ORIGINAL ARTICLE

Intensive Risk-Adjusted Follow-up With the CEA, TPA, CA19.9, and CA72.4 Tumor Marker Panel and Abdominal Ultrasonography to Diagnose Operable Colorectal Cancer Recurrences

Effect on Survival

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Hypothesis: Intensive risk-adjusted follow-up leads to improved resectability of tumor recurrences and better overall survival among patients who have undergone surgery for colorectal cancer.

Design: Long-term observational single-center study.

Setting: University of Pisa, Pisa, Italy.

Patients: One hundred eight disease-free patients who had undergone surgery for colorectal cancer were submitted to long-term follow-up with the serum CEA, TPA, CA19.9, and CA72.4 tumor marker (TM) panel and abdominal ultrasonography.

Main Outcome Measures: Sensitivities and specificities of TMs, abdominal ultrasonography, and abdominal and chest computed tomography (CT); the median survival among patients operated on and those not operated on and the cumulative 5-year overall survival among the entire group.

Results: Twenty-two patients with asymptomatic colorectal cancer recurred 32 times. The CEA, TPA, CA19.9, CA72.4, and TM panel sensitivities were 46.9%, 34.4%, 9.4%, 9.4%, and 81.0%, respectively, and the mean (SD) lead times before confirmation of recurrence were 4.3 (4.8), 4.1 (4.7), 8.3 (10.9), 5.0 (7.0), and 5.3 (5.8) months, respectively. Abdominal and chest CT sensitivities were 100.0%. Among 86 patients without recurrence, specificities of the TM panel and all panel markers were 100.0%, while specificities of abdominal ultrasonography, abdominal CT, and skeletal CT were 99.9%, 99.0%, and 100.0%, respectively. The median survival after first recurrence was 16 months (range, 3-48 months) for 8 patients with recurrence who did not undergo second-line surgery. Among 14 remaining patients who underwent metastasectomy, the median survival after first recurrence was 37 months (range, 12-187 months; $P=.03$). Among the entire group of 108 patients, the cumulative 5-year overall survival was 88.7%.

Conclusions: Long-term intensive risk-adjusted monitoring using the CEA, TPA, CA19.9, and CA72.4 TM panel and abdominal ultrasonography allows early detection of most recurrences. Patients can then undergo radical metastasectomy, with potentially improved overall survival.

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COLORECTAL CANCER (CRC) is the second most common cause of cancer-related deaths in Western countries.[1] After curative resection, adjuvant chemotherapy improves the prognosis among patients with CRC, but more than one-third of them experience recurrence,[2,3] with a median survival of no longer than 2 years.[4] The preferred treatment for patients with recurrent disease is resection of liver or lung metastases, with a 5-year survival rate of 20% to 57%.[5-9]

The aim of postoperative follow-up is early diagnosis of recurrent disease, when radical surgical treatment is possible.[2,10,11] Two meta-analyses[12,13] that pooled results from 5 randomized studies found a survival advantage for patients allocated to intensive follow-up. However, no standardized protocol or consensus exists.[14-17] Carcinoembryonic antigen (CEA) is the most frequent indicator of asymptomatic recurrences,[18-20] and American Society of Clinical Oncology 2006 guidelines[17] recommend postoperative serum CEA testing in patients with stage II or III CRC for at least 3 years. If confirmed by retesting, an elevated CEA level warrants further evaluation for metastatic disease. In most intensive fol-

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low-up studies conducted in the last decades, serum CEA testing and (in some of them) abdominal ultrasonography (US) were serially and differently performed up to 5 years after primary surgery.[4,19,21-25]

For many years, we have been performing an intensive risk-adjusted follow-up focused on the use of serum tumor markers (TMs) and abdominal US to detect early recurrent disease.

METHODS

PATIENTS

Between January 1, 1993, and June 30, 2008, a total of 108 patients, aged 37 to 83 years (mean age, 60 years), with CRC (69 colon and 39 rectal), underwent intensive risk-adjusted postoperative follow-up. Dukes stages (modified by Astler and Coller[26]) were A in 14 patients, B1 in 15 patients, B2 in 41 patients, C1 in 6 patients, and C2 in 32 patients. All patients underwent baseline chest radiograph (CXR), abdominal US, abdominal computed tomography (CT), and serum CEA, tissue polypeptide antigen (TPA), cancer antigen 19.9 (CA19.9), and CA72.4 testing; bone scintigraphy (BS) was performed in 57 patients with Dukes stages B2, C1, and C2.

FOLLOW-UP PERIOD

All patients were followed up for at least 12 months (mean [SD], 99 [57] months; range, 13-179 months). Control visits were regularly scheduled every 4 months for patients with Dukes stages B2, C1, and C2 and every 6 months for patients with Dukes stages A and B1. At each control visit, an accurate history was obtained, along with a clinical examination, routine blood testing, and a CEA, TPA, CA19.9, and CA72.4 TM panel. Abdominal US was regularly performed every 8 months, with colonoscopy performed every 6 months during 2 years following surgery and thereafter every 12 months. Abdominal CT was performed at 2 and 5 years after surgery. In 14 patients, whole-body positron emission tomography (positron emission tomography with fluorodeoxyglucose F 18 [FDG-PET]) was performed basally or during the follow-up period for more accurate and complete restaging.

Serum CEA, TPA, CA19.9, and CA72.4 were measured in fasting patients by chemiluminescent microparticle immunoassay (Abbott, Rome, Italy) for CEA and CA19.9, by immunoenzymatic assay (DRG, Marburg, Germany) for TPA, and by electrochemiluminescent immunoassay (Roche Diagnostics, Milan, Italy) for CA72.4. The within-assay and between-assay coefficients of variation for CEA, TPA, CA19.9, and CA72.4, respectively, were less than 4.0%, less than 5.0%, less than 5.0%, and less than 3.5%, while the cutoff values were 3 ng/mL, 95 IU/L, 40 U/mL, and 6.9 U/mL (to convert CEA level to micrograms per liter, multiply by 1.0; TPA to international units per liter, multiply by 1000; and cancer antigen level to kilounits per liter, multiply by 1.0). In the case of a high value in 1 or more markers, another blood sample was drawn 2 weeks to 1 month after the previous elevated value. If the remeasured TM level had decreased to a normal value, the initial elevated level was considered an isolated elevated value. A TM increase was considered progressive when it was 30.0% or higher in the sample that followed the initial elevated value. Otherwise, 2 high values were regarded as a constant elevation (CE).[27-30] Concomitant benign pathologic findings were identified considering the patient history recorded at baseline and that at any successive visit.

SUSPECTED PATIENTS AND CONFIRMATION OF RECURRENCE

In previous follow-up studies[27,28,31] of patients with cancer, isolated elevated TM levels had no value in predicting metastases. Therefore, patients with CE or progression in 1 or more markers of the CEA, TPA, CA19.9, and CA72.4 panel that was unexplained by concomitant benign pathologic findings were suspected of having tumor recurrence.[27,29,30,32] Moreover, in any patient with concomitant benign pathologic findings possibly explaining a significant (CE or progression) TM increase, TM monitoring was intensified, and an additional 2 to 3 blood samples were obtained every 1 to 2 weeks. Despite concomitant benign pathologic findings, patients with rising TM levels were suspected of having recurrence, unlike those with a fluctuating TM pattern. In the latter situation, no further increase or decrease even to normal values was observed. In addition to the CEA, TPA, CA19.9, and CA72.4 TM panel, a patient's history, physical examination, and abdominal US results were used to diagnose a suspected recurrence, while a CXR was obtained for initial thoracic evaluation. Computed tomography or magnetic resonance imaging was used to confirm a suspected recurrence. If necessary, cytohistologic findings were also obtained.

STATISTICAL ANALYSIS

Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were defined as usual. Survival was evaluated by Kaplan-Meyer analysis, and 5-year cumulative overall survival (OS) was assessed among the entire group of 108 patients. Moreover, comparison of survival curves between patients operated on and those not operated on was performed using the log-rank (Mantel-Cox) test. The level of significance was $P < .05$.

RESULTS

PATIENTS WITHOUT RECURRENCE

Tumor Markers

Among 86 patients without CRC recurrence, the mean (SD) follow-up was 99 (57) months (range, 13-179 months), and the total number of CEA, TPA, CA19.9, CA72.4, and TM panel determinations was 1662. The most common type of increase was CE for all TMs except CA72.4, which had isolated elevated values. The proportion of patients with 1 or more CEs or progression during the follow-up period for CEA, CA19.9, and CA72.4, ranged from 5.8% to 13.9%, while 56.9% of patients had 1 or more CEs or progression for TPA. When TMs were considered as a panel, the most common type of increase was CE. Constant elevation or progression occurred in 1 or more TM panels among 60 patients (69.8%). All CEs or progressions for most TMs were clearly explained by concomitant benign pathologic findings or for CEA by a smoking history and fluctuating serum TM pattern; therefore, specificities of the TM panel and all panel markers were 100.0%. Significant increases in TPA were likely due to acute inflammation and transient liver failure in 10.5% of patients and due to diabetes mellitus or hepatosteatosis in 51.2% of patients. A smoking history was present in 5.8% of patients with a significant CEA increase. Existing illnesses likely ex-

Table 1. Initial Suspicion and Confirmation of 32 Colorectal Cancer Recurrences Among 22 Asymptomatic Patients[a]

Recurrences			First Suspicion of Recurrence						
No. of Patients	Site	No. of Recurrences	sTMi	sTMi and Abdominal US	sTMi and Whole-Body PET	Abdominal US	CXR	Abdominal CT	Whole-Body PET
15	Liver	**20**	13	3	. . .	3	. . .	1	. . .
4	Lung	**8**	6	. . .	1	. . .	1	. . .	
3	Locoregional	**4**	3	. . .	. . .	. . .	. . .	. . .	1

Recurrences			Diagnosis of Recurrence		False-Negative Examination Result at Diagnosis				
No. of Patients	Site	No. of Recurrences	CT	CT Plus Cytohistologic Findings	sTMi	Abdominal US	CXR	CT	Whole-Body PET
15	Liver	**20**	9	11	2	6	. . .	0	0
4	Lung	**8**	5	3	0	. . .	2	0	1
3	Locoregional	**4**	1	3	0	. . .	. . .	0	0

Abbreviations: CT, computed tomography; CXR, chest radiograph; ellipses, not applicable; PET, positron emission tomography; sTMi, significant tumor marker panel increase; US, ultrasonography.

[a] Patients with more relapses were counted once, referring to the site of the first relapse.

plained significant increases in CEA and TPA (for patients with chronic obstructive bronchopneumopathy) and in TPA and CA19.9 (for patients with hypertension) in 2.3% to 9.3% of patients. Concomitant chronic liver failure was another likely cause of CE or progression in all panel markers except CEA.

Procedural Examinations

The numbers of BS, abdominal US, FDG-PET, CXR, and CT procedures performed at baseline (BS) and during the follow-up period (US, FDG-PET, CXR, and CT) were 57, 745, 10, 86, and 118 (111 abdominal CT and 7 bone CT), respectively. One patient was falsely suspected of having liver metastases on abdominal US. This patient had equivocal results of abdominal CT "aimed" at the liver. Subsequent follow-up (53 months) excluded the presence of metastases; therefore, abdominal US and skeletal CT specificities were 99.9% and 99.0%, respectively. In 7 patients, baseline BS findings were equivocal, resulting in a specificity of 88.0%. Skeletal CT aimed at suspected bone areas showed no abnormal findings in all cases, demonstrating 100.0% specificity. In 8 patients falsely suspected of having recurrence on abdominal US (1 patient) and BS (7 patients), all panel markers remained in the normal range except for 1 patient in whom there were 4 consecutive CEs. These were likely caused by concomitant chronic liver failure and had a fluctuating pattern. For CXR and FDG-PET, no false-positive results were found.

PATIENTS WITH RECURRENCE

Initial Pathologic Finding and Confirmation of Recurrence

At the time of study analysis, 22 patients (20.4%) had experienced recurrence. Among these patients, there were 32 recurrences (20 liver, 8 lung, and 4 locoregional). Dukes stages at the time of primary surgery were as follows: B1 in 1 patient, B2 in 7 patients, C1 in 1 patient, and C2 in 13 patients. **Table 1** gives the initial pathologic findings among 32 recurrences. In 20 liver metastases, a significant TM panel increase alone (13 recurrences) or with abdominal US (3 recurrences) or abdominal US without TM panel increase (3 recurrences), or abdominal CT (1 recurrence) was the initial pathologic finding. Recurrences were confirmed by CT (9 recurrences) and by CT plus cytohistologic findings (11 recurrences). In 8 lung metastases, a significant TM panel increase alone (6 recurrences) or with FDG-PET (1 recurrence) or CXR (1 recurrence) was the initial pathologic finding. Recurrences were confirmed by CT (5 recurrences) and by CT plus cytohistologic findings (3 recurrences). In 4 locoregional metastases, a significant TM panel increase (3 recurrences) or FDG-PET results (1 recurrence) were the initial pathologic finding. Recurrences were confirmed by CT (1 recurrence) and by CT plus cytohistologic findings (3 recurrences). A significant CEA increase alone (n=12) or with other markers (n=3) was the initial pathologic finding in 9 liver recurrences, in 4 lung recurrences (1 concomitant with PET results), and in 2 locoregional recurrences. A significant TPA increase alone (n=8) or with other markers (n=3) was the initial pathologic finding in 7 liver recurrences (2 concomitant with abdominal US results), in 2 lung recurrences, and in 2 locoregional recurrences. A significant CA19.9 increase alone (n=2) or with other markers (n=1) was the initial pathologic finding in 2 liver recurrences and in 1 lung metastasis. A significant CA72.4 increase alone (n=1) or with other markers (n=2) was the initial pathologic finding in 1 liver metastasis and in 2 locoregional recurrences. Therefore, early recurrences were detected by CEA (15 recurrences), TPA (11 recurrences), CA19.9 (3 recurrences), and CA72.4 (3 recurrences) levels, demonstrating sensitivities of 46.9%, 34.4%, 9.4%, and 9.4%, respectively; the mean (SD) lead times before confirmation of recurrence were 4.3 (4.8), 4.1 (4.7), 8.3 (10.9), and 5.0 (7.0) months, respectively. A CEA and TPA association was the initial patho-

Table 2. Specificities and Sensitivities of the CEA, TPA, CA19.9, and CA72.4 Tumor Marker Panel and Abdominal Ultrasonography in Early Detection of Colorectal Cancer Recurrences

Variable	No./Total No.[a]				Percent				
	True Positive	True Negative	False Positive	False Negative	Specificity	Sensitivity	Positive Predictor Value	Negative Predictive Value	Accuracy
Significant tumor marker panel increase	**26/32**	**1662/1662**	**0/1662**	**6/32**	100.0	81.3	100.0	99.6	99.6
Abdominal ultrasonography	14/20	744/745	1/745	6/20	99.9	70.0	93.3	99.2	99.1

[a] Analyses were performed based on the numbers of recurrences and patients (32 recurrences in 22 asymptomatic patients), the number of liver recurrences (n=20), the number of tumor marker panel determinations (n=1662) and the number of abdominal ultrasonography procedures (n=745) in the patients who have remained disease-free during the follow-up.

Table 3. Number and Site of Recurrences and Survival Among 14 Patients Who Underwent Metastasectomy for Colorectal Cancer Recurrences

Recurrences, No.	Patients, No.	Site								Total Recurrences		Overall Survival, Median (Range), mo	Patients Surviving	
		Liver		Lung		Locoregional		Total						
		No.	OO	No.	OO	No.	OO	No.	OO	No.	OO		Total No.	Disease-Free, No.
First Recurrence														
1	6	3	3	1	1	2	2	**14**	**14**	**24**	**17**	**25 (10-187)**	**5**	**3**
2	6	5	5	1	1	...	...					**27 (14-82)**	**1**	**0**
3	2	2	2	...	...	...	...					**53 (37-69)**	**0**	**0**
Second Recurrence														
1	6	...	...	...	...	...	...	**8**	**3**					
2	6	3	1	2	...	1	...							
3	2	1	1	1	1	...	...							
Third Recurrence														
1	6	...	...	...	...	...	...	**2**	**0**					
2	6	...	...	...	...	...	...							
3	2	1	...	1	...	...	...							

Abbreviations: Ellipses, not applicable; OO, operated on.

logic finding in 23 of 32 recurrences, a 71.9% sensitivity, and the mean (SD) lead time was 4.4 (4.8) months. A CEA, TPA, and CA19.9 association was the initial pathologic finding in 25 of 32 recurrences, a 78.1% sensitivity, and the mean (SD) lead time was 5.0 (5.7) months. When the CEA, TPA, CA19.9, and CA74.4 TM panel was taken into account, a significant increase in 1 or more markers alone (22 recurrences) or with abdominal US (3 recurrences) or FDG-PET (1 recurrence) was the initial pathologic finding in 26 recurrences, demonstrating 81.0% sensitivity; the mean (SD) lead time was 5.3 (5.8) months (range, 0-21 months). In 6 of 26 recurrences with concomitant benign pathologic findings, rising serum TM levels occurred. In 4 of 6 recurrences with a TM panel in the normal range at the initial suspicion of recurrence, a significant increase in and rising serum TM levels occurred when metastases were confirmed. Therefore, at confirmation of recurrence, sensitivity of the TM panel was 94.0%.

Procedural Examinations

Procedural examinations performed were abdominal US (20 procedures), CXR (8 procedures), FDG-PET (4 procedures), and CT (32 procedures [24 abdominal and 8 chest]). Results of abdominal US were pathologic in 14 of 20 liver metastases. The specificity and sensitivity for early diagnosis of recurrence are given in **Table 2** for the TM panel and for abdominal US.

The CXR radiographs were abnormal in 6 of 8 patients with lung metastases. Four patients with recurrences underwent FDG-PET, resulting in false-negative findings in 1 of them. Therefore, sensitivities at confirmation of diagnosis were 70.0%, 75.0%, and 75.0% for abdominal US, CXR, and FDG-PET, respectively. Abdominal and chest CT images were true positive in all patients having recurrences, a 100.0% sensitivity. Overall, the diagnostic accuracy of abdominal CT was 99.3%.

Clinical Outcome

The mean (SD) disease-free interval after primary surgery was 22.9 (22.7) months (range, 0-105 months) in 22 patients with recurrence, and 15 of them died. Fourteen of 22 patients (63.6%) with recurrence underwent metastasectomy. **Table 3** gives the number and site of recurrences in these patients who were operated on. Six patients had 1 recurrence, 6 patients had 2 recurrences, and 2 patients had 3 recurrences. Therefore, there were 24 recurrences in these 14 patients who were operated on. Thirteen patients underwent adjuvant chemotherapy, and 17 recurrences were "radically" removed by surgery. The mean (SD) disease-free interval after primary colectomy was 25 (26) months (median, 19 months; range, 0-105 months), and the median survival after first recurrence was 37 months (range, 12-187 months). Eight of 14 patients died. Six patients are alive to date, and 3 of them are disease free 187, 57, and 19 months after op-

eration for the first recurrence. Eight patients who had liver (5 patients), lung (2 patients), and locoregional recurrence (1 patient) did not undergo second-line surgery, and 7 of them have died. Their mean (SD) disease-free interval after colectomy was 19 (16) months (median, 15 months; range, 3-46 months), and their median survival after first recurrence was 16 months (range, 3-48 months) ($P = .03$) (**Figure**). Among the entire group of 108 patients, the cumulative 5-year OS was 88.7%.

COMMENT

In CRC, follow-up practices and guidelines vary widely after potentially curative surgery.[33] Among patients receiving intensive surveillance, a significant reduction in cancer-related deaths is seen following surgery with curative intent.[12,13,34] Intensive follow-up is recommended for up to 5 years, as CRC typically recurs within the first 2 years after initial resection and rarely after 5 years.[15,19,21,35,36] Accordingly, in this study, 21 of 22 patients (95.5%) experienced recurrence earlier than 60 months, while the last patient experienced recurrence 103 months after primary surgery. Procedural examination–based follow-up of patients after curative resection of CRC can lead to unnecessary cost.[36,37] Serum TMs are inexpensive and simple measurements for routine use. The CEA has proven effective in identifying patients with early recurrences[38]; its sensitivity has been reported to range from 58% to 89%, with a specificity of 75% to 98%.[35,38] Other serum TMs such as CA19.9 have been proposed, but they are not routinely recommended. In this study, consistent with the principal aim, all 22 patients were asymptomatic at the time of their first recurrence. Sensitivity for early detection of recurrences ranged from 9.4% for CA19.9 and CA72.4 to 46.9% for CEA. The sensitivity of CEA herein was lower than that reported by other authors.[35,38] However, unlike most intensive follow-up protocols[4,19,21-25] in which CEA was the only marker measured, TM measurement in our study included TPA, CA19.9, and CA72.4. In addition, abdominal US was serially performed.

Inclusion of TPA increased CEA sensitivity from 46.9% to 71.9%, although the lead time was only slightly extended (4.4 vs 4.3 months). When consecutively added to the CEA and TPA association, CA19.9 and CA72.4 increased sensitivity from 71.9% to 78.1% and 81.3%, and the lead time was extended from 4.4 to 5.3 months. Therefore, TPA increased CEA sensitivity more than CA19.9 and CA72.4, while CA19.9 and CA72.4 extended CEA lead time more than TPA.

In this study, the principal aim was to detect as many recurrences as early as possible so that patients could undergo curative surgery. Therefore, even if only marginally able to increase sensitivity or extend the lead time, any additional marker was considered worthwhile to include in the panel. Notably, no decrease in specificity occurred. In fact, the criteria used resulted in 100.0% specificity for the CEA, TPA, CA19.9, and CA72.4 TM panel. If our results are confirmed among more patients, the number of procedural examinations could be reduced. In the 6 recurrences with concomitant benign pathologic findings, rising TM levels obviated any equivocal interpretation.

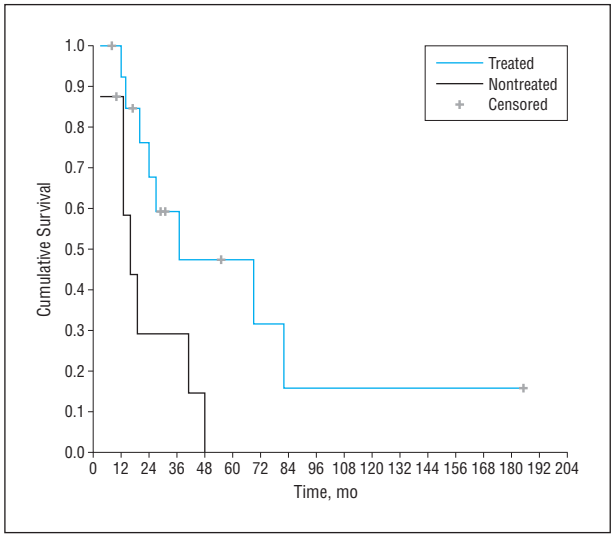

Figure. Cumulative survival among 14 patients who were operated on (blue line) and 8 who were not operated on (black line) after recurrence of colorectal cancer.

No study evaluating abdominal US findings alone has shown a convincing survival advantage among patients with cancer.[1,16] However, abdominal US has been shown to detect potentially resectable hepatic recurrences from CRC.[39] In our study overall, abdominal US demonstrated abnormal findings early among 70.0% of 20 liver metastases. This suggests a relevant role for abdominal US in early detection of liver metastases among patients with CRC.

Chest radiographs have been reported[35] to identify 2% to 12% of patients with resectable lung lesions. In our study, false-negative findings in 2 of 8 patients with suspected recurrence suggest limited usefulness in early diagnosis of lung metastases, although the specificity of CXR at baseline was 100.0%. Baseline BS demonstrated low specificity (88.3%), with 7 false-positive suspected recurrences.

Whole-body FDG-PET has shown high sensitivity, specificity, and accuracy[40,41] and is recommended for detecting extrahepatic metastases.[42] In our study, whole-body FDG-PET demonstrated 100.0% specificity and 75.0% sensitivity. However, these results are inconclusive because of the few examinations performed.[14] In a recent CRC study,[43] CT sensitivity and specificity for all metastases were 75% and 99%, respectively (90% and 99%, respectively, for liver metastases). In our study, abdominal CT showed high diagnostic accuracy (99.3%), and 100.0% sensitivity and specificity were shown for chest and bone CT. These results and the findings of other authors[43] support the use of CT as the principal tool to perform initial staging and to confirm diagnosis in patients suspected of having a recurrence.

Liver, lung, and locoregional involvement are the most common sites of CRC recurrences.[34,44] In 50% to 100% of patients who have metastases to a single organ such as liver or lung or have a local recurrence and who received adjuvant chemotherapy after curative resection, 5-year survival approaches 20% to 25% and may reach

40% to 58% if the liver is the only site of recurrence.[5,6,15,45-48] Asymptomatic rather than symptomatic recurrences are more often resectable.[19] Among 22 patients in our series with recurrences, the median survival after recurrence in 14 patients who were operated on was significantly longer than that in 8 patients who did not undergo operation (37 vs 16 months, $P = .03$). Moreover, 3 patients who were operated on were still disease free 187, 57, and 19 months after surgical removal of liver (2 patients) and lung (1 patient) metastases.

In most CRC studies,[4,19,21-25] recurrence rates have ranged from 26% to 57%, and the cumulative 5-year OS of patients who underwent intensive follow-up ranged from 60% to 80%. Herein, the recurrence rate was 20.4%, and the cumulative 5-year OS was 88.7%. The low recurrence rate could have favorably affected the 5-year OS. However, the high percentage (63.6% [14 of 22]) of patients with recurrences who underwent curative reresection is perhaps more relevant. In fact, among the aforementioned studies, a significant difference in cumulative 5-year OS in favor of the arm that underwent intensive follow-up was found only in investigations reporting curative reresection recurrence rates higher than 30%.

In conclusion, long-term intensive risk-adjusted follow-up of patients with CRC has high accuracy using the serum CEA, TPA, CA19.9, and CA72.4 TM panel and abdominal US. Such monitoring results in early detection of most recurrences. Patients with early detection can then undergo radical metastasectomy, with potentially improved OS.

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