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Bone metastasis from colorectal cancer in autopsy cases

MASARU KATOH,[1] MASAMITSU UNAKAMI,[2] MITSURU HARA,[2] and SOHTARO FUKUCHI[1]

Departments of [1] Gastroenterology and [2] Pathology, Toranomon Hospital, Toranomon 2-chome, Minato-ku, Tokyo 105, Japan

Abstract: The incidence of bone metastasis from colorectal cancer is reported to be 10.7% in autopsy cases. However, the characteristics of the primary cancers, as well as the patterns of bone metastasis, remain unclear. We analyzed the clinical and autopsy records of 118 patients with primary colorectal cancer treated either surgically or conservatively and eventually autopsied between 1970 and 1987 at Toranomon Hospital in Tokyo. Bone metastasis was detected in 23.7% (28/118). The average age of patients with bone metastasis was lower than that in patients without bone metastasis ($P < 0.02$). Cancers to the rectum and cecum were accompanied by bone metastasis more frequently than cancers of other portions of the colon. Signet-ring cell carcinoma showed a high incidence of bone metastasis ($P = 0.041$). Bone metastasis from colorectal cancer was associated with liver or lung metastases ($P < 0.0001$). These results indicated that bone metastasis from colorectal cancer is not as infrequent as previously described.

Key words: colorectal cancer, bone metastasis, hematogenous metastasis

Introduction

Colorectal cancer is one of the most common malignancies worldwide,[1] and colorectal cancer mortality gradually increased in Japan during the period 1960–1990.[2] Because of better primary tumor control and improved patient prognosis, the significance of distant metastasis in patient management has increased. Metastasis of colorectal cancer has been reported to be most frequently found in the liver, occurring in 57.6% (118/205) of autopsy cases, followed in frequency by metastasis to abdominal lymph nodes (48.3%) and lung (37.6%).[3]

The incidence of bone metastasis from colorectal cancer is reported in the English literature to be 8.6%–10.7%[3,4] in autopsy cases, and 4.7%–10.9% in clinical cases.[5–7] However, the characteristics of the primary cancers, as well as the patterns of metastasis in colorectal cancers with bone metastasis, remain unclear. In this report, we investigated the clinicopathological features of bone metastasis from colorectal cancer in autopsy cases.

Patients and methods

Patients

We analyzed the clinical and autopsy records of 118 patients with primary colorectal cancer treated either surgically or conservatively and eventually autopsied between 1970 and 1987 at Toranomon Hospital in Tokyo, Japan. No particular inclusion creteria were employed, but patients with multiple cancer that included colorectal cancer were excluded from this study.

Classification of primary colorectal cancer and bone metastasis

The location, the gross type, and the histological type of colorectal cancer were classified on the basis of General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus by the Japanese Research Society for Cancer of Colon and

Offprint requests to: M. Katoh, Genetics Division, National Cancer Center Research Institute, Tsukiji 5-chome, Chuo-ku, Tokyo, 104 Japan

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Rectum.[8] The gross type of early colorectal cancer was designated type 0, and that of advanced colorectal cancer was classified as type 1 (protruded type), type 2 (localized ulcerative type), type 3 (infiltrating ulcerative type), type 4 (diffuse infiltrating type), or type 5 (unclassified type).

The entire lengths of the thoracolumbar vertebrae, the left femur, and the sternum of all patients were longitudinally saw-cut and examined for gross metastases on autopsy. Other bones were also examined for metastasis according to the symptoms of patients or the clinical findings. In addition, the bone marrow of the ninth thoracic vertebral body, the fourth lumbar vertebral body, the left femur, and the sternum was examined histologically. Other sites with gross metastasis were also examined histologically.

Bone metastasis patterns were classified as solitary, localized, and multiple types, solitary type being bone metastasis limited to a single bone; localized type, bone metastasis spanning several adjacent bones; and multiple type, bone metastasis with discontinuous distribution.

Statistical analysis

The age of patients was expressed as mean ± SD and analyzed by Student's *t*-test. The difference between the incidence of bone metastasis was analyzed by Fisher's exact test or by χ^2 analysis when samples were of sufficient size. A P value of 0.05 or less in two-tailed tests was considered statistically significant.

Results

Clinical features

Bone metastasis was found in 23.7% (28/118) of patients with colorectal cancer at autopsy (Table 1). The average age of the patients with bone metastasis was lower than that of the patients without bone metastasis ($P < 0.02$ by Student's *t*-test, Table 1).

The major symptoms of the patients with bone metastasis were back pain and lumbago (Table 2). Seventeen patients (60%) were asymptomatic. No pathological fracture was observed in our study.

Elevation of alkaline phosphatase or carcinoembryonic antigen was evident in some patients. Statistical analysis was not performed, since the assay system for alkaline phosphatase and carcinoembryonic antigen had changed during the 20-year period in our hospital. Disseminated intravascular coagulation was suspected in six patients with bone metastasis.

Table 2. Symptoms of bone metastasis

Symptom	No. of patients
Back pain	7
Lumbago	6
Femoral pain	3
Shoulder pain	2
Sternal pain	1
Symptom-free	17

Of the 28 patients with colorectal cancer with bone metastasis, 7 had been suspected to have bone metastasis, and had been clinically diagnosed by X-ray examination and ^{99m}Tc-MDP bone scintigram. X-ray examination in these 7 patients, who were examined because of back pain or lumbago, showed osteolytic changes in 5 patients and osteoplastic changes in 2. There were no false negative cases in patients examined by X-ray to detect bone metastasis. The ^{99m}Tc-MDP bone scintigram showed abnormal uptake in all of the patients examined (3/3): 1 with solitary lesion (third lumbar vertebra), 1 with localized lesion (second to fourth lumbar vertebra) and 1 with multiple lesions (tenth thoracic vertebra, seventh rib, and bilateral clavicles).

Characteristics of primary colorectal cancer

The association between the incidence of bone metastasis and the characteristics of the primary colorectal cancers was analyzed in respect to the location, the gross type, and the histological type (Table 3).

Although no statistical significance could be demonstrated, cancers of the rectum and cecum showed a higher incidence of bone metastasis than those in other parts of the colon, and the incidence of bone metastasis in colorectal cancers of type 4 was higher than that in the other types. The histological type of the primary tumor was apparently unrelated to the incidence of bone metastasis, except for signet-ring cell carcinoma, which showed a high incidence of bone

Table 1. Clinical features of bone metastasis

	No. of patients	Age (years)	Sex (male/female)
Bone metastasis (+)	28	58.7 ± 12.1*	22/6
Bone metastasis (−)	90	65.2 ± 13.5*	67/23

* $P < 0.02$ by Student's *t*-test

Table 3. Incidence of bone metastasis according to location and type of colorectal cancer

Location	Incidence	G type	Incidence	H type	Incidence
Rectum	32.4% (12/37)	Type 0	0.0% (0/6)	Well	17.5% (7/40)
Sigmoid colon	17.1% (6/35)	Type 1	10.0% (1/10)	Mod	25.5% (13/51)
Descending colon	20.0% (1/5)	Type 2	20.0% (13/65)	Por	16.7% (1/6)
Transverse colon	18.2% (2/11)	Type 3	31.6% (6/19)	Sig	75.0% (3/4)*
Ascending colon	18.8% (3/16)	Type 4	50.0% (3/6)	Muc	25.0% (2/8)
Cecum	30.8% (4/13)	Type 5	40.0% (2/5)	Undiff	100% (1/1)

* $P = 0.041$ by Fisher's exact test
G type, Gross type; *H type*, histological type; *well*, well differentiated adenocarcinoma; *mod*, moderately differentiated adenocarcinoma; *por*, poorly differentiated adenocarcinoma; *sig*, signet-ring cell carcinoma; *muc*, mucinous adenocarcinoma; *undiff*, undifferentiated adenocarcinoma

metastasis (3/4, 75.0%, $P = 0.041$ by Fisher's exact test, Table 3).

Patterns of bone metastasis

The pattern of bone metastasis in the 28 patients was solitary type ($n = 10$), localized type ($n = 2$), and multiple type ($n = 16$).

Bone metastasis to lumbar and thoracic vertebrae was frequently observed (Table 4). Six solitary type and 2 localized type were located in the lumbar vertebrae. Two solitary type were located in the thoracic vertebra and the sternum, respectively. Pelvic or long bone metastases were always accompanied by metastases to the lumbar vertebrae.

Association of bone metastasis with other metastasis

All patients with bone metastasis had accompanying liver metastasis, and 21 of the 28 patients with bone metastasis had accompanying lung metastasis ($P < 0.0001$ by χ^2 analysis, Table 5).

Discussion

In this report, we analyzed the clinicopathological features of bone metastasis from colorectal cancer in patients that were autopsied. The incidence of bone metastasis from colorectal cancer (23.7%) was higher than that in previous reports,[3,4] probably because we looked carefully for bone metastasis as a routine procedure.

Table 4. Site of bone metastasis

Site	No. of patients
Lumbar vertebra	21
Thoracic vertebra	17
Sternum	5
Rib	5
Femur	5
Sacral vertebra	4
Cervical vertebra	2
Ileum	2

Table 5. Association between bone metastasis and other distant metastasis

	Incidence of other distant metastasis	
	Liver	Lung
Bone metastasis (+)	100% (28/28)*	75.0% (21/28)**
Bone metastasis (−)	54.0% (49/90)*	32.0% (29/90)**

*; ** $P < 0.0001$ by χ^2 analysis

The average age of patients with bone metastasis was lower than that of those without bone metastasis ($P < 0.02$). This tendency has also been reported in gastric cancer.[9] Some genetic alterations may be implicated in the higher incidence of bone metastasis in the younger group.

Cancers of the rectum showed a higher incidence of bone metastasis than those of other portions of the colon (Table 3), which finding agrees with previous peports.[4–7] Multiple genetic alterations occur during multi-step carcinogenesis.[10,11] Colorectal cancer can evolve through the stepwise acquisition of mutations at certain critical genetic loci.[12] In colorectal cancer, activation of the K-*ras* gene, as well as inactivation of the *APC* gene, the *p53* gene, and the *DCC* gene occur.[13] Accumulation of multiple genetic alterations is more common in lesions of the distal colon,[14] which finding may explain, in part, the higher incidence of bone metastasis in rectal cancer.

The incidence of bone metastasis from colorectal cancer was higher in signet-ring cell carcinoma than that in other histological types (Table 3). This tendency is also observed in gastric cancer. Depressed type lesions of gastric cancer (type 3 and type 4), as well as the poorly differentiated type of gastric cancer (signet-ring cell carcinoma and poorly differentiated adeno-

carcinoma), show higher incidences of bone metastasis than other types.[9]

The process of cancer metastasis consists of a series of steps resulting in the spread of malignant cells beyond the site of origin, and the formation of metastases in distant organs. The initiation of bone metastasis begins with the invasion of surrounding normal stroma. Invading cells detach from the primary lesion and are transported to the bone. There are four routes by which tumor cells reach the bone: (a) Tumor cells reach the liver through the portal vein, go to the lungs, and then are distributed through the arterial tree. (b) Tumor cells reach the lungs through the inferior vena cava, and are then spread to the bone. (c) Tumor cells are distributed along lymphatic chains before the lymphatic ducts drain into the venous system. (d) Tumor cells reach the bone directly through the vertebral vein system, described by Batson;[15] this includes internal vertebral veins constituting a longitudinal anastomotic plexus, intraosseous vertebral veins lying within the bone of each vertebra, postvertebral veins, and prevertebral veins. The routes through the lungs may be a major mechanism of bone metastasis, since lung metastasis was detected in 75% (21/28) of the patients with bone metastasis. However, it is also possible that the tumor cells migrate directly from primary lesions to the bone through the vertebral vein system of Batson,[15] since 25% (7/28) of the patients with bone metastasis did not have lung metastasis.

The successful metastatic cell must be viewed as a cell receptive to its environment.[16,17] The outcome of bone metastasis depends not only on anatomical factors such as the blood flow but also on the interaction of unique tumor cells with the microenvironment in the bone. The molecular basis of the intrinsic capacity of the poorly differentiated type of gastric or colorectal cancer cells to colonize the bone is under intense investigation. The identification of specific genetic alterations, as well as the identification of specific tumor markers associated with increased potential for bone metastatsis will lead to improved prognosis for cancer of the gastrointestinal tract.

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