JAMA Oncology | Original Investigation

# Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer
## A Systematic Review and Meta-analysis

Fausto Petrelli, MD; Gianluca Tomasello, MD; Karen Borgonovo, MD; Michele Ghidini, MD; Luca Turati, MD; Pierpaolo Dallera, MD; Rodolfo Passalacqua, MD; Giovanni Sgroi, MD; Sandro Barni, MD

**IMPORTANCE** Primary tumor location is emerging as an important prognostic factor owing to distinct biological features. However, the side of origin of colon cancer (CC) still does not represent a prognostic parameter when deciding for adjuvant or palliative chemotherapy.

**OBJECTIVE** To determine the prognostic role of left vs right-sidedness of primary tumor location in patients with CC.

**DATA SOURCES** We searched PubMed, EMBASE, The Cochrane Library, Web of Science, LILACS, CINAHL, and SCOPUS for prospective or retrospective studies reporting data on overall survival for left-sided colon cancer (LCC) compared with right-sided colon cancer (RCC).

**STUDY SELECTION** Studies were selected if: (1) side of CC was reported among variables entered into survival analysis, (2) survival information was available (overall survival [OS] was reported in the article as hazard ratio (HR) according to multivariate analysis, (3) articles were published in the English language.

**DATA EXTRACTION AND SYNTHESIS** Data were pooled using HRs for OS of LCC vs RCC according to fixed or random-effects models. Subgroup analysis and multivariate random-effects model meta-regression was also implemented adjusting for stage distribution, sample size, race, year of publication, type and quality of studies, and adjuvant chemotherapy.

**MAIN OUTCOMES AND MEASURES** HRs for OS (the primary outcome measure) were pooled to provide an aggregate value. In this analysis, all HRs with 95% CIs were pooled to obtain prognostic information on the location of the primary tumor (left vs right location site of CC) independent of other common clinicopathological covariates.

**RESULTS** An analysis was made from the 66 studies conducted. It included 1 437 846 patients with a median follow-up of 65 months. Left sided primary tumor location was associated with a significantly reduced risk of death (HR, 0.82; 95% CI, 0.79-0.84; $P < .001$) and this was independent of stage, race, adjuvant chemotherapy, year of study, number of participants, and quality of included studies.

**CONCLUSIONS AND RELEVANCE** Based on these results, CC side should be acknowledged as a criterion for establishing prognosis in all stages of disease. It should be considered when deciding treatment intensity in metastatic settings, and should represent a stratification factor for future adjuvant studies.

*JAMA Oncol*. 2017;3(2):211-219. doi:10.1001/jamaoncol.2016.4227
Published online October 27, 2016. Corrected on November 17, 2016.

Supplemental content

CME Quiz at jamanetworkcme.com and CME Questions page 287

**Author Affiliations:** Oncology Unit, Oncology Department, ASST Bergamo Ovest, Treviglio (BG), Italy (Petrelli, Borgonovo, Barni); Oncology Unit, Oncology Department, ASST Ospedale di Cremona, Cremona, Italy (Tomasello, Ghidini, Passalacqua); Surgical Oncology Unit, Surgery Department, ASST Bergamo Ovest, Treviglio (BG), Italy (Turati, Dallera, Sgroi).

**Corresponding Author:** Fausto Petrelli, MD, Oncology Unit, Oncology Department, ASST Bergamo Ovest, Piazzale Ospedale 1, 24047, Treviglio (BG) Italy (faupe@libero.it).

According to the recent EUROCARE 5 analysis,[1] colon and rectal cancer presented a minimal but significant increase in 5-year survival across years by about 4 to 6%, with worst survival with increasing age. In particular, colon cancer (CC) cases diagnosed with screening colonoscopy have lower stage disease at presentation but also have better outcomes independent of their staging.[2] Standard clinicopathological risk factors for disease progression and death that lead to the prescription of postsurgical therapy are stage (node positive disease), grade, obstructing and/or perforating presentation, vascular invasion, and pT4 classification. All these variables are taken into account for selecting patients for adjuvant chemotherapy in stage II and III disease, according to major guidelines. In metastatic CC, the extent of cancer and aim of therapy (operable vs inoperable metastases), *RAS* mutation, and performance status guide the choice of systemic therapy.

There are suggestions that localization of CC (right CC [RCC][3,4] sided up to splenic flexure and left CC [LCC], including descending, and sigmoid and/or rectosigmoid cancers) potentially influences prognosis owing to differing biological features. Clinical presentation is also different: iron deficiency anemia from occult blood loss is more prevalent in patients with right-sided CCs; conversely, hematochezia and change in bowel habits is a more common presenting symptom for left-sided CCs.[3] From a molecular point of view, RCC and LCC are 2 different entities, with RCC associated with defective mismatch repair (MMR) genes, mutations of *KRAS* and *BRAF*, and microRNA-31, whereas LCC is associated with CIN, p53, *NRAS*, microRNA-146a, microRNA-147b, and microRNA-1288.[4] Location of primary tumor seems to influence the outcome with adjuvant therapy and the survival with palliative chemotherapy or targeted therapy in stage IV disease. In fact, in the phase III N0147 trial[5] comparing FOLFOX and FOLFOX plus cetuximab LCC was associated with an overall better disease-free survival as compared with RCC. Similarly, Weiss et al[6] showed a better outcome for left-sided compared with right-sided diseases in stage III but not in stage II CCs. In the same manner, metastatic LCCs exhibited a better outcome than RCCs in previously untreated patients.[7]

In this systematic review and meta-analysis, we evaluated the independent prognostic value of site of primary tumor (left-sided vs right-sided primary location) in patients with cancer of the colon.

### Key Points

**Question** What is the prognostic role of primary tumor location (left vs right) in patients with colon cancer?

**Findings** In this systematic review and meta-analysis which included 66 studies with more than 1.4 million patients, a significant prognostic impact of tumor site on overall survival was found with a 20% reduced risk of death for cancers arising on the left side.

**Meaning** Based on these results, colon cancer primary tumor sidedness should be acknowledged as a criterion for establishing prognosis in both earlier and advanced stages of disease.

## Methods

We performed this systematic review and meta-analysis in accordance with PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.

### Search Strategy

References for this systematic review and meta-analysis were identified through searches of PubMed, the Cochrane Library, SCOPUS, Web of Science, EMBASE, LILACS, and CINAHL from inception to February 2016. A manual update of meeting abstracts presented at 2016 American Society of Clinical Oncology was also performed. Searches included the terms: "colon or colorectal" "cancer or carcinoma" and "right or left or site or side or descending or sigmoid or proximal or distal or cecum" and "hazard ratio" and "multivariate or Cox regression". Manual selection of relevant studies was carried out based also on the related articles function. The citation lists of all retrieved articles were analyzed to identify other potentially relevant reports.

### Study Selection and Data Extraction

The following criteria for eligibility among studies were set before collecting the articles: (1) site of CC was reported (right vs left side or as other subsites), (2) survival information (OS or cancer-specific survival [CSS]) at specific follow-up was reported in the article as HRs according to multivariate cox regression analysis, after primary tumor location was associated with significant results in univariate analysis, (3) articles were published in the English language, (4) when several articles were published by the same authors or group, the newest or most informative single article was selected. Exclusion criteria were the following: (1) no information on OS was provided, (2) letters to editor and/or commentary, reviews, articles published in a book, or papers published in a nonEnglish language, (3) clinical studies reporting odds ratios or risk ratios, or only univariate analyses, and (4) studies comparing colon cancer with rectal cancer. If studies compared RCC with LCC including some rectal and rectosigmoid cancers, they were included, provided that rectal cancer was the minority of presented cases.

Two authors (F.P. and G.T.) conducted the search and identification independently, and the selection of an article was reached by consensus with a third author (S.B.). The following information was extracted from each report by the 2 authors independently: author, year of publication, country, patient number, type of study, side of primary tumor rates (right vs left CCs, %), chemotherapy exposure (rate), survival data (HRs), and covariates investigated in multivariate analysis.

### Statistical Analysis

For analysis of survival results, HRs were pooled to provide an aggregate value. In this analysis, all HRs with 95% CIs obtained from multivariate analysis (adjusted for the maximum number of covariates significantly associated with OS in univariate analysis) and available in the articles were combined

to obtain prognostic information on the location of the primary tumor (left vs right side of CC) independent of other clinicopathological covariates. Sensitivity analysis was performed according to race of participants (Asian vs nonAsian origin, the number of patients > vs < of the median number), stage (I-III vs IV), year of publication (<2006 vs 2006-2016), quality (high vs low quality papers), and type of study (retrospective vs prospective). To explore the impact of interstudy variability in the inclusion of different stages of CCs, we also conducted a multivariate random-effects model meta-regression of OS adjusted for the proportion of patients with stage I, II, III, and IV disease, the rate of patients that received chemotherapy in stage II disease, and Newcastle-Ottawa Scale (NOS) assessment. Data were entered into the Comprehensive Meta-Analysis software (version 3.3.070, Biostat). The Cochran's test was used to assess the heterogeneity of included studies. For heterogeneity tests, P values less than .05 were considered to indicate significance. If the test of heterogeneity was significant ($P < .05$ or $I^2 > 50\%$), the random-effects model was used to pool the estimate across studies with the Der Simonian-Laird method. Otherwise, the fixed-effects model was used. By convention, an observed HR of <1 implied better survival for patients with left-sided cancers.

We used the NOS for risk of bias assessment.[8,9] This scale assesses the likelihood of bias in 3 domains: (1) selection of the study groups; (2) comparability of groups; and (3) ascertainment of exposure and outcome. Studies with scores of 7 or higher were considered as having a low risk of bias, scores of 4 to 6 as having a moderate risk of bias, and scores less than 4 as having a high risk of bias. We assessed that follow-up was adequate if the median follow-up was more than 5 years for early stages of CC and more than 3 years for stage IV CC.

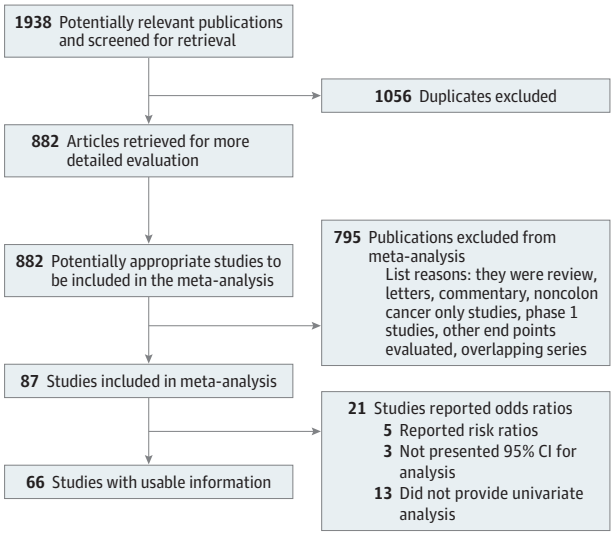
We finally investigated the publication bias for OS meta-analyses with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's τ[10] and Egger's bias test.[11] Moreover, in the presence of publication bias for the primary analysis, we conducted a trim and fill adjusted analysis[12] to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric about the (new) effect size. This analysis was performed including in the main analysis those studies with a nonsignificant association of side with OS from univariate analysis.

## Results

A total of 1938 potentially relevant citations were reviewed (**Figure 1**). Among them, 29 reported OS data either as risk ratios, odds ratios, or not provided multivariate analysis, or they did not report 95% CI for inclusion in the final analysis. Ultimately, 66 studies[6,7,13-76] published from 1995 to 2016, that reported the prognostic value of CC site were analyzed. The total number of patients included was 1 437 846 ranging from 87 to 279 623 patients per study (median, 880). The major characteristics are shown in eTable 1 and 2 in the Supplement.

In 59 publications, a retrospective analysis of patients with CC was presented; all other papers reported a prospective cohort series or studies of surgically treated patients with CC. According to race, the majority of patients were white (n = 56); the remaining 10 publications included Asian participants. Twenty studies reported on stage IV disease and 25 reported on stages I to III. Twenty papers included all stages of disease and in 1 study stages were not reported. Rates of RCCs ranged from 17.6% to 67% and LCCs from 10% to 71% of all included patients (data not available only in 3 articles). The quality of article expressed by the NOS scale ranged from 5 to 9, with 75% including studies of high quality (NOS scores ranging from 7-9).

Figure 1. Overview of Trials Search and Selection




### Meta-Analysis of Overall Survival

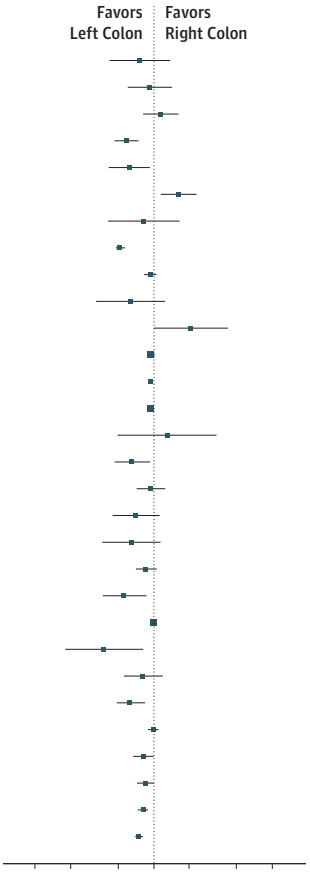
Because the heterogeneity test showed a high level of heterogeneity ($I^2 = 93\%$; $P < .001$) between the studies, a random-effects model was used for the analysis. A pooled HR of 0.82 (95% CI, 0.79-0.84; $P < .001$) from multivariate analysis showed that patients with LCC were associated with an increased survival rate (**Figures 2** and **3**).

### Subgroup Analysis and Meta-Regression

The subgroup analysis performed according to the number of patients (> or < of the calculated median number), showed that in the largest studies (>880 participants), the effect size was inferior to the smallest studies (<880 participants) with HRs of 0.84 (95% CI, 0.81-0.87) and 0.7 (95% CI, 0.65-0.76), respectively ($P < .001$ for subgroups difference). Analysis according to race (Asian vs nonAsian race of included patients) leads to a similar effect on OS for LCCs: HRs of 0.8 (95% CI, 0.71-0.89) and 0.82 (95% CI, 0.79-0.85; $P < .001$), respectively. Both studies with prospective (HR, 0.82; 95% CI; 0.73-0.91) and retrospective design (HR, 0.82; 95% CI, 0.78-0.84) and higher vs lower quality (HR, 0.81; 95% CI, 0.78-0.84 and HR, 0.82; 95% CI, 0.75-0.88 respectively; $P < .001$ and $P < .001$, respectively) gave identical results. Results did not change according to year of publication (1995-2005 and 2006-2016). Studies that included only patients with stage IV disease

Figure 2. Meta-analysis (Forest Plot) of 66 Studies Assessing Overall Survival of Left vs Right Site in Patients With Colon Cancer

| Study or Subgroup | Log Hazard Ratio | SE | Hazard Ratio IV, Random, 95% CI | Weight, % |
|---|---|---|---|---|
| Mulder et al,[52] 1995 | -0.2614 | 0.2973 | 0.77 (0.43-1.38) | 0.3 |
| Liang et al,[42] 2002 | -0.0736 | 0.2231 | 0.93 (0.60-1.44) | 0.5 |
| Ward et al,[73] 2003 | 0.1484 | 0.1708 | 1.16 (0.83-1.62) | 0.8 |
| Chafai et al,[20] 2005 | -0.5276 | 0.116 | 0.59 (0.47-0.74) | 1.4 |
| Negri et al,[53] 2005 | -0.4652 | 0.2053 | 0.63 (0.42-0.94) | 0.6 |
| Lanza et al,[39] 2006 | 0.4941 | 0.1691 | 1.64 (1.18-2.28) | 0.8 |
| Al-Mulla et al,[14] 2006 | -0.1912 | 0.353 | 0.83 (0.41-1.65) | 0.2 |
| Johnson et al,[34] 2006 | -0.6539 | 0.0408 | 0.52 (0.48-0.56) | 2.8 |
| George et al,[26] 2006 | -0.0619 | 0.0574 | 0.94 (0.84-1.05) | 2.5 |
| Deschoolmester et al,[51] 2008 | -0.4463 | 0.338 | 0.64 (0.33-1.24) | 0.3 |
| Koo et al,[38] 2008 | 0.7227 | 0.3687 | 2.06 (1.00-4.24) | 0.2 |
| Meguid et al,[45] 2008 | -0.0419 | 0.0157 | 0.96 (0.93-0.99) | 3.2 |
| Le et al,[40] 2009 | -0.0587 | 0.0187 | 0.94 (0.91-0.98) | 3.2 |
| Wray et al,[74] 2009 | -0.0471 | 0.013 | 0.95 (0.93-0.98) | 3.2 |
| Horst et al,[30] 2009 | 0.2624 | 0.4875 | 1.30 (0.50-3.38) | 0.1 |
| Peeples et al,[62] 2010 | -0.4155 | 0.1732 | 0.66 (0.47-0.93) | 0.8 |
| Roth et al,[66] 2010 | -0.0492 | 0.1362 | 0.95 (0.73-1.24) | 1.1 |
| Farina-Sarasqueta et al,[24] 2010 | -0.3425 | 0.2327 | 0.71 (0.45-1.12) | 0.5 |
| Magnusson et al,[44] 2010 | -0.4246 | 0.2948 | 0.65 (0.37-1.17) | 0.3 |
| Suttie et al,[68] 2011 | -0.1485 | 0.0997 | 0.86 (0.71-1.05) | 1.6 |
| Katoh et al,[37] 2011 | -0.5621 | 0.2069 | 0.57 (0.38-0.86) | 0.6 |
| Weiss et al,[6] 2011 | -0.0101 | 0.0157 | 0.99 (0.96-1.02) | 3.2 |
| Katkoori et al,[36] 2012 | -0.9676 | 0.3812 | 0.38 (0.18-0.80) | 0.2 |
| Kalady et al,[35] 2012 | -0.1985 | 0.1855 | 0.82 (0.57-1.18) | 0.7 |
| Mekenkamp et al,[46] 2012 | -0.4463 | 0.1363 | 0.64 (0.49-0.84) | 1.1 |
| Van Steenbergen et al,[70] 2012 | 0 | 0.0486 | 1.00 (0.91-1.10) | 2.6 |
| Sinicrope et al,[67] 2012 | -0.1863 | 0.0943 | 0.83 (0.69-1.00) | 1.7 |
| Nitsche et al,[54] 2013 | -0.1508 | 0.0836 | 0.86 (0.73-1.01) | 1.9 |
| Wallace et al,[71] 2013 | -0.2021 | 0.0478 | 0.82 (0.74-0.90) | 2.7 |
| Jess et al,[33] 2013 | -0.2771 | 0.0298 | 0.76 (0.71-0.80) | 3.0 |




(continued on figure 3)

(n = 20) compared with those that included patients with stages I to III only (n = 25) showed a significantly greater effect on mortality for patients with LCC (HR, 0.73; 95% CI, 0.69-0.78 vs HR, 0.84; 95% CI, 0.79-0.89; $P < .001$ for subgroups difference).

Meta-regression showed that the effect size did not depend on stage ($P = .35$, 0.48, 0.41 and 0.41 after adjustment for stage I, II, III and IV, respectively). When meta-regression was performed according to the rate of patients that received adjuvant chemotherapy in stage II (virtually all stage III and IV received systemic treatment and none received it for stage I disease) the results remained significant even after adjustment for adjuvant treatment (coefficient, −0.36; $P = .11$). Therefore, the high heterogeneity could be partially explained by the different population included in the meta-analysis, with both early and metastatic tumors and with similar effect in stages II, III, and IV.

Under the random-effects model, the pooled HR obtained from both multivariate and univariate HRs (the latter studies excluded from the main analysis) was 0.85 (95% CI, 0.82-0.88; $P < .001$), and this was confirmed even in high quality studies (HR, 0.81; 95% CI, 0.77-0.84; $P < .001$). The funnel plot (**Figure 4**) and Egger test ($P = .079$) did not indicate the existence of obvious publication bias. Trim and fill analysis also did not change the pooled estimates of the meta-analysis.

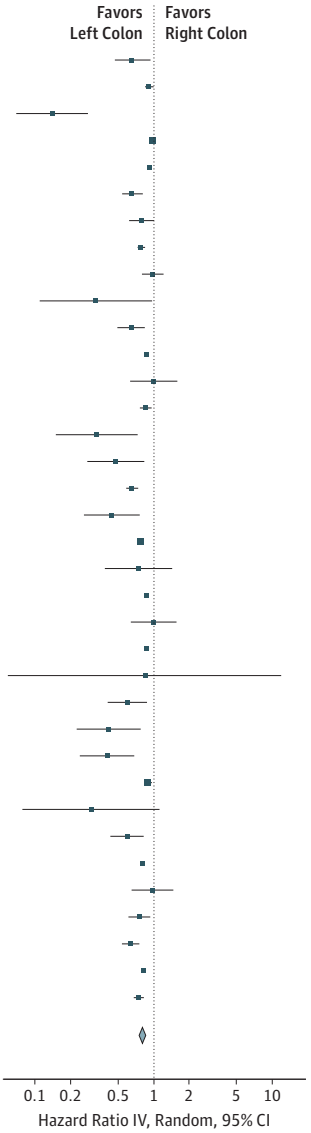
## Discussion

An increasingly large amount of evidence is accumulating showing that colon tumors proximal and distal to splenic flexure are distinct clinical and biological entities. Apart from having a different embryological origin—proximal colon from midgut and distal colon and rectum from hindgut—the right colon displays peculiar differences in mucosal immunology, probably owing to differences in gut microbiota.[77] A higher concentration of eosinophils and intraepithelial T cells in the proximal colon compared with the distal colorectum has been reported.[78-80] It has been hypothesized that this could be the result of the delicate balance that immune cells have to maintain between immunogenicity against pathogens and tolerance for the commensal microbiota, which is much more represented in the distal colorectum. This observation could also explain the differences in immunological response to tumors developing in the proximal colon characterized by an increased immune activity and, in turn, reflect the specific differences in pathogenesis and outcome. Tumors arising on the right side of the colon, in fact, seem to follow different molecular pathways of oncogenesis. These RCCs more commonly are diploid and characterized by mucinous histology,

Figure 3. Meta-analysis (Forest Plot) of 66 Studies Assessing Overall Survival of Left vs Right Site in Patients With Colon Cancer (Continued)

| Study or Subgroup | Log Hazard Ratio | SE | Hazard Ratio IV, Random, 95% CI | Weight, % |
|---|---|---|---|---|
| Ferrand et al,[25] 2013 | -0.4155 | 0.1732 | 0.66 (0.47-0.93) | 0.8 |
| Lykke et al,[43] 2013 | -0.0856 | 0.0393 | 0.92 (0.85-0.99) | 2.8 |
| Merok et al,[47] 2013 | -1.9661 | 0.3537 | 0.14 (0.07-0.28) | 0.2 |
| Gleisner et al,[28] 2013 | -0.0253 | 0.0133 | 0.98 (0.95-1.00) | 3.2 |
| Bhangu et al,[16] 2013 | -0.0812 | 0.0101 | 0.92 (0.90-0.94) | 3.3 |
| Boisen et al,[17] 2013 | -0.4155 | 0.0977 | 0.66 (0.54-0.80) | 1.7 |
| Park et al,[60] 2013 | -0.2231 | 0.1219 | 0.80 (0.63-1.02) | 1.3 |
| Renfro et al,[65] 2014 | -0.2357 | 0.03 | 0.79 (0.74-0.84) | 3.0 |
| Ogura et al,[56] 2014 | -0.0101 | 0.1087 | 0.99 (0.80-1.23) | 1.5 |
| Oue et al,[58] 2014 | -1.1209 | 0.5543 | 0.33 (0.11-0.97) | 0.1 |
| Modest et al,[49] 2014 | -0.4308 | 0.1339 | 0.65 (0.50-0.85) | 1.2 |
| Budde et al,[19] 2014 | -0.1347 | 0.01 | 0.87 (0.86-0.89) | 3.3 |
| Moritani et al,[50] 2014 | 0.009 | 0.2259 | 1.01 (0.65-1.57) | 0.5 |
| Ishihara et al,[31] 2014 | -0.1393 | 0.0557 | 0.87 (0.78-0.97) | 2.5 |
| Crosara Teixeira et al,[23] 2015 | -1.1087 | 0.4023 | 0.33 (0.15-0.73) | 0.2 |
| Cohen et al,[21] 2015 | -0.734 | 0.275 | 0.48 (0.28-0.82) | 0.4 |
| Loupakis et al,[7] 2015 | -0.414 | 0.0588 | 0.66 (0.59-0.74) | 2.4 |
| Pentheroudakis et al,[63] 2015 | -0.8052 | 0.2726 | 0.45 (0.26-0.76) | 0.4 |
| Tarantino et al,[69] 2015 | -0.2536 | 0.0113 | 0.78 (0.76-0.79) | 3.2 |
| Cremolini et al,[22] 2015 | -0.2877 | 0.3336 | 0.75 (0.39-1.44) | 0.3 |
| Hawk et al,[29] 2015 | -0.1416 | 0.0107 | 0.87 (0.85-0.89) | 3.2 |
| Paquet et al,[59] 2015 | 0 | 0.2198 | 1.00 (0.65-1.54) | 0.5 |
| Wang et al,[72] 2015 | -0.137 | 0.0124 | 0.87 (0.85-0.89) | 3.2 |
| Jeong et al,[32] 2015 | -0.1744 | 1.3465 | 0.84 (0.06-11.76) | 0.0 |
| Lee et al,[41] 2015 | -0.5108 | 0.1943 | 0.60 (0.41-0.88) | 0.7 |
| Pectasides et al,[61] 2015 | 0.8747 | 0.3148 | 0.42 (0.22-0.77) | 0.3 |
| Miyamoto et al,[48] 2015 | -0.9014 | 0.264 | 0.41 (0.24-0.68) | 0.4 |
| Ahmadi et al,[13] 2015 | -0.1054 | 0.0352 | 0.90 (0.84-0.96) | 2.9 |
| Gilardoni et al,[27] 2015 | -1.204 | 0.6744 | 0.30 (0.08-1.13) | 0.1 |
| Brulè et al,[18] 2015 | -0.5108 | 0.1582 | 0.60 (0.44-0.82) | 0.9 |
| Price et al,[64] 2015 | -0.2231 | 0.0064 | 0.80 (0.79-0.81) | 3.3 |
| Andre et al,[15] 2015 | -0.0202 | 0.2017 | 0.98 (0.66-1.46) | 0.6 |
| Oh et al,[57] 2016 | -0.2705 | 0.1059 | 0.76 (0.62-0.94) | 1.5 |
| Venook et al,[76] 2016 | -0.4385 | 0.0822 | 0.65 (0.55-0.76) | 1.9 |
| Schrag et al,[75] 2016 | -0.1779 | 0.0148 | 0.84 (0.81-0.86) | 3.2 |
| Noren et al,[55] 2016 | -0.2877 | 0.05 | 0.75 (0.68-0.83) | 2.6 |
| **Total (95% CI)** | | | **0.82 (0.79-0.84)** | 100 |

Heterogeneity: $\tau^2 = 0.01\%$, $\chi^2 = 950.69$, df = 65 ($P < .001$), $I^2 = 93\%$,
Test for overall effect: $Z = 11.43$ ($P < .001$)

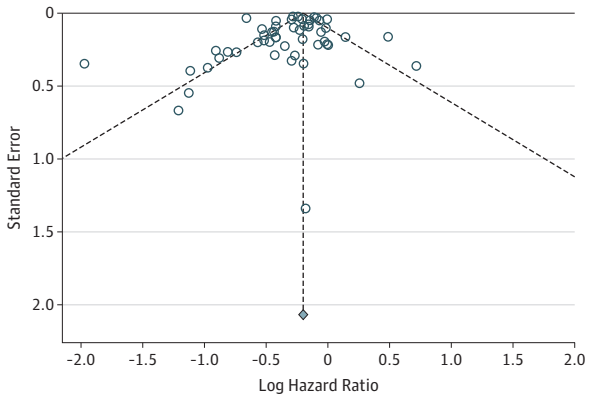



high microsatellite instability, CpG island methylation, and *BRAF* mutations.[81-85] Conversely, LCCs were found to have frequently p53 and *KRAS* mutations.[86]

In stage II completely resected CC, the presence of MSI has been associated with a more favorable prognosis and a lack of benefit from fluorouracil-based adjuvant chemotherapy.[84] More recently, Sinicrope et al[5] evaluated the prognostic impact of deficient DNA MMR in patients with stage III enrolled in a randomized trial of FOLFOX-based adjuvant chemotherapy and found that among deficient MMR cancers only proximal tumors had favorable outcome.

Results from our analysis clearly demonstrate that primary tumor location has a critical role in determining CC prognosis, being a surrogate of different and poor biology. This analysis included 66 published studies and analyzed 1 437 846 CC patients with overall survival data available. To our knowledge, this is the first meta-analysis that describes the site of colon cancer (right vs left) as an independent prognostic factor in both early and advanced disease. Specifically, bearing a tumor originating in the left side of the colon was significantly associated with an absolute 19% reduced risk of death. Such a survival benefit was independent of race, stage (II, III, and IV), year of publication, and type of studies, and deeper for smallest (<880 patients) compared with largest series. As a possible consequence of the higher representation of MSI-positive cases in proximal cancers and of the associated better prognosis, the difference, although again significant, was less pronounced for early stages as compared with the advanced ones. When meta-regression was performed, side remained prognostic in patients with stage II disease after adjusting for adjuvant chemotherapy received. Finally, the prognostic information of side remained significant after adjustment for all stages. Our work confirms and emphasizes previous reports indicating an increasing importance of primary

Figure 4. Funnel Plot for Publication Bias (All Studies Included) of Overall Survival Meta-analysis




tumor location in clinical decision-making processes.[6,45,87] In particular, the prognostic impact of CC side of origin, has been recently assessed in about 2000 patients with previously untreated metastatic CC receiving first-line chemotherapy plus bevacizumab in 3 independent cohorts: a prospective pharmacogenetic study (PROVETTA) and 2 randomized phase 3 trials, AVF2107g and NO16966.[7] In all cohorts considered, patients with left-sided tumors showed superior OS. Finally, at multivariate analysis, right-sided location was confirmed to be a negative prognostic variable independent of mucinous histology and *BRAF* mutational status. Unfortunately, our data did not allow an analysis according to histology and mutational status.

Apart from intrinsic biological differences (ie, higher rate of *BRAF* mutant cases) related to a more aggressive clinical behavior, we believe that several other factors must be taken into account to explain the worse overall prognosis for patients with RCC.

The first possible reason may involve the surgical technique. Similar to total mesorectal excision (TME), which was the cause of a significant decline in the incidence of local recurrence after its introduction as standard approach in mid and low rectal cancer, complete mesocolic excision (CME) has been advocated by many as the better option for tumors arising in the right colon. Complete mesocolic excision consists of complete removal of the intact mesentery and high ligation of the vascular supply at its origin.[88] The rationale behind this procedure is that a more extensive surgery, by reducing the risk of local recurrence, might guarantee superior disease-free and overall survival. A retrospective study[88] analyzed 1329 patients who had undergone CME in a single center and showed very promising results with 5-year cancer specific survival rates of 91.4% in patients with stage II and 70.2% in patients with stage III disease. More recently, a case-control study[89] from Denmark confirmed that CME represents a valid and potentially better option associated with significant disease-free survival benefit in patients with stages I to III CC compared with conventional surgery. However, in the absence of prospective randomized trials, a consensus conference agreed that there are sound oncological reasons for recommending a more radical surgical approach.[90]

Further hypotheses can be advanced to explain the better outcomes of LCCs. Among these, a different sensitivity to chemotherapy has been postulated. As reported from a FIRE3 and CALGB/SWOG 80405 trial subgroup analysis, it has been suggested that anti-EGFR therapy has a decreased benefit in patients with right-colon tumors.[76,91] Since *RAS* mutational status is the only accepted predictor of effectiveness from such treatments so far, these provocative results suggest that other biomarkers and clinical parameters deserve to be investigated. Again, beyond the higher rate of *BRAF* mutations, right-colon tumors are more likely to have MSI or to display a CpG island methylator phenotype. In fact, worsened PFS for patients with CpG island methylator phenotype-high *RAS*-wt and/or *BRAF*-wt tumors treated with anti-EGFR therapy, has been recently reported.[92] Moreover, a meta-analysis of 463 *RAS*-wt and/or *BRAF*-mut colorectal patients showed that anti-EGFR drugs, when added to standard therapy or best supportive care, do not confer any significant advantage in response rate, PFS, or OS, as compared with control regimens.[93]

In addition to the need for improving molecular selection of patients with CC to achieve better outcomes, patients with right-sided tumors may deserve more aggressive treatments, especially in advanced settings and, potentially, in stage II tumors, when there are no other adverse prognostic factors. Indeed, as described in the clinical subgroup analysis of the TRIBE trial,[94] a trend toward a PFS benefit from the intensification of the chemotherapy backbone in patients with RCC emerged (HR, 0.66 for RCC vs HR, 0.82 for LCCs; $P = .20$). Therefore, one may speculate that the corresponding worse prognosis of proximal tumors in advanced stages could also be related to the use of suboptimal systemic treatment.

## Limitations

Our study has some intrinsic weaknesses that must be addressed. First, we observed notable heterogeneity owing to retrospective and different populations included. We attempted to take it into account with a random effects model analysis and with subgroup analysis and meta-regression. Significant difference was observed for metastatic vs locoregional populations, and this was the only significant variable evaluated with meta-regression. Size of studies, race, year of publication, NOS quality scale, and rate of patients who received chemotherapy were not significant to explain heterogeneity in subgroup analysis. Second, this meta-analysis is based on published data instead of individual patient data. Finally, we have excluded 29 articles where primary tumor location was not significantly associated with OS or HR data were not obtainable from publications. Nevertheless, even after adding 13 trials with HRs derived from univariate analysis only, the main analysis would have not changed significantly the effect size. The strength of our analysis is represented by the overall number of patients included (more than 1 400 000 patients with CC), the independent prognostic significance of CC side according to multivariate analysis, and the lack of significant and obvious biases with funnel plot and Egger's test.

## Conclusions

Based on the results of this study, the side of origin of CC (left vs right) should be acknowledged as a criterion

for establishing prognosis in both earlier and advanced stages of disease. Moreover, primary tumor location should be carefully considered when deciding treatment intensity in metastatic and locoregional settings, and should represent an important stratification factor for future adjuvant studies.

## ARTICLE INFORMATION

**Correction:** This article was corrected online on November 17, 2016 to fix a typographical error in the Conclusions section. The first word of the first paragraph was not capitalized.

**Published Online:** October 27, 2016. doi:10.1001/jamaoncol.2016.4227

**Author Contributions:** Dr Petrelli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Petrelli, Tomasello, Turati, Sgroi, Barni.
*Acquisition, analysis, or interpretation of data:* Petrelli, Tomasello, Borgonovo, Ghidini, Dallera, Sgroi, Barni.
*Drafting of the manuscript:* Petrelli, Tomasello, Ghidini.
*Critical revision of the manuscript for important intellectual content:* Petrelli, Tomasello, Borgonovo, Turati, Dallera, Sgroi, Barni.
*Statistical analysis:* Petrelli, Tomasello, Dallera.
*Administrative, technical, or material support:* Borgonovo.
*Study supervision:* Ghidini, Sgroi, Barni.
*No additional contributions:* Turati.

**Conflict of Interest Disclosures:** None reported.

## REFERENCES

1. Holleczek B, Rossi S, Domenic A, et al; EUROCARE-5 Working Group. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. *Eur J Cancer*. 2015; S0959-8049(15)00704-2.

2. Amri R, Bordeianou LG, Sylla P, Berger DL. Impact of screening colonoscopy on outcomes in colon cancer surgery. *JAMA Surg*. 2013;148(8):747-754.

3. Saidi HS, Karuri D, Nyaim EO. Correlation of clinical data, anatomical site and disease stage in colorectal cancer. *East Afr Med J*. 2008;85(6):259-262.

4. Shen H, Yang J, Huang Q, et al. Different treatment strategies and molecular features between right-sided and left-sided colon cancers. *World J Gastroenterol*. 2015;21(21):6470-6478.

5. Sinicrope FA, Mahoney MR, Smyrk TC, et al. Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX-based adjuvant chemotherapy. *J Clin Oncol*. 2013;31(29):3664-3672.

6. Weiss JM, Pfau PR, O'Connor ES, et al. Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results--Medicare data. *J Clin Oncol*. 2011;29(33):4401-4409.

7. Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst*. 2015;107(3):dju427.

8. Deeks JJ, Dinnes J, D'Amico R, et al; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess*. 2003;7(27):iii-x, 1-173.

9. Wells G, Shea B, O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomizes studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed December 29, 2015.

10. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101.

11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.

12. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463.

13. Ahmadi O, Stringer MD, Black MA, McCall JL. Clinico-pathological factors influencing lymph node yield in colorectal cancer and impact on survival: analysis of New Zealand Cancer Registry data. *J Surg Oncol*. 2015;111(4):451-458.

14. Al-Mulla F, Hagan S, Behbehani AI, et al. Raf kinase inhibitor protein expression in a survival analysis of colorectal cancer patients. *J Clin Oncol*. 2006;24(36):5672-5679.

15. André T, de Gramont A, Vernerey D, et al. Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study. *J Clin Oncol*. 2015;33(35):4176-4187.

16. Bhangu A, Kiran RP, Slesser A, Fitzgerald JE, Brown G, Tekkis P. Survival after resection of colorectal cancer based on anatomical segment of involvement. *Ann Surg Oncol*. 2013;20(13):4161-4168.

17. Boisen MK, Johansen JS, Dehlendorff C, et al. Primary tumor location and bevacizumab effectiveness in patients with metastatic colorectal cancer. *Ann Oncol*. 2013;24(10):2554-2559.

18. Brulé SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur J Cancer*. 2015;51(11):1405-1414.

19. Budde CN, Tsikitis VL, Deveney KE, Diggs BS, Lu KC, Herzig DO. Increasing the number of lymph nodes examined after colectomy does not improve colon cancer staging. *J Am Coll Surg*. 2014;218(5):1004-1011.

20. Chafai N, Chan CL, Bokey EL, Dent OF, Sinclair G, Chapuis PH. What factors influence survival in patients with unresected synchronous liver metastases after resection of colorectal cancer? *Colorectal Dis*. 2005;7(2):176-181.

21. Cohen SA, Wu C, Yu M, et al. Evaluation of CpG island methylator phenotype as a biomarker in colorectal cancer treated with adjuvant oxaliplatin. *Clin Colorectal Cancer*. 2016;15(2):164-169.

22. Cremolini C, Di Bartolomeo M, Amatu A, et al. BRAF codons 594 and 596 mutations identify a new molecular subtype of metastatic colorectal cancer at favorable prognosis. *Ann Oncol*. 2015;26(10):2092-2097.

23. Crosara Teixeira M, Marques DF, Ferrari AC, et al. The effects of palliative chemotherapy in metastatic colorectal cancer patients with an ECOG performance status of 3 and 4. *Clin Colorectal Cancer*. 2015;14(1):52-57.

24. Fariña-Sarasqueta A, van Lijnschoten G, Moerland E, et al. The BRAF V600E mutation is an independent prognostic factor for survival in stage II and stage III colon cancer patients. *Ann Oncol*. 2010;21(12):2396-2402.

25. Ferrand F, Malka D, Bourredjem A, et al. Impact of primary tumour resection on survival of patients with colorectal cancer and synchronous metastases treated by chemotherapy: results from the multicenter, randomised trial Fédération Francophone de Cancérologie Digestive 9601. *Eur J Cancer*. 2013;49(1):90-97.

26. George S, Primrose J, Talbot R, et al; Wessex Colorectal Cancer Audit Working Group. Will Rogers revisited: prospective observational study of survival of 3592 patients with colorectal cancer according to number of nodes examined by pathologists. *Br J Cancer*. 2006;95(7):841-847.

27. Gilardoni E, Bernasconi DP, Poli S, et al. Surveillance for early stages of colon cancer: potentials for optimizing follow-up protocols. *World J Surg Oncol*. 2015;13:260.

28. Gleisner AL, Mogal H, Dodson R, et al. Nodal status, number of lymph nodes examined, and lymph node ratio: what defines prognosis after resection of colon adenocarcinoma? *J Am Coll Surg*. 2013;217(6):1090-1100.

29. Hawk NN, Long TE, Imam MH, et al. Clinicopathologic Features and Outcome of Young Adults With Stage IV Colorectal Cancer. *Am J Clin Oncol*. 2015;38(6):543-549.

30. Horst D, Kriegl L, Engel J, Jung A, Kirchner T. CD133 and nuclear beta-catenin: the marker combination to detect high risk cases of low stage colorectal cancer. *Eur J Cancer*. 2009;45(11):2034-2040.

31. Ishihara S, Nishikawa T, Tanaka T, et al. Prognostic impact of tumor location in stage IV colon cancer: a propensity score analysis in a multicenter study. *Int J Surg*. 2014;12(9):925-930.

32. Jeong DH, Kim WR, Min BS, Kim YW, Song MK, Kim NK. Validation of a quantitative 12-multigene expression assay (Oncotype DX(®) Colon Cancer Assay) in Korean patients with stage II colon cancer: implication of ethnic differences contributing to differences in gene expression. *Onco Targets Ther*. 2015;8:3817-3825.

33. Jess P, Hansen IO, Gamborg M, Jess T; Danish Colorectal Cancer Group. A nationwide Danish cohort study challenging the categorisation into right-sided and left-sided colon cancer. *BMJ Open*. 2013;3(5):e002608.

34. Johnson PM, Porter GA, Ricciardi R, Baxter NN. Increasing negative lymph node count is independently associated with improved long-term

survival in stage IIIB and IIIC colon cancer. *J Clin Oncol*. 2006;24(22):3570-3575.

**35**. Kalady MF, Dejulius KL, Sanchez JA, et al. BRAF mutations in colorectal cancer are associated with distinct clinical characteristics and worse prognosis. *Dis Colon Rectum*. 2012;55(2):128-133.

**36**. Katkoori VR, Shanmugam C, Jia X, et al. Prognostic significance and gene expression profiles of p53 mutations in microsatellite-stable stage III colorectal adenocarcinomas. *PLoS One*. 2012;7(1):e30020.

**37**. Katoh H, Yamashita K, Wang G, Sato T, Nakamura T, Watanabe M. Prognostic significance of preoperative bowel obstruction in stage III colorectal cancer. *Ann Surg Oncol*. 2011;18(9):2432-2441.

**38**. Koo JH, Jalaludin B, Wong SK, Kneebone A, Connor SJ, Leong RW. Improved survival in young women with colorectal cancer. *Am J Gastroenterol*. 2008;103(6):1488-1495.

**39**. Lanza G, Gafà R, Santini A, Maestri I, Guerzoni L, Cavazzini L. Immunohistochemical test for MLH1 and MSH2 expression predicts clinical outcome in stage II and III colorectal cancer patients. *J Clin Oncol*. 2006;24(15):2359-2367.

**40**. Le H, Ziogas A, Taylor TH, Lipkin SM, Zell JA. Survival of distinct Asian groups among colorectal cancer cases in California. *Cancer*. 2009;115(2):259-270.

**41**. Lee I, Baek S-H, Kim H, et al. Survival analysis for colon subsite and rectal cancers: experience from a single surgeon. *Korean J Clin Oncol*. 2015;11:114-119.

**42**. Liang JT, Huang KC, Cheng YM, et al. P53 overexpression predicts poor chemosensitivity to high-dose 5-fluorouracil plus leucovorin chemotherapy for stage IV colorectal cancers after palliative bowel resection. *Int J Cancer*. 2002;97(4):451-457.

**43**. Lykke J, Roikjaer O, Jess P; Danish Colorectal Cancer Group. The relation between lymph node status and survival in Stage I-III colon cancer: results from a prospective nationwide cohort study. *Colorectal Dis*. 2013;15(5):559-565.

**44**. Magnusson C, Mezhybovska M, Lörinc E, Fernebro E, Nilbert M, Sjölander A. Low expression of CysLT1R and high expression of CysLT2R mediate good prognosis in colorectal cancer. *Eur J Cancer*. 2010;46(4):826-835.

**45**. Meguid RA, Slidell MB, Wolfgang CL, Chang DC, Ahuja N. Is there a difference in survival between right- versus left-sided colon cancers? *Ann Surg Oncol*. 2008;15(9):2388-2394.

**46**. Mekenkamp LJ, Heesterbeek KJ, Koopman M, et al. Mucinous adenocarcinomas: poor prognosis in metastatic colorectal cancer. *Eur J Cancer*. 2012;48(4):501-509.

**47**. Merok MA, Ahlquist T, Røyrvik EC, et al. Microsatellite instability has a positive prognostic impact on stage II colorectal cancer after complete resection: results from a large, consecutive Norwegian series. *Ann Oncol*. 2013;24(5):1274-1282.

**48**. Miyamoto Y, Baba Y, Sakamoto Y, et al. Negative Impact of Skeletal Muscle Loss after Systemic Chemotherapy in Patients with Unresectable Colorectal Cancer. *PLoS One*. 2015;10(6):e0129742.

**49**. Modest DP, Schulz C, von Weikersthal LF, et al. Outcome of patients with metastatic colorectal cancer depends on the primary tumor site (midgut vs. hindgut): analysis of the FIRE1-trial (FuFIRI or mIROX as first-line treatment). *Anticancer Drugs*. 2014;25(2):212-218.

**50**. Moritani K, Hasegawa H, Okabayashi K, Ishii Y, Endo T, Kitagawa Y. Difference in the recurrence rate between right- and left-sided colon cancer: a 17-year experience at a single institution. *Surg Today*. 2014;44(9):1685-1691.

**51**. Deschoolmeester V, Van Damme N, Baay M, et al. Microsatellite instability in sporadic colon carcinomas has no independent prognostic value in a Belgian study population. *Eur J Cancer*. 2008;44(15):2288-2295.

**52**. Mulder TP, Verspaget HW, Sier CF, et al. Glutathione S-transferase pi in colorectal tumors is predictive for overall survival. *Cancer Res*. 1995;55(12):2696-2702.

**53**. Negri FV, Wotherspoon A, Cunningham D, Norman AR, Chong G, Ross PJ. Mucinous histology predicts for reduced fluorouracil responsiveness and survival in advanced colorectal cancer. *Ann Oncol*. 2005;16(8):1305-1310.

**54**. Nitsche U, Zimmermann A, Späth C, et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. *Ann Surg*. 2013;258(5):775-782.

**55**. Norén A, Eriksson HG, Olsson LI. Selection for surgery and survival of synchronous colorectal liver metastases; a nationwide study. *Eur J Cancer*. 2016;53:105-114.

**56**. Ogura T, Kakuta M, Yatsuoka T, et al. Clinicopathological characteristics and prognostic impact of colorectal cancers with NRAS mutations. *Oncol Rep*. 2014;32(1):50-56.

**57**. Oh BY, Huh JW, Park YA, et al. Prognostic factors in sporadic colon cancer with high-level microsatellite instability. *Surgery*. 2016;159(5):1372-1381.

**58**. Oue N, Anami K, Schetter AJ, et al. High miR-21 expression from FFPE tissues is associated with poor survival and response to adjuvant chemotherapy in colon cancer. *Int J Cancer*. 2014;134(8):1926-1934.

**59**. Paquet ER, Cui J, Davidson D, et al. A 12-gene signature to distinguish colon cancer patients with better clinical outcome following treatment with 5-fluorouracil or FOLFIRI. *J Pathol Clin Res*. 2015;1(3):160-172.

**60**. Park JH, Kim TY, Lee KH, et al. The beneficial effect of palliative resection in metastatic colorectal cancer. *Br J Cancer*. 2013;108(7):1425-1431.

**61**. Pectasides D, Karavasilis V, Papaxoinis G, et al. Randomized phase III clinical trial comparing the combination of capecitabine and oxaliplatin (CAPOX) with the combination of 5-fluorouracil, leucovorin and oxaliplatin (modified FOLFOX6) as adjuvant therapy in patients with operated high-risk stage II or stage III colorectal cancer. *BMC Cancer*. 2015;15:384-395.

**62**. Peeples C, Shellnut J, Wasvary H, Riggs T, Sacksner J. Predictive factors affecting survival in stage II colorectal cancer: is lymph node harvesting relevant? *Dis Colon Rectum*. 2010;53(11):1517-1523.

**63**. Pentheroudakis G, Raptou G, Kotoula V, et al. Immune response gene expression in colorectal cancer carries distinct prognostic implications according to tissue, stage and site: a prospective retrospective translational study in the context of a hellenic cooperative oncology group randomised trial. *PLoS One*. 2015;10(5):e0124612.

**64**. Price TJ, Beeke C, Ullah S, et al. Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? *Cancer*. 2015;121(6):830-835.

**65**. Renfro LA, Grothey A, Xue Y, et al; Adjuvant Colon Cancer Endpoints (ACCENT) Group. ACCENT-based web calculators to predict recurrence and overall survival in stage III colon cancer. *J Natl Cancer Inst*. 2014;106(12):dju333.

**66**. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol*. 2010;28(3):466-474.

**67**. Sinicrope FA, Foster NR, Yoon HH, et al. Association of obesity with DNA mismatch repair status and clinical outcome in patients with stage II or III colon carcinoma participating in NCCTG and NSABP adjuvant chemotherapy trials. *J Clin Oncol*. 2012;30(4):406-412.

**68**. Suttie SA, Shaikh I, Mullen R, Amin AI, Daniel T, Yalamarthi S. Outcome of right- and left-sided colonic and rectal cancer following surgical resection. *Colorectal Dis*. 2011;13(8):884-889.

**69**. Tarantino I, Warschkow R, Worni M, et al. Prognostic Relevance of Palliative Primary Tumor Removal in 37,793 Metastatic Colorectal Cancer Patients: A Population-Based, Propensity Score-Adjusted Trend Analysis. *Ann Surg*. 2015;262(1):112-120.

**70**. van Steenbergen LN, Lemmens VE, Rutten HJ, Wymenga AN, Nortier JW, Janssen-Heijnen ML. Increased adjuvant treatment and improved survival in elderly stage III colon cancer patients in The Netherlands. *Ann Oncol*. 2012;23(11):2805-2811.

**71**. Wallace K, Hill EG, Lewin DN, et al. Racial disparities in advanced-stage colorectal cancer survival. *Cancer Causes Control*. 2013;24(3):463-471.

**72**. Wang R, Wang MJ, Ping J. Clinicopathological Features and Survival Outcomes of Colorectal Cancer in Young Versus Elderly: A Population-Based Cohort Study of SEER 9 Registries Data (1988-2011). *Medicine (Baltimore)*. 2015;94(35):e1402.

**73**. Ward RL, Cheong K, Ku SL, Meagher A, O'Connor T, Hawkins NJ. Adverse prognostic effect of methylation in colorectal cancer is reversed by microsatellite instability. *J Clin Oncol*. 2003;21(20):3729-3736.

**74**. Wray CM, Ziogas A, Hinojosa MW, Le H, Stamos MJ, Zell JA. Tumor subsite location within the colon is prognostic for survival after colon cancer diagnosis. *Dis Colon Rectum*. 2009;52(8):1359-1366.

**75**. Schrag D, Weng S, Brooks G, Meyerhardt JA, Venook AP. The relationship between primary tumor sidedness and prognosis in colorectal cancer. *J Clin Oncol*. 2016;34 (suppl abstr, 3505).

**76**. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). *J Clin Oncol*. 2016;34(suppl, abstr 3504).

**77**. Gill SR, Pop M, Deboy RT, et al. Metagenomic analysis of the human distal gut microbiome. *Science*. 2006;312(5778):1355-1359.

**78**. Kirby JA, Bone M, Robertson H, Hudson M, Jones DE. The number of intraepithelial T cells decreases from ascending colon to rectum. *J Clin Pathol*. 2003;56(2):158.

**79**. Lowichik A, Weinberg AG. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. *Mod Pathol*. 1996;9(2):110-114.

**80**. Selby WS, Janossy G, Jewell DP. Immunohistological characterisation of intraepithelial lymphocytes of the human gastrointestinal tract. *Gut*. 1981;22(3):169-176.

**81**. Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. *Cancer*. 2011;117(20):4623-4632.

**82**. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. *Ann Intern Med*. 1990;113(10):779-788.

**83**. Distler P, Holt PR. Are right- and left-sided colon neoplasms distinct tumors? *Dig Dis*. 1997;15(4-5):302-311.

**84**. Hutchins G, Southward K, Handley K, et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. *J Clin Oncol*. 2011;29(10):1261-1270.

**85**. Iacopetta B. Are there two sides to colorectal cancer? *Int J Cancer*. 2002;101(5):403-408.

**86**. Breivik J, Lothe RA, Meling GI, Rognum TO, Børresen-Dale AL, Gaudernack G. Different genetic pathways to proximal and distal colorectal cancer influenced by sex-related factors. *Int J Cancer*. 1997;74(6):664-669.

**87**. Benedix F, Schmidt U, Mroczkowski P, Gastinger I, Lippert H, Kube R; Study Group "Colon/Rectum Carcinoma (Primary Tumor)". Colon carcinoma—classification into right and left sided cancer or according to colonic subsite?—analysis of 29,568 patients. *Eur J Surg Oncol*. 2011;37(2):134-139.

**88**. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. *Colorectal Dis*. 2009;11(4):354-364.

**89**. Bertelsen CA, Neuenschwander AU, Jansen JE, et al; Danish Colorectal Cancer Group. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. *Lancet Oncol*. 2015;16(2):161-168.

**90**. Søndenaa K, Quirke P, Hohenberger W, et al. The rationale behind complete mesocolic excision (CME) and a central vascular ligation for colon cancer in open and laparoscopic surgery: proceedings of a consensus conference. *Int J Colorectal Dis*. 2014;29(4):419-428.

**91**. Heinemann V, Modest DP, Fischer von Weikersthal L. Gender and tumor location as predictors for efficacy: influence on endpoints in first-line treatment with FOLFIRI in combination with cetuximab or bevacizumab in the AIO KRK 0306 (FIRE3) trial. *J Clin Oncol*. 2014;32:5s (suppl abstr, 3600).

**92**. Lee MS, Overman MJ, Maru DM. Association of CpG island methylator phenotype (CIMP) with inferior progression-free survival with anti-EGFR monoclonal antibody therapy in metastatic colorectal cancer. *J Clin Oncol*. 2014;32:5s(suppl abstr, 3633).

**93**. Pietrantonio F, Petrelli F, Coinu A, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. *Eur J Cancer*. 2015;51(5):587-594.

**94**. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med*. 2014;371(17):1609-1618.