Dynamics of Serum Levels of Tumour Markers and Prognosis of Recurrence and Survival after Liver Surgery for Colorectal Liver Metastases

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Abstract. *Background: The authors present a statistical analysis of the dynamics of tumour markers and compare these with single serum levels in patients before and after liver surgery for colorectal liver metastases (CLM). Patients and Methods: The serum levels of tumor markers conventionally used in clinical practice (CA19-9, CEA, CA72-4) and markers informing of the proliferation activity of malignancy (TK, TPA, TPS) were statistically analysed. The authors studied 144 patients who underwent liver surgery for colorectal liver metastases between September 1999 and June 2005. Serum levels of tumor markers before surgery (maximally two weeks before the operation), after surgery (maximally one month after the operation – usually on the day of dismission), six months (± one month) and twelve months after the surgery (± one month) were determined. The Log Rank test and the Wilcoxon test were used for statistical evaluation. The survival rate and disease-free intervals (DFI) were computed using the Kaplan-Meier method. Results: The statistical analysis of tumour marker dynamic after liver surgery (speed and power of recurrence) supported the dynamics of CA 19-9 and CEA as excellent prognostic factors of early recurrence of CLM in contrast to proliferative tumor markers. Conclusion: The results of the study suggest the importance of tumour markers for the prediction of a short survival rate or DFI. This approach would be very helpful for the planning of palliative oncological treatment for patients with liver malignancies that cannot be treated by surgical therapy. Current patients with a high tendency of recurrence of CLM after liver surgery should be followed up more thoroughly to increase the possibility of successful reoperation.*

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The radical resectability of colorectal liver metastases (CLM) is only about 15% and this proportion is further decreased after radical surgical therapy by early recurrence of the metastatic process (1) that is rarely identified in time. It is a fact that repeated liver resections for CLM are associated with as goog a survival rate as single resections, hence it is important, that prompt diagnosis of early liver metastases recurrence is made. One way to distinguish patients with a tendency for early recurrence is the use of tumour markers. Under early recurrence of malignancy, relapse after radical surgical therapy can be determined by following tumour marker levels earlier than supposed from the statistical time difference between radical and paliative therapy. This means that patients are burdened with operations without any distinct survival benefit.

Tumor markers should not only be used as static prognostic levels with many single serum levels and any level of cut-off, but their dynamics should also be studied in order to understand their physiological or pathological role in the disease process. Patients with a tendency for a short disease-free interval (DFI) could then be identified swiftly, improving their prognosis and helping in the development of appropriate follow-up strategies. Routine tumour markers (CEA, CA19-9, CA72-4) and proliferative tumour markers (TK, TPS, TPA) are commonly expressed not only by the primary tumour mass but also in metastatic tissues (2, 3). In previous studies, the importance of the statistical analysis of these tumour markers was demonstrated for a predictive prognosis of disease, mainly for the prediction of relapse of malignancy during the follow-up period. Proliferative tumour markers express the proliferative activity of a tumour and can reflect the aggressiveness of a tumour. The serum level of conventional tumour markers, however, depends on tumour mass (4, 5).

Some scoring systems for prediction of early recurrence of the CLM process after surgical therapy use tumour markers as one of the predictive factors (6-8). The tumour

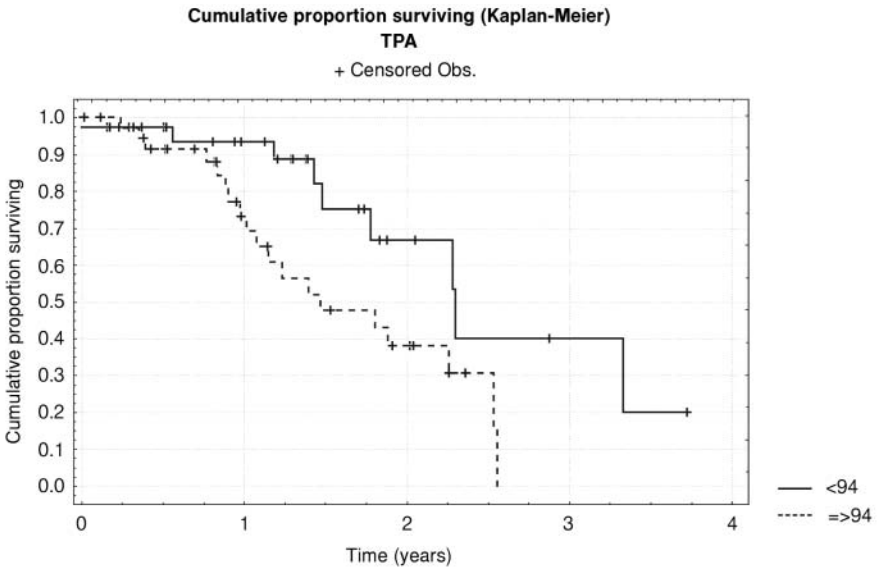

Figure 1. *Overall survival using the preoperative serum level of TPA as a prognostic factor of survival rate after surgery for colorectal liver metastases (cut-off 94 IU/L).*

marker most often used is CEA (9). The authors present a statistical analysis of the dynamics of tumour markers and compare them with single serum levels in patients after liver surgery for colorectal liver metastases

Patients and Methods

One hundred and forty-four 144 patients, who underwent radical surgical therapy for colorectal liver metastases between September 1999 and November 2005 were retrospectively included into this study. From this group patients were chosen, from whom marker serum levels were acquired during a postoperative period of one year: *i.e.* 82 patients with CLM who were operated on between September 1999 and June 2005. The purpose was to study the dynamics of tumour markers after radical surgery and determine any association with survival rate and the disease-free interval. The serum levels of routine tumour markers (CEA, CA 19-9, CA 72-4) and proliferative tumour markers (TPS, TPA, TK) were determined from blood samples collected before the operation (maximum two weeks before the operation), after the operation (maximum one month after the operation – usually on the day of release), and six (±1 month) and twelve months after the operation (±1 month). In the dynamics study the ratios of preoperative (D 14-0) and postoperative (I. D1-30, II. after 6±1 month, III. after 12±1 month) serum levels of the named tumour markers were compared. All the time deviations were taken into account during the statistical analyses.

The tumor markers were monitored using the following immunoanalytical methods: carcinoembryonic antigen (CEA): IRMA (immuno-radiometric assay), Immunotech, Czech Republic (ng/mL); carbohydrate antigen (CA 19-9): Shering-CIS, France (kIU/L); carbohydrate antigen (CA 72-4): IRMA, Shering-CIS, France (kIU/L); tissue polypeptide antigen (TPA): IRMA, DIASORIN (kIU/L); tissue specific polypeptide antigen (TPS): IRMA, IDL, Sweden (kIU/L); thymidine kinase (TK): REA, Immunotech (kIU/L).

The statistical analysis of both cohorts of patients was processed using S.A.S. version 8.02 (Statistical Analysis Software, Inc.) using Kaplan-Maier curves. The statistical significance was determined using the Log-rank and the Wilcoxon tests. The cut-off of tumour markers was estimated using the quartile system.

Results

The survival rate for patients after radical surgical therapy of CLM was found to be dependent on the preoperative serum level of the proliferative tumour markers TPS and TPA ($p<0.05$) and the classical tumour markers CA19-9 and CA72-4 ($p<0.05$) (Figures 1 and 2). The survival rate was dependent on the postoperative (day 1-30) serum level of TPA and CEA (both $p<0.05$). The DFI in the same group was found to be dependent on the prepoperative serum level of the proliferative tumour marker TPS and CA72-4 (both $p<0.05$). The DFI was also dependent on the postoperative serum level (day 1-30) of CEA (p-value <0.05). Postoperative serum levels of tumour markers can be influenced by the half-life of the serum tumour marker (10). The statistical analysis of repeated serum levels of named tumour markers demonstarted that the ratio of preoperative and postoperative serum levels of CA19-9 and CEA were statistically significant for the prediction of early recurrence ($p<0.05$). The dynamics study (again increased or decreased serum level) showed that dynamic changes of CA19-9 and CEA were excellent prognostic factors of the DFI of CLM in contrast to the proliferative tumour markers (Figure 3). The statistical analysis did not demonstrate proliferative tumour markers as prognostic factors for early recurrence. The

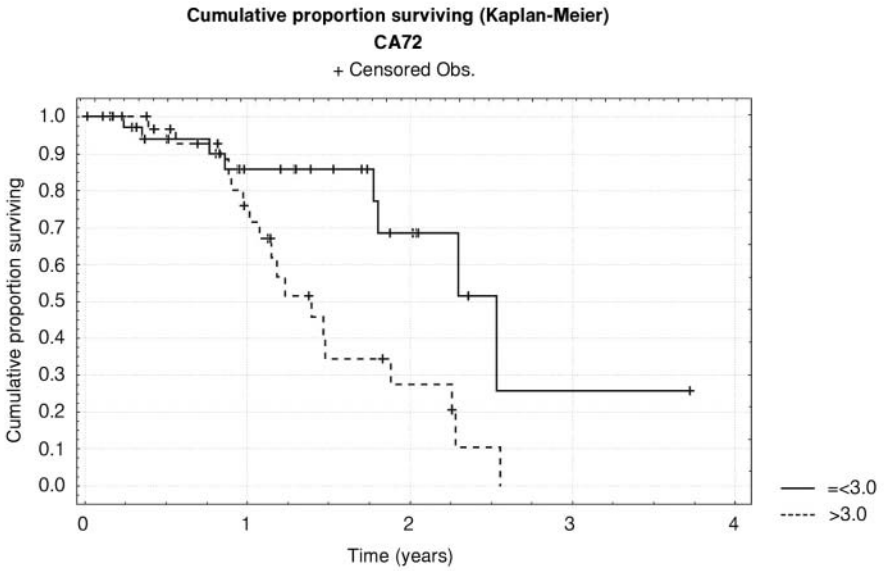

Figure 2. *Overall survival using the preoperative serum level of CA72-4 as a prognostic factor of survival rate after surgery for colorectal liver metastases (cut-off 3.0 IU/L).*

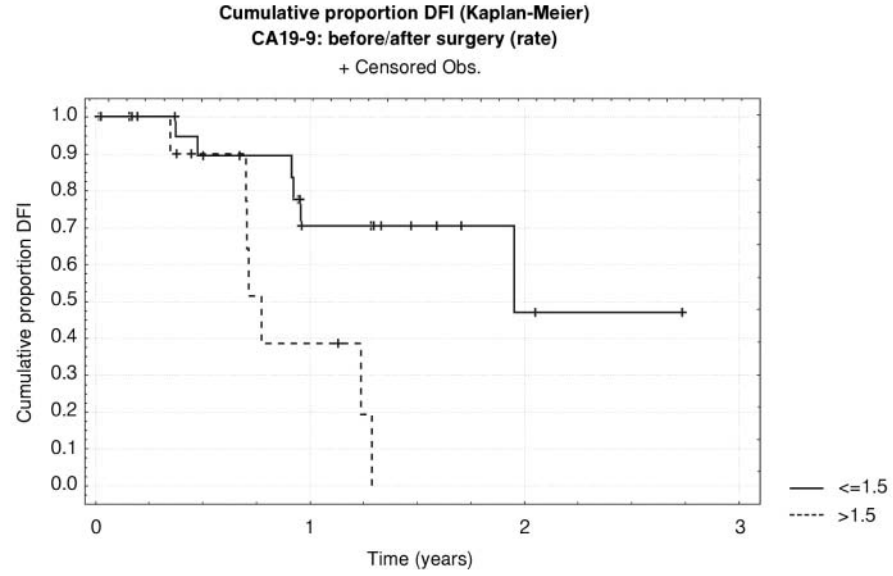

Figure 3. *The disease-free interval using the ratio of the preoperative and postoperative serum levels of CA19-9 as a prognostic factor of early recurrence after surgery for CLM (cut-off 1.5).*

statistical analysis of the ratio of preoperative and late (6 and 12 months) postoperative serum levels of both groups of tumour markers were not statistically significant for the prediction of the DFI or survival rate.

Discussion

The survival rate of patients with surgically untreated malignancy of the liver depends on tumour mass and whether the liver parenchyma is affected by malignancy. The survival rate and DFI of patients after surgery for CLM also depend on the preoperative tumour mass and the proliferative activity of the tumour. Early postoperative levels of tumour markers in patients who underwent surgery for CLM were not so important for the prediction of recurrence or survival. The dynamics (increase) of the serum level of classical tumour markers has been shown here to be a prognostic factor for the early recurrence of CLM after surgery. The dynamics of proliferative tumour markers has not been shown as a prognostic factor of early recurrence. The postoperative serum

levels found in the early postoperative period (maximum 30 days after operation) may have been distorted by the longer half life of tumour markers. During the postoperative period, the regeneration and hypertrophy of liver parenchyma commences as a consequence of surgical resection and the necessity for compensation of the parenchymal functional capacity. This process is realised through proliferation. Some of the named proliferative tumour markers are involved in this proliferation process. We did not find any statistically significant changes in serum levels of the proliferative tumour markers in the perioperative period that could reflect the behaviour of CLM after radical surgical therapy.

The question of the significance of the ratio of preoperative and late postoperative serum levels of tumour markers for the prediction of early recurrence remains partially unanswered. This may have been influenced by the small fraction of patients with early recurrence in our patients' cohort or it was not possible to distinguish between early and late recurrence.The use of tumour markers for the prediction of survival rate or the DFI of patients with CLM in clinical practice should be influenced by the actual clinical situation and individual patient history (11-13). Recognition of the clinical situation for which the tumour markers are assessed is crucial for the validity of the results and to enable patients to profit from tumour marker measurement. The interpretation of tumour markers depends on the art of processing, which should be chosen with regard to "the clinical question asked" (14). Understanding the behaviour of tumour markers during the follow up period after surgery for liver malignancy is the most important factor in selecting the follow up strategy. Tumour markers could be used safely as prognostic factors in extended follow-up guidelines for patients with an increased risk ratio of early recurrence of CLM. Their clinical relevance will make it possible to increase the number of timely detected recurrences and the number of repeated resections, and this will increase the overall survival rate in CLM.

Conclusion

In this study, we demonstrated that the preoperative serum level of the proliferative tumour markers TPS, TPA and the conventional tumour markers CA19-9, CA72-4 was as statistically significant for the prediction of the survival rate. The DFI was dependent on the prepoperative serum level of the proliferative TPS and CA72-4. The statistical analysis of repeated serum levels of named tumour markers demonstrated the ratio of preoperative to postoperative serum levels of CA19-9 and CEA as statistically significant for the prediction of early recurrence. We could use these facts to improve our follow-up guidelines to achieve early detection of recurrence. This could raise the number of patients who, with repeated surgical therapy, could achieve the same survival rate as patients having had a single surgical operation.

Acknowledgements

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