Colorectal cancer (CRC) represents a major health burden in the Western world. Carcinogenesis spans over several years, providing an opportunity for early detection. However, risk predictors for long-term (metachronous) colorectal cancer (mCRC) development in patients with sporadic adenomas are lacking. Furthermore, since 30–40% of patients undergoing surgery develop recurrent disease, surveillance is advocated, albeit with various means. Currently, carcinoembryonal antigen (CEA) is the only biomarker in clinical use for CRC, but has suboptimal accuracy. New and better biomarkers are therefore strongly needed.

Thus, biomarkers predictive of metachronous colorectal cancer (mCRC) in patients with sporadic colorectal adenomas from 374 consecutive patients were evaluated. The prognostic value of classical clinicopathologic and morphometry features were evaluated using quantitative image analysis. Of the 171 adenomas, 50 (29%) had so-called MPECs (monotonous population of elongated cells), of which 9 (18%) patients developed mCRC at follow-up. Elevated expression of cell-cycle regulators \( p16, p21, \) and \( \beta \)-catenin correlated with increased CRC risk, as did elevated expression of the antiapoptosis protein survivin and human telomerase reverse transcriptase (hTERT). Survivin, hTERT, and nuclear \( \beta \)-catenin were the most predictive molecular markers. The features were validated in a second set of patients (\( n = 227 \)), and evaluated by receiver-operating characteristics (ROC) curve analysis for optimal cutoffs. On multivariate risk evaluation hTERT (HR 11.3, 95% CI 3.9–33.1; \( p < 0.001 \)) and survivin (HR 7.0, 95% CI 2.4–20.5; \( p < 0.001 \)) were the strongest predictors. The combination of survivin and hTERT yielded high mCRC risk when both were positive (15/51 = 29%; OR 14.3, 5.6–36.5), modest for one positive (survivin 4/90 = 4.4%; hTERT 4/60 = 6.7%), and no risk if both were negative (0/144 = 0%).
A study on a CRC postsurgery surveillance\textsuperscript{3–6} national program was evaluated. Twenty-one patients (11\%) were operated on for curable recurrence, and 18 patients (9\%) were disease free after curative surgery for recurrence at evaluation. CEA interval measurement had to be made most frequently (534 tests needed) to detect one asymptomatic curable recurrence. Overall compliance with the surveillance program was 66\%, being lowest for colonoscopy (55\%) and highest for ultrasonography of the liver (85\%). The total diagnostic yield with regard to disease-free survival after surgery for recurrence was 9\% (4). Further, the diagnostic accuracy of serial measurements of CEA was performed using ROC analysis of various cutoffs and the slope of increase in CEA.\textsuperscript{5} Depending on the chosen cutoff value of CEA, the diagnostic accuracy (DA) varied. CEA $> 4$ U/ml provided the highest sensitivity (0.78) and specificity (0.91). A threefold increase of CEA in an individual patient had the same DA as the best cutoff value ($> 4$ U/ml).

Finally, the effect of microsatellite instability (MSI) and DNA ploidy was evaluated in relation to survival and risk of recurrence or distant metastasis in 186 patients.\textsuperscript{6} PCR technique was used to analyze for MSI using quasi-monomorphic markers (BAT-26, BAT-25, NR-21, NR-24, and NR-27). MSI tumors were significantly more often found in proximal colon, were larger, were of more invasive nature (pT3-4), were diploid and low histologic grade, and had a more advanced stage (stages II or III) than their MSS counterparts. MSI was not associated with increased risk for any recurrence, but had a higher OR for developing locoregional recurrence (27\% versus 11\%, respectively; OR 2.9, 95\% C.I. 1.2–7.0; $P = 0.016$). Also, a trend toward shorter time to locoregional recurrence ($P = 0.060$) was noted for MSI cancers. This could be of clinical importance for the choice of surveillance modality.

REFERENCES


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The present Ph.D. thesis of Kjetil Søreide focuses on two important aspects of colorectal cancer (CRC): The risk of developing metachronous CRC after the diagnosis of an adenomatous polyp in the colorectum\(^1\)–\(^3\) and the risk of recurrent disease after curative surgery for CRC.\(^4\)–\(^6\)

Traditionally, decisions of clinical management of patients with colorectal adenomas are mainly based on conventional histopathological examination. However, better prognostic tools with regard to the risk of metachronous CRC are needed to focus on high-risk patients, and to avoid unnecessary follow-up procedures. In our studies, molecular biomarkers were investigated as possible predictors for CRC. This novel approach identified hTERT and survivin as independent predictors for metachronous CRC development. The study was done in consecutively collected adenomas from a large unselected population. We regard these findings as clear indication for the potential of biomarkers in this context, and of great significance for the follow-up strategies in patients with colorectal adenomas. Our findings warrant further prospective studies in large populations.

Follow-up after curative resection for CRC is commonly recommended, although the scientific basis for its benefit is weak. Norwegian guidelines for follow-up aim at the early detection of asymptomatic, and hopefully curable recurrence. Follow-up includes imaging of liver and lungs, endoscopy and monitoring of serum-Carcinoembryonic antigen (CEA). The significance of this study\(^4\) is that many patients undergoing surveillance never develop any recurrence, while patients with asymptomatic recurrence either are incurable at the time of diagnosis, or develop symptomatic recurrence during follow-up intervals. Serial serum-CEA monitoring has not been as promising as desired when the analysis became available during the 1970s. The scientific evaluation of this test has been far from satisfactorily due to the diversity of statistical approaches and variability of chosen cutoff. Our analysis\(^5\) of the diagnostic accuracy of CEA with regard to asymptomatic recurrences is the first one applying receiver operating characteristics (ROC) curve analysis, and thus revealing the best cutoff value within the whole spectra of the test. This cutoff is not necessarily the upper normal range as commonly used in clinical practice. Furthermore, our study deals with the problem of the clinical significance of minor changes of consecutive CEA values. A triple increase even within the normal range indicated the presence of recurrence.

In follow-up of CRC, better predictors of risk of recurrent CRC are highly desirable in order to select high-risk patients from those of low risk. Microsatellite instability (MSI) has recently been in the focus of interest. Our study (paper 6) indicates that MSI positive tumors tended to behave differently from microsatellite
stable (MSS) tumors in terms of increased local aggressiveness. The significance of our findings of increased risk of locoregional recurrence and shorter time to relapse in MSI positive patients is that molecular biomarkers probably have the potential for a more individually tailored follow-up strategy as compared to current general follow-up schemes.