Tumor Markers as Useful Predictors of Survival Rate after Exploratory Laparotomy for Liver Malignancies

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Abstract. Background: Tumor markers are used for the prediction of relapse and in determining the effect of postoperative or post-oncological therapy as a standard component of follow-up. Metastatic processes of the liver and primary malignancies of the liver and gall bladder are very common in the European population. The aim of this study was to demonstrate the behaviour of malignancy in patients who have not undergone surgical therapy and to study serum levels of the monitored tumor markers in relation to the life expectancy of these patients. Patients and Methods: The Log-rank test and Wilcoxon test were used for statistical evaluation. Survival was computed using the Kaplan-Meier method. Serum levels of the tumor markers conventionally used in clinical practice in patients with gastrointestinal tumors (CEA, CA19-9, C724) and the markers of the proliferation activity in malignancy (TK, TPA, TPS) were studied. Results: One hundred and nine patients who underwent exploratory laparotomy without any surgical therapy between September 1999 and June 2005 were studied. For patients with a serum level of CEA, CA19-9 and CA72-4 that was higher than the calculated cut-off, hazard ratios of early death were respectively 3-, 5- and 9-fold higher than for patients with serum levels of the same tumor markers below the calculated cut-off. Preoperative serum levels of proliferative tumor markers (TK, TPA and TPS) were not statistically significant for the prediction of early death. Conclusion: The results of the pilot study suggest the importance of tumor markers for the prediction of the short-term survival rate. These markers could be used to supplement classic clinical, laboratory and radiodiagnostic parameters. It would be very helpful for the planning of palliative oncological therapy for patients with liver malignancies who cannot be treated by surgical therapy.

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Key Words: Liver malignancy, exploratory laparotomy, prediction, tumor markers.
The Log-rank and Wilcoxon tests for statistical evaluation (S.A.S., Statistical Analysis Software, release 8.02) were used. The survival period was computed using survival analysis with the Kaplan-Meier method (Figure 1).

For the tumor marker assessment, venous blood from the cubital vein was sampled under standard conditions between 7 and 9 a.m. The serum acquired through centrifugation was stored at a temperature of –20°C until laboratory analysis. Tumor markers were assessed using commercial laboratory kits in accordance with the manufacturers’ recommendations. The following tumor markers were assessed: carcinoembryonic antigen (CEA; IRMA, Immunotech, Czech Republic), carbohydrate antigens CA 19-9 and CA 72-4 (IRMA, CIS Bio International, France), TPA (IRMA, Diasorin, Italy), TPS (IRMA, IDL, Sweden).

Cut-off values were defined first as the median of the presented tumor marker level in the cohort being studied and subsequently optimal cut-off values were calculated for particular tumor markers, where the maximal difference in survival period between the compared cohorts was achieved. For calculation of the optimal cut-off we used the Cox regression model.

Results

For the statistical analysis of CA 19-9 the preoperative serum level of 52 patients was used. The serum level of CA19-9 with an estimated cut-off of 56.7 IU/L (median of serum levels) was not statistically significant. Using the Cox regression model, we calculated an optimal cut-off at 420 IU/L ($p<0.01$, Figure 2). For the statistical analysis of CA72-4, the preoperative serum level of 42 patients was obtained. The estimated cut-off of 3.1 IU/L (median of serum levels) was not statistically significant. For the serum level of CA72-4, a cut-off of 12 IU/L ($p<0.01$, Figure 3) was calculated as statistically significant. The estimated cut-off of 3.1 IU/L was not proved. For the statistical analysis of CEA, the preoperative serum levels of 38 patients were used. A serum level of CEA higher than the estimated cut-off (9.2 ng/mL, median of serum levels) was not statistically significant whilst that above calculated cut-off of 9.5 ng/mL was statistically significant ($p<0.05$, Figure 4). For patients with a serum level of CEA, CA19-9, or CA72-4 higher than the respective calculated cut-off, the hazard ratio of early death was 3-, 5- and 9-fold higher respectively than for patients with a serum level of the same tumor markers below the calculated cut-off.

Preoperative serum levels of the proliferative tumor markers (TK, TPA and TPS) were not statistically significant for the prediction of early death. For statistical analysis, the serum levels of 42, 42 and 43 patients, respectively, were accepted. The estimated cut-off, as the median of serum levels, was not statistically significant (9.75, 150.5, 190 IU/L, $p<0.05$ for all). The Cox regression model did not show any other statistical significance for the preoperative serum levels of the proliferative tumor markers that we studied.

Discussion

Although surgery is the most effective therapeutic method in patients with a tumor disease of the gastrointestinal tract, the surgery is very often performed at a stage when the tumor is
Figure 2. Survival rate dependence upon calculated cut-off of CA19-9 (420 IU/L).

Figure 3. Survival rate dependence upon calculated cut-off of CA72-4 (12 IU/L).
inoperable and only exploratory laparotomy is possible. Up
to one third of patients are at an inoperable stage at the time
of surgery (4). In these patients, there is another variant of
oncological treatment, most often palliative chemotherapy
(5). The main aims of chemotherapy in patients with an
advanced tumor disease are to prolong survival, control
symptoms and to improve their quality of life (6). It is,
however, necessary to be able to give at least an approximate
prognosis for the patient in order to permit the optimal
choice of chemotherapy. In inoperable tumors, the
possibilities are very limited. We can proceed from the
advance of the tumor disease, histological verification of the
tumor (if such has been performed) and the patient’s status
performance (7). In order to make the prognosis more
accurate, it is necessary to look for other prognostic factors.

The use of tumor markers seems to be appropriate. The
prognostic relevance of tumor markers has often been
described (8-10). However, this refers mostly to primary
surgery, when a tumor is completely removed, in relation to
asymptomatic and overall survival. Second-look surgery based
solely on a rising CEA level has been recommended by
several investigators (8). In more than 90% of these patients,
a residual tumor has been found, but this was resectable in
only 7-43% of the patients. The problem of using CEA in
second-look surgery is the time that elapses between the
observation of the rising CEA titres and the decision to
proceed with surgery (8, 10). Nevertheless CEA can be a
prognostic indicator. Several studies have demonstrated that
gastrointestinal tract cancer patients with high preoperative
levels of CEA have a worse prognosis than those with low
levels (9, 10). Furthermore, in many of these reports the
prognostic impact of CEA was found to be independent of
the traditional staging systems (11). After CEA, CA 19-9 is
the most widely investigated gastrointestinal (GIT) tumor
marker. The preoperative levels of CA 19-9 may also provide
independent prognostic information, especially in patients
with colorectal carcinoma (10, 12). CA 72-4 tumor marker
has, with the exception of stomach carcinoma, a smaller
prognostic significance than CEA and CA 19-9 (9, 13). TPA,
which measures fragments of cytokeratin 8, 18 and 19, and
TPS, which detects fragments of cytokeratin 18, have also
been subjected to only limited evaluation in GIT cancers.
Because of the lack of sensitivity and specificity, neither TPA
nor TPS can be recommended for the detection of GIT
cancers. In some studies it has been shown that high levels of
cytokeratins were associated with aggressive disease and poor
prognosis, but cytokeratins did not provide independent
prognostic information (3, 9, 13).

Figure 4. Survival rate dependence upon calculated cut-off of CEA (9.5 ng/mL).
The results of our pilot study suggest the importance of tumor markers for prediction of the short-term survival rate of patients who have undergone exploratory laparotomy because of an inoperable GIT tumor. We can conclude that we can use the classic tumor markers (CEA, CA19-9, CA72-4) as a suitable supplement to classic clinical, laboratory and radiodiagnostic parameters. It could be very helpful in the planning of palliative oncological therapy for patients with liver malignancies which cannot be operated on. We did not show any correlation between early death and increased proliferative activity of liver malignancy in the preoperative period. We suppose that the prognosis of patients with an inoperable liver malignancy is more dependent upon the advanced stage of the disease than upon the proliferative activity of malignant cells.

Acknowledgements


References


Received June 19, 2006
Revised January 3, 2007
Accepted January 22, 2007