Diagnosis of Colorectal Tumor Invasion by Endoscopic Miniature Probe Ultrasonography

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Summary: We evaluated the diagnostic efficacy of high-frequency (20 MHz) ultrasound probe (HFUP) for the staging of invasive depth of colorectal tumors. The subjects were 27 patients with colorectal tumorous lesions who were treated by endoscopic or surgical operation (11 patients with lesions remaining in the mucosa, 13 patients with submucosal cancer, and 3 patients with cancer invading the muscularis propria or deeper layers). Considering the previous reports that endoscopic mucosal resection (EMR) is indicated in cases of tumors remaining in the mucosa or cancer slightly invading the submucosal layer, we divided the submucosal layer vertically into three equal areas (most superficial, middle and deepest areas which were referred to as sm1, sm2 and sm3, respectively). The depth of tumor invasion in histological specimens was compared to the depth of tumor invasion as assessed preoperatively using the HFUP. The HFUP-based diagnosis was identical to the histological diagnosis in 86.4% of all cases, when the depth of tumor invasion was rated on a three-point scale: (i) m-sm1, (ii) sm2-sm3 or (iii) mp or deeper. These results indicate that the HFUP is very useful in selecting a therapeutic method for colorectal tumors.

Key words colorectal tumor, endoscopic ultrasonography, miniature probe, diagnosis of tumor invasion

INTRODUCTION

In recent years, the superficial colorectal tumors have been frequently detected at many medical facilities [1-3], and endoscopic mucosal resection (EMR) has often been used in these cases [1,4]. The selection of a therapeutic method for early colorectal cancer, especially determination of the indication of endoscopic treatment for this cancer, is a clinically important. Cases of superficial colorectal cancer without lymph node metastasis are absolutely indicated for endoscopic treatment. Cancers remaining in the mucosa are usually free of lymph node metastasis and can be regarded as being indicated for endoscopic treatment. Endoscopic treatment of submucosal cancer is reported to involve several problems. Submucosal (sm) cancers are equally subdivided vertically into sm1, sm2 and sm3, depending on whether or not cancer has invaded the most superficial (sm1), middle (sm2) or deepest (sm3) layer of

the submucosa. Cancers invading the sm1 or less deeply are considered to be indicated for endoscopic treatment, because lymph node metastasis is rare in these cases. Cancers invading the sm2 or sm3 involve higher probability of lymph node metastasis and some probability of distant metastasis, and are therefore considered to be indicated for radical operation, combined with lymph node excision. As to the cancer invading the muscularis propria or more deeper, it is considered to be indicated for more wide area excision of lymph node than sm2 or sm3 cancer. To select the optimum therapeutic method for a given case, it is necessary to accurately assess the depth of tumor invasion on a three-point scale: (i) lesions remaining in the mucosa (m) or sm1, (ii) lesions reaching the sm2 or sm3, and (iii) lesions invading the muscularis propria (mp) or more deeply.

X-rays and endoscopy have conventionally been used to assess the depth of tumor invasion. Following the recent development of a high-frequen-

cy small-diameter ultrasound probe (HFUP), the usefulness of this probe in assessing the depth of colorectal tumor invasion has begun to be reported [5-10].

The present study was undertaken to assess the usefulness of endoscopic ultrasonography using an HFUP (20 MHz) in assessing the depth of invasion of colorectal tumorous lesions.

MATERIALS AND METHODS

The subjects were 27 patients with colorectal tumorous lesions who had undergone endoscopic ultrasonography and subsequent endoscopic or surgical operation at the Second Department of Internal Medicine or the Division of Gastroenterology of the Kurume University Hospital between July 1994 and December 1995 and in whom the resected tissue was examined histopathologically. There were 5 cases of adenoma, 6 cases of m cancer, 13 cases of sm cancer, and 3 cases of advanced cancer. The shape of lesions was macroscopically classified into the following types according to the macroscopic classification system established by the Japanese Research Society for Cancer of the Colon and Rectum: type I (protruding type), type II (superficial type), nodule-aggregating type and advanced type. Type I was subdivided into type Ip (pedunculated), Isp (subpedunculated) and Is (sessile). Type II was subdivided into IIa (superficial elevated type), IIb (superficial flat type) and IIc (superficial depressed type). One lesion was rated as type Ip, one lesion as

type Isp, one lesion as type Is, 11 lesions as type IIa, no lesion as type IIb, 8 lesions as type IIc, 2 lesions as nodule-aggregating type and 3 lesions as advanced type (Table 1).

A high-frequency ultrasound miniature probe (sp501, 20 MHz, Fuji Corp, Tokyo, Japan) was used for endoscopic ultrasonography by the degassed water filling method.

The normal colonic wall has a five-layer structure. The first and second layers were the mucosal layers. The third layer corresponded to the submucosal layer. The fourth layer was the muscularis propria. The fifth layer was the serosa. The submucosal layer (sm) was equally divided vertically into three areas, i.e., the most superficial (SM1), middle (SM2) and deepest (SM3) areas. The histological depth of tumor invasion of the submucosal layer was rated on three areas according to the classification of Kudo et al. [11]: sm1, sm2 and sm3.

The ability of endoscopic ultrasonography to provide images of the structure of tumorous lesions was analyzed in relation to the height of lesions. Cases in which the five-layer structure of the colorectal wall adjacent to the lesion was visible were classified as cases in which lesions could be visualized. Cases in which lesions and the five-layer structure of the adjacent area were not visible were classified as cases in which lesions could not be visualized. The height of lesions, i.e., the distance from the surface of normal marginal mucosa to the top of the lesion, was measured under a microscope.

In cases where lesions were clearly visible, the

TABLE 1.
Macroscopic classification and histologic depth of invasion

Gross appearance	Histology					Total
	m*	sm1	sm2	sm3	mp	
Protruding type (I)	1		(1)	(1)		1 (2)
Superficial elevated type (IIa)	7 (2)		2			9 (2)
Superficial depressed type (IIc)		2	4	2		8
Nodule-aggregating lesion	1		(1)			1 (1)
Borrmann 2					3	3
Total	9 (2)	2	6 (2)	2 (1)	3	22 (5)

m: mucosal cancer; sm: submucosal cancer; mp: cancer extending into the muscularis propria

*Includes adenoma (): invisible lesions

depth of tumor invasion as assessed by endoscopic ultrasonography was compared with the histological depth of invasion, and the coincidence rate was calculated. Furthermore the coincidence rate for the selection of therapeutic methods was analyzed by dividing the lesions into three groups: (i) m or sm1 lesions, (ii) sm2 or sm3 lesions and (iii) mp or deeper lesions. When the depth of tumor invasion was determined by endoscopic ultrasonography, the presence or absence of destruction of the five-layer structure due to tumor-associated low echoes was checked for, in accordance with the method reported by Aibe et al. [12]. Cases in which low echoes were visible in the first and second layers but were absent in the third and subsequent layers were rated as having m lesions. Cases in which low echoes were visible in the third layer but absent in the fourth and deeper layers were rated as having sm lesions.

The ability of endoscopic ultrasonography to allow accurate diagnosis of the depth of tumor invasion (the accurate diagnosis rate) was analyzed, by comparing the depth of tumor invasion as determined by endoscopic ultrasonography with the depth as determined histopathologically for tumors classified by the maximum diameter into four groups: 6-10 mm, 11-15 mm, 16-20 mm and over 21 mm. Furthermore, the accurate diagnosis rate was analyzed for three categories of tumor depth (m-sm1, sm2-3 and mp or deeper).

RESULTS

The ability to obtain images of the five-layer structure of the colonic wall and the tumor height (Table 2)

The five-layer structure of lesions was visible in 22 (81.5%) of the 27 cases but not in 5 (18.5%) when examined by endoscopic ultrasonography. The tumor height in cases where the structure was not visible (5.73 ± 4.44 mm) was greater than that in cases where it was visible (3.16 ± 2.52 mm), although the difference was not significant.

The relationship between accurate diagnosis rate and the depth of tumor invasion

For the 22 lesions which were depicted well by endoscopic ultrasonography, the accurate diagnosis rate was analyzed in relation to the depth of tumor invasion assessed histopathologically.

Accurate diagnosis rate in relation to the depth of tumor invasion (Table 3): The accurate diagnosis rate was 63.6% (14/22) for all patients, 44.4% (4/9) for m lesions, 50.0% (1/2) or sm1 lesions, 83.3% (5/6) for sm2 lesions, 50.0% (1/2) for sm3 lesions, and 100.0%

TABLE 2.
The ability to obtain images of the five-layer structure of the colonic wall and tumor height

	Height of lesions (mm)
Invisible lesions (n=5)	5.73 ± 4.44
Visible lesions (n=22)	3.16 ± 2.52

TABLE 3.
Accurate diagnosis rate in relation to the depth of tumor invasion

Histology	HFUP					Total	Accuracy (%)
	M*	SM1	SM2	SM3	MP		
m*	4	3		2		9	4/9 (44.4)
sm1		1	1			2	1/2 (50.0)
sm2			5	1		6	5/6 (83.3)
sm3			1	1		2	1/2 (50.0)
mp					3	3	3/3 (100)
Total	4	4	7	4	3	22	14/22 (63.6)

*Includes adenoma HFUP: high-frequency ultrasound probe

TABLE 4.
Accurate diagnosis rate in relation to the depth of tumor invasion clinically used
for the selection of therapeutic methods

Histology	HFUP			Total	Accuracy (%)
	M* - SM1	SM2 - SM3	MP -		
m* - sm1	8	3		11	8/11 (72.7)
sm2 - sm3		8		8	8/ 8 (100)
mp -			3	3	3/ 3 (100)
Total	8	11	3	22	19/22 (86.4)

*Includes adenoma HFUP: high-frequency ultrasound probe

(3/3) for mp lesions. In 5 cases where histological diagnosis was mucosal tumor, the evaluation of the depth of tumor invasion by endoscopic ultrasonography were sm1 or sm3. Thus, the depth of tumor invasion tended to be overestimated in cases of mucosal lesions.

Accurate diagnosis rate in relation to three categories of tumor invasion depth clinically used for the selection of therapeutic methods (Table 4): When the accurate diagnosis rate was analyzed in relation to three categories of tumor invasion depth (m-sm1, sm2-3 and mp or deeper), the accurate diagnosis rate was 86.4% (19/22) for all patients, 72.7% (8/11) for m-sm1 cases, 100.0% (8/8) for sm2-3 cases and 100.0% (3/3) for mp or deeper cases. Thus, the accurate diagnosis rate was high for all three categories.

Assessment of the depth of tumor invasion in relation to the tumor size

Tumor size and the accuracy in assessing the depth of tumor invasion (Fig. 1): The percentage of cases in which the depth of tumor invasion was assessed accurately was 100.0% (4/4) when the tumor diameter was 6-10 mm, 41.7% (5/12) at a tumor diameter of 16-20 mm, and 66.7% (2/3) at a tumor diameter over 21 mm. Thus, the percentage did not correlate with the tumor diameter.

Relationship between tumor diameter and accurate diagnosis rate using three categories of tumor depth (Fig. 2): When the percentage of cases in which tumor invasion depth (m-sm1, sm2-3 and mp or deeper) was assessed accurately was analyzed in relation to tumor diameter, the percentage was 100.0% (4/4) when the tumor diameter was 6-10

Fig. 1. Relationship between the tumor diameter and accurate diagnosis of the depth of tumor invasion. Five categories of the depth of tumor invasion (m, sm1, sm2, sm3 and mp or deeper) are used in evaluating the invasive degree. Closed squares indicate the accurate diagnosis rate. Open squares indicate the erroneous diagnosis rate.

Fig. 2. Relationship between tumor diameter and tumor depth assessment using three categories of tumor depth. Three categories of the depth of tumor invasion (m-sm1, sm2-3 and mp or deeper) are used in evaluating the invasive degree. Closed squares indicate the accurate diagnosis rate. Open squares indicate the erroneous diagnosis rate.

mm, 91.7% (11/12) at a tumor diameter of 11-15 mm, 66.7% (2/3) at a tumor diameter of 16-20 mm and 66.7% at a tumor diameter over 21 mm. The percentage tended to be higher in smaller tumors than in larger tumors, although the difference was not significant. Thus, no significant correlation was observed between the tumor diameter and the accurate assessment of tumor invasion depth using the three-category classification of tumor depth.

Case illustration

Firstly, a representative case of accurate diagnosis evaluated using endoscopic ultrasonography is described. Colonoscopy detected a superficial elevated tumor with central depression in the sigmoid colon (Fig. 3A). Use of the dye-spraying technique

more clearly delineated the lesion (Fig. 3B). Use of the HFUP showed that the lesion had invaded the middle of the third layer (Fig. 3C). Histologically, the section shows that the lesion involved two-thirds of the submucosal layer (Fig. 3D). Secondly, a representative case of the erroneous diagnosis evaluated using endoscopic ultrasonography is described. Colonoscopy detected a superficial depressed tumor with a central nodule in the transverse colon using dye-spraying technique (Fig. 4A). Use of the HFUP showed that the lesion had invaded two-thirds of the third layer (Fig. 4B). Histology revealed that the lesion had involved one-third of submucosal layer. The lesion of high magnification showed the abundant fibrosis under the nodule (Fig. 4C, D).

Fig. 3. A case of accurate diagnosis. A: Colonoscopy revealed a reddish superficial elevated tumor with central depression in the sigmoid colon. B: The dye-spraying technique demonstrates the lesion more clearly. C: HFUP showed that the lesion had invaded the middle of the third layer. (low echoic) (SM2) D: Histology revealed that the lesion involved two-thirds of the submucosal layer. (sm2)

Fig. 4. A case of erroneous diagnosis. A: Colonoscopy revealed superficial depressed tumor in the transverse colon. B: HFUP showed that the lesion had invaded two-thirds of the third layer. (SM2) C: Histology revealed that the lesion had involved one-third of submucosal layer. (sm1) D: Section showed the abundant fibrosis around the tumor frontier area in high magnification of lesion.

DISCUSSION

Due to the spread of colorectal examination, the number of colorectal cancer detected in early stages has been increasing. Radical treatment by polypectomy or EMR is possible for cancers remaining in the mucosa (m cancer). In cases of cancer which has invaded the submucosal layer (sm cancer), the indications for endoscopic treatment or surgical operation (combined with lymph node excision) need to be determined carefully, taking into account the possibility of residual cancer, lymph node metastasis and distant metastasis.

The depth of invasion by colorectal cancer has conventionally been assessed using X-rays and endoscopic findings [13-15]. These methods, however, do not allow direct assessment of deep invasion of tumors. Instead they only allow indirect assessment of the depth of tumor invasion on the basis of extent

and height of lesions on X-rays and endoscopic findings. For more accurate assessment of the depth of tumor invasion, endoscopic ultrasonography, which provides direct images of tumor invasion in the vertical direction, has been increasingly used in addition to conventional methods. The usefulness of endoscopic ultrasonography has been suggested in recent reports [16-22].

At present, two types of endoscopic ultrasonography are used. One type is the conventional instrument composed of an ultrasound vibrator attached to the tip of an endoscope (EUS). The other is a high-frequency ultrasound miniature probe (HFUP) which is inserted through the forceps channel of an endoscope. The EUS uses either 7.5 MHz or 12 MHz frequency. Since ultrasound attenuation is small, the EUS is useful when diagnosing lesions with a great height or extra intestinal lesions. Lesions with small height such as superficial tumors are difficult to be

detected by the EUS. Insertion of the EUS deeply into the large intestine requires considerably high skill [23]. The HFUP uses a fairly high frequency (20 MHz). Since ultrasound attenuation is large, the HFUP is primarily used to evaluate superficial tumors. Since the HFUP is usually inserted through the forceps channel of a video endoscope, ultrasound images can be taken while monitoring the lesions endoscopically. Furthermore, it is easy to insert video endoscope deeply into large intestine.

In the present study, we assessed the usefulness of HFUP in diagnosing the depth of colorectal tumorous lesions. Regarding the relationship between the height of lesions and the ability to provide images of the layered structure of lesions, Ashiwaru et al. [24] have reported that the accurate diagnosis rate was high for lesions below 7 mm in size, but that the rate was lower for lesions larger than 8 mm. Matsunaga et al. [25,26] also reported that 90-100% of superficial tumors were visible with this technique, but that only about 65% of lesions with large height were visible. In the present study, the height of lesions was 3.16 ± 2.52 mm for lesions visible with this technique and 5.73 ± 4.41 mm for lesions not visible, although the difference was not significant. This difference is probably because an increase in tumor height accelerates ultrasound attenuation and thus makes imaging of the deepest area of the tumor impossible.

Reports from other facilities showed that this technique allowed accurate assessment of the depth of tumor invasion in 80 - 94% of all cases, indicating the usefulness of this technique [5,24,26-28]. In the present study, the percentage of cases in which this technique allowed accurate assessment of the depth of tumor invasion was low (63.3%, 14/22). However, when the depth of tumor invasion was divided into three categories (m-sm1, sm2-3 and mp or deeper), which are often used clinically when selecting therapeutic methods, the accurate diagnosis rate was higher, i.e., 86.4% (19/22) for the entire population, 72.7% (8/11) for m-sm1 cases and 100% (11/11) for sm2 or deeper cases. Although the accurate diagnosis rate for m-sm1 cases was not satisfactorily high, this will not cause any problem when selecting endoscopic treatment or surgical operation, since the depth of tumor invasion is usually assessed based on a general evaluation of X-ray, endoscopic and ultrasound findings, instead of relying solely on ultrasound findings.

Few studies have examined the relationship between the width of lesions and the usefulness of

endoscopic ultrasonography in accurate assessment of the depth of tumor invasion. Yoshimoto et al. [29] reported that the accurate diagnosis rate was 81% for lesions smaller than 30 mm and 14% for lesions over 30 mm. In the present study, no particular relationship was observed between the tumor size and the accurate diagnosis rate. However, when the depth of tumor invasion was divided into three categories (m-sm1, sm2-3 and mp or deeper), the accurate diagnosis rate tended to decrease as the tumor diameter increased. This is probably because ultrasound scanning of the entire lesion is difficult for larger lesions. The depth of tumor invasion cannot be accurately assessed unless the deepest part of the tumor can be scanned. It is not easy to scan a large lesion completely, including its deepest portion. The small-diameter ultrasound probe used in the present study can be inserted through the forceps channel of an ordinary video endoscope. If the deepest area of the tumor identified by endoscopic observation is scanned with this probe, the accurate diagnosis rate will be improved.

In the 9 cases where the ultrasound diagnosis of the depth of tumor invasion was discrepant from the histological diagnosis, the discrepancy is probably because infiltration of inflammatory cells [30], fibrosis of the tumor frontier region [31] and the presence of lymph follicles caused overestimation of the depth of tumor invasion by endoscopic ultrasonography.

In the present study, a HFUP was used to assess the depth of invasion by colorectal tumorous lesions. This probe was found to have the following advantages. It was easier to insert and manipulate than the conventional probes used for endoscopic ultrasonography (EUS). The use of this probe allows ultrasound imaging under endoscopic guidance and subsequent efficient endoscopic treatment when needed. Ultrasonic checks for deep tumor invasion under endoscopic guidance is easier with this probe. A disadvantage with this probe is that in cases of tumors with large height, the ability to obtain images of minute invasion in the deep area is low. This problem needs to be resolved.

A HFUP was used to obtain images of 27 colorectal tumorous lesions. Its ability to provide images of these lesions and to accurately assess the depth of tumor invasion was examined. This probe was found to be very useful in obtaining images of superficial tumors with low height. Endoscopic ultrasonography using this probe is expected to provide a useful means of determining the indications of early colorectal cancer for endoscopic resection if its find-

ings are combined with findings from conventional X-ray and video endoscopy.

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