# An explorative study on the clinical utility of baseline and serial serum tumour marker measurements in advanced upper gastrointestinal cancer

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**Abstract.** The value of early tumour marker changes during palliative chemotherapy in patients with upper gastrointestinal adenocarcinoma (UGIA) is unclear. Seventy-three patients with advanced UGIA were randomised to receive 45 mg/m$^2$ docetaxel or 180 mg/m$^2$ irinotecan with 5-FU/leucovorin. After every 2nd course the patients were crossed over to the other regimen. Serum was sampled before start of chemotherapy and every 2nd week during 8 weeks for CEA, TPA, TPS, CA72-4, CA19-9 and CA242 measurements. Eighteen patients (25%) had partial response (PR) and 21 patients had stable disease for at least 4 months (SD4). All baseline marker levels, except CA72-4, correlated with time to progression and survival. Patients with normal levels, except CA72-4, also had more clinical responses (PR+SD4) than patients with elevated values. Tumour marker changes early during treatment provided modest predictive information for tumour response and survival. A model combining baseline level, the change and the interaction between them gave the best prediction of outcome, however, insignificantly better than baseline level for all markers except CA242. Baseline tumour marker levels provide prognostic information for patients with UGIA on palliative chemotherapy. Early changes generally failed to provide accurate information for tumour response and survival.

## Introduction

In metastatic upper gastrointestinal adenocarcinoma (UGIA), i.e. gastric (GC), pancreatic (PC) and biliary cancer (BC), chemotherapy can favourably influence the quality and quantity of life (1-4). The effects are usually short-lived, although by most considered sufficient for routine use. There is a great need to explore new drug combinations with greater efficacy, to identify, prior to treatment initiation, the patients who will benefit from treatment and to early identify those who will not respond. Changes in serum tumour markers have been explored for the latter purpose. Small patient series in PC have indicated that changes in CA19-9 during treatment provide clinically relevant information (5-10), but the value of these changes is far from established (11-13).

We recently reported a randomised exploratory phase II trial on the value of planned sequential combination chemotherapy in UGIA (14). The main aim was to explore the possibilities to monitor the administration of chemotherapy using serial measurements of tumour markers during the first two months after treatment initiation. Since there is no knowledge, with the exception of CA19-9 in PC (5-13), about the value of any tumour marker in the monitoring of palliative chemotherapy in UGIA, the study was exploratory and included several markers of potential interest. All selected markers have been used in gastrointestinal cancer, including colorectal cancer (CRC), and discussed in clinical guidelines (12,15,16). We now report on the prognostic and predictive utility of the measurements at baseline and early during treatment in the trial.

## Patients and methods

*Patients*. Patients with advanced UGIA were eligible if they had measurable disease, were 18-75 years old, had an ECOG performance status of 0-2, and adequate haematologic, liver and kidney functions. Patients with previous malignancy, cardiac problems precluding treatment or CNS metastases were excluded. Radiological staging using computed tomography was done within 3 weeks prior to randomisation. All patients provided written informed consent, and the study was approved by the ethics committees at participating centres.

*Randomisation, treatment and response evaluation*. Patients were randomised to start with 2 cycles of docetaxel (45 mg/m$^2$

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day 1) with 5-FU/leucovorin (FLv-DOCE) or irinotecan (180 mg/m$^2$ day 1) with 5-FU/leucovorin (FLv-IRI) followed by 2 cycles of the other combination (14). Cycles were repeated every 14 days. Tumour response was evaluated according to RECIST criteria by imaging every 2 months. At the first evaluation all patients had been treated with 2 cycles each of FLv-DOCE and FLv-IRI. Treatment continued sequentially for totally 12 cycles if there were no signs of progression and treatment was well tolerated. Clinical response was defined as partial remission (PR) or stable disease for at least 4 months (SD4). Patients who had stable disease after 2 months (SD2), but progressive disease (PD) before the evaluation after 4 months and those with PD before or at the first evaluation were clinical non-responders.

*Tumour marker analyses*. Serum for marker analyses were taken at baseline within one week prior to the first cycle and immediately (1-3 days) prior to cycles 2-5. Immediately after sampling, aliquots were frozen at -20˚C.

CEA and CA19-9 were analyzed on a Modular Analytics E170 (Roche Diagnostics, Mannheim, Germany). The total coefficient of variation (CV) for the CEA assay was 2.6% at 3.6 $\mu$g/l and 1.7% at 22.8 $\mu$g/l and for the CA19-9 assay 2.9% at 9.7 kU/l and 2.8% at 39 kU/l. The reference intervals were <3.4 $\mu$g/l for CEA and <37 kU/l for CA19-9.

Tissue polypeptide antigen (TPA) was analysed on a Liaison instrument (DiaSorin, Saluggia, Italy). The total CV was 7.9% at 696 U/l and 5.6% at 927 U/l. The reference interval was <95 U/l.

Tissue polypeptide-specific antigen (TPS) was analysed on an Immulite One instrument (Diagnostic Products Corp., Los Angeles, CA, USA). The total CV was 6.9% at 91 U/l and 4.2% at 415 U/l. The reference interval was <85 U/l.

CA72-4 was analyzed on an Elecsys 2010 (Roche Diagnostics). The total CV was 4.0% and the reference interval <6 kU/l.

CA242 was analysed by microtitre plate EIA assay (Fujirebio Diagnostics, Gothenburg, Sweden) in batch mode. The within-run CV for CA242 was 3.8-4.7% and the between-day CV was 2.2-3.8%. The reference interval was <25 kU/l.

*Statistics*. The Gehan method was used to power the clinical phase II study (14). Sixty patients with at least 20 patients for each diagnosis were considered adequate in this explorative study to get a good idea of whether sufficiently large tumour marker changes occurred to early guide sequential administration of chemotherapy in advanced UGIA.

All analyses were according to intention to treat. Log-linear regression was applied to obtain individual estimates of the changes in tumour marker levels during treatment. The slope estimates changes in level of the marker, in relation to the intercept (estimated baseline level) per day and corresponds to the tumour marker doubling time in days (td = Ln2/slope) if the slope is positive and to the tumour marker half time if the slope is negative (th = Ln0.5/slope) (17,18).

In logistic regression models, we examined the effect of the baseline level, the slope and the combined effect of the slope, intercept and the interaction between the two variables on clinical response. We developed receiver operating characteristic (ROC) curves for these models. The areas under the curves (AUC) were compared using the method by DeLong (19). Optimal cut-off levels were calculated based on the Youden index (20) where sensitivity and specificity were considered equally important.

Overall survival (OS) and time to tumour progression (TTP) were calculated from the date of randomisation and a linear regression model was used, since there were no censored observations. The explanatory value ($R^2$) is a measurement of each marker's ability to predict OS and TTP. In the model, OS or TTP is the dependent variable and the marker level the explaining variable. Correlations were studied with Spearman's rank correlation test and comparisons of proportions between groups by $\chi^2$. Cox proportional hazard models were used to study the effect of baseline tumour marker levels on clinical response rate, TTP and OS. All baseline markers were log-transformed. When analyzing the relations between marker changes and survival, the landmark method was used to compensate for the guarantee-time of those with a change (21). A p-value of $p<0.05$ was considered statistically significant.

Table I. Patient characteristics at baseline and treatment outcome.

| | All[a] |
|---|---|
| Total | 73 |
| Gastric cancer | 22 |
| Pancreatic cancer | 28 |
| Biliary cancer | 23 |
| Age, mean (range) years | 62 (40-75) |
| Male/female | 38/35 |
| WHO 0/1/2 | 47/22/3 |
| Metastatic/locally advanced | 70/3 |
| Haemoglobin mean (range) g/l | 126 (101-163) |
| ALP mean (range) $\mu$kat/l | 11.7 (1.1-65) |
| ALP elevated >1.9 $\mu$kat/l | 49 |
| Response category | |
| PR | 18 (25%) |
| SD4 | 21 (29%) |
| Clinical (PR+SD4) | 39 (54%)[b] |
| SD2+PD | 34 (46%) |
| OS months (median) | 8.2 |
| TTP months (median) | 4.4 |

[a]Number of patients unless otherwise indicated. [b]Sixty-four percent for gastric cancer, 61% pancreatic cancer and 35% biliary cancer. ALP, alkaline phosphatase; PR, partial remission; >30% decrease decrease in the sum of the longest tumour diameters, SD4, stationary disease for at least 4 months; SD2; stationary disease for 2 but not 4 months, PD, progressive disease; >20 increase of the longest diameters or new lesions, or not evaluated (death prior to the first evaluation, usually in progressive disease). OS, overall survival; TTP, time to tumour progression.

Table II. Serum tumour marker levels at baseline.

| | GC | PC | BC | All |
|---|---|---|---|---|
| CEA | 104 (2.3) | 180 (5) | 356 (7.5) | 214 (5.0) |
| Mean (median) (range) | (1-2074) | (2-3043) | (1-6603) | (1-6603) |
| % elevated (>3.4 $\mu$g/l) | 39 | 61 | 70 | 58 |
| TPA | 417 (199) | 782 (134) | 1287 (459) | 824 (219) |
| Mean (median) (range) | (76-3364) | (26-8795) | (53-8682) | (26-8795) |
| % elevated (>95 U/l) | 95 | 57 | 95 | 81 |
| TPS | 218 (142) | 459 (108) | 901 (438) | 510 (198) |
| Mean (median) (range) | (39-1224) | (36-4565) | (32-3910) | (32-4565) |
| % elevated (>85 U/l) | 68 | 58 | 95 | 72 |
| CA72-4 | 59 (15.5) | 54 (7.6) | 60 (9.5) | 58 (8.4) |
| Mean (median) (range) | (0.4-531) | (0.7-527) | (0.8-600) | (0.2-600[a]) |
| % elevated (>6 kU/l) | 60 | 54 | 57 | 56 |
| CA19-9 | 845 (19) | 29954 (321) | 93950 (1534) | 40154 (116) |
| Mean (median) (range) | (3.1-1.1x$10^4$) | (5-3.8x$10^5$) | (23-1.7x$10^6$) | (1.1-1.7x$10^6$) |
| % elevated (>37 kU/l) | 36 | 71 | 67 | 60 |
| CA242 | 355 (10) | 2652 (40) | 30349 (38) | 11264 (27) |
| Mean (median) (range) | (<1.0-3863) | (<1.0-19179) | (<1.0-586163) | (<1.0-586163) |
| % elevated (>25 kU/l) | 35 | 54 | 77 | 54 |

[a]Maximum assay value 600. CEA, carcinoembryonic antigen; TPA, tissue polypeptide antigen; TPS, tissue polypeptide-specific antigen; CA, carbohydrate antigen.

## Results

*Patients and treatment*. Between August 2003 and April 2005, 73 patients were randomised; 22 with GC, 28 with PC and 23 with BC. Patient characteristics are shown in Table I. One patient rapidly deteriorated and never started chemotherapy. Of the 72 patients who started treatment, 9 dropped-out prior to the tumour evaluation after 4 cycles, 21 stopped treatment before the evaluation after 8 cycles, and 24 (33%) completed 12 cycles. Tumour progression was the main reason for treatment interruption. There were no differences in response rates, TTP and OS according to whether FLv-DOCE or FLv-IRI was given first, why the results are not separated.

*Tumour outcome and survival*. The objective response rate (PR) was 25% and the clinical response rate (PR+SD4) was 54% (Table I). There were no significant differences in TTP and OS between the diagnoses. Toxicity, symptomatic improvement and quality of life are detailed separately (14).

*Baseline tumour marker levels and outcome*. At baseline, the frequency of elevated markers ranged between 54 and 81% (Table II). Elevated levels were seen more often in BC (57-95%) than in PC (54-71%) and GC (35-95%). CA242 was least commonly elevated. The median number of markers elevated was 4 (range 0-6). All patients but 3 had at least one marker elevated at baseline. The baseline levels of TPA and TPS (Spearman's rho 0.83) and CA19-9 and CA242 (rho 0.81) were strongly and those between CEA and CA19-9 (rho 0.51) and between CEA and CA242 (rho 0.47) moderately correlated (all $p<0.0001$).

The proportion of PRs did not differ according to whether baseline values were normal or elevated (data not shown). More clinical responses were, however, seen if the baseline values were normal compared with elevated for CA242 [70% (23/33) vs. 39% (15/38), $p=0.02$]. A tendency was seen for all other markers (68-79% vs. 43-51%, p=0.12-0.06), except for CA72-4 (data not shown). However, not even very high levels of a marker excluded a response. The highest baseline values observed for responders (PR or clinical) were CEA 3.043 $\mu$g/l, TPA 8.795 U/l, TPS 1.620 kU/l, CA72-4 1.620 U/l, CA19-9 45.962 kU/l and CA242 10.960 kU/l.

Baseline levels of all markers but CEA and CA72-4, used as continuous variables, inversely correlated to clinical response, TTP and OS (Table III). ALP and performance status correlated with OS, and diagnosis with clinical response. When dichotomized (normal vs. elevated), all markers but CA72-4 gave prognostic information with longer survival for those with normal levels (data not shown). In multivariate analyses, performance status and TPA provided independent prognostic information for OS, TPS for TTP and CA19-9 for clinical response (Table III).

Table III. Cox proportional hazard analyses of OS, TTP and clinical response.

| | Overall survival | | TTP | | Clinical response PR+SD4 vs.SD2-PD | |
|---|---|---|---|---|---|---|
| Characteristics | Univariate HR | Multivariate HR CI (95%) | Univariate HR | Multivariate HR CI (95%) | Univariate HR | Multivariate HR CI (95%) |
| Age | 1.00 | | 0.98 | | 0.99 | |
| Sex | 1.01 | | 1.23 | | 1.47 | |
| Diagnosis | | | | | | |
| Biliary (ref) | 1.00 | | 1.00 | | 1.00 | |
| Gastric | 0.98 | | 0.65 | | 0.27 p=0.038 | |
| Pancreatic | 0.78 | | 0.66 | | 0.31 p=0.050 | |
| Performance status | 2.01 p=0.008 | 2.76 (1.44-5.30) p=0.002 | 1.63 | | 2.39 | |
| Haemoglobin | 0.99 | | 0.99 | | 0.98 | |
| ALP | 1.02 p=0.033 | | 1.01 | | 1.02 | |
| CEA | 1.40 p=0.018 | | 1.28 | | 1.91 | |
| TPA | 1.97 p=0.002 | 1.98 (1.22-3.22) p=0.006 | 1.69 p=0.018 | | 2.76 p=0.036 | |
| TPS | 2.20 p=0.002 | | 2.46 p=0.001 | 2.32 (1.27-4.26) p=0.006 | 4.50 p=0.007 | |
| CA72-4 | 1.08 | | 1.13 | | 1.17 | |
| CA19-9 | 1.32 p=0.003 | | 1.28 p=0.008 | | 2.12 p=0.001 | 1.99 (1.24-3.22) p=0.005 |
| CA242 | 1.43 p=0.001 | | 1.29 p=0.020 | | 2.1 p=0.002 | |

TTP, time to tumour progression; ALP, alkaline phosphatase; HR, hazard ratio, see Table II for the tumour markers. All tumour markers are for baseline measurements and were log-transformed. Only p-values <0.05 are shown. The multivariate analyses included the variables that were statistically significant in the univariate analyses.

*Changes in tumour marker levels and outcome*. During treatment, the marker levels changed rapidly in many patients. A decrease by (arbitrarily) >50% in the patients who had elevated levels at baseline was seen in 4-41% at 4 weeks and in 13-42% at 8 weeks (data not shown). Some patients had decreases by >90%, or to normal values (6-32%) after 4 and 8 weeks. Increases by more than 100% (maximum 320% after 8 weeks) were seen for all markers (data not shown). TPA and TPS decreased more rapidly and in more patients than the other markers. Some patients had marker levels below the upper normal limit (UNL) throughout the 8 weeks assessment period. This was most common for CA242.

A distinctly different tumour marker response during the first 4 weeks from that during the subsequent 4 weeks (e.g. first a >50% decrease and then a >50% increase), when the other combination was given, was seen in many (30-60%) patients for one or several tumour markers. However, except for one patient, where three markers initially decreased and then increased, no consistent pattern emerged. Actually, in some patients, some markers decreased and others increased

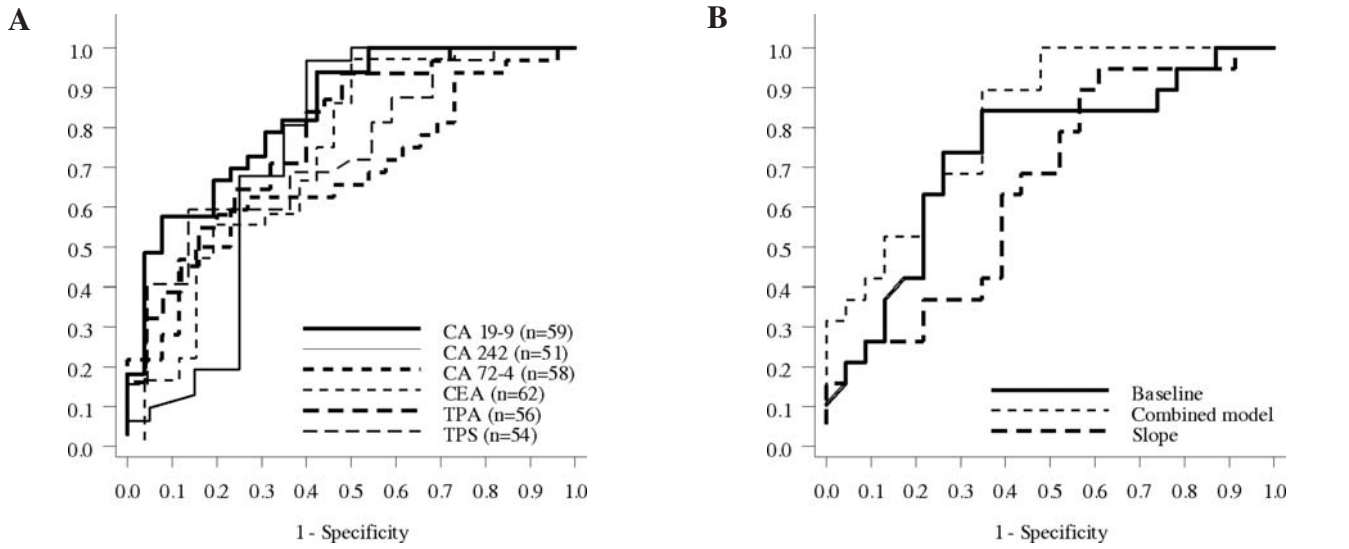


Figure 1. A, ROC curves for prediction of clinical response for the combined model integrating the estimated baseline value and the slope are shown for all 6 tumour markers. B, ROC curves for prediction of clinical response for the baseline value, the slope and the combined model illustrated for S-CA19-9, being typical for all markers. Results are presented for patients with at least one value above normal at baseline or during treatment (n=42).

Table IV. ROC AUCs and p-values from logistic regression for the different markers and methods for clinical response (PR+SD4).

| | AUC (95% confidence limits) (p-value)[a] | | |
|---|---|---|---|
| | Baseline | Slope | Combined |
| CEA (n=62) | 0.642 (0.496-0.789) | 0.635 (0.489-0.780) | 0.730 (0.594-0.866) (p<0.001) |
| TPA (n=56) | 0.657 (0.513-0.801) (p=0.033) | 0.516 (0.362-0.670) | 0.781 (0.659-0.903) (p<0.001) |
| TPS (n=54) | 0.735 (0.597-0.874) (p<0.001) | 0.649 (0.503-0.796) (p=0.046) | 0.737 (0.603-0.871) (p=0.011) |
| CA72-4 (n=58) | 0.597 (0.450-0.744) | 0.524 (0.369-0.679) | 0.680 (0.542-0.819) (p=0.011) |
| CA19-9 (n=59) | 0.783 (0.662-0.903) (p<0.001) | 0.585 (0.429-0.741) | 0.836 (0.733-0.938) (p<0.001) |
| CA242 (n=51) | 0.657 (0.488-0.825) | 0.737 (0.586-0.889) (p=0.002) | 0.740 (0.573-0.908) (p=0.005) |

[a]Only p-values <0.05 are shown. See Table II for abbreviations of tumour markers. The slope is the estimated slope from a log-linear regression of the predictors and combined is the intercept, the slope and the interaction between the intercept and the slope from the log-linear regression of the predictors.

during the first period, with the opposite pattern during the second period.

*Changes in tumour marker levels and clinical response*. The ability of predicting clinical response by the baseline value, the slope and the combined intercept, slope and interaction model was studied using logistic regression and ROC curves (Fig. 1 for the combined model). The combined model yielded the largest AUC values (Table IV), but the additional information in terms of larger AUC gained by using the combined model was not statistically significantly better than the information given by the baseline values only for any marker but CA242 (data not shown). An association between clinical response and slope was seen only for

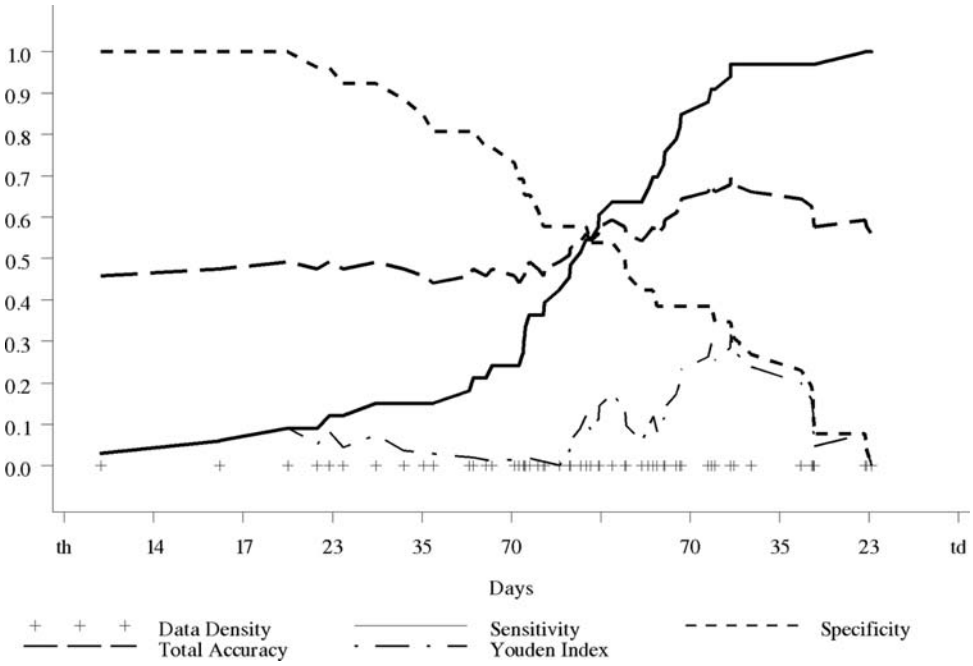


Figure 2. Prediction of clinical response for tumour marker kinetics (slope) during therapy for UGIA. The results of CA19-9 for patients with baseline and at least two values during treatment are presented (n=59). th is the tumour marker half time seen to the left of the x-axis and td is the tumour marker doubling time seen to the right of the x-axis. Note that th or td is infinite in the middle when the slope is zero (no change in marker levels). The sensitivity for a clinical response markedly increases when the th increases above about 70 days to reach almost 100% when the td becomes shorter than about 70 days. Correspondingly, the specificity continuously decreases with longer th's to shorter td's. An increase in marker levels during treatment, i.e. a positive slope gives the highest total accuracy score (about 65% for td's between 50-30 days). The total accuracy for a clinical response is the same (about 50%) irrespective of the th value (corresponding to negative slopes). The same pattern is basically seen for all tumour markers.

Table V. Marker prediction explanation ($R^2$ from a regression analysis) of outcome in per cent for overall survival (OS) and time to tumour progression (TTP).

| | CEA (n=62) (%) | TPA (n=56) (%) | TPS (n=54) (%) | CA72-4 (n=58) (%) | CA19-9 (n=59) (%) | CA242 (n=51) (%) |
|---|---|---|---|---|---|---|
| OS | | | | | | |
| Combined | 22.4 | 17.3 | 19.2 | 3.2 | 42.0 | 44.3 |
| Slope | 3.41[a] | 3.1 | 5.5 | 0.0 | 17.6[a] | 23.5 |
| Baseline | 11.7 | 13.7 | 11.3 | 2.0 | 19.9 | 13.1[b] |
| TTP | | | | | | |
| Combined | 15.1 | 22.7 | 21.8 | 15.8 | 38.2 | 30.6 |
| Slope | 6.3 | 0.2 | 7.8 | 0.5 | 9.6[a] | 26.2 |
| Baseline | 5.0 | 13.3 | 20.9 | 7.9 | 18.7 | 5.5[b] |

[a]Statistically significant difference ($p<0.05$) between the slope and the combined model; [b]between the baseline value and the combined model. For abbreviation of the tumour markers, see Table II and for calculations of the slopes and the combined model, see Table IV. A landmark time of 56 days, excluding two patients with short survival time was used.

CA242 (Table IV). No single cut-off value for the measure of marker slope yielded high sensitivity combined with high specificity (illustrated for CA19-9 in Fig. 2).

It was not possible to identify a negative slope within a clinically interesting range (-0.004 to -0.03, corresponding to decreasing values by >25% at 8 weeks to >90% at 4 weeks) having a significant relation with clinical response for any marker. For TPS, the most marked decreases (slopes -0.04 to -0.06) were seen in a few non-responding patients.

In patients with normal marker levels during the first 2 months, 78-85% had clinical response. PR was seen in 17-33% in those with a level consistently below UNL, except for CEA where it was 44%.

*Changes in tumour marker levels and survival*. In analyses of the relations between marker changes during treatment, restricted to patients with baseline values and at least two follow-up values, the slope used as a continuous variable for

CA19-9 and CA242 explained about 18-24% of the variability in OS [corresponded to HR (95% CI), 1.20 (1.02-1.41) and 1.25 (1.06-1.48), unit % change per day]. CA242 explained 26% of TTP [1.36 (1.12-1.65)] (Table V). When the slope values were divided into quarters, prognostic information for OS was provided only by the quarter with the steepest raising slope [doubling-times <77 days for CA19-9 (HR:Q4 vs. Q1:2.23, 1.05-4.73) and 56 days for CA242 (HR:Q4 vs. Q1:2.37, 1.12-5.02)]. Baseline values of all markers except CA72-4 were predictive of OS and TTP (marginally for CA242 and CEA) (Table V). The predictive value for the combined model was numerically larger than for the baseline value but statistically significantly only for CA242 (p=0.03 for OS and p=0.04 for TTP).

## Discussion

When several serum tumour markers, all previously explored in patients with gastrointestinal cancer, were measured in patients with advanced UGIA, elevated levels were found for at least one in virtually all patients. Not all markers have been analysed in the tumour types investigated here before, but when done, the proportion of patients with elevated levels were in concordance with what has been reported (5-10,13,22-24). No major differences were seen between diagnoses. Since patients with CRC frequently also have elevated levels of these markers (12,15,25,26), it is concluded that none of them are sufficiently specific for either of the GI-cancers. Thus, none of them can sufficiently discriminate between the different gastrointestinal cancers, e.g. when searching for the primary cancer in a metastatic setting.

The baseline levels of most markers, whether analyzed dichotomised or continuously provided prognostic information on survival and response. Again, similar findings have been reported in a few studies (13,22). This information can be used clinically, e.g. when the patients are informed about future outcome and for stratification in trials, but there is no consensus, except for CA19-9 in PC, about which marker that is recommended for routine use. The performance of CA19-9 in PC was, however, not better than in GC or BC (data not shown), although the small number of patients preclude firm conclusions. In a multivariate analysis, performance status gave the strongest prognostic value for OS, although TPA gave additional information. CA72-4 provided no prognostic information, and since it performed poorly also in a study of CRC patients (27), it is not valuable as a gastrointestinal cancer marker.

Whether the baseline level of either of the markers should have an impact on the decision to start palliative chemotherapy or choose between regimens have been much debated. In CRC, the levels of some of the markers used here, particularly TPS, provide prognostic information, but it was not possible to detect a level that influenced the treatment decision (28). This was also supported from the present study, i.e. we could not define a clinically useful level above which there was no or very low chance of response.

Elevated baseline marker levels provided prognostic information, and early significant changes (>50-90% decreases and >100% increases) were frequently seen. Thus, the possibility for the tumour markers to provide clinically important information based on early changes seemed strong. However, we consider the information provided by the changes (the slope) during the first two months too low to recommend them for routine use to assess chemotherapy efficacy. The slope did not significantly increase the prognostic or predictive value of the baseline values for any marker but CA242. Very high sensitivities for clinical response were found, but only when the increase was not pronounced (slope >0.01). The overall accuracy did not appreciably change when different levels of decrease (slope <-0.005 to <-0.03) were explored. Thus, tumour marker changes during the first two months of treatment do not provide sufficiently reliable information to guide treatment decisions. When this has been studied before, using CA19-9 in PC, the conclusion was the same (11-13), although small studies had indicated a clinical value (5-10). Using CEA in CRC, the same overall conclusion was made in the ASCO recommendations (12). The recommendations state that 'when tumour imaging is not possible, tumour marker changes can at least provide some clinically useful information'. In UGIA, we question this use within the first two months after treatment initiation. Due to the design, we can not exclude that measurements beyond two months of treatment could provide more useful information. In a pooled analysis of 3 studies in PC, where decreases by >50% or >89% of CA19-9 predicted survival (10), the median time to nadir was 3 months. An initial surge, i.e. an increase in marker levels by more than 20% after a few cycles followed by a decrease by more than 20% in clinically responding patients, has been reported in CRC (29) and GC (24). When examining each patient in detail, we could see this in one or two patients for most markers (data not shown), but this phenomenon (30) could not explain the poor performance of repeated marker measurements early during therapy.

In conclusion, baseline tumour marker levels in upper UGIA provide prognostic information on the outcome and efficacy of sequential combination chemotherapy. Although markedly increasing levels indicated lower possibilities to respond, early, repeated measurements of tumour markers were not useful to provide accurate information for tumour response and survival. When further exploring the concept of planned sequential combination chemotherapy in UGIA, we decided to change the regimen to only after two months of treatment when a radiological evaluation had been done.

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