Palliative resection of a primary tumor in patients with unresectable colorectal cancer: could resection type improve survival?

Hyun Seok Jang, Jae Kyun Ju, Chang Hyun Kim[1], Soo Young Lee[1], Hyeong Rok Kim[1], Young Jin Kim[1]

Department of Surgery, Chonnam University Hospital, Gwangju, [1]Department of Surgery, Chonnam University Hwasun Hospital, Gwangju, Korea

Purpose: The aim of this study was to evaluate the impact of extended resection of primary tumor on survival outcome in unresectable colorectal cancer (UCRC).
Methods: A retrospective analysis was conducted for 190 patients undergoing palliative surgery for UCRC between 1998 and 2007 at a single institution. Variables including demographics, histopathological characteristics of tumors, surgical procedures, and course of the disease were examined.
Results: Kaplan-Meier survival curve indicated a significant increase in survival times in patients undergoing extended resection of the primary tumor (P < 0.001). Multivariate analysis showed that extra-abdominal metastasis (P = 0.03), mini-mal resection of the primary tumor (P = 0.034), and the absence of multimodality adjuvant therapy (P < 0.001) were signi-ficantly associated poor survival outcome. The histological characteristics were significantly associated with survival times. Patients with well to moderate differentiation tumors that were extensively resected had significantly increased survival time (P < 0.001), while those with poor differentiation tumors that were extensively resected did not have increase survival time (P = 0.786).
Conclusion: Extended resection of primary tumors significantly improved overall survival compared to minimal resection, especially in well to moderately differentiated tumors (survival time: extended resection, 27.8 ± 2.80 months; minimal re-section, 16.5 ± 2.19 months; P = 0.002).
[Ann Surg Treat Res 2016;91(4):172-177]

Key Words: Colorectal neoplasms, Palliative care, Colorectal surgery

INTRODUCTION

Approximately one-fifth of colorectal cancer patients are diagnosed with synchronous metastasis, despite the wide-spread screening for early detection of colorectal cancer [1]. Chemotherapy and other palliative modalities are currently proposed as part of palliative care for these patients to manage pain and improve their quality of life. In addition, in the era of systemic treatment, less than 15% of patients require surgical and/or other primary interventions. Therefore, the role of surgical resection of primary tumors is controversial and has been proposed as an aggressive approach for unresectable colorectal cancer (UCRC) [2-7].

Although many retrospective studies have suggested that the surgical resection of a primary tumor has a positive impact on patient survival [2-5], the impact on whether minimal resection or extended resection of primary tumors on overall survival (OS) in patients is not clear [8]. The primary objective of this study was to evaluate the impact of extended resection of primary tumor on survival outcome. For this, we analyzed the results

Corresponding Author: Jae Kyun Ju
Department of Surgery, Chonnam University Hospital, 42 Jebong-ro, Dong-gu, Gwangju 61469, Korea
Tel: +82-62-220-6456, **Fax:** +82-62-227-1635
E-mail: jkju@jnu.ac.kr

of palliative surgery (extended resection or minimal resection) performed at a single institution.

METHODS

A retrospective analysis was performed on patients undergoing palliative resection for primary tumors for UCRC between 1998 and 2007 at the Chonnam National University Hospital. UCRC is when it is impossible to achieve complete and macroscopically curative resection of metastatic lesions because residual tumor tissue was present in the surgical field, the presence of malignant ascites/peritoneal carcinomatosis, and unresectable distant metastases. Patients' demographics, tumor location, adjuvant therapy, pathologic grade, tumor size, metastases pattern, and the extent of resection were all collected from a database.

Over a 10-year period, 206 patients with UCRC underwent surgery including resection, bypass, and exploratory surgery. Exclusion criteria included the following: (1) age >80 years, (2) performance status ≥ 3, (Eastern Cooperative Oncology Group performance status), (3) resection with curative intent, (4) patients who had undergone ostomies and bypass surgery, (5) presence of metachronous/synchronous cancer of other organs, and (6) death due to non-cancer-related factors. After the application of exclusion criteria, 190 patients were enrolled in the present study. Data for patients lost to follow-up were excluded.

Extended resection of a primary tumor was defined as standard lymph node dissection (D2 + D3), *en bloc* multivisceral resection in cases where the primary tumor invaded an adjacent organ, and severe cases included para-aortic lymph node dissection and partial peritonectomy based on the surgeon's decision. Minimal resection was defined as the resection of the involved segment with lymph node dissection less than D2. Treatment modalities were classified into 4 groups according to resection and multimodality adjuvant therapy: Extended resection with or without adjuvant therapy or minimal resection with or without adjuvant therapy. Chemotherapy regimen was limited to 5-fluorouracil (5-FU) with oxaliplatin, 5-FU without oxaliplatin, 5-FU with irinotecan, or 5-FU without irinotecan. In some cases, capecitabine was used. All surgeries were performed using the open method.

For statistical analysis, the chi-square test and Fisher exact test were used for categorized variables and the Student t-test was used for continuous variables. Survival curves were evaluated by the Kaplan-Meier method compared to the generalized Breslow Wilcoxon test. Cox regression model was used for multivariate analysis. The difference was considered statistically significant for P-value < 0.05.

RESULTS

One hundred seventy-four patients underwent minimal or extended resection of the primary tumor, whereas 16 patients underwent bypass or exploration. One hundred ten patients underwent minimal resection of the primary tumor, and 64 patients underwent extended resection. The most common location of the primary tumor was the rectum (minimal resection, 65 cases; extended resection, 27 cases). The majority of patients had hepatic metastasis (minimal resection, 44 cases; extended resection, 39 cases). and/or peritoneal carcinomatosis (minimal resection, 55 cases; extended resection, 19 cases)and 17 patients had extra-abdominal metastasis: lung in 15, bone in 1, and brain in 1. Twenty-two patients had multiple distant metastases. Tumor size, tumor location, nodal status, and meta-

Table 1. Patients' characteristics according to the extent of surgical resection

Variable	Minimal resection (n = 110)	Extended resection (n = 64)	P-value
Age (yr)			0.344
<65	81 (73.6)	42 (65.6)	
≥65	29 (26.4)	22 (34.4)	
Sex			0.454
Male	61 (55.5)	40 (62.5)	
Female	49 (44.5)	24 (37.5)	
Tumor size (cm)			0.029
<10	91 (82.7)	61 (95.3)	
≥10	19 (17.3)	3 (4.7)	
Tumor location			0.046
Colon	45 (40.9)	37 (57.8)	
Rectum	65 (59.1)	27 (42.2)	
Histologic differentiation			0.063
WD	24 (21.8)	17 (26.6)	
MD	51 (46.4)	37 (57.8)	
PD	35 (31.8)	10 (15.6)	
Nodal status			0.033
Positive	63 (93.8)	59 (92.2)	
Negative	18 (6.2)	5 (7.8)	
Cannot checked	29 (23.6)	0 (0)	
Metastasis			0.021
Hepatic metastasis	44 (40.0)	39 (61.0)	
Peritoneal metastasis	55 (50.0)	19 (29.7)	
Other metastasis	11 (10.0)	6 (9.3)	
Symptom at diagnosis			0.913
No	21 (19.1)	11 (17.2)	
Yes	89 (80.9)	53 (82.8)	
Postoperative morbidity			0.690
No	98 (89.1)	59 (92.2)	
Yes	12 (10.9)	5 (7.8)	

Values are presented as number (%).
WD, well differentiation; MD, moderate differentiation; PD, poor differentiation.

stasis were significantly different between both groups (Table 1).

Symptoms at diagnosis

Thirty-two patients (16.8%), at the time of diagnosis, did not have any symptoms related to problems of the gastrointestinal tract. The 2 most common symptoms were abdominal pain and change in bowel movement.

Postoperative morbidity

Postoperative complications occurred in 17 patients (9%). Of the 2 patients who developed postoperative sepsis, 1 died due to acute myocardial infarction. (postoperative mortality: n = 1, 0.7%). The difference in the mean survival times of patients with and without postoperative complications was 16.5 and 15.5 months, respectively, which was not significantly different. Complications occurred in 4 of 19 patients (21.1%) who had undergone emergency surgery, compared to (number, %, and total in non-ER surgeries) and the difference was not statistically significant (P = 0.249). Patients who underwent stoma formation (n = 37, 24.7%) such as Hartmann procedure had a significantly higher complication rate when compared to 9 patients (n = 9, 24.3%) who underwent primary anastomosis

Survival

In total, 174 patients underwent follow-up for a median 17.5 months. Extended resection was identified as a significant predictive factor. Mean survival times of the extended resection group and the minimal resection group were 27.8 months and 16.5 months, respectively (P = 0.002). Fig. 1 shows survival times according to surgical extent including adjuvant chemotherapy. As shown, adjuvant chemotherapy could not improve OS. We also examined the prognostic significance of other clinic-pathologic factors (Table 2). The 5-year OS correlated with age, tumor size, tumor differentiation, lymph node status (Table 2). Significant factors in the univariate analysis were included in the multivariate analysis and are shown in Table 3. Extended resection (P < 0.001), age (P = 0.008), tumor size (P = 0.036), and poor tumor differentiation (P < 0.001) remained significant prognostic factors in the multivariate analysis. In the subgroup analysis, 110 patients (73.3%) had well or moderately differentiated tumors. In this group, multivariate analysis showed that extended resection of primary tumors was the single most important factor associated with significantly improved survival outcomes (hazard ratio, 2.80; 95% confidence interval, 1.862–4.273; P < 0.001).
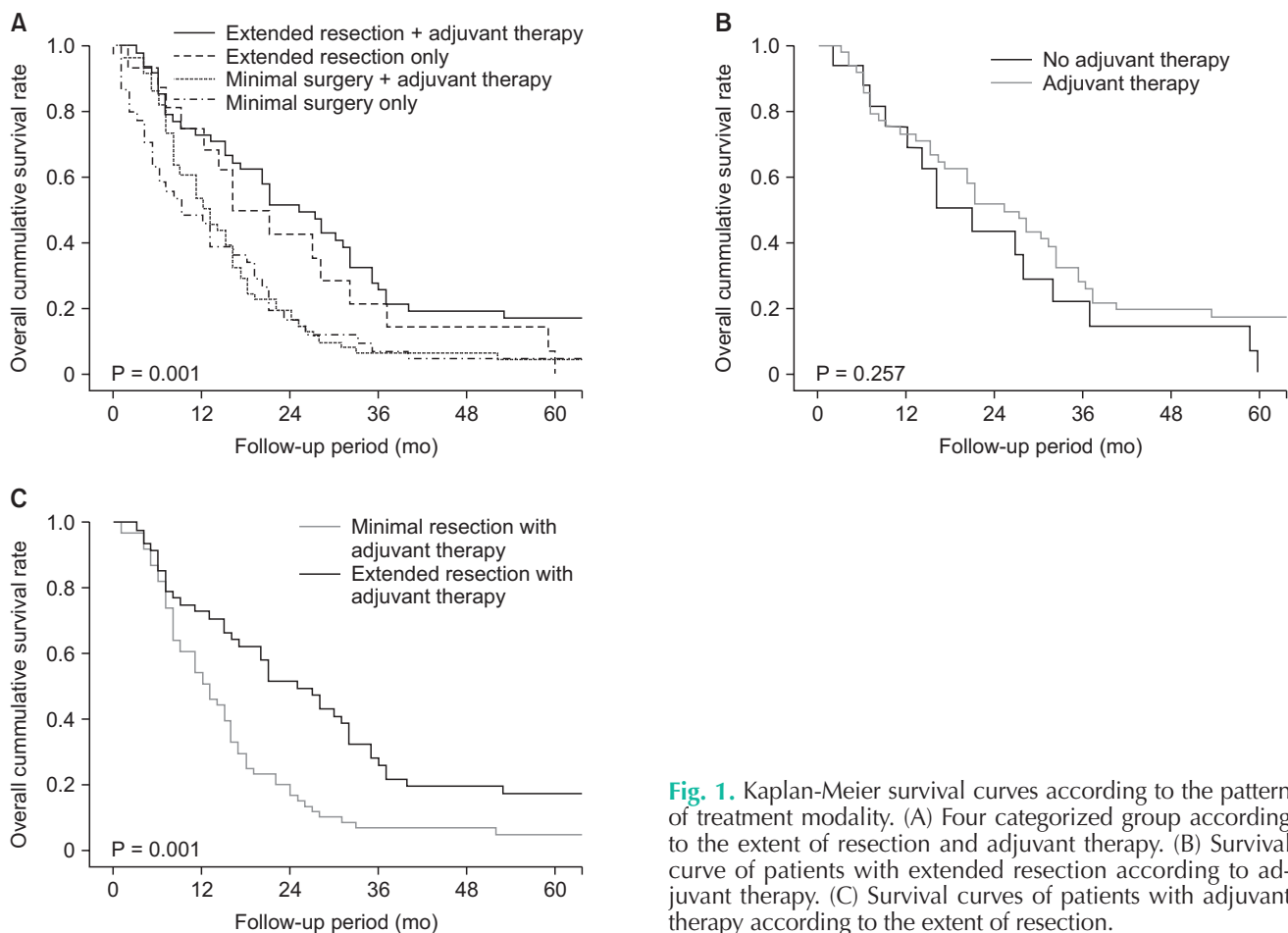

Fig. 1. Kaplan-Meier survival curves according to the pattern of treatment modality. (A) Four categorized group according to the extent of resection and adjuvant therapy. (B) Survival curve of patients with extended resection according to adjuvant therapy. (C) Survival curves of patients with adjuvant therapy according to the extent of resection.

Table 2. Univariate analysis of factor which was associated with survival in palliative resection group

Variable	No. of patients (n = 174)	Survival time (mo), mean ± SD	P-value
Age (yr)			0.036
<65	123	22.8 ± 2.25	
≥65	51	15.6 ± 2.54	
Sex			0.602
Male	101	19.87 ± 2.30	
Female	73	21.8 ± 2.77	
Tumor size (cm)			0.035
<10	152	21.9 ± 1.93	
≥10	22	12.4 ± 3.84	
Tumor location			0.215
Right sided colon	40	24.9 ± 4.84	
Left sided colon	42	15.9 ± 2.35	
Rectum	92	20.9 ± 2.35	
Tumor growth pattern			0.353
Ulcerofungating	83	22.4 ± 2.71	
Ulceroinfiltrative	91	19.1 ± 2.30	
Differentiation			0.001
Well to moderate	129	24.2 ± 2.25	
Poorly	45	10.5 ± 1.41	
Node status			0.003
Negative	23	35.2 ± 7.68	
Positive	122	19.5 ± 1.86	
Cannot checked	29	13.9 ± 2.81	
Hepatic metastasis			0.456
(−)	91	21.9 ± 2.57	
(+)	83	19.3 ± 2.41	
Peritoneal dissemination			0.885
(−)	100	20.4 ± 2.23	
(+)	74	20.9 ± 2.88	
Other metastasis			0.507
(−)	157	20.9 ± 1.87	
(+)	17	16.3 ± 4.32	
Resection extent			0.002
Minimal resectoin	110	16.5 ± 2.19	
Extended resection	64	27.8 ± 2.80	
Adjuvant therapy			0.129
Yes	111	22.7 ± 2.26	
No	63	17.1 ± 2.26	

SD, standard deviation.

Table 3. Multivariate analysis of factor which was associated with survival in palliative resection group (n = 174)

Variable	Odds ratio	95% CI	P-value
Age (yr), <65 vs. ≥65	1.616	1.135–2.300	0.008
Tumor size (cm), <10 vs. ≥10	1.71	1.035–2.825	0.036
Pathologic grade, W, M vs. P	2.005	1.374–2.924	<0.001
Resection extent, ≥D2 vs. <D2	1.937	1.368–2.739	<0.001

CI, confidence interval; W, well; M, moderate; P, poor.

in patients with poorly differentiated tumors.

The benefits of palliative resection of primary tumors in patients with stage IV UCRC is controversial [9-11]. However, many reports have suggested the positive prognostic impact of primary tumor resection in UCRC [2,12].

In a multicenter retrospective study by Karoui et al. [13], primary tumor resection followed by chemotherapy improved OS. For patients with well differentiated colon cancer with metastasis to the liver, resection of the primary tumor followed by chemotherapy in association with target therapy may be the best therapeutic option.

Moreover, in a propensity score analysis in a multicenter retrospective study by Ishihara et al. [14], patients treated with primary tumor resection had significantly better OS than those who did not undergo tumor resection. Furthermore, among patients treated with primary tumor resection, patients treated with D3 lymph node dissection showed significantly better OS than those with less extensive lymph node dissection. In an agreement with this study, our study also indicates that extended resection of primary tumors is defined as standard lymph node dissection including D2 + D3, and has similar results with those of this study.

Extended resection of the primary tumor can prevent locoregional complications. Furthermore, as primary tumors and remaining regional lymph nodes can be sources of immunosuppressive cytokines, such as transforming growth factor beta, granulocyte-macrophage colony-stimulating factor, and prostaglandin E2 [15], extended primary tumor resection can dampen the immunosuppressive microenvironment. These remaining lymph nodes have immune cells and stromal cells that express various molecules to prolong cancer cell survival, and recent reports suggest that CD8+ T cells kill myeloid cells in lymph nodes to prevent colonization of tumor cells [16]. Therefore, remaining lymph nodes have important roles in tumor progression.

In contrast to these studies, however, some recent studies have emphasized the nonoperative management of UCRC. A single center retrospective analysis and a nonrandomized study by Bajwa et al. [17] showed that surgical resection and response of the primary tumor to chemotherapy may be associated with

DISCUSSION

This study revealed that extended resection of primary tumors significantly improved OS compared to minimal resection, especially in well or moderately differentiated tumors (survival time: extended resection 27.8 ± 2.80 months; minimal resection 16.5 ± 2.19 months, P = 0.002). In addition, improved survival outcomes were associated with the extent of resection whether they received adjuvant chemotherapy. However, the survival benefit was not significantly associated with resection

improved survival, but proximal or multiple cancers predict poor outcomes in patients with asymptomatic CRC and unresectable metastatic disease. Further, a study by Kleespies et al. [18] showed that palliative resection is associated with a particularly unfavorable outcome in rectal cancer patients presenting with a locally advanced tumors.

In our study, regardless of extended resection, survival improvement was not shown in the poorly differentiated tumor group. Similar to our study, several studies revealed that people with well to moderately differentiated tumors have significantly better survival than those with poorly differentiated tumors in UCRC [19-21].

In addition to the oncologic outcome mentioned above, postoperative morbidity and mortality are risks that should be considered [14]. Galizia et al. [22] reported that the risks of postoperative morbidity and mortality in patients with metastatic UCRC who have undergone surgery are 20%–30% and 1%–6%, respectively. In our study, the morbidity rate was 12.1% (17 patients). The mean survival of patients with postoperative complication was 16.5 months, not significantly different compared with 15.5 months of patients without complications. The postoperative morbidity rate measured in the present analysis was similar to those reported previous studies.

There are several limitations associated with this study. First, this study has selection bias due to the retrospective nature of the analysis. In addition, extended primary tumor resection may be preferentially performed in patients with less advanced disease, so this could be factor for better prognosis. Further-more, the decision to surgically resect primary colorectal lesions in UCRC remains difficult, particularly for patients without symptoms related to primary lesions, such as bowel obstruction, perforation, and bleeding [12,23]. In our study, 44 patients (29.3%) underwent resection of a primary tumor due to gastrointestinal tract symptoms. As a result, specific indications for extended resection could not be concluded owing to the retrospective nature of our study.

In summary, we analyzed 174 patients who were diagnosed with UCRC within a 10-year period. Our study demonstrates that UCRC patients who underwent extended resection followed by adjuvant chemotherapy had significantly improved survival times compared to those who had minimal resection with/without adjuvant chemotherapy, or only extended resection. These results suggest that extended resection can improve survival of patients with UCRC. Further prospective randomized studies are needed to draw any conclusions.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

REFERENCES

1. Mella J, Biffin A, Radcliffe AG, Stamatakis JD, Steele RJ. Population-based audit of colorectal cancer management in two UK health regions. Colorectal Cancer Working Group, Royal College of Surgeons of England Clinical Epidemiology and Audit Unit. Br J Surg 1997;84:1731-6.

2. Ruo L, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD. Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients. J Am Coll Surg 2003; 196:722-8.

3. Sarela AI, Guthrie JA, Seymour MT, Ride E, Guillou PJ, O'Riordain DS. Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer. Br J Surg 2001;88:1352-6.

4. Carne PW, Frye JN, Robertson GM, Frizelle FA. Stents or open operation for palliation of colorectal cancer: a retrospective, cohort study of perioperative outcome and long-term survival. Dis Colon Rectum 2004;47:1455-61.

5. Benoist S, Pautrat K, Mitry E, Rougier P, Penna C, Nordlinger B. Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases. Br J Surg 2005;92:1155-60.

6. Law WL, Chan WF, Lee YM, Chu KW. Non-curative surgery for colorectal cancer: critical appraisal of outcomes. Int J Colorectal Dis 2004;19:197-202.

7. Nash GM, Saltz LB, Kemeny NE, Minsky B, Sharma S, Schwartz GK, et al. Radical resection of rectal cancer primary tumor provides effective local therapy in patients with stage IV disease. Ann Surg Oncol 2002;9:954-60.

8. Costi R, Mazzeo A, Di Mauro D, Veronesi L, Sansebastiano G, Violi V, et al. Palliative resection of colorectal cancer: does it prolong survival? Ann Surg Oncol 2007; 14:2567-76.

9. Cummins ER, Vick KD, Poole GV. Incurable colorectal carcinoma: the role of surgical palliation. Am Surg 2004;70:433-7.

10. Poultsides GA, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving

combination chemotherapy without surgery as initial treatment. J Clin Oncol 2009;27:3379-84.

11. Tebbutt NC, Norman AR, Cunningham D, Hill ME, Tait D, Oates J, et al. Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. Gut 2003;52:568-73.

12. Verhoef C, de Wilt JH, Burger JW, Verheul HM, Koopman M. Surgery of the primary in stage IV colorectal cancer with unresectable metastases. Eur J Cancer 2011;47 Suppl 3:S61-6.

13. Karoui M, Roudot-Thoraval F, Mesli F, Mitry E, Aparicio T, Des Guetz G, et al. Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study. Dis Colon Rectum 2011;54:930-8.

14. Ishihara S, Hayama T, Yamada H, Nozawa K, Matsuda K, Miyata H, et al. Prognostic impact of primary tumor resection and lymph node dissection in stage IV colorectal cancer with unresectable metastasis: a propensity score analysis

in a multicenter retrospective study. Ann Surg Oncol 2014;21:2949-55.

15. Ogawa F, Amano H, Eshima K, Ito Y, Matsui Y, Hosono K, et al. Prostanoid induces premetastatic niche in regional lymph nodes. J Clin Invest 2014;124:4882-94.

16. Pereira ER, Jones D, Jung K, Padera TP. The lymph node microenvironment and its role in the progression of metastatic cancer. Semin Cell Dev Biol 2015;38:98-105

17. Bajwa A, Blunt N, Vyas S, Suliman I, Bridgewater J, Hochhauser D, et al. Primary tumour resection and survival in the palliative management of metastatic colorectal cancer. Eur J Surg Oncol 2009;35:164-7.

18. Kleespies A, Fuessl KE, Seeliger H, Eichhorn ME, Muller MH, Rentsch M, et al. Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer. Int J Colorectal Dis 2009;24:1097-109.

19. Harris GJ, Senagore AJ, Lavery IC, Church JM, Fazio VW. Factors affecting survival

after palliative resection of colorectal carcinoma. Colorectal Dis 2002;4:31-5.

20. Chafai N, Chan CL, Bokey EL, Dent OF, Sinclair G, Chapuis PH. What factors influence survival in patients with unresected synchronous liver metastases after resection of colorectal cancer? Colorectal Dis 2005;7:176-81.

21. Yun HR, Lee WY, Lee WS, Cho YB, Yun SH, Chun HK. The prognostic factors of stage IV colorectal cancer and assessment of proper treatment according to the patient's status. Int J Colorectal Dis 2007;22:1301-10.

22. Galizia G, Lieto E, Orditura M, Castellano P, Imperatore V, Pinto M, et al. First-line chemotherapy vs bowel tumor resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases. Arch Surg 2008;143:352-8.

23. Stelzner S, Hellmich G, Koch R, Ludwig K. Factors predicting survival in stage IV colorectal carcinoma patients after palliative treatment: a multivariate analysis. J Surg Oncol 2005;89:211-7.