Table 4 Local recurrence rates by histological type

Type	Adenoma	M-ca	SM-ca	Unevaluated	Total
En-bloc	1.1%* (2/181)	0.4%* (1/253)	0% (0/5)	0% (0/1)	0.7% (3/440)
Piecemeal	17.1% (6/35)	26.1% (23/88)	25% (2/8)	0% (0/1)	23.5% (31/132)
Total	3.7% (8/216)	7.0% (24/341)	15.4% (2/13)	0% (0/2)	5.9% (34/572)

M-ca intramucosal carcinoma, *SM-ca* submucosal invasive carcinoma
*$P<0.001$

Twenty-eight of the 34 lesions with local recurrence were detected by the first follow-up colonoscopy that occurred at a median of 114 days (range 74–471) after resection. Local recurrence was detected in the remaining six lesions at the second or subsequent colonoscopy that occurred at a median of 726 days (range 337–910). For four of the six local recurrences that were missed by the first colonoscopy, the colonoscopy was performed within 3 months of resection.

The cumulative rate of local recurrence using the Kaplan–Meier method is shown in Fig. 3. The 6-, 12-, and 24-month cumulative local recurrence rate of the en-bloc group was 0.24%, 0.49%, and 0.81%. The 6-, 12-, and 24-month cumulative local recurrence rate for the piecemeal group was 18.4%, 23.1%, and 30.7%. Local recurrences were significantly frequent in the piecemeal group (log rank test, $P<0.001$). Therefore, we considered the proper first follow-up interval for the piecemeal group to be 6 months. The treatment for local recurrence endoscopic resection was performed in 32 cases (94.1%), and almost all of them were performed in a single session (mean 1.1, range 1–2; Fig. 1). Neither bleeding nor perforation occurred during endoscopic treatment. Two patients required additional surgery (Fig. 1), and the finding was intramucosal carcinoma without lymph node metastasis. The rate of additional surgery after endoscopic en-bloc and piecemeal resection was 0.23% (1/440) and 0.75% (1/132).

Discussion

Endoscopic resection for an early colorectal tumor has been used throughout the world since the 1970s [9, 10]. An endoscopic mucosal resection (EMR) with submucosal saline injection technique [1, 11–14] allowed us to remove a large colorectal tumor that appeared to be not only sessile but also flat and depressed. However, local recurrences frequently occurred after endoscopic piecemeal resection for large sessile tumors, which is a serious problem. Previous studies have reported the rate of local recurrence following piecemeal resection to be 25–50% [1, 2, 6]. Consequently, a combination of snare polypectomy and argon plasma coagulator (APC) [4, 5] or YAG laser [3, 15] was attempted to reduce local recurrence. One randomized controlled study demonstrated that there were fewer local recurrences with APC than without APC (1/10 vs. 7/11) [5]. However, the randomized group consisted of the patients in whom initial polypectomy was apparently complete, and local recurrence frequently occurred despite APC in patients with incomplete polypectomies (6/13). On the other hand, Palma et al. [15] reported that YAG laser reduced remnant tumor in ≥40-mm adenomas. However, the number of treatments with the YAG laser were frequently as many as three, which is a disadvantage of the method. The effort to reduce the local recurrence of piecemeal resection has stalled.

In pathologic staging, it is often difficult to evaluate the surgical margins and invasion depth after piecemeal removal of lesions because specimens may be difficult to reconstruct [16]. On the other hand, surgical margins and invasion depth are easily assessed after en-bloc resection

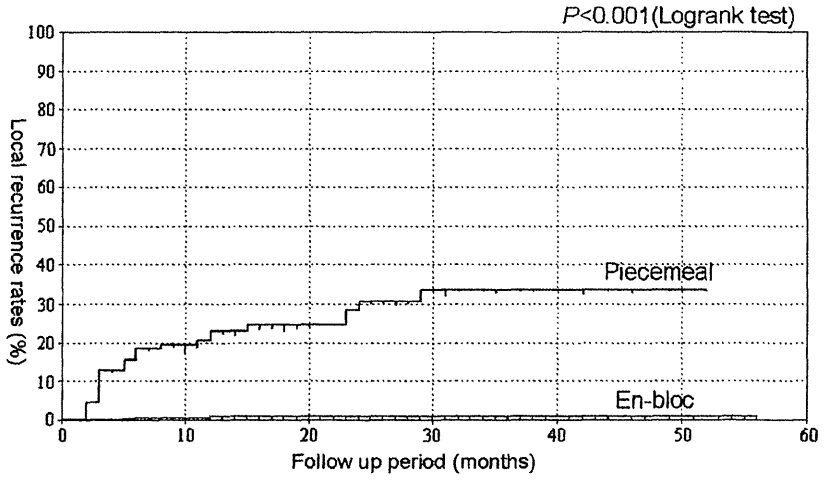

Fig. 3 Cumulative local recurrence rates after endoscopic resection (Kaplan–Meier method)

[16]. Moreover, one can easily evaluate the lateral margin after an en-bloc procedure by immediate observation of the retrieved specimen.

Could the en-bloc method reduce local recurrence after endoscopic resection? In the present study of 572 colorectal tumors that were endoscopically resected, local recurrence occurred for 34 lesions (5.9%). Furthermore, the local recurrence rate for the en-bloc group was significantly lower (0.7%) than that for the piecemeal group (23.5%; $P<0.001$). The difference was maintained in subgroups with different lesion sizes (i.e., 10–19 vs. 20–29 mm). We could rationalize that the 10- to 19-mm lesions in which local recurrence occurred were difficult to locate, and therefore, we could not perform en-bloc resection.

Localization of the lesion in the large bowel is an important factor for the detection of remnant tumor immediately after endoscopic resection. Moreover, neither the macroscopic nor the histological type affected the local recurrence rate. Therefore, en-bloc resection appears to be an important factor for reducing local recurrences. lishi et al. [17]. reported that of 56 large sessile colorectal polyps, the local recurrence after an en-bloc resection was less than that after piecemeal resection (0% vs. 50%). We confirmed this result in a large number of cases in the present study, and we added a detailed analysis for each factor. Although we routinely use magnifying observation of artificial ulcer's edges after endoscopic resection, local recurrence rate of the piecemeal group was significantly higher than the en-bloc group. We speculate this reason that there were micro-residual lesions made by intra-plural snaring method in the center of artificial ulcers, which were difficult to diagnose by observation of ulcer edges. Moreover, higher local recurrence rate might be caused by detailed detection during follow-up colonoscopy using magnified observation.

For the part of large rectal lesions, transanal endoscopic microsurgery (TEM) was considered for an alternative therapy for endoscopic resection. Local recurrence rates (0–10%) of TEM were reported [18], and these were better than our data of endoscopic piecemeal resection. However, TEM required experienced techniques and special instruments, and some complications such as incontinence and urinary retention which never arose in endoscopic resection occur [18].

Recently, several Japanese endoscopists [19, 20] developed novel techniques for large en-bloc resection, endoscopic submucosal dissection (ESD). Gotoda et al. [19] reported EMR on two rectal tumors using an insulation-tipped knife with which they cut the normal mucosa surrounding the target lesions before snaring. Yamamoto et al. [20] successfully removed a 40-mm rectal laterally spreading tumor with submucosal injection of a large amount of sodium hyaluronate. They also cut normal mucosa surrounding the target lesions with a needle knife before snaring. There are several problems with these novel techniques, including technical difficulty, the inability to determine the rate of perforation, and long procedure time. For those reasons, ESD is not widely used.

Based on our result, local recurrence is rare following en-bloc resection. Therefore, the 3- to 5-year interval for surveillance colonoscopy suggested by the national polyp study [7] and the guidelines of the American Gastroenterological Association (AGA) [21] should be appropriate after en-bloc resection. Definite surveillance intervals after incomplete resection have not been proposed by the AGA [21]. In our piecemeal resection group, local recurrence increased gradually from 18.4% at 6 months to 30.8% at 24 months. Based on those findings, an earlier surveillance colonoscopy (e.g., 3 months) would have missed local recurrence. Therefore, a 6-month interval for surveillance colonoscopy after piecemeal resection seems appropriate. That interval will provide accurate diagnosis of local recurrences >50% of the time.

The limitations of our study include using retrospective analysis and being non-randomized. Prospective randomized controlled studies are necessary for determining the appropriate interval for surveillance colonoscopy after piecemeal resection.

In our study, only two instances of local recurrence required additional surgery; the remainder were treated with additional endoscopic resection. We consider piecemeal resection an acceptable treatment until the efficacy and safety of large en-bloc resection are established.

In the future, an effective injection fluid or snare should be developed for safer and larger en-bloc resection based on conventional EMR procedures. We recently injected 10% glycerin solution into the submucosa during EMR, which resulted in a better en-bloc resection rate compared to normal saline [22]. Furthermore, we should make an effort to establish an ESD technique while paying a great deal of attention to safety.

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ORIGINAL ARTICLE – COLORECTAL CANCER

Successful Complete Cure En-Bloc Resection of Large Nonpedunculated Colonic Polyps by Endoscopic Submucosal Dissection: A Meta-Analysis and Systematic Review

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ABSTRACT

Background. Endoscopic submucosal dissection (ESD) has emerged as one of the techniques to successfully resect large colonic polyps en bloc. Complete resection prevents the patient from going through transabdominal colonic resection. We sought to evaluate the proportion of successful en-bloc and complete cure en-bloc resection of large colonic polyps by ESD.

Methods. Studies that use ESD technique to resect large colonic polyps were selected. Successful en-bloc resection was defined as resection of the polyp in one piece. Successful complete cure en-bloc resection was defined as one piece with histologic disease-free-margin polyp resection. Articles were searched in Medline, PubMed, and Cochrane control trial registry. Pooled proportions were calculated by both fixed and random-effects model.

Results. The initial search identified 2,120 reference articles; 389 relevant articles were selected and reviewed. Data were extracted from 14 studies ($n = 1,314$) that met the inclusion criteria. The mean ± standard error size of the polyps was 30.65 ± 2.88 mm. Pooled proportion of en-bloc resection by the random-effects model was 84.91% (95% confidence interval, 77.82–90.82) and complete cure en-bloc resection was 75.39% (95% confidence interval, 66.69–82.21). The fixed-effects model was not used because of the heterogeneity of studies.

Conclusions. ESD should be considered the best minimally invasive endoscopic technique in the treatment of large (>2 cm) sessile and flat polyps because it allows full pathological evaluation and cure in most patients. ESD offers an important alternative to surgery in the therapy of large sessile and flat polyps.

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Endoscopic submucosal dissection (ESD), which was pioneered in Japan for the treatment of early gastric cancers, has now been applied to the colorectum. ESD has an advantage over other endoscopic techniques in that it allows en-bloc removal of large (>2 cm) colonic lesions.[1] ESD uses an electrosurgical cutting device to purposely dissect the deeper layers of the submucosa to remove neoplastic mucosal lesions.

ESD has an advantage over the older technique of endoscopic mucosal resection in that its effectiveness is not limited by the size of the lesion or its configuration. Multiple electrosurgical knives have been used, from a conventional needle knife to other modified accessories.[1–3]

Adenomas represent the single most important premalignant lesions of the colorectum. Pedunculated adenomas are easily removed by loop snare. However, this technique frequently results in piecemeal removal when applied to sessile and flat polyps.[4] ESD has been found to be particularly useful for the removal of sessile or flat adenomatous lesions.[2,3] En-bloc removal is advantageous because it allows full histological evaluation of the complete resection and is associated with a lower recurrence rate when compared with piecemeal removal.[3,5]

With such an important difference in treatment and prognosis between en-bloc versus piecemeal resection, it is important to evaluate the proportion of successful en-bloc and complete cure en-bloc resection of large colonic polyps by ESD. Because of this inconsistency, as well as the clinical importance of ESD for treatment and prognosis, we

performed a meta-analysis to evaluate the proportion of successful en-bloc and complete cure en-bloc resection of large colonic polyps by ESD.

METHODS

Study Selection Criteria

Studies that used the ESD technique to resect large colonic polyps were selected. Successful en-bloc resection was defined as resection of the polyp in one piece. Successful complete cure en-bloc resection was defined as one piece with histologic disease-free-margin polyp resection.

Data Collection and Extraction

Articles were searched in the following databases: Medline (through PubMed, an electronic search engine for published articles and Ovid), Japanese Language Literature, PubMed, Ovid journals, Cumulative Index for Nursing and Allied Health Literature, ACP journal club, DARE, International Pharmaceutical Abstracts, old Medline, Medline nonindexed citations, OVID Healthstar, and Cochrane Central Register of Controlled Trials (CENTRAL). Both English- and Japanese-language literature was searched. The search was performed for studies published in the years 1966 to June 2008. The search terms used were ESD, endoscopic submucosal dissection, colon polyps, lateral spreading tumors, large polyps, nonpolypoid colon lesions, flat colon polyps, and flat adenomas. Two authors (S.P. and Y.K.) independently searched and extracted the data into an abstraction form. Any differences were resolved by mutual agreement.

Quality of Studies

Clinical trials designed with a control and treatment arms can be assessed for quality of the study. A number of criteria have been used to assess this quality of a study (e.g., randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome).[6,7] There is no consensus on how to assess studies without a control arm. Hence, these criteria do not apply to studies without a control arm.[7] Therefore, for this meta-analysis and systematic review, studies were selected on the basis of completeness of data and inclusion criteria.

Statistical Methods

This meta-analysis was performed by calculating pooled proportions (i.e., pooled proportion of en-bloc resection and complete cure en-bloc resection). First the individual study, proportions of successful resection were transformed into a quantity by Freeman–Tukey variant of the arcsine square root–transformed proportion. The pooled proportion was calculated as the backtransform of the weighted mean of the transformed proportions; inverse arcsine variance weights were used for the fixed-effects model, and DerSimonian–Laird weights were used for the random-effects model.[8,9] Forrest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forrest plots indicates the assigned weight to that study. The heterogeneity among studies was tested by Cochran's Q-test on the basis of inverse variance weights.[10] If the P value is $>.10$, it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested by the Begg–Mazumdar bias indicator.[11] Also, funnel plots were constructed to evaluate potential publication bias by means of the standard error and diagnostic odds ratio.[12,13]

RESULTS

Initial search identified 2,120 reference articles; from these, 389 relevant articles were selected and reviewed. Data were extracted from 14 studies ($n = 1{,}314$) that met the inclusion criteria.[3,14–26] The search results are shown in Fig. 1. The mean ± standard error size of the polyps was 30.65 ± 2.88 mm. There were 1,105 successful en-bloc resections.

Pooled proportion of successful en-bloc resection by the random-effects model was 84.91% (95% confidence interval, 77.82–90.82). The Forrest plot in Fig. 2 depicts the individual study proportion of successful en-bloc resection in relation to the pooled estimate. The pooled proportion for successful complete cure en-bloc resections

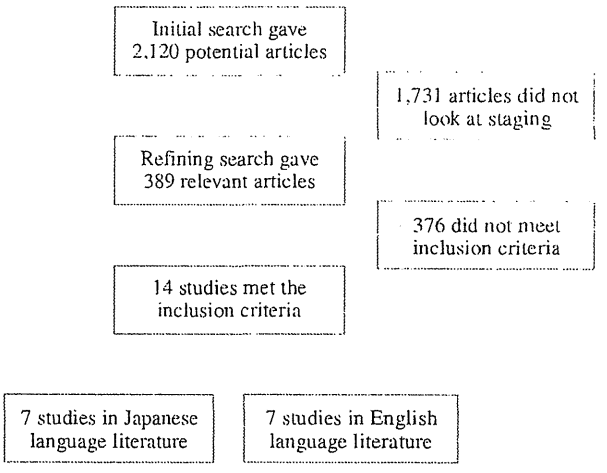

FIG. 1 Search results

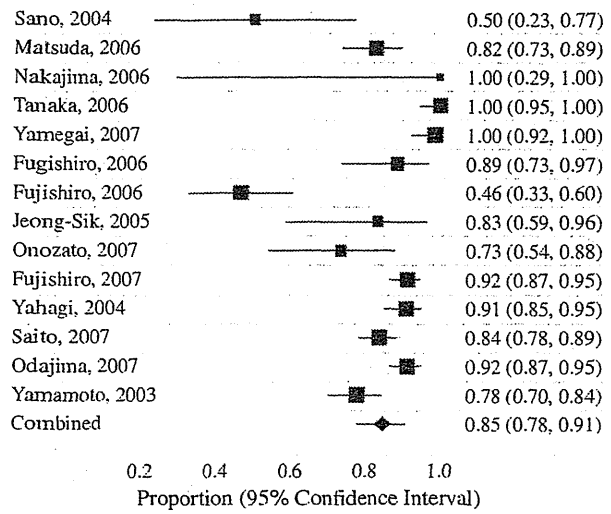

FIG. 2 Forrest plot showing successful en-bloc resection

by the random-effects model was 75.39% (95% confidence interval, 66.69–82.21). Figure 3 shows a Forrest plot depicting the individual study successful cure en-bloc resection in relation to the pooled estimate. The fixed-effects model was not used because of the heterogeneity of studies.

Subgroup analysis was performed by grouping studies according to the study population. This was done because the expertise required to perform procedures might affect the outcome. Studies were grouped into two groups: <100 patients and >100 patients. The proportion for successful en-bloc and successful cure en-bloc resections are shown in Table 1. The proportions shown in Table 1 were obtained by the random-effects model.

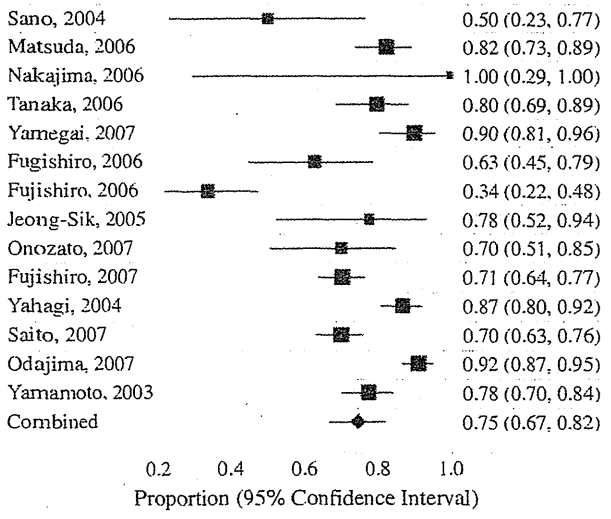

FIG. 3 Forrest plot showing successful complete cure en-bloc resection

The publication bias calculated by Begg-Mazumdar bias indicator for successful en-bloc resection gave a Kendall's tau b value of $-.31$ ($P = .14$), and for successful cure en-block resection, it was $-.16$ ($P = .38$). The funnel plot in Fig. 4 shows the publication bias for successful cure en-bloc resection.

DISCUSSION

Most colorectal cancers develop from adenomas. The risk of high-grade dysplasia and cancer has been found to increase with the size of the lesion.[27] Although traditional loop snare polypectomy has been found to be effective to treat large pedunculated neoplasias, its effectiveness in the therapy of sessile and flat polyps has been disappointing, frequently requiring piecemeal resection and additional procedures or therapies.[28,29] Surgical therapy of these large sessile and flat lesions continues to be an important alternative to endoscopic therapy, especially in the Western world.[30]

Although the procedure was initially developed to treat early gastric cancers, ESD has been found to be effective in the therapy of large (>2 cm) benign colorectal neoplastic lesions and early colorectal malignancy. ESD has an advantage over traditional loop snare polypectomy and endoscopic mucosal resection in that its effectiveness is not constrained by the size of the snare or by the configuration of the lesion.[1,3]

Our meta-analysis revealed that ESD en-bloc resection is achieved in 84.91% of lesions, and clear vertical and lateral margins are achieved in 75.39%. These results compare well to en-bloc resections achieved by conventional polypectomy snare, which have been reported to be between 7% and 34% for the treatment of large sessile polyps.[4,29] Our meta-analysis also reveals that experience with ESD plays an important role in achieving a better en-bloc resection and en-bloc cure. Studies with >100 lesions reported a pooled successful en-bloc resection of 87.77%, and clear vertical and lateral margins were achieved in 79.67%. In studies with <100 lesions, the pooled successful en-bloc resection drops to 82.6%, and clear vertical and lateral margins were achieved in 71.2%.

A limitation of this meta-analysis is that there was heterogeneity among studies; we thus used the random-effects model instead of the fixed-effects model. However, to overcome any potential bias, we looked into the world literature, which included articles published in Japanese. We think that our results are a true reflection of the status of ESD in the therapy of large polyps of the colon.

ESD is an innovative technique for resection of large nonpedunculated polyps of the colon, and we think that it should be considered the best minimally invasive

TABLE 1 Pooled proportion of successful en-bloc and cure en-bloc resection based on study size

Study size	No. of studies	Successful en-bloc resection, % (95% CI)	Complete cure en-bloc resection, % (95% CI)
<100 patients	9	82.60 (66.45–94.22)	71.23 (57.17–83.46)
>100 patients	5	87.77 (85.55–89.84)	79.67 (76.97–82.25)

95% CI, 95% confidence interval

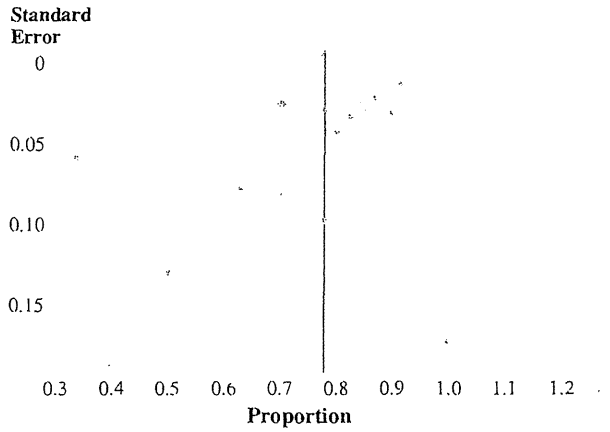

FIG. 4 Funnel plot showing publication bias for successful complete cure en-bloc resection

endoscopic technique in the treatment of large (>2 cm) sessile and flat polyps because it allows full pathological evaluation and cure in most patients. In addition, improvement in techniques and equipment are likely to improve complete cure en-bloc resection. ESD offers an important alternative to surgery in the therapy of large sessile and flat polyps.

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CURRENT STATUS AND FUTURE PERSPECTIVE OF ENDOSCOPIC TREATMENT FOR COLORECTAL NEOPLASIA

ENDOSCOPIC SUBMUCOSAL DISSECTION IN THE COLORECTUM: PRESENT STATUS AND FUTURE PROSPECTS

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Endoscopic submucosal dissection (ESD) can successfully resect early stage gastrointestinal tumors, but colorectal ESDs are not widely performed, even by Japanese endoscopists, because of several negative factors. Besides being considerably more difficult in terms of technical demands, colorectal ESDs involve a longer procedure time and have a higher complication rate compared to gastric ESDs. In addition, most colorectal lesions are adenomas or intramucosal cancers that despite their large size that can be curatively treated by endoscopic mucosal resection including piecemeal resection.

There is, however, no doubt about ESD having a major therapeutic advantage in being able to achieve a higher en-bloc resection rate resulting in enhanced curability and more accurate histopathological assessment. Continued improvement in the technical skills of endoscopists, further refinement of such devices as electrical surgical knives and a special colonoscope as well as the development of more effective submucosal injection solutions and new traction systems are expected to facilitate easier, faster and safer colorectal ESD procedures in the relatively near future.

Key words: colorectum, endoscopic submucosal dissection (ESD), perforation, thin endoscope assisted-ESD (TEA-ESD), training.

INTRODUCTION

Endoscopic submucosal dissection (ESD) can successfully resect early stage gastrointestinal tumors *en bloc* including large lesions and lesions with submucosal fibrosis and ulceration scarring.[1–9] The acceptance of ESD for treating early gastric cancer has steadily increased in many Japanese medical centers, but colorectal ESDs are not widely performed by endoscopists in Japan because of a greater level of technical difficulty, longer procedure times and a higher risk of complications, such as perforations, compared to gastric ESDs.[5,10–16]

This review focuses on the present status of colorectal ESD, taking into account recent advances as well as future prospects for this very promising procedure, with continued improvement in technical skills and further refinement and development of new endoscopic devices, materials and techniques.

TECHNICAL ISSUES ASSOCIATED WITH COLORECTAL ESD

Lack of education and training programs

There are no education and training programs for colorectal ESD in Japan at the present time. The first author, for example, is the only endoscopist currently capable of performing this procedure at his hospital.

Given the increased level of technical difficulty involved in colorectal ESD and the complete lack of any existing education and training programs, it is, therefore, strongly recommended that endoscopists obtain the requisite experience by performing a sufficient number of gastric ESDs before attempting colorectal ESD. We recommend at least 20 such gastric ESDs as a minimum and the initial colorectal ESDs should be performed in the rectum because rectal lesions are technically less difficult to treat endoscopically with a lower risk of perforation.

Longer procedure time

The reported procedure times for colorectal ESDs have ranged between 70 and 110 minutes.[10,12–14] The actual time required depends on a number of factors, of course, particularly an individual lesion's characteristics, but it is generally regarded that colorectal ESD requires more time than gastric ESD.

The graph in Fig. 1 indicates the relationship between procedure time and lesion size in our hospital. Although it seems obvious, the necessity of longer procedure times as lesion size increased was clearly indicated with a high correlation coefficient.

Perforation

The narrow angulated lumen and thinner wall in the colorectum make it difficult to control the endoscope and resect

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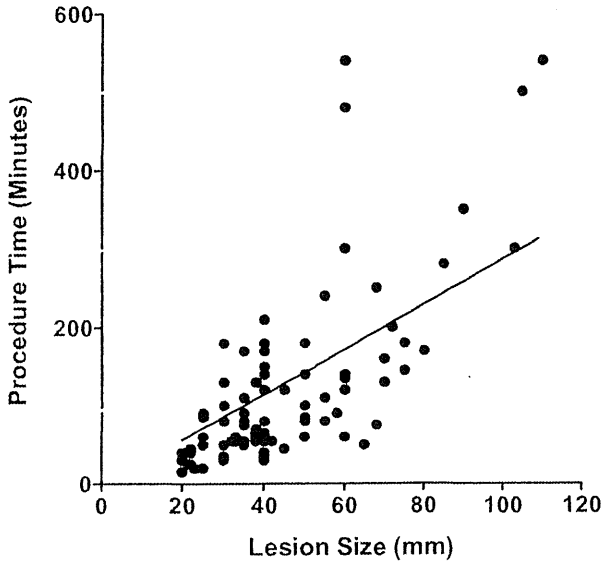

Fig. 1. Relationship between lesion size and procedure time at our hospital. The endoscopic submucosal dissection procedure took longer as lesion size increased, with a correspondingly high correlation coefficient (0.6386, $P < 0.001$).

safely during colorectal ESD. Perforation is a serious complication requiring immediate management especially in the colorectum because of the greater possibility of peritonitis due to the presence of fecal fluid.

When colorectal ESDs were initially being performed, the perforation rate was reported to have been approximately 10%.[17,18] More recent reports from medical centers specializing in ESDs, however, have indicated better results attributable to improved technical ability and the refinement of new endoscopic devices and techniques.[19]

Endoscopic submucosal dissection specialists have also mastered effective complication management methods such as the use of endoclips.[17,20] Successful endoscopic closure of perforations and the administration of antibiotics following ESD procedures have now made it possible to conservatively treat most patients with perforations, and emergency surgery has become quite rare.

MINIMIZING NEGATIVE FACTORS

In order to reduce the effect of these negative factors, further refinement of such devices as electrical surgical knives and a special colonoscope in addition to the development of improved submucosal injection solutions and better traction systems will be necessary.

Combination use of electrical surgical knives

Early ESD pioneers developed various surgical knives, but most endoscopists now performing colorectal ESD combine the use of different electrical surgical knives during the actual procedure. Using a combination of various electrical surgical knives is preferred because it shortens the procedure time while ensuring a higher level of safety in virtually all situations.

The combined use of a Flex knife (Olympus Co., Tokyo, Japan) and a Hook knife (Olympus)[5,8,13] and a Flush knife (FTS, Omiya, Japan) together with a Hook knife[9] have both been reported previously. We primarily use a bipolar current needle knife (B-knife, Zeon Medical Inc., Tokyo, Japan),[10-12,16,21] which has been specifically designed so high-frequency current sent to the muscle layer is reduced for better control and safer use with the current flowing back from the knife towards the sheath tip, in combination with an insulation-tipped knife (IT knife; Olympus) to shorten the procedure time[10,12] and/or a Mucosectom (PENTAX Co., Tokyo, Japan)[7] for safer dissection of submucosal fibrosis and ulceration scar tissue with satisfactory clinical treatment outcomes.

Among 137 ESDs performed between April 2006 and October 2008 in our hospital, the en-bloc resection rate was 91%, the median procedure time was 75 minutes and the mean size of resected specimens was 43 mm. Perforations that occurred in 3% of all cases could be successfully managed using endoclips without the necessity for surgical treatment.

Thin endoscope assisted-ESD

We developed a thin endoscope assisted-ESD (TEA-ESD) traction system to improve direct visualization of the submucosal layer cutting line.[16] This procedure is performed (Fig. 2) with a primary gastroscope and a second thinner endoscope, 6.5 mm in diameter, each of which is operated by a different endoscopist. After a circumferential incision and partial exfoliation have been completed, an endoclip is attached to the edge of the exfoliated mucosa. The thinner endoscope is then inserted into the lumen and a snare is used to grasp the positioned endoclip and pull the lesion away from the muscle layer. Traction direction is easily controlled because of the flexibility of the thinner endoscope and direct cutting line visualization is maintained by retracting the submucosal layer tissue resulting in a safe dissection.

As a result of improved direct visualization having been achieved with the TEA-ESD traction system, it is expected that continued use of this technique will result in both reducing the perforation rate and shortening the colorectal ESD procedure time. We are now prospectively performing TEA-ESDs to remove laterally spreading tumors >20 mm located in the rectum and sigmoid colon to evaluate the safety and efficacy of this procedure.

Special colonoscope for colorectal ESD

Recently, a special 10.5 mm-diameter pediatric type EMR/ESD colonoscope with a water-jet function (PCF-260JI; Olympus) has become available in Japan facilitating even safer and more efficient ESD colorectal procedures. This colonscope's small caliber, shorter bend at the top and increased flexibility make it easier to use the retroflex position in the narrow colorectal lumen. Water is supplied through the accessory channel when the endoscopist simply steps on a foot switch. The water-jet function helps to improve direct cutting line visualization and identify any bleeding points without the necessity of taking various devices like an electrical surgical knife or coagulation forceps

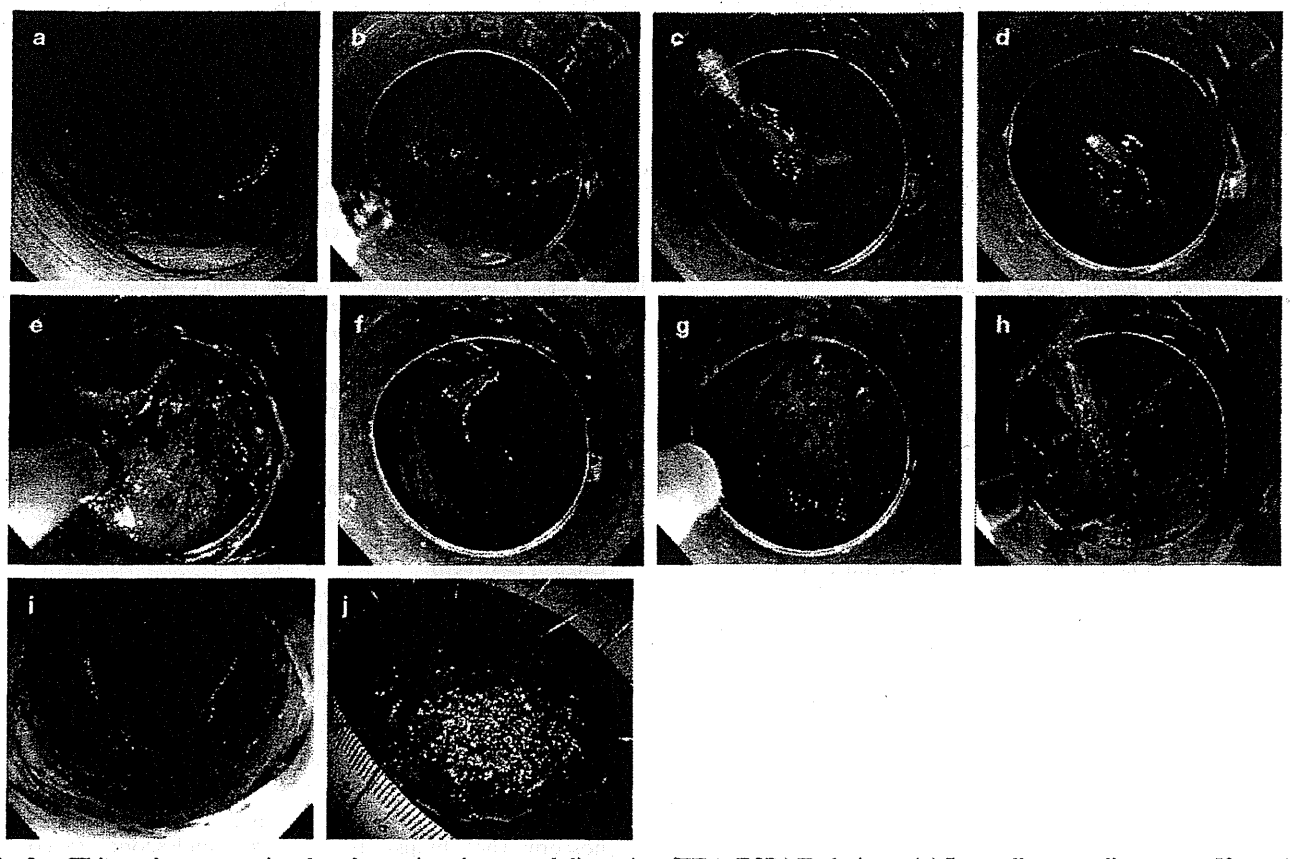

Fig. 2. Thin endoscope assisted-endoscopic submucosal dissection (TEA-ESD) Technique. (a) Laterally spreading tumor 50 mm in diameter located in lower rectum. (b) After submucosal injection, we performed circumferential incision and partial exfoliation. (c) Endoclip attached to edge of exfoliated mucosa. (d) Second thinner endoscope inserted into lumen and snare introduced through working channel grasped endoclip and pulled lesion away from muscle layer. (e) Thinner endoscope provided sufficient traction. (f) Thinner endoscope facilitating sufficient traction easily controlled by flexible endoscope. (g) Submucosal dissection safely and successfully performed by TEA-ESD. (h) Final stage of TEA-ESD. (i) Successful en-bloc resection without complication. (j) Histopathological diagnosis revealed well-differentiated adenocarcinoma, M, lymphovascular invasion (-) and cut end (-).

in and out during the procedure. Use of this function should contribute to shorter procedure times and safer submucosal dissections.

FUTURE PROSPECTS

Further refinements in colorectal ESD devices and techniques are expected to be standardized in the future. Colonoscopes will have enhanced features such as greater flexibility and be multifunctional including the ability to release and retract multiple devices instantly. Control of electrical surgical knives and traction forceps will also be considerably more flexible than with the devices currently in use.

In order to assist endoscopists in acquiring the necessary colorectal ESD skills more efficiently, the development of a simulation system involving an ESD training model such as the stomach of a pig is important. Eventually, a robotic system with remote control of newly developed devices and techniques may be feasible.

There is no doubt about ESD being a significant advancement in therapeutic endoscopy with the major advantage of being able to achieve a higher en-bloc resection rate resulting in enhanced curability and more accurate histopathological assessment. While still in the developmental stages at the present time, it is certainly conceivable that colorectal ESD could become the standard procedure for treating large lesions and lesions with submucosal fibrosis and ulceration scarring as continued advances are made that facilitate easier, faster and safer procedures in the relatively near future.

CONFLICT OF INTEREST

No conflict of interest has been declared by T Uraoka, Y Kawahara, J Kato, Y Saito or K Yamamoto.

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BRIEF ARTICLES

Meta-analysis and systematic review of colorectal endoscopic mucosal resection

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Abstract

AIM: To evaluate the proportion of successful complete cure *en-bloc* resections of large colorectal polyps achieved by endoscopic mucosal resection (EMR).

METHODS: Studies using the EMR technique to resect large colorectal polyps were selected. Successful complete cure *en-bloc* resection was defined as one piece margin-free polyp resection. Articles were searched for in Medline, Pubmed, and the Cochrane Control Trial Registry, among other sources.

RESULTS: An initial search identified 2620 reference articles, from which 429 relevant articles were selected and reviewed. Data was extracted from 25 studies (n = 5221) which met the inclusion criteria. All the studies used snares to perform EMR. Pooled proportion of *en-bloc* resections using a random effect model was 62.85% (95% CI: 51.50-73.52). The pooled proportion for complete cure *en-bloc* resections using a random effect model was 58.66% (95% CI: 47.14-69.71). With higher patient load (> 200 patients), this complete cure *en-bloc* resection rate improves from 44.19% (95% CI: 24.31-65.09) to 69.17% (95% CI: 51.11-84.61).

CONCLUSION: EMR is an effective technique for the resection of large colorectal polyps and offers an alternative to surgery.

INTRODUCTION

The use of endoscopic mucosal resection (EMR), pioneered in Japan for the treatment of early gastric cancer, has expanded to include therapy of other early gastrointestinal malignancies and pre-cancerous lesions such as adenomas. At the same time, this technique has gained acceptance in Europe and in the US, especially for the treatment of Barrett's esophagus with high grade dysplasia[1-3]. Several variations of the EMR technique have been devised such as inject-lift-cut, strip biopsy, suction cup (EMRC), and EMR with a ligating device.

Throughout the world, adenomas of the colorectum represent the single most important premalignant lesion of the GI tract. Large (> 2 cm) colorectal polyps have been found in 0.8%-5.2% of patients undergoing colonoscopies for different indications[4].

Large sessile and flat polyps represent a major technical challenge to conventional snare resection. Additional procedures and therapies such as Argon plasma coagulation are frequently needed to destroy remnant tissue after resection[5]. When these techniques are not used or possible, patients are frequently referred for surgical resection[6].

EMR has been shown to be useful in the removal of large colorectal sessile and flat lesions[7]. However, there are limits to the size of lesions which can be removed *en-bloc* with the various EMR techniques, with 1.5-2 cm generally being the upper limit[8].

En-bloc removal of large polyps is desirable as it facilitates thorough histological evaluation related to the

completeness of resection, and is associated with a lower recurrence rate as compared to piecemeal removal[9-14].

MATERIALS AND METHODS

Study selection criteria

Studies using EMR technique to resect large (> 2 cm) colorectal polyps were selected. Successful cure *en-bloc* resection was defined as one piece removal with tumor-free vertical and lateral margins.

Data collection and extraction

Articles were searched for in Medline, Pubmed, Ovid journals, Japanese language literature, Cumulative Index for Nursing & Allied Health Literature, ACP journal club, DARE, International Pharmaceutical Abstracts, old Medline, Medline non-indexed citations, OVID Healthstar, and the Cochrane Controlled Trials Registry. The search terms used were EMR, endoscopic mucosal resection, colon polyps, lateral spreading tumors, large polyps, nonpolypoid colon lesions, flat colon polyps, and flat adenomas. Two authors (SP and YK) independently searched and extracted the data for revising into an abstracted form. Any differences were resolved by mutual agreement.

Quality of studies

Clinical trials with a control arm can be assessed for the quality of the study. A number of criteria have been used to assess the quality of a study (e.g. randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome)[15,16]. There is no consensus regarding how to assess studies without a control arm. Hence, these criteria do not apply to studies without a control arm[16]. Therefore, for this meta-analysis and systematic review, studies were selected based on completeness of data and inclusion criteria.

Statistical methods

This meta-analysis was performed by calculating pooled proportions, i.e. pooled proportion of *en-bloc* resections and complete cure *en-bloc* resections. Firstly, the individual study proportions of successful resections were transformed into a quantity using Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion was calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-Laird weights for the random effects model[17,18]. Forrest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forrest plots indicated the assigned weight to that study. The heterogeneity among studies was tested using Cochran's Q test based upon inverse variance weights[19]. If P value was > 0.10, the null hypothesis was rejected that the studies were heterogeneous. The effects of publication and selection bias on the summary estimates were tested by Begg-Mazumdar bias indicator[20]. Also, funnel plots were constructed to evaluate potential publication bias using the standard error and diagnostic odds ratio[21,22].

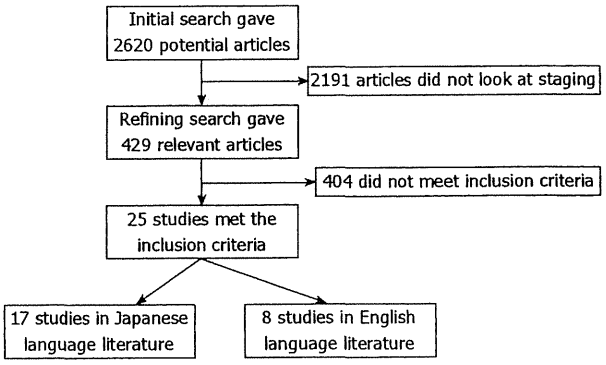

Figure 1 Search results.

RESULTS

An initial search identified 2620 reference articles from which 429 relevant articles were selected and reviewed. Data was extracted from 25 studies (n = 5221) which met the inclusion criteria[23-46]. The search results are shown in Figure 1. All the studies used snare to perform EMR. Two studies used a strip biopsy technique[42,43]. The mean size of the polyps was 22.48 ± 4.52 mm. There were 3755 successful *en-bloc* resections. The study characteristics are shown in Table 1.

The pooled proportion of *en-bloc* resections using a random effect model was 62.85% (95% CI: 51.50-73.52). Forest plot in Figure 2A depicts the individual study proportion of successful *en-bloc* resections in relation to the pooled estimate. The pooled proportion for complete cure *en-bloc* resections using a random effect model was 58.66% (95% CI: 47.14-69.71). Figure 2B shows Forrest plot depicting the individual study successful cure *en-bloc* resections in relation to the pooled estimate. The fixed effect model was not used because of the heterogeneity of studies.

Subgroup analysis was carried out by grouping studies according to the study population. This was done because the expertise needed to perform procedures might have affected the outcome. Studies were categorized into three groups: < 100 patients, 100-200 patients and > 200 patients. The proportions for successful *en-bloc* and successful cure *en-bloc* resections are shown in Table 2.

The publication bias calculated by Begg-Mazumdar bias indicator for successful cure *en-bloc* resections concluded that the Kendall's tau b value was -0.19 (P = 0.17). The funnel plot in Figure 3 shows that there was no publication bias for successful cure *en-bloc* resections.

DISCUSSION

Some colorectal cancers develop from adenomas. The risk of high grade dysplasia and cancer increases with the size of the lesion. Endoscopic removal of large (> 2 cm) sessile and flat polyps represents a difficult challenge for conventional snare resection and they are frequently managed by piecemeal resection or surgically[6,47]. EMR was the definitive procedure in all the collated studies. The data for complications was not available for the majority of the studies, so this data was not collected. EMR is a technique that can be applied to sessile and flat

	Author, yr	Instrument used	*n*	Type of polyp	Technique
1	Matsushita *et al*[23], 2003	Snare	935	No information	EMR
2	Imai *et al*[24], 1999	Snare	30	No information	EMR
3	Igarashi *et al*[25], 1999	Snare	884	No information	EMR
4	Oka *et al*[26], 2005	Snare	410	Lateral spreading tumor	EMR
5	Sano *et al*[27], 2004	Snare	392	Lateral spreading tumor	EMR
6	Hotta *et al*[28], 2003	Snare	284	Protrusion 68, flat 213, depressed 3	EMR
7	Matsuda *et al*[29], 2006	Snare	154	Is,Isp 33, LST-G 96, NG 25	EMR
8	Yasumoto *et al*[30], 2005	Snare	240	LST-G 180, NG 60	EMR
9	Terai *et al*[31], 2003	Snare	223	Lateral Spreading tumor	EMR
10	Nozaki *et al*[32], 2006	Snare	198	Ip 3, Isp 34, Is 7, LST-G 85, NG 28	EMR
11	Watari *et al*[33], 1998	Snare	186	Lateral spreading tumor	EMR
12	Sugisaka *et al*[34], 2003	Snare	162	No information	EMR
13	Matsunaga *et al*[35], 1999	Snare	134	No information	EMR
14	Nomura *et al*[36], 2001	Snare	54	No information	EMR
15	Kobayashi *et al*[37], 1999	Snare	131	No information	EMR
16	Nakajima *et al*[38], 2006	Snare	52	No information	EMR
17	Cho *et al*[39], 1999	Snare	34	No information	EMR
18	Saito *et al*[40], 2001	Snare	170	Lateral spreading tumor	EMR
19	Tanaka *et al*[13], 2001	Snare with needle spike	81	Lateral spreading tumor	EMR
20	Ahmad *et al*[41], 2002	Snare with suction	41	Colon and rectum	EMR
21	Hurlstone *et al*[42], 2004	Strip technique of Karita	80	Rectal villous adenoma	EMR
22	Hurlstone *et al*[43], 2005	Strip technique of Karita	62	Rectal villous adenoma	EMR
23	Su *et al*[44], 2005	Snare with needle spike	152	Colonic nonpolypoid lesions	EMR
24	Uraoka *et al*[45], 2005	Snare	113	Lateral spreading tumor	EMR
25	Kawamura *et al*[46], 1999	Snare	19	Submucosal invasive colorectal cancers	EMR

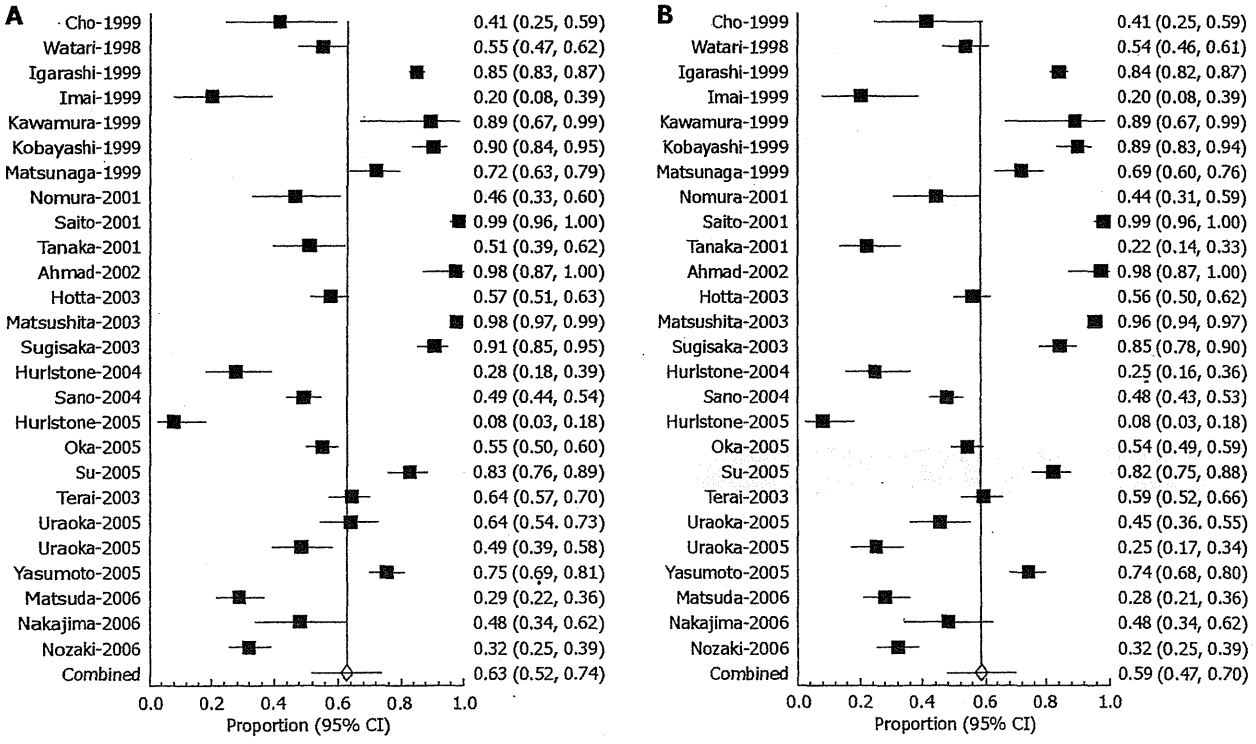

Figure 2 Forrest plot showing successful *en-bloc* (A) and cure *en-bloc* (B) resection.

lesions. Though initially used for the treatment of early gastric cancer in Japan, the technique has been expanded to the therapy of large colorectal neoplasms[7].

This meta-analysis revealed that *en-bloc* resection was achieved in 62.85% of lesions and tumor-free vertical and lateral margins were achieved in 58.6%. These results compare well to *en-bloc* resection rates achieved by conventional polypectomy snare, which have been reported to be between 7% and 34% for large sessile polyps[6,48].

Furthermore, our meta-analysis revealed that experience performing EMR plays an important role in achieving a better *en-bloc* resection and cure *en-bloc* tumor-free rate. Studies reporting more than 200 lesions removed reported a 71.39% *en-bloc* resection of lesions and tumor-free vertical and lateral margins in 69.17% of cases, while studies reporting less than a 100 lesions reported a

Study size	No. of studies	Successful *en-bloc* resection (95% CI)	Successful cure *en-bloc* resection (95% CI)
< 100 patients	9	48.07% (28.36-68.09)	44.19% (24.31-65.09)
100-200 patients	9	68.93% (50.39-84.76)	63.32% (43.50-81.04)
> 200 patients	7	71.39% (52.24-87.20)	69.17% (51.11-84.61)

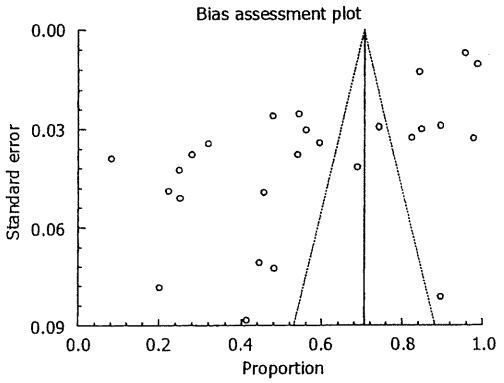

Figure 3 Funnel plot showing publication bias for successful cure *en-bloc* resection.

48.07% *en-bloc* removal and tumor-free vertical and lateral margins in 44.19% of cases. This indicates that experience in the technique of EMR increase the cure *en-bloc* rate.

In the present meta-analysis we searched the world literature which included articles published in Japanese language literature. We believe that our results are a reasonable reflection of the status of EMR in the therapy of large colorectal polyps.

EMR is an effective technique for resection of large colorectal polyps. The technique offers an alternative to surgery. This meta-analysis shows that the success rate for *en-bloc* margin-free resection is not high but improves with experience. Improvements in techniques and equipment are needed to increase complete cure *en-bloc* resection rates.

COMMENTS

Background

Endoscopic mucosal resection (EMR) has emerged as an alternative to surgery for the resection of large colorectal polyps. Complete cure with tumor-free lateral and vertical margins would prevent further therapy. Published data regarding successful *en-bloc* resection with tumor-free margins by EMR has been varied.

Innovations and breakthroughs

EMR has been shown to be useful in the removal of large colorectal sessile and flat lesions. However, there are limits to the size of lesions which can be removed *en-bloc* with the various EMR techniques, with 1.5-2 cm generally being the upper limit. *En-bloc* removal of large polyps is desirable as it facilitates thorough histological evaluation related to the completeness of resection, and is associated with a lower recurrence rate as compared to piecemeal removal.

Applications

EMR is an effective technique for resection of large colorectal polyps and offers an alternative to surgery. This meta-analysis shows that the success rate for *en-bloc* margin-free resection is not high but improves with experience. Improvements in techniques and equipment are needed to increase complete cure *en-bloc* resection.

Peer review

The authors evaluated the proportion of successful complete cure *en-bloc* resections of large colorectal polyps achieved by EMR. They found that EMR is an effective technique for resection of large colorectal polyps. This article is well written and easy to read.

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BRIEF ARTICLE

CO_2 insufflation for potentially difficult colonoscopies: Efficacy when used by less experienced colonoscopists

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Abstract

AIM: To clarify the effectiveness of CO_2 insufflation in potentially difficult colonoscopy cases, particularly in relation to the experience level of colonoscopists.

METHODS: One hundred twenty potentially difficult cases were included in this study, which involved females with a low body mass index and patients with earlier abdominal and/or pelvic open surgery or previously diagnosed left-side colon diverticulosis. Patients receiving colonoscopy examinations without sedation using a pediatric variable-stiffness colonoscope were divided into two groups based on either CO_2 or standard air insufflation. Both insufflation procedures were also evaluated according to the experience level of the respective colonoscopists who were divided into an experienced colonoscopist (EC) group and a less experienced colonoscopist (LEC) group. Study measurements included a 100-mm visual analogue scale (VAS) for patient pain during and after colonoscopy examinations, in addition to insertion to the cecum and withdrawal times.

RESULTS: Examination times did not differ, however, VAS scores in the CO_2 group were significantly better than in the air group ($P < 0.001$, two-way ANOVA) from immediately after the procedure and up to 2 h later. There were no significant differences between either insufflation method in the EC group ($P = 0.29$), however, VAS scores for CO_2 insufflation were significantly better than air insufflation in the LEC group ($P = 0.023$) immediately after colonoscopies and up to 4 h afterwards.

CONCLUSION: CO_2 insufflation reduced patient pain after colonoscopy in potentially difficult cases when performed by LECs.

Key words: CO_2 insufflation; Colonoscopy; Difficult colonoscopy; Experienced colonoscopist; Training

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INTRODUCTION

Colonoscopy has a high profile because of its increasingly important role in successfully preventing, detecting and treating colorectal cancer[1,2], however, some patients experience considerable abdominal pain and discomfort when the procedure is performed using air insufflation. In particular, the so-called "difficult colonoscopy" cases[3-6], which involve female patients with a relatively

low body mass index (BMI), patients with a history of abdominal and/or pelvic open surgery and male patients with diverticulosis, often require prolonged insertion to the cecum, thus this procedure can cause increased abdominal pain and discomfort for such patients.

Factors accounting for longer examination times and increased abdominal pain and discomfort can be derived from both a patient's condition and the examining colonoscopist's skill and experience[7-9]. Novice and even moderately skilled colonoscopists must improve their technical abilities by gaining experience in successfully handling difficult colonoscopies to become qualified experts, as a suitably high-level colonoscopy training environment has not been established as yet[10,11].

CO_2 insufflation has been reported to reduce patient abdominal pain and discomfort during and after colonoscopies[12-15]. Although the safety and efficacy of CO_2 insufflation during colonoscopies have been assessed in earlier studies, air insufflation is still the standard method due to a lack of suitable equipment and inadequate information as to when and on whom CO_2 insufflation should be used during colonoscopy examinations.

We decided to conduct a prospective randomized controlled trial to test the hypothesis that CO_2 insufflation reduces patient abdominal pain and discomfort during and after colonoscopy examinations in potentially difficult cases.

MATERIALS AND METHODS

Study protocol

Consecutive patients considered potentially difficult cases for colonoscopic intubation were included in this prospective randomized controlled trial which took place between September 2006 and October 2007. The aim of this study was to clarify the effectiveness of CO_2 insufflation during colonoscopy examinations, with the primary objectives of assessing both patient tolerance and the safety of CO_2 insufflation in these potentially difficult cases. A secondary objective was to clarify any differences between the two insufflation methods in relation to the experience level of the participating colonoscopists. This study was approved by the Ethics Committee at Okayama University Hospital.

Patients

Patients considered potentially difficult colonoscopy cases, based on published information and clinical experience, were selected, and included females with a relatively low BMI (BMI < 22), patients with a history of abdominal and/or pelvic open surgery, with the exception of low risk procedures for adhesions such as appendectomy or hernia repair, and male patients with previously diagnosed left-side diverticulosis[3-6].

The indications for colonoscopy examination were the standard clinical criteria: colorectal cancer screening, surveillance for polyps, a positive fecal occult blood test, abdominal symptoms or anemia. Exclusion factors included severe heart or lung disease, a prior colorectal resection, inflammatory bowel disease, severe hematochezia and repeat colonoscopy for therapeutic procedures including polypectomy.

Written informed consent was obtained from each patient and enrolled patients were randomly divided into two groups for colonoscopy examinations using either CO_2 or standard air insufflation. Group allocation for both patients and colonoscopists was performed by specially assigned nurses using standard randomization lists which contained consecutive patient numbers. Each number was linked to one of the two study groups for allocation purposes. These lists were not accessible by the participating colonoscopists.

Colonoscopy using CO_2 insufflation

Patients underwent bowel preparation with sodium picosulfate the day before their examinations and two liters of polyethylene glycol solution-containing lavage the morning of their colonoscopies. Scopolamine butylbromide (20 mg) was administered intramuscularly to suppress bowel movement, while patients with cardiac disease or benign prostatic hypertrophy received glucagon (1 IU) intramuscularly. Patients were not sedated, although midazolam (2-3 mg, iv) was administered based on the examining colonoscopist's judgment or when requested by the patient due to abdominal pain or distension. Examinations were performed using a pediatric variable-stiffness colonoscope (PVSC) with a distal tip diameter of 11.3 mm (PCF-Q260AI, Olympus Co, Tokyo, Japan).

Procedures were randomly performed by eight colonoscopists who had earlier been divided into two groups according to their colonoscopy experience: four highly experienced colonoscopists (EC) group each of whom had been in colonoscopy practice for over 10 years (TU, JK, KT and SH), and four less experienced colonoscopists (LEC) group with 5-7 years of colonoscopy practice during which each had performed 900-1500 colonoscopies (MK, SI, KH and HF).

If an examining colonoscopist from the LEC group failed to pass through the sigmoid-descending colon junction within 15 min or a patient complained of severe pain, a colonoscopist from the EC group replaced the initial examiner before midazolam was administered and continued insertion to the cecum. When such a case involved a colonoscopist from the EC group as the initial examiner, a more experienced member of the EC group would continue the procedure. After reaching the cecum, the initial examiner proceeded with withdrawal of the colonoscope.

A "complete colonoscopy" was defined as successful insertion to the cecum bottom or terminal ileum. Insertion to the cecum and withdrawal time was recorded for every colonoscopy.

CO_2 insufflation and monitoring system

CO_2 was administered using a commercial CO_2 regulator (Gas Regulator, Crown, Model FR-IIS-P; Yutaka Engineering, Tokyo, Japan) connected to a CO_2 bottle.

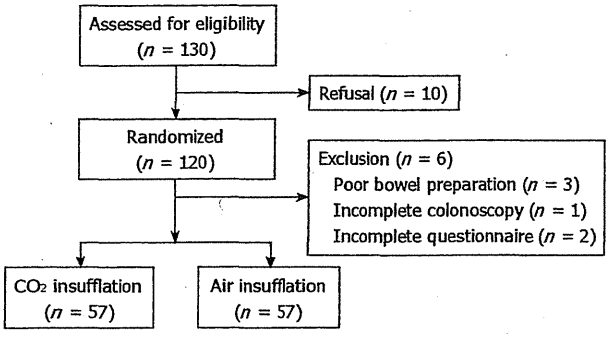

Figure 1 Patient flow chart.

The regulator delivered CO_2 at the rate of 2 L/min. CO_2 and air insufflations were used in a blind fashion both to patients and colonoscopists with full-day colonoscopy sessions randomly assigned CO_2 or air insufflation to avoid unblinding caused by set-up changes between patients.

CO_2 partial pressure was continuously measured using a transcutaneous CO_2 monitoring system (TOSCA 500; Radiometer Basel AG, Switzerland). Processed transcutaneous CO_2 readings ($PtcCO_2$) correlate closely with directly obtained arterial blood gas results[16,17]. Sensors were attached to a patient's ear lobe with a monitor-specific clip. A colonoscopy assistant recorded readings and an independent observer monitored gas readings to avoid potential serious side effects. CO_2 insufflation was stopped immediately if $PtcCO_2$ registered > 60 mmHg during any colonoscopy examination.

Pain and discomfort measurement

A 100-mm visual analogue scale (VAS) consisting of a horizontal line 100 mm in length was used for measuring patient abdominal pain and discomfort (0 mm = painless, 100 mm = extremely painful)[18]. Patients recorded the pain level experienced upon reaching the cecum bottom, immediately following their examinations and 30 min, 1, 2, 4 and 6 h afterwards. The VAS score was the distance measured to the nearest millimeter from the left end of the line to the point of the patient's mark.

Another member of the medical staff, who did not know how the procedures were performed, interviewed the patients 30 min after completion of their colonoscopies. A questionnaire was then given to the patients to take home to complete as instructed at intervals of 1, 2, 4 and 6 h and the completed forms were then mailed to the hospital the following day. The completed questionnaires were subsequently mailed to our medical office. No follow-up phone calls were made as 98% of all questionnaires were promptly returned.

Statistical analysis

A preliminary pilot study was conducted to estimate the SD in pain measurements. With an assumed SD of 19 mm, the study sample size was calculated at 110 patients in order to have an 80% power with two-sided α levels of 0.05 to detect any differences in VAS scores between the two insufflation groups ($\geq$ 10 mm was considered clinically important).

The outcomes for our secondary objective to clarify any differences between the two insufflation methods in relation to the experience level of participating colonoscopists were analyzed on an intention-to-treat basis, given the fact that a number of the initial examining colonoscopists were replaced during the insertion phase of the procedure. Statistical comparisons were made using chi-square and Fisher's exact tests. ANOVA was used for repeated measures statistical analysis of pain. Some variables were not distributed normally, thus the Wilcoxon rank sum test was applied for supplementary analysis to compare groups at each measurement point. Statistical analyses were performed using Prism version 5.0 (GraphPad Software, San Diego, CA, USA) and JMP version 6.3 (SAS Institute, Cary, NC, USA). A P value < 0.05 was considered significant.

RESULTS

Baseline characteristics

A total of 130 patients were asked to participate and 120 consenting patients were randomized into two groups prior to their colonoscopy examinations (Figure 1). Three poor bowel preparation patients were not included and one (0.85%, 1/117) incomplete intubation patient in the air insufflation group with a history of abdominal and pelvic open surgery, whose examination was performed by an EC, was not submitted for consideration. Completed questionnaires were received from 98% of the 116 remaining patients, thus a final total of 114 patients (68% female/32% male) were analyzed in this study. Exactly half or 57 patients were examined using CO_2 insufflation and the other 57 patients were examined with air insufflation. There were no significant differences in baseline patient characteristics including eligibility criteria for potentially difficult cases between the two groups (Table 1).

Outcome measures comparing CO_2 and air insufflation groups

There were no significant differences in procedure times including intubation, withdrawal and total time between the two groups (Table 2). Midazolam was administered to two patients (4%) in each group. There were no instances of $PtcCO_2$ > 60 mmHg in the CO_2 insufflation patients or any procedure-related complications in either group.

Figure 2 shows the mean VAS scores during and after colonoscopy examinations. VAS scores in the CO_2 insufflation group were significantly better than those in the air insufflation group (P < 0.001, ANOVA for repeated measures). The overall mean difference was 5.3 mm (95% CI: 3.5-7.1, P < 0.001). Comparison by nonparametric analysis at each measurement point produced results favoring CO_2 insufflation immediately following the examinations and up to 2 h afterwards. The maximum mean difference of 9.2 mm (95% CI: 0.4-18.0, P = 0.0049) was recorded 30 min after the examinations.