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Functional folate status as a prognostic indicator of toxicity in clinical trials of the multitargeted antifolate LY231514. *Peter H. Zervos[1], Robert H. Allen[2], Donald E. Thornton[1], and Patricia A. Thiem[1]. [1]Eli Lilly and Co., Indianapolis, IN., [2]University of Colorado, Health Sciences Center, Dept. of Biochemistry, Biophysics and Genetics. Denver, CO.*

Studies in animal models and humans have revealed that folate nutritional status may be correlated with toxicity and antitumor activity of antifolates. Supplemental folic acid may play a role in protecting against the toxicities associated with antifolate drugs. LY231514 is a multi-targeted antifolate that inhibits Thymidylate synthase, Dihydrofolate reductase and Glycinamide ribonucleotide formyltransferase. Functional folate status, based on serum concentrations of homocysteine (HCYS), cystathione (CYSTAT), and methylmalonic acid (MMA), was assessed in 116 patients participating in Phase 2 studies of LY231514. This drug was administered as a 10-minute infusion once every 21 days. Samples were taken prior to initiation of therapy and prior to the start of each cycle. CTC toxicity scores (hematologic and non-hematologic) were assigned at the end of each cycle of therapy. Eight pts were found to be folate deficient (elevated HCYS and CYSTAT and normal MMA). All experienced CTC grade 3 or 4 toxicity which was primarily hematologic. From this data, we would conclude that functional folate status appears to be a reliable prognostic indicator of hematologic toxicity that may be experienced from treatment with LY231514. Further investigation is warranted to support this conclusion.

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Sphincter sparing treatment for distal rectal adenocarcinoma: a phase II intergroup study. *GD Steele[1], JE Herndon[1], AM Burgess[2], R Bleday[3], AH Russell[4], AB Benson[5], MA Hussain[4], RJ Mayer[3]. [1]Cancer and Leukemia Group B (CALGB); [2]Radiation Therapy Oncology Group (RTOG); [3]Eastern Cooperative Oncology Group (ECOG); [4]Southwest Oncology Group (SWOG).*

Uncontrolled series from single institutions have suggested that the anal sphincter can be preserved in patients (pts) with superficial distal rectal adenocarcinomas (DRA) but this concept has not been validated in a multiinstitutional setting. CALGB, with ECOG, RTOG, and SWOG, gathered 180 pts (PS 0-2) having histologically documented T1/T2 adenocarcinomas without clinical evidence of progression through bowel wall or spread to lymph node or distant sites (ECOG/RTOG registered T3 as well). No tumor could be > 4cm in diameter or encompass > 40% bowel wall circumference or be > 10 cm from the dentate line. Pts with tumor fixation, anal cancer, other histologies, or prior therapy were ineligible. A full thickness local excision was attempted in 164/180 registered pts. For this analysis, the 3 pts with T3 lesions were not included. Forty eight other pts were declared ineligible because of; involved margins, tumor > 4cm, stage > T2, and stage < T1. Of the remaining 113 eligible pts, the 60 T1 pts received no further treatment and were observed for recurrence and survival on a specified schedule. The 53 T2 pts were treated with external beam radiation 5400 cGY/30 fractions 5days/week to begin ≤ 6 weeks post local excision and 5-FU 500mg/m^2 IV bolus d1-3, 29-31, and then followed in a similar fashion. Surgical complications were minimal; wound (5%), GI (4%), and GU (5%). Chemoradiation was well tolerated with grade 3 + toxicities of lymphocytopenia (25%), diarrhea (18%), skin (12%), and neutropenia (10%). After a median follow-up of 24 months, 4/113 pts have died of their malignant disease, 2/4 having distant recurrence only. Two pts have been successfully treated for second colorectal tumors. Only 2/113 experienced isolated local recurrences; both have undergone subsequent resection and remain alive. One pt with T2 disease died after 43 months from unrelated cardiovascular disease. These data indicate that sphincter preservation can be achieved with excellent cancer control without sacrifice of anal function in selected pts with superficial DRA.

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Preoperative chemoradiation therapy appears superior to preoperative radiation alone in the management of clinical T3/T4 rectal cancer. *N.R. Ahmad, P.R. Anne, D.A. Nagle, L.J. Rose, E.P. Mitchell, and R.D. Fry. Thomas Jefferson University, Philadelphia, PA.*

Advantages of preoperative radiation therapy (RT) in rectal cancer include increased resectability and sphincter-sparing surgery. This analysis assesses the influence of concurrent chemotherapy (CT) on the outcome of patients (pts) treated with preoperative RT for clinical stage T3/T4 (cT3/T4) rectal cancer. Two hundred three pts with cT3/T4 cancers received preoperative RT (median 55.8 Gy) followed by surgery. Forty-seven received concurrent CT (CRT group) and 156 did not (RT group). CT consisted of protracted venous infusion 5-FU (300/mg/m^2/day) in 32 pts, weekly bolus 5-FU (500/mg/m^2/week) and leucovorin in 10 pts, and other 5-FU-based CT in 5 pts. Following surgery, 36 pts received adjuvant 5-FU CT for 3 to 18 months; 26 in the CRT group and 10 in the RT group. The median follow-up times for the CRT and RT groups were 36 and 49 months, respectively. Clinically fixed cancers constituted 57% (27/47) of the CRT group and 48% (75/156) of the RT group. Postoperative pathologic stage was T3/T4 in 22/47 (47%) of the CRT group and 95/156 (61%) of the RT group. The 5-year actuarial local control (LC), distant metastasis-free survival (DMFS) and overall survival (OS) rates are summarized below:

	LC%	p <	DMFS%	p <	OS%	p <
RT	80	ns	61	0.02	62	0.007
CRT	96		90		92	

Grade 3/4 acute GI toxicity was significantly greater in the CRT group (24%) vs. the RT group (5%, $p < 0.005$, χ^2). We conclude that in this series, the DMFS and OS rates following preoperative CRT appear superior to those obtained with preoperative RT alone or postoperative CRT. The increased acute toxicity of CRT is acceptable in light of the improved patient outcome.

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Multivariate analysis of tissue-based prognostic markers in stage II-III colorectal carcinoma. *J.M. Jessup, I.C. Summerhayes, D. Shibata, G. Cangi, P.T. Lavin, A.M. Mercurio, F. Fogt, M. Loda. Boston Biostatistics, Inc., Framingham, MA and Beth Israel Deaconess Medical Center, Boston, MA.*

Expression of molecules associated with the cell cycle (p27Kip1, cdc 25B), drug response (topoisomerase IIα), differentiation (sucrase-isomaltase (S-I)), or neoplastic transformation (DCC - deleted in colon cancer) may define subsets of patients whose outcome differs from that of the stage-specific average. We tested this postulate in 149 patients with AJCC stage II or III colorectal adenocarcinoma resected for cure without adjuvant therapy at the Deaconess Hospital between 1965 and 1977. Median follow-up is 115 months with 51% of patients dying of cancer. Tissue sections of paraffin-embedded tissues were stained with antibodies and scored in a coded fashion as Absent or Present (≥ 1% tumor cells stained). Standard clinical, stage, and grade variables were assessed in Kaplan-Meier analyses (K-M A). Variables with a Wilcoxon p value < 0.10 were then included in a Cox Proportional Hazards (PH) model:

	K-M A		Cox PH		
	p value	Category	p value	Rel. Risk of Death	95% C.I.
p27	0.066	Absent	0.002	3.39	1.5 - 7.4
DCC	0.025	Absent	0.013	7.22	1.5 - 34.4
S-I	0.015	Absent	0.053	0.54	0.3 - 1.01
Stage	<0.0001	II	0.007	0.41	0.2 - 0.8
Grade	0.0001	Not Poor	0.005	0.26	0.1 - 0.7
Site	0.057	Colon	0.153	0.62	0.3 - 1.2

Age, sex, vascular invasion, cdc 25B, topoisomerase IIα, and primary site were not significant covariates. Expression of S-I tends to increase the risk of death from cancer. However, expression of p27 and DCC strongly decreased the risk of cancer death even with stage and grade in the Cox PH model. Intratumoral expression of p27 and/or DCC are strong prognostic factors and may identify stage II - III colorectal cancer patients with better prognosis.

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