Adjuvant Therapy for Rectal Cancer

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Type of Session: Scientific

Background
- Based on data published in the Journal of Clinical Oncology, it has become apparent that 5-year follow-up data are not sufficient for rectal cancer clinical trials.
- The standard adjuvant regimen for rectal cancer includes either continuous infusion 5-FU or oral 5-FU, known as capecitabine (based on the data published in the X-ACT trial).
- Initially, patients with resectable rectal cancer were shown to benefit from adjuvant therapy if they were found to have node positive or T3/T4 disease at the time of surgery.
- Recent data presented at ASCO 2003 suggests that the overall benefit to adjuvant radiation therapy for T3N0 patients is small, and may not be worth the added morbidity it can cause.
- The standard of care for locally advanced rectal cancer has changed since the finding that preoperative chemoradiotherapy is beneficial.
- Potential advantages to preoperative therapy include improved rates of sphincter preservation and decreased toxicity.
- An American trial, the NSABP R-03, was developed to determine the optimal timing of adjuvant therapy, either preoperatively or post-operatively, but this study was closed early secondary to poor accrual.
- The data from the limited numbers of patients treated on the R-03 trial demonstrated improvements in local control and survival with preoperative therapy, although these improvements were not statistically significant.
- The German CAO/ARO/AIO trial, recently published in NEJM, clearly demonstrated a benefit to preoperative chemoradiotherapy with infusional 5-FU and 50.4 Gy, when compared with the same regimen given post-operatively.
- Benefits to preoperative therapy in the German trial included higher rates of sphincter-sparing procedures (39% vs 20%, p=0.004), decreased acute and long term toxicity, and improved local control rates (13% vs 6%, p=0.006).
- Overall survival was not affected by the timing of adjuvant therapy in the German trial (76% pre vs 74% post, p=ns).
- Further analysis of this trial presented at ASCO 2005 showed that patients who responded to preoperative therapy (either with a pathologic complete response or tumor downstaging), had improved survival outcomes compared to patients who did not.

Materials and Methods
- In many Northern European trials, preoperative radiation without chemotherapy is given in a short course over one week (5Gy x 5days).
- This is in contrast to the American strategy which employs radiation over 5-6 weeks.
- The Dutch trial of short course, intensive therapy randomized T1-T3 patients to either 5 Gy x 5 days followed by total mesorectal excision (TME), or TME alone.
- The 5-year local recurrence rate with surgery alone was 12%, but this dropped to 6% with preoperative radiation therapy.
- The 5-year local recurrence rate for stage III patients who underwent surgery alone was 20%.
- The only randomized preoperative therapy trial which ever revealed a significant advantage in overall survival was the Swedish Rectal Cancer Trial, which employed a short, intensive course of radiation.
- Subsequent meta-analyses have demonstrated mixed results on the subject.
- It is not possible to compare the local recurrence and survival data between the short, intensive course trials and the conventional fractionation used in because most of the trials which employed the short course included patients with
T1/T2 disease, unlike trials using conventional fractionation.
- A Polish preoperative trial attempted to determine which strategy is superior; either short course one week intensive radiation therapy (5 Gy x 5days) or conventional fractionation with 5-FU (50.4 Gy in 1.8 Gy fractions).
- 316 patients were eligible, and none of the patients had involvement of the sphincter.
- Pathologic complete response rate (PCR) for the short course was 1% and was 16% for the conventional fractionation scheme.
- The sphincter-sparing surgery rate for the short course and conventional fractionation were the same (61% vs 58%).

**Results**
- The EORTC 22921 study of preoperative therapy had 4 arms: 45 Gy preop with no further therapy, 45 Gy preop with 5-FU following surgery, 45 Gy with 5-FU preop and no further therapy after surgery, and 45 Gy with 5-FU preop, followed by more 5-FU following surgery.
- The study enrolled 1,011 patients, with a median follow-up of 5.4 years.
- This study was presented in abstract form at ASCO 2005.
- This study showed a significant improvement in local control for patients who received chemotherapy (10% vs 17%, p=0.002), but did not demonstrate a survival benefit when adding chemotherapy.
- A French study of preoperative therapy had two arms: 45 Gy followed by surgery and then 5-FU vs. 45 Gy with 5-FU followed by surgery and more 5-FU.
- This study showed an improvement in PCR rate with the addition of chemotherapy (12% vs 4%, p<0.0001), but did not show any improvement in survival (68% vs 67%, p=NS).

**Author's Conclusions**
- One of the problems with preoperative therapy is that some patients (up to 20%) may be over-treated, because they actually are node-negative.
- Radiation therapy is a necessary component of adjuvant therapy for rectal cancer.
- Newer chemotherapeutic agents (like oxaliplatin), when used with 5-FU and radiation, have been demonstrated to improve pathologic complete response rates.
- New combined modality regimens containing novel chemotherapeutics and targeted therapies may improve outcomes.
- The NSABP R-04 study is open, and it is a preoperative study which is randomizing patients to either capecitabine +/- oxaliplatin and radiation or continuous infusion 5-FU +/- oxaliplatin and radiation.
- The ECOG Intergroup trial is open and is randomizing patients to FOLFOX6 +/- bevacizumab following preoperative therapy and surgery.

**Clinical/Scientific Implications**

Dr. Minsky presented a clear and concise review of the relevant issues surrounding adjuvant therapy for rectal cancer. Dr. Minsky makes a very important point when he states that the standard of care should be preoperative chemoradiotherapy for locally advanced rectal cancers. The German trial was instrumental in proving this concept. The issue regarding a short course versus a long course of radiation therapy has not yet been settled, and may not be for some time. Few people would argue that chemotherapy is not required for locally advanced patients, given the data presented. With the proven efficacy of oxaliplatin, bevacizumab, and cetuximab in colon cancer, the future directions of clinical research in rectal cancer treatment are likely going to involve the introduction of these agents either before, during, or after radiation therapy.