Chapter 14
Utility of Primary Tumor Resection in Asymptomatic, Unresectable Metastatic Colon and Rectal Cancer

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Introduction

One in five patients diagnosed with colorectal cancer (CRC) present with synchronous metastatic disease, and of these, only 13 % survive to 5 years [1]. Curative resection of the primary tumor and metastases can improve 5-year overall survival (OS) to 30–50 % [2]. Unfortunately, about three-quarters of patients with metastatic CRC present with unresectable disease to the liver [3]. In this setting, the principal treatment is chemotherapy, with an overall median survival in randomized-controlled trials of >20 months [4, 5]; in fact, a recent phase III study suggested that patients who were able to receive all currently available systemic treatment options had a median OS of nearly 30 months [6].

While receiving chemotherapy, about 10–20 % of patients may develop symptoms from the primary colonic tumor (e.g. obstruction, perforation, and severe bleeding) that necessitate acute intervention [7–11]. Upfront resection of the primary colon cancer prior to the development of symptoms could potentially prevent morbidity, and improve outcomes. Early retrospective data has suggested a survival benefit with primary colon resection, combined with chemotherapy, in the presence

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Table 14.1 Clinical question

P	Patient population	Unresectable, metastatic colon cancer with an asymptomatic primary tumor
I	Intervention	Primary tumor resection (colectomy) followed by 1st line chemotherapy,
C	Comparator	1st line chemotherapy with primary tumor resection only if/when patient becomes symptomatic
O	Outcomes	Overall survival, Hazard Ratio

of unresectable metastases [8, 12]. However, up to half of the patients in these analyses did not receive chemotherapy after surgery, and these patients had no survival benefit when compared to those receiving chemotherapy alone [12].

As a surgeon, it is difficult to draw conclusions from the literature, which is limited to retrospective data, with considerable susceptibility to selection bias. Further complicating the decision to pursue upfront surgery is the fact that there have been significant survival gains over the last decade as a result of multi-drug regimens and targeted therapies [13–20]. Depending on one's perspective, the improved survival associated with modern-era systemic therapy may either obviate the need for resection by providing significant reduction in tumor size and control of local symptoms, or may result in a greater number of patients developing symptoms from the primary tumor because they live longer, thereby requiring surgery. No good data exists regarding the likelihood of curative resection after chemotherapy in patients who present with initially unresectable disease; thus, the clinical choices in this setting are primarily colon resection followed by chemotherapy, or chemotherapy alone. In this chapter, we examine emerging data regarding primary tumor resection with chemotherapy in patients with unresectable metastatic disease and an asymptomatic primary, versus patients receiving upfront multidrug chemotherapy (Table 14.1).

Search Strategy

A detailed search of the Embase-Medline databases was conducted for current medical literature published from 2010 to 2015. The following search terms were employed to identify relevant articles: ("colon" OR "colorectal") AND ("cancer" OR "carcinoma" OR "adenocarcinoma") AND ("metastatic" OR "Stage IV" OR "Stage 4") AND "asymptomatic" AND ("surgery" OR "colectomy" OR "resection"). Duplicate articles were excluded. We included 14 articles, published from 2010 to 2015, that were identified in a Cochrane review and meta-analysis on this specific topic, and were not identified in our initial literature search [21, 22]. The title and abstracts of English-language articles were assessed for relevance. We excluded articles for the following reasons: not relevant, no comparator group (trend

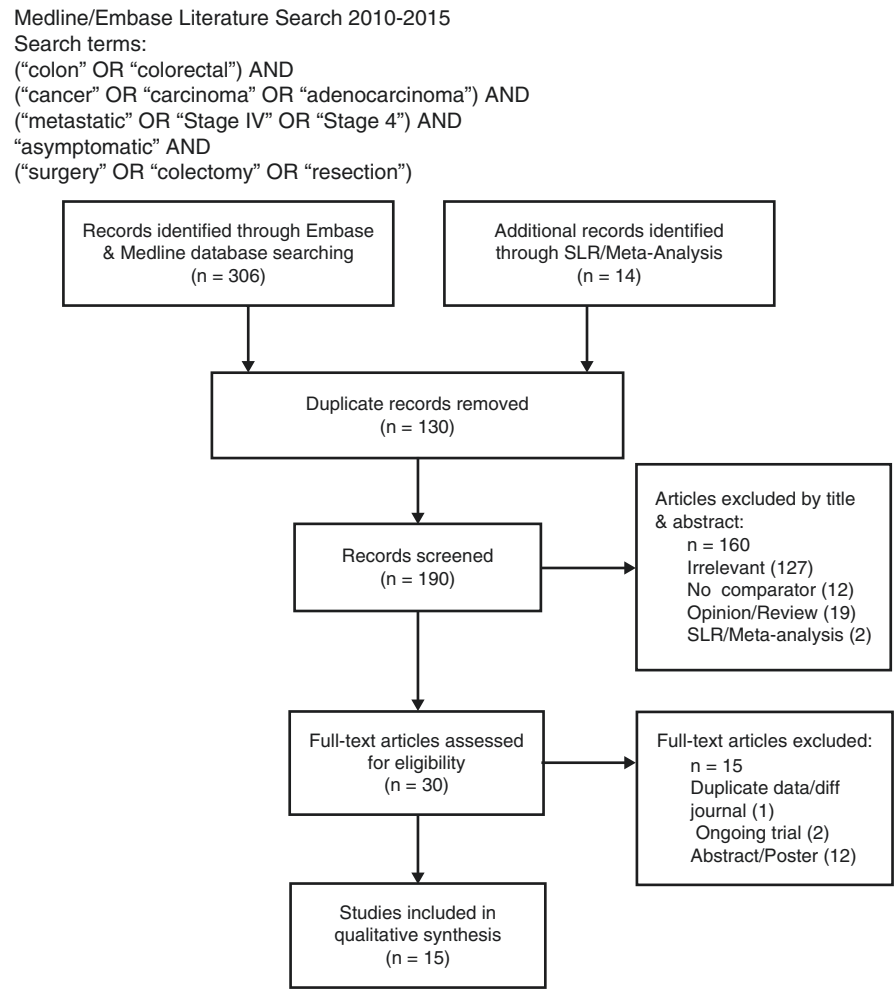

Fig. 14.1 PRISMA diagram, systematic literature search results

analysis), review/opinion articles without primary data, and systematic literature reviews/meta-analyses. A total of 30 articles met the inclusion criteria for full review. Full-text articles were excluded if they were limited to an abstract/poster, contained data duplicated in a different journal, or reported on ongoing trials without reporting any preliminary data. Fifteen manuscripts remained for analysis, five of which were identified from the Cochrane Review and meta-analysis. The literature review process, following PRISMA guidelines, is detailed in Fig. 14.1. Selected articles were abstracted for several variables including study design, time interval, patient population, chemotherapy, survival, and quality (Table 14.2).

Table 14.2 Literature search results

First author	Year	Study design	Interval	Patient population	Chemotherapy regimen(s)	Patients (n)		Median overall survival (mo)		Survival	Acute surgery (*NR*)	Quality of evidence
						R	*NR*	*R*	*NR*	*HR*	%	
Seo	2010	Retrospective cohort	2001–2008	umCRC + APT	FL ± Ox/Iri ± Bev/Cetux	196	83	22	14	–	8.4	Low
Chan	2010	Retrospective cohort	2000–2002	mCRC	Not reported	286	125	14	6	–	–	Very low
Venderbosch	2011	Retrospective review of RCT (CAIRO I)	2003–2004	mCRC	CAPOXIRI	258	141	16.7	11.4	0.63	–	Very low
	2011	Retrospective review of RCT (CAIRO II)	2005–2006	mCRC	CAPOX/Bev ± Cetux	159	289	20.7	13.4	0.65	–	Very low
Karoui	2011	Retrospective cohort, propensity scored	1998–2007	umCC ± APT	FL ± Ox/Iri ± Bev/Cetux	85	123	30.7	21.9	–	19	Low-Mod
Verberne	2011	Retrospective cohort	2002–2006	mRC ± APT	Not reported	26	21	26	17	0.5	–	Very low
Cetin	2013	Retrospective cohort	2006–2010	umCRC + APT	CAPOX/IFL/ FOLFIRI ± Bev	53	46	23	17	–	4.4	Low
Boselli	2013	Retrospecitve cohort	2010–2011	umCRC + APT	FOLOX ± Bev	17	31	4	5	–	–	Very low
Ferrand	2013	Retrospective review of RCT (FFCD 9601)	1997–2001	mCRC (mCC)	FL	156	56	16.3 (15.2)	9.5 (11.1)	–	7	Low

Yun	2014	Retrospective cohort, propensity matched	2000–2008	umCRC + APT umCRC + APT	± FL ± Ox/ Iri ± Bev/ Cetux	113 (286)	113 (198)	17.2	14.4	–	4.5	Moderate
Watanabe	2014	Retrospective cohort	2002–2009	umCRC + APT	FL ± Ox/ Iri ± Bev/ Cetux	46	112	19.9	19.0	–	21	Low
Yoon	2014	Retrospective cohort, propensity matched	2000–2007	umCRC ± APT	FL/Cape ± Ox/ Iri ± Bev/ Cetux	51 (195)	51 (66)	16.5	12	0.68	-	Low-Mod
Matsumoto	2014	Retrospective cohort	2005–2011	umCRC + APT	Fl ± Ox/ Iri ± Bev/ Cetux	41	47	23.9	23.6	0.72	25.5	Low
Tsang	2014	Retrospective cohort (SEER)	1996–2007	mCRC	Not reported	8599	3117	21	10	–	–	Very low
Tarantino	2015	Retrospective cohort, propensity scored (SEER)	1998–2008	mCRC	Not reported	22858	17575	–	–	0.40	–	Very low
Ahmed	2015	Retrospective cohort	1992–2005	mCRC + APT	Not reported	521	313	18.0	8.1	0.52	–	Very low

APT asymptomatic primary tumor, *Bev* bevacizumab, *Cape* capecitabine, *CAPOX* capecitabine/oxaliplatin, *CAPOXIRI* capecitabine/oxaliplatin/irinotecan, *Cetux* cetuximab, *FL* fluropymidine/leucovorin, *FOLFOX* leucovorin/infusional 5-FU/oxaliplatin, *FOLFIRI* leucovorin/infusional 5-FU/irinotecan, *Iri* irinotecan, *mCC* metastatic colon cancer, *mCRC* metastatic colorectal cancer, *mRC* metastatic rectal cancer, *Ox* oxaliplatin, *umCC* unresectable metastatic colon cancer, *umCRC* unresectable metastatic colorectal cancer.

Results

Our literature search identified 15 recently published retrospective studies, in which patients received primarily multi-drug chemotherapy. No prospective observational or randomized controlled trials (RCTs) have been published to date, and secondary analyses of these trials are limited.

Four RCTs were initiated to address this question, although two have already closed due to poor accrual [23, 24]. The Dutch Colorectal Cancer Group (CAIRO4) and the German SYNCHRONOUS trial group have opened multicenter, randomized, superiority trials comparing primary tumor resection + fluoropyrimidine-based regimens with targeted therapy, vs. fluoropyrimidine-based regimens with targeted therapy alone [25, 26]. The results of these trials are not anticipated for several years, but will obviously have a significant impact on surgical decision-making. Until that time, the data from our literature search represents the body of knowledge available on which surgeons may base decisions. Many studies report upfront resection vs. no resection, but do not address the more important question of upfront surgery and chemotherapy vs. chemotherapy alone. Among both groups, there were limited or no data regarding chemotherapy received, and need for acute surgery while on chemotherapy. Recognizing these limitations, a review of the current literature does provide some guidance to the practicing surgeon who is attempting to decide whether or not to resect the primary colon tumor before initiating chemotherapy in patients with unresectable metastatic disease.

Overall Survival

Twelve of the 15 studies identified in our search demonstrated better OS with primary tumor resection vs. no resection in patients with metastatic colon cancer, with a median survival benefit of 7 months. At face value, these results suggest superior OS with primary tumor resection prior to the development of symptoms in patients with unresectable metastatic CRC. Yet on closer analysis, there are serious limitations to these findings, and they should therefore be interpreted with ample skepticism.

To reduce the impact of selection bias and potential confounders, four studies used propensity score modeling, with variable results. Two groups from Korea used propensity scores to match patients who underwent initial primary tumor resection + chemotherapy vs. chemotherapy alone. The smaller of these studies found a statistically significant OS benefit with primary tumor resection (16.5 vs. 12 months, $p = 0.048$) [21], whereas the other, much larger study found no statistical difference in OS between these groups (17.2 vs. 14.4 months, $p = 0.27$) [27, 28]. In the remaining two studies, the data were not sufficiently defined or granular, and the results are less compelling [29, 30]. A French publication reported that OS was superior with primary tumor resection + chemotherapy vs. chemotherapy (30.7 vs. 21.9 months, $p = 0.031$) even after propensity analysis; however, a significant pro-

portion of patients in both groups had obstructive primary tumors at initial presentation (38.8 % vs 26.5 %), and it remains unclear if the survival advantage was from primary resection vs. stent placement or chemotherapy [29]. Similarly, a large U.S. SEER Database analysis demonstrated a dramatic survival advantage with primary tumor resection vs. no resection (HR = 0.40, $p < 0.001$) even after propensity matching (for such factors as age, grade, baseline carcinoembryonic antigen level), but potential confounders such as chemotherapy, performance status, comorbidity, and metastatic disease extent/resectability were not reported [30]. In the end, after controlling for confounding and sufficiently defining the target population, the data did not suggest a significant survival advantage with upfront surgery in asymptomatic patients.

Chemotherapy and Survival

A central criticism of earlier retrospective studies comparing primary tumor resection vs. initial chemotherapy has been the reliance on 5-fluorouracil (5-FU)/leucovorin monotherapy, which was the only chemotherapy agent available prior to the early 2000s. To restrict our literature search to modern chemotherapeutic regimens, we limited our investigation to studies published from 2010 to the present. Despite these efforts, seven of the selected articles included patients receiving 5-FU/leucovorin or the oral 5-FU pro-drug capecitabine alone [27–29, 31–34], and five studies failed to report whether chemotherapy was even administered [30, 35–38]. Furthermore, considerable heterogeneity in chemotherapy regimens existed in all but three of the studies. In these three studies, patients received only irinotecan- or oxaliplatin-based chemotherapy, with or without the monoclonal antibodies bevacizumab (anti-vascular endothelial growth factor) and cetuximab (anti-epidermal growth factor receptor) [39–41]. One of these studies retrospectively analyzed two RCTs and demonstrated a 5-month survival benefit with primary tumor resection and subsequent palliative chemotherapy; however, this study was limited by the fact that patients in the chemotherapy-only group had a statistically greater metastatic disease burden [39]. In the two remaining studies, primary resection followed by chemotherapy vs. chemotherapy alone did not significantly improve OS [40, 41].

The delay in initiating chemotherapy has frequently been considered a drawback to primary tumor resection. In the three studies reporting time-to-chemotherapy in asymptomatic patients who underwent upfront surgery, the data demonstrate a median 4–5 week delay in chemotherapy initiation, compared to patients who had upfront chemotherapy [31, 33, 41]. In addition to this delay, the data suggest that a significant proportion (15–50 %) of asymptomatic patients who undergo upfront surgery do not proceed to chemotherapy most likely due to debilitation from surgery [28, 33, 34, 37, 41] and only one of these studies showed an improved OS with upfront surgery [37]. Two publications included patients for either strategy only if they had received some chemotherapy; one of the two studies reported that primary tumor resection was associated with a significantly better OS (30.7 vs. 21.9 months, $p = 0.03$ [29]; 23 vs. 17 months, $p = 0.32$ respectively) [40]. These

data suggest that OS is potentially optimized in patients who have upfront surgery *when* they are able to receive postoperative chemotherapy. Identification of those patients who will be able to proceed from surgery to chemotherapy in an expeditious manner remains challenging.

Metastatic Disease Burden and Survival

Careful patient selection for upfront surgery is critical, as the disease burden of metastatic CRC has a dramatic influence on candidacy for curative resection and OS. Of the studies that reported a survival benefit with primary tumor resection [27, 29–32, 35–40], more than half did not report the extent or resectability of metastatic disease [30, 32, 35–39]. For example, two studies attempting to identify an optimal strategy through examination of SEER data reported that patients with stage IV CRC lived significantly longer after primary resection [30, 35]. However, neither study described the extent and resectability of metastatic disease, receipt of chemotherapy, or symptoms related to the primary tumor.

In a retrospective analysis of two Dutch RCTs (CAIRO I and II), OS was better with resection compared to no resection (16.7 vs. 11.4 months, $p = 0.004$; 20.7 vs. 13.4 months, $p < 0.0001$), although there was evidence to suggest that patients who did not have surgery were more likely to have an abnormal LDH, more extrahepatic disease, and oligo-metastases, all independent predictors of poor survival [39].

Amongst the eight manuscripts that provided sufficient documentation of the burden of unresectable metastatic disease, the majority of studies found that primary tumor resection did not provide a significant survival advantage over chemotherapy [27–29, 31, 33, 34, 40, 41]. Only two demonstrated a significant difference in median OS with upfront primary resection vs. initial chemotherapy (30.7 vs. 21.9 months, $p = 0.03$) [29], (21 vs. 10 months, $p < 0.001$) [27]. In a study by Chan et al., patients receiving chemotherapy first were significantly more likely to be of older age, to have adjacent organ invasion, extensive liver metastases, poorer performance status, and a rectal primary tumor, all of which are poor prognostic features. In the studies showing no survival benefit, three were of relatively small sample size ($n < 100$), and two limited primary resection to patients with non-traversable tumors only [33, 34, 40, 41]. However, in the overwhelming majority of studies with documented unresectable metastatic disease, OS was not significantly different between groups.

Further Considerations

While there is no compelling evidence that supports upfront surgery vs. chemotherapy with respect to survival benefit, surgeons face additional issues when deciding between primary surgery and chemotherapy. These deserve further discussion.

Acute Surgery During Chemotherapy

Removal of the primary tumor in an elective setting prior to the development of obstruction, perforation or severe bleeding should theoretically result in lower morbidity and mortality. Within our selected studies, 4–25 % of patients receiving chemotherapy first developed symptoms requiring acute surgery [22, 24–28]; and except for differences in the study sizes, no discernible trend could be found between low- and high-incidence studies with respect to patient population, chemotherapy received, or time interval. In three of the four largest studies (n > 200 patients), less than 10 % of patients required acute surgery while on chemotherapy; the most frequent indication was obstruction, and rarely tumor perforation or bleeding [28, 31, 32]. If the theoretical primary benefit of upfront resection is to avoid acute surgery at a later time, somewhere between five and ten patients would receive an unnecessary intervention in order to prevent acute surgery in one patient. Thus, the prevention of acute surgery with elective resection is less common than is purported. Additionally, one cannot ignore the potential delay in chemotherapy initiation, and the potential deterioration in performance status associated with serious surgical complications. From a prevention standpoint, primary tumor resection does not provide a significant benefit for most patients.

Postoperative Complications: Elective Versus Acute Surgery

Colorectal resection, even in the elective setting, is plagued by a variety of complications, and can delay the initiation of chemotherapy. Understandably, acute surgery comes with an even greater risk for complications that may significantly delay or prevent the re-institution of palliative chemotherapy. No study in our search reported on the delay or completion of chemotherapy associated with complications. Three studies reported complications after surgery [31, 33, 34], one of which provided data only on complications after elective resection, thus preventing inter-group comparisons [31]. The results from the remaining two publications failed to show a difference with regards to the incidence of complications, after either elective or acute surgery [33, 34]. The smaller of the two studies found similar rates of severe complications (Clavien-Dindo Grade 3 and 4) [34]; paradoxically, the larger study found that elective surgery was associated with more complications [33]. Although primary tumor resection should intuitively be associated with the lower morbidity of elective surgery, no study has actually demonstrated any such difference in morbidity between elective vs. acute surgery.

Systemic Inflammation and Primary Resection

Emerging evidence suggests that the benefits of primary tumor resection may involve more than the prevention of primary tumor symptoms. Tumor-associated systemic inflammation is associated with significant reductions in survival in patients with

solid-tumor cancers [42]. Increased neutrophil-to-lymphocyte ratio (NLR) is a well-established biomarker of systemic inflammation, and can be calculated with a simple complete blood count. However, none of the manuscripts identified in this search included NLR in their analyses. Two retrospective studies of patients with metastatic CRC who underwent primary tumor resection in the setting of asymptomatic disease, demonstrated a persistent survival benefit with a low NLR or reversal of NLR from high to low [43, 44]. Both studies stratified outcomes by NLR level; reversal of NLR with tumor resection was associated with an 11-month survival benefit compared to a persistently high NLR. These two studies were limited by the fact that they were retrospective analyses, lacked comparator groups, and did not clarify the extent of metastatic burden (other than reporting the presence of oligo-metastases). Nevertheless, these observations are intriguing and should be validated prospectively.

Recommendations

No definitive evidence supports upfront primary tumor resection in patients with unresectable, metastatic CRC and an asymptomatic primary who plan to receive multi-drug chemotherapy. Existing evidence for or against primary tumor resection is severely limited by data that is mostly retrospective and observational. There is considerable potential for selection bias when healthier patients with predicted better survival pursue surgery. No recent studies support primary tumor resection for the prevention of future symptoms, as none have clearly shown a diminished morbidity with upfront surgery. A meta-analysis and Cochrane Review have demonstrated no survival benefit with primary tumor resection in asymptomatic patients.

Given the paucity of data, the National Cancer Center Network (NCCN) Guidelines for colon cancer do not endorse resection of a primary tumor in the setting of unresectable synchronous liver and/or lung metastasis, unless the patient is at imminent risk for obstruction or severe bleeding [45]. Furthermore, the guidelines recommend synchronous or staged resection in the setting of resectable disease. Although the emerging retrospective evidence linking improved survival to lower systemic inflammation after primary resection in CRC is intriguing, many more basic science and clinical investigations are warranted. Randomized controlled trials are needed in order to clarify the benefits of primary tumor resection in asymptomatic individuals; biomarker and correlative analyses are essential to the attempt to identify a subpopulation that might benefit from initial surgery.

Personal View of the Data

My current practice embraces chemotherapy first in asymptomatic patients with unresectable, metastatic colon cancer, except in the cohort with lung-only metastases, as these patients tend to have more indolent metastatic disease. Less than 7 % of

patients at our institution ever require surgery for their primary tumor while receiving initial chemotherapy [11]. In this setting, multi-drug chemotherapy has proven effective and safe in the long-term treatment of metastatic disease. Moreover, in a subset of patients, current multimodality therapies have substantially improved our ability to obtain a curative resection at a later date. Given the survival benefits of a staged or synchronous resection, treatment should focus on improving the probability of resection. Clinical judgment, however, should ultimately direct decision-making, with the goal of optimizing survival and quality of life. In determining a treatment plan, I very carefully evaluate the patient for symptoms, reviewing colonoscopy reports and CT scans. In patients who present with anemia, I generally find that the symptoms can be managed medically, and this improves within 2–4 cycles of chemotherapy. In patients with mild obstructive symptoms, I tend to recommend upfront chemotherapy with careful observation, and find it quite common to see resolution of symptoms within 2 cycles of treatment. This approach is supported by data on our patients with locally advanced rectal cancer, in whom we routinely administer oxaliplatin-based induction chemotherapy and observe high radiographic, clinical and pathologic complete response rates [46]. For patients with significant symptoms and/or evidence of proximal dilation on CT scan, I recommend resection, bearing in mind the increased risk of complications and potential delay in chemotherapy. Although the data do not support primary tumor resection in patients with unresectable disease, there is considerable equipoise between strategies, and there is need for a randomized trial in the future.

Recommendations

- Patients with unresectable, metastatic colon cancer and an asymptomatic or minimally symptomatic primary tumor should not undergo resection of the primary tumor (Evidence quality low, weak conditional recommendation)

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