PRACTICE GUIDELINE

Consensus statement: the 16th Annual Western Canadian Gastrointestinal Cancer Consensus Conference; Saskatoon, Saskatchewan; September 5–6, 2014

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ABSTRACT

The 16th annual Western Canadian Gastrointestinal Cancer Consensus Conference was held in Saskatoon, Saskatchewan, September 4–5, 2014. The Consensus Conference is an interactive, multidisciplinary event attended by health care professionals from across western Canada (British Columbia, Alberta, Saskatchewan, and Manitoba) involved in the care of gastrointestinal cancer. Surgical, medical, and radiation oncologists; pathologists; radiologists; and allied health care professionals participated in presentation and discussion sessions for the purposes of developing the recommendations presented here. This consensus statement addresses current issues in the management of colorectal cancer.

KEY WORDS

Colorectal cancer, rectal cancer, EGFR inhibitors, chemotherapy, liver-directed therapy, surgery, magnetic resonance imaging, radiation therapy, consensus statement

1. TERMS OF REFERENCE

1.1 Purpose

The purpose of the Consensus Conference is to develop the consensus opinion of oncologists and allied health professionals from across western Canada about best care practices and to improve care and outcomes for patients with gastrointestinal cancer.

1.2 Participants

The conference draws the participation of medical oncologists, radiation oncologists, colorectal and hepatobiliary surgeons, surgical oncologists, pathologists, radiologists, and allied health professionals from western Canada who are involved in the care of patients with gastrointestinal malignancies (Table I).

1.3 Target Audience

The audience for this consensus statement are health care professionals involved in the care of patients with colorectal cancer (CRC).

1.4 Basis of Recommendations

The recommendations reported here are based on presentation and discussion of the best available evidence. Where applicable, references are cited.

2. RECOMMENDATIONS

2.1 Question 1

What, if any, are the indications for first-line epidermal growth factor receptor inhibitor (EGFRI) therapy in *RAS* wild-type metastatic CRC?

Recommendations: First-line EGFRI therapy represents an option to consider, especially in patients with relative contraindications to bevacizumab. The

TABLE I   Attendees at the 16th Annual Western Canadian Gastrointestinal Cancer Consensus Conference

Name	Position	Site
Ahmed, Shahida	Radiation oncologist	Cancer Care Manitoba
Ahmed, Osama	Internal medicine resident	University of Saskatchewan
Ahmed, Shahid	Medical oncologist	Saskatoon Cancer Centre
Arnold, Florence	Medical oncologist	Saskatoon Cancer Centre
Beck, Gavin	Hepatobiliary surgeon	University of Saskatchewan
Berry, Scott	Medical oncologist	University of Toronto
Brigden, Malcolm	Medical oncologist	Jack Ady Cancer Centre
Buie, Donald	Surgical oncologist	University of Calgary
Chalchal, Haji	Medical oncologist	Saskatchewan Cancer Agency
Cheung, Winson	Medical oncologist	BC Cancer Agency
Chua, Neil	Medical oncologist	Cross Cancer Institute
Davies, Janine	Medical oncologist	BC Cancer Agency– Centre for the Southern Interior
Dhaliwal, Dhali HS	Medical oncologist	Cancer Care Manitoba
Dhalla, Sonny	General surgeon	Brandon Regional Health Centre
Doll, Corinne	Radiation oncologist	Tom Baker Cancer Centre
Elzinga, Christine	Clinical associate	Tom Baker Cancer Centre
Fairchild, Alysa	Radiation oncologist	Cross Cancer Institute
Gordon, Vallerie	Medical oncologist	Cancer Care Manitoba
Groot, Gary	Director of research and grad studies Director of surgical oncology	University of Saskatchewan
Haider, Kamal	Medical oncologist	Saskatoon Cancer Centre
Hardy, Edward	Medical oncologist	BC Cancer Agency
Havixbeck, Lisa	Pharmacist	Cancer Care Manitoba
Horsman, Susan	Nurse practitioner	Alberta Health Services
Johnson, Kate	Radiation oncology resident	Cancer Care Manitoba
Jones, Edward	Clinical pathologist	Regina Qu'Appelle Health Region
Kanthan, Selliah	Colorectal surgeon	University of Saskatchewan
Kellett, Curtis	Pharmacist	Cancer Care Manitoba
Kennecke, Hagen	Medical oncologist Professional practice leader	BC Cancer Agency
Kim, Christina	Medical oncologist	Cancer Care Manitoba
Krahn, Marianne	Medical oncologist	Cancer Care Manitoba
Le, Lyly	Medical oncologist	BC Cancer Agency
Le, Duc	Radiation oncologist	Saskatoon Cancer Centre
Lim, Howard	Medical oncologist	BC Cancer Agency
Lund, Chad	Radiation oncologist	Fraser Valley Cancer Centre
Luo, Yigang	Hepatobiliary surgeon	Saskatoon Health Region
Maroun, Jean	Medical oncologist	The Ottawa Hospital
McConnell, Yarrow	Surgical oncologist	BC Cancer Agency
McGhie, John Paul	Medical oncologist	BC Cancer Agency
Melosky, Barbara	Medical oncology	BC Cancer Agency
Nashed, Maged	Radiation oncologist	Cancer Care Manitoba

TABLE I   Continued

Name	Position	Site
Park, Jason	Surgical oncologist	Cancer Care Manitoba
Price Hiller Julie	Medical oncologist	Cross Cancer Institute
Rashidi, Farid	Diagnostic radiologist	University of Saskatchewan
Salim, Muhammad	Medical oncologist	Saskatchewan Cancer Agency
Sam, Veronica	Clinical associate	Tom Baker Cancer Centre
Sami, Amer	Medical oncologist	Saskatoon Cancer Centre
Sawyer, Michael	Medical oncologist	Cross Cancer Institute
Scarfe, Andrew	Medical oncologist	Cross Cancer Institute
Shewchuk, Chelsey	Pharmacist	Saskatoon Cancer Centre
Sollid, David	Pharmacist	Saskatoon Cancer Centre
Tan, K.T.	Interventional radiologist	University of Saskatchewan
Wong, Ralph	Medical oncologist	Cancer Care Manitoba
Woo, Nobby	General surgeon	Concordia Hospital
Zaidi, Adnan	Medical oncologist	Saskatoon Cancer Centre

evidence is evolving. The decision should be made after discussion with the patient, with consideration given to quality of life and patient preference.

Expanded *RAS* (*KRAS* and *NRAS*) testing provides optimal patient selection and should be considered the standard of care for EGFRI treatment.

Summary of Evidence: Infusional FOLFIRI (fluorouracil–leucovorin–irinotecan) and FOLFOX (fluorouracil–leucovorin–oxaliplatin) have been demonstrated to be equal in efficacy for treatment-naïve patients with stage IV CRC. However, the optimal first-line monoclonal antibody—bevacizumab (an inhibitor of vascular endothelial growth factor A) or an EGFRI such as cetuximab or panitumumab—remains unclear. The efficacy of the EGFRI alone or in combination with cytotoxic agents has been reported in both chemotherapy-refractory and untreated advanced CRC[1–5]. Unlike bevacizumab, cetuximab and panitumumab are both active as single agents in chemorefractory advanced CRC. However, the activity of the EGFRIS is confined to *RAS* wild-type tumours; patients harboring *KRAS* mutations in codon 12 or 13 at exon 2 do not benefit from EGFRIS whether given alone or in combination with chemotherapy[6–8]. A mutation in the *KRAS* gene is found in 30%–40% of CRCs. In a randomized trial, 1198 chemotherapy-naïve patients were randomized to FOLFIRI with or without cetuximab. Compared with FOLFIRI alone, combination treatment in patients with a *KRAS* wild-type tumour was associated with a significantly better median overall survival (MOS): 23.5 months versus 20 months[5]. Likewise, in patients with a *KRAS* wild-type tumour and chemorefractory disease who were treated with cetuximab, the MOS was 9.5 months compared with 4.8 months with best supportive care[3]. Recent data have demonstrated that 15%–25% patients carry mutations in *KRAS* exons 3 (codon 61) and 4 (codons 117 and 146) and in *NRAS* exons 2, 3, and 4, and do not respond to EGFRIS[9–11]. For instance, a reanalysis of the addition of panitumumab to FOLFOX in the PRIME study in the *KRAS, NRAS,* and *BRAF* wild-type subgroup noted statistically significant improvements in progression-free survival (PFS) and OS in the panitumumab arm[9]. Furthermore, patients with a mutated *RAS* tumour experienced shorter PFS and OS when treated with combination therapy.

At least three trials have compared first-line EGFRI or bevacizumab in combination with chemotherapy[12–14]. The largest, the phase III Cancer and Leukemia Group B (CALGB)/SWOG 80405 trial, compared first-line therapy with bevacizumab or cetuximab in combination with FOLFOX or FOLFIRI for patients with *KRAS* wild-type (codons 12 and 13) stage IV CRC[14]. Overall, 73.4% of patients in the trial received FOLFOX as the chemotherapy backbone. The preliminary results were presented at the 2014 American Society of Clinical Oncology annual meeting. Patients treated with bevacizumab experienced a MOS of 29 months, compared with 29.9 months for those receiving cetuximab [hazard ratio (HR): 0.925; $p = 0.34$]. Median PFS was 10.8 months with bevacizumab and 10.4 months with cetuximab (HR: 1.04; $p = 0.55$). Approximately 10% of the patients underwent curative surgery. The toxicity profiles were as expected for these agents, with the incidences of grades 3 and 4 rash (7% vs. 0%) and diarrhea (11% vs. 8%) being increased in the cetuximab arm, and the incidences of grades 3 and 4 hypertension (1% vs. 7%) and gastrointestinal events (0.5% vs. 2%) being increased in the bevacizumab arm. Updated patient-reported survey data about dermatology-specific quality of life confirmed that

skin rash was a significant concern for patients ($p <$ 0.0001); however, the same concern was not reflected in the data from the European Organisation for Research and Treatment of Cancer (EORTC) global quality of life survey ($p = 0.0546$). When comparing efficacy in the two chemotherapy groups, the results were the same, suggesting that the chemotherapy backbone did not affect the overall results. The preliminary result for the expanded wild-type *RAS* population was presented at the 2014 European Society for Medical Oncology annual meeting. In that population, the MOS improved to beyond 30 months. Although neither cetuximab nor bevacizumab, both in combination with chemotherapy, was noted to be associated with a significant difference in MOS (32 months vs. 31.2 months) or PFS, the expanded *RAS* population in the cetuximab arm experienced a higher response rate (68.6% vs. 53.6%, $p < 0.01$)[15].

The smaller phase III FIRE-3 trial compared FOLFIRI plus either cetuximab or bevacizumab in patients with *KRAS* wild-type stage IV CRC[13]. Although no significant differences between bevacizumab and cetuximab were noted with respect to response rate and PFS, a 3.7-month OS advantage was seen with cetuximab. That OS advantage was not seen until about 1 year after completion of the study therapy. In a preliminary report of a subsequent analysis of the FIRE-3 trial, patients with expanded wild-type *RAS* status experienced an even more pronounced survival benefit with cetuximab than with bevacizumab (MOS: 33.1 months vs. 25.9 months; HR: 0.70; $p = 0.01$), but no difference in PFS (median: 10.5 months vs. 10.4 months). The investigators recently presented an independent radiology review at the 2014 European Society for Medical Oncology annual meeting[16]. Based on that review, FOLFIRI plus cetuximab was associated with a significantly higher overall response rate, a greater rate of early tumour shrinkage, and an increased depth of response than was FOLFIRI plus bevacizumab. In the *RAS* wild-type population, the overall response rate was 72% in the cetuximab arm and 56.1% in the bevacizumab arm ($p = 0.003$). The foregoing response-related outcomes might in part explain the significant OS advantage observed with the use of FOLFIRI plus cetuximab in the expanded *RAS* wild-type study population.

Lastly, in a phase II study (PEAK), 285 patients with previously untreated metastatic *RAS* wild-type CRC were randomly assigned to FOLFOX plus either panitumumab or bevacizumab[12]. Progression-free survival was similar in both arms, but the MOS was significantly better with panitumumab (34 months vs. 24 months; HR: 0.62). When the analysis was expanded to all patients with *RAS* wild-type tumours, panitumumab was associated with a significant improvement in PFS. The difference in MOS, although clinically meaningful, was not statistically significant (41 months vs. 29 months).

Current evidence highlights the efficacy of two treatment options for patients with stage IV CRC. Chemotherapy plus bevacizumab or plus cetuximab are two potential first-line options in all patients with *RAS* wild-type advanced CRC. In settings in which tumour shrinkage is a relevant therapeutic goal, EGFRI in combination with chemotherapy might be the preferable first-line option. Future information about treatment characteristics (duration, second-line treatments, and so on), depth of response, and early tumour shrinkage from the largest first-line trial (CALGB/SWOG 80405) could potentially influence selection of the initial therapeutic approach. Recent updates on patient outcomes in relation to expanded *RAS* testing strongly support all-*RAS* testing in making better selections of patients for EGFRI.

2.2 Question 2

What is the best way to define the rectum and to determine the location of a rectal tumour in clinical practice?

Recommendations: A multimodality assessment incorporating both endoscopic and radiographic findings is recommended if there is any question about the location of the tumour in the rectum compared with the sigmoid colon.

Standardized preoperative magnetic resonance imaging (MRI) in combination with clinical and endoscopic examination by a surgeon who treats rectal cancer is recommended to determine the location of a rectal cancer for staging and treatment purposes.

Standardized synoptic reporting of the findings from MRI is recommended. The report should assist a treatment decision by describing tumour location, depth, lymph node status, extramural vascular invasion, and distance of tumour or lymph nodes to the mesorectal fascia ("circumferential resection margin").

Summary of Evidence: The rectum extends from the anorectal junction to the sigmoid colon; it measures 12–15 cm in length. Most studies have arbitrarily defined three parts of the rectum: the low rectum (up to 5 cm from the anal verge), the mid-rectum (5 cm to <10 cm), and the upper rectum (10–15 cm)[17]. Tumours with distal extension to 15 cm or less from the anal margin (as measured by rigid sigmoidoscopy) are classified as rectal; more proximal tumours are classified as colonic cancer[17,18].

The decision between upfront surgery and neoadjuvant treatment is based largely on preoperative locoregional staging. Magnetic resonance imaging and endorectal ultrasonography are both options for that purpose. On balance, the more recent literature favours the use of MRI for staging, and currently, phased-array pelvic MRI is recommended for the preoperative assessment of tumour location (rectal versus sigmoid, lower versus upper rectum), depth (T1 or 2 vs. T3 or T4), lymph node status (abnormal

nodes in the mesorectum or pelvic side wall), extramural vascular invasion, and distance of tumour or lymph nodes to the mesorectal fascia (circumferential resection margin status). However, endorectal ultrasonography might provide an advantage in differentiating the depth of invasion in early tumours (T1 vs. T2)[19].

In prospective comparative studies using histopathology, staging by MRI correlated strongly with depth of tumour invasion (82%) and extramural depth of invasion (95%)[20,21]. Lymph nodes with a short axis greater than 5 mm in size or with a spiculated and indistinct border or a mottled heterogeneous appearance are considered clinically positive. However, not all positive lymph nodes meet those criteria. A recent meta-analysis involving 1249 patients from 23 studies showed a pooled sensitivity of 77% and specificity of 71% for MRI assessment of nodal involvement[22]. The low sensitivity with the use of size criteria can be explained only by the fact that, in rectal cancer, small lymph nodes still have a high prevalence of malignancy, 9% in 1-mm to 2-mm nodes, and 17% in 2-mm to 5-mm nodes respectively[23]. However, with improvements in MRI techniques, staging accuracy for lymph nodes has increased to 91%, with a high sensitivity of 89%[24]. In radiographic assessments using MRI, the point of peritoneal reflection can clearly be seen and is of variable height. Typically, tumours at or below the peritoneal reflexion are, by definition, rectal tumours. Magnetic resonance imaging is also used to measure the distance of a tumour from the mesorectal fascia or the circumferential radial margin (CRM). Involvement of the CRM is defined as a tumour within 1 mm of the mesorectal fascia. The MERCURY Study Group prospective trial showed 92% specificity for the preoperative MRI predictions of a clear CRM with surgery[21]. Overall, pelvic MRI is a robust tool (high accuracy and reproducibility) for preoperative staging and assessment of CRM involvement.

2.3 Question 3

What are the current indications for radiotherapy (RT) in early-stage rectal cancer?

Recommendations: For clinically T3/4 or node-positive rectal cancer, preoperative radiation is recommended.

If downstaging is required, chemoradiation (CRT) therapy is the preferred option.

Chemoradiation therapy is recommended after upfront resection for patients with T3 or T4 tumours, a positive circumferential margin, or lymph node involvement.

Low-risk stage 2 rectal cancers such as T3 lesions with a wide CRM as defined by high-resolution MRI should be discussed at a multidisciplinary team meeting for optimal management.

Summary of Evidence: Prognosis in rectal cancer is largely determined by TNM staging. Adjuvant fluorouracil-based CRT has been associated with 10%–12% reductions in the rate of local failure and 10%–15% improvements in survival[25]. The status of the CRM is an important prognostic factor for survival and local recurrence[26,27]. With the introduction of total mesorectal excision (TME), local recurrence rates have dropped to 10%–15% with surgery alone. However, the Dutch TME study showed a local control benefit for adding preoperative RT to TME surgery[28]. That result was subsequently confirmed by the U.K. Medical Research Council 07 trial, which found that, even in the setting of a high-quality TME, RT appears to improve local control rates[29]. The German Rectal Study Group compared preoperative CRT with postoperative CRT in patients with clinically T3/4 or node-positive rectal cancer. At a median follow-up of 46 months, the pelvic relapse rate was 6% in the preoperative CRT group and 13% in the postoperative CRT group[30]. The U.S. National Surgical Adjuvant Breast and Bowel Project R-03 trial (which closed prematurely) demonstrated better disease-free survival (DFS) with preoperative CRT[31]. The German trial established preoperative RT as a standard treatment option for T3/4 or node-positive rectal cancer. The EORTC 22921 and French phase III Fédération Francophone de Cancérologie Digestive 9203 trials demonstrated the benefit of combining fluorouracil-based chemotherapy with preoperative RT by improving rates of pathologic complete response and local control with acceptable toxicity[32,33]. At least three phase III trials (the Swedish Rectal Cancer trial, the Dutch TME study, and the Medical Research Council trial) evaluated short-course preoperative RT and demonstrated improved local control with short-course preoperative RT followed by surgery compared with surgery alone[28,29,34]. Several randomized trials and a meta-analysis have evaluated the role of concurrent CRT with conventional-fractionation RT. Using a 2×2 factorial design, EORTC 22921 compared preoperative CRT with RT alone with or without adjuvant chemotherapy. A high rate of pathologic complete response and better local control with CRT was revealed[35]. Two other trials, the Polish trial and the Trans-Tasman Radiation Oncology Group trial compared short-course RT (5×5-Gy fractions) with conventional-fractionation CRT[36,37]. No significant differences were noted with respect to the rates of local relapse, DFS, and OS. Nevertheless, a meta-analysis of six randomized trials favoured CRT[38]. The addition of concurrent chemotherapy to neoadjuvant RT was associated with better local control [odds ratio for local recurrence: 0.56; 95% confidence interval (CI): 0.42 to 0.75]. However, a higher rate of adverse effects was reported with CRT (odds ratio: 3.96; 95% CI: 3.03 to 5.17).

The utility of preoperative high-resolution MRI for selecting patients with T3 disease for preoperative

therapy based on the depth of extramural tumour invasion was reported in an analysis from the prospective MERCURY trial[39]. The local recurrence rate for patients predicted to have a good-prognosis tumour on MRI was 3%. Likewise, pooled data from 2551 patients enrolled in three North American rectal trials revealed that patients staged pT3N0 had a 6%–8% risk of local recurrence and might not derive benefit from adjuvant radiation[40]. Hence, in selected patients with T3N0 upper rectal cancer with clear resection margins and favourable prognostic features after upfront surgery, chemotherapy alone can be considered. Low-risk stage 2 rectal cancer such as T3 with a wide CRM as defined by high-resolution MRI should be discussed at a multidisciplinary team meeting for optimal management.

2.4 Question 4

What is the preferred adjuvant treatment in rectal cancer after neoadjuvant CRT?

Recommendations: The decision about adjuvant treatment is guided largely by evidence extrapolated from the colon cancer literature and is based on preoperative staging.

For patients who received chemotherapy as part of long-course preoperative chemoradiotherapy, fluoropyrimidine-based chemotherapy with or without oxaliplatin for a total of 4 months is recommended.

Summary of Evidence: The use of adjuvant treatments in patients with rectal cancer after preoperative RT or CRT and TME is based largely on extrapolation from data for colon cancer and postoperative adjuvant therapy before the era of neoadjuvant therapy. The results of a Cochrane meta-analysis support the use of fluorouracil-based postoperative adjuvant chemotherapy for patients with rectal cancer. Twenty-one eligible randomized controlled trials involving 9785 patients with rectal cancer were identified. The results showed a 25% relative reduction in the risk of disease recurrence (HR: 0.75; CI: 0.68 to 0.83) and a 17% reduction in the risk of death (HR: 0.83; CI: 0.76 to 0.91) among patients treated with adjuvant chemotherapy[41]. However, preoperative CRT was administered to all patients in only one of the included trials. Currently, evidence about the benefit of adjuvant chemotherapy in patients treated with preoperative therapy and TME is limited[42].

At least four randomized trials have evaluated the benefit of adjuvant chemotherapy in rectal cancer patients after neoadjuvant RT or CRT therapy[43–46]. Although EORTC failed to demonstrate a benefit for adjuvant chemotherapy, their trial suffered from substantial drop-out and dose reductions in the chemotherapy arm. Hence, the trial cannot be interpreted as definite evidence of a lack of benefit for adjuvant chemotherapy in rectal cancer[43]. An Italian trial conducted between 1993 and 2003 did not report a survival benefit for adjuvant fluorouracil compared with observation alone in patients with clinical T3/4 rectal cancer[44]. The U.K. CHRONICLE and Dutch PROCTOR/SCRIPT trials also evaluated the benefit of adjuvant chemotherapy after neoadjuvant therapy in stage II and III rectal cancer. Although no differences in DFS or OS were seen between the adjuvant chemotherapy and observation groups in either study, both trials were closed prematurely because of poor patient accrual[45,46]. Despite negative results, the available data are insufficient to conclude that postoperative chemotherapy in this setting offers no benefit. Guidelines from the U.S. National Comprehensive Cancer Network and the European Society for Medical Oncology support adjuvant chemotherapy in rectal cancer[47,48].

The optimal adjuvant chemotherapy in rectal cancer is not known. The benefit of adjuvant oxaliplatin-based chemotherapy has been demonstrated in node-positive colon cancer[49,50]. Three prospective trials evaluated oxaliplatin-based regimens after neoadjuvant therapy in rectal cancer, two of which favoured adding oxaliplatin to fluorouracil-based adjuvant chemotherapy[51–53]. In the German trial, patients with cT3/4 or cN+ rectal cancer were randomized to preoperative CRT with or without oxaliplatin, followed by TME and 4 cycles of bolus fluorouracil or 8 cycles of adjuvant FOLFOX. The 3-year DFS was 71.2% in the fluorouracil group and 75.9% in the FOLFOX group ($p = 0.03$)[51]. A South Korean randomized phase II trial compared adjuvant FOLFOX with fluorouracil–leucovorin in rectal cancer patients whose postoperative stage was II or III after preoperative CRT[52]. At a median follow-up of 38.2 months, the 3-year DFS was 71.6% in the FOLFOX arm and 62.9% in the fluorouracil arm (HR: 0.657; $p = 0.047$). The PETAAC-8 trial evaluated the benefit of adjuvant capecitabine–oxaliplatin (CAPOX) compared with capecitabine alone and reported no difference in 3-year DFS between the two arms (75% vs. 74%, $p = 0.78$)[53]. However, adjuvant therapy was not received by 38% of patients in the CAPOX arm and 23% of patients in the capecitabine arm. Furthermore, only 53% of patients in the CAPOX arm and 68% of patients in the capecitabine arm received all intended adjuvant chemotherapy cycles.

Taking all the evidence together, fluoropyrimidine-based chemotherapy with or without oxaliplatin for a total of 4 months is recommended in patients who received chemotherapy as part of long-course preoperative CRT.

2.5 Question 5

What is the best sequence of treatments in patients with resectable primary rectal cancers and synchronous resectable or borderline resectable liver metastases?

Recommendations: The best sequence of systemic and local therapies, including the sequencing of surgery, is not well defined in patients with resectable primary rectal cancers and synchronous resectable or borderline resectable liver metastases.

For borderline resectable liver disease, upfront systemic therapy is a preferred option.

After discussion in a multidisciplinary team meeting, treatment should be individualized based on the extent of primary and liver disease, patient characteristics, and local expertise.

Summary of Evidence: The optimal sequence of systemic and local therapy in patients with resectable or borderline resectable stage IV rectal cancer remains unknown. Data about optimal treatment approaches in these patients is very limited. Curative treatment usually entails a multimodality approach, with surgical resection of the primary tumour and metastatic disease, and incorporation of systemic therapy with or without RT. Most primary tumours in patients with stage IV rectal cancer represent T3/4 disease with regional lymph node involvement, which necessitates the use of RT. Furthermore, the need for surgical treatment at two different sites makes overall patient management complex, particularly with respect to sequencing surgery with chemotherapy and RT. Additionally, a two-stage approach to hepatic resection might be needed in the presence of multiple bilobar metastases. Several strategies have been developed to combine the various treatment modalities. Initial treatment options for rectal cancer with synchronous resectable liver metastases include preoperative combination chemotherapy with or without a biologic agent, preoperative CRT therapy, or even an upfront surgical approach.

Reports in the literature describe three approaches with respect to the appropriate timing of surgical resection of primary and metastatic tumours:

- Classical approach, whereby the primary is resected first, and liver metastases are resected in a second operation
- Simultaneous approach, in which both resections are performed in the same procedure[54]
- Liver-first approach, in which the resection of liver metastases precedes resection of the primary tumour[55,56]; however, such a strategy can be applied only to primary tumours without symptoms that render the surgical management of the rectal site urgent (for example, obstruction and perforation)

A systematic review evaluating clinical studies compared the timing and sequence of surgical interventions in patients with synchronous liver metastases[57]. Despite the relatively large number of published studies on surgical management of synchronous liver metastases, no randomized controlled trials have been reported; all published studies are observational, usually retrospective, and often noncomparative. The review suggested that none of the three surgical strategies (primary first, liver first, or simultaneous) is inferior to the others. Another review[58] suggested that a liver-first approach is safe and feasible in selected patients with CRC and synchronous liver metastases. Based on local expertise, combined and staged surgeries of the primary and metastatic disease are both appropriate options.

Chemotherapy can be used before liver resection as neoadjuvant treatment between the two procedures and after the CRC resection. Systemic chemotherapy can be sequenced with CRT either before or after local treatment for the primary tumour. Radiation therapy should be incorporated for T3/4 or N+ rectal cancer. A phase II study evaluated preoperative short-course pelvic RT (5×5 Gy) followed by CAPOX in combination with bevacizumab before radical surgical treatment in patients with potentially resectable stage IV rectal cancer[59]. Radical surgical treatment was possible in 36 of 50 patients (72%). The 2-year rates of recurrence and OS were 64% and 80% respectively. This treatment scheme yielded a pathologic complete response of the primary tumour in 26% of patients and a pathologic near-complete response in 16% of patients.

For patients with resectable metastatic disease, oxaliplatin-based systemic therapy is the preferable option[60]. Few studies have assessed outcomes in patients with rectal cancer treated with neoadjuvant chemotherapy alone. A small retrospective study evaluated outcomes in patients with colon and rectal cancers who received preoperative FOLFOX alone, either because of metastatic disease or contraindications to, or refusal of, RT. Of the 20 patients who received FOLFOX or FOLFOX plus bevacizumab without RT, 7 (35%) achieved a complete pathologic response. Of the 6 patients with rectal cancer who were treated with preoperative FOLFOX, 2 achieved a complete pathologic response, and an additional 3 experienced a 90% positive treatment effect[61]. In the setting of potentially operable liver metastases, a preliminary report of the EPOC trial (FOLFOX with or without cetuximab for 12 weeks before and 12 weeks after surgery) showed that the addition of cetuximab was associated with a significantly worse PFS (14.8 months vs. 24.2 months) and should be avoided[62].

2.6 Question 6

What is the role of liver-directed therapy in patients with stage IV CRC with unresectable liver-only disease?

Recommendations: The role of liver-directed therapy in patients with stage IV CRC with unresectable liver-only disease is currently not well defined.

Such therapy can be considered in selected patients after discussion in a multidisciplinary team meeting.

Summary of Evidence: Liver metastases develop in approximately 40% of patients with CRC[63]. In patients with liver metastases and limited extrahepatic disease, local control of the liver disease can result in better overall survival[64]. Several liver-directed therapies have been developed to improve disease control. Radiofrequency ablation has been used in liver-limited metastatic disease as an adjunct to surgery or single treatment for a lesion smaller than 3 cm. For smaller lesions, local recurrence rates with radiofrequency ablation are comparable to those with resection of the liver metastases[65]. Image-guided transarterial chemoembolization (TACE) is the procedure most commonly performed for liver tumours. It is also used as salvage therapy for patients with liver metastases from neuroendocrine tumours and chemorefractory CRC. Other treatments such as transarterial chemotherapy infusion, transarterial embolotherapy, and radioembolization with ^{90}Y are less commonly used[63]. More recently, a new method called DEB-TACE has been introduced, in which polymer-based microparticles [drug-eluting beads (DEBS)] replace lipiodol. Compared with conventional TACE, DEB-TACE enhances drug delivery to the tumour and significantly reduces systemic drug exposure.

Limited data suggest that hepatic arterial embolization and TACE can achieve disease stabilization in 40%–60% of treated patients, but the survival benefit relative to systemic chemotherapy alone is uncertain. Several studies suggest that conventional TACE is associated with improved survival in patients with chemorefractory CRC with liver metastases[66,67]; however, most studies lack a control group. Phase II/III trials using DEB-TACE have reported response rates of approximately 70%, with PFS durations of 7–8 months and a mOS of 22–25 months[68–70]. Nonetheless, larger randomized trials are needed to confirm those results before it can be concluded that hepatic artery chemoembolization provides outcomes superior to those with standard intravenous systemic chemotherapy.

3. ACKNOWLEDGMENTS

4. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SA has received speaker fees and fees as an advisory board member for Roche and Amgen; SB has received honoraria from Roche and Amgen; SG has received honoraria from Amgen and Bristol–Myers Squibb; HK has received research funding and honoraria from Roche, Sanofi, and Amgen; HL has received fees as an advisory board member for Roche, Amgen, Bayer, and Sirtex, and his institution receives funding from Roche, Bayer, and Lilly for a trial in which he is co-investigator; and KM has received personal fees and nonfinancial support from Novartis Canada and Lilly Canada outside the submitted work. The remaining authors have no conflicts of interest to disclose.

5. REFERENCES

1. 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;351:337–45.

2. Douillard JY, Siena S, Cassidy J, *et al.* Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697–705.

3. Jonker DJ, O'Callaghan CJ, Karapetis CS, *et al.* Cetuximab for the treatment of colorectal cancer. *N Engl J Med* 2007;357:2040–8.

4. 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;25:1658–64.

5. Van Cutsem E, Köhne CH, Hitre E, *et al.* Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408–17.

6. 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;26:1626–34.

7. 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;359:1757–65.

8. Van Cutsem E, Köhne CH, Láng I, *et al.* Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor *KRAS* and *BRAF* mutation status. *J Clin Oncol* 2011;29:2011–19.

9. Douillard JY, Oliner KS, Siena S, *et al.* Panitumumab–FOLFOX4 treatment and *RAS* mutations in colorectal cancer. *N Engl J Med* 2013;369:1023–34.

10. Stintzing S, Jung A, Rossius L, *et al.* Analysis of *KRAS/NRAS* and *BRAF* mutations in FIRE-3: a randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) *KRAS* (exon 2) metastatic colorectal cancer (mCRC) patients [abstract LBA 17]. *Eur J Cancer* 2013;49(suppl 3):. [Available online at: http://2013.europeancancercongress.org/Scientific-Programme/Abstract-search?abstractid=8953; cited February 28, 2015]

11. Ciardiello F, Lenz HJ, Kohne CH, *et al.* Treatment outcome according to tumor *RAS* mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to

FOLFIRI with/without cetuximab [abstract 3506]. *J Clin Oncol* 2014;32:. [Available online at: http://meetinglibrary.asco.org/content/127862-144; cited February 15, 2015]

12. Schwartzberg LS, Rivera F, Karthaus M, *et al.* PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type *KRAS* exon 2 metastatic colorectal cancer. *J Clin Oncol* 2014;32:2240–7.

13. Heinemann V, von Weikersthal LF, Decker T, *et al.* FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1065–75.

14. Venook A, Niedzwiecki D, Hollis D, *et al.* Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients with untreated metastatic adenocarcinoma of the colon or rectum (mCRC): CALGB 80203 preliminary results [abstract 3509]. *J Clin Oncol* 2006;24:. [Available online at: http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/3509; cited February 15, 2015]

15. Lenz H, Niedzwiecki D, Innocenti F, *et al.* CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded *ras* analyses untreated metastatic adenocarcinoma of the colon or rectum (mCRC) [abstract 501O]. Presented at the 2014 Annual Meeting of the European Society for Medical Oncology; Madrid, Spain; September 26–30, 2014. [Available online at: https://www.webges.com/cslide/library/esmo/browse/itinerary/478/2014-09-29#9faw03oW; cited February 28, 2015]

16. Stintzing S, Modest D, von Weikersthal LF, *et al.* Independent radiological evaluation of objective response rate, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final *RAS* evaluable population [abstract LBA11]. *Ann Oncol* 2014;25:1–41.

17. Salerno G, Sinnatamby C, Branagan G, Daniels IR, Heald RJ, Moran BJ. Defining the rectum: surgically, radiologically and anatomically. *Colorectal Dis* 2006;8(suppl 3):5–9.

18. Schoellhammer HF, Gregorian AC, Sarkisyan GG, Petrie BA. How important is rigid proctosigmoidoscopy in localizing rectal cancer? *Am J Surg* 2008;196:904–8.

19. Bartram C, Brown G. Endorectal ultrasound and magnetic resonance imaging in rectal cancer staging. *Gastroenterol Clin North Am* 2002;31:827–39.

20. Brown G, Richards CJ, Newcombe RG, *et al.* Rectal carcinoma: thin-section MR imaging for staging in 28 patients. *Radiology* 1999;211:215–22.

21. MERCURY Study Group. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. *Radiology* 2007;243:132–9.

22. Al-Sukhni E, Milot L, Fruitman M, *et al.* Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2012;19:2212–23.

23. Wang C, Zhou Z, Wang Z, *et al.* Patterns of neoplastic foci and lymph node micrometastasis within the mesorectum. *Langenbecks Arch Surg* 2005;390:311–18.

24. Winter L, Bruhn H, Langrehr J, Neuhaus P, Felix R, Hänninen LE. Magnetic resonance imaging in suspected rectal cancer: determining tumor localization, stage, and sphincter-saving resectability at 3-Tesla-sustained high resolution. *Acta Radiol* 2007;48:379–87.

25. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;264:1444–50.

26. Adam IJ, Mohamdee MO, Martin IG, *et al.* Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994;344:707–11.

27. Hall NR, Finan PJ, al-Jaberi T, *et al.* Circumferential margin involvement after mesorectal excision of rectal cancer with curative intent. Predictor of survival but not local recurrence? *Dis Colon Rectum* 1998;41:979–83.

28. Kapiteijn E, Marijnen CA, Nagtegaal ID, *et al.* on behalf of the Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638–46.

29. Sebag–Montefiore D, Stephens RJ, Steele R, *et al.* Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomized trial. *Lancet* 2009;373:811–20.

30. Sauer R, Becker H, Hohenberger W, *et al.* on behalf of the German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731–40.

31. Roh MS, Colangelo LH, O'Connell MJ, *et al.* Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol* 2009;27:5124–30.

32. Gerard JP, Conroy T, Bonnetain F, *et al.* Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3–4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006;24:4620–5.

33. Bosset JF, Collette L, Calais G, *et al.* on behalf of the EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;355:1114–23. [Erratum in: *N Engl J Med* 2007;357:728]

34. Birgisson H, Påhlman L, Gunnarsson U, Glimelius B on behalf of the Swedish Rectal Cancer Trial Group. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol* 2005;23:8697–705.

35. Bosset JF, Calais G, Mineur L, *et al.* Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. *J Clin Oncol* 2005;23:5620–7.

36. Bujko K, Nowacki MP, Nasierowska–Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;93:1215–23.

37. Ngan SY, Burmeister B, Fisher RJ, *et al.* Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol* 2012;30:3827–33.

38. McCarthy K, Pearson K, Fulton R, Hewitt J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. *Cochrane Database Syst Rev* 2012;12:CD008368.

39. Taylor FG, Quirke P, Heald RJ, *et al.* on behalf of the MERCURY study group. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multi-center, European study. *Ann Surg* 2011;253:711–19.

40. Gunderson LL, Sargent DJ, Tepper JE, *et al.* Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. *J Clin Oncol* 2004;22:1785–96.

41. Petersen SH, Harling H, Kirkeby LT, Wille–Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012;3:CD004078.

42. Bujko K, Glynne–Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. *Ann Oncol* 2010;21:1743–50.

43. Bosset JF, Calais G, Mineur L, *et al.* on behalf of the EORTC Radiation Oncology Group. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014;15:184–90.

44. Cionini L, Sainato A, De Paoli A, *et al.* Final results of randomized trial on adjuvant chemotherapy after preoperative chemoradiation in rectal cancer. *Radiother Oncol* 2012;96(suppl 1):S113–14.

45. Breugom AJ, van den Broek CBM, van Gijn W. The value of adjuvant chemotherapy in rectal cancer patients after preoperative radiotherapy or chemoradiation followed by TME-surgery: the PROCTOR/SCRIPT study [abstract 1]. *Eur J Cancer* 2013;49(suppl 3):. [Available online at: http://2013.european cancercongress.org/Scientific-Programme/Abstract-search.aspx?abstractid=5779; cited March 7, 2015]

46. Glynne–Jones R, Counsell N, Quirke P, *et al.* CHRONICLE: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014;25:1356–62.

47. Glimelius B, Tiret E, Cervantes A, Arnold D on behalf of the ESMO Guidelines Working Group. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24(suppl 6):vi81–8.

48. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Colon Cancer.* Ver. 3.2011. Fort Washington, PA: NCCN; 2011. [Current version available online at: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (free registration required); cited September 12, 2014]

49. André T, Boni C, Navarro M, *et al.* Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;27:3109–16.

50. Yothers G, O'Connell MJ, Allegra CJ, *et al.* Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011;29:3768–74.

51. Rodel C, Liersch T, Fietkau R, *et al.* Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: results of the German CAO/ARO/AIO-04 randomized phase III trial [abstract 3500]. *J Clin Oncol* 2014;32:. [Available online at: http://meetinglibrary.asco.org/content/133115-144; cited February 16, 2015]

52. Hong YS, Nam BH, Kim K, *et al.* Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 2014;15:1245–53.

53. Schmoll HJ, Haustermans K, Price TJ, *et al.* Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: disease-free survival results at interim analysis [abstract 3501]. *J Clin Oncol* 2014;32:. [Available online at: http://meetinglibrary.asco.org/content/134502-144; cited February 16, 2015]

54. Fahy BN, Fischer CP. Synchronous resection of colorectal primary and hepatic metastasis. *J Gastrointest Oncol* 2012;3:48–58.

55. de Jong MC, van Dam RM, Maas M, *et al.* The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience. *HPB (Oxford)* 2011;13:745–52.

56. Valadão M. Reverse approach: a new paradigm in the treatment of synchronous liver metastasis from colorectal cancer. *Rev Col Bras Cir* 2010;37:314–15.

57. Lykoudis PM, O'Reilly D, Nastos K, Fusai G. Systematic review of surgical management of synchronous colorectal liver metastases. *Br J Surg* 2014;101:605–12.

58. Lam VW, Laurence JM, Pang T, *et al.* A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. *HPB (Oxford)* 2014;16:101–8.

59. Van Dijk TH, Tamas K, Beukema JC, *et al.* Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. *Ann Oncol* 2013;24:1762–9.

60. Nordlinger B, Sorbye H, Glimelius B, *et al.* on behalf of the EORTC Gastro-Intestinal Tract Cancer Group, Cancer Research UK, the ALM-CAO, the Australasian Gastro-Intestinal Trials Group, and the Fédération Francophone de Cancérologie Digestive. 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;371:1007–16.

61. Cercek A, Weiser MR, Goodman KA, *et al.* Complete pathologic response in the primary of rectal or colon cancer treated with FOLFOX without radiation [abstract 3649]. *J Clin Oncol* 2010;28:. [Available online at: http://meetinglibrary.asco.org/content/47789-74; cited February 16, 2015]

62. Primrose JN, Falk S, Finch–Jones M, *et al.* A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in *K-ras* wild-type patients with operable metastases from colorectal cancer: the new EPOC study [abstract 3504]. *J Clin Oncol* 2013;31:. [Available online at: http://meetinglibrary.asco.org/content/112298-132; cited February 16, 2015]

63. Fiorentini G, Aliberti C, Mulazzani L, *et al.* Chemoemboliza-tion in colorectal liver metastases: the rebirth. *Anticancer Res* 2014;34:575–84.

64. Stillwell AP, Ho YH, Veitch C. Systematic review of prognos-tic factors related to overall survival in patients with stage IV colorectal cancer and unresectable metastases. *World J Surg* 2011;35:684–92.

65. Mulier S, Ni Y, Jamart J, Michel L, Marchal G, Ruers T. Radio-frequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? *Ann Surg Oncol* 2008;15:144–57.

66. Albert M, Kiefer M, Sun W, *et al.* Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, Ethiodol, and polyvinyl alcohol. *Cancer* 2011;117:343–52.

67. Vogl TJ, Gruber T, Balzer JO, Eichler K, Hammerstingl R, Zangos S. Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: prospective study. *Radiology* 2009;250:281–9.

68. Aliberti C, Fiorentini G, Muzzio PC, *et al.* Trans-arterial chemoembolization of metastatic colorectal carcinoma to the liver adopting DC Bead, drug-eluting bead loaded with irinotecan: results of a phase II clinical study. *Anticancer Res* 2011;31:4581–7.

69. Martin R, Joshi J, Robbins K, *et al.* Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unre-sectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study. *Ann Surg Oncol* 2010;18:192–8.

70. Fiorentini G, Aliberti C, Tilli M, *et al.* Intra-arterial infu-sion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. *Anticancer Res* 2012;32:1387–95.

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