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RAPID COMMUNICATION

Immunoscintigraphy of local recurrent rectal cancer with ^{99m}Tc-labeled anti-CEA monoclonal antibody CL58

Yun-Feng Yao, Zhi Yang, Zhen-Fu Li, Jin Gu

Yun-Feng Yao, Zhi Yang, Zhen-Fu Li, Jin Gu, Peking University School of Oncology, Beijing 100036, China
Supported by National High-Tech R&D Program of China (863 Program), No. 2004AA215270
Correspondence to: Dr. Jin Gu, Peking University School of Oncology, Fucheng Road #52, Haidian District, Beijing 100036, China. zlguj@bjmu.edu.cn
Telephone: +86-10-88141032 Fax: +86-10-88141032
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Abstract

AIM: To explore a specific diagnostic method for local recurrent rectal cancer.

METHODS: Immunoscintigraphy with ^{99m}Tc-labeled anti-CEA monoclonal antibody (MoAb) CL-58 was performed for patients suspected of having a postoperative local recurrent rectal cancer and the findings were compared with the results of conventional imaging and pathology.

RESULTS: A total of 36 patients with a suspected local recurrent rectal cancer underwent immunoscintigraphy with ^{99m}Tc-conjugated CL58. Local recurrence of rectal cancer was identified in 31 patients and established in 30 during operation, endoscopy and pathological examination. No local recurrence was found in 5 patients without specific accumulation of ^{99m}Tc during the follow-up. Immunoscintigraphy had a positive rate of 86.11%, a specificity of 83.33%, and a sensitivity of 100%.

CONCLUSION: Immunoscintigraphy has a highly specific and predictive value for detecting local recurrent rectal cancer, especially after abdominal perineal resection (APR).

Key words: Immunoscintigraphy; Rectal cancer; Recurrence; Monoclonal antibody

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INTRODUCTION

Surgical intervention is the main therapeutic method for rectal cancer. However, local recurrence and metastasis are still two critical factors that determine the long-term survival and life quality of the patients. Early detection of any recurrent lesions can provide critical information for further therapy. Once recurrence or metastasis of rectal cancer is determined, early surgical intervention may help to gain long-term survival. Adjuvant chemotherapy, radiotherapy or other palliative modalities can improve the quality of life[1].

Based on the National Comprehensive Cancer Networks (NCCN) standard, serum CEA levels should be measured every three months in the first 2 postoperative years to monitor disease progression. For high-risk patients, CT scan and fibrocolonoscope should be performed every six months. However, these procedures often do not provide sufficient evidence for a final diagnosis of recurrent lesions. Although fibrocolonoscope can provide the pathological diagnosis, this method is suitable only for some patients undergoing low anterior resection (LAR). Ultrasonography or CT-guided needle biopsy is invasive with a higher risk. Moreover, the experience of different operators may lead to different outcomes. The advent of positive emission tomography (PET) can detect both local recurrent and distant metastatic lesions[2,3].

Monoclonal antibodies (MoAbs) against tumor-associated antigens have been utilized in targeted delivery of agents to tumor cells either for diagnostic imaging purposes or for therapeutic purposes[4,5]. Immunoscintigraphy is a targeted imaging technique that employs a radiolabeled MoAb specifically bound to a particular tumor antigen[6]. This approach produces a clear image of lesions expressing the specific tumor antigen, thus representing a highly specific method for detecting tumor recurrence.

This study was to assess whether immunoscintigraphy with ^{99m}Tc-labeled anti-CEA MoAb CL58 can provide useful information on the diagnosis and treatment of recurrent rectal cancer.

MATERIALS AND METHODS

Patients

The study group consisted of 36 consecutive patients (20 males, 16 females, mean age 58.8 + 3.30 years) with a suspected local recurrent rectal cancer treated at Peking University School of Oncology from September 2000 to December 2004. Patients were excluded from this study if they had bowel obstruction or extra-abdominal disease. Written informed consent was obtained from each patient. All the patients underwent total mesorectal excision (TME)

in accordance with the R0 criteria during the past 7-26 mo, of them 24 underwent low anterior resection (LAR) and 12 abdominal perineal resection (APR). Standard pathologic analysis of rectal specimens was performed. The rectal tumor was staged according to the American Joint Committee on Cancer (AJCC) Staging Manual, 6th edition. Postoperative staging of tumor, node and metastasis (TNM) showed that 2 cases were in stage Ⅰ, 5 in stage Ⅱ and 29 in stage Ⅲ. The distance from the anal margin in these patients ranged 4-15 cm. During the Follow-up (average 34 mo), 4 patients underwent a second operation, 28 adjuvant chemotherapy, and 14 pelvic radiotherapy. At the end of this study, 25 patients survived and 11 died. The average postoperative tumor-free survival time was 32 mo.

Clinical detection of local recurrence

Suspected local recurrence was defined as at least one lesion detected by radiology (CT, ultrasonography, endorectal ultrasound or PET) and/or fibrocolonoscopy. Patients after LAR were biopsied *via* fibrocolonoscopy. Others with suspected perineal recurrence after APR were biopsied under ultrasonography guidance if the tumor was reachable. For those cases post-APR with recurrent tumors invaded perineal skin, local cell smears or biopsies were used for pathological diagnosis. Of the 36 patients, 31 were positive and 5 were negative for recurrent tumors.

Anti-CEA antibody

CL58 is a murine anti-CEA monoclonal immunoglobulin (Ig)-G1. Hybridoma cell line was produced by cell fusion of spleen cells from human CEA-immunized Balb/c mice with SP2/0 myeloma cells. MoAb CL-58 hybridoma was grown in mouse ascites, CL-58 MoAb was purified on protein A affinity column (MAPS-100, Bio-Rad) and high performance hydroxylapatite (HPHT) column (Bio-Rad). Purity was more than 95% as confirmed by SDS-PAGE. The affinity constant of CL58 was 7.4×10^9 mol/L) as measured by competition ELISA. CL58 bound to colorectal cell line (CL-187, HT-29 and B-80) with a high affinity. Normal cells such as mixed lymphocytes, red blood cells, fibroblasts and bone marrow cells were proved negative for rectal cancer by ELISA. The specific CEA in colorectal and normal tissues recognized by CL-58 was confirmed by immunohistochemistry.

Radio labeling of CL58 McAb

^{99m}Tc-labeled CL58 was prepared by Schwartz method. Briefly, CL58 was reduced by 2-mercapthonal and purified on PD-10 column (Pharmacia, Sweden). One mg of the reduced CL58 was mixed with 1 mg glucoheptonate, followed by adding 5-10 μg of freshly prepared $SnCl_2$ (Sigma, American). Then about 0.5-1 mL of fresh e $Na^{99m}TcO4$ was added to the mixture with slight shake. The mixture was incubated at room temperature for 15 min before labeling efficacy was tested. When the labeling efficiency was less than 90%, the mixture was purified by running through a PD-10 column (Pharmacia, Sweden) and sterilized by filtration through a 0.22 μm filter (Millipore, USA). The agents produced by using the one- or two- step freeze drying method could be used to prepare antibodies for direct ^{99m}Tc labeling. Because the conjugation rate was greater than 90% and the level of free ^{99m}Tc was less than 2%, the produced ^{99m}Tc-labeled antibodies were not further purified for clinical application.

Immunoscintigraphy

Thirty-six patients with suspected recurrence of rectal cancer received immunoscintigraphy with ^{99m}Tc-labeled CL58. Single photon emission computed tomography (SPECT) was performed using an E.CAM^{TM} dual-head emission imaging system (Siemens, Germany). The patients needed to have clear fecal residue before imaging. Head/neck-pelvis tomography was performed 4 and 22 h after intravenous injection of 1.11 GBq of ^{99m}Tc labeled CL58. To discriminate imaging artifacts in the intestinal tract, abdomen-pelvis tomography was conducted 28 h after CL58 injection. In addition, patients received abdominal CT, ultrasonography, and fibrocolonoscopy. Two- and three- dimensional immunoscintihtsphy images were analyzed by at least two experienced radiologists after completion of immunoscintigraphy. The areas of specific accumulation of ^{99m}Tc were regarded as malignant tumors. All images on X-ray films, abdominal CT and ultrasonography were compared except for the normal imaging sites in liver, spleen, kidney, bladder and major blood vessels.

Statistical analysis

Statistical evaluation was performed using the Student's *t* test and the positive predictive values were evaluated by Fisher's exact test using SPSS 11.0 software. $P < 0.05$ was considered statistically significant.

RESULTS

Imaging results

A total of 36 patients underwent immunoscintigraphy with ^{99m}Tc-labeled CL58. Tumor status and immunoscintigraphy data are summarized in Table 1. Of the 36 patients, 31 (86.11%) were positive for local tumor recurrence. Forty lesions were found in the pelvis: 20 in tissues adjacent to the bladder, 15 in presacral region, 2 in colon and 3 in peritoneal region (Table 2).Ten lesions were distant metastases: 1 in liver, 2 in sternum, 1 in retroperitoneal lymph nodes, 1 in free abdominal cavity, 4 in lung and 1 in tissues adjacent to the stomach (Table 3). Focal trace accumulation was found in bladder and lungs. Fourteen patients were found to have two lesions.

Tumor recurrence was pathologically confirmed in 30 of the 31 patients. Five patients with negative immunoscintigraphy had no pathological evidence of recurrence even though isolated masses were detected in the pelvis area. The overall positive rate was 86.11%, the specificity was 83.33%, and the sensitivity was 100%.

Immunoscintigraphy following APR

In this study, 12 patients underwent APR. Immunoscintigraphy showed local recurrence in 11 patients and negative imaging in 1 patient. Of the 11 patients with a

Table 1 Surgical procedure, serum CEA level and immunoscintigraphy data

Patients	Gender	Operation LAR/APR*	RⅡ result	Serum CEA level
1	M	LAR	+	16.4
2	F	LAR	+	25.4
3	M	APR	+	25.4
4	M	LAR	+	16.4
5	M	LAR	+	13.3
6	M	LAR	+	2.1
7	F	APR	+	23.9
8	F	LAR	-	0.9
9	M	LAR	+	8.2
10	M	LAR	+	6.0
11	M	APR	+	52.8
12	F	APR	+	9.0
13	M	LAR	+	50.0
14	F	LAR	+	52.0
15	F	LAR	+	500.0
16	M	LAR	+	33.9
17	F	LAR	+	317.7
18	M	APR	+	51.8
19	M	APR	+	68.7
20	F	LAR	+	17.9
21	M	APR	+	14.5
22	F	APR	+	27.5
23	M	APR	+	34.2
24	M	APR	+	6.8
25	F	LAR	+	8.9
26	M	LAR	+	1.0
27	F	APR	+	7.5
28	F	LAR	+	6.1
29	M	LAR	+	13.7
30	F	LAR	-	1.3
31	M	LAR	+	24.9
32	F	LAR	-	7.7
33	F	APR	-	2.4
34	M	LAR	+	13.0
35	M	LAR	-	1.5
36	F	LAR	+	14.0

positive immunoscintigraphy finding, 7 were pathologically confirmed to have local recurrence by biopsy, 4 not confirmed by biopsy were eventually confirmed to have recurrence by pathology when the tumors invaded skin (Table 4).

Comparison of immunoscintigraphy with CT, ultrasonography and PET

To assess the reliability of immunoscintigraphy, we collected the pathological data from all cases which were compared with conventional diagnostic methods including CT, ultrasonography and fibrocolonoscope. Of the 31 patients with recurrences, radiolabled immunoscitigraphy (RⅡ), CT, and fibrocolonoscope identified lesions in 4 patients, accounting for 12.90%; RⅡ, CT and ultrasonography suggested recurrence in 20 patients, accounting for 64.52%; in the remaining 7 patients (22.58%) only ultrasonography and RⅡ suggested recurrence.

Immunoscintigraphy and serum CEA levels

Of the 31 patients with confirmed recurrence by positive CL-58 immunoscintigraphy, 29 had elevated serum CEA levels: 2-fold higher in 2 patients, 3-fold higher in 6 patients, and 4-fold higher in 19 patients.

DISCUSSION

TME can significantly reduce local recurrence of rectal cancer its recurrence rate[7]. It is estimated that approximately 8% of rectal cancer patients would experience a local recurrence even after TME. Most local recurrences of rectal cancer present only in the pelvic area, especially in stage T3 tumor with invaded serosa[8]. Diagnosis of local recurrence of rectal cancer in patients having undergone LAR is primarily based on pelvic CT and transrectal ultrasonography, partially on biopsy[9,10]. However, all these procedures are limited in the diagnosis of local recurrence of rectal cancer, especially following APR. Contrast-enhanced CT scan is difficult to discriminate small recurrent tumor nodules from postoperative scars[11]. Percutaneous punctures might injure adjacent organs. These methods are not sufficient to make a definitive diagnosis and it is difficult to treat it based only on conventional imaging and serum CEA levels[12]. About 40% of patients with rectal cancer, especially low rectal cancer, need to receive APR[13]. Because their rectum and anus are resected, the diagnosis of local recurrence of rectal cancer is difficult. Furthermore, a recent study revealed that the 5-year survival rate of patients with distant metastasis and local recurrence is 36.1% and 24% , respectively[14].

Immunoscintigraphy can obtain important information about tumors including their size and location. This technology is based on the principle that radioisotope-labeled anti-tumor antibodies can specifically bind to the corresponding tumor-specific antigens. It is characterized by a high specificity and sensitivity, and has been used in clinical practice[15]. Immunoscintigraphy with ^{99m}Tc-labeled anti-CEA antibodies appears to produce clear images and provide the precise location of recurrent rectal cancer, suggesting that it is an effective method for the identification of local recurrent rectal cancer, especially for the suspected local recurrent rectal cancer after APR. The sensitivity of immunoscintigraphy ranged 70%-100% for rectal cancer and the detection rate of abdominal and hepatic lesions is 86%. Our group has successfully used ^{99m}Tc labeled immuconjugates in more than 200 clinical cases. Based on previous preclinical experiments that assessed toxicity, body distribution, stability and availability of CL58 in animals[6]. we used ^{99m}Tc-labeled CL58 to detect malignancies in patients. In our study, of the 36 patients with suspected recurrent rectal cancer, 31 (86.1%) had positive immunoscintigraphy. Of the 54 recurrent lesions in 30 patients, 40 (74.07%) occurred in the pelvis.

Our data indicate that CL-58 immunoscintigraphy can detect small local recurrent lesions. Post-APR recurrent lesions which were too small to be detected by CT could be diagnosed by immunoscintigraphy in 7 patients. RⅡ can also be used to detect metastases of rectal cancer in the liver, lung, and peritoneum, and discriminate between recurrent malignancies and benign scar in the pelvic cavity. In addition, the cost of RⅡ is significantly lower than that of PET.

The detection rate of different methods for recurrent lesions at various locations is different. Ultrasonography is difficult to identify relatively small lesions and CT is

Table 2 Sites of local recurrence

Patients	Gender	Operation LAR/APR*	RⅡ (+/-)	CEA (+/-)	Parabladder	Presacral	Colon	Perineal
1	M	LAR	+	16.4	+	+	-	-
2	F	LAR	+	25.4	+	-	-	-
3	M	APR	+	25.4	-	+	-	-
4	M	LAR	+	16.4	+	+	-	-
5	M	LAR	+	13.3	+	-	-	-
6	M	LAR	+	2.1	+	+	-	-
7	F	APR	+	23.9	-	+	+	-
9	M	LAR	+	8.2	+	-	-	-
10	M	LAR	+	6.0	-	+	-	-
11	M	APR	+	52.8	+	-	-	-
12	F	APR	+	9.0	-	+	-	-
13	M	LAR	+	50.0	-	-	-	-
14	F	LAR	+	52.0	+	-	-	-
15	F	LAR	+	500.0	+	+	-	-
16	M	LAR	+	33.9	+	-	-	+
17	F	LAR	+	317.7	+	-	-	-
18	M	APR	+	51.8	-	-	-	-
19	M	APR	+	68.7	+	-	-	-
20	F	LAR	+	17.9	+	+	-	+
21	M	APR	+	14.5	+	-	-	-
22	F	APR	+	27.5	-	-	-	-
23	M	APR	+	34.2	-	+	-	-
24	M	APR	+	6.8	-	+	-	+
25	F	LAR	+	8.9	+	+	-	-
26	M	LAR	+	1.0	+	-	-	-
27	F	APR	+	36.2	-	-	-	-
28	F	LAR	+	6.1	+	-	+	-
29	M	LAR	+	13.7	+	+	-	-
31	M	LAR	+	24.9	+	+	-	-
34	M	LAR	+	13.0	-	-	-	-
36	F	LAR	+	14.0	+	+	-	-

Table 3 Distant metastases

Patients	Gender	Operation LAR/APR*	CEA (+/-)	Liver	Sternum	RPLN	FAC	Lung	Parastoma
1	M	LAR	16.4	-	-	-	-	-	-
2	F	LAR	25.4	-	-	-	-	+	-
3	M	APR	25.4	-	-	-	-	-	-
4	M	LAR	16.4	-	-	-	-	-	-
5	M	LAR	13.3	-	-	-	-	-	-
6	M	LAR	2.1	-	-	-	-	+	-
7	F	APR	23.9	-	-	-	-	-	-
9	M	LAR	8.2	-	-	-	-	-	-
10	M	LAR	6.0	-	-	-	-	-	-
11	M	APR	52.8	-	-	-	-	-	-
12	F	APR	9.0	-	-	-	-	-	-
13	M	LAR	50.0	-	+	-	-	-	-
14	F	LAR	52.0	-	-	-	-	-	-
15	F	LAR	500.0	-	-	-	-	+	-
16	M	LAR	33.9	-	-	-	-	-	-
17	F	LAR	317.7	-	-	+	-	-	-
18	M	APR	51.8	-	-	-	+	-	-
19	M	APR	68.7	-	-	-	-	-	-
20	F	LAR	17.9	-	-	-	-	-	-
21	M	APR	14.5	-	-	-	-	-	-
22	F	APR	27.5	-	-	-	-	-	+
23	M	APR	34.2	-	-	-	-	-	-
24	M	APR	6.8	-	-	-	-	-	-
25	F	LAR	8.9	-	-	-	-	-	-
26	M	LAR	1.0	-	-	-	-	-	-
27	F	APR	36.2	+	-	-	-	-	-
28	F	LAR	6.1	-	-	-	-	-	-
29	M	LAR	13.7	-	-	-	-	-	-
31	M	LAR	24.9	-	-	-	-	-	-
34	M	LAR	13.0	-	+	-	-	+	-
36	F	LAR	14.0	-	-	-	-	-	-

RPLN: Retroperitoneal lymph nodes; FAC: Free abdominal cavity.

Table 4 Immunoscintigraphy following APR

Patients	Gender	Operation LAR/APR*	Path (+/-)	CEA (+/-)	Parabladder	Presacral	Colon	Perineal	Liver	Sternum	RPLN	FAC	Lung	Parastoma
3	M	APR	Puncture	25.4	-	+	-	-	-	-	-	-	-	-
7	F	APR	LTS	23.9	-	+	+	-	-	-	-	-	-	-
11	M	APR	Puncture	52.8	+	-	-	-	-	-	-	-	-	-
12	F	APR	FTG	9.0	-	+	-	-	-	-	-	-	-	-
18	M	APR	Puncture	51.8	-	-	-	-	-	-	-	+	-	-
19	M	APR	Puncture	68.7	+	-	-	-	-	-	-	-	-	-
21	M	APR	Puncture	14.5	+	-	-	-	-	-	-	-	-	-
22	F	APR	Puncture	27.5	+	-	-	-	-	-	-	-	-	-
23	M	APR	LTS	34.2	-	+	-	-	-	-	-	-	-	-
24	M	APR	FTG	6.8	-	+	-	+	-	-	-	-	-	-
27	F	APR	Puncture	36.2	-	-	-	-	+	-	-	-	-	-

Puncture: Biopsy and pathological examination; LTS: Local tissue smear tumors invaded skin; FTG: Further tumor growth.

not able to discriminate between recurrent malignancies and benign postoperative scarring. Compared with these examination procedures, RⅡ has a higher sensitivity and specificity for both local recurrent lesions and metastases following surgery. Immunoscintigraphy in this study identified some suspected recurrent lesions not detected by CT, suggesting that RⅡ in combination with CT and ultrasonography may provide more accurate findings following tumor resection.

In our study, there was no false negative case, indicating that this method is highly specific. False positivity occurred only in the early period of this study mainly due to the vicinity of the bladder. Patients selected to undergo immunoscintigraphy were highly suspected of having recurrence. Since immunoscintigraphy is not routinely used after operation, there were few negative cases. This sampling bias limited the diagnostic specificity when it is routinely used after operation. We expect that ^{99m}Tc CL-58 immunoscintigraphy would provide more precise and specific data.

Serum CEA detection has become an important follow-up method after rectal cancer surgery[16]. CEA levels are increased in 75% of patients with rectal tumors[17]. We subjected 29 patients with suspected tumor recurrence to immunoscintigraphy because of elevated CEA serum levels. Immunoscintigraphy successfully identified local recurrence and metastasis in these patients. Moreover, it appeared to be more sensitive than blood CEA testing or other diagnostic modalities in detecting recurrent rectal cancer. Therefore, even when serum CEA levels are normal, immunoscintigraphy can be used as a routine screening method for early detection of recurrence and metastasis of rectal cancer.

Although immunoscintigraphy is highly specific, it cannot directly provide a pathological diagnosis. Furthermore, immunoscintigraphy has toxicity and side effects.

In conclusion, ^{99m}Tc CL-58 immunoscintigraphy after rectal cancer surgery has a high specificity and provides early diagnosis of local recurrence and distant metastasis of rectal cancer especially after APR. The eventual incorporation of this technique into the postoperative standard of care for rectal cancer patients may contribute to the early diagnosis of recurrent rectal cancer and prolong the survival time of such patients.

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