Localized Rectal CANCER

Egyptian National Guidelines for Localized rectal Cancer

➢ Acknowledgments

- We would like to acknowledge the Oncology Committee of the Egyptian Health Council (EHC) Guidelines, for adapting these Guidelines.
- Chair of the Oncology Committee of Egyptian Health Council Guidelines: Prof Hussein Khaled.
- The Oncology Committee Members: Emad Hamada, Samir Shehata, Hesham Elghazaly, Hesham Tawfik, Fouad Abuotaleb, Ebtesam Saad Eldin, Ihab Khalil, Khaled Abdelkarim, Lobna EZZ Elarab, Mary Gamal, Mohamed Abdel Mooti, Mohamed Gamil, Nervana Hussein, Ola Khorshid, Omar Sherif Omar, Rasha Fahmi, Rasha Shaltout, Yousri Wasef & Yousri Rostom.
- Chair of the GIT Cancer Scientific Committee: Prof Yousri Rostom
- The rectal cancer Scientific Group Members: (Alphabitical order): Ahmed EL Kassed, Fouad Aboutaleb, Khaled Abdelkarim, Manal EL Mahdy, Omar S. Omar, and Yousri Wasef.

➢ Abbreviations

5FU	fluorouracil
cCR	clinical complete remission
CEA	carcinoembryonic antigen
CRT	chemo-radiotherapy
CT	computed tomography
DRE	digital rectal examination
EMVI	extramural venous invasion
ERUS	endorectal ultrasound
LE	local excision
MDT	multidisciplinary team
MRF	mesorectal fascia
MRI	magnetic resonance imaging
PME	partial mesorectal excision
RT	radiotherapy
SCRT	Short course radiotherapy
TME	total mesorectal excision
TNT	total neoadjuvant treatment

➢ Executive Summary

Recommendations	*Strength of the recommendation*
DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY	
● From diagnosis, a dedicated multidisciplinary team (MDT) of expert medical oncologists, radiologists, surgeons, radiation oncologists and pathologists should attend regular meetings to discuss patients	**Good practice statement.**
● A full medical history and physical examination, including digital rectal examination (DRE), complete blood count, liver and renal function	**Good practice statement.**

tests and measurement of serum CEA, should be carried out	
● Preoperative colonoscopy to the caecal pole and MRI are recommended to determine tumour level. Tumor height must be defined: low = 0 to <5 from anal verge , mid 5 to <10 cm, upper >10 cm.	**Strong**
● ERUS (if available) is recommended for T staging of localized tumors in cases of cT1 versus cT2.	**Conditional**
● MRI (rectal protocol) is mandatory as part of the staging work-up to stratify for risk-adapted treatment	**Strong**
● MRI reports should include description of tumour infiltration depth, node status, lateral lymph nodes, EMVI status and MRF status	**Strong**
● The recommended high-risk criteria are cT4a or cT4b, involved or threatened mesorectal fascia (MRF+), cN2 (4 uspicious nodes), EMVI + and lateral lymph node enlargement of 7 mm .	**Strong**
● Contrast-enhanced CT of the chest and abdomen is recommended for distant staging (if possible)	**Strong**
● Fertility risk discussion is recommended in appropriate patients.	**Good practice statement.**
MANAGEMENT OF LOCALISED DISEASE	
RT and CRT	
For lower or middle third tumours when surgery is intended:	
● Preoperative RT followed by LE cannot generally be recommended in patients with cT2 N0 tumours <4 cm but may be considered for selected patients (e.g. elderly or frail patient at high surgical risk).	**Conditional**
● Neoadjuvant SCRT or CRT (not TNT) is recommended for patients with cT2 N+, cT3 N0 or cT3 N1 tumours.	**Strong**
For lower or middle third tumours when watch-and-wait approach is intended:	
● SCRT or CRT is recommended for patients with cT1-cT2 N0 tumours.	**Strong**

Total neoadjuvant therapy (TNT).	
● RT should be offered as long-course CRT (50-50.4 Gy in 25-28 fractions with concomitant capecitabine or infusional 5-FU) or SCRT (25 Gy in five fractions)	**Strong**
● Consolidation or induction chemotherapy (CAPOX or FOLFOX) should be administered for 4-6 cycles (i.e. 3-4.5 months)	**Strong**
● If FOLFIRINOX regimen is used, it may be administered in line with the protocol of the PRODIGE 23 trial (indications and doses), see Annex.	**Conditional**
For upper third tumours:	
● TNT should be offered to patients with cT4 or involved or threatened MRF.	**Strong**
● CRT or SCRT should be considered if TNT is not feasible.	**Strong**
For lower or middle third tumours when surgery is intended:	
● TNT should be offered to patients with high-risk criteria.	**Strong**
For lower or middle third tumours when watch-and-wait approach is intended:	
● TNT is recommended for patients with high-risk criteria and patients with cT2 N+ or cT3 any N	**Strong**
● Upfront CRT followed by consolidation chemotherapy is recommended to increase the likelihood of cCR.	**Strong**
Neoadjuvant Chemtherapy	
● When considering neoadjuvant chemotherapy, the inclusion criteria of the PROSPECT study should be used (T2 N+, T3 any N, distance to the CRM ≥3 mm, continence-preserving surgery possible).	**Strong**
● Neoadjuvant chemotherapy should comprise 3 months of CAPOX or FOLFOX .	**Strong**
For upper third tumours:	
● Neoadjuvant chemotherapy is recommended for patients with cT2 N+ or cT3 any N disease.	**Strong**
● Neoadjuvant chemotherapy is recommended for patients with cT4 any N disease.	**Strong**
For lower or middle third tumours when surgery is intended:	

● Neoadjuvant chemotherapy is recommended for patients with cT2 N+, cT3 N0 or cT3 N1 disease.	**Strong**
● Salvage RT is recommended in case of intolerance to, or progression on, neoadjuvant chemotherapy.	**Strong**
Restaging before surgery or watch-and-wait approach	
● Restaging should comprise MRI, endoscopy and DRE.	**Strong**
● In case of a cCR, biopsies are not recommended to determine a watch-and-wait approach, as their value in this setting is unclear.	**Strong**
Surgery	
● PME and TME are the recommended surgical procedures for rectal cancer	**Strong**
● Open surgery and minimally invasive approaches are both recommended as they lead to similar oncological results	**Strong**
● A distance of >1 mm from tumour to CRM and other organs is recommended. In case of MRF + or T4b, beyond TME surgery is recommended.	**Strong**
● The distal mesorectal margin should be >5 cm.	**Strong**
● A distal resection margin of >1 cm is recommended.	**Strong**
● Lateral lymph nodes with a short axis of >7 mm should be resected after neoadjuvant treatment	**Strong**
For upper third tumours:	
● PME and TME are both equally recommended.	**Strong**
● LE is recommended as an alternative to PME or TME for low-risk tumours (pT1 without unfavourable pathological features).	**Strong**
For lower or middle third tumours when surgery is intended:	
● TME is the recommended surgical procedure.	**Strong**
● LE should be considered as an alternative to TME for low-risk tumours (pT1 without unfavourable pathological features).	**Strong**
For lower or middle third tumours when watch-and-wait approach is intended:	
● Surgery, with the resection method depending on clinical assessment, is recommended for patients who do not achieve a cCR following CRT or TNT	**Strong**

● In case of local (endorectal) regrowth after a watch-and-wait procedure, salvage resection should be offered to all patients.	**Strong**
Watch and wait approach	
● For lower or middle third tumours, a watch-and-wait strategy is recommended in patients with cCR when organ preservation is intended.	**Strong**
● Discussion with patients about the importance of adherence to strict follow-up investigations is mandatory.	**Good Practice Statement**
● Follow-up examinations should comprise MRI, endoscopy and DRE every 3 months for the first 2 years and every 6 months thereafter. CT scans of the chest and abdomen should be carried out every 6 months for the first 2 years and annually thereafter.	**Strong**
Adjuvant therapy	
For upper third tumours:	
Adjuvant Chemotherapy with a fluoropyrimidine and (potentially) oxaliplatin should be offered (according to clinical risk assessment) following PME or TME alone.	**Strong**
In patients who did not receive preoperative RT, adjuvant CRT should be offered in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME.	**Strong**
For lower or middle third tumours after surgery:	
● Adjuvant therapy with a fluoropyrimidine and (potentially) oxaliplatin should be offered (according to clinical risk assessment) following TME alone.	**Strong**
● Adjuvant therapy with a fluoropyrimidine and (potentially) oxaliplatin is recommended after neoadjuvant CRT or SCRT.	**Strong**
● In patients who did not receive preoperative RT, adjuvant CRT should be offered in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME.	**Strong**
For lower or middle third tumours for watch-and-wait approach:	
● An adjuvant fluoropyrimidine oxaliplatin combination can be offered on a case-by-case basis after RT or fluoropyrimidine-based CRT in patients achieving cCR with initial cN+ disease	**Conditional**
● Post-neoadjuvant systemic treatment following TNT (irrespective of surgical or nonsurgical local	**Conditional**

approach) cannot be generally recommended due to toxicity considerations. This approach should be discussed individually within an MDT.	
FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP	
● Proactive surveillance for local recurrence can be considered in patients at high risk of recurrence (e.g. involved CRM).	**Good practice statement.**
● Clinical assessment should be carried out every 3 months for 2 years	**Good practice statement.**
● Serum CEA measurements can be recommended every 3-4 months for the first 3 years.	**Good practice statement.**
● Annual (minimum) CT scan of the chest, abdomen and pelvis can be recommended after the first 2 years for detection of distant metastases.	**Good practice statement.**
● A completion colonoscopy is recommended within the first year (preferably after 6 months) if not carried out at the time of diagnostic work-up (e.g. if an obstruction was present)	**Good practice statement.**
● Medical history and colonoscopy with resection of colonic polyps can be recommended every 5 years up to the age of 75 years	**Good practice statement.**
● Long-term side-effects of treatment should be monitored	**Good practice statement.**

➢ Introduction

Colo-rectal cancer is the 7th most common cancer in the Egyptian population with more than 5900 newly diagnosed cases and more than 3000 deaths in 2022 (4).

Purpose and scope

These guidelines will help to improve the quality of care for localized rectal cancer patients via providing a uniform standard of care across the country to help in early diagnosis and treatment for localized rectal cancer, with less aggressive treatment options and improved clinical outcomes. These guidelines cover primary diagnosis, staging, treatment and follow-up of localized rectal cancer patients.

➢ Target audience

Clinicians who are involved in the care and treatment of patients with localized rectal cancer, including medical oncologists, radiation oncologists, clinical oncologists, onco- and gastrointestinal surgeons, radiologists and pathologists.

➢ Methodology

A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation. inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guidelines must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence). - Selecting only national and/or international guidelines.
- Specific range of dates for publication (using Guidelines published or updated 2015 and later).
- Selecting peer reviewed publications only.
- Selecting guidelines written in English language.
- Excluding guidelines written by a single author not on behalf of an organization to be valid and comprehensive, a guideline ideally requires multidisciplinary input.
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations.

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cutoff point or rank the guidelines (any guideline scoring above 50% on the rigor dimension was retained)

The NCCN, ESMO, NICE guidelines are the main sources used while formulating the national guidelines for bladder cancer (1-3).

➢ Evidence assessment

According to WHO handbook for Guidelines we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available through the on the following sites:

. GRADE working group: http://www.gradeworkingroup.org

. GRADE online training modules: http://cebgrade.mcmaster.ca/

. GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality of evidence in GRADE

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 2: Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3: Factors that determine how to upgrade or downgrade the quality of evidence.

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

➢ The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to the recommendation:

Strong recommendations: With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations: These are made when there is greater uncertainty about the four factors above (Table 2) or if local adaptation must account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations; when there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

➢ Recommendations

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

- From diagnosis, a dedicated multidisciplinary team (MDT) of expert medical oncologists, radiologists, surgeons, radiation oncologists and pathologists should attend regular meetings to discuss patients

Good practice statement.

- A full medical history and physical examination, including digital rectal examination (DRE), complete blood count, liver and renal function tests and measurement of serum CEA, should be carried out

Good practice statement.

- Preoperative colonoscopy to the caecal pole and MRI are recommended to determine tumour level. Tumor height must be defined: low = 0 to <5 from anal verge , mid 5 to <10 cm, upper >10 cm.

Strong recommendation, low grade evidence (5).

- ERUS (if available) is recommended for T staging of localized tumors in cases of cT1 versus cT2.

Conditional recommendation, high grade evidence (6).

- MRI (rectal protocol) is mandatory as part of the staging work-up to stratify for risk-adapted treatment

Strong recommendation, high grade evidence (6)

- MRI reports should include description of tumour infiltration depth, node status, lateral lymph nodes, EMVI status and MRF status

Strong recommendation, low grade evidence (7).

- The recommended high-risk criteria are cT4a or cT4b, involved or threatened mesorectal fascia (MRF+), cN2 (4 uspicious nodes), EMVI + and lateral lymph node enlargement of 7 mm .

Strong recommendation, low grade evidence (8).

- Contrast-enhanced CT of the chest and abdomen is recommended for distant staging.

Strong recommendation, low grade evidence (9).

- Fertility risk discussion is recommended in appropriate patients.

Good practice statememt

MANAGEMENT OF LOCALISED DISEASE
RT and CRT
For lower or middle third tumours when surgery is intended:

- Preoperative RT followed by LE cannot generally be recommended in patients with cT2 N0 tumours <4 cm but may be considered for selected patients (e.g. elderly or frail patient at high surgical risk).

Conditional recommendation, low grade evidence (10).

- Neoadjuvant SCRT or CRT (not TNT) is recommended for patients with cT2 N+, cT3 N0 or cT3 N1 tumours

Strong recommendation, high grade evidence (11,12).

For lower or middle third tumours when watch-and-wait approach is intended:

- SCRT or CRT is recommended for patients with cT1-cT2 N0 tumours

Strong recommendation, high grade evidence (11,12).

Total neoadjuvant therapy (TNT).

- RT should be offered as long-course CRT (50-50.4 Gy in 25-28 fractions with concomitant capecitabine or infusional 5-FU) or SCRT (25 Gy in five fractions)

Strong recommendation, high grade evidence (13-15).

- Consolidation or induction chemotherapy (CAPOX or FOLFOX) should be administered for 4-6 cycles (i.e. 3-4.5 months)

Strong recommendation, high grade evidence (16).

- If FOLFIRINOX regimen is used, it may be administered in line with the protocol of the PRODIGE 23 trial (indications and doses), see Annex.

Conditional recommendation, high grade evidence (17).

For upper third tumours:

- TNT should be offered to patients with cT4 or involved or threatened MRF

Strong recommendation, high grade evidence (18).

- CRT or SCRT should be considered if TNT is not feasible

Strong recommendation, high grade evidence (19).

For lower or middle third tumours when surgery is intended:

- TNT should be offered to patients with high-risk criteria

Strong recommendation, high grade evidence (13).

For lower or middle third tumours when watch-and-wait approach is intended:

- TNT is recommended for patients with high-risk criteria and patients with cT2 N+ or cT3 any N

Strong recommendation, high grade evidence (20).

- Upfront CRT followed by consolidation chemotherapy is recommended to increase the likelihood of cCR.

Strong recommendation, high grade evidence (20).

Neoadjuvant Chemtherapy

- When considering neoadjuvant chemotherapy, the inclusion criteria of the PROSPECT study should be used (T2 N+, T3 any N, distance to the CRM ≥3 mm, continence-preserving surgery possible)

Strong recommendation, high grade evidence (21-23).

- Neoadjuvant chemotherapy should comprise 3 months of CAPOX or FOLFOX

Strong recommendation, high grade evidence (21-23).

For upper third tumours:

- Neoadjuvant chemotherapy is recommended for patients with cT2 N+ or cT3 any N disease

Strong recommendation, high grade evidence (21-23).

- Neoadjuvant chemotherapy is recommended for patients with cT4 any N disease.

Strong recommendation, very low grade evidence (24).

For lower or middle third tumours when surgery is intended:

- Neoadjuvant chemotherapy is recommended for patients with cT2 N+, cT3 N0 or cT3 N1 disease

Strong recommendation, high grade evidence (21-23).

- Salvage RT is recommended in case of intolerance to, or progression on, neoadjuvant chemotherapy

Strong recommendation, high grade evidence (25).

Restaging before surgery or watch-and-wait approach

- Restaging should comprise MRI, endoscopy and DRE

Strong recommendation, high grade evidence (26,27).

- In case of a cCR, biopsies are not recommended to determine a watch-and-wait approach, as their value in this setting is unclear.

Strong recommendation, low grade evidence (28,29).

Surgery

- PME and TME are the recommended surgical procedures for rectal cancer

Strong recommendation, low grade evidence (30).

- Open surgery and minimally invasive approaches are both recommended as they lead to similar oncological results

Strong recommendation, high grade evidence (31).

- A distance of >1 mm from tumour to CRM and other organs is recommended. In case of MRF + or T4b, beyond TME surgery is recommended.

Strong recommendation, low grade evidence (32).

- The distal mesorectal margin should be >5 cm.

Strong recommendation, low grade evidence (32).

- A distal resection margin of >1 cm is recommended.

Strong recommendation, low grade evidence (33,34).

- Lateral lymph nodes with a short axis of >7 mm should be resected after neoadjuvant treatment

Strong recommendation, very low grade evidence (35).

For upper third tumours:

- PME and TME are both equally recommended.

Strong recommendation, low grade evidence (36).

- LE is recommended as an alternative to PME or TME for low-risk tumours (pT1 without unfavourable pathological features).

Strong recommendation, low grade evidence (37).

For lower or middle third tumours when surgery is intended:

- TME is the recommended surgical procedure.

Strong recommendation, low grade evidence (38).

- LE should be considered as an alternative to TME for low-risk tumours (pT1 without unfavourable pathological features).

Strong recommendation, low grade evidence (37).

For lower or middle third tumours when watch-and-wait approach is intended:

- Surgery, with the resection method depending on clinical assessment, is recommended for patients who do not achieve a cCR following CRT or TNT.

Strong recommendation, high grade evidence (39).

- In case of local (endorectal) regrowth after a watch-and-wait procedure, salvage resection should be offered to all patients.

Strong recommendation, low grade evidence (37).

Watch and wait approach

- For lower or middle third tumours, a watch-and-wait strategy is recommended in patients with cCR when organ preservation is intended.

Strong recommendation, high grade evidence (40).

- Discussion with patients about the importance of adherence to strict follow-up investigations is mandatory.

Good Practice Statement

- Follow-up examinations should comprise MRI, endoscopy and DRE every 3 months for the first 2 years and every 6 months thereafter. CT scans of the chest and abdomen should be carried out every 6 months for the first 2 years and annually thereafter

Strong recommendation, high grade evidence (41).

Adjuvant therapy

For upper third tumours:

- Adjuvant Chemotherapy with a fluoropyrimidine and (potentially) oxaliplatin should be offered (according to clinical risk assessment) following PME or TME alone

Strong recommendation, high grade evidence (42,43).

- In patients who did not receive preoperative RT, adjuvant CRT should be offered in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME

Strong recommendation, low grade evidence (44).

For lower or middle third tumours after surgery:

- Adjuvant therapy with a fluoropyrimidine and (potentially) oxaliplatin should be offered (according to clinical risk assessment) following TME alone

Strong recommendation, high grade evidence (42,43).

- Adjuvant therapy with a fluoropyrimidine and (potentially) oxaliplatin is recommended after neoadjuvant CRT or SCRT.

Strong recommendation, low grade evidence (45).

- In patients who did not receive preoperative RT, adjuvant CRT should be offered in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME.

Strong recommendation, low grade evidence (44).

For lower or middle third tumours for watch-and-wait approach:

- An adjuvant fluoropyrimidine oxaliplatin combination can be offered on a case-by-case basis after RT or fluoropyrimidine-based CRT in patients achieving cCR with initial cN+ disease

Conditional recommendation, high grade evidence (42,43).

- Post-neoadjuvant systemic treatment following TNT (irrespective of surgical or nonsurgical local approach) cannot be generally recommended due to toxicity considerations. This approach should be discussed individually within an MDT

Conditional recommendation, high grade evidence (42,43).

CLINICAL MONITORING, LONG-TERM IMPLICATIONS, AND SURVIVORSHIP

- Clinical examination, pelvic MRI and/or CT can be recommended for detection of locoregional recurrence.

Good practice statement.

- Proactive surveillance for local recurrence can be considered in patients at high risk of recurrence (e.g. involved CRM)

Good practice statement.

- Clinical assessment should be carried out every 3 months for 2 years

Good practice statement.

- Serum CEA measurements can be recommended every 3-4 months for the first 3 years

Good practice statement.

- Annual (minimum) CT scan of the chest, abdomen and pelvis can be recommended after the first 2 years for detection of distant metastases.

Good practice statement.

- A completion colonoscopy is recommended within the first year (preferably after 6 months) if not carried out at the time of diagnostic work-up (e.g. if an obstruction was present)

Good practice statement.

- Medical history and colonoscopy with resection of colonic polyps can be recommended every 5 years up to the age of 75 years

Good practice statement.

- Long-term side-effects of treatment should be monitored

Good practice statement.

➢ Research Gaps

- Evaluation of real world data on the use on new targeted and immune-therapeutic agents in bladder cancer in Egypt.
- Cost effective analysis of new therapeutic agents in Egypt.
- Define the molecular biologic profiles of our Egyptian patients

➢ Update of the guideline

- This guideline will be updated whenever there is new evidence.

➢ References

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➢ Annexes

Annex 1.

American Joint Committee on Cancer (AJCC) TNM Staging Classification for Rectal Cancer 8th ed., 2017

Table 1. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres** to adjacent organs or structures

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive
M	**Distant Metastasis**
M0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

American Joint Committee on Cancer (AJCC)
TNM Staging System for Rectal Cancer 8th ed., 2017

Table 2. **Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

Annex 2.

REGIMENS (PERIOPERATIVE THERAPY)

<u>Perioperative Chemotherapy</u>:

- **mFOLFOX 6**
  Oxaliplatin 85 mg/m^2 IV, day 1, leucovorin 400 mg/m^2 IV day 1, 5-FU 400 mg/m^2 IV bolus on day 1, followed by 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 months perioperative therapy.

- **CAPEOX**
  Oxaliplatin 130 mg/m^2 IV day 1. Capecitabine 1000 mg/m^2 PO twice daily for 14 days every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy.

- **FOLFIRINOX**
  Oxaliplatin 85 mg/m² IV on day 1, leucovorin 400 mg/m² IV over 2 hours on day 1, irinotecan 180 mg/m² IV over 30–90 minutes on day 1, 5-FU 400 mg/m² IV push day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks.

- **Modified FOLFIRINOX**

Oxaliplatin 85 mg/m² IV on day 1, leucovorin 400 mg/m² IV over 2 hours on day 1, irinotecan 150 mg/m² IV over 30–90 minutes on day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks.

Dosing Schedules for Concurrent Chemotherapy/RT:

- **RT + continuous infusion 5-FU**

  5-FU 225 mg/m^2 IV over 24 hours daily on days 1–5 or days 1–7 for 5 weeks with RT

- **RT + capecitabine**

  Capecitabine 825 mg/m^2 PO BID, Monday–Friday, on days of radiation treatment only, throughout the duration of RT (typically 28–30 treatment days)

- **RT + 5-FU/leucovorin**

  5-FU 400 mg/m^2 IV bolus + leucovorin 20 mg/m^2 IV bolus for 4 days during weeks 1 and 5 of RT

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

- **mFOLFOX 6**
  Oxaliplatin 85 mg/m2 IV day 1z Leucovorin 400 mg/m2 IV day 1aa
  5-FU 400 mg/m2 IV bolus on day 1, followed by 1200 mg/m2/day x 2 days (total 2400 mg/m2 over 46–48 hours) IV continuous infusion
  Repeat every 2 weeks

- **mFOLFOX 7**
  Oxaliplatin 85 mg/m2 IV day 1z Leucovorin 400 mg/m2 IV day 1aa
  5-FU 1200 mg/m2/day x 2 days (total 2400 mg/m2 over 46–48 hours) IV continuous infusion
  Repeat every 2 weeks
- **FOLFOX + bevacizumab**
  Bevacizumab mg/kg IV, day 1 Repeat every 2 weeks
- **FOLFOX + panitumumab (KRAS/NRAS/BRAF WT)**
  Panitumumab 6 mg/kg IV over 60 minutes, day 1 ---Repeat every 2 weeks
- **FOLFOX + cetuximab (KRAS/NRAS/BRAF WT)**
  Cetuximab 400 mg/m2 IV over 2 hours first infusion, followed by 250 mg/m2 IV over 60 minutes weekly or Cetuximab 500 mg/m2 IV over 2 hours, day 1, every 2 weeks (preferred for every 2 weeks)
- **CAPEOX8**
  Oxaliplatin 130 mg/m2 IV day 1z
  Capecitabine 1000cc mg/m2 twice daily PO for 14 days
  Repeat every 3 weeks

- **CAPEOX + bevacizumab**
  Oxaliplatin 130 mg/m2 IV day 1z
  Capecitabine 1000cc mg/m2 PO twice daily for 14 days
  Bevacizumab 7.5 mg/kg IV day 1 Repeat every 3 weeks

CAPEOX + cetuximab (KRAS/NRAS/BRAF WT)
Cetuximab 400 mg/m2 IV over 2 hours first infusion, followed by 250 mg/m2 IV over 60 minutes weekly or Cetuximab 500 mg/m2 IV over 2 hours, day 1, every 2 weeks (preferred for every 2 weeks)

CAPEOX + panitumumab9-11 (KRAS/NRAS/BRAF WT)
Panitumumab 6 mg/kg IV over 60 minutes, day 1 Repeat every 2 weeks

FOLFIRI
Irinotecan 180 mg/m2 IV over 30–90 minutes, day 1
Leucovorinaa 400 mg/m2 IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m2 IV bolus day 1, followed by 1200 mg/m2/day x 2 days (total 2400 mg/m2 over 46–48 hours) continuous infusion
Repeat every 2 weeks

- **FOLFIRI + bevacizumab**
  Bevacizumab 5 mg/kg IV, day 1 Repeat every 2 weeks
- **FOLFIRI + cetuximab (KRAS/NRAS/BRAF WT)**
  Cetuximab 400 mg/m2 IV over 2 hours first infusion, followed by 250 mg/m2 IV over 60 minutes weekly or Cetuximab 500 mg/m2 IV over 2 hours, day 1, every 2 weeks (preferred for every 2 weeks)

- **FOLFIRI + panitumumab (KRAS/NRAS/BRAF WT)**
  Panitumumab 6 mg/kg IV over 60 minutes, day 1 Repeat every 2 weeks
- **FOLFIRINOX20**
  Oxaliplatin 85 mg/m² IV on day 1,z leucovorin 400 mg/m² IV over 2 hours on day 1, irinotecan 165–180 mg/m² IV over 30–90 minutes on day 1, 5-FU 400 mg/m² IV push day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion.
  Repeat every 2 weeks
- **Modified FOLFIRINOX**
  Oxaliplatin 85 mg/m² IV on day 1,z leucovorin 400 mg/m² IV over 2 hours on day 1, irinotecan 150 mg/m² IV over 30–90 minutes on day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks
- **FOLFIRINOX or mFOLFIRINOX + bevacizumab**
  Bevacizumab 5 mg/kg IV, day 1
  Repeat every 2 weeks

- **IROX**
  Oxaliplatin 85 mg/m2 IV
  followed by irinotecan 200 mg/m2 over 30–90 minutes every 3 weeks
- **IROX + bevacizumab**
  Bevacizumab 7.5 mg/kg IV on day 1 Repeat every 3 weeks

- **Bolus or infusional 5-FU/leucovorin Roswell Park regimen**
  Leucovorin 500 mg/m2 IV over 2 hours, days 1, 8, 15, 22, 29, and 36
  5-FU 500 mg/m2 IV bolus 1 hour after start of leucovorin,

days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

- **Simplified biweekly infusional 5-FU/leucovorin (sLV5FU2)**
  Leucovorinaa 400 mg/m2 IV over 2 hours on day 1,
  followed by 5-FU bolus 400 mg/m2 followed by 1200 mg/m2/day x 2 days (total 2400 mg/m2 over 46–48 hours) continuous infusion Repeat every 2 weeks
  Weekly Leucovorin 20 mg/m2 IV over 2 hours on day 1, 5-FU 500 mg/ m2 IV bolus injection 1 hour after the start of leucovorin. Repeat weekly27
  or
  5-FU 2600 mg/m2 by 24-hour infusion plus leucovorin 500 mg/m2 Repeat every week
- **Bolus or infusional 5-FU + bevacizumab**
  Bevacizumab 5 mg/kg IV on day 1
  Repeat every 2 weeks
- **Capecitabine**
  Capecitabine 850–1250 mg/m2 PO twice daily for 14 days Repeat every 3 weeks
- **Capecitabine + bevacizumab**
  Bevacizumab 7.5 mg/kg IV, day 1 Repeat every 3 weeks
- **Irinotecan**
  Irinotecan 125 mg/m2 IV over 30–90 minutes, days 1 and 8 Repeat every 3 weeks
  or Irinotecan 180 mg/m2 IV over 30–90 minutes, day 1 Repeat every 2 weeks
  or Irinotecan 300–350 mg/m2 IV over 30–90 minutes, day 1 Repeat every 3 weeks
- **Irinotecan + cetuximab (KRAS/NRAS/BRAF WT)**
  Cetuximab 400 mg/m2 first infusion, followed by 250 mg/m2 IV weekly32
or Cetuximab 500 mg/m2 IV over 2 hours, day 1, every 2 weeks16
(preferred for every 2 weeks)
- Irinotecan + panitumumab17,33 (KRAS/NRAS/BRAF WT)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

- Irinotecan + bevacizumab34,bb Irinotecan 180 mg/m2 IV, day 1
Bevacizumab 5 mg/kg IV, day 1 Repeat every 2 weeks
or
Irinotecan 300–350 mg/m2 IV, day 1
Bevacizumab 7.5 mg/kg IV, day 1 Repeat every 3 weeks
Cetuximab (KRAS/NRAS/BRAF WT)
Cetuximab 400 mg/m2 first infusion, followed by 250 mg/m2 IV weekly32
or Cetuximab 500 mg/m2 IV over 2 hours, day 1, every 2 weeks16
(preferred for every 2 weeks)
Panitumumab35 (KRAS/NRAS/BRAF WT)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

- **Trastuzumab + pertuzumab**
(HER2-amplified and RAS and BRAF WT)
  Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, followed by 6 mg/kg IV every 21 days
  Pertuzumab 840 mg IV loading dose on day 1 of cycle 1, followed by 420 mg IV every 21 days
- **Trastuzumab + lapatinib**
(HER2-amplified and RAS and BRAF WT)
  Trastuzumab 4 mg/kg IV loading dose on day 1 of cycle 1, followed by 2 mg/kg IV weekly

Lapatinib 1000 mg PO daily

Annex 3. PRODIGE 23 TRIAL PROTOCOL (Indications and doses)

Eligible patients:

- adults aged 18–75 years,
- newly diagnosed,
- biopsy-proven,
- staged cT3 or cT4 M0
- WHO performance status of 0–1.

Doses, and procedures

- oxaliplatin 85 mg/m2, irinotecan 180 mg/m2, leucovorin 400 mg/m2, and fluorouracil 2400 mg/m2 intravenously every 14 days for 6 cycles),
- chemoradiotherapy (50 Gy during 5 weeks and 800 mg/m2 concurrent oral capecitabine twice daily for 5 days per week),
- total mesorectal excision,
- 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]).