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p53, p21, p27 and bcl-2 as predictors for clinical outcome in rectal cancer

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Purpose: The purpose of this study was to examine whether molecular markers, including p53, p21, p27 and bcl-2, can be used to predict tumor response to pre-operative radiotherapy/chemoradiotherapy in rectal cancer.

Methods: From January 1998 to June 2002, there were 77 patients with rectal cancer enrolled. The preoperative chemoradiotherapy delivered radiation with 45 Gy in 25 fractions over 5 weeks with continuous infusion 5-flurouracil (300 mg/m^2/day). Surgery, such as LAR or APR, was performed 4 weeks after completion of chemoradiotherapy. Immunohistochemistry of p53, p21, p27 and bcl-2 were performed in the pre-radiation biopsy of specimen of 70 patients and in the post operation specimen of 53 patients. The end-points for evaluation of tumor response were down-staging (DS), tumor-shrinkage (TS), and tumor-shrinkage more than 50% (50%-TS). Besides, fair response (FS), including complete regression and tumor in situ, was also evaluated. Meanwhile, the relationship between those molecular markers and overall survival rate and disease free survival rate were evaluated.

Results: The percentages of patients of DS, TS, 50%TS and FS were 50%, 94.8%, 70.7% and 17.7% respectively. In the pre-radiation biopsy of specimen, the positive rate of p53, p21, p27 and bcl-2 were 63.3%, 16.3%, 37.2% and 16.7%, but in the post operation specimen, the positive rate was increased, 69.4%, 20.4%, 73.5% and 41.7%, accordingly (p=0.58, 0.79, 0.001 and 0.012). Of the pre-radiation biopsy of specimen for DS and TS patients, there was no significant difference in molecular markers p53, p21, p27, and bcl-2. For 50%-TS patients, the significant differences were found in p21 and bcl-2 (p=0.005 and 0.046). As for FR patients, the significant findings were noted in p53, p27 and bcl-2 (p=0.006, 0.012 and 0.027). The 3-year disease-free and overall survival rates in our patients were 75% and 85%. The 3-year overall survival rates for pathologic specimen p27 (+) and p27(-) patients were 87% and 78% respectively (p=0.029). However, there was no significant finding between molecular markers, no matter pre-radiation or post operation, and disease free/overall survival rates, with all p values more than 0.05.

Conclusions: After neoadjuvant therapy, the positive rates of all molecular markers, including p53, p21, p27 and bcl-2, increased. In the pre-radiation biopsy of specimen, the p21 (-) and bcl-2 (+) were good predictors for 50%-TS while p53 (-), p27 (+) and bcl-2 (+) were good for FR. More p27 (+) patients survived over 3 years, but other molecular markers could not predict disease free and overall survival.

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Survivin expression: an independent prognostic factor in rectal cancer patients with and without radiotherapy

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Background: Survivin blocks apoptosis by inhibiting caspase 3 and 7. This protein is undetectable in many normal tissues and is re-expressed in several types of human cancers. The survivin expression in rectal cancer patients who received preoperative radiotherapy alone has not been studied. Our aim was to analyze the relationship of survivin expression with radiotherapy, clinicopathological variables, apoptosis, Ki-67 and p53 in rectal cancer patients who participated in a trial of preoperative radiotherapy.

Methods: We investigated survivin expression by using immunohistochemistry on 98 rectal tumors with 74 cases that had normal mucosa adjacent to the tumors. Fifty-seven patients had curative tumor resection alone and 41 received preoperative radiotherapy, 25 Gy before surgery.

Results: The survival rate of the patients with survivin positive tumors was significantly reduced compared to those with survivin negative tumors independently of clinicopatholgical variables (P = 0.02). The patients with survivin positive tumors tended to have a higher risk of local (P = 0.12) and distant (P = 0.11) recurrence. In subgroups analyzes of non-irradiated or irradiated patients, the positive expression tended to associate with unfavorable survival (P = 0.08, P = 0.19). After radiotherapy, survivin expression in the normal mucosa was increased (33% of the cases vs 67% of the cases, P = 0.057) but not in the tumors (P = 0.71).

Conclusion: Survivin positive expression was independently related to unfavorable survival in rectal cancer patients who participated in a trial of preoperative radiotherapy. Compared to tumor tissue, survivin expression in normal mucosa was greatly up-regulated after radiotherapy. Survivin protein does not predict the response to radiotherapy of rectal tumours.

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Quality of life in patients with rectal carcinomas treated by preoperative radiotherapy: a longitudinal prospective study

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Background: Recently it was shown that preoperative radiotherapy (RT) reduces local recurrences and may improve overall survival. Although RT is believed to increase treatment sequela, data on quality of life (QoL) after such a therapeutic strategy are scarce. The present study aimed to assess prospectively the QoL of patients treated by preoperative RT for locally advanced rectal cancers.

Patients and Methods: Forty-three patients accepted to participate in the present study. All patients were enrolled in two successive phase I-II trials and treated preoperatively with 50 Gy in 40 fractions of 1.25 Gy over 4 weeks with or without concomitant chemotherapy (gemcitabine). Rectal surgery was scheduled 6 weeks after completion of RT. QoL was assessed using two self-rating questionnaires developed by the European Organization for Research and Treatment of Cancer: one for cancer-specific QoL (EORTC QLQ-C30) and one for site-specific QoL (EORTC QLQ-CR38). Participants were asked to complete the questionnaires before RT and one-year post-treatment. We hypothesized that at least some scores of the various scales would vary between the 2 analyses. The two-tailed paired t-test was used to compare the mean values of the different scores.

Results: Compared to pre-RT scores, at one year patients reported a significant improvement in the emotional function (median: 92 vs 75, p=0.003), their perspective for the future (median: 100 vs 67, p=0.003) and their global quality of life (p=0.015) as well as a decrease in gastrointestinal symptoms such as constipation (p=0.006) and diarrhea (p=0.035). However, the sexual dysfunction score increased significantly, particularly for males (median: 33 vs 83, p=0.005), and body image score decreased significantly (median: 100 vs 67, p=0.007). The latter score was significantly correlated to the severity of late complications (p=0.02) as well as defecation and stoma problems.

Conclusion: The present prospective study highlights some significant score changes in functions as well as symptoms one year after treatment compared to the pre-RT base line scores. While body image and sexual functioning decreased significantly, global quality of life and the perspective for the future were significantly improved. Any further improvement in QoL outcome may require refinements in the RT and surgical techniques to reduce late sequela, particularly operative procedures allowing preservation of sexual function.

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Preoperative radiochemotherapy with capecitabine in locally advanced rectal cancers - a phase-II-study

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Experimental findings have demonstrated that thymidine phosphorylase, which is necessary for the final conversion of the prodrug capecitabine, is predominantly expressed in tumor cells and is further upregulated by radiotherapy (XRT) in malignant but not in healthy tissue. Based on these findings, the concurrent administration of radiotherapy and capecitabine may improve tumor response and/or reduce toxicity. As shown in our previous phase I dose finding study (J Clin Oncol 2002, 20: 3983-91), the concurrent administration of daily capecitabine with pelvic XRT appears to be feasible and effective in advanced rectal cancer. The objective of the present expanded phase II trial is to establish the use of this combined modality approach in a multicenter setting, focussing on its application as neoadjuvant treatment of locally advanced (cT3-4) or primarily inoperable tumors. A total irradiation dose of 50.4 to 55.8Gy was administered in conventional daily doses of 1.8