Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. National Cancer Institute. *Comprehensive Cancer Information*. http://www.cancer.gov/cancertopics/types/colon-and-rectal. Accessed 5 January 2012.	15	N/A	Estimated new cases and deaths from colon and rectal cancer in the United States in 2012.	New cases: 103,170 (colon); 40,290 (rectal), Deaths: 51,690 (colon and rectal combined)	4
2. Rich T, Gunderson LL, Lew R, Galdibini JJ, Cohen AM, Donaldson G. Patterns of recurrence of rectal cancer after potentially curative surgery. *Cancer* 1983; 52(7):1317-1329.	4	142 cases	To determine patterns of recurrence of rectal cancer after potentially curative surgery.	The incidence of local failure as any component of failure was found to be strongly dependent on the pathologic stage, and for Dukes' A was 8.0% (3/39); Dukes' B, 31% (18/59), and Dukes' C, 50% (22/44). The incidence of local failure for tumors without lymph node metastasis was 17% with only microscopic extension through the wall (modified Astler-Coller Stage MAC-B2m), but increased to 54% in tumors that were adherent to or invading adjacent organs and structures (MAC-B3). Similarly, in tumors with positive lymph nodes, there was a 36% incidence of local failure for tumors confined to the wall or with only microscopic extension through the wall (MAC-C1/C2m), compared to a 67% incidence for tumors with adherence or involvement of adjacent organs (MAC-C3). Other predictors of local recurrence were the tumor location, grade, number of lymph nodes, and blood vessel invasion. The pathologic factors predicting distant metastasis are also presented. Five-year survival for Dukes' A was 77% (30/39); Dukes' B, 44% (26/59); and Dukes' C, 23% (10/44). The implications for future adjuvant therapy based on the identification of patients with the highest risk for local and distant failure are discussed.	3

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3. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; 351(17):1731-1740.	1	823 total patients; 421 patients received preoperative chemoradiotherapy; 402 patients received postoperative chemoradiotherapy	To compare preoperative chemoradiotherapy with postoperative chemoradiotherapy for locally advanced rectal cancer.	The overall 5 year survival rates were 76% and 74 %, respectively (P=0.80). The 5 year cumulative incidence of local relapse was 6% for patients assigned to preoperative chemoradiotherapy and 13% in the postoperative-treatment group (P=0.006). Grade 3 or 4 acute toxic effects occurred in 27% of the patients in the preoperative-treatment group, as compared with 40% of the patients in the postoperative-treatment group (P=0.001); the corresponding rates of long-term toxic effects were 14% and 24%, respectively (P=0.01). Preoperative chemoradiotherapy, as compared with postoperative chemoradiotherapy, improved local control and was associated with reduced toxicity but did not improve OS.	1
4. Bernstein TE, Endreseth BH, Romundstad P, Wibe A. Circumferential resection margin as a prognostic factor in rectal cancer. *Br J Surg* 2009; 96(11):1348-1357.	3a	3,196 patients with known CRM status	To examine the prognostic impact of the CRM in patients with rectal cancer treated by TME with or without RT.	5 year local recurrence, distant metastasis and OS rates were 23.7%, 43.9% and 44.5% respectively for patients with a CRM of 0-2 mm, compared with 8.9%, 21.7% and 66.7% respectively for those with wider margins. A CRM of ≤2 mm had an impact on the prognosis of T2 and T3 tumors located 6-15 cm above the anal verge, but not on lower tumors. CRM also had a prognostic impact on the three endpoints in patients who received preoperative RT, but with less precision. A CRM of ≤2 mm confers a poorer prognosis and patients should be considered for neoadjuvant treatment.	2

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5. Tilney HS, Rasheed S, Northover JM, Tekkis PP. The influence of circumferential resection margins on long-term outcomes following rectal cancer surgery. *Dis Colon Rectum* 2009; 52(10):1723-1729.	3a	435 patients	To assess the influence of various circumferential margins on long-term outcome from rectal cancer surgery.	Median follow-up, 70.4 months. Cancer-specific survival at 5 years was 80.8%, 69.2%, 59.2%, and 34.1% for tumors with a CRM of >10 mm, 3-10 mm, 2 mm, and ≤1mm, respectively (P<0.001). Local recurrence at 5 years was 9.0%, 14.7%, and 25.8% for margins >10 mm, 2-10 mm, and ≤1 mm, respectively (P=0.001). Independent predictors of cancer-specific mortality were circumferential margins of ≤1 mm vs >10 mm (OR=3.38, P=0.014) or 2 mm (OR=2.24, P+0.029), Dukes Stage (C2 vs A: OR=15.18, P<0.001), and vascular invasion (present vs absent: OR=1.51, P=0.033). Local recurrence was predicted by a margin of ≤1 mm (OR=2.29, P=0.041), gender (female vs male: OR=0.25, P=0.002), Dukes Stage (C2 vs A: OR=28.89, P=0.003), and vascular invasion (extramural vs none: OR=2.04, P=0.24). Circumferential margins ≤2 mm are associated with significantly reduced cancer-specific survival, and margins ≤1 mm with increased local recurrence, when other factors are accounted for, challenging the assumption that a CRM of ≤1 mm is safe.	2
6. Gosens MJ, Klaassen RA, Tan-Go I, et al. Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. *Clin Cancer Res* 2007; 13(22 Pt 1):6617-6623.	3a	201 consecutive patients	To evaluate circumferential margin involvement as a prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma.	Local recurrence occurred in only 8% of the patients with a free CRM compared with 43% in case of CRM involvement (P<0.0001). None of the four regression systems were associated with prognosis, not even when corrected for CRM status. However, we did observe a higher degree of tumor regression after radiochemotherapy compared with RT (P<0.001). Absence of tumor regression was associated with increasing invasion depth and a positive CRM (P=0.02 and 0.03, respectively). Assessment of CRM involvement is the most important pathologic variable after radiochemotherapy. Although tumor regression increases the chance on a free CRM, in cases with positive resection margins prognosis is poor irrespective of the degree of therapy-induced regression.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
7. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 2009; 373(9666):821-828.	4	1,156 patients	To prospectively assess the effect of the involvement of the CRM and the plane of surgery achieved.	HR was 0.32 (95% CI, 0.16-0.63, P=0.0011) with 3-year local recurrence rates of 6% (5%-8%) and 17% (10%-26%) for patients who were negative and positive for CRM, respectively. For plane of surgery achieved, HRs for mesorectal and intramesorectal groups compared with the muscularis propria group were 0.32 (0.16-0.64) and 0.48 (0.25-0.93), respectively. At 3 years, the estimated local recurrence rates were 4% (3%-6%) for mesorectal, 7% (%5-11%) for intramesorectal, and 13% (8%-21%) for muscularis propria groups. The benefit of short-course preoperative RT did not differ in the three plane of surgery groups (P=0.30 for trend). Patients in the short-course preoperative RT group who had a resection in the mesorectal plane had a 3-year local recurrence rate of only 1%. In rectal cancer, the plane of surgery achieved is an important prognostic factor for local recurrence. Short-course preoperative RT reduced the rate of local recurrence for all three plane of surgery groups, almost abolishing local recurrence in short-course preoperative RT patients who had a resection in the mesorectal plane. The plane of surgery achieved should therefore be assessed and reported routinely.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
8. Mohiuddin M, Winter K, Mitchell E, et al. Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: Radiation Therapy Oncology Group Trial 0012. *J Clin Oncol* 2006; 24(4):650-655.	1	106 total patients; 103 evaluable	Randomized trial to evaluate the rate of pCR and toxicity of neoadjuvant chemoradiation for advanced T3/T4 distal rectal cancers in a randomized phase II study.	The overall resectability rate was 93%. The median time to surgery was 7 weeks. Tumor downstaging was observed in 78% of patients in both arms. The pCR rate for all assessable patients was 26% in each arm. For patients who had surgery, the pCR rate was also the same (28%) in both arms. Acute and late toxicity was also similar. Grade 3 and 4 acute hematologic and nonhematologic toxicity occurred in 13% and 38% in arm 1 and 12% and 45% in arm 2, respectively. Although the overall complete response rate and toxicity seems similar in both arms, this is the first multi-institutional study to establish a relatively high (28%) pCR rate after neoadjuvant therapy.	2
9. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991; 324(11):709-715.	1	204 patients	A randomized trial to develop a combination regimen to optimize the contribution of chemotherapy, decrease recurrence, and improve survival as compared with adjuvant radiation alone.	After a median follow-up of more than 7 years, the combined therapy had reduced the recurrence of rectal cancer by 34% (P=0.0016; 95% CI, 12%-50 %). Initial local recurrence was reduced by 46% (P=0.036; 95% CI, 2%-70%), and distant metastasis by 37% (P=0.011; 95% CI, 9%-57%). In addition, combined therapy reduced the rate of cancer-related deaths by 36% (P=0.0071; 95% CI, 14%-53%) and the overall death rate by 29% (P=0.025; 95% CI, 7%-45%). The combination of postoperative local therapy with radiation plus 5-FU and systemic therapy with a 5-FU-based regimen significantly and substantively improves the results of therapy for rectal carcinoma with a poor prognosis, as compared with postoperative radiation alone.	1
10. Thomas PR, Lindblad AS. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumor Study Group experience. *Radiother Oncol* 1988; 13(4):245-252.	1	227 patients	Randomized trial to evaluate adjuvant postoperative RT and chemotherapy in rectal carcinoma.	The results of the study showed an advantage for CMT over no adjuvant therapy for time to recurrence (P=0.005) and for survival (P=0.01). Severe acute toxicity was frequent in the combined modality arm (61%) but late effects, including radiation enteritis, have been infrequent. We conclude that postoperative adjuvant therapy is indicated in certain stages of rectal carcinoma and that the present state of knowledge suggests CMT.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
11. Tveit KM, Guldvog I, Hagen S, et al. Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes B and C rectal cancer. Norwegian Adjuvant Rectal Cancer Project Group. *Br J Surg* 1997; 84(8):1130-1135.	1	136 patients	To investigate whether a 1-month regimen of postoperative RT combined with 5-FU could reduce the local recurrence rate and improve survival in patients with Dukes B and C rectal cancer.	The adjuvant treatment was well tolerated. After an observation time of 4-8 years, patients in the adjuvant treatment group had a cumulative local recurrence rate of 12% compared with 30% in the group that had surgery only (P=0.01). The 5-year recurrence-free and OS rate was 64% in the adjuvant group compared with 46% (P=0.01) and 5% (P=0.05) respectively in the surgery group. The adjusted RR of recurrence and death for the adjuvant group was 0.48 (95% CI, 0.28-0.82) and 0.56 (0.33-0.94), respectively. The 1-month postoperative combination regimen improved treatment results in patients with Dukes B and C rectal cancer, in terms of local recurrence rate, recurrence-free survival and OS, without serious side-effects.	1

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12. Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst* 1988; 80(1):21-29.	1	555 total patients; 184 no further treatment; 187 postoperative adjuvant chemotherapy with MOF; 184 postoperative RT	Randomized trial to evaluate postoperative adjuvant chemotherapy or RT for rectal cancer.	The chemotherapy group, when compared with the group treated by surgery alone, demonstrated an overall improvement in DFS (P=.006) and in survival (P=.05). Employing the proportional hazards model, a global test was used to determine the presence of treatment interactions. Investigation of stratification variables employed in this study indicated that sex, and to a lesser extent age and Dukes stage, made individual contributions to the DFS and the survival benefit from chemotherapy. When evaluated according to sex, the benefit for chemotherapy at 5 years, both in DFS (29% vs 47%; P<.001; relative odds, 2.00) and in survival (37% vs 60%; P=.001; relative odds, 1.93), was restricted to males. When males were tested for age trend with the use of a logistic regression analysis, chemotherapy was found to be more advantageous in younger patients. When the group receiving postoperative radiation (4,600-4,700 rad in 26-27 fractions; 5,100-5,300 rad maximum at the perineum) was compared to the group treated only by surgery, there was an overall reduction in local-regional recurrence from 25% to 16% (P=.06). No significant benefit in overall DFS (P=.4) or survival (P=.7) from the use of radiation has been demonstrated. The global test for interaction to identify heterogeneity of response to radiation within subsets of patients was not significant. In conclusion, this investigation has demonstrated a benefit from adjuvant chemotherapy (MOF) for the management of rectal cancer. The observed advantage was restricted to males. Postoperative RT reduced the incidence of local-regional recurrence, but it failed to affect overall DFS and survival.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
13. Wolmark N, Wieand HS, Hyams DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. *J Natl Cancer Inst* 2000; 92(5):388-396.	1	694 total patients; 348 postoperative adjuvant chemotherapy alone; 346 chemotherapy with postoperative RT	To determine whether the addition of RT results in improved DFS and OS.	The average time on study for surviving patients is 93 months as of September 30, 1998. Postoperative RT resulted in no beneficial effect on DFS (P=.90) or OS (P=.89), regardless of which chemotherapy was utilized, although it reduced the cumulative incidence of locoregional relapse from 13% to 8% at 5-year follow-up (P=.02). Male patients who received 5-FU plus leucovorin demonstrated a statistically significant benefit in DFS at 5 years compared with those who received MOF (55% vs 47%; P=.009) but not in 5-year OS (65% vs 62%; P=.17). The addition of postoperative RT to chemotherapy in Dukes' B and C rectal cancer did not alter the subsequent incidence of distant disease, although there was a reduction in locoregional relapse when compared with chemotherapy alone.	1
14. Smalley SR, Benedetti JK, Williamson SK, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. *J Clin Oncol* 2006; 24(22):3542-3547.	3a	1,917 patients	To evaluate 3 postoperative 5-FU radiochemotherapy regimens.	Median follow-up was 5.7 years. Lethal toxicity was <1%, with grade 3 to 4 hematologic toxicity in 49% to 55% of the bolus arms vs 4% in the protracted venous infusion arm. No DFS or OS difference was detected (3-year DFS, 67%- 69% and 3-year OS, 81%-83% in all arms). Locoregional failure at first relapse was 8% in arm 1, 4.6% in arm 2, and 7% in arm 3. Locoregional failure in T1-2, N1-2, and T3, N0-2 primaries who received low anterior resection (those most suitable for primary resection) was 5% in arm 1, 3% in arm 2, and 5% in arm 3. All arms provide similar RFS and OS, with different toxicity profiles and central catheter requirements.	2

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15. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994; 331(8):502-507.	1	660 patients	To determine whether the efficacy of chemotherapy could be improved by administering 5-FU by protracted infusion throughout the duration of RT and whether the omission of semustine would reduce the toxicity and delayed complications of chemotherapy without decreasing its antitumor efficacy.	With a median follow-up of 46 months among surviving patients, patients who received a protracted infusion of 5-FU had a significantly increased time to relapse (P=0.01) and improved survival (P=0.005). There was no evidence of a beneficial effect in the patients who received semustine plus 5-FU. A protracted infusion of 5-FU during pelvic RT improved the effect of combined-treatment postoperative adjuvant therapy in patients with high-risk rectal cancer. Semustine plus 5-FU was not more effective than a higher dose of systemic 5-FU given alone.	1
16. Tepper JE, O'Connell MJ, Petroni GR, et al. Adjuvant postoperative fluorouracil-modulated chemotherapy combined with pelvic radiation therapy for rectal cancer: initial results of intergroup 0114. *J Clin Oncol* 1997; 15(5):2030-2039.	1	1,696 patients	Randomized trial to determine whether the efficacy of adjuvant postoperative 5-FU-modulated chemotherapy combined with pelvic RT could be improved by the addition of leucovorin and/or levamisole.	With a median follow-up duration of 48 months, there is no statistically significant advantage to any of the treatment regimens compared with bolus 5-FU alone. There is evidence of increased GI toxicity with the three-drug combination compared with bolus 5-FU alone. Statistical analysis suggests it is very unlikely that either levamisole-containing combination will be shown to be of value with further follow-up evaluation. There is no evidence at present for a beneficial effect of levamisole in the adjuvant treatment of rectal cancer. Definitive evaluation of the effect of the addition of leucovorin to 5-FU and pelvic radiation will require further follow-up evaluation.	1
17. Lee JH, Lee JH, Ahn JH, et al. Randomized trial of postoperative adjuvant therapy in stage II and III rectal cancer to define the optimal sequence of chemotherapy and radiotherapy: a preliminary report. *J Clin Oncol* 2002; 20(7):1751-1758.	1	274 patients	A prospective randomized trial to define the optimal sequence of chemotherapy and RT of postoperative adjuvant treatment in stage II and III rectal cancer.	With a median follow-up of 37 months for surviving patients, DFS was significantly prolonged in arm I compared with arm II (8% vs 70% at 4 years; P=.043). 23 recurrences occurred in arm I and 38 in arm II (P=.047). OS was not significantly different between arms I and II (84% vs 82% at 4 years; P=.387). Early RT with concurrent chemotherapy after resection of stage II and III rectal cancer demonstrated a statistically significant advantage for DFS compared with late RT with chemotherapy.	1

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18. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 2005; 23(24):5644-5650.	1	1,168 patients	To evaluate the long-term effects on survival and recurrence rates of preoperative RT in the treatment of curatively operated rectal cancer patients.	Median follow-up time was 13 years (range, 3 to 15 years). The OS rate in the irradiated group was 38% vs 30% in the nonirradiated group (P=.008). The cancer-specific survival rate in the irradiated group was 72% vs 62% in the nonirradiated group (P=.03), and the local recurrence rate was 9% vs 26% (P<.001), respectively. The reduction of local recurrence rates was observed at all tumor heights, although it was not statistically significant for tumors >10 cm from the anal verge. Preoperative RT with 25 Gy in 1 week before curative surgery for rectal cancer is beneficial for OS and cancer-specific survival and local recurrence rates after long-term follow-up.	1
19. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; 336(14):980-987.	1	1,168 patients	To evaluate the survival rates of preoperative RT in resectable rectal cancer.	The irradiation did not increase postoperative mortality. After 5 years of follow-up, the rate of local recurrence was 11% (63/553 patients) in the group that received RT before surgery and 27% (150/557) in the group treated with surgery alone (P<0.001). This difference was found in all subgroups defined according to Dukes' stage. The overall 5-year survival rate was 58% in the RT-plus-surgery group and 48% in the surgery-alone group (P=0.004). The cancer-specific survival rates at 9 years among patients treated with curative resection were 74% and 65%, respectively (P=0.002). A short-term regimen of high-dose preoperative RT reduces rates of local recurrence and improves survival among patients with resectable rectal cancer.	1

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20. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol* 2005; 23(34):8697-8705.	1	1,147 patients	To analyze the occurrence of subacute and late adverse effects in patients treated with preoperative irradiation for rectal cancer.	Irradiated patients were at increased risk of admissions during the first 6 months from the primary treatment (RR=1.64; 95% CI, 1.21-2.22); these were mainly for GI diagnoses. Overall, the 2 groups showed no difference in the risk of admissions more than 6 months from the primary treatment (RR=0.95; 95% CI, 0.80-1.12). Regarding specific diagnoses, however, RR were increased for admissions later than 6 months from the primary treatment in irradiated patients for unspecified infections, bowel obstruction, abdominal pain, and nausea. GI disorders, resulting in hospital admissions, seem to be the most common adverse effect of short-course preoperative RT in patients with rectal cancer. Bowel obstruction was the diagnosis of potentially greatest importance, which was more frequent in irradiated than in nonirradiated patients.	1
21. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Late gastrointestinal disorders after rectal cancer surgery with and without preoperative radiation therapy. *Br J Surg* 2008; 95(2):206-213.	1	908 total patients; 454 preoperative RT; 454 surgery alone	To analyze late GI disorders necessitating hospital admission following rectal cancer surgery and to determine their relationship to preoperative RT.	Irradiated patients had an increased RR of late small bowel obstruction (RR 2.49 (95% CI, 1.48 to 4.19)) and abdominal pain (RR 2.09 (95% CI, 1.03 to 4.24)) compared with patients treated by surgery alone. The risk of late small bowel obstruction requiring surgery was greatly increased (RR 7.42 (95% CI, 2.23 to 24.66)). Irradiated patients with postoperative anastomotic leakage were at increased risk for late small bowel obstruction (RR 2.99 (95% CI, 1.07 to 8.31)). The risk of small bowel obstruction was also related to the radiation technique and energy used. Small bowel obstruction is more common in patients with rectal cancer treated with preoperative RT.	1

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22. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; 345(9):638-646.	1	1,805 patients	A multicenter, randomized trial to determine whether the addition of preoperative RT increases the benefit of TME.	The overall rate of survival at 2 years among the eligible patients was 82.0% in the group assigned to both RT and surgery and 81.8% in the group assigned to surgery alone (P=0.84). Among the 1,748 patients who underwent a macroscopically complete local resection, the rate of local recurrence at 2 years was 5.3%. The rate of local recurrence at 2 years was 2.4% in the RT-plus-surgery group and 8.2% in the surgery-only group (P<0.001). Short-term preoperative RT reduces the risk of local recurrence in patients with rectal cancer who undergo a standardized TME.	1
23. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; 373(9666):811-820.	1	1,340 total patients from 80 centers	Randomized trial to compare short-course preoperative RT vs initial surgery with selective postoperative chemoradiotherapy.	Median follow-up of surviving patients was 4 years. 99 patients had developed local recurrence (27 preoperative RT vs 72 selective postoperative chemoradiotherapy). A reduction of 61% was noted in the RR of local recurrence for patients receiving preoperative RT (HR 0.39, 95% CI, 0.27-0.58, P<0.0001), and an absolute difference at 3 years of 6.2% (95% CI, 5.3-7.1) (4.4% preoperative RT vs 10.6% selective postoperative chemoradiotherapy). A relative improvement was recorded in DFS of 24% for patients receiving preoperative RT (HR 0.76, 95% CI, 0.62-0.94, P=0.013), and an absolute difference at 3 years of 6.0% (95% CI, 5.3-6.8) (77.5% vs 71.5%). OS did not differ between the groups (HR 0.91, 95% CI, 0.73-1.13, P=0.40). Taken with results from other randomized trials, the findings provide convincing and consistent evidence that short-course preoperative RT is an effective treatment for patients with operable rectal cancer.	1

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24. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; 355(11):1114-1123.	1	1,011 patients	To evaluate the addition of chemotherapy to preoperative RT and the use of postoperative chemotherapy in the treatment of rectal cancer.	The combined 5-year OS rate for all 4 groups was 65.2%. The 5-year cumulative incidence rates for local recurrences were 8.7%, 9.6%, and 7.6% in the groups that received chemotherapy preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive chemotherapy (P=0.002). The rate of adherence to preoperative chemotherapy was 82.0%, and to postoperative chemotherapy was 42.9%. In patients with rectal cancer who receive preoperative RT, adding 5-FU-based chemotherapy preoperatively or postoperatively has no significant effect on survival. Chemotherapy, regardless of whether it is administered before or after surgery, confers a significant benefit with respect to local control.	1
25. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006; 24(28):4620-4625.	1	733 patients	Randomized trial to compare preoperative RT with chemoradiotherapy.	Grade 3 or 4 acute toxicity was more frequent with chemoradiotherapy (14.6% vs 2.7%; P<.05). There was no difference in sphincter preservation. Complete sterilization of the operative specimen was more frequent with chemoradiotherapy (11.4% vs 3.6%; P<.05). The 5-year incidence of local recurrence was lower with chemoradiotherapy (8.1% vs 16.5%; P<.05). 5-year OS in the two groups did not differ. Preoperative chemoradiotherapy despite a moderate increase in acute toxicity and no impact on OS significantly improves local control and is recommended for T3-4, N0-2, M0 adenocarcinoma of the middle and distal rectum.	1

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26. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol* 2009; 27(31):5124-5130.	1	254 total patients; 123 preoperative chemotherapy 131 postoperative chemotherapy	To compare neoadjuvant vs adjuvant chemoradiotherapy in the treatment of locally advanced rectal carcinoma.	Surviving patients were observed for a median of 8.4 years. The 5-year DFS for preoperative patients was 64.7% vs 53.4% for postoperative patients (P=.011). The 5-year OS for preoperative patients was 74.5% vs 65.6% for postoperative patients (P=.065). A complete pathologic response was achieved in 15% of preoperative patients. No preoperative patient with a complete pathologic response has had a recurrence. Preoperative chemoradiotherapy, compared with postoperative chemoradiotherapy, significantly improved DFS and showed a trend toward improved OS.	1
27. Roh MS, Colangelo L, Wieand S, et al. Response to preoperative multimodality therapy predicts survival in patients with carcinoma of the rectum. *J Clin Oncol* 2004; 22(14S):3505.	1	253 total patients; 123 preoperative chemotherapy; 130 postoperative chemotherapy	To compare preoperative neoadjuvant to postoperative adjuvant chemoradiation.	Among the 78 preoperative patients evaluable for response, 25.6% had a complete clinical response, 48.7% had partial, 23.1% stable and 2.6% progressive but operable disease. In the complete clinical response group, OS was 100% as compared to 95% in the partial group and 83% in the stable group (P=0.02 for complete clinical response vs other). Corresponding values were 95%, 78%, 66% (P=0.004) for DFS and 95%, 80%, 70% (P0.01) for RFS. Compared with postoperative adjuvant, preoperative neoadjuvant appears to result in improved OS, DFS and RFS. Complete responders at surgery have a significant improvement in overall, disease-free and RFS.	1

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28. Kim TH, Chie EK, Kim DY, et al. Comparison of the belly board device method and the distended bladder method for reducing irradiated small bowel volumes in preoperative radiotherapy of rectal cancer patients. Int J Radiat Oncol Biol Phys 2005; 62(3):769-775.	3c	20 patients	To determine the most effective method to reduce the irradiated small bowel volume when using a belly board device, a distended bladder, or both in patients with rectal cancer undergoing preoperative pelvic RT.	All patients underwent four sets of CT scan under the conditions of four different methods as follows: Group I = empty bladder without the use of belly board; Group II = empty bladder with the use of belly board; Group III = distended bladder without the use of belly board; and Group IV = distended bladder with the use of belly board. It was found that the volume of irradiated small bowel decreased in the order of Group I, Group II, Group III, and Group IV at all dose levels ($P<0.05$). Compared with Group I, the mean volume reduction rate (reduced volume) of irradiated small bowel in Group II varied between 14.5% and 65.4% (15.5-80.4 cm(3)), in Group III it varied between 48.1% and 82.0% (21.6-163.1 cm(3)), and in Group IV between 51.4% and 96.4% (28.6-167.1 cm(3)). The distended bladder was more effective than the belly board device for reducing the volume of irradiated small bowel in rectal cancer patients receiving pelvic RT. The combination of the belly board device and distended bladder showed an additive effect and was the most effective method for reducing the irradiated small bowel volume.	3

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
29. Siddiqui F, Shi C, Papanikolaou N, Fuss M. Image-guidance protocol comparison: supine and prone set-up accuracy for pelvic radiation therapy. Acta Oncol 2008; 47(7):1344-1350.	10	30 patients; 829 mega-voltage CT; 299 prone set-up on belly board; 530 supine set-up	To retrospectively investigate the impact of prone vs supine patient set-up and use of various image-guidance protocols on residual set-up error for RT of pelvic malignancies. To identify an optimal frequency and protocol for image-guidance.	The protocol with the highest imaging frequency, alternate day imaging with a running mean (50% imaging frequency), provided the best set-up error reduction. This protocol would have reduced the average length of 3D corrective vector shifts derived from daily image-guidance from 15.2 and 13.5 mm for prone and supine set-up, to 5 and 5.4 mm, respectively. A No Action Level protocol, averaging shifts of the first 3 fractions (No Action Level3), would have reduced the respective set-up variability to 6.3 (prone), and 7.5 mm (supine). An extended No Action Level protocol, averaging shifts of the first 3 fractions plus weekly imaging, would have reduced the daily positioning variability to 6 mm for both prone and supine set-ups. Daily image-guidance yielded set-up corrections >10 mm in 64.3% for prone and 70.3% for supine position. Use of the No Action Level 3 protocol would have reduced the respective frequency to 14.4%, and 21.2% for prone, and supine positioning. In comparison, the alternate day running mean protocol would have reduced the frequency of shifts >10 mm to 5.5% (prone), and 8.3% (supine), respectively. In this comparison, high frequency image-guidance provided the highest benefit with respect to residual set-up errors. However, both No Action Level and extended No Action Level protocols provided significant set-up error reduction with lowered imaging frequency. While the mean 3D vector of corrective shifts was longer for prone set-up compared to the supine set-up, using any image-guidance protocol would have reduced shifts for prone set-up to a greater extent than for the supine set-up. This indicates a greater risk for systematic set-up errors in prone set-up, and larger random errors using a supine patient set-up.	3

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
30. Drzymala M, Hawkins MA, Henrys AJ, Bedford J, Norman A, Tait DM. The effect of treatment position, prone or supine, on dose-volume histograms for pelvic radiotherapy in patients with rectal cancer. Br J Radiol 2009; 82(976):321-327.	4	19 consecutive patients	To evaluate the volume of bowel and dose received in the prone and supine positions in patients undergoing preoperative rectal cancer chemoradiation.	At 5 Gy and 10 Gy dose levels, a significantly higher volume of bowel was irradiated in the supine position (P<0.001). At 15 Gy, it was marginally significant (P=0.018). From 20-45 Gy, there was no significant difference in the volume of bowel irradiated with each 5 Gy increment. This study demonstrates that the volume of bowel irradiated at doses associated with bowel toxicity in concurrent chemoradiation is not significantly higher in the supine position. This position could be adopted for patients undergoing pre-operative rectal cancer chemoradiation.	3
31. Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann Surg Oncol* 2008; 15(10):2661-2667.	3a	132 patients	To assess whether the time interval between neoadjuvant therapy and surgery affects the operative and postoperative morbidity and mortality, the pCR rate and disease recurrence in locally advanced rectal cancer.	The groups were demographically comparable except for the group A patients being younger at operation. The median interval between chemoradiation and surgery was 56 days (range 13-173 days). 37 patients (28%) had a pCR and near pCR. 53 patients (40%) had complications. There was no in-hospital mortality. Surgery type, operative time, number of intraoperative blood transfusions, postoperative complications, and length of hospitalization were not influenced by the interval length. The pCR and near pCR rates were higher with longer interval: 17% in group A, 35% in group B (P=0.03). Patients operated at an interval >7 weeks had significantly better DFS (P=0.05). A neoadjuvant-surgery interval >7 weeks was associated with higher rates of pCR and near pCR, decreased recurrence and improved DFS.	2

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
32. Habr-Gama A, Perez RO, Proscurshim I, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? *Int J Radiat Oncol Biol Phys* 2008; 71(4):1181-1188.	3a	250 patients	To retrospectively evaluate whether this interval has an impact on survival.	There were no statistical differences in OS (86% vs 81.6%) or DFS rates (56.5% and 58.9%) between patients according to interval (≤12 vs >12 weeks). Patients with intervals of 12 weeks or less had significantly higher rates of stage III disease (34% vs 20%; P=0.009). The delay in surgery was caused by a suspected clinical complete response in 23 patients (interval, 48 +/- 10.3 weeks). 5 year overall and DFS rates for this subset were 84.9% and 51.6%, not significantly different compared with the remaining group (84%; P=0.96 and 57.8%; P=0.76, respectively). Delay in surgery for the evaluation of tumor response after neoadjuvant chemoradiation therapy is safe and does not negatively affect survival. These results support the hypothesis that shorter intervals may interrupt ongoing tumor necrosis.	2
33. Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. *ASCO Meeting Abstracts* 2011; 29(15_suppl):3503.	1	1,608 total patients	Randomized trial to compare the efficacy of 4 chemotherapy regimens administered concomitantly with preoperative RT.	From July 2004 to August 2010 patients were obtained and randomly assigned. No significant differences in the rates of pCR, sphincter-saving surgery, or surgical downstaging were identified between the 5-FU and capecitabine regimens or between the regimens, with and without oxaliplatin. Patients treated with oxaliplatin experienced significantly more grade 3/4 diarrhea. Administration of capecitabine with preoperative RT achieved similar rates of pCR, sphincter-saving surgery, and surgical downstaging compared to continuous IV infusion 5-FU. The addition of oxaliplatin did not improve preliminary outcomes but added significant toxicity. The definitive analysis of local tumor control will be performed in fall 2013.	1

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
34. Hofheinz R, Wenz FK, Post S, et al. Capecitabine (Cape) versus 5-fluorouracil (5-FU)-based (neo)adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): Long-term results of a randomized, phase III trial. *ASCO Meeting Abstracts* 2011; 29(15_suppl):3504.	1	392 evaluable patients: Arm A n=197; Arm B n=195. Stratum I n=231; Stratum II n=161.	To report long-term data of a non-inferiority phase III trial investigating (neo-) adjuvant chemoradiotherapy with capecitabine in comparison with 5-FU.	At a median follow-up of 52 months, the local recurrence rate was equal (capecitabine 6%, 5-FU 7%, P=0.665), while significantly less pts developed distant metastases in the Cape arm (18.8% vs 27.7%; P=0.037). A total of 93 patients had died, 55 of whom in the 5-FU arm. Capecitabine was non-inferior to 5-FU regarding 5-year OS (capecitabine 75.7% vs 5-FU 66.6%; P=0.0004). The test for superiority showed borderline significance in favor of capecitabine (P=0.053). 3-year DFS was significantly better with capecitabine (75.2% vs 66.6%; P=0.034). Capecitabine patients developing hand-foot skin reactions had better 3-year DFS (83.2%) and 5-year OS (91.4%) in comparison with the remaining patients (P=0.004 for DFS and P<0.0001 for OS). In view of the advantageous safety profile, an improved nodal-downstaging in neoadjuvant stratum and the favorable survival data Cape may replace 5-FU in the perioperative treatment of locally advanced rectal cancer.	1
35. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; 28(10):1638-1644.	1	598 patients 299 received capecitabine (Cap 45 group); 299 capecitabine and oxaliplatin (Capox 50 group)	Randomized trial to compare neoadjuvant RT plus capecitabine with dose-intensified RT plus capecitabine and oxaliplatin.	More preoperative grade 3 to 4 toxicity occurred in the Capox 50 group (25% vs 1%; P<.001). Surgery was performed in 98% of patients in both groups. There were no differences between groups in the rate of conservative surgery (75%) or postoperative deaths at 60 days (0.3%). The complete sterilization of the operative specimen rate was 13.9% with Cap 45 and 19.2% with Capox 50 (P=.09). When complete sterilization of the operative specimen was combined with yp few residual cells, the rate was respectively 28.9% with Cap 45 and 39.4% with Capox 50 (P=.008). The rate of positive circumferential rectal margins (between 0 and 2 mm) was 19.3% with Cap 45 and 9.9% with Capox 50 (P=.02). The benefit of oxaliplatin was not demonstrated and this drug should not be used with concurrent irradiation. Cap 50 merits investigation for T3-4 rectal cancers.	1

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
36. Valentini V, Coco C, Minsky BD, et al. Randomized, multicenter, phase IIb study of preoperative chemoradiotherapy in T3 mid-distal rectal cancer: raltitrexed + oxaliplatin + radiotherapy versus cisplatin + 5-fluorouracil + radiotherapy. *Int J Radiat Oncol Biol Phys* 2008; 70(2):403-412.	1	164 patients accrued in 10 Italian centers: 83 patients in cisplatin, 5-FU and RT (PLAFUR arm); 81 in the raltitrexed, oxaliplatin, and RT (TOMOX-RT arm)	To prospectively compare the rates of pathologic response, acute toxicity, and sphincter preservation with two different schedules of preoperative chemoradiotherapy in patients with cT3 mid-distal rectal cancer.	Overall, tumor regression grade 1-2 was observed in 76 patients (46.4%) and ypT0 in 49 (29.9%). The tumor regression grade 1-2 rate was 41.0% vs 51.9% (P=0.162) and the ypT0 rate was 24.1% vs 35.8% (P=0.102) for the PLAFUR vs TOMOX-RT arm, respectively. The overall rate of tumor regression grade 1 and ypN+ was 4.6%. The occurrence of ypT downstaging was significantly greater in the TOMOX-RT arm (P=0.035). Grade 3-4 acute toxicity occurred in 19 patients (11.6%): 7.1% in the PLAFUR arm vs 16.4% in the TOMOX-RT arm. Sphincter-saving surgery was performed in 143 patients (87.2%) overall: 87.9% in the PLAFUR arm and 86.4% in the TOMOX-RT arm.	1
37. Kiran RP, Nisar PJ, Pelley RJ, Fazio VW, Lavery IC. Role of routine adjuvant chemotherapy after neoadjuvant chemoradiotherapy and resection in low-risk patients with rectal cancer. *ASCO Meeting Abstracts* 2011; 29(15_suppl):e14032.	3a	1,363 total patients: 798 (58.5%) received adjuvant chemotherapy (+chemo group); 565 (41.5%) did not (–chemo group)	To identify specific groups where adjuvant chemotherapy may reasonably be avoided.	The median follow up time was 53 months. Treatment with adjuvant chemotherapy was associated with improved survival for patients with lymph nodal involvement on pathological staging and stratified as AJCC stages II and III. The findings of this study suggest that the decision whether to perform adjuvant chemotherapy after chemoradiation and resection for rectal cancer patients can be stratified based on lymph node status and AJCC stage. Adjuvant chemotherapy may reasonably be avoided, without adversely affecting survival, in selected low risk patients. OS (%) for patients receiving adjuvant vs no adjuvant chemotherapy following surgery for rectal cancer with preoperative chemoradiotherapy.	2

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
38. Garofalo M, Moughan J, Hong T, et al. RTOG 0822: A Phase II Study of Preoperative (PREOP) Chemoradiotherapy (CRT) Utilizing IMRT in Combination with Capecitabine (C) and Oxaliplatin (O) for Patients with Locally Advanced Rectal Cancer. *Int J Radiat Oncol Biol Phys* 2011; 81(2):S3-S4.	3a	68 patients	To determine whether the acute GI toxicity seen in RTOG 0247 (C/O/RT arm) could be reduced using inverse-planned IMRT optimized to limit dose to the small bowel.	By grade (G), the incidence of preoperative GI toxicity was 31% (G1), 28% (G2), 22% (G3) and 1% (G4). 51% of patients (35/68) developed Grade 2 preoperative GI toxicity. By comparison, the rate of preoperative Grade 2 GI toxicity in the C/O/RT arm of RTOG 0247 was 58% (30/52; P=0.31). 21% (14/68) of patients underwent an APR. The pCR rate was 15% (10/68). Patterns of failure and survival analyses are ongoing. RTOG 0822 is the first multi-institutional, prospective study of the use of IMRT in the preoperative treatment of rectal cancer and is the largest such Phase II clinical experience to date. Inverse-planned rectal IMRT was feasible with a high rate of contouring and planning compliance, likely attributable to utilization of the RTOG anorectal contouring atlas. IMRT-based preoperative chemoradiotherapy in RTOG 0822 resulted in reduced preoperative Grade 2 GI toxicity when compared with RTOG 0247; however, this did not reach statistical significance. The pCR rate suggests that tumor coverage was not compromised with highly conformal therapy. A regression analysis of the DVH and toxicity data is currently being performed toward identifying optimal IMRT planning criteria for future studies.	2

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
39. Samuelian JM, Callister MD, Ashman JB, Young-Fadok TM, Borad MJ, Gunderson LL. Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2012; 82(5):1981-1987.	3a	92 consecutive patients	To evaluate IMRT to treat rectal cancer and report patient clinical outcomes.	Patients who received IMRT had significantly less GI toxicity. 62% of patients undergoing chemoradiotherapy experienced ≥Grade 2 acute GI side effects, compared with 32% among IMRT patients (P=0.006). The reduction in overall GI toxicity was attributable to fewer symptoms from the lower GI tract. Among chemoradiotherapy patients, ≥Grade 2 diarrhea and enteritis was experienced among 48% and 30% of patients, respectively, compared with 23% (P=0.02) and 10% (P=0.015) among IMRT patients. There was no significant difference in hematologic or genitourinary acute toxicity between groups. In addition, pCR rates and postoperative morbidity between treatment groups did not differ significantly.	2
40. Fuller CD, Nijkamp J, Duppen JC, et al. Prospective randomized double-blind pilot study of site-specific consensus atlas implementation for rectal cancer target volume delineation in the cooperative group setting. *Int J Radiat Oncol Biol Phys* 2011; 79(2):481-489.	1	14 contour sets	Prospective randomized double-blind study to determine the effect of a consensus guideline-based visual atlas on contouring the target volumes.	Among 1 expert and 7 Group A and 6 Group B observers, greater agreement was found for the GTV (mean CN, 0.75) than for the CTVs (mean CN, 0.46-0.65). Atlas exposure for Group A led to significantly increased interobserver agreement for CTVA (mean initial CN, 0.68, after atlas use, 0.76; P=.03) and increased agreement with the expert reference (initial mean CN, 0.58; after atlas use, 0.69; P=.02). For the GTV and CTVB, neither the interobserver nor the expert agreement was altered after atlas exposure. Consensus guideline atlas implementation resulted in a detectable difference in interobserver agreement and a greater approximation of expert volumes for the CTVA but not for the GTV or CTVB in the specified case. Visual atlas inclusion should be considered as a feature in future clinical trials incorporating conformal RT.	1

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
41. Fuller CD, Nijkamp J, Rasch CR, et al. Impact of rectal cancer target volume consensus atlas implementation in the cooperative group setting: Preliminary results from a prospective randomized double-blind pilot study. *2010 Gastrointestinal Cancers Symposium*: American Society of Clinical Oncology 2010:Abstrast No: 458.	10	N/A	To determine the effect of a consensus guideline-based visual atlas on physician contouring of rectal cancer target volumes.	In 28 evaluable contour sets (1 expert, 7 Group A, 6 Group B), there was greater agreement for GTV (mean CN 0.75) than CTV (mean CN 0.46-0.65). Atlas exposure for Group A led to significantly increased interobserver agreement for CTV-A (mean initial CN 0.68, post-atlas 0.76, P=0.031), as well as increased agreement with the expert reference (initial mean CN 0.58, 0.69 post-atlas, P= 0.016). For CTV-B, neither interobserver nor expert agreement was altered after atlas exposure. Consensus guideline atlas implementation resulted in a detectable difference in target volume agreement between users, allowing greater approximation of expert volumes for CTV-A.	3
42. Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys* 2009; 74(3):824-830.	15	N/A	To develop a RTOG atlas of the elective CTV definitions to be used for planning pelvic IMRT for anal and rectal cancers.	The panel achieved consensus CTV definitions to be used as guidelines for the adjuvant therapy of rectal cancer and definitive therapy for anal cancer. The most important difference from similar atlases for gynecologic or genitourinary cancer is mesorectal coverage. Detailed target volume contouring guidelines and images are discussed.	4
43. Taylor N, Crane C, Skibber J, et al. Elective groin irradiation is not indicated for patients with adenocarcinoma of the rectum extending to the anal canal. *Int J Radiat Oncol Biol Phys* 2001; 51(3):741-747.	3a	536 patients 186 patients had anal canal involvement	To evaluate the inguinal nodal failure rate in patients with locally advanced rectal cancer with anal canal involvement treated with pelvic chemoradiation without elective inguinal irradiation.	The median follow-up was 50 months. Only 6 of 184 anal canal involvement patients who had clinically negative inguinal nodes at presentation developed inguinal nodal recurrence (5-year actuarial rate 4%); 4 of the 6 cases were isolated. Two patients underwent successful salvage. Only one died of uncontrolled groin disease. Local control was achieved in both patients with inguinal nodal disease at presentation, but both died of metastatic disease. Only 3 patients with tumors >4 cm from the verge developed inguinal recurrence (5-year actuarial rate <1%). Inguinal nodal failure in rectal cancer patients with anal canal involvement treated with neoadjuvant or adjuvant chemoradiation is not high enough to justify routine elective groin irradiation.	2

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
44. Gunderson LL, Sargent DJ, Tepper JE, et al. Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer: a pooled analysis. *Int J Radiat Oncol Biol Phys* 2002; 54(2):386-396.	1	2,551 total patients: 200 patients in NCCTG 79-47-51; 656 patients in NCCTG 86-47-51; 1,695 patients in INT 114	To determine the rates of survival and disease control by TNM and MAC stage in three randomized North American rectal adjuvant studies.	5 year follow-up was available in 94% of patients and 7-year follow-up in 84%. OS and DFS were dependent on both TN stage and NT stage. Even among N2 patients (4 or more LN+), T stage influenced 5-year OS (T1-2, 69%; T3, 48%; T4, 38%). 3 risk groups of patients were defined: 1) Intermediate: T3N0, T1-2N1, 2) Moderately high: T4N0, T1-2N2, T3N1, and 3) High: T3N2, T4N1, T4N2. For Group 1, 5-year OS was 74% and 81%, and 5-year DFS was 66% and 74%. For Group 2, 5-year OS ranged from 61% to 69%. For Group 3, OS ranged from 33% to 48%, as seen in the survival analyses. Patients with a single high-risk factor of either extension beyond the rectal wall (T3N0) or nodal involvement (T1-2N1) have improved OS, DFS, and disease control when compared to those with both high risk factors. Different treatment strategies may be indicated for intermediate- (T3N0, T1-2N1) vs moderately high or high-risk patients in view of differential survival and rates of relapse. For future trial design, it may be preferable to perform separate studies, or a planned statistical analysis, for the "intermediate-risk" vs the "moderately high" or "high-risk" subsets of patients.	1

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
45. Gunderson LL, Sargent DJ, Tepper JE, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. *J Clin Oncol* 2004; 22(10):1785-1796.	1	3,791 total patients; 179 surgery alone; 281 RT alone; 779 RT + 5-FU +/- semustine bolus chemotherapy; 325 RT + protracted venous infusion chemotherapy; 1,695 RT + 5-FU +/- leucovorin or levamisole bolus chemotherapy; 532 chemotherapy alone	To determine survival and relapse rates by T and N stage and treatment method in 5 randomized phase III North American rectal adjuvant studies.	5 year follow-up was available in 94% of surviving patients, and 8-year follow-up, in 62%. OS and DFS were dependent on TN stage, NT stage, and treatment method. Even among N2 patients, T substage influenced 5-year OS (T1-2, 67%; T3, 44%; T4, 37%; P<.001). Three risk groups of patients were defined: 1) Intermediate (T1-2/N1, T3/N0). 2) Moderately high (T1-2/N2, T3/N1, T4/N0). 3) High (T3/N2, T4/N1, T4/N2). For intermediate-risk patients, those receiving surgery plus chemotherapy had 5-year OS rates of 85% (T1-2/N1) and 84% (T3/N0), which was similar to results with surgery plus RT plus chemotherapy (T1-2/N1, 78% to 83%; T3/N0, 74% to 80%). For moderately high-risk lesions, 5-year OS ranged from 43% to 70% with surgery plus chemotherapy, and 44% to 80% with surgery plus RT plus chemotherapy. For high-risk lesions, 5-year OS ranged from 25% to 45% with surgery plus chemotherapy, and 29% to 57% with surgery plus RT plus chemotherapy. Different treatment strategies may be indicated for intermediate-risk vs moderately high or high-risk patients based on differential survival rates and rates of relapse. Use of trimodality treatment for all patients with intermediate-risk lesions may be excessive, since surgery plus chemotherapy resulted in 5-year OS of approximately 85%; however, 5-year DFS rates with surgery plus chemotherapy were 78% (T1-2/N1) and 69%(T3/N0), indicating room for improvement.	1

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
46. Guillem JG, Diaz-Gonzalez JA, Minsky BD, et al. cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. *J Clin Oncol* 2008; 26(3):368-373.	10	188 patients	To determine the accuracy of pre-CMT ERUS or MRI staging and to explore the validity of a nonpreoperative CMT approach for cT3N0 disease.	Tumors were located a median of 5 cm from the anal verge. Sphincter-preserving surgery was performed in 143 patients (76%). Overall pCR was 20% and 41 patients (22%) had pathologically positive mesorectal lymph nodes. The incidence of positive lymph nodes significantly increased with T stage: ypT0, 3%; ypT1, 7%; ypT2, 20%; ypT3-4, 36% (P=.001). The accuracy of preoperative ERUS/MRI for staging mid to distal cT3N0 rectal cancer is limited because 22% of patients have undetected mesorectal lymph node involvement despite CMT. Therefore, ERUS-/MRI-staged T3N0 rectal cancer patients should continue to receive preoperative CMT. Although 18% may be overstaged and therefore overtreated, our data suggest that an even larger number would be understaged and require postoperative CMT, which is associated with significantly inferior local control, higher toxicity, and worse functional outcome.	2
47. Garcia-Aguilar J, Shi Q, Thomas CR, Jr., et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. *Ann Surg Oncol* 2012; 19(2):384-391.	4	90 total patients	Phase II trial to assess the efficacy and safety of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer.	Among 77 eligible patients who underwent local excision, 34 patients achieved a pCR (44%) and 49 (64%) tumors were downstaged (ypT0-1), but 4 patients (5%) had ypT3 tumors. Five local excision specimens contained lymph nodes; one T3 tumor had a positive node. All but one patient had negative margins. 33 (39%) of 84 patients developed chemoradiation-related grade ≥3 complications. Rectal pain was the most common PC. Chemoradiation before local excision for T2N0 tumors results in a high pCR rate and negative resection margins. However, complications during chemoradiation and after local excision are high. The true efficacy of this approach will ultimately be assessed by the long-term oncologic outcomes.	3

Resectable Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
48. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J Gastrointest Surg* 2006; 10(10):1319-1328; discussion 1328-1319.	3a	361 total patients	To evaluate patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy.	Mean follow-up was 59.9 months. There were 13 (13.1%) recurrences: 5 (5%) endorectal, 7 (7.1%) systemic and 1 (1%) combined recurrence. All 5 isolated endorectal recurrences were salvaged. Mean recurrence interval was 52 months for local failure and 29.5 months for systemic failure. There were 5 cancer-related deaths after systemic recurrences. OS and DFS 5-year rates were 93% and 85%. Even though surgery remains the standard treatment for rectal cancer, nonoperative treatment after complete clinical response following neoadjuvant chemoradiation therapy may be safe and associated with good survival rates in a highly selected group of patients. Survival in these patients is significantly affected by systemic failure. Exclusive local failure occurs late after chemoradiation therapy completion and is frequently amenable to salvage therapy.	2

Evidence Table Key

Study Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
    a. Cohort
    b. Cross-sectional
    c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations Key

5-FU = Fluorouracil

CI = Confidence interval

CMT = Combined-modality therapy

CN = Conformation number

CRM = Circumferential resection margin

CT = Computed tomography

CTV = Clinical target volume

DFS = Disease-free survival

ERUS = Endorectal ultrasound

GI = Gastrointestinal

GTV = Gross tumor volume

HR = Hazard ratio

IMRT = Intensity-modulated radiotherapy

MOF = 5-fluorouracil, semustine, and vincristine

MRI = Magnetic resonance imaging

OR = Odds ratio

OS = Overall survival

pCR = Pathologic complete response

RFS = Relapse-free survival

RR = Relative risk

RT = Radiation therapy

TME = Total mesorectal excision