Evidence tabel Uitgangsvraag 8 Follow-up

| Auteurs, jaartal Land | Mate van bewijs | Studie type Follow-up | Populatie (incl. steekproef-grootte) | Patiënten kenmerken | Interventie (aantal pts) | Controle (aantal pts) | Resultaten | Conclusie | Opmerkingen |
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| Bohner, 2000<br><br>Germany | B | Retrospectiv e cohort study | 67 pts who had probable or confirmed recurrence after gastrectomy for gastric cancer | Mean age 58.8 yrs; 46% males | Asymptomatic recurrence (n=15) | Symptomatic recurrence (n=52) | Overall recurrence rate 49.6% (67/135). Most useful test to detect recurrence in asymptomatic group: US (8/15) and tumor markers (6/15)<br>Time till recurrence was not different between the groups (17.1% vs 18.0 months). Chemotherapy was performed more frequently in the asymptomatic group (p=0.0028) and survival after recurrence was longer (8.4 vs 5.9 months, p=0.017). The time the asymptomatic patients lived longer was not higher than the time the 9 untreated asymptomatic patients remained free of symptoms despite recurrence. | Routine follow-up does not contribute to early detection of gastric cancer recurrence. It has no benefit with respect to treatment and survival. | Retrospective study design, small sample size |
| Bennett, 2005<br><br>US | B | Retrospectiv e cohort study | 561 pts who had a recurrence after a curative gastrectomy. Complete data were available on 382 patients. | Median age at time of recurrence 64 for men and 63 for women; 70% males | Asymptomatic recurrence (n=99) | Symptomatic recurrence (n=283) | Of 1,172 patients who underwent a curative gastrectomy, 561 (48%) had a documented recurrence.<br><br>Median time to recurrence was 10.8 months for asymptomatic patients and 12.4 for symptomatic patients (not significant). Median disease-specific survival (DSS) from recurrence to death was 13.5 months for asymptomatic patients and 4.8 months for symptomatic patients (p<0.01). Median DSS from resection to death was 29.4 for asymptomatic patients and 21.6 for symptomatic patients (p<0.05).<br><br>Variables predictive of poor post-recurrence survival included: symptomatic recurrence, advanced stage (III/IV), poor differentiation, short disease-free interval (<12 months) and multiple sites of recurrence. | Follow-up did not identify asymptomatic recurrence earlier than symptomatic recurrence. Patients with symptomatic recurrence may have more aggressive disease with a shorter postrecurrence survival. | Retrospective study design |
| Tan, 2007<br><br>Singapore | B | Retrospectiv e cohort study | 102 pts with gastric carcinoma who had undergone gastrectomy between 1995-98 | Mean age 59.9 yrs (SD 8.2); 57% males | Intensive follow-up (FU) (n=49) | Regular follow-up (n=53) | *Results for intensive vs regular FU*<br>Mean length FU: 3.4 yrs (SD 0.5) vs 3.4 yrs (SD 0.3)<br>Mean no. visits / yr: 3.8 (SD 0.3) vs 3.6 (SD 0.4)<br>Mean no. CT / yr: 1.6 (SD 0.3) vs 0.6 (SD 0.2)<br><br>Recurrence rate: 49% vs 43% (p=0.57)<br>Detection after average period of 11.5 mo (SD 2.1) vs 19.2 mo (SD 2.7) (p=0.02)<br><br>5-yr survival: 43% vs 34% (p=0.36)<br>Length of survival: 4.1 yrs (SD 0.5) vs 3.8 (SD 0.4) (p=0.46)<br><br>Overall recurrence rate: 46%<br>Most useful modality to detect recurrences: CT scan (detected 60%), followed by esophagogastroscopy (detected 23%). | Intensive follow-up resulted in earlier detection of recurrences. However, there was no survival benefit from this regimen. CT was most useful for detecting recurrences | Retrospective study design<br><br>More patients from the intensive follow-up group received adjuvant therapy. |

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| Kodera, 2003<br><br>Japan | B | Retrospective cohort study | 197 pts with gastric carcinoma who had recurrent disease after a potentially curative resection<br><br>No evidence of distant metastasis before or at initial surgery | Mean age 62 yrs in asymptomatic and 60 yrs in symptomatic group; 68% males<br><br>FU consisted of history, physical examination and blood tests (every 3 mo for the first yr and every 6 mo for at least 5 yrs; chest X-ray and abdominal US or CT (every 6 mo); and Endoscopy (annually) | Asymptomatic recurrence (n=88) | Symptomatic recurrence (n=109) | Recurrences were diagnosed within 1 year of surgery in 50% of patients and within 2 years in 75%.<br><br>Asymptomatic recurrence occurred in 45%.<br><br>Asymptomatic recurrence frequently represented distant metastasis (42/88 in asymptomatic vs 21/109 in symptomatic group)<br><br>Although early detection improved survival after diagnosis of recurrent disease (P<0.0001), disease-free survival was shorter. Thus no difference in overall survival was observed. | Early detection of asymptomatic recurrence did not improve overall survival of patients with recurrence after curative resection. | Retrospective study design |

Tumor markers

| Auteurs, jaartal Land | Mate van bewijs | Studie type<br><br>Follow-up | Populatie | Patiënten kenmerken | Index test | Controle | Resultaten | Conclusie | Opmerkingen, commentaar |
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| Marrelli, 2001<br><br>Italy | B | Prospective comparative study<br><br>Mean follow-up time for the entire population: 41 +/- 33 months | 133 pts who had undergone potentially curative surgery | Mean age 66 yrs; 60% males<br><br>Recurrence in 75 (56%) patients | Serum tumor markers CEA, CA 19-9, and CA 72-4 | Clinical examination, hematological analyses, abdominal ultrasound, chest radiograph, endoscopy of the upper digestive tract. Abdominal computed tomography (CT) scan | Preoperative positivity was 16% for CEA, 35% for CA 19-9, and 20% for CA 72-4.<br><br>Marker sensitivity in recurrent cases was 44% for CEA, 56% for CA 19-9, and 51% for CA 72-4; the combined use of the three markers increased sensitivity to 87%, which reached 100% in patients with positive preoperative levels. Marker specificity, evaluated in 58 disease-free patients, was 79% for CEA, 74% for CA 19-9, and 97% for CA 72-4. | The combined assay of CEA, CA 19-9, and CA 72-4 may be useful for early diagnosis of recurrence of gastric cancer; however, only CA 72-4 positivity should be considered a specific predictor of tumor recurrence. | Reference test is not gold standard |
| Takahashi, 2003<br><br>Japan | B | Prospective comparative study | 321 pts with advanced gastric cancer of more than stage II | Median age 59 yrs; 64% males | Serum levels of CEA and CA19-9 were examined preoperatively and every 3 months post-operatively | Diagnostic imaging such as chest X-ray, computed tomography (CT), and ultrasonography every 3 months, to check for recurrence, for at least 3 years. | 120 patients had recurrences<br>Sensitivities for CEA and CA19-9, and combinations of the two markers, for indicating recurrence were 65.8%, 55.0%, and 85.0%, all of which values were sign higher than the preoperative positivities (28.3%, 29.2%, and 45.0%, respectively; $p$<0.001 for all.) the specificities of serum CEA and CA19-9 for recurrence were 81.1% and 93.7%, respectively<br><br>Recurrent diseases were detected at -5 to 12 months (mean, 3.1$\pm$3.6 (SD) months) for CEA monitoring and at -10 to 13 months (mean, 2.2$\pm$3.9 months) for CA19-9 monitoring before detection by imaging. | Monitoring for recurrence by serum CEA and/or CA19-9 levels is useful in most patients with gastric cancers. However, suggest that we should monitor imagings mainly, rather than monitoring these markers, in the remaining patients with low pre- | Reference test is not gold standard |

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| | | | | | | | | operative levels of these markers. | |
| Studie designs met patiënten en controles | | | | | | | | | |
| Auteurs, jaartal Land | Mate van bewijs | Studie type<br><br>Follow-up | Marker | Patiënten kenmerken | Patiënten | Controle | Resultaten | Conclusie | Opmerkingen, commentaar |
| Tani, 2007<br><br>Japan | B | Case-control study | Circulating cell-free mRNA | Mean age 65 yrs; 65% males<br><br>Stage<br>I and II=65%<br>III and IV=35% | 52 pts with gastric cancer (40 preoperatively and 12 one yr after gastric-tomomy | Healthy people (n=20) | Preoperative, 6 (15%) patients were positive for at least one tumor-related mRNA.<br>In de follow up patients, 2 out of 12 patients were positive for circulating cell-free tumor-related mRNA. One of these two showed definite findings of recurrence. The other patients developed recurrence 5 months later.<br><br>Circulating tumor cells were detected in 4 patients (2 pre, 2 post) using the CEA-specific RT-PCR assay and aberrant methylation of a least one gene was detected in 12 patients (8 pre, 4 post) with the MSP assay. | The detection of circulating cell-free mRNA might serve as a new complementary marker for gastric cancer. The assay might be helpful in detecting clinically occult recurrences during the follow-up period after a gastrectomy. | Retrospective study design |
| Choi, 2006<br><br>Korea | B | Case-control study | CEA, CA19-9, and AFP measured prior to surgery, and every 6 mo postoperatively (for at least 3 yrs) | Mean age 55 yrs; 62% males<br><br>Tumor stage<br>T1=31%,T2=42%, T3=28%,N0=41%, N1=38%,N2=21% | Pts who underwent gastrectomy for gastric adenocarcinoma with recurrence (n=52) | Pts who underwent gastrectomy for gastric adenocarcinoma without recurrence after more than 3 yrs of follow up (n=52) | At least one of the three tumor markers tested was positive preoperatively in 7 (13.4%) of the patients without recurrence compared to 20 (38.5%) of those with a recurrence (p=0.007).<br><br>Postoperatively, at least one marker was present in ten patients (19.2%) in the control group including two in whom it was positive preoperative compared to 40 (76.9%) in the recurrence group ($p< 0.001$)<br><br>Specificities of the serum AFP, CEA and CA19-9 for recurrence were 96.2, 86.5 and 86.5%.<br>At a combination of tests (i.e., AFP/CEA, AFP/CA19-9, CEA/CA19-9) the sensitivity for predicting recurrence increased from 59.6 to 73.1% compared to single tests (30.8–51.9%) ($p< 0.01$). | An elevated tumor marker at diagnosis or during follow up may identify patients at higher risk for a recurrence. | Retrospective study design<br><br>The tumor size was slightly smaller, and the tumor stage was lower in the control group |
| Teng, 2006<br><br>China | B | Case-control study<br><br>Median FU 19 mo (range 2-32) | Big ET-1 levels were examined pre-operatively and on post-operative days (POD) 1,3 and 10 and every 3 mo thereafter until recurrence | Mean age 57 yrs; 66% males<br><br>TNM stage<br>I=12%<br>II=41%<br>III=34%<br>IV=13% | 106 pts diagnosed with gastric cancer | 20 healthy controls with no known history of cancer | Big ET-1 levels of patients with stage II, III and IV were higher compared with the healthy controls (p=0.000).<br><br>Recurrence occurred in 48 out of 86 patients.<br>Big ET-1 levels immediately before relapse in stage II patients were increased compared with the $10^{th}$ POD ($6.16\pm0.80$ vs. $6.56\pm0.88$, p=0.011). No similar alterations were observed in stage III and IV recurrent patients ($6.06\pm 0.79$ vs. $6.15\pm0.79$, p=0.087; $6.45\pm1.10$ vs. $6.56\pm1.11$, p=0.099, respectively) | Plasma Big ET-1 levels might be a reliable marker to determine the severity of gastric carcinoma. In stage II patients Big ET-1 levels were valuable in predicting recurrences. | Retrospective study design<br><br>Big ET-1= Big Endothelin-1 |
| Xu, 2005<br><br>China | B | Case-control study | Expression of CK18 mRNA in lymph nodes and in peripheral blood | 54 patients; mean age 51.2 yrs; 56% males | In lymph nodes: 35 patients with gastric carcinoma (298 nodes) | In lymph nodes: Control group I : 10 patients with peptic ulcer (20 nodes) | Correlation between expression of CK 18 mRNA in lymph nodes and tumor invasion, and lymph node metastasis is significant ($p<0.05$). Correlation with tissue differentiation and TNM stage not significant. | RT-PCR with CK18 mRNA as a molecular marker is highly sensitive and specific in detecting lymph node micro-metastases of | Retrospective study design |

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| | | | | | In peripheral blood: 54 patients with gastric carcinoma | In peripheral blood: Control group II: 10 healthy people | Correlation between expression of CK 18mRNA in peripheral blood and tissue differentiation, and lymph node metastasis, and TNM stage is significant ($p<0.05$). Correlation with tumor invasion is not significant. | gastric carcinoma. | |
| Tajima, 2004<br><br>Japan | B | Prospective cohort study | The phenotypic marker expression of the tumour was determined by examining the expression of human gastric mucin (HGM), MUC6, MUC2 and CD10<br><br>every 3 mo for the first postoperative yr and then at intervals of between 6 and 12 mo for at least 5 yrs | Mean age 69 yrs; 69% males | Pts who had undergone a curative resection (D2/3), who died from recurrence (n=97)<br><br>Recurrence: Peritoneal=60 Haemato-genous=32 Locoregional= 18 | Pts who had undergone a curative resection (D2/3), alive without recurrence (n=116) | The expressions of HGM, MUC6, MUC2 and CD10 were observed in 73.3, 61.7, 30.0 and 15.0% of patients in the peritoneum recurrence group, respectively;<br>in 43.8, 43.8, 37.5 and 43.8% of patients in the haematogenous recurrence group, respectively;<br>in 66.7, 66.7, 50.0 and 16.7% of patients in the locoregional recurrence group, respectively;<br>and in 54.3, 62.9, 61.2 and 23.3% of patients in the control group, respectively.<br><br>Peritoneal recurrence was associated with HGM-positive tumours ($p=0.022$) and MUC2- negative tumours ($p=0.0002$), compared with the control group. Haematogenous recurrence was associated with MUC2-negative tumours ($p=0.028$) and CD10-positive tumours ($p=0.039$).<br><br>Peritoneal recurrence was associated with G-phenotype tumours, compared with the control group ($p=0.0002$). | The gastric and intestinal phenol-typic marker expression of the tumour, determined by immunohistochemical staining for HGM, MUC6, MUC2 and CD10, can be used to predict the pattern of gastric carcinoma recurrence after curative resection. | Confounding not clearly addressed |

*Afkortingen:*
CEA= carcinoembryonic antigen
CA 19-9, CA 72-4= carbohydrate antigen
AFP= alpha fetoprotein
CK-18= cytokeratin 18
HGM, MUC6, MUC2 and CD10= ‘human gastric mucin’ genes