ORIGINAL ARTICLE

Colorectal Cancer: Guidelines to Management

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ABSTRACT

Colon cancer is the third leading cause of cancer deaths in Jamaica. Unique features may exist in this predominantly black population that impact management. Additionally, there is rationalization of some resources that may impose restrictions on the widespread applicability of some international guidelines. We have developed here guidelines that are consistent with the best available evidence and which are appropriate to use in our local context.

Screening: *We recommend that screening should start at age 45 for the average risk patient and may take the form of yearly stool testing (three serial samples) followed by colonoscopy where positive. Endoscopic evaluation with flexible sigmoidoscopy every five years in combination with stool testing, or colonoscopy every 10 years are all acceptable options. Computed tomography (CT) colonography every five years is especially useful in some patients.*

Staging: *Staging patients by CT scan of the chest, abdomen and pelvis is desirable. Other options may be used but are of inferior accuracy. Magnetic resonance imaging (MRI) for staging is acceptable where CT contrast reactions exist. Rectal cancer requires additional local staging by MRI or the less desirable transrectal ultrasound. Positron emission tomography/ computed tomography (PET/CT) has limited role in confirming or localizing metastatic disease.*

Surgery: *Oncologic outcomes are the same with open and laparoscopic approaches, however, patient postoperative mobilization and cosmetic outcomes are better with the laparoscopic approach. The required advanced minimally invasive surgical skills are not universally available. Extent of resection is determined based on curative versus palliative intent and tumour location in relation to vascular supply. Total mesorectal or mesocolon resections are desirable. Stapled anastomoses may be advantageous over hand sewn but suffer from reduced availability and increased cost of stapling devices.*

Metastases: *Patients with metastatic disease are best managed by multidisciplinary teams with a view to neoadjuvant chemotherapy, multi-visceral resection and intraperitoneal chemotherapy.*

Pathological Assessment: *Apart from tumour confirmation the pathologist assists with quality control (*eg *regional lymph node harvest) and suggestions on genetic and histochemical testing. Better clinical information and specimen orientation would assist the pathologist in providing clearer guidance. Ideally, fresh specimens should be received/ retrieved but this may be impossible in most institutions. A pathology reporting checklist is strongly advised in order to achieve standardization.*

Adjuvant Therapy: *Stage 1 and low risk Stage 2 disease patients are generally not offered adjuvant chemotherapy. Patients with Stage 4 disease should be tested for mutations in the KRAS and NRAS gene and offered EGFR agents like cetuximab and pantuximab.*

Surveillance for survivors: *No internationally agreed guidelines exist. We suggest the following for average risk patients managed with curative intent: Every six months for five years, patients should have clinical evaluation, carcinoembryonic antigen (CEA) [if indicated] and CT scans of the chest, abdomen and pelvis. Other modalities like abdominal ultrasound and*

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chest X-ray may substitute if CT is unavailable. A colonoscopy should be done one year after surgery and then every five years. Surveillance for high-risk patients would be different.

The Management Flowchart in Appendix 1 captures this summary.

Keywords: Colonoscopy, neoadjuvant, oncology, screening, surveillance

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INTRODUCTION

Colorectal cancer is the third leading cause of cancer death in Jamaican men and women (1). Over the past decade there has been a reduction in the average age of diagnosis in the Jamaican population and approximately 20% of patients are diagnosed before age 50 (2, 3). Though colorectal cancer is common in the Jamaican population, there are no locally developed guidelines for the management of these patients. The lack of locally developed guidelines has led to the adaptation of various guidelines from all over the world though there is strong evidence that the disease presentation varies between populations (4). In addition, data from the United States of America have also showed that African Americans do poorly compared to Caucasians (5). With this in mind, locally developed guidelines will allow more uniform usage of the resources available in the region in accordance with current evidence in the medical literature.

Screening

Colorectal cancer presents at an earlier age in the black population and is associated with a worse prognosis (4). The selection of the ideal screening programme for a patient should be based on the age of the patient, previous history of colorectal cancer or cancers known to be associated with colorectal cancer syndromes and family history of the patient inclusive of any known genetic syndrome. Patients can be divided into average risk and high-risk groups.

For the average risk group, we recommend that screening should begin at age 45 years with any of the following modalities:

- **Stool testing:** Faecal occult blood testing, faecal immunochemicical testing (FIT) or multiplex stool DNA (FIT-DNA). Guaiac based occult blood tests, if used, should be done yearly and consist of three stool samples taken on different days. Faecal immunochemicical testing can be done yearly on a sample while combination test (FIT-DNA) can be done on a single sample every three years. A positive stool test should be followed by a colonoscopy. The faecal occult blood testing can be associated with false positive results in patients consuming meat rarely up to two weeks before testing, the use of medications such as iron tablets, cimetidine and the consumption of foods such as horseradish. This risk is reduced with the use of FIT. Faecal occult blood testing has been shown to reduce the mortality associated with colon cancer (6).
- Faecal immunochemical testing is more sensitive for advanced adenomas and colon cancer compared to faecal occult blood testing and as a result it is anticipated that the reduction in colon cancer mortality should be superior to faecal occult blood testing and may be the screening test of choice in our population.
- Faecal DNA tests evaluate for DNA mutations and methylation markers. When combining FIT with faecal DNA tests, FIT-DNA demonstrated a 92.3% sensitivity at CRC detection (7).
- **Endoscopic evaluation:** it can be done with flexible sigmoidoscopy and colonoscopy. The flexible sigmoidoscope evaluates the left-side of the colon up to the splenic flexure. Though it does not evaluate the entire colon, this method of endoscopic evaluation is useful since left-sided cancers are more common than right-sided cancers. However, it is important to note that the incidence of right-sided cancers is increasing (8). Sedation and oral bowel preparation are not usually required for this procedure, bowel preparation can be done with an enema. As a result, complications such as electrolyte abnormalities, dehydration, respiratory depression and colonic perforation are reduced in flexible sigmoidoscopy compared to colonoscopy. If a colonic cancer or polyp is found at flexible sigmoidoscopy, a colonoscopy should be performed to ensure there are no synchronous lesions. If flexible sigmoidoscopy is used for screening, it should be repeated every five years in patients with average risk. Since the right colon is not evaluated in flexible sigmoidoscopy, right-sided cancers or polyps can be missed. Stool tests can be combined with flexible sigmoidoscopy to improve the sensitivity. Colonoscopy allows for a full evaluation of the colon. It allows the location of tumours or polyps to be determined, the

presence of synchronous lesions to be determined and for biopsies to be taken for histological confirmation. Oral bowel preparation and sedation are required for the procedure. Dehydration especially in the elderly, electrolyte abnormalities, respiratory depression and colonic perforation are all complications of colonoscopy. Every patient with colorectal cancer should get a full colonic evaluation before surgery once there is no bowel obstruction or contraindications to colonoscopy, such as emergency presentation. Patients at average risk and with a normal colonoscopic screening should have a repeat in 10 years. The costs and availability of this test limits its usefulness as the screening method of choice in our population.

- **Radiological test:** CT colonography (CTC) is the newest modality of screening being used for colorectal cancer. It is less invasive compared to colonoscopy and the risk of bowel perforation is significantly reduced. This may be a suitable modality for use especially in the elderly population but oral bowel preparation is usually required. Techniques minimizing catharsis with stool tagging can be done in patients for whom full bowel preparation is difficult or contraindicated (9). Computed tomography colonography is also indicated in evaluating the remainder of the colon in patients with failed or incomplete colonoscopy or in whom colonoscopy is contraindicated (10). Every patient found to have a polyp or cancer on CTC should go on to have a colonoscopy. Computed tomography colonography does not allow biopsy for histological evaluation. Computed tomography colonography is repeated every five years when used for screening. Double contrast barium enema is no longer recommended as a screening modality for colorectal cancer but it retains a role in patients with incomplete colonoscopy.

Clinical staging of colorectal cancer

If possible, all patients with colorectal cancer should undergo CT scan of the chest, abdomen and pelvis before elective surgery (11). This is important because the liver is the most common site of metastasis and the lung is the second most common site of metastasis. Carcinomatosis is seen more often in patients with full thickness involvement of the bowel wall extending into the peritoneal cavity (12). Regional and distant nodal involvement are also well evaluated with CT scan. Synchronous colorectal metastasis is seen in approximately 25% of patients with colorectal cancer and approximately 50% will eventually develop metastasis to the liver (13). With this in mind, the staging CT scan is not only used to detect synchronous metastases but also forms a baseline for future reference with subsequent surveillance CT scans. The staging CT scan should be a triphasic scan with IV contrast of thin slices (14). For patients in whom administration of iodinated contrast material is contraindicated, a non-contrast CT scan of the chest and gadolinium based contrast MRI of the abdomen can be used for staging (15).

If CT or MRI is not available, chest X-ray and abdominal ultrasound can be substituted though the sensitivity of these investigations is significantly reduced compared to a CT scan of the chest, abdomen and pelvis (16).

Additional staging investigations are required for rectal cancer to determine the tumour (T) and node (N) stage. This is important because treatment decisions such as the use of neoadjuvant chemoradiotherapy will be dependent on this. The T and N stage can be assessed using pelvic MRI and transrectal ultrasound. Pelvic MRI utilizing a surface coil is preferred for the assessment of the T and N stage for rectal cancer. Transrectal endoscopic ultrasound (TEUS) is an option for assessing early stage tumours (T1-2, N0) but due to lack of depth penetration, is limited in large tumours and for other organ invasion. Pelvic MRI is superior to TEUS for the assessment of the circumferential resection margin.

The initial assessment of the circumferential resection margin is important since patients with a positive resection margin have a higher risk of local recurrence and a poorer prognosis. Patients whose initial assessment indicates a positive circumferential resection margin are candidates for neoadjuvant chemoradiotherapy. The presence of tumour or lymph nodes with metastases within 1mm from the resection margin is considered a positive circumferential resection margin (18).

The routine use of a PET/CT is not recommended for staging of colorectal cancers. Positron emission tomography/computed tomography may have a role to play in situations where the CEA is elevated but a metastasis cannot be found. It is also useful for indeterminate lesion detected by MRI or contrast enhanced CT scan and in the detection of local recurrence (19).

Surgical management

Colonic resection can be performed laparoscopically or open. There is no difference in oncologic outcomes with the method of resection chosen (20). However, laparoscopic resection provides additional benefits, which include: reduced postoperative pain, shorter hospital stay and better cosmetic outcome (21). Whichever method

is chosen, it is very important to ensure that sound oncologic principles are followed with the resection of colon cancer. Laparoscopic colectomy should only be performed by a surgeon who has advanced training or experience in laparoscopic colectomy (22). Patients who have an obstructing tumour, locally advanced tumour (T4) and extensive adhesions may not be candidates for laparoscopic colectomy (22).

Irrespective of the method chosen, at the beginning of the surgery, a thorough intra-abdominal examination should be performed to check for peritoneal metastasis, omental deposits and metastasis to solid organs such as the liver and spleen. Though imaging would have been performed before surgery, metastases that are sub-centimetre in size can be missed (14). If on examination, there is a suspicion of peritoneal metastasis, this can be confirmed by frozen section of a biopsy or cytological evaluation of peritoneal fluid or washings (23). Metastasis to solid organs can be confirmed by a wedge resection or core biopsy once there is no bleeding risk. The presence of peritoneal metastasis or metastasis to solid organs is considered Stage 4 disease and a decision should be made if the goal of treatment remains curative or now palliative. Such a scenario may warrant a resubmission of the patient's case for a multidisciplinary discussion.

The colectomy to be performed is determined by the presence of the tumour along with the arcade of vessels supplying the bowel. The regional lymph nodes draining the bowel containing the tumour will be present in this vascular arcade (24). A minimum of 12 lymph nodes should be resected for the lymphadenectomy to be considered adequate (25).

The names of the various colectomies based on these vascular arcades are:
- Right hemicolectomy
- Extended right hemicolectomy
- Left hemicolectomy
- Sigmoid colectomy
- Anterior resection
- Low anterior resection

A total mesorectal excision (TME) is the surgical procedure to ensure adequate lymphadenectomy in patients undergoing curative resection for rectal cancer (26). The mesorectum provides a natural boundary for rectal cancer spread. A TME excision should be done with sharp dissection, taking great care to remove the fascial envelope intact with the tumour. By removing the fascial envelope intact, this will reduce the spillage of tumour cells and the prevention of divest in the specimen that could result in tumour or cancer laden lymph nodes being left behind. Rectal cancers to the upper third/above the peritoneal reflection are treated similar to colon cancers where chemoradiation before surgery is not routinely practised (27). Rectal cancer to the middle third and lower third are treated with neoadjuvant chemoradiotherapy if the lesion is T3 or T4 and also if there is evidence of lymph node involvement. Upper and mid rectal tumour are treated with a low anterior resection, with a mesorectal horizontal transection 5 cm below the lower edge of the tumour to ensure removal of the lymph nodes draining the tumour. Rectal cancers to the distal third are treated with ultralow anterior resection with coloanal anastomosis or abdominoperineal resection (26). Abdominoperineal resection is the procedure of choice when the tumour encroaches on the anal sphincter (18). A distal resection margin of 2 cm or more is preferred for low rectal cancer. For patients undergoing an ultralow anterior resection, especially after neoadjuvant chemoradiotherapy, a temporary diverting loop ileostomy is sometimes used to protect the anastomosis, as the anastomotic leak risk exceeds 10%. Patients with anastomotic leaks have increased perioperative mortality and reduced cancer specific survival.

A Hartmann's type procedure is performed predominantly in patients who are assessed to have a high-risk of anastomotic leak, patients with pre-existing faecal incontinence, the elderly, emergency surgery and patients with large tumours. In this procedure, the rectosigmoid portion of the bowel is removed and the proximal colon is used to fashion an end-colostomy. The distal rectum or anus is closed as a pouch. A high percentage of patients with Hartmann's procedure will never get restoration of bowel continuity and every effort should be made to restore continuity at the initial surgery, if it is not risky for the patient.

Suspicious nodes outside the field of nodes draining the tumour should be sampled but extended lymphadenectomy is not recommended (29). Ideally a proximal and distal margin of 5 to 7 cm should be obtained to ensure removal of the pericolonic lymph nodes in colonic cancers (30). A positive resection margin confers a poor prognosis for the patient, hence the surgeon should be prepared to do an en bloc multivisceral resection and/ or resection of any adhesions involving the tumour to obtain a negative resection margin (31). Computed tomography or MRI will often indicate the need for multivisceral resection before surgery. The identification of the need for multivisceral resection before surgery will

allow the necessary specialties to be a part of multidisciplinary planning for the surgery. Patients requiring multivisceral resection may also be candidates for neoadjuvant therapies. Multivisceral resections for T4 rectal cancers commonly include the bladder, ovary, vagina and uterus. If the urinary bladder is involved, a partial cystectomy with or without re-implantation of the ureters maybe required. If the tumour invades the trigone of the bladder, a complete cystectomy with an ileal conduit or a neo-reservoir is required.

If the colon cancer is synchronous the options for resection are extended colectomy or segmental bowel resections. Extended colectomy is preferred when the synchronous tumour is due to underlying causes such as ulcerative colitis and FAP (32). Whenever possible, without putting the patient at increased risk, a primary bowel anastomosis should be performed. The anastomosis can be performed with staples or hand sewn. Stapled bowel anastomoses are quicker to perform and are associated with a reduced rate of anastomotic leakage, especially when used by more inexperienced surgeons (33).

Colonic cancer can also present with emergencies such as obstruction, bleeding and perforation. The management of colonic obstruction from cancer is dependent on whether the obstruction is right-sided or left-sided, as well as the age and clinical condition of the patient. Right-sided obstructing colonic cancer can be managed with a right hemicolectomy with primary anastomosis provided there are no contraindications to anastomosis and the patient is fit for surgery. There is increasing evidence that colonic stenting is an option for right-sided tumour. Obstructing left-sided colon cancer can be managed with colectomy, proximal diversion or colonic stenting as a bridge to resuscitation and resection at a later date (34). Colonic stenting can be associated with perforation of the colon and increase the risk of recurrence in patients with potentially curable disease (35).

Management of metastatic colon cancer

About 50% of patients with colon cancer will develop metastases (13). The common sites of metastases from colon cancer are liver, lung, ovary, retroperioneum and the peritoneal cavity (37). Most patients with colon cancer metastases will not be candidates for curative surgical resection. All cases of metastatic colorectal cancer should be discussed in a multidisciplinary meeting to determine the best method of management. Patients with resectable liver and/ or lung metastases should be offered surgery since surgery represents the only chance of a cure (38). The five-year survival of patients having R0 liver resection of colorectal metastases is 50% and survival at 10 years is 25% (39). Survival results of patients having liver resection for colorectal metastases continue to improve with the advances in chemotherapeutic agents and biologics. Metastatic colon cancer can present as synchronous metastases or metachronous metastases. Resectable synchronous metastatic disease to liver or lung can either be resected with the primary tumour or as a staged procedure (40).

Techniques such as downsizing of the tumour with chemotherapy, two staged liver resection and portal vein embolization can be used to make patients who are borderline resectable candidates for liver resection (41). Metastasectomy is not only recommended for patients with liver and lung metastasis, but also for select patients with metastasis to areas beyond the lung and the liver (42). The majority of patients undergoing metastasectomy will require perioperative chemotherapy (43). For patients with isolated metastases to the peritoneum, cytoreductive surgery and heated intraperiotoneal chemotherapy has been shown to be more effective than systemic chemotherapy (44).

If the metastatic disease is not resectable, a resection of the primary is only recommended for colonic obstruction, bleeding and perforation. Chemotherapy is a standard method of palliation for patients who are not candidates for metastasectomy but are fit enough for therapy (45). Colonic obstruction can be palliated with colonic stents and bleeding may be palliated with endoscopic methods or angiography with embolization.

Pathological assessment of the specimen

The role of the pathologist in evaluating specimens for colorectal cancer has changed dramatically, as they are no longer just for confirmation of malignant disease, but serves as clinical docent that help to ensure maintenance of high quality surgical care and onco-therapeutic management. In some centres they may even be the prompters for the genetic evaluation for hereditary disease.

It is very important that the pathologist be provided with as much information as possible. The use of preoperative therapies such as chemoradiotherapy can cause a complete pathologic response, especially in rectal carcinomas. If the pathologist is aware that preoperative therapies were given and the location of the tumour was provided, extra efforts can be made to assess for any residual cancer cells or fibrosis in response to treatment. Ideally, the pathologist should examine the specimen fresh since fixation with formalin can cause significant shrinkage of tissue. However, an examination of the

fresh specimen by the pathologist may not be possible in centres that do not have a pathologist on staff or in the case when the surgeries are conducted after work hours. The specimen should be oriented by the surgeon for the pathologist and the proximal and distal margins should be identifiable. Any points of close or potentially positive margin should be marked for identification.

Not all colonic tumours present to the pathologists in the form of colectomy specimens. In early stage disease, *ie* neoplastic glandular invasion through the muscularis mucosae into but not beyond the submucosa, pT1 tumours; they can be removed endoscopically *via* polypectomy and endoscopic submucosal dissection (ESD). These tumours are then evaluated microscopically for resection margin status and the possibility of harbouring high-risk features of lymph node involvement, which serves as a statistical guide to determine whether or not to offer surgical resection (46).

The margins of all resected specimens (endoscopic or otherwise) should be marked by the pathologist and the distance of the tumour from the margins reported. The distal and proximal luminal margins of colectomy specimens are rarely ever involved. It has been argued in cases that if the tumour lies > 5 cm away from the margin macroscopically, the chances that these margins are positive approaches zero (47), and we have never seen a case where this is not true. The surgical resection margin that is now currently in vogue is the circumferential/radial margin (CRM). This margin is the adventitial soft-tissue margin in closest proximity to the deepest point of tumour penetration. This tumour extension could be direct, within lymph nodes, or within or around neural or vascular structures. If the tumour comes to within 1 mm of this margin it is considered to be positive and the risk of local recurrence is increased (48). Technically, the serosal surface is not a surgical margin, however, tumours that invade along the antimesenteric border has the potential to extend to involve this surface, which results in an increased risk or peritoneal dissemination. If the tumour extends beyond the elastic lamina of the serosa it is said to have a lower disease free survival than those that do not, but this still remains controversial (49).

The anatomical site of the tumour must be recorded and it is also advised that its location below or above the peritoneal reflection should be too, if applicable. The tumour sidedness may impact screening, follow-up and given the possible difference in tumour biology, it may even assist in guiding therapy (50).

Rectal carcinomas highlight the role that surgical competence plays in the management of colorectal disease. The complete removal of the mesorectal envelope with the diseased rectum intact have been shown to achieve an adequate CRM and remove the most likely involved lymph nodes which results in a decrease in the recurrence rate and prolongs the patient's overall survival (51).

Perforation of colonic viscera with tumour, iatrogenic and otherwise, is rare. When this is present it is associated with increased mortality not only from peritonitis but it may also result in seeding of the peritoneum by tumour cells and increased local recurrence rate (52).

The majority of colorectal carcinomas are conventional adenocarcinomas and the other common types are medullary carcinomas, neuroendocrine carcinomas (small cell > large cell), mixed carcinomas (adenoneuroendocrine, adenosquamous, *etc*) and pure squamous cell carcinoma. Medullary carcinoma is a distinctive subtype of carcinomas which are strongly associated with right-sidedness, increased tumour infiltrating lymphocytes and microsatellite instability [MSI] (53). This subtype can be seen in acquired DNA mismatch repair (MMR) gene abnormalities and in Lynch syndrome. Certain subtypes of adenocarcinomas, *eg* mucinous and signet ring cell variants may also be associated with MSI-H status or other genetic abnormalities but even when not associated with such, they have an infiltrating pattern of growth which is a poor prognostic factor.

Tumour grading (in colorectal carcinoma) for the most part has been unchanged since the time of Dukes' seminal paper (36). Currently grading in pathology has become somewhat contracted and the World Health Organization (WHO) two-tiered grading system has been shown to be most reproducible while still maintaining prognostic significance (54). Nevertheless, for gastrointestinal (GI) tumours three- or four-tiered systems are still currently in use. The overall grade ascribed to colonic tumours is the predominant grade pattern identified under the microscope.

The depth of tumour invasion is one of the most important tenets in colon cancer reporting and this indicates what the pT portion of the pTNM stage is going to be. The pT staging is as follows:

- pTis: Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae).
- pT1: Tumour invades the submucosa (through the muscularis mucosae but not into the muscularis propria).

- pT2: Tumour invades the muscularis propr.
- pT3: Tumour invades through the muscularis propria into pericolorectal tissues.
- pT4: Tumour invades the visceral peritoneum or invades or adheres to adjacent organ or structure.
  - o pT4a: Tumour invades through the visceral peritoneum (including gross perforation of the bowel through tumour and continuous invasion of tumour through areas of inflammation to the surface of the visceral peritoneum).
  - o pT4b: Tumour directly invades or adheres to adjacent organs or structures.

The majority of tumours seen in our institution are pT3 tumours (55), however, we tend to see a fair share of pT4. The sequelae of serosal surface involvement is mentioned above.

It is recommended that a minimum of 12 regional lymph nodes should be examined in order to properly stage the patient, however, efforts should be made to examine all nodes present in the specimen. The pN staging is as follows:

- pN0: No regional lymph node metastasis.
- pN1: One to three regional lymph nodes are positive (tumour in lymph nodes measuring ≥ 0.2 mm), or any number of tumour deposits are present and all identifiable lymph nodes are negative.
  - o pN1a: One regional lymph node is positive.
  - o pN1b: Two or three regional lymph nodes are positive.
  - o pN1c: No regional lymph nodes are positive, but there are tumour deposits in the subserosa, mesentery, or non-peritonealized pericolic, or perirectal/mesorectal tissues.
- pN2: Four or more regional lymph nodes are positive
  - o pN2a: Four to six regional lymph nodes are positive
  - o pN2b: Seven or more regional lymph nodes are positive.

In the majority of cases the recommended twelve lymph nodes are identified, however, in situations where the surgical excision of the pericolonic tissues borders on inadequacy and the patient has undergone neoadjuvant oncotherapy, it may be difficult to attain the recommended standard. Complete removal and fixation of the pericolonic fat in Bouin's solution may assist in achieving higher lymph node yields. One must note, that in some cases, even with the use of ancillary tests (histochemical and immunohistochemical stains), it may be difficult to determine whether or not a tumour deposit is a completely effaced lymph node. If no lymph nodes are positive the tumour should be ascribed a nodal status of N1c, however, if positive nodes are present in the specimen the tumour deposits are separately recorded.

Lymphovascular [small vessel] (56), vascular (large vessel) and perineural invasion (57) have all been established adverse prognostic factors that should be recorded on colorectal carcinoma pathology reports. Both small vessel disease and perineural involvement are associated with nodal tumour involvement. Large vessel disease can either be intramural or extramural. These are best identified with the use of elastin stains. Extramural mural venous involvement is an independent predictor of liver metastasis (49).

Tumour budding is defined as tumour cells arranged singly or in small clusters of < 5 cells. They are usually at the leading edge of the tumour, however, intratumoural tumour buds may also be identified. Nevertheless, reporting of tumour buds remains optional. But just like its most similar counterpart, lymphovascular invasion, it will most likely become mandatory. High-risk tumour budding is associated with nodal involvement and has attained the status as a poor prognostic factor (58). The extent of lymph node resection in our population can be further optimised (58).

The pathological staging of colon cancer is currently being done by the 8th edition of the AJCC. In this edition,
T1 - tumours involve the submucosa;
T2 - tumours penetrate through the submucosa into the muscularis propria;
T3 - tumours penetrate through the muscularis propria;
T4a - tumours directly penetrate to the surface of the visceral peritoneum; and
T4b - tumours directly invade or are adherent to other organs or structures.

N1a - (1 positive lymph node)
N1b - (2–3 positive lymph nodes)
N1c - (tumour deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis *ie*, satellite tumour nodules)
N2a - (4–6 positive nodes)
N2b - (7 or more positive nodes)

M1a - when metastases are to only one site/solid organ (including to lymph nodes outside the primary tumour regional drainage area) are positive.
M1b - is used for metastases to multiple distant sites or solid organs, exclusive of peritoneal carcinomatosis.

M1c - category for peritoneal carcinomatosis with or without blood-borne metastasis to visceral organs (59).

At a minimum, the pathologist should provide the following: tumour grade, depth of penetration, involvement of adjacent organs, perforation, lymphovascular invasion, perineural invasion, number of lymph nodes involved, margins (proximal, distal and circumferential margins), as well as, the presence of distant metastases.

To ensure that the base requirements are submitted it is strongly advised that a colorectal cancer reporting checklist is used (60). An example of one that is currently utilized our institution is present below [Appendix 2].

Adjuvant therapy

The decision to offer systemic adjuvant therapy is dependent on the stage of the disease and the risk assessment of the patient. Patients are classified as high-risk if they have poorly differentiated histology or any of the following: MSI-H, LVI, less than 12 nodes removed, bowel obstruction, perineural invasion, localized perforation, close or positive margins. Low-risk patients have Stage 1 disease or MSI-high disease. The prognosis for low-risk disease is so good that adjuvant chemotherapy is not recommended.

Patients with low risk Stage 2 disease are usually not offered adjuvant chemotherapy. If chemotherapy is offered the agents of choice are capecitabine or 5-fluorouracil and leucovorin (5-FU/LV). High-risk Stage 2 patients are treated with either observation or chemotherapy. The chemotherapeutic agents of choice are 5-FU/LV, capecitabine, CapeOX, FOLFOX or FLOX (28). Oxaliplatin offers no additional benefit in Stage 2 disease without high-risk features (61).

Chemotherapy is recommended for all Stage 3 diseases. The regimens of choice are FOLFOX or CapeOX (62, 63).

It is now standard practice to test colon cancer patients for microsatelitte instability (MSI) because this can help in the decision-making process for adjuvant chemotherapy. Microsatelitte instability occurs when the MMR protein is defective. A defective MMR gene can occur from mutation or modification such as methylation. Mutations of the MMR gene, such as MLH1, MSH2, MSH6, PMS and EpCAM, are associated with Lynch syndrome. Tumours with MSI are further classified in to MSI-high or MSI low. Microsatelitte instability-high tumours are often associated with Stage 2 and rarely associated with Stage 4 disease, as such MSI-high tumours typically confer a good prognosis. Despite the positive prognosis, MSI-high tumours have been shown to have reduce benefit from fluoropyrimidine chemotherapeutic agents. Patients with Stage 2 disease and MSI-high have a good prognosis and do not require chemotherapy, even if the colon cancer is poorly differentiated.

Routine testing of Stage 1, 2 and 3 disease for KRAS/NRAS is not recommended. However, patients with metastatic colon cancer should be tested for mutations in the KRAS and the NRAS genes. Patients with these genes mutation should not be treated with anti-EGFR (epidermal growth factor receptor) agents, such as cetuximab and panitumumab, because they have been shown to have no benefit as immunotherapy whether for single or combination use. Patients who do not test positive for the KRAS and NRAS mutations are said to have wild type KRAS and NRAS genes. Interestingly enough, though some patients with wild type KRAS and NRAS will respond to anti-EGFR agents, not all patients with wild type KRAS and NRAS genes will respond to those medications. As such, additional testing is required for these patients to determine if they have a mutation in the BRAF gene, which will help to predict which patient with wild type KRAS/NRAS will not respond to anti-EGFR medications.

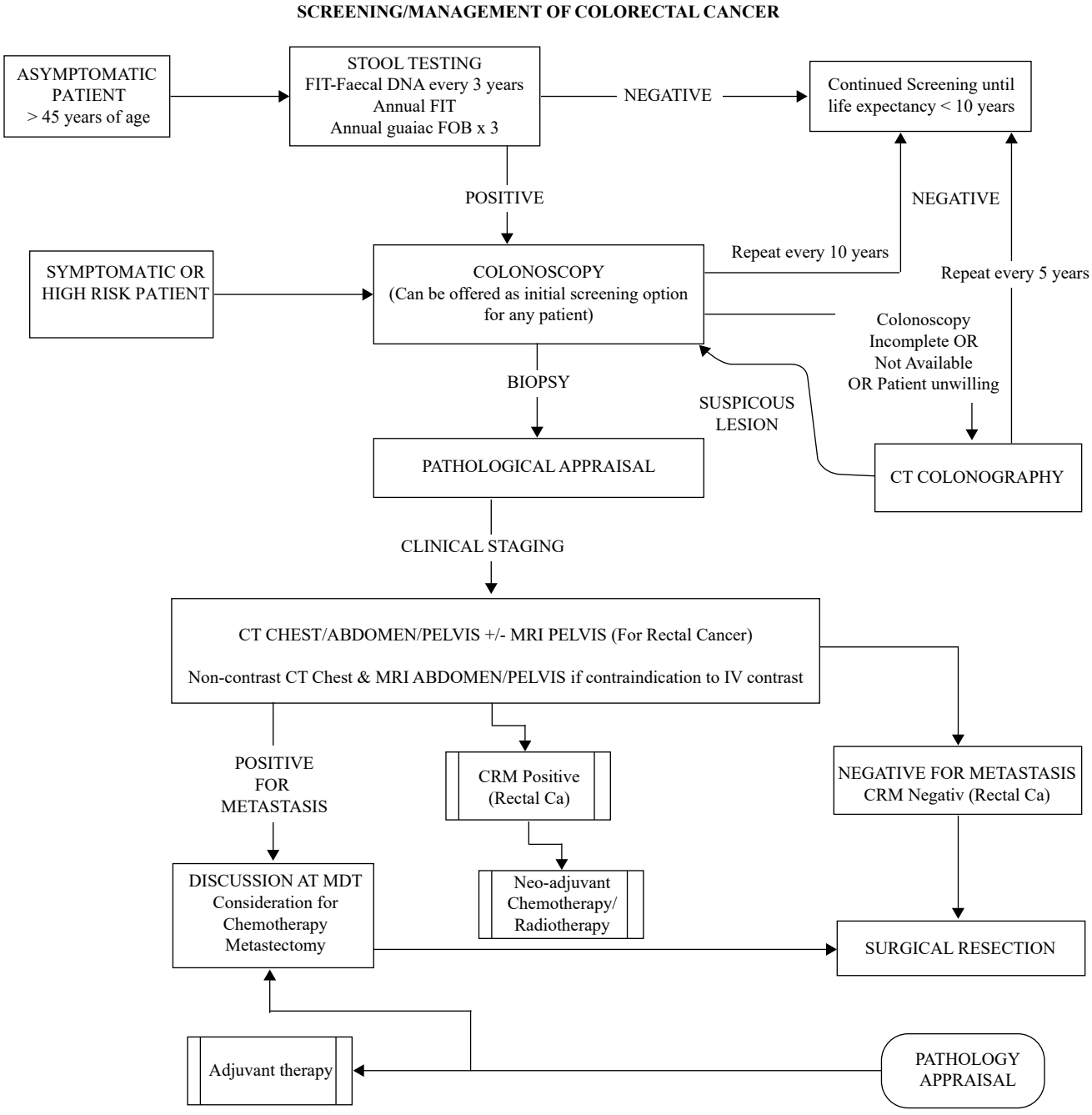
Monitoring of colon cancer survivors

There is no agreed international standard on how to manage colorectal cancer survivors. We recommend that patients treated for Stage 2 and 3 disease should be seen regularly because of the risk for recurrence and also because some patients with recurrence are candidates for curative treatment. A physical examination every six months for five years along with six monthly CEA for five years in those patients with CEA that was elevated before surgery but normalized after surgery. A CT scan of the chest, abdomen and pelvis every six months for five years although recommended may be excessive and done annually for the first three years after surgery when it is likely to give maximum benefit is more practical. As with preoperative staging, follow-up with non-contrast CT chest and MRI abdomen for those patients in whom iodinated contrast cannot be administered is an option. Although not preferred, abdominal ultrasound and chest X-ray can be substituted if CT scan or MRI is not available. Patients who have a high-risk of recurrence and patients who potentially resectable may require more intensive three monthly follow-up. A colonoscopy should be performed within a year of the initial curative surgery for colorectal cancer. The frequency of subsequent colonoscopies will be dependent on the outcome of the previous colonoscopy. If the colonoscopy performed

after curative surgery is normal, subsequent colonoscopies can be performed every five years (64). Patients with a persistently elevated CEA or a rising CEA after surgery should be assessed with a complete history, examination, CT scan of the chest, abdomen and pelvis as well as a colonoscopy PET/CT is recommended when a cause for the elevated CEA cannot be found. Positron emission tomography/computed tomography is also recommended in patients who are candidates for resection of metastasis, to exclude metastasis elsewhere.

For young patients with colorectal cancer and patients from high-risk families, genetic testing should be done to exclude known genetic conditions, such as familial adenomatous polyposis syndrome and hereditary non-polyposis colon cancer syndrome. A positive test for genetic conditions causing colon cancer will allow secondary prevention measure such as, increase surveillance, prophylactic colectomy and screening for others cancers that are associated with that particular syndrome.

Appendix 1: Management Flowchart



Appendix 2: Pathology Reporting Checklist for Colorectal Cancer

Type of Procedure:
Tumour Type:

Grade (Differentiation):	Well	} Low Grade
	Moderately	}
	Poorly	} High Grade
	Undifferentiated	}

Location:
Size (greatest dimension):
Depth of invasion:

Perforation:	Absent:	Present:	Tumour:	Inflammatory:
Lymphovascular invasion: [Small vessel- intratumoural]		Present	Absent	Indeterminate
Venous invasion: [Large vessel- peritumoural]		Present	Absent	Indeterminate
Perineural:		Present	Absent	Indeterminate
Borders:		Infiltrating		Pushing
Infiltrating Lymphocytes:		Absent		Present:
Intraepithelial	Peritumoural		Crohn's-like	

Treatment Effects: (Mandard): Not applicable TRG1 (No residual)
TRG2 (Rare residual cells) TRG3 (Fibrosis > tumour)
TRG4 (Tumour > fibrosis) TRG5 (No regression)

Margins:

Proximal:	Involved	Not Involved	:
Distal:	Involved	Not Involved	:
Circumferential (Radial):	Involved	Not Involved	: Distance_____
Visceral peritoneum:	Involved	Not Involved	:

Lymph nodes:	Macro#: _____ (≥ 2 mm)	Micro#:_____ (0.2- < 2.0 mm)	ITC#: _____ (< 0.2 mm)

Non-tumourous bowel:

Staging: TNM: pT N M

REFERENCES

1. Gibson TN, Blake G, Hanchard B, Waugh N, McNaughton D. Age-specific incidence of cancer in Kingston and St Andrew, Jamaica, 1998-2002. West Indian Med J 2008; **57:** 81–9.
2. McFarlane MEC, Plummer JM, Leake PA, Williams, NP, Ferron-Boothe D, Meeks-Aitken N. Colorectal cancer in Jamaica: patterns and anatomical distribution, West Indian Med J 2014; **63: (Suppl 4)** 48.
3. Plummer JM, Leake PA, Ferron-Boothe D, Roberts PO, Derek I, McFarlane ME et al. Colorectal cancer survival in Jamaica. Ann Med Surg 2016; **6:** 26e29
4. Tammana VS, Laiyemo AO. Colorectal cancer disparities: issues, controversies and solutions, World J Gastroenterol 2014; **20:** 869–76.
5. Rahman R, Schmaltz C, Jackson CS, Simoes EJ, Jackson-Thompson J, Ibdah JA. Increased risk for colorectal cancer under age 50 in racial and ethnic minorities living in the United States. Cancer Med 2015; **4:** 1863–70.
6. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993; **328:** 1365–71.
7. Ladabaum U, Mannalithara A. Comparative effectiveness and cost effectiveness of a Multitarget Stool DNA Test to screen for colorectal neoplasia. Gastroenterology 2016; **151:** 427.
8. Leung WK, Chen WQ, Gu L, Long D, Law WL. Distributions of colorectal cancer in two Chinese cities with contrasting colorectal cancer epidemiology. J Gastroenterol Hepatol 2015; **30:** 1726–30.
9. Utano K, Nagata K, Honda T, Mitsushima T, Yasuda T, Kato T et al. Diagnostic performance and patient acceptance of reduced-laxative CT colonography for the detection of polypoid and non-polypoid neoplasms: a multicenter prospective trial. Radiology 2017; **282:** 399–407.
10. Scalise P, Mantarro A, Pancrazi F, Neri E. Computed tomography colonography for the practicing radiologist: a review of current recommendations on methodology and clinical indications. World J Radiol 2016; **5:** 472–483.
11. Engstrom PF, Arnoletti JP, Benson AB 3rd, Chen YJ, Choti MA, National Comprehensive Cancer Network et al. NCCN clinical practice guidelines in oncology: rectal cancer. J Natl Compr Canc Netw 2009; **7:** 838–81.
12. Sugarbaker PH. Colorectal cancer: prevention and management of metastatic disease. BioMed Research International 2014. Article ID: 782890.
13. Meyerhardt J, Saunders M. (eds) Dana Farber Cancer Insitute: Colorectal Cancer. Philadelphia, USA: Mosby; 2003.
14. So JS, Cheong C, Oh SY, Lee JH, Kim YB, Suh KW. Accuracy of preoperative local staging of primary colorectal cancer by using computed tomograpgy. Ann Coloproctol 2017; **33:** 192–96.
15. Fowler KJ, Kaur H, Cash BD, Feig BW, Gage KL, Garcia EM et al. Expert panel on gastrointestinal imaging. ACR appropriateness criteria (®) pretreatment staging of colorectal cancer. J Am Coll Radiol 2017; **14:** 234–44.
16. Simunovic M, Stewart L, Zwaal C, Johnston M and the Diagnostic imaging guidelines panel. Cross-sectional imaging in colorectal cancer. April 12, 2006. www.cancercare.on.ca/pdf/pebcdicrc.pdf
17. Purkayastha S, Tekkis PP, Athanasiou T, Tilney HS, Darzi AW, Heriot AG. Diagnostic precision of magnetic resonance imaging for preoperative prediction of the circumferential margin involvement in patients with rectal cancer. Colorectal Dis 2007; **9:** 402–11.
18. Smith A, Driman D, Spithoff K, McLeod R, Hunter A, Rumble RBv et al. Optimization of surgical and pathological quality performance in radical surgery for colon and rectal cancer: Margins and Lymph Nodes Guideline Based Care (PEBC) and CCO's Surgical Oncology Program. Developed by the expert panel on colon and rectal cancer surgery and pathology. Cancer Care Ontario Evidence-Based Series#17-4: Section 1. Report Date: April 17, 2008
19. Falconer R, Connor S, Balasingam A, Eglinton T. Does positron emission tomography/computed tomography change management in colorectal cancer? (published online ahead of print October 27, 2016). ANZ J Surg. doi: 10.1111/ans.13798. Accessed July 23, 2017.
20. Green BL, Marshall HC, Collinson F, Quirke P, Guillou P, Jayne DG et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 2013; **100:** 75–82.
21. Ng LW, Tung LM, Cheung HY, Wong JC, Chung CC, Li MK. Hand-assisted laparoscopic versus total laparoscopic right colectomy: a randomized controlled trial. Colorectal Dis 2012; **14:** 612–17.
22. Ota DM, Nelson H, Weeks JC. Controversies regarding laparoscopic colectomy for malignant diseases. Curr Opin Gen Surg 1994: 208–13.
23. Kanellos I, Demetriades H, Zintzaras E, Mandarali A, Mantzoros I, Betsis D. Incidence and prognostic value of positive peritoneal cytology in colorectal cancer. Dis Colon Rectum 2003; **46:** 535–9.
24. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P et al. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol 2010; **28:** 272–78.
25. Jessup JM, Goldberg RM, Asare EA, Benson III AB, Brierley JD, Chang GJ et al. Colon and rectum. In: Armin MB, Greene FJ, Byrd DR,

Brookland RK, Washington MK, eds. AJCC Cancer Staging. 8th ed. New York, NY: Springer; 2017.
26. Lindsetmo R, Joh Y, Delaney CP. Surgical treatment for rectal cancer: an international perspective on what the medical gastroenterologist needs to know. World J Gastroenterol 2008 7; **14:** 3281–89.
27. Schrag D. Evolving role of neoadjuvant therapy in rectal cancer. Current Treat Oncol 2013; **14:** 350–64.
28. Benson AB, 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004; **22:** 3408–19.
29. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y et al. Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol 2012; **17:** 1–29.
30. Hashiguchi Y, Hase K, Ueno H, Mochizuki H, Shinto E, Yamamoto J. Optimal margins and lymphadenectomy in colonic cancer surgery. Br J Surg 2011; **98:** 1171–78.
31. Gezen C, Kement M, Altuntas YE, Okkabaz N, Seker M, Vural S et al. Results after multivisceral resections of locally advanced colorectal cancers: an analysis on clinical and pathological t4 tumors. World J Surg Oncol 2012; **10:** 39.
32. Ross H, Steele SR, Varma M, Dykes S, Cima R, Buie WD et al. Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for the surgical treatment of ulcerative colitis. Dis Colon Rectum 2014; **57:** 5–22.
33. Slieker JC, Daams F, Mudler IM, Jeehel J, Lange JF. Systematic review of the techniques of colorectal anastomosis. JAMA Surg 2013; **148:** 190–201.
34. Huang X, Lv B, Zhang S, Meng L. Preoperative colonic stents versus emergency surgery for acute left-sided malignant colonic obstruction: a meta-analysis. J Gastrointest Surg 2014; **18:** 584–91.
35. Lee J-M, Byeon J-S. Colorectal stents: current ttatus. Clin Endosc 2015; **48:** 194–200.
36. Dukes C. The classification of cancer of the rectum. J Pathol 1932; **35:** 323–32.
37. Abeloff M, Marmitage J, Niederhuber J, Kastan MB, McKenna WG(eds). Clinical Oncology. 3rd edition. Philadelphia, USA: Elsevier Churchill Livingstone, 2004.
38. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Komprat P, Gonen M et al. Actual 10-year survival after resection of colorectal liver metastases de nes cure. J Clin Oncol 2007; **25:** 4575–80.
39. Shah SA, Bromberg R, Coates A, Rempel E, Simunovic M, Gallinger S. Survival after liver resection for metastatic colorectal carcinoma in a large population. J Am Coll Surg 2007; **205:** 676–83.
40. Quan D, Gallinger S, Nhan C, Auer RA, Biagi JJ, Fletcher GG et al. The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review. Surgery 2012; **151:** 860–70.
41. Folprecht G, Gruenberger T, Bechstein W, Raab HR, Weitz J, Lordick F et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). Ann Oncol 2014; **25:** 1018–25.
42. Elias D, Liberale G, Vernerey D, Pocard M, Ducreux M, Boige V et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. Ann Surg Oncol 2005; **12:** 900–9.
43. Nordlinger B, Van Cutsem E, Gruenberger T, Glimelius B, Poston G, Rougier P et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. Ann Oncol 2009; **20:** 985–92.
44. Cashin PH, Mahteme H, Spång N, Syk I, Frodin JE, Torkzad M et al. Cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases: a randomised trial. Eur J Cancer 2016; **53:** 155–62.
45. Alawadi Z, Phatak UR, Hu CY, Bailey CE, You YN, Kao et al. Comparative effectiveness of primary tumor resection in patients with stage IV colon cancer. Cancer 2017; **123:** 1124–33.
46. Beaton C, Twine CP, Williams GL, Radcliffe AG. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. Colorectal Dis 2013; **15:** 788–97.
47. Keighley MR, Hall C. Anastomotic recurrence of colorectal cancer--a biological phenomenon or an avoidable calamity? Gut, 1987.
48. Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, Dixon MF, Mapstone NP et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg 2002; **235:** 449–57.
49. Grin A, Messenger DE, Cook M, O'Connor BI, Hafezi S, El-Zimaity H et al. Peritoneal elastic lamina invasion: limitations in its use as a prognostic marker in stage II colorectal cancer. Hum Pathol 2013; **44:** 2696–705.
50. Cremolini C, Antoniotti C, Lonardi S, Bergamo F, Cortesi E, Tomasello G et al. Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Ann Oncol 2018 Apr 20. doi: 10.1093/annonc/mdy140. [Epub ahead of print]
51. Arbman G, Nilsson E, Hallbook O, Sjodahl R. Local recurrence following total mesorectal excision for rectal cancer. Br J Surg 1996; **83:** 375–79.
52. Bundgaard NS, Bendtsen VO, Ingeholm P, Seidelin UH, Jensen KH. Intraoperative tumor perforation is associated with decreased 5-Year survival in colon cancer: a Nationwide Database Study. Scand J Surg 2017; **106:** 202–10.
53. Fiehn AM, Grauslund M, Glenthøj A, Melchior LC, Vainer B, Willemoe GL. Medullary carcinoma of the colon: can the undifferentiated be differentiated? Virchows Arch 2015; **466:** 13–20.
54. Darragh TM, Colgan TJ, Thomas-Cox J, Heller DS, Henry MR, Members of the LAST Project Work Groups et al. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Int J Gynecol Pathol 2013; **32:** 76–115. Erratum in: Int J Gynecol Pathol 2013; **32:** 432. Int J Gynecol Pathol 2013; **32:** 241.
55. Graham RP, Plummer JM, West KA, Williams NP. Adequacy of lymph node harvesting in colorectal cancer management: improving standards, ensuring quality. West Indian Med J 2012; **61:** 134–8.
56. Lim SB, Yu CS, Jang SJ, Kim TW, Kim JH, Kim JC. Prognostic significance of lymphovascular invasion in sporadic colorectal cancer. Dis Colon Rectum 2010; **53:** 377–84.
57. Ueno H, Shirouzu K, Eishi Y, Yamada K, Kusumi T, Kushima R et al; Study Group for Perineural Invasion projected by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). Characterization of perineural invasion as a component of colorectal cancer staging. Am J Surg Pathol 2013; **37:** 1542–49.
58. Lugli A, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol 2017; **30:** 1299–311.
59. Amin MB, Edge S, Greene FL, Byrd DR, Brookland RK, Washington MK et al. eds. AJCC Cancer Staging Manual (8th Edition). New York: Springer; 2016.
60. Sluijter CE, van Lonkhuijzen LR, van Slooten HJ, Nagtegaal ID, Overbeek LI. The effects of implementing synoptic pathology reporting in cancer diagnosis: a systematic review. Virchows Arch 2016; **468:** 639–49.
61. Casadaban L, Rauscher G, Aklilu M, Villenes D, Freels S, Maker AV. Adjuvant chemotherapy is associated with improved survival in patients with stage II colon cancer. Cancer 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27417445
62. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004; **350:** 2343–51.
63. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011; **29:** 1465–71.

64. Earle C, Annis R, Sussman J. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer. Cancer Care Ontario 2013.