Comparative Effectiveness in Colon and Rectal Cancer

Christine C. Jensen and Robert D. Madoff

Abstract

Treatment of colorectal cancer is becoming more uniform, with wider acceptance of standardized guidelines. However, areas of controversy exist where the appropriate treatment is not clear, including:

- should a segmental colectomy or a more extensive resection be performed in hereditary nonpolyposis colorectal cancer?
- should an asymptomatic primary cancer be resected in the presence of unresectable metastatic disease?
- what is the role of extended lymph node resection in colon and rectal cancer?
- are there clinically significant benefits for a robotic approach to colorectal resection versus a laparoscopic approach?

This chapter will examine these issues and discuss how they may be resolved.

Keywords

Hereditary nonpolyposis colorectal cancer · Complete mesocolic excision · Metastatic colon cancer · Robotic surgery

Contents

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1 Extended Versus Segmental Resection for Hereditary Nonpolyposis Colorectal Cancer

Persons with hereditary nonpolyposis colorectal cancer (HNPCC) are at increased risk for metachronous cancers compared to the general population. This risk has been estimated to be 40 % by 10 years [1]. In addition, the adenoma-carcinoma sequence appears to be accelerated in HNPCC, so that persons with HNPCC can progress from a normal colonoscopy to carcinoma within 2–3 years, [2, 3] mandating colonoscopy every 1–2 years. Such surveillance has been shown to decrease the risk of subsequent cancer by more than 63 %, even when conducted only every 3 years, and also decreases the risk of death related to colorectal cancer [4]. However, some studies have shown a significant risk for development of cancer despite intensive surveillance, ranging from 6 to 25 % [2, 5, 6]. In addition, the rate of missed adenomas on colonoscopy has been found to be as high as 55 % in HNPCC, [7] suggesting that there continues to be significant risk of subsequent cancer even with intensive surveillance. Because of this uncertainty, the NCCN guidelines recommend the surgeon "consider more extensive colectomy for patients with a strong family history of colon cancer or young age (<50)," but stop short of recommending this [8].

The ability to detect microsatellite instability and defective mismatch repair genes preoperatively has blossomed over the last several years. Patients with likely HNPCC can be diagnosed preoperatively using germline testing when there is an established family history of HNPCC. The diagnosis can also be suggested when immunohistochemistry testing fails to show intact mismatch repair enzymes or when there is microsatellite instability in a biopsy specimen, even if there is no suggestive family history. Now much more frequently than before, an individual is known to be an HNPCC carrier prior to surgery. Thus, the question arises whether patients with a colorectal cancer in the setting of HNPCC should have a more extensive resection, such as a subtotal or total colectomy or an ileoanal pouch. This may reduce their risk of a subsequent cancer more than having a segmental resection but is associated with functional consequences. Also undetermined is whether a known HNPCC carrier should have a prophylactic colectomy, and if so which procedure should be performed.

Several attempts have been made to compare these operative strategies. In a study of colorectal cancer patients in known HNPCC families, Mecklin and Jarvinen [9] found metachronous cancers in 41 % of patients who had undergone segmental resection versus 24 % who had subtotal colectomy during 7 years of follow up. Similarly, Van Dalen [10] found no metachronous cancer among patients who had total colectomies versus 16 cancers in 70 patients who had segmental resections (although the rate of metachronous cancer in this group was quite different depending on whether the patients had been followed up at the original institution or another institution). These results would suggest that patients with HNPCC may benefit from a more extensive resection.

Decision analysis has also been used as a tool to model outcomes between the two strategies. Maeda et al. [11] performed a decision analysis of segmental versus total abdominal colectomy for a hypothetical cohort of 30-year-old patients with HNPCC. For this population, total abdominal colectomy led to an improvement in survival of 0.7 years and no appreciable difference in quality-adjusted life years. Which operation was preferred was dependent on the quality of life associated with each operation, the patient's age and the hypothesized risk of metachronous cancer, so the authors recommended the procedure to be performed should be chosen on a case-by-case basis taking these factors into account. Cappel et al. [12] in a study that did not examine quality of life, found a predicted 2.3-year survival benefit among a cohort of 27-year-old patients with cancer undergoing total abdominal colectomy as compared to segmental resection, although this survival benefit decreased with age.

Despite the predominance of right-sided cancers in HNPCC, approximately 15 % of initial cancers in HNPCC patients will be rectal cancers [13]. For a patient with rectal cancer in the setting of HNPCC, the functional difference between a segmental and extended resection becomes more stark, as extended resection would require an ileoanal pouch, as has been recommended by some [14]. There are few studies examining this specific area, other than the case series by Kalady et al. [2] demonstrating a greater than 50 % risk of high-risk adenoma or carcinoma after proctectomy, despite colonoscopic surveillance. In that series, one patient developed a metachronous cancer within 2 years of a normal colonoscopy.

For a patient known to have HNPCC who has not yet been diagnosed with a colorectal cancer, there is little data on whether they should be offered a prophylactic colectomy. Some authors have suggested prophylactic colectomies for known gene carriers may be appropriate in certain situations [14, 15]. A decision analysis study by Syngal et al. [16] found that for a hypothetical 25-year-old HNPCC carrier, prophylactic proctocolectomy was associated with an increase in survival of 15.6 years versus no intervention, whereas intensive surveillance was associated with an increase of 13.5 years. With increasing age prophylactic proctocolectomy became less beneficial, and when health-related quality of life was considered, surveillance led to greater benefit than prophylactic proctocolectomy. However, there is no retrospective or prospective data to guide this decision making.

There are several barriers that have prohibited more conclusive research in this area. First, HNPCC represents approximately only 3 % of colorectal cancers, so obtaining adequate numbers of patients would require a multi-institutional study or a study spanning many years at a single institution. Second, the functional consequences of a segmental resection versus a more extensive resection mean that patients may have a strong preference for one option versus another, and some patients may not be a candidate for a more extensive resection due to pre-existing incontinence or diarrhea. Third, the diagnosis of HNPCC has historically been based on the Amsterdam criteria rather than genetic testing, leading to exclusion of patients from studies if their family history was not strongly suggestive of HNPCC due to a small family size or de novo genetic mutation. Patients may also have been incorrectly classified as having HNPCC based on the Amsterdam criteria even when their genetic predisposition was instead due to another cause such as Familial Colorectal Cancer Type X.

The time may be right for a randomized controlled trial of extended versus segmental resection for established colorectal cancer, which would clearly provide the best quality evidence regarding the optimal surgical procedure. The ability to diagnose HNPCC prior to surgery, even in persons who may not have been suspected to have HNPCC based on family history, and the ability for institutions to collaborate through the use of registries may lead to a sufficient number of patients being available for enrollment in a study. The risks and benefits of a segmental versus extended resection do not currently show one of these strategies to be clearly superior and therefore it is acceptable from an ethical standpoint to enroll patients in a randomized trial on this subject. With metachronous cancer rates being as high as 40 % at 10 years, [1] the randomized trial may not require an extensive period of time to show whether there is an effect on the rate of metachronous cancer, provided enough patients can be enrolled. At a minimum, the use of a centralized registry of HNPCC patients would allow for a case series to be conducted with larger number of patients than the studies already in existence, thus providing more reliable information regarding the risk of subsequent cancer.

It would be difficult to use a randomized controlled trial to evaluate surgical options for HNPCC patients presenting with rectal cancer or persons known to carry a mismatch repair gene defect who have not yet developed cancer. In these patients, the functional differences between standard resection and total proctocolectomy for the rectal cancer patients, and no surgery and total proctocolectomy for the mismatch repair gene defect patients, are disparate enough that it would likely be difficult to recruit patients to this sort of trial. Since both of these situations represent a very small minority of the colorectal cancer patients seen by the typical surgeon, this is a case where a centralized registry may help with compiling such cases and allow analysis of outcomes through a case series. Ideally, quality of life data would also be gathered, but this would be difficult given the likely large number of contributors to the registry.

Thus, there are no compelling data that mandate the appropriate surgery for a patient with HNPCC and colon cancer. At present, the decision must be individualized based upon the patient’s age, disease status, bowel function and individual preference. Even less clear is what should be done for the patient with an HNPCC-associated rectal cancer, or a mismatch repair gene defect carrier who has not yet developed a colorectal cancer. However, due to an increased ability to identify mismatch repair gene carriers, there is great promise for future research in this area.

2 Resection of an Asymptomatic Primary Tumor in Unresectable Metastatic Disease

As many as 20–25 % of patients will have metastatic disease at the time of presentation with colorectal cancer [17]. Even within this group, presentations can vary, from the patient with a symptomatic primary and minimal metastatic disease, to the patient with no symptoms from the primary and extensive metastatic disease, to the patient with both primary and metastatic disease that may become resectable after chemotherapy. The patient with an asymptomatic primary tumor and unresectable metastatic disease represents a special case. In this situation, the NCCN guidelines recommend chemotherapy with monitoring of response every 2 months. Surgery is recommended only if both the primary and the metastases become completely resectable [8].

In reality, the situation may not be so straightforward. Resection of the asymptomatic primary may be advisable for two reasons. First, it may prevent complications from the tumor during chemotherapy, such as perforation or obstruction, or allow use of additional chemotherapeutic agents such as bevacizumab. Second, and more controversially, it may prolong survival even in the presence of unresectable metastatic disease.

The risk of tumor complications from an unresected primary tumor during chemotherapy has been widely variable in the literature (Table 1). Complications can include perforation, bleeding and obstruction. There have been particular concerns about the use of bevacizumab contributing to an increased risk of tumor perforation, leading some oncologists to avoid use of bevacizumab when there is an intact primary tumor. Other authors have not found this to be the case and have recommended use of bevacizumab with an intact primary tumor [18].

Resection of the primary has its own risks. The risk of mortality with resection of the primary has been found to be between 1.6 and 4.6 % [19, 20]. Resection of the primary tumor delays initiation of systemic therapy, particularly if postoperative complications occur, potentially allowing progression of metastases. Rarely, patients may still be at risk for complications from the primary tumor, such as

Table 1 Risk of complications from primary tumor during chemotherapy with unresectable metastatic disease

Author, year	Complications due to primary (%)
Benoist, 2005	15
Cellini, 2010	67
Galizia, 2008	30
Karoui, 2011	19
McCahill, 2012	14
Muratore, 2007	8.6
Ruo, 2003	29
Scoggins, 1999	8.7
Seo, 2010	19.9
Tebutt, 2003	9.8

obstruction or perforation, if there is recurrence of the tumor either at an anastomosis or at another site in the bowel. In fact, a recent Cochrane review concluded there was no significant reduction in the risk of complications when surgery as the initial therapy was compared to chemotherapy and/or radiation as the initial therapy [21]. These findings have lead several authors to recommend avoidance of resection for asymptomatic primary tumors, [18, 20, 22, 23] while others recommend resection, particularly for patients who are low-risk for surgery from a medical standpoint [24, 25].

Resection of the primary could also theoretically slow the progression of the disease by debulking the tumor, allowing chemotherapy to work more effectively on the remaining disease. Many studies have examined the possibility of a survival benefit with resection of the primary tumor, but these have been hampered by the strong influence of patient selection since these were retrospective studies. Often patients who were in better medical condition or those who were thought to have a possibility of cure with from a combination of resection and chemotherapy were chosen for resection, leading to a bias toward much more advanced disease in the nonresected subjects. Results of such studies have varied widely. For studies limited to patients with asymptomatic primary tumors and unresectable metastatic disease, some studies have shown a survival benefit while the majority have not (Table 2). The authors of these studies have been split on whether resection of the primary is beneficial. Some have advocated for this approach [26] whereas others have not [20, 27–29]. If the criteria are expanded so that studies that include symptomatic primaries or resectable metastatic disease are included (Table 3), the picture becomes even more clouded. In these studies, it is difficult to determine how much of the improvement in survival, if demonstrated, could be due to patients who are curable. Some multivariate analyses have found tumor resection to be an independent predictor of survival [30–32] while others have not [33]. A Cochrane review on the subject concluded there is no consistent improvement in overall survival with resection of the primary tumor [21].

Thus, retrospective data have been very limited in their ability to allow reliable conclusions about the role of resection of the primary due to issues with patient selection. Ideally, a randomized controlled trial could be done among patients with asymptomatic primaries and unresectable metastatic disease who are medically fit to undergo resection, thus eliminating these patient selection factors that have plagued retrospective studies. However, recruitment for such studies has been difficult, with at least two studies being closed due to lack of recruitment [34, 35]. This difficulty with recruitment likely relates to patients being unwilling to undergo surgery for unclear benefit, or care providers encouraging them to have resection due to the perceived risk of complications from the primary. There is currently another randomized controlled trial on this subject underway, [36] which one hopes will provide definitive data as to whether primary tumor resection is associated with decreased complications or lengthened survival.

Other important issues in these cases are quality of life and patient preferences. Since surgery can be associated with short-term decreases in quality of life, this could be a major consideration in patients who likely have a limited life expectancy.

Table 2 Case series evaluating resection of primary in unresectable metastatic colon and rectal cancer with asymptomatic primary tumors

Author, year	Number of patients	Follow up, months	Survival, months	Comments
Benoist, 2005				Difference in survival not significant
Resection of primary	32	Not stated	2-year OS: 44 %	
No resection	27		2-year OS: 41 %	
Galizia, 2008				$p = 0.03$ for difference in survival
Resection of primary	42	16	15	
No resection	23	12	12	
Ruo, 2003				$p < 0.001$ for difference in survival
Resection of primary	127	>80 % followed until death	16	
No resection	103		9	
Scoggins, 1999				Difference in survival not significant
Resection of primary	66	Not stated	14.5	
No resection	23		16.6	
Seo, 2010				Survival different in univariate but not multivariate analysis
Resection of primary	144	49	22.0	
No resection	83		14.0	
Tebutt, 2003				Difference in survival not significant in multivariate analysis
Resection of primary	280	30	14.0	
No resection	82	19	8.2	

Unless otherwise noted, follow up and survival numbers are reported as medians
OS overall survival

Patient preferences in this area could be examined with the time-trade-off method, where patients are given a hypothetical scenario where the typical postoperative course for surgery is described in detail and patients are asked if an increased survival of 6 months, for example, would lead them to choose surgery and its associated recovery in order to gain this survival benefit. The anticipated increase in survival is then lessened and the same question asked again, with the process repeated until the patient no longer reports they would be willing to have surgery for the anticipated survival benefit. Such a study could provide information as to whether most patients would consider resection of the primary, even if it were proven to be associated with some definite increase in survival.

Thus, it remains unclear whether resection of the primary tumor is associated with a decrease in complications from the primary tumor or an increase in survival. Patient preferences in this area have not been well studied and are likely to play a significant role in whether surgical intervention for the primary tumor is pursued.

Table 3 Studies evaluating resection of primary in metastatic colon and rectal cancer, resectable metastatic disease and symptomatic primaries included

Author, year	Number of patients	Follow up, months	Survival, months	Comments
Cellini, 2010				Difference in survival not significant
Staged primary and liver	13	23	50	
Synchronous primary and liver	30		54	
Primary only	22		32	
No resection	9		37	
Chan, 2010				
Resection of primary	286	Variable	14	
No resection	125		6	
Chew, 2012				Patients routinely received primary resection unless contraindication
Resection of primary	696	9	1-year cancer-spec.: 48.7 %	
No resection	22		1-year cancer-spec.: 9 %	
Cook, 2005				Analysis of the SEER database
Resection of primary	17,658	Not stated	11 colon, 16 rectal	
No resection	9,097		2 colon, 6 rectal	
Karoui, 2011				Resection independent predictor of survival in multivariate analysis
Resection of primary	85	19.7	30.7	
No resection	123		21.9	
Konyalian, 2007				Resection independent predictor of survival in multivariate analysis
Resection of primary	62	Not stated	12.3	
No resection	47		4.5	

Unless otherwise noted, follow up and survival numbers are reported as medians
SEER Surveillance, Epidemiology and End Results

3 Standard Versus Extended Lymph Node Resection for Colon and Rectal Cancer

Great emphasis has been placed on ensuring appropriate oncologic resection for colon and rectal cancer, with 12 nodes in the specimen being a generally accepted standard to ensure an adequate resection and accurate staging. This standard does not take into account factors that are associated with decreased lymph node number (such as radiation, left-sided resections or variations in pathology practice), [37] or whether an increased number of lymph nodes was obtained by resecting a greater length of bowel, a longer segment of the feeding vessel, or a more complete mesocolic/mesorectal excision. Some have advocated a more aggressive resection of the lymph nodes, beyond this numerical standard, for both colon cancer and for rectal cancer. It remains unclear whether this results in better oncologic outcomes.

3.1 Colon Cancer

For colon cancer, more aggressive resection is termed complete mesocolic excision (CME). For the right colon, this entails a Kocher maneuver with mobilization of the mesenteric root up to the base of the superior mesenteric artery, including dissection of the mesentery off of the uncinate process of the pancreas and duodenum. For the left colon, this involves takedown of the splenic flexure and resection of the transverse mesocolon at the lower edge of the pancreas [38]. In both cases, close attention is paid to maintaining an intact mesocolic fascia. Some authors also resect a greater length of colon as part of this approach [39, 40]. Similar to total mesorectal excision in rectal cancer, the theory is that maintaining intact embryologic planes and ensuring complete resection of the mesentery will improve oncologic outcomes.

Results of this approach have generally shown acceptable operative times, blood loss and postoperative complications [38, 41, 42]. CME has also been demonstrated to result in a greater incidence of an intact mesocolon and a greater number of lymph nodes resected [39, 40]. Attempts have been made to determine whether this results in improved oncologic outcomes. Hohenberger et al. [38] showed that among node-negative patients, those with resection of 28 or more lymph nodes had 96.3 % cancer-related 5-year survival versus 90.7 % if less than 28 lymph nodes were resected, but a similar analysis among node-positive patients was not significant. CME was the standard practice at that institution, so the differences in survival were not associated with whether CME was attempted. Other studies have shown improved outcomes with preservation of anatomic planes [43, 44] or more extensive resection [45]. However, it remains unclear whether there is a benefit in terms of survival or local recurrence. The primary problem is that individual centers tend to pursue either CME or standard resection exclusively, and there are therefore no appropriate patients to serve as comparators. Comparing outcomes from patients operated on at different centers introduces an increased risk that any differences observed are due to factors other than the surgical approach.

Conclusive evidence demonstrating whether there is a benefit to CME would require a randomized clinical trial of CME versus more standard resection. However, the number of patients required to demonstrate this difference could be prohibitive, depending on the endpoints chosen for the study. As an example, power calculations can be estimated using the local recurrence rate (4.8 %) and cancer-specific survival rate (85.2 %) from Weber et al.'s [42] study of 1,452 patients undergoing CME who were followed for at least 5 years. Assuming an 80 % power and a significance level of 0.05, 11,136 patients would be required to demonstrate a 25 % difference in local recurrence. In contrast, 792 patients would be required to demonstrate a 10 % difference in cancer-specific survival. While this latter example may represent a feasible number of patients to recruit to such a study, the number of patients required is exquisitely sensitive to the estimated difference in cancer-specific survival, and the 10 % difference estimate may be too high. Changing the estimated difference in cancer-specific survival to 5 % rather than 10 % increases the number of patients required to 2,614.

A more feasible approach may be a pathology-based study. CME could be performed in patients, and the surgeon could delineate which areas of the specimen they believe would have been removed in a standard resection and which areas were resected only as a result of the CME. It may be best to have two surgeons come to an agreement regarding these boundaries, to prevent the surgeon from under- or overestimating the amount of tissue that would have been removed with a standard resection, as Spasojevic et al. [46] found surprising lengths of artery remaining after what were reportedly standard resections with high ligation. The two areas of the specimen could then be dissected apart and processed separately. If additional nodal metastases or tumor deposits are found frequently in the additional tissue, this would lend more credence to the argument to perform a more extensive resection. If, however, metastasis is infrequent in the additional tissue, this would make it unlikely that CME contributes to a clinically significant difference in outcomes. A similar study, looking at the location of lymph node metastases in right-sided colon cancers, found less than 1 % of lymph node metastases were located more than 10 cm from the primary tumor (Fig. 1) [47].

3.2 Rectal Cancer

In contrast to colon cancer, in rectal cancer dissection along embryologic planes is accepted practice. However, controversy remains about whether more extensive lymph node dissection is of benefit. Particularly in Japan, a more aggressive

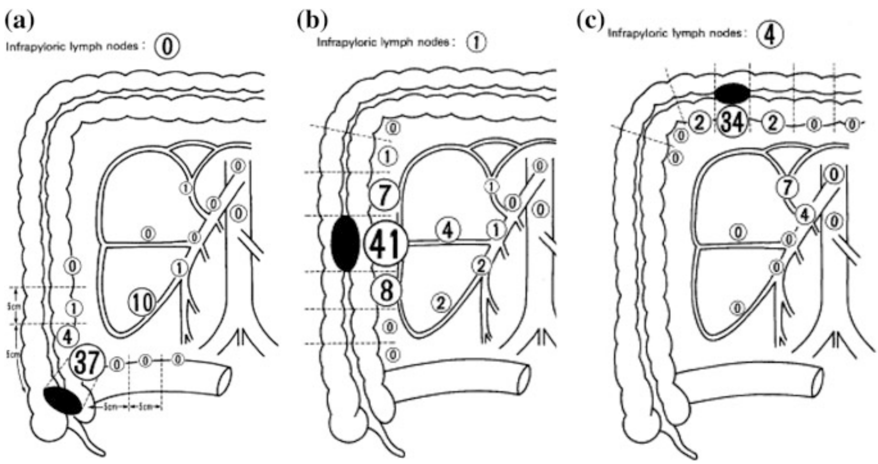

Fig. 1 Rates of lymph node metastases for cecal (**a**), ascending (**b**) and transverse colon cancers (**c**). From Toyota et al. [47]

resection is often used, including dissection of the lateral pelvic lymph nodes. This has been shown to result in increased survival [48, 49] in some studies, although other studies have shown no difference [50, 51]. A recent meta-analysis showed no difference in overall or disease-free survival (Fig. 2) [52].

There are a few issues that make it difficult to determine whether extended lymph node resection for rectal cancer is associated with a benefit. For the studies demonstrating a survival advantage with more aggressive lymph node resection, stage migration could be a confounding issue. More accurate staging due to a larger number of lymph nodes being resected could theoretically correctly classify some early stage III cancers that would have been erroneously classified as stage II, thus improving the survival of both stage II and stage III cancers as a whole, even if there is no actual survival benefit for extended lymph node resection. Another pertinent issue is the use of radiation. Many of these patients do not receive preoperative chemotherapy and radiation. However, in other countries where preoperative radiation for node-positive rectal cancer is more common, such as the United States, extended node dissection is not standard practice. There is some evidence that these two approaches have similar effectiveness [53]. However, it is unclear whether adding extended node dissection to radiation may further improve outcomes. Finally, the average body mass index is generally much lower in countries which practice extended lymph node resection, raising the question of whether this technique can be generalized while maintaining the same results.

Whether lateral node dissection should be undertaken is particularly important because there can be significant adverse effects. In this dissection, the pelvic nerves

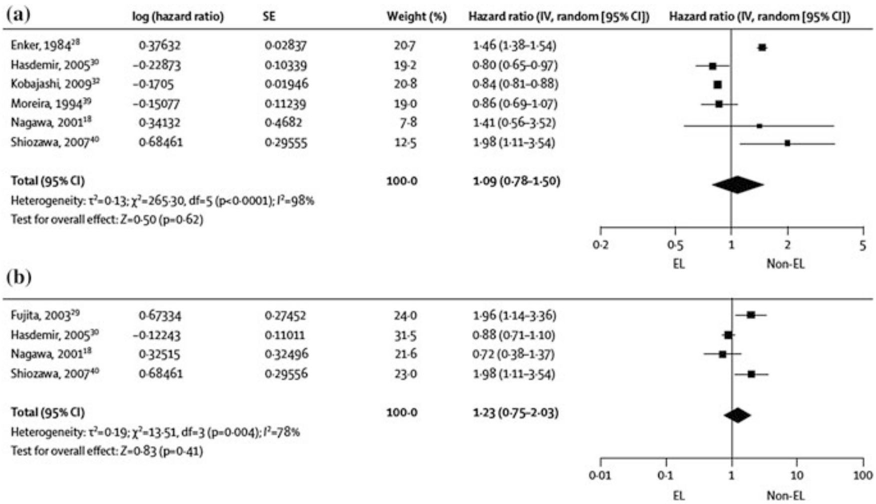

Fig. 2 Meta-analysis of 5-year overall (**a**) and disease-free survival (**b**) following extended versus non-extended lymphadenectomy for rectal cancer. *Squares* are point estimates of the treatment effect, with 95 % CI indicated by *horizontal bars*. *Diamonds* are the summary estimate from the pooled studies with 95 % CI. From Georgiou et al. [52]

are often damaged or even intentionally sacrificed, and this results in a very high incidence of urinary and sexual dysfunction [50, 54, 55]. For example, Akasu et al. [54] found that with unilateral or bilateral pelvis plexus sacrifice, rates of inability to have sexual intercourse at 1 year were 55 and 100 %, respectively. Urinary symptoms were present in 100 % of male and 90 % of female patients in one study, and 1 year after surgery 44 % of men and 17 % of women still required self-catheterization [55]. Lateral node dissection has also been associated with increased operative time [50, 52, 56] and blood loss [52, 56].

Ideally, a randomized controlled trial would determine whether extended lymph node resection contributes any additional benefit among patients who have undergone preoperative chemotherapy and radiation. Indeed, this study has already been performed by Nagawa et al. [57]. They found no difference in survival between patients undergoing a standard resection versus an extended lymph node resection after preoperative chemotherapy and radiation. However, only 45 patients were enrolled in this study, severely limiting its ability to detect a difference in survival. In addition, patients with evidence of lateral pelvic or para-aortic lymph node metastasis were excluded, although it seems this staging may have been done after chemotherapy and radiation were completed.

A more informative study may be obtained by selecting only patients who have evidence of lateral pelvic or para-aortic lymph node metastasis before chemotherapy and radiation, then randomizing them to standard versus extended lymph node resection after neoadjuvant therapy. Limiting this analysis to patients who are preoperatively known to have advanced nodal metastasis achieves two ends. One, it increases the likelihood of local recurrence [49] and therefore decreases the sample size needed to demonstrate a difference related to extended node dissection, similar to the discussion of CME for colon cancer. Second, it could help resolve the ethical dilemma of exposing patients to the high risk of urinary and sexual dysfunction associated with lateral node dissection; if patients are strongly suspected to have lateral node metastasis prior to radiation these risks may be more acceptable in light of an increased risk of poor outcome. Thus, the pertinent question seems to be not whether radiation or extended lymph node resection is preferable, but if extended resection can improve upon the outcomes already obtained with preoperative chemotherapy and radiation in cases of known lateral pelvic or para-aortic lymph node metastasis, and whether the combination of radiation and extended lymph node resection would lead to prohibitively severe morbidity.

While extended lymph node resection for colon and rectal cancer seems as if it would be preferable, current data do not allow conclusions to be drawn about whether this approach has benefits that would justify any increase in operative time or complications. A variety of methods may be used to provide additional data in this area.

4 Robotic Versus Laparoscopic Resection for Colorectal Cancer

When reports of laparoscopic colon and rectal resection first appeared, the relative merits of laparoscopic and open surgery were hotly debated. Many surgeons now believe that laparoscopic resection is associated with improved postoperative recovery and similar oncologic outcomes, but even so both open and laparoscopic surgery continue to have their proponents, and only 10.5 % of elective colon resections in the United States were performed laparoscopically as recently as 2007 [58]. The appearance of robotic surgery has renewed the debate regarding the optimal approach to colorectal cancer resections.

Potential benefits of the robotic approach center around the ability to have seven degrees of freedom in movement, and the increased visibility resulting from a three-dimensional view and greater magnification (Table 4). Particularly in the pelvis, where dissection can be quite difficult due to the bony pelvis, patient obesity and a bulky tumor, these may be significant advantages. Laparoscopic resections in this area can be difficult due to the fulcrum effect of the laparoscopic instruments on the sacral promontory. The robot also stabilizes physiologic tremor. Robotic surgery has thus been hypothesized to result in a better surgical specimen, with some evidence to support this [59].

Potential drawbacks of the robotic approach include operative time and cost. The majority of studies have found that robotic surgery is associated with increased operative times, which can range from a difference of 42–64 min for a low anterior or abdominoperineal resection [60–67]. Only a few studies have shown operative times to be similar, [68–71] and one showed a decreased operative time for robotic compared to laparoscopic low anterior resections [72]. Increased operative time exposes patients to increased risk of certain complications, in particular venous thromboembolism [73]. In addition, there are some technical drawbacks of the robot. Colorectal resections often encompass dissection over a large area of the abdomen, such as from the splenic flexure to the pelvis, which can result in the need to re-dock the robot several times to perform the dissection robotically. More

Table 4 Potential advantages of robotic colorectal surgery as compared to laparoscopic surgery

Potential advantages of robotic surgery
Increased degrees of freedom and “wristed” movements
Improved visualization due to magnification and steady camera
Stabilization of physiologic tremor
Absence of fulcrum effect during mesorectal dissection
Potential advantages of laparoscopic surgery
Decreased operative time
Decreased expense
Greater familiarity with technique among surgeons
Haptic feedback

instruments may be needed than there are available robotic arms, leading some surgeons to use a laparoscopic port and an assistant during the robotic dissection. Because of these factors, surgeons often approach a portion of the operation laparoscopically or through an open incision, and there is great variation in how individual steps of the operation are completed (Table 5).

Four studies have addressed the cost of the robot in comparison to laparoscopy, and all have found the robotic approach to be more expensive. Delaney et al. [60] found that equipment cost was $350 greater in robotic resections (in 2003 dollars) and did not account for the costs of maintenance or depreciation; robot maintenance can be approximately $100,000 per year. DeSouza et al. [61] compared 40 robotic and 135 laparoscopic right colectomies and found total cost was $15,192.00 for robotic cases versus $12,361.50 for laparoscopic cases. Similarly, a randomized controlled trial of right colectomies by Park et al. [65] found the cost to be higher with robotic resections versus laparoscopy ($12,235 vs. $10,320). Tyler et al. [73] reviewed the Nationwide Inpatient Sample and found robotic colon resections cost an average of $3,424 more than laparoscopic resections.

Perioperative results are similar in laparoscopic and robotic cases. Most studies have found no difference in intraoperative complications, [62, 66, 73] estimated blood loss, [60, 61, 65, 66, 68, 70, 72] postoperative complications, [61, 62, 64–66, 68–70, 72–74] anastomotic leak rate, [64, 72] conversion rate, [61, 62, 64–66, 69] readmission [66, 68] and length of stay [60–62, 65, 68, 70, 73, 74]. However, a few studies have found differences in these outcomes, including decreased conversion rates with the robot, [68, 74] decreased blood loss in robotic cases [62] and decreased length of stay for robotic compared to laparoscopic but not hand-assisted laparoscopic cases [66].

Oncologic results have generally been found to be equivalent between the laparoscopic and robotic approaches (Table 6). Both approaches result in a similar number of lymph nodes resected, rates of positive margins and survival data. Although the robotic approach has been promoted as ensuring a more complete mesocolic excision, there is little data to support this claim nor any impact of a more complete excision on survival or local recurrence.

Obtaining high-quality data in this area has been difficult. Many of the currently published studies are case series or case-matched studies that document the early experience with robotic colorectal resections and therefore may not be representative of current results. Few have long-term follow up to assess oncologic outcomes, and most of these do not go beyond two- to three-year follow up. Therefore, even in the absence of a more rigorous study such as a randomized controlled trial, more current case-matched studies with longer follow up could provide valuable information on the results of robotic colon and rectal surgery now that some of the initial learning curve has passed. Prior to embarking on additional prospective studies, a few considerations should be taken into account. First, any potential study should split resections that include a rectal dissection from those that do not, as rectal dissection is where the majority of the potential benefit from the robotic approach appears to lie. It would also be useful if a consensus approach to dissection, resection and anastomosis on the left side could be developed, given the

Table 5 Differences in robotic technique for left-sided resections

Author, year	Stage of operation					Comments
	Transection of vessels	Flexure mobilization	Rectal dissection	Rectal transection	Anastomosis	
Baek, 2013	R	R	R	R	R or TA	
Bianchi, 2010	R	25 % L 75 % R	R	R	L	
Choi, 2009	R	R	R	L	L	Laparoscopy for initial exposure
D'Annibale, 2004	R	R	R	R	L or TA	
Delaney, 2003	R	R	R	O	O	Laparoscopy for takedown of adhesions
DeSouza, 2011	L (R if APR)	L (R if APR)	R	R or TA	R or TA	
Kwak, 2011	R	R	R	L	L	Laparoscopy for initial exposure
Luca, 2009	R	R	R	R	R	
Patriti, 2009	L	L	R	R	R? or TA	Unclear whether anastomosis was R or L
Pigazzi, 2010	L	L	R	L	R?	
Ragupathi, 2011	R	L	R	R	R	

R robotic, *L* laparoscopic, *O* open, *TA* transanal

Table 6 Oncologic outcomes in robotic and laparoscopic colorectal cancer resections

Author, year	Lymph nodes, mean		Positive circumferential margin (%)		Survival	
	Robotic	Laparoscopic	Robotic	Laparoscopic	Robotic	Laparoscopic
Baek, 2013	10.6	14.1	2.1	8.1	3-year OS 86.5 %	3-year OS 90.7 %
Baik, 2013 [76]	15.6	n/a	5.7	n/a	3-year OS 93.1 %	n/a
Bianchi, 2010	18	17	0	4.0		
Choi, 2009 [77]	20.6	n/a	2.0	n/a		
D'Annibale, 2004	17	16	0	0		
deSouza, 2011	15.0	16.8	0	5.9		
deSouza, 2010	14	n/a	0	n/a		
Kwak, 2011	20	21	0.9	0	Recurrence 5.5 % over median 17 months	Recurrence 5.6 % over median 13 months
Luca, 2009	18.5	n/a	0	n/a		
Patel, 2011	17.3	20.9	0	0		
Patriti, 2009	10.3	11.2	0	0	No difference in OS or DS over mean follow up of 29 (robotic) and 19 months (laparoscopic)	
Pigazzi, 2010 [78]	14.1	n/a	0.7	n/a	Robotic only; 3-year overall survival 97 % with no local recurrence at mean follow up of 17 months	

No differences in this table were significant at $p < 0.05$ or less
OS overall survival

variation in technique detailed in Table 5. Even if a study were to examine robotic versus laparoscopic left-sided resections, it would be difficult to generalize the data to robotic resections performed by other surgeons, given the variations in technique. A difference in the number of re-dockings required, the technique of anastomosis, or the use of laparoscopy for a portion of the procedure can greatly affect the operative times, cost and complications associated with robotic surgery. Of course, a randomized controlled trial would provide even more reliable information on the outcomes of these two approaches. There is currently a randomized controlled trial entitled "Robotic versus Laparoscopic Resection for Rectal Cancer" (ROLARR) which will attempt to answer these questions for rectal cancer [75]. This study will include quality of life and cost data to allow a cost-effectiveness analysis to be performed. Cost-effectiveness analysis lends itself particularly well toward comparing robotic and laparoscopic colorectal resections for cancer. Since most studies have found similar outcomes, the question becomes whether the difference in cost between laparoscopic and robotic resections is justified by an improvement in quality of life.

Robotic and laparoscopic surgery in colorectal resections thus have much more similar results than a similar comparison between laparoscopic and open resection, but a much greater difference in cost and operative times. Areas of future research should therefore focus on quality of life and cost in addition to surgical and oncologic outcomes to provide information on whether robotic surgery is the preferred approach in colon and rectal cancer.

5 Conclusion

Surgical treatment in colon and rectal cancer has become more standardized, but there remain a number of areas of controversy, ranging from surgical treatment of HNPCC to the role of robotic surgery, where the appropriate choices are not clear. Further study in these areas can be accomplished by a variety of approaches, with certain methods being more likely than others to provide a solid evidence base for future surgical practice.

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