

## S1

### *Center and period bias assessment*

The endoscopic centers were divided into three groups (only EMR, only ESD, or EMR and ESD). The grouping was not an independent predictor of recurrence-free survival ( $P = 0.316$ ). The recurrence-free survival rate within the third tertile of the inclusion period was similar in each tertile period ( $P = 0.284$ ) (**Supplementary figure 1**).

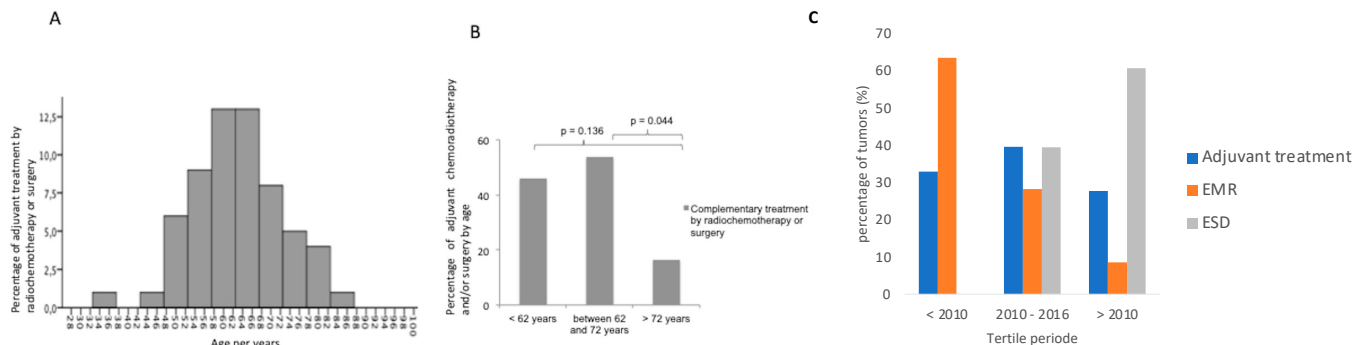
### *Complications after endoscopic resection*

The overall complication rate was 8% and was similar in the ESD (12.1%) and EMR (4.2%) groups ( $P = 0.089$ ). Intraoperative perforations occurred in six procedures (one EMR, five ESD). In all cases the treatment was conservative, using a self-expandable metallic stent and antibiotics. Delayed bleeding occurred in 1.5% of procedures (2/137). During follow-up, the rate of postoperative strictures was 17.5% (24/137). Patients with strictures were successfully treated by endoscopy, and any patient with a refractory stricture required secondary surgery.

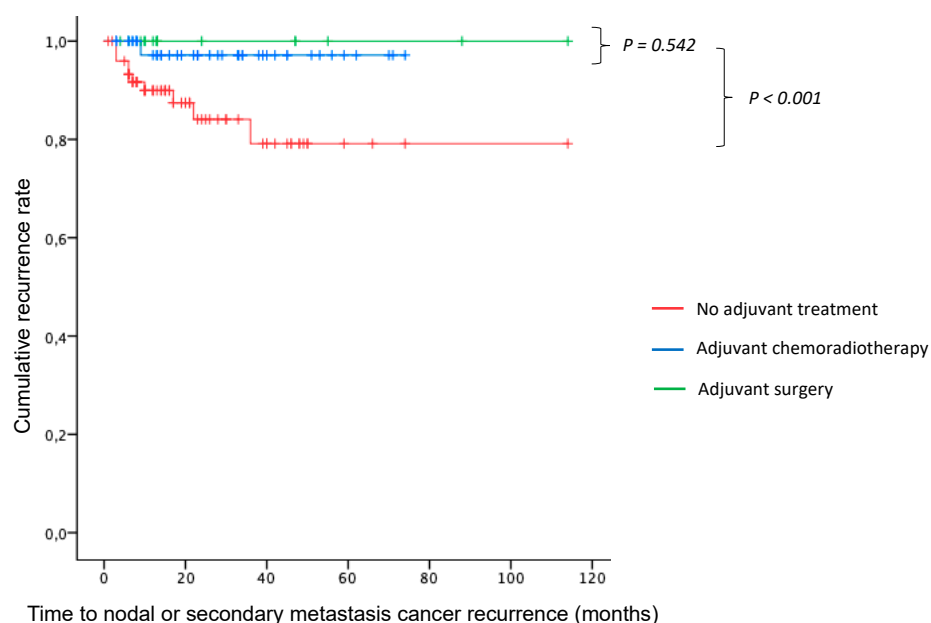
### *Local recurrence*

The rate of local recurrence was 21.1% in the EMR group and 3% in the ESD group and this difference was statistically significant ( $P = 0.016$ ) (Supplementary Table 2 and 3). In univariable analyses resection by EMR ( $P = 0.016$ ), piecemeal resection ( $P = 0.012$ ), and non-tumor-free lateral margin ( $P < 0.001$ ) were associated with local recurrence. However, in the multivariable analysis no factor was significantly associated with local recurrence (Supplementary Table 3).

## S2



**Supplementary Figure S1.** Adjuvant chemoradiotherapy and/or surgery by age. Panel A: Percentage of adjuvant chemoradiotherapy and/or surgery by age; Panel B: Comparison of rates of adjuvant chemoradiotherapy and/or surgery by age group (< 62 years; between 62 and 72 years; and > 72 years). Panel C: Comparison of rates of adjuvant chemoradiotherapy, and endoscopic resection by EMR or ESD.



**Supplementary Figure S2.** Nodal or metastatic recurrence-free survival rates in patients with tumors invading the muscularis mucosae (pT1a-m3) or the submucosa (pT1b-Sm) with and without adjuvant chemoradiotherapy and/or surgery.

**Supplementary Table S1.** Number of EMR and ESD procedures performed per center.

Centre, n(%)	ESD group (n=66)	EMR group (n=71)
1	5(7.6)	6(8.5)
2	11(16.7)	0(0.0)
3	0(0.0)	8(11.3)
4	0(0.0)	10(14.1)
5	16(24.2)	1(1.4)
6	9(13.6)	0(0.0)
7	3(4.5)	0(0.0)
8	0(0.0)	11(15.5)
9	3(4.5)	34(47.9)
10	17(25.8)	0(0.0)
11	2(3.0)	1(1.4)

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection.

**Supplementary Table S2.** Comparisons of the EMR and ESD groups were performed in intention-to-treat, choice between EMR or ESD was decided before to start the endoscopic resection.

	EMR group (n = 71)	ESD group (n = 66)	P-value*
Male n (%)	57 (80.3)	46 (69.7)	0.152
Mean age (years, (range))	63.6 (35-87)	64.1 (44-90)	0.189
Median size (mm, (range))	15.0 (3.0-30.0)	35.7 (8.0-90.0)	<0.001
Tumor circumference of the esophageal lumen > 1/3 n (%)	34 (47.9)	50 (75.8)	0.001
Piecemeal resection n (%)	48 (67.6)	2 (3.0)	<0.001
Lateral margin-free cancer (%) (R0; R1; Rx) <sup>a</sup>	(14.1; 18.3; 67.6)	(90.9; 6.1; 3.0)	<0.001
Tumor infiltration depth m3-sm1 n (%)	48 (67.6)	43 (65.2)	0.761

Adjuvant treatment by chemoradiotherapy or/and surgery n (%)	30 (42.3)	31 (47.0)	0.579
Mean follow-up (months, (range))	41.4 (1-135)	17.6 (3-55)	<0.001

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; m3, cancer invading the muscularis mucosae, sm1: cancer invading the submucosa. \*Univariate analyses were carried out by chi-squared test for qualitative variables. For tumor size and age, <sup>a</sup> univariate t-test was used. <sup>a</sup> Lateral margins were considered R0 for tumor-free margins, R1 for non-tumor-free margins and Rx when the pathology was not evaluable, for example due to piecemeal resection.

**Supplementary Table S3.** Results according to local cancer recurrence during the follow-up.

	Local cancer recurrence		Univariate analysis
	Yes (n =17)	No (n =120)	P-value <sup>1</sup>
Male n (%)	12 (70.6)	91 (75.8)	0.407
Mean age, (years, (range))	65.7 (51-78)	63.6 (35-90)	0.074
Median tumor size, (mm, (range))	20.0 (10.0-40.0)	25.0 (3.0-90.0)	0.210
Tumor circumference of the esophageal lumen > 1/3 n (%)	8 (47.1)	76 (63.3)	0.278
EMR resection n (%)	15 (88.2)	56 (46.7)	0.016
Piecemeal resection n (%)	12 (70.6)	38 (31.7)	0.012
Tumor infiltration depth > Sm1 n (%)	6 (35.3)	40 (33.3)	0.854
Differentiation G2 and G3 <sup>‡</sup> , n (%)	4 (23.5)	38 (31.7)	0.696
Lymphovascular invasion, n (%)	1 (5.9)	18 (15.0)	0.397
R1 or Rx <sup>a</sup> lateral margins n (%)	17 (100.0)	50 (24.2)	<0.001
Adjuvant treatment by chemoradiotherapy n (%)	5 (29.4)	56 (46.7)	0.126
Median follow-up (months, (range))	46.0 (9-135)	20.5 (1-115)	0.074

CI, confidence interval; EMR, endoscopic mucosal resection; m3, cancer invading the muscularis mucosae, sm, cancer invading the submucosa; R1, margin not tumor free; SCC, squamous cell carcinoma. <sup>a</sup> R1 for non-tumor-free margins and Rx when the pathology was not evaluable, for example, due to piecemeal resection. <sup>1</sup> Univariate analyses were carried out using the log-rank test for qualitative variables. For age and tumor size, a univariate Cox model was used. All significant factors, together with those of borderline significance ( $P < 0.2$ ), were included in the multivariate analysis, which used the Cox proportional hazards model. In the multivariate models, only variables with a  $P < 0.05$  were retained.

**Supplementary Table S4.** Characteristics of adjuvant chemoradiotherapy and/or surgery.

	Complementary treatment		Univariate analysis
	Chemoradiotherapy (n = 46)	surgery (n = 15)	P value*
Male, n (%)	36 (78.3)	11 (73.3)	0.730
Age, mean (range), years	63.8 (35-83)	60.0 (44-81)	0.190
ASA score $\geq 3$ , n (%)	24 (52.2)	8 (53.3)	0.938

Tumor size, median (range), mm	25 (5-65)	30 (10-81.7)	0.022
EMR resection, n (%)	24 (52.2)	6 (40.0)	0.413
Piece-meal resection, n(%)	15 (32.6)	4 (26.7)	0.757
Tumor infiltration depth m3–sm1, n (%)	27 (58.7)	7 (46.7)	0.415
Differentiation G2 and G3 <sup>‡</sup> , n (%)	17 (37.0)	5 (33.3)	0.800
Lymphovascular invasion, n (%)	9 (19.6)	2 (13.3)	0.716
Local recurrence cancer, n (%)	5 (10.9)	0 (0.0)	0.321

ASA, American Society of Anesthesiologists; EMR, endoscopic mucosal resection; m3, invasive carcinoma limited to the muscularis mucosae; sm, invasive carcinoma limited to the submucosa. \*Univariate analyses were carried out by chi-squared test for qualitative variables. For age and tumor size, a univariate t-test was used. For local recurrence, a univariate Cox model was used. <sup>‡</sup>G2 was moderately differentiated and G3 was poorly differentiated.

**Supplementary Table S5.** Characteristics of adjuvant chemoradiotherapy.

	Adjuvant treatment by chemoradiotherapy		Univariate analysis
	Yes (n = 46)	No (n = 76)	P value*
Male, n (%)	36 (78.3)	56 (73.7)	0.570
Age, mean (range), years	63.8 (35-83)	64.7 (44-90)	0.886
ASA score ≥3, n (%)	24 (52.2)	39 (51.3)	0.927
History of head-and-neck cancer n (%)	19 (41.3)	28 (36.8)	0.624
Tumor size, median (range), mm	25 (5-65)	20 (3-90)	0.861
EMR resection, n (%)	24 (52.2)	6 (40.0)	0.413
Piece-meal resection, n(%)	15 (32.6)	31 (40.8)	0.366
Tumor infiltration depth m3–sm1, n (%)	27 (58.7)	57 (75.0)	0.059
Differentiation G2 and G3 <sup>‡</sup> , n (%)	17 (37.0)	20 (26.3)	0.215
Lymphovascular invasion, n (%)	9 (19.6)	8 (10.5)	0.162

ASA, American Society of Anesthesiologists; EMR, endoscopic mucosal resection; m3, invasive carcinoma limited to the muscularis mucosae; sm, invasive carcinoma limited to the submucosa. \*Univariate analyses were carried out by chi-squared test for qualitative variables. For age and tumor size, a univariate t-test was used. <sup>‡</sup>G2 was moderately differentiated and G3 was poorly differentiated.

**Supplementary Table S6.** Risk factors associated with nodal or distal metastasis recurrence during.

	Nodal or secondary metastasis cancer recurrence	Univariate analysis	Multivariate analysis
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	Yes (n =11)	No (n =111)	P-value <sup>1</sup>	Hazard ratio (95% CI)
Male n (%)	8 (75.7)	84 (72.7)	1.000	
Mean age, (years, (range))	70.2 (56-83)	63.8 (35-90)	0.030	1.083(1.015-1.156)
History of head-and-neck cancer n (%)	4 (36.4)	43 (38.7)	1.000	
Median tumor size, (mm, (range))	20.0 (7.0-71.5)	25.0 (3.0-90.0)	0.478	
Tumor circumference of the esophageal lumen > 1/3 n (%)	4 (36.4)	69 (62.2)	0.115	
EMR resection n (%)	7 (63.6)	58 (52.3)	0.470	
Piecemeal resection n (%)	6 (54.5)	40 (36.0)	0.328	
R1 or Rx <sup>a</sup> lateral margins, n (%)	6 (54.5)	54 (48.6)	0.709	
Rx <sup>a</sup> depth margins, n (%)	3 (27.3)	18 (16.2)	0.400	
Tumor infiltration depth > Sm1 n (%)	6 (54.5)	32 (28.8)	0.095	4.446(1.286-15.515)
Differentiation G2 and G3 <sup>‡</sup> , n (%)	6 (54.5)	31 (30.1)	0.171	
Lymphovascular invasion, n (%)	1 (9.1)	16 (15.8)	1.000	
No adjuvant treatment by chemoradiotherapy n (%)	1 (9.1)	45 (40.5)	0.051	8.072(1.006-64.802)
Median follow-up (months, (range))	34.0 (9-112)	23.0 (1-135)	0.180	

CI, confidence interval; EMR, endoscopic mucosal resection; sm1, cancer invading the submucosa; R1, margin not tumor free. <sup>a</sup> R1 for microscopic margins positive for tumor and Rx when the pathology was not evaluable, for example due to piecemeal resection and/or coagulation artifacts. <sup>1</sup> Univariate analyses were carried out by log-rank test for qualitative variables. For age and tumor size, a univariate Cox model was used. All significant factors, together with those of borderline significance ( $P < 0.2$ ), were included in the multivariate analyses, which used the Cox proportional hazards model. In the multivariate models, only variables with a  $P < 0.05$  were included.