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Tumor Markers (CEA, CA19-9, TPA) in Portal Blood in Colorectal Cancer Patients

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ABSTRACT : The Carcinoembryonic antigen (CEA), CA19-9 and Tissue Polypeptide Antigen (TPA) levels in portal blood in colorectal cancer patients were studied in correlation with the peripheral blood levels and histopathologic findings in order to know serum levels increased. 1) Portal blood CEA, CA19-9 and TPA increased by operative maneuver. 2) Mean values of these markers in portal blood were higher than those in peripheral blood. 3) Portal blood CEA was correlated with Dukes' staging, and revealed higher positive rates than CEA in peripheral blood in each stage. Portal CA19-9 changed within normal value and strikingly rose in Dukes' D stage. Portal TPA tends to be higher in all stages and correlated with grades, but the value in Dukes' D were lower than that of peripheral blood. 5) Moderately differentiated adenocarcinoma revealed the highest level of portal CEA ($P<0.05$), but portal CA19-9 and TPA did not indicate any correlation with cell differentiation. 6) The mean values of portal and peripheral CEA, CA19-9 and TPA showed significant elevation in those with infiltration of cancer cells extending through the proper muscle layer. This study suggests that the mechanism of these markers' transfer from tumor into the portal vein is the most important decisive factor of the peripheral levels.

INTRODUCTION

Among various tumor markers of colorectal cancer, the carcinoembryonic antigen (CEA) is the most valuable tumor marker and its assay is now widely used[1~4]. On the other hand, CA19-9 and Tissue Polypeptide Antigen (TPA) are also used for colorectal cancer, althoug these assays increased in carcinomas of hepatobilliary tract, pancreas, stomach and intestine[5~7]. However, about half of the patients with colorectal cancer do not indicate elevated levels of these markers in peripheral blood. It has been considered that the level of these markers in peripheral blood does not fully reflect the cancer tissue. Most researches about the mechanism of elevated blood levels of the markers have been concerned with the assessment of the markers in peripheral blood, using the histopathological findings of the tumor[6~8], and the measurement of markers in extracts of tumor,

but a few has studied portal markers levels[3, 10]. In the present study, we measured portal CEA, CA19-9 and TPA levels from the blood of the drainage vein which was drawn during the surgical operations of the patients with colorectal cancer, and studied the relationship between portal and peripheral levels of the markers and histopathological findings.

MATERIALS AND METHODS

Patients

One-hundred and thirty patients who underwent resection for primary colorectal cancer at the First Deparment of Surgery, Nagasaki University Hospital sine 1983 were examined. The number of cases which were studied portal CEA, CA19-9 and TPA were shown in **Table 1.** Those who were affected with multiple cancer and/or double cancer were excluded.

Blood-collecting from the portal vein

A catheter was inserted into the main trunk of the drainage veins from the primary tumor, and collected the blood sample from the marginal vein close to the tumor. To avoid the influence of the surgical maneuver, blood collecting was done immediately after laparotomy. On the other hand, to know the alterations of the portal blood levels of CEA, CA19-9 and TPA caused by the surgical maneuver, portal blood sample was also collected at the time of resection of the colon and rectum.

Radioimmunoassay

The radioimmunoassays using in this study were: Sandwich method using Dinabot-RIA Kit in CEA, RIA Kit in CA19-9 and RIA double antibody method (Centcorner Co.) in TPA.

Histopathological Study

The section for histological study of the tumor was obtained from the central part and bilateral part of the tumor, and they were fixed in 10% formaldehyde and embedded in paraffin and stained by hematoxylin and eosin. Dukes' staging classification was employed as a measure of the clinical staging of the colon and rectum.

RESULTS

Alteration of Portal Levels of CEA, CA19-9 and TPA during the Operation

In order to know the alterations of the portal blood levels of the markers which were caused by the surgical maneuvers, the portal blood samples were collected on laparotomy and on resection of the tumor. Portal blood levels on resection were higher than those on laparotomy in each markers (**Fig. 1**). The mean CEA levels on laparotomy was significantly differed from that on resection. The mean values of CA19-9 and TPA on laparotomy were higher than those on resection. However, there were no significant differences between the levels immediately after laparotomy and those after surgical maneuver, respectively.

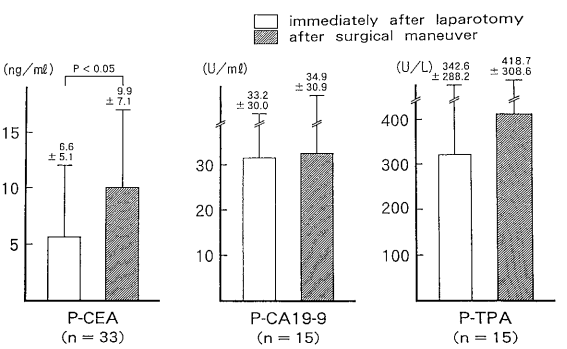

Fig. 1. Alterations of the Portal CEA levels by the Surgical Maneuvers

Table 1. Portal and Peripheral Blood Levels of CEA, CA19-9 and TPA

Markers	No. of patients	Portal values		Peripheral values		Pv>Sv (%)
		Mean ± SD	Positive rate (%)	Mean ± SD	Positive rate (%)	
CEA (2.5ng/ml)	77	13.2 ± 32.3	57.1	8.0 ± 10.2	48.5	75.0
CA19-9 (37U/ml)	44	38.4 ± 64.9	23.4	38.8 ± 54.7	28.5	83.8
TPA (100U/L)	47	160 ± 267	65.2	157.8 ± 89.8	55.2	57.9

( ): Cut off levels Pv: Portal levels Sv: Peripheral levels

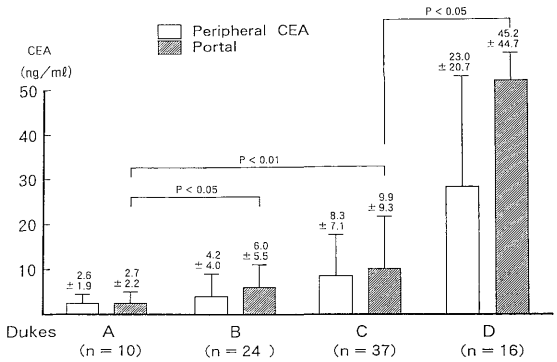

Fig. 2. Dukes' stage, Portal CEA and Peripheral CEA

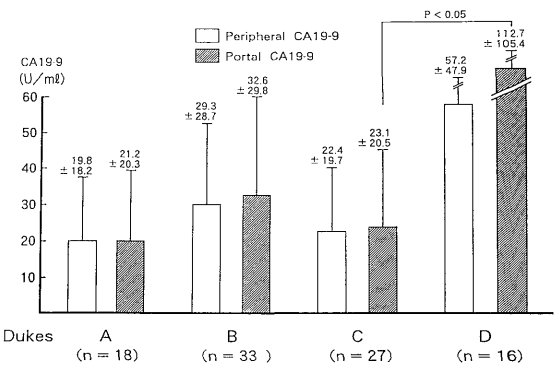

Fig. 3. Dukes' stage, Portal CA19-9 and Peripheral CA19-9

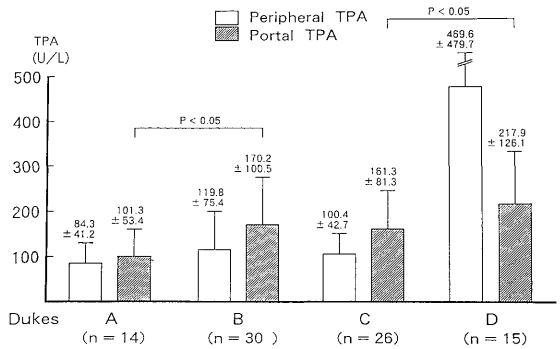

Fig. 4. Dukes' stage, Portal TPA and Peripheral TPA

Portal and Peripheral Values of CEA, CA19-9 and TPA

Table 1 showed the mean values and positive rates of CEA, CA19-9 and TPA in portal and peripheral blood. In peripheral blood, the positive rates were 48.5% in CEA, 28.5% in CA19-9 and 55.2% in TPA. The mean values of CEA and TPA were higher than those of cut off levels, and the portal values were higher than the peripheral ones, but the mean values of portal and peripheral CA19-9 were the same of cut off levels. The incidence of the cases in which the portal levels were higher than the peripheral levels were 75% in CEA, 83.8% in CA19-9 and 57.9% in TPA.

Dukes' Staging and Portal Levels of CEA, CA19-9 and TPA

The relationship between Dukes' staging and portal and peripheral levels of CEA, CA19-9 and TPA were shown in **Fig. 2, 3** and **4**. The mean value of serial CEA in peripheral blood and in the portal blood on Dukes' D stage was significantly higher than those on Dukes' A and Dukes' B and Dukes' C. In portal CA19-9, Dukes' D stage which were accompanying peritoneal dissemination and/or liver metastasis revealed a remarkable rise with a mean values of 112.7± 105.4ng/ml. However, there was no close correlation between portal and peripheral levels. TPA levels in portal blood tend to be higher in all stages with correlation with grades. Significant difference between Dukes' A and Dukes' B was observed in portal TPA, and the levels of Dukes' D were significantly higher than those of other stages. But the mean values of portal TPA in Dukes' D were lower than that of peripheral blood.

Cancer Invason in Colorectal Wall and Portal and Peripheral Levels of CEA, CA19-9 and TPA

The mean values of portal and peripheral CEA showed significant elevation in those with infiltration of cancer cells extending through the proper muscle layer (pm). The positive rate of portal CEA in those with subserosal or serosal invasion was higher than that of peripheral CEA. Significant elevation was also noted in portal and peripheral CA19-9, same as those of CEA, between proper muscle layer and subserosal layer, but the changes of values were within normal values. The mean values of portal and peripheral TPA were higher in those with subserosal layer than in those with proper muscle layer, but there was no significant difference between the values of proper muscle layer and that of subserosal layer (**Table 2**).

Table 2. Cancer Invasion in Colorectal Wall and Portal and Peripheral Levels of CEA, CA19-9 and TPA (Mean ± SD)

Cancer invasion	CEA (ng/ml)		CA19-9 (U/ml)		TPA (U/L)	
	Portal	Peripheral	Portal	Peripheral	Portal	Peripheral
pm	3.2 ± 2.4*	3.1 ± 2.3*	14.0 ± 9.9*	15.7 ± 12.3*	105.7 ± 69.0	83.9 ± 62.8
ss	10.2 ± 11.3	8.2 ± 10.2	36.3 ± 29.5	34.7 ± 37.1	157.4 ± 88.0	200.0 ± 251.9
s	33.6 ± 31.7	8.7 ± 8.9	28.8 ± 35.6	30.7 ± 22.6	215.1 ± 107.2	125.3 ± 67.5
si	22.2 ± 13.1	12.3 ± 13.1	20.7 ± 17.6	43.9 ± 40.6	169.8 ± 62.3	159.1 ± 122.9

pm: proper muscle layer ss: subserosal layer s: serosal layer
* Significant difference in cancer invasion extending through pm ($p<0.01$) by the Student's *t* test

Table 3. Tumor Differentiation, Portal Values of CEA, CA19-9 and TPA (Mean ± SD)

Cell differentiation	CEA (ng/ml)	CA19-9 (U/ml)	TPA (U/L)
Well	6.0± 7.8*	22.7±10.5	140.8± 57.2
Moderately	18.0±41.4	29.2±27.5	167.0± 98.2
Poorly	5.1± 3.7	21.5±19.8	384.2±427.3
Mucinous	6.5± 3.1	43 ±31.7	119.7± 88.0

* Significant difference between well and moderately differentiated adenocarcinoma ($p<0.05$)

Tumor Differenciation and Portal levels of CEA, CA19-9 and TPA

The mean values of portal CEA of moderately differentiated adenocarcinoma was significantly higher than that of well differentiated andenocarcinoma ($p<0.05$) (**Table 3**). However, there was no significant correlation between cell differentiation of adenocarcinoma and peripheral blood CEA. Two out of five patients with poorly differentiated or mucinous carcinoma were positive of portal CEA, but the mean values of CEA were lower than that of moderatelety differentiated adenocarcinoma.

The mean values of portal CA19-9 and TPA did not indicate the significant correlation with any cell differentiations.

DISCUSSION

In patients with colorectal cancers, several factors contributing to elevated peripheral levels of tumor markers were pointed out[11~13]; 1) markers' productivity of tumor 2) release of markers from tumor into blood stream 3) clearance of circulating tumor markers. In this study, we found that portal levels of CEA, CA19-9 and TPA were higher than peripheral levels and elevated after surgical maneuvers. This fact suggests that most of these markers flows from tumor tissues into peripheral blood vessels via the portal vein.

Portal CEA levels correlated with Dukes' grading and reflected the progression of the cancer better than peripheral CEA levels. Portal CEA levels were especially high in the case of tumors with invasion over the intestinal walls. What is more, portal CEA levels were found to correlate with the differentiation of tumor. Pathologically, portal CEA levels were most strongly correlated with the progression of cancer, that is, cases with cancerous invasion over intestinal walls tended to indicate high portal CEA levels. In terms of tumor differentiation, moderately differentiated adenocarcinoma showed significantly higher portal CEA levels than well differentiated ones. This fact is assumed to reflect the phenomenon that moderately differentiated adenocarcinoma contains a large amount of CEA and has wide distribution of CEA shown by immunohistochemical staining[2, 3, 11, 14]. On the other hand, well differentiated adenocarcinoma revealed low portal CEA levels in comparison with other tumor type, though it contained a large amount of CEA[14]. This can be explained by that most of the CEA in the tumor was excreted into the lumen of intestine and only a little was released into portal vein. Poorly differentiated adenocarcinoma and mucinous cancer showed low portal CEA levels. This appears to reflect the fact that these carcinomas contained low CEA[3]. Portal CEA levels correlated well with invasion of tumor, but not with peripheral CEA levels. This difference might be caused mainly by the metabolism in the liver, since CEA flows

the portal vein into the systemic circulation through the liver[13].

Portal CA19-9 levels changed within normal value and showed a striking rise in Dukes' D stage accompaing peritoneal dissemination and/or liver metastasis. It has been reported that positive rate of serum CA19-9 for colorectal cancer patients ranged from 21%-36%[4, 5, 15]. In the present syudy, we also found low positive rates of portal CA19-9 as well as those of peripheral one. Eighty-five per cent of the cases, however, had a higher portal CA19-9 levels than peripheral CA19-9 levels. It has been reported that the colorectal carcinoma contained high CA19-9[6]. These findings suggests that CA19-9 transfer from tumor into the portal vein, and that the high levels in Dukes' D might be caused by production of metastatic lesion.

General agreement has been obtained by many investigators that serial TPA was not specific for colorectal carcinoma, because most of the patients with gastrointestinal cancer showed a remarkable rise of TPA, and that the positive rates of serial TPA for colorectal cancer patients were 50%-70%[4, 16, 17]. In this study, the portal values tend to correlate with Dukes' staging, but the mean values of portal TPA in Dukes' D were lower than that of peripheral blood. This difference might be caused by transfer from metastatic tumors and/or by specificity of TPA per se such as cytotoxicity or acute phase reactant[7,17]. It has been also recognized that the cancerous tissues of colon and rectum contained as high as ten times of TPA values as compared to normal colorectal mucosa[7]. We found that 58% of the cases showed higher levels in portal TPA than that in peripheral blood. These findings suggest that the mechanism of TPA transfer from tumor into portal vein is the most important factor to evaluate the TPA values in peripheral blood vessels.

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