Colon Cancer

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3.1 Epidemiology, Risk and Protective Factors

With ≈1 million of new cases per year separated into 72% for the colon and 28% for the rectum, colorectal cancer (CRC) is the fourth most common cancer in men (after cancer of the lung, prostate and stomach) and the third most common in women (after cancer of the breast and cervix) without significant differences in incidence by sex (male:female ratio of 1.2:1). The areas with the highest incidence rates are Australia and New Zealand, North America, Japan and western Europe [1]. In 2002, it resulted in ≈8% of the 6,724,000 registered deaths for cancer. It is estimated that 83% of cases occur in patients aged >60 years and the average age at diagnosis is 70 years. Unfortunately, the incidence of CRC is escalating in patients younger than 50 years, with an increased rate of 56% for patients aged 40–44 years over the past two decades [2]. Five-year survival is stage-dependent, being 90% in localized disease, 68% for regional disease, and 10% if distant metastases are present. Familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), personal or in the first- and second-degree relative history of high-risk polyp or colonic cancer and a personal history of inflammatory bowel disease (IBD) are the most important innate risk factors. Race is also important: 20% more African–Americans develop colon cancer than Caucasians. However, geographic factors can modify racial risk: Native Alaskan Americans have an incidence rate of 102.6/100,000 if living in Alaska and 21.0/100,000 if residing in the southwest of the USA. Smoking and diet are the most important variables and acquired risk factors. Diets high in red or

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processed meats can increase the risk of developing CRC, especially in smokers (relative risk [RR], 1.5) [3]. A body mass index (BMI) >25 and physical inactivity augment the risk of colon cancer. Smoking and heavy use of alcohol worsen the prognosis of CRC.

Interesting evidence about the protective role of certain drugs is emerging. Taking aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) such as sulindac and celecoxib is associated with a lower risk of CRC and has been shown to reduce the formation of adenomatous polyps in people with FAP. It also seems that statins and angiotensin-converting enzyme (ACE) inhibitors help lower the risk of polyps and CRC and of relapse. Aspirin can cause stomach ulcers and other side effects, but the association is strong enough that the Aspirin in Dukes C and High-risk Dukes B Colorectal Cancer (ASCOLT) trial was created to study the use of this drug as an adjuvant medication [4].

3.2   New Developments in Genetic-based Treatments

Recent discoveries of inherited genes that increase a person's risk of developing CRC are being used in genetic tests to inform people most at risk. Anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab and panitumumab) have been available for some years and have good efficacy for the treatment of metastatic colorectal cancer (mCRC) and in chemotherapy-refractory cases. EGFR regulates cancer-cell proliferation, apoptosis and tumor-induced neo-angiogenesis. Unfortunately, efficacy is limited to a subset of patients: EGFR-independent, constitutive activation of the RAS or RAF kinase pathways impairs the response to anti-EGFR drugs. KRAS links growth-promoting signals from the cell surface to the nucleus. It is a member of the RAS protein group of guanosine triphosphate/ guanosine diphosphate (GTP/GDP) binding proteins, and the wild-type gene works transiently only if growth factor receptors (such as the EGFR) are activated. However, when specific mutations in the KRAS gene occur (usually in codons 12 or 13), the resulting KRAS protein can be constitutively active (it can then function independently of upstream growth factor receptor-driven signals and remain active), thereby verifying the block of anti-EGFR monoclonal antibodies. A different and (not equally clearly defined) mechanism allows a mutation in the gene for B-RAF kinase to permit replication of tumoral cells independently from the EGFR. This is why everyone with advanced colon cancer who is considering an EGFR-targeted therapy such as Erbitux® or Vectibix® should have testing for KRAS and BRAF before treatment starts to spare them (mutation is present in ≈40% of cases) from receiving unnecessary treatments. Data from important and well-powered multicenter studies demonstrated that the KRAS and BRAF mutation was significantly associated with more rapid and aggressive metastatic behavior in CRC, short-interval liver metastases, poor survival after resection of the colon and liver, and a worse prognosis [5]. In a Korean study on patients with metasta-

tic or recurrent CRC, lung metastasis was more frequently the initial metastatic site in patients with KRAS mutations [6]. By better understanding the interactions between KRAS and other genes, we may then take advantage of these synthetic lethal combinations to provide additional options to treat chemotherapy- or cetuximab-refractory CRC patients harboring KRAS mutations. Knowledge of these synthetic lethal interactions may also enable the development of improved targeted therapies that may be more effective without the toxicities of traditional chemotherapy due to off-target killing of normal cells. Continued prospective studies and basic science research is critical in the effort to improve outcomes in CRC patients with this mutation.

3.3 Earlier Detection and Diagnosis

The "adenoma–carcinoma" multistep model of CRC is one of the best known models of carcinogenesis. The aim of a screening program is to detect a polyp before its transformation or a cancer at its earlier stage [7]. The common pattern of tests in program of screening for colon cancer are stool and endoscopic (colonoscopy or sigmoidoscopy) or radiologic (virtual colonscopy and air contrast barium enema) tests. The age to begin screening differs between people with an average risk (start screening at 50 years) or with a family history (start screening at 40 years or 10 years before the age when a relative was diagnosed of with colon cancer). The recent evidence of a younger onset associated with more advanced stage, more aggressive histopathological characteristics, and a worse prognosis when compared with older patients as well as a relative rightward shift over the past three decades of the colonic distribution of cancer are encouraging a preference for colonoscopy over sigmoidoscopy and an ever more early age of screening. Screening colonoscopy also involves risks [8]; perforation and bleeding in the case of polypectomy are estimated to be near 0.1% and 1%, respectively. Chromoendoscopy (which involves the application of stains or pigments) and magnification endoscopy (with or without staining) allows the endoscopist to better visualize mucosal details with up to 100-fold image enhancement. Narrow-band imaging colonoscopy allows better visualization of vascular changes in superficial lesions. The value of these techniques in screening for colon cancer has yet to be established. The effectiveness of colonoscopy is dependent upon the skill and experience of the endoscopist to not only reach the cecum but also to identify small lesions. Despite criticism about the cost and potential morbidity, colonoscopy remains the "gold standard" to evaluate the colonic mucosa. A recent long-term prospective study validated colonoscopic polypectomy, with a 53% reduction in mortality [9]. New imaging and laboratory tests are also being developed. Newer, more accurate ways to look for changes in stools that might indicate CRC have been developed. These include tests that are better able to detect blood in stools and tests that can be used to detect changes in the DNA of cells in the stool ("fecal immunochemical tests").

3.3.1   Double-contrast Barium Enema (DCBE)

Retrospective studies have found that DCBE may miss 15% to 22% of CRCs [10]. Even if abnormalities are found, this test must be followed by colonoscopy for biopsy or excision. The use of DCBE for screening has been declining with the increasing use of endoscopic procedures and computed tomography (CT) colonography (also known as virtual colonoscopy (VC)), but retains its value in areas where colonoscopy resources are limited. It has no role in the surveillance of colon cancer but may be used to evaluate the colon by radiographic means if a stoma reversal is being consiered.

3.3.2   VC

VC is a special type of CT that provides endoluminal visualization of the colon based on two- and three-dimensional imaging that enables the detection of many colorectal polyps and cancers early. To enhance accuracy, patients frequently undergo bowel preparation before the procedure, but recent studies found that it could be helpful in screening even without the patient having to drink large amounts of liquid laxative first. The colon is then insufflated with air or carbon dioxide (or, in some cases, water) to facilitate colonic distention and detection of intraluminal lesions. In addition to its non-invasive nature, VC is associated with enabling the diagnosis of extra-colonic disease and establishing the presence of synchronous lesions in the setting of an obstructive distal cancer that does not permit colonoscopy. Synchronous lesions are thought to occur in 1% to 7% of patients, and a 100% sensitivity rate for the detection of proximal synchronous cancers in the setting stenosing cancers has been observed. Sensitivities and specificities increase according to increasing polyp size (≈80% for polyps of diameter >9 mm and ≈100% for lesions of diameter >15 mm) [11,12].

3.3.3   CT

In newly diagnosed colon cancer, preoperative abdominal and pelvic CT demonstrated variable sensitivity for detecting distant metastasis (75% to 87%), nodal involvement (45% to 73%) or the depth of transmural invasion (≈50%) as well as tumor-related complications such as obstruction, perforation, and fistula formation [13]. CT is not a reliable diagnostic test for low-volume tumors on peritoneal surfaces. The sensitivity for detecting peritoneal implants is <40% neither for large lesions (diameter, 5 mm to 50 mm). The most important feature of preoperative CT is the planning of eventual simultaneous or staged liver metastasectomy or eventual neoadjuvant therapy for high-volume and diffuse, metastatic, non-stenosing and non-bleeding colon cancer. Intraoperative ultrasonography and manual palpation of the liver may

provide a better yield than preoperative CT [14], but the latter is precluded in laparoscopic colon resections, and both methods can be hindered by supramesocolic adhesions from previous surgery. A preoperative CT of the chest might be of more value for rectal cancer than for colon cancer depending on the different types of venous drainage.

3.3.4   Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET)

Contrast-enhanced MRI and PET or PET/CT have no role in screening or in the routine staging of colon cancer. However, they may have a role in patients thought to be candidates for resection of isolated liver metastases of colon cancer (especially in patients who have not previously undergone therapy), which changes surgical plans in a consistent percentage of patients [15].

Recently, increasing attention has been placed on the application of PET to assist with early detection of disease recurrence, in differentiating it from postoperative scarring, or in the evaluation of patients with unexplained increasing levels of carcinoembryonic antigen (CEA) after initial surgery. In this setting, PET can potentially be used to localize occult disease, permitting the selection of patients who may benefit from exploratory surgery. PET is frequently used in conjunction with CT and demonstrates high sensitivities and specificities (>90%) in association with contrast-enhanced or non-contrast CT [16].

3.4   Preoperative Preparation

Recent demonstration of low septic and anastomotic complications in emergency colectomy without mechanical bowel preparation (MBP) [17], together with the results of prospective studies demonstrating safety in elective surgery of the colon and rectum with avoidance of mechanical bowel cleaning, are changing conceptions about the central role of MBP with or without oral antibiotics in preventing postoperative complications [18,19]. In elderly patients, MBP can produce intravascular depletion and electrolyte abnormalities, thereby increasing surgical risks [20]. A meta-analysis involving seven randomized clinical trials [21], revealed a higher rate of anastomotic dehiscence among patients in the MBP group compared with patients in the non-MBP group (5.6% *vs* 2.8%, respectively, $p = 0.03$) with similar septic peritoneal or wound infections. A review of 26 trials [22] on various intravenous and oral preoperative antibiotic regimens demonstrated that antibiotic prophylaxis decreased the overall infection rate from 36% to 22% and mortality rates from 11.2% to 4.5%, suggesting that antibiotic prophylaxis for colorectal procedures is merited. Some studies based on replacing routine MBP with a single preoperative enema [23] noted significant increases in postoperative morbidity (26 *vs* 9, $p = 0.004$) and wound infection (7 *vs* 1, $p = 0.041$). A well-

powered study to assess the relative benefits of no preparation *vs* mechanical preparation alone or in conjunction with antibiotics is required.

3.4.1 Goal-directed Fluid Management

Several recent studies [24, 25] have suggested that a restricted goal-directed fluid regimen that avoids excess fluid administration causing adverse cardiovascular and pulmonary effects and even leading to impairments in wound healing may improve postoperative outcomes in colectomy. A too-restricted fluid regimen can lead to tissue hypoperfusion, anastomotic leaks, and sepsis. Dehydration from preoperative MBP and prolonged perioperative nil-by-mouth regimens can create difficulty in optimizing fluid management that is equally [26] challenging in the operating room. This is because the various medications and anesthetic agents administered can affect urine output and the cardiac parameters commonly used in the assessment of volume status. Given this challenge, several surrogate markers have been used to help guide fluid administration in the perioperative period, including serum lactate levels and mixed venous oxygen saturation. The recent introduction of intraoperative esophageal Doppler to monitor cardiac output by directly measuring flow in the descending aorta seems to be a very good guide for balanced fluid administration [27], mitigating the risk of gut hypoperfusion that can occur. Consequently, application of this method should be considered for patients undergoing colectomy.

3.4.2 Enhanced Recovery After Surgery (ERAS)

Colectomy is a common and major procedure which, unfortunately, is associated with significant morbidity and costs to healthcare systems. Over the past 20 years, there have been two important developments in elective major abdominal surgery—the introduction of laparoscopic surgery and implementation of ERAS programs (also referred to as "fast track" (FT) perioperative care)—with the aims of reducing the length of hospital stay, morbidity and mortality, length of time to return to full function, and to improve patient satisfaction [28,29]. During the mid-1990s, FT perioperative care was pioneered by Henrik Kehlet. FT programs consist of a multidisciplinary approach (dieticians, nurses, surgeons, anesthesiologists) and aim at reducing surgical-stress responses, organ dysfunction, and morbidity, thereby promoting faster recovery after surgery.

FT perioperative care comprises extensive preoperative counselling, no bowel preparation, no sedative premedication, carbohydrate-loaded liquids up to 2 h before surgery, and effective multimodal pain management with short-acting anaesthetics (blocking the neurohormonal response to surgery). The goal is to reduce the risk of organ dysfunction and complications, enable ade-

quate perioperative goal-directed fluid management, use small incisions, and to not use drains and nasogastric tubes. Intraoperative care involves the prevention of hypothermia (because it reduces sympathetic responses), undesirable cardiac events, and wound morbidity [30]. Postoperative care involves early oral feeding, enforced mobilization, early removal of urinary catheters, and standard use of laxatives. NSAID agents and epidural anesthesia/analgesia are used to reduce the perioperative inflammatory responses, leading to a reduction in mediator release and catabolism. Optimal analgesia can permit early ambulation, and diet introduction is probably the most important (and least appreciated) component of an ERAS program [31]. The Laparoscopy and/or FT Multimodal Management Versus Standard Care (LAFA) trial [32] has provided interesting data regarding which of these components is essential to improved outcomes: the focus is on laparoscopy, analgesia, early ambulation, and early resumption of diet. A recent multicentric Dutch trial confronting the four combinations of laparoscopy, open surgery, standard and FT perioperative care showed that the combination of laparoscopic surgery with FT care resulted in a significantly faster recovery after colonic surgery than all other combinations [33]. The challenge of building and enabling the organizational structure around the necessary multidisciplinary group for a successful ERAS program is well documented, but encouraging results are pointing towards such implementation. The multidisciplinary approach of any ERAS program should address the oft-quoted question raised by Henrik Kehlet: "why is the patient in hospital today?"

3.4.3 Stadiation

The American Joint Committee on Cancer (AJCC) has published the seventh edition of its staging manual [34]. Tables 3.1 and 3.2 report the new tumor/node/metastasis (TNM) classification for CRC report, which should be compared with the previous classifications of Dukes and Astler–Coller.

3.4.3.1 Staging Information
The features of the revised staging give more importance to the poor prognostic features of the depth of invasion despite fewer positive nodes.
- T4 is divided between penetration to the surface of the visceral peritoneum and direct gross adherence to adjacent structures;
- T1–2N2 is downstaged from stage IIIC to IIIA or IIIB depending on the number of nodes involved
- Shift T4bN1 from IIIB to IIIC;
- Subdivide T4/N1/N2;
- Resolution of staging for issue of mesenteric deposits where nodal tissue is not identified;
- Revised sub-staging of stage II based on depth of invasion, with addition of stage IIC;

Table 3.1 TNM classification for colon cancer

Primary tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T*is* Carcinoma *in situ*: intra-epithelial or invasion of lamina propria
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into pericolorectal tissues
T4a Tumor penetrates to the surface of the visceral peritoneum
T4b Tumor directly invades or is adherent to other organs or structures
Regional lymph nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1–3 regional lymph nodes
N1a Metastasis in 1 regional lymph node
N1b Metastasis in 2–3 regional lymph nodes
N1c Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis
N2 Metastasis in ≥4 lymph nodes
N2a Metastasis in 4–6 regional lymph nodes
N2b Metastasis in ≥7 regional lymph nodes
Distant metastasis (M)
M0 No distant metastasis
M1 Distant metastasis
M1a Metastasis confined to 1 organ or site (e.g., liver, lung, ovary, non-regional node)
M1b Metastases in >1 organ/site or the peritoneum

- Revised sub-staging of stage III based on node number (N1a, 1 node; N1b, 2–3 nodes; N2a, 4–6 nodes; N2b, ≥7 or more nodes);
- Division of metastases to ≥1 sites in recognition of the possibility of a curative approach for aggressive treatment of a single site of metastases.

The seventh edition considers, together with the classic anatomic bases of T, N and M, some other important anatomic and serological prognostic factors validated by clinical studies and which are evidence-based and which assume prognostic value that influences patient care. Among the important anatomical factors are lymphatic vessel invasion (Lx: cannot be assessed; L0: absent; L1: present), venous invasion (V0: absent; V1: microscopic; V2: macroscopic), perineural invasion (PN: 1 present or 0 absent) and the residual tumor (Rx:

Table 3.2 Anatomic stage/prognostic groups

Stage	T	N	M	Dukes	MAC
0	T*is*	N0	M0	--	--
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	--	--
IVB	Any T	Any N	M1b	--	--

T tumor, *N* node, *M* metastasis, *MAC* modified Astler-Coller.

cannot be assessed; R0: no residual; R1: microscopic residual; R2: macroscopic residual). The two principal serological prognostic factors are CEA (Cx: not assessed; C0: <5 ng/mL – normal; C1: >5 ng/ml – elevated) and microsatellite instability (MSI). MSI is a marker of the functionality of the DNA repair enzyme system operating during cellular replication. MSI (higher (H) or lower (L) level) is especially significant in HNPCC and in ≈20% of sporadic cancers.

3.4.4 Sentinel Lymph Node (SLN) Biopsy

Since the 1980s, many studies have been conducted focusing on intraoperative identification of SLNs and/or complete mapping of lymph nodes using different technologies (e.g., vital coloration, intraoperative ultrasound and/or radioimmunoguided nodal mapping) [35,36]. The first aim was to eventually modify the extension of the resection that could be more limited in small lesions (frequently diagnosed in screening programs and eventually removed endoscopically) with negative SLNs, or more extended over the boundaries of classic lymphadenectomy in cases of aberrant lymphatic drainage. Furthermore, microscopic evaluation of node status in colon cancer is based

on hematoxylin and eosin (H&E) staining, and has a non-negligible percentage of false-negative values (especially if we consider micrometastases), and cell clusters of diameter <0.2 mm are also associated with relevant recurrence of disease and lower 5-year survival rates. Correct identification of this false stage-II population can be achieved by a more sensible (but more expensive) immunohistochemical (IHC) test. The individualization of a SLN could help to reach this aim.

3.5 Treatment According to Stage of Colon Cancer

3.5.1 Stages

Stage 0: These cancers are in the inner lining of the colon; polypectomy or local excision through a colonoscope is often all that is needed. Colectomy may occasionally be needed if a tumor is too big to be removed by local excision.

Stage I: Several layers of the colon are penetrated from the cancer without spread outside the colon wall (or into nearby lymph nodes). Partial colectomy (i.e., surgery to remove the section of colon that has cancer and nearby lymph nodes) is the standard treatment without the need for additional therapy.

Stage II: Many of these cancers have grown through the wall of the colon and may extend into nearby tissue. They have not yet spread to the lymph nodes. Colectomy is usually the only treatment needed. However, adjuvant chemotherapy may be recommended if the cancer has a higher risk of returning because of certain factors: it looks very abnormal (is high grade) or has a dangerous histotype; shows MSI; has grown into nearby organs; the surgeon did not remove all the cancer and ≥12 lymph nodes; the cancer obstructs the colon or causes a perforation in the colon wall. Many research teams have studied the way to identify stage II because the risk of recurrence is greater. Petersen et al. [37] proposed a sub-classification of the prognostic index (PI) based on four elements subsequently considered by many other authors. Three of them have a score of 1: peritoneal involvement with or without ulceration; extramural or submucosal venous spread; or a involved or inflamed margin. The last element, perforation through the tumor, has a score of 2. Patients in stage II with a PI of ≥2 are to be considered at high risk and could be candidates for adjuvant therapy (see below). Even the pathological aspects of tumor necrosis as well as host systemic and local inflammatory responses are taken into account. Different criteria have been used to measure these variables, such as the Glasgow Prognostic Score [38] for systemic inflammatory responses, the Klintrup–Makinen criteria [39] for local inflammatory infiltrates and for the assessment of tumor necrosis. Richards et al. [40] confirmed by statistical means that tumor necrosis is a marker of a poor prognosis, independent of pathological stage, and that it is associated directly with an increase in the

systemic inflammatory response and a decrease in local inflammatory cell infiltrates. This finding suggests that the impact of tumor necrosis on survival from CRC may be explained by close relationships with host inflammatory responses. Patients in stage II with extensive tumor necrosis are to be considered at high risk and could be candidates for adjuvant therapy.

Stage III: There is a spread to nearby lymph nodes, but cancer has not yet spread to other parts of the body. Partial colectomy followed by adjuvant chemotherapy is the standard treatment for this stage.

Stage IV: Distant organs and tissues such as the liver, lungs, peritoneum or ovaries can be affectted by colon cancer. If only a few small metastases are present in the liver or lungs and can be completely removed along with the colon cancer, surgery may prolong life and sometimes may even cure. Chemotherapy is typically given before and/or after surgery. Other options to destroy tumors in the liver include hepatic artery infusion, cryosurgery, radiofrequency ablation, or other non-surgical methods. If the cancer is too widespread to try to cure with surgery, colectomy or diverting colostomy may be needed in cases of bleeding or occlusion. Sometimes, such surgery can be avoided by inserting a stent into the colon during colonoscopy to keep the lumen patent. Most patients with stage-IV cancer will receive chemotherapy and/or targeted therapies to control the cancer.

3.5.2   Recurrent Colon Cancer

Recurrent cancer means that the cancer has returned after treatment. If the cancer comes back locally, surgery (often with previous and/or after chemotherapy) can stop recurrence, prolong life, and eventually cure the patient. If the cancer comes back at a distant site (liver, lung, others), surgery may be an option in some cases. If needed, chemotherapy can be tried first to shrink the tumor(s), and may be followed by surgery. If the cancer is too widespread for a surgical approach, chemotherapy and/or targeted therapies may be used depending on which (if any) drugs were received before the cancer returned and how long ago the patient received them, as well as general health status. Radiotherapy may be an option to relieve symptoms in some cases.

3.6   Adjuvant Therapy

In previous years, the standard of care for stage-III and -IV disease (and even some high-risk stage-II disease) was treatment with 5-fluorouracil (5FU) and leucovorin (LV) for six cycles with surgery or these agents alone in cases without a surgical indication. From 2004, with the results of the Multicenter International Study of Oxaliplatin/5-fluorouracil (FU)/leucovorin (LV) in the

Adjuvant Treatment of Colon Cancer (MOSAIC) trial [41], oxaliplatin became part of the chemotherapy regimen. Also, irinotecan was demonstrated to improve the effectiveness of 5FU and LV. Hence, the principal protocol of adjuvant therapy was FOLFOX (5FU, LV, and oxaliplatin) or FOLFIRI (5FU, LV, and irinotecan). In addition to this regimen, especially in stage-IV disease or stage III refractory to chemotherapy, targeted therapies (see above) [42] have become the first-line therapy in recent years. They demonstrate a good decrease in median progression-free survival and better quality of life in the absence of mutations of KRAS or BRAF.

3.7 Surgical Treatment

3.7.1 Laparoscopic Colectomy (LC)

Laparoscopic surgery for CRC has undergone slow (but tremendous overall) advancement since 1991, when first laparoscopic colonic resection for cancer was described. LC can today be considered the gold standard surgical treatment for colon cancer when indicated appropriately. Randomized clinical trials have shown that this method is safe and effective for malignant disease with oncologic outcomes equivalent to open surgery [43–45]. LC results in a shorter hospital stay as well as less morbidity and postoperative pain than open colorectal surgery.

Nevertheless significant socioeconomic disparities in the use of minimally invasive surgery (MIS) for colorectal disease remain. A recent revision of 211,862 colorectal resections carried out at high-volume hospitals in 2008 in the USA [46] demonstrated that only 16,637 (7.3%) colorectal resections were done using MIS. It was found that racial and socioeconomic factors influenced appreciably the access to MIS for CRC treatment. Laparoscopic surgery for colon cancer is the cornerstone of enhanced recovery programs thanks to its lower level of injury to potentially complex, immune-challenged hosts. The underlying philosophy of FT programs is to capitalize upon small differences to effectuate more important global benefits in overall patient recovery in the hope that the short-term advantages of enhanced-recovery colonic surgery may have important cumulative long-term benefits. Clearly, further investigation is warranted. Under the impact of an ever advancing technology, enhancing the ergonomics and extending the boundaries of MIS, the next few years are expected to be very promising for laparoscopic surgery of colon cancer with prospective randomized studies reaching full maturity and having the possibility to extend the follow-up to a more significant period of 10 years. The integration of enhanced-recovery regimens with laparoscopic methods should also provide greater uniformity of clinical outcomes throughout the world. Furthermore, the previously arduous learning curve will predominantly be addressed in the postgraduate training period. The comparisons of experiences will probably lead, in this decade, to an evermore important technical standardization of colectomies.

3.7.2 Single-incision Laparoscopic Colectomy (SILC)

Single-incision laparoscopic surgery (SILS) represents the latest development in laparoscopic surgery and has been promoted to improve the cosmetic effect and incisional and/or parietal pain as well as to reduce port site-related complications. The initial increases in surgical costs associated with purchasing new equipment do not seem to be mitigated by a significant reduction in morbidity and duration of hospital stay [47]. SILS has several disadvantages compared with multiport laparoscopic surgery with regard to surgical instruments and methods. One of the biggest challenges associated with SILS is the optimal positioning of instruments. Therefore, SILS requires an experienced surgeon to overcome the difficulties of triangulation, pneumoperitoneum leaks, and instrument crowding. In fact, many cases require conversion to open or multiport laparoscopic procedures to get better retraction or aid in colonic mobilization. Some investigators recommend utilizing articulating instruments or variable-length tools, including a bariatric-length bowel grasper or an extra-long laparoscope to minimize external clashing. Most of the experiences in SILC have been in the setting of right hemicolectomy [48] (Fig. 3.1). This is because this procedure was proposed as an intracorporeal ileocolic anastomosis using an Endo stapler and closure of the orifice left from the stapler by the endostitch that requires limited wrist movements to avoid interference with the endoscope. It was also to avoid mesenteric traction occurring with extracorporeal sutures, which often involve enlarging the incision of the multiport device [49]. Further advantages can be gained from the use of particular access ports to allow the introduction of several trocars multiple times, for example using Gelport™, in which trocars can be kept apart for as long as possible to maintain instrument triangulation and to prevent clashing outside the abdomen. It has recently been suggested [50] that the implementation of robotic technology to SILC could help overcome some of the difficulties associated with conventional SILS.
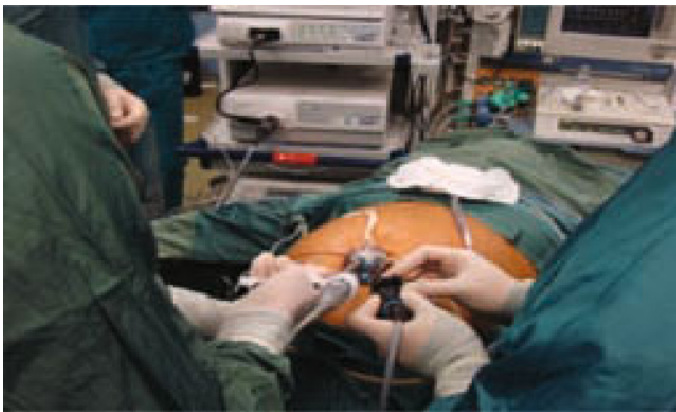

Fig. 3.1 Position of monotrocar in SILS right colectomy

3.7.3   Natural Orifice Transluminal Endoscopic Surgery (NOTES)

In specialist centers around the world efforts are being made to assess various possibilities to transform the new concept of NOTES from the experimental setting into clinical practice. The common focus of these concepts is to minimize trauma to the abdominal wall while gaining access to the peritoneal cavity and/or extracting the surgical specimen through a natural orifice such as the mouth, anus or vagina as well as reducing the incisional complications of pain, infections and hernia. Endoscopic technology is not available to carry out NOTES exclusively for complex procedures such as a colon resection, so a hybrid solution has emerged.

In this setting, there has been renewed interest in a classically described method of natural orifice specimen extraction (NOSE), which was originally proposed by Franklin. This hybrid method uses a natural orifice for instruments and tasks that need a larger diameter of access (>5 mm) to the abdominal cavity. NOSE also allows for laparoscopic assistance *via* small-size trocars to reduce the trauma of access and morbidity. An interesting combination of laparo-endoscopic single-site (LESS) and NOSE was also developed and experimented in sigmoidectomy to push the technical limits of MIS of the colon [52]. A recent review of transvaginal specimen extraction in colorectal surgery [53] reported on 130 patients of which 67 had colonic cancer. Two significant complications, pelvic seroma and rectovaginal fistula, were likely to have been related to transvaginal extraction. The duration of follow-up was specified in only one study. Harvested nodes and negative margins were adequate and reported in 70% of oncological cases. There is relative skepticism about the possibility of propagation of these procedures considering the high costs in terms of instrumentation and prolonged operating time due to the technical difficulties of these procedures.

3.7.4   Robotic Colon Surgery

Theoretically, the demerits of laparoscopic methods such as unstable camera platforms, limited degrees of freedom, two-dimensional imaging, and ergonomic constraints could be overcome by robotic surgery. Its implementation has gained acceptance in rectal surgery, appearing able to ensure a more refined total mesorectal excision accurate with nerve sparing. However, it remains unclear if robot-assisted colectomy (RAC) has significant clinical advantages over laparoscopically assisted colectomy (LAC) in treating colonic cancer. The use of robotic technology for colon resections has been reported in several small series in the past years. In 2004, D'Annibale and colleagues [54] reported on 53 patients undergoing robotic colorectal surgery in which 22 patients underwent surgery for malignant disease. In this series, no significant difference in total operating time was noted between laparoscopic and robotic groups (although a longer time was required to prepare the operating room in the robotic group). Specimen length, number of lymph nodes harvested, intraoperative blood loss, and duration of hos-

pital stay were comparable between the groups. In 2011, Luca and colleagues [55] published the results of a case-matched series in which the outcomes of patients undergoing right hemicolectomy for cancer were compared with patients undergoing open resections. Although the operating time was longer in the robotic cohort, patients in this group demonstrated reduced intraoperative blood loss and a shorter duration of hospital stay than patients in the open surgery cohort. Consistent with the report by D'Annibale and colleagues, patients in both groups had similar specimen lengths and number of lymph nodes harvested.

Despite these promising reports, several challenges must be addressed before robotic technology can be adopted for colon surgery. Robotic surgery is associated with substantive costs, which may prohibit the widespread implementation of this method. Limited robotic instrumentation for intra-abdominal surgery is available, highlighting the importance of continued development of devices. The required machinery is bulky, resulting in difficulties with maneuvering and the need for substantial space in the operating room. As with all new technologies, specialized training and proficiency is required before implementation. With increased experience and familiarity with the procedure, the longer operating times associated with robotic colon resections have been shown to decrease. The feasibility and safety of RAC have been confirmed but prolonged operating time and elevated costs without actual significant benefit to justify the greater cost were reported recently from Shin et al. [56]. Continued advances are undoubtedly expected, although the ultimate utility of this method for routine colon resections remains to be seen.

3.8   Conclusions

Colon cancer remains a major therapeutic challenge. In many ways, the encouraging results achieved from the improvement and dissemination of screening, the good outcomes of MIS and ERAS programs, as well as the deepening of genetic knowledge with the introduction of targeted therapies, has allowed significant progress in the battle against colon cancer. There is no consensus on the role of robotic SILS and NOTES colectomy in the treatment of this serious disease. Technological progress and the results of the first multicenter studies in progress may clarify the true costs and benefits of these treatments.

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