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*REVIEW*

# Evolving management of colorectal cancer

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## Abstract

This article reviews recent advances in surgical techniques and adjuvant therapies for colorectal cancer, including total mesorectal excision, the resection of liver and lung metastasis and advances in chemoradiation and foreshadows some interventions that may lie just beyond the frontier. In particular, little is known about the intracellular and extracellular cascades that may influence colorectal cancer cell adhesion and metastasis. Although the phosphorylation of focal adhesion kinases and focal adhesion associated proteins in response to integrin-mediated cell matrix binding ("outside in integrin signaling") is well described, the stimulation of cell adhesion by intracellular signals activated by pressure prior to adhesion represents a different signal paradigm. However, several studies have suggested that increased pressure and shear stress activate cancer cell adhesion. Further studies of the pathways that regulate integrin-driven cancer cell adhesion may identify ways to disrupt these signals or block integrin-mediated adhesion so that adhesion and eventual metastasis can be prevented in the future.



**Key words:** Adhesion; Colorectal; Signaling; Cancer; Surgery

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## INTRODUCTION

Colorectal cancer is a common cause of morbidity and mortality. Although the basic principles of screening, surgical resection when possible, and adjuvant therapy when indicated remain valid, considerable new information offers the possibility of substantially improving outcomes for such patients in the future. This review will briefly summarize current epidemiologic and prognostic information about this disease for context, and then will focus on new approaches to surgery, adjuvant therapy, the management of established metastasis, and the prevention of metastasis. Although screening for colorectal neoplasm is critical for prevention, early diagnosis, downstaging, and improved survival, this subject has been extensively reviewed elsewhere[1-4] and is beyond the scope of the current review.

## INCIDENCE AND PREVALENCE

Colorectal cancer is the third most common cancer and the third leading cause of cancer related mortality in the United States[5]. Colorectal cancer is also very common in Western Europe, Australia and New Zealand, whereas the age standardized incidence rate of colorectal carcinoma is very low in India and Africa[6,7]. There seems to be an association of higher incidence rates in colorectal cancer with increasing affluence[8]. Over the past decade, colorectal cancer rates have modestly decreased or remained level. Until age 50, men and women have similar incidence and mortality rates; after age 50, men are more vulnerable[5]. Colorectal cancer is generally a malignancy associated with the elderly, with a mean age at diagnosis of 73 years[9]. In the Netherlands, statistics showed that a peak incidence of colorectal cancer for both men and women occur between the age of 70-79 years[10]. Before the age of 75 years, men and

women in the Netherlands have a 4.67% and 3.34% cumulative incidence to develop colorectal cancer[11]. By the age of 70 years, at least 50% of the western population will develop some form of colorectal tumor, spanning the spectrum from an early benign polyp to an invasive adenocarcinoma.

## STAGE OF COLORECTAL DISEASE

The stage of disease is one of the most important prognostic factors for survival in patients with colorectal cancer. It is therefore clinically significant to know the relative incidence for each stage of the disease. The incidence of Stage Ⅰ disease in the United States has increased over the past years due to better screening and is currently around 30%. This is an important development since the detection of early stage disease increases the chance for R0 resection and potential cure for colorectal cancer. The incidence of Stage Ⅱ and Ⅲ disease are respectively 27% and 24%, while Stage Ⅳ disease is present in 19% of patients in the United States. A remarkable observation is that older patients are diagnosed more frequently at an early stage (Stage 0 and 1) and diagnosed three times less frequently with stage Ⅳ disease than younger patients. A possibility is that younger patients feel less at risk and ignore symptoms for a longer period of time and are therefore diagnosed at a later stage[12].

The relative 5-year survival rates in the United States show that when the disease is detected early, at a localized stage, survival rates for Stage Ⅰ colon and rectal cancer are 93% and 92%, respectively. At Stage Ⅱ disease the 5-year survival rates are between 72%-85% for colon cancer and between 56%-73% for rectal cancer. The fluctuations in Stage Ⅱ survival rates are due to the fact that Stage Ⅱ disease includes both T3 (Stage ⅡA) and T4 (Stage ⅡB) tumors. For more advanced disease at diagnosis, the survival rates drop significantly. At Stage Ⅲ, the 5-year survival rates for colon and rectal cancer vary from 44%-83% and 30%-67% respectively. Again the wide range of survival rates reflects the fact that Stage Ⅲ disease is further categorized into the following sub-categories, Stage ⅢA (T1-2, N1, M0), Stage ⅢB (T3-T4, N1, M0) and Stage ⅢC (any T, N2, M0) disease. For Stage IV colorectal disease the 5-year survival rate may be as low as 8%[13,14].

## SURGICAL TREATMENT

Surgical management is the primary treatment of potentially curable colorectal cancer. In most cases, this involves resection of the primary tumor and regional lymph nodes. However, treatment of curable colorectal cancer patients may vary from endoscopic polypectomy for malignant polyps or local excision in carefully selected patients with limited rectal carcinomas to multimodality management for locally advanced rectal cancers or cancers invading adjacent organs. The objective in all cases is to maximize both oncologic and functional results. Due to the improvements in surgical techniques, as well as better screening and new developments in adjuvant therapy, the ratio of people with potentially curable disease has increased over the past decades. This evolution has included the development of total mesorectal excision, the introduction of laparoscopic surgery, the sentinel lymph node technique, curative resections of liver and lung metastasis and improvements in adjuvant therapies such as chemotherapy and radiotherapy.

En bloc resection and the no-touch technique were first described in 1967 by Trumbell *et al* and remain valid and important[15]. The best prevention strategy of potential tumor cell distribution is maintained by the surgeon strictly using the principles of en-bloc resection. As the likelihood of lymph node involvement increases with depth of tumor invasion (5.6% for $pT_1$, 10% for $pT_2$, 36.7% for $pT_3$, and 77.7% for $pT_4$ colon carcinoma)[16], invasive adenocarcinomas require ligation and resection of the lymphovascular pedicle directly draining the intestinal segment containing the tumor. When the lesion is equidistant between two pedicles, then both should be encompassed in the resection. Another surgical option is the no-touch isolation technique with primary ligation of the corresponding vessels, and dissection of the lymph nodes[17-20]. The concept of this technique is to avoid tumor manipulation during surgery so that shedding of tumor cells into the lymphatic or vascular circulation is kept to a minimum. The presence of free cancer cells within the lymphatic, vascular circulation or in the peritoneal cavity can be detected by mRNA coding using qPCR and is associated with a poorer prognosis for patients undergoing curative colorectal cancer surgery[21,22]. However, there seems to be limited benefit in the no-touch isolation group; the morbidity and mortality rates after a 5-year follow-up of patients were equal[20]. More recently, a study by Hayashi *et al* has suggested that the no-touch isolation technique may be useful to prevent cancer cells from being shed into the portal vein during surgical manipulation[23]. Today, en-bloc resection without the primary ligation of corresponding vessels is still the more common technique.

Other advances in surgical techniques have resulted in less tumor recurrence and given patients with advanced colorectal disease the opportunity to undergo surgery with curative intent. In 1982 Heald developed an important surgical technique for the treatment of rectal cancer. The concept of total mesorectal excision (TME) was introduced in conjunction with low anterior resection (LAR) as a means of procuring all perirectal fat while facilitating sphincter preservation[24]. Recent studies have reported local recurrence rates of around 10% in various TME series[25-30]. In the study by Moore *et al*, local recurrence rates of less than 5% have been reported with a distal margin of 1 cm, provided that the mesorectum can be excised as a complete lymphovascular package[31]. Today TME has been successfully taught as a standardized procedure and translated to other colorectal surgical environments with reproducible cancer-specific outcomes[32].

Advances in laparoscopic equipment and technique have revolutionized the surgical approach to many diseases. Laparoscopic surgery for colorectal cancer is currently considered an acceptable alternative to open resection for colorectal cancer. There are small but measurable short term benefits such as decreased post-operative narcotic use, earlier return of bowel function, shorter length of stay and better cosmetic results. Today there is no question that laparoscopic surgery can be performed safely and effectively by experienced surgeons. There is enough evidence that survival rates are not compromised by the laparoscopic approach[33,34].

Although the first laparoscopic colon resection was reported in 1991[35], the adoption of minimally invasive colon resection has been impeded by several factors. First, laparoscopic colon surgery is technically demanding. Second, and more importantly, there has been historical concern about whether minimally invasive surgery for colonic malignancies would achieve adequate oncologic resection. The most recent studies, including retrospective and prospective registries, as well as comparative studies clearly demonstrate that oncologic principles are not compromised by laparoscopic techniques, and the yield of lymph nodes, surgical margins (proximal, distal and radial), and length of bowel resected were comparable to open cancer surgery[17,36,37]. Another problem that has been discussed controversially is the issue of whether laparoscopic surgery is associated with an increased hematogenous and intraperitoneal tumor cell distribution. Some studies have shown that there is a higher incidence of intraperitoneal tumor cell dissemination during laparoscopic resection for colorectal cancer when compared to open surgery for colorectal cancer[38,39]. On the other hand, other studies have contradicted this observation[40,41]. Finally, another concern has been the incidence of port-site metastasis after laparoscopic resection[16,42-45]. Although port-site metastases have not been restricted to laparoscopic surgery for colorectal cancer, the major impact of this phenomenon has been in this field. A closer look at the literature reveals most reports with a high incidence rate were small series published in the early 1990s[44,45]. Within the last ten years, three large trials of laparoscopic surgery for colorectal cancer have been published that clearly demonstrated a low incidence of wound recurrence not statistically significantly increased compared to wound recurrence after open laparotomy sites[33,34,46]. However, it should be cautioned that these trials were not adequately powered to fully address the question. Moreover, in the COST-trial[33], wound recurrence rates demonstrated an incidence of port site recurrence that, although both low and not statistically significantly different from that after open surgery, was nevertheless more than twice the rate of wound implantation seen after open surgery (0.5% incidence in the laparoscopic arm *vs* 0.2% in the open surgical arm of the trial). Although the question therefore still has not been completely addressed, it appears that the incidence is quite low and within acceptable clinical range, and it seems dubious that a randomized trial of sufficient size ever will be conducted to settle conclusively this issue. It seems likely that insufficient technical skills and experience at the beginning of the laparoscopic era contributed to the early reports that described considerably higher rates of port site recurrence.

Many cancers, including colorectal cancer, spread first to the lymph nodes before reaching other parts of the body. Lymph node status remains one of the most important prognostic factors in the management of colorectal cancer. In patients without nodal disease, recurrent tumors still develop in about 15% to 20% of cases within 5 years of diagnosis[47]. The reasons for this are unclear, but may depend upon the quality of surgical resection and conventional pathologic review. Node-negative patients are usually not treated with adjuvant chemotherapy outside a clinical trial because of the lack of definitive evidence of survival benefit. Patients with nodal disease, on the other hand, should be treated with adjuvant chemotherapy because of potential reduction of mortality up to 33%[48]. Therefore, it is critical to avoid pathological understaging of the specimen. Standard pathologic evaluation may overlook low volume nodal metastasis, thereby failing to identify nodes imperative to accurate staging. Inconsistencies in number of nodes harvested at time of pathologic processing impact significantly colon cancer staging accuracy. This nodal sampling error serves as the basis for guidelines establishing a 12 node minimum for adequate staging utilizing conventional techniques[49]. Up to 78% of metastases are identified in subcentimeter nodes that may be overlooked during standard gross pathologic dissection of resected specimens[49-51]. Microscopic examination of 1 or 2 hematoxylin and eosin-stained sections of a 5-mm node limits pathologic assessment to < 1% of the entire node, making identification of small tumor cell aggregates challenging. In a study by Saha *et al*, sentinel lymph node mapping appears superior to conventional pathologic review and may therefore be a useful method to avoid understaging[47]. Nodal positivity was 48% for the group assigned sentinel-lymph-node mapping, compared with 35% for the group assigned conventional staging ($P < 0.001$). In this study, sentinel lymphatic mapping accounts for the upstaging of 13% of colon cancer. In other studies, sentinel lymph node mapping accounts for the upstaging of 19%-24% of patients[52-57]. The consequence of upstaging is that these patients now become candidates for adjuvant chemotherapy. After a minimum of 2 years follow-up, patients assigned nodal mapping ($n = 153$) had an overall recurrence of 7%, compared with 25% ($n = 162$) for the patients assigned conventional staging ($P = 0.001$)[47,58]. As the sentinel lymph node technique has developed, some investigators describe over 90% success in identifying the sentinel node and accuracy rates of approximately 90%[47,53-56].

In patients with colorectal metastases, advances in surgical techniques have made it possible that the goal of surgery is no longer palliative but of curative intent. Therefore, a complication such as wound recurrence may have grave clinical consequences for patients that

are operated on with curative intent. It thus becomes increasingly important that surgeons minimize tumor spill into the peritoneal cavity or into the lymphatic/vascular systems during surgical procedures for colorectal cancer. If not, tumors may recur and compromise a potentially curative resection.

The liver is the most common site for colorectal metastasis, since the venous outflow of the gut first reaches the liver through the portal system before flowing back into the systemic circulation. Approximately one-third of patients diagnosed with colorectal cancer will develop synchronous or metachronous metastases to the liver. The incidence of synchronous metastasis has ranged from 23.0% to 46.8%[59-62] and the 5-year survival rate after hepatic resection has been reported to be 14% to 40% in studies with more than 100 or more patients[60,61]. Several studies have suggested that careful selection of patients for hepatic resection of colorectal metastases can result in favourable survival[63-65]. A recent study by Rees *et al* found 7 risk factors (Basingstoke Prediction Index) that were found to be independent predictors of poor survival in a multivariate analysis[66]. The 7 risk factors were number of hepatic metastases > 3, node positive primary, poorly differentiated primary, extrahepatic disease, tumor diameter ⩾ 5 cm, carcinoembryonic antigen level > 60 ng/mL, and positive resection margin. The first 6 of these criteria were used in a preoperative scoring system and the last 6 in the postoperative setting. Patients with the worst postoperative prognostic criteria had an expected median cancer-specific survival of 0.7 years and a 5-year cancer-specific survival of 2%. Conversely, patients with the best prognostic postoperative criteria had an expected median cancer-specific survival of 7.4 years and a 5-year cancer-specific survival of 64%[66]. It is therefore very important to preoperatively assess if resection is achievable, most preferably with a 1 cm margin[67,68]. It is often difficult to measure a 1 cm distance to the tumor edge on the specimen because of dissection or cautery artifact. Other times a surgical margin of 1 cm cannot be obtained because of the relation of the tumor to the hepatic veins, portal veins, or vena cava. When tumor is left behind after surgery, meaning that RO resection is not achieved, the survival is not different than that in the nonresected group.

While surgical resection remains the gold standard of therapy, only a few patients are suitable candidates for curative surgical resection because of the presence of liver malignancy in unresectable locations, the number of and anatomic distribution of tumor lesions, or the presence of extrahepatic disease or poor liver function. An alternative treatment to control and potentially cure liver disease has been developed for use in patients with malignant liver tumors. Radiofrequency ablation (RFA), also known as "radiofrequency thermal ablation", is a recently developed thermoablative technique. It induces temperature changes by using high-frequency alternating current applied *via* electrodes placed within the tissue to generate areas of coagulative necrosis and tissue desiccation[69,70]. Overall recurrence for colorectal cancer was most common after RFA (84% *vs* 64% RFA and resection *vs* 52% resection only, $P = 0.001$)[71]. Thus, RFA has been reserved as an adjunctive tool to resection, when complete resection is not possible, either alone or in combination with resection[72-74]. The study by Abdalla *et al* demonstrates that RFA alone or in combination with resection for unresectable patients does not provide survival comparable to resection, and provides survival only slightly superior to nonsurgical treatment[71].

After colorectal metastases to the liver, the lungs are the second most common site of metastasis. The number of possibly resectable cases of lung metastasis after primary surgery for colorectal cancer has increased considerably over the past 20 years. The typical pattern of lung metastasis is single or multiple nodules rather than miliary tumors or lymphangitis carcinomatosa. No effective chemotherapy regimen has been found for metastatic disease. Hence, a surgical procedure to eliminate pulmonary metastases is generally accepted as the only potentially curative treatment. In favor of surgery is the recent trend toward earlier detection of pulmonary metastases as small peripheral densities with increasingly common use of screening with spiral or high-resolution computed tomography. The reported 5-year survival rates for lung metastectomy surgery were 24% to 63%, and most were around 40%[75-90]. The criteria for resection of pulmonary metastases from colorectal carcinoma included unilateral or bilateral excisable lung lesions per preoperative chest radiography, no local recurrence of primary lesions, and no extrapulmonary lesions with the exception of associated prior or simultaneous resectable hepatic metastases. Elevated CEA level and the number of metastasis are the most significant prognostic factors for overall survival after resection of lung metastases from colorectal cancer[91].

## ADJUVANT THERAPY

For the treatment of rectal cancer, adjuvant radiotherapy has become a standard procedure. The following two schedules of treatment have been explored over the last decades: short term treatment that delivers 25 Gy in 5 fractions during 1 wk, followed immediately by surgery, and conventional schedules that deliver 40 Gy to 50 Gy in 20-25 fractions during 4 to 5 wk, followed by surgery 3-6 wk later. Regardless of the schedule, preoperative radiotherapy decreases local recurrence rates by 50%-60% when compared to surgery alone[92,93]. The conventional schedules are delivered in combination with chemotherapy to patients with locally advanced rectum cancer (T3-T4 tumors and N+ disease). The radiobiological dose delivered in a short term treatment schedule is too low for adequate response in locally advanced rectal tumors. In 2001, a study by Marijnen *et al* demonstrated that short term treatment with 25 Gy during 1 wk did not achieve tumor down staging for T1-T3 tumors within a period of 10 d[94]. However, a schedule of 50.4 Gy given over a period of 6 wk in combination with 5-FU and leucovorin did cause

down staging of locally advanced rectum tumors[95]. Today the standard treatment for locally advanced rectum carcinoma is pre-operative radiotherapy in combination with 5-FU and leucovorin[96]. In addition, it has been demonstrated that timing of chemoradiation for locally advanced tumors is important, since less toxicity and better local control may be achieved when chemoradiation is given pre-operatively instead of post-operatively[97]. Thus far, there has been no conclusive demonstration of a gain in overall survival for patients with locally advanced rectal tumors treated with adjuvant chemoradiation[98].

During the past years, various phase Ⅰ and Ⅱ trials have been performed with capecitabine[98,99]. It is a form of chemotherapy that is administered orally and is a tumor activated fluoropyrimidine carbonate. During the last of three enzymatic processes, thymidine phosphorylase converts capecitabine to 5-FU. The enzyme thymidine phosphorylase is found in high concentrations in rectal tumors and it is therefore less likely that healthy tissue within the radiation field is subjected to 5-FU. The advantages of this form of therapy are less toxicity, oral administration, and less chance of infections since a venous port access catheter is no longer necessary. Although the phase Ⅱ trials with capecitabine in combination with radiotherapy for locally advanced rectum tumors show promising results, there are currently no phase Ⅲ trials that give information about local recurrence during a long term follow-up period. However, the National Surgical Breast and Bowel Project trail in the United States is planning on performing such a study in the near future. If the results from this study show acceptable local recurrence rates, then capecitabine may replace the 5-FU/leucovorin schedule. A study by Kim *et al* suggests that the addition of leucovorin to capecitabine does not work synergetically but actually seems more toxic[100]. For this reason a combined capecitabine and leucovorin schedule does not seem desirable. Other phase Ⅰ and Ⅱ studies have tried to combine capecitabine with oxaliplatin[101-103]. The results seem promising as well, and grade Ⅲ/Ⅳ toxicity does not seem greater than the capecitabine and 5-FU/leucovorin schedules. Although there are many new developments, 5-FU and leucovorin in combination with radiotherapy remains the standard of neo-adjuvant treatment in most countries for patients with locally advanced rectum carcinoma.

Although research efforts continue to be directed at deriving new cytotoxic and antiproliferative agents directed specifically at cancer cells, the concept of targeting the angiogenic support of tumors has recently become of interest, and angiogenesis inhibitors have also been introduced for treatment of cancer. Bevacizumab is an anti-VEGF antibody. When combined with conventional chemotherapy, this agent has been reported to prolong survival in patients with advanced colorectal cancer treated in a palliative setting[104,105]. Additionally, recent trials with neo-adjuvant chemotherapy suggest that irresectable liver metastases can be downstaged with this agent. Thus, an increasing number of patients with colorectal metastases to the liver may now become candidates for liver resection. Indeed, in such patients preoperative treatment with bevacizumab and chemotherapy may be associated with less blood loss compared to chemotherapy alone[106]. If bevacizumab and chemotherapy are discontinued at least 8 wk before hepatic resection, the addition of bevacizumab to preoperative irinotecan and oxaliplatin does not increase morbidity after hepatic resection[106,107]. Unfortunately, there are no studies yet that compare whether the combination of bevacuzimab and chemotherapy allows for better downstaging of liver metastases than conventional chemotherapy alone. This will be an important subject for future study, as will the long term outcomes of patients downstaged with these agents and then subjected to liver resection of the remaining obvious metastases.

Despite all of these advances in surgical techniques and adjuvant therapies, colorectal tumor recurrence remains a problem. Manfredi *et al* described a 5-year cumulative rate of local recurrence of 12.8% and a 25.6% per cent rate of distant metastases[108]. During surgery it is important that tumor free margins of the resected specimen are achieved and that tumor spill is avoided. Unfortunately, some tumor spill occurs in approximately half of patients that are operated for colorectal cancer[109]. Many research studies have provided evidence for direct implantation of the port site or surgical wound by exfoliated cancer cells, hematogenous seeding, tissue manipulation, serolization by pneumoperitoneum, patient's positioning and immune dysfunction as potentially etiologic factors. Approximately 0.2%-1% of patients will eventually develop wound recurrence[33,110]. Many of these patients also exhibit more diffuse peritoneal recurrence, although approximately half exhibit isolated wound recurrence. Either phenomenon has a negative impact on survival for those patients that are operated with curative intent. Since more than 80% of patients with colorectal disease are initially operated with curative intent, a complication such as wound or peritoneal recurrence may drastically influence their 5-year survival rate in a negative manner.

## TUMOR CELL ADHESION

The contrast between the high rates of tumor cell spillage and circulating tumor cells and the much lower rates of clinical tumor metastasis or implantation after surgery suggests that tumor implantation may be regulated in some way. The mechanisms that determine which tumor cells adhere to target organs and tissues are poorly understood. Normally, if a cell is unable to attach to the extracellular matrix, it dies through induction of the cell suicide program known as apoptosis. Cancer cells, however, develop a means to avoid death in this situation. Cells that have suffered irreparable DNA damage activate specific proteases and nucleases that destroy the proteins and DNA of the cell, thereby effectively limiting the spread of potentially deleterious mutations. Cancer cells often exhibit mutations in genes

involved in regulating this pathway.

Since not all cancer cells that are shed into the peritoneal cavity undergo apoptosis, there is always a possibility that these cells will eventually cause wound metastasis. Tumor implantation begins with the adhesion of tumor cells to the matrix proteins in the wound. The extracellular matrix consists chiefly of type Ⅰ and Ⅳ collagens, laminins, heparin sulfate proteoglycan, fibronectin, and other noncollagenous glycoproteins[111]. Cell adhesion to extracellular matrix proteins is mediated by diverse receptors, most notably by members of the integrin family. Integrins, heterodimeric transmembrane proteins, are composed of noncovalently associated alpha and beta subunits that define the integrin-ligand specificity[112], and their pattern of expression is likely to promote specific cellular adhesions. Both the physiologic status of the cell[113] and divalent extracellular divalent cation concentrations[114] can influence the affinity between integrins and their ligands. After adhesion of the cell, proliferation and angiogenesis are then required to support tumor growth, invasion and subsequent metastasis.

### *Treatments to prevent wound or peritoneal metastasis*

During the past years not much progress has been booked in reducing wound recurrence in patients with curable colorectal cancer. The application of topical ointments[115,116], abdominal irrigation[117] and port-site resection of wounds[118] have had limited success. The most promising results to date are probably the studies that investigate the anticancer effect of COX-2 inhibitors. Various studies have shown that COX-2 inhibitors have both antiangiogenic[119,120] and apoptotic effects[121,122] on human colon cancer cells. A more recent study demonstrated that COX-2 inhibitors down-regulated β1-integrin expression, with consequent impairment of the ability of colon cancer cells to adhere to and migrate on extracellular matrix in an *in vitro* study[115]. It is therefore possible that these drugs may reduce wound recurrence since they may interfere with the adhesion of the cell to extracellular matrix. However, to date, the mechanisms of drug action and interaction are still far from clear, and their roles within the clinical setting are yet to be observed. It is therefore important to further investigate factors that may be of significance during wound implantation and eventual tumor formation.

### *Extracellular influences on colon cancer cell adhesion*

Interaction between cells and the extracellular matrix are in large part mediated by integrins in divalent cation-dependent processes. This means that extracellular processes that alter divalent cation concentrations may also influence colon cancer cell adhesion to the extracellular matrix. Local shifts in the concentrations of extracellular $Mg^{2+}$ and $Ca^{2+}$ occur during wound healing, impacting the function of divalent cation-dependent cell surface molecules responsible for cell-cell and cell-extracellular matrix interactions[123]. Early in the process, when cell migration into the wound is initiated, $Mg^{2+}$ is elevated and $Ca^{2+}$ is reduced. As wound healing progresses, wound concentrations of $Mg^{2+}$ and $Ca^{2+}$ return to normal plasma levels. Ebert *et al* reported that $Mn^{2+}$ and $Mg^{2+}$ stimulate binding of HT-29 colon cancer cells to extracellular matrix proteins[124], and similar effects have been described in SW 620 and Caco-2 human colon cancer cells[125]. However, calcium inhibits adhesion of SW 620 and Caco-2 human colon cancer cells to collagen Ⅰ, which is the dominant collagen of the interstitial matrix[125]. Furthermore, $Mg^{2+}$ and $Mg^{2+}$ potentiate cancer cell adhesion to murine surgical wounds and subsequent tumor development. In contrast, $Ca^{2+}$ inhibits cancer cell adhesion to murine surgical wounds and subsequent tumor development[126]. The biological and chemotherapeutic response characterization of transplantable mouse colon tumors suggests that they are reasonable models for colon cancer in humans[127]. Although more studies are required, these results raise the possibility that in the future, manipulation of divalent cation concentrations in irrigation of the surgical site may diminish perioperative tumor implantation.

### *Effects of physical forces on colon cancer cell adhesion*

Cancer cells are subjected to pressure during surgical manipulation and passage through the venous and lymphatic system. Cells that are shed into the peritoneal cavity postoperatively are also subjected to increased pressure from postoperative edema. Surgical manipulation during either laparoscopic or open procedures is likely to result in the direct application of much higher pressures to tumors or lymphatic channels containing malignant cells. For instance, during laparoscopic colectomy for cancer, intra-abdominal pressure is often increased by 15 mmHg as the abdominal cavity is expanded to provide room to operate. The pressure engendered by a surgical forceps grasping tissue may be as high as 1500 mmHg[128]. Although pressure by the surgeon's hand during tumor dissection has not been quantified to our knowledge, parallel studies suggest that intraocular pressures may exceed 50 mmHg during ocular manipulation during enucleation[129]. Normal portal venous pressures may be as high as 10 mmHg, and this may increase substantially in portal hypertension. Mesenteric venous pressures may exceed this under normal circumstances to generate portal flow and might be accentuated by intra-abdominal pressure generated by ascites, Valsalva maneuvers, or bowel edema after surgery. Mesenteric lymphatic pressures in the setting of tumor infiltration into the lymphatics are unclear but might also be expected to be of similar orders of magnitude. Tumor cells in the systemic arterial circulation, of course, are exposed to substantially higher pressures.

Physical forces such as shear stress, and pressure have been reported to affect colon cancer cells[130]. Increasing ambient pressure and the application of shear stress increased cell adhesion of several colon cancer cell lines and primary human colon cancer cells isolated directly from surgical specimens[130,131]. Indeed, an increase of

15 mmHg above ambient pressure had a maximum effect on colon cancer cell line adhesion *in vitro*[130]. An interesting observation is that during colorectal cancer surgery cells are shed into the abdominal cavity and subjected to increases in shear during irrigation and increased pressure during and after surgical procedures. Such increases in pressure may enhance the adhesion of shed cells to surgical sites. Although these original studies were performed *in vitro*, 30 min exposure to 15 mmHg increased pressure has more recently been demonstrated to increase cancer cell adhesion to murine surgical wounds[132] and to adversely affect survival in a murine transplantable tumor model[133]. There are obviously manifest differences between transplantable tumors in mice and the pathophysiology of human colon cancers, but as these same signal events have also been described in primary human colon cancer cells[130,131], the animal data are suggestive that the same pathway might affect the development of metastatic tumors in humans.

### *The effect of pressure on focal adhesion-associated proteins*

If pressure and shear stimulate the adhesion of cancer cells[125,130], it may then be important to unravel the intracellular mechanisms that mediate this effect so that interventions can ultimately be targeted to prevent cancer cell adhesion. In many cells, the focal adhesion kinase FAK transduces signals after adhesion through association with the cytoplasmic domains of integrin subunits[134]. However, "inside-out signaling" by which intracellular events modulate integrin function is less well understood. A study by Cooke *et al* suggests that mechanical stimulation of enterochromaffin-derived BON cells directly or indirectly stimulates a G protein-coupled receptor that activates Gαq, mobilizes intracellular calcium, and causes 5-HT release[135]. Although this study did not portray increased adhesion due to mechanotransduction, it did show that shear stress on carcinoid cells activate an intracellular cascade that releases 5-HT. Consistent with such force-activated intracellular signaling, Thamilselvan *et al* demonstrated that extracellular pressure may increase integrin affinity and promote colon cancer adhesion *in vitro via* actin-dependent inside-out FAK and Src signals[136]. Indeed, it is likely that the intracellular cascade involved in colon cancer cell adhesion to extracellular matrix is very complex. Recently, the activation of PI 3-kinase/Akt signaling pathway has been correlated with prostatic metastasis[137], colon cancer cell invasion[138] and post-operative growth[139]. The overexpression of the PI 3-kinase/Akt pathway has also been described in human cancers including ovarian and colonic carcinomas[140,141]. Recent studies suggest that the PI 3-kinase/Akt pathway may also be required for pressure-stimulated cancer cell adhesion[142], acting specifically via Akt-1[143].

Several key structural proteins also seem to be involved in the mechanotransduction pathway, including cytoskeletal elements[144], the adapter proteins paxillin[145,146] and alpha actinin-1[147]. Both paxillin and alpha actinin-1 facilitate focal adhesion formation and physically link integrin-associated focal adhesion complexes with the cytoskeleton. These focal adhesion associated proteins are often abnormally expressed or mutated in cancer cells[148-150]. Therefore, they may be important in tumor biology in general. Although these focal adhesion associated proteins are not kinases themselves, these proteins facilitate the interaction of various kinases and other proteins required for this pathway to function. This makes them a promising target to uncouple the pathway required for force-activated adhesion without actually inhibiting cellular kinases, possibly leading to fewer side effects. Indeed, in a preliminary proof of principle, knockout of alpha actinin-1 has been shown to abolish the effect of pressure on tumor-free survival in a murine transplantable tumor model[133].

## CONCLUSION

Over the past decades, screening for colorectal neoplasm has shown to be critical for prevention, early diagnosis, downstaging, and improved survival. Beyond intensified screening programs, surgical techniques have evolved over the past years. Total mesorectal excision has improved survival rates for rectal cancer[92]. Other major advances have included liver and lung resections for patients with colorectal metastasis, so that at least some of these patients are no longer candidates for palliative treatment but instead can be treated with curative intent. Besides improvements in surgical techniques, adjuvant therapies such as radiotherapy and chemotherapy also have undergone improvement. At this moment, sentinel lymph node mapping is a technique that lies on the frontier, as does the proper role of anti-angiogenesis agents. Some studies suggest that the sentinel lymph node technique may upstage a significant number of patients who then become candidates for chemotherapy, while anti-angiogenic therapy may downstage patients who then become candidates for surgical resection of known metastases. However, before conclusions are made on these points, further follow-up of patient cohorts will be necessary. The cellular biochemistry involved in metastasis currently lies beyond the frontier. Unfortunately, little is known about the intracellular and extracellular cascades that may influence colorectal cancer cell adhesion and metastasis. Several studies have suggested that increased pressure and shear stress activate cancer cell adhesion. Further studies of the pathways that regulate integrin-driven cancer cell adhesion may identify ways to disrupt these signals or block integrin-mediated adhesion so that perioperative adhesion and eventual metastasis can be prevented in the future, adding yet another strategy to combat colorectal malignancy.

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