Adjuvant Radiochemotherapy of Stage II and III Rectal Adenocarcinoma: Role of CEA and CA 19-9

CHRISTIAN WEISSENBERGER1, GEORG VON PLEHN1, FLORIAN OTTO2, ANNETTE BARKE1, FELIX MOMM1 and MICHAEL GEISSLER3

1Department of Radiology, Division of Radiotherapy,
2Department of Internal Medicine I, Division of Oncology,
and 3Department of Internal Medicine II,
Division of Gastroenterology University Hospital of Freiburg, Freiburg, Germany

Abstract. Background: This analysis was undertaken to evaluate the impact of pre-radiotherapy CEA and CA 19-9 values on clinical outcome of locally advanced rectal cancer. Patients and Methods: Retrospective data were collected from patients (n=203) with UICC stage II and III rectal adenocarcinomas, who underwent low anterior or abdominoperineal resection and received post-operative or pre-operative radiochemotherapy from January 1989 until July 2002. The rates of survival and distant and local recurrences were evaluated using Kaplan-Meier survival analysis, Log-rank test and Cox's proportional hazards (median follow-up 8 years). Multivariate analysis was used to assess the prognostic value of CEA and CA 19-9. Results: The 5-year actuarial rates for patients with normal (n=118) and elevated (n=88) CEA values were as follows: overall survival 62.4% and 32.0% (p<0.001), local control 73.5% and 55.0% (p=0.007), and absence of distant metastasis 83.3% and 88.0% (n.s.), respectively. Similar results were obtained for patients with normal (n=82) and elevated (n=10) CA 19-9 values: overall survival 60.7% and 14.0% (p=0.007), local control 83.7% and 80.0% (n.s.), and absence of distant metastasis 64.9% and 75.0% (n.s.), respectively. After adjustment for TNM stage, sex, age, LDH, tumor site and grading, the elevation of CEA proved to be an independent prognostic factor for overall survival (relative risk of 1.01 per ng/ml, CI 1.002 – 1.01; p=0.005). Conclusion: This study confirmed the prognostic value of pre-radiotherapy CEA and CA 19-9 in patients with stage II or III rectal carcinoma.

An improved therapeutic strategy for stage II and III rectal adenocarcinomas is urgently needed because up to 30% of patients still develop recurrent disease after curative surgical resection (1). Several studies are ongoing, aiming at the evaluation of new multimodality treatment strategies (2). Recent results have raised the question of whether the current “monolithic approaches” (3) or new risk-adapted strategies should prevail in future. Thus, in future, decision-making will need more accurate data about individual risk of tumor relapse, preferably obtained by non-invasive methods or routine laboratory diagnostics.

Several functions have been attributed to CEA (oncofetal glycoprotein antigen): involvement in cell adhesion, inhibition of cell death induced by loss of anchorage to the extracellular matrix, and cooperation in cellular transformation with proto-oncogenes like Bcl2 and C-Myc (4). CEA is present in embryonic tissues and certain epithelial malignancies. Progressive elevation of CEA may indicate tumor recurrence 1 – 3 years before clinical evidence of metastases. Local recurrences are accompanied by a small rise of CEA, hepatic metastasis by a large rise. CEA has been shown to be the most cost-effective approach to detect potentially resectable metastases from colon cancer (5).

With the long-term outcome in mind, our study aimed to evaluate the impact of increased levels of CEA and CA 19-9 in the combined-modality treatment for stage II and III rectal carcinoma, performed during the past 14 years at the Department of Radiotherapy, University Hospital of Freiburg, Germany.

Patients and Methods

Inclusion and exclusion criteria. Male or female patients between 20 and 90 years, with histologically confirmed rectal adenocarcinoma scheduled for conventional radiotherapy of the pelvic region (6 / 18 MeV linear accelerator) in the adjuvant or neoadjuvant setting, were included in this study. Exclusion criteria were: heavy smoking
Patients with metastatic or recurrent tumors were not included. Pre-treatment evaluation included complete blood test, chemistry profile, chest radiography, liver ultrasonography and computer tomography (CT) of the abdomen and pelvis. Blood samples for estimation of tumor markers were collected prior to radiotherapy, at three-monthly intervals for two years afterwards, and at six-monthly intervals for five years afterwards. CEA and CA 19-9 were defined as "elevated" if they exceeded 3 ng/ml and 60 U/ml, respectively (6). For smokers the same cut-off value for CEA was taken.

Regarding surgical intervention, patients treated by low anterior resection (LAR) or by abdominoperineal resection (APR) were eligible. Patients who were defined as "radically resected" (proximal and distal surgical margins were microscopically free of tumor, R0) were scheduled for 6 cycles of chemotherapy according to the NIH protocol: bolus application of 500 mg/m² 5-FU for 3 days during cycles 1-3 and for 5 days during cycles 4-6. In contrast, patients with microscopic or macroscopic residual tumors received continuous infusion over 24 hours for 14 days: 350 mg/m² 5-FU i.v. Additionally, bolus applications of 200 mg/m² leucovorin and 4 mg/m² mitomycin C were given daily.

Statistical methods. Kaplan-Meier curves (7) were used to estimate the distribution of overall survival (OAS). For analysis adjusting the rates of treatment failures, local-relapse-free survival (LRS) and distant-relapse-free survival (DRS) were determined as life-table analysis referring to freedom of locoregional relapse and freedom of distant metastases. Log-rank tests (Cox-Mantel) were used to compare the survival distributions between different patient subgroups (8). The influence of CEA and CA 19-9 was studied by Cox's proportional-hazard regression analysis (9).

Results

Patient data. Complete data about CEA were available for 132 men and 71 women with stage II or III tumors treated with pre- or post-operative adjuvant radiochemotherapy (between January 1989 and July 2002). These 203 patients were enrolled in the study. Ages ranged from 34 to 83 years old (median 60 years). The distribution of stages is shown in Table I. One hundred and sixty-six (81.8%) and 37 (18.2%) patients were treated by post-operative radiochemotherapy and pre-operative radiochemotherapy, respectively. The radiotherapy courses included a total dose of 45 - 56 Gy in 25 - 31 sessions using 6 and 18 MeV linear accelerators. Survival data and CEA values were available for all 203 patients but only 92 patients had documented CA 19-9 values.
Figure 1. Kaplan-Meier analysis of overall survival.

Figure 2. Survival curves for normal and elevated levels of CEA.
Tumor markers CEA and CA 19-9. According to the inclusion criteria, pre-radiotherapy CEA values were available for all patients (Table III). 118 (58.1%) patients showed normal levels of CEA (<3 ng/ml) whereas 85 (41.9%) patients showed elevated levels of CEA (≥3 ng/ml). The 5-year overall survival rate (Figure 2) was significantly lower if CEA was elevated (32.0% versus 62.4%). Median survival decreased from 9.8 to 3.1 years, if CEA was elevated (Hazard ratio 2.4, CI 1.7 – 3.8; \( p < 0.001 \)). Similarly, the local control decreased from 73.5% to 55.0%, if CEA was elevated, whereas the rate of distant metastases was not significantly different.

Eighty-two (89.1%) patients showed normal levels of pre-radiotherapy CA 19-9 (<60 U/ml), whereas 10 (10.9%) patients showed elevated levels of CA 19-9 (≥60 U/ml). CA 19-9 data were missing for 111 patients. Similarly to CEA, elevated levels of CA 19-9 (Figure 3) were associated with a significantly lower 5-year overall survival rate (14.0% versus 60.7%) and median survival (2.6 vs. 6.1 years, Hazard ratio 3.0, CI 1.6 – 19.1; \( p < 0.001 \)) compared to normal CA 19-9 levels, but not with the rates of local control or distant metastases.

As potential prognostic factors, age, sex, stage, CEA, LDH, localization of tumor and grading were tested in a multivariate model. CEA (relative risk [RR] 1.01 per ng/ml, Table III. Patient characteristics (Chi-square test).

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<tr>
<th>Increase of CEA</th>
<th>Increase of CA 19-9</th>
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<td>(85/203 tumors)</td>
<td>(10/92 tumors)</td>
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<td>39</td>
<td>45.9%</td>
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<tr>
<td>&gt;Median age of 60</td>
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<td>54.1%</td>
<td>5</td>
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<td>Stage</td>
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<td>20</td>
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<td>III</td>
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<td>76.5%</td>
<td>8</td>
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<td>Tumor localization</td>
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<td>33</td>
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Figure 3. Survival curves for normal and elevated levels of CA 19-9.
CI 1.00 – 1.02; \( p=0.04 \), age (relative risk [RR] 1.03 per year, CI 1.00 – 1.05; \( p=0.02 \)) and, as a trend, stage (II vs. III, relative risk [RR] 0.78, CI 0.58 – 1.02; \( p=0.06 \)) turned out to be independent prognostic factors for overall survival.

Using the Chi-square test, we searched for potential associations between increase of CEA and CA 19-9 and age, stage, treatment (pre- or post-operative radiochemotherapy), grading and tumor localization (Table III). Significant associations with CEA increase were found for stage (II vs. III: 23.5% vs. 76.5%, respectively) and treatment (post-operative vs. pre-operative radiochemotherapy: 75.3% vs. 24.7%). Using a patient cohort of smokers of less than 40 cigarettes per day, no correlation between CEA levels and smoking was seen. Further, treatment (post-operative vs. pre-operative radiochemotherapy) was significantly correlated with an increase of CA 19-9. However, the sample size was low as only 10 patients showed elevated levels of CA 19-9.

**Discussion**

Prognostic factors CEA and CA 19-9. Patients who showed elevated CEA values in our study had significantly lower 5-year overall survival rates and local control (32.0% and 55.0%) compared to patients with normal CEA values (62.4% and 73.5%, respectively). Similarly, patients with elevated CA 19-9 values had significantly lower overall survival rates than other patients (14.0% vs. 60.7%, \( p=0.007 \)). This is consistent with several previous studies (10-16) which demonstrated that CEA and CA 19-9 levels are reliable tumor markers for rectal cancer. In a study of Belbehi et al. (17), patients with pre-operatively elevated CEA levels had a 2-year disease-free survival of 25%, whereas patients without CEA elevation had a 2-year disease-free survival of 71%. In a multivariate analysis, Lee et al. identified a non-significant trend of CEA as an independent prognostic factor for survival (18). Similar results were described by Myerson et al. (19).

However, the majority of studies referred to pre-operative CEA and CA 19-9 values and no data about long-term outcome were given. Our study revealed the importance of pre-radiotherapy values of CEA and CA 19-9 in long-term prognosis. Furthermore, after adjustment TNM stage, sex, age, LDH, tumor site and grading, CEA values continued to provide independent predictive information on survival in multivariate analysis. Additionally, an increase of CEA values during radiotherapy was associated with a decreased overall survival rate (Table II). Using Chi-square tests, a significant association between stage and elevation of CEA was observed. If lymph nodes were involved, the patient had higher levels of CEA, indicating that CEA was associated with dissemination of tumor cells and progressive disease.

Using a nude mouse model with rectal carcinoma xenografts (20), we had previously shown that CEA was significantly associated with increased levels of multidrug resistance, which is known to predict poor outcome even if a broad panel of chemotherapeutics is used (21). A possible interaction between MDR and sensitivity to radiotherapy was reported by Wenz et al. (22), while other studies negated such interactions (23, 24). Nevertheless, data about sensitivity to radio- or chemotheraphy is extremely helpful (e.g. in the selection of the sequence of pre- or post-operative adjuvant therapy), and the CEA value before treatment may provide some additional information to estimate the prognosis of rectal cancer.

Our patient collective was not homogeneous since patients with pre-operative and post-operative radiochemotherapy were included. However, analysis of survival data showed no differences concerning overall survival, local control, or distant metastases. Smokers of more than 40 cigarettes per day were excluded; other smokers showed no correlation between number of cigarettes and CEA levels.

Physicians seem not to be convinced of the potential benefits from CEA or CA 19-9 measurements, or they may not know of the recommendations for the use of tumor markers in colorectal cancer given by the ASCO guidelines (25). Nevertheless, routine determination of CEA and CA 19-9 is easy, established in clinical practice, and the results are reliable and comparable between different laboratories (26).

In most reports about the prognostic value of CEA and CA 19-9, adjuvant chemotherapy and/or radiotherapy was not routinely applied or the information about it was incomplete. Furthermore, different cut-off levels for CEA (3 μg/l to 5 μg/l) and CA 19-9 (14 kU/l to 60 kU/l) have been used. For our patient cohort, complete data about radiochemotherapy courses were available, and routinely CEA and CA 19-9 were defined as "elevated" if they exceeded 3 ng/ml and 60 U/ml, respectively. Smokers of more than 40 cigarettes per day were excluded. Smokers of less than 40 cigarettes per day were included without adjustment of the cut-off value. Further, radiation therapy, as well as the hepatotoxicity of anti-neoplastic drugs, is known to induce a transient rise in CEA. Since all patients received complete courses of the same radiochemotherapy scheme, any potential effects applied to all patients.

**Perspectives of rectal cancer.** Recently, much effort has been put into identifying novel prognostic factors. Alterations in DNA ploidy has been investigated, assuming that a aneuploid DNA content may preclude a higher radiosensitivity than that of diploid tumors. The pre-irradiation biopsy specimens of 72 patients with colorectal cancer treated by pre-operative radiotherapy were investigated by Qiu et al. (27). Among the examined parameters of microsatellite instability, microvessel count, immunohistochemistry for proliferating cell nuclear
antigen, p53, p21, bcl-2 and VEGF, only the presence of positive nodes and p21 expression were significantly associated with tumor response to pre-operative radiation. Considering that patients with low thymidylate synthase levels, an enzyme involved in DNA biosynthesis, showed improved outcome, measurement of this enzyme was regarded as useful in predicting response to 5-FU-based therapy (28). Rödel et al. reported promising results analyzing survivin, a novel member of the inhibitor of apoptosis family (29). Low survivin expression was related to an increased rate of disease-free survival, a reduced risk of distant metastases and local failure.

An important milestone for cancer treatment would be to establish new screening methods with the following properties: easy-to-handle in day-to-day clinical practice, reliable and showing significant impact on outcome (i.e., correlation between elevation of values and survival, local relapse and distant recurrences). Though CEA results should only be used in conjunction with further clinical evidence, our study confirmed, for a defined collective of patients treated with standard adjuvant or neoadjuvant radiochemotherapy, that CEA and CA 19-9 are valuable prognostic tumor markers.

Conclusion

Our study demonstrated that patients with locally advanced colorectal cancer and elevated CEA values had significantly lower 5-year overall survival rates and local control. Elevation of the CA 19-9 values also indicated significantly lower rates of overall survival.

Acknowledgements

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References


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