

## Advanced colorectal cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

E. J. D. Van Cutsem<sup>1</sup> & J. Oliveira<sup>2</sup>

On behalf of the ESMO Guidelines Working Group\*

<sup>1</sup>Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium; <sup>2</sup>Service of Medical Oncology, Portuguese Institute of Oncology, Lisbon, Portugal

### incidence

In 2006 there were 412 900 new cases of colorectal cancer in Europe. This is 12.9% of all cancer cases. Colorectal cancer is responsible for 217 400 deaths in Europe in 2006. This represents 12.2% of all cancer deaths.

### diagnosis

Clinical suspicion of metastatic disease should always be confirmed by adequate radiologic imaging [usually a computed tomography (CT) scan] and/or scintigraphic examination. Histopathologic or cytologic confirmation should be obtained whenever there is atypical presentation or very late presentation after the primary tumor. Resectable metastases do not need histologic or cytologic confirmation before resection. Evaluation of the general condition, concomittant pathology and organ function determines therapeutic strategy.

### staging and treatment strategy

In order to identify patients with potentially curative surgical options the staging should include clinical examination, blood counts, liver and renal function tests, carcinoembryonic antigen (CEA), chest X-ray and a CT scan of the abdomen. Baseline performance status and lactate dehydrogenase level are the strongest individual prognostic factors. CT scan of the chest and additional examinations as clinically needed are recommended before major abdominal surgery with potentially curative intent. An FDG–PET can give additional information on unequivocal lesions before resection of metastatic disease or can identify new lesions in case of planned resection of metastases.

The strategy should be discussed from a multidisciplinary perspective.

### treatment

Surgery should be considered for solitary or confined liver or pulmonary metastases. Long term survivors can be obtained in experienced hands. In patients with resectable liver metastases perioperative combination chemotherapy with 5-fluorouracil (5-FU)/leucovorin (LV)/oxaliplatin improves the outcome (improved progression-free survival). Initially unresectable liver metastases can become resectable after downsizing with chemotherapy.

First-line palliative chemotherapy should be considered early and consists of a fluoropyrimidine (i.v. 5-FU or oral fluoropyrimidines) in various combinations and schedules. Infused regimens of 5-FU/LV are generally less toxic than bolus regimens. The oral fluoropyrimidines capecitabine and uracil–ftorafur (UFT)/LV are an alternative to intravenous 5-FU/LV as monotherapy.

Combination chemotherapy with 5-FU/LV/oxaliplatin (FOLFOX regimens) or 5-FU/LV/irinotecan (FOLFIRI regimens) provides better survival than 5-FU/LV. FOLFOX and FOLFIRI have similar activity, but different toxicity profiles. The combination of capecitabine plus oxaliplatin has a similar activity to the combination 5-FU/LV/oxaliplatin. The combination of capecitabine/irinotecan might be more toxic than 5-FU/LV/irinotecan.

The duration of chemotherapy for metastatic colorectal cancer remains controversial. Treatment interruptions of combination chemotherapy may be considered, especially if cumulative toxicity occurs and if disease control is reached. Maintenance treatment with a fluoropyrimidine may be considered if an interruption of the combination chemotherapy is proposed. Reintroduction of combination chemotherapy is usually indicated in the case of progression.

Second-line chemotherapy should be proposed for patients with good performance status. In patients refractory to FOLFOX an irinotecan-based regimen can be proposed in the second-line treatment. In patients refractory to FOLFIRI, FOLFOX can be proposed in second-line treatment.

Monoclonal antibodies against vascular endothelial growth factor (VEGF) and against the epidermal growth factor receptor (EGFR) in combination with chemotherapy should be considered in selected patients with metastatic colorectal

\*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland

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cancer. Validated molecular markers for the selection of anti-VEGF and anti-EGFR antibodies are not yet available.

Bevacizumab increases survival and progression-free survival in first-line treatment in combination with an irinotecan-based chemotherapeutic cancer regimen and progression-free survival in combination with a fluoropyrimidine plus oxaliplatin. Cetuximab and panitumumab are active as single agents in chemorefractory metastatic colorectal cancer. The combination of cetuximab with irinotecan is more active than cetuximab monotherapy.

The antibodies against VEGF and EGFR have a specific spectrum of adverse events.

## response evaluation

History, physical examination, CEA if initially elevated and a CT scan of the involved region are recommended after 2–3 months of palliative chemotherapy.

## note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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