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ORIGINAL PAPER

Different Roles of Tumor Marker Monitoring after Curative Resections of Gastric and Colorectal Cancers

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Abstract We previously demonstrated that false-positive findings for tumor markers are frequently observed, and that the sensitivity of marker monitoring for early detection of the recurrence is low after curative resection of gastric cancer. The aim of this study was to investigate whether such characters are specific to gastric cancer. Serum carcinoembryonic antigen and/or carbohydrate antigen 19-9 were periodically assessed in 258 patients who underwent curative gastrectomy for gastric cancer (n = 161) or curative resection for colorectal cancer (n = 97). The frequency of false-positive findings for the tumor markers, the sensitivity of the marker monitoring for detection of the recurrence, and the characteristics of such cases were compared between these two cancer groups. During the median follow-up period of 30 months, recurrence developed in 14% of gastric cancer and 23% of colorectal cancer patients. A false positive with the tumor marker was frequently observed in patients after gastrectomy compared with after colorectal surgery. The sensitivity of the marker monitoring regarding early detection of recurrence was higher in patients with colorectal cancer than those with gastric cancer, especially in cases of advanced stage. As a result, the accuracy of marker monitoring for the detection of recurrence was higher in patients after the resection of colorectal cancer than that of gastric cancer. Surgeons and oncologists should thus be aware that the role of the tumor marker monitoring after a curative operation differs between patients with gastric and colorectal cancers.

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Introduction

Various kinds of tumor markers are widely used to detect recurrence after curative resection for malignant diseases. There is a consensus that monitoring tumor-specific markers after treatment is useful for the early detection of the recurrence as well as to predict prognosis [1–10]. On the other hand, tumor markers occasionally increase even in patients without malignant diseases, a phenomenon known as false-positive findings for tumor marker [11–16], and in some cases after the treatment of cancer it is difficult to distinguish the false-positive finding from a true positive. We previously demonstrated that a false-positive finding for tumor markers is frequently observed (~15%) after curative resection of gastric cancer (GC), especially in those with early-stage cancer and those with chronic benign diseases such as liver dysfunction, renal failure, and pulmonary diseases. These findings can be distinguished from a true positive in most cases by the frequent evaluation of markers in combination with radiological examinations [17]. In addition, it seemed that the true-positive rate for early detection of the recurrence after curative gastrectomy was low [17]. These observations suggest that the high frequent false-positive findings for markers might be specific to patients after curative gastrectomy, and that routine marker monitoring would not be required after curative resection for any cases of GC. The aim of this study was to clarify these questions, by comparing the changes in tumor marker level after the curative resections of GC and colorectal cancer (CRC).

Methods

The medical records of 349 patients who underwent curative resection for gastric cancer ($n = 211$) and for colorectal cancer ($n = 138$) between 2002 and 2005 at the Department of Surgery, Saga University Hospital, were retrospectively reviewed (gastric cancer stage I–III according to the Japanese Classification of Gastric Carcinoma, 13th edition, 1999; and colorectal cancer stage 0–III according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus, 7th edition, 2006). All patients showed no residual cancer macroscopically as well as histologically. The frequency and characteristics of false-positive findings for tumor markers after curative gastrectomy in the 211 patients with gastric cancer were described in a previous report, and have been followed up for a longer time [17]. The tumor markers assessed in this study were serum carcinoembryonic antigen (CEA, a Latex immunoassay, Mitsubishi Chemical Ltd., Japan, normal ≤5.0 ng/ml) and/or carbohydrate antigen 19-9 (CA19-9, a Latex immunoassay, Mitsubishi Chemical Ltd., Japan, normal ≤37 ng/ml). These two markers were also examined preoperatively in all patients and the follow-up schedule of the tumor markers and physical examination after the operation were: every 1–3 months during the initial 6 months after the operation, every 3–6 months from 6 months to 2 years, and every 6–12 months during 2–5 years after the operation. Radiological examinations including abdominal ultrasonography, computed tomography (CT), chest X-ray, gastrointestinal series, and/or endoscopic evaluation were performed every 6–12 months during the follow-up period. Marker evaluations and physical/radiological examinations were performed at shorter-term intervals than those described above in patients with suspected recurrence, those undergoing chemotherapy, or in those demonstrating marker elevations.

A false-positive finding for a tumor marker was defined as an elevation of the tumor marker over the normal limit without any sign of recurrence based on physical and radiological examinations after the operation, and the value of the marker either spontaneously decreasing or continuously showing a stable level without any treatment such as chemotherapy, radiotherapy, or operation [17]. The patients with false positive marker results were divided into two subtypes, as described previously [17]: (1) type FP-A, in which the value of marker was normal preoperatively and elevated over the normal limit after the operation and then immediately decreased to a normal level (in some cases, two or three episodes of single-point elevation), or continued to be high for several months, but then finally decreased (in some cases, to within the normal limit) without any treatment, (2) FP-B, which showed continuously high levels of tumor markers during the preoperative and postoperative periods. There are also two subtypes in the true-positive group: (1) TP-A, in which the marker elevation was observed prior to or at the same time as the physiological and/or radiological findings of recurrence and (2) TP-B, physiological and/or radiological findings were prior to marker elevation [17]. "Sensitivity" included both TP-A and TP-B; however, from the point of view of clinical importance, TP-B seems not to be useful for early detection of the recurrence. Therefore, "real sensitivity" was defined as the frequency of TP-A. Histories of chronic benign diseases possibly influencing the tumor marker elevation were bronchitis, renal dysfunction, liver dysfunction, cholangitis, diabetes mellitus, rheumatic diseases, and inflammatory bowel diseases [11–17].

Comparisons between the two groups were assessed by either the Mann–Whitney test, chi-square test or the Fisher's exact test. A probability value of less than 0.05 was considered to be statistically significant.

Results

Among the 349 patients, 46 with a history of other malignancies before or after the operation were excluded (GC $n = 23$, including seven patients with synchronous and three with metachronous resections of GC and CRC; CRC $n = 23$). Forty-five patients were lost to follow-up in terms of marker evaluation after the operation (GC $n = 27$, CRC $n = 18$). Therefore, the data of the remaining 258 patients were available in this study (GC $n = 161$, CRC $n = 97$) (Fig. 1).

The patients with GC included 106 males and 55 females with a median age of 68 years (range 26–88 years). A total of 12 of the 161 patients showed a positive finding for tumor markers preoperatively (8%, four patients with CEA and eight with CA19-9). The procedures performed were distal gastrectomy in 104 patients, total gastrectomy in 56 patients, and partial resection in the remaining patient. A history of chronic benign diseases or smoking was observed in 46 patients (29%): 17 with diabetes mellitus, 11 with liver dysfunction, eight with pulmonary disease, eight smoking, two with renal dysfunction, and three others (a total of 51 histories). Regarding stage, 108 were pathological stage I, 24 were stage II, and 29 were stage III. While the patients with CRC consisted of 55 males and 42 females with a median age of 70 years (range 37–86 years). A positive finding for tumor marker before operation was observed in 25 patients (26%) with 16 CEA and 13 CA19-9. The tumor location was right-side colon in 32 patients, left-side colon in 32, rectum in 30, and multiple locations in the remaining three. Histories of chronic benign diseases or smoking were observed in 34 patients

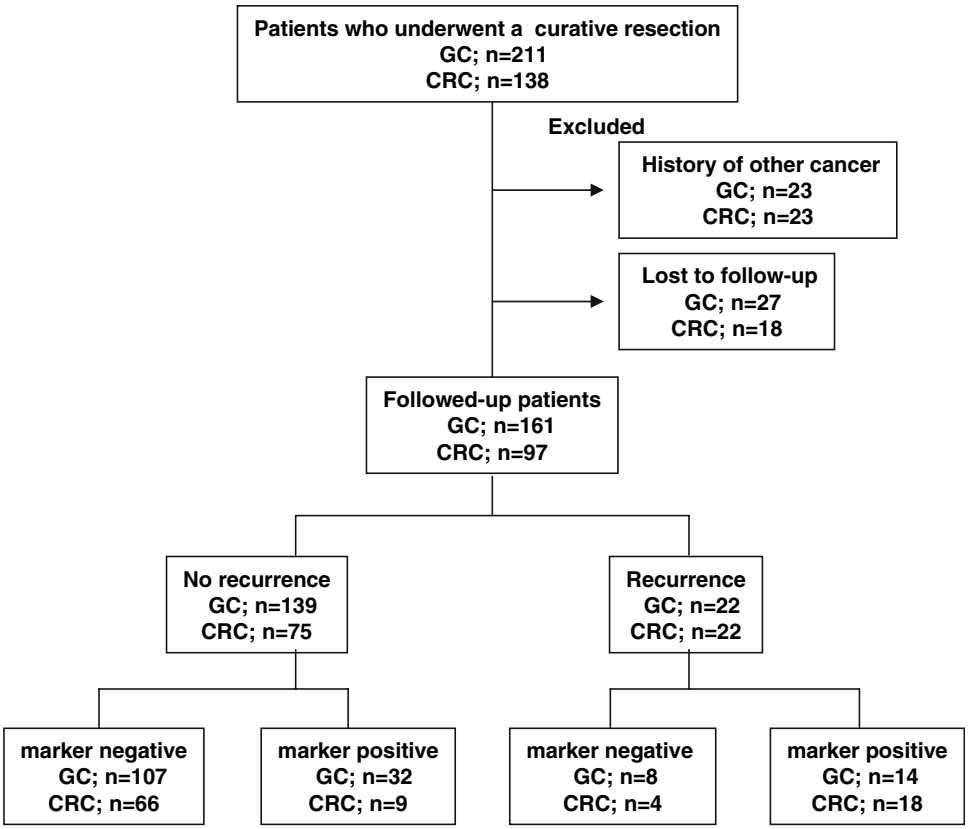

Fig. 1 A flow diagram of the 349 patients who underwent a curative gastrectomy for gastric cancer (n = 211) or a resection of colorectal cancer (n = 138)

(35%): 19 with diabetes mellitus, ten liver dysfunction, three pulmonary disease, three renal dysfunction, two smoking, and five others (a total of 41 histories). Pathological stage was 0 in eight patients, I in 12, II in 37, and III in 40.

Recurrence developed in 22 of 161 patients after gastrectomy (14%), with a median follow-up period of 29.4 months. Initial recurrent sites were peritoneal dissemination in 11 patients, lymph node in five, liver in four, and other sites in four (a total of 24 sites). In patients after resection for colorectal cancer, 24 initial recurrent sites were observed in 22 patients (23%) with a median follow-up period of 30.6 months: liver in six, lymph node in six, peritoneal dissemination in six, and another site in six. The patients' background is shown in Table 1. Because of the larger population of advanced stage of CRC ($P < 0.01$), the preoperative abnormal elevation of tumor marker was observed more frequently in patients with CRC (8% versus 29%, $P < 0.01$), and the rate of adjuvant chemotherapy was higher after colorectal surgery, compared with those with GC (16% versus 35%, $P < 0.01$). Histopathological study demonstrated that most cases of CRC were differentiated adenocarcinomas, while over half of the cases of GC were undifferentiated-type carcinomas ($P < 0.01$).

In 161 GC patients, 107 patients were true negative, 32 were false positive, eight were false negative, and 14 were true positive (Fig. 1). The sensitivity, specificity, and accuracy of the marker evaluation for the detection of recurrence in this study population were 63%, 77%, and 75%, respectively (Table 2). In the false-positive group, one patient showed high levels of both CEA and CA19-9, and as a result there were 17 patients who were CEA positive and 16 who were CA19-9 positive. There were ten patients who were CEA and four who were CA19-9 positive in the true-positive group. On the other hand in 97 CRC patients, 66 patients were true negative, nine were false positive, four were false negative, and 18 were true positive (Fig. 1). The sensitivity, specificity, and accuracy in this study population were 82%, 88%, and 87%, respectively (Table 2). In the false-positive group, there were five patients who were CEA positive and four who were CA19-9 positive. Three patients showed high levels of both CEA and CA19-9, and thus there were 17 patients who were CEA positive and four who were CA19-9 positive in the true-positive group. In the CRC group, the sensitivity tended to be higher (P = 0.06), and the accuracy was significantly higher (P = 0.03) than those in the GC group (Table 2).

Table 3 shows more detailed comparative analyses of postoperative changes in tumor markers between the GC and CRC groups. The population of subtypes of the false-positive findings FP-A and FP-B were 27 and five in GC group, and six and three in the CRC group, respectively.

Table 1 Comparison of the characteristics between the patients with gastric and colorectal cancers

	Gastric cancer $n = 161$	Colorectal cancer $n = 97$	P-value
Age (years)			
Median (range)	68 (26–88)	70 (37–86)	0.11
Gender (male/female)	106/55	55/42	0.14
Chronic diseases or smoking[a]	46 (29%)	34 (35%)	0.17
Preoperative marker elevation	12 (8%)	25 (29%)	<0.01
Operation[b]			
DG/TG/other	104/56/1	–	–
Ri/L/Re/M	–	32/32/30/3	–
Stage (0–I/II–III)	108/53	20/77	<0.01
Pathology (diff/undiff/other)[c]	73/82/6	89/6/2	<0.01
Adjuvant therapy	25 (16%)	34 (35%)	<0.01
Recurrence	22 (14%)	22 (23%)	0.08
Follow-up period (months)			
Median (range)	29.4 (6.4–61.3)	30.6 (6.4–62.2)	0.63

[a] History of chronic benign disease possibly influencing the marker elevation, such as bronchitis, renal dysfunction, liver dysfunction, diabetes mellitus, and inflammatory bowel disease

[b] DG, distal gastrectomy; TG, total gastrectomy; Ri, right-side colon; L, left-side colon; Re, rectum; M, multiple locations

[c] Diff, differentiated adenocarcinoma; Undiff, undifferentiated carcinoma

Table 2 Recurrence and the sensitivity, specificity, and accuracy of tumor marker monitoring

	Marker positive	Marker negative	Total
(A) Gastric cancer			
Recurrence (+)	14	8	22
Recurrence (–)	32	107	139
Total	46	115	161
(B) Colorectal cancer			
Recurrence (+)	18	4	22
Recurrence (–)	9	66	75
Total	27	70	97

(C) Comparisons of the sensitivity, specificity, and accuracy between patients with gastric cancer and those with colorectal cancer

	Gastric cancer (%)	Colorectal cancer (%)	P-value
Sensitivity	63	82	0.31
Specificity	77	88	0.06
Accuracy	75	87	0.03

False-positive findings for tumor marker in cancer-free patients tended to be more frequently observed after gastrectomy than after colorectal surgery (23% versus 12%, $P = 0.06$). The histories of chronic disease in the FP patients ($P = 0.77$), elevated marker (CEA or CA19-9) ($P = 0.83$), and the time at postoperative marker elevation ($P = 0.93$) were not different between the two groups. FP in the GC group occurred in patients who had an earlier stage of cancer (stage 0–I) than that in the CRC group ($P < 0.01$). Although the prevalence of FP-B was not different between the two groups (4% in each, $P = 0.88$), that of FP-A was significantly higher in the GC group than in the CRC group (19% versus 8%, $P < 0.01$). The population of subtypes TP-A and TP-B were nine and five in the GC group, and 17 and one in the CRC group, respectively. The frequency of true positive was not different between the two groups; however, the real sensitivity to detect recurrence prior to or at least at the same time as radiological/physical examination, indicating TP-A, was higher in the CRC group than that in the GC group (41% versus 77%, $P = 0.03$).

To determine the role of marker monitoring in the early detection of recurrence after operation, the patients were divided into two groups according to the stage contribution (stage 0-I versus stage II-III), and the data were compared between the GC and CRC groups. The recurrence rate of early stage (0–I) was low in both the GC (2.8%) and CRC groups (10%), while in the advanced stage (II–III), the recurrence rate was 36% in GC and 26% in CRC group (Table 4). Notably, the sensitivity of marker monitoring in advanced cancer tended to be higher in the CRC than in GC group (58% versus 85%, $P = 0.06$), and furthermore, the real sensitivity to detect the recurrence prior to or at the same time as the radiological/physical examination (TP-A) was better in the CRC group than in the GC group (37% versus 80%, $P < 0.01$, Table 4).

Table 3 Comparison of the postoperative changes in tumor markers between the gastric and colorectral cancer groups

Recurrence +/–	Gastric cancer 22/139 (n = 161)	Colorectal cancer 22/75 (n = 97)	P-value
Evaluation of false-positive marker			
FP[a] (specificity)	23% (32 of 139)	12% (9 of 75)	0.06
	77%	88%	
FP-A	19% (27 of 139)	8% (6 of 75)	0.03
FP-B	4% (5 of 139)	4% (3 of 75)	0.88
Chronic diseases in FP	50% (16 of 32)	55% (5 of 9)	0.77
Elevated marker (CEA/CA19-9)	17/16[*]	5/4	0.83
Stage at operation (0–I/II–III)	22/10	1/8	<0.01
Operation[b]			
DG/TG/other	14/17/1	–	–
Ri/L/Re/M	–	3/3/2/1	–
POM at marker elevation[c]			
Median (range)	11.2 (1.9–42.8)	15.6 (3.3–34.2)	0.93
Evaluation of recurrence			
TP (sensitivity)[d]	64% (14 of 22)	81% (18 of 22)	0.18
Real sensitivity (TP-A/TP-B & FN[d])	41% (9/13)	77% (17/5)	0.03
Elevated marker (CEA/CA19-9)	10/4	17/4[*]	0.51
Stage at operation (0–I/II–III)	3/19	2/20	>0.99
POM at recurrence[b]			
Median (range)	13.1 (0.7–41.0)	12.5 (3.5–45.5)	0.38

[a] FP, false positive

[b] DG, distal gastrectomy; TG, total gastrectomy; Ri, right-side colon; L, left-side colon; Re, rectum; M, multiple locations

[c] POM, postoperative months. There was no difference between the time at marker elevation of FP and that at recurrence in either gastric and colorectal cancer

[d] TP, true positive; FN, false negative

[*] One patient (gastric cancer) with false-positive marker results and three (colorectal cancer) with true-positive results showed both CEA and CA19-9 elevations postoperatively

Discussion

The present study comparing the changes in tumor marker levels after curative resection of GC and CRC demonstrated several findings: (1) the frequency of false-positive tumor marker after curative gastrectomy, especially FP-A, was significantly higher in the GC group than in the CRC group, while the histories of the benign chronic diseases or smoking did not differ between the two groups, (2) the sensitivity of marker monitoring regarding the early detection of the recurrence was higher in patients with CRC than those with GC, especially in advanced stage, (3) a lower prevalence of false-positive findings and a higher sensitivity for the detection of recurrence seemed to contribute to the higher accuracy of marker monitoring after colorectal surgery, compared with that after a gastrectomy.

We previously demonstrated that patients with false-positive marker results after curative gastrectomy for gastric cancer tend to have a history of chronic benign diseases or smoking [17], and in this study about half of the patients with postoperative false-positive marker results had such histories in both the GC and CRC groups. However, the frequency of the false-positive results following GC was significantly higher than that after CRC, especially in FP-A. FP-B would depend on the patients' preoperative characteristics, while FC-A might be affected by the type of operation. As expected, although the prevalence of FP-B did not differ between the two groups (4% in each), that of FP-A was significantly higher in the GC than in the CRC group (19% versus 8%). Thus, a gastrectomy itself might influence the postoperative elevation of tumor markers even without recurrence. The type of operation such as distal or total gastrectomy does not seem to be a positive factor [17]. A gastrectomy has been reported to cause a deterioration in the glucose metabolism and dumping syndrome due to disruption of the pyrolus ring or hormonal abnormalities and a nonphysiological reconstruction route, and to lead cholestasis and liver dysfunction because of

Table 4 Comparison of the role of tumor marker monitoring in the early detection of recurrence between the gastric and colorectal cancer groups, according to tumor stage

	Gastric cancer	Colorectal cancer	*P*-value
Stage 0–I	*n* = 108[a]	*n* = 20	
Recurrence	3 (2.8%)	2 (10%)	0.13
TP (sensitivity)[b]	100% (3 of 3)	50% (1 of 2)	0.17
Real sensitivity (TP-A/TP-B&FN[c])	67% (2/1)	50% (1/1)	0.71
Stage II–III	*n* = 53	*n* = 77	
Recurrence	19 (36%)	20 (26%)	0.23
TP (sensitivity)[b]	58% (11 of 19)	85% (17 of 20)	0.06
Real sensitivity (TP-A/TP-B & FN[c])	37% (7/12)	80% (16/4)	<0.01

[a] Stage 0 is not available for gastric cancer

[b] TP, true positive

[c] FN, false negative

disruption of the vagal nerve [18–20]. These factors might accelerate the elevation of the markers in some cases, even without recurrence after a curative gastrectomy. Further investigation is required to clarify the precise mechanism behind the frequent observation of false-positive tumor markers after a gastrectomy.

Twenty-two of the 32 patients (69%) with false-positive findings for tumor markers had stage I of GC. In addition, as shown in Table 4, recurrence occurred in only 2.8% of stage I gastric cancer. Marker monitoring after a gastrectomy might not be applied routinely for all the patients with stage I of GC, because of the low recurrence rate as well as frequent findings for false-positive markers. Furthermore, even in the advanced stage of GC, the sensitivity of marker monitoring for early detection of cancer recurrence is not very high (37%, compared with 80% of CRC). On the other hand, marker monitoring might be recommended after the curative resections for CRC, because of the high population of advanced stage under the current operative indications for CRC, the high sensitivity for detection of the recurrence, and the low rate of false-positive findings for tumor markers. Several reports have demonstrated the efficacy of tumor marker monitoring for the detection of recurrence after curative resections of both GC and CRC [3–10]. However, there is little data available on the characteristics of false-positive findings for tumor markers and comparison of the role of marker monitoring after curative resections of those cancers. The current study might provide the critical information in reconsidering the different roles of marker monitoring after curative resections of GC and CRC.

Recent advances in endoscopic techniques provide excellent screening for the early detection and treatment of gastrointestinal malignancy. However, the different biological behavior of cancers in each site and anatomical problems influence the choice of treatment [20–23]. Many patients with early GC still underwent a gastrectomy, because of the high prevalence of undifferentiated carcinoma, which is a contraindication for endoscopic submucosal dissection in many institutions, and the difficulty in endoscopic treatment due to the anatomical location or the unclear margin of the lesion [20–23]. On the other hand, most early colon cancers show a polyploid appearance with a differentiated type of adenocarcinoma, which is suitable for endoscopic resection [24]. As a result, surgeons encounter advanced-stage cases of CRC more frequently than for GC. As described above, there are several differences in the patients' background between GC and CRC, and there might be a difference in the postoperative courses in those patients. The current study was attempted to investigate such a different postoperative course with regard to tumor marker monitoring.

In conclusion, a false-positive finding for tumor markers was frequently observed after curative resection for gastric cancer, especially in patients with an early stage of cancer. The sensitivity of marker monitoring regarding early detection of recurrence was higher in patients after operation for colorectal cancer than that for gastric cancer. Therefore, surgeons and oncologists should be aware that the efficacy of tumor marker monitoring after curative operation differs between patients with GC and CRC.

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