clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v93–v97, 2010
doi:10.1093/annonc/mdq222

Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment

E. Van Cutsem[1], B. Nordlinger[2] & A. Cervantes[3]
On behalf of the ESMO Guidelines Working Group*

[1]*Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium;* [2]*Ambroise Paré, Hospital, Boulogne, France;* [3]*Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain*

incidence

In 2006 there were 412 900 new cases of colorectal cancer (CRC) in Europe. This is 12.9% of all cancer cases. CRC was responsible for 217 400 deaths in Europe in 2006. This represents 12.2% of all cancer deaths. Approximately 25% present with metastases at initial diagnosis and almost 50% of patients with CRC will develop metastases, contributing to the high mortality rates reported for CRC.

diagnosis

Clinical or biochemical suspicion of metastatic disease should always be confirmed by adequate radiological imaging [usually a computed tomography (CT) scan or alternatively magnetic resonance imaging (MRI) or ultrasonography]. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan can be useful in determining the malignant characteristics of tumoral lesions, especially when combined with CT scan. FDG-PET scan is especially useful to characterize the extent of metastatic disease when the metastases are potentially resectable. Histology of the primary tumour or metastases is always needed before chemotherapy is started. For metachronous metastases histopathological or cytological confirmation of metastases should be obtained, if the clinical or radiological presentation is atypical or very late after the initial diagnosis of the primary tumour. Resectable metastases do not need histological or cytological confirmation before resection because of a low chance of seeding.

Evaluation of the general condition, organ function and concomitant non-malignant diseases determines the therapeutic strategy for patients with metastatic CRC.

**Correspondence to:* ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland;
E-mail: clinicalrecommendations@esmo.org

Approved by the ESMO Guidelines Working Group: April 2002, last update March 2010. This publication supercedes the previously published version-Ann Oncol 2009; 20 (Suppl 4): iv61-iv63

Conflict of interest: Prof. Van Cutsem has reported that he has received research funding from Amgen, MerckSerono, Pfizer, Roche and Sanofi-Aventis; Prof. Nordlinger has reported no conflicts of interest; Dr Cervantes has reported that he is currently conducting research sponsored by Roche, Amgen and MerckSerono and that he is a member of the speakers' bureau for MerckSerono.

determination of the treatment strategy

The optimal treatment strategy of patients with metastatic CRC should be discussed in a multidisciplinary team.

In order to identify the optimal treatment strategy for patients with metastatic CRC, the staging should include at least clinical examination, blood counts, liver and renal function tests, carcinoembryonic antigen (CEA), CT scan of the abdomen and chest (alternatively, MRI). The general condition and performance status of the patient are strong prognostic and predictive factors. Known biochemical prognostic factors are white blood cell count, alkaline phosphatase level, lactate dehydrogenase, serum bilirubin and albumin. Additional examinations as clinically needed, are recommended before major abdominal or thoracic surgery with potentially curative intent. An FDG-PET can give additional information on equivocal lesions before resection of metastatic disease or can identify new lesions in the case of planned resection of metastases.

treatment of metastatic CRC

The majority of patients have metastatic disease that initially is not suitable for resection. It is, however, important to select patients in whom the metastases are suitable for resection and those with initially unresectable disease in whom the metastases can become suitable for resection after a major response has been achieved with combination chemotherapy. The aim of the treatment in the last group of patients may therefore be to reverse initially unresectable metastatic CRC to resectable CRC.

unresectable metastatic CRC

The optimal treatment strategy for patients with clearly unresectable metastatic CRC is rapidly evolving. The treatment of patients should be seen as a continuum of care in which the determination of the goal of the treatment is important: prolongation of survival, cure, improving tumour-related symptoms, stopping tumour progression and/or maintaining quality of life.

The outcome of patients with metastatic CRC has clearly improved during the last years with median survival now reaching almost 24 months.

The backbone of first-line palliative chemotherapy consists of a fluoropyrimidine [intravenous (i.v.) 5-fluorouracil (5-FU) or

oral fluoropyrimidines] in various combinations and schedules. Infused regimens of 5-FU/leucovorin (LV) are generally less toxic than bolus regimens. The most frequently used regimens are a 48 h bolus and infused regimen of 5-FU/LV every 2 weeks (LV5FU2 regimens). The oral fluoropyrimidines capecitabine and uracil–ftorafur (UFT)/LV are an alternative to intravenous 5-FU/LV as monotherapy. The experience and database with capecitabine is more extensive than with UFT.

Combination chemotherapy with 5-FU/LV/oxaliplatin (FOLFOX) or 5-FU/LV/irinotecan (FOLFIRI) provides higher response rates, longer progression-free survival and better survival than 5-FU/LV [I, B]. FOLFOX and FOLFIRI have a similar activity, but a different toxicity profile: more alopecia and diarrhoea for irinotecan and more polyneuropathy for oxaliplatin [I, B]. Both regimens consist of a 48 h administration every 2 weeks (q2weeks). The dose of oxaliplatin in combination regimens with 5-FU/LV is between 85 mg/m^2 and 130 mg/m^2 q2weeks; there is, however, no evidence that the dose at the higher range is more active. Therefore usually a dose of 85 mg/m^2 is proposed. Two randomized studies showed that combination chemotherapy was not superior to sequential treatment in terms of overall survival, and therefore sequential therapy starting with fluoropyrimidine monotherapy remains a valid option in selected and frail patients [I, B]. Nevertheless, when an objective response is the primary goal in a specific patient (e.g. in view of surgical resection of metastases or when the metastases are symptomatic), combination chemotherapy remains the preferred option. There are, however, no perfect selection criteria for determining which patients are still candidates for upfront fluoropyrimidine therapy. It is estimated that today ~15% of patients are treated initially with a fluoropyrimidine alone.

The exposure to all three cytotoxics (fluoropyrimidines, oxaliplatin and irinotecan) in various sequences, results in the longest survival.

The combination of capecitabine plus oxaliplatin (CAPOX; capecitabine 2000 mg/m^2/day; day 1-14 q3weeks and oxaliplatin 130 mg/m^2 day 1 q3weeks) is an alternative to the combination of infused 5-FU and oxaliplatin [I, A] based on similar activity and safety. The original 3 weekly regimen of capecitabine/irinotecan (capecitabine 2000 mg/m^2/day for 2 weeks and irinotecan 250 mg/m^2 day 1 q3 weeks) seems to be more toxic than 5-FU/LV/irinotecan. This regimen is therefore less well established and less frequently used in its original form. A dose-reduced regimen seems be less toxic, while maintaining the activity (capectitabine 1600 mg/m^2/day for 2 weeks and irinotecan 200 mg/m^2 day 1 q3weeks).

The optimal duration of chemotherapy for metastatic CRC remains controversial. Options are a fixed treatment period (3–6 months) and treatment until progression or toxicity. Treatment interruptions of combination chemotherapy or less intensive cytotoxic treatment should be considered if cumulative toxicity occurs, if the metastases are not resectable and if disease control is reached. Maintenance treatment with a fluoropyrimidine alone prolongs the progression-free survival compared with a complete treatment break, after an initial period of combination chemotherapy [I, B]. Reintroduction of combination chemotherapy is usually indicated in the case of progression.

Second-line chemotherapy should be proposed for patients with good performance status and adequate organ function. In patients refractory to a fluoropyrimidine in monotherapy, second-line treatment must consist of a combination with oxaliplatin or irinotecan. In patients refractory to FOLFOX or CAPOX, an irinotecan-based regimen is proposed in the second-line treatment. Irinotecan monotherapy (350 mg/m^2 q3weeks) and FOLFIRI are options. There is no strong evidence that 5-FU significantly increases the activity of irinotecan in this setting, but there are clear safety advantages of the FOLFIRI regimen, compared with irinotecan monotherapy. In patients refractory to FOLFIRI, FOLFOX or CAPOX is proposed as second-line treatment [I, B].

Monoclonal antibodies against vascular endothelial growth factor (VEGF) and against the epidermal growth factor receptor (EGFR) in combination with chemotherapy should be considered in patients with metastatic CRC, since they improve the outcome of selected patients with metastatic CRC.

Bevacizumab, an anti-VEGF antibody, should be considered in patients with metastatic CRC, as it increases the activity of an active cytotoxic regimen. It increases the survival, progression-free survival and response rate in first-line treatment in combination with 5-FU/LV/irinotecan and in combination with 5-FU/LV or capecitabine alone [I, B]. Bevacizumab improves the progression-free survival in combination with a fluoropyrimidine plus oxaliplatin in the first-line treatment of metastatic CRC [I, B]. Bevacizumab improves also the survival and progression-free survival in combination with FOLFOX in second-line treatment [I, B]. Bevacizumab has specific class-related side-effects: hypertension, proteinuria, arterial thrombosis, mucosal bleeding, gastrointestinal perforation and wound healing problems. Patients older than 65 years with a history of arterial thrombotic events are at significantly higher risk for having an arterial thrombosis while being treated with bevacizumab.

There are no validated predictive molecular markers available for bevacizumab. There is no strong evidence for post-progression continuation of bevacizumab. Bevacizumab is usually continued in combination with a cytotoxic agent (fluoropyrimidine alone ± oxaliplatin or irinotecan) until progression, toxicity or until the metastases are resectable.

The anti-EGFR antibodies cetuximab and panitumumab are active as single agent in chemorefractory metastatic CRC. The activity of the anti-EGFR antibodies is confined to KRAS wild-type tumours [I, B].

It has been shown that cetuximab improves the survival of chemorefractory patients compared with best supportive care (BSC) [I, B]. Panitumumab improves the progression-free survival compared with BSC in chemorefractory metastatic KRAS wild-type CRC [I, B]. The panitumumab trial did not show a survival difference due to the cross-over design of the trial. The combination of cetuximab with irinotecan is more active than cetuximab monotherapy in chemorefractory patients [II, A]. The combination of cetuximab and irinotecan has become the reference treatment in fit chemorefractory KRAS wild-type metastatic CRC patients.

Anti-EGFR antibodies also increase the activity of a backbone reference cytotoxic regimen in earlier lines of treatment of KRAS wild-type metastatic CRC.

Cetuximab increases the activity of a cytotoxic doublet in the first-line treatment in KRAS wild-type patients. A survival, progression-free survival and response rate advantage has been demonstrated for the combination FOLFIRI/cetuximab compared with FOLFIRI alone in the first-line treatment of KRAS wild-type patients [I, B]. An improved response rate and progression-free survival of the combination of FOLFOX and cetuximab in KRAS wild-type patients has been reported, but not consistently confirmed in first-line treatment. The progression-free survival and response rate were improved for the combination cetuximab/irinotecan compared with irinotecan alone in the second-line treatment of metastatic CRC [I, B]. The panitumumab studies in first- and second-line treatment of KRAS wild-type metastatic CRC also showed an increased progression-free survival for panitumumab when combined with FOLFOX in first-line treatment and an increased response rate and progression-free survival when combined with FOLFIRI in second-line treatment. No survival advantage has been shown in these trials [I, B].

There are no phase III results available of studies comparing the activity of bevacizumab and cetuximab or panitumumab in KRAS wild-type tumours. The anti-EGFR antibodies should not be combined with bevacizumab [I, B].

The activity of the anti-EGFR antibodies is confined to KRAS wild-type tumours and they should not be used in KRAS mutant CRC [I, B]. Approximately 40% of metastatic CRCs are KRAS mutant; 5%–10% of CRC are BRAF mutant. KRAS mutations and BRAF mutations are usually mutually exclusive. The activity of the anti-EGFR antibodies in chemorefractory CRC seems also to be confined to BRAF wild-type CRC. BRAF mutations have a strong prognostic value in early lines of treatment. A predictive value of BRAF mutation status for anti-EGFR antibodies in combination with cytotoxics could not be demonstrated until now in early lines of treatment. Other emerging markers (e.g. the ligands amphi- and epiregulin) are under investigation, but the prognostic and predictive role of these markers needs validation.

The anti-EGFR antibodies induce in most treated patients an acneiform rash. Hypomagnesaemia is another class-related side-effect. Cetuximab is a chimeric antibody that gives slightly more frequent allergic reactions than the human monoclonal antibody panitumumab.

In patients presenting synchronously with a primary colon cancer and metastases and suffering from symptoms of the primary tumour (e.g. occlusion, bleeding), a resection of the primary tumour should be considered before starting chemotherapy. In patients with metastatic rectal cancer with symptoms of the primary tumour, irradiation (possibly combined with chemotherapy) of the primary tumour should be considered after discussion with the radiation oncologist in order to obtain optimal symptom control of the primary tumour.

resection of metastatic disease

Surgical resection should be considered for solitary or confined liver metastases, since it offers patients with metastatic CRC the best chance of long-term survival with actuarial 5-year survival rates (following hepatic resection) ranging from 30%–35% to >50% in some selected series. Unfortunately, 60%–75% of these patients will suffer a relapse following resection of their hepatic metastases, with the majority occurring in the liver [II, A]. There is no role for partial palliative resection of metastases.

Radiofrequency ablation, in combination with systemic treatment, is under investigation as an alternative or a complement to surgical resection of liver metastases in cases where this is not possible or complete.

In patients with resectable liver metastases, perioperative combination chemotherapy with the FOLFOX regimen improves the progression-free survival by 7%–8% at 3 years [I, B]. The perioperative chemotherapy is given for 3 months (six cycles) before and 3 months after the surgical resection of the metastases. In the case that no preoperative chemotherapy can be or has been administered, postoperative adjuvant treatment with FOLFOX should be considered. There is no evidence yet that adding a biological to a cytotoxic doublet improves the outcome in resectable metastases compared with a cytotoxic doublet alone in combination with resection of the metastases.

Resection of resectable lung metastases offers also 25%–35% 5-year survival rates in carefully selected patients.

Initially unresectable liver metastases can become resectable after downsizing with chemotherapy and, if so, resection should be considered after multidisciplinary discussions. For patients with initially unresectable liver metastases, a strong correlation between response rate and resection rate in the neoadjuvant treatment of metastatic CRC has been demonstrated. Pathological response seems to be a surrogate for predicting the outcome. Thus, the strategy when treating patients with initially unresectable disease is to try to achieve high response rates in order to convert unresectable metastases to resectable metastases. Diminution of the metastases in number only should not be considered as the majority of metastases in complete radiological remission still contain microscopic viable tumour cells. In patients in whom the metastases have disappeared on standard imaging, microscopic disease is often still present and a multidisciplinary discussion for the optimal strategy has to take place. Standard combination chemotherapy regimens comprising 5-FU/LV in combination with either irinotecan, typically FOLFIRI, or oxaliplatin (FOLFOX) have been reported to facilitate the resection of 7%–40% of patients with initially unresectable metastases depending upon the initial selection of patients. However, 75%–80% of these patients experience cancer relapse within 2 years of resection. Data emerging from randomized trials suggest that the addition of a targeted agent (bevacizumab or cetuximab) or even scarce data of phase II trials on the combination with a third cytotoxic plus or minus a targeted agent, might be even more effective, although concerns about toxicity limit the use of this triple cytotoxic regimen to highly selected cases. The combination of a doublet of cytotoxics plus cetuximab has led to higher resection rates (although still low in absolute numbers) in patients with liver limited unresectable metastatic KRAS wild-type CRC. The combination of FOLFOX/cetuximab and FOLFIRI/cetuximab has led to similar response rates and resection rates in KRAS wild-type tumours. The combination of a fluoropyrimidine/oxaliplatin/bevacizumab has led to a non-significant trend in an increased resection rate compared with the cytotoxic backbone alone, although no increase in

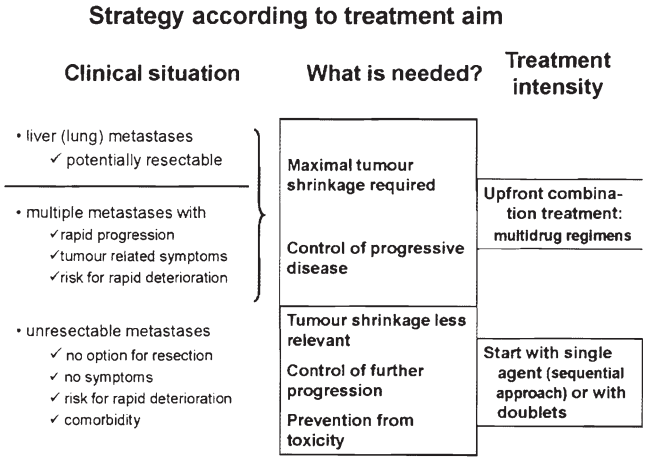

Figure 1. Strategy for the treatment of metastatic CRC (modified from Expert discussion ESMO/WCGIC Barcelona june 2009)

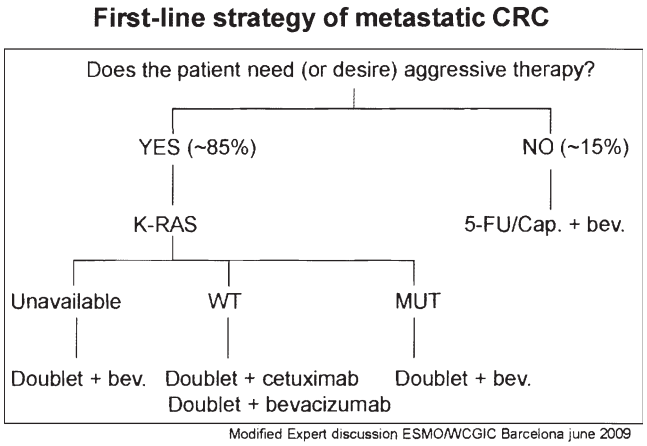

Figure 2. algorithm for first-line treatment of metastatic CRC. WT, wild type; MUT, mutant; Cap., capecitabine; bev., bevacizumab; doublet, doublet of cytotoxics.

response rate was shown. There are no data of randomized studies comparing the activity of a doublet of cytotoxics plus bevacizumab with a doublet plus cetuximab.

Surgery can be performed safely after 4 weeks from the last cycle of chemotherapy plus or minus cetuximab, and 5–8 weeks following chemotherapy plus bevacizumab.

Resection of the metastases should be performed as soon as the metastases are resectable, since unnecessary prolonged administration of chemotherapy may lead to a higher postoperative morbidity. The postoperative morbidity is more related to the duration of the chemotherapy than to the type of chemotherapy that is administered, although oxaliplatin and irinotecan may cause different histological changes in liver parenchyma: oxaliplatin is related to sinusoidal liver lesions and irinotecan to steatohepatitis.

The criteria for resectability of liver metastases are not standardized and have evolved over the last years and are clearly related to the experience of the surgeon and of the multidisciplinary team. Multiple resections can also be performed, provided there is sufficient remnant liver (>30%) and surgery is not too risky due to location. Other considerations must include the presence of questionably resectable extrahepatic disease and poor biology.

conclusion on strategy of treatment of metastatic CRC

In the selection of the optimal treatment options for patients with metastatic CRC, the determination of the treatment goals and strategy are crucial. The possibility of resection of liver (or lung) metastases should be considered. In view of this and also because of the higher activity, multidrug combination regimens are proposed to many patients, although for a subgroup of patients with unresectable metastases without symptoms or risk of rapid deterioration and with comorbidity a sequential approach may be justified (Figures 1 and 2). In patients who are candidates for combination therapy determination of the KRAS status of the tumour can clearly determine the selection of the best combination regimen (Figure 2).

response evaluation

History, including the evaluation of the general condition, the side-effects of the chemotherapy and the impact on the quality of life of the patient, physical examination, CEA if initially elevated and a CT scan of the involved regions are recommended after 2–3 months during palliative chemotherapy. It is recommended that the patient be re-evaluated every 2–3 months if chemotherapy is continued.

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.

literature

1. Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000; 355: 1041–1047.
2. de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000; 18: 2938–2947.
3. Tournigand C, Andre T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004; 22: 229–237.
4. Grothey A, Sargent D, Goldberg R, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 2004; 22: 1209–1214.
5. Van Cutsem E, Hoff PM, Harper P et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised phase III trials. Brit J Cancer 2004; 90: 1190–1197.
6. Rougier P, Van Cutsem E, Bajetta E et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998; 352: 1407–1412.
7. Seymour M, Maughan T, Ledermann J et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced

colorectal cancer (MRC FOCUS): a randomised controlled trial. Lancet 2007; 370: 143–152.
8. Koopman M, Antonini NF, Douma J et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. Lancet 2007; 370: 135–142.
9. Chibaudel B, Maindrault-Goebel F, Lledo G et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J Clin Oncol 2009; 27: 5727–5733.
10. Van Cutsem E, Nordlinger B, Adam R et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer 2006; 42: 2212–2221.
11. Nordlinger B, Sorbye H, Glimelius B et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008; 371: 1007–1016.
12. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335–2342.
13. Saltz LB, Clarke S, Díaz-Rubio E et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008; 26: 2013–2019.
14. Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan refractory metastatic colorectal cancer. N Engl J Med 2004; 351: 337–345.
15. Jonker D, O'Callaghan C, Karapetis C et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007; 357: 2040–2048.
16. Van Cutsem E, Peeters M, Siena S et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007; 25: 1658–1664.
17. Amado RG, Wolf M, Peeters M et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26: 1626–1634.
18. Wong SL, Mangu PB, Choti MA et al. Clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol 2010; 28: 493–508[Oct 19 2009 Epub ahead of print].
19. Karapetis CS, Khambata-Ford S, Jonker DJ et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008; 359: 1757–1765.
20. Saltz LB, Clarke S, Díaz-Rubio E et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008; 26: 2013–2019.
21. Cassidy J, Clarke S, Díaz-Rubio E et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008; 26: 2006–2012.
22. Bokemeyer C, Bondarenko I, Makhson A et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009; 27: 663–671.
23. Van Cutsem E, Köhne CH, Hitre E et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009; 360: 1408–1417.
24. Tol J, Koopman M, Cats A et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009; 360: 563–572.
25. Nordlinger B, Van Cutsem E, Rougier P et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. Eur J Cancer 2007; 43: 2037–2045.
26. Nordlinger B, Van Cutsem E, Gruenberger T et al. European Colorectal Metastases Treatment Group; Sixth International Colorectal Liver Metastases Workshop. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. Ann Oncol 2009; 20: 985–992.
27. Schmoll HJ, Sargent D. Single agent fluorouracil for first-line treatment of advanced colorectal cancer as standard? Lancet 2007; 370: 105–107.