ROYAUME DU MAROC
UNIVERSITE MOHAMMED V DE RABAT
FACULTE DE MEDECINE
ET DE PHARMACIE
RABAT

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NEOADJUVANT TREATMENT IN RECTAL CANCER

THESIS

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BY

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FOR THE DEGREE OF

Doctor of Medicine

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***Enseignant militaire**

DEDICATIONS

A ALLAH

Le tout puissant, le Miséricordieux; ainsi qu'à son prophète Mohamed, paix et salut sur lui.

Par la grâce et la bonté de Dieu qui a toujours guidé nos pas et qui nous a donné la chance et la force d'étudier et d'en arriver là.

Je dédie cette thèse …

À

FEU SA MAJESTE LE ROI HASSAN II

Que Dieu ait son âme en sa Sainte Miséricorde

À

SA MAJESTE LE ROI MOHAMED VI

Chef Suprême et Chef d'Etat-Major Général des Forces Armées Royales.

Roi du MAROC et garant de son intégrité territoriale

Qu'Allah le glorifie et préserve Son Royaume

À

SON ALTESSE ROYALE LE PRINCE

HERITIER MOULAY EL HASSAN

Que Dieu le garde

À

SON ALTESSE ROYALE

LE PRINCE MOULAY RACHID

Que Dieu le protège

À TOUTE LA FAMILLE ROYALE

A

Monsieur le Général de Corps d'Armée

Abdelfattah LOUARAK

Inspecteur Général des Forces Armées Royales

En témoignage de notre grand respect

Et notre profonde considération

A

Monsieur le Médecin Général de Brigade

Mohammed ABBAR

Inspecteur du Service Santé

En témoignant de notre grand respect

Et notre profonde considération

A

Monsieur le Médecin Général de Brigade

El Mehdi ZBIR

Directeur de l'Hôpital Militaire d'Instructions Mohamed V – Rabat

En témoignage de notre grand respect

Et notre profonde considération et sincère admiration

A

Monsieur le Médecin Général de Brigade

BOULAHYA Abdellatif

Directeur de l'Hôpital Militaire Avicenne – Marrakech

En témoignant de notre grand respect et notre profonde considération

A

Monsieur le Colonel Major

Abderrazak SABIR

Médecin Chef du 3ème Hôpital de Laayoune

En témoignant de notre grand respect et notre profonde considération

A

Monsieur le Médecin Colonel

Karim FILALI

Directeur de l'Ecole Royale du Service de Santé Militaire

En témoignage de notre grand respect

Et notre profonde considération.

A

Monsieur le Médecin Colonel Major

Elbaaj Mohammed

Directeur de l'Hôpital Militaire Moulay Ismail - Meknes

En témoignage de notre grand respect

Et notre profonde considération

To my dear wife, Dr. Majdoulin Boubekri EL Marraki:

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LIST
OF ABBREVIATIONS

Abbreviations

AJCC : American Joint Committee on Cancer

ANP : Autonomic nerve preservation

APR : Abdomino-perineal resection

BMI : Body mass index

CAPOX : Capecitabine/oxaliplatin

CCT : Concurrent chemotherapy

CEA : Carcinoembryonic antigen

CRM : Circumferential resection margin

CRT : Chemoradiotherapy

CT : Computed tomography

CTV : Clinical tumor volume

EBRT : External beam radiation therapy

EGFR : Epidermal growth factor receptor

ESMO : European Society for Medical Oncology

FIT : Fecal immunochemical test

FOBT : Fecal occult blood test

FOLFOX : Fluorouracil/oxaliplatin

GTV : Gross tumor volume

HNPCC : Hereditary nonpolyposis colorectal cancer

IMA : Inferior mesenteric artery

IMRT : Intensity-modulated radiation therapy

INO : Institutit National d'Oncologie

ISR : Intersphincteric resection

LAR : Low anterior resection

LCCRT : Long-course chemoradiotherapy

LLND : Lateral lymph node dissection

LV : Leucovorin

MLC : Multileaf collimator

MRI : Magnetic resonance imaging

NAT : Neoadjuvant treatment

NCCN : National Comprehensive Cancer Network

NPVs : Negative predictive values

OARs : Organs at risk

OS : Overall survival

pCR : Pathologic complete response

PET : Positron emission tomography

PPVs : Positive predictive values

PTV : Planning target volume

RT : Radiotherapy

SBRT : Stereotactic body radiation therapy

SCRT : Short-course radiotherapy

SSS : Sphincter sparing surgery

TME : Total mesorectal excision

TNT : Total neoadjuvant treatment

TRUS : Transrectal endoscopic ultrasound

ULAR : Ultra-low anterior resection

VEGF : Vascular endothelial growth factor

VLAR : Very low anterior resection

3D-CRT : Three-dimensional conformal radiation therapy

5-FU : 5-fluorouracil or fluorouracil

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SUMMARY

INTRODUCTION

The rectum is the final step before feces are excreted out of the human body through the anal canal. The electrolytes such as sodium and potassium are absorbed and the indigestible food ingredients are decomposed by anaerobic bacteria, similar to the colon. The stool is thickened by absorption of water and mixed with mucus. Moreover, it is part of the continence organ and performs a key role in the defecation mechanism. [1].

Rectal cancer ranks third in terms of incidence, but second in terms of mortality worldwide. The global burden of colorectal is expected to significantly increase by 60% with the detection of more than 2.2 million new cases and 1.1 million cancer deaths by 2030[2].

Surgery is the main treatment for rectal cancer. Recently, total mesorectal excision is considered the chief surgical procedure, further improving the standard care for rectal cancer, especially locally advanced one.

Neoadjuvant treatment is a standard approach in treating locally advanced rectal cancer. It comprises preoperative radiotherapy and preoperative chemotherapy. It has an essential role in reducing cancer volume and staging, while it increases pathological complete response and facilitates surgical resection of rectal cancer.

Many approaches have been developed as neoadjuvant treatment, such as short-course radiotherapy, long-course chemoradiotherapy, and the recent approach defined as total neoadjuvant treatment.

Each neoadjuvant treatment approach presents its indications, benefits, and disadvantages. So knowing these can surely provide the medical staph with appropriate measures to treat locally advanced rectal cancer and improve the treatment’s outcomes.

Recently, many trials about total neoadjuvant treatment, such as PRODIGE 23 and RAPIDO trials, try to show us new strategies that can provide us with better results compared to the actual standard neoadjuvant treatment.

FIRST CHAPTER: RECTAL CANCER

I. Anatomy reminders

A. External configuration [3], [4]

Collectively, the rectum and the anal canal represent the last segment of the gastrointestinal tract. Initially, the rectum is facing downwards and backwards, and then downwards and forwards until reaching the levator hiatus at which level it becomes continuous with the anal canal. The rectum is an intrapelvic viscus, and it measures 12 to 18 cm in the adult. The anorectal junction is located around 4 cm in front of the tip of the coccyx (Figure 1).

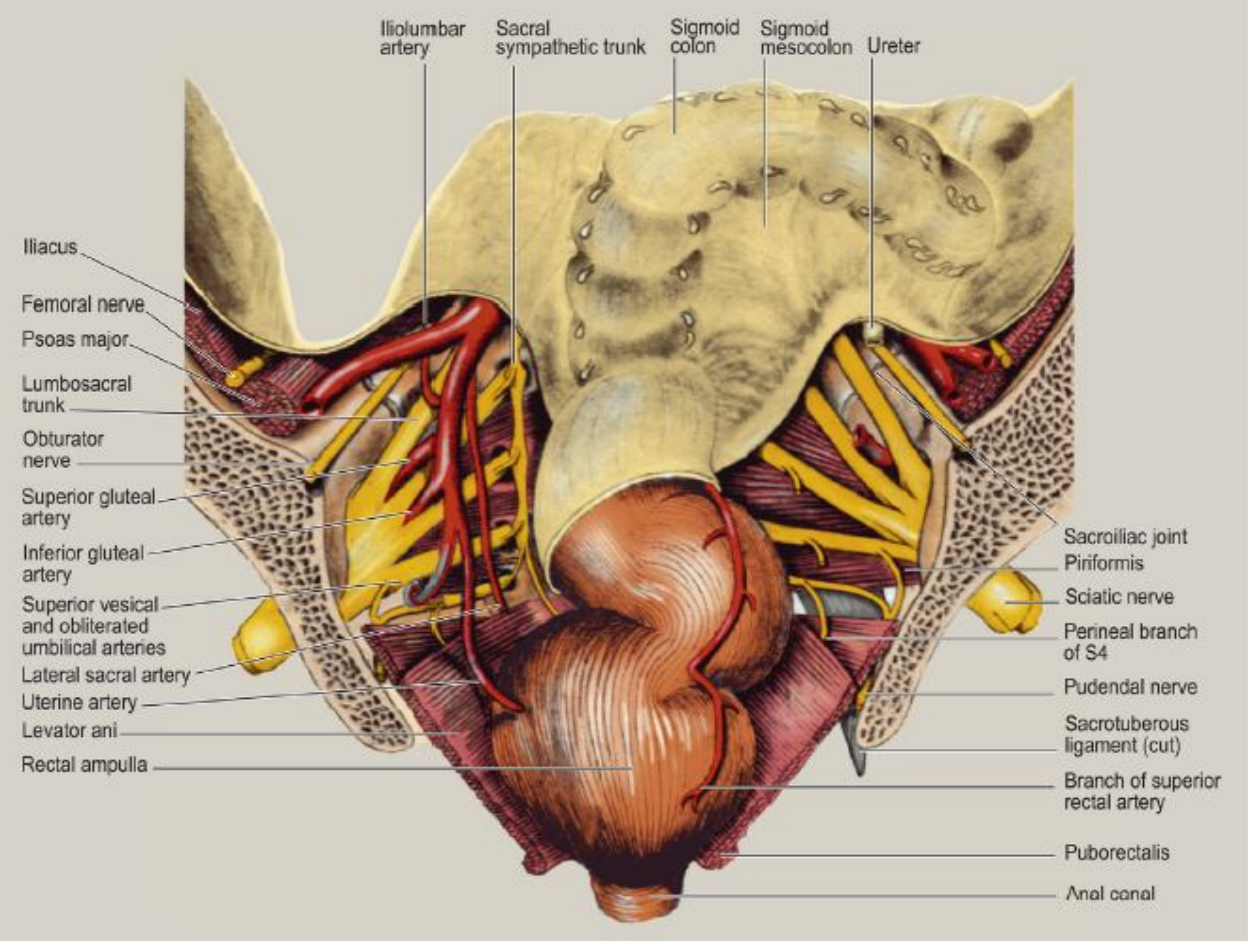

Figure 1. Coronal view of the posterior half of the pelvic cavity, showing the anterior aspect of the rectum.[3]

B. Facial coverings of the rectum [3], [4]

The rectum is almost surrounded by a cuff of fat called the perirectal fat that is usually more abundant posteriorly than anteriorly, and in this perirectal fat, we find the pararectal and epirectal lymph nodes and also the superior rectal vessels that travel by here before entering the rectum. The perirectal fat is enclosed by a specific circumferential fascial layer called the fascia propria of the rectum (Figure 2). The fascia propria surrounding the perirectal fat and the embedded lymph nodes is identified as the mesorectum. Although that term does not mean that the rectum has a suspensory mesentery. Nonetheless, the rectum must be removed with a completely intact mesorectum for a successful result in rectal cancer surgery.

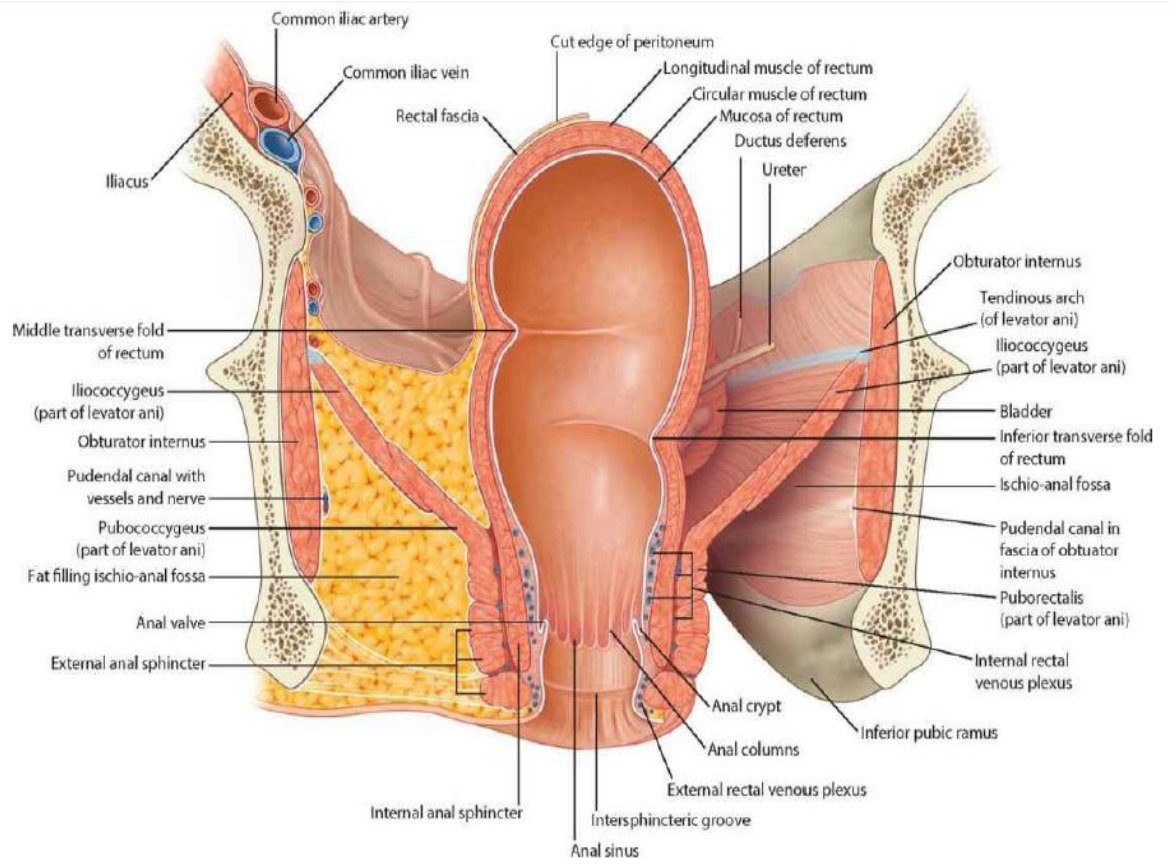

Figure 2. Coronal section through the rectum and the anal canal [5]

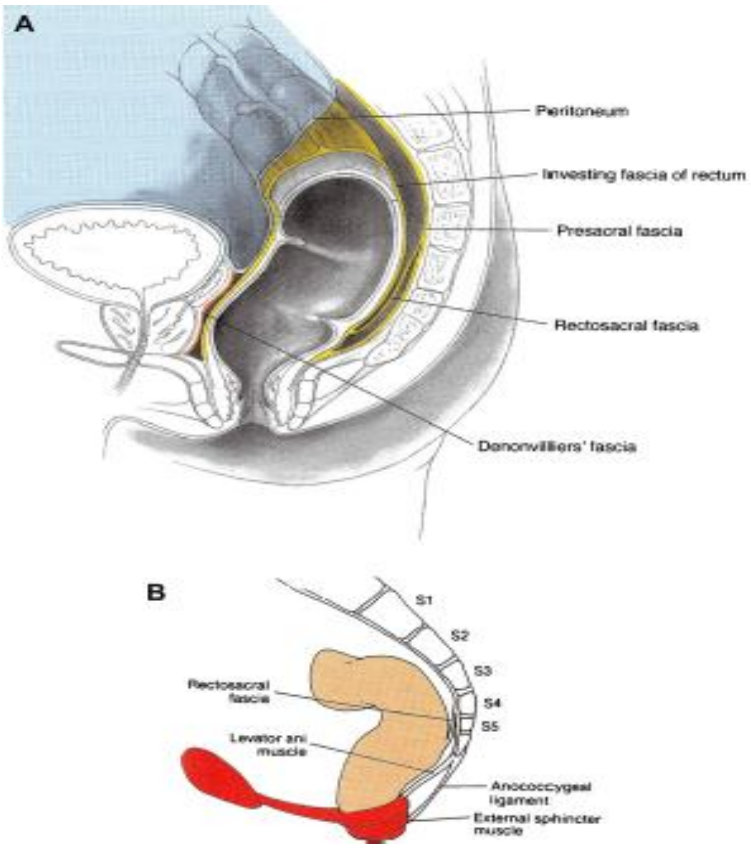

Figure 3. Pelvic fascia. (A) Relation of pelvic fascia to peritoneal layers, prostate, and bladder. (B) Pelvic fascia and Waldeyer ring [6]

C. Internal configuration [4], [6], [7]

The rectum presents 2 to 3 curves in its lumen called the rectal shelves or the valves of Houston which results from the thickened muscle in the rectal wall protruding inwards and covered with overlying mucosa (Figure 5). The rectum wall is composed of colonic epithelium, lamina propria, muscularis mucosae, submucosa, and muscularis propria. The latter is composed of two layers: a longitudinal one that continues as the longitudinal layer of the anal sphincter, and an inner circular layer that thickens at the anorectal junction and forming the internal anal sphincter (Figure 4)

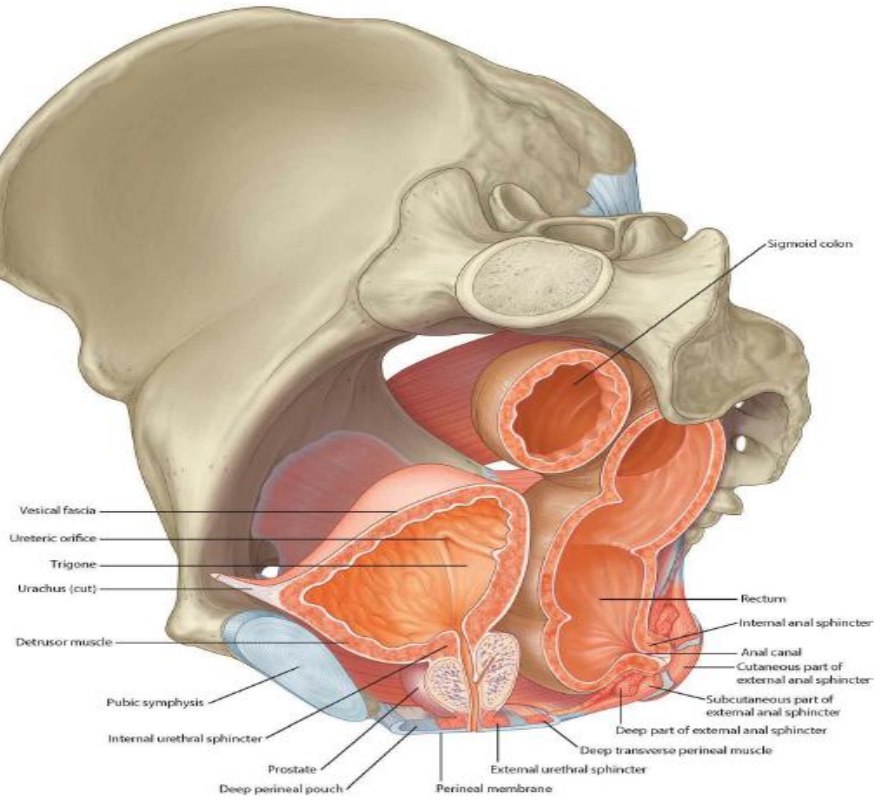

Figure 4. Rectum within the pelvic cavity in men (oblique sagittal view)[5]

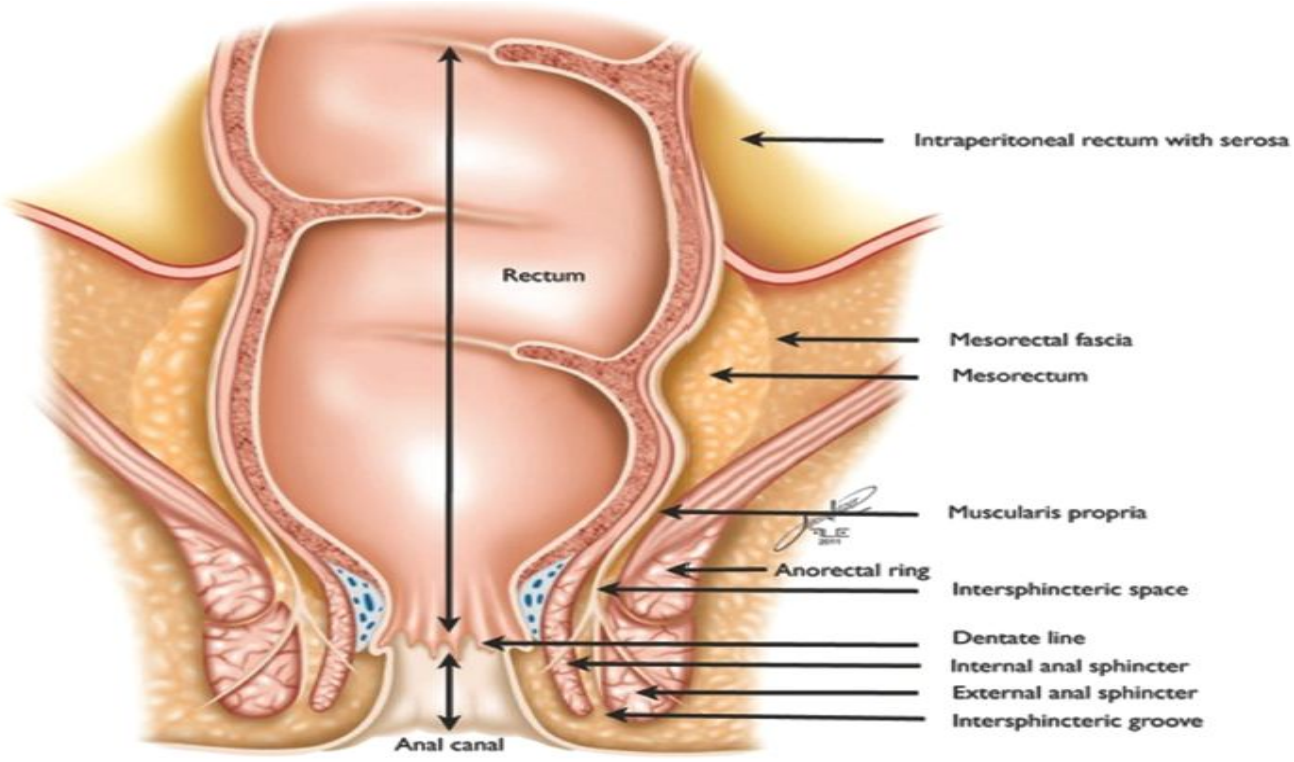

Figure 5. Internal configuration [8]

D. Arterial supply and venous draining

1. Arterial supply [3], [6], [9]

The vascularization of the rectum is ensured by the *superior rectal artery* (which is the inferior mesenteric after crossing the pelvic brim and entering the pelvic cavity), the *middle rectal arteries* (which originates from the internal iliac arteries), the *inferior rectal arteries* (which arise from the internal pudendal artery, which is, in turn, a branch of the internal iliac artery), and the *median sacral artery* (which arises from the posterior aspect of the aorta just proximal to the aortic bifurcation).

The superior rectal artery supplies the rectum and the upper third of the anal canal, the middle rectal artery supplies the distal part of the rectum and the proximal part of the anal canal, the inferior rectal arteries travel the ischioanal fosse on each side of the anal canal nourishing the sphincter muscles. Intramural collaterals are situated between the superior and inferior rectal arteries at the level of the dentate line in the submucosa (Figure 6).

2. Venous drainage [3], [6], [9]

Blood passes from a rich a valveless intramural venous plexus to the valveless perirectal venous plexus, wherefrom rectal blood floats essentially in the superior rectal vein. The latter crosses the pelvic brim from bottom to top, alongside the artery, to become the inferior mesenteric vein, which drains the sigmoid colon, descending colon, and splenic flexure before joining the splenic vein giving birth to the portal vein. Some venous blood from the intramural and perirectal venous plexuses is carried in both sides by the middle rectal veins and drains into the internal iliac veins. Venous blood from these rectal plexuses gets

through the anal wall into the inferior rectal veins which drain into the internal iliac veins via the internal pudendal veins (Figure 6). The anal mucosa and submucosa thereby represent sites of natural portosystemic venous anastomoses. In portal hypertension, these anastomoses get significantly distended and engorged, and if severed, can give rise to grave bleeding.

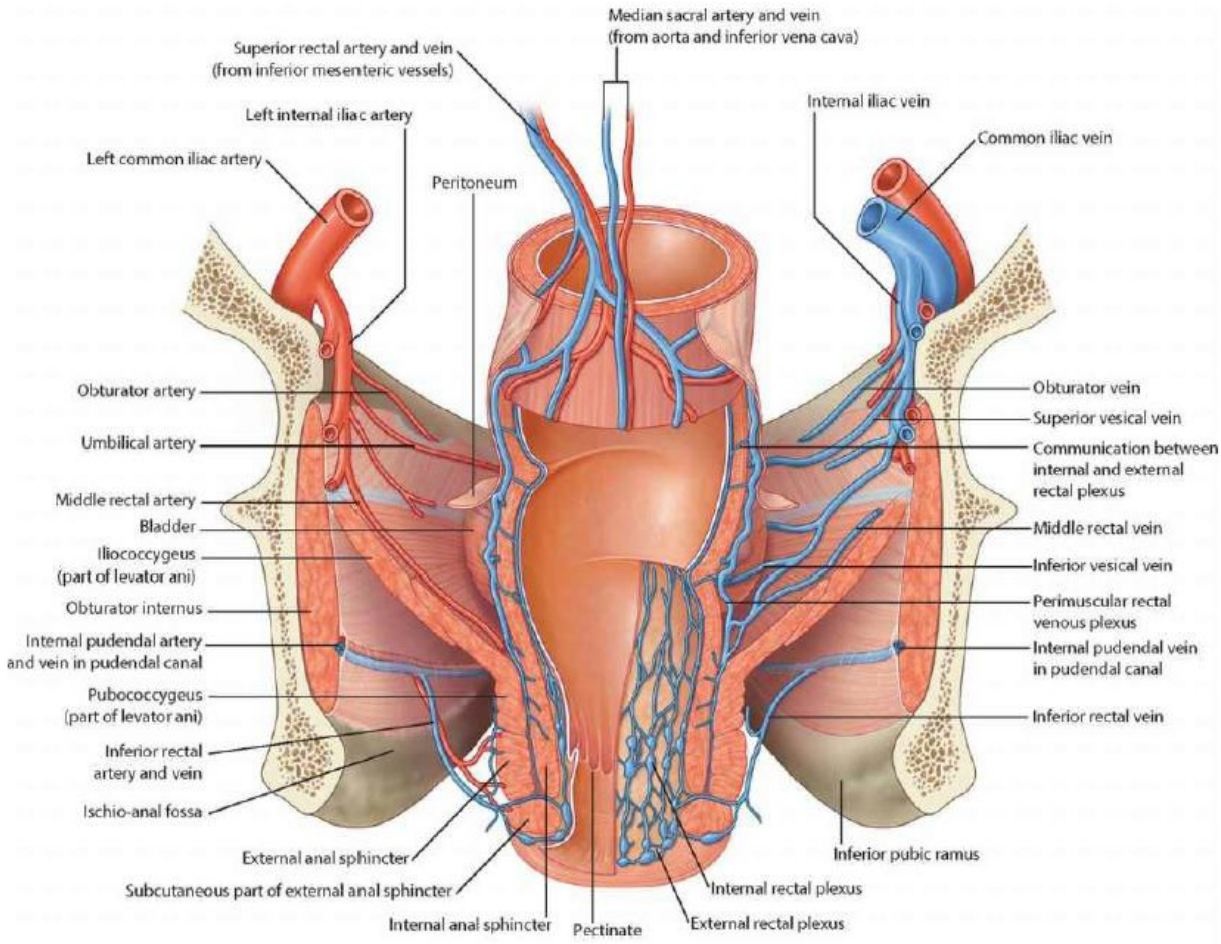

Figure 6. Vasculature of the rectum (posterior view) [5]

E. Lymphatic drainage of the rectum[3], [6], [9], [10]

Most of the lymphatic drainage of the rectum follows the corresponding arteries. The upper two-thirds of the rectum drains into the local lymph nodes along the superior rectal vessels, and then to the inferior mesenteric lymph nodes which are situated around the origin of the inferior mesenteric artery. Lymph from the lower third of the rectum drains into three sets of principal nodes which are the internal iliac lymph nodes bilaterally and the inferior mesenteric lymph nodes. For the TNM cancer classification, the lymph nodes are divided into those close to the rectal wall (N1) and those centrally placed but still inside the mesorectum(N2). Radical extirpative surgery and adjuvant radiotherapy with curative intent must address all these lymph node groups.

F. Innervation[9], [11]

The rectum obtains sensory and autonomic innervation. Parasympathetic nervous supply to the rectum comes from S2-4 via the pelvic splanchnic nerves and inferior hypogastric plexuses. The sympathetic supply comes from lumbar splanchnic nerves and superior and inferior hypogastric plexuses. Visceral afferent (sensory) fibers follow the parasympathetic supply.

G. Topographical relations of the rectum [3], [9], [11]–[13]

Posterior to the rectum lie the ventral surface of the sacrum, the coccyx, the presacral fascia, the presacral space which contains the median sacral vessels and the presacral venous plexus, the sacral sympathetic chain, and the piriformis and the levator ani muscles (Figure 3).

Laterally, the rectum is related to a condensation of pelvic fascia called the lateral ligament, the inferior plexus (whose disruption after radical surgery for cancers of the rectum may cause bladder dysfunction in both sexes and erectile and/or ejaculatory dysfunction in males), the sigmoid colon, and terminal ileum.

The anterior topographical relations of the rectum vary in the two sexes. *In the female*, the rectum beneath the level of the peritoneal reflection is related to the posterior wall of the intra-pelvic vagina. Above the peritoneal reflection lies the pouch of Douglas or the rectouterine pouch, which is inserted between the posterior vaginal fornix and the rectum. Above the vaginal fornix, the rectum is related to the posterior wall of the uterus, and between the two lies loops of the small bowel (Figure 7). *In the male*, the rectum below the peritoneal reflection is related to the posterior aspects of the left and right seminal vesicles, the left and right vas deferens, the inferior segments of the two ureters, the posterior surface of the urinary bladder, and below the bladder neck the posterior surface of the prostate. All the above-named urogenital structures are separated from the fascia propria of the rectum by the fascia of Denonvilliers (known also as the rectovesical fascia and the rectovesical septum). Above the peritoneal reflection, ahead of the upper two-thirds of the rectum lie loops of the small bowel and possibly the free lower and of the greater omentum.

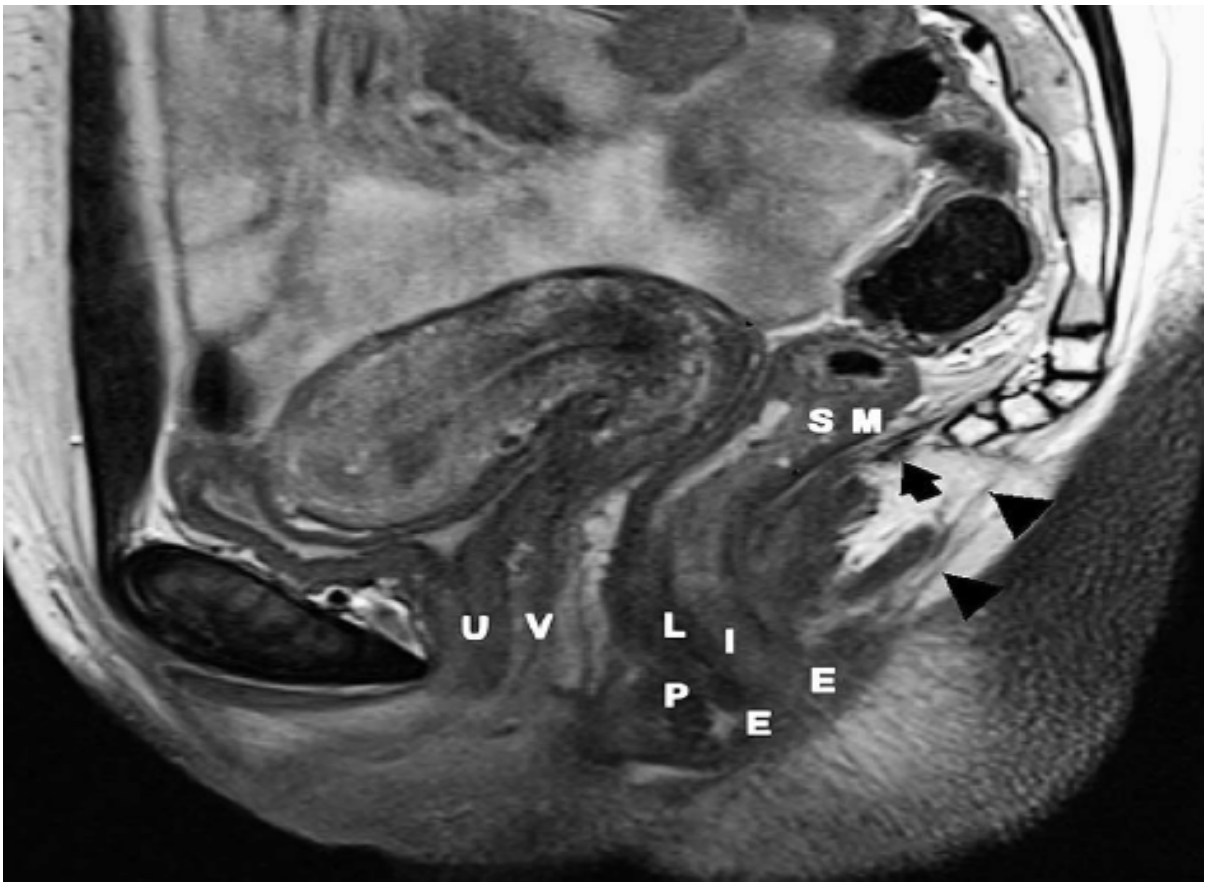

Figure 7. Midsagittal T2 weighted TSE with external coil demonstrates the internal sphincter (I), longitudinal layer (L), external sphincter (E), perineal body (P), anococcygeal ligament (arrowheads), pelvic diaphragm (arrow), vagina (V), and urethra (U). The rectal wall mucosal/submucosal layer (S) and the muscularis propria (M) are demonstrated as separate layers (MRI imagery) [7]

II. Epidemiology

A. Worldwide[14]–[20]

In 2020, the number of new rectal cancer cases worldwide was 732210 (3.8% of all new cancer cases of all sites), and the number of new deaths was 339022 (3.4% of new deaths due to all cancers combined).[14]

Incidence and mortality are slightly different depending on sex (Table 1).

Incidence					
males			Females		
Cases	Age-Standardized rate (world)	Cumulative risk, ages 0-74 years, %	cases	Age-Standardized rate (world)	Cumulative risk, ages 0-74 years, %
443358	9.8	1.18	288852	5.6	0.65
Mortality					
males			Females		
Cases	Age-Standardized rate (world)	Cumulative risk, ages 0-74 years, %	cases	Age-Standardized rate (world)	Cumulative risk, ages 0-74 years, %
204104	4.4	0.50	134918	2.4	0.26

Table 1. Incidence (Cases, Age-Standardized Rate, Cumulative Risk) and Mortality (Deaths, Age-Standardized Rate, Cumulative Risk) for rectal cancer by sex in 2020.[14]

Overall, it is estimated that 1.6 million cases are diagnosed with colorectal cancer each year, with 30% of it being rectal cancer, thus colorectal cancer ranks third in terms of incidence, but second in terms of mortality, with higher incidence rates in transitioned countries in comparison to transitioning countries, although there isn't much difference in mortality rates due to higher fatality in transitioning countries.

Growing incidence has been reported from various parts of Africa which were treated as low incidence areas.

B. Morocco

In morocco, the average age of occurrence of colorectal cancer according to the estimates of the National Institute of Oncology (INO) is 51.5years old with 26.6% of patients under 40 years old for rectal cancer.[21]

In morocco, colorectal cancer ranks 3rd in the incidence of cancer in men after lung and prostate cancers, while it ranks 4th in women after breast, cervical, and thyroid cancers.[22]–[25]

In 2014, the number of men dying of cancer was 12500 (7.4% died from colorectal cancer) while the number of women dying of cancer was 10400 (7.4% died from rectal cancer). The incidence of colorectal cancer in men was 1358 compared to 1126 in women.[22]

C. Risk factors [16], [26]–[33]

It's been noted that many factors contribute to the risk of colorectal cancer, although the studies may differ and the degree and statistical results, they agree that these factors contribute to increasing the incidence of colorectal cancer, noting that most studies evaluate the risk of both colon and rectal cancer at the same time.

It is found that *physical activity* is more associated with colon cancer compared with rectal cancer; many explain it is due to the effects of insulin. While it is noted that *obesity* is considered a risk factor, especially for people with a body mass index exceeding 30. Many studies find a strong association between *smoking* and rectal cancer, even more than colon cancer. When it comes to food, many studies demonstrate that higher *vegetable and fruit* and *whole-grain products* intake is associated with a lower incidence of colorectal cancer, whilst a high intake of *refined grains* is associated with increased colorectal cancer risk. Furthermore, *fat* and *red or processed meat* and *alcohol* increase the risk for colorectal cancer, which has been noted in many recent studies.

Patients with inflammatory bowel diseases such as Crohn's disease and hemorrhagic rectocolitis disease are known to have a bigger risk for colorectal cancer.

3 to 6% of all colorectal cancer is pinned on inherited familial syndromes, like Familial Adenomatous Polyposis, Lynch syndrome, and hamartoma syndromes. Noting that family history remains a big risk factor in rectal cancer even outside of these defined genetic syndrome disorders.

III. Diagnosis

A. Clinical presentations [34]–[37]

Although it is thought that a large number of asymptomatic cases in early stages are diagnosed due to the current screening programs worldwide, it is a fact that in most developing countries rectal cancer is discovered due to clinical signs before confirming it using paraclinical tests, so a practitioner should always be aware of these clinical presentations and symptoms to not overlook and miss any rectal cancer case.

The most common symptom is *rectal bleeding*, either *haematochezia* (the passage of fresh blood through the anus, usually in or with stools, in contrast to melena which is dark black, tarry feces that are associated with upper gastrointestinal bleeding) or *rectorrhagia* (rectal bleeding that is not associated with defecation). Rarely, in tumors located in the upper rectum, we can have *iron deficiency anemia* due to blood loss, although it is usual in colon cancer.

Thus, the rectal examination must be practiced systematically to search for any signs of bleeding, pain, or the presence of abnormalities

Abdominal pain is also found in many cases, usually due to the metastatic migration of the tumor cells. *Change in bowel habit* is also a usual sign, associated with *constipation*, *rectal pain*, *mucus in stools*, and *tenesmus*.

We can also encounter *anorexia*, *nausea*, *vomiting*, and *fatigue* in many patients.

Fever of unknown origin, bacteremia or sepsis, abscesses (as a result of localized perforated cancer), fistula formation into adjacent organs (such as bladder or vagina) has also been reported as rare presentations.

In many cases, physicians(and patients) care more about the severity, frequency, duration, and persistence of symptoms than their presence or absence, which leads many times to miss the diagnosis and wasting precious time that can be used in treating less severe rectal cancer if found earlier. Especially since many studies have found that the duration of symptoms was not associated with the stage of cancer. Thus a physicist should always keep in mind the probability of rectal cancer presence, especially in older patients or patients with risk factors.

B. Paraclinical tests [27], [34], [46]–[53], [38]–[45]

Once rectal cancer is suspected from symptoms and signs or by rectal examination, *colonoscopy* is required. Using a colonoscope (a thin, flexible, lighted tube with a small video camera on the end), the doctor examines the entire length of the rectum and the colon (Figure 8). In rectal cancer, colonoscopy is associated with *rigid proctoscopy* (a thin, rigid, lighted tube with a small video camera on the end) or *sigmoidoscopy*.

Rigid proctoscopy has proved to be a great reproducible method of determining the level of rectal cancer and does not count upon the operator. Sigmoidoscopy permits one to see only the lower part of the colon and rectum. Moreover, colonoscopy helps one to obtain an image of the whole intestine with similar specificity and sensitivity. Both colonoscopy and flexible sigmoidoscopy are usually used for diagnosis and screening in rectal cancer, and although flexible sigmoidoscopy is an accurate diagnostic method for rectal cancer, a colonoscopy is necessary for evaluating other parts of the colon in search of synchronous colonic polyps or other associated tumor sites.

If any suspicious areas are found, the doctor can use surgical tools through the colonoscope to take tissue samples for further histological studies (*biopsy*). A biopsy helps in determining whether the cells are cancer, whether they're aggressive or not, and which genes in the cancer cells are abnormal (like changes in NRAS, KRAS, and BRAF genes).

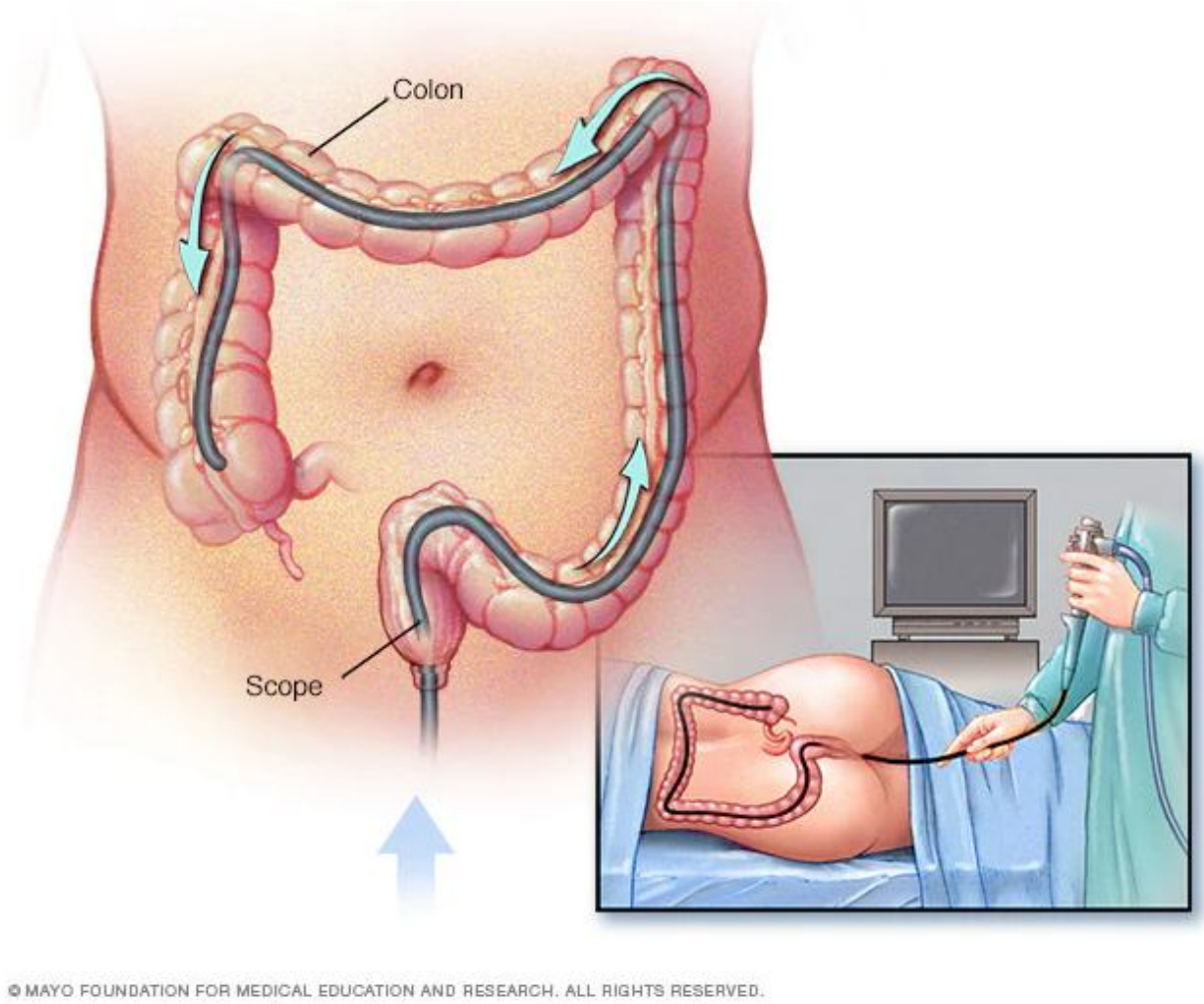

Figure 8. Colonoscopy [39]

Chest, abdomen, and pelvis computed tomography (CT) scan can be used for staging evaluation of rectal cancer and metastasis studying. *Abdominal and endorectal ultrasound* can distinguish localized involving the mucosa and muscularis propria or perirectal fat (Figure 9).

Magnetic resonance imaging (MRI) is very useful in differentiating malignant tissues from the propria and defining tumoral infiltration of the mesorectal fascia (Figure 7). MRI can also be used for staging rectal cancer.

MRI is the modality that has the highest soft tissue contrast, and the introduction of endoluminal coil further improved image resolution and detailed evaluation of rectal wall layers. When it comes to staging using MRI, it is done based on the criteria laid down by AJCC (American joint committee on Cancer) as T staging, T substaging, and N staging through meticulous interpretation of thin-section, high-resolution, and small FOV T2-weighted images acquired perpendicular to the rectal wall.

MRI is used also in post-treatment assessment, especially after neoadjuvant treatment and before surgery. In case of effective tumor response to the treatment, the tumor is shown on MRI either as hypointense foci on T2W high-resolution images portraying fibrosis or in some cases as hyperintense fluid signal thanks to colloid response. Tumor tissue appears as intermediate signal foci.

To evaluate the effect of neoadjuvant chemoradiotherapy, the MRI should describe:

- Morphological image of the tumor

- Height of treated tumor from anal verge in comparison with baseline pretreatment images
- Distance to potential circumferential resection margin and whether this looks conceivably involved or clear
- MR imaging T stage and T substage, taking into consideration the depth of extramural spread
- Existence of extramural venous invasion
- Mesorectal and pelvic sidewall nodal status

MRI is usually performed 6 to 8 weeks after finishing chemoradiotherapy, and it can show tumor volume shrinkage. Moreover, when it comes to the detection of an involved mesorectal fascia, it is reported that MRI has negative predictive values (NPVs) as high as 90% (at the expense of 50% positive predictive values [PPVs]), which suggests that it can precisely assess clearance from formerly suspicious invaded mesorectal resection margin. Because of its larger field of view and more detailed information on pelvic anatomy, MRI is superior to endorectal ultrasonography in this setting.[53]

When using MRI results to assess the tumor response to neoadjuvant treatment, one has to bear in mind that there can be intra- and interobserver variability in measuring geometrically irregular tumors like rectal cancer, which then cannot be reproduced without difficulty. Moreover, a complete response is described as the complete disappearance of the tumor, while a partial response is defined as a reduction in tumor length > 30%, and progression is defined as at least a 20% increase in tumor length. Furthermore, stable disease is described as neither sufficient shrinkage nor sufficient increase of disease.

Furthermore, the prognosis of rectal cancer is greatly dependent on the early detection of liver metastases. In many studies, MRI proved its high specificity and sensitivity for the detection of live metastases[51]. Also, many studies showed the diagnostic superiority of combining diffusion-weighted imaging and gadoxetic acid-enhanced MRI, particularly in terms of per lesion sensitivity, compared to CT and FDG-PET[50].

The chest x-ray is used to examine the lungs in search of metastatic sites. *Positron emission tomography (PET) scan* can also be used in the metastatic evaluation, although it is used less and less in practice. Angiography can show the arteries that supply blood to those tumors existing within the liver and helps surgeons decide if the liver tumors can be removed and if so, it can help plan the operation.

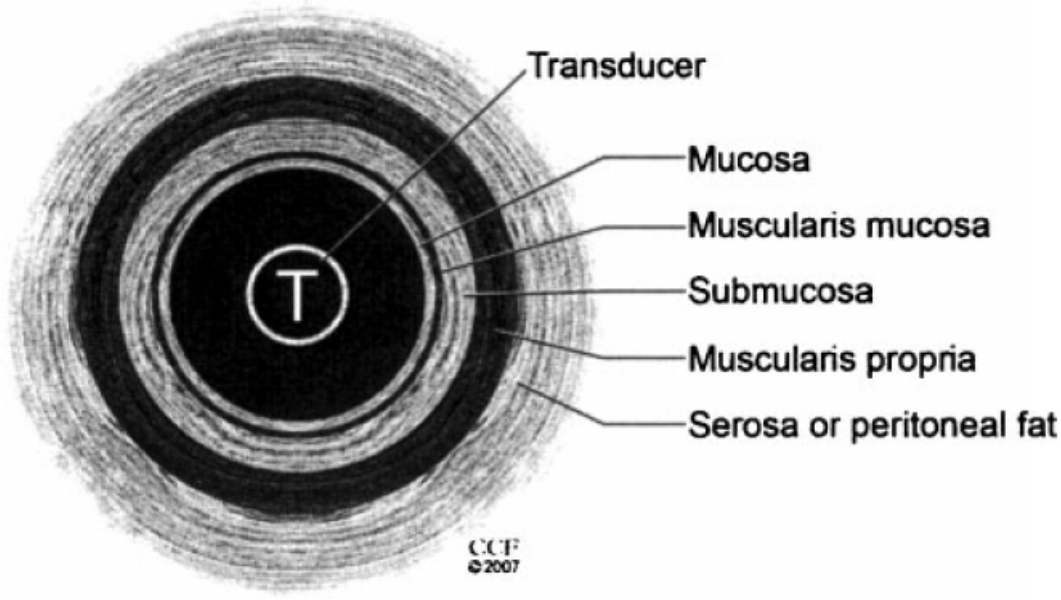

Figure 9. Five-layer model for the interpretation of endorectal ultrasound. [54]

When it comes to Noninvasive diagnostic methods, the *Fecal occult blood test (FOBT)* which reveals hemoglobin in feces, and *Fecal immunochemical tests (FIT)* appear to be accurate for detecting colorectal cancer, and they require the patient to collect 1 to 3 samples of stool from a bowel movement. A *stool DNA test* (also known as FIT-DNA or a multitargeted stool DNA test [MT-sDNA]) looks for certain abnormal sections of DNA from cancer or polyp cells and also for occult (hidden) blood.

Blood studies have a goal of assessing patients' organ function (liver, kidneys) in anticipation of diagnostic and therapeutic procedures and also to estimate tumor burden, they may include *Complete blood cell count, Liver function tests, Renal function tests, Serum chemistries, Serum carcinoembryonic antigen (CEA) level* (An elevated level of CEA in serum can be connected with carcinogenesis), *carbohydrate antigen (CA 19-9) level* (it is used in diagnostics of gastric, pancreatic, and colorectal cancer), *tissue polypeptide specific antigen (TPS) level* (it is used in diagnostics and monitoring of chemotherapy in bronchial tumors and gastrointestinal tract tumors (mainly colorectal and pancreatic)), and *tumor-associated glycoprotein (TAG-72) level.*

C. Histopathology[55]–[60]

It is noted that more than 90% of colorectal carcinoma are adenocarcinomas (cancer that begins in glandular (secretory) cells) originating from epithelial cells of colorectal mucosa. While there are other rare types of colorectal carcinomas like neuroendocrine, spindle cell, adenosquamous, squamous cell, and undifferentiated carcinomas. Typical adenocarcinoma is identified by glandular formation, which is the basis for histologic tumor grading. Poorly differentiated adenocarcinoma is largely solid with less than

50% gland formation. In moderately differentiated adenocarcinoma between 50% and 95% is gland formation. Well-differentiated adenocarcinoma shows more than 95% gland formation. In practice, most colorectal adenocarcinoma(roughly 70%) are diagnosed as moderately differentiated (Figure 10), while 10% are well-differentiated carcinomas and 20% are poorly differentiated carcinomas.

The biopsy needs to be well done because if it is poorly oriented or superficial, the microscopic examination becomes difficult especially when looking for evidence of invasion. In a microscopic examination, if the muscularis mucosae can be recognized, it is essential to determine whether it is disrupted by neoplastic cells because invasive carcinoma usually invades through the muscularis mucosae into the submucosae. The presence of desmoplasia or desmoplastic reaction is another feature of invasion (Figure 11). Invasive carcinoma can also present characteristic necrotic debris in glandular lumina which are called dirty necrosis (Figure 12)

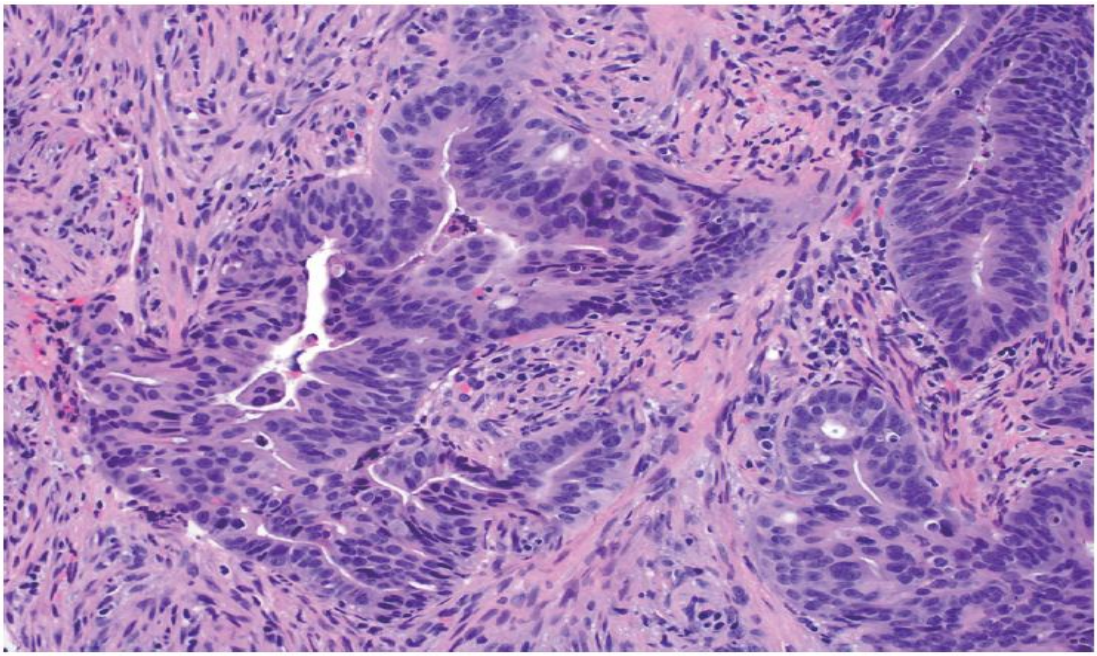

Figure 10. An example of moderately differentiated adenocarcinoma showing complicated glandular structures in a desmoplastic stroma (original magnification x400) [55]

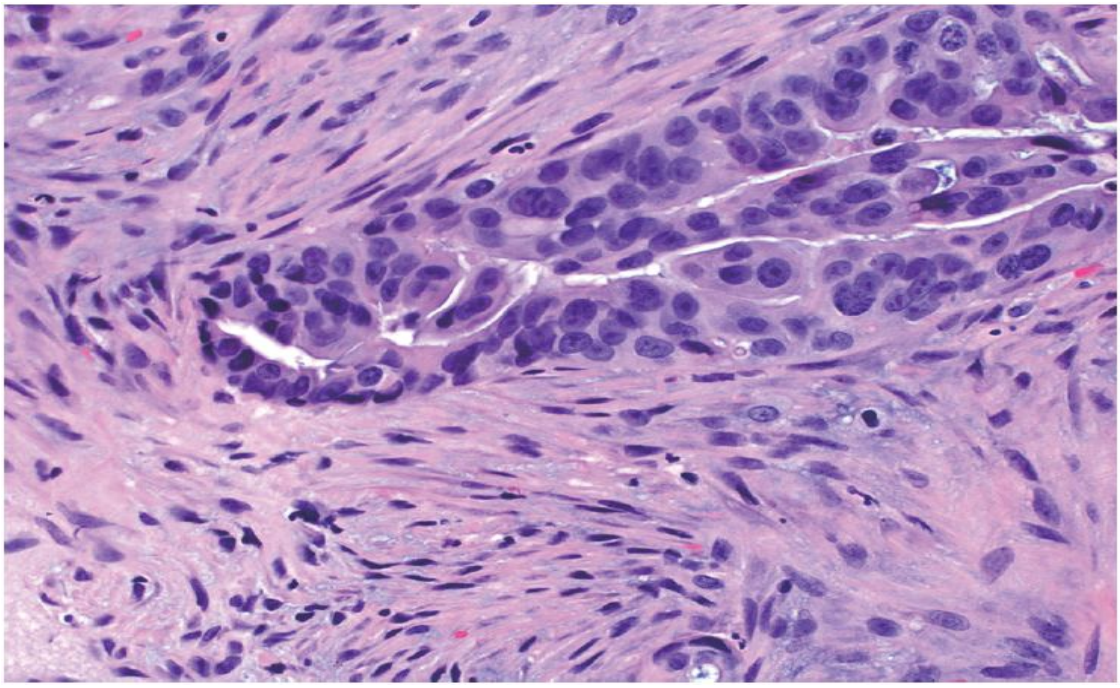

Figure 11. Desmoplastic reaction characterized by proliferation of spindle cells surrounding an adenocarcinomatous gland (original magnification x400) [55]

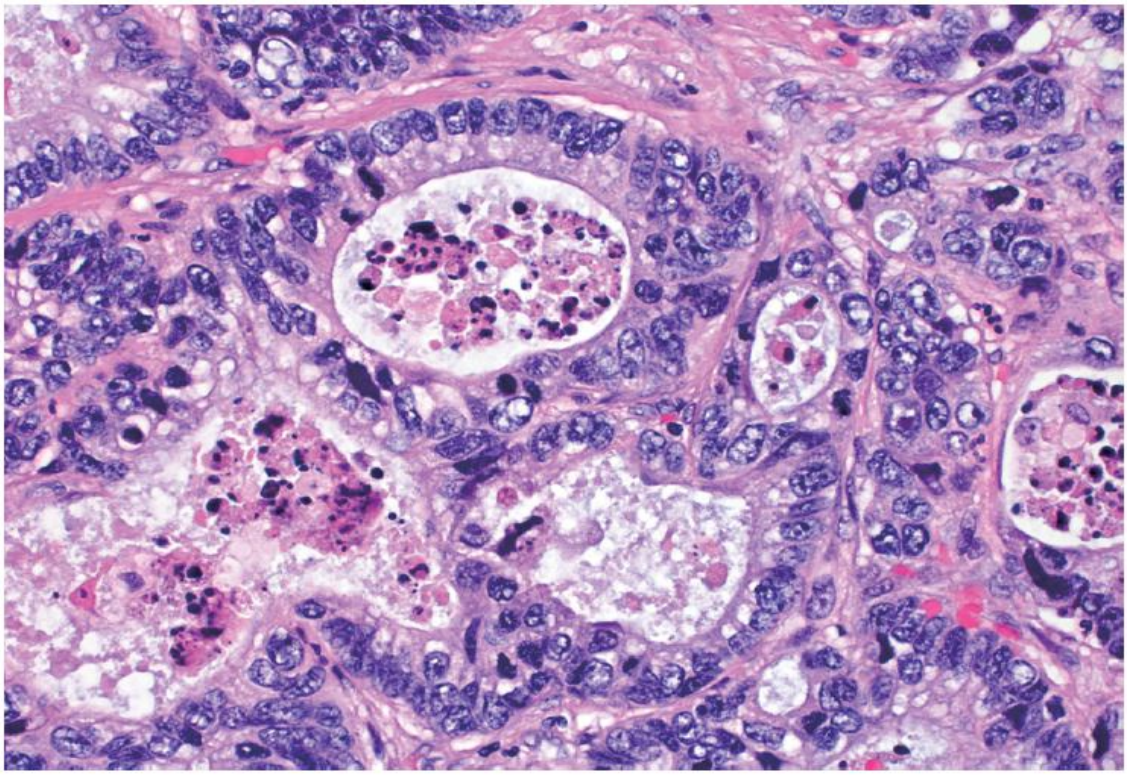

Figure 12. Dirty necrosis (necrotic debris) within the lumina of adenocarcinomatous glands (original magnification x400) [55]

Some studies [20] found that Mucinous carcinoma and signet ring carcinoma were more common in patients under 40 years old, while well-differentiated adenocarcinoma was more common in patients above 40 years old.

The fundamental difference between malignancy and dysplasia is invasion. Malignancy is revealed by the destroyed basement and sporadical dysplasia glands.

Many immunohistochemical markers for colorectal adenocarcinoma are used in immunohistochemical phenotyping. The most used are CK7, CK20, and CDX2.

We find two general descriptions of the histogenesis of colorectal cancer. the first is the *Adenoma-carcinoma sequence theory*, which demonstrates that cancer develops from a preexisting adenoma. While the second is the *Novo carcinoma theory*, which considers that cancer arises directly from the nonneoplastic tubules of the lamina propria of the mucosa.

IV. Staging [16], [27], [64]–[73], [34], [74]–[76], [47], [48], [54], [55], [61]–[63]

Once the diagnosis of rectal cancer is well-established, cancer's local and distant extension must be determined to establish a suitable therapeutic approach. Thus it is well known that an accurate staging holds the key to successful treatment of cancer, especially with the advances in surgical techniques and the advent of neoadjuvant treatment.

We start with an extensive physical examination associated with blood tests, followed by sigmoidoscopy and colonoscopy coupled with biopsy. All these procedures help define the malignancy of the tumor and may help to guide other more specific imaging tools.

Imaging has an essential role in defining the extent of cancer and providing the surgeon with an accurate and clear preoperative road map of the tumor and its relationship to other anatomical structures, and it also provides information on the systemic spread of the disease.

Usually, abdominopelvic CT, MRI, and transrectal endoscopic ultrasound (TRUS) coupled with the histologic examination are enough for locoregional evaluation. While chest CT, liver MRI, and PET scan can be used to detect distant metastasis.

The TNM (T for tumor, N for node, and M for metastasis) staging system for colorectal cancers is widely used to describe cancer's spreading.

T defines the extent of the tumor, which means how far cancer has grown into the wall of the rectum and specifies which layers are concerned.

N describes the spreading of cancer to nearby nodes. Lymph nodes near the rectum are called regional lymph nodes; the other lymph nodes are considered metastatic sites (Figure 13).

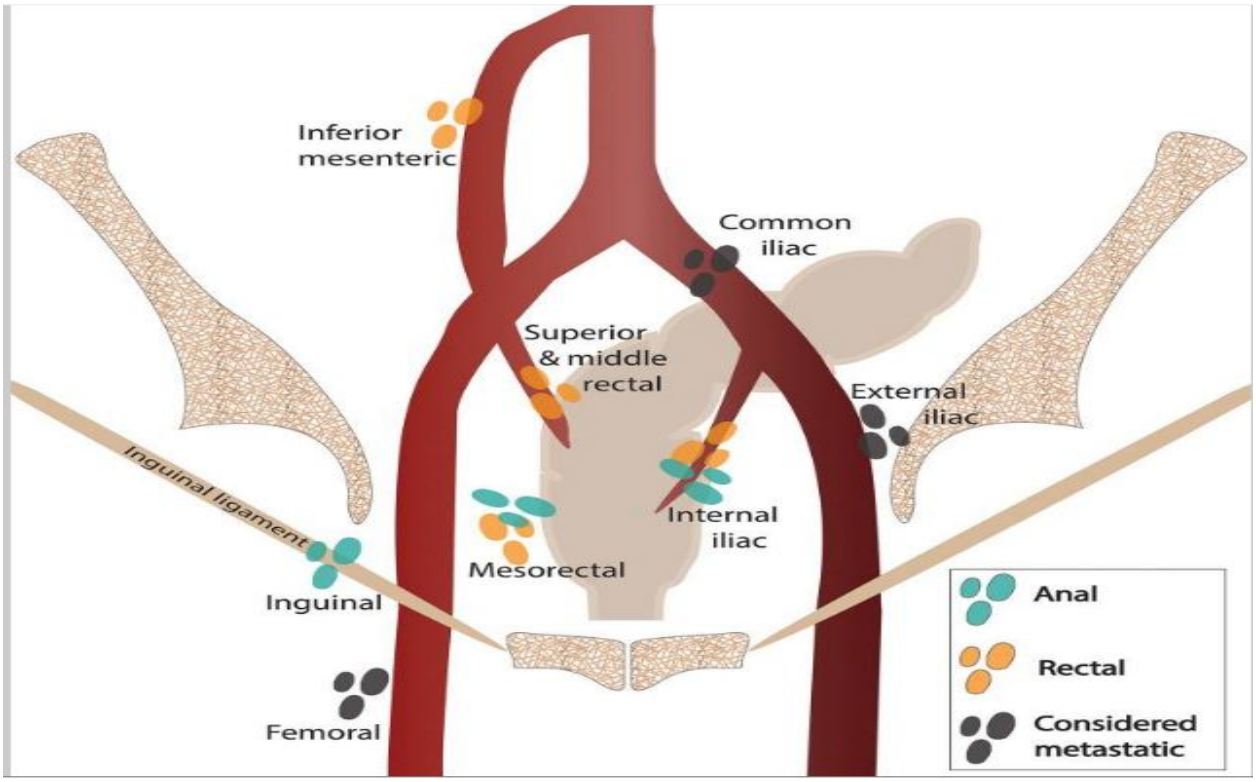

Figure 13. Coronal drawing showing the nodal stations relevant to anal and rectal cancers. Regional nodal stations are shown for anal cancers (blue-green) and rectal cancers (orange). Nodal stations considered metastatic for both anal and rectal cancer are shaded dark gray. [66]

M stands for metastasis, which means the spread of cancer to distant sites (distant lymph nodes and distant organs such as the liver or the lung).

The TNM staging system that is provided by the American Joint Committee on Cancer (AJCC) 8th edition (2017) is currently used worldwide.

- T (the primary tumor)
  - TX: the primary tumor cannot be assessed
  - T0: no evidence o the primary tumor
  - Tis: carcinoma in situ, intramucosal carcinoma (a lesion with invasion into the lamina propria with no extension through muscularis mucosae)
  - T1: tumor invading submucosa (through the muscularis mucosa but not into the muscularis propria)
  - T2: tumor invading muscularis propria
  - T3: tumor invading through the muscularis propria into the pericolorectal tissues
  - T4:
    - T4a: tumor invading through the visceral peritoneum (including gross perforation of the bowel through the tumor and continuous invasion of the tumor through areas of inflammation to the surface of the visceral peritoneum)
    - T4b: tumor directly invading or adhering to other adjacent structures or organs

- N (regional lymph nodes)
  - NX: the regional lymph nodes cannot be assessed
  - N0: no regional lymph node metastasis was found
  - N1: metastasis found in 1 - 3 regional lymph nodes
    - N1a: metastasis found in 1 regional lymph node
    - N1b: metastasis found in 2 - 3 regional lymph nodes
    - N1c: no regional lymph node metastasis are found but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirectal/mesorectal tissues
  - N2: metastasis found in 4 or more regional lymph nodes
    - N2a: metastasis found in 4 - 6 regional lymph nodes
    - N2b: metastasis found in 7 or more regional lymph nodes
- M (distant metastasis)
  - M0: no distant metastasis is found by imaging; no evidence of tumor is found in other sites or organs (this category is NOT assigned by pathologists)
  - M1: distant metastasis are found
    - M1a: metastasis confined to one organ or site without peritoneal metastasis
    - M1b: metastasis to two or more sites or organs is identified without peritoneal metastasis
    - M1c: metastasis to the peritoneal surface is found alone or with other site or organ metastases

NOTES:

- A minimum of 12 regional lymph nodes must be recovered for lymph node staging to be considered accurate in curative resections
- It has been reported that the number of recovered nodes correlates with a better prognosis, most likely due to more accurate staging
- Metastasis to nonregional lymph nodes outside of the drainage area of the tumor, i.e. those not found along vascular arcades of the marginal artery or pericolonic, perirectal, or mesorectal nodes should be considered distant metastasis (M1a)
- Multiple metastases in an organ, even paired organs (ovaries, lungs), are still M1a disease

The stage of cancer describes how much cancer is in the body (Table 2).

Stage	T	N	M
0	Tis	N0	M0
I	T1-2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-4a	N1/N1c	M0
	T2-3	N2a	M0
	T1-2	N2b	M0
IIIC	T4a	N2a	M0
	T3-4a	N2b	M0
	T4b	N1-2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

Table 2. Tumor-node-metastasis stages in the AJCC 8th edition[77]

V. Prognosis [78], [79], [88]–[97], [80], [98]–[100], [81]–[87]

Disease stage (TNM) has been validated as a prognostic factor in multi-institutional prospective studies. Clinical, pathologic, and molecular parameters have also been studied, yet none has been validated in multi-institutional prospective trials.

Moreover, other factors are related to the prognosis of patients with rectal cancer, including the following:

- Age (older patients are usually associated with less overall survival (OS))
- BMI (body mass index)
- Ethnic and racial differences (a shorted overall survival has been noted in black patients compared to white ones)
- Absence or presence of tumor involvement in the lymph nodes and the number of positive lymph nodes
- Absence or presence of distant metastasis
- Obstruction or perforation of the rectum
- Tumor adherence to or invasion of adjacent organs
- Depth of penetration of the tumor through the bowel wall or Circumferential resection margin (CRM), which is defined as the retroperitoneal or peritoneal adventitial soft-tissue margin closest to the deepest penetration of tumor (Measured in millimeters)

- Absence or presence of high-risk pathologic features, including the following:
  - Lymphovascular invasion
  - Poorly differentiated histology
  - Positive surgical margins
  - Perineural invasion

In morocco, in 2020, the 5-year prevalence in all ages numbered 4541 cases, and the proportion (per 100000) was 12.30.[100]

In the United States, the 5-year survival rates for rectal cancer are 88% for stage I, 81% for stage IIA, 50% for stage IIB, 83% for stage IIIA, 72% for stage IIIB, 58% for stage IIIC, and 13% for stage IV.[84]

VI. Treatment

A. Therapeutic means

1. Surgery[2], [8], [106]–[115], [27], [116]–[125], [34], [126]–[135], [47], [136]–[138], [101]–[105]

Surgery is the removal of the tumor and some surrounding healthy tissue during an operation. It is the most common treatment in rectal cancer and the cornerstone of curative therapy, especially for cases with resectable rectal cancer. Surgical treatment can be performed as the sole treatment modality or in combination with neoadjuvant and/or adjuvant therapies depending on the location of the tumor and its stage. Bowel continuity and anorectal sphincter preservation are also considered as goals of the surgical treatments.

a) Radical resection

When cancer spreads into the wall of the rectum, the surgeon removes the section of the rectum with cancer and nearby healthy tissue. Sometimes, he removes also the tissue between the rectum and the abdominal wall. The lymph nodes near the rectum are removed to be studied. Many types of resection are used depending on specific criteria and factors like:

- Level of the lesion (especially the distance of the lower edge of cancer from the dentate line)
- Nature of carcinoma
- Patient factors like age and medical fitness
- Mesorectal lymph node status

When the cancer is surgically removed, the surgeon will sew the healthy parts of the rectum together, by sewing either the colon to the remaining rectum or the colon to the anus. This is doing an **anastomosis**.

Many types of anastomosis have been studied. There is the *straight coloanal anastomosis, the colonic J-pouch reconstruction* (in which a small pouch is made by doubling back a short piece of the colon), and the *coloplasty* (in which a segment of the colon is enlarged). The last two options are favored for imitating a small reservoir that provides storage for feces like the rectum did before the surgery.

A **colostomy** is a procedure that creates an opening for the colon through the abdomen, and it may be temporary or permanent. Due to the modern surgical techniques and the use of neoadjuvant treatments before surgery when needed, most patients who receive treatment for rectal cancer do not need a permanent colostomy. Ileostomy, which is a stoma between the ileum and the abdominal wall, can also be used.

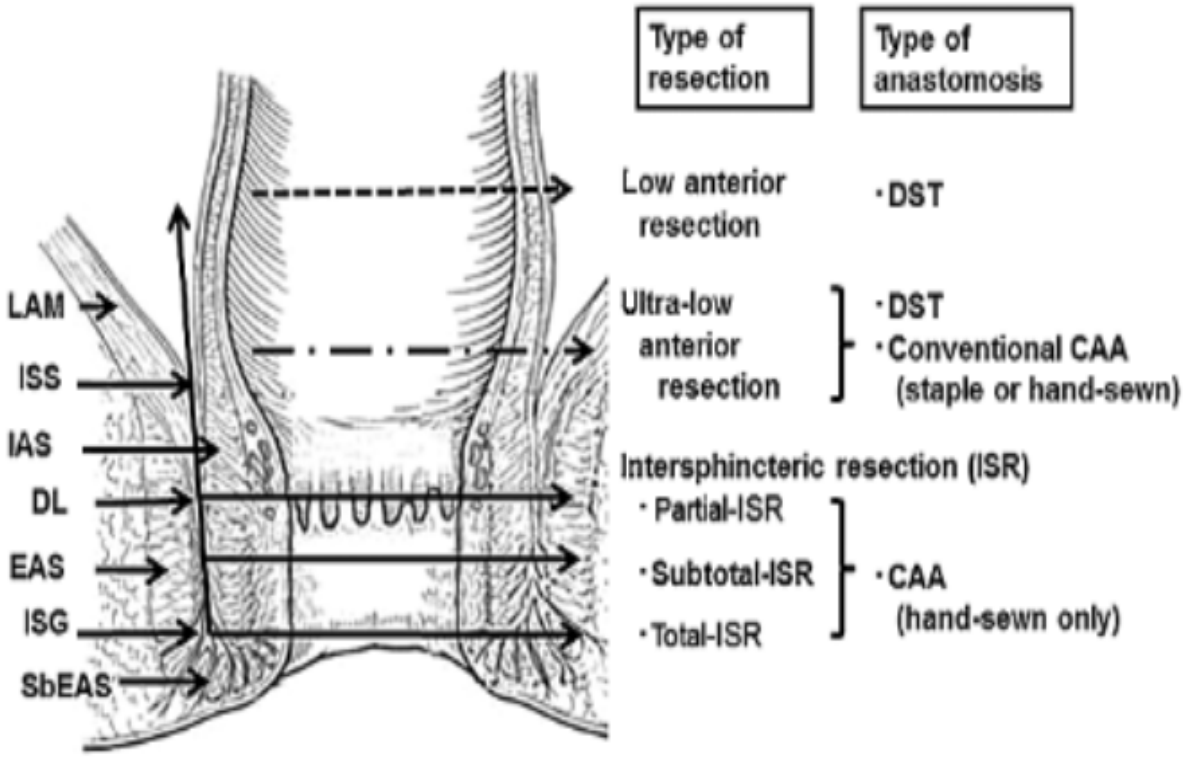

Figure 14. Definition of intersphincteric resection. The resection line of the rectum or anal canal varies depending on the location of the tumor from the anal verge. Total intersphincteric resection (total-ISR) is defined as an internal sphincter resection at the intersphincteric groove (ISG), subtotal-ISR is between the dentate line (DL) and ISG, and partial-ISR is at the DL. CAA, coloanal anastomosis; DST, double stapling technique; EAS, external anal sphincter; IAS, internal anal sphincter; ISS, intersphincteric space; LAM, levator ani muscle; SbEAS, subcutaneous part of external anal sphincter[128]

(1) Total mesorectal excision (TME)

TME is considered a standard surgery for rectal cancer in which the rectum and the mesorectum are removed up to the mesorectal fascia. Superiorly, the dissection is up to the root of the inferior mesenteric artery including superior rectal and inferior rectal nodes.

Both NCCN and ESMO (European Society for Medical Oncology) share the same criteria for TME, which insists that a mesorectal margin of 5cm from the tumor edge must be achieved[120].

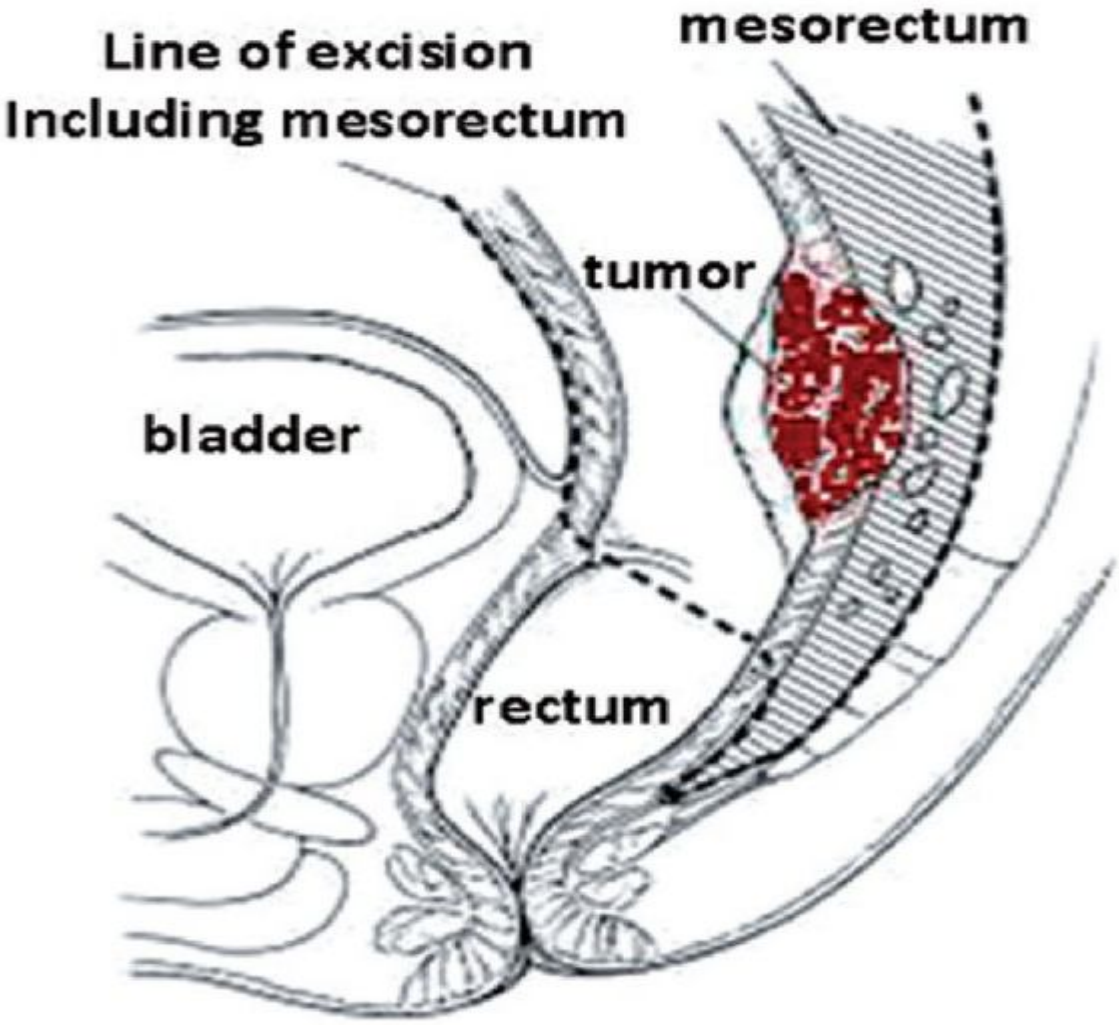

Figure 15. Sketch showing the principles and extent of TME[120]

(2) Intersphincteric resection (ISR)

Intersphincteric resection of low rectal tumors is a surgical procedure extending rectal resection into the intersphincteric space. This technique is performed by a synchronous abdominoperineal approach with mesorectal excision and excision of the entire or part of the internal sphincter.

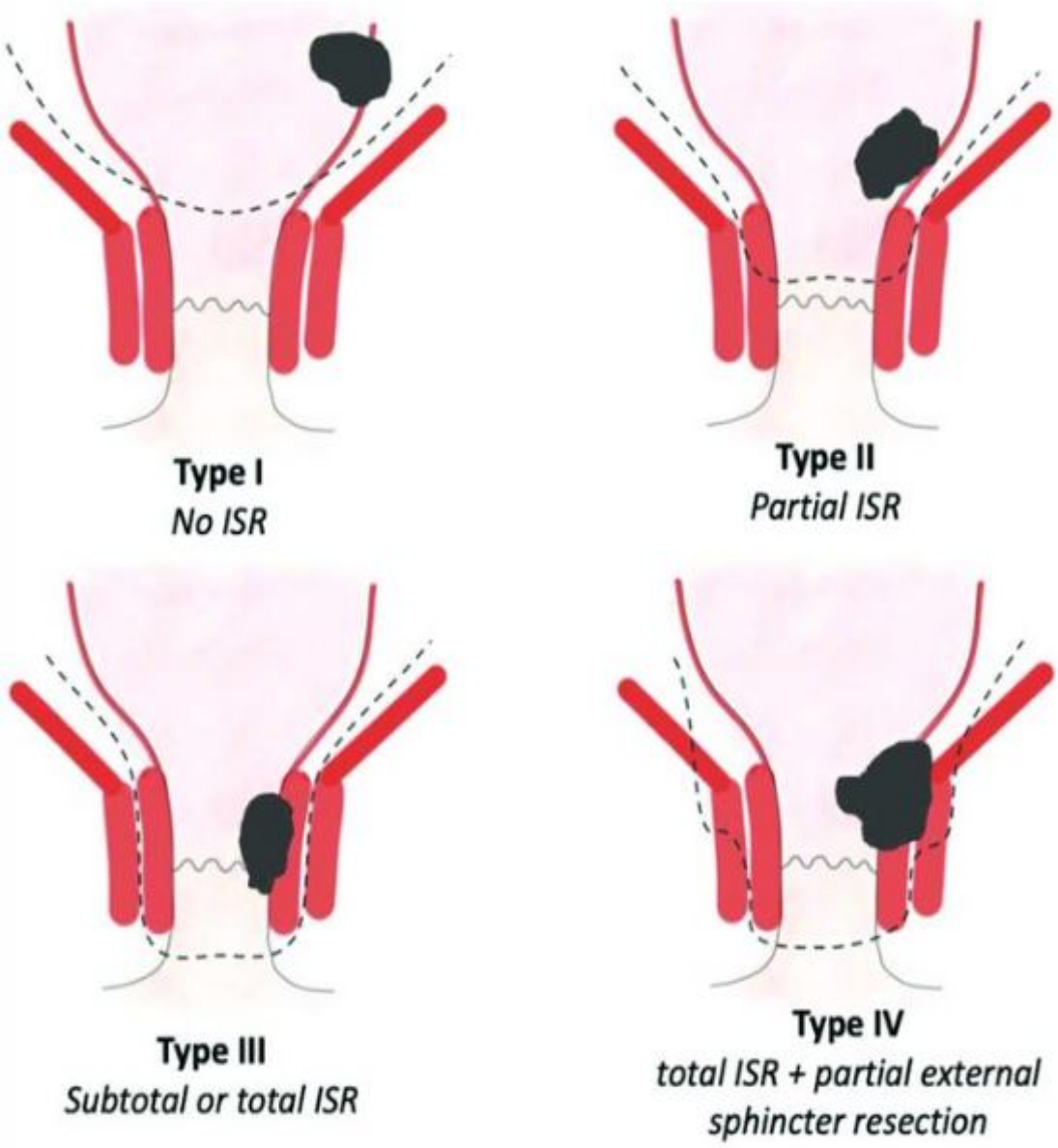

Figure 16. Different options of intersphincteric resection[125]

(3) Low anterior resection (LAR)

LAR consists of removing the part of the rectum containing the tumor. Afterward, the lower part of the colon is attached to the remaining part of the rectum (Figure 18). This type of surgery concerns cancers that are located in the upper part of the rectum, mostly stage II and III. The caudal extent of the surgery where the anastomosis is located is situated below the anterior peritoneal reflection, but it is positioned above the anorectal junction and the sphincter is entirely preserved (Figure 17). For tumors located in the distal rectum without invasion to the anal sphincter, it is recommended to do a very low anterior resection (VLAR) or ultra-low anterior resection (ULAR).

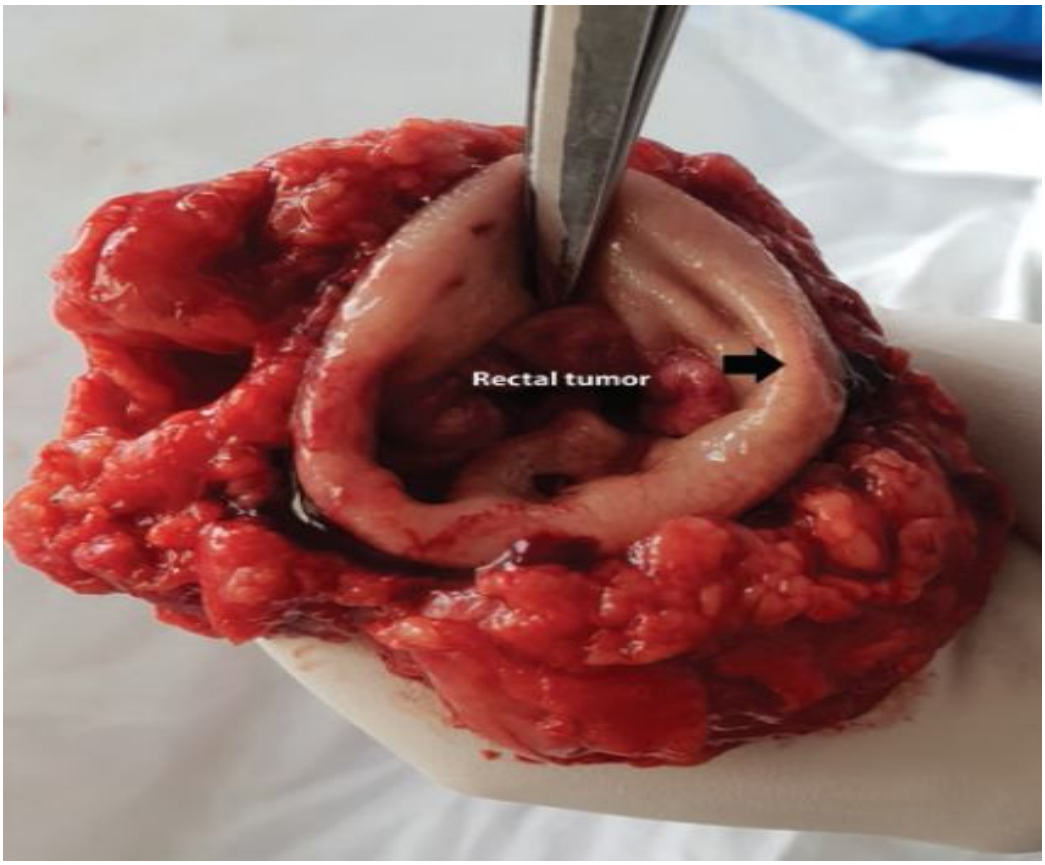

Figure 17. Low anterior resection specimen; when measured on fresh resected specimen a 2 cm distal safe margin was found [106]

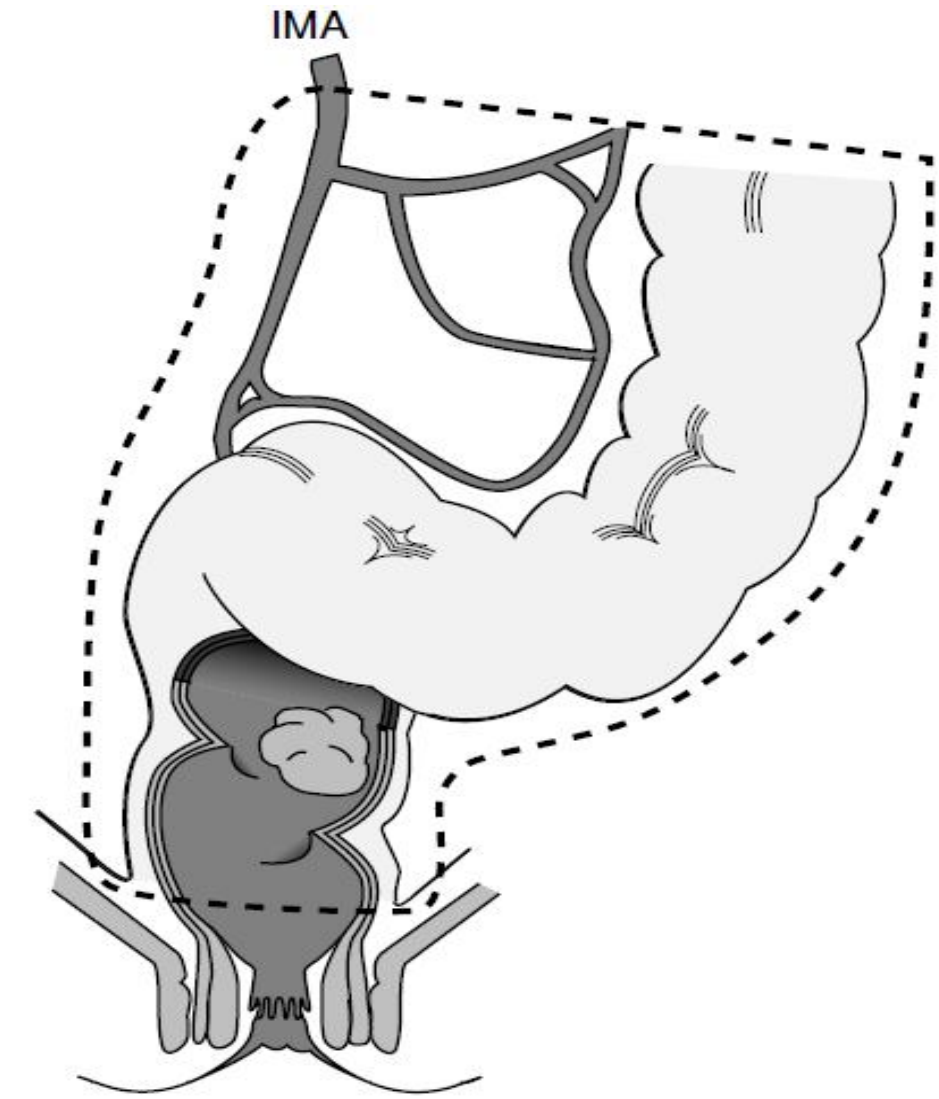

Figure 18. Anterior resection for rectal cancer; IMA, inferior mesenteric artery.[111]

(4) Abdomino-perineal resection (APR)

APR is a kind of TME surgery where the distal resection margin is situated below the anorectal junction, thus the entire anal canal/sphincter complex is removed and the patient gets a permanent colostomy. It is considered more involved than LAR, and it is used to treat many stages II and III cancers located in the lower part of the rectum (Figure 19).

The introduction of neoadjuvant treatments and the improvement of surgical techniques led to an increase in the number of interventions that aim to maintain the anal sphincter in cases of low rectal cancer, thus decreasing the number of APRs been done.

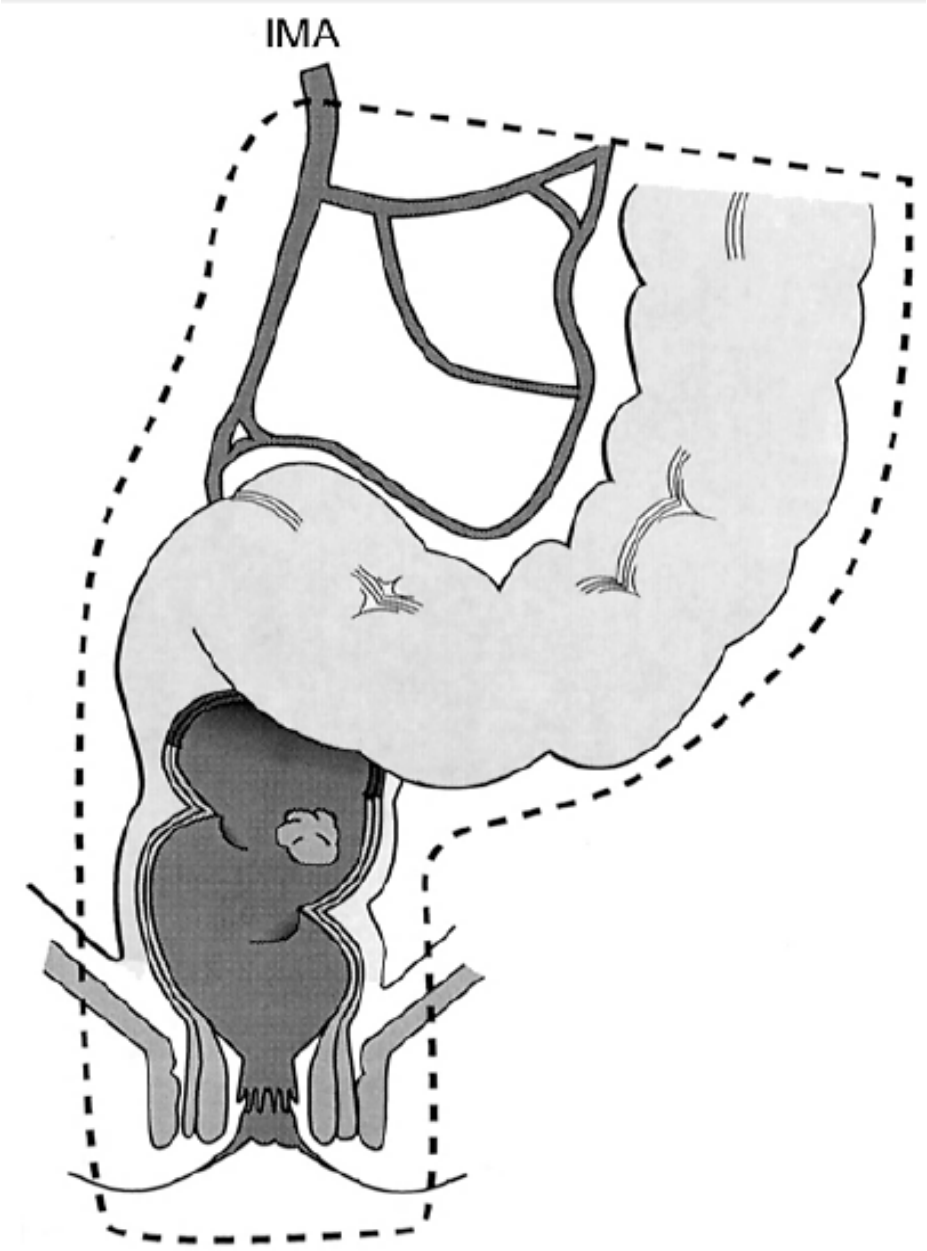

Figure 19. Abdominoperineal resection of the rectum; IMA, inferior mesenteric artery.[111]

(5) Hartmann's resection

This procedure consists of an anterior resection of the rectum without an anastomosis. It is followed by intraperitoneal closure of the rectal stump associated with a colostomy (Figure 20). This method was initially used in obstructive colorectal cancer, while nowadays it is usually used as an intervention in complex emergency cases or as a palliative procedure.

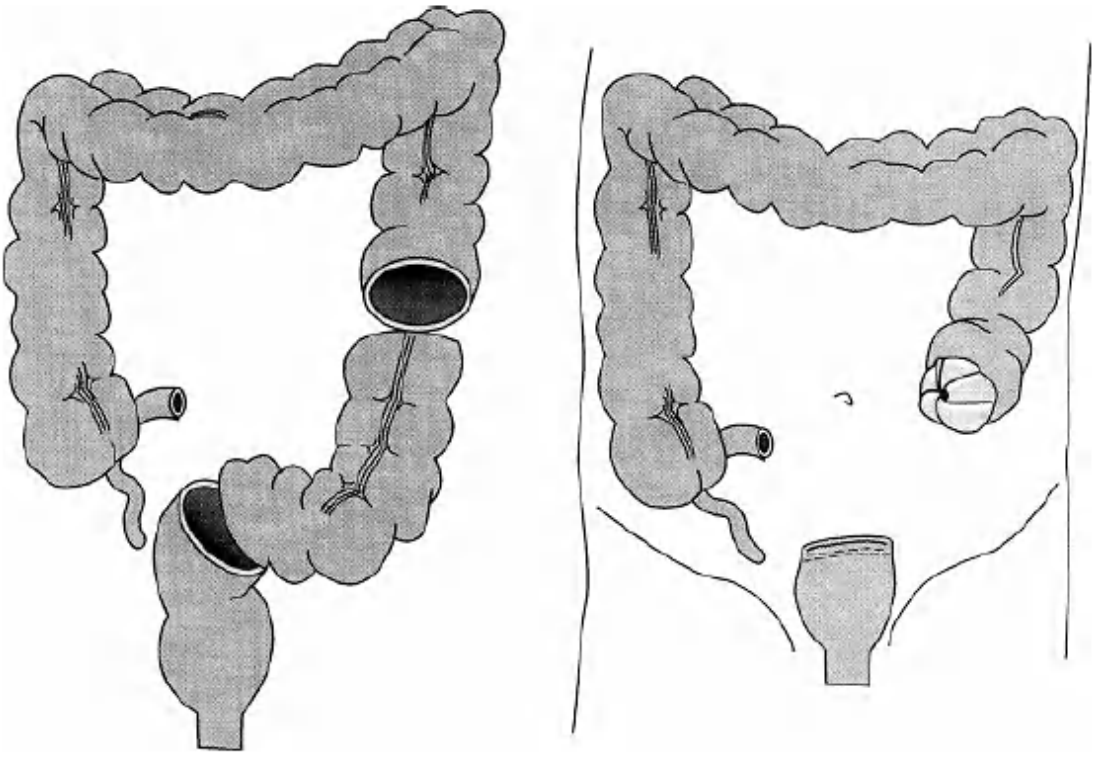

Figure 20. Hartmann's procedure for cancer of the sigmoid colon or upper rectum and sigmoid end colostomy[111]

b) Pelvic exenteration

When cancer spreads to other organs near the rectum, a pelvic exenteration should be done. It is a major operation, in which the surgeon must remove the rectum as well as any nearby organs that cancer has reached, such as the bladder, prostate (in men), uterus, cervix, vagina, and ovaries (in women). A colostomy is a must after pelvic exenteration, and so is a urostomy if the bladder is removed.

c) Lymph node dissection in rectal cancer

The lymphatic spread of rectal cancer can be done in three directions or lymphatic flow routes: the upper route is along the superior rectal artery to the inferior mesenteric artery, the lateral one goes from the middle rectal artery toward the pelvis alongside the internal iliac artery, and the third one spreads downward to the inguinal lymph nodes

The upper route is enveloped in the mesorectum, and by consequence is removed in standard TME. The downward one is involved solely concerned when cancer growth has infiltrated into the anal canal. The lateral one appears to be involved particularly in low and more advanced rectal cancers and is left in situ with total mesorectal excision alone.

The lateral lymph nodes comprise the obturator artery lymph nodes, the internal iliac lymph nodes, the external iliac lymph nodes, and the common iliac lymph nodes.

Lateral lymph node dissection is a surgical technique used to excise adipose tissue together with lymph nodes from the closed cavity between the internal and external iliac arteries, the urinary bladder cavity, and the lateral

portion of the rectal cavity surrounded by the internal iliac artery. Initially, both ureters are taped beside the anterior aspect of the common iliac artery and drugged laterally. Next, the hypogastric nerve is taped and dragged medially, conserving the autonomic nerves. The lymph nodes located at the anterior aspect of the common iliac artery in the region ranging from the bifurcation of the aorta to the bifurcation of the internal and external iliac arteries are excised along with the adipose tissue. The dissection is enlarged to uncover the lateral wall of the pelvis and the posterior sciatic nerve; the obturator nerve and obturator artery and vein can then be distinctly seen. Obturator lymph node dissection is then finished.

Afterward, the surrounding tissue is excised alongside the internal iliac artery, and the superior vesical artery is confirmed. Because the pelvic nerve plexus is situated inferiorly and medially, the blood vessels should be taped and dragged laterally, and space should be made between the pelvic nerve plexus and blood vessels to prevent neural injury. Peripherally, the inferior vesical vein, the obturator artery, and the pelvic nerve (S3, 4) are preserved, and the surrounding adipose tissue is excised. This step finishes the lateral lymph node dissection.[132]

In Japan, the standard approach for treating advanced lower rectal cancer (located at or below the peritoneal reflection) is TME and lateral lymph node dissection (LLND) with autonomic nerve preservation (ANP).

While in Europe and North America, LLND used to be executed, but it resulted in increased blood loss, dysfunction, and complications, with no improvement in overall survival. Thus, LLND is no longer performed. As a replacement, a multidisciplinary treatment combining neoadjuvant chemoradiotherapy with TME is now the standard treatment for advanced rectal cancer.

The number of nodes detected in dissection is considered to be representative of rectal cancer quality surgery and has to be between 12 and 15. Because nodal metastases in rectal cancer are usually found in small lymph nodes (<5 mm in diameter), a punctilious search is needed on gross examination by the pathologist. Moreover, if less than 12 lymph nodes are retrieved, reexamining the specimen may be useful. Usually, in specimens from patients treated with neoadjuvant therapy, the number of recovered lymph nodes is lower than 12 despite a careful search. Many studies have reported that the total number of lymph nodes evaluated after surgical resection is an important prognostic factor in colorectal cancer[2], [132]

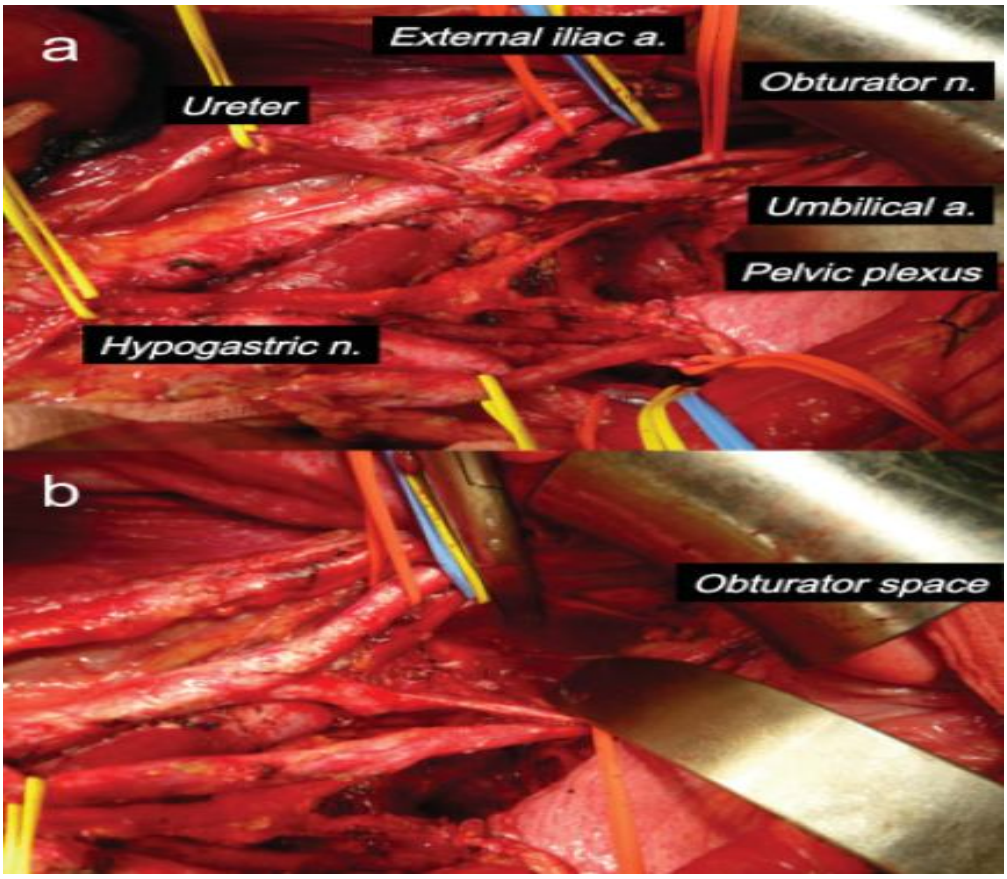

Figure 21. Pictures after LLND by traditional open approach. LLND, lateral lymph node dissection.[138]

2. Radiotherapy [8], [102], [144]–[153], [103], [154]–[163], [104], [164]–[166], [166]–[169], [105], [139]–[143]

Radiotherapy or **Radiation therapy** is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. It is commonly used to treat rectal cancer. It can be used before, during, and after surgery depending on the type and the stage of cancer, patient fitness, and the oncologist's recommendations. It is used, as neoadjuvant treatment, before surgery to decrease the size of cancer and to facilitate its surgical removal. It is also used as a palliative treatment when surgery cannot be done. Its duration, doses, and type are chosen depending on the characteristic of cancer.

Because radiotherapy is considered a localized treatment, defining the tumor and the target volumes for radiotherapy is crucial to its success. So, the finest achievable characterization of the location and extent of the tumor is needed. As a consequence, practitioners defined three main volumes in radiotherapy planning. They are:

- Gross tumor volume (GTV): defined as the position and extent of the gross tumor, in other words, what can be seen, palpated, or imaged. Together with the primary site, the gross tumor involving lymph nodes or spread into adjacent soft tissue have to be included in the gross tumor volume. Usually, it is assumed that the gross tumor volume matches the part of the tumor where the tumor cell density is the maximum. This can have implications when choosing a radiotherapy dose because tumor control demands a higher dose if the initial tumor cell number is bigger.

- Clinical target volume (CTV): surrounds the gross tumor volume and describes the extent of microscopic, un-imageable tumor spread, in other words, it includes gross tumor volume adding it to a margin for sub-clinical disease spread that cannot be completely imaged. The clinical target volume is essential considering that this volume has to be properly treated if a cure is to be accomplished. It is considered that the tumor cell density in the clinical target volume is less than in the gross tumor volume, thus the radiotherapy dose may be lower. Because it cannot be precisely defined for an individual patient, the clinical target volume is considered to be the most difficult volume to be defined. Nonetheless, future developments in imaging, especially towards the molecular level, should permit a more specific delineation of the clinical target volume.

- Planning target volume (PTV): is a geometric concept created to guarantee that the radiotherapy dose is delivered to the clinical target volume. It is considered as a volume that is more related to the isocentre of the linear accelerator than to the anatomy of the patient. As a consequence, the planning target volume can extend beyond anatomical barriers such as bony margins, and can even expand outside the patient.

a) External-beam radiation therapy (EBRT)

EBRT is considered the primary radiation technique used for neoadjuvant and adjuvant treatment. It uses a machine outside the body to deliver radiation therapy to the rectal wall harboring the primary tumor and to the complete mesorectum (Figure 22). Because it exposes the sphincter complex and the perianal skin to radiation, it can cause toxicity and deterioration of the anorectal function. Recently, newer EBRT techniques are showing better results like *three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT),* and *stereotactic body radiation therapy (SBRT).*

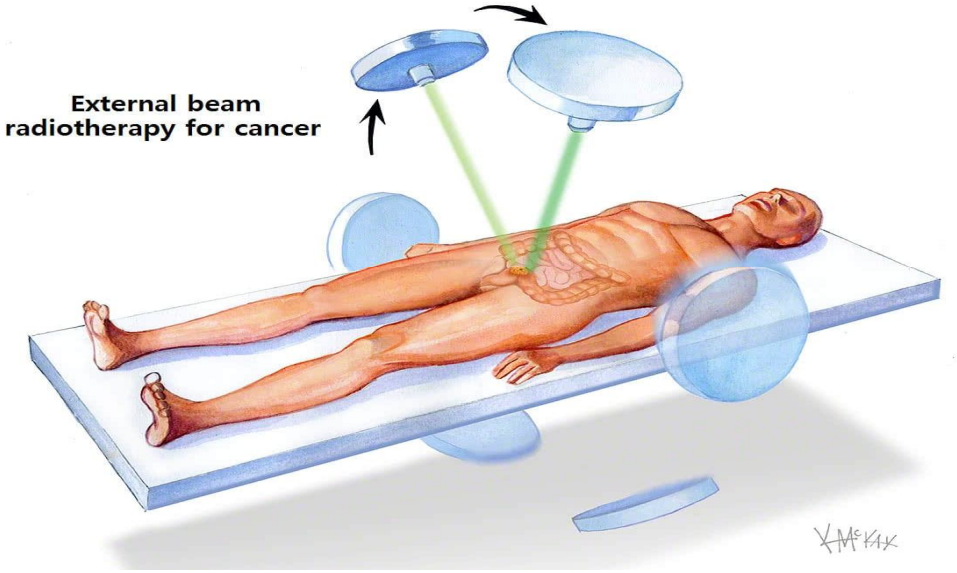

Figure 22. The EBRT technique [170]

(1) Three-dimensional conformal radiation therapy (3D-CRT)

3D conformal radiation therapy is a radiation therapy technique that requires CT and/or MRI planning where the volume to be treated is determined on a 3D data set. Therefore, OARs can be traced and be protected, thus reducing treatment side effects. Radiotherapy planning software serves to conceive complicated beam arrangements and to evaluate dose-volume histograms for the tumor and OARs.

In its basic form, 3D conformal radiation therapy utilizes a multileaf collimator (MLC) in a step and shot technique. An MLC generally is made of 40-80 tungsten leaves, which can move independently into the beam path and create almost limitless beam shapes. Many of these conformal beams would then be delivered from various angles to treat the tumor volume.

(2) Intensity-modulated radiation therapy (IMRT)

Intensity-modulated radiation therapy is defined as a type of conformal radiation therapy where both the shape and the intensity profile (fluence) of each beam are varied, therefore, superior to 3D conformal radiation therapy.

First implementations implicated building up a fluence by summing smaller beam segments until the wanted profile was achieved. The beam was shut down while the multi-leaf collimator (MLC) leaves were in motion and only switched on for a specific duration to deliver each segment.

(3) Stereotactic radiation therapy

Stereotactic radiation therapy or stereotactic body radiotherapy (SBRT) is a type of external beam radiotherapy that uses stereotactic principles for localization and can deliver multiple beams to well-defined targets in few fractions. It presents the possibility of reducing mechanical error margins and enabling the delivery of higher doses of radiation therapy.

High-resolution ct images (1 mm axial) provide a bigger conformality to target volume and avoidance of organs at risk (OARs) than conventional external-beam radiotherapy. Moreover, Gold fiducial markers can be inserted percutaneously to provide real-time fiducial tracking. Furthermore, the stereotactic principles in localization permit bigger doses per fraction (about 5 to 16 Gy) to be delivered to tumors because of reduction in mechanical error margin and better organ at risk sparing.

b) Contact radiotherapy

Contact radiotherapy is a type of internal radiation therapy. This method permits a direct delivery of radiation therapy to the rectal wall by using a rigid proctoscope and a specially designed radiotherapy machine. It has minimal toxicity but also minimal to no activity within the mesorectum.

c) Intraoperative radiotherapy

Intraoperative radiotherapy uses a single, high dose of radiation therapy that can be delivered during surgery by using an electron beam or high dose rate brachytherapy. It delivers radiation precisely to the tumor or tumor bed when the area is exposed during surgery. It is limited by the inconvenience of transporting the patient mid-operation to the radiation oncology suite or the expense of retrofitting an operating room.

3. Therapies using medication [15], [27], [177]–[186], [47], [187]–[190], [190]–[195], [106], [196]–[205], [171], [206]–[212], [172]–[176]

An oncologist uses medication to destroy cancer cells and improve the results of other treatments such as surgery and radiotherapy. Systemic therapy indicates medication that is given through the bloodstream to reach cancer cells throughout the body. Regional therapy consists of medication that is applied directly to cancer or kept in a single part of the body. The main medications used for treating rectal cancer are **chemotherapy, targeted therapy,** and **immunotherapy**.

When this medication is given before the main treatment, which is usually surgery, it is called **neoadjuvant therapy**. The latter's goal is to help reduce the size of the tumor and kill cancer cells that have spread.

When medication is given after the main treatment, it is called **adjuvant treatment**, whose goal is to destroy the remaining cancer cells or to prevent cancer recurrence.

a) Chemotherapy

Chemotherapy is a cancer treatment that uses drugs to destroy cancer cells, either by directly killing them or by stopping their growth and/or mitosis. **Systemic chemotherapy** consists of swallowing drugs by mouth or injecting them into a vein or a muscle. If chemotherapy is placed directly in an organ, in the cerebrospinal fluid, or a body cavity, it is called **regional chemotherapy.**

A chemotherapy schedule, or regimen, consists of a precise number of cycles given over a specific period. Moreover, a patient can either receive one drug at a time or receive a combination of different drugs at the same time.

Chemotherapy can be associated with other medications such as targeted therapy drugs or with radiotherapy.

Chemotherapy can be given a palliative treatment to help elevate the symptoms and slow the spread of advanced rectal cancer (**palliative chemotherapy**).

Drugs usually used for rectal cancer include:

- 5-fluorouracil (5-FU)
- Oxaliplatin
- Capecitabine
- Trifluridine
- Irinotecan
- Tipiracil

b) Targeted therapy

Targeted therapy targets cancer's specific proteins, genes, or the tissue environment that helps cancer to grow, spread, and to survive.

Studies show that patients of all ages can benefit from targeted therapies. Moreover, the expected side effects are manageable most of the time.

Furthermore, not all cancers have the same targets; so many tests must be done to look for the genes, the proteins, and the other factors specific to each rectal cancer case. This makes it possible for the oncologist to give the most appropriate treatment to each patient.

Different kinds of targeted therapies are used to treat rectal cancer, which include the following:

- **Monoclonal antibodies**: monoclonal antibody therapy uses antibodies made in a laboratory from a single type of immune system. Monoclonal antibodies can pinpoint substances on cancer cells or normal substances that can encourage cancer cells to grow. Monoclonal antibodies can be used alone or to carry toxins, radioactive material, or drugs directly to cancer cells. There exist many types of monoclonal antibody therapy:
    - ***Vascular endothelial growth factor (VEGF) inhibitor therapy***: VEGF is a substance made by cancer cells to induce the formation of new blood vessels within the tumor (**angiogenesis**) and to facilitate its growth. VEGF inhibitors block VEGF, thus new blood vessels can't be formed, which leads eventually to the death of the cancer cells. *Ramucirumab*, Ziv-aflibercept, and *bevacizumab* are VEGF inhibitors and angiogenesis inhibitors.

- ***Epidermal growth factor receptor (EGFR) inhibitor therapy:*** epidermal growth factors attach to the EGFR's (which are proteins located on the surface of some cells, including cancer cells), and encourage the cells to divide and to grow. EGFR inhibitors block these receptors, thus prevent the epidermal growth factor from attaching to the cancer cell. As a consequence, the tumor is incapable of dividing and growing. *Panitumumab* and *cetuximab* are EGFR inhibitors.

- **BRAF inhibitors:** Less than 10% of rectal cancer cells have mutations in the BRAF gene. BRAF is a kinase enzyme that helps control cell growth and signaling. Abnormal BRAF protein boosts cancer cell growth, thus some drugs target this abnormal BRAF protein. *Encorafenid* is a BRAF inhibitor.

c) Immunotherapy

Immunotherapy is designed to help the body's immune system to fight cancer. It uses substances created either by a laboratory or the body to improve, target, or restore immune system function.

Checkpoints are proteins in the immune cells that have to be turned on or off to start an immune response. They help the immune system stop itself from attacking the body's normal cells. But some rectal cancer cells can use these checkpoints to evade the immune system attack. Drugs called checkpoint inhibitors are used in treating some cases of rectal cancer.

Pembrolizumab and nivolumab are PD-1 inhibitors. Ipilimumab is a CTLA-4 inhibitor.

B. Surveillance [213]–[222]

The Postoperative surveillance of patients with rectal cancer is very important and crucial, and it offers many benefits such as improving overall survival, ensuring better monitoring of the outcome of the treatment, identifying other treatable diseases found during follow- up and providing immense psychological support.

The major goals of postoperative surveillance are: to measure the efficiency of the initial therapy, assess metachronous or new malignancies, and detect potentially curable recurrence.

Nonetheless, it is noted that the negative effects of the follow-up techniques on the body, their expenses, and their psychological consequences make it difficult to have perfect and harmless surveillance.

The techniques used, the rhythm and number of sessions, and the total duration of the surveillance depend on the stage of cancer and other factors.

Methods of recurrence detection include:

- **History and physical examination**: regular physician visits help at coordinating care, examining the body, organizing specific tests, answering patient questions and concerns, and educating patients about the state of their disease.
- **Laboratory evaluation**: *carcinoembryonic antigen (CEA)* is widely used to monitor patients for recurrent cancer after curative surgery. *Liver function tests* are important because the liver is the most common site of metastasis from rectal cancer. *Complete blood cell count* and especially *hemoglobin* level are used to look for anemia caused by chronic mild bleeding.

- **Chest radiograph**: chest radiograph is used for screening pulmonary metastasis. Its indication is usually due to its low cost.
- **Ultrasound**: Although ultrasound is also inexpensive, it is quite an operator-dependent modality of detecting liver metastasis and be influenced by bowel gas overlying the liver and obesity. *Transrectal ultrasound* can be used to detect recurrent rectal cancer.
- **Computed tomography (CT) scan**: CT scan is becoming the favorite method for evaluating local recurrence, detecting hepatic recurrence, and other metastasis.
- **Nuclear medicine**: immunoscintigraphy can be used to detect recurrent tumor cells by using radiolabeled monoclonal antibodies to specific tumor antigens such as *anti-CEA antibodies, B72.3 antibodies*, and *anti17-1A antibodies*.
- **Magnetic resonance imaging (MRI**): MRI can be used to detect cancer recurrence, but its cost makes it an ill-favored method.
- **Positron emission tomography (PET) scan**: PET scan is not based on morphological abnormalities, but on physiologic metabolic change within tissue to help detect cancer cells. This increases its usefulness in assessing patients with increased CEA levels, or physical or radiological findings that are indeterminate.
- **Endoscopic evaluation**: colonoscopy is a crucial part of follow-up for rectal cancer. Anastomotic and local recurrence occurs often in rectal cancer, which highlights the importance of using colonoscopy to look for any recurrences. It is also quite useful in detecting new polyps and new cancers.

VII.Prevention [34], [223], [232], [233], [224]–[231]

Cancer prevention means taking actions to minimize the chance of getting cancer. Although rectal cancer can not be completely prevented, decreasing the chance of developing one is no small deed.

It is important to avoid risk factors for rectal cancer when possible, such as avoiding smoking and alcohol, increasing fruit and vegetable intake, and doing physical exercises regularly.

Screening for rectal cancer is very important; it aims to adequate target population coverage to reduce mortality through detecting early-stage adenocarcinomas and removing adenomatous polyps. Screening protocols differ depending on the degree of risk.

The average risk population includes patients with:

- Age superior 50 years old
- No history of inflammatory bowel disease
- No history of adenoma or colorectal carcinoma
- Negative family history (Not having 1 first-degree or 2 second-degree relatives with colorectal cancer or multiple cases of Lynch syndrome/HNPCC-related cancer)

The increased risk population includes patients with:

- Personal history of adenoma/sessile serrated polyp, colorectal cancer, and inflammatory bowel diseases such as ulcerative colitis and Crohn’s disease.
- Positive family history

The high increased risk population includes patients with:

- Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)
- Polyposis syndromes:
  - MYH-associated polyposis
  - Hyperplastic polyposis syndrome
  - Attenuated familial adenomatous polyposis
  - Juvenile polyposis syndrome
  - Classical familial adenomatous polyposis
  - Peutz-Jeghers syndrome

Colonoscopy is used as the main method for colorectal cancer screening in average- and high-risk populations. It is favored for its ability to detect and remove all suspicious colorectal lesions.

Flexible sigmoidoscopy and stool-based screening such as fecal immunohistochemical testing can also be used.

SECOND CHAPTER: NEOADJUVANT TREATMENT IN RECTAL CANCER

I. The definition of neoadjuvant treatment[234]–[241]

"**Neo**" stems from the Greek word *neos*, which means new. "**Adjuvan**t" derives from the Latin word *adjuvare*, which means to help. Thus, the word "**Neoadjuvan**t" combines two languages, while it may also combine two or more modalities.

In the Medical Subject Headings (MeSH) of the U.S National Libruary of Medicine, neoadjuvant treatment is defined as the preliminary cancer therapy (radiation therapy, chemotherapy, hormone/endocrine therapy, hyperthermia, immunotherapy, etc.) that precedes a necessary second modality of treatment.[242]

Other terms such as *protoadjuvant therapy, preoperative chemotherapy, basal chemotherapy, induction chemotherapy,* and *primary chemotherapy* have been proposed. A notable amount of ink has been spilled in debating the best term for a field whose contribution to therapy is still poorly defined, but because of the existence of a periodic, international conference on 'neo-adjuvant chemotherapy,' this term has achieved the widest acceptance.

NAT is often viewed as a personalized in vivo drug sensitivity test because it permits rapid evaluation of tumor response to a given therapy and consequent adjustment of further treatment planning. NAT is a crucial tool for in-human testing of new therapeutic compounds, as it deals with yet chemonaive patients and allows pathological and molecular analysis of treatment-exposed tumor tissues.

II. The evolution of neoadjuvant treatment in rectal cancer throughout history [47], [229], [251]–[260], [243], [261]–[265], [244]–[250]

In the 1970s, it was noted that patients with locally advanced rectal cancer managed with surgical resection had rates of recurrence that is above 50%. The evolution of total mesorectal excision helped to lower the local recurrence rate.

Nonetheless, many adjuvant treatment strategies were suggested hoping to reduce local recurrences, such as **Gastrointestinal Tumor Study Group (HITSG)**, which showed that adjuvant therapy, especially adjuvant chemotherapy, helped reduce recurrence rate better than surgery alone[255].

Because local recurrence continued to be common despite the combined adjuvant treatment, many European groups studied whether giving radiotherapy alone in the preoperative setting could reduce local recurrence more and improve other treatment-related consequences. These researchers theorized that malignant cells could be more sensitive to neoadjuvant radiotherapy, because of the better preoperative blood supply and tissue oxygenation.

The **Swedish rectal cancer trial**[257], which was performed between 1987 and 1990, randomized 1168 patients to get either surgery alone or surgery preceded by short-course preoperative radiotherapy. 5-year survival increased from 48% to 58% (P=0.004), and local recurrence was decreased from 27% to 11% with surgery alone and short-course preoperative radiotherapy (P<0.001), respectively[256].

The **Dutch CKVO 95-04**[258], which was performed between 1996 and 1999, randomized 1861 patients to receive either surgery alone or neoadjuvant short-course radiotherapy followed by surgery, but with standardized total mesorectal excision (TME)[258]. It was noted that even with TME, short-course preoperative radiotherapy provided a 5-year locoregional recurrence rate benefit (5% vs. 11%, $p<0.0001$), but there were no differences in overall survival after 12 years of follow-up[259], [260]. This trial confirmed that preoperative radiotherapy gives more benefit even when the surgical technique is optimized.

At first, chemotherapy wasn't generally added to preoperative radiotherapy, but further trials showed the synergistic efficacy of combining radiotherapy with fluorouracil.

The **European Organization for Research and Treatment of Cancer (EORTC) 22921 trial**, which was performed between 1993 and 2003, randomized 1011 patients to receive either neoadjuvant chemoradiotherapy (long course preoperative radiotherapy with concurrent 5FU leucovorin) or neoadjuvant radiotherapy and also adjuvant chemotherapy or no chemotherapy[261].

Patients who received neoadjuvant chemoradiation had smaller tumors, less advanced T and N stages on surgical pathology, and a higher rate of pathologic complete response (14% vs. 5%, $p=0.005$), compared to those who received neoadjuvant radiotherapy alone. Also, those who received radiotherapy and concurrent and/or adjuvant chemotherapy had lower rates of local recurrence compared to those who received radiotherapy and no chemotherapy (8-10% vs.17%).

The **Federation Francophone de Cancerologie Digestive (FFCD) 9203 trial**, which was performed between 1993 and 2003, randomized 762 patients to receive either preoperative radiotherapy or preoperative chemoradiotherapy[264].

Patients who received preoperative chemoradiotherapy had higher rates of pathologic complete response (11% vs 4%, p=0.001) and lower rates of local recurrence (17% vs. 8%, p=0.004). Thus, preoperative chemoradiotherapy showed increased efficacy, associated somehow with increased toxicity, compared to preoperative long-course radiotherapy alone.

EORTC 22921 and FFCD 9203 revealed that the addition of 5FU/LV was connected with an increase in acute toxicity and pathological downstaging. And although they reported a significant reduction in the rate of local recurrence, they presented no difference in disease-free or overall survival.

To evaluate the difference between preoperative chemoradiotherapy and postoperative chemoradiotherapy, three separate trials were launched. The two trials in the USA have closed ahead of time because of low enrollment. The third trial was led by the German Rectal Cancer Study Group[265].

The **German Rectal Cancer Study Group trial**, which was performed between 1995 and 2002, directly compared preoperative and postoperative 5FU chemoradiotherapy. It randomized 823 patients with cT3-4N+ rectal cancer to receive either preoperative or postoperative chemoradiotherapy[265].

Patients who received preoperative chemoradiotherapy had lower rates of local recurrence compared to those who received postoperative chemoradiotherapy (6% vs. 13%, p=0.006). Late and acute toxicity was less

observed in patients who received preoperative chemoradiotherapy. Overall and disease-free survival rates were similar between the two groups.

The trials mentioned above, especially the German trial, are considered the landmark that defined neoadjuvant chemoradiotherapy as the standard of care for patients with stage II and III rectal cancer.

The **National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial**, which was performed between 1993 and 1999, randomized 267 patients to receive either preoperative or postoperative chemoradiptherapy[266].

Patients who received preoperative chemoradiotherapy had higher 5-year overall survival rates (75% vs. 65%, P = 0.065) and higher 5-year disease-free survival rates (65% vs. 53%, P = 0.011) compared to those who received postoperative chemoradiotherapy.

Nonetheless, it should be pointed out that the NSABP R-03 trial allowed 6 additional weeks of preoperative chemoradiotherapy compared with the German Rectal Cancer trial. Yet, both these studies support the benefit of preoperative 5-FU based chemoradiotherapy for locally advanced rectal cancer compared with postoperative chemoradiotherapy.

III. Benefits and indications of neoadjuvant treatment in rectal cancer

A. Benefits of neoadjuvant treatment in rectal cancer [15], [229], [271]–[275], [234], [243], [254], [265], [267]–[270]

The neoadjuvant treatment presents many benefits when it is associated with surgery, especially when it comes to locally advanced rectal cancer (stages II and III).

Although the benefits of neoadjuvant treatment differ depending on the modalities used, the schedule of their implementation, and other factors related to the protocols used, we can find benefits related to neoadjuvant therapy in general.

The advantages of preoperative chemoradiotherapy are:

- The preoperative tumor is sensitive to radiotherapy and the treatment effect is superior to that of postoperative radiotherapy because the local blood supply is not damaged and tumor oxygenation is important for radiation sensitivity.
- Neoadjuvant chemoradiotherapy can downstage tumors, which is demonstrated through decreased numbers of metastatic lymph nodes and the decreased thickness of the invaded intestinal wall, even to pathological complete response. Therefore, neoadjuvant chemoradiotherapy can decrease the positive rate of surgical margin and increase the R0 resection rate and anal sphincter preservation rate for low rectal cancer.

- After neoadjuvant chemoradiotherapy, it is noted that tumor tissue seems necrosis and fibrosis with different degrees, active tumor cells are considerably reduced, the probability of tumor cells falling off, spreading, and planting during the operation are largely reduced, thereby the local reoccurrence reduces.

Other benefits are associated with neoadjuvant treatment, such as:

- Decreasing local recurrence and minimizing toxicity
- Improving local control
- Providing favorable impact on disease-free survival and recurrence-free survival
- Providing favorable impact on cancer-specific survival and local recurrence-free survival
- Granting a high likelihood of complete clinical and pathological responses
- Decreasing the rates of venous, perineural, or lymphatic invasion
- increasing the chances of sphincter-saving surgery

Optimization of the sequence of the neoadjuvant treatment modalities (radiotherapy and chemotherapy) and surgery, and selecting favorable risk patients for de-escalation via omission of a treatment modality promises to further improve the benefits of rectal cancer treatment, especially neoadjuvant therapy.

B. Indications of neoadjuvant treatment in rectal cancer [2], [16], [278]–[284], [34], [74], [252], [254], [275]–[277], [277]

Locally advanced rectal cancer includes stage II (T3-4, N0, M0) and stage III (T3-4, N1-2, M0).

Neoadjuvant treatment (short-course preoperative radiotherapy or long-course radiotherapy associated with chemotherapy) is mainly indicated in treating locally advanced rectal cancer before surgery (which is usually TME).

For patients with locally advanced rectal cancer, treatment decisions regarding neoadjuvant therapy has to be based on preoperative, MRI-predicted circumferential resection margin (less or equal 1 mm), extramural vascular invasion, and more advanced T3 substages, which can define the risk of both local recurrence and/or synchronous and subsequent metastatic disease. For resectable cancers, where there is no indication on MRI that surgery is probably to be associated with either an R2 or an R1 resection (R: residual tumor classification), standard total mesorectum excision should achieve a curative resection. The use of short-course radiotherapy or chemoradiotherapy aims to decrease the rate of local recurrence.

The adoption of a preoperative approach in locally advanced rectal cancer is based more on the multidisciplinary team decision regarding the risk of a CRM+ at TME surgery. If circumferential resection margin (CRM) and/or R0 resection status are predicted at risk, chemoradiotherapy is advised. Otherwise, either chemoradiotherapy or short-course radiotherapy can be administered.

Some studies found that preoperative radiotherapy or chemoradiotherapy decreases the rate of local recurrence without improvement of overall survival for mid/low stage II/III rectal cancers but is associated with considerably worse sexual and intestinal functions after surgery.

Upper rectal cancer (>12cm from the anal verge) that is situated above the peritoneal reflection doesn’t benefit from neoadjuvant treatment and should be treated like colon cancer.[16], [284]

Neoadjuvant treatment can also be applied in advanced rectal cancer curative approaches.

Choosing between neoadjuvant treatment modalities depends on many factors that are discussed more in the next chapters.

IV. The current standard of care for locally advanced rectal cancer

A. Neoadjuvant regiments

1. Short-course radiotherapy (SCRT)[2], [34], [288]–[293], [249], [252], [254], [275], [283], [285]–[287]

Short-course radiotherapy consists of 25Gy in 5 fractions without concurrent chemotherapy, which means that patients who undergo short-course radiotherapy receive a bigger dose per fraction and complete a biologically equivalent radiation therapy course with 5Gy per day for 5 days total. Patients generally proceed to surgery 1 to 2 weeks following radiotherapy.

Supporters of the short course radiotherapy propose that the lower dose of pelvic radiation will result in fewer complications while maintaining efficacy in tumor control. Earlier surgery hypothetically may prevent tumor progression.

The Swedish rectal cancer trial and the Dutch trial showed the benefits of neoadjuvant short-course radiotherapy followed by surgery compared to surgery alone.

The **polish trial,** which was performed between 2008 and 2014, randomized 515 patients to receive either neoadjuvant short-course radiotherapy (5×5Gy over 5 days) with concurrent chemotherapy (three cycles of FOLFOX4) followed by TME or long-course chemoradiotherapy (50.4 Gy in 28 fractions combined with two 5-day cycles of bolus 5-Fu 325 mg/m(2)/day and leucovorin 20 mg/m(2)/day during the first and fifth week of irradiation along with five infusions of oxaliplatin 50 mg/m(2) once weekly) followed by TME[285], [290]. Long term outcomes are:

- *The difference in overall survival was insignificant* (a previous analysis

carried out after a median 3 years of follow-up showed benefit in OS in the short-course/CCT group compared to long-course chemoradiotherapy, but at 8 years follow-up showed the disappearance of the difference in overall survival because median overall survival was 89 months versus 81 months in the short-course/ CCT group versus the chemoradiation group, respectively)

- *There was no difference in disease-free survival* (at 8 years, disease-free survival was 43% versus 41% (p=0.65) in the short-course/CCT group versus the chemoradiation group, respectively)
- *The rates of patients with late complications did not differ* (grade 3+ being 11% versus 9% (p=0.66) in the short-course/ CCT group versus the chemoradiation group, respectively)

A landmark Australian/New Zealand head-to-head trial, that compared short-course radiotherapy and long-course chemoradiotherapy, showed noninferiority in oncological outcomes between the two approaches. Also called **Trans-Tasman Radiation Oncology Group Trial 01.04**, it randomized 326 patients to receive either short-course radiotherapy (5×5Gy in one week) followed by early surgery and six courses of adjuvant chemotherapy or long-course chemoradiotherapy (50Gy, 1.8Gy/fraction, in 5.5 weeks, with continuous infusional fluorouracil 225 mg/m2) followed by surgery after 4 to 6 weeks and four courses of adjuvant chemotherapy[286].

This trial showed that three-year local recurrence rates between long-course chemoradiotherapy (LCCRT) and short-course radiotherapy (SCRT) were not statistically significantly different (4.4% for LCCRT and 7.5% for SCRT, p=0.24). Also, no differences in rates of local recurrence, overall survival, relapse-free survival, or late toxicity were found.

Another **trial** [289] randomized 312 patients to receive either short-course radiotherapy (25 Gy in 5 fractions of 5 Gy) and surgery within 7 days or long-course chemoradiotherapy (50.4 Gy in 28 fractions of 1.8 Gy, bolus of leucovorin and 5-fluorouracil) followed by surgery after 4-6 weeks. It showed that there were no significant differences between short-course radiotherapy and long-course chemoradiotherapy in local control, late toxicity (p=0.360), or overall survival (p=0.960).

The ideal time interval between radiotherapy and surgery remains controversial. **A multicenter trial** randomized the patients to receive either short-course radiotherapy (5×5 Gy) and surgery within one week, short-course radiotherapy and surgery after 4 to 8 weeks, or long course radiotherapy (25×2 Gy) followed by surgery after 4 to 8 weeks. Short-course radiotherapy followed by immediate surgery had a tendency towards more postoperative complications, but only if surgery was delayed beyond 10 days after the start of radiotherapy, and the highest complication rate was noted in patients who received short-course radiotherapy with surgery 11 to 17 days after the start of radiotherapy, so these results indicate that surgery should be performed immediately after short-course RT, within approximately 5 days after the last RT fraction, or be delayed for more than 4 weeks[287], [288].

A multi-center prospectively randomized study of the Berlin Cancer Society randomized patients with histological proven rectal cancer stagedT2N+ or T3 to receive either long-course chemoradiotherapy (50.4 Gy in 28 fractions of 1.8 Gy associated with continuous infusion of 5-fluorouracil) followed by TME 4-6 weeks later or short-course radiotherapy (5×5 Gy) followed by TME within 5 days. Also, all patients receive adjuvant chemotherapy (12 weeks

continuous infusional 5-FU) and are followed up for 5 years[291]. This study includes a larger number of patients for adequate power, applies quality-controlled TME, and tries to avoid the adjuvant treatment bias by mandatory adjuvant chemotherapy in both groups. Results couldn't be found on scientific sites.

The Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 (MRC CR07/NCIC CTG C016) trial randomized more than 1200 patients with operable rectal cancer to receive either preoperative radiotherapy (25 Gy in five fractions) or surgery followed by postoperative chemoradiotherapy (45 Gy in 25 fractions with concurrent 5FU)[292], [293].

A 61% reduction in the relative risk of local recurrence was observed in patients who received preoperative radiotherapy and an absolute difference at 3 years of 6.2% (10.6% selective postoperative chemoradiotherapy vs 4.4% preoperative radiotherapy). Also, doctors noted a relative improvement in disease-free survival of 24% for patients receiving preoperative radiotherapy and an absolute difference at 3 years of 6.0%. But, overall survival wasn't different between the groups.

The use of short-course radiotherapy varies between countries, it is broadly used in Europe, and it is considered less time-consuming, less expensive, and more convenient for patients than long course chemoradiotherapy. However, long course chemoradiotherapy is widely used in the United States.

2. Long course chemoradiotherapy (LCCRT)[2], [8], [295]–[304], [27], [305]–[314], [243], [315]–[324], [252], [325]–[334], [254], [335]–[343], [273], [275], [283], [294]

a) radiotherapy

Patients who receive long-course chemoradiotherapy regimens get a total of 45 to 54 Gy of external-beam radiotherapy over 25 to 28 daily fractions while also receiving concomitant radiation-sensitizing fluoropyrimidine-based chemotherapy. Radiosensitizing chemotherapy prevents DNA repair of radiation-damaged tumor cells with the use of oral capecitabine, continuous infusional 5-fluorouracil, or bolus 5-fluorouracil with leucovorin. The choice of sensitizing chemotherapy will likely be guided by patient fitness and the experience of the partnering medical oncologist.

Long-course radiotherapy (1.8 to 2 Gy each day in ≈25 fractions) was first given as postoperative treatment. During this time, concomitant chemotherapy was also started and when data became obvious that the treatment should be given preoperatively, the issue of the timing of surgery was again part of the debate. Since patients suffer acute toxicity (diarrhea and sometimes leucopenia) and are time and again not in an ideal state for immediate surgery, delayed surgery was favored. There was actually on this background, however, no real knowledge regarding the best timing of surgery, but empirically it was based upon the fact that the majority of the acute toxic reactions to radiotherapy had subsided by 4 weeks. Therefore, the recommendation was to operate upon patients after long-course chemoradiation in 4–5 weeks after the end of the radiotherapy.

EORTC 22921 trial, FFCD 9203 trial, German Rectal Cancer Study Group Trial, and NSABP R-03 trial showed the benefits of neoadjuvant chemoradiation followed by surgery in rectal cancer.

EORTC 22921 trial and FFCD 9203 showed that concurrent preoperative chemoradiotherapy considerably improved the pathologic complete response and local control rate, while it decreased the pathological staging compared with preoperative radiotherapy, but failed to ameliorate the long-term survival and retention rate of anal sphincter.

The timing of surgery following long-course chemoradiotherapy is still a matter of debate. Delaying resection may enhance the clinical response to chemoradiotherapy and result in a higher proportion of patients having a pathologic complete response (pCR). Routinely, the shortest acceptable interval between chemoradiotherapy and surgery has been 6 to 8 weeks to grant time for downstaging and tumor cell death. Nonetheless, anecdotal evidence has suggested that radiation-associated fibrosis results in more difficult operations in a time-dependent fashion. **GRECCAR6 multi-institutional randomized control trial** supports these beliefs and has demonstrated that waiting 11 weeks after radiochemotherapy did not increase the rate of pCR after surgical resection, while a longer waiting period can get involved in higher morbidity and more difficult surgical resection[338]–[340].

A systematic review and meta-analyses[273] showed a beneficial impact of preoperative radiotherapy on local recurrence in rectal cancer patients. The higher perioperative mortality in patients with short-course radiotherapy should prompt further strategies to enhance the risk-benefit ratio. As preoperative chemoradiotherapy improved local recurrence-free survival compared to

preoperative radiotherapy with no benefit in long-term survival, the results of further studies are required to evaluate if more active chemotherapy protocols or targeted therapy in the preoperative setting prolong survival after curative resection.

b) Therapies using medications

(1) Chemotherapy

(a) fluorouracil

Fluorouracil (5FU) is a standard neoadjuvant chemotherapy used in locally advanced rectal cancer and is administered either as a bolus or as a continuous intravenous infusion. It is a cytotoxic chemotherapy drug, and it is classified as an antimetabolite.

The German Rectal Cancer Study Group Trial showed that using fluorouracil-based neoadjuvant chemoradiotherapy yields superior results.

The short half-life of fluorouracil offers the rationale for the usage of prolonged venous infusions, which permits delivery of near to maximum doses with minimal toxicity.

A **clinical investigation**[343] showed that infusional rather than bolus fluorouracil during long course chemoradiotherapy increases the probability of pathological complete response in patients with locally advanced rectal cancer.

Randomized phase III trials of neoadjuvant chemoradiotherapy in resectable locally advanced rectal cancer show that the addition of fluorouracil to neoadjuvant radiotherapy increases the pathological complete response rate over radiotherapy alone and improves locoregional control, but has not improved overall survival or disease-free survival[306]–[310]

(b) Capecitabine

Capecitabine, as an orally active fluoropyrimidine, is orally administered and converts to fluorouracil in tumor tissue, with the help of thymidine phosphorylase. By consequence, capecitabine imitates the pharmacologic activity of continuous intravenous infusion of fluorouracil. Radiation provokes the synthesis of thymidine phosphorylase, which supports the rationale that capecitabine combined with radiotherapy improves the therapeutic effect of chemoradiotherapy.

NSABP R-04 demonstrated that the administration of capecitabine with neoadjuvant radiotherapy achieved rates similar to continuous infusional fluorouracil for surgical downstaging, pathological complete response, and sphincter sparing surgery.

In 2016, a meta-analysis compared capecitabine and fluorouracil as neoadjuvant chemoradiotherapy for locally advanced rectal cancer[332]. The meta-analysis included seven retrospective studies and two randomized controlled trials and showed that capecitabine was considerably more effective than fluorouracil. Another meta-analysis[335] indicated that, compared with fluorouracil, capecitabine is probably associated with an increased rate of pathological complete response and a lower rate of toxic effect, even though the differences were not statistically substantial. Because capecitabine is delivered orally and there is less risk of infection, bleeding, and thrombosis that is associated with fluorouracil intravenous infusion, a good alternative would best balance toxicity and efficacy. Therefore, capecitabine can be deemed to substitute fluorouracil as the neoadjuvant chemoradiotherapy regime for locally advanced rectal cancer.

In 2019, a meta-analysis compared fluorouracil and capecitabine as neoadjuvant chemoradiotherapy for locally advanced rectal cancer[334]. The meta-analysis showed that capecitabine improved pathological complete response and R0 resection rate. There were no statistically important differences either in the overall downstaging rate or in the tumor downstaging rate, but there was an important difference in the nodal downstaging rate between the two groups. There were no statistically important differences in sphincter preservation rate, in 3-year disease-free-survival and grade 3 to 4 acute toxicity during chemoradiotherapy between the two groups.

(c)Oxaliplatin

Oxaliplatin is a platinum analog that makes adducts with the double-stranded DNA structure and which intercalates to impede strand separation generally required for transcription and replication. Because it has little activity as a single agent in colorectal cancer and is more effective when used in association usually with a fluoropyrimidine, oxaliplatin is typically given along with other drugs like fluorouracil and leucovorin. Thus, combinations of oxaliplatin and capecitabine (XELOX) and oxaliplatin and infusional fluorouracil (FOLFOX) are existing therapies in neoadjuvant chemoradiotherapy. In preclinical studies, it is considered a potent radiosensitizing agent.

STAR-01 randomized trial (which investigated the effect of adding oxaliplatin to preoperative fluorouracil-based chemoradiotherapy in patients with resectable locally advanced rectal cancer)[330] and **ACCORD 12/0405 randomized trial** (which investigated the effect of adding oxaliplatin to preoperative capecitabine-based chemoradiotherapy in patients with resectable

locally advanced rectal cancer)[329] showed that the addition of oxaliplatin considerably increased toxicity without improving the pathological complete response or sphincter sparing surgery. NSABP R-04 also found that the addition of oxaliplatin to fluorouracil or capecitabine didn't improve the chemoradiotherapy outcome, but it increased toxicity.

(d) Leucovorin

Leucovorin is a reduced folic acid that is used in combination with other chemotherapy drugs to either enhance effectiveness or as a chemoprotectant. It enhances the binding of fluorouracil to an enzyme inside of the cancer cells. Thus, fluorouracil stays in the cancer cell longer and exerts its effect better.

A Korean single-center phase II study [322] showed that the combination of oxaliplatin, continuous infusional fluorouracil, and leucovorin in neoadjuvant chemoradiotherapy was associated with bigger rates of sphincter preservation and downstaging.

A **phase II study** [325] studied the effect of preoperative radiotherapy combined with UFT (tegafur/uracil) and leucovorin on tumor response, sphincter preservation, and tumor control in patients with rectal cancer. This approach downstaged 63% of tumors and allowed a sphincter-preserving procedure in some patients, while toxicity was moderate. Other studies[326], [327] also showed the effect of adding leucovorin in neoadjuvant chemoradiotherapy.

(e)Irinotecan

Irinotecan (CPT-11) is a semisynthetic derivative of camptothecin. It appears to exert its antitumor activity by binding to topoisomerase I, which inhibits DNA replication, transcription, and repair

A study made in 2010 evaluated the usefulness of neoadjuvant systemic chemotherapy using irinotecan, 5-FU, and leucovorin (LV) for the treatment of locally advanced rectal cancer and showed that this combination may be beneficial to the prognoses of patients with locally advanced rectal cancer[324].

Radiation Therapy Oncology Group Trial 0012 randomized 106 patients to receive either radiotherapy coupled with continuous venous infusion fluorouracil and irinotecan or radiotherapy and continuous venous infusion fluorouracil alone. Surgery was done 4 to 10 weeks after completion of neoadjuvant therapy[324]. In both arms, pathological complete response and acute/late toxicity were the same.

A Radiation Therapy Oncology Group randomized study (RTOG 0247) randomized 96 patients to receive preoperative radiotherapy (50.4 Gy in 1.8 Gy fractions) associated with either (1)capecitabine and irinotecan or (2)capecitabine and oxaliplatin. Surgery was performed 4 to 8 weeks after chemoradiotherapy[241][344]. After chemoradiotherapy, nodal downstaging was 46% and 40%, and tumor downstaging was 52% and 60%, for arms 1 and 2, respectively. Pathological complete response rates were 21% in the oxaliplatin arm and 10% in the irinotecan arm. Thus, irinotecan has no additional benefit in clinical response and it increases treatment-related toxicities.

(2) Targeted therapies

(a) <u>EGFR inhibitors</u>

EGFR inhibitors: overexpression of EGFR is considered a negative prognostic factor and is associated with resistance to radiotherapy. In retrospective analyses, patients with EGFR-expressing rectal cancer undergoing

preoperative radiotherapy had a considerably lower disease-free survival and lower chance of attaining a pathological complete response[275], [311]–[317].

Two kinds of EGFR inhibitors have been tested in patients with locally advanced rectal cancer in the neoadjuvant setting: monoclonal antibody to EGFR (cetuximab) and small-molecule EGFR tyrosine kinase inhibitor (gefitinib).

(i) Cetuximab

Cetuximab is a chimeric monoclonal antibody that binds to and inhibits epidermal growth factor receptors, and it is given by intravenous infusion. Cetuximab can be safely combined with chemoradiotherapy in the neoadjuvant treatment of rectal cancer.

A phase I-II study investigating cetuximab delivered with oxaliplatin/capecitabine-based chemoradiotherapy[302] and a **phase II study** investigating cetuximab delivered with fluorouracil-based chemoradiotherapy[301] yielded disappointing pathological complete response rates of only 9% and 5%, respectively.

A phase II study [306] investigated the safety and efficacy of preoperative cetuximab, capecitabine, and radiotherapy for patients with locally advanced rectal cancer. It found that neoadjuvant treatment with cetuximab and capecitabine-based chemoradiotherapy is well tolerated and safe. The pathological complete response rate, overall survival rate, and 3-year disease-free survival rate are not superior to the rate of neoadjuvant chemoradiotherapy using two or more cytotoxic agents. Toxicities were acceptable.

Another **phase II study**[303] investigated neoadjuvant treatment with single-agent cetuximab followed by fluorouracil, cetuximab, and pelvic radiotherapy, and it found that neoadjuvant treatment with fluorouracil, cetuximab, and pelvic radiotherapy is feasible with acceptable toxicities; Nonetheless, the rate of pathologic responses is disappointingly low.

(ii) Gefitinib

Gefitinib is an EGFR tyrosine kinase inhibitor that suspends signaling through the epidermal growth factor receptor in target cells. Precisely, this agent competes with the binding of ATP to the tyrosine kinase domain of EGFR, therefore inhibiting receptor autophosphorylation and resulting in inhibition of signal transduction.

A **phase I trial from Duke University** combined gefitinib, capecitabine, and radiotherapy in rectal cancer and the combination resulted in significant toxicity, and no recommended phase II dose could be determined[300].

In contrast, **an Italian phase I and II Trial study**[299] evaluated infusional fluorouracil with gefitinib and radiotherapy, and it showed that Gefitinib can be associated with fluorouracil-based neoadjuvant chemoradiotherapy at the dose of 500 mg without any life-threatening toxicity and with a pathological complete response rate of 30.3%.

A **phase I trial**[297] showed that the combination of gefitinib, capecitabine, and radiation in rectal cancer patients resulted in significant toxicity.

(b) VEGF inhibitors

(i) Bevacizumab

Bevacizumab is a humanized anti-VEGF monoclonal IgG antibody. It is an **anti-angiogenic agent** that modifies and normalizes the existing vasculature, inhibiting new blood vessel formation and improving the delivery of cytotoxic drugs. It is approved for the treatment of advanced colorectal cancer in combination with chemotherapy[27][296].

The addition of bevacizumab to fluorouracil-based chemoradiotherapy offers encouraging pathological complete response rates and does not increase acute toxicity.

A **multidisciplinary phase II**[295] study investigated the efficacy and safety of neoadjuvant bevacizumab with standard chemoradiotherapy in locally advanced rectal cancer. It found that adding bevacizumab to chemoradiotherapy appeared active and safe and yielded promising survival results in locally advanced rectal cancer.

Another **phase II study** investigated neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer[294]. It found that The addition of bevacizumab to neoadjuvant chemoradiation caused a promising pathologic complete response without an increase in acute toxicity. Moreover, the effect of bevacizumab on the perineal wound and anastomotic healing due to concurrent bevacizumab required further study.

3. Total neoadjuvant treatment[15], [248], [347]–[356], [249], [357]–[366], [252], [367]–[369], [254], [268], [275], [283], [345], [346]

Total neoadjuvant treatment (TNT) includes different strategies, some comprise of receiving long-course chemoradiotherapy followed by chemotherapy before surgery (**consolidation neoadjuvant chemotherapy**), others comprise of receiving chemotherapy followed by long course chemoradiotherapy before surgery (**induction neoadjuvant chemotherapy**). Receiving short-course radiotherapy followed by chemotherapy before surgery is also a TNT approach.

a) Induction chemotherapy followed by LCCRT

Multimodality therapy for patients with locally advanced rectal cancer comprises radiotherapy, chemotherapy, chemoradiotherapy, surgery, and eventual use of molecularly targeted agents. The optimum order of these procedures is being debated. Furthermore, rectal cancer local recurrence rates are today less than 10%. The leading mode of failure in rectal cancer is the development of distant metastases (30–35%). Thus, the chief aim of adding induction chemotherapy is not to increase local efficacy, but to better control the distant disease.

Induction neoadjuvant chemotherapy presents many theoretical advantages. We note that:

- It can be correlated with improved treatment compliance and can permit full systemic doses of chemotherapy to be given.
- It has the possibility of tumor shrinking or downstaging, therefore encouraging more efficient local treatment and early treatment of micrometastasis.

- Tumor shrinkage potentially permits better tumor vascularity. Moreover, the consequences of this are better oxygenation and greater intratumoral concentration of cytotoxic drugs.
- It presents the potential to exterminate distant micrometastases at an early stage in the evolution, and it has the possibility of using the embryonic tumor blood supply (in contrast to surgical scars). Moreover, it offers treatment of fit patients before surgery.

UNICANCER-PRODIGE 23 phase III trial is a phase III multicenter randomized clinical trial investigating the role of neoadjuvant mFOLFIRINOX before preoperative chemoradiotherapy (total neoadjuvant treatment) with TME-surgery and adjuvant chemotherapy in resectable locally advanced rectal cancer[365][364]. Between 2012 and 2017, the authors randomized 461 patients to receive either ***(1) neoadjuvant chemotherapy*** with FOLFIRINOX (leucovorin 400 mg/m2, irinotecan 180 mg/m2, oxaliplatin 85 mg/m2, and fluorouracil 2400 mg/m2 intravenously every 14 days for 6 cycles), followed by chemoradiation (50 Gy during 5 weeks associated with 800 mg/m2 concurrent oral capecitabine twice daily for 5 days per week), before total mesorectal excision and adjuvant chemotherapy (3 months of modified FOLFOX6 [intravenous oxaliplatin 85 mg/m2 and leucovorin 400 mg/m2, followed by intravenous 400 mg/m2 fluorouracil bolus and then continuous infusion at a dose of 2400 mg/m2 over 46 h every 14 days for six cycles] or capecitabine [1250 mg/m2 orally twice daily on days 1-14 every 21 days]), or ***(2) neoadjuvant chemoradiotherapy*** followed by total mesorectal excision and adjuvant chemotherapy (for 6 months). We note that the primary endpoint was disease-free survival assessed in the intention-to-treat population at three years.

Moreover, it was noted that more than 90% of patients received all planned cycles of FOLFIRINOX and that the total neoadjuvant treatment did not decrease patient compliance with radiotherapy, while only 8% of arm 1 discontinued capecitabine before completing radiotherapy[367][368].

The authors found at a median follow-up of 46·5 months that *3-year disease-free survival rates* were 76% and 69% (p=0.034), *3-year metastasis-free survival rates* were 79% and 72% (p=0.017), *noncurative surgery rates* were 0% and 3.7% (p=0.007), *pathological complete response (ypT0N0) rates* were 28% and 12% (p<0.001), in arms 1 and 2, respectively. They also found that in arm 1, the most common grade 3-4 adverse events were neutropenia (38 [17%] of 225 patients) and diarrhea (25 [11%] of 226), thus neoadjuvant mFOLFIRINOX was reported to be well tolerated. Moreover, global quality-of-life were alike, but a longer time to deterioration (P = .006) and less impotence (P = .077) were reported in arm 1. During adjuvant chemotherapy, the most common grade 3-4 adverse events were neutropenia (9 [6%] of 161 in arm 1 vs 28 [18%] of 155 in arm 2), lymphopenia (18 [11%] of 161 in arm 1 vs 42 [27%] of 155 in arm 2), and peripheral sensory neuropathy (19 [12%] of 162 in arm 1 vs 32 [21%] of 155 in arm 2).

The authors concluded that intensification of chemotherapy using FOLFIRINOX before neoadjuvant chemoradiotherapy considerably enhanced outcomes in comparison to neoadjuvant chemoradiotherapy in patients with cT3 or cT4 M0 rectal cancer. The considerably increased disease-free survival in the neoadjuvant chemotherapy group and the reduced neurotoxicity demonstrates that the perioperative approach is more efficient and tolerated than adjuvant chemotherapy.

The Grupo cancer de recto 3 study randomized 108 patients with locally advanced rectal cancer to receive either (1) preoperative long-course chemoradiotherapy (CRT) with capecitabine, oxaliplatin, and concurrent radiation followed by surgery and four cycles of postoperative adjuvant capecitabine and oxaliplatin (CAPOX) or (2) induction CAPOX followed by long course chemoradiotherapy and surgery[358].

Postoperative adjuvant CAPOX and induction CAPOX before chemoradiotherapy had a similar pathological complete response and complete resection rates. But, induction CAPOX before CRT achieved more favorable compliance and toxicity profiles.

A Spanish study compared efficacy in terms of pathologic complete response in patients with locally advanced rectal cancer treated with preoperative chemoradiotherapy, with or without a short-intense course of induction oxaliplatin[357].

114 patients were treated with preoperative chemoradiotherapy (45–50.4Gy and oral Tegafur 1200 mg/day). Among them, 52 patients received induction FOLFOX-4 followed by the previously described preoperative chemoradiotherapy.

Short-intense induction FOLFOX-4 considerably increased pathologic complete response in locally advanced rectal cancer patients treated with tegafur-sensitized neoadjuvant chemoradiotherapy.

A multicentric phase II study randomized fifty-seven patients with T2-T4/N+ rectal adenocarcinoma to receive either (1) neoadjuvant chemoradiotherapy with fluorouracil continuous infusion followed by surgery or (2) induction oxaliplatin, folinic acid, and fluorouracil followed by chemoradiotherapy and surgery[356].

In a published interim analysis, the authors reported no differences in the rates of primary downstaging (34.5 % in group 1 vs. 32 % in group 2), R0 resection (97 vs. 96 %), pathological complete response (28 vs. 25 %), or sphincter preservation. Also, toxicity wasn't different in both groups. surprisingly, pathologic response rates in group 1 were considerably bigger than previously published figures, suggesting some patients may have been overstaged. In total, the authors concluded short intense induction oxaliplatin is feasible in locally advanced rectal cancer patients without compromising the neoadjuvant chemoradiotherapy completion even though analysis didn't indicate an enhanced locoregional impact on standard therapy.

A multicenter randomized phase II clinical trial (EXPERT-C study) randomized 165 patients to receive either (1) induction capecitabine/oxaliplatin (CAPOX) followed by capecitabine chemoradiotherapy, surgery, and adjuvant CAPOX or (2) induction cetuximab and capecitabine/oxaliplatin (CAPOX) followed by capecitabine chemoradiotherapy, surgery, and adjuvant CAPOX[355].

Cetuximab caused an important increase in radiological response and overall survival in patients with KRAS/BRAF wild-type rectal cancer, but the primary endpoint of improved complete response was not met.

A retrospective cohort analysis using Memorial Sloan Kettering Cancer Center (MSK) records from 2009 to 2015 compared 320 patients who received chemoradiotherapy with planned adjuvant chemotherapy and 308 patients who received total neoadjuvant treatment (induction fluorouracil- and oxaliplatin-based chemotherapy followed by chemoradiotherapy)[354].

The complete response rate, including both pathological complete response and clinical complete response at 12 months post-treatment, was better in the total neoadjuvant treatment cohort compared to the group with planned adjuvant chemotherapy (37% vs. 22%). Moreover, patients in the total neoadjuvant treatment group got a greater percentage of planned fluorouracil and oxaliplatin. However, there was no difference in distant metastatic-free survival despite a higher number of cT4 and cN+ tumors in the total neoadjuvant treatment group.

Finally, the authors concluded that total neoadjuvant treatment is a viable treatment strategy for rectal cancer and is affiliated with higher rates of pathological complete response and clinical complete response as well as nodal downstaging.

In **A systematic review and meta-analysis**[268], the authors found that the overall pathological complete response can be increased with total neoadjuvant treatment compared with when chemoradiotherapy is administered alone. Moreover, distant and local metastases are potentially lesser, and this can decrease the risk of relapse and mortality, as noticed in the comparative series. The treatment seemed feasible, and almost all patients finished total neoadjuvant treatment with moderate toxicity in line with the treatment received (proctitis, diarrhea, hematological toxicities, and dermatitis)

A phase II single-center pilot trial from Memorial Sloan Kettering Cancer Center studied the use of induction FOLFOX-bevacizumab-based chemotherapy with or without neoadjuvant chemoradiotherapy for patients with clinical stage II-III rectal cancer (but not T4 tumors) who were candidates for sphincter-sparing surgery[349]. In this study, patients were treated with 6 cycles of FOLFOX. Bevacizumab was included for cycles 1 to 4. Patients then were re-

examined, re-imaged, and had repeat sigmoidoscopy with endorectal ultrasound performed by their surgeon to evaluate the primary tumor response. Those with stable/progressive rectal cancer were to be referred for neoadjuvant fluorouracil-based chemoradiotherapy, followed by surgery, and those with clinical regression were to have surgery without neoadjuvant chemoradiotherapy. Adjuvant fluorouracil-based chemoradiotherapy was planned for any patient who did not have an R0 resection. Adjuvant chemotherapy was left to investigator discretion, however, 6 cycles of FOLFOX were recommended.

This pilot study indicated that FOLFOX-bevacizumab-based neoadjuvant chemotherapy alone can be sufficient for local and distant disease control in carefully selected patients.

In conclusion, induction chemotherapy in patients with locally advanced rectal cancer is possible, does not undermine chemoradiotherapy or surgical resection, and permits chemotherapy to be delivered in adequate dose and intensity.

b) Neoadjuvant LCCRT followed by consolidation neoadjuvant chemotherapy

Preliminary results from **the Organ Preservation of Rectal Adenocarcinoma (OPRA) trial** [363] found a considerably bigger rate of organ preservation in the consolidative total neoadjuvant treatment group compared with the induction total neoadjuvant treatment group, but there was no important difference when it came to 3-year disease-free or distant metastasis-free survival.

A multicenter nonrandomized phase II prospective trial [351], [352] studied the effect of consolidation mFOLFOX6 chemotherapy after chemoradiotherapy in patients with locally advanced rectal cancer. It assigned patients to receive chemoradiotherapy (with concurrent fluorouracil) followed by chemotherapy (mFOLFOX6) then surgery.

The pathologic complete response rate was bigger in patients who obtained additional chemotherapy and longer intervals before surgery, and no patient experienced disease progression during neoadjuvant chemotherapy was found. The authors found that adding neoadjuvant mFOLFOX6 not only increased pathological complete response but also improved disease-free survival. Overall survival was not significantly different.

A multi-center randomized phase II trial from Germany, CAO/ARO/AIO-12 [350] sought to determine the optimal scheduling of neoadjuvant chemoradiotherapy and chemotherapy. It randomized 306 patients to receive either (1) induction chemotherapy using three cycles of fluorouracil, leucovorin, and oxaliplatin before fluorouracil/oxaliplatin chemoradiotherapy or (2) consolidation chemotherapy after chemoradiotherapy.

The authors found that group 2 had lower grades 3 or 4 toxicities (27% vs. 37%) and higher compliance (92% vs. 85%). Pathological complete response was achieved in 17% vs. 25%, in group 1 vs. group 2, respectively. They found also that the longer interval between completion of chemoradiotherapy and surgery in group 2 (median 90 v 45 days in group 1) did not increase surgical morbidity. They concluded that chemoradiotherapy followed by consolidative chemotherapy had higher compliance.

c) Neoadjuvant Short-course radiotherapy followed by consolidation neoadjuvant chemotherapy

Short-course radiotherapy looks, as a part of total neoadjuvant treatment, like a promising approach for several reasons. A period of delay between completion of short-course radiotherapy and surgery can permit tumor downstaging. Thus, this “downtime” can instead be used to deliver multi-agent chemotherapy and improve disease control, assuming there is an adequate time between therapies to avoid overlap of toxicities. Moreover, in contrast to total neoadjuvant treatment with long course chemoradiotherapy, delivering short-course radiotherapy can decrease the duration between the start of neoadjuvant treatment and radical surgery. In comparison to induction neoadjuvant chemotherapy regimens, total neoadjuvant treatment with short-course radiotherapy reduces the time to starting multi-agent chemotherapy while also offering early local therapy and is more suitable for patients given the shorter duration of daily radiotherapy.

The international multicenter phase III RAPIDO trial randomized 920 MRI-diagnosed locally advanced rectal cancer patients, with either cT4a/b, cN2, extramural vascular invasion, involved mesorectal fascia or enlarged lateral lymph nodes considered to be metastatic, from 54 centres in the Slovenia, Netherlands, Denmark, Spain, Norway, and the USA[366], [369], to receive either **(1)** Short-course radiotherapy (5 × 5 Gy) followed by six cycles of CAPOX (oxaliplatin 130 mg/m² intravenously on day 1, capecitabine 1000 mg/m² orally twice daily on days 1–14, and a chemotherapy-free interval between days 15–21) or nine cycles of FOLFOX4 (leucovorin [folinic acid] 200 mg/m² intravenously on days 1 and 2, oxaliplatin 85 mg/m² intravenously on

day 1, followed by bolus fluorouracil 400 mg/m² intravenously and fluorouracil 600 mg/m² intravenously for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3–14), followed by total mesorectal excision after 23 to 24 weeks (Choice of FOLFOX4 or CAPOX was per hospital policy or physician discretion), or **(2)** Capecitabine-based chemoradiotherapy (25–28 × 2.0–1.8 Gy, per physician discretion or hospital policy) followed by total mesorectal excision and optional adjuvant treatment with 12 cycles of FOLFOX4 or 8 cycles of CAPOX. All investigators were masked for the primary endpoint until a prespecified number of events was reached. The primary endpoint was 3-year disease-related treatment failure, defined as the first occurrence of locoregional failure, new primary colorectal tumor, distant metastasis, or treatment-related death, evaluated in the intention-to-treat population. Moreover, safety was evaluated by intention to treat. Median follow-up was 4·6 years.

The authors found that pathological complete response rates were 27.7% in arm 1vs 13.8% in arm 2 ($p<0.001$). They also found that at three years, the cumulative probability of disease-related treatment failure was 23.7% in arm 1 and 30.4% in arm 2 ($p = 0.02$). Moreover, probability at three years of distant metastasis and locoregional failure were, in arms 1 and 2, 19.8% vs 26.6% ($p = 0.004$) and 8.7% vs 6.0% ($p = 0.10$), respectively. They noted that they found no differences in disease-related treatment failure between hospitals with or without a policy for postoperative chemotherapy ($p = 0.37$). Furthermore, quality of life ($p=0.125$), overall health ($p=0.192$), and low anterior resection syndrome score ($p=0.136$) were almost similar between the two treatment arms.

The authors found that there were more grade ≥ 3 toxicities during neoadjuvant treatment in arm 1, including more neurologic toxicity (4.3% vs 0.2%), more vascular disorders (8.5% vs 4.1%), and more diarrhea (17.6% vs 9.3%). During postoperative adjuvant therapy, diarrhea was observed in 7% of the arm 2.

The authors concluded that a lower rate of disease-related treatment failure, as a consequence of a lower rate of distant metastases, in high-risk locally advanced rectal cancer patients can be achieved with neoadjuvant short-course radiotherapy, followed by chemotherapy and total mesorectal excision than by conventional chemoradiotherapy. In addition, the high pathological complete response rate, achieved with the treatment regimen in arm 1 can benefit organ preservation. This treatment can be regarded as a new standard of care for locally advanced rectal cancer.

In a single-arm phase II trial at Washington University, 69 patients with cT3-4 cN0-2 rectal cancer obtained a near-total neoadjuvant treatment consisting of short-course radiotherapy followed by 4 cycles of FOLFOX and a subsequent 4–9-week delay before total mesorectal excision, with or without up to 8 cycles of adjuvant FOLFOX-based chemotherapy[347], [348]. In comparison to **a stage-matched cohort** of patients who received neoadjuvant long-course chemoradiotherapy and adjuvant FOLFOX-based chemotherapy, patients undergoing the near-total neoadjuvant treatment regimen showed ameliorations in pathologic downstaging of the primary tumor (75% vs. 41%) and 3-year disease-free survival (85% vs. 68%), with no important difference in 3-year actuarial local control (92% vs. 96%).

Supplementary patients from **a Stanford University cohort** were further included in the comparison group to decrease bias, and total neoadjuvant treatment stayed associated with a lower risk of recurrence. Comparable local control between groups can indicate that the improvement in disease-free survival and distant metastasis-free survival is due to earlier delivery of multi-agent chemotherapy. There were expectedly more preoperative grades 3–4 acute hematologic toxicities in the neat total neoadjuvant treatment cohort (22% vs. 0%), but these findings are similar to toxicity profiles during adjuvant chemotherapy, and patient-reported quality of life was unfluctuating from pre-treatment to 1 year after surgery[345]. . Moreover, 28% of patients in the near-total neoadjuvant treatment cohort had a pathological complete response compared to 16% in the matched cohort. While not considerably different, the rate of pathological complete response in the near-total neoadjuvant treatment group was high regarding historical controls, particularly considering the high-risk disease characteristics prevalent in this cohort (75% cN1-2, 76% with one or more adverse features including tumor < 5 cm from the anal verge, circumferential, fixed, or near-obstructing).

A **single-institution experience report** about the feasibility and early oncologic outcomes of short-course neoadjuvant radiotherapy (5 Gy x 5 fractions) followed by consolidation neoadjuvant chemotherapy studied twenty-five patients who underwent a median of 4 cycles (range 3 to 8) of mFOLFOX6 (with one cycle consisting of two weeks). It was noted that one patient received 3 cycles of capecitabine and oxaliplatin, all patients completed short-course radiotherapy, and 81% completed the full course of neoadjuvant chemotherapy with 19% requiring dose reductions in chemotherapy, most commonly due to neuropathy[345].

The authors concluded that short-course neoadjuvant radiotherapy followed by consolidation neoadjuvant chemotherapy was well-tolerated and achieved oncologic outcomes that compare satisfyingly with neoadjuvant long-course chemoradiotherapy or neoadjuvant short-course radiation therapy alone. This approach is affiliated with high rates of clinical and pathologic complete response.

B. The interest of the intensification of current neoadjuvant treatments [250], [341], [378], [370]–[377]

Over the last decades, rising attention concerning intensified neoadjuvant treatment has been noticed, mostly focused on locally advanced and metastatic rectal cancer. Employing the standard chemoradiotherapy strategy, only about 11–18% of patients will achieve a pathological complete response[341]. Because this minor group of patients presents an improved overall prognosis in comparison to others with less or no response, several approaches have been studied to enhance the pathological complete response rate or even exclude surgery in selected cases. Those approaches include:

- The use of more intensive chemotherapy regimens concurrent to radiation
- Addition of targeting agents to concurrent chemoradiotherapy
- Escalation of radiotherapy dose or the use of altered fractionations
- The sequential use of chemoradiotherapy and intensified induction or consolidation chemotherapy regimens in the neoadjuvant setting known as total neoadjuvant therapy

Those strategies are further studied in previous chapters.

The total neoadjuvant treatment strategy is likely the most promising since it targets not only pathological complete response rate but also appears to decrease distant failure rates with enhanced treatment compliance and acceptable toxicity.

A single-institution retrospective study investigated surgical complications in 387 patients who received oncological resection for rectal cancer between January 2000 and December 2009, from which 106 patients received an intensified radiochemotherapy. Perioperative morbidity and mortality were studied and analyzed retrospectively with special attention to complication rates after intensified radiochemotherapy[370]. Most neoadjuvant-treated patients underwent an intensified neoadjuvant radiochemotherapy, which varied within the observation period. From January 2000 to January 2002, patients underwent a combination of continuous infusion fluorouracil (250 mg/m2 per day) over 31 days, seven weekly doses of irinotecan (40 mg/m2), and a local radiotherapy five days a week with a single dose of 1.8 Gy adding up to 50.4 Gy.

From February 2002, fluorouracil was replaced by a daily dose of capecitabine with a single dose between 1000 and 1650 mg/m2. Doses of radiotherapy were no longer decreased and attained a cumulative dose of 55.8 Gy. Oxaliplatin had been received instead of irinotecan in eight patients. Also, for each patient exposed to neoadjuvant treatment a patient without neoadjuvant treatment was matched in the following order for tumor height, discontinuous resection/extirpation, T-category of the TNM-system, dividing stoma, and UICC stage

The authors found that of all patients operated for rectal cancer, 27.4% underwent an intensified neoadjuvant treatment and tumor location in the matched patients were in the lower third (55.2%), middle third (41.0%), and upper third (3.8%) of the rectum. Postoperatively, surgical morbidity was greater after intensified neoadjuvant treatment. In the subgroup with low anterior resection, the anastomosis leakage rate was bigger (26.6% vs. 9.7%) and in the subgroup of patients with rectal extirpations, the perineal wound infection rate was larger (42.2% vs. 18.8%) after intensified radiochemotherapy. Thus, they concluded that, in rectal cancer, the decision for an intensified neoadjuvant treatment is associated with along with an increase of anastomotic leakage and perineal wound infection. Also, the quality of life is usually reduced significantly and has to be balanced against the potential benefit of intensifying neoadjuvant radiochemotherapy.

It is noted that the treatment intensification of the standard neoadjuvant schedule (LCCRT or SCRT) has been tried by many researchers. However, early results of these treatment intensification trials demonstrated no significant benefit and are coupled with higher toxicity. There is an unfulfilled need to stratify patients based on risk to assign them to long-course chemoradiotherapy or short-course radiotherapy. Actual evidence does not support the employment of adjuvant chemotherapy in patients who received neoadjuvant (chemo) radiotherapy. Neoadjuvant radiotherapy seems to increase disease control with a favorable toxicity profile and there is very little to choose between long-course chemoradiotherapy and short-course radiotherapy (as seen in previous chapters). Nonetheless, long-course chemoradiotherapy can be favorable for patients with high-risk features such as positive circumferential resection margin and

extramural spread of >5mm. There seems to be no role for adjuvant chemotherapy in patients who were treated preoperative (chemo)radiotherapy[377]

In **a review** comparing the current approaches in the intensification of long-course chemoradiotherapy in locally advanced rectal cancer[378], the authors found that the total neoadjuvant treatment has a brighter future, considering the strength of results and power of the clinical trials, compared to radiotherapy intensification and concurrent chemotherapy intensification.

CONCLUSION

Neoadjuvant treatment is now a pillar in the standard care for locally advanced rectal cancer. A lot of research and studies aim to specify the best strategy and approach to increase pathological complete response, local and distant control while decreasing local and distant metastasis and toxicities.

The standard care for locally advanced rectal cancer saw many changes. First, it consisted of surgery alone, afterward surgery and adjuvant treatment, and now neoadjuvant treatment followed by surgery.

The neoadjuvant treatment presented many advantages, such as tumor downstaging, improving local control, disease-free survival and local recurrence-free survival rates, complete pathological response, and the chances of sphincter-saving surgery.

Neoadjuvant treatment, including short-course radiotherapy and long-course chemoradiotherapy, is mainly indicated in treating locally advanced rectal cancer.

Short-course radiotherapy consists of 25Gy in 5 fractions without concurrent chemotherapy, followed by surgery 1 to 2 weeks afterward.

Long-course chemoradiotherapy consists of 45 to 54 Gy of external-beam radiotherapy over 25 to 28 daily fractions while also receiving concomitant radiation-sensitizing fluoropyrimidine-based chemotherapy.

Recently, total neoadjuvant treatment (TNT) is receiving more attention. It consists of different strategies, some comprise of receiving long-course chemoradiotherapy followed by chemotherapy before surgery (**consolidation neoadjuvant chemotherapy**), others comprise of receiving chemotherapy followed by long course chemoradiotherapy before surgery (**induction neoadjuvant chemotherapy**). Receiving short-course radiotherapy followed by chemotherapy before surgery is also a TNT approach.

Science generally and medicine specifically achieved huge progress in treating cancer especially rectal cancer. The association of neoadjuvant treatment and surgery showed a mighty effect in saving many patients and improving their survival.

More trials are going on, trying to improve the current standard of care. Some may not achieve their goals, but the ones that will do it will surely be marked as historical moments, the same way previous ones did.

ABSTRACTS

ABSTRACT

Title: Neoadjuvant treatment in rectal cancer: a review of literature

Author: Youssef EL MARRAKI

Keywords: Rectal cancer; Neoadjuvant treatment; Radiotherapy; Chemotherapy

Background: Neoadjuvant treatment is a pillar of the current standard care of locally advanced rectal cancer. Many approaches are used as neoadjuvant treatment, while more are analyzed and studied to further improve the current ones.

Aim: To investigate the neoadjuvant treatment as a current standard of care for locally advanced rectal cancer

Methods: A review of the literature was performed to investigate and evaluate the neoadjuvant treatment in the current standard of care for locally advanced rectal cancer. The review includes original articles published in English, included and not limited to systematic reviews, prospective studies, and retrospective ones. It also included chapters and data from different books and scientific sites.

Results: Short-course radiotherapy and long-course chemoradiotherapy have comparable results, while total neoadjuvant treatment seems like a promising approach, although more studies are needed. Moreover, intensified neoadjuvant treatment's results differ depending on the strategy used, and they show new directions for a better treatment approach.

Conclusion: Neoadjuvant treatment shows clearly its advantages in treating locally advanced rectal cancer, especially when it comes to improving local control and increasing pathological complete response.

Résumé

Titre: les traitements néoadjuvants dans le cancer du rectum: revue de la littérature

Auteur: Youssef EL MARRAKI

Mots clés: Cancer du rectum; Traitement néoadjuvant; Radiothérapie; Chimiothérapie

Contexte: Le traitement néoadjuvant est un pilier du traitement standard actuel du cancer du rectum localement avancé. De nombreuses approches sont utilisées comme traitement néoadjuvant, tandis que d'autres sont analysées et étudiées pour améliorer les approches actuelles.

Objectif: Étudier le traitement néoadjuvant en tant que norme de soins actuelle pour le cancer du rectum localement avancé.

Méthodologie: Une revue de la littérature a été réalisée afin d'étudier et d'évaluer le traitement néoadjuvant dans la norme actuelle de soins pour le cancer du rectum localement avancé. La revue comprend des articles originaux publiés en anglais, incluant et ne se limitant pas à des revues systématiques, des études prospectives et rétrospectives. Elle inclut également des chapitres et des données provenant de différents livres et sites scientifiques.

Résultats: La radiothérapie courte et la chimioradiothérapie longue donnent des résultats comparables, tandis que le traitement néoadjuvant total semble être une approche prometteuse, bien que des études supplémentaires soient nécessaires. De plus, les résultats du traitement néoadjuvant intensifié diffèrent en fonction de la stratégie utilisée, et ils montrent de nouvelles directions pour une meilleure approche thérapeutique.

Conclusion: Le traitement néoadjuvant montre clairement ses avantages dans le traitement du cancer du rectum localement avancé, notamment lorsqu'il s'agit d'améliorer le contrôle local et d'augmenter la réponse pathologique complète.

ملخص

العنوان: العلاج الابتدائي المساعد في سرطان المستقيم

المؤلف: يوسف المراقي

الكلمات الأساسية: سرطان المستقيم, العلاج الابتدائي المساعد, العلاج الإشعاعي, العلاج الكيميائي.

السياق: العلاج الابتدائي المساعد هو أحد أعمدة الرعاية القياسية الحالية لسرطان المستقيم المتقدم محليًا. يتم استخدام العديد من الأساليب كعلاج مساعد جديد، بينما يتم تحليل المزيد منها ودراستها لتحسين الأساليب الحالية

المقصد: التحقيق في العلاج الابتدائي المساعد كمعيار حالي للرعاية لسرطان المستقيم المتقدم محليًا

المنهجية: بهدف دراسة و تقييم المعيار الحالي المتعلق بالعلاج الابتدائي المساعد لعلاج سرطان المستقيم المتقدم محليا, تمت مراجعة الأدبيات ذات الصلة بالموضوع. شملت هذه المراجعة مقالات أصلية منشورة باللغة الإنجليزية و اللتي تتضمن دون أن تنحصر في المراجعات المنهجية و الدراسات الإستباقية و الإسترجاعية. كما شملت أيضا فصولا و بيانات مستمدة من مختلف المؤلفات و المواقع العلمية

النتائج: يعطي العلاج الإشعاعي القصير والعلاج الكيميائي الإشعاعي الطويل نتائج مماثلة ، بينما يبدو أن العلاج المساعد الجديد هو نهج واعد ، على الرغم من الحاجة إلى مزيد من الدراسات. بالإضافة إلى ذلك ، تختلف نتائج العلاج المساعد الجديد اعتمادًا على الاستراتيجية المستخدمة ، وتظهر اتجاهات جديدة لنهج علاجي أفضل.

الخلاصة: يظهر العلاج الابتدائي المساعد بوضوح مميزاته في علاج سرطان المستقيم المتقدم محليًا ، خاصة عندما يتعلق الأمر بتحسين السيطرة الموضعية وزيادة الاستجابة المرضية الكاملة.

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Serment d' H ippocrate

Au moment d'être admis à devenir membre de la profession médicale, je m'engage solennellement à consacrer ma vie au service de l'humanité.

- *Je traiterai mes maîtres avec le respect et la reconnaissance qui leur sont dus.*
- *Je pratiquerai ma profession avec conscience et dignité. La santé de mes malades sera mon premier but.*
- *Je ne trahirai pas les secrets qui me seront confiés.*
- *Je maintiendrai par tous les moyens en mon pouvoir l'honneur et les nobles traditions de la profession médicale.*
- *Les médecins seront mes frères.*
- *Aucune considération de religion, de nationalité, de race, aucune considération politique et sociale ne s'interposera entre mon devoir et mon patient.*
- *Je maintiendrai le respect de la vie humaine dès la conception.*
- *Même sous la menace, je n'userai pas de mes connaissances médicales d'une façon contraire aux lois de l'humanité.*
- *Je m'y engage librement et sur mon honneur.*

قسم أبقراط

بسم الله الرحمان الرحيم

أقسم بالله العظيم

في هذه اللحظة التي يتم فيها قبولي عضوا في المهنة الطبية أتعهد علانية:

- بأن أكرس حياتي لخدمة الإنسانية.
- وأن أحترم أساتذتي وأعترف لهم بالجميل الذي يستحقونه.
- وأن أمارس مهنتي بوازع من ضميري وشرفي جاعلا صحة مريضي هدفي الأول.
- وأن لا أفشي الأسرار المعهودة إلي.
- وأن أحافظ بكل ما لدي من وسائل على الشرف والتقاليد النبيلة لمهنة الطب.
- وأن أعتبر سائر الأطباء إخوة لي.
- وأن أقوم بواجبي نحو مرضاي بدون أي اعتبار ديني أو وطني أو عرقي أو سياسي أو اجتماعي.
- وأن أحافظ بكل حزم على احترام الحياة الإنسانية منذ نشأتها.
- وأن لا أستعمل معلوماتي الطبية بطريق يضر بحقوق الإنسان مهما لاقيت من تهديد.
- بكل هذا أتعهد عن كامل اختيار ومقسما بالله.

والله على ما أقول شهيد.

المملكة المغربية
جامعة محمد الخامس بالرباط
كلية الطب والصيدلة
الرباط

سنـة : 2021 أطروحة رقم:326

العلاج الابتدائي المساعد في سرطان المستقيم

أطروحة

قدمت ونوقشت علانية يوم : / /2021

من طرف
السيد يوسف المراقي
المزداد في 25 أكتوبر 1995 بالدريوش
من المدرسة الملكية لمصلحة الصحة العسكرية – الرباط

لـنـيـل شـهـادة

دكـتـور فـي الطب

الكلمات الأساسية : سرطان المستقيم؛ العلاج الابتدائي المساعد؛العلاج الإشعاعي؛ العلاج الكيميائي

أعضاء لجنة التحكيم:

السيد حسن صفات أستاذ في العلاج بالأشعة	**رئيس**
السيد محمد المرجاني أستاذ في العلاج بالأشعة	**مشرف**
السيد ياسر سبيطي أستاذ في علم السرطان	**عضو**
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