

Treatment of Locally Advanced Rectal Cancer: Current Concepts

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Case Presentation

- 62 y.o. man with history of hematochezia for several months; never had colorectal cancer screening
- 35 lb weight loss
- Referred to colorectal surgeon, found to have 10 cm tumor in rectum, marginally resectable
- CEA 10 ng/ml
- Referred for neo-adjuvant chemo-radiation therapy



Case Presentation, cont.

- Treated with radiation and concomitant Xeloda, then underwent resection
- At resection, had tumor invading into muscularis propria with four negative lymph nodes; received no chemotherapy post-operatively
- One year after surgery was found to have rising CEA and liver metastases
- No evidence of local recurrence

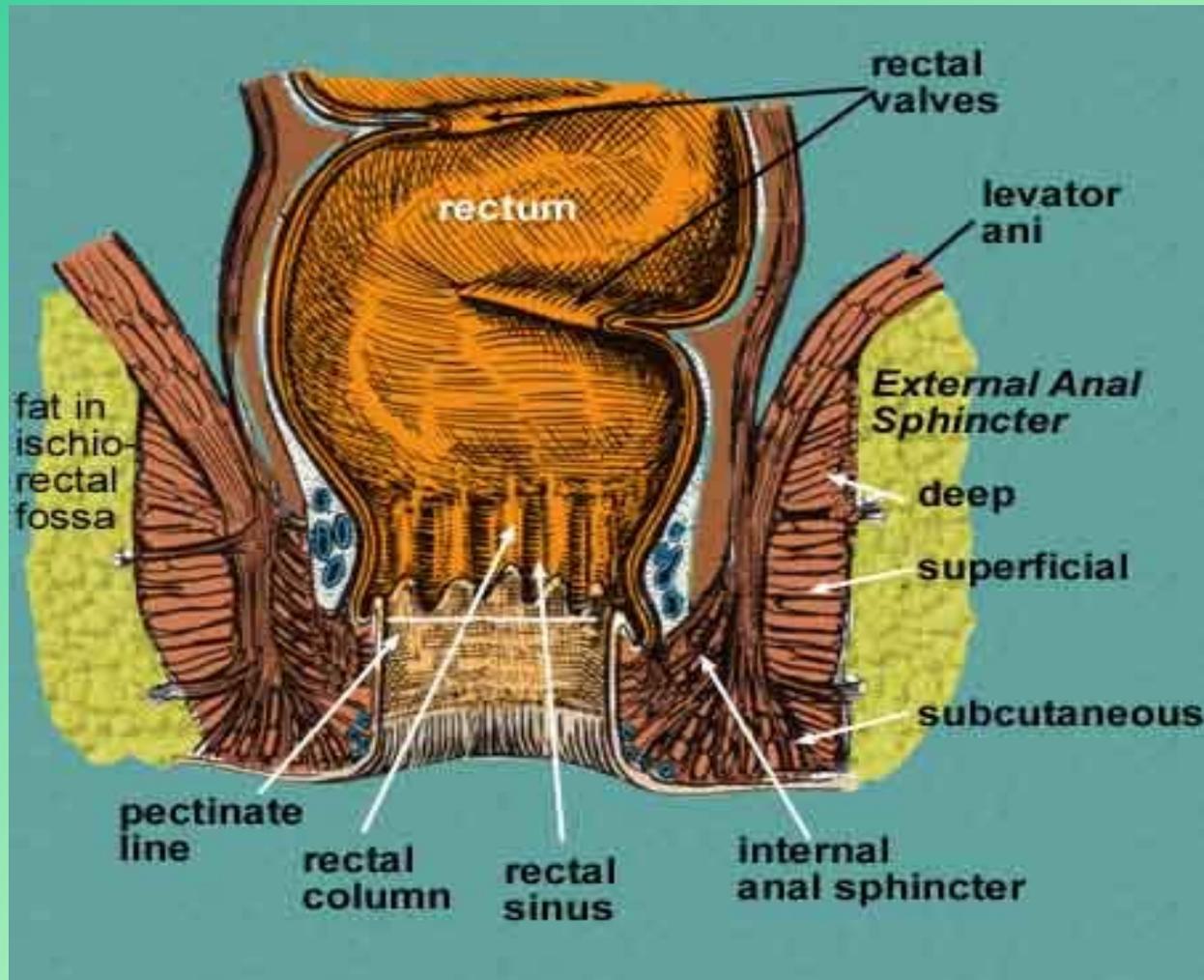


Historical Basis for Combined Modality Treatment for Rectal Cancer

- Starting in 1970's oncologists have recognized special status of rectal cancer – i.e., that local control is a problem...



Anatomy of the Rectum



Historical Basis for Combined Modality Treatment for Rectal Cancer

- Starting in 1970's oncologists have recognized special status of rectal cancer – i.e., that local control is a problem...
- Combinations of radiation and chemotherapy tried, with hopes of increasing local control rate and survival
- Initial results published in 1980's suggested that both local control and overall survival were improved...



GITSG Protocol 7175*

- Four-arm study (small, only 200 patients)
 - Surgery only
 - Radiation only
 - Chemo only (MeCCNU + 5FU)
 - Radiation and Chemo
 - All patients treated postoperatively
- Results
 - Control: 55% recurred locally, distantly or both
 - Combined group: 33% recurred
 - RT only, chemo only: less benefit
 - Small sample size; $p=N.S.$ “underpowered” by contemporary standards but highly suggestive of benefit
- Historical perspective: RT doses low by modern standards; chemo inferior as well, but basis for further investigation established



Next Question for Investigators: Give the chemo and RT before surgery or after?

- Starting in 1980's surgeons and oncologists began to appreciate the role of pre-operative downstaging with chemo alone (breast cancer) or chemo and radiation together (head-and-neck cancer, rectal cancer)
- Allowed organ preservation in selected patients (breast conservation, rectum preservation, larynx preservation)
- Optimal interdigitation of various modalities investigated ever since while drugs and RT techniques have continued to improve...moving target
- Has led to current series of trials in rectal cancer and evolution of current thinking

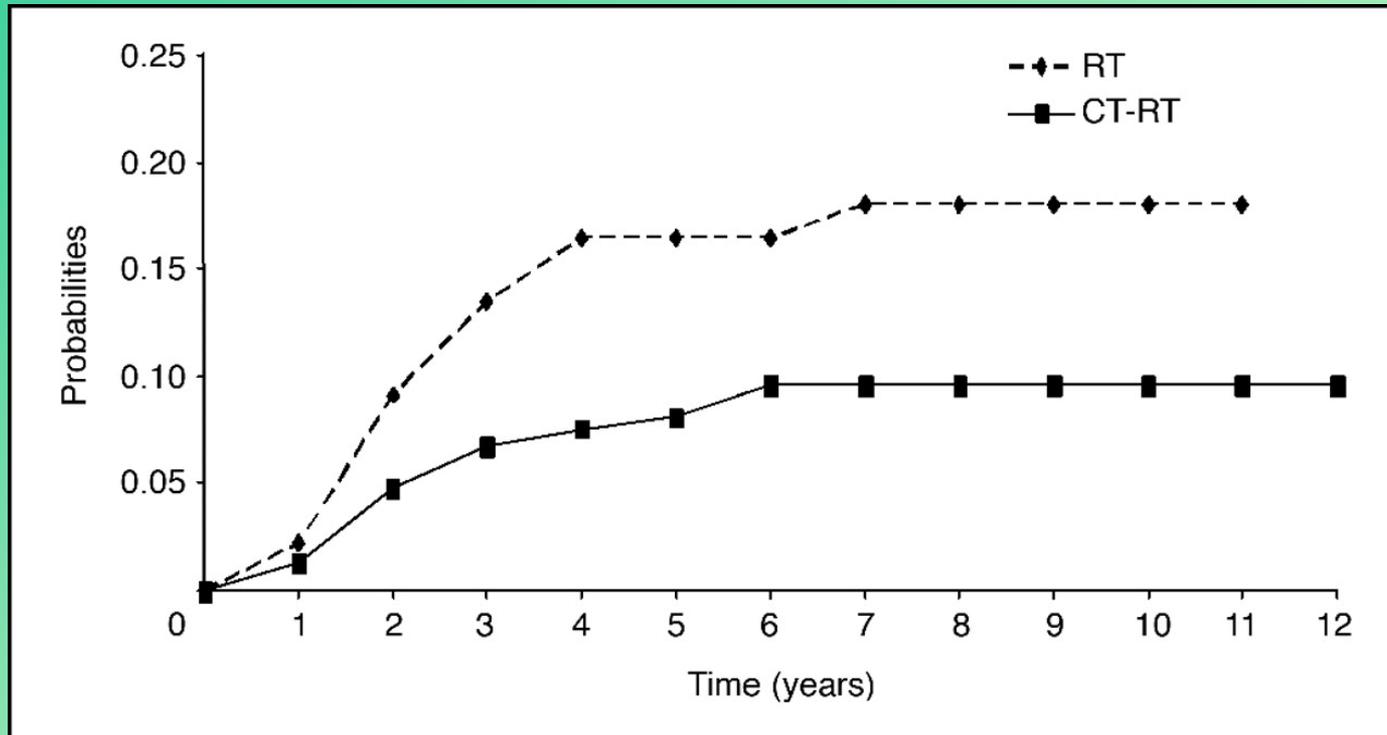


Diversionary Question Being Asked: In Pre-Operative Setting is Chemotherapy Needed in Addition to Radiation?

- Recent publication confirms conclusion of several earlier studies that chemotherapy is necessary for full benefit...
 - Not surprising in light of landmark GITSG study from the '80's



Cumulative incidence of local recurrence among 661 patients with treatment randomly assigned between preoperative radiotherapy (RT) and preoperative chemotherapy and radiotherapy (CT-RT)



Gerard, J.-P. et al. J Clin Oncol; 24:4620-4625 2006

OK... So chemo is needed; do you give package of treatment before or after surgery?

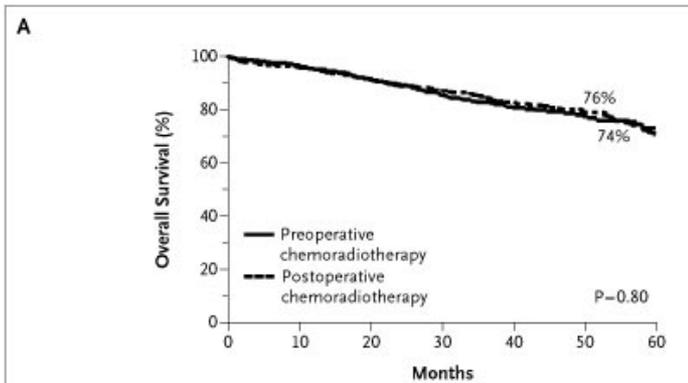


Timing of Radiation and Chemotherapy in Rectal Cancer

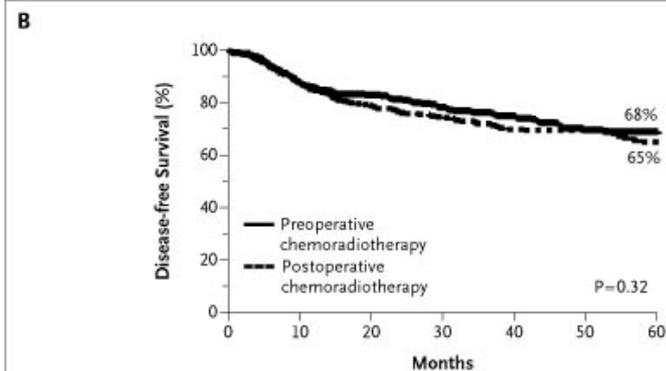
- Given pre-operatively:
 - Chance to save rectum
 - Early administration of systemic therapy to try to prevent micrometastatic disease from gaining a foothold
- Given post-operatively:
 - Allows full surgical staging without downstaging effect of chemo-RT in evaluating prognosis and designing future therapy
 - In theory some patients with less advanced disease can be spared chemotherapy if surgically staged at diagnosis
- Several trials done to try to resolve this conundrum



Overall Survival (Panel A) and Disease-free Survival (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis



No. at Risk	0	10	20	30	40	50	60
Preoperative chemoradiotherapy	397	372	321	253	193	144	90
Postoperative chemoradiotherapy	384	355	314	251	196	135	98



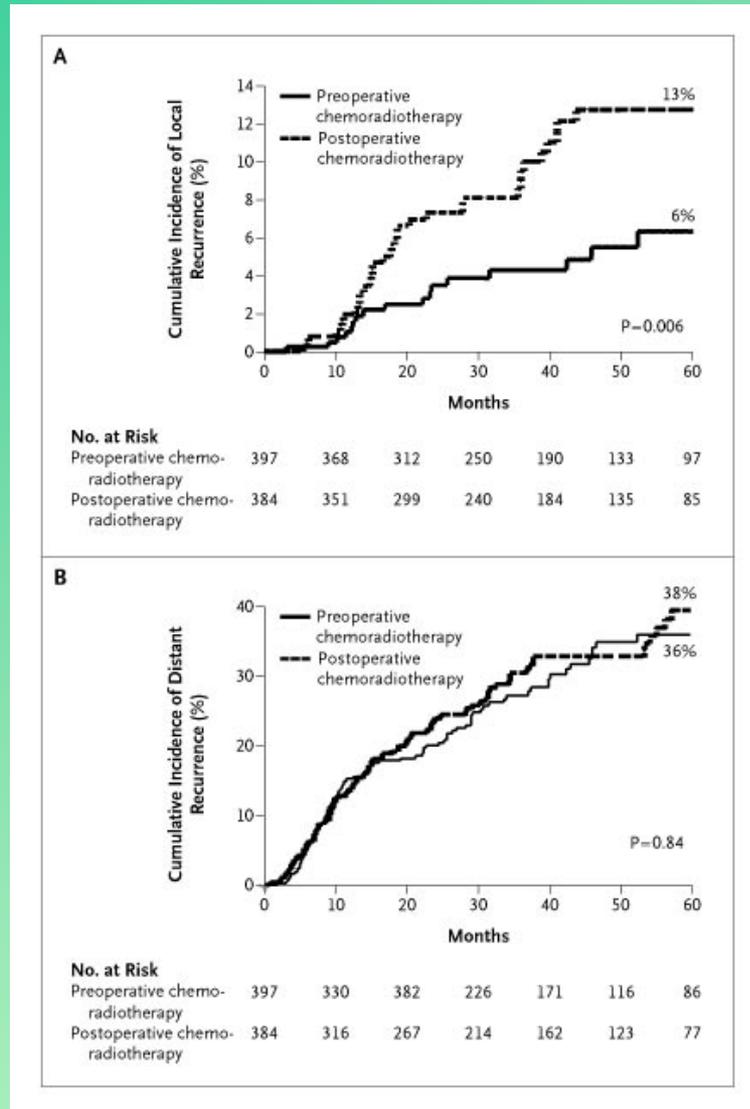
No. at Risk	0	10	20	30	40	50	60
Preoperative chemoradiotherapy	397	331	280	224	169	115	85
Postoperative chemoradiotherapy	384	314	259	209	159	117	73

No difference in overall or disease-free survival

As opposed to earlier trials there was no observation-only treatment arm



Cumulative Incidence of Local Recurrences (Panel A) and Distant Recurrences (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis



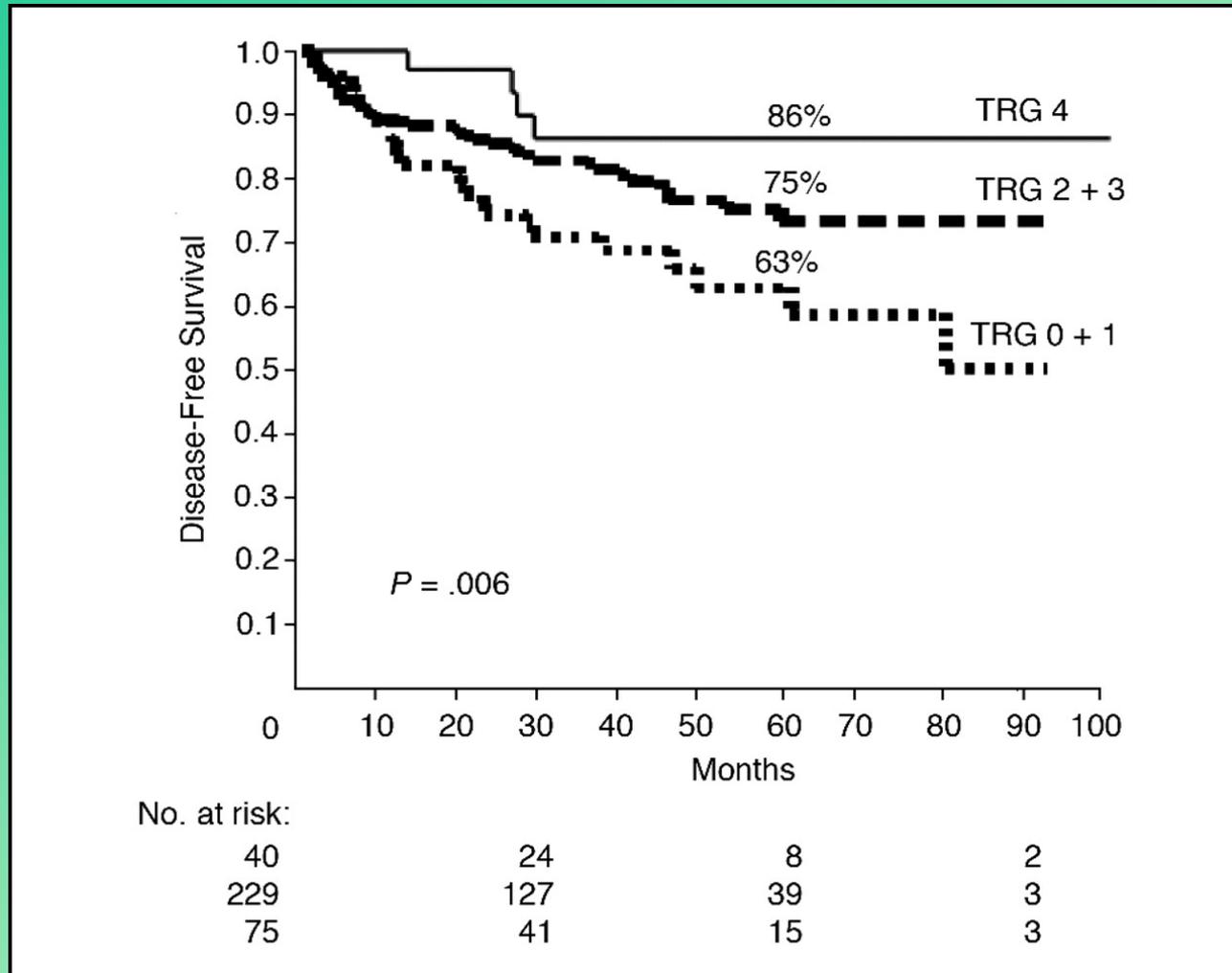
Only local recurrence rate affected by changing timing of treatment

Effect of Chemo-RT on Surgical Specimen

- Pre-op chemo/RT affords unique opportunity to assess efficacy of treatment: the post-treatment pathology specimen, obtained at definitive resection
- Does degree of tumor killing matter to prognosis?

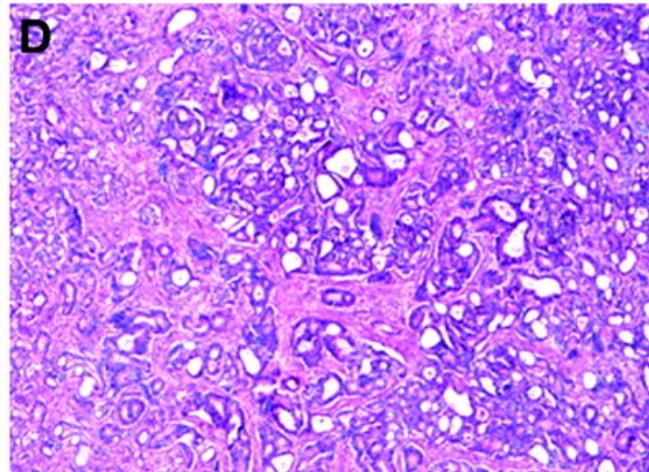
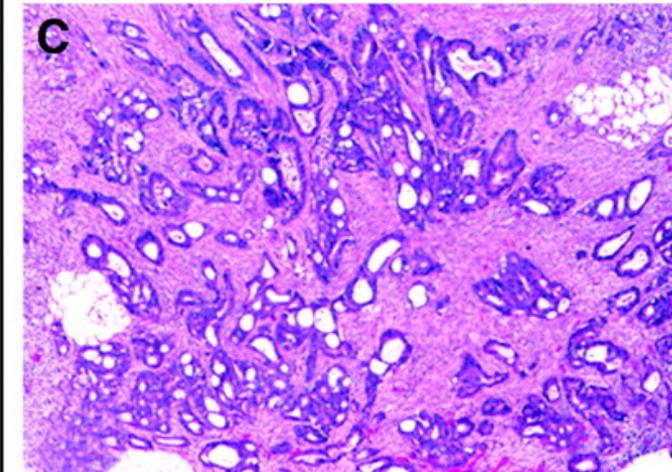
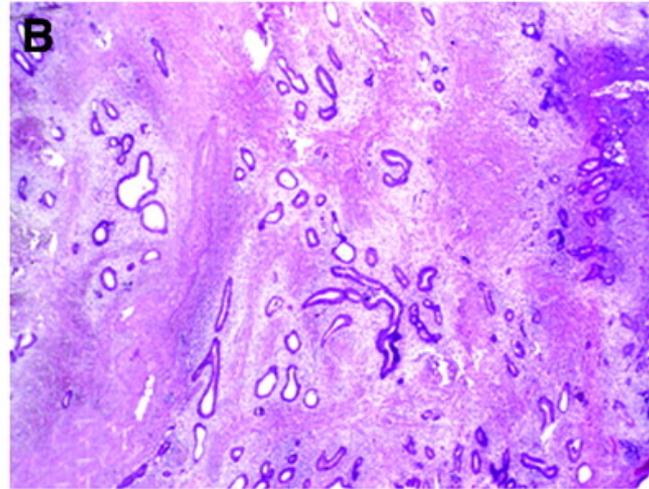
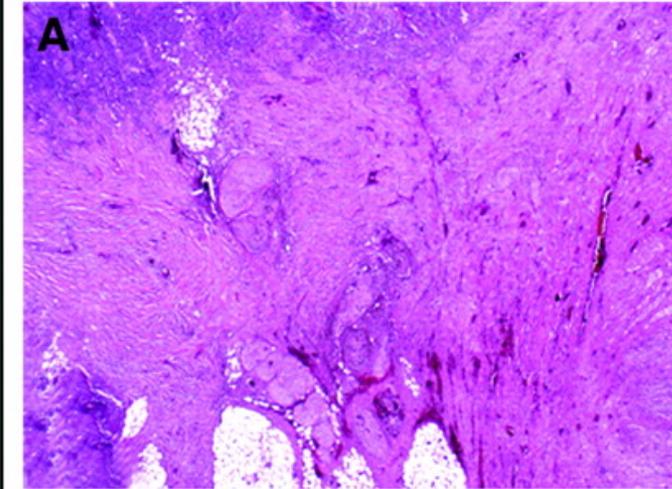


Disease-free survival of 344 patients with rectal carcinoma after preoperative chemoradiotherapy and curative resection (R0 resection), according to tumor regression grading (TRG)



The
answer is:
yes

Tumor regression grading (TRG) after preoperative chemoradiotherapy : (A) total regression, no viable tumor cells, only fibrotic mass, TRG 4; (B) dominant fibrosis outgrowing the tumor mass (>50% tumor regression), TRG 3; (C) dominant tumor mass with obvious fibrosis in 26% to 50% of the tumor mass, TRG 2; (D) minor regression, fibrosis in only 25% or less of the tumor mass, TRG 1



Back to Our Patient

- Clearly the greatest benefit of his treatment to date has been in preventing local recurrence
- The effect of chemotherapy on prevention of metastasis and overall survival in rectal cancer is still modest
- His presentation – with a huge primary tumor, having never been screened – predicted for a poor outcome
 - Nodal status probably understated since nodes were sampled after chemo-RT; nonetheless, based on current guidelines he received no post-operative adjuvant chemo



Conclusions

- Current approach has made some inroads into local and systemic control of rectal cancer
- Pros and cons of current sequencing still up for debate
- As with out patient, the impact of failure to enroll patients in an organized screening program cannot be cured with aggressive cancer therapy



For more information...

- Visit us on the web (www.StarkOncology.com) or at the office...

