ADVANCED/ METASTATIC CRC

Egyptian National Guidelines for Advanced/Metastatic CRC

➢ Acknowledgments

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➢ Abbreviations

5FU	fluorouracil
AEs	adverse events
CEA	carcinoembryonic antigen
ChT	chemotherapy
CT	computed tomography
CRC	colo-rectal cancer
CRLMs	colo-rectal liver metastases
EGFR	Epidermal growth factor receptor
EMV	extramural venous invasion

FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FISH	Fluorescence In Situ Hybridization
IHC	Immunohistochemistry
mCRC	metastatic colo-rectal cancer
MDT	mulocal treatmentidisciplinary team
mAb	monclonal antibody
MRI	magnetic resonance imaging
OMD	oligometastatic disease
PS	performance status
SBRT	Stereotactic Body Radiation Therapy

➢ Executive Summary

Recommendations	***Strength of the recommendation***
1. DIAGNOSTIC WORK UP FOR ADVANCED/METASTATIC DISEASE	
Complete work-up should be carried out to achieve an accurate histological diagnosis of the primary tumor, assess the baseline characteristics of the patient and determine the extent of the disease.	**Strong**
Besides a comprehensive physical examination, request blood tests including complete blood count and chemistry profile.	**Strong**
In addition, serum levels of CEA should be evaluated and monitored during the follow-up period to help evaluate response to treatment.	**Strong**
CT of the thoracic, abdominal and pelvic cavities with i.v. contrast administration is the preferred radiological method for the evaluation of the extent of CRC.	**Strong**
A Triphasic CT or Dynamic liver MRI is recommended to characterise non-typical liver lesions on CT scans or when liver metastases seem resectable or potentially resectable.	**Strong**
FDG-PET/CT scan can be useful, particularly in patients with increased tumour markers without evidence of metastatic disease, or to define the extent of metastatic disease on potentially resectable metastases.	**Conditional**
FDG-PET/CT is NOT USEFULL in mucinous and sigent ring differentiation.	**Strong**

Testing for KRAS, NRAS exon 2, 3 and 4 and BRAF mutations is recommended in all patients at the time of mCRC diagnosis	**Strong**
RAS testing is mandatory before treatment with antiEGFR monoclonal antibodies and can be carried out on either the primary tumour or other metastatic sites.	**Strong**
BRAF mutation status should be assessed simultaneously with the evaluation of RAS, for prognostic assessment and for the option of treatment with antiEGFR mAbs.	**Strong**
Identification of HER2 amplification by IHC or FISH is recommended in RAS-wt patients to detect those who may benefit from HER2 blockade.	**Strong**
2.TREATMENT OF POTENTIALLY RESECTABLE ADVANCED AND METASTATIC DISEASE	
In patients with resectable metastases, favorable prognostic criteria and a feasible surgical approach, preoperative / post-operative systemic treatment may not be needed.	**Conditional**
In patients with resectable metastases, the use of perioperative oxaliplatin-based chemotherapy is recommended where the prognostic situation is unclear.	**Strong**
Anti-EGFR monoclonal antibodies in left-sided RAS-wt patients should be used as conversion therapy, when complete resection is the aim.	**Strong**
In patients with right-sided and RAS-mutant disease, FOLFOXIRI-bevacizumab and, to a lesser extent, a cytotoxic doublet-bevacizumab should be considered the best choice depending on patients' ability to tolerate triplet chemotherapy.	**Strong**
Patients unresponsive to first-line chemotherapy should not be denied resection or ablation of metastases since the outcome of resected patients after second-line treatment could be also favorable	**Conditional**
In case of peritoneal metastasis only, complete cytoreductive surgery may be carried out.	**Conditional**
Intent and choice of local treatment.	
Local treatment can be used primarily as a metastasis-directed treatment to halt local failure , further dissemination, and/or following systemic therapy as a consolidation treatment, to delay or pause further treatment.	**Conditional**
Frequent radiological reevaluations of the potential applicability of surgery or other local treatment techniques should be carried out, generally every 8-12 weeks.	**Strong**

Local ablation treatment	
In patients with unresectable CRLMs only, or OMD in the liver, thermal Ablation can be considered for small metastases.	**Conditional**
Thermal Ablation is a valid treatment option for recurrent disease after surgical resection for small CRLMs.	**Strong**
In patients with lung-only metastases or OMD including lung lesions, thermal ablation may be considered along with resection, according to tumor size, number, location, the extent of lung parenchyma loss, or other comorbidities.	**Conditional**
SBRT may be considered as a local treatment option.	**Conditional**
3.MANAGEMENT OF ADVANCED AND METASTATIC DISEASE WITHOUT POTENTIAL CONVERSION	
First-line therapy	
Determining the RAS mutational status on a tumour biopsy is mandatory to guide the best treatment decision.	**Strong**
Delivering a biological therapy in combination with chemotherapy in the first-line setting is recommended, unless contraindicated.	**Strong**
First-line treatment will consist of doublet of chemotherapy (FOLFOX, FOLFIRI, CAPOX) combined with an anti-VEGF or anti-EGFR mAbs unless contraindicated..	**Strong**
In RAS-wt and BRAF-wt left-sided tumours, doublet chemotherapy plus an anti-EGFR mAbs is the preferred option.	**Strong**
In RAS-wt right-sided tumours, chemotherapy + bevacizumab is the recommended treatment unless contraindicated	**Strong**
Anti-EGFR mAbs should be combined with the doublets FOLFOX or FOLFIRI.	**Strong**
Bevacizumab should be combined with single fluoropyrimidines, irinotecan or oxaliplatin-based doublet of ChT (FOLFOX, CAPOX, FOLFIRI) or triplets (FOLOXIRI).	**Strong**
A triplet with FOLFOXIRI plus bevacizumab could also be an option for selective patients with good PS and without comorbidities.	**Conditional**
Triplets including FOLFOXIRI should not be used in patients >75 years old, with PS2 or in patients with significant comorbidities.	**Strong**

In patients with comorbidities, older age or with metastatic disease not amenable to a curative treatment strategy and no significant disease-related symptoms, monotherapy with a fluoropyrimidine bevacizumab is recommended	**Strong**
In frail or elderly patients unable to tolerate chemotherapy, whose tumours are left-sided and RAS-wt, monotherapy with anti-EGFR mAbs can be considered.	**Conditional**
Maintenance and subsequent therapy	
After first-line therapy with ChT based on oxaliplatin and bevacizumab, maintenance therapy with a fluoropyrimidine is recommended in nonprogressive patients after at least 6 months of treatment.	**Strong**
Reintroduction of an initial successful induction therapy may be done after progressive disease while on maintenance therapy.	**Conditional**
After failure of first-line oxaliplatin-based therapy, second-line treatment with irinotecan-based or monotherapy is recommended unless contraindicated	**Strong**
After failure of first line irinotecan-based therapy , second line treatment with oxaliplatin-based therapy (FOLFOX or CAPOX) is recommended unless contraindicated .	**Strong**
In RAS-wt patients not previously treated with an anti- EGFR moAb, treatment with chemotherapy (FOLFIRI or irinotecan) and cetuximab or panitumumab is recommended for left-sided colon tumours.	**Strong**
In patients previously treated with chemotherapy alone, a combination of doublet chemotherapy + bevacizumab or anti EGFR (Left side) is recommended.	**Strong**
Bevacizumab can be combined with a fluoropyrimidine doublet with oxaliplatin or irinotecan, depending on the first-line chemotherapy backbone delivered.	**Conditional**
Reintroduction of the initial induction therapy can be considered after second-line therapy, as long as the patient did not progress during the induction course of first-line chemotherapy. Treatment should be based upon previous treatment lines, AEs, and PS.	**Conditional**
Follow up and monitoring	
History and physical examination and CEA level determination are recommended every 3-6 months for 3 years and every 6-12 months at years 4 and 5 after surgery.	**Strong**
Colonoscopy must be carried out at year 1 and every 3-5 years thereafter, looking for metachronous adenomas and cancers.	**Strong**

CT scan of chest , abdomen and pelvis every 6-12 months for the first 3 years is recommended in patients who are at higher risk of recurrence according to the TNM classification.	**Strong**
Long-term follow-up, rehabilitation and survivorship care programmes should be implemented, aiming at detection of recurrent or new cancers, assessment and management of late and psychosocial effects and implementation of healocal treatmenth promotion measures.	**Strong**

➢ 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 (1).

Purpose and scope

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

➢ Target audience

Clinicians who are involved in the care and treatment of patients with Advanced/Metastatic CRC, 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 mulocal treatmentidisciplinary 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 metastatic colorectal cancer (2-4).

➢ 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

1. DIAGNOSTIC WORK UP FOR ADVANCED/METASTATIC DISEASE

- A complete work-up should be carried out to achieve an accurate histological diagnosis of the primary tumor, assess the baseline characteristics of the patient and determine the extent of the disease

Strong recommendation, High grade evidence (5)

- Besides a comprehensive physical examination, request blood tests including complete blood count and chemistry profile.

Strong recommendation, High grade evidence (5).

- In addition, serum levels of CEA should be evaluated and monitored during the follow-up period to help evaluate response to treatment.

Strong recommendation, Low grade evidence (6-8)

- CT of the thoracic, abdominal and pelvic cavities with i.v. contrast administration is the preferred radiological method for the evaluation of the extent of CRC.

Strong recommendation, High grade evidence (9,10)

- .A Triphasic CT or Dynamic liver MRI is recommended to characterise non-typical liver lesions on CT scans or when liver metastases seem resectable or potentially resectable.

Strong recommendation, High grade evidence (11).

- FDG-PET/CT scan can be useful, particularly in patients with increased tumour markers without evidence of metastatic disease, or to define the extent of metastatic disease on potentially resectable metastases.

Conditional recommendation, High grade evidence (8,12).

- FDG-PET/CT is NOT USEFULL in mucinous and sigent ring differentiation

Strong recommendation, High grade evidence (8,12).

- .Testing for KRAS, NRAS exon 2, 3 and 4 and BRAF mutations is recommended in all patients at the time of mCRC diagnosis.

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

- RAS testing is mandatory before treatment with antiEGFR monoclonal antibodies and can be carried out on either the primary tumour or other metastatic sites.

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

- BRAF mutation status should be assessed simultaneously with the evaluation of RAS, for prognostic assessment and for the option of treatment with antiEGFR mAbs.

Strong recommendation, Low grade evidence (16,17).

- Identification of HER2 amplification by IHC or FISH is recommended in RAS-wt patients to detect those who may benefit from HER2 blockade

Strong recommendation, Low grade evidence (18).

2. TREATMENT OF POTENTIALLY RESECTABLE ADVANCED AND METASTATIC DISEASE

- In patients with resectable metastases , favorable prognostic criteria and a feasible surgical approach, preoperative / post-operative systemic treatment may not be needed.

Conditional recommendation, low grade evidence (19).

- In patients with resectable metastases, the use of perioperative oxaliplatin-based chemotherapy is recommended where the prognostic situation is unclear.

Strong recommendation, high grade evidence (20).

- Anti-EGFR monoclonal antibodies in left-sided RAS-wt patients should be used as conversion therapy, when complete resection is the aim.

Strong recommendation, high grade evidence(21).

- In patients with right-sided and RAS-mutant disease, FOLFOXIRI-bevacizumab and, to a lesser extent, a cytotoxic doublet-bevacizumab should be considered the best choice depending on patients' ability to tolerate triplet chemotherapy.

Strong recommendation, high grade evidence (21).

- Patients unresponsive to first-line chemotherapy should not be denied resection or ablation of metastases since the outcome of resected patients after second-line treatment could be also favorable.

Conditional recommendation, low grade evidence (22).

- In case of peritoneal metastasis only, complete cytoreductive surgery may be carried out.

Conditional recommendation, high grade evidence (23).

Intent and choice of local treatment

- Local treatment can be used primarily as a metastasis-directed treatment to halt local failure , further dissemination, and/or following systemic therapy as a consolidation treatment, to delay or pause further treatment

Conditional recommendation, low grade evidence (24,25).

- Frequent radiological reevaluations of the potential applicability of surgery or other local treatment techniques should be carried out, generally every 8-12 weeks.

Strong recommendation, very low grade evidence(26).

Local ablation treatment

- In patients with unresectable CRLMs only, or OMD in the liver, Thermal Ablation can be considered for small metastases.

Conditional recommendation, low grade evidence (27-29).

- Thermal Ablation is a valid treatment option for recurrent disease after surgical resection for small CRLMs

Strong recommendation, high grade evidence (30).

- In patients with lung-only metastases or OMD including lung lesions, thermal ablation may be considered along with resection, according to tumor size, number, location, the extent of lung parenchyma loss, or other comorbidities.

Conditional recommendation, low grade evidence (27-29).

- SBRT may be considered as a local treatment option

Conditional recommendation, low grade evidence (31).

3. MANAGEMENT OF ADVANCED AND METASTATIC DISEASE WITHOUT POTENTIAL CONVERSION

First-line therapy

- Determining the RAS mutational status on a tumour biopsy is mandatory to guide the best treatment decision.

Strong recommendation, high grade evidence (32).

- Delivering a biological therapy in combination with chemotherapy in the first-line setting is recommended, unless contraindicated.

Strong recommendation, high grade evidence (33).

- First-line treatment will consist of doublet of chemotherapy (FOLFOX, FOLFIRI, CAPOX) combined with an anti-VEGF or anti-EGFR mAbs unless contraindicated .

Strong recommendation, high grade evidence (34).

- In RAS-wt and BRAF-wt left-sided tumors, doublet chemotherapy plus an anti-EGFR mAbs is the preferred option.

Strong recommendation, high grade evidence (34).

- In RAS-wt right-sided tumors, chemotherapy + bevacizumab is the recommended treatment unless contraindicated ,

Strong recommendation, high grade evidence (35).

- Anti-EGFR mAbs should be combined with the doublets FOLFOX or FOLFIRI.

Strong recommendation, high grade evidence (33,36).

- Bevacizumab should be combined with single fluoropyrimidines, irinotecan or oxaliplatin-based doublet of ChT (FOLFOX, CAPOX, FOLFIRI) or triplets (FOLOXIRI)

Strong recommendation, high grade evidence (37-39).

- A triplet with FOLFOXIRI plus bevacizumab could also be an option for selective patients with good PS and without comorbidities

Conditional recommendation, high grade evidence (37-39).

- Triplets including FOLFOXIRI should not be used in patients >75 years old, with PS2 or in patients with significant comorbidities.

Strong recommendation, very low grade evidence (40).

- In patients with comorbidities, older age or with metastatic disease not amenable to a curative treatment strategy and no significant disease-related symptoms, monotherapy with a fluoropyrimidine bevacizumab is recommended

Strong recommendation, high grade evidence (41).

- In frail or elderly patients unable to tolerate chemotherapy, whose tumours are left-sided and RAS-wt, monotherapy with anti-EGFR mAbs can be considered

Conditional recommendation, very low grade evidence (42).

Maintenance and subsequent therapy

- After first-line therapy with ChT based on oxaliplatin and bevacizumab, maintenance therapy with a fluoropyrimidine is recommended in nonprogressive patients after at least 6 months of treatment.

Strong recommendation, high grade evidence (43).

- Reintroduction of an initial successful induction therapy may be done after progressive disease while on maintenance therapy

.**Conditional recommendation, high grade evidence (37).**

- After failure of first-line oxaliplatin-based therapy, second-line treatment with irinotecan-based or monotherapy is recommended unless contraindicated

Strong recommendation, high grade evidence (44, 45).

- After failure of first-line Irinotican-based therapy, second-line treatment with Oxaloplatin-based therapy (FOLFOX or CAPOX) is recommended unless contraindicated

Strong recommendation, high grade evidence (22).

- In RAS-wt patients not previously treated with an anti- EGFR moAb, treatment with chemotherapy (FOLFIRI or irinotecan) and cetuximab or panitumumab is recommended for left-sided colon tumours.

Strong recommendation, high grade evidence (46).

- In patients previously treated with chemotherapy alone, a combination of doublet chemotherapy + bevacizumab or anti EGFR (Left side) is recommended.

Strong recommendation, high grade evidence (46).

- Bevacizumab can be combined with a fluoropyrimidine doublet with oxaliplatin or irinotecan, depending on the first-line chemotherapy backbone delivered.

Conditional recommendation, high grade evidence (46).

- Reintroduction of the initial induction therapy can be considered after second-line therapy, as long as the patient did not progress during the induction course of first-line chemotherapy. Treatment should be based upon previous treatment lines, AEs, and PS.

Conditional recommendation, low grade evidence.

➢ Follow up and monitoring (47-53)

- History and physical examination and CEA level determination are recommended every 3-6 months for 3 years and every 6-12 months at years 4 and 5 after surgery.

Strong recommendation, high grade evidence.

- Colonoscopy must be carried out at year 1 and every 3-5 years thereafter, looking for metachronous adenomas and cancers.

Strong recommendation, moderate grade evidence.

- CT scan of chest , abdomen and pelvis every 6-12 months for the first 3 years are recommended in patients who are at higher risk of recurrence according to the TNM classification.

Strong recommendation, high grade evidence.

- Long-term follow-up, rehabilitation and survivorship care programmes should be implemented, aiming at detection of recurrent or new cancers, assessment and management of late and psychosocial effects and implementation of healocal treatmenth promotion measures.

Strong recommendation, low grade evidence.

➢ Research Gaps

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

➢ Update of the guideline

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

➢ 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.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

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