Leeds Institute of Molecular Medicine

UNIVERSITY OF LEEDS

Section of Pathology and Tumour Biology

How to report Upper GI EMR/ESD specimens

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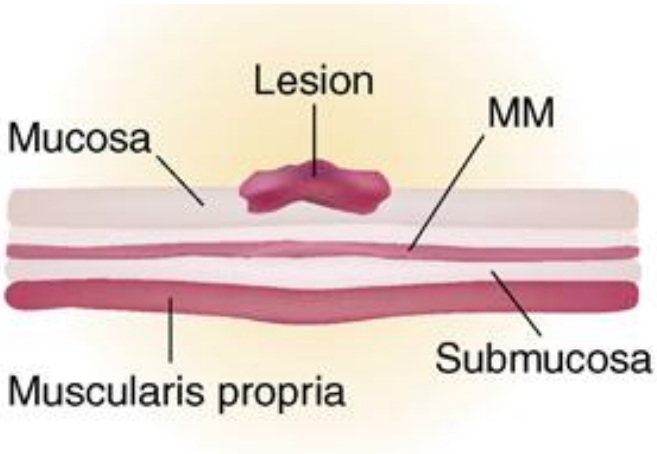
Warning ….

Most of the criteria, methodologies, evidence presented in this talk are based on studies in early gastric cancer in Japan.

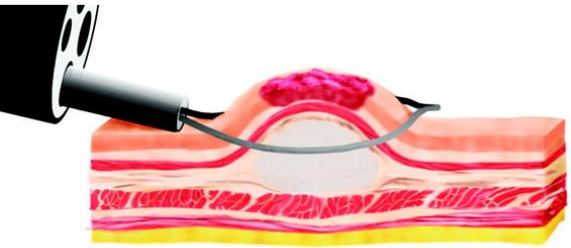
Relative few studies have been published investigating early carcinoma of the oesophagus.

Endoscopic mucosal resection (EMR)



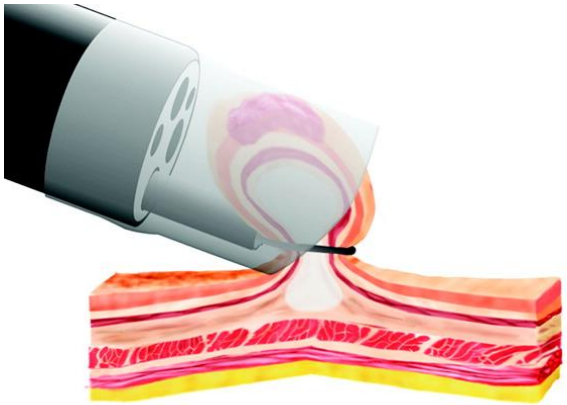
1. Lift the mucosa by injecting saline

JCO 2005;23:4490-4498, Mod Pathol 2009; 22:489-498



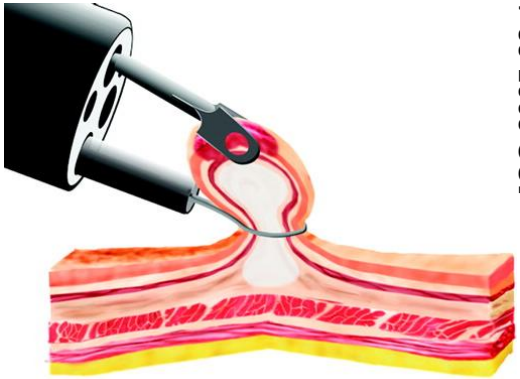
2a. Cut using a snare

or



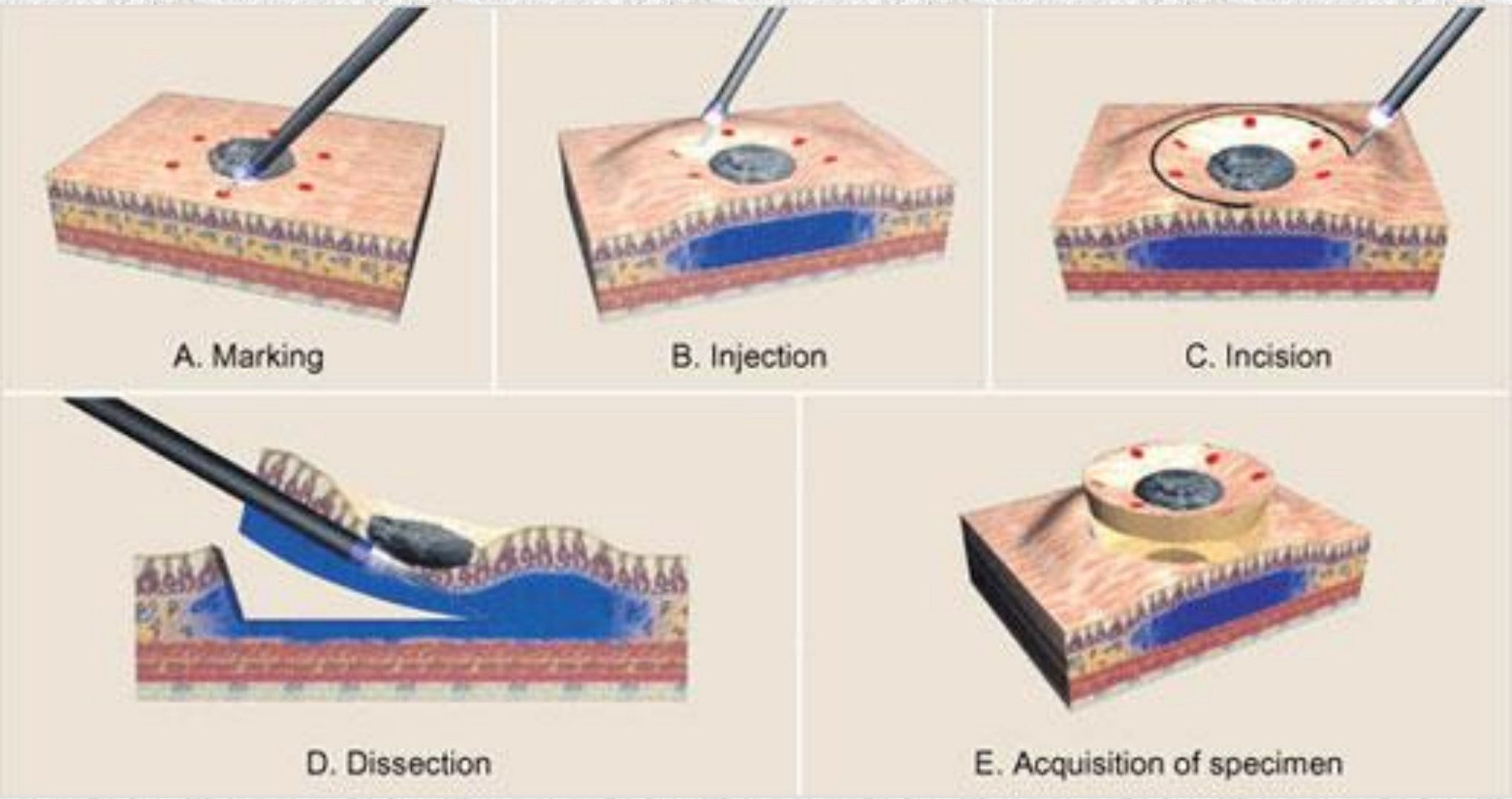
2b. Suck into cap and cut using a snare

or



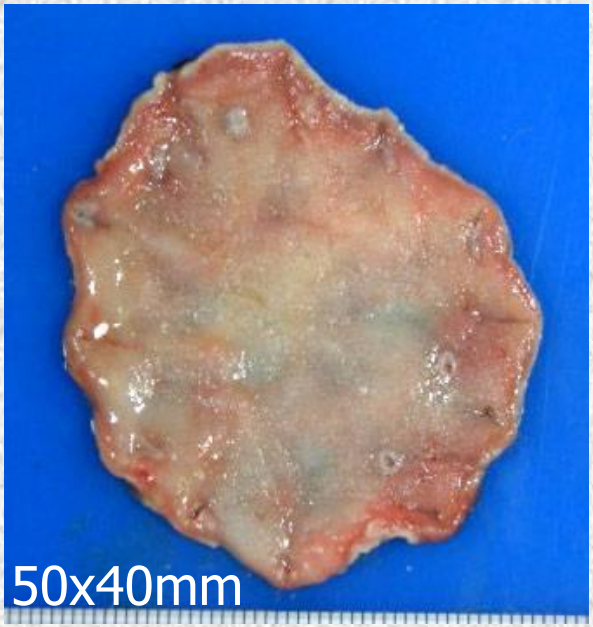
2c. Lift with forceps and cut using a snare

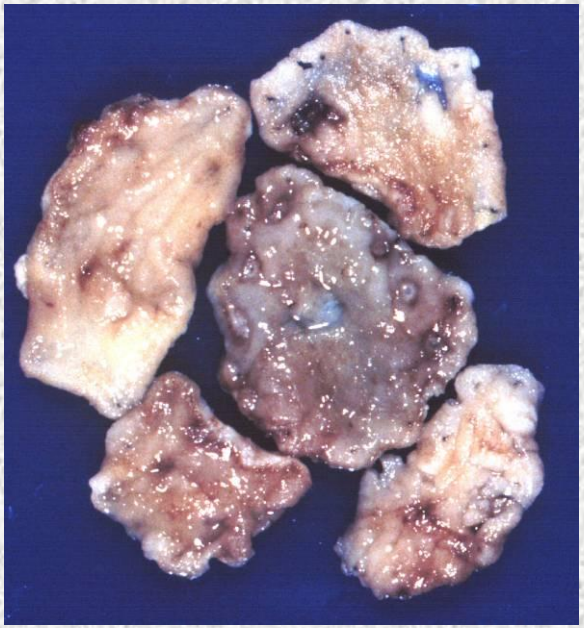
Endoscopic submucosal dissection (ESD)



www.tradekorea.com

Comparing ESD and EMR





Pictures from T Sano, Tokyo

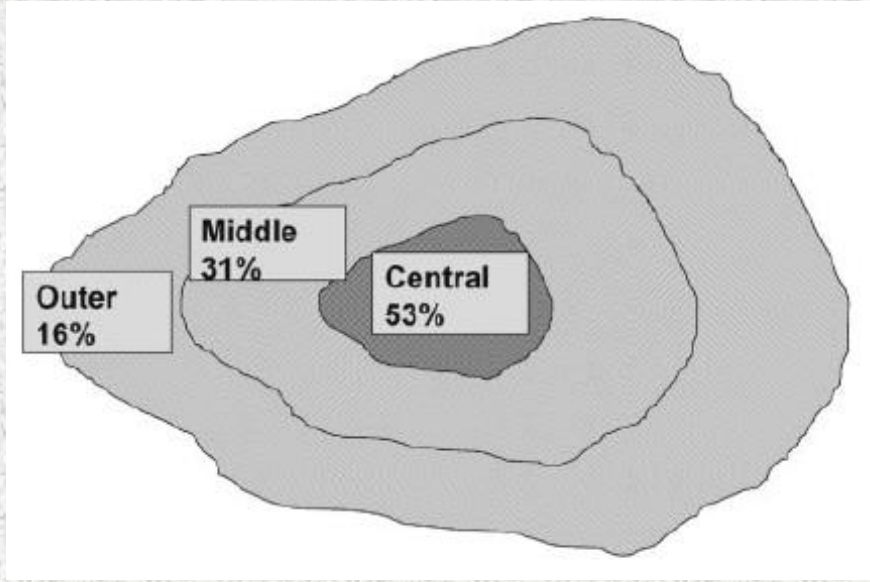
92% En bloc
82% R0
<1% recurrence
4% perforation

48% Piecemeal
42% R0
6% recurrence
<1% perforation

Meta-analysis by Lian J et al Gastrointestinal Endoscopy 76: 763-770, 2012

Pathological factors and distribution of the deepest point of submucosal invasion in EGC

Characteristics	Number	Central	Middle	Outer	*P**
Macro type					
Raised	66	35	23	8	0.967
Depressed	129	68	37	24	
Tumor size (mm)					
≤20	93	47	25	21	0.542
>20	102	56	35	11	
Ulcer finding					
No	122	65	35	22	0.868
Yes	73	38	25	10	
Location					
U	37	22	13	2	0.105
M	99	57	23	19	
L	59	24	24	11	
ly–v					
No	162	86	46	30	0.869
Yes	33	17	14	2	
Histological type					
Well	162	84	47	31	0.156
Mod	30	18	11	1	
Pap	3	1	2	0	
Total	195	103	60	32	

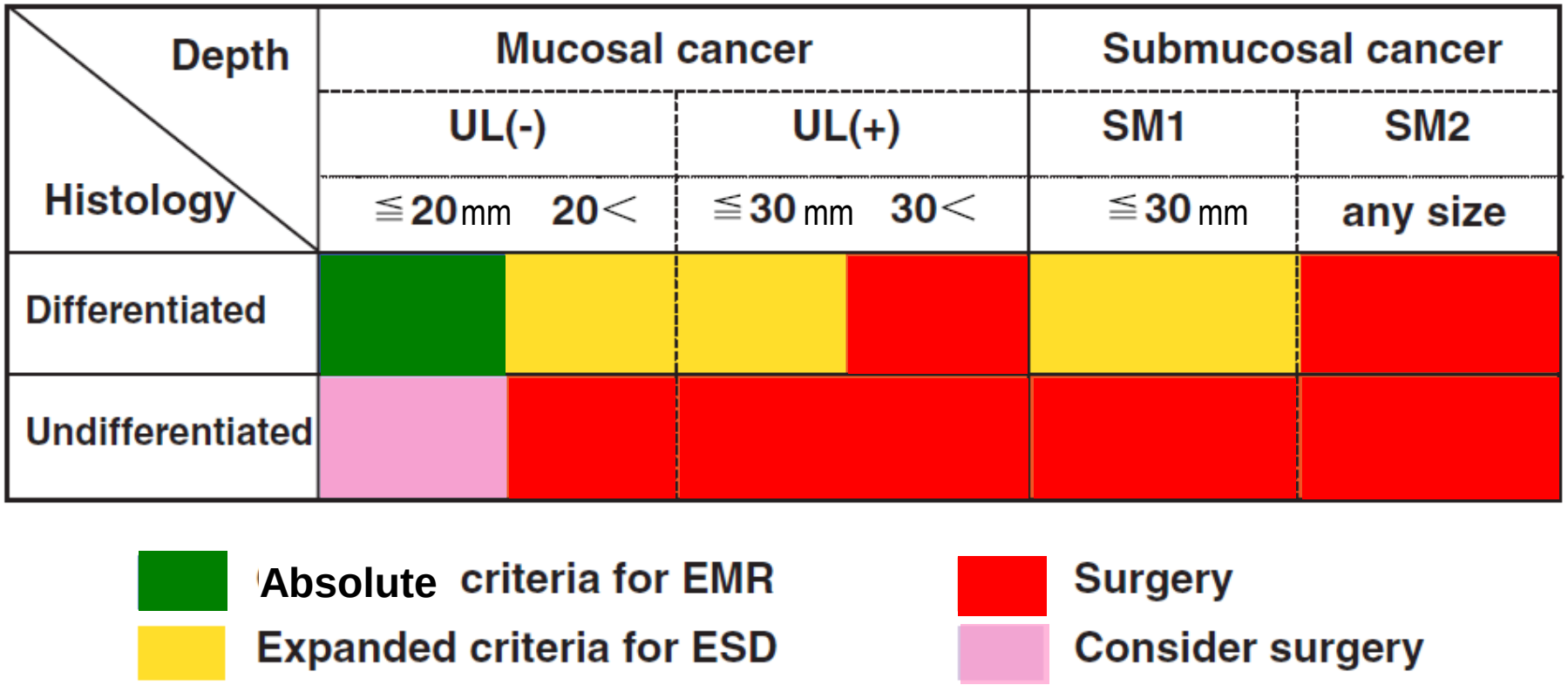


Deepest infiltration not always central and cannot be predicted based on pathology.

The only way to assess true tumour depth is to resect the entire lesion in one piece and avoid burn effects inside the lesion.

Jpn J Clin Oncol 2005;35(10)587–590

Absolute and expanded indication for EMR/ESD

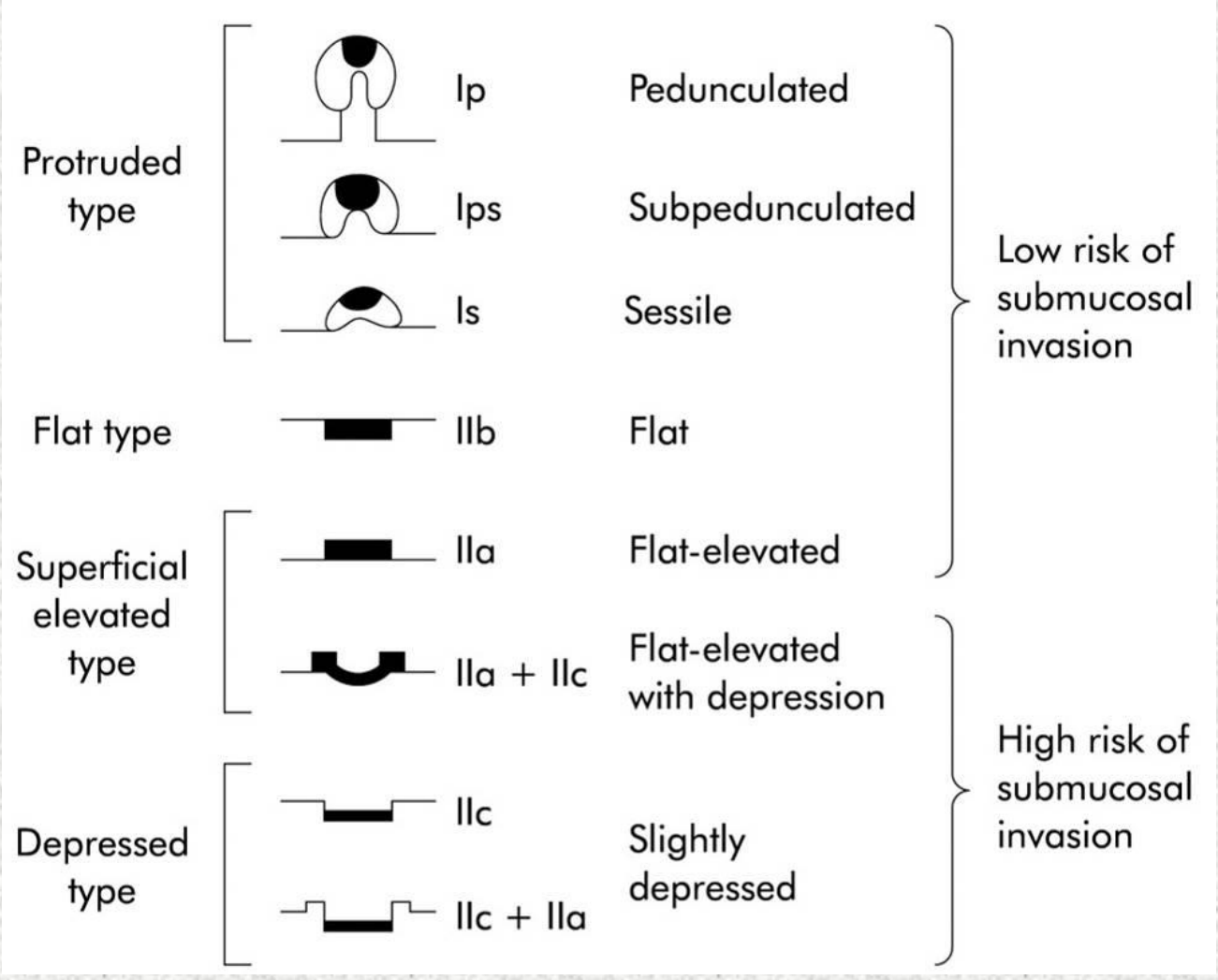


Notes:
Depth of invasion is diagnosed based on macroscopic type.
Expanded indication is considered 'investigational treatment'.

Soetikno R et al. JCO 2005;23:4490-4498

Macroscopic type and risk of submucosal invasion

Updated Paris classification of superficial neoplastic lesions

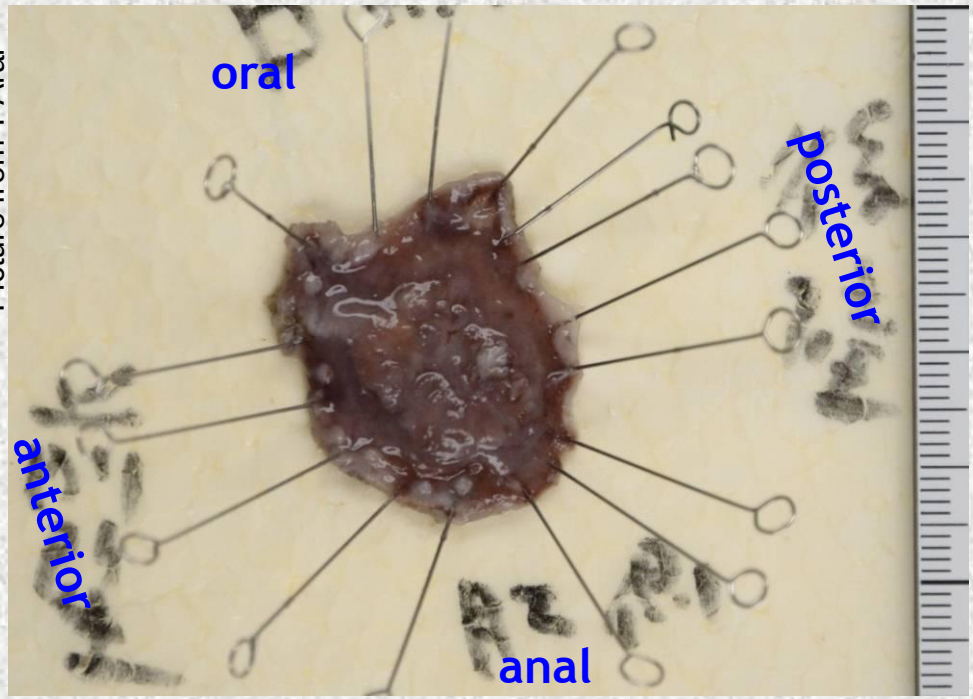


Gut 2004;**53**:1222-1224

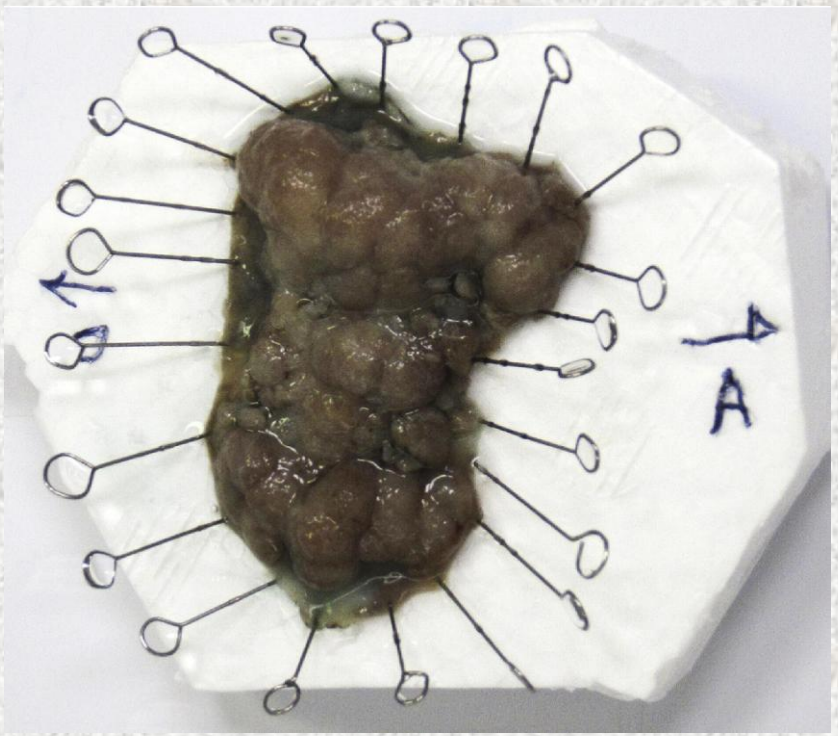
How to prevent curling up of small specimens

Place specimen between histology sponges in regular size cassette or megablock cassette.

Specimen ideally pinned out by endoscopist



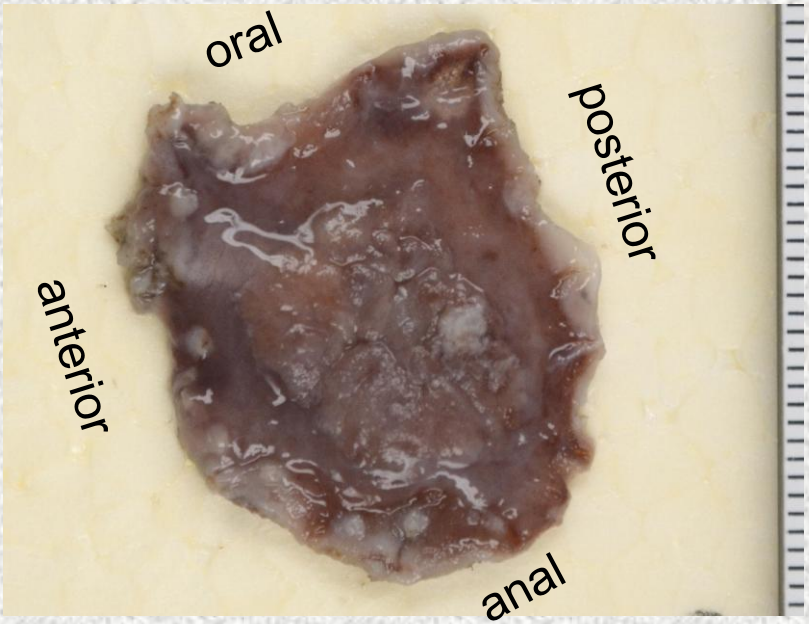
Picture from T Arai



Techniques in Gastrointestinal Endoscopy (2011) 13, 95-99

The larger the specimen the more important it becomes that the specimen arrives in the lab pinned out ‘orientated’ to facilitate repeat EMR/ESD for positive lateral margins.

Macroscopic description

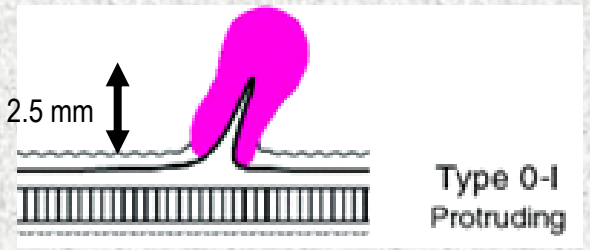


Photograph (optional)

Measurements:
- Specimen in 3 dimensions
- Lesion incl. distance to margin

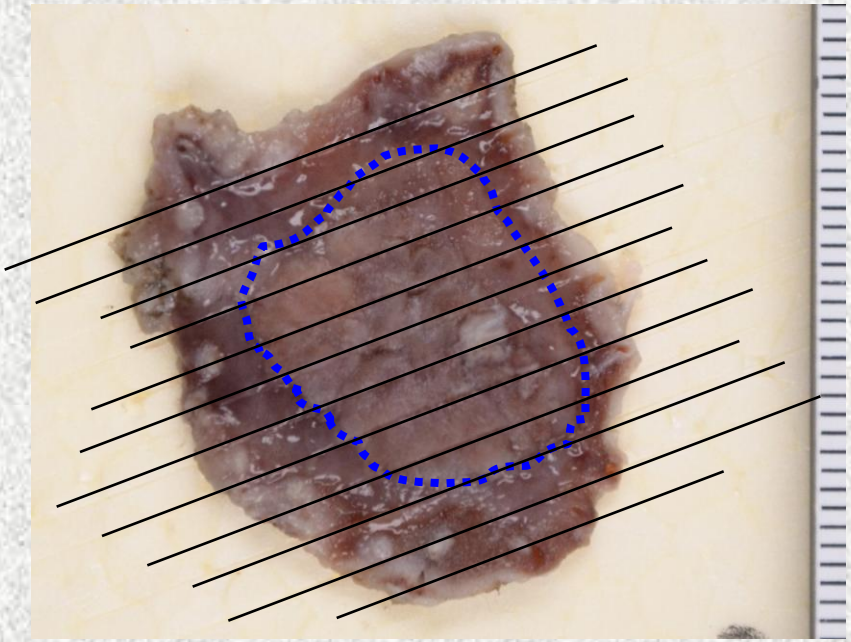
Determine macroscopic type
if not provided by endoscopist
(Paris classification)

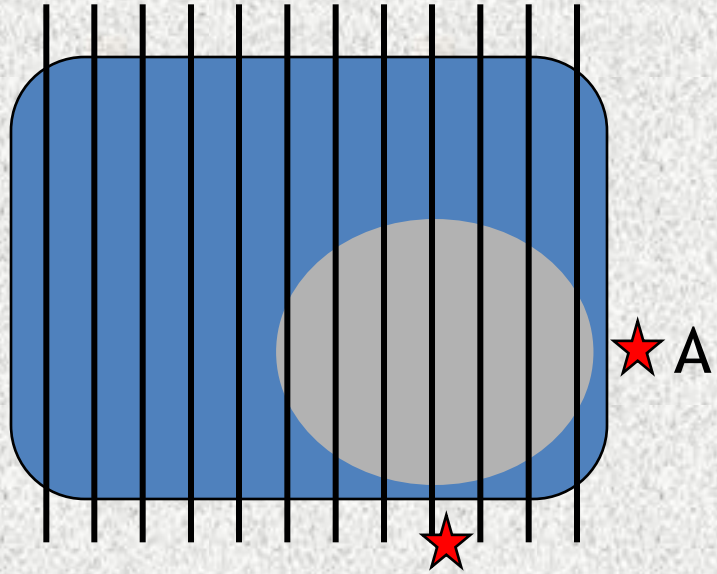
Ink deep margin (optional)



(Gastric Cancer 2011; 14: 101-112)

Cutting up the specimen





2 to 3mm wide sectioning

Direction optimised to demonstrate distance to lateral margin.

If lesion in the centre, then cut perpendicular to longest axis.

Block sections systematically and ask to be cut ‘on edge’.

If lesion close to two lateral margins, then position section (A) ‘flat’ to cut from the margin towards the lesion.

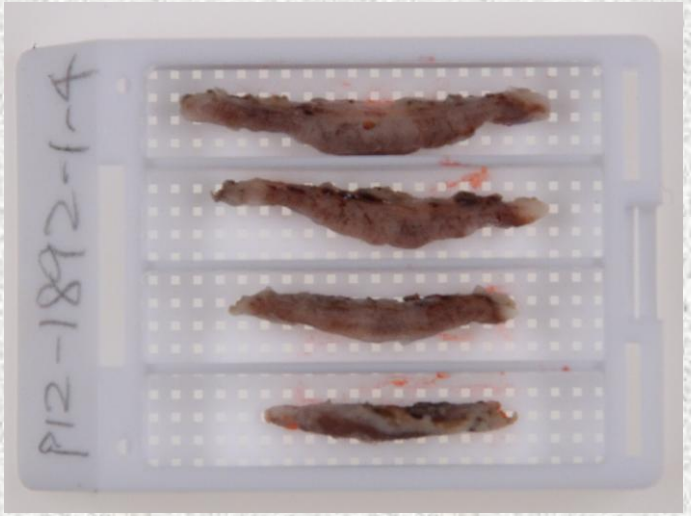
Processing the specimen

Mojtahed A et al

3 sections in a 40x12.5mm 'megablock'
> ideal for large ESDs

(Note: this type of cassette is currently not available in the EU)

Another option by M Vieth from Bayreuth



Regular size cassette with dividers
> my preferred option!

Histological evaluation – Resection margin

1. **Deep (vertical) margin**
   VM0 – not involved (measure distance to margin)
   VM1 – involved VMx – cannot be assessed

2. **Lateral (horizontal) margin**
   HM0 – not involved (measure distance to margin)
   = No cancer in first and last section. No cancer at both sides of all other sections. Measure distance cancer to margin.

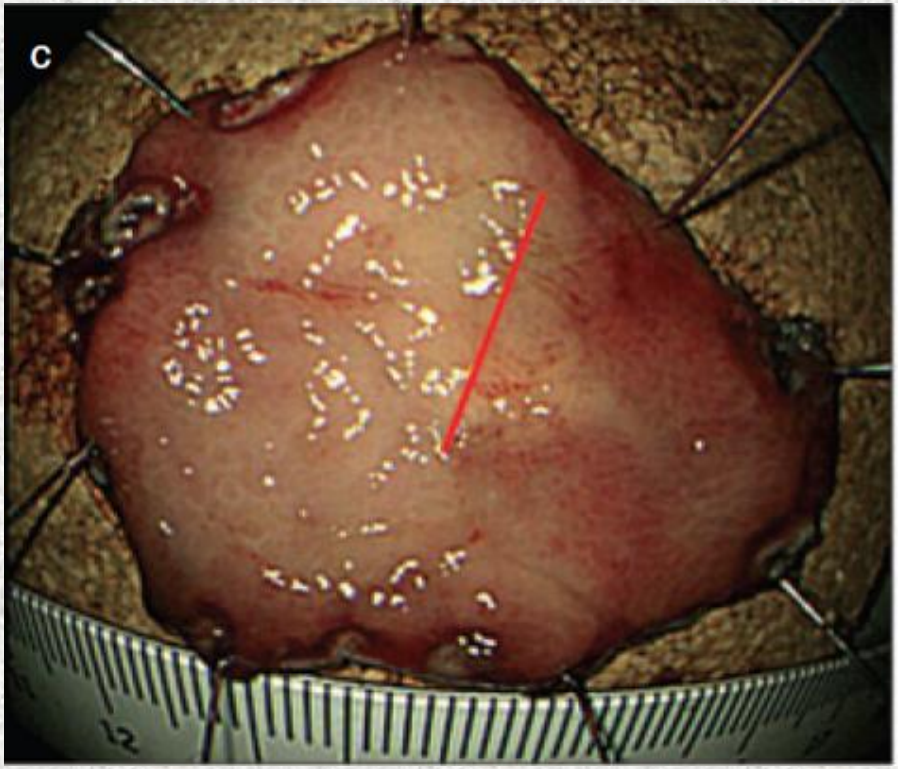
   HM1 – involved.
   The number of sections with HM1 should be recorded.
   If one section HM1 > no further treatment,
   if more than 1 section positive > immediate repeat EMR/ESD

   HMx – cannot be assessed

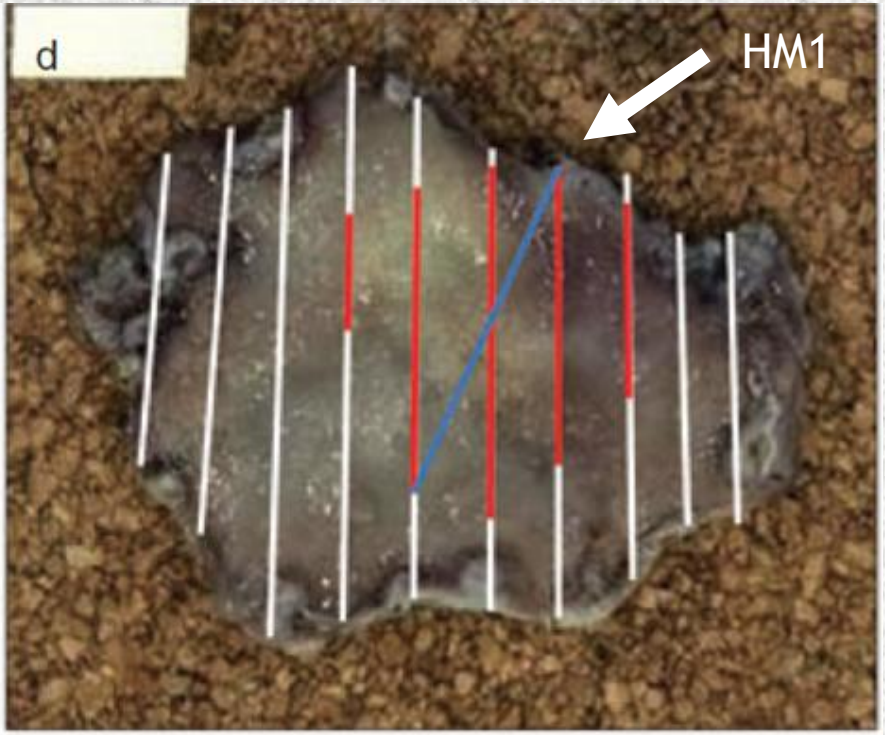
Note: Definition of 'positive' EMR/ESD resection margin: no evidence!
Japanese pathologists: cancer within 2mm; Japanese endoscopists: cancer 'at' the margin
UK: ?? 1mm

Histological evaluation – Size of tumour

Size of the tumour needs to be confirmed on histology as size may be underestimated on macroscopy



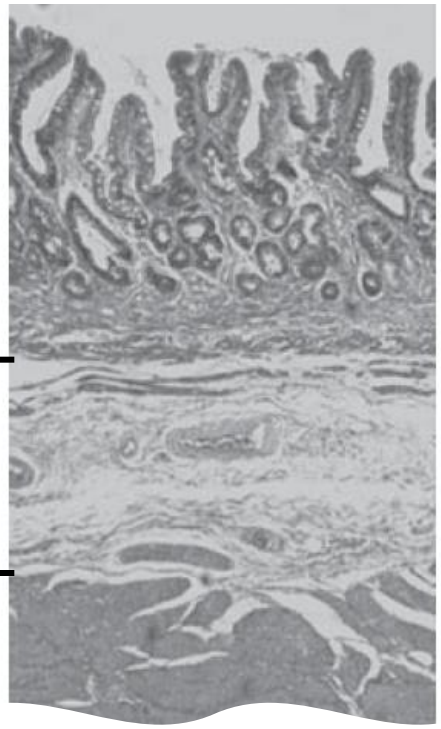
Max tumour diameter (macro): 15mm (red line)



Max tumour diameter (micro): 23mm (blue line), also R1 (HM)

Digestive Endoscopy (2010) **22**, 112–118

Histological evaluation – Depth of invasion ‘extended’ TNM classification



pT1a

pT1b

pT2

M — m1 (in situ/HGD)

M — m2 (lamina propria)

MM — m3

SM — sm1 (≤ 500 µm; SCC: ≤ 200 µm)

SM — sm2 (> 500 µm; SCC: > 200 µm)

Alternatively proposed:
sm1: (1/3), sm2: (2/3), sm3: (3/3)

Notes:
Depth of invasion is only assessed if the deep margin is negative.
SM classification ambiguous, provide absolute measurement from MM instead!

Histological evaluation – Depth of invasion
Duplicated muscularis mucosae: which system to use?

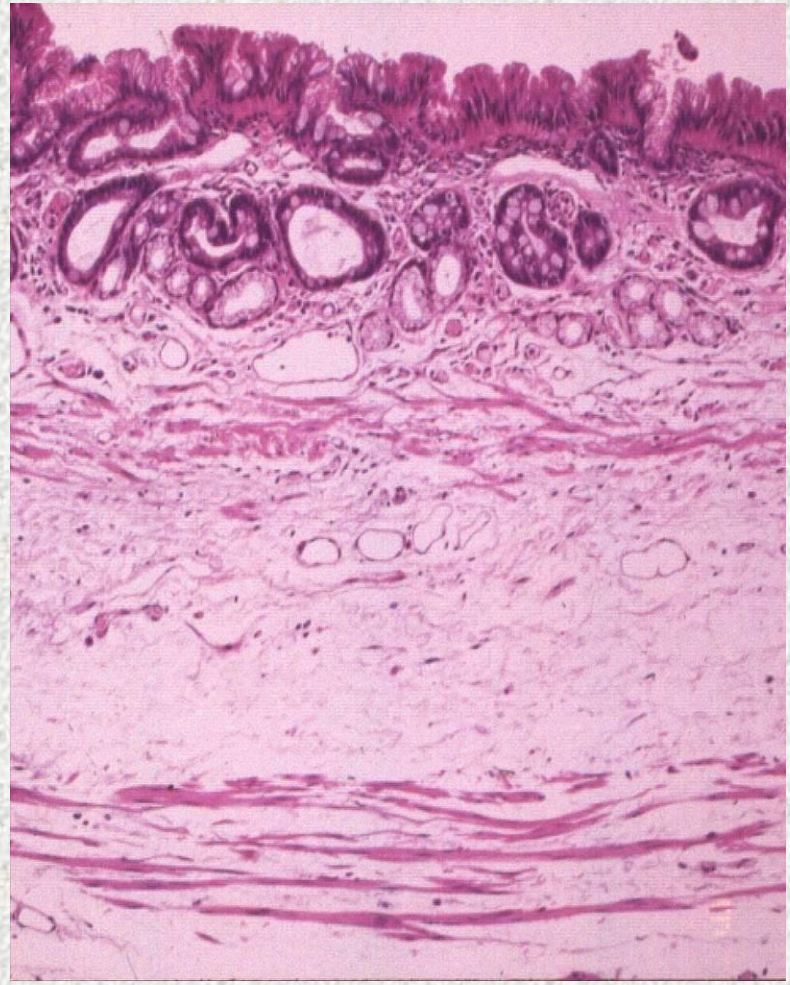
Westerterp et al.
Virchows Arch 2005

m1 (in situ/HGD)

m2 (lamina propria)

m3
(both layers of musc. mucosae + space in between)

sm1



Vieth M, Stolte M . Best Pract Res Clin Gastroenterol 2005

m1 (lamina propria)

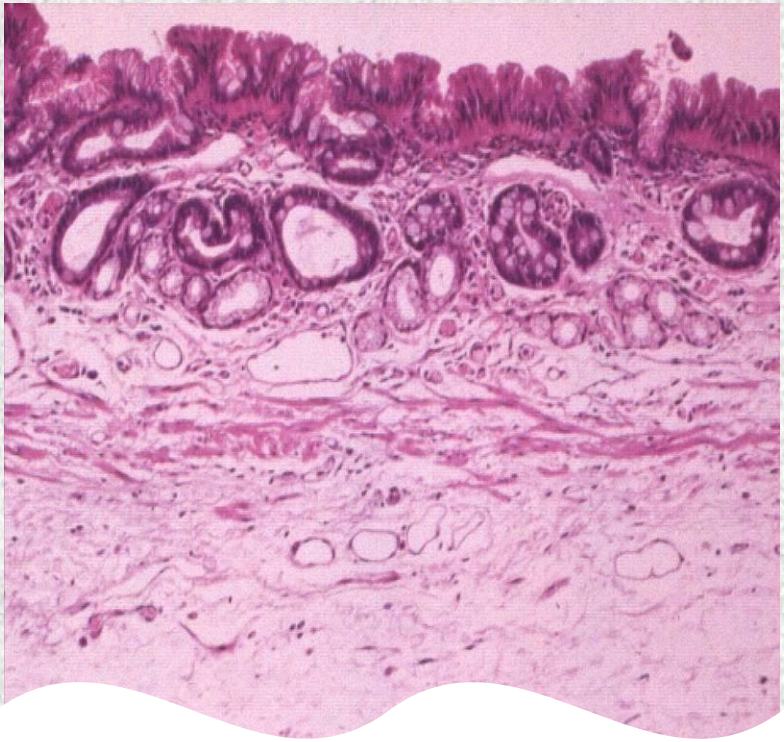
m2 (superficial layer musc. mucosae)

m3 (between the 2 layers)

m4 (deep layer musc. mucosae)

sm1

Histological evaluation – Depth of invasion
How to report Barrett's specimens?

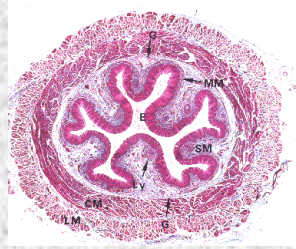


If cancer in mucosa or infiltrating into directly adjacent smooth muscle
> intramucosal cancer

If cancer infiltrates beyond the directly adjacent smooth muscle, depth of invasion is uncertain:
intramucosal if double MM
OR
submucosal if single MM

Frequency of lymph node metastases

Mucosal oesophageal cancer

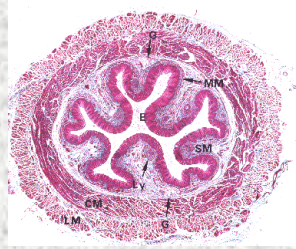


Author	Year	Patients (n)	LNM (%)
Squamous cell carcinoma			
Endo[23]	2000	112	2.7
Chibana[24]	2005	5	0
Bollschweiler[8]	2006	7	0
Shimada[25]	2006	40	5.0
Higuchi[26]	2007	8	12.5
Tachibana[27]	2007	51	2.0
Ancona[6]	2008	12	0
Total		235	3.0%
Adenocarcinoma			
Hagen[28]	2001	16	0
Rice[29]	2001	53	3.8
Stein[30]	2003	27	0
Liu[10]	2005	53	3.8
Westerterp[9]	2005	54	1.9
Bollschweiler[8]	2006	26	0
Oh[31]	2006	23	4.4
Ancona[6]	2008	15	6.7
Cen[32]	2008	48	4.2
Sepesi[11]	2010	25	0
Leers[12]	2011	75	1.3
Total		415	2.4%

(*Ann Surg* 2011;254:802–808)

Frequency of lymph node metastases

Submucosal oesophageal cancer

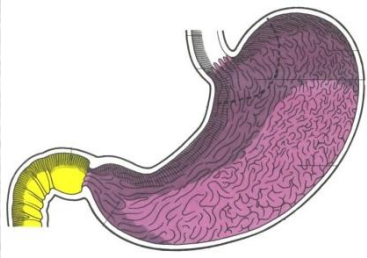


Author/Year	Histology	Patients With Submucosal (pT1b) Carcinoma	sm1		sm2		sm3	
			Patients	% LNM	Patients	% LNM	Patients	% LNM
Liu et al. 2005[10]	AC	37	12	8.3	—	—	25	36.0
Westerterp et al 2005[9]	AC	66	25	0	23	26.1	18	66.7
Ancona et al. 2008[6]	AC/SCC	71	36	8.3	7	28.6	28	53.6
Badreddine et al. 2010[7]	AC	80	31	12.9	23	21.7	26	19.2
Sepesi et al. 2010[11]	AC	29	14	21.4	11	36.4	4	50.0
Leers et al. 2011 [12]	AC	51	19	21.1	9	11.1	23	26.1
Present study	AC/SCC	101	30	13.3	26	19.2	45	55.6
Total	AC/SCC	435	167	11.4	99	23.2	169	43.8

(*Ann Surg* 2011;254:802–808)

Frequency of lymph node metastases

Mucosal and submucosal gastric cancer

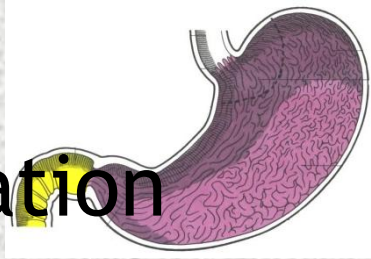


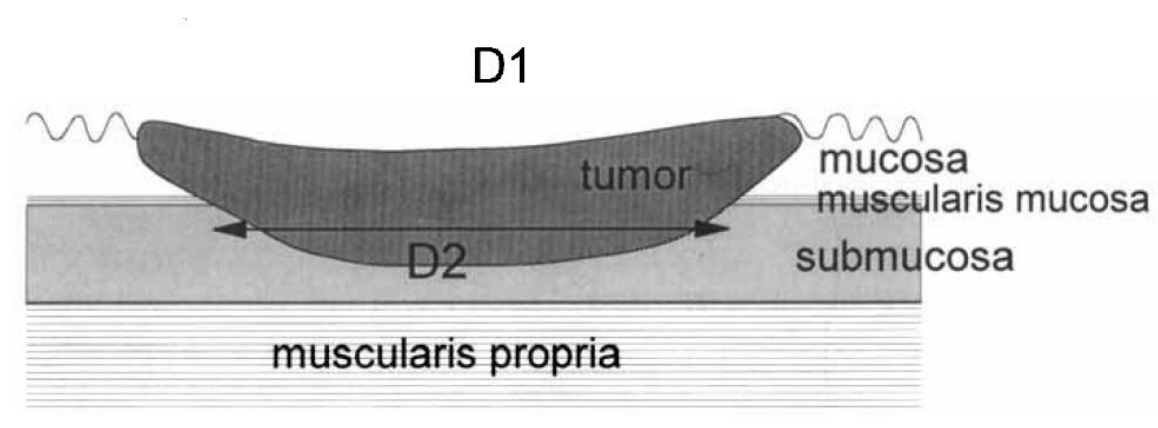
			pT1a		pT1b	
Author	**Year**	**Origin**	**n**	**% LNM**	**n**	**% LNM**
Folli et al[32]	1995	Italy	117	4	106	23
Hayes et al[33]	1996	Germany	14	21	14	64
Bösing et al[19]	1998	Germany	33	9	24	17
Popiela et al[22]	2002	Poland	113	6	125	21
Roviello et al[28]	2006	Italy	330	5	322	24
Hölscher et al	2009	Germany	47	11	79	25
		Europe	654	6.5	670	23.9
Kitamura et al[34]	1997	Japan	326	1	308	16
Tachibana et al[20]	1999	Japan	59	2	41	32
Skoropad et al[35]	2005	Russia	60	0	89	20
Nasu et al[36]	2006	Japan	169	5	118	24
Ishikawa et al[37]	2007	Japan	156	4	122	23
Xu et al[38]	2007	China	152	6	170	22
Ha et al[39]	2008	Korea	847	2	673	23
Park et al[4]	2008	Korea	118	3	116	22
Ye et al[5]	2008	Korea	339	3	252	27
		Asia	2226	2.7	1889	22.1
Total		All	2880	3.2	2559	22.5

(*Ann Surg* 2009;250: 791–797)

Frequency of lymph node metastases

Depth and width of submucosal infiltration



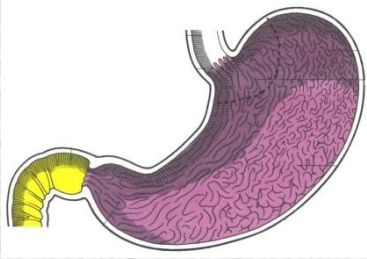


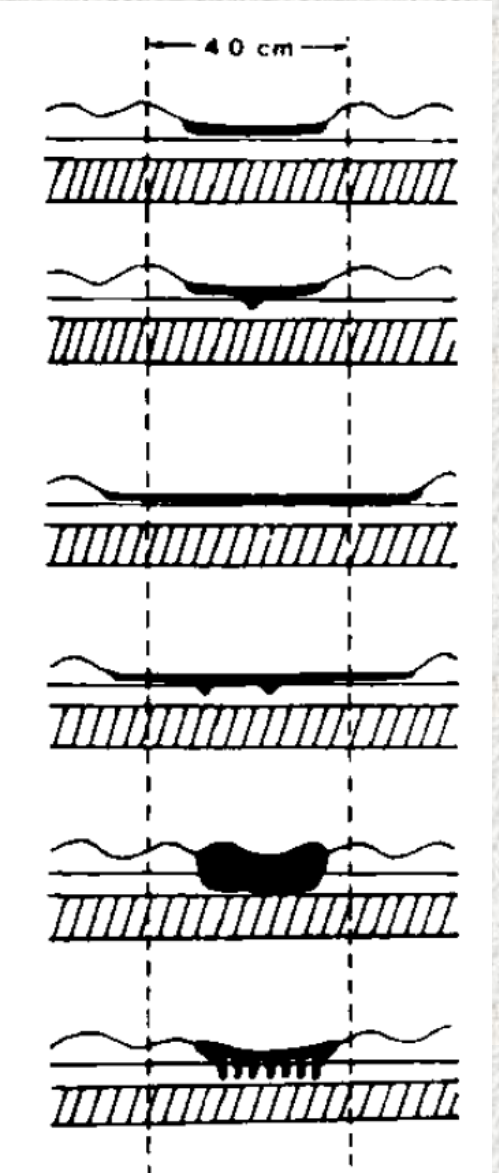
Variable	Odds ratio (95% CI)	*p*-Value
Width of SM invasion >6000 μm	8.54 (2.24–41.2)	0.0034
Lymphatic involvement	4.39 (1.55–14.1)	0.0077
Undifferentiated histologic type at the deepest invasive portion	4.30 (1.44–15.3)	0.014
Depth of SM invasion >1000 μm	3.92 (1.07–15.5)	0.042
Tumor diameter >30 mm	3.42 (1.40–8.71)	0.0078
Venous involvement	–	NS

Scand J Gastroenterol 2010; 45: 1480-1487

Frequency of lymph node metastases

Pattern of submucosal infiltration





Small mucosal M

Small mucosal SM

Super M

Super SM

Pen A

Pen B

Super: superficially spreading
Lymph node met: 11%
Bvi: 0%

Pen A: expansive growth with complete destruction of MM
Lymph node met: 25%
Bvi: 25%

Pen B: infiltrative growth with ‘fenestration’ of MM
Lymph node met: 8%
Bvi: 0%

Kodama Y et al. Cancer 1983; 51:320-326

Histological evaluation – Tumour type

Differentiated type

- papillary adenocarcinoma
- well and moderately diff. tubular adenocarcinoma

Undifferentiated type

- poorly differentiated adenocarcinoma
- signet-ring carcinoma
- mucinous adenocarcinoma

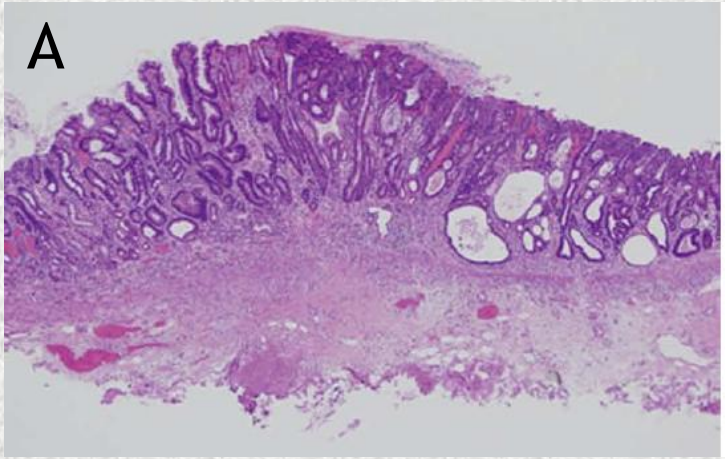
If both types: report predominant type

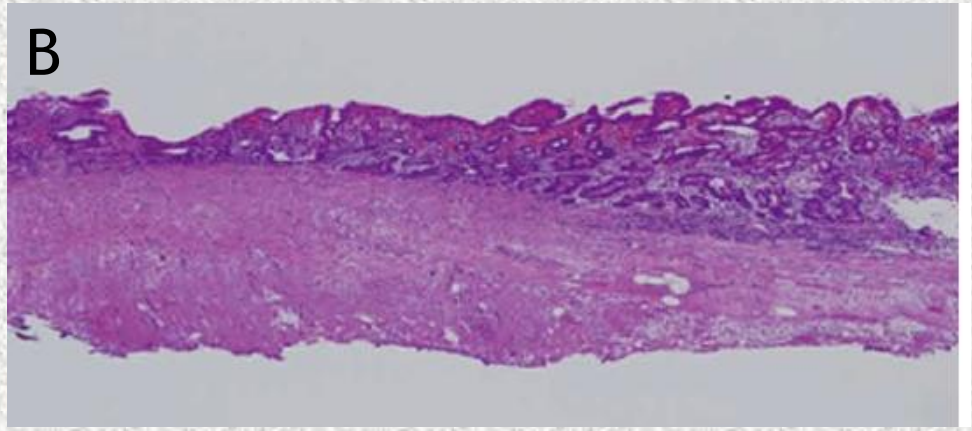
If SM1: also report the type of the invasive portion

Histological evaluation – Ulceration/scar

UL(-): intratumoral ulcer or ulcer scar is absent

UL(+): intratumoral ulcer or ulcer scar is present

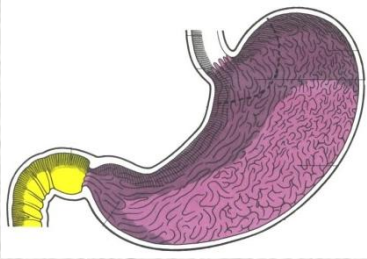




Challenge:
Scarring due to biopsy (A: usually small and circumscribed) vs. scarring after ulceration (B: usually expansive lesion).
Only scar due to tumour ulceration counts!

Complete resection rate

Presence of ulceration



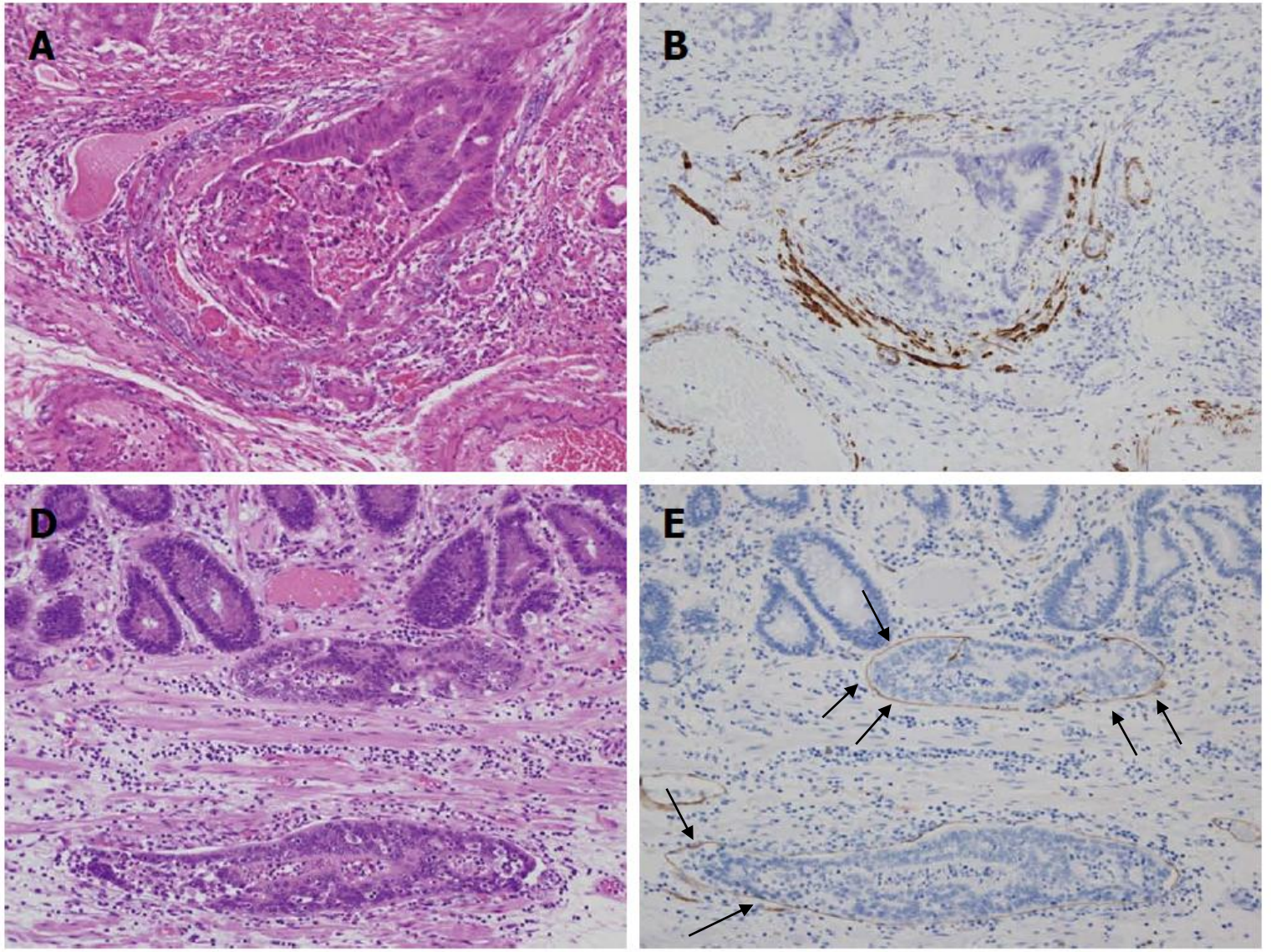
	Size, mm	EMR, % (n)	ESD, % (n)	*P* value
Ulceration (−)				
	≤10	34.6 (142/410)	95.1 (39/41)	<.01
	11-20	15.5 (43/278)	94.4 (85/90)	<.01
	≥21	8.8 (9/102)	86.8 (33/38)	<.01
	Total	24.6 (194/790)	92.8 (157/169)	<.01
Ulceration (+)				
	≤10	14.2 (1/14)	40.0 (2/5)	NS
	11-20	0 (0/16)	20.0 (2/10)	NS
	≥21	0 (0/5)	9.1 (1/11)	NS
	Total	2.9 (1/35)	19.2 (5/26)	<.05

NS, Not significant.

(Gastrointest Endosc 2006;64:877-83.)

Note: Massive drop in complete resection rate in the presence of ulceration

Histological evaluation – Lymphovascular invasion

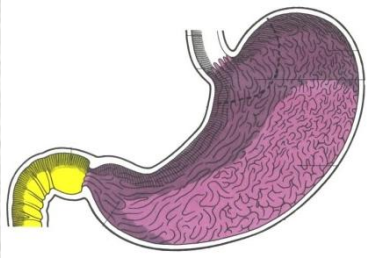


Desmin for smooth muscle in the vessel wall

CD31/34 for endothelial cells

D2-40 for lymphatic endothelial cells.

Pathological features associated with venous and lymphatic involvement



Venous involvement

Clinicopathological feature	OR (95 % CI)	*P* value
Macroscopic type (elevated)	2.6 (1.1–6.3)	0.032
Depth ≥SM2 (≥ 500 μm)	96.5 (30.7–302.6)	<0.0001
Undifferentiated-type adenocarcinoma component, present	2.7 (1.1–6.8)	0.032

Lymphatic involvement

Clinicopathological feature	OR (95 % CI)	*P* value
Size >20 mm	2.5 (1.2–5.2)	0.011
Depth ≥SM1	58.7 (22.2–155.7)	<0.0001
Papillary adenocarcinoma component, present	8.1 (3.2–20.6)	<0.0001
Undifferentiated-type adenocarcinoma component, present	4.8 (2.2–10.2)	<0.0001

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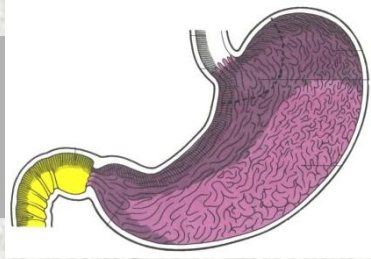
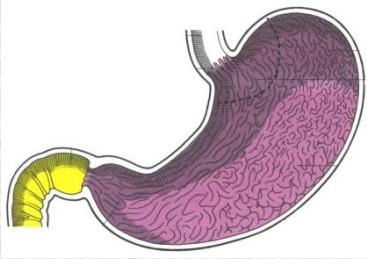
Curative resection (standard criteria)



- en-bloc resection of lesion
- tumour size ≤ 2cm (Paris type 0-IIa)
- tumour size < 1cm (Paris type 0-IIb/IIc)
- differentiated type
- intramucosal (m1 – m3)
- negative resection margins
- no lymphovascular invasion
- no ulcer or ulcer scar

Curative resection (expanded criteria)



En-bloc resection, R0, no lymphovascular invasion

and

(a) tumour ≤ 2cm, undifferentiated, pT1a, UL(-)

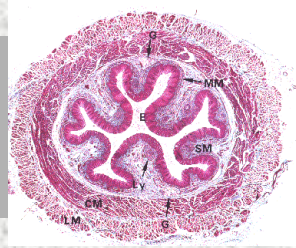
(b) tumour > 2cm, differentiated, pT1a, UL(-)

(c) tumour ≤ 3cm, differentiated, pT1a, UL(+)

(d) tumour ≤ 3cm, differentiated, pT1b (SM1, < 500μ)

Any undifferentiated component in (b) to (d) requires surgical resection.

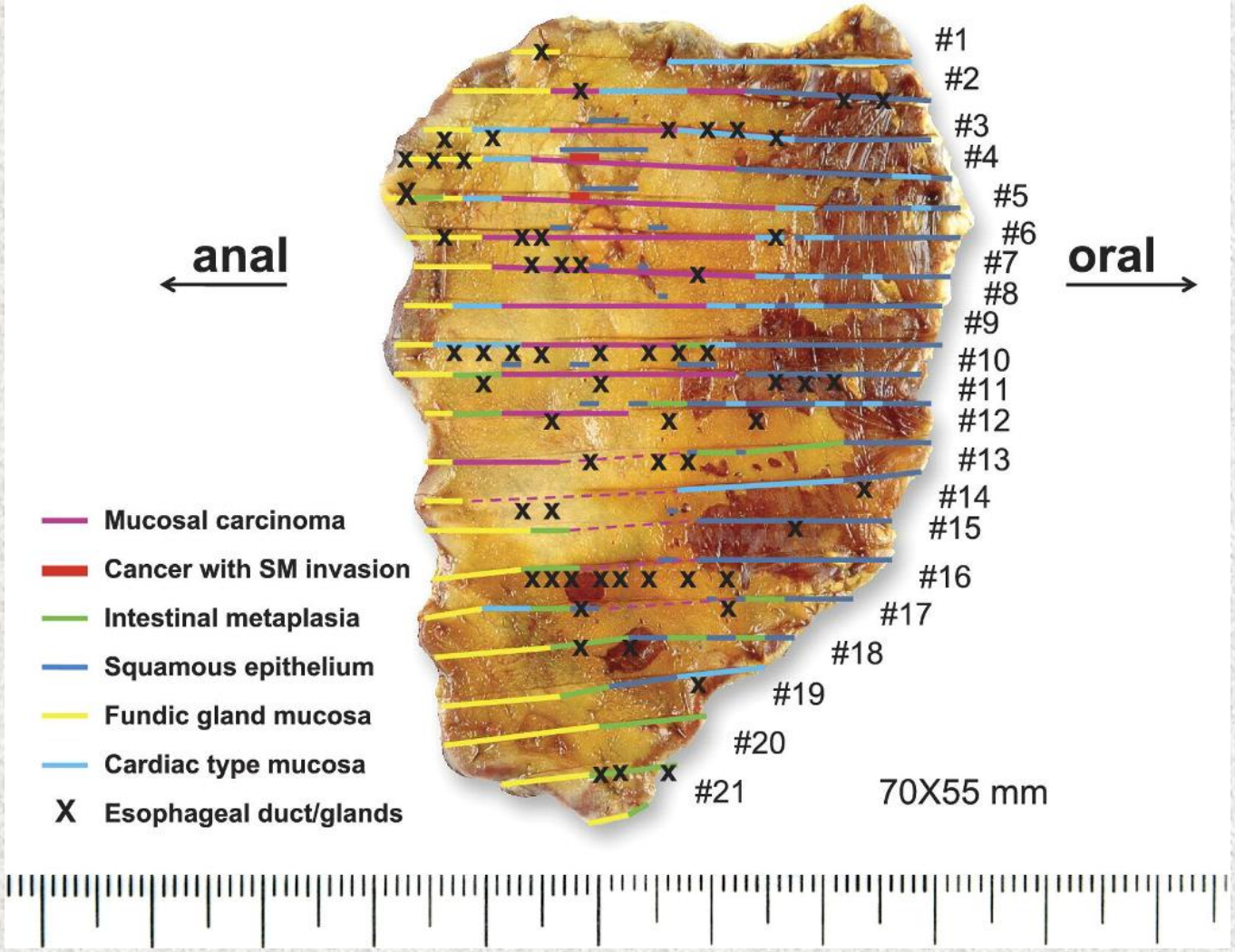
Curative resection (oesophageal cancer)



- en-bloc resection of lesion
- max tumour size not established, should be less than 1/3 of circumference
- Paris type 0-IIa and 0-IIb lesions
- well and moderately differentiated
- m1-m3 (adenoca), m1-m2 (SCC), HGD
- negative resection margins
- no lymphovascular invasion

Mapping back histology onto macro image

Standard in Asia – 'Bonus' feature in the UK?



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Items for the EMR/ESD pathology report Summary

- Number of specimens (en bloc vs. piecemeal resection)
- Size of the specimen, size of the lesion (macro/micro)
- Macroscopic tumour type (Paris classification)
- Histological tumour type (different. vs. undifferent.)
- Depth of invasion (extended TNM)
- Presence of intratumoral ulcer
- Presence of lymphovascular invasion
- Resection margin status (deep and lateral)
- Curative resection (yes/no)

Conclusions

- EMR/ESDs can be very challenging and time consuming (levels, special stains, 2nd opinion)
- Adjust minimum data set according to local endoscopy practice
- High quality pathology reporting of EMR/ESD specimen - the key to determine risk of lymph node metastases, local recurrence and hence patient management!