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ORIGINAL ARTICLE

# Benefit of Surgical Resection of the Primary Tumor in Patients Undergoing Chemotherapy for Stage IV Colorectal Cancer with Unresected Metastasis

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**Abstract**

*Purpose* Resection of the primary tumor in patients with unresected metastatic colorectal cancer is controversial, and often performed only for palliation of symptoms. Our goal was to determine if resection of the primary tumor in this patient population is associated with improved survival.

*Methods* This is a retrospective cohort study of the National Cancer Data Base from 2004 to 2012. The study population included all patients with synchronous metastatic colorectal adenocarcinoma who were treated with systemic chemotherapy. The study groups were patients who underwent definitive surgery for the primary tumor and those who did not. Patients were excluded if they had surgical intervention on the sites of metastasis or pathology other than adenocarcinoma. Primary outcome was overall survival.

*Results* Of the 65,543 patients with unresected stage IV colorectal adenocarcinoma undergoing chemotherapy, 55% underwent surgical resection of the primary site. Patients who underwent surgical resection of the primary tumor had improved median survival compared to patients treated with chemotherapy alone (22 vs 13 months, $p < .0001$). The surgical survival benefit was present for patients who were treated with either multi-agent or single-agent chemotherapy (23 vs 14 months, $p < 0.001$; 19 vs 9 months, $p < 0.001$). Surgical resection of the primary tumor was also associated with improved survival when using multivariate analysis with propensity score matching (OR = 0.863; 95% CI [0.805–.924]; HR = 0.914; 95% CI [0.888–0.942]).

*Conclusions* Our results show that in patients with synchronous unresected stage IV colorectal adenocarcinoma undergoing single- or multi-agent chemotherapy, after adjusting for confounding variables, definitive resection of the primary site was associated with improved overall survival. Large randomized controlled trials are needed to determine if there is a causal relationship between surgery and increased overall survival in this patient population.

**Keywords** Colorectal neoplasms · Chemotherapy · Neoplasm metastasis

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## Introduction

Colon adenocarcinoma is one of the most common cancers in the USA.[1,2] Unfortunately, even with increasing awareness regarding screening guidelines, approximately 20% of patients present with metastasis at time of diagnosis,[3] with 75–90% of these patients having unresectable metastatic disease.[4] Of these patients, only a minority (9–29%) present with symptoms, including bleeding or obstruction.[5] Historically, resection of the primary tumor has only been recommended if the patient is symptomatic. Current National Comprehensive

Cancer Network (NCCN) guidelines do not recommend surgical resection of the primary tumor as first line treatment for this patient population.[6] Because of this, there has been a significant decrease in the rate of primary tumor resection over time from 68 to 74% in 1998 to 51–56% in 2015.[2,7,8] However, there is recent literature suggesting a benefit from surgical resection of the primary tumor.[4,9–12]

Controversy exists regarding the long-term benefit of prophylactic resection of the primary tumor in the setting of unresectable stage IV disease. By removing the primary tumor, the goal of intervention is to prevent future morbidity and mortality associated with complications including obstruction, bleeding, and perforation. Many prior studies have addressed this issue, with some suggesting a benefit to surgical resection[4,9–12] and others suggesting that there is no benefit to surgical resection of the primary tumor.[5,7,13,14]

One critique of these studies has been that multimodality treatment has improved survival over time, and that this improvement in nonsurgical treatment is the cause of this increased survival. We sought to minimize confounding factors by only analyzing the subset of patients treated with chemotherapy, but not surgical resection of metastatic disease. This is the largest study to date addressing this question, including over 60,000 patients.

## Materials and Methods

This is a retrospective cohort study of the National Cancer Data Base (NCDB) from 2004 to 2012. The study population includes all patients with synchronous metastatic colorectal adenocarcinoma treated with systemic chemotherapy who did not undergo surgical resection of metastatic disease. The study groups compared patients who underwent surgical removal of the primary tumor to those who did not (Fig. 1) and excluded patients that had surgery on the metastatic site. Primary outcome was overall survival of patients undergoing definitive surgical resection for the primary colorectal cancer versus no surgery. Multivariate cox proportional hazards regression was adjusted for chemotherapy group, age, gender, race, insurance status, facility type, histology, tumor grade, and comorbidity score to obtain propensity score matching. According to the Commission on Cancer, an academic comprehensive cancer program is defined as a participating institution that has more than 500 newly diagnosed cancer cases per year and provides multiple subspecialties of postgraduate medical training. A community cancer program is defined as an institution that has more than 100 but fewer than 500 newly diagnosed cancer cases per year and training resident physicians is optional.

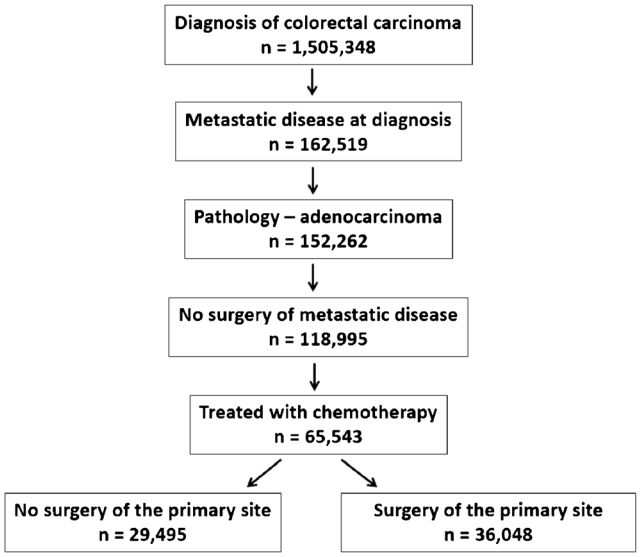


**Fig. 1** Flowchart for NCDB patient selection

## Results

Of the 65,543 patients with unresected stage IV colorectal adenocarcinoma undergoing chemotherapy, 55% underwent surgical resection of the primary site (Table 1). The patients in the surgery group were more likely to be younger, female, white, treated with multi-agent chemotherapy, and have a more aggressive tumor pathology ($p < 0.0001$). Patients with private insurance and those treated at a community hospital were also more likely to have undergone surgery ($p < 0.0001$). The Charlson-Deyo scores were similar between the two groups.[15] Most patients received chemotherapy in the adjuvant setting (Table 1). The mean hospital stay was 7.6 days following surgery.

On univariate analysis, there was no difference in mortality when comparing males to females (HR = 0.987; 95% CI [0.968–1.005]). Blacks had a 13% increased risk of mortality when compared to non-hispanic whites (HR = 1.127; 95% CI [1.097–1.157]) and privately insured patients had a 16% decreased risk of mortality when compared to the uninsured patients (HR = 0.835; 95% CI [0.811–0.860]). In addition, treatment at an academic/research hospital was associated with an 8% decreased risk of mortality when compared to a community hospital (HR = 0.915; 95% CI [0.888–0.944]). Multi-agent chemotherapy was associated with a 10% decreased risk of mortality when compared to single-agent chemotherapy (HR = 0.896; 95% CI [0.874–0.918]). Presence of bone metastasis and brain metastases increased mortality by 84 and 140%, respectively (HR = 0.914; 95% CI [0.888–0.942]).

On multivariate analysis, there remained no difference in mortality when comparing males to females (HR = 0.986; 95% CI [0.965–1.008]). Blacks had an 8% increased risk of

**Table 1** Patient characteristics

| | No surgery, $n$ = 29,495 | Surgery, $n$ = 36,048 | $p$ value |
|---|---|---|---|
| Total | | | < 0.0001 |
| | 45% | 55% | |
| Age | | | < 0.0001 |
| 18–40 | 4.9% | 5.3% | |
| 41–60 | 39.0% | 41.0% | |
| 61–80 | 47.8% | 47.0% | |
| 81–90 | 9.3% | 6.7% | |
| Sex | | | < 0.0001 |
| Male | 57.2% | 54.4% | |
| Female | 42.8% | 45.6% | |
| Race | | | < 0.0001 |
| White | 77.9% | 80.9% | |
| Black | 15.8% | 13.8% | |
| Hispanic | 6.3% | 5.4% | |
| Grade | | | < 0.0001 |
| Well differentiated | 6.9% | 5.9% | |
| Moderately differentiated | 67.5% | 63.0% | |
| Poorly differentiated | 24.3% | 27.9% | |
| Undifferentiated | 1.4% | 3.1% | |
| Insurance status | | | < 0.0001 |
| None | 16.9% | 13.0% | |
| Private | 39.3% | 46.0% | |
| Government | 43.8% | 41.0% | |
| Charlson-Deyo score | | | < 0.0001 |
| 0 | 78.9% | 77.6% | |
| 1 | 15.9% | 18.0% | |
| 2 | 5.2% | 4.5% | |
| Facility type | | | < 0.0001 |
| Community | 12.5% | 13.7% | |
| Comprehensive Community | 50.9% | 57.1% | |
| Academic/research | 36.7% | 29.1% | |
| Type of chemotherapy | | | < 0.0001 |
| Single-agent | 17.8% | 15.1% | |
| Multi-agent | 82.2% | 84.9% | |
| Timing of chemotherapy | | | < 0.0001 |
| Preoperative | | 10.8% | |
| Postoperative | | 84.5% | |
| Both | | 4.7% | |
| Location of metastases | | | < 0.0001 |
| Bone | 8.4% | 2.6% | |
| Brain | 1.3% | 0.6% | |
| Liver | 79.6% | 71.7% | |
| Lung | 32.1% | 17.2% | |
| Overall median survival | | | < 0.0001 |
| Months | 13 | 22 | |

mortality when compared to non-hispanic whites (HR = 1.088; 95% CI [1.054–1.123]) and privately insured patients had a 15% decreased risk of mortality when compared to the uninsured patients (HR = 0.853; 95% CI [0.823–

**Table 2** Prognostic factors for overall survival adjusted for age, sex, race, grade, insurance status, comorbidity score, facility type, and type of chemotherapy

| | No surgery, $n$ = 29,495 | | | Surgery, $n$ = 36,048 | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | $p$ value | HR | 95% CI | $p$ value |
| Age | | | | | | |
| 18–40 | 1.194 | 0.804–1.772 | 0.3791 | 1.694 | 1.338–2.143 | 0.0001 |
| 41–60 | 0.834 | 0.645–1.080 | 0.1684 | 1.176 | 1.011–1.368 | 0.0357 |
| 61–80 | 0.781 | 0.632–0.964 | 0.0216 | 0.979 | 0.866–1.107 | 0.7371 |
| 81–90 | Reference group | | | Reference group | | |
| Sex | | | | | | |
| Female | 1.003 | 0.967–1.040 | 0.8796 | 0.977 | 0.951–1.003 | 0.0835 |
| Male | Reference group | | | Reference group | | |
| Race | | | | | | |
| Hispanic | 0.776 | 0.715–0.843 | 0.0001 | 0.853 | 0.799–0.912 | 0.0001 |
| Black | 1.099 | 1.043–1.158 | 0.0004 | 1.077 | 1.035–1.121 | 0.0003 |
| White | Reference group | | | Reference group | | |
| Grade | | | | | | |
| Moderately differentiated | 1.103 | 1.025–1.187 | 0.0088 | 1.148 | 1.080–1.219 | 0.0001 |
| Poorly differentiated | 1.691 | 1.563–1.829 | 0.0001 | 1.724 | 1.619–1.836 | 0.0001 |
| Undifferentiated | 1.688 | 1.428–1.996 | 0.0001 | 1.704 | 1.551–1.873 | 0.0001 |
| Well differentiated | Reference group | | | Reference group | | |
| Insurance status | | | | | | |
| Government | 0.971 | 0.905–1.040 | 0.4 | 0.899 | 0.850–0.950 | 0.0002 |
| Private | 0.874 | 0.826–0.924 | 0.0001 | 0.839 | 0.802–0.878 | 0.0001 |
| Uninsured | Reference group | | | Reference group | | |
| Charlson-Deyo score | | | | | | |
| 2 | 1.384 | 1.276–1.501 | 0.0001 | 1.25 | 1.175–1.331 | 0.0001 |
| 1 | 1.119 | 1.065–1.176 | 0.0001 | 1.088 | 1.051–1.126 | 0.0001 |
| 0 | Reference group | | | Reference group | | |
| Facility type | | | | | | |
| Academic/research | 0.892 | 0.841–0.945 | 0.001 | 0.865 | 0.828–0.904 | 0.0001 |
| Comprehensive community | 0.968 | 0.916–1.022 | 0.2418 | 0.959 | 0.922–0.998 | 0.0375 |
| Community | Reference group | | | Reference group | | |
| Type of chemotherapy | | | | | | |
| Multi-agent | 0.861 | 0.821–0.903 | 0.0001 | 0.926 | 0.892–0.961 | 0.0001 |
| Single-agent | Reference group | | | Reference group | | |

0.883]). Treatment at an academic/research hospital was associated with a 13% decreased risk of mortality when compared to a community hospital (HR = 0.873; 95% CI [0.843–0.904]). Multi-agent chemotherapy was associated with a 10% decreased risk of mortality when compared to single-agent chemotherapy (HR = 0.901; 95% CI [0.875–0.928]) (Table 2).

Actuarial survival analysis demonstrated that surgical resection of the primary tumor was associated with improved survival compared to treatment with chemotherapy alone (median survival 22 vs 13 months, $p < 0.0001$) (Fig. 2). The surgical survival benefit was present in patients treated with either multi-agent or single-agent chemotherapy (23 vs 14 months, $p < 0.001$; 19 vs 9 months, respectively, $p < 0.001$).

To further substantiate our results from the univariate and multivariate regression analyses, we used propensity score matching and weighting, using the same variables employed for the multivariable analysis which showed that surgery demonstrated a similar protective effect on survival (OR = 0.863; 95% CI [0.805–0.924]; HR = 0.914; 95% CI [0.888–0.942]) (Table 3).

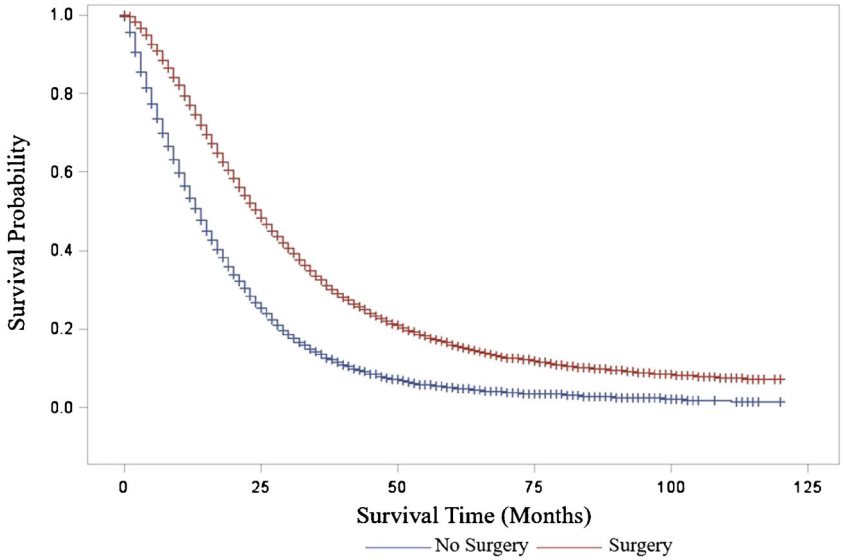


**Fig. 2** Kaplan-Meier survival curve comparing mortality from time of diagnosis of chemotherapy patients who underwent surgical resection of the primary tumor to those who did not ($p < 0.001$)

## Discussion

Historically, in patients with unresectable metastatic colorectal cancer, surgery is usually performed for palliative purposes. However, recent literature has shown an association with increased survival in patients undergoing resection of the primary site of disease.[4,9,11,12] Prior studies have shown that surgical removal of the primary tumor in combination with chemotherapy is associated with improved survival compared to chemotherapy or surgery alone.[7] However, previous studies have typically only included two groups, surgery vs no surgery. We reduced confounding factors by only analyzing the subset of patients undergoing chemotherapy and performing a multivariate analysis with propensity score matching.

The intent of removal of the primary tumor in the setting of incurable disease is to prevent future tumor-related complications including bleeding, obstruction, and perforation. In addition, by intervening prior to the onset of symptoms, an ostomy may be avoided, thereby avoiding the decreased quality of life associated with the formation of an ostomy. Symptomatic obstruction requiring surgical intervention occurs in 19–29% of patients prior to death with proximal diversion being the most common procedure performed.[5,11] Left-sided lesions, rectal cancers, and near-obstructing lesions were more likely to become symptomatic, with 64% of near-obstructing lesions requiring surgery in the first year after diagnosis.[5,11] In palliative surgery for bowel obstruction in stage IV colorectal cancer, mortality ranges from 3 to 40%, morbidity from 32 to 64%, and median survival is 64 days.[16–18] With elective bowel resection in this patient population, 30-day mortality is significantly lower at 1.6–7.7%, with morbidity at 18–50%.[5,9,11]

Our data show that surgical resection in combination with chemotherapy is associated with improved survival when compared to patients treated with chemotherapy alone. The surgical survival benefit was present in both multi-agent or single-agent chemotherapy and persisted even when controlling for confounding variables using multivariate analysis and propensity score matching.

The increase in survival in our data is likely multifactorial. First of all, there is certainly a selection bias in which patients who are fit enough to undergo surgery for their primary tumor are more healthy, and would be expected to live longer. We attempted to remove some of this selection bias by performing multivariate analysis and propensity score matching in a large number of patients. However, it is likely that the variables available to us do not capture all of the confounding covariates, and the only way to definitively answer this question is with a prospective randomized trial. Second, improving survival with multi-agent chemotherapy increases the time that

**Table 3** Summary table with the hazard ratios for survival adjusted for chemotherapy group, age, gender, race, insurance status, facility type, histology, tumor grade, and comorbidity score

| Surgery vs no surgery | | |
|---|---|---|
| Models | HR | 95% CI |
| Univariate Cox PH regression (HR) | 0.907 | 0.885–0.930 |
| Multivariate Cox PH regression (HR) | 0.901 | 0.875–0.928 |
| Multivariate logistic regression with propensity scores matching (OR) | 0.863 | 0.805–0.924 |
| Multivariate Cox PH regression with propensity scores matching (HR) | 0.914 | 0.888–0.942 |

patients may be exposed to complications from the primary tumor, possibly leading to an increase in mortality associated with complications from the primary tumor. Third, emergent surgical intervention for symptomatic patients due to obstruction or bleeding from the primary tumor can result in a significant delay or a failure to initiate or resume beneficial chemotherapy, therefore this patient population is likely to benefit from early elective resection of the primary as opposed to emergent or urgent resection at a later date. Lastly, a recent article from Ghiringhelli et al., has suggested that the addition of bevacizumab to chemotherapy is only beneficial in patients who have undergone primary tumor resection.[19] This gives increasing support to the hypothesis shown by various animal models that there is a more complex tumor angiogenic network in the primary tumor when compared to the metastatic lesions, leading to a difference in efficacy of the various chemotherapy regimens on different sites of disease.[20,21]

A recent study using the Surveillance, Epidemiology, and End Results (SEER) database found that palliative primary tumor resection was associated with improved overall and cancer-specific survival.[22] However, this study did not adjust for variable of the benefit of chemotherapy, which likely contributed to confounding when calculating the survival benefit. Our study used a larger database and a larger patient population allowing us to only analyze the subset of patients undergoing chemotherapy to reduce confounding and obtain a more accurate representation of the association between surgical resection of the primary tumor and potential survival benefit.

Another study, using the NCDB, again demonstrated an overall survival benefit associated with surgical resection of the primary tumor.[10] This study selected database patients listed as "palliative care" limiting the sample size to a surgical resection group of only 231 patients. This small sample size limits the generalizability of this study.

There are currently multiple ongoing prospective randomized controlled trials regarding this important topic. These studies include the GRECCAR 8 study, which is a multicenter, randomized controlled trial of French hospitals comparing the survival of patients with rectal cancer and unresectable synchronous metastasis undergoing primary tumor resection and chemotherapy to those undergoing chemotherapy alone.[23] The SYNCHRONOUS trial is German multicenter randomized controlled trial comparing resection of the primary tumor versus no resection prior to systemic therapy in patients with colon cancer and synchronous metastases not amenable to curative therapy.[24] Additionally, the CAIRO4 study from the Dutch Colorectal Cancer Group is a phase III multicenter randomized controlled trial with the same primary outcome, but additionally analyzing secondary endpoints of progression free survival, surgical morbidity, quality of life, and resection of the primary tumor in the control group.[25] The results of these ongoing studies will further guide the treatment of this complex patient population.

Limitations to our study are similar to all retrospective database studies, including selection bias, confounding, and veracity of the data. In addition, symptom status, targeted therapies, and radiofrequency ablation were not captured in the NCDB.

## Conclusion

Our results show that in patients with synchronous unresected stage IV colorectal adenocarcinoma who receive single- or multi-agent chemotherapy, definitive surgery of the primary site was associated with improved overall survival. The results of ongoing large randomized controlled trials are needed to determine if there is a causal relationship between surgery and increased overall survival in this patient population.

**Author Contribution** All authors listed have made substantial contributions to the conception and design of this manuscript, including analysis and interpretation of data, revising the draft, and have approved the final version as it is now submitted. They are in agreement that they are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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