

Treatment of esophago-gastric junction and stomach cancer; differences and similarities

Are ESD indications same?

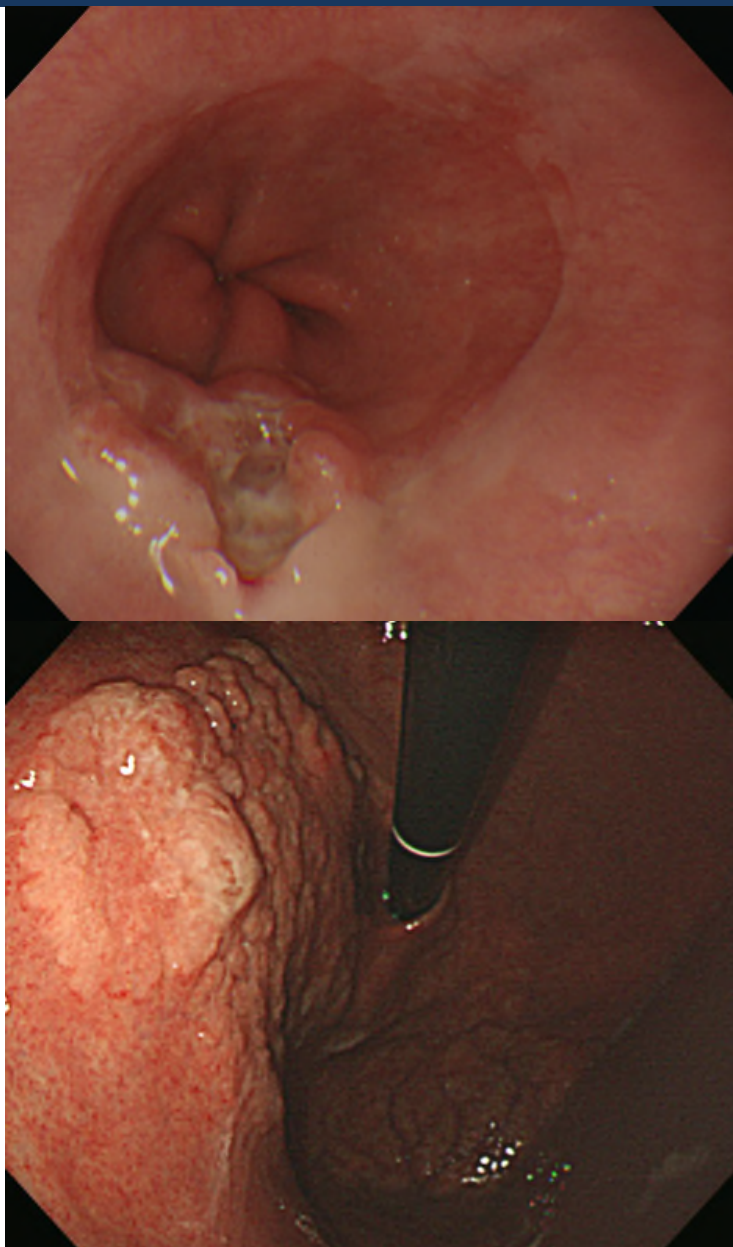
**Division of Gastroenterology,
Department of Internal Medicine,
Kosin University Gospel Hospital,
Sung Eun Kim**

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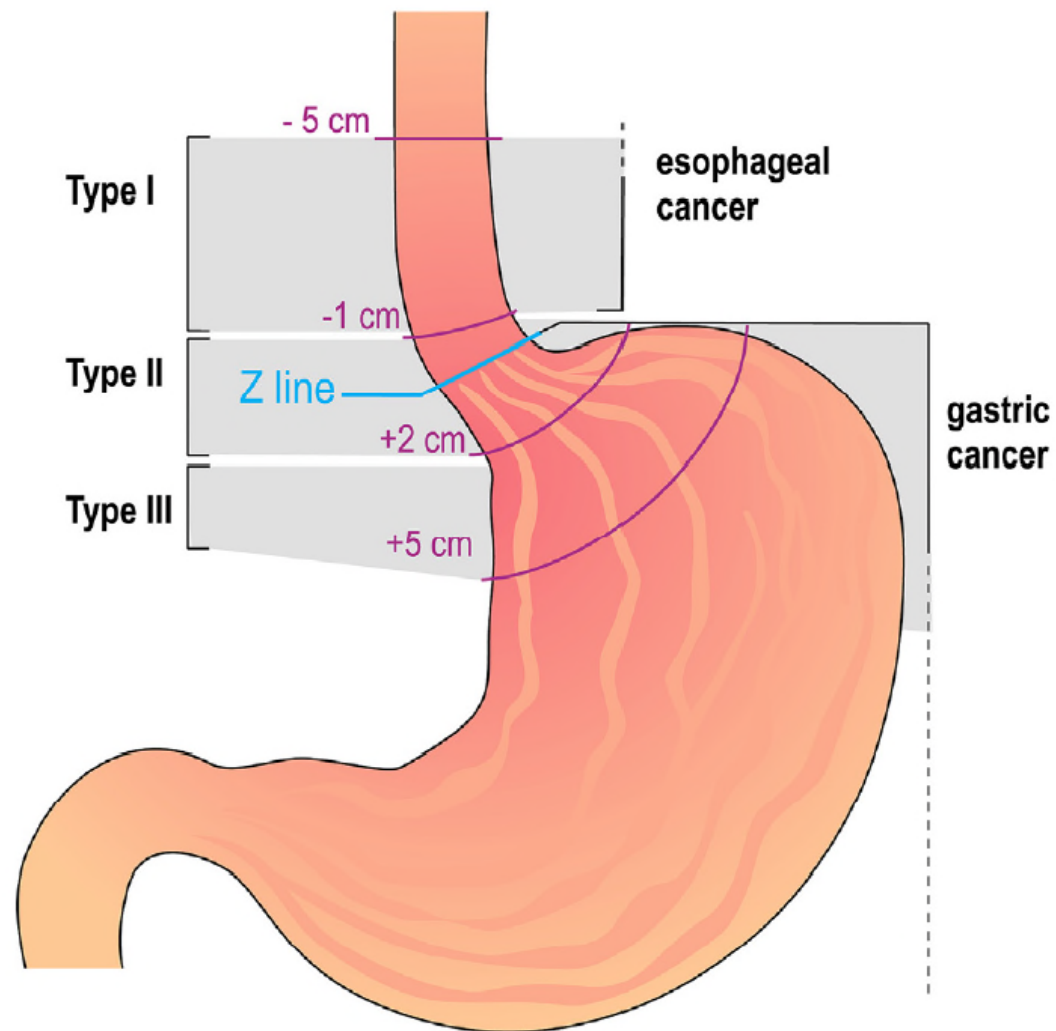
Overview of EGJ cancer

The Siewert classification



Siewert classification

WHO classification



Incidence of EGJ cancer in West

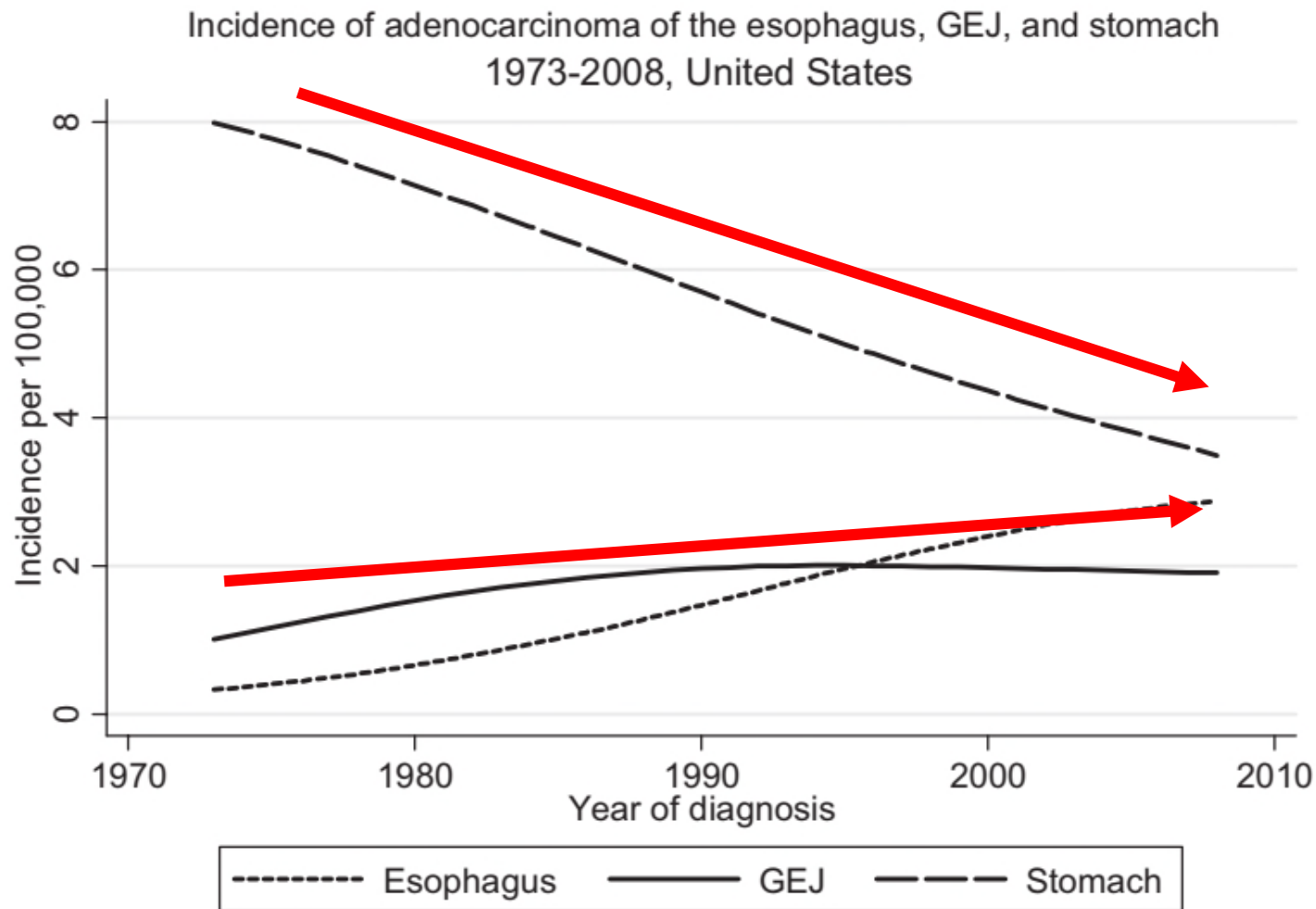


Figure 1 Trends in incidence of adenocarcinoma of the esophagus, gastroesophageal junction (GEJAC), and noncardia stomach in the United States, 1973-2008 (per 100,000, adjusted for age, race, and sex to the 2000 U.S. standard population, with loess smoothing).

Incidence of EGJ cancer in East

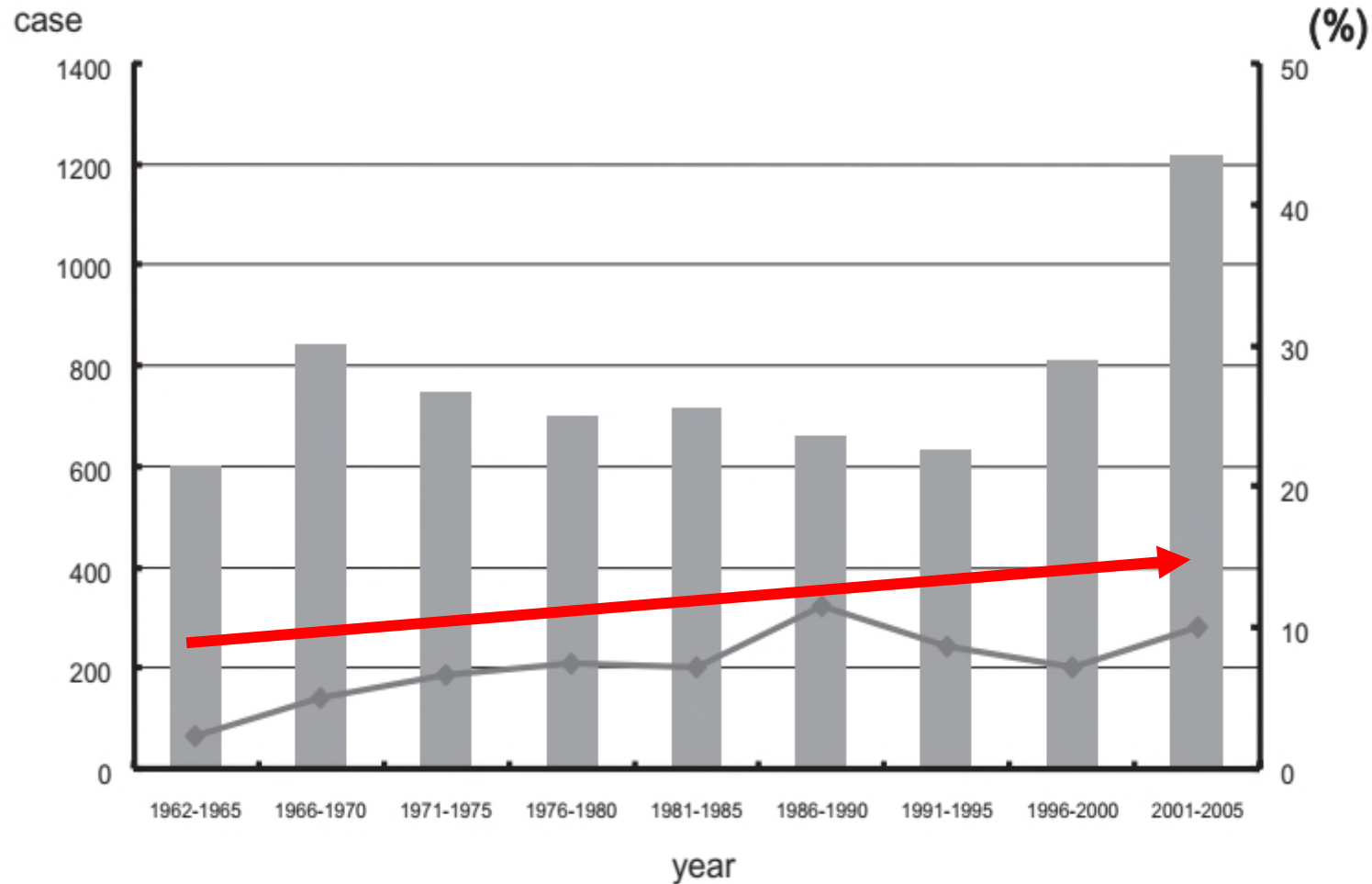
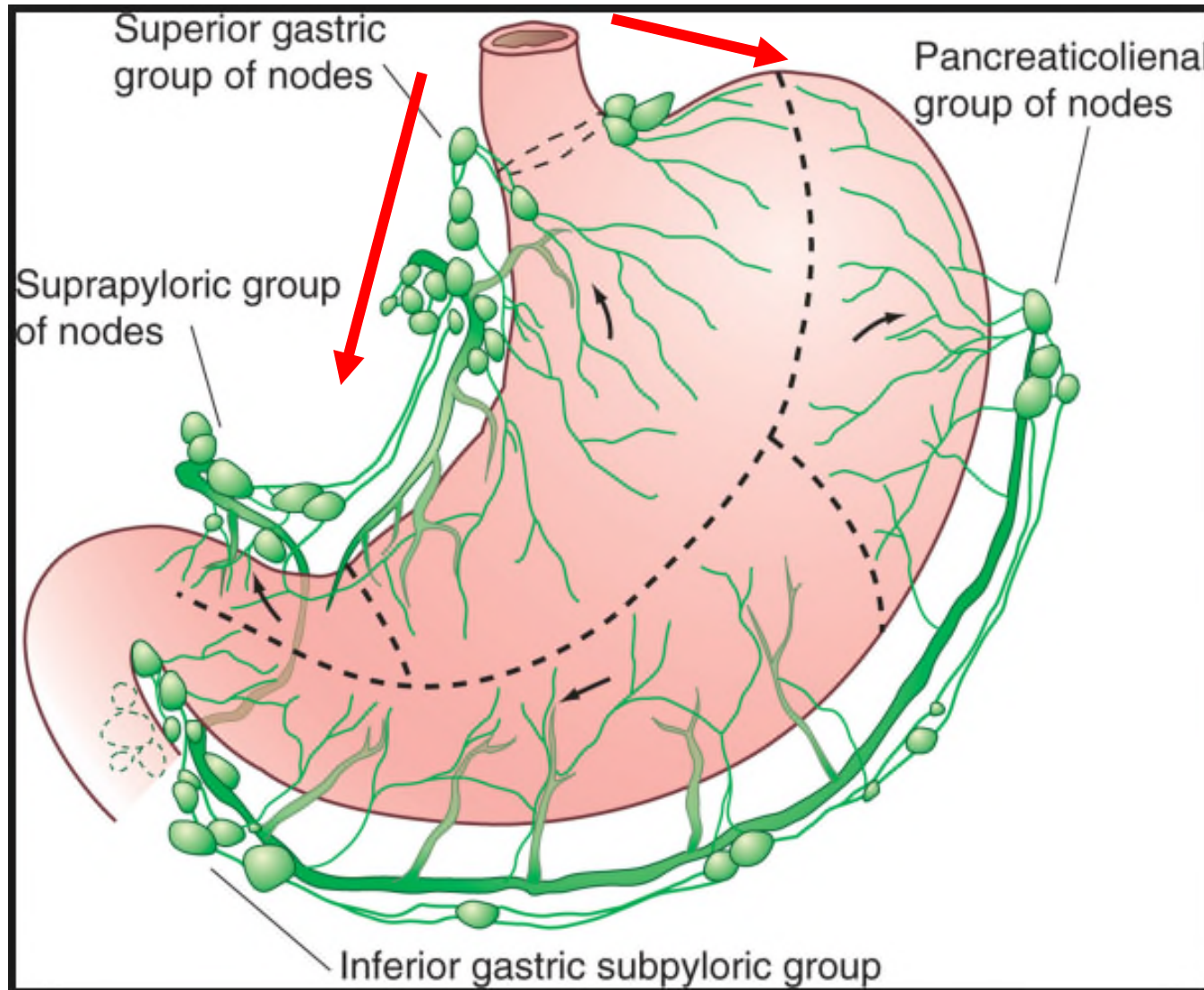


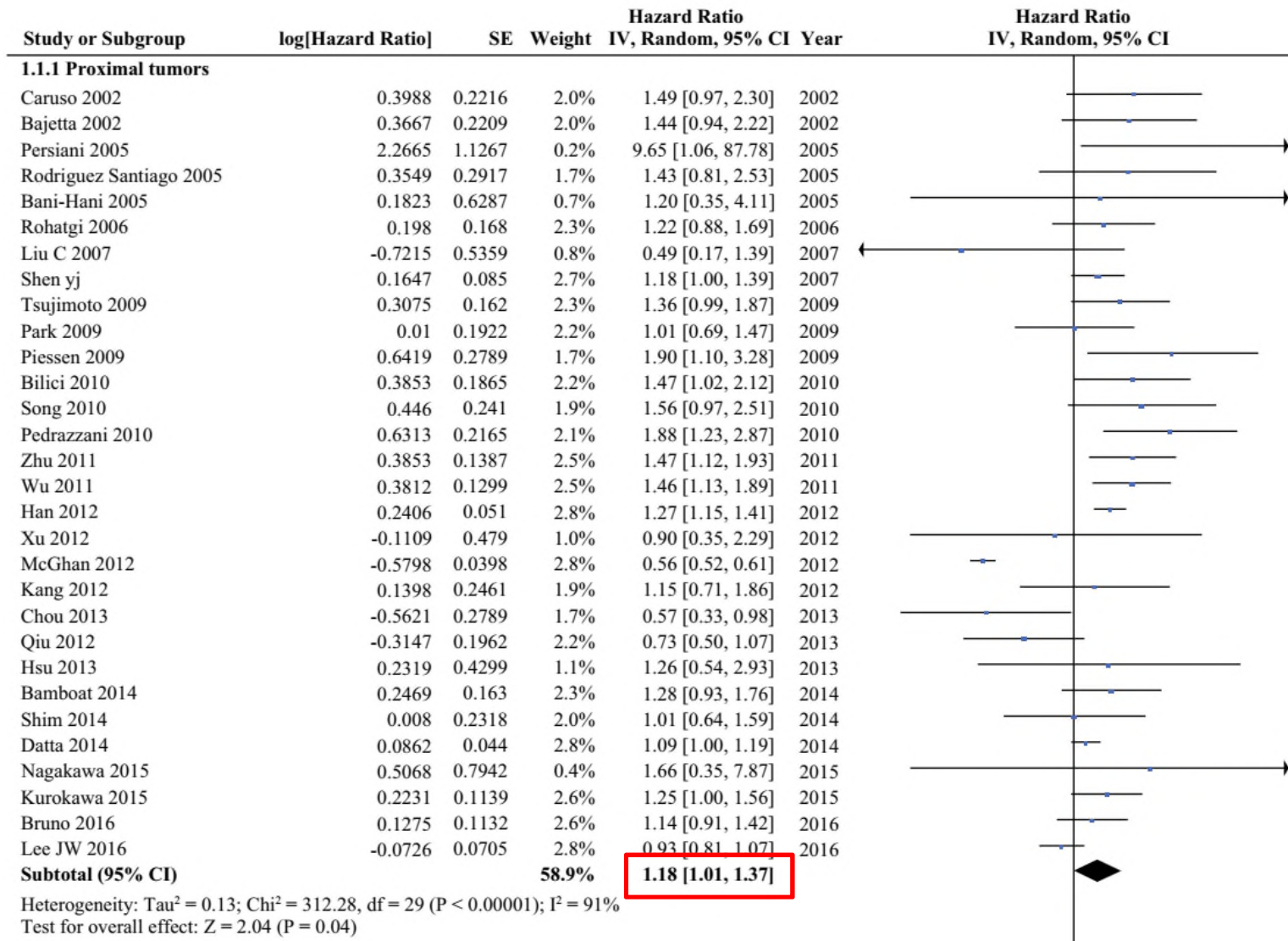
Figure 1 Changing rate in adenocarcinoma of esophagogastric junction (EGJ) among all gastric adenocarcinoma. (■), no. of gastric adenocarcinoma; (◆), proportion of adenocarcinoma of EGJ among all gastric adenocarcinoma.

Stomach lymphatic drainage



Overall survival for proximal gastric cancer

- Meta-analysis, 50 studies (N=123,268)



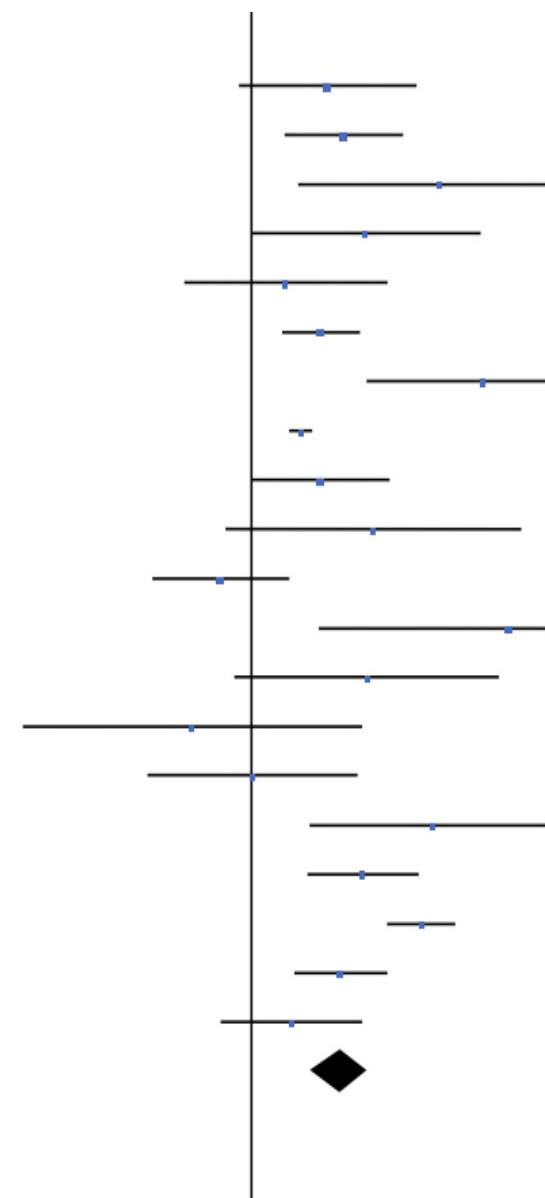
Overall survival for EGJ cancer

1.1.2 cardias/GEJ

Bouche 2005	0.3507	0.2051	2.1%	1.42 [0.95, 2.12]	2005
Kim 2005	0.4253	0.1369	2.5%	1.53 [1.17, 2.00]	2005
Marchet 2007	0.8713	0.3307	1.5%	2.39 [1.25, 4.57]	2007
Marrelli 2009	0.5247	0.2677	1.8%	1.69 [1.00, 2.86]	2009
Yu 2010	0.157	0.2337	2.0%	1.17 [0.74, 1.85]	2010
Strauss 2010	0.3221	0.0886	2.7%	1.38 [1.16, 1.64]	2010
Deans 2011	1.0647	0.2695	1.8%	2.90 [1.71, 4.92]	2011
Kunz 2012	0.2343	0.024	2.9%	1.26 [1.21, 1.32]	2012
Smyth 2012	0.3221	0.1593	2.4%	1.38 [1.01, 1.89]	2012
Jacome 2013	0.5653	0.3422	1.4%	1.76 [0.90, 3.44]	2013
Nelen 2013	-0.1393	0.1566	2.4%	0.87 [0.64, 1.18]	2013
Posteraro 2014	1.1848	0.4439	1.1%	3.27 [1.37, 7.81]	2014
Postlewait 2015	0.5306	0.3078	1.6%	1.70 [0.93, 3.11]	2015
Gu 2015	-0.2666	0.3938	1.2%	0.77 [0.35, 1.66]	2015
Liu K 2015	0.0119	0.2418	1.9%	1.01 [0.63, 1.63]	2015
Squires 2015	0.8372	0.2855	1.7%	2.31 [1.32, 4.04]	2015
Fiteni 2016	0.5158	0.1266	2.5%	1.67 [1.31, 2.15]	2016
Wang 2016	0.7816	0.0767	2.7%	2.18 [1.88, 2.54]	2016
In 2016	0.4114	0.1072	2.6%	1.51 [1.22, 1.86]	2016
Shen GS 2016	0.1906	0.1625	2.3%	1.21 [0.88, 1.66]	2016
Subtotal (95% CI)			41.1%	1.50 [1.32, 1.72]	

Heterogeneity: $\tau^2 = 0.05$; $\text{Chi}^2 = 84.48$, $\text{df} = 19$ ($P < 0.00001$); $I^2 = 78\%$

Test for overall effect: $Z = 6.00$ ($P < 0.00001$)



ESD indications for EGC

ESD indications for EGC

- Gotoda T, *et al.* Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219-25.
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;14:113-23.
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017;20:1-19.

Expanded criteria of endoscopic treatment for EGC

Pathology	Mucosal				Submucosal	
	Ulcer (-)		Ulcer (+)		<500 μm	>500 μm
	≤ 2 cm	> 2 cm	≤ 3 cm	> 3 cm	≤ 3 cm	Any size
Differentiated type	EMR /ESD	ESD	ESD	Surgery	ESD	Surgery
Undifferentiated type	Consider surgery	Surgery	Surgery	Surgery	Surgery	Surgery

Japanese gastric cancer treatment guideline 2014 (ver. 4)

Pathology	Mucosal				Submucosal	
	Ulcer (-)		Ulcer (+)		<500 μ m	>500 μ m
	\leq 2 cm	> 2 cm	\leq 3 cm	> 3 cm	\leq 3 cm	Any size
Differentiated type	EMR /ESD	ESD	ESD	Surgery	ESD	Surgery
Undifferentiated type	ESD	Surgery	Surgery	Surgery	Surgery	Surgery

Clinical outcomes of ESD for early EGJ cancer

Outcome parameters

- **En bloc resection**; a resection in a single piece
- **Complete resection**; successful en bloc resection, with lateral and vertical margins histologically free of carcinoma
- **Curative resection**; a complete resection that fulfilled the following pathological criteria
 - (1) intramucosal cancer, differentiated-type adenocarcinoma, no LVI, no ulcer findings, irrespective of tumor size
 - (2) intramucosal cancer, differentiated-type adenocarcinoma, no LVI, ulcer findings, tumor size ≤ 3 cm
 - (3) minute submucosal cancer invasion $\leq 500 \mu\text{m}$, differentiated-type adenocarcinoma, no LVI, tumor size ≤ 3 cm
 - (4) intramucosal cancer, undifferentiated-type adenocarcinoma, no LVI, no ulcer findings, tumor size ≤ 2 cm.

Complication

- **Bleeding;** bleeding proven by endoscopic evaluation within 24-48 h, clinical evidence of melena or hematemesis, or massive bleeding requiring transfusion
- **Perforation;** endoscopically diagnosed during the procedure or by the presence of free air on plain chest radiography after ESD
- **Stenosis;** present when a standard 10-mm diameter endoscope could not be passed through the EGJ

Clinical Outcomes of Endoscopic Submucosal Dissection for Adenocarcinoma of the Esophagogastric Junction

Eun Jeong Gong¹ · Do Hoon Kim¹ · Hoonsub So¹ · Ji Yong Ahn¹ ·
Kee Wook Jung¹ · Jeong Hoon Lee¹ · Kee Don Choi¹ · Ho June Song¹ ·
Gin Hyug Lee¹ · Hwoon-Yong Jung¹ · Jin-Ho Kim¹

- Dec. 2004-Dec. 2011

Patients (number)	88
Age (years)	66 (59–71)
Male sex	80 (90.9)
Histologic differentiation	
Differentiated ^a	80 (90.9)
Undifferentiated ^b	8 (9.1)
Barrett's cancer	3 (3.4)
Macroscopic type	
Elevated	34 (38.6)
Flat	21 (23.9)
Depressed	33 (37.5)
Size of tumor (mm)	20 (14–25)
Depth of invasion	
Mucosa	65 (73.9)
Submucosa	23 (26.1)

Therapeutic outcomes

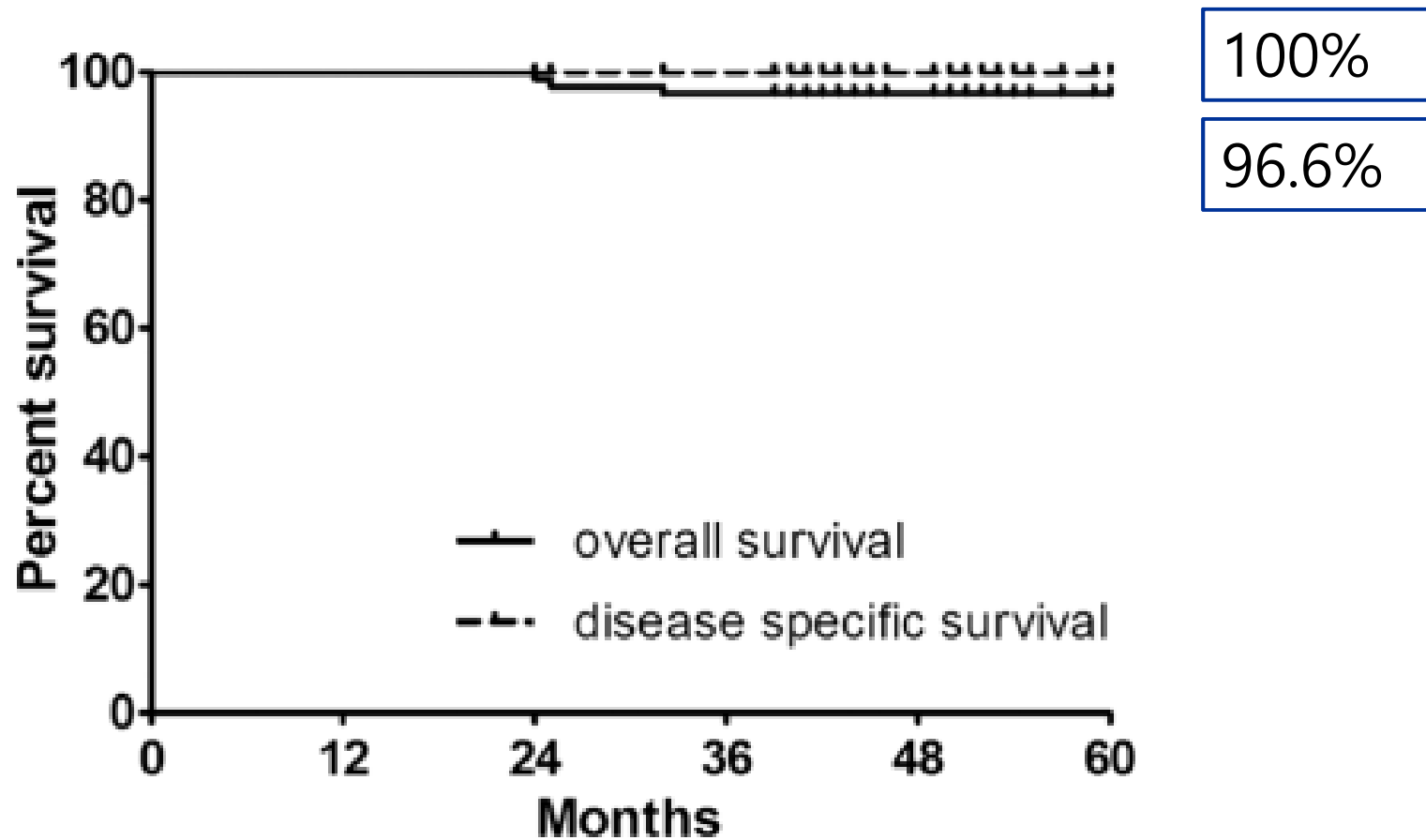
Adverse events	9 (10.2)
Bleeding	6 (6.8)
Immediate	1
Early delayed	4
Late delayed	1
Microperforation	3 (3.4)
Stricture	0 (0.0)
Hospital stay (days)	4 (4–5.3)
Result of resection	
En bloc resection	78 (88.6)
Complete resection	73 (83.0)
Curative resection	53 (60.2)
Lymphovascular invasion	2 (2.4)
Clinical outcome	
Local recurrence	2/84 (2.4)
Metachronous lesion	6/84 (7.1)

Predictive factors for non-curative resection

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	<i>P</i> value	OR (95 % CI)	<i>P</i> value
Differentiation				
Differentiated	1		1	
Undifferentiated	13.0 (1.522–111.05)	0.019	18.682 (2.06–169.45)	0.009
Macroscopic type				
Depressed	1		1	
Flat	1.333 (0.407–4.372)	0.635	1.181 (0.316–4.417)	0.805
Elevated	3.378 (1.215–9.389)	0.020	4.154 (1.391–12.402)	0.011
Size of tumor				
<20 mm	1			
≥20 mm	1.385 (0.586–3.269)	0.458		

Overall and disease-specific survival rates

- Median follow-up period; 68.5 mo (range; 24.4–123.5 mo)



Curative vs. non-curative resection

Surgery (n=9)
pN0 stage
; 9 (100%)

	Curative (n = 53)	Noncurative (n = 35)	P value
Differentiation			0.006
Differentiated	52 (98.1)	28 (80.0)	
Undifferentiated	1 (1.9)	7 (20.0)	
Macroscopic type			0.045
Depressed	24 (45.3)	9 (25.7)	
Flat	14 (26.4)	7 (20.0)	
Elevated	15 (28.3)	19 (54.3)	
Size of tumor			0.457
<20 mm	27 (50.9)	15 (42.9)	
≥20 mm	26 (49.1)	20 (57.1)	
Criteria			<0.001
Absolute	31 (58.5)	7 (20.0)	
Expanded	22 (41.5)	8 (22.9)	
Beyond expanded	0 (0.0)	20 (57.1)	

Clinical outcomes of ESD for early EGJ cancer

- Meta-analysis, 6 studies (359 lesions), 2010-2014
- Single-center, retrospective studies conducted in Japan.

Author	Age, year	Male (%)	Siewart classification	Histologic type of lesion	Lesion size (mm)	Deep submucosal invasion ^a (%)	LVI (%)
Hirasawa et al. [12]	Mean 69.3 (range 36–85)	79.3	Type II	BA: 1, GC: 57	Mean 20.3 (range 3–50)	8.6	6.9
Hoteya et al. [13]	BA: mean 63.5 (SD 12.5) GC: mean 68.8 (SD 9.3)	83.6	Type II	BA: 25, GC: 103	BA: mean 20.2 (SD 17.6) GC: mean 21.8 (SD 15.8)	N/A	BA: 24.0 GC: 9.7
Omae et al. [14]	Mean 70.0 (range 42–84)	90.9	Type II	BA: 13, GC: 31	Mean 17 (range 5–47)	11.4	2.3
Yamada et al. [15]	Median 68 (range 39–88)	84.9	Type II	BA: 28, GC: 25	Median 20 (3–47)	24.5	7.5
Imai et al. [16]	Median 72 (range 41–89)	87.8	Type II	BA: 7, GC: 43	Median 22 (range 5–70)	22.0	10.0
Kagemoto et al. [17]	Mean 63 (SD 10)	91.3	N/A	BA: 26	Mean 19.0 (SD 13.6)	23.1	0.0

LVI, lymphovascular invasion; ESD, endoscopic submucosal dissection; BA, Barrett's adenocarcinoma; GC, gastric cardia cancer; IT, insulation-tipped

^a SM2 invasion (>500 μm from the muscularis mucosa) or more.

(A)

En-bloc resection

Author

Event rate and 95% CI

Event rate	Lower limit	Upper limit	Total	Relative weight
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(B)

Complete resection

Author

Event rate and 95% CI

Event rate	Lower limit	Upper limit	Total	Relative weight
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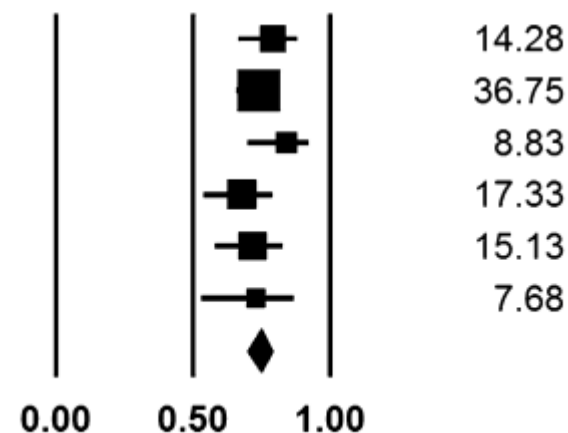
(C)

Curative resection

Author

Event rate and 95% CI

Author	Event rate	Lower limit	Upper limit	Total
Hirasawa <i>et al.</i> [12]	0.793	0.670	0.879	46 / 58
Hoteya <i>et al.</i> [13]	0.742	0.660	0.811	95 / 128
Omae <i>et al.</i> [14]	0.841	0.702	0.922	37 / 44
Yamada <i>et al.</i> [15]	0.679	0.543	0.790	36 / 53
Imai <i>et al.</i> [16]	0.720	0.581	0.827	36 / 50
Kagemoto <i>et al.</i> [17]	0.731	0.533	0.866	19 / 26
	0.746	0.698	0.789	



(A)

Post-ESD bleeding

Author

Event rate and 95% CI

Event rate	Lower limit	Upper limit	Total	Relative weight
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(B)

Perforation

Author

Event rate and 95% CI

Event rate	Lower limit	Upper limit	Total	Relative weight
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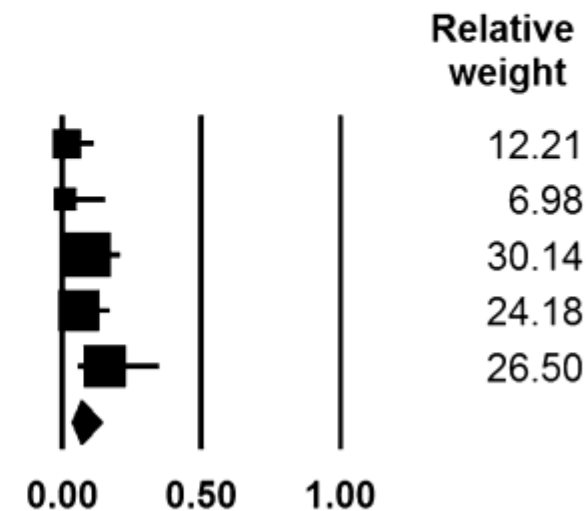
(C)

Stenosis

Author

Event rate and 95% CI

Author	Event rate	Lower limit	Upper limit	Total
Hirasawa <i>et al.</i> [12]	0.017	0.002	0.112	1 / 58
Omae <i>et al.</i> [14]	0.011	0.001	0.154	0 / 44
Yamada <i>et al.</i> [15]	0.094	0.040	0.207	5 / 53
Imai <i>et al.</i> [16]	0.060	0.019	0.170	3 / 50
Kagemoto <i>et al.</i> [17]	0.154	0.059	0.345	4 / 26
	0.069	0.032	0.140	




Long-term clinical outcomes of ESD for EGJ cancer

- Period of follow-up; median 35.8 mo (range, 33.0-73.2 mo)

Curative resection criteria	Curative resection		Non-curative resection		Cause-specific mortality
	Local recur	Distant mets	Local recur	Distant mets	
Gastric cancer (GC)	0/46	0/46	0/12	0/12	0/58
GC	0/95	0/95	0/33	1/33	1/128
GC	0/37	0/37	0/7	0/7	0/44
GC	0/36	0/36	3/17	0/17	2/53
GC	0/36	0/36	0/14	1/14	0/50
Esophageal cancer	0/19	0/19	0/7	0/7	0/26
Total	0/269	0/269	3/90 (3.3%)	2/90 (2.2%)	3/359

Indication for endoscopic resection in patients with gastric cancer metastasis

Jeung Hui Pyo¹ · Hyuk Lee²  · Yanqiang Heejin Yoo⁴ · Soohyun Ahn⁴ · Jae J. Kim³

- Jan. 2002-Mar. 2017

	Total (n = 256)	LNМ (-) (n = 235)	LNМ (+) (n = 21)	P value
Age (years), mean ± SD	60.0 ± 9.6	60.1 ± 9.6	58.6 ± 10.0	0.590
Sex, n (%)				1.000
Male	204 (79.7)	187 (79.6)	17 (81.0)	
Female	52 (20.3)	48 (20.4)	4 (19.0)	
Siewert type, n (%)				0.092
II	168 (65.6)	158 (67.2)	10 (47.6)	
III	88 (34.4)	77 (35.8)	11 (52.4)	
Extent of surgery, n (%)				1.000
Total gastrectomy	239 (93.4)	219 (93.2)	20 (95.2)	
Proximal gastrectomy	17 (6.6)	16 (6.8)	1 (4.8)	
Extent of nodal dissection, n (%)				0.938
D1 +	19 (7.4)	18 (7.7)	1 (4.8)	
D2	127 (49.6)	117 (49.8)	10 (7.9)	
D2 +	110 (43.0)	100 (42.6)	10 (9.1)	
Number of dissected lymph nodes, mean ± SD	41.3 ± 17.9	41.3 ± 18.4	40.9 ± 10.9	0.890
Macroscopic type, n (%)				0.048
Elevated	54 (21.1)	45 (19.1)	9 (42.9)	
Flat	47 (18.4)	45 (19.1)	2 (9.5)	
Depressed	141 (55.1)	133 (56.6)	8 (38.1)	
Mixed	14 (5.5)	12 (5.1)	2 (9.5)	
Tumor size (cm), mean ± SD	3.2 ± 2.0	3.1 ± 1.7	4.8 ± 3.1	0.003
Histology, n (%)				0.649
Differentiated	157 (61.3)	143 (60.9)	14 (66.7)	
Undifferentiated	99 (38.7)	92 (39.1)	7 (33.3)	
Depth of invasion, n (%)				< 0.001
M	94 (36.7)	94 (40.0)	0 (0)	
SM1	46 (18.0)	44 (18.7)	2 (9.5)	
SM2	43 (16.8)	36 (15.3)	7 (33.3)	
SM3	73 (28.5)	61 (26.0)	12 (57.1)	
Lymphovascular invasion, n (%)				< 0.001
Negative	213 (83.2)	204 (86.8)	9 (42.9)	
Positive	43 (16.8)	31 (13.2)	12 (57.1)	

Predictive factors for LN metastasis

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value ^a
Age	0.97 (0.93–1.02)	0.278		
Sex		0.883		
Male	1.00			
Female	1.09 (0.34–3.52)			
Macroscopic type		0.237		
Elevated or flat	1.00			
Depressed	0.57 (0.23–1.44)			
Tumor size	1.43 (1.14–1.78)	0.002	1.42 (1.10–1.82)	0.007
Histology		0.662		
Differentiated	1.00			
Undifferentiated	0.81 (0.31–2.12)			
Depth of invasion		0.056		
SM1	1.00			
SM2/3	4.31 (0.96–19.31)			
Lymphovascular invasion		< 0.001		0.002
Negative	1.00		1.00	
 Positive	5.63 (2.15–14.71)		5.13 (1.88–14.06)	

No LNM in T1a cancers

Incidence of LN metastasis in Siewert II/III cancer

	Mucosal cancer				Submucosal cancer		
	UL (-)		UL (+)		SM1		SM2/3
	≤ 2 cm	> 2 cm	≤ 3 cm	> 3 cm	≤ 3 cm	> 3 cm	Any size
Differentiated (n %, 95% CI)	0/94 (0)				0/19 (0)		1/20 (5.0, 0.0–14.6) 13/70 (18.6, 9.5–27.7)
Undifferentiated (n %, 95% CI)					1/7 (14.3, 0.0–40.2)		6/46 (13.0, 3.3–22.8)

LVI lymphovascular invasion, *UL* ulcer, *SM1* submucosal invasion <500 μm

Conclusions; Tumor size and LVI were associated with LNM in patients with early Siewert type II/III gastric cancer, and the expanded indication for endoscopic resection may be used.

Summary

- **EGJ cancer is difficult** in many ways.
- The treatment outcomes of ESD for early stage EGJ cancer are generally acceptable.
 - > **a practical treatment option**
- Few studies have considered ESD indication for EGJ cancer (including LN metastasis).
 - > Curative resection
 - > **Non-curative resection -> LN metastasis (?)**
 - > **Distant metastasis (2.2%)**
- Further prospective studies with large number of patients are acquired to confirm the reliable ESD indication for EGJ cancer.



THANK YOU FOR YOUR ATTENTION.