Diseases of the Large Intestine—Neoplastic diseases—

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Abstract: Neoplastic lesions of the large intestine are increasing in Japan in conjunction with the changes in the dietary life of the population. Exact diagnosis of the diseases of the large intestine are still being debated. However, recent advances in diagnostic imaging provide improved diagnosis of neoplastic lesions of the large intestine without undue stress on the patient. In this paper, recent diagnosis, treatment and surveillance of neoplastic lesions such as early cancer, advanced cancer, mucosa-associated lymphoid tissue tumor (MALToma) and gastrointestinal submucosal tumor (GIST) are discussed.

Key words: Large intestine; Neoplastic lesion; Colorectal cancer; EMR; MALToma; GIST; Virtual

Introduction

Recently, there has been increased interest in diseases of the large intestine due to the growing number of patients with colorectal cancer. In particular, rapid progress has been made in the diagnosis and treatment of neoplastic diseases of the large intestine including colorectal polyps.

The large intestine consists of the cecum, colon, and rectum. The characteristics of diseases of the large intestine differ according to the part of the large intestine. With a focus on early cancer, this paper reports on recent trends in the diagnosis and treatment of colorectal cancer. It also discusses carcinoid, mucosa-associated lymphoid tissue (MALT) lymphomas and gastrointestinal stromal tumors (GIST) which have been the focus of recent interest, despite the limited number of cases.

New Diagnostic Methods for Neoplastic Lesions of the Large Intestine

The main diagnostic tool for neoplastic lesions of the large intestine is colonoscopy. However, this examination places a significant onus on the patient and requires trained skills.
commonly in the large intestine and that they have significant importance as the beginning of colorectal cancer. These lesions, which spread on the surface, are called laterally spreading tumors (LST). LSTs are classified into two subtypes—granular type LSTs, which have a nodular and granular form, and non-granular type LSTs, which do not have these morphological features.

Gene analysis has shown that granular type LSTs have a high incidence of mutations of the oncogene $K\text{-}ras$ and they are presumed to adopt the carcinogenesis of the adenoma-carcinoma sequence. Non-granular type LSTs have few $K\text{-}ras$ mutations, but mutations of the cancer suppressor gene $p53$ are observed over a wide area, suggesting that the non-granular type may undergo a de novo carcinogenesis. In both cases, the incidence of cancer increases as the lesion increases in size and special attention should be paid to non-granular type LSTs because of the greater risk of their infiltrating into the submucosa.

It should be noted that these lesions are not defined in the “Japanese Classification of Colorectal Carcinoma” (ed. Japanese Society for Cancer of the Colon and Rectum, Kanehara & Co., Ltd.) which may result in some confusion. However, the clinical features of these lesions are easily identified in certain circumstances and further studies of their subtypes and significance are needed.

### Table 1 Merits and Demerits of Virtual Endoscopy by Helical CT Scanning

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<th>Merits</th>
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<tr>
<td>1. Minimal onus on patient with little discomfort</td>
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<td>2. Examination requires short time (minutes)</td>
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<td>3. Provides information on lesion depth, involvement of lymph nodes, and relationship with peripheral organs</td>
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<td>4. Possible to diagnose proximal lesions, even with obstruction and stenosis</td>
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<td>5. Possible to obtain complete image of lesion from any direction</td>
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<td>6. Reproducibility</td>
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<table>
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<tr>
<th>Demerits</th>
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<tr>
<td>1. Difficult to diagnose submerged lesions because contrast with air is required</td>
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<tr>
<td>2. Poor resolution of images</td>
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<td>3. Not possible to determine color and hardness</td>
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<td>4. Not possible to perform histological examinations</td>
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<tr>
<td>5. Image processing requires a long time</td>
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<td>6. Equipment is expensive</td>
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Three-dimensional diagnostic imaging, or virtual endoscopy, offers a solution to these problems. Virtual endoscopy uses computer processing of image datasets obtained by helical CT scanning to reconstruct 3D images. In fact, virtual endoscopy requires the same preparation as for colonoscopy, and the CT scan is performed after introducing air via the anus. The merits and demerits of this procedure are outlined in Table 1.

It has been reported that virtual endoscopy can detect protruded lesions of 5 mm or more and flat and/or depressed lesions of 10 mm or more. Since the problems associated with the method are mainly computer-related issues, which are expected to be resolved with rapid advances in this area, it is anticipated that virtual endoscopy will be used in the clinical setting as a screening test in the near future.

### Laterally Spreading Tumors

The wide use of colonoscopy has resulted in the detection of neoplastic lesions of various shapes. It has been recognized that polyps as well as flat and/or depressed tumors occur

### Recent Trends in the Treatment of Colorectal Cancer

#### 1. Early cancer

In the case of early cancer, it is quite feasible to obtain a complete cure of intramucosal carcinoma by endoscopic polypectomy or endoscopic mucosal resection (EMR). The choice of treatment becomes a problem when the resected margin is positive, namely, in the case of an incomplete resection, or when the resection is complete but the lesion has infiltrated into the submucosa (sm). If the only resected
stump of the mucosal surface is positive based on a thorough pathological examination of the resected specimen, the endoscopic examination may be repeated three months later if there are no risk factors for lymph node metastasis. In the absence of problems, the patient should be followed periodically. Surgery is indicated if the resected stump in the submucosa is positive.

In contrast, if the resection was complete but submucosal carcinoma is evident and there are no risk factors for lymph node metastasis (e.g., positive vascular infiltration of lymphatics and veins, poor differentiation of cancerous tissue, the depth of cancer infiltration is moderate or more), the patient should be followed carefully by endoscopy. If even one of these risk factors is evident, colectomy with lymphadenectomy is required. Dissection of the second lymph node group (N2) is sufficient and laparoscopically-assisted colectomy, a minimally invasive procedure, is indicated.

It should be noted that in the case of the rectum, QOL is decreased following rectal amputation or low anterior resection due to an artificial anus, micturition disorders, and/or sexual dysfunction. Therefore, the recommended treatment is initially a local excision of the rectum with lymphadenectomy in the neighbouring mesorectum; and the necessity of additional surgery should be discussed depending on the absence or presence of lymph node metastasis (Fig. 1).

2. Advanced cancer

With the aim of maintaining and improving
post-operative QOL, laparoscope-assisted colectomy is becoming widespread as the best surgical option for the patient. While early colorectal carcinoma is a good indication for this procedure, the case for advanced cancer is controversial. In terms of recurrence and metastasis, there is a lack of consensus. Some maintain that this procedure is indicated if the cancer has not invaded the serosa surface while others believe that it is needed in all cases of advanced cancer. A randomized controlled trial (RCT) is required but there are several difficulties with the implementation of such a trial. Although this problem is being investigated overseas, the extent of lymph node excision and the techniques used are different from those in Japan, preventing a direct application of the results obtained overseas.

**Surveillance Following Resection of Neoplasms of the Large Intestine**

Surveillance following endoscopic resection or surgical resection of neoplasms of the large intestine is an important issue. This surveillance serves a double purpose. The first is early detection of the recurrence of cancer and the second is the early detection of colorectal carcinoma of multifocal origin. For patients with colorectal carcinoma, 5 to 10 percent will experience synchronous or metachronous multifocal lesions. The question is how often surveillance should be carried out in what kind of patient.

In the case of adenomatous lesions of the large intestine, endoscopic resection should be performed for multifocal lesions until all lesions have disappeared, followed by three-yearly endoscopic examinations. In the case of localized lesions, it is sufficient to revert to the usual test for colorectal carcinoma of fecal occult blood following resection.

It is a little different in the case of cancer. In the case of multifocal colorectal carcinoma, recent gene analysis has reported a high incidence of abnormalities in DNA repair genes or microsatellite instability (MSI), the cause of hereditary non-polyposis colorectal cancer (HNPCC). The incidence of colorectal carcinoma and malignant neoplasms of other organs in family members is known to be also high. Therefore, patients with this genetic abnormality or with a family history of colorectal carcinoma must be followed post-operatively by annual endoscopic examinations. In other cases, it is sufficient to test patients with colorectal carcinoma annually for five years after surgery and, providing there is no evidence of carcinoma, at three-yearly intervals thereafter.

**Submucosal Neoplasms**

The final section will discuss submucosal neoplasms of the large intestine which are important in terms of diagnosis and treatment, despite the relatively low incidence of cases.

1. **Carcinoid tumors of the large intestine**

In Japan, the most common site of carcinoid tumors in the digestive tract is the rectum, followed by the duodenum, stomach, and appendix. In America, in contrast, the most common site is the appendix, followed by the rectum and ileum, with few cases reported in the stomach and duodenum. It is presumed that endocrine cells deep in the mucosa give rise to gastrointestinal carcinoid tumors and, because of the ease with which they progress to submucosal levels, they are often handled clinically as submucosal neoplasms.

Morphologically, carcinoid tumors of the large intestine are hemispherical (Yamada classification: type II or III) with a slight depression on the surface, and are often slightly yellowish in color. In terms of site, they almost invariably develop within six centimeters from the anal verge. These tumors occur in a younger age cohort (mean age: about 50 years) than cancer patients.

While small carcinoid tumors of the large intestine may be treated by endoscopic resec-
tion, some tumors of about one centimeter in size metastasize to the lymph nodes or liver. Therefore, the patient must be treated for cancer.

2. Mucosa-associated lymphoid tissue lymphoma

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a well-known lymphoma of low-grade malignancy which develops due to inflammation of the gastric mucosa associated with a Helicobacter pylori infection. It has been reported that gastric MALT lymphoma often disappears in many people with gastric MALT lymphoma following eradication therapy.

Recently it has been reported that MALT lymphoma has also been detected in the large intestine and, as in the case of the stomach, the MALT lymphoma of the large intestine disappears following eradication therapy of the Helicobacter pylori infection. However, the mechanism by which H. pylori, which are primarily active in and inhabit the stomach only, are involved in the development of MALT lymphoma in the large intestine is unclear.

Based on gene analysis, translocation involving the No.11 and No.18 genes is frequently observed in cases of MALT lymphoma in the large intestine. When translocation occurs, it has been reported that H. pylori eradication is ineffective even against gastric MALT lymphoma. Therefore, further studies of the development and treatment of MALT lymphoma in the large intestine are warranted.

3. Gastrointestinal stromal tumor (GIST)

Submucosal neoplasms of the gastrointestinal tract which is assumed to arise from spindle-shaped cells have previously been classified as smooth muscle type neoplasms and neural type neoplasms. Recent studies using markers for both types, however, have shown that the majority of GISTs do not stain for either marker (Tables 2, 3). It has also been shown that these tumors are characterized by genetic abnormalities known as c-kit and that they grow and metastasize by tyrosine autophosphorylation.

These tumors are thought to originate in interstitial cells of Cajal which are known as pacemaker cells in the gastrointestinal tract. For further information, several books have recently been published on various aspects of GISTs, including their definition, classification, and gene analysis.

GISTs of the gastrointestinal tract are most common in the stomach, followed by the small intestine. GISTs in the large intestine are uncommon. The usual method of diagnosis is diagnostic imaging but, in most cases, endoscopic biopsy does not lead to a confirmed diagnosis. Recently, endoscopic ultrasonography-guided fine needle aspiration biopsy has been employed in the differential diagnosis between benign and malignant GISTs. It has been reported that the degree of malignancy increases in tumors five centimeters or more in size and with increasing mitosis of tumor cells. Most malignant GISTs metastasize to the liver or recur in the peritoneum, with lymph node metastasis being extremely rare.

As treatment, local resection of the gastrointestinal tract including the primary lesion is sufficient, with a laparoscope-assisted operation indicated. In the case of metastatic lesions, it

Table 2 Classification of GIST

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<th>Type</th>
<th>Description</th>
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<tr>
<td>smooth muscle type</td>
<td>Smooth muscle actin, desmin</td>
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<tr>
<td>neural type</td>
<td>S-100, neuronspecific enolase</td>
</tr>
<tr>
<td>combined muscle-neural type</td>
<td>Vimentin</td>
</tr>
<tr>
<td>uncommitted type (GIST in narrow sense)</td>
<td>CD34, c-kit protein (CD117)</td>
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(Classification of Rosai et al. Source: Ackerman’s Surgical Pathology, 8th ed., Mosby, St. Lois, 1996; pp.645–646)
has been reported that the tyrosine kinase inhibitor STI 571 (Glivec®), which has been approved as a therapeutic drug for chronic leukemia, is effective because, as mentioned previously, activation of tyrosine kinase is closely involved in the metastasis of tumors. We have also obtained a complete response (CR) of tumors by administering this drug to a malignant gastric GIST patient with liver metastasis. This treatment method promises to be a significant addition to the armamentarium for malignant GISTs.

This paper has focused on recent issues in the diagnosis and treatment of neoplastic lesions of the large intestine aimed at improving patient care. It is hoped that the information will be of help in daily clinical practice.

REFERENCES

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