Neoadjuvant Management of Cancer Rectum

Essay

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By

Reham Mohammed Faheim
M.B; B.Ch

supervised by

Prof. Dr. Soheir Helmy Mahmoud

Prof. of Radiation Oncology and Nuclear Medicine
Ain Shams University

Dr. Tarek Hussein Kamel

Ass. Prof. Of Radiation Oncology And Nuclear Medicine
Ain Shams University

Dr. Hesham Ahmed Elghazaly

Lecturer Of Radiation Oncology And Nuclear Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
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العلاج الكيماوى والإشعاعى المستخدم قبل إجراء العملية الجراحية لسرطان المستقيم

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مقدمه من

الطبيبه / ريهام محمد فهيم

تحت إشراف

الأستاذة الدكتورة / سهير حلمى محمود

أستاذ علاج الأورام بالإشعاع والطب النووى
كلية الطب – جامعة عين شمس

الدكتور / طارق حسين كامل

أستاذ مساعد علاج الأورام بالإشعاع والطب النووى
كلية الطب – جامعة عين شمس

الدكتور / هشام احمد الغزالى

مدرس علاج الأورام بالإشعاع والطب النووى
كلية الطب – جامعة عين شمس

كلية الطب
جامعة عين شمس
٢٠٠٧

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Introduction

The rectum is the final straight portion of the large intestine, terminating in the anus. The human rectum is about ١٢ cm long. The rectum hooks up with the sigmoid colon superiorly and with the anal canal inferiorly. The rectum has neither mesentery nor haustra, and it has an almost complete outer longitudinal muscular coat rather than teniae and lower third empty except during defecation ***(Robert et al., ٢٠٠٧).***

Estimated new cases of rectal cancer in radiation oncology and nuclear medicine department of Ain Shams University in ٢٠٠٧: ٢٨ new cases. Estimated new cases of rectal cancer in the United States In ٢٠٠٧: ٤١,٤٢٠ ***(Linda et al, ٢٠٠٧).*** Relative frequency Incidence of rectal cancer in radiation oncology and nuclear medicine department of Ain Shams University in ٢٠٠٧: ٢ %.

The incidence is slightly higher in males than in females ***(Elizabeth et al., ٢٠٠٧).*** Incidence peaks in the seventh decade; however, cases have been reported in young children ***(Elizabeth et al., ٢٠٠٧).***

Adenocarcinoma is the most common type of cancer rectum. It accounts for over ٩٠-٩٥٪ of cancers originating in the rectum. Other types of cancer including carcinoid (٠,١٪), lymphoma (١,٣٪), and sarcoma (٠,٣٪) also originate in the rectum, but are not referred to as rectal cancer. Very rare cases of squamous cell carcinoma of the rectum have been reported ***(Harvey, ٢٠٠٤).***

The exact cause of rectal cancer is unknown, but rectal cancer appears to be multifactorial in origin and studies showing concentration in areas of higher economic development suggest a relationship to diet (excess saturated animal fat). Causes of rectal cancer are probably environmental in the sporadic cases (٨٠٪), and genetic in the hereditary − predisposed (٢٠٪) cases, other factors include: other diseases of the digestive tract and history of ulcerative colitis ***(Will et al., ٢٠٠٦).***

Germline mutations responsible for inherited conditions that predispose to the development of rectal cancers, such as the *APC* gene in familial adenomatous polyposis coli (FAP) and the mismatch repair genes in hereditary non-polyposis colon cancer (HNPCC). But FAP and HNPCC account for only about ٥٪ of all colorectal cancers, and the identification of genetic polymorphisms that predispose to the development of colorectal cancer may be more important in the population as a whole ***(*Park and Kim, ٢٠٠٥).***

Molecular techniques have been employed in the diagnosis of colorectal cancer, and mutated copies of the *APC*, *K-ras* and *P٥٣* genes have been detected in the stools of patients with malignancies as have DNA sequences demonstrating microsatellite instability ***(Lawes et al., ٢٠٠٣).*** Rectal cancers expressing the mutant P٥٣ protein tend to be resistant to radiotherapy, whilst those expressing the *p٢١* gene seem more sensitive to its effects. Cancers that express high levels of the enzyme thymidylate synthase show resistance to ٥-fluorouracil whilst those demonstrating microsatellite instability seem to respond well to ٥-fluorouracil. Cancers with mutations of the *K-ras, DCC* and *p٥٣* genes tend to have a poor prognosis ***(Devita et al., ٢٠٠٥).***

Cyclooxygenase-٢ (COX-٢) expression correlates with size and invasiveness of colorectal carcinomas. When its expression levels increase, the size and the depth of tumor invasion increase. COX-٢ expression in primary lesions of colorectal cancer is closely related to the occurrence of metachronous liver metastasis and patient survival outcome ***(Takeyoshi; et al, ٢٠٠٤).***

Colorectal cancer patients with EGFR-negative tumors have the potential to respond to cetuximab-based therapies. EGFR analysis by current IHC techniques does not seem to have predictive value and selection or exclusion of patients for cetuximab therapy on the basis of currently available EGFR IHC does not seem warranted ***(KiYoung et al., ٢٠٠٥).***

All patients should undergo a complete history, including a family history and assessment of risk factors for the development of rectal cancer. Many rectal cancers produce no symptoms and are discovered during digital or proctoscopic screening examinations. Bleeding per rectum is the most common symptom of rectal cancer and occurs in ٦٠٪ of patients. Change in bowel habits present in ٤٣٪ of patients. Often, it occurs in the form of diarrhea, particularly if the tumor has a large villous component. Partial large-bowel obstruction may cause colicky abdominal pain and bloating and is present in ٢٠٪ of cases. Also unexplained weight loss and malaise**.** Physical examination is performed including digital rectal examination, routine laboratory studies, CEA, (CA) ١٩-٩, fecal occult blood test and imaging Studies, such as, double contrast barium enema, proctosigmoidoscopy, endorectal ultrasound and metastatic workup ***(Elizabeth et al., ٢٠٠٧).***

Staging is an important part of diagnosis, treatment planning, and predictions of long term survival. Various

staging systems have been used for rectal cancer, the most popular being that proposed by Dukes. It is based on the degree of bowel wall penetration and lymph node metastases. The Dukes system does not include the degree of bowel wall penetration in node-positive patients. Surgeons and oncologists are increasingly using the unified TNM stage system of the UICC (Union International Contre le Cancer) and AJCC (American Joint Committee on Cancer), as it separately identifies each component of a tumour's risk; tumour stage (T), node stage (N) and metastasis (M) ***(Elizabeth et al., ٢٠٠٧).***

Neoadjuvant therapy: This can be defined as any form of treatment the patient receives prior to definitive surgical intervention, with the aim of limiting the scope of surgery required ***(Prab .et al., ٢٠٠٢).***

Preoperative radiation therapy among the potential advantages of the preoperative approach are downstaging and downsizing effects that possibly enhance curative surgery in locally advanced, e.g. T٤-rectal cancer, and sphincter preservation in low-lying rectal cancer. Moreover, neoadjuvant therapy may be advantageous also in resectable rectal cancer as sterilization of the tumor cells prior to surgery may reduce the risk of tumor cell spillage during surgery. Technically, there are two approaches to preoperative radiation therapy. The first one is an intensive short-course radiation, for one week & the second includes ٥ to ٦ weeks of conventional fractionation **(Rolf, ٢٠٠٢).**

Neoadjuvant therapy used in locally advanced rectal cancer is neoadjuvant CRT that consisted of ٥٠,٤ Gy in ٢٨ fractions to the tumor and pelvic lymph nodes and concomitant ٥-FU continuous infusion during weeks ١ and ٥. All patients also received ٤ additional cycles of ٥-FU adjuvant chemotherapy and a ٥,٤ Gy small-volume boost._Neoadjuvant XELOX-RT ٥٠,٤ Gy consists

of preoperative radiation therapy with concomitant Xeloda and Eloxatin ***(Charles et al, ٢٠٠٣).***

Pathologic complete response rates by using a neoadjuvant approach range from ٣٪ to ٣٠٪.Complete clinical response after treatment range from ٧٪ to ١٤٪ and has been judged by combinations of examination, proctoscopy, CT-scan, endorectal ultrasound, and biopsy***(Mark et al., ٢٠٠١).***

Enhancing Sphincter preservation another major goal of neoadjuvant therapy is the conversion of a low-lying tumor, that was declared by the surgeon to require an abdominoperineal resection (APR), into a lesion amenable to sphincter-preserving procedures (SPP).Technically, two surgical approaches have been used after preoperative therapy: local excision and a low anterior resection with or without a coloanal anastomosis ***(Rolf, ٢٠٠٢).***

The prognosis and treatment options depend on the stage of the cancer (whether it affects the inner lining of the rectum only, involves the whole rectum, or has spread to other places in the body), the patient's general health and whether the cancer has just been diagnosed or has recurred. Disease recurs in ٥-٣٠٪ of patients, usually in the first year after surgery ***(Elizabeth et al., ٢٠٠٧).***

THE CONTENTS

THE ABBREVIATIONS

AJCC	*American Joint Committee on Cancer*
AP	*anterioposterior*
APC	*adenomatous polyposis coli*
APR	*abdominoperineal resection*
ASTRO	*American Society of Therapeutic Radiology and Oncology*
BIT	*bi-ischial tuberosity*
BMI	*body mass index*
CA	*cancer antigen*
CAA	*colonanal anastomosis*
CEA	*carcinoembryonic antigen*
cm	*Centimeter*
COX-۲	*Cyclooxygenase-۲*
CRT	*chemoradiation*
C-T	*Computed tomography*
DFS	*disease free survival*
DRE	*digital rectal examination*
DSC	*distance of sacrococcyx*
EBRT	*external beam radiation therapy*
EGFR	*the epidermal growth factor receptor*

EORTC	*European Organisation for Research and Treatment of Cancer*
ERUS	*Endorectal ultrasound*
FOBT	*fecal occult blood test*
GI	*gastrointestinal*
HART	*High accelerated RT*
HNPCC	*hereditary nonpolyposis colorectal cancer*
IBD	*inflammatory bowel disease*
IHC	*Immunohistochemical*
IORT	*Intraopertive RT*
LAR	*low anterior resection*
MIN	*microsatellite instability*
MMP	*metalloproteinases*
MMR	*mismatch repair*
MRI	*Magnetic resonance imaging*
NCI	*National Cancer Institute*
pCR	*pathologic complete response*
PET	*positron emission tomography*
RT	*radiotherapy*
R1	*Positive resection margin*

R٢	*Direct visualization and irradiation of the persistent tumour*
SCRCs	*sporadic colorectal cancers*
SIPS	*inferior pubis to sacrococcyx*
SPP	*sphincter preservation procedure*
SUPS	*upper pubis to the sacrococcyx*
TME	*Total mesorectal excision*
TP	*thymidine phosphorylase*
TPR	*total pathological remissions*
TS	*thymidylate synthase*
U.S.A	*the United States*
UC	*ulcerative colitis*
UICC	*Union International Contre le Cancer*
UICC	*the International Union against Cancer*
UPC	*upper pubis to coccyx*
S.N.٤	*the fourth sacral nerve*
٣D	*three-dimensionally*
٥*FU*	٥*-fluorouracil*

THE FIGURES