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Rectal cancer: a review

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Abstract

Rectal cancer is the second most common cancer in large intestine. The prevalence and the number of young patients diagnosed with rectal cancer have made it as one of the major health problems in the world. With regard to the improved access to and use of modern screening tools, a number of new cases are diagnosed each year. Considering the location of the rectum and its adjacent organs, management and treatment of rectal tumor is different from tumors located in other parts of the gastrointestinal tract or even the colon. In this article, we will review the current updates on rectal cancer including epidemiology, risk factors, clinical presentations, screening, and staging. Diagnostic methods and latest treatment modalities and approaches will also be discussed in detail.

Keywords: Rectal cancer, Treatment, Review, Screening, Diagnosis, Staging, Treatment.

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Introduction

Rectal cancer is one of the frequent human malignant neoplasms and the second most common cancer in large intestine. Colorectal cancers (CRCs) are the second most common cancers in human and major public health problems worldwide (1).

Considering the different embryonic origin of the colon and the rectum, cancers arising from these two locations of the large bowel have several different distinctive features. The colon is arising from the midgut and the rectum from the hindgut. Gradient of hormone receptors are also different. These two serve different functions as well. The rectum is exposed to a more concentrated fecal matter in a direct way. Moreover, undigested matter traveling through the colon is coated with alkaline mucus. The different levels of pH in the colon and rectum may also influence susceptibility to environmental factors. (2) Therefore, different risk factors may be involved in these tumors.

With due regard to the location of the rectum within the pelvic cavity and its relation with genitourinary organs, rectal tumors may present with special clinical manifestations different from other cancers within the gastrointestinal tract. During the past few years, diagnosis and management of rectal tumors as a separate entity from other parts of the colon has been considered greatly. With the help of rectosigmoidoscopy and new imaging modalities, these cancers can be diagnosed at earlier stages. Multimodality treatment approaches, including surgery, preoperative and postoperative chemo- or radiotherapies, have led to a better survival in these patients.

In this review article, we will review the current updates on rectal cancer. An overview on anatomy, epidemiology and risk factors will be discussed first and then we will go through clinical presentations, current staging and screening protocols and latest approaches on diagnosis and treatment modalities of rectal cancer.

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Anatomy of Rectum

The rectum is final portion of the large intestine between the sigmoid colon and the anal canal. It starts from the rectosigmoid junction at the level of the third sacral vertebra or the sacral promontory and terminates at the level of the anorectal ring. It is about 12-15 centimeters in length with an internal caliber similar to the sigmoid colon at the commencement. It dilates near its termination, forming the rectal ampulla.

Anatomic landmarks of rectum should be considered due to its importance in tumor staging, assessment of resectability and planning of surgery. The anal verge, most distal part of the anal canal, is an important surgical landmark. Lower border of the tumor located in rectum should be determined relative to this line. At the junction of the upper two-thirds and lower one-third, rectum separates into intra- and extraperitoneal portions by the anterior peritoneal reflection. Rectovesical pouch is a peritoneum-lined recess between the rectum and the posterior aspect of the bladder. The rectum is separated posteriorly from the pelvic nerves and the presacral venous by the presacral fascia. Denonvilliers' (rectoprostatic) fascia is located between the anterior aspect of the rectum and the prostate and seminal vesicles in men and the vagina in women.

Anatomic position of the rectal tumor in relation to anal sphincters is also an important issue in selecting patients for sphincter preservation surgery. Anal sphincter complex include internal and external sphincters separated by an intersphincteric plane. The internal sphincter is a thickened continuation of the inner smooth muscle layer of the rectum. The external sphincter is an extension of the puborectalis muscle and begins at the inferior insertion of the levator ani muscles.

Rectal wall comprises five layers including mucosa, submucosa, inner circular muscle, outer longitudinal muscle, and serosa. The proximal one third of the rectum is covered by peritoneum; but the mid and lower rectum lack serosa. Valves of Houston are three mucosal folds extending into the rectal lumen. The dentate or pectinate line is the transitional zone between columnar rectal mucosa and squamous anoderm. It is surrounded by columns of Morgagni which are longitudinal mucosal folds.

Anal transition zone is the 1 to 2 cm of mucosa just proximal to the dentate line with histologic characteristics of columnar, cuboidal, and squamous epithelium. (3-5)

Epidemiology

Rectal cancers are the second most common (28%) cancers in large intestine after proximal colon cancers (42%) (1). Therefore, rectal cancers have always been considered as a part of CRCs in related epidemiological studies. CRC, as one of the major public health problems, is the third most common cancer in men and the second in women in the world with a lifetime probability of 4.7-5% (6). It has also been reported as the third leading cause of cancer death in men and women in the United States (1).

Although geographical incidence of CRC varies worldwide, its pattern is similar among men and women. Currently, CRCs seem to be more common in developed regions of the world. The highest estimated rates is in Australia/New Zealand (44.8 and 32.2 per 100,000 in men and women respectively), and the lowest in Western Africa (4.5 and 3.8 per 100,000) (6). According to a recent data from the United States, approximately 136,830 new cases of CRC are diagnosed annually, including 40,000 rectal cancers (7). It is also estimated that 71,830 men and 65,000 women will be diagnosed with colorectal cancer and 26,270 men and 24,040 women will die of the disease in this country in 2014 (1).

With regard to the improved access to and use of screening and standard treatment, overall incidence rate has decreased by approximately 3% per year during the past decade. Although a large drop in the number of rectal cancers has been found in adults aged 65 and older (-1.5% for 50-64 years and 4.3% for ages above 65), this rate

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has increased by 1.8% annually for rectal cancers among adults younger than 50 years. In contrast to proximal and distal colon cancers, the median age at diagnosis for rectal cancer is younger (63 years in men and 65 years in women). There is also a significant variation in tumor location by age, with a notable decrease in rectal tumors in older age. Male to female incidence rate ratio for rectal cancers also varies among different age groups as follows: 1.10 for 0-49 years, 1.19 for 50-64 years, 1.27 for 50-79 years, and 1.29 for those 80 years and older (1).

Rectal cancer's overall 5-year survival rate (66.5%) is slightly higher than for colon cancers (64.2%), but stage-specific survival is similar. Moreover, the survival rates do not vary significantly by sex. Mortality rate is 30-40% higher in men than in women, though this difference varies by age. Race and ethnicity can also affect the mortality rate; for instance recent reports from the United States show death rates in blacks are more than double those in Asians/Pacific Islanders (1). Although CRCs are more common in more developed regions, their mortality seems to be higher in the less developed regions of the world, reflecting a poorer survival in these countries. Highest estimated mortality rates in both sexes has been reported from Central and Eastern Europe (20.3 per 100,000 for men, 11.7 per 100,000 for women), and the lowest from Western Africa (3.5 and 3.0, respectively) (6).

Risk Factors

A large number of reviews and studies have considered risk factors in CRCs generally, however, a limited number of them have tried to separate environmental and genetic factors that can affect the likelihood of colon and rectal cancers (2,8).

Studies have confirmed that a family history of colorectal cancer appears to affect risk for colon cancer more strongly than risk for rectal cancer (2). Hereditary syndromes such as familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), and MUTYH-associated polyposis (MAP) are samples of familial colon cancer syndromes. Moreover, patients with a personal history of CRCs or adenomatous polyps of the colon are at risk for the future development of colon cancer. Prevalence of K-ras mutations and mutation patterns in the p53 gene in rectal cancers are also different from those seen in colon cancers (9).

Age and gender are important risk factors affecting both colon and rectal cancers (2). A statistically significant increased risk for colon cancer has been reported with increased height. For the Body Mass Index (BMI), there is a different effect on CRCs between men and women. A systematic review has reported that each 5 kg/m2 increase in BMI is associated with a 24% and 9% increased incidence of CRCs in men and women, respectively (10). Moreover, there is a meaningful increased risk in the highest category of BMI among the women for rectal cancer (2).

Environmental factors such as diet and physical activity can also affect the risk. Contradictory results have been published on the role of calcium on rectal cancers. Wei et al (2) showed that patients with rectal cancers tended to have slightly higher folate and slightly lower calcium intake, whereas Wu et al. (11) found a significant association between calcium and cancers arising in the distal colon. It has also been shown that diets with higher milk and dairy product are associated with a significant reduction in the risk of colon cancer, not affecting the risk of rectal cancer (12). An inverse association has been shown between magnesium intake and the risk of both colon and rectum cancers in women (13). Physical activity has been found to be more strongly associated with colon cancer than rectal cancer. Beef, pork or lamb as a main dish, processed meat and alcohol are related to colon cancers (2). A slightly stronger association is reported between cigarette smoking and rectal cancer in comparison to colon cancer (2, 14). A history of radiation therapy for prostate cancer

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is another risk factor of rectal cancer (15). According to a meta-analysis, risk of colon and rectal cancers among patients with diabetes mellitus was approximately 38% and 20% higher than non-diabetic patients, respectively (16).

Clinical Presentations

Although a large number of asymptomatic cases in early stages are diagnosed as a result of current screening programs worldwide, a significant number of cases are diagnosed after the onset of symptoms. Extension of a rectal tumor into adjacent organs or into the lumen of gastrointestinal tract leads to symptomatic presentation. Therefore, symptoms usually reflect at least a locally advanced cancer.

Rectal bleeding is the most common presentations of rectal cancer. In later stages of the disease, other symptoms such as tenesmus, incomplete stool evacuation, diminished caliber of stools cramping, pelvic and rectal pain or obstructive symptoms might present. Comparing the presenting symptoms of CRCs in general, we will notice that clinical manifestations differ depending on tumor location (i.e. ascending, transverse, or sigmoid colon, or rectum) (17). Hematochezia and change in bowel habit are more common in rectal cancers and left-sided CRCs; however, iron deficiency anemia from an unrecognized origin is more often caused by right-sided cancers. Abdominal pain can occur in both left- and right-sided tumors. It can be a symptom of partial obstruction, peritoneal dissemination of the tumor, intestinal perforation or even peritonitis. Patients suffering from metastatic rectal cancer may present with clinical symptoms referable to their metastatic site. Based on the venous drainage of the upper rectum via the portal system, most common site of hematogenous metastasis is liver, followed by the lungs and bone; however, distal rectum drains into the inferior rectal vein (and then into the inferior vena cava) and it may metastasize initially to the lungs (18-20).

In rare situations, rectal tumors can also present emergently with intestinal obstruction, acute gastrointestinal bleeding or peritonitis following its perforation into the peritoneal cavity. Fistula formation into adjacent organs (such as bladder), fever of unknown origin, abscesses (due to a localized perforated cancer), bacteremia or sepsis (due to Streptococcus bovis or Clostridium septicum) has also been reported as other rare presentations (21-23).

Screening

The goal of colon and rectal cancer screening is to reach adequate target population coverage in order to reduce mortality through detection of early-stage adenocarcinomas and removal of adenomatous polyps. This leads to a reduction in incidence of advanced cancers (24). It is documented that around 30% of all CRCs are diagnosed by screening in asymptomatic individuals (25).

Screening in average-risk population

CRC screening in this group is performed using structural exams or stool tests which may be used alone or in combination to improve sensitivity. Structural exams can help in diagnosing both adenocarcinoma and adenomatous polyps, while stool tests are suited for detection of cancers. Structural exams, also called one step screening program, include colonoscopy, flexible sigmoidoscopy (FSIG), double-contrast barium enema (DCBE) and computed tomographic colonography (CTC). Stool tests are the initial method of a two-step program. Fecal occult blood tests (FOBT) can be done using guaiac-based (gFOBT), immunochemical-based (iFOBT or FIT) or fecal DNA methods. Currently, gFOBT is the most frequently used test in the CRC screening programs worldwide. In cases of positive FOBT, further evaluation with the structural exams has been recommended (24, 26). Although a group of rectal cancers can be detected on digital rectal examination, it is not recommended in current screening guidelines. (27)

A number of guidelines on CRC screen-

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Table 1. Joint colorectal cancer screening guideline published by the American Cancer Society and the United States Multi-Society Task Force (ACS-MSTF)

Class:	Test	Interval
Tests that detect Adenomatous Polyps and Cancers	Flexible Sigmoidoscopy (FSIG)	Every 5 years, or
	Colonoscopy	Every 10 years, or
	Double-Contrast Barium Enema (DCBE)	Every 5 years, or
	Computed Tomographic Colonography (CTC)	Every 5 years
Tests that primarily detect Cancers	Guaiac-Based Fecal Occult Blood Test (gFOBT) with high sensivity for cancer	Annual, or
	Fecal Immunohistochemical Test (FIT) With High Sensivity For Cancer	Annual, or
	Stool DNA Test With High Sensivity For Cancer	Uncertain Interval

ing are available. The joint guideline published in 2008 by the American Cancer Society, the United States Multi-Society Task Force on Colorectal Cancer (ACS-MSTF) and the American College of Radiology is one of the major protocols (24). Moreover, other guidelines have been issued by the National Comprehensive Cancer Network (NCCN) in 2013 (28), the Council of the European Union (CEU) in 2013 (29), the American College of Physicians (ACP) in 2012 (30), the American College of Gastroenterology (ACG) in 2009 (31), and the United States Preventive Services Task Force (USPSTF) in 2008 (32).

ACS-MSTF guideline (24) offers CRC screening beginning at age 50 for average-risk patients. Screening can be discontinued when the individual's estimated life expectancy is less than 10 years. It has a more stress on prevention rather than early detection and recommends that patients can choose specific tests within each class. The guideline has been summarized in Table 1. The gFOBT or FIT should be performed on three consecutive stool samples using a sensitive guaiac test. Positive tests need to be followed by colonoscopy. In patients who prefer FSIG, it should be done with insertion to 40cm or to splenic flexure.

Other guidelines have recommended different approaches for CRC screening. For instance, the CEU (29) guideline has recommended only the FOBT for screening individuals aged 50 to 74 years; whereas, colonoscopy is the preferred test in the NCCN (28) and the ACG (31) guidelines. Moreover, the ACG recommends screening beginning at age 45. The ACP suggests screening average-risk patients starting at age 50 and stopping at age 75 years or in adults with a life expectancy less than 10 years. The USPSTF (32) recommends screening of adults age 50 to 75 years using annual sensitive FOBT, FSIG every 5 years in addition to sensitive FOBT every 3 years, or colonoscopy every 10 years.

Screening in high-risk population

Genetic predisposition is one of the most important risk factors for development of colon and rectum cancers. It is estimated that family history is a risk factor in 25% of patients with colorectal cancer. Patient with cancer susceptibility syndromes such as HNPCC and FAP are also at an increased risk (33). Multiple affected family members, history of CRC in first-degree relatives, and development of CRC at an early age (younger than 50 years) in the relatives are important risk factors (34, 35). Moreover, CRCs occur earlier in patients with a family history (36).

According to the latest guideline from the American College of Gastroenterology (ACG), screening with colonoscopy is recommended every 10 years beginning at age 50 for persons with a single first-degree relative diagnosed at age 60 or older with CRC or an advanced adenoma (larger than or equal to 1cm, high-grade dysplasia, or villous components). Whereas, in cases with a single first-degree relative diagnosed before 60 years with CRC or an advanced adenoma, or two or more first-degree relatives with these conditions at any age, screening with colonoscopy is recommended at age 40 or 10 years before the young-

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est relative's diagnosis; and it needs to be repeated every five years (31).

The risk of CRC is increased in patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn disease (CD) (37). Duration and extent of the inflammation are two important factors affecting the risk in UC. For instance, patients with pancolitis have the greatest risk after 8-10 years following the onset of symptoms (38, 39). The risk increases after 15-20 years in patients with left-side colitis (40). In contrast, the risk of cancer does not increase in patients with ulcerative proctitis and proctosigmoiditis (41). The American Gastroenterological Association (AGA) guideline recommends screening started after 8 years in patients with pancolitis and after 15 years in patients with left-side colitis, using colonoscopy every 1-2 years (37). Moreover, the American Society for Gastrointestinal Endoscopy (ASGE) has recommended four biopsies obtaining from every 10 cm of the colon from the cecum to the rectum during in each colonoscopy (42). In contrast, according to the American College of Gastroenterology (ACG) guideline, only patients who are surgical candidates are suggested for the annual surveillance colonoscopy (43). The British Society of Gastroenterology (BSG) recommends a surveillance colonoscopy 10 years after the onset of symptoms in all the patients irrespective to the extent and severity of the disease; but the interval depends on the duration and extent of disease and presence of additional risk factors (44). Patterns and factors affecting the risk of CRC in CD are similar to UC (45). Therefore, the AGA and the BSG guidelines have applied the same recommendations for CD.

An increased risk of CRC has also been detected in polyp syndromes such as HNPCC, or Lynch syndrome, FAP, MAP, juvenile polyposis (JPS) and Peutz–Jeghers syndrome (PJS). Biennial colonoscopy surveillance starting from age 25 to the age of 70-75 years has been offered for patients with HNPCC. In FAP mutation carriers, annual flexible sigmoidoscopy is recommended from diagnosis; but in families where genetic linkage analysis is not possible, annual surveillance from age 13–15 until age 30 years, and every 3–5 years thereafter until age 60 should be done. In at-risk individuals and mutation carriers for the JPS, screening every 1–2 years is offered starting from age 15–18 years. For patients who are bi-allelic MUTYH carriers, screening with colonoscopy every 2–3 years is recommended from age 25. CRC screening has been recommended in patients with the PJS every 2 years from age 25 (44).

Diagnosis

Rectal cancers may be suspected from signs and symptoms or by rectal examination. Once suspected, a colonoscopy or an imaging study is required. It may also be discovered by the screening. Histologic tissue examination is then required to confirm the diagnosis followed by a proper staging.

Sigmoidoscopy and colonoscopy are two commonly used diagnostic and screening modalities for rectal cancers. Although flexible sigmoidoscopy is an accurate diagnostic method for rectal cancers, a colonoscopy is still required to evaluate other parts of the colon for synchronous colonic polyps or tumors that is found in 4% of patients. (46) Moreover, colonoscopy can remove polyps, biopsy lesions and visualize flat or non-polypoid adenomas throughout the large bowel. It is a precise tool with a miss rate of about 2.3% for rectal and sigmoid cancers. (47)

Double contrast barium enema (DCBE) is another diagnostic and screening tool used alone or together with flexible sigmoidoscopy. It has also been found to be superior to the Response Evaluation Criteria in Solid Tumors (RECIST) in evaluating the effect of chemoradiotherapy and predicting the likelihood of tumor recurrence (48), but its diagnostic yield is less than colonoscopy (49). Additionally, colonoscopy is recommended for all detected lesions by the DCBE to establish the histology and search for synchronous lesions.

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Computed tomographic colonography (CTC) (also known as virtual colonoscopy) is another non-invasice and safe diagnostic tool. Not only CTC provides endoluminal visulization of the colon and rectum, but also it enables the examination of extracolonic organs (50). In a trial done by Atkin et al (51), the SIGGAR trial, CTC was recommended as a similarly sensitive, less invasive alternative to colonoscopy. CTC has also been suggested as a sensitive tool for detection of synchronous lesions in situations which a complete colonoscopy is not possible due to technical reasons (such as an obstructing cancer) or patient intolerance (52).

Other imaging modalities such as magnetic resonance imaging (MRI), endoscopic ultrasound (transrectal or transvaginal) are also used to determine the stage of the tumor. Transrectal ultrasound (TRUS) can distinguish localized cancers involving the mucosa and submucosa from those involved the muscularis propria or perirectal fat. (53) MRI is another accurate imaging test for staging evaluation of rectal cancer. Not only it has an established role in initial staging of the tumor, but also it can be utilized for evaluation of treatment response and local recurrence (5). The role of these two modalities in tumor staging will be discussed further in the staging section.

A number of serum markers have also been suggested for colon and rectum cancers, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9). Due to their low sensitivity for early-stage disease and possibility to increase in non-cancer medical conditions, they cannot be used as a screening or diagnostic test for CRCs (54, 55). CEA have also values in post-treatment follow-up, surgical treatment planning, and the evaluation of prognosis (54).

Staging

Once the diagnosis of rectal cancer is established, the local and distant extent of the tumor should be determined for further therapeutic approach. Imaging modalities such as abdominopelvic CT or MRI and transrectal endoscopic ultrasound (TRUS) are frequently used for locoregional evaluation. Distant metastasis can be detected by chest CT, liver MRI or positron emission tomography (PET) scan.

In patient with diagnosed rectal cancer, CT scan is a helpful staging test for identifying local and distant metastasis and evaluation of tumor-related complications (such as obstruction, perforation or fistula formation) (56). The sensitivity of CT for detecting distant metastasis is higher than for detecting malignant lymph nodes or the local transmural tumor invasion (57). Although sensitivity of CT for assessment of perirectal lymph nodes is less than TRUS or MRI, its sensitivity for detection of malignant lymph nodes in rectal cancers is higher than colon cancers (58). Additionally, CT scan is not reliable in detecting small implants on peritoneal surfaces, with a sensitivity of 37% for peritoneal lesions 0.5-5cm in size (59, 60). Therefore, clinical benefit of routine abdominal and pelvic CT is controversial (61). Performing routine preoperative chest CT in rectal cancers has also been a matter of debate; but with due regard to the venous drainage of the lower rectum through the hemorrhoidal veins into the vena cava and higher probability of lung metastasis in rectal cancers, preoperative chest CT seems to be of more value in these tumors (62).

MRI is a useful modality in differentiating malignant tissues from the muscularis propria, and defining tumoral infiltration of the mesorectal fascia. MRI staging of rectal cancer can be performed using an endorectal surface coil, gradient coil systems or high resolution surface coils. Due to the ability of MRI to detect intranodal signals and irregularity of their borders, MRI has a higher sensitivity than EUS for the assessment of perirectal nodal involvement (63-66). According to a meta-analysis of 21 studies, published by Al-Sukhni et al, (66) MRI had 87% and 77% sensitivity for evaluation of the tumor size and nodal involvement, respectively. It specificity was

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75% for the size and 71% for the nodal status. Based on another meta-analysis, done by Niekel et al, (67) MRI has also been recommended as the preferred first-line imaging study for evaluating CRC liver metastases in patients who have not previously undergone therapy.

TRUS is an accurate modality for locoregional staging of rectal cancers using its ability to distinguish tumors involving the mucosa and submucosa from those involved the muscularis propria or perirectal fat (53). Comparing to CT and MRI, the TRUS has been superior for T staging of rectal cancer (68). In a meta-analysis published by Bipat et al, (69) TRUS was found to be more sensitive than CT and MRI in evaluation of both muscularis propria invasion and perirectal tissue invasion. In contrast, TRUS accuracy in evaluation of regional lymph nodes seems to be similar to CT and MRI (70). TRUS and MRI are also valuable modalities in evaluation of circumferential resection margin (CRM) before the surgical procedure. Involvement of the mesorectal fascia, which is the CRM during the surgical resection, is an important prognostic factor highly predictive of residual tumor and local recurrence. For anterior rectal tumors, the CRM can be evaluated by TRUS or MRI, while MRI has been suggested for posterior tumors (71-75).

PET scans has not been recommended in routine preoperative staging of rectal cancers (76); while, as an adjunct to other tests it might be helpful in evaluation of patients with isolated colorectal cancer liver metastases to reduce the number of nontherapeutic laparotomies (77, 78) or localizing the site of recurrence in patients with a rising serum CEA level (79).

An accurate staging system can be helpful in choosing the best therapeutic option for patients suffering from cancers. It can also help physician to evaluate results of their management. The TNM (Tumor, Node and Metastasis) staging system for colorectal cancers provided by the American Joint Committee on Cancer (AJCC) (80) is currently used worldwide. The most recent 7th edition (2010) defines a revised staging system. Subdivision of T4, N1, N2, and M1 in addition to substaging of stage II is among the changes in the new edition. According to the recent staging system, the TNM classification for the staging of colorectal cancer is summarized in Tables 2 and 3.

Table 2. TNM (Tumor, Node and Metastasis) definition of colorectal cancers

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial 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 one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

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Table 3. Staging of colorectal cancers

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

Treatment

Different types of treatment modalities have been proposed for patients with rectal cancer. Surgery is the mainstay of treatment for cases with resectable rectal cancers. According to the location of the tumor and the stage, surgical resection can be performed as the sole treatment modality or in combination with other neoadjuvant and/or adjuvant therapies (81).

Surgical Resection

Complete removal of the tumor and related lymphatic tissues is the primary goal of surgical resection. Other goals such as bowel continuity and anorectal sphincter preservation should also be considered when possible. The surgical options for resectable rectal cancers are local excision, sphincter-sparing procedures (such as low, very low, or ultra-low anterior resections), and abdominal perineal resection. Although more radical resections can be offered as potentially curative approaches for resectable tumors, other options such as local excision or sphincter-sparing procedures can be suggested to selected groups of patients. The choice of procedure is determined by the stage of the tumor, the location of the cancer from the dentate line and accommodating features of the pelvis (82).

The total mesorectal excision (TME) technique has been replaced the previous practice of blunt dissection of rectum from surrounding structures with better local control and survival rates (83-85). Currently, it has been accepted as the standard surgical approach during sphincter-sparing procedures or abdominoperineal resections. TME is the removal of the perirectal areolar tissues including lateral and circumferential margins of the mesorectum using sharp and meticulous dissection in the avascular plane between the parietal and visceral pelvic fascia. A 5 cm mesorectal excision beyond the primary rectal tumor seems to be adequate (86-88). Reduced risk of postoperative genitourinary dysfunction due to preservation of the pelvic autonomic nerves is another advantage of this technique (89).

Obtaining histologically negative proximal, distal, and radial surgical margins of resection should also be considered in order to reduce the risk of a local recurrence (90). A 5 cm negative proximal margin seems to be adequate for most rectal cancers (87). In conjunction with a TME, a 2 cm negative distal margin is adequate for rectal cancers; however, a 1 cm distal negative margin has been accepted for cancers located at or below the mesorectal margin (82, 87, 91, 92). Preservation of the anorectal sphincter is recommended if it is possible to obtain the 1 cm negative distal margin (81).

Minimally invasive approach for surgical resection of rectal tumors has been found to be comparable to open surgery (93). Compared with the open techniques, the laparoscopic approach has resulted in similar completeness of resection and circumferential resection margins in addition to median tumor distance to the distal resection margin (94). Although no difference has been found between the female sexual function between these two techniques (open and laparoscopic), an increased risk of sexual dysfunction has been reported for men. Rates of bladder dysfunction are also similar following these two techniques (95). In another study, except for the mean operative time, patients undergoing a laparoscopic proctectomy had shorter length of hospital stay and lower rates of blood transfusion and postoperative complications (96).

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Local Excision

Distal rectal tumors with nonaggressive features can be resected by local excision; however, it is not recommended for tumors located in proximal part of rectum. It can be performed through transanal, transsphincteric, or transsacral approaches. A local recurrence rate of 7% to 21% for T1 tumors has been reported for these procedures, therefore an annual follow-up with a sigmoidoscopy after five years has been recommended (82, 97-100).

Selected rectal T1N0M0 tumors located in middle to distal rectum with a diameter of less than 3 cm depicting favorable histological features (such as well differentiated, no vascular and/or neural invasion) are candidate for local excision. Presence of concurrent comorbidities that preclude a radical surgical operation and refusal of other surgical option are other indications for local excision. In the setting of a clinical trial, it may also be recommended for tumors deeper than the submucosa (>T1) with a complete response after neoadjuvant chemoradiation (82).

Transanal excision (TAE) is the most common local resection procedure for early rectal tumors. It is full-thickness excision of the rectal cancer with a negative deep margin and a minimum lateral margin of 1 cm. In cases with positive margins, an additional local or radical resection is needed (101, 102). Fewer postoperative complications (103) and high recurrence rate (104) are pros and cons of this technique, respectively. Transanal endoscopic microsurgery (TEM) is an alternative performed for tumors located 4-18 cm from the anal verge. The TAE approach is recommended for higher tumors (105-109). The transsphincteric approach (TSA), also called York-Mason procedure, used for cancers in the middle portion of the rectum beyond the reach of a TAE, but with a higher morbidity. Levator ani, puborectalis muscle and external anal sphincter are divided followed by a segmental resection and a primary closure. The transsacral approach, or the Kraske procedure, can be performed for tumors located in the middle and posterior aspects of the rectum. In this approach, the rectum is circumferentially mobilized followed by partial or segmental resection of the rectum and a primary closure (110-112).

Low anterior resections (sphincter-sparing procedures):

A low anterior resection (LAR) is used for tumors located in the upper to middle parts of the rectum. The sigmoid colon and rectum is resected to a level where the distal margin is free of tumor followed by a primary anastomosis between the descending colon and the distal rectum.

For cancers located in the distal rectum without invasion to the anal sphincter, a very low anterior resection (VLAR) or ultra low anterior resection (ULAR) have been recommended (113). Provided the distal margin is clear of malignant cells, the anastomosis between the colon and anal sphincter can be performed as a straight side-to-end reservoir, a colonic J-pouch reservoir, or a transverse coloplasty. The side-to-end coloanal anastomosis has been reported with a 51% success (complete fecal continence) in previous studies (114). The colonic J-pouch provides a larger reservoir with a side-to-side anastomosis at the distal 8 cm of the colon to create a pouch with an undistended volume capacity of 60-105 mL (115-119). Patients undergoing a colonic J-pouch have better short-term bowel function and lower morbidity, but long-term function and mortality are comparable in these two methods (120-122). The transverse coloplasty is created by an 8-10 cm longitudinal colotomy between the colonic tenia, beginning 4-6 cm proximal to the distal end of the mobilized descending colon, and approximating the incision transversely. It is offered to patients who are not good candidates for the straight or J-pouch anastomosis (123).

In order to protect the anastomosis, a temporary diverting ileostomy has been recommended if the anastomosis is low, under tension, presence of an air leak on

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proctoscopic testing, preoperative chemoradiation, or history of immunosuppressive medication. (123, 124)

Abdominoperineal Resection

Abdominoperineal resection (APR) is an accepted surgical approach for low rectal tumors not indicated for sphincter-sparing procedures. It includes the resection of sigmoid colon, rectum, and anus followed by a permanent colostomy. It is indicated when achieving a negative distal margin is not possible with the sphincter-sparing procedures or as a salvage procedure for local recurrence or locally advanced rectal tumors. The introduction of circular stapling devices for low rectal anastomoses, the use of neoadjuvant therapy for downsizing rectal cancers and recent advances in sphincter saving procedures has resulted in an increase use of low anterior resections for low rectal tumors without sphincteric involvement (125).

Neoadjuvant Therapy

Neoadjuvant therapy has been strongly recommended for locally advanced cancers located in the middle or distal rectum. Presence of T4 rectal cancer is the most important indication for neoadjuvant treatment. It is also recommended in patients with node positive disease as well (82). Short-course radiotherapy (SCRT) and long-course chemoradiotherapy (LCCRT) are accepted approaches for delivering preoperative neoadjuvant therapy. The SCRT is done using a daily radiation dose of 5 Gy over 5 days. The LCCRT uses doses of 1.8-2 Gy over 5-6 weeks (to a total dose of 45-50.4 Gy) in addition to concurrent administration of 5-fluorouracil-based chemotherapy. Surgical resection is performed 8-12 weeks later (126, 127). Although neoadjuvant SCRT has been the preoperative treatment of choice in Northern Europe and Scandinavia, in North America and in some European countries LCCRT has become more accepted (82). Comparing SCRT and LCCRT, rates of sphincter preservation, local recurrence, disease free survival and overall survival have been similar; however, complete pathological response was higher in patients receiving LCCRT (128, 129).

Several chemotherapeutic regimens have been used for the neoadjuvant therapy of rectal cancers. These regimens include infusional or bolus fluorouracil alone (130), and leucovorin plus fluorouracil (131). Other agents such as oral fluoropyrimidines (eg. Capecitabine) (132), Oxaliplatin (133), Irinotecan (134), Bevacizumab (135), Cetuximab (136), and Panitumumab (137) have also been studied.

The combination of neoadjuvant radiotherapy (LCCRT and SCRT) and optimal mesorectal excision has resulted in lower recurrence of rectal tumors, especially in tumors located 5-10 cm from the anal verge, with lymph node involvement and negative circumferential margins (138, 139). Long-term side effects including chronic bowel dysfunction and sexual dysfunction has also been reported in this setting (82). Patients who received preoperative SCRT had lower local recurrence and higher 5-year survival in comparison with the patients underwent surgery alone (140). Tumor regression and down-staging resulted from neoadjuvant LCCRT may also help complete resection of the tumor and may make a sphincter-saving procedure possible in low rectal tumors (130, 141-143). Therefore, SCRT is typically used in patients whose tumor margin threatens the mesorectal fascia and tumor down-staging would not improve resection or sphincter preservation (82).

Prognosis in patients undergoing neoadjuvant chemoradiotherapy is related to the final tumor stage and presence of lymph node involvement in the surgical specimen. Tumor Regression Grade (TRG), which is defined by degree of fibrosis and percentage of viable tumor, is another factor affecting the prognosis (144-146).

Adjuvant Therapy

Adjuvant therapy, in general, has been highly recommended for patients with stage

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III or high-risk stage II rectal cancer. Postoperative chemoradiotherapy is the preferred adjuvant therapy for patients who have not received neoadjuvant therapy; while, postoperative chemotherapy is suggested for patients previously treated with neoadjuvant therapy (82). Adjuvant chemoradiotherapy has been shown to be effective in reducing local recurrence and mortality from the rectal cancer. Impaired perineal wound healing and small bowel toxicity are the disadvantages (147-149). Patients with a downstaged tumor due to a preoperative chemoradiation may also benefit from postoperative chemotherapy. In these cases, it is recommended to base adjuvant treatment decisions on the preoperative staging of the tumor (82).

Several regimens have been studied and used for the chemotherapy component of adjuvant treatment of rectal cancers. These regimen include bolus or infusional fluorouracil (150), the Roswell Park regimen (weekly bolus fluorouracil plus leucovorin) (151), the de Gramont regimen (short-term infusional fluorouracil and leucovorin) (152), capecitabine (an orally active fluoropyrimidines) (153) or oxaliplatin-based regimen such as FOLFOX (infusional fluorouracil and leucovorin plus oxaliplatin) (154) or CAPOX (Capecitabine plus oxaliplatin) (155) regimen.

Treatment of rectal cancer with liver metastases

Depending on the resectability of the primary tumor and the liver metastases, several treatment options are available for these patients. For patients with resectable colon cancer with resectable liver metastases, resection of the primary tumor followed by hepatic resection is the preferred strategy. In these cases a combined resection in one stage may also be performed. This approach is more complex for rectal cancers with potentially resectable liver metastases (156).

For rectal cancers, treatment may start with short-course radiotherapy or a long course chemoradiation followed by resection of the rectal cancer (156). Liver metastases will be resected at a later stage (157, 158). Treatment of liver metastases consists of radical resection and/or local ablative therapy (e.g. radiofrequency ablation) combined with adjuvant chemotherapy (159). A 5-year overall survival of around 30 % has been achieved after resection of all resectable primary and metastatic disease (160). However, some other studies showed a comparable survival rates after simultaneous colorectal and liver resection (161-164). Liver-first approach is another alternative, in which resection of the liver metastases is performed first followed by a radiation therapy to the rectum and resection of the rectal cancer at a later stage. Neoadjuvant chemotherapy has also been recommended for this approach (165-169).

Another treatment dilemma occurs in patients presenting with resectable rectal cancer but unresectable synchronous liver metastases. Palliation is the principal goal of treatment in symptomatic patients (170). The most common treatment strategy is to perform a palliative colorectal resection in order to treat or prevent complications of the primary tumor such as intestinal obstruction, perforation, or hemorrhage. Chemotherapy is administered after the resection to treat the metastatic disease (171-174). In asymptomatic patients, chemotherapy may be considered as the initial treatment (175). However, there is no clear evidence available on the best approach; initial resection of the primary tumor or initial systemic therapy (156).

Treatment of unresectable rectal cancer

A clear definition for unresectability of a rectal tumor has not been established yet. A fixed or adhesive tumor that cannot be resected from adjacent organs without leaving microscopic or gross residual disease at local site might be consider as an unresectable tumor. Thin cut MRI with pelvic phased-array coil is the modality of choice in evaluating the local tumor resectability. Depth of transmural invasion, nodal involvement, invasion into adjacent struc-

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tures and circumferential margins can be assessed using MRI. In comparison, CT scan and endorectal ultrasound are less helpful in evaluation of local tumor resectability (176-180).

According to the guidelines, a multimodality plan including preoperative neoadjuvant chemoradiotherapy, multivisceral surgical resection (with or without intraoperative radiotherapy) and postoperative adjuvant chemotherapy are the current approach for unresectable rectal cancers (82, 87, 181, 182). Multivisceral resections, such as total pelvic exenteration (TPE) or its modifications, have led to good local control and survival (183-186). The TPE involves the removal of the rectum, anus, lower ureters, urinary bladder, and prostate in males; the uterus, ovaries and vagina are also removed in females (187, 188). Posterior pelvic exenteration has also been studied as a surgical modality in females with rectal tumor adherent or invaded to the uterus and vagina. It involves the removal of the rectum, sigmoid colon, internal reproductive organs, draining lymph nodes and pelvic peritoneum in women (189-191). A supralevator pelvic exenteration is another option which involves the en bloc removal of the compromised organs similar to the TPE, preserving an adequate distal margin in the rectum. In this procedure, the perineal floor will be preserved; so, a primary colorectal anastomosis can be performed (192, 193). In a systematic review on 1049 patients underwent multivisceral resection for their rectal cancers, a local recurrence rate of 4.8- 61%, a complication rate of 37-100%, and a perioperative mortality rate of 0-25% was reported (194).

Treatment of locally recurrent rectal cancer

Proper management of locally recurrent rectal cancer has been a matter of debate. Depending on previous therapies and local extent of the recurrent tumor, treatment modalities such as surgery alone or with radiation therapy has been recommended. There are no strong data on the use of adjuvant chemotherapy for these patients.

Providing the possibility of complete resection of the tumor with negative margins, extensive surgical procedures such as pelvic exenteration (including partial sacrectomy) may result in long-term survival (195-201). Recurrent tumor involving nerve roots above the level of L1-2, proximal sacrum (S1, S2) extending to the sacral promontory, and involvement of paraaortic lymph nodes or the iliac vessels are not recommended for curative radical surgery. Extension through the greater sciatic notch, bilateral urethral obstruction and circumferential involvement of the pelvic wall are other contraindications for the curative radical surgery. Depending on possible curative resection, presence of liver or long metastases may not be a contraindication (202, 203). Pelvic radiotherapy is generally not recommended for previously irradiated patients; however, it has been reported in some studies (204-206). Intraoperative radiation therapy has also been reported with favorable results (207-211).

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