Table 3. Comparisons of mRNA levels in the non-metaplastic and metaplastic glands between the control group and the cancer group before and after eradication

		Control	Cancer	p values*
Non-metaplastic glands				
Number of samples[1]	before	10	24	
	after	13	31	
CDX2	before	0 (0–10)	10 (0–20)	0.32
	after	0	0	0.54
	p values	0.02	0.01	
MUC2	before	0 (0–35)	0 (0–38)	
	after	0	0	0.96
	p values	0.40	0.11	0.67
MUC5AC	before	6,390 (3,545–27,780)	15,530 (9,415–28,650)	0.51
	after	16,260 (6,440–42,490)	11,745 (6,490–34,570)	
	p values	0.40	0.43	0.48
MUC6	before	150 (40–550)	60 (3–208)	0.22
	after	110 (40–600)	90 (40–320)	0.95
	p values	0.40	0.19	
Metaplastic glands				
Number of samples[1]	before	5	19	
	after	5	15	
CDX2	before	110 (60–415)	40 (20–123)	0.23
	after	20 (20–140)	20 (10–120)	0.56
	p values	0.07	0.28	
MUC2	before	1,150 (750–5,190)	510 (180–855)	0.03
	after	390 (140–1,620)	280 (150–1,425)	0.59
	p values	0.14	0.20	
MUC5AC	before	1,170 (0–5,510)	840 (95–3,898)	0.66
	after	200 (100–670)	470 (330–8,890)	0.94
	p values	0.27	0.35	
MUC6	before	0 (0–105)	10 (0–105)	0.23
	after	20 (0–160)	0 (0–25)	0.11
	p values	0.47	0.13	

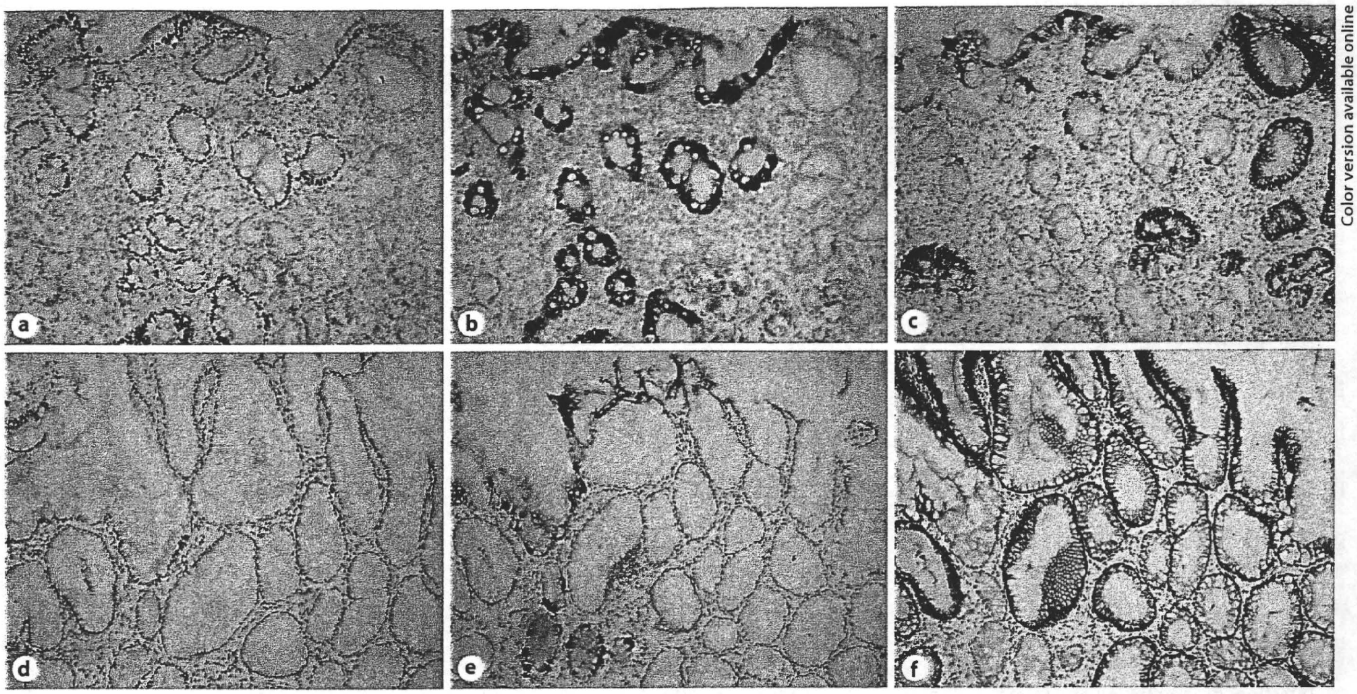
Values are expressed relative ($\times 10^{-3}$) to the control gene β-actin as the median with a 25–75% range.

* p values for the comparisons between the cancer group and the controls were calculated using the non-parametric Mann-Whitney U test. p values for the comparisons between before and after eradication were calculated using the Wilcoxon signed rank test.

[1] Number of samples corrected by laser capture containing enough non-metaplastic or metaplastic glands in the cancer group and the controls. The samples contained too small targets for non-metaplastic or metaplastic glands were excluded.

molecular mechanisms how eradication suppress aberrant *CDX2* expression.

MUC2 and CDX2 were repressed in the metaplastic glands isolated from patients who had undergone mucosal resection of early gastric cancer compared to the controls. Tsukamoto et al. [25] analyzed *MUC2* and *CDX2* mRNA levels in isolated gastric glands from surgically resected antral mucosa and demonstrated that *MUC2* and *CDX2* expressions were progressively upregulated with intestinalization from the gastric type to the gastric/intestinal-mixed type to the intestinal type. In our previous immunohistochemical studies, there is a significant association between types of IM and atrophic scores or serum pepsinogen levels [33]. The most incomplete IM (types II and III) preserving gastric mucin was the gastric and intestinal mixed (GI) type, whereas the complete type expressing MUC2 and CD10 was the intestinal (I) type. Incomplete or gastric/intestinal-mixed type IM was detectable in the mucosa of gastric cancer patients significantly more frequently (58 vs. 38%, $p < 0.001$) than in the controls [33].



Color version available online

Fig. 4. CDX2 (**a**, **d**), MUC2 (**b**, **e**) and MUC5AC (**c**, **f**) immunohistochemical staining of serial sections of the patient with gastric cancer in the corpus greater curve before (**a–c**) and after eradication (**d–f**). Orig. magnif. ×40.

Moreover, CDX2 expression increased in patients in the ascending order of those without IM, those with complete IM and those with incomplete IM ($p < 0.001$) [34]. Although both *MUC5AC* and *MUC6* gene expressions were not significantly different between the two groups, the lower levels of *MUC2* and *CDX2* mRNA in the cancer group of the present study may reflect a higher proportion of those with gastric/intestinal-mixed type IM.

In summary, we first indicated that *CDX2* aberrant expression was detected at the gastric glands without goblet cells in the corpus and disappeared after *H. pylori* eradication. *H. pylori* eradication reversed the gastric phenotype only in the control group. We propose that *CDX2* expression is a feature denoting the early phases of intestinalization of gastric glands and eradication may prevent extension of intestinalization even in the high-risk group for gastric cancer. Depending on the extent and severity of corpus gastritis/atrophy, *H. pylori* eradication can reverse corpus atrophy and have the greatest benefit in reducing gastric cancer risk.

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References

1 Graham DY, Shiotani A: The time to eradicate gastric cancer is now. Gut 2005;54:735–738.
2 Sipponen P, Kimura K: Intestinal metaplasia, atrophic gastritis and stomach cancer: trends over time. Eur J Gastroenterol Hepatol 1994;6(suppl 1):S79–S83.
3 Correa P: Human gastric carcinogenesis: a multistep and multifactorial process – First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992;52:6735–6740.
4 Gendler SJ, Spicer AP: Epithelial mucin genes. Annu Rev Physiol 1995;57:607–634.
5 Williams SJ, McGuckin MA, Gotley DC, Eyre HJ, Sutherland GR, Antalis TM: Two novel mucin genes down-regulated in colorectal cancer identified by differential display. Cancer Res 1999;59:4083–4089.
6 Lapensee L, Paquette Y, Bleau G: Allelic polymorphism and chromosomal localization of the human oviductin gene (MUC9). Fertil Steril 1997;68:702–708.

7 Shankar V, Pichan P, Eddy RL Jr, Tonk V, Nowak N, Sait SN, Shows TB, Schultz RE, Gotway G, Elkins RC, Gilmore MS, Sachdev GP: Chromosomal localization of a human mucin gene (MUC8) and cloning of the CDNA corresponding to the carboxy terminus. Am J Respir Cell Mol Biol 1997;16:232–241.
8 Macdonald PM, Struhl G: A molecular gradient in early drosophila embryos and its role in specifying the body pattern. Nature 1986;324:537–545.
9 Moreno E, Morata G: Caudal is the Hox gene that specifies the most posterior Drosophile segment. Nature 1999;400:873–877.
10 Silberg DG, Swain GP, Suh ER, Traber PG: Cdx1 and Cdx2 expression during intestinal development. Gastroenterology 2000;119:961–971.
11 Mutoh H, Sakurai S, Satoh K, Tamada K, Kita H, Osawa H, Tomiyama T, Sato Y, Yamamoto H, Isoda N, Yoshida T, Ido K, Sugano K: Development of gastric carcinoma from intestinal metaplasia in Cdx2-transgenic mice. Cancer Res 2004;64:7740–7747.
12 Beck F, Chawengsaksophak K, Waring P, Playford RJ, Furness JB: Reprogramming of intestinal differentiation and intercalary regeneration in Cdx2 mutant mice. Proc Natl Acad Sci USA 1999;96:7318–7323.
13 Phillips RW, Frierson HF Jr, Moskaluk CA: Cdx2 as a marker of epithelial intestinal differentiation in the esophagus. Am J Surg Pathol 2003;27:1442–1447.
14 Silberg DG, Sullivan J, Kang E, Swain GP, Moffett J, Sund NJ, Sackett SD, Kaestner KH: Cdx2 ectopic expression induces gastric intestinal metaplasia in transgenic mice. Gastroenterology 2002;122:689–696.
15 Matsumoto K, Mizoshita T, Tsukamoto T, Ogasawara N, Hirata A, Shimizu Y, Haneda M, Yamao K, Tatematsu M: Cdx2 expression in pancreatic tumors: relationship with prognosis of invasive ductal carcinomas. Oncol Rep 2004;12:1239–1243.
16 Piscitelli D, Ingravallo G, Resta L, Fiore MG, Maiorano E: Oncocytic adenocarcinoma of the rectum with diffuse intraluminal microcalcifications: the first reported case. Virchows Arch 2003;443:579–582.
17 Kaimaktchiev V, Terracciano L, Tornillo L, Spichtin H, Stoios D, Bundi M, Korcheva V, Mirlacher M, Loda M, Sauter G, Corless CL: The homeobox intestinal differentiation factor Cdx2 is selectively expressed in gastrointestinal adenocarcinomas. Mod Pathol 2004;17:1392–1399.
18 Mizoshita T, Tsukamoto T, Nakanishi H, Inada K, Ogasawara N, Joh T, Itoh M, Yamamura Y, Tatematsu M: Expression of Cdx2 and the phenotype of advanced gastric cancers: relationship with prognosis. J Cancer Res Clin Oncol 2003;129:727–734.
19 Seno H, Oshima M, Taniguchi MA, Usami K, Ishikawa TO, Chiba T, Taketo MM: Cdx2 expression in the stomach with intestinal metaplasia and intestinal-type cancer: prognostic implications. Int J Oncol 2002;21:769–774.
20 Shiotani A, Uedo N, Iishi H, Tatsuta M, Ishiguro S, Nakae Y, Kamada T, Haruma K, Merchant JL: Re-expression of sonic hedgehog and reduction of Cdx2 after *Helicobacter pylori* eradication prior to incomplete intestinal metaplasia. Int J Cancer 2007;121:1182–1189.
21 Shiotani A, Kamada T, Yamanaka Y, Manabe N, Kusunoki H, Hata J, Haruma K: Sonic hedgehog and cdx2 expression in the stomach. J Gastroenterol Hepatol 2008;23(suppl 2):S161–S166.
22 Shiotani A, Iishi H, Uedo N, Ishiguro S, Tatsuta M, Nakae Y, Kumamoto M, Merchant JL: Evidence that loss of sonic hedgehog is an indicator of *Helicobater pylori*-induced atrophic gastritis progressing to gastric cancer. Am J Gastroenterol 2005;100:581–587.
23 Ravizza M: Does *Helicobacter pylori* eradication modify intestinal metaplasia evolution in the stomach? Minerva Gastroenterol Dietol 2002;48:165–167.
24 Satoh K, Mutoh H, Eda A, Yanaka I, Osawa H, Honda S, Kawata H, Kihira K, Sugano K: Aberrant expression of Cdx2 in the gastric mucosa with and without intestinal metaplasia: effect of eradication of *Helicobacter pylori*. Helicobacter 2002;7:192–198.
25 Tsukamoto T, Inada K, Tanaka H, Mizoshita T, Mihara M, Ushijima T, Yamamura Y, Nakamura S, Tatematsu M: Down-regulation of a gastric transcription factor, Sox2, and ectopic expression of intestinal homeobox genes, Cdx1 and Cdx2: inverse correlation during progression from gastric/intestinal-mixed to complete intestinal metaplasia. J Cancer Res Clin Oncol 2004;130:135–145.
26 Vauhkonen M, Vauhkonen H, Sipponen P: *Helicobacter pylori* infection induces a reversible expression of the Cdx2 transcription factor protein in human gastric epithelium. Scand J Gastroenterol 2008;43:915–921.
27 Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK: *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of china: a randomized controlled trial. JAMA 2004;291:187–194.
28 Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M: Effect of eradication of helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008;372:392–397.
29 Yasunaga Y, Shinomura Y, Kanayama S, Yabu M, Nakanishi T, Miyazaki Y, Murayama Y, Bonilla-Palacios JJ, Matsuzawa Y: Improved fold width and increased acid secretion after eradication of the organism in *Helicobacter pylori*-associated enlarged fold gastritis. Gut 1994;35:1571–1574.
30 Gutierrez O, Melo M, Segura AM, Angel A, Genta RM, Graham DY: Cure of *Helicobacter pylori* infection improves gastric acid secretion in patients with corpus gastritis. Scand J Gastroenterol 1997;32:664–668.
31 El-Omar EM, Oien K, El-Nujumi A, Gillen D, Wirz A, Dahill S, Williams C, Ardill JE, McColl KE: *Helicobacter pylori* infection and chronic gastric acid hyposecretion. Gastroenterology 1997;113:15–24.
32 Ruiz B, Correa P, Fontham ET, Ramakrishnan T: Antral atrophy, *Helicobacter pylori* colonization, and gastric pH. Am J Clin Pathol 1996;105:96–101.
33 Shiotani A, Haruma K, Uedo N, Iishi H, Ishihara R, Tatsuta M, Kumamoto M, Nakae Y, Ishiguro S, Graham DY: Histological risk markers for non-cardia early gastric cancer. Pattern of mucin expression and gastric cancer. Virchows Arch 2006;449:652–659.
34 Shiotani A, Iishi H, Uedo N, Ishihara R, Ishiguro S, Tatsuta M, Nakae Y, Kumamoto M, Hinoi T, Merchant JL: *Helicobacter pylori*-induced atrophic gastritis progressing to gastric cancer exhibits sonic hedgehog loss and aberrant CDX2 expression. Aliment Pharmacol Ther 2006;24(suppl 4):71–80.

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連　載

手技の解説

治療困難例に対するダブルスコープESD(シングルトランスシステム)

田辺　聡* 樋口　勝彦* 佐々木　徹*
堅田　親利* 東　瑞智* 石戸　謙次*
中谷　研斗* 阿江太佳子* 小泉和三郎*

はじめに

早期胃癌に対する内視鏡的粘膜下層剝離術(ESD)[1]は2006年に保険収載され，施行する施設も増加し標準化しつつある．また，従来の内視鏡的粘膜切除術(EMR)では切除困難であった潰瘍合併例や大型病変などの適応拡大[2]も模索されている．ESDの最大の利点は一括切除が可能であり，正確な病理学的評価ができることである．一方では，胃体部小弯や大弯，また潰瘍合併例や大型病変などの適応拡大病変では切除に困難を極めることも少なくない．以前よりESDの手技は「片手でリンゴを剝くような手技」に例えられてきた．すなわち，外科手術の際の「助手の左手」がない状態で行う制限された治療と考えられる．

そこで，われわれは切除を行う主となる内視鏡に加えて細径内視鏡を同時に挿入し，かつ一つの光源のみを用いる方法を考案した．本稿では単光源を用いたダブルスコープESDの手技とコツについて解説する．

Ⅰ．準備する機材(図1)

基本となるメインスコープはオリンパスメディカルシステムズ社製Q260Jまたは2TQ260M，切開ディバイスは針状ナイフ，IT knife2，高周波装置はVIOを用いている．病変を牽引する細径スコープはXP260，把持鉗子にはFG-4L-1を用いている．局注液にはグリセオール®とムコアップ®を1：1で混合して使用している．

Ⅱ．ダブルスコープESDが適応となる病変

本法が有効な病変は，大型病変や瘢痕病変すなわち適応拡大病変が良い適応となる．とくに，瘢痕病変については細径スコープでトラク

Key words：早期胃癌，治療困難例，ダブルスコープESD

Satoshi Tanabe／Katsuhiko Higuchi／Tohru Sasaki／Chikatoshi Katada／Mizutomo Azuma／Kenji Ishido／Kento Nakatani
Takako Ae／Wasaburo Koizumi
*北里大学医学部消化器内科学(〒252-0380 神奈川県相模原市南区麻溝台2-1-1)

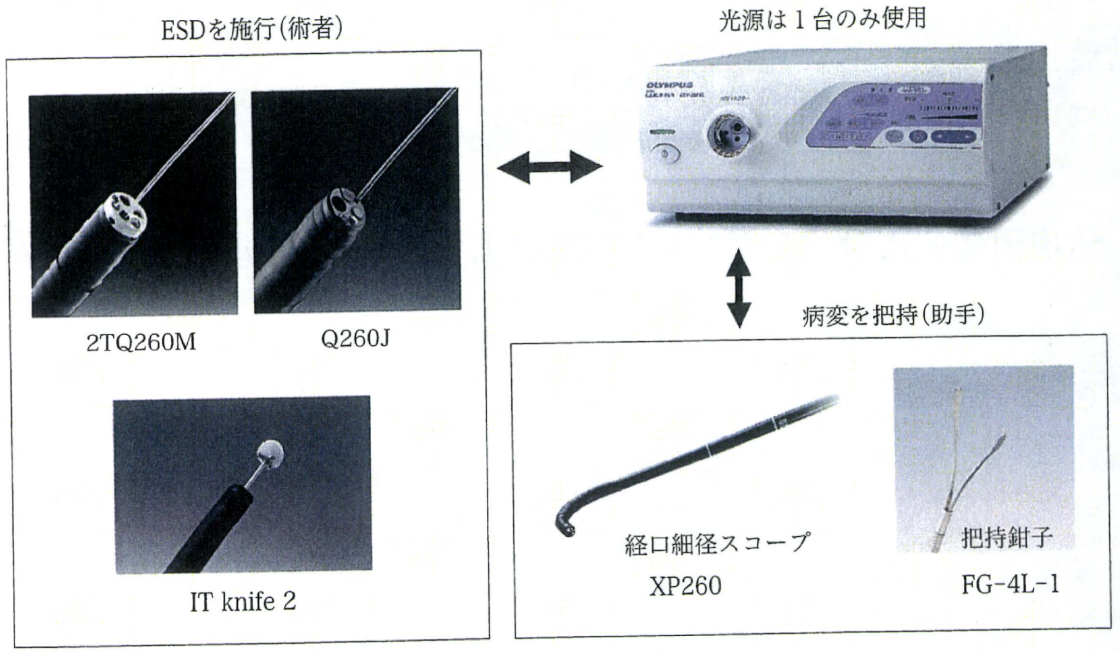


図1 ダブルスコープESDで使用する機器
(すべてオリンパスメディカルシステムズ社製)

ションをかけることにより，深切りによる穿孔や病変内の切り込みを回避することが可能となる．また，トラクションがかかることにより切除効率が向上し，時間の短縮にもつながる．病変の部位では，胃体中下部，胃角の小弯はスコープの近接が困難な場所であり，ダブルスコープが威力を発揮する．前庭部は安易な場所と認識されているが，小弯側は切開ディバイスが垂直になり剥離に難渋する場合もみうけられる．トラクションを少しかけるだけでも切開，剥離効率は各段に上昇する．

Ⅲ．術者・助手の配置図

図2に術者(メインスコープ)と助手(細径スコープ)，その他の介助者の配置図を示す．患者の頭側に術者，尾側に助手が並び，その横に把持鉗子を補助する者が立つ．術者の後ろに立つ介助者が，ITナイフを補助している．

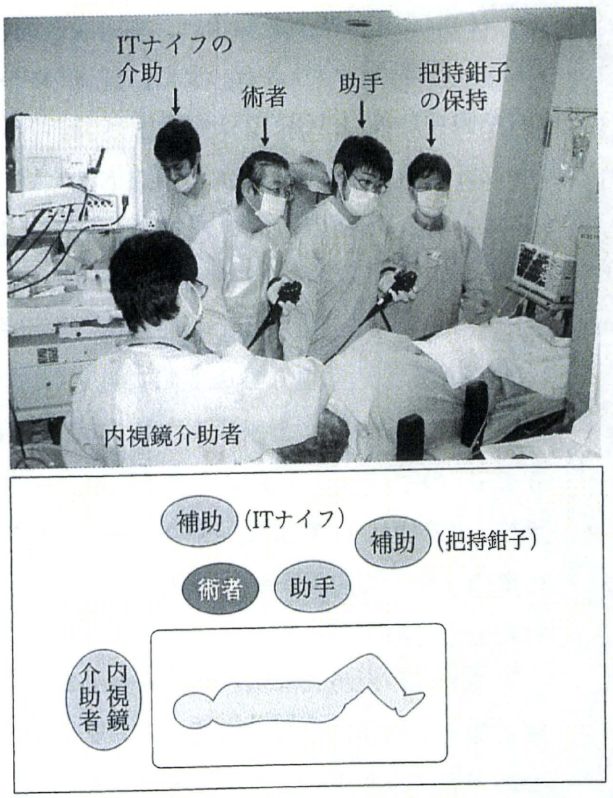


図2 患者，術者の配置図

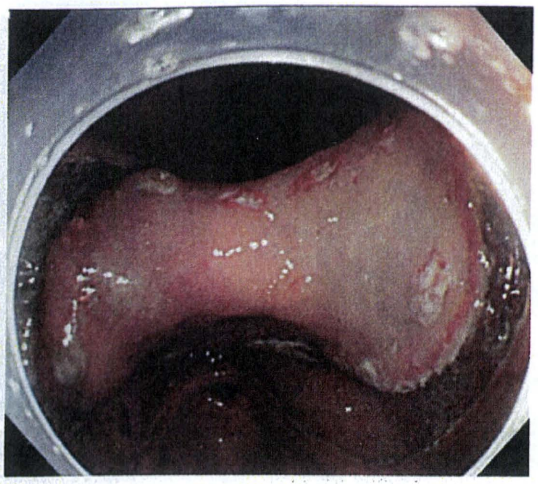


図3　全周切開後
全周切開後は，口側，肛門側をある程度剝離しておく．ここまでは通常のESD手技と同様に行う．

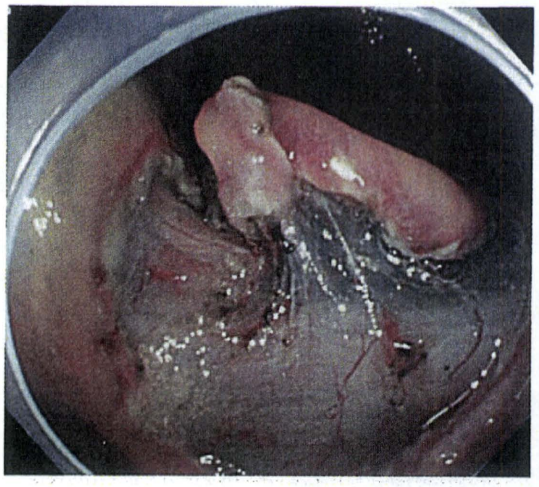


図5　細径スコープによる病変の把持
病変の肛門側を把持し，reverse viewで剝離を行う．適度な牽引により良好な視野が確保できる．

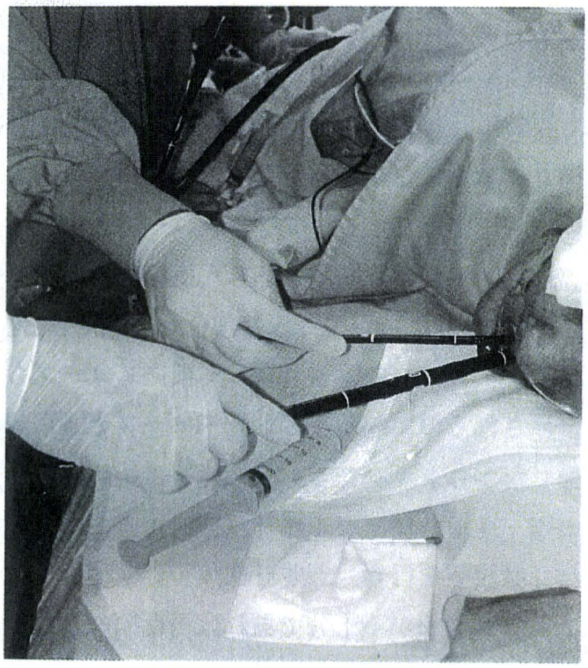


図4　細径スコープの挿入
メインスコープを胃内に留置したまま，メインスコープを光源から外し，細径スコープに差し替える．メインスコープに添わせるように細径スコープを挿入する．

図6　メインスコープによる粘膜下層剝離
細径スコープを光源から外し，再度メインスコープへ差し替え，粘膜下層剝離を継続する．

Ⅳ．ダブルスコープESDの手技

1．メインスコープによる全周切開

通常の手技と同様にメインスコープにより，病変周囲にマーキングを行い全周切開を開始する．その後，粘膜下層の剝離を全周にわたってある程度行う．とくに，小弯病変では肛門側の剝離を十分に行うことにより，細径スコープより挿入した把持鉗子の摑む部分ができる(**図3**)．

2．細径スコープの挿入

把持鉗子で摑む部分がある程度剝離された後，メインスコープを胃内に残したまま光源装置から外し，細径スコープを光源装置に装着する．細径スコープをメインスコープに添わせるようにして挿入する(**図4**)．この際，マウスピースのみでオーバーチューブは使用しない．ほとんど干渉は感じないが，下部食道から食道胃接合部付近が屈曲している場合もあるので，管腔を確認しながら進める．

3．細径スコープによる病変の把持

病巣を確認し，細径スコープの鉗子口から把持鉗子(FG-4 L-1)を挿入し，病変の辺縁を把持する．反転操作による小弯側の病変は肛門側を，順視による大弯側の病変は口側を把持する(**図5**)．細径スコープを光源装置から外し，メインスコープを光源装置に装着し直す．助手はメインスコープで観察しながら細径スコープの位置を調整して，適切なトラクションがかかるようにアングルで調節を行う．この際，あまり大きく細径スコープを動かさなくとも，アングル操作やスコープの捻りなどで微調整が可能である．

4．メインスコープによる粘膜下層剝離

良好なポジショニングが完了した後に，メインスコープで剝離を進めていく(**図6**)．瘢痕症例では，病変が挙上されているため良好な視野が確保され，穿孔や病変への切り込みのリスクが回避される．さらに，トラクション効果により，1回の剝離操作で処理される面積が多く，治療時間の短縮も可能になる．

表 ダブルスコープESD(シングルトランスシステム)のコツ

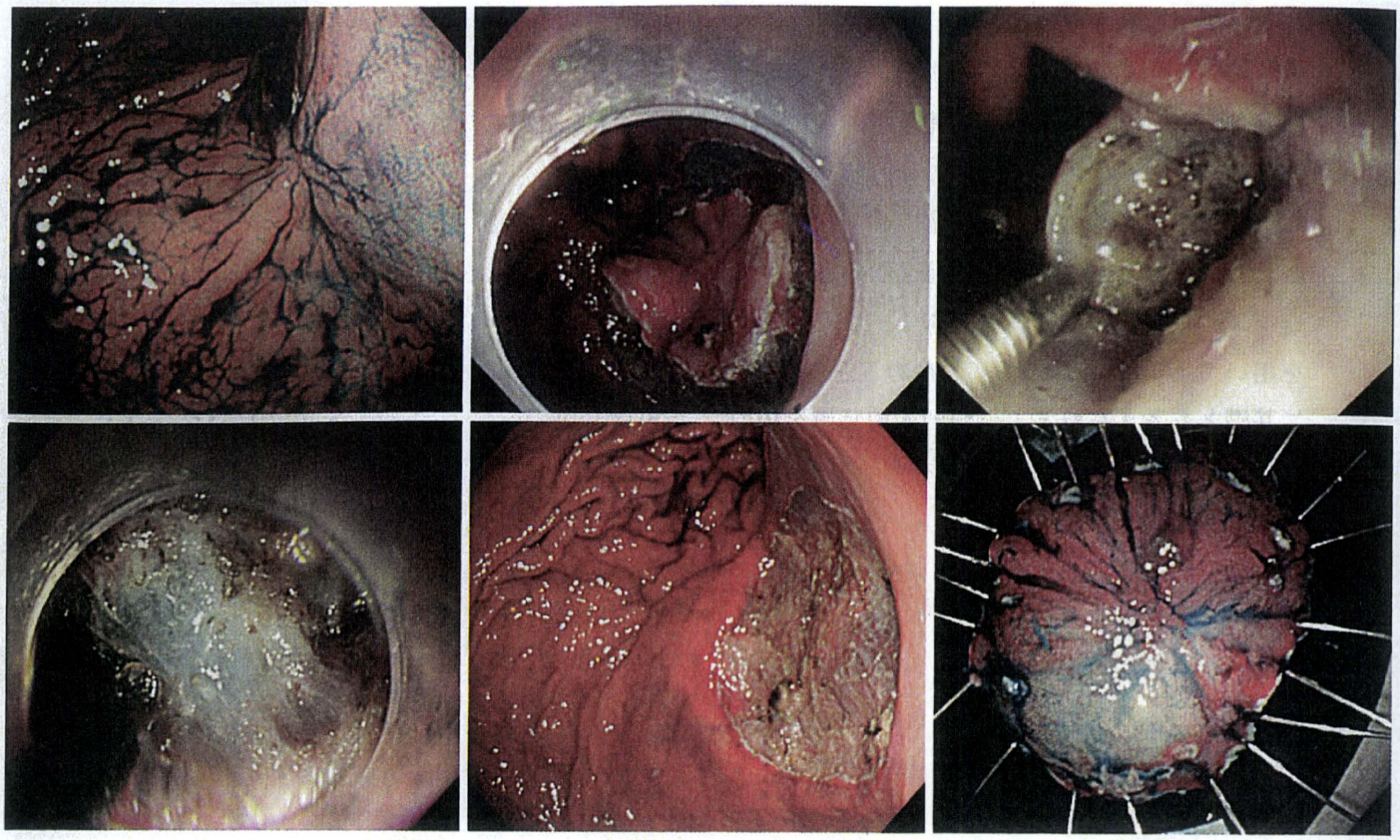
①細径内視鏡(XP260 or XP260N)，把持鉗子(FG-4L-1)を準備．
②全周切開後，病変の肛門側と口側の剝離を行っておく．
③病変の肛門側を把持し，reverse viewで剝離を行う．
④アングル操作，把持鉗子の出し入れで，病変にカウンタートラクションをかける．
⑤病変を引っ張りすぎない．

Ⅴ．ダブルスコープESD(シングルトランスシステム)のコツ(表)

瘢痕症例や大型病変など本法が必要となる可能性がある症例に際しては，細径内視鏡(XP260あるいはXP260N)，把持鉗子(FG-4 L-1)を準備しておくことにより，ダブルスコープ法へスムースに移行できる．ダブルスコープを用いる際には，口側，肛門側をある程度剝離しておくことにより，把持鉗子で摑む部位が確保できる．メインスコープの動きによって細径スコープも干渉されるので，助手は細径スコープを適宜調節しながらトラクションの状態を維持する．その際，助手はアングル操作，把持鉗子の出し入れで微調整を行う．剝離を進めていく過程で，トラクションが不十分であれば再度摑み直しを行う．牽引の程度も引っ張りすぎると標本が損傷したり，筋層が挙上することにより筋層へ切り込む危険性もあるので注意する．

Ⅵ．症例提示(図7)

症例は胃体上部後壁の高度な瘢痕症例である(図7a)．まず，通常のESDと同様にメインスコープにて全周切開と周囲のトリミングを行う(図7b)．その後，メインスコープを胃内に留



7a|7b|7c
7d|7e|7f

図7　胃体上部後壁の高度瘢痕症例
a：高度瘢痕症例
b：全周切開とトリミング後
c：細径スコープによる把持，牽引
d：メインスコープによる粘膜下層剝離
e：切除後の潰瘍
f：切除標本

置した状態で，細径スコープに差し替え，把持鉗子にて病変の肛門側を把持し牽引する(図7c)．再度メインスコープに差し替え，トラクションの状態を調整し，粘膜下層の剝離を行う(図7d)．スコープ挿入から抜去まで104分(ダブルスコープ施行時間15分)で治療が終了した(図7e)．切れ込みのない標本が切除された(図7f)．

Ⅶ．考　　察

ESDは従来のEMRと比較し，大型病変や瘢痕病変など従来のEMRでは切除が困難であった病変を一括で確実に切除できるすばらしい方法であるが，一方では技術的な難易度が高く，治療時間も長いなどの問題点が指摘されている．

ESDは通常の外科手術と異なり，助手による補助がないため，切除する場所の視野の確保が難しく，先端アタッチメントを内視鏡の先端に装着することにより粘膜下層に入り込んで切除を行う．手術と同様にトラクションをかける試みがさまざまなされてきた．小山ら[3]の糸付きクリップ法，今枝ら[4]の把持鉗子，本橋ら[5]のインパクトシューターなどであるが，手技や準備が大変な場合や，十分なトラクションがかか

らない場合もありうる．

2本の内視鏡を挿入して行うダブルスコープ法は1983年に平尾ら[6]により報告されている．実際には手術室において二つの光源装置を用いて，それぞれのスコープが観察できる状態で行われた．当時は現在のようなESDのさまざまなディバイスは開発されておらず，針状ナイフを用いて切除がなされた．現在のESDのまさに基礎とも考えられる．二つの光源装置を用いたために光の干渉が問題となった．森田ら[7]も二つの光源装置と特殊なオーバーチューブ(トップ社製スプリットバレル)を用いたダブルスコープ法を報告している．

今回のわれわれの方法では，一つの光源装置によりスコープを差し替えて用いるため，光の干渉は起こらない．また，内視鏡室のワーキングスペースが犠牲にならず，設置などの準備や画像ファイリングの統合なども不要である．細径スコープと把持鉗子の準備があれば，ESDの途中で困難な局面に遭遇した場合に，ただちにダブルスコープへ切り替えることが可能である．

おわりに

早期胃癌治療困難例に対する単光源装置によるダブルスコープESD法の手技について解説した．大型病変や瘢痕症例などの病変に対して本ダブルスコープ法は有用であり，困難な局面に直面した際には試みていただきたい．

文　献

1) Ono, H., Kondo, H., Gotoda, T., et al.：Endoscopic mucosal resection for treatment of early gastric cancer. Gut 48；225-229, 2001
2) Gotoda, T., Yanagisawa, A., Sasako, M., et al.：Incidence of lymph node metastasis from early gastric cancer：estimation with a large number of cases at two large centers. Gastric Cancer 3：219-225, 2000
3) 高橋亜紀子，小山恒男：胃ESDにおける穿孔予防の工夫：糸付きクリップ法．第81回日本胃癌学会総会抄録集2009，p. 361
4) 今枝博之，細江直樹，井田陽介，他：「胃ESD」手技の基本と困難例克服のコツ．消化器の臨床 12；212-218，2009
5) 本橋 修，西村 賢，中山昇典，他：内視鏡手技における私の工夫(粘膜把持鉗子用チャンネル付き透明フードを用いるESD)．Prog. Dig. Endosc. 71；25-27，2007
6) 平尾雅紀，小林多加志，長谷良志男：胃の腫瘍性病変に対する内視鏡的切除法．Gastroenterol. Endosc. 25；1942-1953，1983
7) 森田圭紀，豊永高史，東 健：胃ESDにおける困難例に対する対応 早期胃癌に対するESD治療困難症例の克服 スプリットバレルによるDouble scope-ESD．Gastroenterol. Endosc. 51(Suppl. 2)；2140，2009

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SURGERY TODAY

Original Article

Survival of Patients Treated by an Autonomic Nerve-Preserving Gastrectomy for Early Gastric Cancer

SHINSUKE SASADA, MOTOKI NINOMIYA, MASAHIKO NISHIZAKI, MASAO HARANO, YASUTOMO OJIMA, HIROYOSHI MATSUKAWA, SHIGEHIRO SHIOZAKI, SATOSHI OHNO, and NORIHISA TAKAKURA

Department of Surgery, Hiroshima City Hospital, Hiroshima, Japan

Abstract

Purpose. Autonomic nerve preservation in a gastrectomy for gastric cancer improves the postoperative quality of life. We retrospectively examined the survival of patients treated by an autonomic nerve-preserving gastrectomy in comparison to the survival of the patients treated by a conventional gastrectomy.

Methods. The survival of 385 patients treated by an autonomic nerve-preserving gastrectomy for clinical early gastric cancer (the ANP group) was compared with that of 285 patients treated by a conventional gastrectomy (non-ANP group).

Results. Among the ANP group, the numbers of patients with tumor invasion to the mucosa, submucosa, and muscularis propria were 210, 166, and 9, respectively, whereas the numbers of patients with lymph node metastasis grades of N0, N1, and N2 were 360, 21, and 4, respectively. The overall 5-year survival rate of the ANP group was 94.7%, which was superior to that of the non-ANP group (90.4%; $P = 0.003$). The 5-year survival rates of patients with lymph node metastasis were 94.9% and 91.8% in the ANP and non-ANP groups, respectively ($P = 0.733$). Only 3 patients in the ANP group died from gastric cancer.

Conclusions. The survival of patients treated by an autonomic nerve-preserving gastrectomy was equivalent to that of patients treated by a conventional gastrectomy, thus suggesting that an autonomic nerve-preserving gastrectomy could be a useful procedure for the treatment of early gastric cancer.

Key words Gastric cancer · Gastrectomy · Autonomic nerve preservation · Survival

Reprint requests to: S. Sasada, Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
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Introduction

Function-preserving surgery for early gastric cancer is now widely performed in Japan.[1] There are various types of function-preserving operations, including those involving a reduced extent of gastrectomy, autonomic nerve preservation, sphincter preservation, and formation of a neostomach.[2] Because the preservation of the vagus nerve has been demonstrated to improve the postoperative quality of life in patients who undergo either a vagotomy and/or gastrectomy,[3–14] we have performed an autonomic nerve-preserving gastrectomy for early gastric cancer since December 1994. Although autonomic nerve preservation has been considered to maintain the curability of patients,[15,16] the long-term survival rate after an autonomic nerve-preserving gastrectomy has not been fully assessed to date. We retrospectively examined the survival of patients after an autonomic nerve-preserving gastrectomy for early gastric cancer.

Patients and Methods

Between December 1994 and July 2003, 385 patients were treated by an autonomic nerve-preserving gastrectomy for clinical early gastric cancer at our institute (ANP group). The indications for this operation included tumor invasion into the mucosal or submucosal layer (T1), and the absence of lymph node involvement and distant metastases according to clinical and surgical findings (N0/M0). All patients underwent gastrointestinal fiberscopy, a gastrointestinal series, and computed tomography for the preoperative evaluation. If regional lymph node metastasis was suspected by the intraoperative findings, a frozen-section analysis of the lymph node was performed and the patients with positive nodes were excluded from the study. With regard to the specific procedures, a distal gastrectomy was

performed in 210 cases, a proximal gastrectomy was performed in 31 cases, a total gastrectomy was performed in 17 cases, and a pylorus-preserving gastrectomy was performed in 127 cases. Ten patients were treated by laparoscopy-assisted surgery. Lymph node dissection was performed for D1+α, D1+β or D2, where α refers to lymph nodes 7 and 8a in cases of lower third cancer, and β refers to lymph nodes 7, 8a, and 9. Cases with local and segmental resection and lymph node dissection less than D1 were excluded. Staging and classification were determined according to the general rules for surgical and pathological gastric cancer studies in Japan.[17] The control group was 285 patients treated by a conventional gastrectomy for early gastric cancer based on their clinical stages between 1991 and 1998 (non-ANP group), because we began performing an autonomic nerve-preserving gastrectomy in 1994 and have performed this procedure for almost all patients with a clinical T1 N0 M0 stage after 1999.

Operative Procedure

The preserved autonomic nerves included the hepatic branch originating from the anterior trunk of the vagus nerve and the celiac branch, the plexus surrounding the common hepatic artery and the splenic artery, and the pancreatic branch and the hepatic branch originating from the posterior trunk of the vagus nerve. The celiac branch was followed upward from the root of the left gastric artery or downward from the posterior trunk of the vagus nerve, taped, and preserved. The left gastric artery was divided at the peripheral side of the confluence of the celiac branch (Fig. 1).

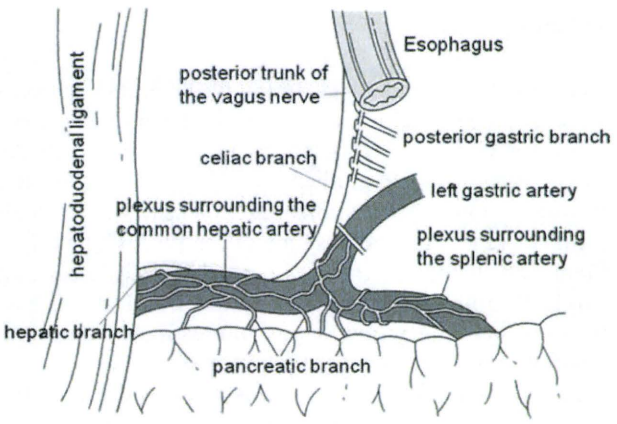

Fig. 1. Preserved autonomic nerves and cutting lines (*double lines*) for the left gastric artery and the posterior gastric branches

Statistical Analysis

The clinicopathological features and survival rates of the ANP group were compared with those of the non-ANP group. The median follow-up time was 5.7 years. Statistical analyses were conducted using the Statcel version 2.0 software program (OMS, Tokyo, Japan). Statistically significant differences were determined using the χ^2 test or Student's *t*-test. The survival rates were calculated using the Kaplan–Meier method and the log-rank test. The level of significance was set at $P < 0.05$.

Results

Clinicopathological Features

Table 1 shows the clinicopathological data for both groups. Fewer patients in the ANP group were treated by a total gastrectomy in comparison to the non-ANP group. In the histological analyses, the numbers of patients with tumor invasion to the mucosa, submucosa, muscularis propria, and subserosa were 210, 166, 9, and 0 in the ANP group and 166, 98, 15, and 6 in the non-ANP group, respectively. Although the non-ANP group contained significantly more patients with tumors exhibiting deeper invasion than the ANP group, the extent of lymph node metastasis and tumor staging were similar in the two groups. The number of dissected lymph nodes was greater in the ANP group than in the non-ANP group. In the ANP group, the number of patients with lymph node metastasis was 25 (6.5%) and the number of patients over stage T1 N0 M0 was 32 (8.3%).

Survival

The overall 5-year survival rates were 94.7% in the ANP group and 90.4% in the non-ANP group ($P = 0.003$) (Fig. 2). The 5-year survival rates of patients at stages IA, IB, and II were 94.8%, 96.2%, and 83.3% in the ANP group, and 89.5%, 96.2%, and 83.3% in the non-ANP group, respectively (Fig. 3). The survival rate in the ANP group was superior to that in the non-ANP group for stage IA ($P = 0.003$). Because there was no significant difference in the disease-specific survival rates for stage IA (99.7% vs 98.5%, $P = 0.571$, Fig. 4), the difference in the survival rates of the stage IA patients between the ANP and non-ANP groups may have been caused by death from other diseases. In contrast, the 5-year survival rates of the patients in the ANP group were 94.9% in those without lymph node metastasis and 91.8% in those with metastasis, respectively, with no significant difference (Fig. 5).

Table 1. Clinicopathological findings of patients who underwent a gastrectomy with or without the preservation of the autonomic nerves

	ANP (n = 385)	Non-ANP (n = 285)	P value
Age, years (range)	62.6 (25–88)	62.0 (28–85)	0.451
Sex			0.436
Male	251	194	
Female	134	91	
Tumor location			0.053
U	44	31	
M	244	158	
L	97	96	
Tumor size (mm)	27.5	28.3	0.579
Lymph node dissection			0.391
D1	85	71	
D2	300	214	
Operation method			<0.001
DG	210	222	
PG	31	7	
TG	17	32	
PPG	127	24	
Depth of tumor invasion			0.001
pM	210	166	
pSM	166	98	
pMP	9	15	
pSS	0	6	
Lymph node metastasis			0.894
pN0	360	268	
pN1	21	15	
pN2	4	2	
fStage			0.297
IA	353	251	
IB	26	28	
II	6	6	
Histologic type			0.124
Differentiated	246	202	
Undifferentiated	138	83	
Unknown	1	0	
Number of dissected lymph nodes (range)			
All	37.8 (5–110)	32.4 (2–127)	<0.001
Group2[a]	13.9 (0–52)	10.9 (0–72)	<0.001

U, upper third; M, middle third; L, lower third; DG, distal gastrectomy; PG, proximal gastrectomy; TG, total gastrectomy; PPG, pylorus-preserving gastrectomy; M, mucosa and/or muscularis mucosa; SM, submucosa; MP, muscularis propria; SS, subserosa
[a] Group 2 lymph nodes refer to Nos. 7, 8a, 9, and 11

Although 26 patients died in the ANP group and 50 patients died in the non-ANP group, only 3 and 5 deaths, respectively, were disease-specific. Among these patients, only one in each group had lymph node metastasis (Table 2). The mortality was only one patient in each group.

Discussion

In gastric cancer patients, there are two types of postgastrectomy syndrome that are classified based on their etiology, namely, postgastrectomy syndrome from resection of the stomach and injury to the vagus nerve from lymph node dissection.[18] Many limited gastrectomy techniques have been developed to reduce the incidence of postgastrectomy syndrome, including pylorus-preserving gastrectomy, proximal gastrectomy, segmental gastrectomy, and local resection. The hepatic and celiac branches of the vagus nerve innervate the region from the pylorus to the large intestine as far as the distal portion of the transverse colon, the biliary tract, and the other upper abdominal organs. Preservation of the vagus nerve minimizes the loss of digestive and absorptive functions, thereby improving recovery of postoperative bodyweight and reducing diarrhea.[5,10,13–15] Furthermore, vagus nerve preservation decreases the incidence of cholelithiasis[3,13,14] and pre-

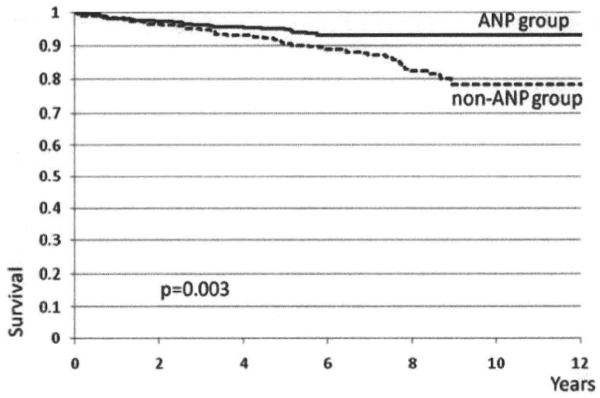

Fig. 2. Survival curves of the patients who underwent a gastrectomy with (*ANP*) and without (*non-ANP*) the preservation of the autonomic nerves. The overall 5-year survival rates are 94.7% in the ANP group and 90.4% in the non-ANP group ($P = 0.003$, log-rank test)

serves pancreatic insulin release.[9,11] We previously reported the superiority of this procedure.[10,13]

We designated our nerve-preserving procedure an "autonomic nerve-preserving gastrectomy," although it has also been referred to as a vagus nerve-preserving gastrectomy in previous reports. The reason for this designation is that the procedure preserves the plexus surrounding the common hepatic artery and the splenic artery, the pancreatic branch, and the hepatic branch originating from the posterior trunk of the vagus nerve as well as the sympathetic nervous system from the celiac ganglia.[19] It seems reasonable that the preservation of both the sympathetic and parasympathetic nervous systems is important for maintaining the function of the upper gut after a gastrectomy.[20,21]

A gastrectomy with extensive nodal dissection appears to prevent recurrence and improve cancer-specific survival in early gastric cancer patients with

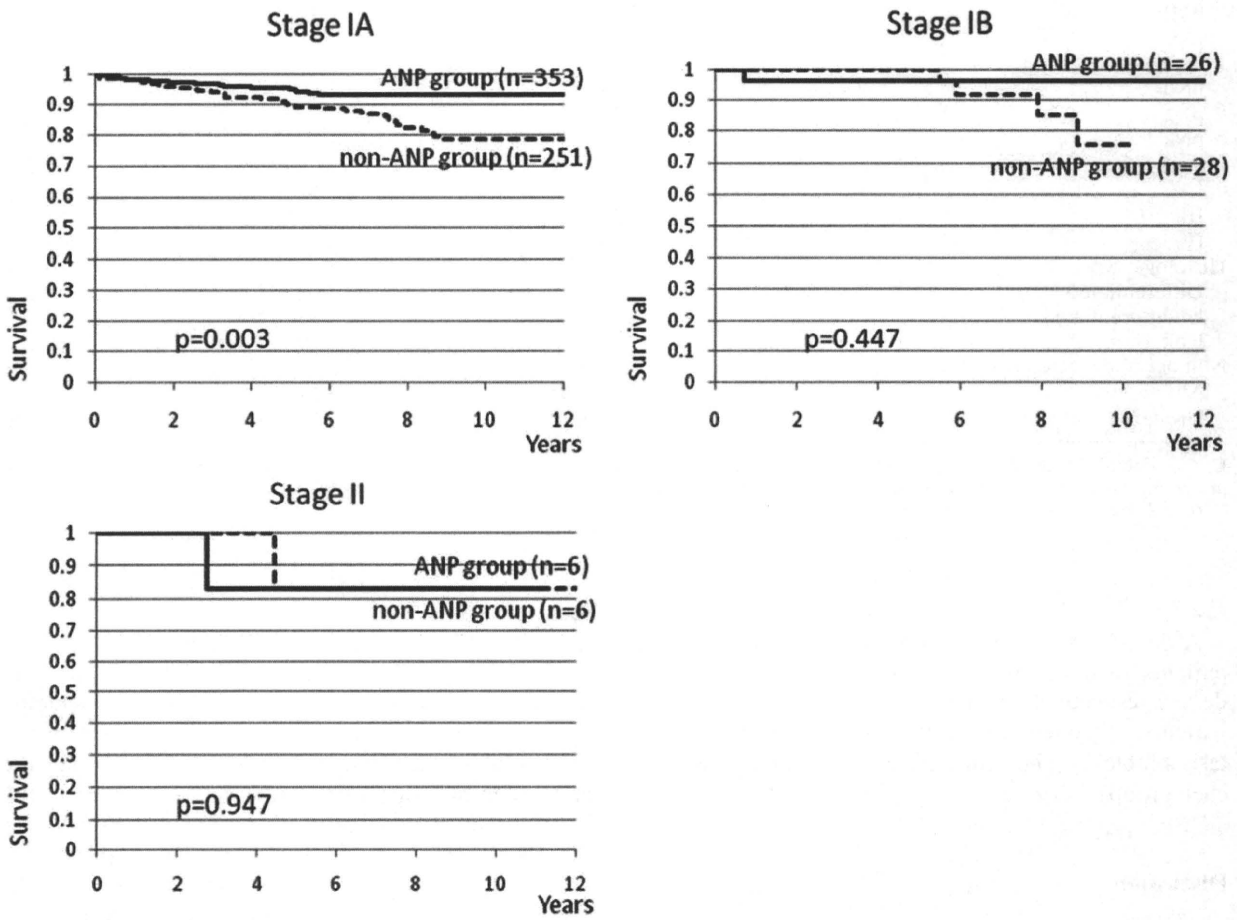

Fig. 3. Survival curves for stage IA, IB, and II patients who underwent a gastrectomy with (*ANP*) and without (*non-ANP*) the preservation of the autonomic nerves. The survival rate in the ANP group is superior to that in the non-ANP group for stage IA ($P = 0.003$, log-rank test). The survival rates between the ANP and non-ANP groups do not differ significantly for stages IB ($P = 0.433$, log-rank test) and II ($P = 0.947$, log-rank test)

Table 2. Patient mortality due to gastric cancer

pT	pN	fStage	Lesion of nodal metastasis	No. of nodal metastases	Organ of recurrence
ANP group					
M	N0	IA	—	0	Remnant stomach, liver, LN
SM	N0	IA	—	0	Liver
SM	N2	II	Nos. 1, 3, 4d, 6, 7, 8a, 9, 11	25	Peritoneum, LN
Non-ANP group					
M	N0	IA	—	0	Brain
M	N0	IA	—	0	Mediastinum, LN, bone
M	N0	IA	—	0	Unknown
M	N0	IA	—	0	Unknown
M	N1	IB	No.4d	1	Peritoneum

M, mucosa and/or muscularis mucosa; SM, submucosa; LN, lymph node

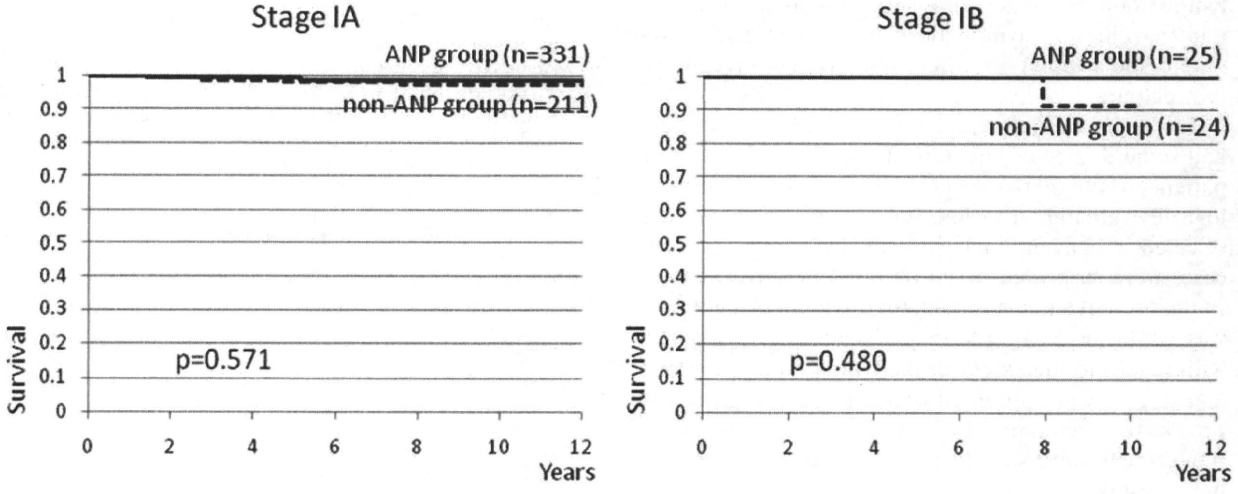

Fig. 4. Disease-specific survival curves for stage IA and IB patients who underwent a gastrectomy with (*ANP*) and without (*non-ANP*) the preservation of the autonomic nerves. The survival rates between the ANP and non-ANP groups do not differ significantly for stages IA ($P = 0.571$, log-rank test) and IB ($P = 0.480$, log-rank test)

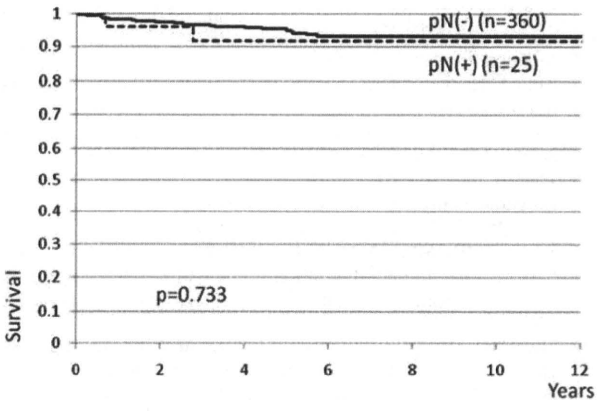

Fig. 5. Five-year survival rates of the patients in the ANP group are 94.9% in those without lymph node metastasis and 91.8% in those with metastasis ($P = 0.733$, log-rank test)

nodal metastasis in comparison to a gastrectomy with a limited lymph node dissection.[22] However, a recent study reported no significant difference in the survival rates between the standardized D2 lymphadenectomy and the D2 plus para-aortic lymphadenectomy in gastric cancer surgery.[23,24] The purpose of a nerve-preserving gastrectomy is to maintain both the postoperative quality of life and the curability of the patient. The left gastric artery and the common hepatic artery are enveloped in connective tissue, and the lymphatics along the arteries encircle this connective tissue. The nerves are dispersed within the connective tissue surrounding the arteries.[15,16] Therefore, an autonomic nerve-preserving gastrectomy may provide a curative operation even for patients with intracapsular microscopic metastases.[15,16] The number of dissected lymph nodes was actually greater in the ANP group than in the non-ANP group

although the dissection levels of both groups were equal. We achieved technical improvement of the dissection by confirming the location of the autonomic nerves. Although macroscopic diagnosis of lymph node metastases is possible, a previous study found that 15 of 158 gastric cancer patients with macroscopically negative nodes had lymph node metastases, and the false-negative rate was 3.8%.[25] In the present study the false-negative rate was 6.5%, and the survival of such patients was same in both groups. In addition, only one patient experienced recurrence in comparison to the four patients who had metastasis to lymph nodes near the celiac branch, such as No. 1 or No. 7. Therefore, our retrospective study indicates that an autonomic nerve-preserving gastrectomy did not reduce the patient survival rate, even in patients with microscopic lymph node metastases, thus suggesting that this procedure can eliminate lymphatic invasion (including microscopic metastases) as effectively as a conventional gastrectomy.

This study was a retrospective analysis and therefore had some degree of bias. Given that significantly more patients in the non-ANP group had tumors with histologically greater invasion, the surgeons may have selected a conventional gastrectomy when advanced cases were suspected based on intraoperative findings. In the present study, although the most important factor was lymph node metastasis, no significant differences with regard to the extent of the lymph node metastasis and staging were observed between the two groups. A prospective randomized trial is therefore necessary in the future to solve and elucidate the problems identified in our study.

In conclusion, an autonomic nerve-preserving gastrectomy did not reduce the survival of patients with early gastric cancer as compared with a conventional gastrectomy. Therefore, an autonomic nerve-preserving gastrectomy appears to be a useful function-preserving procedure for the treatment of clinical early gastric cancer. In addition, we recently started to perform a laparoscopy-assisted autonomic nerve-preserving gastrectomy,[26] and this method is expected to be both a function-preserving and minimally invasive treatment modality.

References

1. Hotta T, Taniguchi K, Kobayashi Y, Johata K, Sahara M, Naka T, et al. Postoperative evaluation of pylorus-preserving procedures compared with conventional distal gastrectomy for early gastric cancer. Surg Today 2001;31:774–9.
2. Katai H. Function-preserving surgery for gastric cancer. Int J Clin Oncol 2006;11:357–66.
3. Freedom GT, Kannel WP, Dawber TR. Epidemiology of gallbladder disease: Observation of the Framingham study. J Chron Dis 1966;19:273–81.
4. Mujahed Z, Evans JA. The relationship of cholelithiasis to vagotomy. Surg Gynecol Obstet 1971;133:656–8.
5. Goligher JC, Pulvertaft CN, Irvin TT, Johnston D, Walder B, Hall RA, et al. Five- to eight-year results of truncal vagotomy and pyloroplasty for duodenal ulcer. Br Med J 1972;1:7–13.
6. Csendes A, Laeach J, Godoy M. Instance of gallstone development after selective hepatic vagotomy. Acta Chir Scand 1978; 144:289–91.
7. Sapala MA, Sapala JA, Soto AD, Bouwman DL. Cholelithiasis following subtotal gastric resection with truncal vagotomy. Surg Gynecol Obstet 1979;148:36–8.
8. Ihasz M, Griffith CA. Gallstones after vagotomy. Am J Surg 1981; 141:48–50.
9. Nordback I, Harju E. Immediate effect of vagotomy on pancreatic insulin secretion. Gut 1991;32:303–5.
10. Ninomiya M, Ikeda T, Asakura H, Moriyama Y, Onoda T, Shiozaki S, et al. The clinical significance of gastrectomy with preservation of autonomic nerves and the pylorus accompanied with D2 dissection for early gastric cancer (In Japanese with English abstract). Nihon Syokakigeka Gakkaizasshi (Jpn J Gastroenterol Surg) 1997;30:2239–46.
11. Kinami S, Miwa K, Sato T, Miyazaki I. Section of the vagal celiac branch in man reduces glucagon-stimulated insulin release. J Auton Nerv Syst 1997;64:44–8.
12. Suzuki H, Mikami Y, Seino K, Baba T, Takahashi S, Kawasaki H, et al. Evaluation of the vagus preserving gastrectomy aiming at prevention of postgastrectomy gallstone formation (In Japanese with English abstract). Nihon Syokakigeka Gakkaizasshi (Jpn J Gastroenterol Surg) 1998;31:813–8.
13. Ninomiya M, Sasaki H, Ikeda Y, Harano M, Aoki H, Takakura N. Distal gastrectomy with preservation of autonomic nerves for early gastric cancer (In Japanese). Rinshogeka 2003; 58:1341–5.
14. Tsuji H, Andoh S, Sakakibara K. The clinical evaluation of vagus nerve preserving gastric operation with D2 lymph node dissection for early and advanced gastric cancer (In Japanese with English abstract). Nihon Syokakigeka Gakkaizasshi (Jpn J Gastroenterol Surg) 2003;36:78–84.
15. Miwa K, Kinami S, Sato T, Fujimura T, Miyazaki I. Vagus-saving D2 procedure for early gastric carcinoma (In Japanese with English abstract). Nihon Geka Gakkaizasshi (J Jpn Surg Soc) 1996;97:286–90.
16. Ando S, Tsuji H. Surgical technique of vagus nerve-preserving gastrectomy with D2 lymphadenectomy for gastric cancer. Aust NZ J Surg 2008;78:172–6.
17. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. Gastric Cancer 1998;1:10–24.
18. Uyama I, Sakurai Y, Komori Y, Nakamura Y, Syoji M, Tonomura S, et al. Laparoscopic gastrectomy with preservation of the vagus nerve accompanied by lymph node dissection for early gastric carcinoma. J Am Coll Surg 2005;200:140–5.
19. Aoki T, Hanyu N, Furukawa Y. Innervation and motor function of GI tract — application to surgical procedure preserving autonomic nerves for gastric cancer- (In Japanese with English abstract). Jpn J Cancer Clin 1999;45:531–8.
20. Marlett JA, Code CF. Effects of celiac and superior mesenteric ganglionectomy on interdigestive myoelectric complex in dogs. Am J Physiol 1979;237:E432–3.
21. Siadati MR, Murr MM, Foley MK, Duenes JA, Steers JL, Sarr MG. In situ neural isolation of the entire canine upper gut: Effects on fasting and fed motility patterns. Surgery 1997;121: 174–81.
22. Miwa K, Miyazaki I, Sahara H, Fujimura T, Yonemura Y, Noguchi M, et al. Rationale for extensive lymphadenectomy in early gastric carcinoma. Br J Cancer 1995;72:1518–24.
23. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008; 359:453–62.

24. Hu JK, Yang K, Zhang B, Chen XZ, Chen ZX, Chen JP. D2 plus para-aortic lymphadenectomy versus standardized D2 lymphadenectomy in gastric cancer surgery. Surg Today 2009;39:207–13.
25. Natsugoe S, Aikou T, Yotsumoto K, Yoshinaka H, Shimazu H. Comparative study on macroscopic and histological diagnosis for lymph node metastasis in cancer patients (In Japanese with English abstract). Nihon Geka Gakkaizasshi (J Jpn Surg Soc) 1987;88:258–65.
26. Nishizaki M, Urano S, Onishi T, Harano M, Ojima Y, Aoki H, et al. A trial for standardization of laparoscopy assisted autonomic nerve-preserving gastrectomy with D1 plus β lymph node dissection (In Japanese). Med J Hiroshima City Hosp 2008; 61:104–6.

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Safety of carbon dioxide insufflation for upper gastrointestinal tract endoscopic treatment of patients under deep sedation

Satoru Nonaka · Yutaka Saito · Hajime Takisawa · Yongmin Kim · Tsuyoshi Kikuchi · Ichiro Oda

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Abstract
Background It is well known that carbon dioxide (CO_2) is absorbed faster in the body than air and also that it is rapidly excreted through respiration. This study aimed to investigate the safety of CO_2 insufflation used for esophageal and gastric endoscopic submucosal dissection (ESD) in patients under deep sedation.
Methods Patients with either early gastric or esophageal cancers that could be resected by ESD were enrolled in this study from March 2007 to July 2008 and randomly assigned to undergo ESD procedures with CO_2 insufflation (CO_2 group) or air insufflation (air group). A TOSCA measurement system and TOSCA 500 monitor were used to measure and monitor both transcutaneous partial pressure of CO_2 ($PtcCO_2$) and oxygen saturation (SpO_2).
Results The study enrolled 89 patients and randomly assigned them to a CO_2 group (45 patients) or an air group (44 patients). The mean CO_2 group versus air group measurements were as follows: $PtcCO_2$ (49.1 ± 5.0 vs. 50.1 ± 5.3 mmHg; nonsignificant difference [NS]), maximum $PtcCO_2$ (55.1 ± 6.5 vs. 56.8 ± 7.0 mmHg; NS), $PtcCO_2$ elevation (9.1 ± 5.4 vs. 11.4 ± 5.6 mmHg; $p = 0.054$), SpO_2 ($99.0 \pm 0.7\%$ vs. $99.0 \pm 1.0\%$; NS), minimum SpO_2 ($96.5 \pm 2.4\%$ vs. $95.4 \pm 3.3\%$; $p = 0.085$), and SpO_2 depression ($2.4 \pm 2.3\%$ vs. $3.3 \pm 2.9\%$; NS). The $PtcCO_2$ and SpO_2 measurements were similar in the two groups, but the CO_2 group was better than the air group in $PtcCO_2$ elevation and minimum SpO_2.
Conclusions The findings demonstrated CO_2 insufflation to be as safe as air insufflation for upper gastrointestinal tract ESDs performed for patients under deep sedation without evidencing any adverse effects.

Keywords Carbon dioxide insufflation · Deep sedation · Endoscopic submucosal dissection · Transcutaneous partial pressure of carbon dioxide · Upper gastrointestinal tract

Several recent studies investigating colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) have reported that carbon dioxide (CO_2) insufflation reduces abdominal pain and discomfort caused by bowel hyperextension and can be used as safely as air insufflation [1–6]. It is well known that CO_2 is absorbed faster in the body than air and that it also is rapidly excreted through respiration unless some type of pulmonary dysfunction exists [1, 2]. To date, almost all endoscopic procedures have been performed using air insufflation, although it has led to some problems of abdominal pain and discomfort in routine examinations and perforation-related subcutaneous or mediastinal emphysema and pneumoperitoneum in endoscopic treatments [7, 8].

With the relatively recent development and increasingly widespread use of endoscopic submucosal dissection (ESD) as a minimally invasive treatment, performance of ESD for early gastrointestinal (GI) neoplasm in the esophagus, stomach, and colorectum has increased dramatically [9–16]. Quite naturally, the number of complications also has increased as a direct result, including perforations that occur during the technically difficult ESD procedure itself and the delayed bleeding experienced afterward [7, 8, 14, 17, 18]. In fact, the reported ESD perforation rate is 7% for cases involving the esophagus,

S. Nonaka · Y. Saito (✉) · H. Takisawa · Y. Kim · T. Kikuchi · I. Oda
Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: ytsaito@ncc.go.jp

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4% for cases involving the stomach, and 5% for cases involving the colorectum [10, 14, 15]. Perforation can cause peritonitis and mediastinitis, and possibly also thromboembolism due to blood flow congestion (compartment syndrome) when significant pneumatic leakage results in excess internal pressure [19–24]. It is anticipated that such associated problems will be minimized by further use of CO_2 insufflation.

Colonoscopy with conscious sedation and the use of CO_2 insufflation has become more generally accepted since the demonstration of the safety and effectiveness of CO_2 insufflation in a previously published reported [5]. We previously conducted a case–control study that showed CO_2 insufflation to be both safe and effective for colorectal ESD with conscious sedation [25]. However, the safety of CO_2 insufflation has not been established for upper GI tract endoscopic treatment such as ESD with deep sedation in which CO_2 retention and decreased oxygenation are more important factors than in colonoscopy performed with conscious sedation.

This study aimed to investigate the safety of CO_2 insufflation for esophageal and gastric ESDs with deep sedation. Both operations are lengthy procedures.

Materials and methods

Patients

We prospectively assessed the safety of CO_2 insufflation for upper GI tract ESDs performed with the patient under deep sedation compared with air insufflation from March 2007 to July 2008 at the National Cancer Center Hospital (NCCH) in Tokyo, Japan. The study enrolled 89 patients with either early gastric or esophageal cancer that could be resected by ESD and randomly assigned them to undergo ESD procedures with CO_2 insufflation (CO_2 group) or air insufflation (air group).

The study excluded patients with severe pulmonary disease including either chronic obstructive pulmonary disease (COPD) or disease resulting in less than 80% of vital capacity (%VC) or less than 70% of the forced expiratory volume in 1 s as a percentage of the forced vital capacity (FEV1%), patients with severe cardiovascular disease including NYHA III or IV heart failure or arrhythmia with any treatment history, patients with hepatic or renal dysfunction, and patients with a change in insufflation methods from CO_2 to air or from air to CO_2 for any reason during their ESDs.

Endoscopic procedures

All ESD procedures were performed with Olympus video endoscopes and a standard videoendoscope system (EVIS LUCERA; Olympus Optical Co., Ltd., Tokyo, Japan). For ESD procedures, an insulation-tipped diathermic knife (IT-knife; Olympus) was used from March to October 2007 and an improved IT-knife (IT-knife 2; Olympus) from November 2007 to July 2008 [11, 26, 27].

First, marking dots were made around the lesion using a needleknife (Olympus). This was followed by injection of diluted epinephrine with normal saline (1:200,000) to lift the submucosal layer and allow the tip of the IT-knife or IT-knife 2 to be inserted into the submucosal layer. A small initial incision then was made by a needleknife, and a complete circumferential mucosal incision around the periphery of the marking dots was performed with the IT-knife or IT-knife 2. After an additional submucosal injection, the submucosal layer beneath the lesion was directly dissected using the same IT-knife or IT-knife 2.

Although all ESDs were generally performed in this manner, we sometimes used not only other devices such as an argon plasma coagulation probe for the marking dots and a bipolar needleknife (B-knife; XEMEX Co., Tokyo, Japan) for the initial incision and submucosal dissection [15, 28], but also another injection solution, sodium hyaluronate (MucoUp; Johnson & Johnson Co., Ltd., Tokyo, Japan) diluted with normal saline (1:1), especially for esophageal ESDs [12, 29–31]. The final objective was to achieve successful en bloc resections for precise pathologic evaluations.

Patients received midazolam, propofol, or both for deep sedation, and oxygen (O_2) was administered nasally (2 l/min) during ESD. Initially, 3–5 mg of midazolam was used for induction of venous anesthesia, with an additional 1–3 mg given repeatedly as necessary based on the judgment of the individual endoscopist. Propofol was administered initially at a dosage of 20 mg for induction, with another 0.1–0.5 mg/kg/h given continuously for maintenance depending on the condition of the patient.

CO_2 insufflation and transcutaneous measurements

A CO_2 regulator prototype (Olympus) connected to a CO_2 bottle was used for CO_2 insufflation until the Olympus UCR (Fig. 1) became commercially available in Japan in May 2008 [25]. During the procedure, CO_2 insufflation was set at a constant rate of 1.2 l/min, which is a moderate level. In upper GI endoscopy, the UCR has three insufflation levels, which can be controlled by the use of three types of connecting tubes. These insufflation amounts are almost equivalent to the original three regulation levels of the EVIS LUCERA (Olympus).

Measurement of the arterial partial pressure of CO_2 (partial pressure of carbon dioxide [PCO_2] and arterial partial pressure of carbon dioxide [$PaCO_2$]) is an invasive, intermittent, and unpleasant process widely used for

Fig. 1 UCR (CO_2 regulator). The UCR in upper gastrointestinal endoscopy has three levels of insufflation which can be controlled by using three types of connecting tubes. These amounts of insufflation are almost equivalent to the original three regulation levels of the EVIS LUCERA

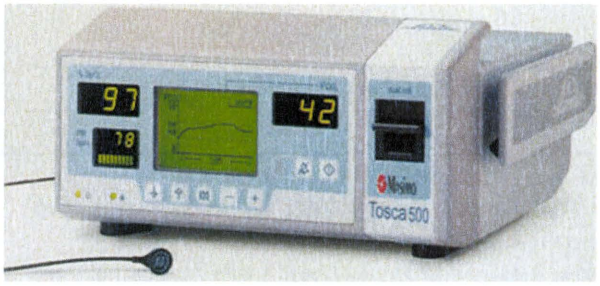

Fig. 2 The TOSCA measurement system and TOSCA 500 monitor, a noninvasive and continuous monitoring device for transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) that takes measurements using a sensor attached by a low-pressure clip to the patient's earlobe

various patients as the gold standard, but determining the variation of $PaCO_2$ during ESD using CO_2 insufflation has proved to be quite difficult.

In this study, a TOSCA measurement system and TOSCA 500 monitor (Linde Medical Sensors, Basel, Switzerland) (Fig. 2) was used to measure and monitor both transcutaneous partial pressure of CO_2 ($PtcCO_2$) and oxygen saturation (SpO_2). This system, which takes measurements using a sensor attached by a low-pressure clip to the patient's earlobe, is a noninvasive, continuous, trend-monitoring device for $PtcCO_2$ reported in several studies to provide general agreement between $PtcCO_2$ and $PaCO_2$ measurements [32–37]. We used a default temperature setting of 42°C for the earlobe sensor and recalibrated the TOSCA system to minimize the possibility of measurement error before each ESD. Procedure time was measured from endoscope insertion to its completed withdrawal after ESD, with $PtcCO_2$ and SpO_2 recorded every 3 s for both groups using the TOSCA system.

Statistical analysis

All variables in this study were described in terms of mean ± standard deviation as well as median and range. We used chi-square and *t*-tests to compare baseline characteristics and measurements between the two groups. All statistical analyses were performed using the SAS Statistical Package (SAS Institute, Tokyo, Japan), and a p value less than 0.05 was considered statistically significant.

Ethics

The ethics committee at NCCH approved the study protocol, and written informed consent was obtained from all patients before they were enrolled in the study.

Results

No significant differences in patient characteristics between the two groups were observed (Table 1). The CO_2 group study consisted of 45 patients (39 men and 6 women) with 52 lesions. These 45 patients (involving 15 esophageal and 30 gastric ESD cases) had a mean age of 68.5 ± 8.8 years (range, 50–84 years). The air group consisted of 44 patients (38 men and 6 women) with 51 lesions. These 44 patients (involving 12 esophageal and 32 gastric ESD cases) had a mean age of 67.6 ± 8.0 years (range, 43–84 years).

The macroscopic types of tumors included 13 elevated lesions, 32 flat and depressed lesions, 6 combined lesions, and 1 residual lesion in the CO_2 group and 11 elevated lesions, 34 flat and depressed lesions, 5 combined lesions, and 1 residual lesion in the air group (nonsignificant difference [NS]). In the CO_2 group, the median size of the tumors, determined histopathologically, was 13 mm (range, 5–60 mm), and the 35 adenocarcinomas included 2 Barrett's carcinomas, 15 squamous cell carcinomas (SCCs), and 2 adenomas. The median size of the tumors in the air group was 19 mm (range, 5–55 mm), and the 37 adenocarcinomas included 2 Barrett's carcinomas, 13 SCCs, and 1 adenoma. The difference between the two groups was not significant. The median specimen size was 35 mm (range, 20–75 mm) in the CO_2 group and 35 mm (range, 20–68 mm) in the air group (NS). The median procedure time was 115 min (range, 30–575 min) in the CO_2 group and 96 min (range, 38–309) in the air group (NS). Midazolam was received by 30 patients at a median

Table 1 Patient characteristics

	CO_2 (*n*)	Air (*n*)	*p* Value
Patients/lesions	45/52	44/51	
Mean age (years)	68.5 ± 8.8	67.6 ± 8.0	NS
Male/female	39/6	38/6	NS
Esophagus/stomach	15/30	12/32	NS
Macroscopic type			
Elevated	13	11	
Flat and depressed	32	34	
Combined	6	5	
Residual	1	1	NS
Histopathologic type			
SCC	15	13	
Adenocarcinoma	35	37	
Adenoma	2	1	NS
Median tumor size: mm (range)	13 (5–60)	19 (5–55)	NS
Median specimen size: mm (range)	35 (20–75)	35 (20–68)	NS
Median procedure time: min (range)	115 (30–575)	90 (38–309)	NS
Perforations	3	0	NS
Patients receiving midazolam	30	31	NS
Patients receiving propofol	15	13	NS
Dosage of midazolam: mg (range)	12 (5–20)	12 (4–23)	NS
Dosage of propofol: mg (range)	640 (130–2460)	370 (180–1116)	NS

CO_2 carbon dioxide, *NS* not significant, *SCC* squamous cell carcinoma

dosage of 12 mg (range, 5–20 mg) in the CO_2 group and by 31 patients at a median dosage of 12 mg (range, 4–23 mg) in the air group (NS), and propofol was received by 15 patients at a median dosage of 640 mg (range, 130–2,460 mg) in the CO_2 group and by 13 patients at a median dosage of 370 mg (range, 180–1,116) in the air group (NS).

All the tumors were resected en bloc by ESD except in one esophageal case in the air group, In this case, the patient's main lesion was resected en bloc by ESD, whereas another smaller synchronous lesion was treated by using endoscopic mucosal resection (EMR) with a cap-fitted panendoscope, resulting in a piecemeal resection [38].

Measurements of $PtcCO_2$ and SpO_2

The mean CO_2 group versus air group measurements were as follows: $PtcCO_2$ (49.1 ± 5.0 vs. 50.1 ± 5.3 mmHg; NS), maximum $PtcCO_2$ (55.1 ± 6.5 vs. 56.8 ± 7.0 mmHg; NS), $PtcCO_2$ elevation (9.1 ± 5.4 vs. 11.4 ± 5.6 mmHg; $p = 0.054$), SpO_2 (99.0 ± 0.7% vs. 99.0 ± 1.0%; NS), minimum SpO_2 (96.5 ± 2.4% vs. 95.4 ± 3.3%; $p = 0.085$), and SpO_2 depression (2.4 ± 2.3% vs. 3.3 ± 2.9%; NS) (Table 2; Fig. 3A–F). The $PtcCO_2$ and SpO_2 measurements were similar in the two groups, but in $PtcCO_2$ elevation and minimum SpO_2, the CO_2 group was better than the air group.

The patient characteristics did not differ significantly between the two groups when esophageal and gastric ESD cases were considered separately, nor did the $PtcCO_2$ and SpO_2 measurements differ significantly between the two groups when only esophageal ESD cases were considered. The CO_2 group versus air group measurements in gastric ESD cases were as follows: $PtcCO_2$ elevation (8.0 ± 5.2 vs. 10.8 ± 5.7 mmHg; $p = 0.049$) and SpO_2 depression (1.9 ± 1.8% vs. 2.8 ± 2.5%; $p = 0.087$). Although the $PtcCO_2$ and SpO_2 measurements again were similar for the two groups, when only gastric ESD cases were considered, the CO_2 group was better than the air group in $PtcCO_2$ elevation and SpO_2 depression.

Table 2 Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) and oxygen saturation (SpO_2) measurements

	CO_2	Air	*p* Value
Mean $PtcCO_2$ (mmHg)	49.1 ± 5.0	50.1 ± 5.3	NS
Maximum $PtcCO_2$ (mmHg)	55.1 ± 6.5	56.8 ± 7.0	NS
$PtcCO_2$ elevation (mmHg)	9.1 ± 5.4	11.4 ± 5.6	0.054
Mean SpO_2 (%)	99.0 ± 0.7	99.0 ± 1.0	NS
Minimum SpO_2 (%)	96.5 ± 2.4	95.4 ± 3.3	0.085
SpO_2 depression (%)	2.4 ± 2.3	3.3 ± 2.9	NS

NS not significant

Five CO_2 group patients and five air group patients experienced a maximum $PtcCO_2$ exceeding 60 mmHg that continued for more than 5 min (NS). The median duration time was 12 min (range, 6–166 min) for the CO_2 group and 35 min (range, 10–148 min) for the air group (NS). The