Material and methods: Between 1993 and 2002, 183 patients with locally advanced rectal cancer (cT3/T4 or N+) were enrolled in this study. Preoperative chemoradiation consisted of 50.4 Gy of pelvic radiation with concurrent 5-fluorouracil+leucovorin bolus i.v. chemotherapy in 94 patients or oral capecitabine in 89 patients. Surgery was performed 6 weeks after chemoradiation. EGFR expression in the pretreatment paraffin-embedded tumor biopsy specimens was assessed by immunohistochemistry using an EGFR pharmDx kit (DakoCytomation). EGFR expression was determined from the intensity and extent of staining. The staining threshold for a positive result was 1+intensity in 1% of the tumor cells. EGFR immunostaining was graded as a categorical variable using an immunoreactive score (IRS) that ranged from 0 (negative staining) to 7 (strong staining) and was defined as low (IRS 0 to 3) or high (IRS 4 to 7) expression. Tumor downstaging was defined as a reduction in the pretreatment T stage by one level compared with the pathological stage. The predictive value of EGFR expression for tumor downstaging was evaluated using the chi-square test and logistic regression analysis.
Results: The median age of the patients was 59 years, and there were 111 males and 72 females. The preoperative clinical T stage was T3 in 163 patients (89%) and T4 in 20 patients (11%). Tumor downstaging occurred in 97 patients (53%). The tumor showed a pathologic complete response in 27 patients (15%). Positive EGFR expression was observed in 140 of 183 patients (76%). The grade of EGFR expression was low in 113 patients (62%) and high in 70 patients (38%). High EGFR expression was not correlated with gender, age, tumor mobility, tumor size, tumor distance from the anal verge, cT stage, cN stage, or pN stage, but was correlated with pT stage ($p = 0.043$). EGFR expression and age were marginally significant predictive factors for tumor downstaging in the univariate analysis ($p = 0.063$ and 0.081, respectively). In the logistic regression analysis, including the variables EGFR expression, age, tumor mobility, and cN stage, high EGFR expression was the only significant predictive factor for tumor downstaging (hazard ratio 0.515, 95% confidence interval 0.276 to 0.963, $p = 0.038$).
Conclusions: High EGFR expression is a significant predictive molecular marker for tumor downstaging in locally advanced rectal cancer treated with preoperative chemoradiation.

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Prevalence of high-risk lesions in prophylactic mastectomy specimens of 82 BRCA1 and BRCA2 mutation carriers

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Purpose: Women with a hereditary predisposition for breast cancer have a very high risk (up to 85%) of developing invasive breast carcinoma and consider prophylactic mastectomy to avoid this risk. Together with cancer-free survival, the effectiveness of prophylactic mastectomy in *BRCA1* and *BRCA2* carriers may be established by the spectrum of high-risk lesions in their mastectomy specimens. Little is known about differences between early stages of breast cancer development in *BRCA1* and *BRCA2* mutation carriers. It is unknown whether the prevalence of high-risk lesions in *BRCA1* and *BRCA2* mutation carriers is different. There may be differences in breast cancer development in *BRCA1* and *BRCA2* mutation carriers because the features of invasive breast cancer lesions are different.
Patients and methods: A prospective series of 68 *BRCA1*- and 14 *BRCA2*-prophylactic mastectomy specimens was analyzed by radiography and macroscopic inspection of 5 mm tissue slices and histological examination of suspicious lesions and random samples from each quadrant of the breast and the nipple area.
Results: Patient characteristics of the two groups were comparable for age at time of prophylactic mastectomy (36 $\pm$ 9 years), presence of previous breast cancer (35%), age at previous breast cancer (42$\pm$9 years), postmenopausal status (46%) and previous oophorectomy (23%). The earliest age of breast cancer occurrence was significantly younger (35 $\pm$ 9 years) in *BRCA1* than *BRCA2* families (44$\pm$9 years; $p = 0.02$). High-risk lesions are equally frequent among women with a *BRCA1* or a *BRCA2* mutation: all high-risk lesions 44% versus 36% ($p = 0.56$), atypical lobular hyperplasia 26% versus 21% ($p = 0.69$), atypical ductal hyperplasia 18% versus 14% ($p = 0.70$), lobular carcinoma-in-situ (LCIS) 16% versus 7% ($p = 0.38$) and ductal carcinoma-in-situ (DCIS) 9% versus 7% ($p = 0.83$).
Conclusions: The high prevalence of high-risk lesions associated with an increased risk of malignancy, substantiates the generalized nature of incipient malignant changes both in *BRCA1* and *BRCA2* mutation carriers and confirms the indication for prophylactic mastectomy. Surveillance does not detect these high-risk lesions.

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Cytoplasmic p27 kip-1 expression is an indicator of good prognosis in colorectal cancer patients

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Introduction: The p27kip-1 protein inhibits certain cyclin-CDK complexes in the cell nucleus, thereby preventing uncontrolled cellular proliferation. Recent data suggests that cytoplasmic p27kip1 may have an alternative function, inhibiting the activity of cytoplasmic Rho proteins which co-ordinate cytoskeletal remodelling and underlie changes in cell adhesion and migration. Our aim was to evaluate the prognostic significance of cytoplasmic and nuclear p27kip-1 in a large series of colorectal cancer patients.
Methods: Using high-throughput Tissue microarray (TMA) technology, we analysed p27kip-1 cytoplasmic and nuclear expression in a series of over 400 paraffin embedded colorectal tumor specimens. Data derived from this analysis was associated with known patient and tumor variables, and with long-term patient outcome data, in order to gain further insight into the mechanisms by which p27kip-1 may influence tumor development.
Results: 74/418 tumours expressed both cytoplamsic and nuclear p27kip-1 which was not associated with the known clinicopathological variables including tumor stage, tumor grade or the presence of vascular invasion. However, on survival analysis using the Kaplan-Meier method there was a significant correlation between p27kip-1 expression and disease specific survival ($p = 0.037$), with patients whose tumours express both nuclear and cytoplamsic p27kip1 having a good prognosis. In contrast, expression of nuclear p27kip-1 alone was observed in 217/418 (51.9%) tumours, and this did not demonstrate any correlations with clinicopathological variables or survival.
Conclusions: For tumours to metastases, cells must alter their connections to their neighbours and their substrate, and then migrate. Efficient migration requires a tight balance between activation and deactivation of Cdc42, Rac and RhoA in both time and space. Sequestration of RhoA by cytoplasmic p27kip-1 may inhibit migration by preventing cells from achieving sufficiently strong adhesion and traction to move forward. In this study cytoplasmic expression of p27kip-1 was always associated with nuclear expression. These tumours would therefore have controlled proliferation and reduced migration resulting in a less aggressive tumour and a good prognosis. These finds support recent evidence that cytoplamsic p27kip1 expression has an important biological role that can influence tumour outcome.

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Bromodeoxyuridine labelling index as an indicator of tumour response to neoajuvant radiotherapy in patients with rectal cancer

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Background: In clinical practice there are no certain methods to predict tumour response to neoadjuvant radiotherapy (RT). Therefore the aim of the study is an assessment of tumour proliferation rate based on Bromodeoxyuridine labelling index (BrdUrd LI) to predict tumour response to neoadjuvant RT in patients with rectal cancer.
Material and methods: Tumour samples were taken twice from each of 65 patients with rectal carcinoma qualified to neoadjuvant RT: before RT and during surgery. Tumour fragments were incubated with BrdUrd for 1 hour at 37°C, and after fixation and staining the cell preparations were analysed with flow cytometer. The BrdUrd LI was calculated as a percentage of BrdUrd-labelled cells in a sample which incorporated BrdUrd. S-phase fraction (SPF), DNA ploidy, and apoptosis were also evaluated. Patients were treated according to two RT schedules: I, short RT for 5 days with 5 Gy/fraction and surgery about one week after RT, or II schedule: short RT (5×5 Gy) with longer interval, 4–5 weeks before surgery. Tumour response after RT has been evaluated by a patologist on the basis of tumour material taken during surgery.
Results: Thirty-one patients were treated according to schedule I, in which the mean interval before surgery was 8 days (range 2–14). In 34 patients schedule II was applied, in which mean break was 32 days (range 17–45). Mean BrdUrd LI before RT was 7% (range 1.0–24.2%) and the mean value did not differ between the two schedules. After RT, tumours treated according to both schedules showed statistically significant growth inhibition (reduction of BrdUrdLI and percentage of SPF cells) in comparison with the values obtained before RT. Because the interval