Saudi Oncology Society clinical management guideline series

Colorectal cancer 2014

Shouki N. Bazarbashi, *MBBS,* ***Ali M. Alzahrani,*** *MBChB, FRCR,* ***Mohammed M. Rahal,*** *MD, PhD,* ***Ahmed S. Al-Shehri,*** *MBChB, FRCPC,* ***Ali H. Aljubran,*** *MD,* ***Nasser A. Alsanea,*** *MBChB,* ***Omar A. Al-Obeed,*** *MBBS, FRCSC,* ***Magdy S. Kandil,*** *MD, PhD,* ***Jamal E. Zekri,*** *MBBCh, FRCP (UK),* ***Ashwaq A. Al Olayan,*** *MBBS,* ***Abdullah A. Alsharm,*** *MD,* ***Khaled S. Balaraj,*** *MD, FRCPC,* ***Mosa A. Fagih,*** *MBBS, FRCPC.*

Colorectal cancer ranked first in incidence among Saudi males and third among Saudi females for the last several years according to Saudi Cancer Registry data.[1] A total of 1033 cases accounting for 10.4% of all newly diagnosed cases were reported in 2010.[1] The overall age standardized rate (ASR) was 9.6/100,000 with ASR of 9.9/100,000 for males and 9.2/100,000 for females. The median age at diagnosis was 60 years for males (range 2-100 years) and 55 years for females (range 13-100 years).[1]

A committee of experts in the medical and surgical treatment of colorectal cancer was established under the supervision of the Saudi Oncology Society (SOS). The evidence adopted in these guidelines is rated at 3 levels: 1) Evidence level-1 (EL-1) (highest level) evidence from phase III randomized trials or meta-analyses; 2- EL-2 (intermediate-level) evidence from good phase II trials or phase III trials with limitations; and 3- EL-3 (low-level) from retrospective or observational data and/or expert opinion. This easy-to-follow grading system is convenient for the reader and allows accurate assessment of the applicability of the guideline in individual patients.[4]

Ultimately, it was agreed that all colorectal cancer cases are preferably seen or discussed in a multidisciplinary form

1. **Pre-treatment evaluation:**
    - 1.1. Clinical examination, including rigid proctosigmoidoscopy for rectal cancer
    - 1.2. Blood count, liver, and renal function tests
    - 1.3. Chest x-ray
    - 1.4. Carcinoembryonic antigen (CEA) level
    - 1.5. CT scan of abdomen and pelvis (including chest in rectal cancer cases)
    - 1.6. Full length colonoscopy
    - 1.7. Transrectal ultrasound and magnetic resonance imaging (MRI) for rectal cancer

    Rectal cancer will be defined as tumors within 15 cm from the anal verge on rigid proctosigmoidoscopy, and below the sacral promontory on computed tomography (CT) scan.

From the Section of Medical Oncology (Bazarbashi, Aljubran), Section of Colon and Rectal Surgery (Alsanea), Department of Surgery, Department of Oncology (Zekri), Section of Radiation Oncology (Balaraj), Oncology Center, King Faisal Specialist Hospital and Research Center, Oncology Department (Alzahrani, Kandil) Prince Sultan Military Medical City, Department of Surgery (Al-Obeed), King Khalid University Hospital, King Saud University, Department of Oncology (Al Olayan), King Abdulaziz Medical City, Medical Oncology Department (Alsharm), Anatomic Pathology Department (Fagih), King Fahad Medical City, Riyadh, Department of Oncology (Rahal), Oncology Center, King Fahad Specialist Hospital, Dammam, and the Department of Oncology (Al-Shehri), Princess Nora Oncology Center, King Abdulaziz Medical City, Jeddah, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Shouki N. Bazarbashi, Oncology Center, King Faisal Specialist Hospital and Research Center, PO Box 3354 (MBC 64), Riyadh 11211, Kingdom of Saudi Arabia. Tel. +966 (11) 4423935. E-mail: Bazarbashi@gmail.com

2. **Surgical pathology report requirements:** The following parameters should be mentioned in all surgical pathology reports of colorectal cancer:[3]
    - 2.1 Specimen
    - 2.2 Procedure
    - 2.3 Specimen length
    - 2.4 Tumor site
    - 2.5 Tumor size
    - 2.6 Macroscopic tumor perforation
    - 2.7 Macroscopic intactness of mesorectum
    - 2.8 Histologic type
    - 2.9 Histologic grade
    - 2.10 Histologic features suggestive of microsatellite instability
    - 2.11 Microscopic tumor extension
    - 2.12 Margins
    - 2.12 Treatment effect (applicable to carcinomas treated with neoadjuvant therapy)
    - 2.12 Vascular (large vessel) invasion (V)
    - 2.13 Lymphatic (small vessel) invasion (L)
    - 2.14 Discontinuous extramural extension (irregular tumor nodules in pericolorectal adipose tissue without histologic evidence of residual lymph node)
    - 2.15 Perineural invasion
    - 2.16 Mismatch repair (MMR) status by either immunohistochemistry (IHC) staining or polymerase chain reaction (PCR) in node negative tumors
    - 2.17 Type of pre-existing polyp in which invasive carcinoma arose from
    - 2.18 Pathologic staging (pTNM)

3. **Staging:**
   The American Joint Commission on Cancer (AJCC) - 2007 pathological staging system will be used.[4]

4. **Treatment:**
   4.1. Clinically localized resectable colon cancer:
    - 4.1.1. Surgical resection according to location:
        - 4.1.1.1. Right colonic cancer includes tumors in the cecum, ascending colon, and hepatic flexure, and are treated with a right hemicolectomy (EL-3).
        - 4.1.1.2. Left colonic cancer includes tumors in the transverse colon, splenic flexure, and descending colon, and are treated with a left partial / left hemicolectomy (EL-2)
        - 4.1.1.3. Sigmoid colon cancer includes tumor located in the totally peritonealized part of the colon between the descending colon and the sacral promontory. It is treated with a sigmoid colectomy (EL-2)
        - 4.1.1.4. Laparoscopic assisted resection is equal to open resection[5] (EL-1)
        - 4.1.1.5. A proximal and distal 5 cm margin is needed for colonic cancer colectomies[6] (EL-2)
        - 4.1.1.6. Surgery should be performed by a colorectal surgeon
    - 4.1.2. Stage I: no adjuvant therapy required
    - 4.1.3. Stage II (Node negative), average risk: no indication of adjuvant chemotherapy[7]
    - 4.1.4. Stage II (Node negative), high risk: treatment will depend on the MMR status:
        - 4.1.4.1. Patients with deficient MMR status will be recommended for observation only10 (EL-2)
        - 4.1.4.2. Patients with proficient MMR status will be recommended for adjuvant chemotherapy with one of the following options: single agent capecitabine or Mayo Clinic regimen (5-Fluorouracil and Leucovorin) for 6 months[9] (EL-3)

High risk factors: - T4 lesion
- Less than 12 removed lymph nodes
- Lymphovascular or perinural invasion
- Obstruction
- Perforation
- Poorly differentiated histology
- Positive margin (if not considered for re-resection)

4.1.5. Stage III (node positive): Adjuvant FOLFOX 6 for 6 months (12 cycles)[10] (EL-1), or alternatively 8 cycles of XELOX regimen[11] (EL-1). Elderly patients and those with performance status (PS) of 3 may be offered single agent capecitabine for 6 months[12]

4.1.6. Follow up: clinical examination, CEA level every 6 months for 5 years. A CT-scan annually for first 3 years in node positive patients (EL-3). Colonoscopy within 6 months if not carried out preoperatively then after 3 years, then every 5 years if normal

4.2. Clinically localized resectable rectal cancer:

4.2.1. Surgical resection procedure will depend on the location of the tumor (anterior resection versus abdomino-perineal resection). The following should be ascertained:

4.2.1.1. Rectal cancer includes tumors between the dentate line in the anal canal and the sacral promontory

4.2.1.2. Surgery should be carried out by a colorectal surgeon

4.2.1.3. Total mesorectal excision should be performed[13]

4.2.1.4. For upper third rectal tumors, a distal mesorectal margin of 5 cm should be excised (however, 2 cm distal margin is needed for lower third rectum)[14] (EL-1)

4.2.1.5. Margins less than 2 cm intra-operatively dictate the need for a frozen section to prove negativity

4.2.1.6. The distal doughnut is not considered part of the distal 2 cm distal margin in rectal cancer

4.2.1.7. Patients with a compromised lumen (does not allow intubation by 20 mm rigid proctosigmoidoscope) should have elective stoma (outside radiation field) prior to starting pre-operative radiation

4.2.2. Endo-anal or transsacral resection will be offered to selected patient populations with all the following factors:[15]

4.2.2.1. Tumor up to 8 cm from anal verge. For tumors located more than 8 cm, trans-anal endoscopic microsurgery (TEM) is feasible.

4.2.2.2. Tumor less than 3 cm in maximum diameter

4.2.2.3. Freely mobile tumors

4.2.2.4. T1 on endoscopic ultrasound or MRI

4.2.2.5. Node negative on MRI ± endoscopic ultrasound

4.2.2.6. Well or moderately differentiated tumors

4.2.2.7. Absence of lymphovascular or peri-neural invasion

4.2.2.8. 3 mm negative margin

In case of violation of any of the above, surgery should be offered. If surgery is not an option, adjuvant chemoradiotherapy should be offered (EL-3)

4.2.3. All clinically T3-4 or N positive lesions will receive pre-operative concurrent chemoradiotherapy. The irradiation will consist of 5040 cGy in 28 fractions and the chemotherapy will consist of capecitabine or infusional 5-Fluorouracil[16] (EL-1). Surgery will be performed 6-8 weeks after the end of radiation therapy. Short course radiation 2500 cGy in 5 fractions with surgical resection in one week can be considered if sphincter saving is not an option[17] (EL-1)

4.2.4. All patients with pre-operative clinical stage T3 or 4 and or node positive disease who received pre-operative chemo-radiotherapy will have one of the following options in the adjuvant setting:
4.2.4.1. Observation (EL-1)[18]
4.2.4.2. Single agent capecitabine for 6 cycles[19] (EL-3)
4.2.4.3. FOLFOX or XELOX for 4 months[20,21] (EL-1)

4.2.5. Adjuvant therapy for early stage rectal cancer (who did not receive pre-operative treatment) will be as follows:
4.2.5.1. T2 tumor: no further therapy
4.2.5.2. T3-4 or positive nodes: will receive adjuvant chemoradiotherapy (same as pre-op) followed by adjuvant chemotherapy with either single agent capecitabine, infusional 5-Fluorouracil and leucovorin21 (EL-1) or XELOX / FOLFOX for 4 months[20,21] (EL-3)

4.2.6. Follow up: (see section 4.1.6)

4.3. Locally advanced unresectable or metastatic colon or rectal cancer:

4.3.1. Surgery:
4.3.1.1. Patients with locally advanced or metastatic colon or rectal cancer and compromised colonic lumen should have a colonic stent (for colon cancer), a stoma, or resection (for colon or rectal cancer) prior to treatment (EL-3)
4.3.1.2. Patients with liver-only metastasis or lung-only metastasis can be considered for resection (metastatectomy) up front or after a period of pre-operative chemotherapy if initially potentially unresectable. The decision for resectability will be made by the operating surgeon (EL-2). Following resection of metastatic liver or lung lesions, patients should receive adjuvant chemotherapy with FOLFOX or XELOX for a total of 6 months of chemotherapy (including pre-operative).[24] Options of pre-operative chemotherapy if unresectable metastasis include:
4.3.1.2.1. FOLFIRI + Cetuximab[23] (EL-1) or FOLFOX + panitumumab[24] if RAS wild type (EL-1)
4.3.1.2.2. FOLFOXIRI (regardless of their RAS status)[25] (EL-1)
4.3.1.2.3. FOLFOX, FOLFIRI, or XELOX (+ Bevacizumab) if RAS mutant[26]

4.3.2. Palliative chemotherapy
4.3.2.1. Patients with locally advanced unresectable rectal tumors can be offered palliative systemic chemotherapy (see below) followed by chemoradiotherapy and surgery if they became resectable (EL-3)
4.3.2.2. Unresectable metastatic disease: patients will be treated with chemotherapy with palliative intent. The option of chemotherapy will depend on multiple factors including patient age, performance status, co-morbid conditions, and RAS mutational status
4.3.2.3. Options of palliative chemotherapy for patients with good performance status (PS 0-2), include one of the following:
4.3.2.3.1. FOLFOX, FOLFIRI or XELOX (+ Bevacizumab)[27-30] (EL-1) regardless of RAS status (EL-1)
4.3.2.3.2. FOLFIRI or FOLFOX + cetuximab (for wild type RAS tumors)[22,30] (EL-1)
4.3.2.3.3. FOLFOX + panitumumab[31] (EL-1)
4.3.2.3.4.Patients who might not tolerate oxaliplatin or irinotecan containing regimens may be considered for single agent capecitabine ± bevacizumab[31]

4.3.3. Duration of palliative therapy: Patients should continue chemotherapy until disease progression or unacceptable toxicity. Patients on oxaliplatin containing regimen are preferable to have their oxaliplatin stopped after 6 cycles, with continuation of other medications (LV5FU2 or capecitabine + Bevacizumab)[32-34] (EL-1)

4.3.4. Second line therapy: Patients who progress on first line chemotherapy, and have good PS, will receive second line therapy depending on the first line agents used with the following options:

4.3.4.1. Re-introduction of oxaliplatin if they were on maintenance with capecitabine or LV5FU2 ± bevacizumab[34] (EL-1)

4.3.4.2. FOLFIRI, or single agent Irinotecan if the first line was oxaliplatin based[27,35] (EL-1)

4.3.4.3. FOLFOX/ XELOX, if the first line is irinotecan based[27,36] (EL-1)

4.3.4.4. Consider adding one of the following targeted therapy to the above chemotherapy:

4.3.4.4.1. Cetuximab or panitumumab, if FOLFIRI or single agent irinotecan to be used in tumor with wild type RAS status[37,38] (EL-1) or

4.3.4.4.2. Bevacizumab to any of the above chemotherapy regimens regardless of RAS status[39] (EL-1) or

4.3.4.4.3. Aflibercept, if FOLFIRI is to be used as second line and regardless of the RAS status[40] (EL-1)

4.3.5. Third line therapy: Patients failing second line therapy and those who have good PS and RAS wild type tumor can be offered cetuximab and irinotecan, cetuximab alone, or panitumumab alone if they did not receive them before[41-43] (EL-1)

4.3.6. Fourth line therapy: Patients who progress despite receiving oxaliplatin, irinotecan, fluoropyrimidine, bevacizumab, and cetuximab or panitumumab have the option of best supportive care (BSC) of regorafenib and BSC[44] (EL-1)

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