Clinical Outcomes of Metastatic Colorectal Cancer Following Surgical Resection of the Primary tumor at Hiwa Cancer Hospital, Sulaimani, Iraq

Kadhim Faruq Namiq¹, Kosar Mohammad Ali¹, Mohammed Ibrahim Mohialdeen Gubari²

¹Department of Medicine, College of Medicine, University of Sulaimani, Sulaimani, Iraq.

²Department of Family and Community Medicine, College of Medicine, University of Sulaimani, Sulaimani, Iraq.

Abstract

Background: Colorectal cancer (CRC) is one of the main causes of cancer-related mortality. The surgical resection of primary CRC tumors is a critical line of treatment. The present study investigated the clinical outcomes of the surgical resection of the primary tumor in metastatic CRC patients.

Materials and Methods: In this prospective and retrospective study, 81 metastatic CRC patients were recruited at Hiwa Cancer Hospital in Sulaimani, Iraq from January 2016 to December 2019. Forty-one patients underwent surgical resection of their primary tumor while the remaining 40 patients did not undergo resection. Data regarding patients' clinical outcomes were obtained from the clinical portal system of the hospital and were analyzed using SPSS (version 23.0).

Results: The patients' mean ($\pm$ SD) age was 53.5 ($\pm$ 17.02) years and the male-to-female ratio was 1.3:1. Patients undergoing the surgical resection of their primary tumors had a significantly better one-year survival compared to those who did not undergo resection ($P=0.04$). Based on the results, patients in the surgical resection group continued to have a better overall survival although it was not statistically significant ($P=0.1$). Significantly more patients with colon cancer underwent surgical resection compared to rectal cancer ($P=0.03$), and smoking habit negatively affected the chance to undergo surgical resection ($P=0.009$).

Conclusion: In general, the surgical resection of the primary tumor has a significant favorable impact on one-year survival, but possibly not on overall survival. The primary site of the tumor and smoking habits significantly influence the chance to undergo surgical resection whereas the grade of the tumor or the type of systemic therapy has no significant impact in this regard.

Keywords: Colorectal cancer, Surgical resection, Primary tumor, Clinical outcome, Survival

*Correspondence to

Kosar Mohammad Ali,
Department of Medicine,
College of Medicine,
University of Sulaimani,
Sulaimani, Iraq.
Tel: 009647702472030.
Email: kosar.ali@univsul.edu.iq

Received: January 27, 2021, Accepted: February 27, 2021, ePublished: March 30, 2021

Introduction

Colorectal cancer (CRC) afflicts both men and women and is referred to as the third most common cause of cancer-related deaths all over the world (1). There has recently been a steady decrease in the CRC incidence and the CRC-caused mortality rate (2). In spite of improvements in survival among CRC patients, the median survival of such patients is still low and about one year (3). CRC can be associated with complications such as perforation, bleeding, and/or obstruction in patients with the primary lesions of the rectum and colon. Such complications make the surgical management of such patients more difficult because there is a need for intraoperative decisions that are modified for the situation at hand (4). According to the National Comprehensive Cancer Network guidelines, systemic chemotherapy is the standard treatment for patients who have minimal primary-tumor symptoms and acceptable performance status. This treatment has been claimed and

proved to enhance such patients' survival (5). Probably, due to the addition of multiagent chemotherapy over the past decade, there have been improvements in the overall survival rate from 9 to 24 or 36 (6). According to Ducreux et al (7), major responses were obtained in the majority of previously untreated patients as a result of first-line chemotherapy with FOLFOX or FOLFIRI (i.e., folinic acid, fluorouracil, and irinotecan). Disease cure is rarely obtained through sole systemic therapy, and effective chemotherapy in combination with complete surgical resection of metastatic disease increases the probability of a cure in patients with the resectable disease (8). Adenocarcinomas account for the majority of primary cancers developing in the colon. Localized colon cancer can only be cured through surgical resection. The tumor, the lymphatic drainage basin of the affected colonic segment, and the major vascular pedicles are completely removed in the surgical resection of primary colon cancer (9). The en bloc surgical resection of contiguous structures

is employed in the case of attachment or the infiltration of the tumor into a potentially resectable structure or organ. Moreover, a staged approach to resection might be required for patients with the symptoms of the complicated disease with perforation or obstruction (10). Using curative surgical resection is restricted in the other sites of the metastatic spread of disease with unresectable tumor burden (1). Based on the literature and our experience of the CRC surgical resection in Iraq, it was hypothesized that the cancer surgical resection of CRC could lead to long-term survival improvements. In this regard, the main objective of the present study was to identify differences in the outcomes of metastatic CRC patients who underwent surgical resection compared to those who did not undergo surgery.

Materials and Methods

Study Design and Setting

The current study was a prospective investigation. It consisted of a cohort of 81 patients who were suffering from metastatic CRC (stage IV) and had undergone surgical resection in the Hiwa Cancer Hospital in Sulaimani, Iraq from January 2016 to December 2019.

Patients

A total of 81 patients suffering from CRC participated in the present study and were chosen based on the following inclusion criteria:

- Patients suffering from stage IV colon or rectal cancer;
- Patients with previous localized CRC represented with metastatic recurrence;
- Adenocarcinoma confirmed on the histopathologic examination of the tissue biopsy;
- Patients with recorded and accessible clinical data.

Data Collection and Procedure

The patients' data were obtained from the clinical portal system of Hiwa Cancer Hospital during the mentioned period. This clinical database system records almost all the clinical data and investigations of patients referring to the hospital, including demographics, histopathology reports, imaging reports, diagnosis, multidisciplinary team recommendations, treatment, and follow-ups. For some patients who lacked full information records in the database, their data were obtained from the referring hospital, laboratory, clinic, or directly from patients' documents. The collected data included patients' demographics such as age, gender, date of diagnosis, history of smoking cigarettes and drinking alcohol, last presence in the hospital, and date of death (if dead), colon or rectal tumor, the exact site of the primary tumor, primary tumor resected or not, and the tumor grade.

Statistical Analysis

The data were obtained over a period of 22 months,

from July 2018 to April 2020, and were organized on a Microsoft Excel worksheet using the Microsoft Excel 2016 software program. The organized data were then analyzed using the Statistical Package for Social Sciences (SPSS) software program, version 23.0. Furthermore, one-year and overall survival outcomes were analyzed for the patients who underwent or did not undergo surgical resection of the primary tumor. The overall survival was defined by the time from the initial diagnosis to death from any cause or censored on the date last found alive. An independent sample *t* test was used to compare the mean ages of both groups, a *P* value of less than 0.05 was considered statistically significant.

Results

The study consisted of a total of 81 patients with a mean age of 53.5 ± 17 years. The male-to-female ratio was 1.3:1. Considering the primary site of the tumor, 31 (38%) patients had primary rectal cancer, and the remaining 50 patients (62%) had their tumor originating from the colon (16 patients in the right colon and 34 in the left colon). Furthermore, the histopathological result of the tissue samples showed that the majority of the tumors ($n=57$, 70%) were grade II disease, and the remaining 24 patients were evenly distributed between grades I and III tumors (15% grade I and 15% grade III). Approximately one-third of the patients (38%) were either current or ex-smoker and only 5 out of 81 patients (6%) were ex-alcohol drinkers (Table 1).

With regard to the one-year survival outcome, the analyzed data demonstrated that the 1-year survival of

Table 1. Characteristics of Patients and Their Tumors

Characteristics	Number (%)	
Number of patients		81
Age (year)	Median	55
	Range	20-87
	Mean	53.5
	SD	17.02
Gender (%)	Male	46 (56.8)
	Female	35 (43.2)
	Male/female ratio	1.3:1
Site of tumor	Rectum	31 (38.3)
	Left colon	34 (42.0)
	Right colon	16 (19.8)
Grade of tumor	I	12 (14.8)
	II	57 (70.4)
	III	12 (14.8)
Surgical resection of tumor	Yes	41 (50.6)
	No	40 (49.4)
Smoking (current or ex-smoker)	Yes	31 (38.3)
	No	50 (61.7)

Note. SD: Standard deviation.

patients undergoing the surgical resection of their primary tumor and those not undergoing surgical resection was 77% and 54%, respectively (Figure 1). The hazard ratio was (HR = 0.81) and the difference was statistically significant ($P=0.04$).

Regarding the overall survival outcome, it was found that the positive impact of the surgical resection of the primary tumor on the survival outcomes of the study subjects continued with time (Figure 2). The overall survival analysis represented the frank separation of both study arms although it is not statistically significant ($P=0.1$).

The study results showed that 63% of females underwent surgical resection of their primary tumor whereas only 41% of males underwent resection ($P=0.05$). In addition, more patients (nearly twice) with colon cancer had the chance to undergo surgical resection compared to those with rectal cancer (Table 2), and the difference was statistically significant (60% versus 35%, $P=0.03$).

Figure 1. One-Year Survival Outcomes of Patients Undergoing Surgical Resection Versus Those Not Undergoing the Resection of Their Primary Tumors

Figure 2. Impact of Surgical Resection on the Overall Survival of Metastatic Colorectal Cancer.

Table 2. The Association Between the Surgical Resection of the Primary Tumor and the Primary Site

		Surgical Resection of Primary Tumor		<i>p</i> Value
		Yes	No	
Primary site	Colon (%)	30 (60.0)	20 (40.0)	0.03
	Rectum (%)	11 (35.5)	20 (64.5)	

The results (Table 3) further revealed that smoking negatively influenced the chance to undergo surgical resection. Smoker patients (current or ex-smoker) were significantly less likely to undergo surgical resection of their primary tumors compared to non-smokers ($P=0.009$).

The effect of possible confounders such as the grade of the tumor and the type of the prescribed systemic therapy on the obtained results was investigated using Fisher's exact test. The results (Table 4) indicated that there was no statistically significant difference in the type of systemic therapy given to the study subjects between the resected and non-resected groups ($P=0.85$). Moreover, there was no significant difference in the grade of the tumor between both groups.

Discussion

Patients suffering from stage IV CRC have recently experienced longer survival rates because the resection of isolated metastases by surgery and chemotherapeutic methods have lately improved significantly. However, no significant improvement was found in the overall prognosis of this disease such that the maximum survival period was five years in nearly 14% of the patients (11). In the present study, the precise investigation into patients undergoing surgical resection with an intent to cure revealed that the overall survival improved among the patients with stage IV CRC who underwent a colorectal resection to resect their primary tumor. Moreover, this association remained even after adjustment, as well as in a sub-analysis of patients only with colon cancers. Based on the results, the characteristics of patients with CRC were affected by different factors such as age, gender, the tumor site, tumor grade, and different therapeutic options such as surgical resection of the tumor and smoking.

Additionally, the results of a study conducted by Kim et al indicated that gender is not a determinant factor such that males and females were not significantly different with regard to being affected by CRC. However, they concluded that males over 65 years old had lower mortality while a higher 5-year survival rate of CRC compared to their age-matched female counterparts (12). The results of the present study revealed that stage IV CRC was prevalent in about one-third of patients. Similarly, Lawler et al reported that the major approach to stage IV disease was basically palliative, in which local bowel obstruction is treated through the surgical bypass and local management is carried out via chemo-radiation.

Table 3. The Association Between the Surgical Resection of the Primary Tumor and Smoking

		Surgical Resection of Primary Tumor		P Value
		Yes	No	
Smoking	Yes	10 (24.4)	21 (52.5)	0.009
	No	31 (75.6)	19 (47.5)	

Table 4. Types of Received Perioperative Systemic Therapies by the Study Subjects in Relation to the Surgical Resection of the Primary Tumor

		Surgical Resection		p Value
		Yes	No	
Type of systemic therapy	Chemotherapy & Avastin (%)	27 (48)	29 (52)	0.85
	Chemotherapy alone (%)	3 (75)	1 (25)	
	Chemotherapy & cetuximab (%)	9 (53)	8 (47)	
	No treatment (%)	2 (50)	2 (50)	

However, in the case of colon cancers, the mere surgical therapy for stages I and II disease is wide resection margins (13).

In another similar study, Feo et al found that different factors affect the decision of surgical resection therapy for the primary tumor in patients with stage IV CRC such that the resectability of metastatic disease and the presence of symptoms need to be taken into account. With the appearance of new therapeutic regimens, surgical resection of the primary tumor does not result in a survival benefit when the patient has no symptoms. However, options such as surgical resection therapy, diversion, and endoluminal therapy are available for patients with symptomatic primary tumors (14).

In the present study, the left colon, the rectum, and the right colon were the sites of the tumor in more than two-fifths, about 38%, and less than 20% of participants, respectively. In addition, a significant association was observed between the primary site of the tumor and response to the surgical resection of the tumor. In line with this finding, evidence has shown that response to systemic treatment has partly been referred to as the reason for the relationship between the primary tumor site and different outcomes in metastatic CRC (15-17). Due to the effect of the primary tumor site on response to surgical resection, it has been recommended by the National Comprehensive Cancer Network to take the primary tumor site into account in the first-line treatment of unresectable metastatic CRC (18).

In the same vein, the results of Aljehani et al showed that survival and response to surgical resection in metastatic CRC can be affected by the primary tumor site. It was found that patients with right-sided metastatic CRC had poorer overall survival compared with those with left-sided metastatic CRC regardless of the surgical resection (19). This is in line with the results of the present study and highlights the relationship between the primary tumor site and outcomes in metastatic CRC. Similarly,

other studies reported a significant association between the primary tumor site and the outcomes in patients who underwent surgical resection and bevacizumab such that significantly higher mortality was observed in patients with right-sided metastatic CRC compared to those with left-sided metastatic CRC (20-22).

Based on the results of the present study, the one-year survival outcome of females was higher than that of males. This finding corroborates with that of Stathopoulos and Smith (23), indicating that females have a higher survival duration following the surgical resection of the primary tumor in comparison to males. However, no significant difference was reported between genders in terms of postoperative survival rates.

The results of another similar study by Bugge et al (24) represented that males and females were not significantly different regarding their overall survival. In addition, it was stated that older patients had a significantly higher mortality risk in comparison with younger ones. However, surgical treatment is advantageous in elderly CRC patients following the one-year overall survival among over half of the older patients with metastatic CRC.

The results for both right and left colons, the outcomes of one-year survival following the surgical resection of the primary tumor, the results were equal, and there was no significant difference in the 1-year survival outcome of the colon and the rectum. Moreover, a significant difference was found between patients who underwent surgical resection and those who did not undergo resection of their primary tumors in terms of their one-year survival outcomes. Likewise, Matsuda et al (25) concluded that in spite of rapid advances in surgical technologies such as surgical resection, preparations, along with utmost serious care need to be taken into account in order to ensure favorable outcomes in CRC patients.

One-year survival outcomes also improved due to the recent progress in preoperative and postoperative surgical treatment. However, further improvement in the surgical therapy outcomes of CRC patients depends on the development of new biomarkers (25). In the present study, the grade of primary CRC has a significant effect on the 1-year survival outcome. Moreover, the results revealed that there is a close association between the grade of primary CRC and the overall survival outcome of surgical therapy, and patients with higher grades of CRC achieved weaker survival outcomes.

Based on the obtained data, smokers were significantly less likely to undergo surgical resection of their primary tumors compared to non-smokers. As a consequence, smoking could negatively influence the chance to undergo surgical resection. Conversely, Tsoi et al (26) reported a different outcome. They concluded that smoking is significantly correlated with a risk of CRC elevations. They further indicated the highest risk of CRC among male smokers, particularly those who smoke 20 cigarettes per day or have smoked for more than 30 years.

A possible explanation is that smoking takes around 30 years to cause CRC, therefore, it usually causes cancer at a late age making the patient less fit for surgery. In addition, smoking negatively affects the lung capacity and function, which, in turn, makes the patient high risk for surgery and decreases the chance of being a candidate for surgical resection in such patients (27). The results of a study by Sharma et al demonstrated that smokers with CRC are less likely to undergo surgical therapies because the risk of complications following all kinds of major colorectal surgery smoking is quite high in smokers, particularly in current ones. Therefore, it is recommended that smoking cessation should be highly encouraged in patients who want to undergo elective colorectal surgery (28).

In this study, none of the systemic therapies such as the combination of chemotherapy and Avastin/cetuximab or chemotherapy alone could significantly affect the surgical resection of the primary tumor. On the other hand, there was no statistically significant difference in the type of perioperative systemic therapy to patients who underwent surgical resection. Patients with initially unresectable metastatic CRC can be turned resectable through using systemic chemotherapy and targeted therapy in order to shrink the primary and secondary lesions. This strategy was used for several initially unresectable patients in this study. Indeed, the prognosis of patients with an initially unresectable tumor that turned resectable after receiving systemic therapy and undergoing surgery is nearly identical to that of patients who have undergone surgery from the onset of the disease (29,30).

There is a significant correlation between the activity of the applied systemic therapy for downsizing and shrinking the tumor, and the probability to turn an unresectable tumor into a resectable one. Therefore, one of the major goals of using systemic therapy in patients with initially unresectable metastatic CRC is to shrink and downsize the tumor and induce radical resection in order to improve prognosis. The results of a similar study conducted by Bridgewater et al represented less prognostically favorable baseline characteristics in the group that had undergone chemotherapy plus cetuximab such that more patients had a large metastasis and synchronous disease. Moreover, it was revealed that patients with favorable characteristics experienced harm as a result of cetuximab (31). In this regard, however, it is clinically recommended that a large number of CRC patients with liver metastases should be treated with chemotherapy regardless of the initial resectability status of their metastases (32).

Conclusion

CRC is highly prevalent and its development can be greatly affected by environmental and genetic factors. Therefore, its management requires a high level of surveillance. In this regard, its risk factors such as low physical activity, lifestyle, and diet need to be assessed and monitored at younger ages. The surgical resection of the primary tumor

was associated with improved survival outcomes. Patients with initially unresectable tumors can be turned resectable through using systemic chemotherapy and targeted therapy in order to shrink and downsize the primary and secondary lesions. The outcomes of surgical resection can be highly influenced by the primary site of the tumor. In addition, the surgical resection of primary tumors is significantly less likely to be carried out for ex- or current smokers. To achieve more considerable results, individual factors of CRC patients should be taken into account by a multidisciplinary team prior to primary tumor resection. In this regard, further research is required to decide which patients might benefit from this intervention.

Conflict of Interest Disclosure

The authors declare that they have no conflict of interests.

Acknowledgements

We wish to express our thanks to all those participating in this research project. We would also like to thank all the staff at the Hiwa Hospital for helping us in collecting the data.

Ethical Statement

The study was approved by the Ethics Committee of the University of Sulaimani/College of Medicine (7-27.03.19). Patients' data were kept confidential throughout the research procedure.

Authors' Contributions

The authors equally contributed to providing the proposal, designing the study, and analyzing and interpreting the data. Furthermore, they cooperated on drafting the article and critically revising it for important intellectual content, along with approving the final version of the study for submission.

Funding/Support

The study was supported by the University of Sulaimani.

Informed Consent

The present study was carried out after obtaining informed consent.

References

1. Gulack BC, Nussbaum DP, Keenan JE, Ganapathi AM, Sun Z, Worni M, et al. Surgical resection of the primary tumor in stage IV colorectal cancer without metastasectomy is associated with improved overall survival compared to chemotherapy/radiation therapy alone. *Dis Colon Rectum*. 2016;59(4):299-305. doi: [10.1097/dcr.0000000000000546](https://doi.org/10.1097/dcr.0000000000000546).
2. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(2):104-17. doi: [10.3322/caac.21220](https://doi.org/10.3322/caac.21220).
3. Castleberry AW, Güller U, Tarantino I, Berry MF, Brügger L, Warschkow R, et al. Discrete improvement in racial disparity in survival among patients with stage IV colorectal cancer: a 21-year population-based analysis. *J Gastrointest Surg*. 2014;18(6):1194-204. doi: [10.1007/s11605-014-2515-3](https://doi.org/10.1007/s11605-014-2515-3).
4. De Sousa EMF, Wang X, Jansen M, Fessler E, Trinh A, de Rooij LP, et al. Poor-prognosis colon cancer is defined by a molecularly distinct subtype and develops from serrated precursor lesions. *Nat Med*. 2013;19(5):614-8. doi: [10.1038/nm.3174](https://doi.org/10.1038/nm.3174).
5. Silberhumer GR, Paty PB, Denton B, Guillem J, Gonen M, Araujo RLC, et al. Long-term oncologic outcomes for

- simultaneous resection of synchronous metastatic liver and primary colorectal cancer. *Surgery*. 2016;160(1):67-73. doi: [10.1016/j.surg.2016.02.029](https://doi.org/10.1016/j.surg.2016.02.029).
6. Ducreux M, Malka D, Mendiboure J, Etienne PL, Texereau P, Auby D, et al. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2011;12(11):1032-44. doi: [10.1016/s1470-2045\(11\)70199-1](https://doi.org/10.1016/s1470-2045(11)70199-1).
 7. Ducreux M, Bennouna J, Hebbar M, Ychou M, Lledo G, Conroy T, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. *Int J Cancer*. 2011;128(3):682-90. doi: [10.1002/ijc.25369](https://doi.org/10.1002/ijc.25369).
 8. Ruers T, Punt C, Van Coevorden F, Pierie J, Borel-Rinkes I, Ledermann JA, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Ann Oncol*. 2012;23(10):2619-26. doi: [10.1093/annonc/mds053](https://doi.org/10.1093/annonc/mds053).
 9. Vogel JD, Eskicioglu C, Weiser MR, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the treatment of colon cancer. *Dis Colon Rectum*. 2017;60(10):999-1017. doi: [10.1097/dcr.0000000000000926](https://doi.org/10.1097/dcr.0000000000000926).
 10. Boriani S. En bloc resection in the spine: a procedure of surgical oncology. *J Spine Surg*. 2018;4(3):668-76. doi: [10.21037/jss.2018.09.02](https://doi.org/10.21037/jss.2018.09.02).
 11. Castleberry AW, Güller U, Tarantino I, Berry MF, Brügger L, Warschkow R, et al. Discrete improvement in racial disparity in survival among patients with stage IV colorectal cancer: a 21-year population-based analysis. *J Gastrointest Surg*. 2014;18(6):1194-204. doi: [10.1007/s11605-014-2515-3](https://doi.org/10.1007/s11605-014-2515-3).
 12. Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK. Sex- and gender-specific disparities in colorectal cancer risk. *World J Gastroenterol*. 2015;21(17):5167-75. doi: [10.3748/wjg.v21.i17.5167](https://doi.org/10.3748/wjg.v21.i17.5167).
 13. Lawler M, Johnston B, Van Schaeybroeck S, Salto-Tellez M, Wilson R, Dunlop M, et al. Colorectal cancer. In: Niederhuber JE, Armitage JO, Dorshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 6th ed. Philadelphia, PA: Elsevier; 2020.
 14. Feo L, Polcino M, Nash GM. Resection of the primary tumor in stage IV colorectal cancer: when is it necessary? *Surg Clin North Am*. 2017;97(3):657-69. doi: [10.1016/j.suc.2017.01.012](https://doi.org/10.1016/j.suc.2017.01.012).
 15. Missiaglia E, Jacobs B, D'Ario G, Di Narzo AF, Soneson C, Budinska E, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. *Ann Oncol*. 2014;25(10):1995-2001. doi: [10.1093/annonc/mdu275](https://doi.org/10.1093/annonc/mdu275).
 16. Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 Trials. *JAMA Oncol*. 2017;3(2):194-201. doi: [10.1001/jamaoncol.2016.3797](https://doi.org/10.1001/jamaoncol.2016.3797).
 17. Brulé SY, Jonker DJ, Karapetis CS, O'Callaghan CJ, Moore MJ, Wong R, 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):1405-14. doi: [10.1016/j.ejca.2015.03.015](https://doi.org/10.1016/j.ejca.2015.03.015).
 18. Burt RW, Barthel JS, Dunn KB, David DS, Drelichman E, Ford JM, et al. NCCN clinical practice guidelines in oncology. Colorectal cancer screening. *J Natl Compr Canc Netw*. 2010;8(1):8-61. doi: [10.6004/jnccn.2010.0003](https://doi.org/10.6004/jnccn.2010.0003).
 19. Aljehani MA, Morgan JW, Guthrie LA, Jabo B, Ramadan M, Bahjri K, et al. Association of primary tumor site with mortality in patients receiving bevacizumab and cetuximab for metastatic colorectal cancer. *JAMA Surg*. 2018;153(1):60-7. doi: [10.1001/jamasurg.2017.3466](https://doi.org/10.1001/jamasurg.2017.3466).
 20. Loupakis F, Yang D, Yau L, Feng S, Cremolini C, Zhang W, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst*. 2015;107(3):dju427. doi: [10.1093/jnci/dju427](https://doi.org/10.1093/jnci/dju427).
 21. Wong HL, Lee B, Field K, Lomax A, Tacey M, Shapiro J, et al. Impact of primary tumor site on bevacizumab efficacy in metastatic colorectal cancer. *Clin Colorectal Cancer*. 2016;15(2):e9-e15. doi: [10.1016/j.clcc.2016.02.007](https://doi.org/10.1016/j.clcc.2016.02.007).
 22. Boisen MK, Johansen JS, Dehlendorff C, Larsen JS, Østerlind K, Hansen J, et al. Primary tumor location and bevacizumab effectiveness in patients with metastatic colorectal cancer. *Ann Oncol*. 2013;24(10):2554-9. doi: [10.1093/annonc/mdt253](https://doi.org/10.1093/annonc/mdt253).
 23. Stathopoulos P, Smith WP. Analysis of survival rates following primary surgery of 178 consecutive patients with oral cancer in a large district general hospital. *J Maxillofac Oral Surg*. 2017;16(2):158-63. doi: [10.1007/s12663-016-0937-z](https://doi.org/10.1007/s12663-016-0937-z).
 24. Bugge A, Kongerud J, Brunborg C, Solberg S, Lund MB. Gender-specific survival after surgical resection for early stage non-small cell lung cancer. *Acta Oncol*. 2017;56(3):448-54. doi: [10.1080/0284186x.2016.1253862](https://doi.org/10.1080/0284186x.2016.1253862).
 25. Matsuda T, Yamashita K, Hasegawa H, Oshikiri T, Hosono M, Higashino N, et al. Recent updates in the surgical treatment of colorectal cancer. *Ann Gastroenterol Surg*. 2018;2(2):129-36. doi: [10.1002/ags3.12061](https://doi.org/10.1002/ags3.12061).
 26. Tsoi KK, Pau CY, Wu WK, Chan FK, Griffiths S, Sung JJ. Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Clin Gastroenterol Hepatol*. 2009;7(6):682-8.e1-5. doi: [10.1016/j.cgh.2009.02.016](https://doi.org/10.1016/j.cgh.2009.02.016).
 27. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA*. 2008;300(23):2765-78. doi: [10.1001/jama.2008.839](https://doi.org/10.1001/jama.2008.839).
 28. Sharma A, Deeb AP, Iannuzzi JC, Rickles AS, Monson JR, Fleming FJ. Tobacco smoking and postoperative outcomes after colorectal surgery. *Ann Surg*. 2013;258(2):296-300. doi: [10.1097/SLA.0b013e3182708cc5](https://doi.org/10.1097/SLA.0b013e3182708cc5).
 29. Adam R, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol*. 2009;27(11):1829-35. doi: [10.1200/jco.2008.19.9273](https://doi.org/10.1200/jco.2008.19.9273).
 30. Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol*. 2001;8(4):347-53. doi: [10.1007/s10434-001-0347-3](https://doi.org/10.1007/s10434-001-0347-3).
 31. Bridgewater JA, Pugh SA, Maishman T, Eminton Z, Mellor J, Whitehead A, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020;21(3):398-411. doi: [10.1016/s1470-2045\(19\)30798-3](https://doi.org/10.1016/s1470-2045(19)30798-3).
 32. Nordlinger B, Van Cutsem E, Gruenberger T, Glimelius B, Poston G, Rougier P, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. *Ann Oncol*. 2009;20(6):985-92. doi: [10.1093/annonc/mdn735](https://doi.org/10.1093/annonc/mdn735).