Rectal Cancer-Metastatic Disease at Presentation
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin.* 2014;64(1):9-29.	Review/Other-Tx	N/A	To provide the expected numbers of new cancer cases and deaths in 2014 in the United States nationally and for each state, as well as a comprehensive overview of cancer incidence, mortality, and survival rates and trends using the most current population-based data available. In addition, we estimate the total number of deaths averted since the early 1990s as a result of 2 decades of declining cancer death rates and present the actual number of deaths reported in 2010 by age for the 10 leading causes of death and the 5 leading causes of cancer death.	Cancer death rates have been continuously declining for the past 2 decades. Overall, the risk of dying from cancer decreased by 20% between 1991 and 2010. Progress has been most rapid for middle-aged black men, among whom death rates have declined by approximately 50%. Despite this substantial progress, 5-year survival rates among blacks continue to lag behind whites by as much as 22 percentage points for uterine cancer, 21 percentage points for cancer of the oral cavity, and 17 percentage points for urinary bladder cancer. Further progress can be accelerated by applying existing cancer control knowledge across all segments of the population, with an emphasis on those groups in the lowest socioeconomic bracket and other disadvantaged populations.	4
2. Ward KC, Young Jr. JR, Gloeckler Ries LA. SEER Survival Monograph: Cancer Survival Among Adults: US SEER Program, 1988-2001, Patient and Tumor Characteristics. Cancers of the Colon and Rectum. 2012; http://seer.cancer.gov/publications/survival/surv_colon_rectum.pdf, March 1, 2013.	Review/Other-Tx	N/A	SEER actively follows all previously diagnosed patients on an annual basis to obtain vital status allowing the calculation of observed and relative survival rates.	The lack of substantial variation in survival rates by subsites of the colon and rectum is interesting. This is best explained by the fact that each subsite had a similar stage distribution at diagnosis with 50%-60% in each group being diagnosed early, stage 0/I or II. The poorer survival among patients whose subsite could not be determined is probably explained by the fact that many of these patients had multifocal colon cancer, i.e., simultaneous lesions arising in multiple polyposis; or else occurred in patients whose disease was so extensive within the colon at the time of diagnosis that the point of origin could not be determined.	4

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3. Platell C, Ng S, O'Bichere A, Tebbutt N. Changing management and survival in patients with stage IV colorectal cancer. *Dis Colon Rectum.* 2011;54(2):214-219.	Observational-Tx	313 patients	To compare the treatment and survival for all patients presenting with stage IV colorectal cancer managed over the last 20 years at a tertiary referral center and to define independent predictors for survival.	A total of 313 patients with stage IV colorectal cancer were analyzed. 2-year OS was significantly higher in the 2003 to 2009 cohort (40.3%; 95% CI, 28.6%-51.8%) than in either the 1989 to 1995 cohort (20.6%, 95% CI, 13.5%- 28.6%) or the 1996 to 2002 cohort (19.3%; 95% CI, 12.8%-26.9%). Significant independent predictors for OS included surgical resection with anastomosis (HR, 0.507; 95% CI, 0.371-0.692), surgical resection with stoma (0.578; 0.401-0.833), ASA score 3 (1.493; 1.150-1.941) or score 4 (2.532; 1.505-4.258), receiving palliative chemotherapy (0.64; 0.457-0.885), and receiving palliative radiotherapy (0.543; 0.352-0.835).	2
4. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure. *Oncology.* 2010;78(3-4):237-248.	Review/Other-Tx	N/A	To conduct a computerized search using PubMed and Google Scholar for reports published between January 1993 and August 2009 using mesh headings and key words relating to the treatment of colorectal cancer. If reports identified by these criteria referred to other papers not in the initial search, then these were also reviewed if relevant to metastatic colorectal cancer.	7 new chemotherapy agents have been licensed for the treatment of advanced colorectal cancer, with associated improved median survival from 5 months to 2 years. Complete responses are rare with systemic chemotherapy alone, but higher overall response rates to systemic and intrahepatic chemotherapies have enabled initially unresectable patients to undergo potentially curative surgical resection of metastases. Improved surgical expertise together with the adjunctive use of RFA has further expanded the definition of resectability. Advances in the understanding of tumor biology have resulted in the development of clinically useful biomarkers and the emergence of active biological therapies.	4

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5. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351(17):1731-1740.	Experimental-Tx	421 patients	To compare preoperative chemoradiotherapy with postoperative chemoradiotherapy for locally advanced rectal cancer.	421 patients were randomly assigned to receive preoperative chemoradiotherapy and 402 patients to receive postoperative chemoradiotherapy. 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).	1
6. van Dijk TH, Tamas K, Beukema JC, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. *Ann Oncol.* 2013;24(7):1762-1769.	Observational-Tx	50 patients	To evaluate the efficacy and tolerability of preoperative short-course radiotherapy followed by capecitabine and oxaliplatin treatment in combination with bevacizumab and subsequent radical surgical treatment of all tumor sites in patients with stage IV rectal cancer.	Of 50 included patients, 42 (84%) had liver metastases, 5 (10%) lung metastases, and 3 (6%) both liver and lung metastases. Radical surgical treatment was possible in 36 (72%) patients. The 2-year OS rate was 80% [95% CI 66.3%-90.0%]. The 2-year recurrence rate was 64% (95% CI 49.8%-84.5%). Toxic effects were tolerable. No treatment-related deaths occurred.	1

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7. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg*. 2008;247(1):125-135.	Observational-Tx	929 consecutive patients	To identify risk factors associated with cancer-specific survival and develop a predictive model for patients undergoing primary hepatic resection for metastatic colorectal cancer.	Postoperative mortality and morbidity were 1.5% and 25.9%, respectively. 5-year and 10-year cancer-specific survival were 36% and 23%. On multivariate analysis, 7 risk factors were found to be independent predictors of poor survival: number of hepatic metastases >3, node positive primary, poorly differentiated primary, extrahepatic disease, tumor diameter ≥5 cm, carcinoembryonic antigen level >60 ng/mL, and positive resection margin. The first 6 of these criteria were used in a preoperative scoring system and the last 6 in the postoperative setting. Patients with the worst postoperative prognostic criteria had an expected median cancer-specific survival of 0.7 years and a 5-year cancer-specific survival of 2%. Conversely, patients with the best prognostic postoperative criteria had an expected median cancer-specific survival of 7.4 years and a 5-year cancer-specific survival of 64%. When tested both predictive models fitted the data well with no significant differences between observed and predicted outcomes (P>0.05).	1

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8. Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? *J Am Coll Surg*. 2010;210(6):934-941.	Observational-Tx	156 consecutive patients	To compare indications, perioperative results, and oncologic outcomes in patients with a synchronous presentation of a colorectal primary tumor and colorectal liver metastases, according to these different surgical strategies and to determine predictive factors of survival in patients with synchronous colorectal liver metastases.	142 patients (83%) had resection of all disease. 72 patients underwent classic, 43 combined, and 27 reverse strategies. Median numbers of colorectal liver metastases per patient were 1 in the combined, 3 in the classic, and 4 in the reverse strategy group (P=0.01 classic vs reverse; P<0.001 reverse vs combined). Postoperative mortality rates in the combined, classic, and reverse strategies were 5%, 3%, and 0%, respectively (P=NS), and postoperative cumulative morbidity rates were 47%, 51%, and 31%, respectively (P=NS). 3-year and 5-year OS rates were, respectively, 65% and 55% in the combined, 58% and 48% in the classic, and 79% and 39% in the reverse strategy (NS). On multivariate analysis, liver tumor size >3 cm (HR 2.72, 95% CI, 1.52 to 4.88) and cumulative postoperative morbidity (HR 1.8, 95% CI, 1.03 to 3.19) were independently associated with OS after surgery.	1
9. de Jong MC, van Dam RM, Maas M, et al. The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience. *HPB (Oxford)*. 2011;13(10):745-752.	Observational-Tx	22 patients	To assess the feasibility and outcome of this approach for synchronous colorectal liver metastasis.	Of the 22 patients planned to undergo the liver-first strategy, the approach was completed in 18 patients (81.8%). The main reason for treatment failure was disease progression. Patients who completed treatment and patients who deviated from the protocol had a similar location of the primary tumor, as well as comparable size, number and distribution of colorectal liver metastasis (all P>0.05). Postoperative morbidity and mortality were 27.3% and 0% following liver resection and 44.4% and 5.6% after colorectal surgery, respectively. On an intention-to-treat-basis, overall 3-year survival was 41.1%. However, 37.5% of patients who completed the treatment had developed recurrent disease at the time of the last follow-up.	1

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10. Martin R, Paty P, Fong Y, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. *J Am Coll Surg.* 2003;197(2):233-241; discussion 241-232.	Observational-Tx	240 patients	To review our experience with synchronous colorectal metastasis and to define the safety of simultaneous vs staged resection of the colon and liver.	134 patients underwent simultaneous resection of a colorectal primary and hepatic metastasis in a single operation (Group I), and 106 patients underwent staged operations (Group II). Simultaneous resections tend to be performed for right colon primaries (P<0.001), smaller (P<0.01) and fewer (P<0.001) liver metastases, and less extensive liver resection (P<0.001). Complications were less common in the simultaneous resection group, with 65 patients (49%) sustaining 142 complications, compared with 71 patients (67%) sustaining 197 complications for both hospitalizations in the staged resection group (P<0.003). Patients having simultaneous resection required fewer days in the hospital (median 10 days vs 18 days, P=0.001). Perioperative mortality was similar (simultaneous, n=3; staged, n=3).	2
11. Tanaka K, Shimada H, Matsuo K, et al. Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. *Surgery.* 2004;136(3):650-659.	Observational-Tx	39 consecutive patients	To seek patient selection criteria for simultaneous resection of a colorectal primary and a liver metastasis on the basis of short and long term outcome.	Only the volume of the resected liver was selected as a risk factor for postoperative complications (350 g mean resected liver volume in patients with postoperative complications vs 150 g in those without complications; P<.05). Patient age of 70 years or older (P<.05) and poorly differentiated or mucinous adenocarcinoma as the primary lesion (P<.01) predicted decreased OS by univariate analysis. Multivariate analysis retained histologic differentiation of the colorectal primary as an independent survival predictor (P<.05).	2
12. van der Wal GE, Gouw AS, Kamps JA, et al. Angiogenesis in synchronous and metachronous colorectal liver metastases: the liver as a permissive soil. *Ann Surg.* 2012;255(1):86-94.	Observational-Tx	29 patients	To investigate whether the presence of a primary colorectal cancer is associated with changes in angiogenic status and proliferation/apoptotic rate in synchronous liver metastases and/or adjacent liver parenchyma.	In all 3 groups a higher expression of the angiogenic factors was encountered in adjacent liver parenchyma as compared to the metastases. VEGFR-2 gene expression was abundant in adjacent liver parenchyma in all 3 groups. VEGF-A and VEGFR-1 were prominent in adjacent parenchyma in the SS-group. The SS-group showed the highest Ang-2/Ang-1 ratio both in the metastases and the adjacent liver. This was accompanied by a high turnover of tumor cells.	2

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13. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg.* 2004;240(4):711-717; discussion 717-718.	Observational-Tx	265 total patients	To report overall long-term results of stage 0 rectal cancer following neoadjuvant chemoradiation and compare long-term results between operative and nonoperative treatment.	OS and DFS 10-year rates were 97.7% and 84%. In 71 patients (26.8%) complete clinical response was observed following chemoradiation therapy (Observation group). 22 patients (8.3%) showed incomplete clinical response and pT0N0M0 resected specimens (Resection group). There were no differences between patient's demographics and tumor's characteristics between groups. In the Resection group, 9 definitive colostomies and 7 diverting temporary ileostomies were performed. Mean follow-up was 57.3 months in Observation Group and 48 months in Resection Group. There were 3 systemic recurrences in each group and 2 endorectal recurrences in Observation Group. 2 patients in the Resection group died of the disease. 5-year OS and DFS rates were 88% and 83%, respectively, in Resection Group and 100% and 92% in Observation Group.	1
14. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol.* 2011;29(35):4633-4640.	Observational-Tx	21 patients	To evaluate feasibility and safety of a wait-and-see policy with strict selection criteria and follow-up.	21 patients with clinical complete response were included in the wait-and-see policy group. Mean follow-up was 25 +/- 19 months. One patient developed a local recurrence and had surgery as salvage treatment. The other 20 patients are alive without disease. The control group consisted of 20 patients with a pathologic complete response after surgery who had a mean follow-up of 35 +/- 23 months. For these patients with a pathologic complete response, cumulative probabilities of 2-year DFS and OS were 93% and 91%, respectively.	1

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15. Ciliberto D, Prati U, Roveda L, et al. Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: a systematic review and meta-analysis of randomized controlled trials. *Oncol Rep.* 2012;27(6):1849-1856.	Review/Other-Tx	3 studies; 666 patients	To perform a systematic review of randomized clinical trials and meta-analysis to address the question if current available studies support the use of systemic chemotherapy as an adjunct to surgery in resected/resectable patients.	Three studies randomizing combined treatment vs surgery alone for a total of 666 patients (642 evaluable for survival analysis) were selected and included in the final analysis. Evidence for chemotherapy-induced benefit in terms of both DFS (pooled HR, 0.71; CI, 0.582-0.878; P=0.001) and PFS (pooled HR, 0.75; CI, 0.620-0.910; P=0.003) was demonstrated. However, our meta-analysis failed to demonstrate a significant advantage of combined treatment in terms of OS (pooled HR, 0.743; CI, 0.527-1.045; P=0.088). Chemotherapy combined with surgical resection of colorectal liver metastases improves DFS and PFS whereas the benefit in OS is not demonstrated on the basis of the available results of randomized clinical trials.	4
16. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet.* 2008;371(9617):1007-1016.	Experimental-Tx	364 patients	To assess the combination of perioperative chemotherapy and surgery compared with surgery alone for patients with initially resectable liver metastases from colorectal cancer.	In the perioperative chemotherapy group, 151 (83%) patients were resected after a median of 6 (range 1-6) preoperative cycles and 115 (63%) patients received a median 6 (1-8) postoperative cycles. 152 (84%) patients were resected in the surgery group. The absolute increase in rate of PFS at 3 years was 7.3% (from 28.1% [95.66% CI, 21.3-35.5] to 35.4% [28.1-42.7]; HR 0.79 [0.62-1.02]; P=0.058) in randomized patients; 8.1% (from 28.1% [21.2-36.6] to 36.2% [28.7-43.8]; HR 0.77 [0.60-1.00]; P=0.041) in eligible patients; and 9.2% (from 33.2% [25.3-41.2] to 42.4% [34.0-50.5]; HR 0.73 [0.55-0.97]; P=0.025) in patients undergoing resection. 139 patients died (64 in perioperative chemotherapy group vs 75 in surgery group). Reversible postoperative complications occurred more often after chemotherapy than after surgery (40/159 [25%] vs 27/170 [16%]; P=0.04). After surgery we recorded two deaths in the surgery alone group and one in the perioperative chemotherapy group.	1

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17. Sorbye H, Mauer M, Gruenberger T, et al. Predictive factors for the benefit of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). *Ann Surg.* 2012;255(3):534-539.	Observational-Tx	237 events from 342 eligible patients	To conduct an exploratory retrospective analysis to identify baseline factors possibly predictive for a benefit of perioperative FOLFOX on PFS.	After adjustment for identified prognostic factors, moderately (5.1-30 ng/mL) and highly (>30 ng/mL) elevated carcinoembryonic antigen serum levels were both predictive for the benefit of perioperative chemotherapy (interaction P=0.07; HR = 0.58 and HR = 0.52 for treatment benefit). For patients with moderately or highly elevated carcinoembryonic antigen (>5 ng/mL), the 3-year PFS was 35% with perioperative chemotherapy compared to 20% with surgery alone. Performance status 0 and body mass index lower than 30 were also predictive for the benefit of perioperative chemotherapy (interaction P=0.04 and P=0.02). However, the number of patients with performance status 1 and body mass index 30 or higher was limited. The benefit of perioperative therapy was not influenced by the number of metastatic lesions (1 vs 2-4, interaction HR = 0.98).	3
18. Lubezky N, Geva R, Shmueli E, et al. Is there a survival benefit to neoadjuvant versus adjuvant chemotherapy, combined with surgery for resectable colorectal liver metastases? *World J Surg.* 2009;33(5):1028-1034.	Observational-Tx	105 patients	To report the results of a retrospective analysis of liver resection in patients with primarily resectable colorectal rectal metastases to the liver.	56/105 patients who underwent liver resections for colorectal metastases (2002-2005) are included. The two groups were comparable for demographics, characteristics of disease (including recurrence risk), treatment protocols, and follow-up. The respective 1-, 2-, and 3-year OS rates were 91%, 91%, and 84%, and the event-free survival rates were 63%, 49%, and 49% for the 19 adjuvant patients, and 95%, 91%, and 70%, and 94%, 50%, and 50% for the 37 neoadjuvant patients.	2
19. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg.* 2004;240(4):644-657; discussion 657-648.	Observational-Tx	1,439 patients	Single institution consecutive series of unresectable colorectal liver metastases evaluating the efficacy of neoadjuvant chemotherapy consisting of 5-FU and mostly oxaliplatin (70%).	Among 1,104 unresectable patients, 138 (12.5%) "good responders" underwent hepatic resection. At 49 months, 80% recurred (29% hepatic, 43% hepatic and extrahepatic). Survival and disease free survival rate was 33 and 23% at 5 years and 22 and 17% at 10 years, respectively.	1

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20. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol.* 2005;23(36):9243-9249.	Observational-Tx	42 patients	To evaluate the resectability rate of patients with not optimally resectable advanced colorectal carcinoma confined to the liver after treatment with FOLFOX4.	42/44 patients were assessable for this analysis. 25 patients (60%) had tumor reduction by serial imaging. 17 patients (40%) underwent surgery (surgery-complete response, n=14; surgery-partial response, n=1; and surgery-unresponsive, n=2) after a median of 6 months of chemotherapy. With a median postsurgical follow-up of 22 months (range, 13 to 32 months), 11 recurrences have occurred in the 15 surgery-complete response and surgery-partial response patients. Median survival time was 26 months.	2
21. Masi G, Cupini S, Marcucci L, et al. Treatment with 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer. *Ann Surg Oncol.* 2006;13(1):58-65.	Observational-Tx	74 patients	To evaluate the outcome of patients with initially unresectable metastatic colorectal cancer who were treated with a combination of irinotecan, oxaliplatin, and 5-FU/LV followed by a potentially curative resection of metastases.	4 patients underwent an extended hepatectomy, 9 patients underwent a right hepatectomy, 3 patients underwent a left hepatectomy, and 3 patients had a segmental resection. In 5 patients, surgical removal of extrahepatic disease was also performed. In 7 patients, surgical resection was combined with intraoperative RFA. The median OS of the 19 patients who underwent operation is 36.8 months, and the 4-year survival rate is 37%. The median OS of the 34 patients who were responsive to chemotherapy, but who did not undergo operation, is 22.2 months (P=.0114).	2
22. Kemeny NE, Melendez FD, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol.* 2009;27(21):3465-3471.	Observational-Tx	49 patients	To determine the conversion to resectability in patients with unresectable liver metastases from colorectal cancer treated with hepatic arterial infusion plus systemic oxaliplatin and irinotecan.	92% of the 49 patients had complete (8%) or partial (84%) response, and 23 (47%) of the 49 patients were able to undergo resection in a group of patients with extensive disease (73% with >5 liver lesions, 98% with bilobar disease, 86% with ≥6 segments involved). For chemotherapy-naive and previously treated patients, the median survival from the start of hepatic arterial infusion therapy was 50.8 and 35 months, respectively. The only baseline variable significantly associated with a higher resection rate was female sex. Variables reflecting extensive anatomic disease, such as number of lesions or number of vessels involved, were not significantly associated with the probability of resection.	3

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23. Wicherts DA, de Haas RJ, Andreani P, et al. Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases. *Br J Surg.* 2010;97(2):240-250.	Observational-Tx	364 patients	To evaluate long-term survival in patients with colorectal liver metastases who underwent hepatectomy following portal vein embolization.	Of 364 patients who underwent hepatectomy, 67 had portal vein embolization beforehand and 297 did not. Those who had portal vein embolization more often had more than 3 liver metastases (68% vs 40.9%; P<0.001) that were more frequently bilobar (78% vs 55.2%; P<0.001), and a higher proportion underwent extended hepatectomy (63% vs 18.1%; P<0.001). Postoperative morbidity rates were 55% and 41.1%, respectively (P=0.035), and overall 3-year survival rates were 44% and 61.0% (P=0.001). 32 other patients who were treated by portal vein embolization but did not undergo resection all died within 3 years.	2
24. Goodman KA, Wiegner EA, Maturen KE, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. *Int J Radiat Oncol Biol Phys.* 2010;78(2):486-493.	Observational-Tx	26 patients	Phase I dose-escalation study to explore the feasibility and safety of treating primary and metastatic liver tumors with single-fraction SBRT.	All patients tolerated the single-fraction SBRT well without developing a dose-limiting toxicity. Nine acute Grade 1 toxicities, one acute Grade 2 toxicity, and two late Grade 2 gastrointestinal toxicities were observed. After a median of 17 months follow-up (range, 2-55 months), the cumulative risk of local failure at 12 months was 23%. 15 patients have died: 11 treated for liver metastases and 4 with primary liver tumors died. The median survival was 28.6 months, and the 2-year actuarial OS was 50.4%.	2
25. Rule W, Timmerman R, Tong L, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. *Ann Surg Oncol.* 2011;18(4):1081-1087.	Observational-Tx	27 patients	To identify a tolerable and effective dose for 5-fraction SBRT for hepatic metastases.	27 patients, 9 in each cohort, with 37 lesions were enrolled and treated: 17 men and 11 women; median age 62 (range 48-86) years; most common site of primary disease, colorectal (44.4%). Median follow-up was 20 (range 4-53) months. There was no grade 4 or 5 toxicity or treatment-related grade 3 toxicity. Actuarial 24-month local control rates for the 30-, 50-, and 60-Gy cohorts were 56%, 89%, and 100%, respectively. There was a statistically significant difference for local control between the 60- and 30-Gy cohorts (P=0.009) but not between the 60- and 50-Gy cohorts (P=0.56) or the 50- and 30-Gy cohorts (P=0.091). The maximum tolerated dose was not reached.	1

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26. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol.* 2009;27(10):1572-1578.	Experimental-Tx	47 patients; 63 liver lesions	To evaluate the efficacy and tolerability of high-dose SBRT for one or two liver metastases.	Local progression occurred in only 3 lesions at a median of 7.5 months (range, 7-13 months) after SBRT. Actuarial in-field local control rates at 1- and 2-years after SBRT were 95% and 92%, respectively. Among lesions with maximal diameter of ≤3 cm, 2-year local control was 100%. Median survival was 20.5 months.	1
27. Kennedy TJ, Cassera MA, Khajanchee YS, Diwan TS, Hammill CW, Hansen PD. Laparoscopic radiofrequency ablation for the management of colorectal liver metastases: 10-year experience. *J Surg Oncol.* 2013;107(4):324-328.	Observational-Tx	130 patients	To analyze our 10-year experience with laparoscopic RFA.	In this cohort, median survival was 40.4 months with 5-year survival of 28.8%. Overall, 9.2% of patients had a local recurrence (3.6% for tumors ≤3 cm). On univariate analysis, factors associated with decreased survival were body mass index (P=0.045), rectal primary (P=0.005), and increased tumor size (P=0.002). On multivariate analysis, increased tumor size (HR 1.29 [95% CI: 1.04-1.59]; P=0.020) and bilobar disease (HR 2.06 [95% CI: 1.02-4.15]; P=0.044) were associated with decreased survival. On univariate analysis, only body mass index was found to be associated with disease recurrence (P=0.025).	2
28. Siperstein AE, Berber E, Ballem N, Parikh RT. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. *Ann Surg.* 2007;246(4):559-565; discussion 565-557.	Observational-Tx	234 patients	To assess factors affecting long-term survival of patients undergoing RFA of colorectal hepatic metastases, with attention to evolving chemotherapy regimens.	234 patients underwent 292 RFA sessions from 1997 to 2006, an average of 8 months after initiation of chemotherapy. 23% had extrahepatic disease preoperatively. Patients averaged 2.8 lesions, with a dominant diameter of 3.9 cm. Kaplan-Meier actuarial survival was 24 months, with actual 3 and 5 years survival of 20.2% and 18.4%, respectively. Median survival was improved for patients with ≤3 vs >3 lesions (27 vs 17 months, P=0.0018); dominant size <3 vs >3 cm (28 vs 20 months, P=0.07); chorioembryonic antigen <200 vs >200 ng/mL (26 vs 16 months, P=0.003). Presence of extrahepatic disease (P=0.34) or type of pre/postoperative chemotherapy (5-FU/LV vs FOLFOX/FOLFIRI vs bevacizumab) (P=0.11) did not alter median survival.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
29. Solbiati L, Ahmed M, Cova L, Ierace T, Brioschi M, Goldberg SN. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. *Radiology.* 2012;265(3):958-968.	Observational-Tx	99 consecutive patients	To determine the long-term (10-year) survival of patients with colorectal liver metastases treated with RFA and systemic chemotherapy with intention to treat.	Primary and secondary technical success rates were 93.1% (188/202) and 100% (14/14), respectively. Local tumor progression occurred in 11.9% (24/202) metastases, and 54.2% (13/24) of these were re-treated. Patient survival rates increased with re-treatment vs no re-treatment (P<.001). At follow-up, 125 new liver metastases were found, and of these 32.8% (41/125) were treated with RFA. OS rates were 98.0%, 69.3%, 47.8%, 25.0%, and 18.0% (median: 53.2 months) at 1, 3, 5, 7, and 10 years, respectively. The major complication rate was 1.3% (2/156), and there were no procedure-related deaths. At the time this article was written, 32.3% (32/99) of the patients were alive, and 67.7% (67/99) were deceased, with a median follow-up of 72 months.	2
30. Gulec SA, Pennington K, Wheeler J, et al. Yttrium-90 Microsphere-selective Internal Radiation Therapy With Chemotherapy (Chemo-SIRT) for Colorectal Cancer Liver Metastases: An In Vivo Double-Arm-Controlled Phase II Trial. *Am J Clin Oncol.* 2012.	Observational-Tx	20 patients	To investigate the objective responses obtained by Y microsphere treatment when combined with contemporary chemotherapy in the front-line (first or second line) setting in patients with colorectal liver metastases.	A decrease in total lesion glycolysis on FDG-PET was seen in 19/20 patients. The mean decrease in total lesion glycolysis values in the tumors receiving chemo-selective internal radiation therapy and chemo-only treatment were 86.26%+/-18.57% and 31.74%+/-80.99% (P<0.01), 93.13%+/-11.81% and 40.80%+/-73.32% (P=0.01), and 90.55%+/-19.75% and 54.91%+/-38.55% (P<0.01) at 4 weeks, 2 to 4 months, 6 to 8 months post-treatment, respectively. Functional and anatomic tumor volume changes were in concordance with the total lesion glycolysis changes.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol.* 2010;28(23):3687-3694.	Experimental-Tx	46 patients	A prospective multicenter randomized phase III trial to assess the safety and efficacy of intra-arterial 90Y-resin microspheres in liver-limited metastatic colorectal cancer among patients for whom all other evidence based treatments had failed.	46 patients were randomly assigned and 44 were eligible for analysis (arm A, n=23; arm B, n=21). Median follow-up was 24.8 months. Median time to liver progression was 2.1 and 5.5 months in arms A and B, respectively (HR = 0.38; 95% CI, 0.20 to 0.72; P=.003). Median time to tumor progression was 2.1 and 4.5 months, respectively (HR = 0.51; 95% CI, 0.28 to 0.94; P=.03). Grade 3 or 4 toxicities were recorded in 6 patients after 5-FU monotherapy and in one patient after radioembolization plus 5-FU treatment (P=.10). 25/44 patients received further treatment after progression, including 10 patients in arm A who received radioembolization. Median OS was 7.3 and 10.0 months in arms A and B, respectively (HR = 0.92; 95% CI, 0.47 to 1.78; P=.80).	1
32. Albert M, Kiefer MV, Sun W, et al. Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. *Cancer.* 2011;117(2):343-352.	Observational-Tx	121 patients	To evaluate response and survival after transarterial chemoembolization.	A total of 245 treatments were performed over 141 cycles on 121 patients. 95/141 treatment cycles were evaluable for response: 2 (2%) partial response, 39 (41%) stable disease, and 54 (57%) progression. Median time to disease progression in the treated liver was 5 months, and median time to disease progression anywhere was 3 months. Median survival was 33 months from diagnosis of the primary colon cancer, 27 months from development of liver metastases, and 9 months from chemoembolization. Survival was significantly better when chemoembolization was performed after first- or second-line systemic therapy (11-12 months) than after third- to fifth-line therapies (6 months) (P=.03). Presence of extrahepatic metastases did not adversely affect survival (P=.48).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
33. Ng KM, Chua TC, Saxena A, Zhao J, Chu F, Morris DL. Two decades of experience with hepatic cryotherapy for advanced colorectal metastases. *Ann Surg Oncol.* 2012;19(4):1276-1283.	Observational-Tx	293 patients	To report a single institution's long-term experience with hepatic cryotherapy for advanced colorectal metastases.	A total of 293 patients were included into analysis. The median number of lesions treated per patient was 3 (range, 1-13). The median OS was 29 (range, 3-220) months. The 1-, 3-, 5-, and 10-year survivals were 87%, 41.8%, 24.2%, and 13.3%, respectively. A total of 161 patients developed intrahepatic recurrences: cryosite (23%); edge recurrence (14%); and within the liver remnant (78%). The median DFS was 9 (range, 1-220) months. The 1-, 3-, 5-, and 10-year DFS rates were 37.9%, 17.2%, 13.4%, and 10.8%, respectively. Univariate analysis identified four factors that significantly affect survival: node-positive primary tumor (P=0.001), preoperative carcinoembryonic antigen level (P<0.001), number of lesions (P<0.001), and use of neoadjuvant chemotherapy (P<0.001). However, only primary tumor nodal status was independently prognostic (HR=2.023; 95% CI, 1.444-2.835; P<0.001).	2
34. Vogl TJ, Gruber T, Balzer JO, Eichler K, Hammerstingl R, Zangos S. Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: prospective study. *Radiology.* 2009;250(1):281-289.	Observational-Tx	463 patients	To evaluate local tumor control and survival data after transarterial chemoembolization with different drug combinations in the palliative treatment of liver metastases in patients with colorectal cancer.	Evaluation of local tumor control resulted in partial response (68 patients [14.7%]), stable disease (223 patients [48.2%]), and progressive disease (172 patients [37.1%]). The 1-year survival rate after chemoembolization was 62%, and the 2-year survival rate was 28%. Median survival from date of diagnosis of liver metastases was 38 months and from the start of chemoembolization treatment was 14 months. There was no statistically significant difference between the three treatment protocols.	1
35. 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.	Experimental-Tx	660 patients	To determine whether the efficacy of chemotherapy could be improved by administering 5-FU by protracted infusion throughout the duration of radiation therapy 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.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol.* 2001;19(8):2282-2292.	Experimental-Tx	605 patients	Prospective randomized phase III trial to compare outcomes, efficacy, and toxicity profile of oral capecitabine with 5-FU/LV in previously untreated metastatic colorectal cancer.	Oral capecitabine resulted in improved tumor response rate than 5-FU/LV (24.8% vs 15.5%, P=.005). OS and disease progression were similar in both groups. Oral capecitabine was more tolerable than bolus 5-FU, except for grade 3/4 hand-foot syndrome and hyperbilirubinemia.	1
37. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet.* 2000;355(9209):1041-1047.	Experimental-Tx	387 patients	Randomized multicenter phase III trial to determine the efficacy of adding irinotecan to 5-FU as first-line treatment in patients with metastatic colorectal cancer.	The response rate was higher in patients in the irinotecan group than in those in the no-irinotecan group (49% vs 31%, P<0.001 for evaluable patients). Time to progression was significantly longer in the irinotecan group than in the no-irinotecan group (median 6.7 vs 4.4 months, P<0.001), and OS was higher (median 17.4 vs 14.1 months, P=0.031). Grade 3 and 4 toxic effects were significantly more frequent in the irinotecan group.	1
38. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol.* 2000;18(16):2938-2947.	Experimental-Tx	420 patients	Randomized phase III trial to evaluate whether the addition of oxaliplatin results in improved outcomes compared to the 5-FU/LV every 2 weeks regimen alone as a first-line treatment in metastatic colorectal cancer.	Patients allocated to oxaliplatin plus 5-FU/LV every 2 weeks had a significantly longer PFS (median, 9.0 vs 6.2 months; P=.0003) and better response rate (50.7% vs 22.3%; P=.0001) when compared with the control arm. 5-FU/LV every 2 weeks plus oxaliplatin gave higher frequencies of grade 3/4 neutropenia (41.7% vs 5.3% of patients), grade 3/4 diarrhea (11.9% vs 5.3%), and grade 3 neurosensory toxicity (18.2% vs 0%), but this did not result in impairment of quality of life.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol.* 2007;25(13):1670-1676.	Experimental-Tx	244 patients	A phase III study comparing FOLFOXIRI [irinotecan 165 mg/m2 day 1, oxaliplatin 85 mg/m2 day 1, leucovorin 200 mg/m2 day 1, 5-FU 3,200 mg/m2 48-hour continuous infusion starting on day 1, every 2 weeks] with FOLFIRI.	A total of 244 patients were randomly assigned. An increase of grade 2 to 3 peripheral neurotoxicity (0% vs 19%; P<.001), and grade 3 to 4 neutropenia (28% vs 50%; P<.001) were observed in the FOLFOXIRI arm. The incidence of febrile neutropenia (3% vs 5%) and grade 3 to 4 diarrhea (12% vs 20%) were not significantly different. Responses, as assessed by investigators, were, for FOLFIRI and FOLFOXIRI, respectively, complete, 6% and 8%; and partial, 35% and 58%, (response rate, 41% vs 66%; P=.0002). Response rate confirmed by an external panel was 34% vs 60% (P<.0001). The R0 secondary resection rate of metastases was greater in the FOLFOXIRI arm (6% vs 15%; P=.033, among all 244 patients; and 12% vs 36%; P=.017 among patients with liver metastases only). PFS and OS were both significantly improved in the FOLFOXIRI arm (median PFS, 6.9 vs 9.8 months; HR, 0.63; P=.0006; median OS, 16.7 vs 22.6 months; HR, 0.70; P=.032).	1
40. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol.* 2004;22(2):229-237.	Experimental-Tx	220 patients	Randomized phase III study comparing FOLFIRI and FOLFOX6 in patients with previously untreated colorectal cancer metastasis. At progression patients would receive the alternative regimen.	Median survival was 21.5 months for patients allocated to FOLFIRI then FOLFOX6 vs 20.6 months in 111 patients allocated to FOLFOX6 then FOLFIRI (P=.99). Median PFS was 14.2 months in arm A vs 10.9 in arm B (P=.64). In first-line therapy, FOLFIRI achieved 56% response rate and 8.5 months median PFS, vs FOLFOX6 which achieved 54% response rate and 8.0 months median PFS (P=.26).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. 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.	Experimental-Tx	598 patients	To compare neoadjuvant radiotherapy plus capecitabine with dose-intensified radiotherapy plus capecitabine and oxaliplatin.	598 patients were randomly assigned to receive Cap 45 (n=299) or Capox 50 (n=299). 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 ypCR rate was 13.9% with Cap 45 and 19.2% with Capox 50 (P=.09). When ypCR 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).	1
42. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004;351(4):337-345.	Experimental-Tx	329 patients	Randomized multicenter trial to evaluate the efficacy of cetuximab plus or minus irinotecan in patients who had progressed during or within 3 months after treatment with an irinotecan-based regimen.	The combined regimen of irinotecan and cetuximab resulted in significantly improved rate of response (22.9% vs 10.8%) and time to progression (4.1 vs 1.5 months), but no significant benefit in median survival (8.6 vs 6.9 months). Toxicity was more frequent with the combination regimen.	1
43. Peeters M, Van Custem EV, Siena S, et al. A phase 3, multicenter, randomized controlled trial of panitumumab plus best supportive care (BSC) vs BSC alone in patients with metastatic colorectal cancer. Paper presented at: 97th Annual Meeting of the American Association for Cancer Research 2006; Washington DC. Abstract CP-1.	Experimental-Tx	463 patients	Randomized multicenter phase III trial to compare the efficacy and safety of panitumumab plus BSC vs BSC alone in patients with metastatic colorectal cancer who failed standard chemotherapy.	231 patients were randomized to the panitumumab plus BSC group and 232 patients to BSC alone. 67% had colon cancer, and 33% had rectal cancer. Median follow-up time was 19 weeks. Patients receiving panitumumab had a 46% lower relative progression rate than those receiving BSC alone (HR=0.54, 95% CI: 0.44, 0.66).	1
44. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med.* 2008;359(17):1757-1765.	Review/Other-Tx	572 patients	Correlative analyses to determine whether the mutation status of the K-ras gene modified the effect of cetuximab on OS and PFS in the CO.17 trial and to assess the association of K-ras mutation status with OS and progression free survival among patients receiving BSC alone.	Patients with a colorectal tumor bearing mutated K-ras did not benefit from cetuximab, while patients with a tumor bearing wild-type K-ras benefited from cetuximab. The mutation status of the K-ras gene had no influence on survival among patients treated with BSC alone.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. Van Cutsem E, Rougier P, Köhne C, Stroh C, Schlichting M, Bokemeyer C. 6077 A meta-analysis of the CRYSTAL and OPUS studies combining cetuximab with chemotherapy (CT) as 1st-line treatment for patients (pts) with metastatic colorectal cancer (mCRC): Results according to KRAS and BRAF mutation status. *European Journal of Cancer Supplements.* 2009;7(2):345-345.	Review/Other-Tx	845 patients	Meta-analysis of randomized trials to evaluate OS time, PFS time and best overall response in combined Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) and Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer (OPUS) patient populations, according to KRAS mutation status.	Meta-analysis showed that the addition of cetuximab to chemotherapy provided a significant benefit for the primary study endpoints PFS and overall response and for OS compared with patients receiving chemotherapy alone. Overall, the addition of cetuximab to chemotherapy in patients with KRAS wild-type tumors significantly reduced the risk of disease progression by 34% and increased the likelihood of achieving a response by >2-fold compared with those patients who received chemotherapy alone. Also, OS was significantly longer in KRAS wild-type patients receiving cetuximab plus chemotherapy compared with those receiving chemotherapy alone.	4
46. Maughan TS, Adams RA, Smith C, et al. COIN, CR10: A three arm randomised controlled trial comparing either COntinuous chemotherapy plus cetuximab, or INtermittent chemotherapy with standard continuous palliative combination chemotherapy with oxaliplatin and a fluoropyrimidine in first line treatment of metastatic colorectal cancer. *NCRI Colorectal Clinical Studies Group* http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?s=10].	Review/Other-Tx	Arm A – 815; Arm B – 815; Arm C - 815	Three-arm randomized controlled trial comparing either continuous chemotherapy plus cetuximab or intermittent chemotherapy with standard continuous palliative combination chemotherapy with oxaliplatin and a fluoropyrimidine in first line treatment of metastatic colorectal cancer.	The addition of cetuximab to oxaliplatin based chemotherapy is associated with: For all patients: Increased nonhaematological toxicity, no change in OS or PFS. For KRAS wild-type patients: Increased nonhaematological toxicity, no change in OS or PFS, increased response rate.	4
47. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol.* 2009;27(5):663-671.	Experimental-Tx	344 patients	Randomized multicenter phase II study to assess whether the best overall response rate of cetuximab combined with FOLFOX4 was superior to that of FOLFOX4 alone as first-line treatment for metastatic colorectal cancer.	The confirmed overall response rate for cetuximab plus FOLFOX4 was higher than with FOLFOX4 alone (46% vs 36%). A statistically significant increase in the odds for a response with the addition of cetuximab to FOLFOX4 could not be established. In patients with KRAS wild-type tumors, the addition of cetuximab to FOLFOX4 was associated with a clinically significant increased chance of response and a lower risk of disease progression.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol.* 2010;28(31):4697-4705.	Experimental-Tx	1,183 patients	The Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) was designed to evaluate the efficacy and safety of panitumumab plus FOLFOX4 vs FOLFOX4 alone as initial treatment for metastatic colorectal cancer.	KRAS results were available for 93% of the 1,183 patients randomly assigned. In the wild-type KRAS stratum, panitumumab-FOLFOX4 significantly improved PFS compared with FOLFOX4 (median PFS, 9.6 vs 8.0 months, respectively; HR, 0.80; 95% CI, 0.66 to 0.97; P=.02). A nonsignificant increase in OS was also observed for panitumumab-FOLFOX4 vs FOLFOX4 (median OS, 23.9 vs 19.7 months, respectively; HR, 0.83; 95% CI, 0.67 to 1.02; P=.072). In the mutant KRAS stratum, PFS was significantly reduced in the panitumumab-FOLFOX4 arm vs the FOLFOX4 arm (HR, 1.29; 95% CI, 1.04 to 1.62; P=.02), and median OS was 15.5 months vs 19.3 months, respectively (HR, 1.24; 95% CI, 0.98 to 1.57; P=.068). Adverse event rates were generally comparable across arms with the exception of toxicities known to be associated with anti-EGFR therapy.	1
49. Heinemann V, Fischer von Weikersthal L, Decker T, et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). *ASCO Meeting Abstracts.* 2013;31(15_suppl):LBA3506.	Experimental-Tx	592 patients	A randomized multicenter trial to compare the efficacy of FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in metastatic colorectal cancer patients not pretreated for metastatic disease.	Among 735 patients of the intent-to-treat population, KRAS-WT was identified in 592. Of these, 297 patients were randomized to arm A and 295 to arm B. Median age was 64 years, 66% of patients were male, and ECOG PS 0-1 was observed in 98% of patients. Median duration of treatment was 4.7 months vs 5.3 months, respectively. While in the intent-to-treat analysis, objective response rate was comparable in arms A vs B (62% vs 57%, OR 1.249), a significant superiority was found for assessable patients in arm A. Median PFS of the intent-to-treat population was nearly identical (10.3 vs 10.4 months, HR 1.04, P=0.69), however, OS showed a significantly better outcome in arm A vs arm B (28.8 vs 25.0 months, HR 0.77, P=0.0164, 95% CI: 0.620-0.953). 60-day mortality was low in both arms (1.01% vs 2.71%).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
50. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350(23):2335-2342.	Experimental-Tx	813 patients	Randomized multicenter phase III trial to evaluate the addition of bevacizumab to 5-FU-based combination chemotherapy in patients with metastatic colorectal cancer.	Median survival and PFS for irinotecan, bolus 5-FU, and leucovorin plus bevacizumab vs irinotecan, bolus 5-FU, and leucovorin plus placebo was (20.3 vs 15.6 and 10.6 vs 6.2 months, respectively). Grade 3 hypertension was more common in the bevacizumab group (11% vs 2.3%).	1
51. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Updated efficacy results from XELOX-1/ NO16966, a randomized phase III trial in first-line metastatic colorectal cancer. *J Clin Oncol.* 2007;25(18):4028.	Experimental-Tx	1,401 patients	A randomized phase III trial to compare capecitabine and oxaliplatin vs FOLFOX with and without the vascular endothelial growth factor inhibitor bevacizumab.	The clinical trial demonstrated first that capecitabine was equivalent to infusional 5-FU when combined with oxaliplatin. The overall HR was statistically significant in favor of bevacizumab, but the magnitude of the benefit with the addition of bevacizumab to FOLFOX was not as high as seen with other regimens in other clinical trials. Addition of bevacizumab to oxaliplatin-based chemotherapy regimens significantly improves PFS.	1
52. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol.* 2009;27(5):672-680.	Experimental-Tx	1,053 patients	Randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. Trial evaluated panitumumab added to bevacizumab and chemotherapy (oxaliplatin- and irinotecan-based) as first-line treatment for metastatic colorectal cancer.	Median PFS was 10.0 and 11.4 months for the panitumumab and control arms, respectively; median survival was 19.4 months and 24.5 months for the panitumumab and control arms, respectively. Grade 3/4 adverse events in the oxaliplatin cohort (panitumumab vs control) included skin toxicity (36% vs 1%), diarrhea (24% vs 13%), infections (19% vs 10%), and pulmonary embolism (6% vs 4%). Increased toxicity without evidence of improved efficacy was observed in the panitumumab arm of the irinotecan cohort. K-ras analyses showed adverse outcomes for the panitumumab arm in both wild-type and mutant groups.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med.* 2009;360(6):563-572.	Experimental-Tx	755 patients	Randomized study to examine the effect of adding the anti-epidermal growth factor receptor antibody cetuximab to a combination of capecitabine, oxaliplatin, and bevacizumab for metastatic colorectal cancer. Patients were randomized to capecitabine, oxaliplatin, and bevacizumab or the same regimen plus weekly cetuximab.	Median PFS was 10.7 months in the capecitabine, oxaliplatin, and bevacizumab group and 9.4 in the CBC group (P=0.01). Quality-of-life scores were lower in the capecitabine, oxaliplatin, and bevacizumab plus weekly cetuximab group. The OS and response rates did not differ significantly in the two groups. Treated patients in the capecitabine, oxaliplatin, and bevacizumab plus weekly cetuximab group had more grade 3 or 4 adverse events. Patients treated with cetuximab who had tumors bearing a mutated K-ras gene had significantly decreased PFS as compared with cetuximab-treated patients with wild-type-K-ras tumors or patients with mutated-K-ras tumors in the capecitabine, oxaliplatin, and bevacizumab group.	1
54. D'Angelica M, Kornprat P, Gonen M, et al. Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: a matched case-control study. *Ann Surg Oncol.* 2007;14(2):759-765.	Observational-Tx	32 patients	Patients who underwent hepatectomy for colorectal metastases and received bevacizumab within 12 weeks of surgery were identified and compared with a group of matched historical controls.	16 patients received bevacizumab before surgery and 24 received bevacizumab after surgery. The median time between bevacizumab administration and surgery was 6.9 weeks before (range, 3-15 weeks) and 7.4 weeks after (range, 5-15 weeks). Perioperative complications occurred in 13 patients (40.6%), two of which were considered major complications. There was no significant difference in perioperative morbidity and severity of complications when compared with a set of matched controls. A window of 6-8 weeks between administration of bevacizumab and surgery is still recommended.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
55. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol.* 2005;91(3):173-180.	Review/Other-Tx	426 patients	To assess the wound healing complications in patients who underwent cancer surgery 28-60 days before study treatment and had major surgery during study treatment. Cases were reviewed for wound healing complications occurring ≤60 days after surgery.	Wound healing complications occurred in 3/230 (1.3%) bevacizumab-treated patients and 1/194 (0.5%) control patients. With major surgery during study treatment, 10/75 bevacizumab-treated patients (13%) and 1/29 control patients (3.4%) had wound healing complications. Bevacizumab administered in combination with 5-FU/LV-based chemotherapy 28-60 days after primary cancer surgery caused no increased risk of wound healing complications compared with chemotherapy alone.	4
56. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol.* 2012;30(28):3499-3506.	Experimental-Tx	612 patients receiving aflibercept; 614 patients receiving placebo	To study the effect of adding the novel antiangiogenic agent aflibercept (also known as ziv-aflibercept in the United States) to FOLFIRI in patients with metastatic colorectal cancer previously treated with oxaliplatin, including patients who received prior bevacizumab.	Adding aflibercept to FOLFIRI significantly improved OS relative to placebo plus FOLFIRI (HR, 0.817; 95.34% CI, 0.713 to 0.937; P=.0032) with median survival times of 13.50 vs 12.06 months, respectively. Aflibercept also significantly improved PFS (PFS; HR, 0.758; 95% CI, 0.661 to 0.869; P<.0001), with median PFS times of 6.90 vs 4.67 months, respectively. The effects on OS and PFS exhibited a consistent trend across prespecified subgroup analyses, including bevacizumab pretreated patients. Response rate was 19.8% (95% CI, 16.4% to 23.2%) with aflibercept plus FOLFIRI compared with 11.1% (95% CI, 8.5% to 13.8%) with placebo plus FOLFIRI (P=.0001). Adverse effects reported with aflibercept combined with FOLFIRI included the characteristic anti-vascular endothelial growth factor effects and also reflected an increased incidence of some chemotherapy-related toxicities.	1

Rectal Cancer-Metastatic Disease at Presentation
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
57. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):303-312.	Experimental-Tx	1,052 patients	An international phase 3 trial was done to assess the multikinase inhibitor regorafenib in patients with metastatic colorectal cancer.	Between April 30, 2010, and March 22, 2011, 1,052 patients were screened, 760 patients were randomized to receive regorafenib (n=505) or placebo (n=255), and 753 patients initiated treatment (regorafenib n=500; placebo n=253; population for safety analyses). The primary endpoint of OS was met at a preplanned interim analysis; data cutoff was on July 21, 2011. Median OS was 6.4 months in the regorafenib group vs 5.0 months in the placebo group (HR 0.77; 95% CI 0.64-0.94; one-sided P=0.0052). Treatment-related adverse events occurred in 465 (93%) patients assigned regorafenib and in 154 (61%) of those assigned placebo. The most common adverse events of grade three or higher related to regorafenib were hand-foot skin reaction (83 patients, 17%), fatigue (48, 10%), diarrhea (36, 7%), hypertension (36, 7%), and rash or desquamation (29, 6%).	1
58. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. *N Engl J Med.* 2012;367(17):1616-1625.	Review/Other-Tx	1,193 patients	To characterize the prevalence of the expectation that chemotherapy might be curative and to identify the clinical, sociodemographic, and health-system factors associated with this expectation.	Overall, 69% of patients with lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy was not at all likely to cure their cancer. In multivariable logistic regression, the risk of reporting inaccurate beliefs about chemotherapy was higher among patients with colorectal cancer, as compared with those with lung cancer (OR, 1.75; 95% CI, 1.29 to 2.37); among nonwhite and Hispanic patients, as compared with non-Hispanic white patients (OR for Hispanic patients, 2.82; 95% CI, 1.51 to 5.27; OR for black patients, 2.93; 95% CI, 1.80 to 4.78); and among patients who rated their communication with their physician very favorably, as compared with less favorably (OR for highest third vs lowest third, 1.90; 95% CI, 1.33 to 2.72). Educational level, functional status, and the patient's role in decision making were not associated with such inaccurate beliefs about chemotherapy.	4

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59. Bae SH, Park W, Choi DH, et al. Palliative radiotherapy in patients with a symptomatic pelvic mass of metastatic colorectal cancer. *Radiat Oncol.* 2011;6:52.	Observational-Tx	80 patients	To evaluate the palliative role of radiotherapy and define the effectiveness of chemotherapy combined with palliative radiotherapy in patients with a symptomatic pelvic mass of metastatic colorectal cancer.	Symptom palliation was achieved in 80% of the cases. During the median follow-up period of 5 months (1-44 months), 45% of the cases experienced reappearance of symptoms; the median symptom control duration was 5 months. Median survival after radiotherapy was 6 months. On univariate analysis, the only significant prognostic factor for symptom control duration was BED ≥40 Gy/10 ($P<0.05$), and chemotherapy combined with palliative radiotherapy was a marginally significant factor ($P=0.0644$). On multivariate analysis, BED and chemotherapy combined with palliative radiotherapy were significant prognostic factors for symptom control duration ($P<0.05$).	2

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

5-FU = Fluorouracil

5-FU/LV = Fluorouracil plus leucovorin

BSC = Best supportive care

CI = Confidence interval

DFS = Disease-free survival

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

FOLFIRI = Infusional fluorouracil, leucovorin, and irinotecan

FOLFOX = Infusional fluorouracil, leucovorin, oxaliplatin

FOLFOXIRI = Infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan

FOLFOX4 = Panitumumab plus infusional fluorouracil, leucovorin, and oxaliplatin

HR = Hazard ratio

OR = Odds ratio

OS = Overall survival

PFS = Progression-free survival

RFA = Radiofrequency ablation

SBRT = Stereotactic body radiotherapy