Evidence tabel Early Gastric Cancer

Auteurs, jaartal	Mate van bewijs	Studie type Follow-up	Populatie (incl. steekproef-grootte)	Patienten kenmerken	Interventie	Contole	Resultaat	Conclusie	Opmerkingen
Wang, 2006	B	Systematic review Search up to Feb 2006	Included were: RCTs of early gastric cancer patients involving a treatment arm of EMR and a comparison arm of gastroectomy	-	EMR	Gastrectomy	No RCTs were found	There is a lack of RCTs in which EMR is compared with gastrectomy for early gastric cancer	
Trials geëxcludeerd door Wang vanwege het feit dat studies geen gastrectomie als controle arm hebben of omdat ze niet gerandomiseerd zijn*									
Kim 2000 Korea	B	Controlled trial Mean 35.3 months (range 18-66)	109 pts with EGC or precancerous lesions	EMR: Mean age 59.8; 65% males; 10% pts with tumor size >20 mm Surgery: Mean age 58.1 yrs (range 34-74), 77% males; 51% pts with tumor size >20 mm	EMR-L (20 had EGC, 54 had precancerous lesions including adenoma and dysplasia)	Subtotal gastrectomy (n =35 with EGC) (lesions were confined to mucosa and were negative for lymph node involvements)	Complete resection was made by EMR-L in 67 cases (92.6% precancerous lesions and 85% EGCs). One pt after EMR had recurrent disease (at 12 months). Five cases of minor bleeding occurred during and after EMR-L. One pt in EMR group died (of non-related causes). Comparing EMR-L (n=20) with surgery (n=35) for EGC, no differences were found in 3 year survival (93.3% vs 100%).	This study suggests that EMR-L is a highly safe and effective treatment modality for selective EGC.	Not randomized; Patient groups are not comparable: pts with larger tumors are more likely to get surgery
Matsushita 1997 Japan	B	RCT 1 year	10 pts with gastric tumors; 4 early cancers, 6 adenomas	Mean age 70 yrs (range 53 to 78); 80% males	LC-EMR (Lift and cut EMR) (n=5)	C-EMR (Cutting EMR) (n=5)	Single resections were performed in 2 lesions of the LC-EMR group and 4 of the C-EMR group. One lesion of the LC-EMR group and 4 of the C-EMR group were resected completely. No complications occurred in the LC-EMR group and there were 2 minor bleedings in the C-EMR. No severe bleeding, perforation or other complications occurred. For the subsequent year, no recurrence was found in the C-EMR group, in the LC-EMR there were 3 recurrent tumors.	C-EMR is a potentially curative treatment for gastric mucosal tumors.	Small sample size
Overige studies naar effectiviteit en veiligheid EMR									
Oka, 2006 Japan (Hiroshima)	B	Retrospective cohort study FU not reported	896 pts (1020 lesions) with EGC resected endoscopally	Not reported	Group A: EMR performed from April 90 to May 02 (n=711)	Group B: ESD performed from June 02 to Dec 04 (n=185)	In cases without ulceration, en bloc and complete resection rates were higher with ESD than EMR ($p<0.01$), regardless of tumor size. The frequency of ulceration did not differ between the groups. Average operation time was longer for ESD than EMR, regardless of tumor size. Also, regardless of ulceration, the	ESD increased en bloc and complete resection rates and may	Retrospective cohort study

							incidence of intraoperative bleeding was higher with ESD (22.6%) than with EMR (7.6%). Delayed bleeding did not differ. In cases with ulceration, the incidence of perforation was higher with ESD (53.8%) than with EMR (2.9%). Local recurrences were treated by incomplete EMR, no patient experienced recurrence after ESD.	reduce local recurrence rate. Increased operation times and complication risks with ESD remain problematic.	
Watanabe, 2006 Japan (Saga)	B	Retrospective cohort study FU 5 yrs	229 pts with 245 gastric tumors undergoing EMR 156 early stage, 89 adenomas	Mean age 69.5 yrs (range 38-91) 70% males	Group A: EMR performed from Feb 99 to June 01	Group B: ESD performed from July 01 to March 04 (subgroups: B1: introduction period and B2: more experienced period)	Lesions > 10 mm: en bloc resection rate and rate of completeness of resection of group B was higher than that of group A ($p<0.01$). For lesions <=10 mm no differences were found. Although the required time was longer in group B than A ($p<0.01$), it was shorter in subgroup B2 compared with B1 ($p<0.05$ with lesions <=10 mm. No difference was found in remnant ratio and perforation rate. Perforation occurred in 9 cases and remnant lesions in 10 cases. No major bleedings was observed and there were no treatment-related deaths during this study.	The en bloc resection rate was better with ESD than with conventional EMR. The required time was longer in ESD but this disadvantage might be improved with experience	Retrospective cohort study
Oda, 2006 Japan (Tokyo)	B	Retrospective cohort study Median FU 3.2 yrs (range 0.5 to 5.0 yrs) Pts follow-up < 6 mo were excluded	714 EGC in 655 pts treated by EMR or ESD	Median age 68 yrs (range 28-93) M/F ratio: 3.4	EMR (n=411)	ESD (n=303)	Technically, 511 of the 714 (71.6%) lesions were resected in one piece. The rate of one-piece resection with ESD (92.7%) was higher compared with that for EMR (56.0%; $p<0.01$). Histologically, curative resection was found in 474 (66.3%) lesions. The rate of curative resection with ESD (73.6%) was higher compared with that for EMR (61.1%, $p<0.01$). Blood transfusion because of bleeding was required in only 1 patient (0.1%), perforation was found in 16 (2.2%). The incidence of perforation with ESD (3.6%) was higher than that with EMR (1.2%, $p<0.05$). There was no procedure-related mortality. The 3-year cumulative residual-free/recurrence-free rate and the 3-year overall survival rate were 94.4% and 99.2%, respectively. The 3-year cumulative residual-free/recurrence-free rate in the ESD group (97.6%) was higher than that in the EMR group (92.5%, $p=0.01$).	ER leads to an excellent 3-year survival in clinical practice and could be a possible standard treatment for EGC. ESD has the advantage of achieving one-piece resection and reducing local residual or recurrent tumor.	Retrospective cohort study 19.6% were excluded (had short-term follow-up only)
Kim, 2007 Korea	C	Case series Median 39 months (range 5-71)	514 EGC in 506 pts treated by EMR	Median age 60 yrs (range 45-83) 72% males	EMR performed from Jan 00 to Dec 02	No control group	Complete resection was achieved in 399 lesions (77.6%). In this group median follow-up was 23.5 months and local recurrence was detected in 24 cases (6%). There were three cases with perforation and 71 cases with bleeding. Overall, no deaths were related to	EMR is an effective modality	No control group

							recurrence of gastric cancer. The only factor that was related to outcome after complete resection was the type of EMR technique (EMR-C and EMR-L have highest recurrence rates).		
Treatments aimed to decrease complications									
Uedo, 2007 Japan	A2	RCT 8 weeks	143 pts with EGC who underwent ESD (n=130 analyzed)	Mean age 68.1 (SD 8.5) PPI group and 65.7 (SD 7.6) yrs in H_2RA group Sex: 78% males in PPI; 79% in H_2RA group	Rabeprazole 20 mg (PPI) on day before ESD for 8 wks 73 assigned 66 analyzed	Cimetidine 800 mg (H_2RA) on day before ESD for 8 wks 70 assigned 64 analyzed	Bleeding occurred in 4 pts in PPI group and 11 in H_2RA group (p=0.057). PPI reduced risk of bleeding (adjusted hazard ratio 0.47 (95% CI 0.22, 0.92, p=0.028). One delayed perforation was experienced in the H_2RA group.	PPI therapy more effectively prevented delayed bleeding from the ulcer after ESD compared to H_2RA	No ITT
Ye, 2006 Korea	B	RCT 4 weeks	100 pts who underwent EMR for gastric mucosal neoplasm (n=82 analyzed)	Mean age 61.2 (SD 9.0) OMP-group and 58.5 (SD 9.4) FMT-group. Sex: 68.3% males for OMP-group and 58.5% for FMT-group	Omeprazole (20 mg/d) after EMR for 28 days 50 assigned 41 analyzed	Famotidine (40 mg/d) after EMR for 28 days 50 assigned 41 analyzed	There were 82 ulcers on follow-up. No differences were found with respect to ulcer stage (P=0.137), ulcer reduction ratio (P=0.38) or ulcer related symptoms (P=0.437). No bleeding episode occurred in any of the patients.	No difference was found between the two treatments	No ITT; Allocation concealment not clear
Yamaguchi, 2005 Japan	B	RCT 60 days	57 pts undergoing EMR for mucosal gastric neoplasm (n=57 analyzed)	Mean age OMP group 71.8 (SD 9.2) yrs; FMT group 72.5 (SD 8.6) Sex OMP 69% males; FMT 82% males	Omeprazole (first 2 days 40 mg/d, thereafter 20 mg/d) after EMR 29 assigned 29 analyzed	Famotidine (40 mg/d) after EMR 28 assigned 28 analyzed	No differences were found with respect to the minor bleeding rates (OMP 13.8% vs FMT 17.9%, p=0.47) and size of the EMR-induced ulceration at 1, 30 and 60 days. No major bleeding occurred. Costs were lower for FMT (10420 vs 17782 yen). No side-effects induced by the medicines were found in either treatment.	Famotidine is suggested as a better alternative as it showed a clear cost-benefit and the healing results were similar for the two treatment strategies.	Small sample size; Allocation concealment and blinding not clear
Watanabe, 2006 Japan	B	RCT 8 weeks	102 pts with severe atypical adenoma (n=26) or early stage gastric cancer (n=72), undergoing EMR at the hospital under study (n=98 analysed)	PPI: 37 men with mean age of 71.7 (SD 10.1) yrs and 14 women with mean age of 74.7 (6.5). Control group: 37 men with mean age of 70.9 (8.1) and	PPI group: Lansoprazole (30 mg) for 1 week before EMR 51 analyzed	No pre-operation medication 47 analyzed	In all pts of both groups, EMR-induced artificial ulcers had almost completely healed by 8 weeks after surgery. The rate of remained ulceration at 7 days after EMR was lower in the PPI group (about 50% versus about 62%, p<0.001) Three pts from no-medication group had postoperative bleeding. No adverse reactions were seen.	The results of the study suggest that preoperative administration of PPI before EMR is useful for controlling and preventing bleeding, and for facilitating	Allocation concealment and blinding not clear; no ITT Results read off figure

				10 women with mean age 68.2 (7.7)				the healing of artificial ulcers	
Ueda, 2006 Japan	B	Prospective comparative study 2 months	58 pts with H. pylori infection who had gastric adenoma or cancer and were undergoing EMR in the hospital under study	Mean age 68.1 yrs (range 34 to 88) 69% males	Pts who underwent successful eradiction (n=26)	I: Pts for whom eradiction therapy was unsuccessful (n=6); and II: Pats who did not undergo eradiction therapy (n=26)	Endoscopically, 18 (75%) of 24 ulcers in the eradication group were at the healing stage 1 month after EMR. The ulcer reduction rates were 85.0 +/- 2.6% and 96. 9 +/- 1.1% at 1 and 2 months after EMR, respectively. Ulcer stage and reduction rate did not differ significantly between the eradication group and control group. However, we frequently observed a better quality of ulcer healing (i.e. a flat pattern at the scar stage) in the eradication group than in the control groups ($p < 0.01$).	H. pylori eradication therapy does not accelerate ulcer healing after EMR but may improve the quality of ulcer healing of gastric ulcer after EMR.	Not randomised
Prognostic factors (studies from 1999-2008)									
An, 2007 Korea (Seoul)	B	Retrospective cohort study	1043 pts surgically treated for early gastric cancer with submucosal invasion (Samsung Medical Center 2002-2005)	Age: 78 <40yrs; 208 40-49 yrs; 271 50-59 yrs, 488 >=60 yrs; 70% males	Pts with lymph node metastases (n=202)	Pts without lymph node metastases (n=841)	The tumor size, histologic type, Lauren classification, tumor depth, lymphatic invasion and perineural invasion showed a positive correlation with the rate of lymph node metastasis and N category by univariate analysis. Multivariate analyses revealed the tumor size (>=2 cm) (2-4 cm OR 1.88 95%CI 1.03, 3.45; >=4 cm 1.96, 95%CI 1.34, 2.88) and lymphatic involvement (OR 8.41 95%CI 5.76, 12.29) to be related to lymph node metastasis.	Lymphatic involvement and tumor size are independent risk factors for a lymph node metastasis in early gastric cancer with submucosal invasion	Retrospective study design
Nasu, 2006 Japan (Matsuyama)	B	Retrospective cohort study Median 50.5 months (range 0 to 199)	332 pts with undifferentiated early gastric cancer who underwent gastrectomy with regional lymph node dissection	Mean age 58 yrs (range 20 to 87); 48% males	Pts with lymph node metastases (n=45)	Pts without lymph node metastases (n=287)	Univariate analysis revealed that depth of tumor invasion (submucosa), tumor size (>30 mm) and lymphatic-vascular involvement were associated with lymph node metastasis. Only lymphatic-vascular involvement was found to have an association by multivariate analysis (OR 7.4 95% CI 2.9, 19.0).	Lymphatic-vascular involvement was the only independent predictive risk factor for lymph node metastasis	Retrospective study design

Hyung, 2004 Korea (Seoul)	B	Retrospective cohort study	566 pts with EGC who underwent gastrectomy with D2 or more extended lymph node dissection (Yonsei Univer-sity 1993-1997)	59% was < 60 yrs of age; 62% males 9% tumor size < 1cm and 21% >= 4 cm	Pts with lymph node metastases (n=67)	Pts without lymph node metastases (n=499)	Rate of lymph node metastasis was 3.4% for mucosal and 21.0% for submucosal cancer. In multivariate analysis risk factors were: Undiff histology: RR 2.28 (95% CI 1.14, 4.56) Size >=2 cm: RR 2.84 (1.36, 5.93) Submucosal invasion RR 3.68 (1.67, 8.13) Lymphatic or blood vessel invasion RR 26.56 (12.77, 55.23). None of the pts that were negative for all these factors showed lymph node metastasis.	Minimally invasive treatment can be positively applied for patients with EGC using these four independent risk factors for lymph node metastases in EGC	Retrospective study design
Abe 2002 Japan (Tokyo/ Shizuoka)	B	Retrospective cohort study	276 pts surgically treated for depressed EGC (Seirei Hospital 1987-1991; First Department of Surgery 1992-2000)	Mean age 58.3 yrs (range 17 to 87); 62% males	Pts with lymph node metastases (LNM) (n=38)	Pts without LNM (n=238)	Variables multivariate associated with LNM: female sex (OR 3.2 95% CI 1.3, 7.9) tumor size >= 20 mm (OR 3.4 95% CI 1.3, 9.1) submucosal invasion (OR 4.9 95% CI 1.5, 16.3) lymphatic vessel involvement (OR 7.5 95% CI 3.0, 19.0) 22.7% of the cases with submucosal invasion had LNM. No LNM was observed in patients who had none of the three risk factors, whereas the percentage was 14.3, 23.3 and 86.7% in patients who had one, two or all three factors, respectively.	Submucosal invasion, female sex, tumor size of 20 mm or more and lymphatic vessel involvement were independently associated with the presence of LNM	Retrospective study design
Gotoda 2000 Japan (Tokyo)	B	Retrospective cohort study	5265 pts who had undergone gastrectomy with lymph node dissection for EGC (National Cancer Institute; Cancer Institute Hospital)	67% males 3016 lesions mucosal; 2249 submucosal	Pts with lymph node metastases (n=467)	Pts without lymph node metastases	Incidence of lymph node metastasis in mucosal tumors: 2.2%. Factors univariate related to LN metastasis were: depressed type, tumor size, undifferentiated type, presence of ulcer and lymphatic-vascular involvement. None of the 1230 well differentiated intramucosal cancers of less than 30 mm diameter regardless of ulceration findings, were associated with metastases (95% CI 0-0.3%). None of the 929 lesions without ulceration were associated with nodal metastases (95% CI 0-0.4%) regardless of tumor size. Incidence of lymph node metastasis in submucosal tumors 17.9%. Factors univariate related to LN metastasis were: female sex, elevated type, tumor size, lymphatic-vascular involvement and degree of submucosal penetration. There was a significant correlation between tumor size larger than 30 mm and lymphatic-vascular involvement with an increased risk of LNM. None of the 145 differentiated adenocarcinomas of less than 30-mm-diameter without lymphatic or venous permeation were associated with LNM, provided that the	We propose expansion of the criteria for local treatment. However, accurate histological evaluation of the resected specimens is essential to avoid recurrence for such EGCs that should be cured	Retrospective study design; No multivariate analyses were performed

							lesion had invaded less than 500 µm into the submucosa (95% CI 0-2.5%).		
Tsujitani 1999 Japan (Yonago)	B	Retrospective cohort study	890 pts with EGC who had undergone standard gastrectomy (incl lymph node dissection)	Age and sex not given 441 mucosal; 449 submucosal cancer	Pts with lymph node metastases (n=76)	Pts without lymph node metastases (n=814)	10-yrs survival 79.2% (mucosal) vs 74.0% (submucosal) Recurrence: 5/441 (mucosal) vs 19/449 (submucosal) Lymph node metastasis: 5 (1.1%) vs 71 (15.8%). Independent prognostic factors for lymph node metastasis were lymphatic vessel invasion (p<0.0001) and submucosal invasion (p=0.018). In patients with mucosal cancer of the elevated type, none had lymphatic metastasis. For the depressed type of <10 mm and 11-20 mm, 1 of 39 and 0 of 96, respectively had lymphatic metastasis. In patients with submucosal cancer of the elevated type with tumors < 30 mm, none had lymphatic metastasis. For the depressed type of <10 mm and 11-20 mm, 0 of 25 and 7 of 77, respectively had lymphatic metastasis.	Endoscopic mucosal resection was suitable for cancers of the depressed type of less than 1 cm in diameter and the elevated type of less than 2 cm in diameter.	Retrospective study design
Shimada, 2001 Japan (Kunamoto)	B	Retrospective cohort study	1051 pts with EGC treated by gastrectomy with D1 or D2 lymph node dissection	Mean age 62 yrs; 65% males mucosal tumors (n=621) submucosal tumors (n=430)	Pts with lymph node metastases (n=99)	Pts without lymph node metastases (n=952)	The incidence of lymph node metastasis was 19.8% in submucosal and 2.3% in mucosal tumors (p<0.001). In submucosal cancer, tumor size (p<0.001) and microscopic type (p=0.04) were associated with lymph node metastasis. All mucosal tumors with lymph node involvement, including tumors smaller than 1.5 cm in diameter, had ulceration or ulceration scar in the lesions. Submucosal tumors that had invaded less than 200 microm in depth (SM1a) had significantly less lymph node involvement than those with deeper invasion. The node metastases were confined to epigastric lymph nodes (N1) in both mucosal tumors with ulceration or ulceration scar and SM1a tumors.	All macroscopic mucosal tumors without ulceration or ulceration scar should be considered for endoscopic mucosal resection.	Retrospective study design; No multivariate analyses were performed
Folli 2001 Italy	B	Retrospective cohort study	584 EGC pts who underwent D2 gastrectomy	Age <=65 48% and > 65 yrs 52%; 60% males	Pts with lymph node metastases (n=84)	Pts without lymph node metastases (n=500)	Prognostic factors for lymph node metastasis were: submucosal invarion (OR 2.29 95% CI 1.56, 3.36) Pen A (Kodama type) OR 1.36 95% CI 1.17, 1.58) Diffuse type (OR 5.70 95% CI 2.88, 11.31) or mixed type (OR 4.19 95% CI 1.89, 9.32) compared to intestinal type. Tumor size (per cm) OR 1.34 95% CI 1.13, 1.59). Pts with 3 or fewer lymph nodes presented a better 5-yr prognosis (83%) than those with more than three positive lymph nodes (48%; p=0.0001).	We propose the following therapeutic strategy: 1) D2 gastrectomy is the standard treatment even in EGC; 2) EMR could be considered first in types I, IIa and IIb tumors that are diagnosed as limited to the mucosal	Retrospective study design

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Ishikawa, 2007 Japan	C	Case series	278 EGC pts (histologically proven adenomca), treated with D2 resection	Mean age 62 yrs 156 mucosal and 122 submucosal cancers	Patients received D2 resection	No control group	Of the 278 patients with EGC, 3 had LNM which met the extended indication criteria for EMR or ESD. Of the mucosal cancers without ulcer, none had lymph node metastases. Six of the 41 specimens of the mucosal cancer with ulcers had LNM at N1 level only. One of these had metastases from a tumor measuring less than 3 cm in size. 22 of 122 submucosal cancers had LNM (23%). 20 of these were SM1 tumors and 5 had LNM; 4 of these 5 had LNM despite the absence of vascular invasion	ESD should be limited to mucosal cancers without ulcer or diff type mucosal cancer with ulcers < 2cm. When the depth of tumor invasion is deeper than mucosal then a gastric resection with lymph node dissection is necessary.	No control group

* Three additional trials are not displayed in the table because they are published in Japanese (Misumi 1991, Mizumoto 1992, Nishida 1993). A fourth study is not displayed because it could not be retrieved (Fukase 1994)