

## Minute liver metastases from a rectal carcinoid: A case report and review

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### Abstract

We here report a 43-year-old male patient with minute liver metastases from a rectal carcinoid. Hepatic nodules were diagnosed during surgery, although they were not diagnosed by preoperative computed tomography or ultrasound examination. The rectal carcinoid was resected together with liver metastases and the patient has had no disease recurrence for 5 years following postoperative treatment of hepatic arterial infusion chemotherapy (HAIC) using 5-fluorouracil (5-FU) and oral administration of 1-hexylcarbamoil-5-fluorouracil (HCFU). In 2003, a health check examination indicated presence of occult blood in his stool. Barium enema study revealed a rectal tumor in the lower rectum and colonoscopy showed a yellowish lesion with a size of 30 mm in diameter. Pathological examination of the biopsy specimen indicated that the rectal tumor was carcinoid. Although preoperative imaging examinations failed to detect liver metastases,

2 min nodules were found on the surface of liver during surgery. A rapid pathological examination revealed that they were metastatic tumors from the rectal carcinoid. Low anterior resection was performed for the rectal tumor and the pathological report indicated that there were 4 metastatic lymph nodes in the rectal mesentery. The patient received treatment by HAIC using 5-FU plus oral administration of HCFU and survived for 5 years. We also review world-wide current treatments and their efficacy for hepatic metastases of carcinoid tumors.

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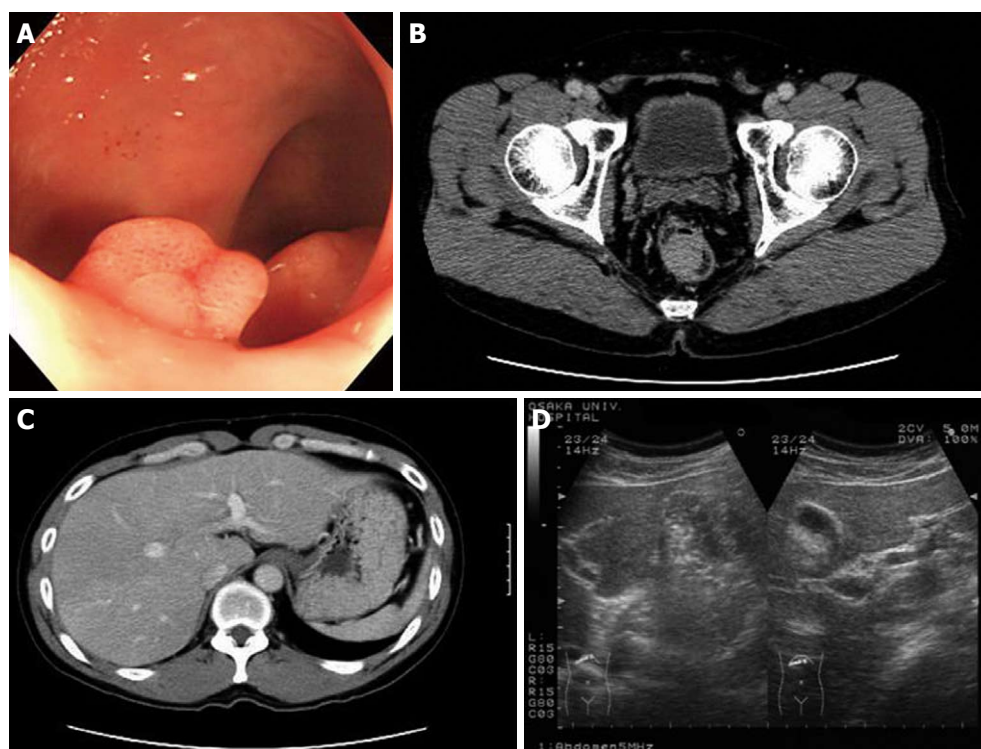
**Key words:** Hepatic arterial infusion chemotherapy; Rectal carcinoid; Liver metastasis; 5-Fluorouracil

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### INTRODUCTION

It is reported that the incidence of liver metastasis from gastrointestinal carcinoids is 16.7% (155 of 928) and the mean life span is approximately 2 years once liver metastasis is diagnosed<sup>[1-2]</sup>. With progress in treatments such as hepatic-artery embolization, radio-frequency thermal ablation, liver transplantation and others, the life span has been improved recently<sup>[3]</sup>. We report here a case of rectal carcinoid in a 43-year-old male with minute liver metastases that were diagnosed during surgery although preoperative computed tomography (CT) and ultrasonography (US) examination did not detect them. We employed hepatic



**Figure 1 Preoperative colonoscopy and image examinations.**

A: Colonoscopy showed an elevated yellowish lesion with a slight central depression of which size was 30 mm in diameter, in the lower rectum; B: A tumor was present on the right wall of the lower rectum by computed tomography (CT) scan; C: Abdominal CT failed to show any obvious abnormalities in the liver; D: No obvious lesions were detected in the liver by ultrasonography.

**Table 1 Blood test and urine 5-HIAA**

WBC	6830/ $\mu$ L	AST	21 IU/L
RBC	506 $\times 10^4$ / $\mu$ L	ALT	21 IU/L
Hb	15.4 g/dL	T.Bil	0.4 mg/dL
Ht	44.4%	T.P.	6.7 g/dL
Plt	20.2 $\times 10^4$ / $\mu$ L	Alb	3.9 g/dL
		CRP	< 0.2 mg/dL
Na	140 mEq/L	CA19-9	< 5.0 U/mL
K	4.2 mEq/L	CEA	1.0 ng/mL
Cl	107 mEq/L		
BUN	14 mg/dL		
Cr	0.8 mg/dL	Urine 5-HIAA	1.3 mg/L

5-HIAA: 5-Hydroxy indole acetic acid.

arterial infusion chemotherapy (HAIC) using 5-fluorouracil (5-FU) and systemic administration of the oral 5-FU derivative 1-hexylcarbonyl-5-fluorouracil (HCFU) as post-operative adjuvant therapy. The patient eventually survived 5 years after surgery without disease recurrence. Although the standard therapy for liver metastasis from carcinoid tumors has not been established in the world, several attractive strategies are currently provided, being reviewed together in this report.

## CASE REPORT

A 43-year-old male patient entered our hospital in March 2003 because of a positive occult blood test on his stool samples. Through a barium enema study, a rectal tumor was suspected. He presented no carcinoid syndrome symptoms such as flushing, diarrhea, pellagra, cyanosis, and others. The results of blood test and level of 5-hydroxy indole acetic acid in the urine was within the normal range (Table 1).

## Colonoscopy

Colonoscopy showed an elevated yellowish lesion in the lower rectum of 30 mm in diameter and with a slight central depression (Figure 1A). Pathological examination of biopsy samples revealed that this was a carcinoid tumor (data not shown).

## Image examinations

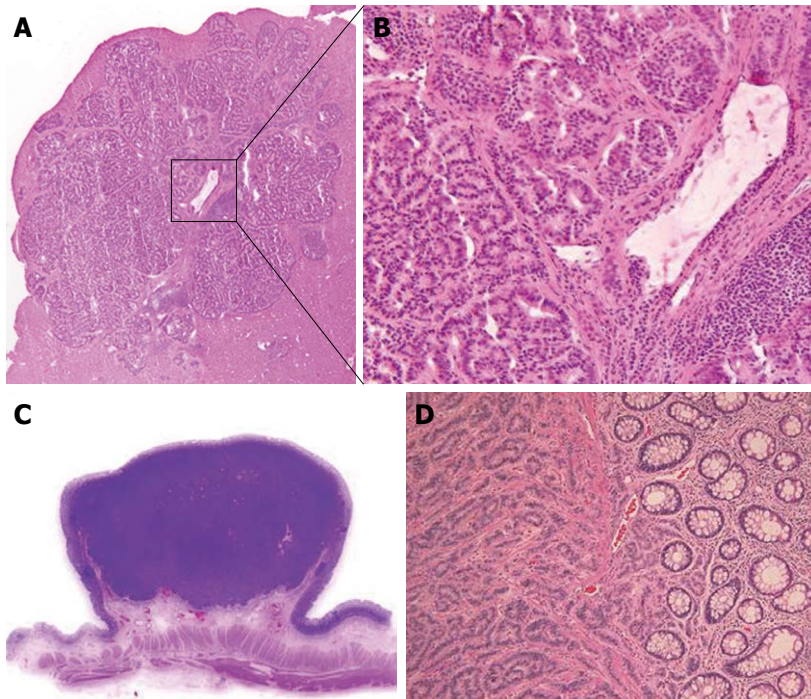
CT scanning showed a tumor on the right wall of the lower rectum (Figure 1B). Abdominal CT failed to show any obvious abnormalities in the liver (Figure 1C). No obvious lesions were detected in the liver by abdominal US (Figure 1D).

## Operation

During surgery, we perceived 2 min nodules through hand palpation of the surface of left liver lobe (S2 and S3). The nodules were hard and white and were both 2 mm in diameter. A rapid pathological examination revealed that the tumors were metastatic carcinoid (Figure 2A and 2B). Other hepatic abnormalities were not detected by intra-operative US. Low anterior resection of the rectum and partial resection of the liver (S2 and S3) were performed. The metastatic tumors were very small, indicating early phase metastases, and it was therefore likely that other latent metastases might be present in the liver. During surgery, we made preparation to carry our HAIC as a post-operative adjuvant chemotherapy, i.e. ligation of the right gastric artery and cholecystectomy to prevent the side effects such as gastric ulcer and cholecystitis, associated with HAIC.

## Histopathological examination

Following staining of the primary rectal tumor with



**Figure 2** Histopathology of liver metastasis and primary tumor. A: Histopathology of a hepatic nodule (Magnification:  $\times 20$ ). A section was stained by hematoxyline & eosin (H&E) solution; B: Magnified image of (A) (Magnification:  $\times 100$ ): The tumor cells were homogeneous and spherical, forming ribbon-like structures, which was compatible with the carcinoid tumor; C: Resected rectal tumor. A loupe image; D: Histopathology of the rectal tumor (Magnification:  $\times 100$ ): Identical histopathological features to that of liver metastasis were confirmed.

**Table 2** Hepatic resection for gastrointestinal carcinoid tumors

Author	n	5-year survival rate (%)	Ref.
Chamberlain <i>et al</i> (2000)	14	78	[14]
Nave <i>et al</i> (2001)	21	48	[15]
Norton <i>et al</i> (2003)	13	77	[16]
Sarmiento <i>et al</i> (2003)	120	62	[17]

**Table 3** Liver transplantation for gastrointestinal carcinoid tumors

Author	n	5-year survival rate (%)	Ref.
Le Treut <i>et al</i> (1997)	15	69	[18]
Lehnert (1998)	36	50	[19]
Coppa <i>et al</i> (2001)	9	70	[20]

hematoxyline and eosin, histopathological examination showed homogeneous spherical cells, forming ribbon-like structures, compatible with the carcinoid tumor (Figure 2C and D). The tumor penetrated into the muscular propria without evidence of venous invasion or lymph duct invasion. There were 4 lymph node metastases within the rectal mesentery.

### Post-operative adjuvant therapy

On the 35th day after surgery, a catheter was inserted from the left subclavian artery and the tip was set along common hepatic artery by the radiologists. HAIC using 5-FU started via the subcutaneous port. A dose of 1250 mg 5-FU was administered every week, and a total of 21 HAICs were performed. In addition, oral 5-FU, HCFU (Carmofur: 300 mg/d) was administered for one and half years as the lymph node metastases were positive. The patient was alive after 5 years without disease recurrence.

**Table 4** Hepatic artery chemoembolization and hepatic artery embolization for metastatic carcinoid tumors

Author	%	Chemotherapy	Ref.
HACE			
Hajarizadeh <i>et al</i> (1992)	50.0 (4/8)	5-FU	[23]
Ruszniewski <i>et al</i> (1993)	33.3 (6/18)	DOX	[24]
Therasse <i>et al</i> (1993)	35.2 (6/17)	DOX	[25]
Kim <i>et al</i> (1999)	25.0 (4/16)	CDDP, DOX	[26]
Roche <i>et al</i> (2003)	42.8 (6/14)	DOX	[27]
	Total 35.6 (26/73)		
HAE			
Carrasco <i>et al</i> (1983)	83.3 (5/6)		[28]
Hanssen <i>et al</i> (1989)	71.4 (5/7)		[29]
Moertel <i>et al</i> (1994)	69.6 (16/23)		[30]
Wangberg <i>et al</i> (1996)	42.5 (17/40)		[31]
Eriksson <i>et al</i> (1998)	37.9 (11/29)		[32]
Loewe <i>et al</i> (2003)	72.7 (16/22)		[33]
	Total 55.1 (70/127)		

HACE: Hepatic arterial chemoembolization; HAE: Hepatic arterial embolization, CR: Complete response; PR: Partial response; CDDP: cisplatin; DOX: Doxorubicin; HAIC: Hepatic arterial infusion chemotherapy.

## DISCUSSION

The 5-year survival rate of colorectal carcinoid is 72%-98%. However, once distant metastasis occurs the prognosis becomes poor<sup>[3-6]</sup>. In cases with liver metastasis, the 5-year survival rate is reported to be 19%-38%<sup>[7]</sup>. In Japan, most colorectal carcinoids are located in the rectum, mainly within 10 cm from the dentate line (80% of rectal carcinoids)<sup>[8]</sup>. Carcinoid tumors originate from the endocrine cells that produce certain amines and peptides. These cells are originally located in the deep mucosa. Once neoplastic changes occur, the tumor looks like a submucosal one following expansive growth.



Table 5 Reports of HAIC for hepatic metastasis of carcinoid tumor in Japan (1993 ~ 2006)

Age (yr)/ Gender	5FU	MMC	ADM	Agents CDDP	MTX	VP16	FAR	Combined therapy	Effects	Ref.
69/M	o	o					o	-	PR	[35]
70/F	o			o				-	IR	[36]
42/M	o		o					-	PR	[37]
65/F	o				o			-	PR	[38]
56/M		o						5-FU	CR	[39]
52/M	o			o				DSM	PR	[40]
42/F	o							MTX + 5-FU	CR	[41]
3 cases	o	o						DSM	PR	[42]
68/M						o		-	PR	[43]
57/M	o	o		o				DSM	PR	[44]
49/F	o							-	CR	[45]

5-FU: 5-Fluorouracil; MMC: Mitomycin; ADM: Adriamycin; CDDP: Cisplatin; MTX: Methotrexate; VP16: Etoposide; FAR: Farmorubicin; DSM: Degradable starch microspheres; CR: Complete response; PR: Partial response; IR: Incomplete response.

With deeper invasion, the metastatic rate becomes correspondingly higher. The most frequent metastatic sites are lymph nodes and liver, followed by bone and lung. It is reported that the frequency of lymph node metastasis was 0% when the tumor is localized in mucosa, 5.3% in T1, 53% in T2 and 85.7% in T3<sup>[9]</sup>. Saito *et al.*<sup>[10]</sup> also reported a relationship between tumor size and incidence of lymph node metastasis. When the tumor diameter is 6 to 10 mm, the metastasis rate is 0.7%, 11-15 mm: 23%, 16-20 mm: 55.6%, and > 21 mm: 66.7%.

There is a report that even 5mm-sized primary carcinoid tumor cause liver metastasis suggesting that a detailed examination of liver is essential before surgery<sup>[11]</sup>. US and CT scans are both standard modalities for detection of liver metastasis. Chiti *et al.*<sup>[12]</sup> reported that the diagnostic sensitivity and specificity was 82% and 92%, respectively for US, and 73% and 93% for CT scans. In the case of the current patient with 2mm-sized liver metastatic lesions, preoperative abdominal US and CT failed to detect them, although such minute nodules could be easily perceived by hand palpation owing to their solidity. Therefore, intra-operative palpation of the liver surface is particularly important and should be done very carefully.

If the liver metastases are completely resected, surgery is the most effective therapy. The surgical indications include uni-lobar hepatic metastases, and multiple tumors expanding to both hepatic lobes with assurance of complete respectability based on good liver function. However, as approximately 90% of hepatic metastases are found to be multiple lesions in both hepatic lobes, complete resection is a rare event in practice<sup>[13]</sup>. The efficacy of hepatic resection for the gastrointestinal carcinoid tumors is summarized in Table 2<sup>[14-17]</sup>.

Liver transplantation is an alternative treatment and widely adopted in patients with liver metastases from carcinoid tumors. The 5-year overall survival rate ranges from 50%-70% (Table 3)<sup>[18-20]</sup>. Lehnert<sup>[19]</sup> reported that the 5-year survival rate was 50% in 36 patients undergoing liver transplantation. He pointed out that the patients with extra-hepatic disease worsened the whole prognosis. Coppa *et al.*<sup>[20]</sup> proposed that selection of patients with

non-resectable metastatic neuroendocrine tumors for liver transplantation should be performed based on the Milan criteria: young patients < 50 years with confirmed by histology, with < 50% of the liver replaced by metastases, with a primary tumor (originating from the gastrointestinal tract) drained by the portal venous system, an absence of extrahepatic disease and stable disease during the pretransplantation period. They reported that the selected 9 cases who satisfied the criteria had a 70% 5-year overall survival rate and a 53% 5-year disease free survival rate.

Treatments by somatostatin analogues, such as interferon and octreotide have been reported. According to the findings, tumor shrinkage was a rare event although the systemic symptoms due to the carcinoid tumor were lessened<sup>[21-22]</sup>.

Since liver metastases from carcinoids display an abundant tumor vascularity, hepatic arterial chemoembolization (HACE) or hepatic arterial embolization (HAE) are employed in western countries. The efficacy of HACE, in which doxorubicin is often used as a principal drug, is 25%-50% (Table 4, upper column)<sup>[23-27]</sup>. Partial response or complete response) cases were reported with HACE treatment. On the other hand, HAE was able to achieve the higher efficacy of 70%-80%, and appears to confer better therapeutic effects than HACE as a whole (Table 4, the lower column)<sup>[28-33]</sup>.

In Japan, HAIC is often used<sup>[34]</sup>. As shown in Table 5<sup>[35-45]</sup>, continuous 5-FU infusion accompanied by other chemotherapeutic drugs is the basic treatment scheme and conferred favorable effects. Based on these reports, we employed HAIC using 5-FU infusion for the current case. Recently, degradable starch microspheres (DSM) have also been used in combination with HAIC<sup>[40,42,44]</sup>. The anti-tumor efficacy when using DSM is attributed to transient obstruction of hepatic artery and subsequent blood reperfusion, which causes high local concentration of chemo-agents during the early phase and induces free radical oxygen as a late effect<sup>[46]</sup>.

As well for primary hepatocellular carcinoma, radio-frequency ablation (RFA) therapy is also applicable to

liver metastatic lesions from carcinoid tumors. The most appropriate application is in cases where tumor size is less than 3 cm in diameter. Hellman *et al.*<sup>[47]</sup> reported that RFA treatment was performed in a group of 21 patients with a total of 43 carcinoid metastatic liver nodules. Therapeutic efficacy was observed in 15 patients, including 4 cases who attained complete ablation.

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