

Radioimmunoguided Surgery for Colorectal Cancer

David J. Bertsch, MD, William E. Burak Jr, MD, Donn C. Young, PhD,
Mark W. Arnold, MD, and Edward W. Martin, Jr, MD

Background: Operations for patients with colorectal cancer are based on traditions established by historical experience. Radioimmunoguided surgery (RIGS) provides new information that challenges these traditions.

Methods: Thirty-two patients with primary colorectal cancer underwent RIGS after being injected with anti-TAG-72 murine monoclonal antibody CC49 labeled with iodine-125. Sixteen of the patients had all gross tumor and RIGS-positive tissue removed (RIGS-negative group), and 16 had only traditional extirpation of the tumor because RIGS-positive tissue was too diffuse (RIGS-positive group).

Results: In the 16 patients having all RIGS-positive tissue removed, five had traditional regional en bloc resections and 11 had additional extraregional tissues resected. Identification of extraregional disease added two liver resections and 25 lymphadenectomies: 10 of the gastrohepatic ligament, five celiac axis, six retroperitoneal, and four iliac. With a median follow-up of 37 months, survival in the RIGS-negative group is 100%. In 14 of 16 patients (87.5%) there is no evidence of disease. In the RIGS-positive group, follow-up shows 14 of 16 patients are dead and two are alive with disease ($p < 0.0001$).

Conclusion: These results suggest that RIGS identifies patterns of disease dissemination different from those identified by traditional staging techniques. Removal of additional RIGS-positive tissues in nontraditional areas may improve survival.

Key Words: RIGS—Colorectal cancer—Disease dissemination—RIGS staging.

The mainstay of colorectal cancer treatment is surgery. In recent years surgery has been augmented by systemic chemotherapy and radiation in selected patients. Two thirds of patients with primary colorectal cancer undergo a "curative" resection, yet nearly 50% develop recurrent disease (1).

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From the Divisions of Surgical Oncology (D.J.B., W.E.B., E.W.M.) and General Surgery (M.W.A.), Department of Surgery, and Department of Biostatistics, Comprehensive Cancer Center (D.C.Y.), Arthur G. James Cancer Hospital and Research Institute, Ohio State University, Columbus, Ohio, USA.

Address correspondence and reprint requests to Dr. Edward W. Martin, Jr., Division of Surgical Oncology, Department of Surgery, Ohio State University Hospitals, 410 West 10th Avenue, Doan N911, Columbus, OH 43210, USA.

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Recognizing that recurrence may be related to inadequate primary surgery, surgeons have tried to determine the extent of surgery needed to improve patient survival and decrease recurrence. Miles's pioneering work in the treatment of rectal cancer yielded important data on the routes of dissemination, resulting in improved survival with wider resection of the avenues of tumor spread (2). Based on the work of Miles and that of others (3-5), a traditional approach to the surgery of colorectal cancer has developed. In essence, the practice of en bloc removal of the tumor with its mesentery and nodes, contiguously involved organs, and high ligation of the named vessel supplying the tumor is current practice. Even with this approach, 10-50% of patients with local or locoregional disease die as a result of recurrence (6), implying the presence of clinically occult disease.

In an effort to improve patient survival, the radioimmunoguided surgery (RIGS) system was developed to increase the accuracy of surgical detection

and removal of cancer. RIGS is an intraoperative tool for detecting occult disease and assessing the extent and dissemination of the malignant process. Using an anti-TAG-72 (anti-tumor-associated glycoprotein) murine monoclonal antibody (MAB) radiolabeled with iodine-125 (^{125}I), the system targets obvious and occult (microscopic) disease. Targeted tissues are detected intraoperatively with a hand-held gamma-detecting probe (GDP) which locates the radioisotope bound to MAB in tissue.

The purpose of this review was to assess use of the RIGS system for detecting disease dissemination and assessing the extent of the malignant process and to determine the impact of this information on patients surgically treated for primary colorectal cancer.

MATERIALS AND METHODS

Thirty-two of 43 patients with primary colorectal cancer enrolled in a nonrandomized National Cancer Institute, Cancer Therapy Evaluation Program (CTEP) RIGS study (T90-0038) were analyzed. This was a phase I/II dose ranging study of ^{125}I -labeled anti-TAG-72 CC49 conducted from July 1990 to April 1992. Four patient cohorts were used in this study:

Cohort 1. Dose: 2 mCi/1 mg CC49. Surgery was performed when precordial GDP counts were < 20 counts/2 s.

Cohort 2. Dose: 2 mCi/0.2 mg CC49. Surgery was performed when precordial GDP counts were < 20 counts/2 s.

Cohort 3. Dose: 2 mCi/10 mg CC49. Surgery was performed when precordial GDP counts were < 20 counts/2 s.

Cohort 4. Dose: A decision related to specific dose depended on findings in cohorts 1, 2, and 3. Surgery was performed when precordial GDP counts were 20–80 counts/2 s.

To be eligible for the study, patients had to be surgical candidates with known or suspected primary or recurrent colorectal cancer. Patients also were required to have a Zubrod performance status grade of 0, 1, or 2, life expectancy > 2 months, and normal renal and liver function.

All patients signed a written consent approved by the Human Subjects Review Board at the Ohio State University before the administration of the radiolabeled antibody. Patients were treated with an oral solution of potassium iodide to block the uptake of radiolabeled monoclonal antibody by

the thyroid. The ^{125}I -CC49 was diluted in 4 ml phosphate-buffered saline solution and administered intravenously. Surgery was scheduled when precordial counts determined by the GDP were < 20 counts/2 s or as otherwise specified in the protocol.

At the time of surgery a thorough traditional examination of the abdomen and pelvis was performed. The findings of this examination were stated by the surgeon and recorded. Then potential tumor sites and other protocol-directed preselected sites were surveyed with the GDP.

Probe counts over the aorta were used as baseline background radioactivity to squelch the GDP's audible signal from inconsequential radioactivity. After the squelch is set, the GDP generates an audio signal only when counts of radioactivity exceed the background counts by a statistically significant amount. A significant or positive count is computed by the probe's control unit by a three-sigma criterion: the baseline count plus three times the square root of the baseline, or greater. These findings are then recorded.

In accordance with the protocol, all tissues containing tumor as determined by palpation and inspection were resected. Biopsy samples of tumor were obtained in cases of unresectable disease. An attempt was made to resect all tissues suspected to contain tumor by the RIGS system unless the extent of RIGS-positive tissue precluded a complete resection.

Depending on the RIGS status at the completion of the surgery, patients were classified as (a) final RIGS negative, all macroscopic and RIGS-positive tissues removed; or (b) final RIGS positive, RIGS-positive tissues remained at the conclusion of the surgery. Patients were also classified by pathologic stage based upon the hematoxylin and eosin (H&E) evaluation of submitted tissue using American Joint Committee on Cancer (AJCC) guidelines.

Regional disease was defined as RIGS-positive or H&E-positive mesenteric lymph nodes that drained the primary tumor, whereas extraregional disease included all RIGS-positive or H&E-positive tissue that was outside the mesentery of the primary tumor.

Data were analyzed for sites of extraregional RIGS-positive tissue identified, survival by traditional staging, and survival by final RIGS status. Survival curves were constructed according to Kaplan-Meier and compared using log rank statistics.

TABLE 1. Characteristics of RIGS groups

	Final RIGS (-)	Final RIGS (+)	Total
Site of lesion			
Right	3	4	7
Left	6	7	11
Rectal	7	7	14
Total	16	16	32
Sex			
M	10	10	20
F	6	6	12
Total	16	16	32
Age (yr)			
Mean	60.2	58.5	59.3
Median (range)	60.5 (37-81)	61.0 (29-87)	60.5 (29-87)
Pathologic stage (AJCC)			
I/II	7	3	10
III	7	4	11
IV	2	9	11
Total	16	16	32
Adjuvant chemotherapy (AJCC)			
Stage I/II	0/7	2/3	2/10
Stage III	7/7	3/4	10/11
Follow-up (mo)			
Mean	43.1	19.0	31.0
Median (range)	42.0 (35+ to 52+)	16.5 (1 to 44+)	37.0 (1 to 52+)

RESULTS

Patient Characteristics

Forty-three patients with primary colorectal cancer were entered in the CTEP study. Eleven patients were excluded from this analysis. Three patients were excluded for failure to localize, and one for having synchronous recurrent rectal carcinoma and primary appendiceal cancer. Seven patients were excluded for having only carcinoma in situ or for being >3 months from their first operation, where they were noted to have extensive regional disease or synchronous hepatic metastasis.

Of the remaining 32 patients, 20 were male and 12 were female. The median age was 60.5 years (range 29-87). There were seven right colon lesions, 11 left colon lesions, and 14 rectal lesions. All patients had standard resections of their primary tumor with its mesentery in addition to removal or biopsy

of suspicious extraregional tissue. Median follow-up was 37 months (range 1 to 52+ months) (Table 1).

All 32 patients had RIGS-positive tissues found at the time of surgery (Fig. 1). Sixteen patients were RIGS negative at the completion of their surgery, whereas 16 patients were RIGS positive.

RIGS-Negative Group

Sixteen of the 32 patients (50%) had no intraabdominal RIGS-positive tissue remaining at the conclusion of surgery. Five of these patients had no extraregional disease noted, and all RIGS-positive tissue was included in the resection of the primary specimen and its mesentery. Eleven of the 16 patients (69%) had extraregional RIGS-positive tissue removed from 27 areas, 25 nodal and two hepatic. Areas of nodal RIGS positivity were gastrohepatic ligament, 10 patients; retroperitoneum, six patients; celiac axis, five patients; and iliac vessels, four patients (Table 2). When examined microscopically, none of these RIGS-positive extraregional nodes had histologic (H&E) evidence of cancer.

When these 16 patients were staged using AJCC guidelines based on H&E histologic evaluation, seven (44%) were AJCC stage I/II, seven (44%) were AJCC stage III, and two (12%) were AJCC stage IV. None of the stage I/II and all seven stage III patients were treated with postoperative chemotherapy.

TABLE 2. Sites of extraregional RIGS-positive tissue removed in final RIGS-negative patients by AJCC stage

	I/II	III	IV	I-IV
Gastrohepatic	3	5	2	10
Celiac	2	3	—	5
Iliac	2	2	—	4
Retroperitoneal	1	5	—	6
Liver	—	—	2	2
Totals	8	15	4	27

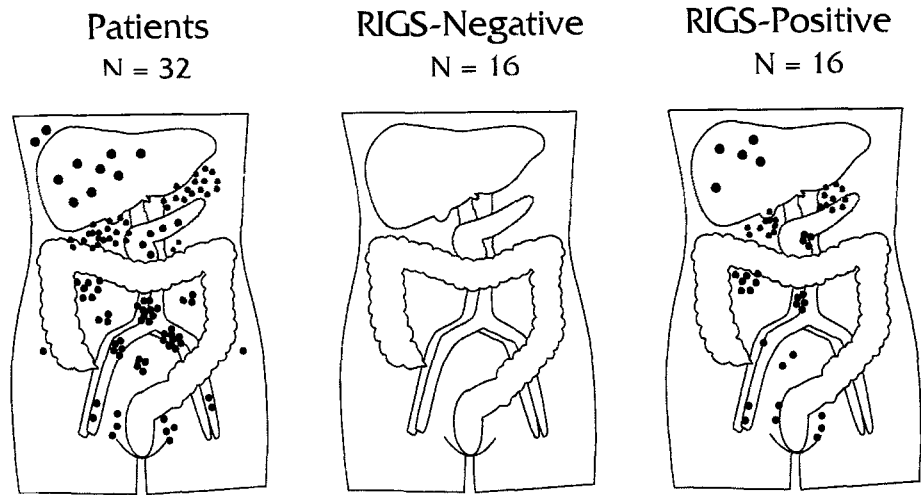


FIG. 1. Initial (left) and final (center, right) RIGS assessment.

RIGS-Positive Group

Sixteen of the 32 patients (50%) were RIGS positive at the conclusion of surgery. These patients had RIGS-positive tissue that could not be completely resected, usually because of widespread retroperitoneal nodal involvement involving multiple anatomic sites (Fig. 1). Ten patients had RIGS-positive celiac nodes, 10 had gastrohepatic ligament nodes, four had peripancreatic nodes, 10 had paraaortic or iliac nodes, and seven had RIGS-positivity in the small bowel mesentery. Five patients had unresectable pelvic RIGS-positive tissue and five had unresectable hepatic disease (RIGS-positive) at the conclusion of surgery.

AJCC staging of these patients showed that three (19%) were stage I/II, four (25%) were stage III, and nine (56%) were AJCC stage IV. Only one of the extraregional sites examined via biopsy or removed in the seven AJCC stage I/II/III final RIGS-positive patients was noted to contain tumor. Two of three stage I/II and three of four stage III patients were treated with adjuvant chemotherapy.

Survival

Of the 32 total patients, 18 patients (56.2%) are alive. Nine of 10 (90%) of the stage I and II patients are alive, two with disease. For AJCC stage III patients, seven of 11 patients are alive, one with disease. Two of 11 (18.2%) stage IV patients are alive, one with recurrence (Table 3, Fig. 2).

By final RIGS status, 16 RIGS-negative patients (100%) are alive, whereas only two of 16 (12.5%) RIGS-positive patients are alive. Both living patients in the latter group have recurrent disease (Fig. 3). Excluding stage IV patients from both RIGS-nega-

tive and RIGS-positive groups, a statistically significant difference in survival is also seen ($p = 0.0002$) (Fig. 4). The median survival for RIGS-positive ($n = 7$) AJCC stage II/III patients is 26 months (range 8 to 44+ months). For RIGS-negative patients ($n = 11$), the median survival has not yet been reached, but the range is 35+ to 52+ months (Table 4).

DISCUSSION

The shortcomings of traditional surgical techniques for treating patients with primary colorectal

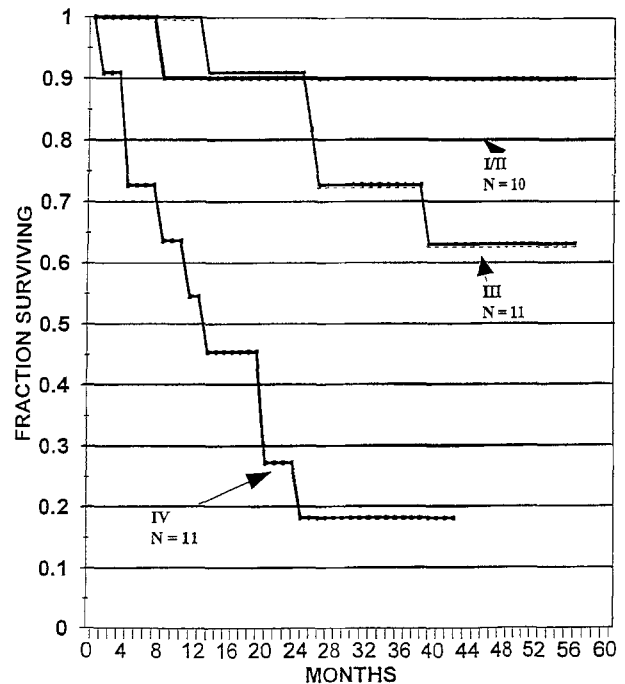


FIG. 2. Survival by AJCC stage.

TABLE 3. Patient survival by AJCC stage and final RIGS status

	Final RIGS(-)	Final RIGS(+)	Total no. studied	NED	Alive with disease	Dead
I/II	7	3	10	7	2	1
III	7	4	11	6	1	4
IV	2	9	11	1	1	9
Total	16	16	32	14	4	14
Alive with disease	2	2	4			
Dead	0	14	14			

NED, no evidence of disease.

cancer are evident from the incidence of recurrent disease. Recurrence is a manifestation of residual disease growth that occurs even after all obvious tumor is removed. Miles (2) recommended overcoming this inability to find and remove all tumor in patients with rectal cancer by performing a wider resection in three directions: lateral, upward, and downward. To remove more lymph nodes, Moynihan (5) described high ligation of the inferior mesenteric artery. Enker et al. (7) reported increased survival for patients with wide anatomic resection. Similarly, Gardner (8) reported encouraging results for patients undergoing multiorgan resection for locally advanced colorectal cancer. All of these approaches deal with adequate clearance of regional disease, but do not address the possible problem of extraregional disease. It was Wangenstein et al. (9) who noted recurrent disease in extraregional areas at second-look surgery, stating that "involvement of the para vena cava and aorta lymph nodes in reentry is usual. No surgeons, however, in the initial operation . . . excise regularly this secondary chain of lymph nodes . . ."

The results of this review suggest that the RIGS

system identifies sites of tissues during first surgery that, as Wangenstein observed, were routinely malignant during his second-look surgeries. The RIGS system targets tissues, mainly nodal tissue, that surgeons do not regularly excise. In the final RIGS-negative patients, diseased tissues were removed from the gastrohepatic ligament, celiac axis, iliac vessels, and retroperitoneum. None of these areas are sites where the surgeon would traditionally remove tissue.

In the seven final RIGS-positive patients (AJCC stage II/III) multiple areas of RIGS-positive tissue were removed and/or examined via biopsy. Residual RIGS-positive tissue remained in the small bowel mesentery nodes in three patients, in the retroperitoneal, paraaortic area near the pancreas in four patients, and in the celiac axis in one patient. Some patients had more than one area of residual RIGS positivity. No gross tumor remained in any of these seven patients, and only one extraregional node contained pathology-confirmed cancer. Of these seven patients with no gross residual disease and only residual RIGS-positive tissues, five patients are dead

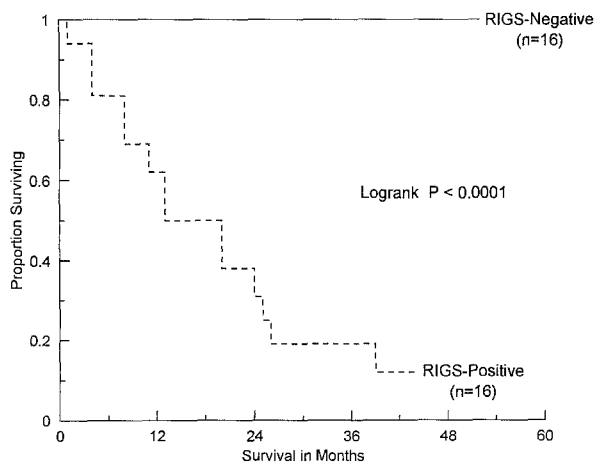
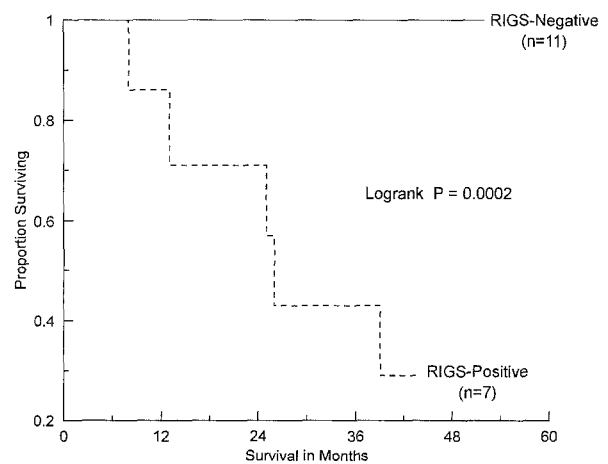
**FIG. 3.** Survival by final RIGS status (all patients).**FIG. 4.** Survival by RIGS status (AJCC stages I-III) only.

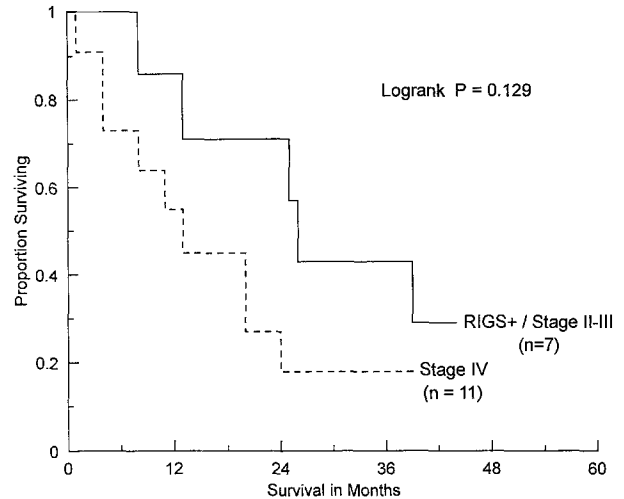
TABLE 4. Median patient survival in months

	Median	Range
Overall n = 32		
Final RIGS (-) (n = 16)	—	35+–52+
Final RIGS (+) (n = 16)	13	1–44+
Stage I/II/III		
Final RIGS (-) (n = 14)	—	35+–52+
Final RIGS (+) (n = 7)	26	8–44+
Stage IV (n = 11)	13	1–38+

and two are alive (44 months each) with advanced recurrence. In these patients with no visible gross disease, the presence of residual RIGS-positive nodal tissue appears to portend a poorer outcome, even though only a small percentage of these residual extraregional lymph nodes demonstrated tumor with H&E staining. This implies that these lymph nodes are biologically significant, either containing nondetectable cancer cells or reflecting an ongoing disease process within these nodes or elsewhere. Complete surgical removal of extraregional RIGS-positive nodes appears to correlate with prolonged survival, although a larger, controlled group of patients will be required to substantiate this observation.

These data suggest that RIGS-positive findings represent new, useful intraoperative staging information. Traditional staging relies on morphological studies. As Steele (10) noted, this traditional approach does not predict the biology of colorectal cancer well or the clinical outcome of the patients. RIGS status appears to be a better predictor of survival than does traditional staging. The difference in survival for all RIGS-negative versus all RIGS-positive patients is highly significant. Even when all stage IV patients are excluded, the difference in survival between stage I–III RIGS-negative versus stage I–III RIGS-positive patients is significant. Without considering RIGS status, survival curves for our patients would be similar to traditionally expected curves. Eighteen of 32 patients (56.3%) are alive. Comparing RIGS-positive stage II/III patients (n = 7) with all stage IV patients (n = 11) shows a similar slope and poor survival (Fig. 5).

The identification of extraregional tissues and the difference in survival suggests that the RIGS system may help overcome the inadequacies of prognosis by morphologic definitions of tumor and better address the issue of systemic disease as discussed by Steele (10). A total of 87.5% of RIGS-negative patients are disease-free, and 87.5% of RIGS-positive patients are dead. In these 32 patients the RIGS

**FIG. 5.** Survival for all AJCC stage IV and RIGS-positive II/III.

system provided information about disease dissemination and survival that is patient specific. This information differs greatly from prognostic information based on traditional staging, which relies on the tissues analyzed by a pathologist. Traditional staging based on ex vivo assessment of excised tissue only allows the surgeon to stratify patients and assign each a statistical risk of success or failure. In contrast, the RIGS system assesses viable tissues in the patient at the time of surgery.

The use of the RIGS system in this small group of primary patients shows its applicability as an intraoperative tool to assess disease dissemination in both regional and extraregional areas. This unique information is specific to each patient and more accurately predicts the patient's survival.

Further studies with a larger number of patients will be needed to support these important findings.

CONCLUSION

Use of the RIGS system for patients with primary colorectal cancer yields new and important information concerning disease dissemination and patient survival that is unavailable by traditional surgical practice or traditional staging methods.

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