

Evidence tabel - Modaliteitsbehandeling

Auteurs, jaartal	Mate van bewijs	Studie type Follow-up	Populatie (incl. steekproef-grootte)	Patienten kenmerken	Interventie groep	Controle groep	Outcome (effectmaat)	Conclusie	Opmerkingen
Neo-adjuvante behandelingen									
Neo-adjuvante chemotherapie									
Oehler, 2006	A2	Systematic review Search 1980-2005	RCTs assessing pre-or postoperative radiotherapy or chemo-radiation in curative treatment approaches for locally advanced gastrointestinal carcinoma	Two RCTs assessed pre-operative chemotherapy	Pre-operative chemotherapy	Surgery	The MAGIC trial showed a benefit such as increased resection rate, prolonged progression-free survival (p=0.002) and improved survival with peri-operative chemotherapy (5-yr survival: 36% with chemotherapy, 23% with surgery alone,p=0.009). A recent Dutch trial failed to show a benefit for chemotherapy.	Pre-operative chemotherapy might improve survival compared to surgery alone, but there is no universal standard of the chemotherapy regimen	Included were: Cunningham, 2005 (A2-MAGIC trial examined peri-operative chemotherapy) and Hartgrink 2004 (B-Dutch trial)
Earle, 2002	A2	Systematic review Search 1966-2002	RCTs,systematic overviews or meta-analyses of randomized trials of adjuvant or neoadjuvant treatments for patients with resectable gastric cancer (T1-4, N1-2, M0)	Three RCTs have examined chemotherapy given before surgery	Neoadjuvant or adjuvant treatments with curative surgery	Curative surgery alone	Only one of the three trials has been published as full paper, and it detected no significant improvement in either the rate of "curative" resection or downstaging in 59 patients with operable gastric cancer.61 The 2 other studies have been published only as abstracts. Neither was able to demonstrate a survival benefit from neoadjuvant treatment.	There is insufficient evidence from randomized trials to recommend neoadjuvant chemotherapy outside a clinical trial.	Included were: Songun 1999 (B-Dutch trial); Fuji, 1999 (abstract only); Kang, 1996 (abstract on advanced cancer)
Janunger, 2002	A2	Systematic review Search up to 2001	RCTs that used systemic and intraperitoneal chemotherapy given before, during or after operation and for advanced disease	19 studies were found on neo-adjuvant chemotherapy; 3 randomized 644 patients	Neoadjuvant chemotherapy	Surgery	Neoadjuvant chemotherapy has shown effects in some patients but no significant benefit was found in the few randomized studies.	There is still not sufficient evidence that chemotherapy given preoperatively results in a higher respectability or curability rate or that this therapy gives a gain in survival. Its routine use is not justified.	Included were: Songun 1999 (B-Dutch trial); Wang 2000 (on cardia cancer); Yonemura, 1994 (on advanced cancer)
Hartgrink, 2004 The Netherlands	B	RCT Median follow-up of 83 months	59 pts with proven adenocarcinoma of the stomach	Age and sex not reported TNM stage I=25% II=29%	Chemotherapy prior to surgery 5-Fluorouracil,	surgery only	<i>5yr survival rate</i> (chemotherapy vs surgery only) 21% vs 34% (p=0.17) <i>5yr survival rate of patients operated with curative intent</i> chemotherapy vs surgery only 32% vs 53% (p=0.07)	This trial could not show a beneficial effect of pre-operative FAMTX Adequate surgery	Trial was stopped prematurely; Small sample size; no ITT

				III=16% IV=30%	doxorubicin and methotrexate (FAMTX) 29 allocated 27 analyzed	30 allocated 29 analyzed		without delay is the best treatment for operable gastric cancer, until proven otherwise.	
Neo-adjuvant radiotherapy									
Fiorica, 2007	B	Meta- analysis Search up to Dec 2006	RCTs comparing mortality of surgery combined with preoperative radiotherapy or postoperative chemoradiothera py to surgery alone in patients without metastases	4 RCTs, including 832 pts, reported on preoperative radiotherapy	Surgery combined with preoperative radiotherapy	Surgery only	3-yr mortality was 209 for treatment versus 279 for control; random effects OR 0.57 (95% CI 0.43, 0.76); 5-yr mortality was 248 for treatment and 308 for control; random effects OR 0.62 (95% CI 0.46, 0.84) Postoperative mortality was 8 for treatment and 14 for control; random effects OR -.61 (95% CI 0.24, 1.57). Compliance with preoperative radiotherapy was generally satisfactory. Preoperative radiotherapy did not increase anastomotic leakage (OR 0.60; 95% CI 0.26, 1.38)	Adjuvant radiotherapy reduces 3-yr and 5-yr all-cause mortality, but the magnitude of the benefit is relatively small.	Included were: one study from China on cardia tumors, two studies from Russia and one from Ukraine
Neo-adjuvant chemotherapy									
Ajani, 2004 US	C	Prospective case series Median follow-up of at least 50 months	33 operable pts with localized gastric adenocarci- noma	Median age 61 yrs (range 39-73); 67% males Baseline stage N0=35% N1=65% T2=6% T3=94%	Chemothera py of fluorouracil, leucovorin, and cisplatin, followed by 45 Gy of radiation plus concurrent fluorouracil before surgery	No control group	Complete pathological response: 36% in patients with surgery (30% in all patients); Partial response: 29% in patients with surgery (24% in all patients) Complete or partial response: 64% in surgery patients, 55% in all patients Median survival in all patients 33.7 months 2yr survival rate 54%	The three-step strategy of preoperative induction chemotherapy followed by chemo- radiotherapy resulted in substantial pathologic response that resulted in durable survival time.	No control group
Peri-operative chemotherapy									
Cunning- ham, 2006 UK MAGIC trial	A2	RCT Median follow-up 4 years	503 pts with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus 372 (74%) pts had stomach cancer	Median age 62 yrs (range 23-85); 79% males Maximum tumor diameter (cm) 0.0-3.9=32% 4.0-7.9=48% 8.0-11.9=16% 12.0-15.9=3% >16.0=1% Unknown=32% Median=5.0 cm	Surgery and perioperative- chemo- therapy: epirubicin, cisplatin and fluorouracil (ECF). 250 allocated	Surgery only 253 allocated	A total of 319 patients died (149 in the perioperative- chemotherapy group and 170 in the surgery group) and 353 patients had disease progression or died (163 and 190, respectively). Hazard ratio for progression 0.66 (95% CI 0.53-0.81) Hazard ratio for death 0.75 (95% CI 0.60-0.93) 5 yr survival rates Chemotherapy 36.3% (95% CI 29.5%-43.0%) Surgery only 23.0% (95% CI 16.6%-29.4%) The median maximum diameter of the resected tumor was smaller in the perioperative-chemotherapy	A perioperative regimen of ECF decreased tumor size and stage and significantly improved progression-free and overall survival	Only 42% in the chemotherapy group completed all protocol treatments and 34% of patients who completed preoperative chemotherapy and surgery did not begin postoperative chemotherapy;

							group than in the surgery group (3 cm vs. 5 cm, P<0.001)			Pts with cardia tumors were included (11%)
							ECF-related adverse effects were similar to those previously reported among patients with advanced gastric cancer.			
Adjuvante behandeligen										
Adjuvante chemotherapie – systematische reviews										
Mari, 2000	A1	Meta-analysis Search 1965-1999	RCTs of adjuvant chemotherapy for gastric cancer compared with surgery alone, published before January 2000	20 RCTs (21 comparisons) 3658 patients, 2180 deaths	Adjuvant chemotherapy after curative resection	Surgery only	Estimated risk of death All studies Subgroups: Mono-chemo ² Poly-chemo, no anthra Poly-chemo, anthra	Hazard ratio (95% CI) 0.82 (0.75-0.89) [21 RCTs] 0.48 (0.35-0.65) [3 RCTs] 0.85 (0.74-0.97) [11 RCTs] 0.87 (0.76-0.99) [7 RCTs]	Chemotherapy produces a small survival benefit. Taking into account the limitations of literature based meta-analyses, adjuvant chemotherapy is still to be considered as an investigational approach.	At least two high quality RCTs included
Earle, 1999	A1	Meta-analysis Search 1966-1999	RCTs of adjuvant chemotherapy versus observation following curative resection of stomach cancer that took place in non-Asian countries	13 RCTs 1990 patients	Adjuvant chemotherapy with curative resection	Curative resection only	The odds ratio for death in the treated group was 0.80 (95% CI 0.66, 0.97), an effect in favor of adjuvant chemotherapy.		Analysis suggests that adjuvant chemotherapy may confer a small survival benefit to patients after curative resection of gastric cancer.	At least two high quality RCTs included ; High quality defined as at least 3 on Jadad scale
Hermans, 1993	A1	Meta-analysis of randomized trials Search up to June 1991	RCTs published since 1980 in which postoperative chemotherapy is compared with surgery for gastric cancer pts	14 RCTs were found and 11 could be analyzed including 2,096 patients	Postoperative chemotherapy	Surgery alone	Pooled odds ratio of death is 0.88 (95% CI 0.72-1.08) comparing the adjuvant treatment with the surgery-only group.		Postoperative chemotherapy cannot be considered as standard adjuvant treatment.	At least two high quality RCTs included
Janunger, 2002	A1	Meta-analysis	Included were: RCTs that used systemic and	21 RCTs used adjuvant systemic chemotherapy	Adjuvant chemotherapy after surgery	Surgery	Odds ratio of death 0.84 (95% CI 0.74-0.96) indicating a survival benefit for the treatment group. The OR for the subgroup of Western studies (n=17) was 0.96 (0.83-1.12)		There is not sufficient evidence that adjuvant	At least two high quality RCTs included

		Search 1969-1996	intraperitoneal chemotherapy given before, during or after operation and for advanced disease	postoperatively 3962 patients, 2488 deaths				chemotherapy with drugs currently used will be of significant benefit for patients with gastric cancer in the western world.	
Earle, 2002	A1	Systematic review Search 1966 - 2002	RCTs, systematic overviews or meta-analyses of randomized trials of adjuvant or neoadjuvant treatments in patients with resectable gastric cancer (T1-4, N1-2, M0)	30 RCTs and 3 meta-analyses reported on adjuvant systemic chemotherapy	Adjuvant treatments with curative surgery	Curative surgery alone	All three meta-analyses found a decreased risk of death in favor of adjuvant chemotherapy. First meta-analysis (n=13) OR 0.82 95% CI 0.68, 0.98 Second (n=13 Western RCTs) OR 0.80 95% CI 0.66, 0.97 Third (20 trials, 21 comparisons) HR 0.82 95% CI 0.75, 0.89). Results of the RCTs were not reported.	Three meta-analyses found a decreased risk of death in favor of chemotherapy. Subgroup analyses suggest that the benefit of chemotherapy may be greatest in patients with lymph-node metastases.	No new data – just summary of results of 3 previous meta-analyses
Adjuvante chemotherapie – RCTs chemotherapie versus operatie in Europese landen									
Bajetta, 2002 Italy	A2	RCT Median follow up 66 months (range 2–83)	274 pts who underwent a radical resection of stomach adenocarcinoma	Median age 57 yrs; 64% males Primary tumor stage T1/2: 48% T3/4: 52%	Chemotherapy etoposide, adriamycin and cisplatin (EAP) and FU and L-leucovorin	Surgery only 137 allocated 135 analyzed	5 yr overall survival rate (Chemotherapy vs Surgery only) 52% vs 48% (HR 0.93 95% CI 0.65, 1.34) 5 yr disease free survival rate (Chemotherapy vs Surgery only) 49% vs 44% (HR 0.83 95% CI 0.59-1.17)	The results show a limited benefit of adjuvant chemotherapy in radically resected gastric cancer patients after adequate surgery.	No ITT
Nitti, 2006 Italy	A2	Prospective combined analysis of two RCTs Median follow-up 6.5 yrs	397 pts who underwent radical resection for adenocarcinoma of the stomach or esophago-gastric junction	Age range 27-71 yrs; 66.5% males 206 pts from EORTC(FAMTX) and 191 from ICCG (FEMTX)	Adjuvant FAMTX or FEMTX chemotherapy after gastrectomy 194 allocated and analyzed	Gastrectomy alone 203 allocated and analyzed	No significant difference was found between the arms for 5-yr disease free survival (HR 0.98, 95% CI 0.72, 1.24) and overall survival (HR 0.98, 95% CI 0.72, 1.24). Five-year disease free survival was 41% (95% CI 34, 48%) in the treatment arm and 42% (95% CI 35, 49%) in the control arm, and 5-year overall survival was 43% (95% CI 36, 50%) in the treatment arm and 44% (95% CI 36, 51%) in the control arm.	No significant differences for were found between patients treated with FAMTX or FEMTX after radical resection and patients who underwent surgery alone.	Concealment of allocation not clear Pts with cardia tumors were included (6.5%)
Chipponi, 2004	A2	RCT Median	209 pts with gastric cancer with lymph node	Mean age 61yrs 66% males	Adjuvant chemotherapy after gastric	Gastric resection only	The hazard ratio comparing the risk of death within 5 yrs after surgery was 39% (95% CI 28.4, 56%) for the control group and 38.7% (95% CI 27.2, 51.5%) for the	This protocol of adjuvant chemotherapy	No ITT 46% of the

France		follow-up 101 months (range 43-140)	or serosal involvement or both	Lymph node involvement Yes=83% Penetration Serosa or beyond=78%	resection folinic acid, 5-fluorouracil, cisplatin	104 allocated 93 analyzed	105 allocated 104 analyzed	chemotherapy group.	failed to improve the 5-year survival after resection for gastric cancer	patients received the nine courses of chemotherapy.
De Vita, 2007 Italy	B	RCT (phase III) Median follow-up 60 months	225 pts with adenocarcinoma of the stomach or gastro-esophageal junction Pts had total or subtotal gastrectomy with at least a D1 lymphoade-nectomy	Median age 63yrs; 66% males Stage IB=2% II=33% IIIA=34% IIIB=32%	Surgery followed by chemo-therapy Epirubicin, leucovorin, 5-fluorouracil and etoposide (ELFE)	113 allocated 112 analyzed	Surgery only 115 allocated 113 analyzed	5 yr disease free survival rate (Chemotherapy vs Surgery) 44% vs 39% (HR 0.88 95% CI 0.66, 1.17) 5 yr overall survival rate (Chemotherapy vs Surgery) 48% vs 43.5% (HR 0.91 95% CI 0.69-1.21)	ELFE failed to improve the survival of patients with gastric cancer in comparison with surgery alone. The only subgroup with a trend to benefit from chemo-therapy was the node-positive population.	Concealment of allocation not clear; no ITT 82% patients completed therapy as planned Pts with cardia tumors were included (13%)
Bouché, 2005 France	B	RCT (phase III) Median follow-up 97.8 months (SE 3.0)	278 pts with stage II-III-IVM0 gastric cancer, who underwent gastrectomy with curative intent	Median age 61 yrs; 72% males UICC stage II=35% IIIA=40% IIIB=13% IV=11% Unknown=1%	Two-stage postoperative chemo-therapy 5-Fluorouracil and cisplatin	138 allocated 127 analyzed	Surgery only 140 allocated 133 analyzed	5 yr overall survival rate (Chemotherapy vs Surgery) 46.6% vs 41.9% (HR 0.74 95% CI 0.54, 1.02) 5 yr disease free survival rate (Chemotherapy vs Surgery) 47.6% vs 39.8% (HR 0.70 95% CI 0.51, 0.97)	There was no statistically significant survival benefit with this toxic cisplatin-based adjuvant chemotherapy, but a risk reduction in recurrence was observed.	Concealment of allocation not clear; no ITT 62.2% completed treatment as planned Pts with cardia tumors were included (16%)
Adjuvante chemotherapie – RCTs 2 soorten chemotherapie in Europese landen										
Cascinu, 2007 Italy	A2	RCT (phase III) Median follow-up 54 months	397 pts with gastric cancer at high risk for recurrence including patients with serosal invasion (stage pT3 N0) and/or lymph node metastasis (stage pT2 or pT3 N1, N2, or N3)	Median age 59 yrs; 64% males Primary tumor stage T3 N0=7% (T any) N1=20% (T any) N2=41% (T any) N3=33%	PELFW cisplatin, leucovorin, epidoxorubicin, 5-fluorouracil, and glutathione	201 allocated and analyzed	5-FU/LV 5-fluorouracil and leucovorin 196 allocated and analyzed	5 yr overall survival rate (PELFW vs 5-FU/LV) 52% vs 50% (HR 0.95 95% CI 0.70, 1.29) 5 yr disease free survival rate (PELFW vs 5-FU/LV) 41% vs 40% (HR 0.98 95% CI 0.75-1.29)	The study did not show any benefit of an intensive adjuvant chemotherapy for curatively resected gastric cancer patients compared with a standard regimen using 5-FU.	Concealment of allocation not clear Treatment completed by 72% and 77% of PELFW and FU/LV pts, respectively
Di Bartolomeo,	A2	RCT (phase III)	166 pts with histologically	Age < 70 yr=82% 70% males	Fluorouracil (FU) with		Mitomycin C (mono)	3 yr disease free survival (poly vs monotherapy) 67.4% vs 50.2% (p=0.0449)	The FOLFIRI regimen and	No ITT

2006 Italy		Median follow up 29 months	confirmed adenocarcinoma treated with nodal positivity or pT3/4 with a radical resection		irinotecan (CPT-11) and docetaxel plus cisplatin (poly) 85 analyzed	81 analyzed	3 yr overall survival (poly vs monotherapy) 73.5% vs 62.4% (p=0.1634) 35% relative risk reduction of disease relapse 30% relative mortality reduction		docetaxel/ cisplatin given in sequence was well tolerated and feasible in adjuvant setting.	Pts with cardia tumors were included (15%)
Adjuvante chemotherapie – RCTs chemotherapie versus operatie in Aziatische landen										
Sakuramoto, 2007 Japan	A2	RCT Median follow-up 2.9 yrs	1059 pts with stage II or III gastric cancer who underwent gastrectomy with extended (D2) lymph-node dissection	Median age 63 yrs; 70% males Cancer stage, TNM classification IB=0% II=52% IIIA=31% IIIB=10% IV=7%	Surgery with adjuvant therapy with S-1 529 allocated and analyzed	Only surgery 530 allocated and analyzed	HR S1 compared to surgery group for death (at 3 yrs) for relapse (at 3 yrs) After 3 years <i>Overall survival rate</i> S-1 group Surgery only group <i>Relapse free survival</i> S-1 group Surgery only group	HR (95% CI) 0.68 (0.52-0.87) 0.62 (0.50-0.77) 80.1% (76.1-84.0%) 70.1% (65.5-74.6%) 72.2% (67.9-76.4%) 59.6% (54.9-64.3%)	S-1 is useful as adjuvant chemotherapy after curative surgery in patients with gastric cancer.	
Nakajima, 2007 Japan	A2	RCT Median follow-up 6.2 yrs	190 pts with T2 N1–2 gastric cancer with curative gastrectomy and D2 dissection (complete (R0) resection)	Median age 64 yrs; 76% males <i>N-stage</i> N1=71% N2=24%	Surgery + Chemo-therapy: Post-operative uracil–tegafur 95 allocated 93 analyzed	Only surgery 95 allocated and analyzed	5yr survival rate Chemo Surgery HR for overall survival: 0.48 (95% CI 0.26, 0.89) In subgroup N1: 0.52 (95% CI 0.26, 1.05) In subgroup N2: 0.40 (95% CI 0.12, 1.34) For relapse free 5yr survival 0.44 (95% CI 0.25, 0.79)	86% 73% (p=0.017)	Analyses revealed a survival benefit for postoperative adjuvant chemotherapy with uracil–tegafur.	No ITT The trial was terminated before the target number of patients was reached because accrual was slower than expected.
Nashimoto, 2003 Japan	A2	RCT (phase II) Median follow-up 69 months	252 pts with adenocarcinoma of the stomach; N2 or less lymph node metastasis; macroscopically serosa-negative, cancer resected without residual disease Excluding T1 N0	Mean age 58yrs 68% males JCGC stage I=42% II=51% III=6%	Adjuvant chemo-therapy mitomycin, fluorouracil (FU) and cytarabine 128 allocated 127 analyzed	Surgery alone 124 allocated 123 analyzed	<i>5 yr relapse free survival rate</i> Chemotherapy Surgery only <i>5 yr overall survival rate</i> Chemotherapy Surgery only	88.8% (95% CI 83.2, 94.3%) 83.7% (77.1, 90.2%) 91.2% (86.2, 96.2%) 86.1% (79.9, 92.2%)	There was no statistically significant benefit with this adjuvant chemotherapy for patients with macroscopically serosa negative gastric cancer after curative resection	No ITT

Chang, 2002 Korea	B	RCT (phase III) median follow-up 91 months (range 6–115)	416 pts with gastric adenocarcinoma, (ii) stage IB, stage II, stage IIIA or stage IIIB tumors 416 allocated 395 analyzed	Median age 53 yrs; 75% males Stage IB=19% II=22% IIIA=26% IIIB=34%	one of the three adjuvant chemo-therapy regimens 1) F group: 5-FU alone (n=133) 2) FM group: 5-FU and MMC (n=131) 3) FAM group: 5-FU, doxorubicin and MMC (n=131)	5 yr overall survival rate (F vs FM vs FAM) 67.2% vs 67.0% vs 66.7% (p=0.97) 5 yr disease free survival rate (F vs FM vs FAM) 62.1% vs 63.3% vs 62.5% (p=0.83)	The addition of MMC and/or doxorubicin to 5-FU for adjuvant chemotherapy did not prolong the survival of patients with resected gastric cancer	Concealment of allocation not clear; no ITT		
Intra-arteriele chemotherapie										
Tentes, 2006 Greece	B	RCT Mean follow-up 52 months (24–102)	40 pts with locally advanced gastric tumors without distant metastases who received curative (D2) gastrectomy 40 allocated and analyzed	Mean age 65 yrs; 75% males Stage II=25% IIIA=45% IIIB=23% IV=8%	Adjuvant intra-arterial chemotherapy (IARC) (n=20)	Surgery only (n=20)	5 yr overall survival rate (Chemotherapy vs Surgery only) 52% vs 54% (p=0.90) Mean survival Chemotherapy 50 months (95% CI 34, 66) Surgery 62 months (95% CI 42, 81) Recurrence in 3 year 55% (11/20) vs 45% (9/20) (p=0.53)	No survival benefit was found for adjuvant IARC for locally advanced gastric tumors	Small sample size	
Adjuvante peritoneale chemotherapie										
Yan, 2007	A1	Meta-analysis Search 1966-2006	RCTs on adjuvant intraperitoneal chemotherapy for resectable gastric cancer (adenocarcinoma of the stomach or gastro-oesophageal junction)	13 RCTs included in review, 10 subject to meta-analysis	Surgery with intraperitoneal chemotherapy	Surgery without intraperitoneal chemotherapy	Overall survival Subgroups based on intervention HIIC ¹ NIIC EPIC HI/EPIC DPIC Local regional recurrence HIIC NIIC EPIC	Hazard ratio (95% CI) 0.60 (0.43, 0.83) [3 RCTs] 0.67 (0.44, 1.01) [4 RCTs] 0.64 (0.37, 1.10) [2 RCTs] 0.45 (0.29, 0.68) [2 RCTs] 0.89 (0.51, 1.55) [1 RCT] Relative risk (95% CI) 0.84 (0.30, 2.31) [1 RCT] 1.00 (0.64, 1.55) [3 RCTs] 0.51 (0.31, 0.84) [1 RCT]	Potential role of HIIC with or without EPIC, in terms of improved overall survival.	Intraperitoneal chemotherapy was also found to be associated with higher risks of intra-abdominal abscess (RR 2.37; 95% CI 1.32, 4.26) and neutropenia (RR 4.33; 95% CI 1.49, 12.61).
Xu, 2004	A1	Meta-analysis Search 1980-2003	RCTs that compared intraperitoneal chemotherapy with gastrectomy alone in patients who received a potential curative surgery for locally advanced gastric cancer.	11 RCTs involving 1161 cases	Intraperitoneal chemotherapy after gastrectomy	gastrectomy alone	Fixed-effect odds ratio for risk of death 0.51 (95% CI 0.40, 0.65) One trial reported serious side effects by IPT (complication rate 35% in IPT group), which terminated the trial ahead of schedule.	Intraperitoneal chemotherapy after curative resection for locally advanced gastric cancer may be beneficial	3 trials of high quality, 8 of low quality (using Jadad scale with concealment allocation added)	

Janunger, 2002	A2	Systematic review Search 1969-1996	Studies that used systemic and intraperitoneal chemotherapy given before, during or after operation and for advanced disease	11 studies used Intraperitoneal chemotherapy, involving 1415 patients	Intraperitoneal chemotherapy (normothermic or hyperthermic intraoperatively, n=7 studies)	Surgery alone (6 studies)	The few studies that reported intraperitoneal therapy showed no detectable survival benefit. In patients with advanced disease, four small RCTs found longer survival in the treated patients (in the range of 3-9 months). There were also improvements in quality of life. Several drug combinations have been tested, however, with no confirmed superiority for a particular regimen.		Chemotherapy given postoperative or as lavage perfusion perioperatively has not been sufficiently tested for safety and efficiency, and should not be used outside controlled trials.	This paper did not report on methodological quality of the trials – not all studies were RCTs																
Sautner, 1994 Austria	B	RCT Mean follow-up 72.5 months (range 36 to 84)	67 pts undergoing surgery for stage 3 and 4 gastric cancer	Mean age 63 yrs	Intraperitoneal chemotherapy with cisplatin (n=33)	Surgery alone (n=34)	Median survival Treatment: 17.3 months (95% CI 12.5, 23.0) Control: 16.0 months (95% CI 9.2, 19.7) Respective 1-, 3- and 5-yr survival rates were 66.8% (SD 8), 33.3% (SD 8) and 21.2% (SD 7) for the treatment group and 57.6% (SD 8), 30.3% (SD 8) and 23.6% (SD 7) for controls		Intraperitoneal chemotherapy with cisplatin does not improve survival after surgery for stage 3 and 4 gastric cancer	Small sample size; concealment of allocation not clear Pts with cardiac tumors were included (24%)																
Adjuvante radiotherapie																										
Hallisey, 1995 UK	A2	RCT Minimum follow-up of 5 years	436 pts with gastrectomy for adenocarcinoma with no prior malignancy; chemotherapy or radiotherapy; stage I, IVAii, or IVB disease; 436 allocated and analyzed	Median age 64 yrs; 70% males Stage II=16% III=51% IV=33%	3 groups: 1. Surgery with chemotherapy (mitomycin, doxorubicin and fluorouracil) (n=138) 2. Surgery with radiotherapy (n=153) 3. Surgery alone (n=145)		<table border="1"> <tr> <td>Treatment</td> <td>Alive after 5yrs</td> </tr> <tr> <td>Surgery</td> <td>20%</td> </tr> <tr> <td>Radiotherapy</td> <td>12%</td> </tr> <tr> <td>Chemotherapy</td> <td>19%</td> </tr> <tr> <td></td> <td>Median survival (in months)</td> </tr> <tr> <td>Surgery</td> <td>14.7</td> </tr> <tr> <td>Radiotherapy</td> <td>12.9</td> </tr> <tr> <td>Chemotherapy</td> <td>17.3</td> </tr> </table>		Treatment	Alive after 5yrs	Surgery	20%	Radiotherapy	12%	Chemotherapy	19%		Median survival (in months)	Surgery	14.7	Radiotherapy	12.9	Chemotherapy	17.3	Surgery remains the standard treatment for this condition and the use of adjuvant treatments should be restricted to controlled trials.	
Treatment	Alive after 5yrs																									
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Florica, 2007	B	Meta-analysis Search up to Dec 2006	RCTs comparing mortality of surgery combined with preoperative radiotherapy or postoperative chemoradiotherapy	5 RCTs, including 869 pts, reported on preoperative radiotherapy	Surgery combined with preoperative chemo-radiotherapy	Surgery only	The largest trial is the SWOG trial accounting for over half of the patients. A reduction of the 5-year mortality rate (OR 0.45 95% CI 0.32, 0.64) was observed when surgery followed by chemoradiation therapy was compared to surgery alone. The OR was 0.79 (95% CI 0.59, 1.05) for the 3-yr mortality.		Radiotherapy in combination with chemotherapy adjuvant reduces the 3 and 5-yr mortality compared to surgery alone.	Four of five studies were published in or before 1990																

			py to surgery alone in patients without metastases						
Oehler, 2006	A2	Systematic review Search 1980-2005	RCTs assessing pre-or postoperative RT or chemo-radiation in curative treatment approaches for locally advanced gastrointestinal carcinoma	1 RCT on gastric cancer (incl cardia tumors) was found	Surgery plus postoperative chemoradiation	Surgery alone	The included study was the SWOG trial. The 3 yr survival was improved from 41% to 50% and median survival from 27 to 36 months. Relapse free survival after 3 yrs increased from 31 to 48%.	After surgery with limited lymphadenectomy, post-operative chemo-radiation might improve survival and can be considered for patients with adequate nutrition status and nutrition possibilities	
MacDonald, 2001 US SWOG trial	A2	RCT Median follow-up 5 yrs	556 pts with resected adenocarcinoma of the stomach or gastro-esophageal junction	Median age 60 yrs; 71.5% males T-stage T1 or T2=31% T3=61.5% T4=7% No. of positive nodes 0=15% 1-3=41.5% ≥4=43%	Surgery plus postoperative chemoradiation, 5-FU/LV +RT ³ 281 allocated and analyzed	Surgery alone 275 allocated and analyzed	<i>3yr survival rate</i> (Chemo-radiation vs Surgery) 50% (141/281) vs 41% (113/275) HR (95% CI) for death in surgery compared with chemo-radiation 1.35 (1.09-1.66) <i>3yr relapse free survival rate</i> (Chemo-radiation vs Surgery) 48% (135/281) vs 31% (96/275) Hazard ratio (95% CI) for relapse in surgery compared with chemo-radiation 1.52 (1.23-1.86)	Local- regional radiotherapy plus fluorinated pyrimidine- based chemotherapy administered as adjuvant treatment significantly improves overall and relapse-free survival	Concealment of allocation not clear 181 (64%) completed treatment Pts with cardia tumors were included (20%)
Adjuvante chemo-immunotherapie									
Sakamoto, 2002	A1	Meta-analysis Search up to 1999	RCTs comparing adjuvant therapy given after curative resection with a standard chemotherapy regimens for gastric cancer. The adjuvant therapy was (intramuscularly or intradermally administration of OK-432 and randomization had to be performed	6 clinical trials; 1522 patients, who were followed-up for at least 3 years after surgery	Adjuvant immunotherapy with OK-432 (or Picibanil) (757 patients)	Standard chemotherapy (765 patients)	Overall 3 yr survival rate Chemotherapy alone 62.6% Immunochemotherapy 67.5% The pooled OR for 3-year overall survival was 0.81 (95% CI 0.65-0.99).	The results of this meta-analysis suggest that immunochemotherapy after surgery with OK-432 can improve the survival of patients with curatively resected gastric cancer.	Evaluation of study quality on limited items only (size and central allocation)

			centrally							
Earle, 2002	B	Systematic review Search 1966 - 2002	RCTs, systematic overviews or meta-analyses of randomized trials of adjuvant or neoadjuvant treatments in patients with resectable gastric cancer (T1-4, N1-2, M0)	30 RCTs and 3 meta-analyses reported on adjuvant systemic chemotherapy	Adjuvant chemo-immunotherapy	Surgery alone	Two Korean studies, a Japanese study and a Polish study detected significant survival benefit favoring immunotherapy, whereas two European and two Japanese studies found no difference in survival.		Results on the effects of adjuvant chemo-immunotherapy compared to surgery alone are inconsistent.	No details on study quality were given
Popiela, 2004 Poland	A2	RCT Postsurgical follow up was carried on for up to 10 years	156 pts with stage III or IV gastric cancer who had undergone curative resection	Mean age 58 yrs; 69% males Stage IIIA=49% IIIB=26% IV=25% Regional lymph nodes N1=55% N2=46%	Adjuvant immuno-chemotherapy with bacille Calmette-Guérin (BCG) and/or (5-fluorouracil, adriamycin, mitomycin C (FAM) Two groups: 1) FAM +BCG (n=51), 2) FAM (n=53) (ITT)	Surgery only 52 patients (ITT)	Hazard ratio (95% CI) for survival BCG+FAM vs. FAM BCG+FAM vs. control FAM vs. control <i>10 yr overall survival rate</i> BCG+FAM FAM Control	0.76 (0.54-1.03) 0.62 (0.45-0.81) 0.82 (0.65-1.01) 47% 30% 15%	This study demonstrates that the addition of BCG as an immunostimulant to adjuvant FAM chemotherapy significantly prolongs the survival of patients with advanced gastric cancer	Concealment of allocation not clear
							The differences between the BCG+FAM group and the two other groups were statistically significant (p< 0.0006 for difference from controls and p=0.037 for difference from FAM)			
Sato, 2004 Japan	A2	RCT	287 pts who underwent curative resection of gastric cancer	Age ≤59=32% 60-69=41% ≥70=27% 71% males pTNM IA=11% IB=24% II=27% IIIA=22% IIIB=13% IV=3%	Adjuvant immunochemotherapy: 5'-DFUR (Furtulon) OK-432 (Picibanil) 144 allocated and analyzed	Chemo-therapy 5'-DFUR (Furtulon) (=5'-deoxy-5-fluorouridine) 143 allocated and analyzed	<i>5 yr overall survival rate</i> Immuno-chemo-therapy Chemotherapy Risk ratio (95% CI) Log-rank test	63.8% 62.9% 0.95 (0.64-1.41) p=0.80	The 5-year survival rates for the two groups were not significant different	Larger study is in progress