23

Prognostic Significance of CEA Levels in Hepatic Resection for Metastatic Colorectal Cancer

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Objective: Carcinoembryonic antigen (CEA) level is amongst the many prognostic factors affecting hepatic resection for colorectal cancer metastases. To determine the prognostic significance of pre-operative CEA levels and post-operative drop of CEA values, we studied 115 out of 229 consecutive liver resection patients in our prospective database who underwent hepatic resections for colorectal cancer metastases. Methods: All data were recorded prospectively. Of the 115 patients in the study, 81 patients had both pre-operative and post-op CEA levels measured. In addition, we also correlated CEA values to other known prognostic factors of survival using both univariate and multivariate analyses. These factors include Dukes staging, margins of resection, R0/R1/R2 resection, presence of extra-hepatic disease, intra-operative blood loss, use of auto-transfusion, number of lesions, DNA index, tumor differentiation, and intra-arterial chemotherapy. Results: Pre-operative CEA values ranged from 1 to 4,000 ug/L. Post-operative CEA values ranged from 0 to 180 ug/L. We divided patients into two groups based on pre-operative CEA levels of < 10 ug/L vs. ± 10 ug/L. Mean survival was significantly better in the group with pre-op CEA < 10. We also divided patients into two groups based on lowest post-operative CEA levels within the first 4 weeks of < 5 ug/L vs. ≥ 5 ug/L. Again, the mean survival was significantly better in the group with lower post-operative CEA levels (Table).

	Survival (mo)	Mean Survival (mo)	p value
Pre-op CEA <10	0.23–106	36.9	<0.05
Pre-op CEA ≥10	0–173	23.3	<0.05
Post-op CEA <5	0.2–173	45.1	<0.001
Post-op CEA ≥5	7.37–41.2	25.8	<0.001

To ascertain that other common prognostic factors as mentioned in Methods did not skew the observed results, we found that these factors were equally distributed among the four groups of patients divided according to CEA levels. Drop of CEA levels was observed from post-operative day 1 to week 4, but the nadir of CEA levels was observed between week 3 to week 4 after the surgery. In order to see the importance of other known prognostic factors in post-operative survival, we correlated them with survival time and did not find any stastically significant difference in survival on univariate analysis. However, on multivariate analysis of groups of prognostic factors, viz., early Dukes stage, R0 resection, absence of extra-hepatic disease, and a segmentectomy were statistically correlated with a better survival. Conclusion: Pre-operative and post-operative CEA levels are important prognostic factors in hepatic resection for metastatic colorectal CA. The ideal time for measuring post-operative CEA level is during post-operative week 3 to week 4 when the level is at its nadir.

24

Correlation of Molecular Markers and Echogenicity in Colorectal Cancer Liver Metastases

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Differences in the echogenicity of colorectal cancer liver metastases (CRCLM) have been shown to be prognostic both after curative resection and after i.a. chemotherapy. Molecular impact of different markers on hypo- or hyperechoic appearance defined during intraoperative ultrasound has been studied immunhistochemically using tumor samples. Standard immunohistochemical techniques were used to stain sections of 67 patients CRCLM for Ki-67, Laminin-5, MMP-9, VEGF, MUC-2, CD3, CD31 and CA19-9. 26 CRCLM with hypoechoic and 41 CRCLM with hyperechoic appearance were analyzed. All patients had undergone curative resection. Uni-, multivariate and survival analyses were performed using SPSS 10.0 for Windows. Mucin staining was identified significantly more often in patients with hypoechoic CRCLM compared to hyperechoic CRCLM (84% vs 44%, $P = .004$). There was a significant overall survival difference between hypoechoic CRCLM patients (med. survival 19.5 months) and hyperechoic ones (41.1 months, $P < .002$) after a mean follow-up of 37 months. Recurrence-free survival was also significantly different (8.8 vs 23.0 months, $P < .001$). In regards to the above mentioned investigated markers a significant correlation with hypoechoic appearance of CRCLM was identified for laminin-5 ($P < .05$), CA 19-9 ($P < .01$) and mucin ($P < .001$). Mucin expression was a significant survival predictor ($P < .05$) irrespective of echogenicity. Cox regression analysis revealed echogenicity ($P = .005$) and mucin ($P = .03$) independently influencing survival in this patients group. Echogenicity seems to be consistently related to mucin content of CRCLM. Patients with hypoechoic CRCLM and thus high mucin expression have a worse prognosis. Tissue remodeling markers and factors involved in neoangiogenesis are not influencing echogenicity. A possible role of chemoresistance to 5-fluorouracil based chemotherapy in mucin producing tumors has to be further explored.

25

Incidence of Liver Metastases in Patients Receiving Adjuvant Chemotherapy After Lymph Node Positive Primary Colon Cancer

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The incidence of liver metastases during follow-up of colon cancer patients under current adjuvant chemotherapeutic protocols following primary tumor resection is essentially unknown. We prospectively documented the incidence of colon cancer liver metastases (CCLM) in an adjuvant clinical trial of lymph node positive colon cancer patients (Studie 90, ABCSG). 598 Dukes C colon cancer patients were randomized to receive one of four treatment regimes after curative colon cancer resection: 5-FU, 5-FU+Levamisol, 5-FU+Interferon-a, 5-FU+Levamisol+IFN-a. Patients were equally distributed among the four treatment groups. Uni- and multivariate analysis of possible risk factors for the development of liver metastases was performed. The Kaplan-Meier method was used for survival analysis. After a median follow-up of 57 months 146 patients (25%) had died. Median overall survival has not been reached, 1-, 3- and 5 year survival were 94%, 84% and 74% respectively. There were 10% T1, T2 tumors, 74% T3 and 16% T4 tumors; 56% patients were N1 positive, 29% N2 and 15% had N3 lymph nodes involved. 69% were well or moderately differentiated, 31% had G3 or G4 tumors. 34% had right sided, 66% left sided colon cancer. Liver metastases were the most frequent recurrence site, in total 94 patients or 15.7%, 29 patients developed local recurrence, 20 patients lung metastases. 46% of the patients with liver metastases underwent surgical resection. Tumor stage significantly influenced the occurrence of liver metastases in uni- and multivariate analysis ($P = .003$). There was no difference in regards to different treatment groups. Treatment strategy of patients developing liver metastases had a significant impact on survival with liver resection prolonging survival most (median 32 months vs 10 months after other treatments, $P < .0001$). Liver resection remains the treatment modality with the most promising overall survival, if patients develop liver metastases during follow-up of colon cancer. Current adjuvant chemotherapeutic approaches seem to reduce the occurrence of liver metastases compared to untreated historical controls. Regular study monitored follow-up of colon cancer patients enable early detection of liver metastases allowing a high percentage of resectabilty.