

PRACTICE GUIDELINES

Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for the Clinical Practice of Hereditary Colorectal Cancer (Translated Version)

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Abstract:

Hereditary colorectal cancer accounts for less than 5% of all colorectal cancer cases. Some of the unique characteristics that are commonly encountered in cases of hereditary colorectal cancer include early age at onset, synchronous/metachronous occurrence of the cancer, and association with multiple cancers in other organs, necessitating different management from sporadic colorectal cancer. While the diagnosis of familial adenomatous polyposis might be easy because usually 100 or more adenomas that develop in the colonic mucosa are in this condition, Lynch syndrome, which is the most commonly associated disease with hereditary colorectal cancer, is often missed in daily medical practice because of its relatively poorly defined clinical characteristics. In addition, the disease concept and diagnostic criteria for Lynch syndrome, which was once called hereditary non-polyposis colorectal cancer, have changed over time with continual research, thereby possibly creating confusion in clinical practice. Under these circumstances, the JSCCR Guideline Committee has developed the “JSCCR Guidelines 2016 for the Clinical Practice of Hereditary Colorectal Cancer (HCRC),” to allow delivery of appropriate medical care in daily practice to patients with familial adenomatous polyposis, Lynch syndrome, or other related diseases. The JSCCR Guidelines 2016 for HCRC were prepared by consensus reached among members of the JSCCR Guideline Committee, based on a careful review of the evidence retrieved from literature searches, and considering the medical health insurance system and actual clinical practice settings in Japan. Herein, we present the English version of the JSCCR Guidelines 2016 for HCRC.

Keywords:

hereditary colorectal cancer, guideline, familial adenomatous polyposis, Lynch syndrome

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Introduction

1. Guideline objectives

In Japan, the incidence of colorectal cancer has been steadily increasing; it is presently one of the most frequently encountered cancers in clinical practice and a cause for great concern. Most colorectal cancers are thought to be caused by the accumulation of gene mutations in the colonic mucosa or adenomas, the occurrence of which is thought to be influenced by lifestyle, environmental factors, advanced age, etc. (sporadic colorectal cancer). Another type of colorectal cancer, called familial colorectal cancer, which accounts for 20-30% of all colorectal cancer cases, is commonly found among relatives (familial clustering). In less than approximately 5% of colorectal cancer cases, the causative genes have been identified, irrespective of the presence or absence of familial clustering, and these cases are collectively referred to as cases of hereditary colorectal cancer. Early age at onset, synchronous/metachronous occurrence, association with multiple cancers in other organs, etc., are usually seen in cases of hereditary colorectal cancer; therefore, this type of cancer should be managed differently from sporadic col-

orectal cancer. However, hereditary colorectal cancer is still not well-recognized by general clinicians.

Familial adenomatous polyposis and Lynch syndrome have high incidence rates in cases of hereditary colorectal cancer. While detection of familial adenomatous polyposis might be facilitated by its common occurrence in 100 or more adenomas of the colonic mucosa, Lynch syndrome, which is the most commonly associated disease with hereditary colorectal cancer, is often missed in daily medical practice owing to its relatively poorly defined clinical characteristics. In addition, Lynch syndrome was once called hereditary non-polyposis colorectal cancer (HNPCC), and its disease concept and diagnostic criteria have changed with continuing research, thereby possibly creating confusion in clinical practice.

Under these circumstances, the “JSCCR Guidelines 2016 for the Clinical Practice of Hereditary Colorectal Cancer” (hereafter referred to as the JSCCR Guidelines 2016 for HCRC), intended for doctors and medical personnel engaged in providing medical care to patients with familial adenomatous polyposis, Lynch syndrome, and other related diseases, have been developed for the following purposes:

(1) To deepen the understanding of the concept of heredi-

tary colorectal cancer

(2) To provide guidance on management strategies, including diagnosis and surveillance, for hereditary colorectal cancer

(3) To emphasize the importance of the need to consider the psychosocial burden caused by hereditary diseases in patients and their families (relatives) as well as their need for support

(4) To enhance mutual understanding between healthcare professionals and patients by making these guidelines available to the public.

2. How to use the JSCCR Guidelines 2016 for HCRC

The JSCCR Guidelines 2016 for HCRC can be used as a tool for the treatment of hereditary colorectal cancer under actual clinical practice settings. More specifically, they can be referred to for the diagnosis/treatment/surveillance of individual patients or for obtaining informed consent for genetic testing and optimal treatment selection etc. from patients and their families. The JSCCR is responsible for the statements in the JSCCR Guidelines 2016 for HCRC. However, the personnel directly in charge of treatment, and not the JSCCR or the Guideline Committee, must take responsibility for treatment outcomes.

3. Method of development for the JSCCR Guidelines 2016

1) Circumstances of the development of JSCCR Guidelines 2016 for HCRC

The JSCCR planned to develop “the JSCCR Guidelines for the Clinical Practice of Hereditary Colorectal Cancer” as a project of the Familial Colorectal Cancer Committee, and published the “JSCCR Guidelines 2012 for HCRC” in July 2012. Subsequently, several new findings and clinical practice guidelines, particularly regarding Lynch syndrome, were published from overseas. In addition, the Familial Colorectal Cancer Committee itself analyzed data from “A Retrospective Multicenter Study of Familial Adenomatous Polyposis” and “Registration and Genetic Analysis of HNPCC-Secondary Study-,” which were studies conducted by the JSCCR, and obtained new findings. Under these circumstances, the clinical genetics departments have been established, mainly in specialized institutions, and hereditary tumors have increasingly become an issue of social concern in Japan. Based on the above, revision of the guidelines published in 2012 was initiated in 2015. A draft revision was prepared after many discussions and submitted to the Guideline Evaluation Committee in May 2016. In addition, a public hearing was held in the 85th annual meeting of the JSCCR in July 2016, and subsequently, the revised points were published on the website of the JSCCR to collect opinions from the public. Further revisions were made by reference to these opinions, and finally the “JSCCR Guidelines 2016 for HCRC” was published in November 2016.

We attempted to develop the JSCCR Guidelines 2016 for HCRC in accordance with the concept of evidence-based medicine. However, the incidence of hereditary colorectal cancer is relatively low, and it is not easy to design high-evidence-level studies. In view of this difficulty in obtaining sufficient evidence, the guidelines have been developed by consensus reached among members of the JSCCR, based on information obtained from literature searches, and considering the medical health insurance system and actual clinical practice situation in Japan. In addition, members of the Japanese Society for Familial Tumors also participated in the Guideline Development Committee.

2) Principles behind Guideline development

The JSCCR Guidelines 2016 for HCRC presents evidence for each management strategy to enable clearer understanding of the management strategies, including the diagnosis, treatment, and surveillance of hereditary colorectal cancer; however, the technical aspects of each treatment method have not been discussed.

3) Extraction and evaluation of evidence

The method adopted for guideline development was in accordance with the concept of EBM. However, because hereditary colorectal cancer is a relatively rare disease and it is difficult to conduct randomized controlled trials, the evidence levels have not been shown.

4. Description method

Familial adenomatous polyposis and Lynch syndrome, which have relatively high incidence rates among cases of hereditary colorectal cancer, were selected, and (1) the disease concept, (2) diagnosis, (3) treatment, (4) postoperative surveillance, (5) management of patients and their families, etc., were briefly described for each disease. Next, contents suitable for inclusion in clinical questions (CQs) were selected and discussed by the Guideline Development Committee.

5. Method for describing the recommendations

Each recommendation in response to a CQ is accompanied, as much as possible, by classifications of the evidence and recommendation categories, based on consensus reached among members of the Guideline Development Committee. In determining the recommendation categories, in addition to an evaluation of the validity of the source of evidence for each recommendation, a comprehensive investigation of the validity and clinical applicability of each recommendation was performed, by ascertaining that the diagnosis and treatment methods are based on clear scientific evidence, are the best and safest available, are minimally invasive, and are in line with those used in actual clinical practice in Japan.

Classification of the recommendation categories are as follows:

- Category A: unanimous recommendation by the Guide-

Table 1. Changes in the Mortality Rates of Various Cancers and Other Conditions Over Time in Patients with Familial Adenomatous Polyposis.

Cause of death	Up to 1980 (n=268)	1981-1990 (n=166)	1990-2003 (n=71)
Colorectal cancer	80.2%	77.7%	60.6%
Desmoid tumor	3.0%	4.8%	9.9%
Gastric cancer	3.0%	2.4%	2.8%
Duodenal/periampullary cancer	1.8%	2.4%	5.6%
Pancreatic cancer	0	0	1.4%
Small bowel cancer	1.2%	1.2%	1.4%
Myocardial infarction/heart failure	1.8%	2.4%	2.8%
Stroke	1.4%	1.2%	2.8%
Lung cancer	0.9%	2.4%	5.6%
Hepatocellular carcinoma	0.7%	0.6%	0
Uterine cancer	0.5%	0.6%	1.4%
Gastric ulcer	0.2%	0	0
Esophageal cancer	0.2%	0	1.4%
Gallbladder cancer	0.2%	0.6%	0
Sarcoma	0.2%	0	0
Ovarian cancer	0.2%	0	0
Thyroid cancer	0	0	1.4%
Accident	2.1%	2.4%	0
Other diseases	1.6%	1.2%	2.8%
Unknown	0.2%	0	0
Suicide	0.2%	0	0
All cases	100%	100%	100%
Age at the time of death (average \pm SD)	41.9 \pm 11.9	44.0 \pm 13.9	46.0 \pm 15.6

Modifications with ref. 2)

line Development Committee based on high-level evidence

- Category B: unanimous recommendation by the Guideline Development Committee based on low-level evidence

- Category C: recommendation that was not agreed upon completely by all the members of the Guideline Development Committee, irrespective of the level of evidence

- Category D: recommendation that was not agreed upon by the members of the Guideline Development Committee

6. Method of literature search

The PubMed and Ichushi-Web databases were selected for the literature search, and the English and Japanese literature was systematically searched in both databases for the period from the earliest possible date to August 2015. The exhaustive literature search was performed for the broad category, namely, “familial adenomatous polyposis,” to obtain articles on familial adenomatous polyposis, and for the broad categories, “Lynch syndrome,” “hereditary non-polyposis colorectal cancer,” “microsatellite instability,” and “mismatch repair,” to obtain articles on Lynch syndrome; manual searching was added as required. The full texts of the articles selected from 25,941 extracted documents with abstracts (familial adenomatous polyposis: 1,049 Japanese arti-

cles and 7,897 English articles; Lynch syndrome: 1,050 Japanese articles and 16,045 English articles) were critically examined. In addition, important articles published from September 2015 onward were also adopted after full examination.

7. Revision

In cooperation with the Japanese Society for Familial Tumors, the JSCCR Guideline Committee and Familial Colorectal Cancer Committee, as the central organizations, shall aim to revise the JSCCR Guidelines 2016 for HCRC in 4 years, in principle.

8. Publication

The JSCCR Guidelines 2016 for HCRC will be published as a pamphlet and will be made available to the public on the website of the JSCCR, etc., so that the guidelines can be widely used under clinical settings throughout Japan.

Table 2. Major Neoplastic Lesions Associated with Familial Adenomatous Polyposis.

<ul style="list-style-type: none"> • Fundic gland polyposis* • Gastric adenoma* • Duodenal adenoma* • Periampullary adenoma* • Jejunal/ileal adenoma* • Desmoid tumor • Skull osteoma/jaw osteoma/unerupted teeth/extra teeth (supernumerary teeth) • Epidermoid cyst • Thyroid cancer • Congenital hypertrophy of the retinal pigment epithelium • Hepatoblastoma • Adrenal tumor* • Brain tumor
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*: possibility of malignant transformation

Chapter 1: Familial Adenomatous Polyposis

1. Outline

● Familial adenomatous polyposis (FAP) is a hereditary autosomal dominant disease caused by germline mutations in the *Adenomatosis Polyposis Coli* (*APC*) gene, and it is characterized by the development of multiple colorectal adenomas (Side Memo 1: Method for describing genomic alterations, germline and somatic mutations; Appendix: II. Method for describing genomic variants).

● If not treated, almost all FAP patients develop colorectal cancer.

● FAP patients can develop not only colorectal cancer, but also various other associated tumorous and non-tumorous lesions in the gastrointestinal tract and other organs.

[Clinical features]

● Some FAP patients have been reported to develop colorectal cancer while still in their teenage years while approximately 50% of the patients develop colorectal cancer by their 40s. If left untreated, almost all patients develop colorectal cancer by around 60 years of age¹⁾. (Attachment I).

● The most common cause of death in FAP patients is colorectal cancer²⁾, which accounted for approximately 80% of all causes of death in FAP patients until the 1980's; however, the proportion has been decreasing toward approximately 60% from the 1990's (Table 1).

● Among the main extracolonic manifestations (Table 2), duodenal cancer and desmoid tumor are major causes of death in addition to colorectal cancer in FAP patients.

[Causative gene]

● *APC* gene on chromosome 5 (5q22.2)

[Mode of inheritance]

● Autosomal dominant inheritance

[Mechanisms of tumorigenesis] (Figure 1A, 1B)

● In addition to a germline mutation in one of the two alleles of the *APC* gene, an acquired second-hit somatic alteration, such as a deletion in the other allele of the *APC* gene in the epithelial cells of the large intestine (loss of heterozygosity [LOH]), is thought to be the cause of aberrant crypt foci (ACF) (Side Memo 1: chromosomal instability, loss of heterozygosity). (Side Memo 1: aberrant crypt foci)³⁾.

● Dysfunction of the APC protein causes accumulation and nuclear translocation of cytoplasmic β -catenin; then, nuclear β -catenin forms a complex with TCF4, which promotes transcription.

● The mechanism via which APC protein malfunction causes chromosomal instability (CIN) remains unknown; however, in the presence of APC protein malfunction, somatic alterations such as LOH tend to occur in oncogenesis-related genes. In the development of colorectal cancer from ACF via the adenoma-carcinoma sequence, additional mutations are thought to occur in carcinogenesis-related genes such as *KRAS* and *TP53* genes (multi-hit theory or multi-stage model)⁴⁾.

[Incidence]

● The estimated incidence of FAP in the overall population is 1:20,000 to 1:10,000 in Western countries, and 1:17,400 in Japan⁵⁾. Less than 1% of all patients with colorectal cancer are estimated to have FAP⁶⁾. According to a JSCCR multicenter study, 0.24% of all colorectal cancer patients have FAP.

Side Memo 1

■ Method for describing genomic alterations, germline and somatic mutations

The description method validated by the Human Genome Variation Society (<http://www.hgvs.org/mutnomen/>) is generally used. So far,

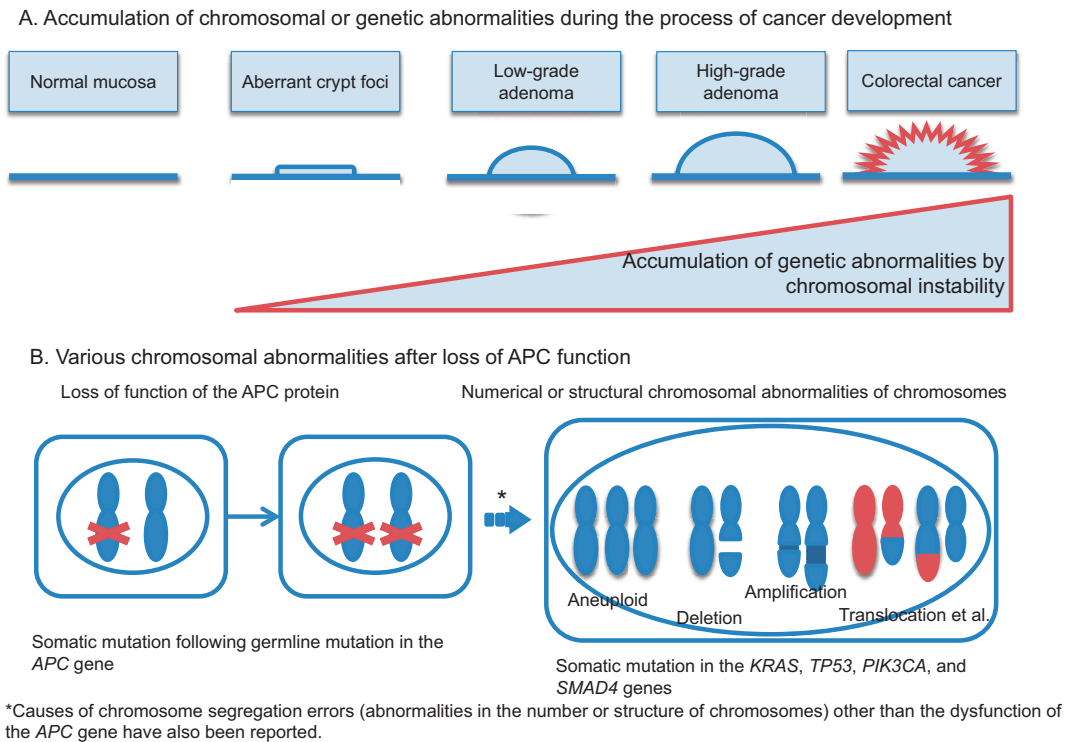


Figure 1. Predicted mechanisms underlying colorectal cancer development in patients with FAP.

changes in genomic sequences have often been represented by terms such as “mutation” and “polymorphism.” However, because the use of these terms may be perceived differently by different individuals, thus causing confusion, the use of terms such as “sequence variant,” “alteration,” and “allelic variant” is recommended. These terms represent the presence of changes compared to reference sequences, but do not indicate any causal relationship with diseases. In addition, the expression “pathogenic” may be used, only after carefully considering what situations it can be used in, and other expressions such as “affect function” may be used in the future.

■ Germline and somatic mutations

Gene mutations transmitted through the sperm or ovum are called germline mutations. Since these mutations are present in the fertilized ovum, all cells of the body have these mutations. On the other hand, new gene mutations in non-germ cells constituting the body, or non-germline mutations, are called somatic mutations.

■ APC gene mutations in FAP

In the tumors of patients with FAP, germline and somatic mutations of the APC gene result in the production of a truncated APC protein, which is thought to be an inactive form of the protein.

■ Chromosomal instability (CIN)

CIN represents abnormalities in the number or structure (deletion, duplication, translocation, etc.) of chromosomes seen in cancer and other cells, and it is thought to cause tumorigenesis.

■ Loss of heterozygosity (LOH)

Heterozygosity indicates the presence of different base sequences in a homologous region of a pair of genetic information inherited from the parents. In the case of FAP, pathogenic mutations are present only in one of the two alleles of the APC gene, and the other allele is normal (wild type) in normal cells. This state is called heterozygosity. However, loss of the wild-type APC allele by deletion, referred to as

LOH, occurs during the process of oncogenesis.

■ Aberrant crypt foci (ACF)

ACF cannot be distinguished from normal mucosa by normal endoscopic observation, and can only be confirmed by magnifying endoscopy as clusters of abnormal crypts showing strong staining with methylene blue. Some ACF are thought to be precursor lesions of adenomas and/or carcinomas.

2. Diagnosis

1) Flow of diagnosis (Figure 2)

● FAP may be diagnosed clinically and/or genetically⁷⁾.

[Clinical diagnosis]

If either of the following criteria (1) or (2) is satisfied, a diagnosis of FAP is made.

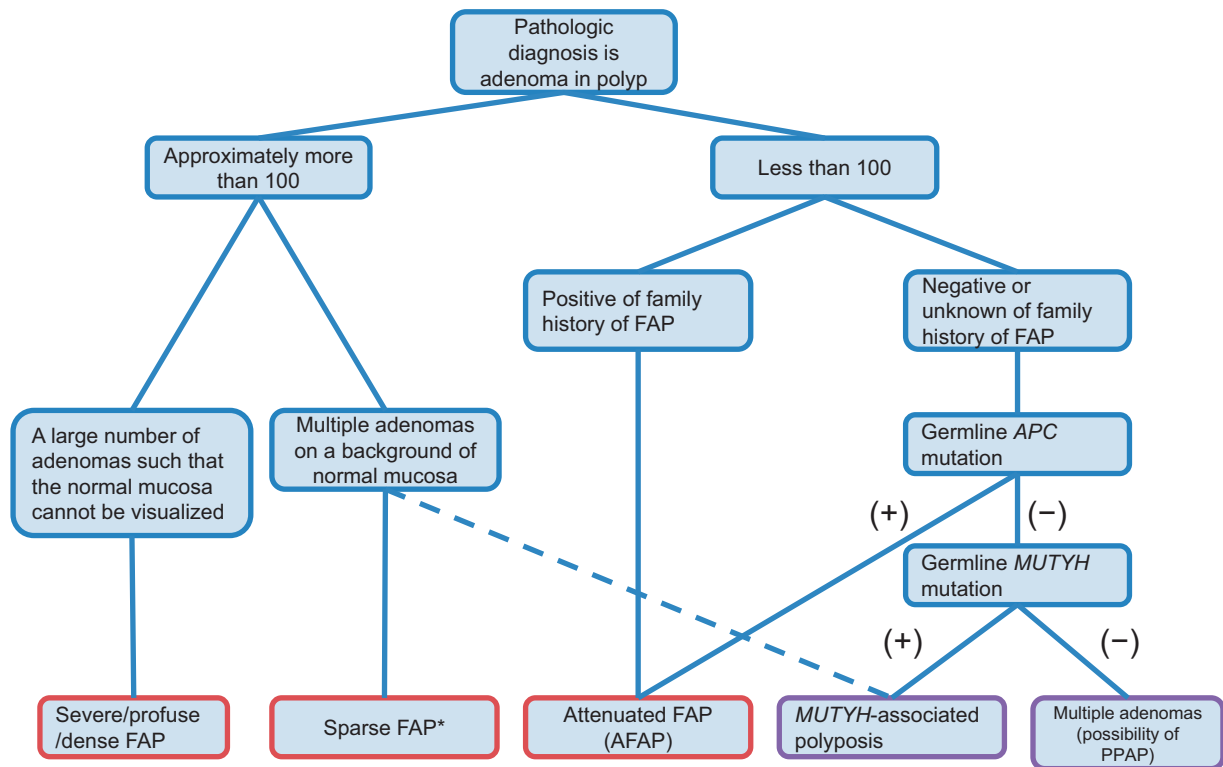
(1) Detection of approximately 100 or more adenomas in the large intestine, irrespective of the presence/absence of a family history of FAP.

(2) Detection of less than 100 adenomas in the presence of a family history of FAP.

[Genetic diagnosis]

If a pathogenic germline mutation is present in the APC gene, a diagnosis of FAP is made.

● There are exceptional pathologies other than FAP that are characterized by the presence of approximately 100 or more adenomas in the large intestine (*MUTYH*-associated polyposis, an autosomal recessive disease). Therefore, a family history consistent with autosomal dominant inheritance is a useful clue for the diagnosis of FAP.



*: If the patient has no family history of FAP, *MUTYH*-associated polyposis cannot be ruled out.
PPAP: polymerase proofreading-associated polyposis

Figure 2. Flow-chart for the diagnosis of FAP.

● Irrespective of the number of colorectal adenomas, the presence of characteristic extracolonic manifestations is a useful clue for the diagnosis of FAP. In 20-40% of patients clinically diagnosed with FAP, no mutations are detected in the *APC* gene^{8,9)}. (CQ1)

● If a patient wishes to undergo genetic testing for his/her own treatment or for the diagnosis in his/her relatives, or if attenuated FAP (AFAP) has to be differentiated from *MUTYH*-associated polyposis and polymerase proofreading-associated polyposis (PPAP), genetic testing of the *APC* gene is considered. This testing can be performed in testing companies (not covered by the national health insurance program) (Side Memo 2: genetic testing) (CQ1).

2) Classification according to the density of the colorectal adenomas

● FAP is sometimes classified as profuse FAP, sparse FAP, and attenuated FAP, according to the density of the adenomas. Profuse FAP and sparse FAP are sometimes collectively called typical (classical) FAP.

● Density of adenomas has been reported to be associated with the site of the germline mutation in the *APC* gene and with the risk of development of colorectal cancer.

● Profuse FAP: Normal mucosa cannot be visualized macroscopically because of the profusion of adenomas (Figure 3) However, often, adenoma density is found to differ

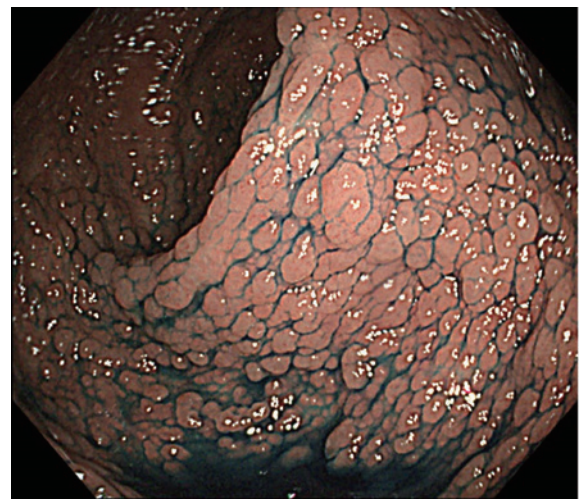


Figure 3. Severe/profuse/dense FAP.

even among regions of the large intestine.

● Sparse FAP: Multiple adenomas can be observed on a background of normal mucosa. The number of adenomas is approximately ≥ 100 (Figure 4).

● Attenuated FAP (AFAP)^{Note 1}: The number of adenomas is approximately ≥ 10 and < 100 (CQ2).

● In cases of profuse FAP, a germline mutation is often

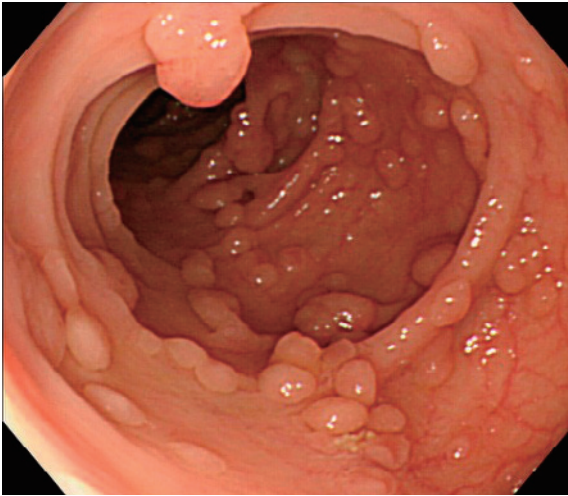


Figure 4. Sparse FAP.

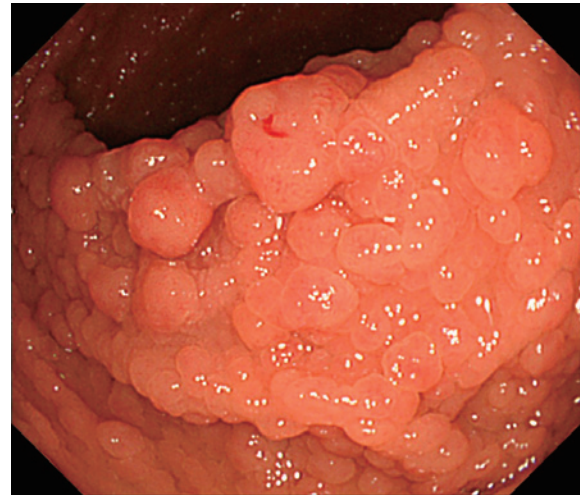


Figure 5. Fundic gland polyposis.

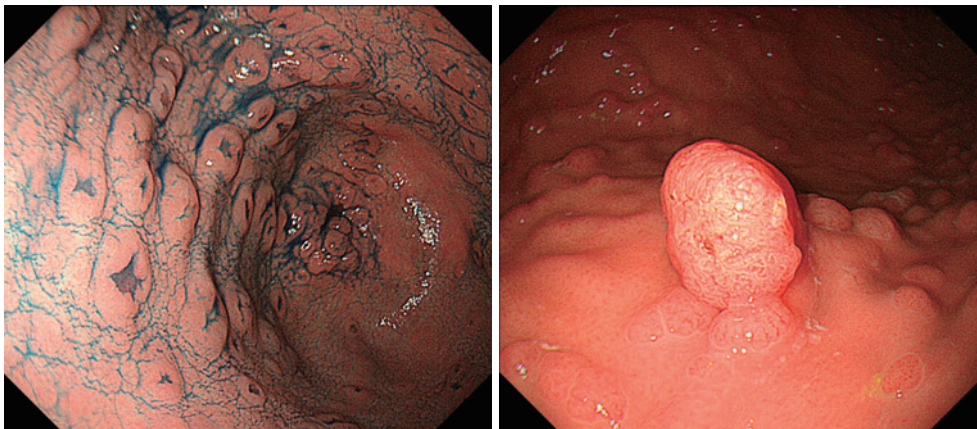


Figure 6. Gastric adenoma (left, depressive type; right, elevated type).

seen between codons 1250 to 1464 (in particular, codon 1309) in the *APC* gene^{10,11}). In AFAP, the germline mutation is often seen in the alternative splicing region (in which an exon is skipped during transcription because of the mutation), or in the 5' or 3' region of the *APC* gene¹²).

According to the JSCCR multicenter study, the age at diagnosis of adenomas and the age at diagnosis of cancer in the colorectum are often lower among patients with profuse FAP than in those with other types of FAP. It has been reported that approximately half of the patients with profuse, sparse, and attenuated types develop colorectal cancer by age 40, 47, and 55 years, respectively.

Side Memo 2

■ Difference between the profuse and sparse types

FAP is sometimes classified according to the number of colorectal adenomas into the profuse (>1,000 or 2,000 adenomas) and sparse (100-1,000 or 2,000 adenomas) types. Many reports classify these types of FAP as typical FAP, and FAP associated with a smaller number (10-99) of adenomas as AFAP. Strict differentiation between the

profuse and sparse types is of little clinical significance.

3) FAP-associated lesions

● FAP is often associated with extracolonic tumorous and/or non-tumorous lesions.

● Presence of tumorous lesions, such as fundic gland polyposis (Figure 5), gastric adenoma (Figure 6) (CQ10), duodenal adenoma (Figure 7) (CQ11), ampullary adenoma (CQ12), desmoid tumor (Figure 8) (CQ14), subcutaneous soft tissue tumor/osteoma, and dental abnormalities (Figure 9) serve as useful clues for the diagnosis of FAP (Side Memo 3: Gardner syndrome).

● FAP patients without *Helicobacter pylori* (*H. pylori*) infection often tend to have fundic gland polyposis, as compared to those with *H. pylori* infection¹³. Surveillance for fundic gland polyposis is required in FAP patients, because of the risk of malignant transformation of fundic gland polyps in these patients.

● FAP patients often develop depressed-type or protruded-type gastric adenomas (Figure 6).



Figure 7. Duodenal adenoma and periampullary adenoma.

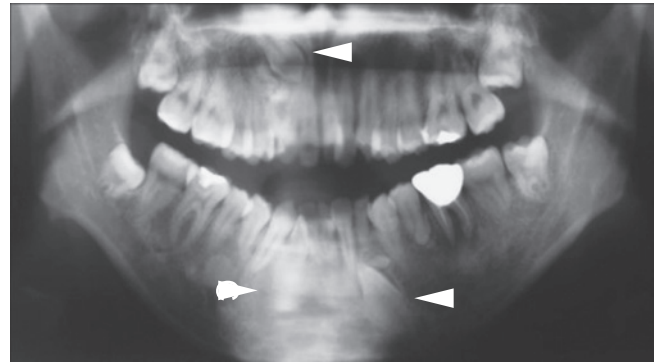


Figure 9. Dental abnormalities (unerupted teeth, arrowheads).

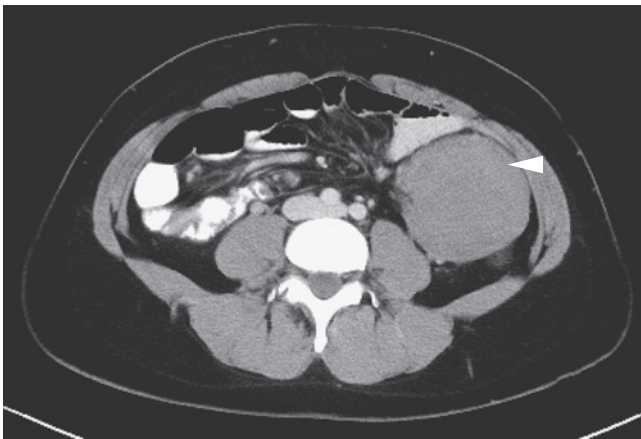


Figure 8. Intra-abdominal desmoid tumor (arrowhead).

● Congenital hypertrophy of the retinal pigment epithelium (Figure 10), a non-tumorous lesion, is detectable before the development of colorectal adenomas in FAP patients, and it is a helpful clue for diagnosis (Side Memo 3: Congenital hypertrophy of the retinal pigment epithelium).

FAP patients may also develop other tumorous lesions, including desmoid tumor, thyroid cancer, adrenal tumor, hepatoblastoma, and brain tumor (Side Memo 3: Turcot syndrome).

Side Memo 3

■ Gardner syndrome

Colorectal polyposis associated with subcutaneous soft tissue tumors, osteomas, dental abnormalities, desmoid tumors, etc., was once called Gardner syndrome, and was regarded as different from FAP, but subsequently, like FAP, this syndrome was also found to be caused by germline mutations in the *APC* gene. At present, the term Gardner syndrome is usually not used.

■ Congenital hypertrophy of the retinal pigment epithelium (CHRPE)

CHRPE is a discontinuous flat pigmented lesion of the retina with-

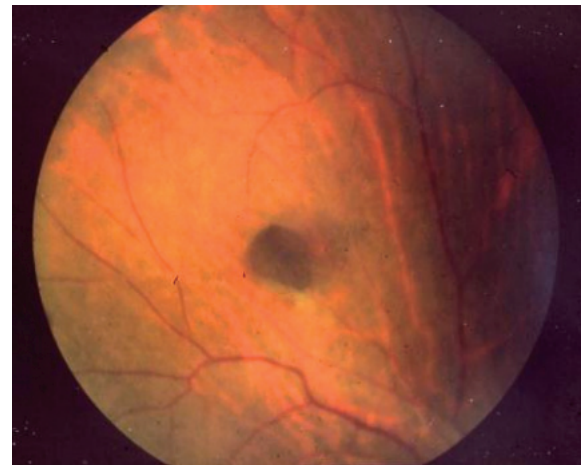


Figure 10. Congenital hypertrophy of the retinal pigment epithelium.

out clinical symptoms, which does not require any treatment. It does not affect visual acuity and does not show malignant transformation. Because approximately 80% of FAP patients have CHRPE, and because it can be detected at birth, it is a helpful clue for the diagnosis of FAP in children.

■ Turcot syndrome (type 2)

Colorectal polyposis associated with brain tumor (mainly cerebellar medulloblastoma), and with a germline mutation in the *APC* gene is called Turcot syndrome, type 2 (see Lynch syndrome for Turcot syndrome, type 1).

4) Diseases and pathological conditions that should be differentiated from FAP

APC mosaicism:

If somatic mutations in the *APC* gene were to occur during the process of tumorigenesis, a mosaic of cells with and without the mutations in the *APC* gene would result. If this abnormality were to occur in cells that differentiate into mucosal cells of the large intestine, multiple colorectal adenomas would develop, like in FAP. It has been reported that *APC* mosaicism occurs in 1.6-4% of FAP patients with identified mutations in the *APC* gene and 11-20% of FAP pa-

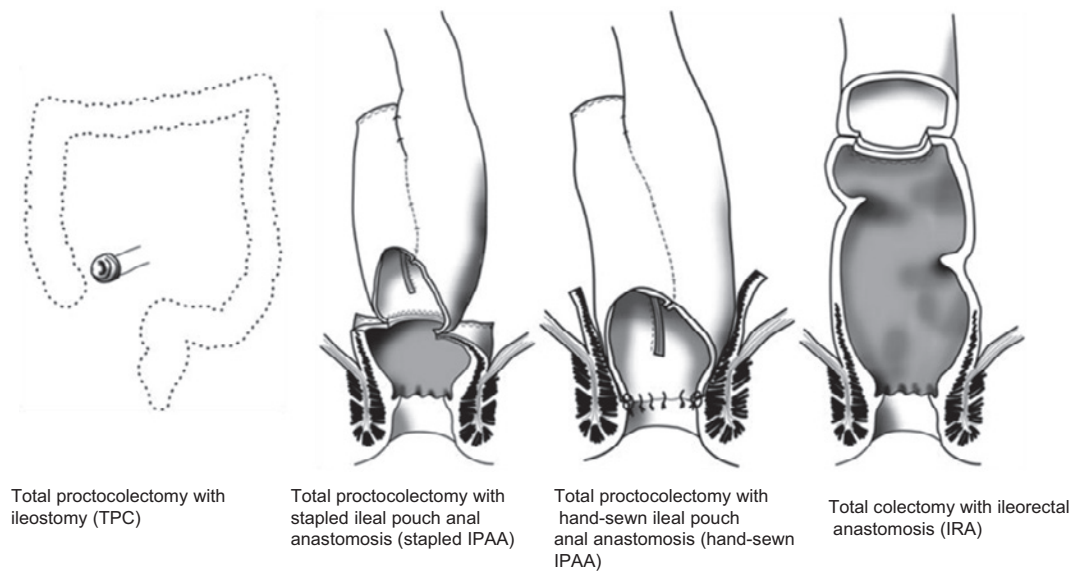


Figure 11. Surgical procedures for FAP (Side Memo 4: Nomenclature of the surgical procedures).

Table 3. Characteristics of Surgical Procedures.

Surgical procedures	Total proctocolectomy with ileostomy	Total proctocolectomy with ileal pouch anal anastomosis	Total colectomy with ileorectal anastomosis
Advantages	<ul style="list-style-type: none"> • Complete prevention of colorectal cancer • Less complications 	<ul style="list-style-type: none"> • Near-complete prevention of most colorectal cancer • Preservation of anal function 	<ul style="list-style-type: none"> • Good anal function • Easy operation • Less complications
Disadvantages	<ul style="list-style-type: none"> • Deteriorated body image and inconvenient stool management by stoma creation 	<ul style="list-style-type: none"> • Complex surgery • Unstable anal function • Possibility of cancer development at remaining rectal mucosa near the anus • Possibility of pouchitis 	<ul style="list-style-type: none"> • Possibility of development of rectal cancer (depending on the number of adenomas, location of the germline mutation in the <i>APC</i> gene, or length of the residual rectum)

tients with a negative family history^{14,15}. Clinically, this condition is managed as FAP. In addition, mutations in the *APC* gene, if present in some germ cells (sex mosaicism), may be passed on to the next generation.

MUTYH-associated polyposis (MAP):

MAP is a hereditary autosomal recessive disease caused by biallelic germline mutation of the *MUTYH* gene, which is one of the base excision repair genes¹⁶. MAP is characterized by the presence of about 10-100 adenomas in the large intestine, although some patients could have as many as 100-1,000 adenomas¹⁷. The incidence of germline mutations in the *MUTYH* gene is unknown among Japanese colorectal cancer patients. The penetrance of colorectal cancer (proportion of individuals who develop colorectal cancer among those with gene mutations) is 43-100% in individuals aged up to 60 years¹⁸. Some MAP patients have been reported to develop a variety of lesions like those found in FAP. In Japan, there are few case reports of MAP, and this disease remains poorly understood. Treatment for MAP is like that for AFAP.

Polymerase proofreading-associated polyposis (PPAP):

PPAP is a hereditary autosomal dominant disease caused by pathogenic germline mutations in the *POLE* or *POLD1* gene, both of which repair errors in DNA replication (proofreading function)¹⁹. Many patients have a few dozen colorectal adenomas, while some patients have been reported to have no adenomas. As extracolonic manifestations, duodenal adenomas/cancers and brain tumors have been reported to develop in patients with PPAP carrying mutation of the *POLE* gene²⁰ and endometrial cancers, breast cancers, and brain tumors have been reported to develop in patients with PPAP carrying mutations of the *POLD1* gene²¹. Tumors of the large intestine (colorectal adenomas and cancers) in PPAP are histologically indistinguishable from these tumors in sporadic cases. Therefore, genetic testing is necessary for a definitive diagnosis.

3. Treatment

1) Treatment of colorectal adenomas

• Proctocolectomy or colectomy prior to the development of colorectal cancer is a reliable prophylactic treatment.

The main surgical procedures adopted are as follows (Figure 11, Table 3):

(1) Total proctocolectomy + permanent ileostomy (TPC)

(2) Restorative proctocolectomy + ileal pouch-anal anastomosis (IPAA)

(3) Total colectomy + ileorectal anastomosis (IRA)

● At present, IPAA is thought to be the standard surgical procedure and it is commonly performed in FAP patients²²⁻²⁵. (CQ3,CQ4)

● In general, it is recommended that patients undergo prophylactic surgery when they are in their 20's. (CQ5)

Side Memo 4

■ Nomenclature of the surgical procedures

In Western countries, ileal pouch anal anastomosis with mucosectomy (IAA) and ileal pouch anal canal anastomosis (IACA) are often collectively called ileal pouch-anal anastomosis (IPAA), without discrimination between them. In addition, IAA is sometimes called hand-sewn IPAA, and IACA is sometimes called stapled IPAA. The height of the anastomosis (length of the residual rectum) is not clearly defined for ileorectal anastomosis (IRA). Total proctocolectomy + permanent ileostomy is often called total proctocolectomy (TPC).

● In recent years, laparoscopic surgery has been increasingly used for prophylactic proctocolectomy (colectomy). (CQ6)

● In cases where desmoid tumors are found in the mesentery during prophylactic surgery, IPAA is generally not recommended, owing to the risk of recurrence or enlargement of desmoid tumors and technical problems, but it may be acceptable under certain conditions. (CQ3)

● Total proctocolectomy for FAP may reduce fertility in females. (CQ7)

● Drug therapy with non-steroidal anti-inflammatory drugs (NSAIDs) has been attempted; however, its usefulness is unclear. (CQ8)

2) Treatment of colorectal cancer

● In FAP patients with locally advanced colorectal cancer, standard treatment for locally advanced colorectal cancer should be undertaken. If curative resection of the colorectal cancer can be expected, the surgical procedure should be selected according to the condition of the FAP.

● In FAP patients with locally advanced colorectal cancer, the surgical procedure should be determined after a comprehensive consideration of the stage and site of the colorectal cancer. If curative resection of the colorectal cancer can be expected, total proctocolectomy or total colectomy with dissection of the regional lymph nodes is an option; on the other hand, if the colorectal cancer cannot be expected to be curatively resected, a surgical procedure like that for sporadic colorectal cancer should be selected.

● Chemotherapy similar to that used for patients with sporadic colorectal cancer should be used for colorectal cancer associated with FAP.

● Even after total proctocolectomy or total colectomy,

chemotherapy selection can be guided by the recommendations in the "JSCCR Guidelines 2016 for the Treatment of Colorectal Cancer."

● If metastatic lesions can be expected to be curatively resected, treatment similar to that for metastases from sporadic colorectal cancer should be used.

3) Examinations for extracolonic manifestations before proctocolectomy (colectomy)

● It is desirable to carry out extensive examinations to check for extracolonic manifestations prior to colorectal resection, irrespective of the presence or absence of associated locally advanced colorectal cancer, although there is little evidence of its usefulness.

● It is recommended to check for the presence of gastroduodenal lesions, including ampullary and desmoid tumors prior to colectomy.

● Examinations for other tumorous lesions can be performed during the surveillance after proctocolectomy (colectomy).

● Presence/absence of adenomas and cancers of the stomach and duodenum, including of the ampulla of Vater, should be checked by upper gastrointestinal endoscopy.

● The presence/absence of desmoid tumors should be checked for by palpation, CT, and/or MRI.

● Ultrasonography to check for thyroid cancer need not necessarily be performed before colectomy, but it must be incorporated into the postoperative surveillance plan, especially in female patients.

● In general, small-bowel follow-through and small-bowel endoscopy (capsule endoscopy) are not performed before proctocolectomy (colectomy) except when there are symptoms/findings (including preoperative diagnostic imaging findings) raising the suspicion of intestinal lesions.

● Because adrenal tumors develop at a low frequency, and hepatoblastomas and brain tumors develop commonly only until 2 to 3 years of age and up to adolescence, respectively, preoperative examinations for these tumorous lesions are, in general, not required.

4. Postoperative surveillance

1) Surveillance specific to proctocolectomy (colectomy)

● If there is any residual colorectal mucosa after prophylactic proctocolectomy (colectomy), regular colonoscopic examination is required, in view of the possibility of new colorectal cancer development.

● In FAP patients undergoing surgery for colorectal cancer, postoperative surveillance similar to that in sporadic colorectal cancer patients should be planned/performed.

● Long-term surveillance to monitor the development of cancer in the remaining rectum is required after IRA (CQ9).

● Usually 2 to 3 cm of rectal mucosa is left behind after stapled IPAA, and a small amount of rectal mucosa may also be left behind after hand-sewn IPAA. Therefore, long-

Table 4. Surveillance for the Remaining Rectum after Surgery and the Major Associated Lesions in Familial Adenomatous Polyposis.

Associated lesions	Initiation age and screening procedures
Remaining rectal adenomas	<ul style="list-style-type: none"> · Annual colonoscopy with polypectomy or ablation after IPAA · Colonoscopy with polypectomy or ablation for the patients after IRA every 6 months (depending on age or density of adenoma)
Duodenal adenoma/cancer (including ampullary lesions)	Baseline upper gastrointestinal endoscopy starting at the time of colectomy or at 20-25 years old, whichever is earlier. Thereafter, upper gastrointestinal endoscopy repeated regularly depending on the severity.
Gastric adenoma/cancer	Upper gastrointestinal endoscopy every year (or simultaneously with examination for duodenal lesions)
Thyroid cancer (for females)	Thyroid ultrasound and palpation every year starting in late teenage
Intra-abdominal desmoid tumor	<ul style="list-style-type: none"> · Abdominal palpation every year · After colectomy, abdominal and pelvic CT or MRI every 3 years for patients with a family history of desmoid tumors
Brain tumor	Radiologic examination every year
Jejunum/ileal adenoma or cancer	Data to support any recommendation are lacking. Simultaneously with radiological examinations (CT/MRI) for desmoid tumors

Modification with ref. 33)

term surveillance of the remaining rectum is required after stapled IPAA and after hand-sewn IPAA.

- Adenomas in the ileal pouch have been reported to develop in 6.7-74% of patients after IPAA²⁶⁻²⁹, and cancer has also been reported to develop^{30,31}. Therefore, long-term surveillance is necessary.

- Pouchitis occurs in approximately 5% of patients undergoing IPAA for FAP, but the incidence is lower than that after surgery for ulcerative colitis³². The condition usually manifests with fever, diarrhea, and anemia, and if these symptoms are noted, colonoscopic examination should be performed immediately.

- In FAP patients with advanced colorectal cancer treated by curative resection, surveillance for recurrence should be performed as in patients with sporadic colorectal cancer.

2) Surveillance for extracolonic manifestations

- Surveillance should be conducted bearing in mind the possible development of desmoid tumors, which tend to develop within 2 to 3 years after colectomy, and the possible development of malignancies such as duodenal cancers.

- Extracolonic manifestations requiring treatment often develop after proctocolectomy (colectomy). A method for surveillance of the remaining rectum and for extracolonic manifestations after proctocolectomy (colectomy) is proposed, as shown in Table 4³³.

[Gastrointestinal tract]

- Polyps in fundic gland polyposis usually show the histological features of hyperplastic polyps, and therefore, do not constitute an indication for surgery. Gastric adenomas develop mainly in the antrum. In Japan, FAP patients are at higher risk of developing gastric cancer than the general population. Gastric surveillance should be conducted simultaneously with duodenal surveillance. (CQ10)

- The incidence of cancer in the duodenum (including ampullary tumors) is high, necessitating regular endoscopic

follow-up and treatment of adenomas. (CQ11, CQ12)

- No recommended method for surveillance of the ileum/jejunum has been established yet. Jejunum/ileal cancer develops rarely. (CQ13)

[Desmoid tumors]

- Desmoid tumors often develop in the abdominal wall, mesentery, or retroperitoneum within 2 to 3 years after proctocolectomy (colectomy)^{26,34}. Palpation and diagnostic imaging should be performed carefully and careful attention should be paid to the clinical symptoms (abdominal pain, abdominal distension, mass, gastrointestinal obstruction, etc.). (CQ14)

[Others]

- Among malignancies, attention should be paid to the development of thyroid cancer (especially in females). Neck palpation and ultrasonography should be performed once a year. (CQ15)

3) Management of families (relatives)

- It is desirable to provide genetic counseling not only to patients, but also to their relatives. (CQ16)

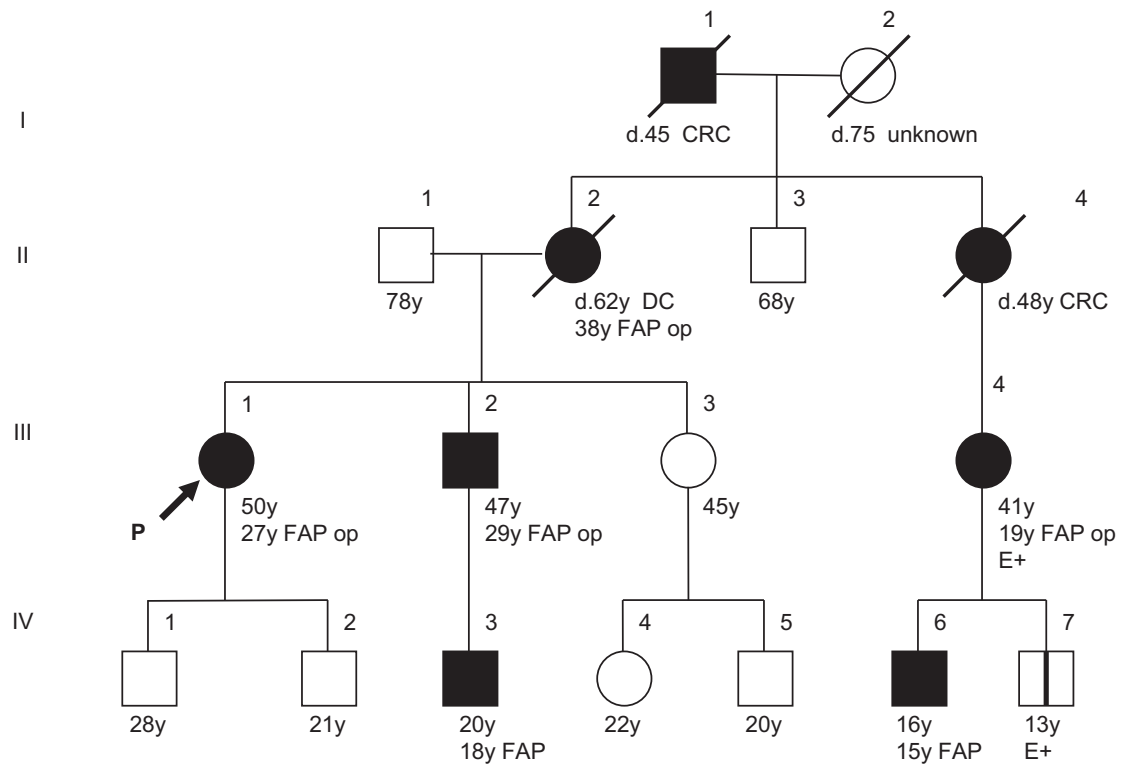
- Surveillance of the gastrointestinal tract, mainly of the large intestine, should be performed in first-degree relatives (parents, children, and siblings) after obtaining informed consent.

- It is indispensable to take a family history in patients with hereditary tumors, including FAP, and it is desirable to accurately describe/record the family history using a pedigree chart^{35,36}. (Figure 12)

- If any relatives have colorectal adenomas (particularly 2 or more colorectal adenomas), the FAP diagnostic chart (Figure 2) should be followed.

- If no adenomas are detected by colonoscopy, colonic examination should be performed approximately every 3 years.

- If no adenomas are detected by multiple colonic exami-



E+: positive for germline mutation of *APC* gene; CRC: colorectal cancer; DC: duodenal cancer; FAP: familial adenomatous polyposis; op: underwent operation



-  : mutation carrier without cancer
-  : Personal numbers can be assigned to the upper right of individuals

Figure 12. Example of description of family tree for FAP.

nations up to 35 years of age, FAP can almost definitely be ruled out.

- If genetic testing is performed, genetic counseling needs to be provided by a physician and/or specialist before and after the testing. (CQ15)

- If a patient has been diagnosed with FAP by genetic testing, his/her relatives can be diagnosed with FAP by genetic testing of a blood sample.

Clinical Questions

CQ1: Under what circumstances is genetic testing required for the diagnosis and treatment of FAP?

Recommendation category: B

Genetic testing of the *APC* gene is required in the following cases.

(1) When the results of genetic testing are planned to be

used as reference for treatment selection or surveillance in patients clinically diagnosed with FAP.

(2) When, in a pedigree in which a pathogenic germline mutation of the *APC* gene has been detected, relatives of the patient wish to undergo genetic testing.

(3) When the results of genetic testing are to be used for the diagnosis of AFAP or in the differential diagnosis of MAP and PPAP.

1. Genetic testing in patients clinically diagnosed as having FAP

FAP is often diagnosed clinically, even in the absence of a family history. However, a relationship between the site of the pathogenic germline mutation in the *APC* gene and the number of colorectal adenomas, other associated lesions, etc., has been reported, and genetic testing is sometimes useful for treatment selection or surveillance³⁷.

*2. Genetic testing in the relatives of a patient with a known pathogenic germline mutation in the *APC* gene*

Genetic testing allows FAP to be diagnosed in the relatives (e.g., children) of a patient with a known pathogenic germline mutation of the *APC* gene.

3. Diagnosis of AFAP or differential diagnosis of *MUTYH*-associated polyposis

Although AFAP can often be clinically diagnosed based on the number of polyps in the colorectum (less than 100) and a family history consistent with autosomal dominant inheritance, extracolonic manifestations, etc., identification of a pathogenic germline mutation in the *APC* gene is useful for a definitive diagnosis. If only the patient or only the sibling(s) of the patient among the family members have less than 100 colorectal adenomas, the patient or the siblings may have *MUTYH*-associated polyposis, and genetic testing of the *APC* gene, followed by, or simultaneously with, genetic testing of the *MUTYH* gene is useful in the differential diagnosis between the two conditions. *MUTYH*-associated polyposis is inherited in an autosomal recessive manner, and it is important to clarify which gene is mutated, considering risk assessment, surveillance, etc., in relatives.

No pathogenic germline mutations of the *APC* gene are identified in some patients who have been clinically diagnosed with FAP. According to a report from Western countries⁹, pathogenic germline mutations of the *APC* gene are identified by usual testing methods in approximately 60% of patients with classical (typical) FAP, and pathogenic *APC* germline mutations and biallelic mutations of the *MUTYH* gene are identified in 10% and 7% of patients respectively, with 20 to 99 colorectal adenomas, and in 5% and 4%, of patients respectively, with 10 to 19 colorectal adenomas. Possible reasons for the failure to detect pathogenic germline mutations of the *APC* gene include: (1) difficulty in the detection of *APC* gene alterations by the analysis method used, (2) presence of unknown causative genes for adenomatous polyposis, (3) *APC* mosaicism, (4) MAP, and (5) PPAP.

The “Guidelines for Genetic Tests and Diagnosis in Medical Practice” of the Japanese Association of Medical Sciences³⁸ and the guidelines of genetics-related societies should be observed, in principle, in genetic testing. Genetic testing under these circumstances is not covered by the national health insurance program in Japan; however, genetic testing of the *APC* gene can be outsourced to testing companies. Approximately 2 to 3 mL of whole blood is required for the genetic testing.

CQ2: What are the points that should be kept in mind while treating attenuated FAP (AFAP)?

Recommendation category: C

Total colectomy + ileorectal anastomosis (IRA) and long-term surveillance by colonoscopy should be considered in patients with AFAP.

It is difficult to confidently diagnose AFAP based only on the number of colorectal adenomas (less than 100); however,

a family history of FAP and fundic gland polyposis, duodenal adenoma, exostosis, desmoid tumor, congenital hypertrophy of the retinal epithelium (CHRPE), etc., that may be associated with FAP or AFAP serve as helpful clues for diagnosis^{39,40}.

If the above-mentioned characteristics are unclear, differentiation from *MUTYH*-associated polyposis and polymerase-proofreading-associated polyposis is difficult, necessitating genetic testing for definitive diagnosis.

In AFAP, pathogenic germline mutations of the *APC* gene are often found in the 5' or 3' region, alternative splicing region (in which an exon is skipped during transcription due to the mutation), etc. of the *APC* gene¹², while no mutations may be identified in many cases.

The mean age of colorectal cancer development is higher in AFAP patients than in typical FAP patients. Burt et al.⁴¹ reported that the mean age at the diagnosis of AFAP was 41 years and that the number of colorectal adenomas was variable, with a mean of 25 (0-470) in 120 individuals from 2 families surveyed. The mean age at onset of colorectal cancer was 58 (21-81) years, and 75% of the patients had cancer of the right colon. The cumulative incidence of colorectal cancer up to 80 years of age (69%) was lower than that in typical FAP patients (almost 100%). According to the JSCCR multicenter study, the mean age at onset of colorectal cancer was 50 years in AFAP patients, and half of the patients developed colorectal cancer by 55 years of age, which was later in life than that in typical FAP patients. Therefore, in AFAP patients without rectal cancer, IRA¹² and long-term follow-up by colonoscopy⁴¹ are valid options.

CQ3: What are the points that should be considered when selecting a surgical procedure for FAP patients?

Recommendation category: B

Total proctocolectomy + ileal pouch-anal anastomosis (IPAA) is the standard surgical procedure. Total colectomy + ileorectal anastomosis (IRA) is also a valid option in patients with sparse FAP and those with a small number of rectal adenomas.

IPAA is the standard surgical procedure for typical FAP²³ (Figure 13). An ileal pouch is generally constructed in a J-shape⁴². IPAA is largely divided into hand-sewn IPAA, in which the rectal mucosa is dissected from the dentate line and an ileal pouch is anastomosed manually to the dentate line, and stapled IPAA, in which stapling anastomosis of the surgical anal canal and ileal pouch is performed. The former procedure leaves only a small amount of rectal mucosa, but requires a greater level of skill in the operator. The JSCCR multicenter study revealed that recently, in Japan, laparoscopic surgery has been used in more than 70% of cases and that hand-sewn IPAA has been selected in an increasing proportion of cases²⁴. (CQ6)

IRA is recommended for AFAP cases. IRA is considered

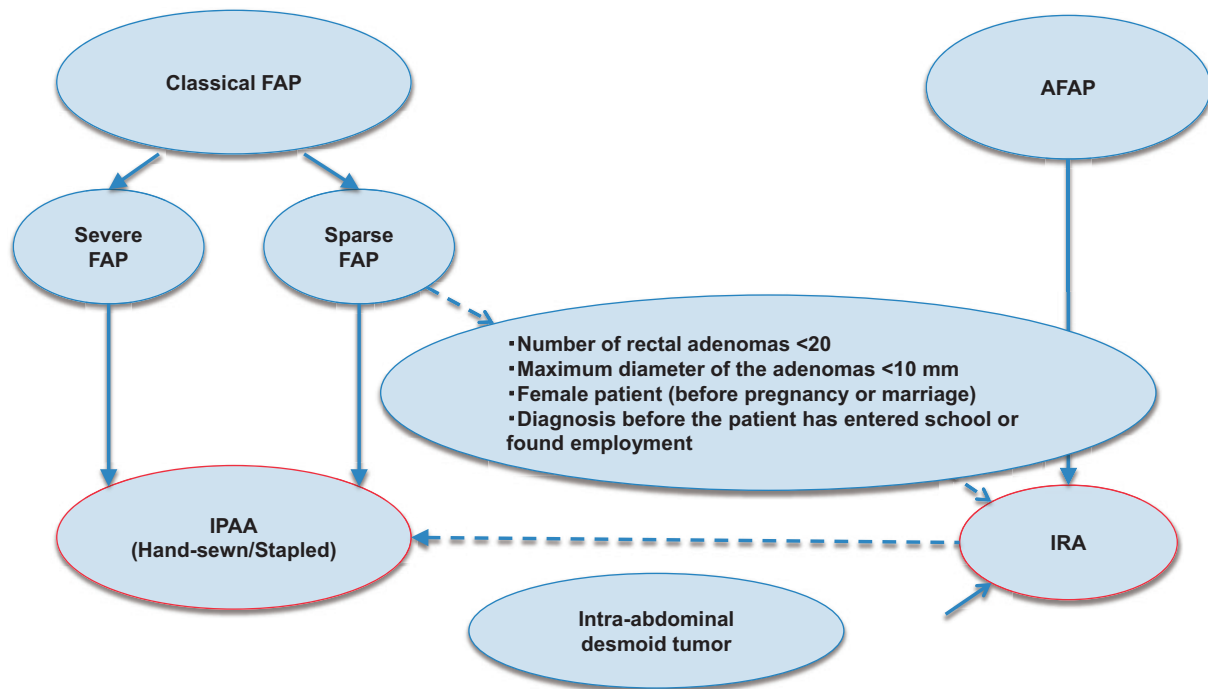


Figure 13. Flow-chart for choice of surgical method of prophylactic colectomy in FAP.

not only in AFAP patients, but also in sparse-type FAP patients who have less than 20 rectal adenomas with a maximum diameter of less than 10 mm, young females who wish to become pregnant, and children/adolescents before school age/employment, etc.^{23,43,44}. A metaanalysis⁴⁵ comparing IPAA and IRA revealed that IRA was better in the improvement of the stool frequency, defecation at night and pad use than IPAA; however, IPAA was better than IRA in the improvement of fecal urgency. The incidence of postoperative complications (within 30 days) was significantly higher after IPAA (23.4% vs. 11.6%). There were no differences in the postoperative sexual function, dietary restriction, long-term complications, or incidence of developing desmoid tumors between IPAA and IRA. It has been reported that the incidence of postoperative complications after IPAA is reduced with increased surgical skill level of the surgical team⁴⁶.

In patients with mesenteric desmoid tumors, it is often difficult to perform IPAA, and IRA is usually selected. However, there is an opinion that if the bottom of the ileal pouch reaches the pelvic floor, IPAA can also be performed.

Total proctocolectomy + permanent ileostomy, which was used before the spread of anus-preserving surgery, is rarely performed as prophylactic surgical treatment. According to the JSCCR multicenter study, this procedure was performed in approximately only 3% of all cases including colorectal cancer²⁴. Total proctocolectomy + permanent ileostomy should be reserved for patients with locally advanced lower rectal cancer, those with poor anal function, and those in whom the ileal pouch does not reach the pelvic floor, etc.

In patients with colorectal cancer, the choice of surgical procedure should be based on a comprehensive consideration of the degree of progression and site of the cancer (See Chapter I; 3. Treatment; 2) Treatment of colorectal cancer).

CQ4: Is temporary ileostomy required in cases undergoing IPAA for FAP?

Recommendation category: None

Temporary ileostomy is not required in all cases, but its need should be determined on a case-by-case basis considering its advantages and disadvantages.

A recent meta-analysis of patients treated by IPAA revealed that patients in whom temporary ileostomy was performed had a lower incidence of anastomotic leakage, but higher incidence of anastomotic stricture and bowel obstruction⁴⁷. It has been reported that temporary ileostomy can be avoided under the following circumstances: in patients with (1) stapling anastomosis, (2) no anastomotic tension, (3) complete anastomosis, (4) sufficient hemostasis, (5) no anastomotic air leak, and (6) no evidence of malnutrition, infection, anemia or regular steroid use⁴⁸. Anastomotic leakage after IPAA may cause an important long-term complication, namely, pouch failure. Anal dysfunction and poor expansion of the ileal pouch have been reported as possible causes of pouch failure. From these points of view, it is considered that temporary ileostomy may be useful in the prevention of anastomotic leakage and pelvic abscess, or suppress the degree of these adverse events as much as possible after IPAA. However, it should be kept in mind that the above studies

included both patients with ulcerative colitis and those with FAP, the latter accounting only for a small proportion of the subjects.

Studies of IPAA conducted on only FAP patients have reported that temporary ileostomy is performed in most patients, except some of those undergoing stapled IPAA^{49,50}. In a study on the usefulness of temporary ileostomy in FAP patients aged less than 20 years old, patients in whom temporary ileostomy was not performed showed favorable long-term defecation control, but had significantly higher incidence of anastomotic leakage within 30 days of surgery (17.2% vs. 0%, $P = 0.002$) and a higher reoperation rate (20.7% vs. 4.6%, $P = 0.02$)⁵¹. However, most subjects included in this study underwent stapled IPAA, and further studies of temporary ileostomy in patients undergoing hand-sewn IPAA are required.

The JSCCR multicenter study showed that temporary ileostomy was performed in 55% of patients who had undergone IPAA²⁵.

A systematic review of the closure of temporary ileostomy⁵² revealed that closure was safe, but that 16.5% of all subjects had postoperative complications, including bowel obstruction in 7.6% (reoperation in 2.9% of all cases), anastomotic leakage in 2.0%, wound infection in 4.0%, and late complications such as incisional hernia in 1.9% and bowel obstruction in 9.4%.

Considering the above, temporary ileostomy can be avoided in selected FAP patients undergoing IPAA, but it is not easy to clearly determine its indications. Therefore, it is practical to determine the need for temporary ileostomy on a case-by-case basis, taking into consideration its advantages and disadvantages.

CQ5: At what age is prophylactic proctocolectomy (colectomy) recommended to prevent colorectal cancer in FAP patients?

Recommendation category: B

In general, the surgery is performed when the patients are in their 20's; however, the decision should be made after comprehensively considering the patient sex, density of colorectal adenomas, presence/absence of malignant transformation of the adenomas, associated lesions, the patient's social background, etc.

The most important considerations in deciding the timing for prophylactic (procto)colectomy in FAP patients are: (1) cumulative prevalence of colorectal cancer²; (2) density of the adenomas⁵³; (3) size and morphology of the adenomas; (4) age at death, age at cancer onset, and presence/absence of desmoid tumors in members of the pedigree⁵⁴; (5) germline mutation site in the *APC* gene⁵⁵; (6) educational, work, and other environments of the patient⁵⁶; (7) fertility⁵⁷ and presence/absence of male sexual dysfunction⁵⁸ after IPAA; (8) presence/absence of gastrointestinal symptoms, such as

diarrhea, abdominal pain and melena; and (9) the histopathological findings of the tumor. Considering the prevalence of colorectal cancer, it is recommended that some classic FAP patients should undergo surgery while in their teens, and that most FAP patients should undergo surgery while they are in their 20's^{59,60}.

According to the JSCCR multicenter study, the cumulative incidence of developing colorectal cancer (excluding intramucosal cancer) was approximately 1% in patients aged 20 years and increased to 9.6% and 21.4% in AFAP and classic FAP patients aged 30 years, respectively. Thus, the incidence is higher in classic FAP patients (Attachments: I. Familial adenomatous polyposis; Attachment Table 3: Cumulative incidence of developing colorectal cancer and duodenal adenoma).

CQ6: Is laparoscopic surgery useful for FAP?

Recommendation category: C

The decision to undertake laparoscopic surgery for FAP should be made after a full informed consent is obtained from the patient, according to the skill of the operator at the institution.

Recently, laparoscopic surgery has been used in an increasing proportion of patients undergoing IPAA or IRA (IPAA: 23-53%; IRA: 58-62%)⁶¹⁻⁶⁴. According to previously published reports, laparoscopic surgery takes a longer time, but there are no differences between laparoscopic and open surgery in the incidence of postoperative complications, mortality, reoperation rate or readmission rate⁶³; furthermore, the laparoscopic approach yields better esthetic outcomes with less intraoperative bleeding. In addition, laparoscopic surgery was also reported to be associated with a lower incidence of postoperative bowel obstruction, due to lower risk of occurrence of intra-abdominal adhesions and a lower incidence of postoperative fertility impairment in females⁶¹. According to the JSCCR multicenter study conducted recently, laparoscopic surgery has been used in more than 70% of cases²⁴, and among the subjects of this study, the laparoscopic approach had been used in 74 out of 171 (43%) patients undergoing IPAA and 52 out of 85 (61%) patients undergoing IRA²⁵.

Concerning the short-term outcomes of laparoscopic surgery, the operation time is long; however, safety is secured. The decision to undertake laparoscopic surgery for FAP should be made after a full informed consent is obtained from the patient, according to the skill of the operating surgeon at the institution.

CQ7: Does IPAA have adverse effects on fertility, pregnancy, and delivery in female patients with FAP?

Recommendation category: None

IPAA may be associated with postoperative reduction in fertility, but has little adverse effect on pregnancy or deliv-

ery.

A study involving 58 female Danish patients with FAP⁶⁵ showed that their fertility rate was 90%, equivalent to that in the general population. A study involving 162 female European patients with FAP demonstrated that the fertility rate in FAP patients who had not undergone any surgery was equivalent to that in the general population. In addition, while the fertility rate of FAP patients who had undergone IRA was also equivalent to that in the general population, the fertility ratio was reduced to 0.46 in FAP patients who had undergone IPAA⁶⁷. On the other hand, a study involving 138 Dutch patients with FAP reported that fertility was not related to the surgical procedure, but to the age at first surgery⁶⁶.

The reduction in fertility after IPAA is thought to be caused by postoperative adhesions. Oresland et al.⁶⁷ reported that hysterosalpingography after total proctocolectomy revealed adhesion of the fallopian tube to the pelvic wall in 48% of the cases, unilateral obstruction of the fallopian tube in 43% and bilateral obstruction of the fallopian tubes in 10% of the cases.

A study in which both patients with FAP and those with ulcerative colitis were included, reported that the fertility was significantly higher after laparoscopic IPAA than after IPAA via open surgery⁶⁸. However, there have been no prospective studies including only FAP patients.

Studies including both patients with FAP and those with ulcerative colitis have reported that pregnancy and transvaginal delivery are safe after IPAA^{69,70}. However, the possibility of anal sphincter muscle damage and nerve damage of the pelvic floor muscles after perineal incision must be considered during transvaginal delivery after IPAA.

CQ8: Is there any effective pharmacotherapy for the adenomas in FAP patients?

Recommendation category: C

NSAIDs have been attempted for colorectal adenomas and duodenal adenomas. Although many studies have reported that NSAIDs reduced polyp number, it is unclear whether they are useful in suppressing the development of new adenomas.

Many studies have evaluated the efficacy of sulindac, one of the NSAIDs, for the control of colorectal adenomas in FAP patients. Treatment with sulindac (150-300 mg/day) for 6 weeks to 98 months reduced the number of colorectal adenomas, or the number of rectal adenomas after total colectomy, by 50% or more, whereas 2-year treatment with 150-300 mg/day of sulindac failed to suppress the development of new adenomas⁷¹.

High-dose (800 mg/day) treatment with celecoxib, one of the selective cyclooxygenase-2 (Cox-2) inhibitors, for 6 months reduced the number of colorectal adenomas by 28% in FAP patients⁷². Celecoxib should be administered at a

high dose for a long period of time for suppressing the development of colorectal adenomas in FAP patients. Rofecoxib, another of the selective Cox-2 inhibitors, was also reported to reduce the number of rectal adenomas by approximately 7% after total colectomy⁷³. However, because long-term treatment with rofecoxib resulted in a high incidence of cardiovascular adverse events⁷⁴, its use for the prevention or treatment of adenomas is not recommended.

So far, no useful pharmacotherapy to suppress the development of new colorectal or duodenal adenomas has been reported.

CQ9: How should the risk of rectal cancer development be managed after total colectomy + ileorectal anastomosis (IRA)?

Recommendation category: C

Long-term surveillance for the development of cancer in the remaining rectum is necessary.

Long-term follow-up after IRA has revealed that 24-43% of patients develop cancer in the remaining rectum^{75,76}. During a 20-year period after IRA, the rectum had to be resected in 10% of patients with AFAP, 39% of patients with sparse FAP, and 61% of patients with profuse FAP³⁷.

With advances in surgical techniques, IPAA has been used in an increasing proportion of cases²²⁻²⁴, and the use of IPAA in patients with a greater number of risk factors for rectal cancer has reduced the proportion of patients undergoing proctectomy after IRA from 40 to 13%, and has also reduced the cumulative incidence of cancer development in the remaining rectum after IRA^{61,77,78}.

CQ10: How should gastric lesions be managed in FAP patients?

Recommendation category: C

FAP patients in East Asia have higher risk of gastric cancer than the general population, necessitating long-term endoscopic surveillance.

Approximately 50% of FAP patients develop multiple protrusive polyps in the fundus to the body (fundic gland polyposis). Foveolar-type adenomas (according to the WHO classification) and pyloric gland adenomas are known to develop in the background of fundic gland polyposis, and although rare, development of invasive cancer has also been reported. Particularly, large polyp clusters, with some showing dysplastic or malignant changes, indicate endoscopic resection^{13,79}. Gastrectomy should not be performed for fundic gland polyposis. Solitary or sporadic, depressed- or elevated-type adenomas develop in the antrum⁸⁰. From the above, adenomas measuring 1 cm or more in diameter, as well as sporadic adenomas not associated with FAP, are relative indicators of endoscopic resection, considering the risk of malignant transformation. While the incidence of gastric cancer in FAP patients has been reported to be equivalent to that in

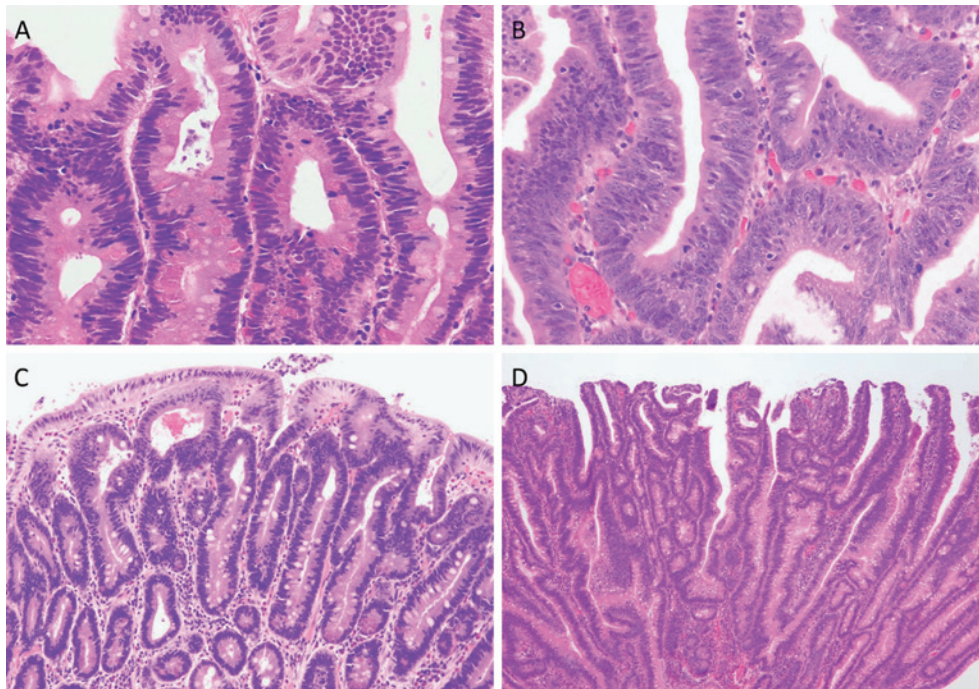


Figure 14. Histology of FAP-associated duodenal adenomas. A: Low-grade adenoma: The tumor glands are rather uniform and the adenomatous epithelial cells show basally oriented, elongated nuclei. B: Intramucosal carcinoma: Tumor glands show significant irregularity, nuclear stratification, and occasional prominent nucleoli. Note that high-grade dysplasia in the Spigelman classification includes non-invasive intramucosal carcinoma in the Japanese classification. C: Tubular adenoma: This lesion shows a relatively regular tubular architecture. D: Tubulo-villous adenoma: This lesion partially exhibits villous architecture, composed of fibrovascular cores lined by dysplastic epithelium.

the general population in Western countries⁸¹), it has been reported to be 3-7 times higher in FAP patients than in the general population in East Asia^{82,83}). It is desirable to perform upper gastrointestinal endoscopy once a year (or simultaneously with surveillance for duodenal adenoma surveillance).

CQ11: How should duodenal adenomas (excluding those of the ampulla) be managed in FAP patients?

Recommendation category: C

No consensus has been reached on the treatment or surveillance for duodenal adenomas, but the Spigelman classification can be referred to for optimal treatment and surveillance.

After excluding colorectal cancer, which accounts for death in the majority (61-69%) of FAP patients, duodenal cancer (including ampullary cancer) ranks as the second most common cause of death after desmoid tumors, and accounts for death in approximately 3% of FAP patients^{2,84}). The relative risk of duodenal cancer in FAP patients as compared with that in the general population is 250-330.8^{81,82}). The cumulative incidence of duodenal cancer by 57 years of age is estimated to be approximately 4.5%⁸⁵). Duodenal ade-

nomas are seen in 30-90% of FAP patients⁸⁶⁻⁸⁸), and the prevalence of adenomas increases after 40 years of age, eventually reaching 90%^{87,88}). Duodenal adenomas grow extremely slowly^{87,89}); however, regular endoscopic surveillance/treatment is necessary. The JSCCR multicenter study found that the cumulative incidence of duodenal adenomas by the age of 50 years was 39.2%, and significantly higher in classic FAP patients than in AFAP patients (42.5% vs. 23.5%)⁹⁰). There exists a clinicopathological classification of duodenal adenomas, called the Spigelman classification⁹¹). In the Spigelman classification, the number and maximum diameter of duodenal adenomas are assessed by endoscopy, and biopsy (Figure 14) is used to evaluate the histology and severity of dysplasia. Over time, some modifications have been introduced to this classification (modified Spigelman classification)⁹¹) (Figure 15). (Side Memo 5: Changes in the evaluation methods for Spigelman classification)

Direct-view endoscopy and side-view endoscopy are used to diagnose duodenal adenomas. A study of 37 Dutch patients with FAP showed that the use of narrow-band imaging increased the number of duodenal adenomas detected, but did not affect the results of classification according to Spi-

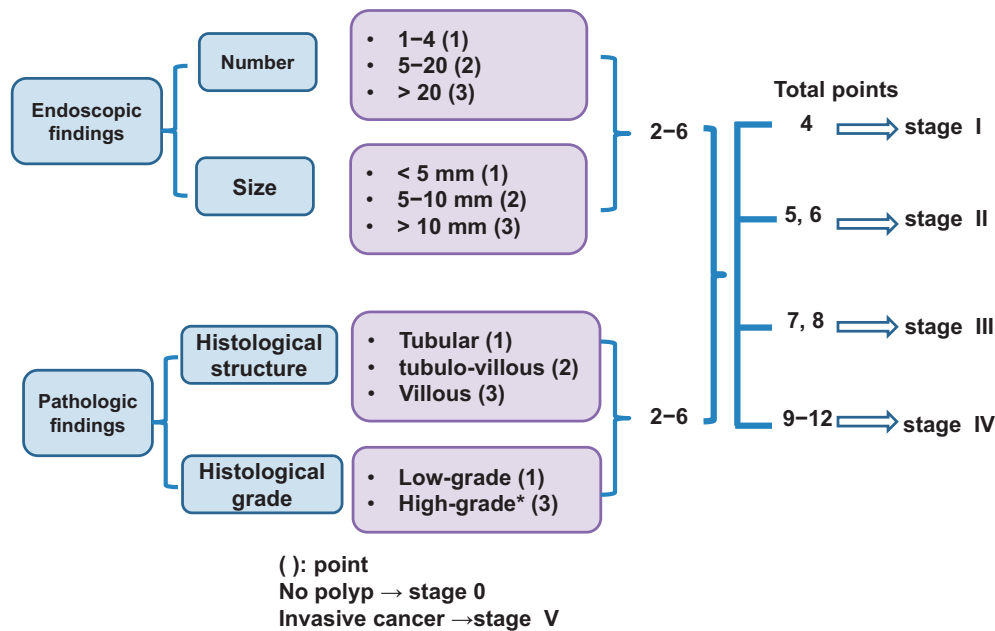


Figure 15. Classification of duodenal adenomas by the modified Spigelman classification.

gelman classification⁹³.

Endoscopic treatments of duodenal adenomas include snare resection, electrocautery, and argon plasma coagulation. Endoscopic electrocautery should be used for adenomas classified as Spigelman stage I/II. Endoscopic or transduodenal resection is not sufficient for patients with many adenomas⁸⁵. It was reported that endoscopic complete resection of adenomas classified as Spigelman stage II/III was associated with a high incidence of complications and a recurrence rate of 50-100%⁸⁶. To date, no clinical trials have been conducted for comparing endoscopic treatment and follow-up of duodenal lesions in FAP patients.

No consensus has been reached on the interval of testing, but it is recommended that testing be performed every 4 to 5 years for cases with stage 0, every 2 to 5 years for cases with stage I, every 2 to 3 years for cases with stage II, and every 6 months to 2 years for cases with stage III duodenal adenomas^{85,88}. Assessment of the indication for surgery or half-yearly to yearly surveillance by a specialist is recommended for patients with stage IV high-grade adenomas, severe adenomatosis, etc. Pancreaticoduodenectomy (PD), pylorus-preserving pancreaticoduodenectomy (PPPD), or pancreas-sparing duodenectomy (PSD) should be considered for patients with stage IV adenomas, because malignant transformation occurs in 7-36% of cases^{85,94}.

Among surgical procedures, PD or PPPD is generally selected, and it was reported that PSD was performed in 13 Danish patients with FAP between 1999 and 2010. Six (46%) of these patients developed postoperative complications, and of these, 3 had anastomotic leakage, but recovered with conservative treatment⁹⁵. According to a report

from the Netherlands, 43 out of 1,066 FAP patients underwent duodenectomy (PSD was performed in 22 of these), and PSD has been the first-line surgical procedure for “prophylactic duodenectomy” since 1999⁹⁶. However, in Japan, PSD is performed in only some hospitals for FAP patients. Management of duodenal adenomas according to the modified Spigelman classification is shown in Figure 16.

Side Memo 5

■ Changes in the evaluation methods for the Spigelman classification

The Spigelman classification is a staging system for duodenal adenomas associated with FAP that was proposed in 1989⁹¹. The polyp number, maximal diameter, histology and severity of dysplasia are assessed on a scale ranging from 1 to 3, and the total score is used to determine the disease stage. In the Vienna classification of 2000⁹⁷, the grading of the severity of dysplasia was changed from 3 levels, that is, mild, moderate, and severe, to 2 levels, namely, low-grade and high-grades, and a modified classification was proposed, in which 1 and 3 points are given to the low and high grades, respectively⁹². Recently, the National Comprehensive Cancer Network (NCCN) Guidelines (Genetic/Familial High-Risk Assessment: Colorectal V.2.2015) proposed a classification that was a simpler form of the Spigelman classification, or the modified Spigelman classification. This classification consists of stages 0 (no adenomas), I (1 to 4 tubular adenomas measuring 1-4 mm in diameter), II (5-19 tubular adenomas measuring 5-9 mm in diameter), III (20 or more adenomatous lesions measuring 1 cm or more in diameter), and IV (dense or high-grade adenomas). No prospective studies of the validity of surveillance or treatment based on these staging systems have been conducted, and this issue needs to be addressed in the future.

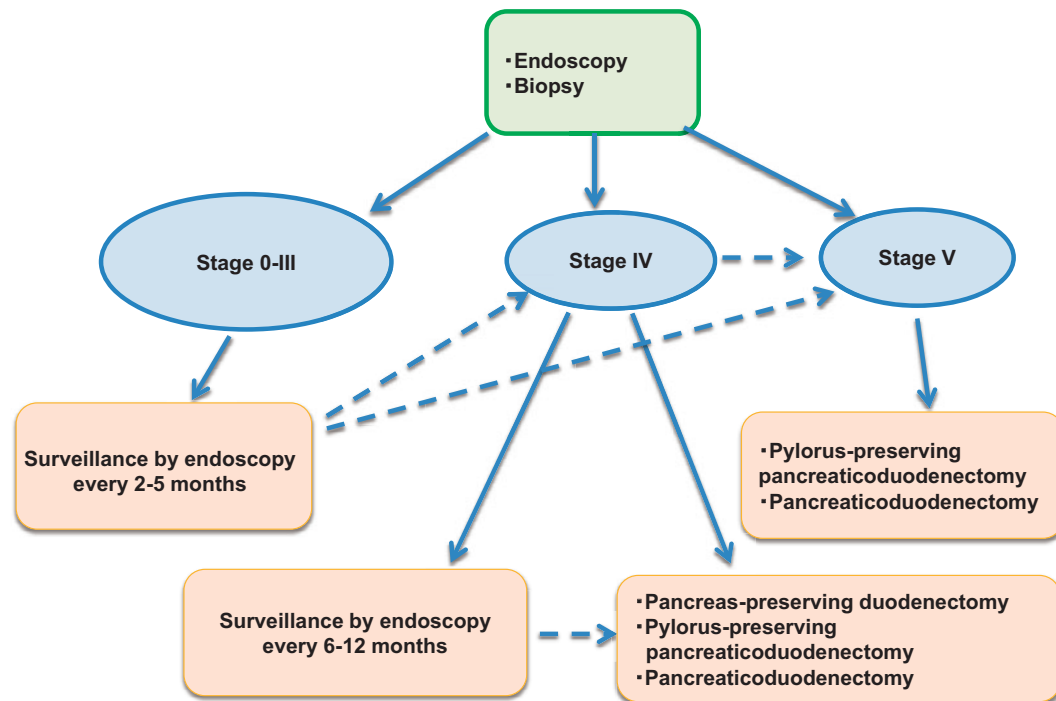


Figure 16. Surveillance of duodenal adenomas based on the modified Spigelman classification.

CQ12: How should ampullary tumors (adenomas/cancers) be managed in FAP patients?

Recommendation category: C

Endoscopic or surgical treatment should be selected for ampullary tumors according to the clinical condition and symptoms.

Approximately 50% of FAP patients develop ampullary tumors^{98,99}. Some AFAP patients also develop ampullary tumors¹⁰⁰. The relative risk of ampullary cancer in FAP patients as compared to that in the general population was reported to be 123.7⁹¹. Endoscopic ampullectomy or transduodenal ampullectomy^{101,102} is indicated for tumors localized to the papilla. The former has often been adopted, with recent advances in colonoscopic treatment techniques.

Electrocautery of periampullary lesions (within 2 cm of the papilla), including those of the papilla, has been reported to be safe and effective¹⁰³, while it has also been suggested that aggressive treatment is not recommended, because the lesions were found to remain benign over long-term observation for more than 10 years¹⁰⁴. Ma et al.¹⁰⁵ retrospectively investigated the data of 26 FAP patients who underwent endoscopic ampullectomy in the United States between 1990 and 2010. Complications in these patients included pancreatitis (19.2%), abdominal pain (7.6%), and bleeding (3.8%). Of the 24 patients who could be followed up, 14 (58.3%) had local recurrence, and the authors called attention to this problem. Gluck et al.¹⁰⁶ reported that endoscopic follow-up of 80 FAP patients for an average of 7.2 years revealed am-

pullary tumors in 38 patients (47.5%), of whom 10 had advanced adenomas (tumor diameter 10 mm or more, villous type, high-grade dysplasia), and that endoscopic ultrasonography (EUS) is important for their diagnosis. In addition, 15 underwent endoscopic ampullectomy, of which 2 eventually underwent surgery for recurrent lesions. Regarding surgery, if there is a periampullary lesion that is difficult to treat endoscopically, pancreas-sparing duodenectomy (PSD)¹⁰⁷ may be selected and if any evidence of malignant change is noted, pancreaticoduodenectomy (PD), pylorus-preserving pancreaticoduodenectomy (PPPD), etc., should be selected.

CQ13: How should jejunal/ileal tumors be managed in FAP patients?

Recommendation category: C

Small-bowel endoscopy and capsule endoscopy have been attempted, but no consensus has been reached on the examination or treatment of jejunal/ileal tumors in FAP patients.

Jejunal/ileal adenomas develop in 60-75% of FAP patients¹⁰⁸⁻¹¹¹. A study using capsule endoscopy showed that patients with duodenal adenomas also tend to have jejunal/ileal adenomas^{109,112}. Most of these adenomas measure 10 mm or less in diameter^{111,113,114}. Studies on relatively large numbers of patients have shown that the number of adenomas tends to be higher in the jejunum and lower in the ileum^{109,114}. In principle, because jejunal/ileal cancer develops rarely¹¹⁵, endoscopic resection is not indicated for jejunal adenomas. However, how jejunal/ileal adenomas should be examined

and treated remains to be established, and this issue needs to be addressed in the future¹¹⁶⁾.

CQ14: What are the management strategies that should be used for desmoid tumors in FAP patients?

Recommendation category: C

No consensus has been reached concerning the treatment of desmoid tumors in FAP patients. Pharmacotherapy, surgery, conservative treatment (follow-up), etc., could be selected according to the site and severity of the tumors.

Management strategy for desmoid tumors should be selected taking into consideration the characteristics of the desmoid tumors, types of treatment available, tumor stage, etc.

1. Characteristics

Desmoid tumor is a type of fibroma, which does not metastasize, but tends to show invasive growth. Desmoid tumors are seen in 8-20% of FAP patients^{54,83,117,118)}, intra-abdominal desmoid tumors accounting for 70% of all cases¹¹⁹⁾. They often develop in the abdominal wall, mesentery or retroperitoneum after (procto)colectomy (in particular, within 2 to 3 years)^{26,34)}, and when developing intra-abdominally (including in the retroperitoneum), they can cause bowel obstruction, perforation, abscess formation, ureteral obstruction, etc., often making treatment difficult. The mortality rate of FAP patients developing desmoid tumors is reported to be 0-14%^{26,83,118,120,121)}.

2. Types of treatment

Desmoid tumors should be treated taking into account their characteristics including: (1) spontaneous decrease of size or size stabilization^{120,122,123)}, and (2) recurrence that has been reported to occur in 10-68% of cases after resection¹¹⁷⁾. Pharmacotherapy (including chemotherapy), surgical resection, radiation therapy, etc., have been used for the treatment of desmoid tumors. In FAP patients, desmoid tumors are often adjacent to the intestine, such as those in the mesentery, and radiation therapy is generally not recommended, because it can cause bowel injury and is poorly effective¹²⁴⁾.

Treatment with sulindac (300 mg/day), which is one of the NSAIDs, and tamoxifen (40 to 120 mg/day) or toremifene (180 mg/day), which are antiestrogens, could be selected for large and/or rapidly growing intra-abdominal or abdominal-wall desmoid tumors^{125,126)}.

Both sulindac and antiestrogens have been reported to have a limited effect in reducing the tumor size, but they suppress tumor growth¹²⁷⁻¹²⁹⁾. Recently, the efficacy of a tyrosine kinase inhibitor, imatinib, has also been examined. Desurmont et al.¹²⁸⁾ reported that imatinib reduced the tumor size or stabilized the tumor size in 36% of treated cases. On the other hand, Chugh et al.¹³⁰⁾ reported a 1-year progression-free rate of 66% in inoperable desmoid tumor patients treated with imatinib, but reduction of the tumor size occurred in only 3% of the patients. Therefore, at pre-

sent, the efficacy of imatinib remains to be clearly established.

Regarding cytotoxic chemotherapy, high response rates were reported with a combination regimen of doxorubicin (DOX) plus dacarbazine (DTIC)¹³¹⁾. In Japan also, DOX + DTIC therapy has been found to be effective¹³²⁾. In addition to DOX + DTIC therapy, methotrexate (MTX) plus vinblastine (VBL) has also been reported to be effective¹³³⁾.

Desurmont et al.¹²⁸⁾ compared the response rates of intra-abdominal desmoid tumors to various pharmacotherapies. They found that the response rates were 77% to treatment with cytotoxic anticancer drugs, 50% to treatment with sulindac + tamoxifen, 40% to treatment with tamoxifen, 36% to treatment with imatinib, and 28% to treatment with sulindac. Thus, the response rate of intra-abdominal desmoid tumors was the highest to treatment with cytotoxic anticancer drugs, and they concluded that cytotoxic anticancer drugs could be the first-line treatment. However, it has not been clearly established in which type of intra-abdominal desmoid tumors cytotoxic anticancer drugs should be used as the first-line treatment.

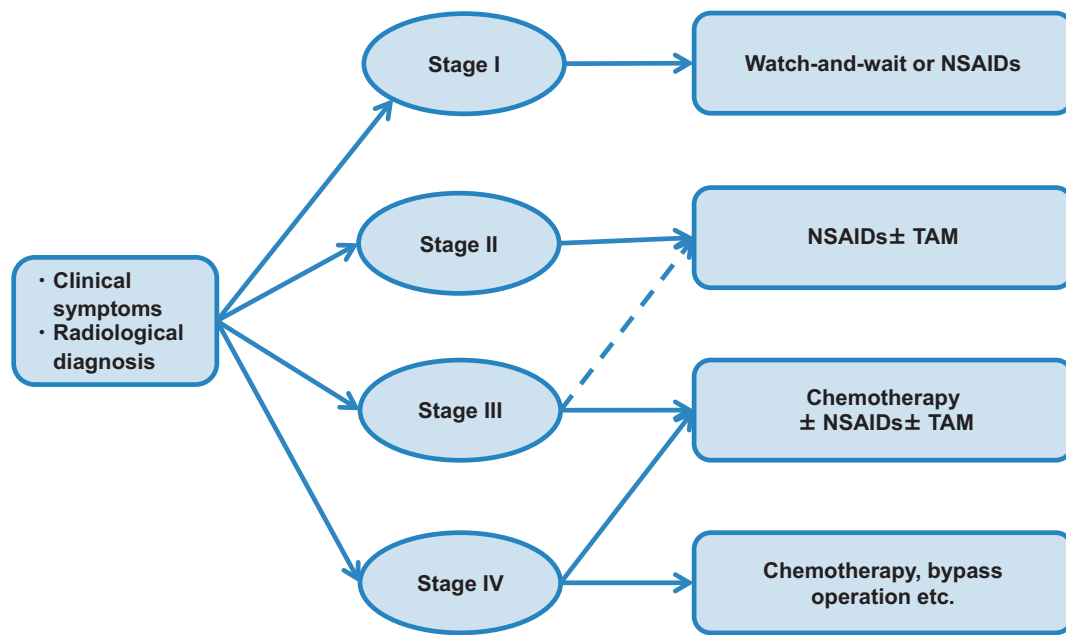
Extra-abdominal desmoid tumors have been reported to show high recurrence rates after resection (20-25%), although the incidence of postoperative complications is low. Because recurrence after resection may not only be caused by incomplete resection, but also possibly by new tumor development at the site of incision, excessive peritumoral resection should be avoided¹³⁴⁾. Although surgery should be considered for bowel obstruction due to intra-abdominal desmoid tumors, it may not be successful due to the difficulty of resection or the necessity for massive intestinal resection¹²⁹⁾. Smith et al.¹³⁵⁾ reported the absence of any difference in survival between patients treated by complete resection and patients not treated by complete resection, including by-pass cases.

3. Treatment of intra-abdominal desmoid tumors based on the Church classification

A staging system for intra-abdominal desmoid tumors has been developed by reference to the classification of Church et al.¹²¹⁾ (Table 5). Although no prospective studies have been conducted, options include follow-up or use of NSAIDs for stage I tumors, surgery and NSAIDs + tamoxifen, if possible, for stage II tumors, NSAIDs + tamoxifen + chemotherapy for stage III tumors, and chemotherapy or by-pass surgery for stage IV tumors (Figure 17). According to one report, mortality was 0 in stage I/II patients and 15% and 44% in stage III and IV patients, respectively. Stent placement is recommended for ureteral obstruction.

Table 5. Staging System for Intra-Abdominal Desmoid Tumors according to Church’s Classification ^{ref. 121)}.

	I	II	III	IV
Maximal size	<10 cm		10-20 cm	>20 cm
Growth speed	No growth within 6 months		Growth within 6 months	More than 50% increase in maximal diameter within 3 months
Uretic obstruction	No		Yes	
Bowel obstruction	No		Yes	
Sensation of tumor	No	Yes		
Pain	No	Yes		
Restriction of daily life	No		Yes	
Hospitalization	Unnecessary			Necessary



TAM: tamoxifen
NSAIDs: nonsteroidal anti-inflammatory drugs

Figure 17. Treatment plan according to the staging system for intra-abdominal desmoid tumors.

CQ15: What malignancies other than those of the gastrointestinal tract should careful attention be paid to in FAP patients?

Recommendation category: None

Thyroid cancer, adrenal cancer, hepatoblastoma, brain tumor, etc., are known to develop in FAP patients, and particularly, many cases of thyroid cancer have been reported. The usefulness of screening tests and surveillance for these tumors has not yet been confirmed.

Thyroid cancer is reported to develop in 1-6.1% of FAP patients^{83,136,137)}, with papillary carcinoma accounting for most

of the cases. Papillary thyroid cancer develops more commonly in females, with a female:male ratio of 44:1¹³⁸⁾. The relative risk of thyroid cancer in female FAP patients as compared to the general population is reported to be 23 to 160^{83,138,139)}. Thyroid cancer in FAP patients often shows a characteristic histology, i.e., the cribriform-morula variant^{140,141)}, and diagnosis of FAP is sometimes made during treatment of the thyroid cancer. Because reported incidences of multiple thyroid cancers and bilateral thyroid cancer are as high as 28.6-69%¹⁴²⁻¹⁴⁴⁾ and 42-67%^{142,145)}, respectively, one report has recommended subtotal thyroidectomy¹⁴⁰⁾. However, papillary thyroid cancer associated with FAP has a fa-

avorable prognosis^{83,146}, and the surgical procedure should be carefully selected. One report recommends ultrasonography in addition to palpation as a screening examination for thyroid cancer in FAP patients¹⁴⁷.

Some FAP patients develop brain tumors (Turcot syndrome, type 2). The incidence is 2.4 times higher in females than in males. Medulloblastoma is the most common tumor (60%), while other tumors such as astrocytoma and ependymoma have also been reported¹⁴⁸. The reported relative risks of brain tumors, overall, and of medulloblastoma in female FAP patients as compared to the general population are 7 and 92, respectively¹⁴⁹. Medulloblastoma commonly develops in childhood to young adulthood.

Adrenal tumors develop in 7.4-13% of FAP patients^{8,150,151}. The reported relative risk of adrenal tumors in FAP patients as compared to the general population is 2.3 to 12.5^{8,150,151}. These tumors are often accidentally detected by CT. In a study by Will et al. of 30 FAP patients¹⁴⁵, 2 (6%) had bilateral adrenal tumors, the age at diagnosis ranged from 26 to 69 years, and there was no gender difference in the incidence. Surgery is indicated for patients with suspected hormone-producing tumors or malignant transformation of the tumor. The incidence of malignant adrenal tumors is unknown in FAP patients.

It is estimated that 0.42-0.75% of children with FAP develop hepatoblastoma¹⁵². The peak age at onset is approximately 3 years, and the relative risk in FAP patients as compared to the general population is reported to be 176 to more than 420^{153,154}. Imaging examinations, including abdominal ultrasonography are used for the diagnosis, and 90% of the patients have high levels of α -fetoprotein (AFP)¹⁵⁵. CHRPE is known to be frequently associated with hepatoblastoma, and FAP patients with a family history of hepatoblastoma are known to be at a higher risk¹⁵⁶. Surgical resection or chemotherapy should be selected for treatment. Patients in whom the tumor is detected early have a favorable prognosis after complete resection^{157,158}, and one report¹⁵⁹ recommends surveillance at the peak age of onset.

CQ16: What are the points that should be kept in mind while providing genetic counseling to FAP patients/their families?

Recommendation category: B

It is necessary to provide information about FAP and psychosocial support while providing genetic counseling for FAP patients and their families (relatives), including at-risk individuals.

Genetic counseling should be provided to FAP patients, irrespective of whether genetic testing has been performed or not. Genetic testing should be performed mainly by a physician at a time and in a place where the patient can talk calmly, in accordance with the "Guidelines for Genetic Tests and Diagnosis in Medical Practice" of the Japanese Associa-

tion of Medical Sciences (February 2011), guidelines of the Japanese Society for Familial Tumors, "Ethical Guidelines for Human Genome/Gene Analysis Research," etc.

In genetic counseling for FAP, comprehensive information about the disease should be provided, including the fact that first-degree relatives of affected individuals have a 50% chance of inheriting the mutation, and that if left untreated, almost a 100% of APC mutation carriers develop colorectal cancer. Furthermore, the significance of genetic testing as one of the options, and its methods, limitations, costs, etc., should be explained, to help the patients and their families make an independent choice about genetic testing. Genetic counseling should be provided not only before and after genetic testing, but also continuously, as necessary.

Genetic or diagnostic testing (colonoscopic examination) of relatives of FAP patients frequently involves minors. When genetic or diagnostic testing is performed in minors, it is desirable to obtain not only the consent of the legal representatives of the subjects, but also informed consent from the subjects themselves after providing them with an explanation according to their level of understanding.

The results of genetic testing of relatives may differ among siblings (mutation carriers and unaffected individuals). Some individuals not carrying the pathogenic mutation have a guilty conscience (survivor guilt), e. g., a feeling that "I alone am safe and I am sorry," and psychological support for family members not carrying the pathogenic mutation is also sometimes required as part of genetic counseling.

Various tumorous and non-tumorous lesions develop in FAP, necessitating collaboration with multiple departments. It is desirable to provide long-term social, economic, and psychological support as a medical team.

Chapter II: Lynch Syndrome

1. Outline

- Lynch syndrome is a hereditary autosomal dominant disease, mainly caused by germline mutations in one of the mismatch repair genes (Side Memo 6: Mismatch repair function; Appendix: II. Method for describing genomic variants).

- These patients and their families are at an elevated risk of developing various malignancies, including colorectal cancer and endometrial cancer.

[Clinical features]

- Colorectal cancers in Lynch syndrome are characterized by early age at onset and occurrence of multiple tumors (synchronous/metachronous), and preferentially develop in the right colon. The frequency of poorly differentiated adenocarcinoma is higher among Lynch syndrome-associated colorectal cancers than among sporadic colorectal cancers. The histological features of colorectal cancer associated with

Lynch syndrome include the presence of tumor-infiltrating lymphocytes, a medullary growth pattern, mucinous/signet-ring cell differentiation, and Crohn's-like lymphocytic reaction^{153,159-161}. (CQ17, CQ18)

● A variety of other Lynch syndrome-associated (malignant) tumors can also develop besides colorectal cancer, including endometrial cancer, ovarian cancer (CQ19), gastric cancer, small-bowel cancer, bile duct cancer, pancreatic cancer, renal pelvic/ureteral cancer, brain tumor, and skin tumor (CQ17). Recently, breast cancer, bladder cancer¹⁶², and prostate cancer¹⁶³ have also been reported to develop in association with Lynch syndrome.

● The risk of development of Lynch syndrome-associated tumors varies depending on the causative gene, the type of mutation, environmental factors, etc.^{153,164-170} (Table 6)

In addition, some individuals carrying the disease-causing genetic mutation remain totally asymptomatic throughout their lives.

[Major causative genes]

● Germline mutations in any of the following genes:

MLH1 gene on chromosome 3

MSH2 and *MSH6* genes on chromosome 2

PMS2 gene on chromosome 7

[Mode of inheritance]

● Autosomal dominant inheritance

[Mechanism of malignant transformation] (Figure 18)

● In Lynch syndrome, a pathogenic germline mutation is present in one allele of one of the mismatch repair genes, and an acquired mutation (or methylation of the promoter region) in the other (wild-type) allele impairs mismatch repair function. As a result, deviations in the number of tandem repeats (microsatellite instability) often occur in the tumors (microsatellites are simple repetitive sequences in the genome.). The genes involved in tumor suppression (such as *TGFBR2*), cell proliferation, DNA repair (such as *MSH3* and *MSH6*), apoptosis (such as *BAX*), etc., contain repetitive sequences in the coding regions and mutations tend to develop in these regions.

● The adenoma-carcinoma sequence has been suggested to underlie the development of colorectal cancer in patients with Lynch syndrome, as in cases of sporadic colorectal cancer (Figure 18); however, the precise mechanisms of carcinogenesis in LS-associated colorectal cancer have not yet been fully clarified.

[Incidence]

● Lynch syndrome has been estimated to account for 2-4% of all colorectal cancer cases^{159,171}.

● The incidence in the overall Japanese population is unknown.

Side Memo 6

■ Changes in the nomenclature of Lynch syndrome

In 1966, Henry T. Lynch et al.¹⁷² reported families in which colorectal cancer and endometrial cancer were more frequently encoun-

Table 6. Cumulative Lifetime Risk of Lynch Syndrome-Associated Neoplasms (Up to the Age of 70 Years).

Malignant tumors	Cumulative risk (%)
Colorectal cancer	54%-74% (Male) 30%-52% (Female)
Endometrial cancer	28%-60%
Stomach cancer	5.8%-13%
Ovarian cancer	6.1%-13.5%
Small-bowel cancer	2.5%-4.3%
Bile duct cancer	1.4%-2.0%
Pancreatic cancer	0.4%-3.7%
Renal pelvic/ureteral cancer	3.2%-8.4%
Brain tumor	2.1%-3.7%
Sebaceous gland tumor	Unknown

Adapted from ref. 153), 164) -169)

tered than in the general population. In 1984, Boland et al.¹⁷³ classified the conditions into two categories; Lynch syndrome I, characterized by an increased risk of development of only colorectal cancer, and Lynch syndrome II, characterized by increased risk of development of not only colorectal cancer, but also cancer of other organs in the family members. These two conditions have come to be collectively called Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC). In 1990, the terms were unified as HNPCC, and in a workshop of the International Collaborative Group on HNPCC (ICG-HNPCC) held in Amsterdam, standardized Amsterdam criteria I¹⁷⁴ were proposed to collect HNPCC pedigrees. Causative genes have been reported one after another since 1993. As a result, it had been found that there are many families that carry a causative gene mutation, but do not meet the Amsterdam criteria I, and many others that meet the Amsterdam criteria I, but in which no causative genes can be identified. Therefore, in 1998, the revised Amsterdam criteria (Amsterdam criteria II) (Table 7), developed taking into consideration the occurrence of malignant tumors other than colorectal cancer, such as endometrial cancer, were proposed, for collaborative research on HNPCC¹⁷⁵). Thereafter, the appropriateness of the term HNPCC was repeatedly discussed, and it came to be thought that the term is inappropriate considering the characteristics of the disease, i.e., the occurrence also of various malignant neoplasms other than colorectal cancer. Currently, the term Lynch syndrome, named after - Dr. Lynch, is commonly used.

■ Mismatch repair function

Cells are equipped with the function of detecting and repairing mismatches that occur during DNA replication. Mismatch repair dysfunction increases the frequency of mispairs and insertions/deletions of simple repeat sequences by 10- to 1,000-fold, which results in microsatellite instability (Side Memo 8: Method for MSI testing and evaluation of the results [p.58]).

■ Recent research on the causative genes of Lynch syndrome

(1) Germline epimutation

Recently, it was found that epimutations are involved in tumorigenesis in some cases of Lynch syndrome. Epimutations refer to modifications of molecules involved in gene expression, such as aberrant DNA methylation, that can cause changes in gene expression without alterations of the DNA sequence. Although rare, aberrant germline methylation (hypermethylation) of the promoter region of the *MLH1*

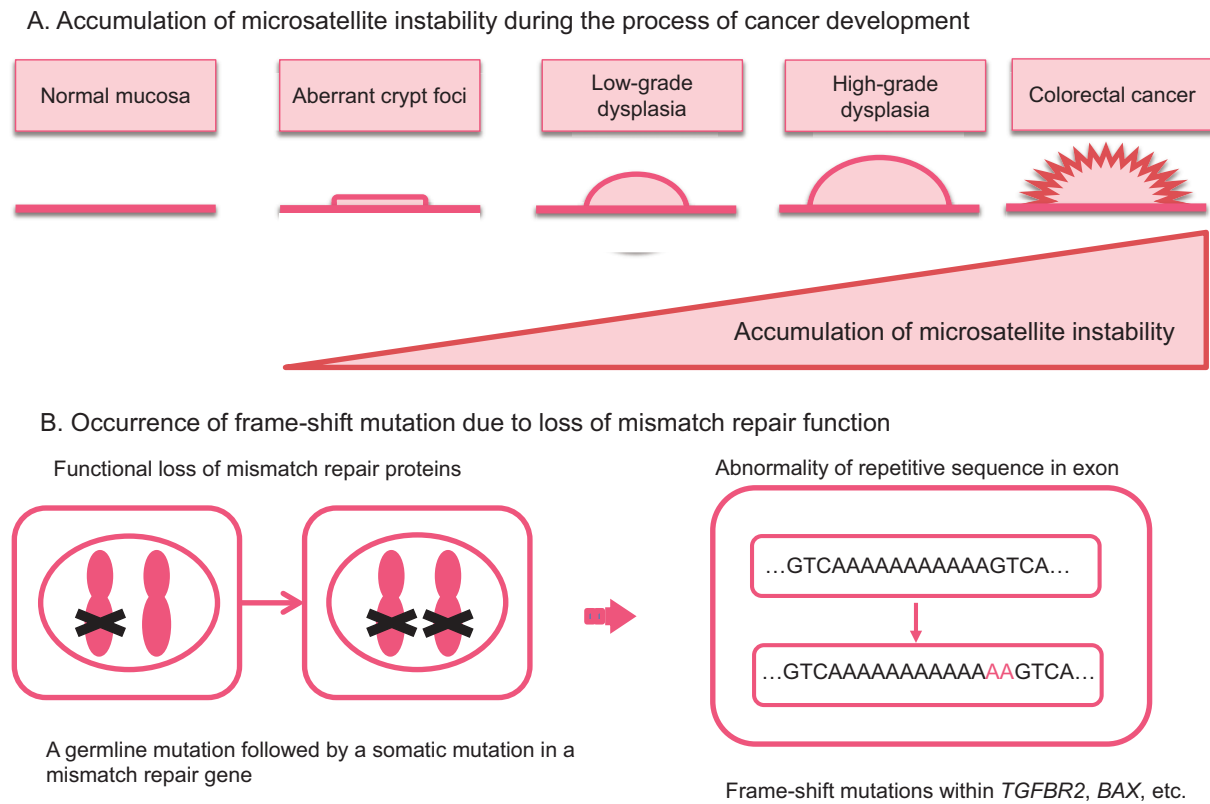


Figure 18. Possible mechanisms underlying colorectal cancer development in patients with Lynch syndrome.

Table 7. Amsterdam Criteria II ^{ref. 175)}.

At least three relatives must have a Lynch syndrome-associated cancer (colorectal, endometrium, small bowel, ureter, or renal pelvic cancer); all of the following criteria should be met:

- One must be a first-degree relative of the other two;
- At least two successive generations must be affected;
- At least one should have been diagnosed before the age 50 years;
- Familial adenomatous polyposis should be excluded; and
- Tumor diagnosis should be confirmed by histopathological examination.

gene has been reported as a cause of Lynch syndrome¹⁷⁶⁾.

(2) *EPCAM* deletion

The *EPCAM* (*TACSTD1*) gene is located upstream of the *MSH2* gene, adjacent to it, and deletion of its 3' region (sequences necessary for transcription termination) can cause Lynch syndrome. The deletion allows the *EPCAM* and *MSH2* genes to be continuously transcribed, thereby inducing aberrant methylation of the promoter region of the *MSH2* gene and loss of expression of the *MSH2* protein. The risk of colorectal cancer development in individuals with *EPCAM* deletions is comparable to that in patients with Lynch syndrome caused by mutations in the *MSH2* gene, although the risk of endometrial cancer development is lower in these individuals¹⁷⁷⁾. *EPCAM* deletions have been reported to account for 1-3% of Lynch syndrome cases¹⁷⁸⁾.

2. Diagnosis

1) Flow of diagnosis

- Definitive diagnosis should be made according to the

following Steps 1 to 3 in patients with clinicopathological findings (including family history) suggestive of Lynch syndrome (Figure 19).

Step 1: It should be checked whether the patient meets the Amsterdam criteria II¹⁷⁵⁾ (Table 7, Figure 20A, 20B) or the revised Bethesda guidelines¹⁷⁹⁾ (Table 8) (primary screening).

Step 2: Microsatellite instability (MSI) testing or immunohistochemistry for the causative gene products in the tumor tissue should be performed to confirm high-frequency MSI (MSI-H) or to confirm the absence of mismatch repair proteins.^{Note 2} (secondary screening) (CQ20, CQ21)

Step 3: Pathogenic germline mutations in the mismatch repair genes should be identified (not covered by the national health insurance program in Japan) for definitive diagnosis. (CQ22, CQ23, CQ24)

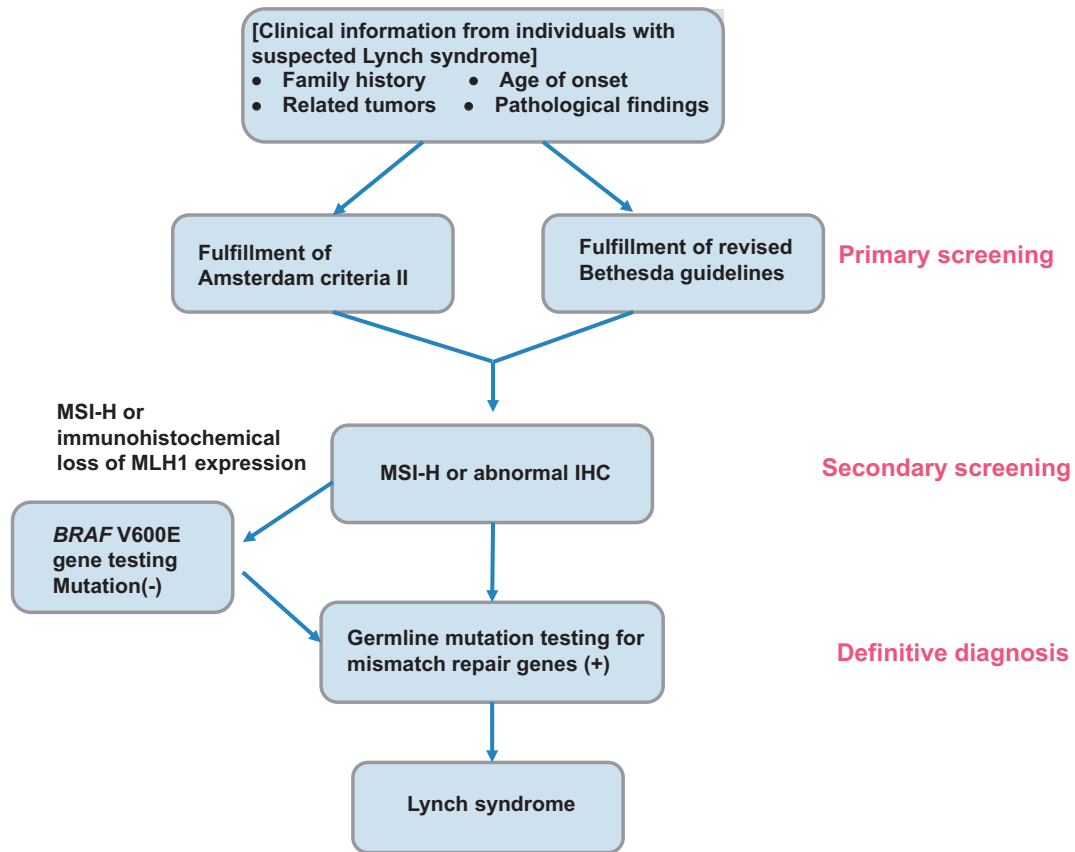


Figure 19. Diagnostic process for Lynch syndrome. Microsatellite instability: MSI, high-frequency MSI: MSI-H.

Recently, it was proposed that all patients (or patients aged 70 years or less) with colorectal cancer be screened for Lynch syndrome, irrespective of the clinicopathological findings or family history (Side Memo 7: universal tumor screening).

Note 2: If MSI testing shows MSI-H or immunohistochemistry shows loss of MLH1 expression, the tumor tissue should be tested for the *BRAF* V600E mutation. If the tumor is positive for this mutation, Lynch syndrome can almost certainly be ruled out. Thus, this allows patients who do not have to proceed to Step 3 to be selected. *BRAF* V600E mutation testing is also not covered by national health insurance in Japan, but can be outsourced to testing companies. It must be noted that the *BRAF* V600E mutation has been reportedly found in some colorectal cancers associated with Lynch syndrome caused by mutations in the *PMS2* gene¹⁸⁰.

Step 1. Criteria for primary screening (Table 7, 8)

● It has been reported that 27-41%^{172,181} of Lynch syndrome families meet the Amsterdam criteria II¹⁷⁵ and that 68-89% meet the revised Bethesda guidelines¹⁷⁹; thus, more patients with Lynch syndrome can be identified using the revised Bethesda guidelines¹⁸¹.

● Approximately one-fourth of all colorectal cancer patients fulfill the revised Bethesda guidelines¹⁸². Namely, a

considerable proportion of non-Lynch syndrome patients with sporadic colorectal cancer also meet the revised Bethesda guidelines¹⁷⁹.

● In the JSCCR project studies, 1.2% of all colorectal cancer patients were found to meet the Amsterdam criteria II¹⁸³.

Step 2. Tests used for secondary screening

MSI testing:

In some tumor cells with impaired mismatch repair function, the number of repeats in microsatellites, which are repetitive sequences of one to several nucleotides in the genome, is different from that in normal cells. This phenomenon is called microsatellite instability (MSI). MSI-H (high-frequency MSI) is usually seen in the tumor tissues in Lynch syndrome. Thus, screening and auxiliary diagnosis of Lynch syndrome has been performed using this phenomenon. This testing is covered by national health insurance (CQ20, Side Memo 8: Method for MSI testing and evaluation of the results).

● In cases with clinical findings suggestive of Lynch syndrome where the results of MSI testing of the colorectal tumor (colorectal adenomas can also be examined, although the detection sensitivity is lower) show MSI-H, Lynch syndrome should be strongly suspected.

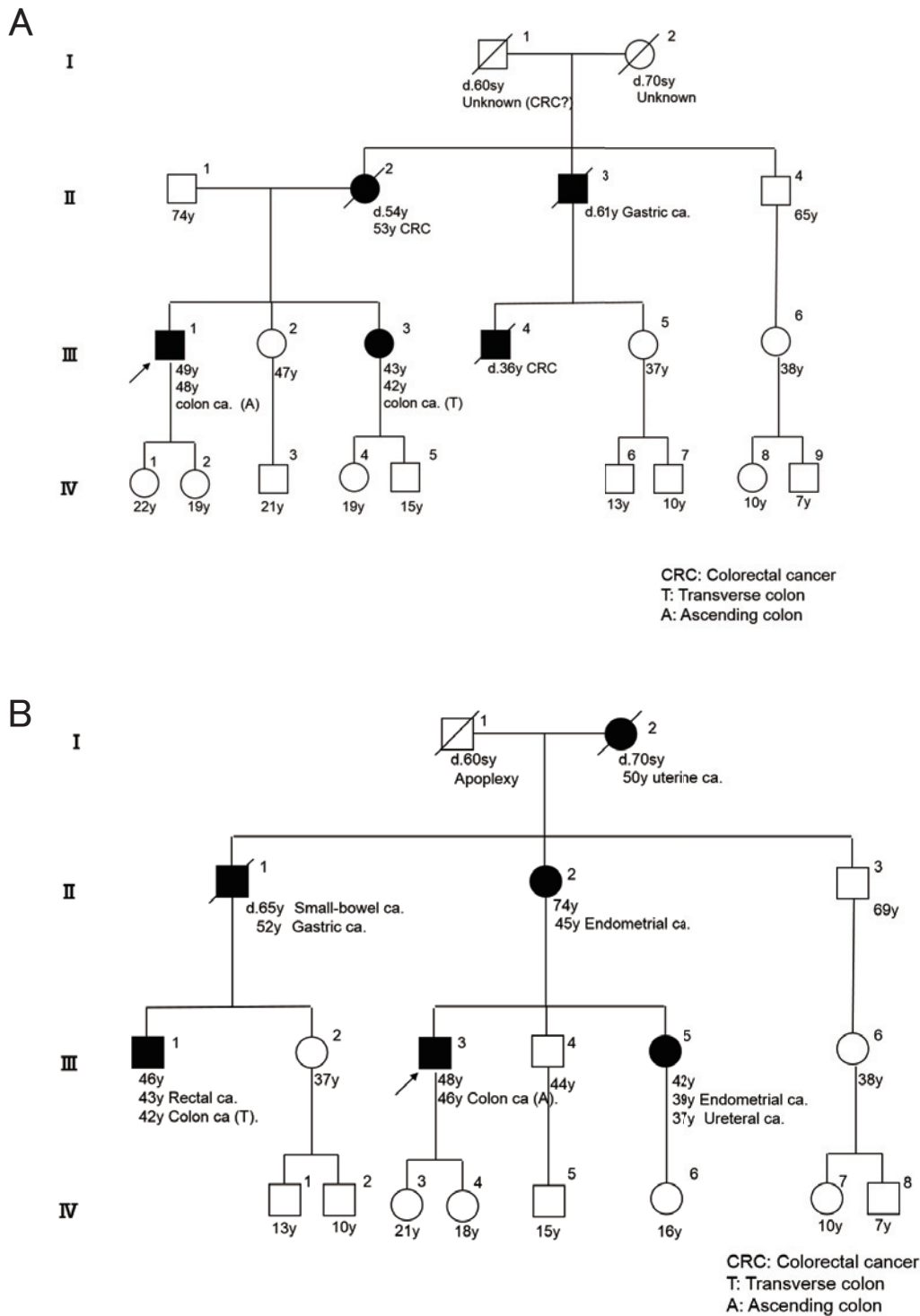


Figure 20. Family tree fulfilling Amsterdam criteria II. (See appendix: Principles in drawing and reading pedigrees) A: Multiple family members with colorectal cancer B: Multiple members with Lynch syndrome-associated extra-colonic cancers.

● In MSI testing, the microsatellite length is compared between normal and tumor tissues, usually using 5 markers (Bethesda markers) (Figure 21). If there are differences in the microsatellite length in the tumor tissue

is judged as showing MSI. MSI detected with 2 or more markers is defined as MSI-H, MSI detected with a single marker is defined as low-frequency MSI (MSI-L), and MSI detected with none of the 5 markers is defined as

Table 8. The Revised Bethesda Guidelines (2004)^{ref. 179)} for Testing Colorectal Tumors for High-frequency Microsatellite Instability (MSI-H).

Tumors from patients with colorectal cancer (CRC) should be tested for MSI in the following situations:

1. CRC diagnosed in a patient less than 50 years old.
2. Presence of synchronous, metachronous colorectal, or other Lynch syndrome (LS)-associated tumors,^{a)} regardless of the age.
3. CRC with MSI-H histology^{b)} diagnosed in a patient less than 60 years old.
4. CRC diagnosed in a patient with one or more first-degree relatives with a LS-associated tumor, with one of the cancers being diagnosed under the age of 50 years.
5. CRC diagnosed in two or more first- or second-degree relatives with LS-associated tumors, regardless of the age.

^{a)} LS-associated tumors include colorectal cancer, endometrial cancer, gastric cancer, small-intestinal cancer, ovarian cancer, pancreatic cancer, renal pelvic/ureteral cancer, biliary tract cancer, brain tumors, sebaceous gland adenomas, and keratoacanthomas.

^{b)} Tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.



Detection of differences in the microsatellite lengths with two (BAT25, D5S346) of the five markers between normal and tumor tissues was interpreted as MSI-H.

Figure 21. An example of MSI analysis using the Bethesda markers.

microsatellite-stable (MSS).

Immunohistochemistry:

Most Lynch syndrome-associated tumors have biallelic inactivation of one of the mismatch repair genes, namely, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and expression of the corresponding protein is lost in most cases. Because MSI-H is caused by mismatch repair deficiency, the results of MSI testing are highly consistent with those of immunohistochemistry for mismatch repair proteins. It has been reported that the results of MSI testing and immunohistochemistry are consistent in 90% of cases and that the false-negative rate of immunohistochemistry for Lynch syndrome is 5-10%^{159,184)}. The great advantage of immunohistochemistry, as compared to MSI testing, is that it allows the causative gene to be deduced. In addition, immunohistochemistry is simpler than MSI testing and has been used increasingly in institutions in Japan. (CQ20, CQ21)

Step 3. Tests for definitive diagnosis

Genetic testing for mutation in the mismatch repair genes:

The patients' blood is used to directly determine the presence or absence of pathogenic germline mutations in the mismatch repair genes. If a pathogenic mutation is identified, the patient is definitively diagnosed as having Lynch syndrome. In Japan, this testing is not covered by the national health insurance program, and it is currently performed at the patient's expense or as research (genetic test-

ing can be outsourced to testing companies). Genetic counseling must be provided before and after the testing. (CQ22, CQ23, CQ24)

- Even if genetic testing for mutations of the mismatch repair genes is considered unnecessary in the screening process, or genetic testing does not reveal any pathogenic mutations in the causative genes, the patient may still have Lynch syndrome.

- For families with clinical features strongly suggestive of Lynch syndrome, genetic testing for mutations in the mismatch repair genes is sometimes performed directly without screening by MSI testing or immunohistochemistry.

- It is desirable to perform genetic testing for mutations in the mismatch repair genes in individuals whose family members show clinical features suggestive of Lynch syndrome (multiple cancers, including colorectal cancer, endometrial cancer, early-onset cancer, etc.)

Side Memo 7

■ Muir-Torre syndrome

Muir-Torre syndrome is a disease characterized by synchronous/metachronous development of various Lynch syndrome-associated tumors, such as colorectal cancer with sebaceous tumors (sebaceous adenoma, sebaceous epithelioma or sebaceous carcinoma), and/or keratoacanthoma. Germline mutations are found mainly in the *MSH2* gene¹⁸⁵⁾.

■ Turcot syndrome (type 1)

Turcot syndrome, type 1, is a disease in which Lynch syndrome-associated colorectal cancer is accompanied by brain tumors, mainly

glioblastoma. Germline mutations in the *MLH1* or *PMS2* gene or hypermethylation of the *MLH1* promoter have been found¹⁸⁶. Caution should be exercised, since brain tumors are reported to be a major cause of death in patients with Lynch syndrome¹⁸⁷. (Side Memo 3: Turcot syndrome, [type 2]).

■ Universal tumor screening

Recently, universal tumor screening, in which MSI testing or immunohistochemistry for mismatch repair proteins is performed in all patients (or patients aged 70 years or less) with colorectal or endometrial cancer, is recommended as a highly sensitive and cost-effective method for the diagnosis of Lynch syndrome in Western countries. The incidence of Lynch syndrome detected by universal tumor screening is reported to be 2.4 to 3.7% of all colorectal cancers^{188,189}.

2) Differential diagnosis

Sporadic colorectal cancer with MSI-H:

Sporadic colorectal cancer with MSI-H is commonly characterized by occurrence in elderly females, occurrence of poorly differentiated adenocarcinoma, right-sided preponderance, etc. The primary cause of MSI-H is considered as an acquired aberrant methylation of the promoter region of the *MLH1* gene¹⁹⁰. In these tumors, immunohistochemistry shows loss of expression of MLH1 protein. In addition, the *BRAF* V600E mutation is found in the tumor tissue in 35-43% of patients^{191,192}. On the other hand, the *BRAF* V600E mutation is not detected in most colorectal cancers associated with Lynch syndrome, even if they show MSI-H¹⁹³. Therefore, checking for the presence or absence of the *BRAF* V600E mutation is sometimes used to differentiate between these diseases.

Polymerase proofreading-associated polyposis (PPAP):

The phenotype of PPAP¹⁹⁻²¹ is sometimes like that of FAP (AFAP) or Lynch syndrome, and PPAP needs to be differentiated from Lynch syndrome (Chapter I. Familial adenomatous polyposis; 2) Diagnosis; 4) Diseases and pathological conditions that need to be differentiated from FAP; Polymerase-proofreading-associated polyposis.)

Familial colorectal cancer type X:

Patients who meet the Amsterdam criteria I,^{174)Note 3} but in whom no pathogenic germline mutations are detected in the mismatch repair genes or the colorectal cancer does not show MSI-H, are unlikely to have Lynch syndrome, and the term “familial colorectal cancer type X”¹⁹⁴ was proposed for the condition. Familial colorectal cancer type X is speculated to comprise multiple diseases. Reports from both Western countries and Japan¹⁹⁵ have shown that the risk of developing Lynch syndrome-associated tumors other than colorectal cancer is significantly lower in cases of familial colorectal cancer type X.

Note 3) Amsterdam criteria I: While colorectal cancer, endometrial cancer, renal pelvic/ureteral cancer and small-bowel cancer are included as Lynch syndrome (HNPCC)-associated tumors in the Amsterdam criteria II, only colorectal cancer is included as Lynch syndrome (HNPCC)-associated tumor in the Amsterdam criteria I¹⁷⁴.

3. Treatment

1) Treatment of colorectal cancer

● The following options exist for the extent of resection of the colorectum (types of surgical procedures) in Lynch syndrome:

(1) Extent of resection equivalent to that adopted for sporadic colorectal cancer

(2) Total colectomy

(3) Total proctocolectomy

● No consensus has been reached on the usefulness of prophylactic colectomy, and it is not generally recommended.

● Because colorectal cancer tends to develop at multiple sites of the colorectum in Lynch syndrome, including synchronous or metachronous development, the entire colorectum should be examined before surgery.

● Some reports from Western countries have recommended extended operations, such as total colectomy for colonic cancer and total proctocolectomy for rectal cancer, for colorectal cancer in Lynch syndrome. However, no prospective studies on their usefulness have been conducted, and no consensus has been reached yet. (CQ25)

● Prophylactic colectomy for Lynch syndrome mutation carriers is not generally recommended, because its efficacy has not been assessed. (CQ25)

● Colorectal cancers in most cases of Lynch syndrome show MSI-H. Although 5-fluorouracil (FU)-based anticancer drugs have been reported to be generally ineffective in colorectal cancers showing MSI-H, the usefulness of chemotherapy specifically in Lynch syndrome-associated colorectal cancer has not yet been clarified. (CQ26)

2) Management of extracolonic tumors

(1) Gastrointestinal tumors (gastric cancer, small-bowel cancer, bile duct cancer, pancreatic cancer, etc.)

(2) Gynecologic tumors (endometrial cancer, ovarian cancer, etc.) (CQ19)

(3) Urological tumors (renal pelvic/ureteral cancer, etc.)

(4) Other tumors (brain tumor, skin tumor, etc.)

● There is no clear evidence of any special considerations required for the above-mentioned tumors (1) to (4), except for the case of gynecologic cancers, in patients with Lynch syndrome. At present, treatment like that for the corresponding sporadic cancers (tumors) is used.

● In Lynch syndrome patients with colorectal cancer, it is desirable to conduct screening for other Lynch syndrome-associated tumors (in particular, gynecologic cancers, urological cancers, and gastrointestinal cancers) prior to elective colectomy.

Table 9. Recommended Surveillance Protocols for Common Lynch Syndrome-Associated Tumors.

Sites	Examinations	Lower age limit (years) for starting surveillance	Surveillance interval (years)
Colorectum	Colonoscopy	20-25	1-2
Uterus, ovary	Transvaginal ultrasound	30-35	0.5-1
	Endometrial biopsy		
	Endometrial cytology		
	Serum CA125 measurement		
Stomach, duodenum	Gastroduodenoscopy	30-35	1-2
Urinary tract	Urinalysis and urinary cytology	30-35	1-2

Modifications with ref. 196)

4. Postoperative surveillance

1) Surveillance for multiple colorectal cancers and resection of adenomas

● Attention should be paid to the possible development of metachronous cancer in the remaining colorectum after surgery for colorectal cancer in patients with Lynch syndrome, and lifelong regular colonoscopic examination is required. (CQ29)

● Surveillance for recurrence of colorectal cancer after resection should be in accordance with the protocol used for cases of sporadic colorectal cancer.

● Colorectal adenomas, if detected, should be resected, because they may develop into colorectal cancer.

2) Surveillance for Lynch syndrome-associated extracolonic tumors

● A specialist group in Europe proposed the following method of surveillance for the main Lynch syndrome-associated tumors (Table 9)¹⁹⁶⁾.

● It was proposed that surveillance be conducted by upper gastrointestinal endoscopy every 1 to 2 years in areas where gastric cancer is common, such as East Asia, and in Lynch syndrome patients with a family history of gastric cancer and their relatives¹⁹⁷⁾.

● No consensus has been reached on the method or interval of regular surveillance for endometrial and ovarian cancers. (CQ19)

● Lynch syndrome-associated urological tumors include renal pelvic/ureteral cancer. This type of cancer has been reported to be common in patients with germline mutations in the *MSH2* gene, but none of the surveillance methods, including regular urinalysis and urinary cytology, have been demonstrated to be useful in improving prognosis.

5. Surveillance of colorectal cancer patients without a genetic diagnosis of Lynch syndrome

● In patients who are suspected to have Lynch syndrome but have not been diagnosed yet by genetic testing, the pos-

sibility of Lynch syndrome should be individually evaluated based on clinical information and the results of MSI testing, which is covered by national health insurance in Japan, and surveillance for Lynch syndrome-associated tumors should be conducted (Figure 22).

● In cases where the patient “meets the Amsterdam criteria II” or “has a past or family history highly suggestive of Lynch syndrome,” in addition to the results of MSI testing showing MSI-H, the patient should be regarded as having Lynch syndrome and surveillance should be conducted even if no genetic testing has been performed.

● In cases where the patient “meets the Amsterdam criteria II” or “has a past or family history highly suggestive of Lynch syndrome,” but the results of MSI testing show MSS or MSI-L (there are no findings strongly suggestive of mismatch repair gene deficiency), Lynch syndrome can certainly not be ruled out (Side Memo 8: MSI testing method and evaluation of the results). In these cases, follow-up should be subsequently performed while paying attention to the personal and family history, with colonoscopic examination for colorectal cancer conducted at least every 3 to 5 years.

● In case the patient “meets the revised Bethesda guidelines, but not the Amsterdam criteria II, or does not have a personal or family history strongly suggestive of Lynch syndrome,” if the results of MSI testing show MSI-H, the patient may have Lynch syndrome (many patients are likely to have sporadic colorectal cancer). Follow-up should be performed while validating the past and family history.

● In MSS or MSI-L colorectal cancer patients who are unlikely to have Lynch syndrome based on the family and medical history, surveillance for Lynch syndrome-associated tumors is not conducted. When patients have symptoms of colorectal cancer, or Lynch syndrome-associated tumors are observed in the patients or their relatives, detailed examination and reevaluation for Lynch syndrome is recommended.

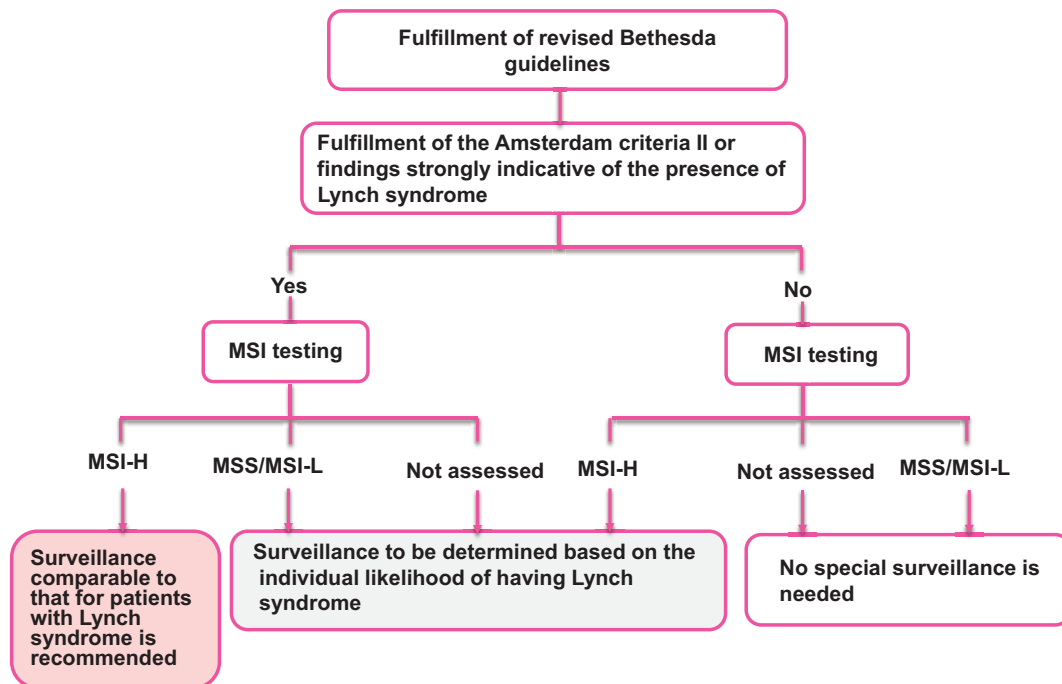


Figure 22. Management of individuals without a definitive diagnosis of Lynch syndrome. MSI testing can be used as a complement to or a surrogate for IHC.

6. Genetic counseling and management of families (relatives)

● It is desirable to provide genetic counseling not only to the patients, but also to their relatives.

● After providing an adequate explanation about the disease to first-degree relatives (parents, children, and siblings) and obtaining their consent, surveillance for Lynch syndrome-associated tumors should be conducted according to the assessed risk.

● For genetic testing, the “Guidelines for Genetic Tests and Diagnosis in Medical Practice” of the Japanese Association of Medical Sciences, guidelines of the Japanese Society for Familial Tumors, “Ethical Guidelines for Human Genome/Gene Analysis Research,” etc., should be observed. In addition, records should be carefully stored, in consideration of the privacy of the subjects.

● In genetic counseling, information about the disease should be provided and the significance of genetic testing as one of the options and its methods, limitations, costs, etc., should be explained to help patients and their families make an independent choice about whether to undergo genetic testing or not. For patients who wish to undergo genetic testing, testing should be performed after obtaining informed consent from the patient. Genetic counseling should be provided not only before and after genetic testing, but also repeatedly, where necessary.

● In principle, because Lynch syndrome-associated tumors generally develop in adulthood, genetic testing should

be performed in adulthood.

● It should be ascertained as to whether the patients (clients) want to be apprised of the results of genetic testing with their family members or not. If a patient does not wish to be informed about the results in the presence of family members, an opportunity should be provided for giving the information individually.

1) *Management of patient families (relatives) who have been diagnosed by genetic testing to have Lynch syndrome (Figure 23)*

● Relatives who are definite mutation carriers or who have not undergone genetic testing should be regarded as having Lynch syndrome and undergo surveillance for Lynch syndrome-associated tumors (Figure 23).

● Relatives who have been confirmed to have no pathogenic mutation should undergo general cancer screening (Figure 23). Information on the necessity of surveillance and significance of genetic diagnosis should be provided to relatives who have reached the age of surveillance for Lynch syndrome-associated tumors. Everyone should decide, of his/her own free will, whether he/she wishes to undergo genetic testing or not through genetic counseling.

2) *Management of patient families (relatives) who are suspected to have Lynch syndrome, but for whom no definitive diagnosis has been made*

● In relatives of patients who have not undergone genetic testing or in whom genetic testing has failed to yield a definitive diagnosis of Lynch syndrome, individual risk assessment should be carried out by reference to the age of onset,

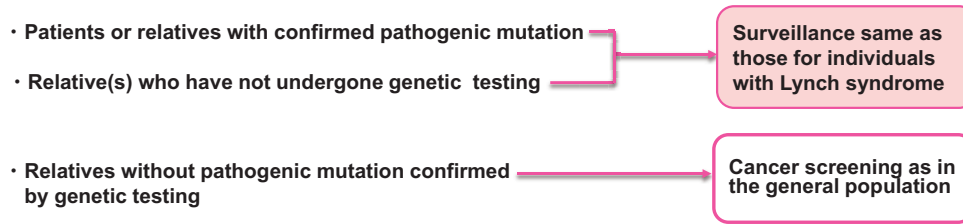


Figure 23. Management of the families (relatives) of patients who have been definitively diagnosed with Lynch syndrome defined by genetic testing.

Table 10. Lifetime Risk of Lynch Syndrome-Associated Tumors According to the Kind of Causative Genes (up to the Age of 70 Years).

	<i>MLH1</i>	<i>MSH2</i>	<i>MSH6</i>	<i>PMS2</i>
Colorectal cancer	41%	48%	10%-22%	15%-20%
Endometrial cancer	18%-54%	21%-30%	16%-71%	15%
Gastric cancer	3%-6%	0.2%-7%	≤3%	-
Ovarian Cancer	13%-20%	9.5%-24%	1%-11%	-
Renal pelvic/ureteral cancer	0.2%-2.9%	2.2%-12%	<1%	-

incidence, etc., of Lynch syndrome-associated tumors in family members, and surveillance for associated tumors should be conducted.

● In relatives of patients suspected as having Lynch syndrome, surveillance should be conducted according to the protocol shown in Table 9, or colonoscopy should be started at an age 5-15 years younger than that of the earliest age at diagnosis of colorectal cancer in the family.

Clinical Questions

CQ17: Do Lynch syndrome-associated tumors require different treatments according to the causative gene of Lynch syndrome?

Recommendation category: C

The risk of developing Lynch syndrome-associated tumors may vary greatly depending on the causative gene. Therefore, it has been proposed that surveillance be conducted according to the organ-specific cancer risk, which is related to the causative gene.

Many studies comparing the major causative genes *MLH1* and *MSH2* have reported that the risk of colorectal cancer is equivalent between patients with *MLH1* mutations and those with *MSH2* mutations, and that the risk of development of Lynch syndrome-associated tumors (in particular, those of the urinary system) other than those of the large intestine is higher in patients with *MSH2* mutations¹⁹⁸. The risk of colorectal cancer development is lower in patients with *MSH6* mutations than in those with *MLH1* or *MSH2* mutations, but the risk of endometrial cancer development in patients with

MSH6 mutations is equivalent to or higher than that in those with *MLH1* or *MSH2* mutations (Table 10). Therefore, it is desirable to bear in mind, while conducting surveillance, that the incidence of Lynch syndrome-associated tumors varies greatly depending on the causative gene in Lynch syndrome. However, the risk of development of Lynch syndrome-associated tumors for each causative gene has not yet been fully assessed in Japanese.

CQ18: What are the important histologic findings that need to be screened for in cases of colorectal cancer associated with Lynch syndrome?

Recommendation category: C

Tumor-infiltrating lymphocytes, a medullary growth pattern, mucinous/signet-ring differentiation and Crohn’s-like lymphocytic reaction are useful in screening not only for sporadic MSI-H colorectal cancer, but also for Lynch syndrome.

Several histological features are significantly more common in MSI-H colorectal cancers than in non-MSI-H (MSI-L or MSS) colorectal cancers, and these findings are useful to screen for patients with suspected Lynch syndrome. Four histologic findings, namely, (1) tumor-infiltrating lymphocytes (TIL), (2) a medullary growth pattern, (3) mucinous/signet-ring differentiation, and (4) Crohn’s-like lymphocytic reaction, are listed in the revised Bethesda guidelines¹⁷⁹ (Figure 24A, 24B, 24C, 24D). However, these histological features are not necessarily specific to Lynch syndrome; they are commonly seen in both Lynch syndrome-associated and sporadic MSI-H colorectal cancers¹⁹⁹.

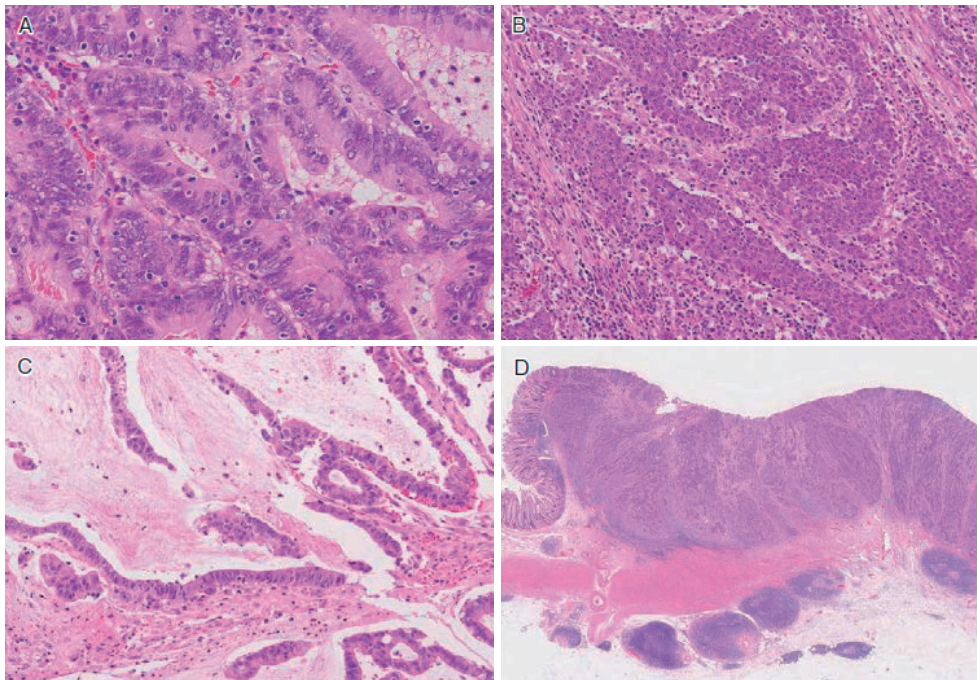


Figure 24. Pathological features of MSI-H colorectal cancer A: Tumor-infiltrating lymphocytes Numerous intra-epithelial lymphocytes showing clear halos. B: Medullary carcinoma Tumor showing a solid growth pattern without glandular structure. C: Mucinous adenocarcinoma showing prominent extracellular mucin. D: Crohn's-like lymphoid reaction characterized by peritumoral lymphocytic aggregates.

CQ19: How should gynecologic cancers be treated in patients with Lynch syndrome (including mutation carriers who have not developed colorectal cancer)?

Recommendation category: C

No surveillance method for endometrial and ovarian cancers in patients with Lynch syndrome has been established. Some experts have proposed that transvaginal ultrasonography must be performed in addition to endometrial cytology or endometrial biopsy as part of surveillance for endometrial cancer.

The Lynch syndrome-associated gynecologic cancers are endometrial cancer and ovarian cancer.

Endometrial cancer is the second most common cancer after colorectal cancer in Lynch syndrome and it is regarded as a “sentinel cancer.” Dysfunctional uterine bleeding is the most common subjective symptom. Surveillance methods include endometrial cytology, endometrial biopsy and transvaginal ultrasonography, and definitive diagnosis is made by histopathological examination. Note that routine Pap smear is performed to screen for cervical cancer, but not for endometrial or ovarian cancer.

At present, risk-reducing surgery is the most effective method for the primary prevention of ovarian cancer. If risk-reducing surgery is not selected, surveillance should be conducted, but its usefulness has not been established. Trans-

vaginal ultrasonography and CA125 testing have not been shown to be sufficiently sensitive or specific for hereditary breast and ovarian cancer syndrome, which is characterized by an increased risk of development of ovarian cancer, like in Lynch syndrome. Transvaginal ultrasonography and CA 125 testing approximately every 6 months are the secondary prophylaxis in clinical practice. However, there is a risk of so-called interval cancer, in which cancer is detected by the appearance of subjective symptoms before the scheduled medical examination, although the previous medical examination was negative for cancer.

Risk-reducing surgery with hysterectomy and bilateral salpingo-oophorectomy can be considered as options for primary prevention of gynecologic cancer in Lynch syndrome patients who have completed childbearing or who are postmenopausal²⁰⁰. In addition, the option of simultaneous hysterectomy and bilateral salpingo-oophorectomy with surgery for colorectal cancer should also be considered for patients with colorectal cancer. Risk-reducing surgery should be performed after obtaining approval from the local ethics committee and carefully considering the medical care system in advance.

The surveillance methods shown in Table 9 ((4) Postoperative surveillance) should be followed in patients who do not wish to undergo risk-reducing surgery and choose to undergo surveillance instead.

CQ20: What are the points that should be kept in mind while conducting screening tests (MSI testing and immunohistochemistry) for Lynch syndrome?

Recommendation category: None

Sensitivity and specificity are equivalent between MSI testing and immunohistochemistry, and immunohistochemistry helps identify the putative causative genes. The costs and convenience of performance of the tests vary from institution to institution, and comprehensive consideration should be given to selection of one of the tests.

It has been reported that more than 90% of colorectal cancers in patients with Lynch syndrome show MSI-H²⁰¹. On the other hand, according to reports from Western countries²⁰¹⁻²⁰³ and Japan^{191,204}, MSI-H colorectal cancer accounts for 12-16% and 6-7% of all colorectal cancers, respectively. Therefore, MSI testing is a useful screening test to shortlist patients with suspected Lynch syndrome. MSI testing has been covered by the national health insurance program since 2006 in Japan as a genetic test for malignancies in colorectal cancer patients with suspected Lynch syndrome. When MSI testing is performed, the possibility of hereditary cancer should be fully explained to the individuals and informed consent should be obtained. Related webpages are linked to the website of the Japanese Society for Familial Tumors (<http://jsft.umin.jp/>).

Clinicians must be aware that some Lynch syndrome patients with germline mutations in the *MSH6* gene do not show MSI-H^{205,206}. Therefore, if the patient shows MSI-L or MSS, but meets the Amsterdam criteria II¹⁷⁵ or if the patient has clinical features (early-onset cancer or multiple cancers) strongly suggestive of Lynch syndrome, genetic testing of mismatch repair genes should be considered³³. MSI testing mainly using mononucleotide repeat markers, which have recently been increasingly used, has also been reported to be highly sensitive in patients with *MSH6* mutations (Side Memo 8: Method for MSI testing and evaluation of the results).

On the other hand, immunohistochemistry for mismatch repair proteins has rapidly become popular as a secondary screening test for Lynch syndrome. Immunohistochemistry can be performed at many institutions. In addition, when immunohistochemistry is performed, a thorough explanation should be provided to individuals and informed consent should be obtained, as for MSI testing. Related webpages are linked to the website of the Japanese Society for Familial Tumors (<http://jsft.umin.jp/>).

MSI testing and immunohistochemistry use different methods, but have equivalent sensitivity and specificity, and immunohistochemistry allows the possible causative gene among 4 MMR genes to be identified. The costs and convenience of performance of these tests vary from institution to institution, and comprehensive consideration, including

the examination system at the institution, should be given to the selection of one of the tests. However, if the patient is clinically suspected as having Lynch syndrome even if one test is negative, implementation of the other test allows complementary screening to be performed.

Side Memo 8

■ Method for MSI testing and evaluation of the results

Clinical testing companies provide MSI testing. Frozen samples or formalin-fixed paraffin-embedded specimens of tumor and non-tumor normal tissues are required for MSI testing (blood samples can be used instead of normal tissues). DNA is extracted from tumor and normal tissues to compare the microsatellite lengths between these tissues. In general, 5 markers (known as the Bethesda markers or NCI panel, consisting of 2 mononucleotide repeat markers and 3 dinucleotide repeat markers) have been used to assess MSI (Step 2. Tests used for secondary screening). Sometimes, when more markers are used, cases in which 30% or more markers show changes in the microsatellite lengths in tumor tissue are defined as having MSI-H. In addition, because mononucleotide repeat markers have high sensitivity, MSI-H is sometimes defined by the presence of instability detected using 3 or more markers. Some MSI tests with mononucleotide repeat markers allow MSI to be assessed using tumor tissue alone, and have rapidly become popular in Japan as well as in other countries.

CQ21: What are the points that must be borne in mind while conducting immunohistochemistry for mismatch repair gene products (proteins)?

Recommendation category: None

From the pattern of loss of the mismatch repair proteins in cell nuclei, genes causing the mismatch repair deficiency can be deduced. When evaluating the staining results, the adequacy of staining should be confirmed using internal positive controls.

1. Internal positive controls

Mismatch repair proteins are localized in the nuclei and are more strongly expressed in proliferating cells. The base of the colonic mucosal glands and germinal centers of lymph follicles are good positive controls in non-tumor tissues (Figure 25). Because tumor tissues generally have high proliferative activity, confirmation of staining of internal positive controls often makes evaluation easier.

2. Staining patterns and evaluation

In tumors without mismatch repair deficiency, all 4 proteins are expressed. In tumors with mismatch repair deficiency, protein expression is lost reflecting the deficiency of mismatch repair genes, but individual mismatch repair gene deficiency does not correspond 1:1 to loss of protein expression (Table 11, Figure 26). Most cases exhibit one of the staining patterns shown in Table 11. If a staining pattern different from any of those shown in Table 11 is obtained, the validity of staining should be checked before considering the possibility of an exceptional case. In principle, invasive cancers show diffuse loss of expression.

The expression of PMS2 in addition to MLH1 is lost in

tumors with *MLH1* mutations, and the expression of MSH6 in addition to MSH2 is lost in tumors with *MSH2* mutations (Table 11). Therefore, the use of only 2 antibodies, anti-PMS2, and anti-MSH6 antibodies, allows the screening of Lynch syndrome to be performed with a sensitivity equivalent to that using 4 antibodies²⁰⁷. If the expression of PMS2 or MSH6 is lost, staining for MLH1 or MSH2, respectively, should be added to deduce the mutated gene.

Side Memo 9

Exceptional staining results

■ Expression of abnormal proteins due to missense mutations

In some cases of missense mutations (Appendix: II. Method for describing genomic variants; 3. Types of changes), non-functional proteins are expressed. This is known to be relatively common in Lynch syndrome patients with *MLH1* mutations, and in most of these cases, only PMS2 expression is lost²⁰⁷. However, there are rare cases in which no abnormalities are detected by immunohistochemistry. Even if no abnormalities are detected by immunohistochemistry, if the patient is clinically strongly suspected as having Lynch syndrome, the addition of MSI testing may allow accurate diagnosis.

■ Secondary mutations in mismatch repair genes due to microsatellite instability

Some mismatch repair genes have repeat sequences, and secondary

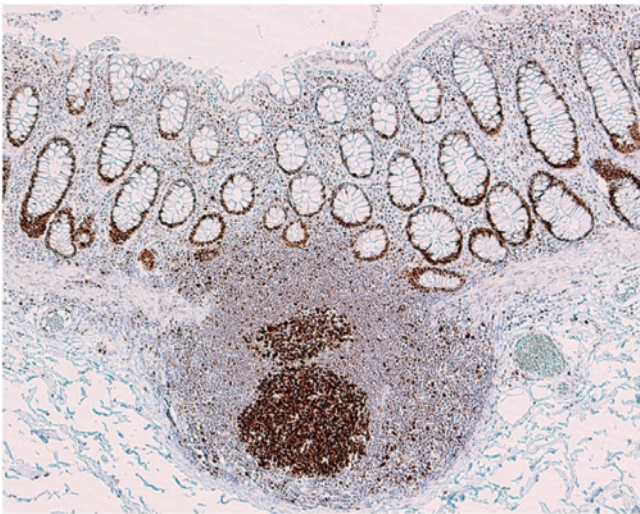


Figure 25. MSH2 expression in normal colon mucosa. Strong staining is seen in the germinal center of a lymphoid follicle and at the bottom of glands.

mutations may occur in these genes. In some patients with *MLH1* gene mutations (loss of MLH1/PMS2), MSH6 expression is lost diffusely or regionally²⁰⁸.

■ Loss of MSH6 expression due to preoperative chemoradiotherapy

It has been reported that in colorectal cancer patients administered preoperative chemoradiotherapy, the tumor MSH6 expression may be lost even in the absence of abnormality in the *MSH6* gene²⁰⁸.

CQ22: What is the significance of genetic diagnosis of Lynch syndrome and what are the important points that should be kept in mind?

Recommendation category: B

Genetic testing of mismatch repair genes is required for a definitive diagnosis of Lynch syndrome. Individuals for genetic testing should be selected carefully, and after genetic counseling is provided, it should be checked with them whether they wish to undergo the testing or not. The results of genetic testing should be evaluated for the genetic diagnosis of individuals' relatives and medical management of the individuals and their relatives.

Pathogenic germline mutations in mismatch repair genes should be identified to make a definitive diagnosis of Lynch syndrome. Individuals (patients/relatives) for genetic testing should be appropriately selected, and genetic counseling should be provided before and after the genetic testing. Genetic testing sometimes fails to determine whether the individual has Lynch syndrome or not, and the results should be interpreted carefully. Testing for mismatch repair genes is not covered by the national health insurance program, but can be outsourced to testing companies.

1. Genetic testing of mismatch repair genes

Genetic counseling should be provided before and after genetic testing, because there are hereditary disease-specific precautions and considerations. In principle, an explanation about the genetic testing should be given by a physician, but the individuals can be referred to institutions with expertise in providing genetic counseling. If the individuals agree to undergo genetic testing, approximately 2 to 3 mL of blood should be collected and sent to the testing company to perform genetic testing. Direct sequencing is generally used for analysis, but if no mutations are identified, multiplex ligation-dependent probe amplification, Southern blotting,

Table 11. Immunohistochemical Expression Patterns of the Mismatch Repair Proteins Associated with Each Suspected Causative Gene.

		Expressions of immunohistochemical staining			
		MLH1	MSH2	PMS2	MSH6
Causative genes	<i>MLH1</i>	-	+	-	+
	<i>MSH2</i>	+	-	+	-
	<i>PMS2</i>	+	+	-	+
	<i>MSH6</i>	+	+	+	-

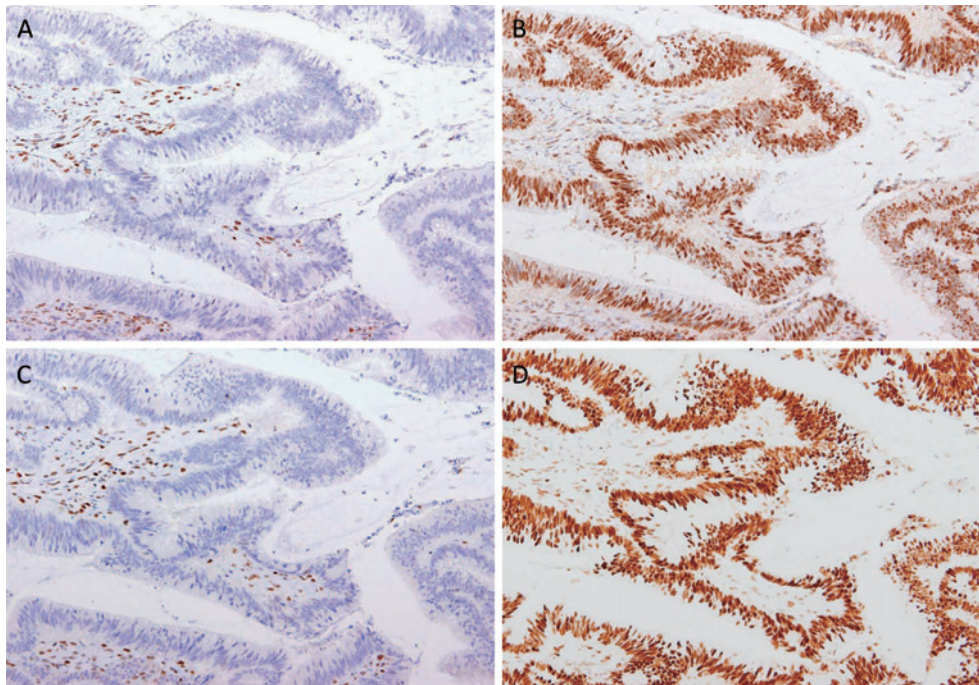


Figure 26. Immunohistochemistry for mismatch repair proteins in the colorectal cancer specimen resected from in a Lynch syndrome patient with a germline *MLH1* mutation. Loss of *MLH1* (A) and *PMS2* (C) and retention of *MSH2* (B) and *MSH6* (D). Stromal cells served as internal positive controls.

etc., should be used, because a part of a gene may be deleted, duplicated, or rearranged.

2. Evaluation of the results of genetic testing

If a gene mutation obviously causing the disease is found, a definitive diagnosis of Lynch syndrome can be made. After disclosing the results of genetic testing, genetic counseling, future surveillance planning and implementation, genetic testing of relatives, etc., should be considered. On the other hand, even if a genetic mutation is found, its causal relationship to the disease is unclear (a variant of uncertain significance [VUS]) in some cases (CQ23). In these cases, subsequent surveillance should be conducted as if no genetic testing had been performed. Even if no mutations are detected by genetic testing, Lynch syndrome cannot be completely ruled out, because there may be gene alterations that are undetectable by current testing methods or unknown causative genes. Risk assessment should be carried out according to the past medical and family history, and surveillance, as appropriate, should be conducted. If genetic testing of the proband reveals no mutation, genetic testing of other relatives is of little significance.

3. Genetic testing of relatives

Detection of a pathogenic gene mutation in the proband makes it possible to check whether his/her relatives have the same mutation. In this case, only the region containing the identified mutation should be tested. Genetic counseling should also be provided before and after genetic testing of

the relatives. Detection of a mutation in one of the causative genes should lead to future surveillance planning and implementation. Unless there is a family history of early-onset (teens to 20s) cancer, genetic testing should generally be performed in adulthood. Everyone should decide, of his/her own free will, about whether he/she should undergo genetic testing or not.

The JSCCR multicenter study showed that in addition to colorectal cancer and endometrial cancer, which are common in Western countries, Lynch syndrome-associated tumors such as gastric cancer, ovarian cancer, and bile duct cancer, were the major causes of death in first-degree relatives of Japanese Lynch syndrome patients. In close relatives with definite Lynch syndrome, it is important to conduct surveillance bearing these malignancies in mind²⁰⁹⁾.

CQ23: How should Lynch syndrome patients in whom genetic testing shows a variant of uncertain significance (VUS) be managed?

Recommendation category: C

Patients with VUS should be managed as if no genetic testing had been performed (Figure 22). If possible, the presence or absence of the variant should be assessed in relatives to investigate its association with tumor development.

The results of genetic testing show a “variant of uncertain significance (VUS)” in some cases. The interpretation of the

clinical significance of VUS sometimes changes because of database updating, etc. There are programs to predict the influence of variants on the protein function (Sorting Intolerant From Tolerant [SIFT], <http://sift.jcvi.org/index.html>; Polymorphism Phenotyping version 2 [PolyPhen-2], <http://genetics.bwh.harvard.edu/pph2>, etc.). In cases where the presence or absence of the variant in relatives is strongly associated with tumorigenesis and in cases where the pattern of loss of mismatch repair proteins as assessed by immunohistochemistry is consistent with the VUS, the variant is most likely a pathogenic mutation, but further examination is required to confirm this.

If no definite information is available, the patient should be managed as follows.

- If a patient who has an MSI-H tumor or in whom immunohistochemistry shows loss of expression of one of the mismatch repair proteins has the clinical features of Lynch syndrome, he/she should be managed under the assumption that he/she has Lynch syndrome.

- If a patient who has an MSI-H tumor or in whom immunohistochemistry shows loss of expression of one of the mismatch repair proteins has no clinical findings suggestive of Lynch syndrome, periodic follow-up should be continued based on the family/past medical history.

CQ24: What are the points that should be considered while providing genetic counseling to patients with Lynch syndrome and their families?

Recommendation category: B

When genetic counseling is provided to patients with suspected Lynch syndrome and their families (relatives), the explanation provided about the disease should include an outline of Lynch syndrome, the mode of inheritance, the tests required for diagnosis, the risk of development of Lynch syndrome-associated tumors, including colorectal cancer, surveillance, etc., information resources on the disease, psychosocial support, etc.

It is important to keep in mind the following points (1) to (4) while providing genetic counseling to patients/their families for Lynch syndrome:

(1) The medical and family histories of the individuals should be taken.

(2) The following information should be provided.

An outline of Lynch syndrome (clinical symptoms, penetrance, natural course, incidence, causative genes, diagnosis, treatment, prophylaxis, etc.), its mode of inheritance (autosomal dominant inheritance), the risk of development of various cancers in the individuals (and their relatives) with or without a pathogenic mutation, the possibility of detecting gene mutations, the risk of various cancers when there is a pathogenic mutation, an outline of tests for Lynch syndrome (MSI testing, immunohistochemistry, genetic testing for mismatch repair genes, etc.), preventive measures (in

particular, surveillance) based on the risk, information resources such as websites and books, information on patient groups, and current state of research in Japan and overseas.

(3) The surveillance protocols for Lynch syndrome-associated tumors according to the risk should be presented.

(4) Psychosocial support should be provided (patients should be asked to give voice to their concerns and anxieties about the disease, conflicts among family members, etc., and should receive empathy from the physician).

CQ25: Which are the surgical procedures that should be selected for colorectal cancer in patients with Lynch syndrome?

Recommendation category: C

No consensus has been reached on whether the same surgical procedures as those for sporadic colorectal cancer should be selected, or extended operations should be adopted, considering the risk of multiple colorectal cancers in patients with Lynch syndrome.

A retrospective cohort study of colorectal cancer in Lynch syndrome reported that the 10-, 20- and 30-year cumulative incidences of development of metachronous colorectal cancer after partial colectomy (segmental resection) were 16%, 41%, and 62%, respectively, and that the risk of development of metachronous colorectal cancer was lower when a longer segment of the intestine was resected²¹⁰.

In addition, according to another retrospective cohort study, approximately 15% of primary colorectal cancers in patients with Lynch syndrome were rectal cancers, and most metachronous colorectal cancers were right colon cancers in patients who underwent proctectomy. Furthermore, endoscopic surveillance at mean intervals of 14 months revealed 10-, 20-, and 30-year cumulative incidences of development of metachronous colorectal cancers of 19%, 47%, and 69%, respectively²¹¹. There are insufficient data on whether total proctocolectomy should be selected or not for primary rectal cancer.

Also, no consensus has been reached on whether prophylactic colectomy should be performed in mutation carriers who have been genetically diagnosed as having a pathogenic mutation in one of the mismatch repair genes, but have not developed colorectal cancer. The lifetime risk of colorectal cancer development in male patients with Lynch syndrome is 54-74%, and that in female patients with Lynch syndrome is 30-52% (Table 6). Furthermore, a substantial number of mutation carriers do not develop colorectal cancer throughout their lifetimes. Therefore, prophylactic colectomy cannot be uniformly recommended, as in the case of patients with FAP. Accordingly, it is desirable to allow mutation carriers to decide for themselves the course of treatment they would wish to receive, after they are provided an explanation about the risk of development of metachronous colorectal cancer in Lynch syndrome, the necessity and limitations of surveil-

lance, the significance of prophylactic surgery, the postoperative QOL, etc.

CQ26-1: Which are the adjuvant chemotherapy regimens effective for colorectal cancer in patients with Lynch syndrome?

Recommendation category: C

There is no clear evidence of the efficacy of postoperative adjuvant chemotherapy specifically for colorectal cancer in patients with Lynch syndrome. Stage III colonic cancer (colorectal cancer) in Lynch syndrome could be an indication for postoperative adjuvant chemotherapy.

Because there is little evidence of chemotherapy specific to colorectal cancer in patients with Lynch syndrome, chemotherapy is often considered in accordance with that for sporadic MSI-H colorectal cancers. However, it has been reported that postoperative 5-fluorouracil (FU)-based adjuvant chemotherapy is not useful in patients with sporadic MSI-H colorectal cancer, but is useful in MSI-H colorectal cancer patients aged less than 50 years with suspected Lynch syndrome²¹², suggesting that colorectal cancer in Lynch syndrome should be considered differently from sporadic MSI-H colorectal cancers. There are almost no useful data on postoperative adjuvant chemotherapy for sporadic MSI-H rectal cancer or Lynch syndrome-associated rectal cancer.

A meta-analysis of the MSI status and efficacy of postoperative adjuvant chemotherapy including 5-FU in cases with stage II/III sporadic colorectal cancer showed that MSI-H colorectal cancer had a better prognosis than MSS colorectal cancer, but that postoperative adjuvant chemotherapy did not improve the survival or recurrence-free survival in patients with MSI-H colorectal cancer^{213,214}. However, the National Surgical Adjuvant Breast and Bowel Project (NSABP)-C07 trial and the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial showed that oxaliplatin had an additive effect in postoperative adjuvant therapy for both MSI-H and MSS colonic cancers²¹⁵. Therefore, at present, it is not recommended to determine whether stage III colonic cancer is an indication for postoperative adjuvant chemotherapy according to the MSI status. The usefulness of postoperative adjuvant chemotherapy has not been established for stage II colorectal cancer, and it is thought to be less useful, particularly in MSI-H cancers, because these cancers have favorable prognoses.

CQ26-2: What are the chemotherapy regimens effective against metastatic colorectal cancer in Lynch syndrome?

Recommendation category: C

There is no clear evidence of the efficacy of chemotherapy exclusively against metastatic colorectal cancer in Lynch syndrome. The same management strategies as those for sporadic colorectal cancer should be selected.

The incidence of MSI-H has been shown to be lower in stage IV than in stage II/III sporadic colorectal cancers^{216,217}. Chemotherapy specific to metastatic colorectal cancers associated with Lynch syndrome or colorectal cancers showing MSI-H has not yet been clearly investigated and no conclusion has been reached. Therefore, regimens generally selected for sporadic colorectal cancers could be indicated for these cancers as well. The response rate to irinotecan as a second-line treatment in cases with acquired resistance to 5-FU was reported to be significantly higher in MSI-H cancers than in other sporadic colorectal cancers²¹⁸. Recent reports on immune checkpoint inhibitors have attracted attention (Side Memo 10: MSI-H tumors and anti-PD-1 antibody drugs).

Side Memo 10

■ MSI-H tumors and anti-PD-1 antibody drugs

Recently, anti-programmed death (PD)-1 antibodies, which are immune checkpoint inhibitors, have been shown to be effective in the treatment of metastatic colorectal cancers, particularly those showing MSI-H, and these antibodies are expected to also be effective against Lynch syndrome-associated colorectal cancer²¹⁹. The response rate to anti-PD-1 antibodies was significantly higher in MSI-H colorectal cancer (40%) and other MSI-H cancers (71%) than in MSS colorectal cancer (0%). However, among the MSI-H cancer cases, a subgroup of 11 patients with Lynch syndrome showed a response rate of only 27%, lower than the response rate in patients with sporadic MSI-H cancers. Anyway, these results suggest that there is much scope for innovation in pharmacotherapy for MSI-H cancers, including those associated with Lynch syndrome.

CQ27: Are there any lifestyle remedies that are effective in preventing carcinogenesis in Lynch syndrome?

Recommendation category: B

Smoking cessation and proper body fat control are recommended to prevent colorectal carcinogenesis in Lynch syndrome.

The effects of smoking, body mass index, alcohol consumption, diets (red meat, processed meat, vegetables, fruits, fish, dairy products, and dietary fiber), etc., have been investigated. Studies, including a prospective cohort study, have shown an association of smoking and body mass index with the risk of carcinogenesis^{220,221}.

The results of the JSCCR multicenter study suggested that smoking is a risk factor for the development of synchronous/metachronous multiple colorectal cancers in Lynch syndrome²²¹.

Based on current evidence, smoking cessation and proper body fat control are recommended to prevent colorectal carcinogenesis in patients with Lynch syndrome.

CQ28: Is there any chemoprophylaxis that is effective in preventing carcinogenesis in Lynch syndrome?

Recommendation category: C

Aspirin may prevent the development of Lynch syndrome-

associated tumors.

The Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) was the first double-blind study to evaluate the efficacy of aspirin in preventing Lynch syndrome-associated tumors and colorectal adenomas. Long-term follow-up revealed that aspirin was significantly effective in preventing the development of colorectal cancer (primary endpoint) and other Lynch syndrome-associated tumors (secondary endpoint)²²². No useful data with respect to the prevention of colorectal adenomas were obtained. The aspirin dose used in this study was 600 mg/day, a dose which is considered difficult to use widely in Japanese patients, who are more susceptible to gastrointestinal disorders caused by aspirin as compared to Europeans and Americans. On the other hand, a study conducted on a large patient cohort, although retrospective, showed the efficacy of aspirin and ibuprofen in preventing the development of colorectal cancer in Lynch syndrome²²³. It remains to be investigated in the future as to what dose and for what duration aspirin should be administered for obtaining this effect. Several studies have reported that low-dose aspirin may prevent the development of sporadic colorectal cancer²²⁴, and a clinical trial of low-dose aspirin in Lynch syndrome patients is ongoing.

CQ29: Is surveillance by colonoscopy effective in patients with Lynch syndrome?

Recommendation category: B

Endoscopic surveillance and resection of adenomas reduce the development of and death from colorectal cancer in cases of Lynch syndrome.

Patients with Lynch syndrome have been shown to be at a high risk of developing colorectal cancer, including those with remaining large intestine after surgery for colorectal cancer, and regular and lifelong endoscopic surveillance with the aim of any resecting precancerous adenomas and early detection of colorectal cancer is required^{225,226}. Many studies have recommended that surveillance be started at the age of 20-25 years¹⁹⁶. Regarding the intervals at which the examinations should be conducted, a prospective study by Järvinen et al.²²⁷ reported that endoscopic surveillance at 3-year intervals decreased the mortality from colorectal cancer by 65%. However, observational studies have confirmed the development of advanced cancer over 3-year periods in endoscopic surveillance, and several studies recommend annual surveillance²²⁸⁻²³⁰.

In Lynch syndrome patients, colorectal adenomas often develop at a young age (less than 40 years)^{228,231}, show MSI-H, show high-grade atypia even if smaller than ordinary adenomas, and undergo malignant transformation within a short period of time^{232,233}. In addition, the cumulative number of colorectal adenomas developing over a lifetime has been reported to be up to approximately 20²³⁴. Therefore, tumor-

ous lesions, if detected, should be actively resected endoscopically, irrespective of their size.

Appendix

I. Principles in drawing and reading pedigrees

1. Points that must be kept in mind while taking the family history (Appendix Figure 1)

- Information on at least 3 generations should be obtained.

- It should be checked whether there are any consanguineous marriages (such as cousin marriages).

- Not only the number of affected individuals, but also the number of unaffected individuals among siblings should be checked.

- Date of taking family history, name of the person providing the information, and name of the person taking the family history should be described in the pedigree.

- Maternal and paternal pedigrees should be separately evaluated.

2. Outline of how to draw pedigrees (Appendix Figure 2)

- The proband (the affected individual leading to the detection of the affected family) should be indicated by P ↗

- The client should be indicated by ↗

- If possible, the husband (male partner) should be listed to the left of the wife (female partner).

- Siblings should be listed from left to right in order of birth.

- The generation number should be indicated in Roman numerals on the left side.

- Individual numbers should be given in Arabic numerals in order from left to right along generation lines.

- Necessary clinical information, such as the age at onset (age at diagnosis), affected site (left or right in the case of bilateral disease), course of treatment, surgical procedure, and pathological diagnosis, should be described.

Symbols generally used to draw pedigrees are shown below.

The first-, second-, or third-degree relatives of the proband are shown below.

II. Method for describing genomic variants

The description method proposed by the Human Genome Variation Society (<http://varnomen.hgvs.org/>) is generally used to describe genomic changes. Usually, information on reference sequences, their location, and any changes should be given in that order.

1. Symbols for reference sequences

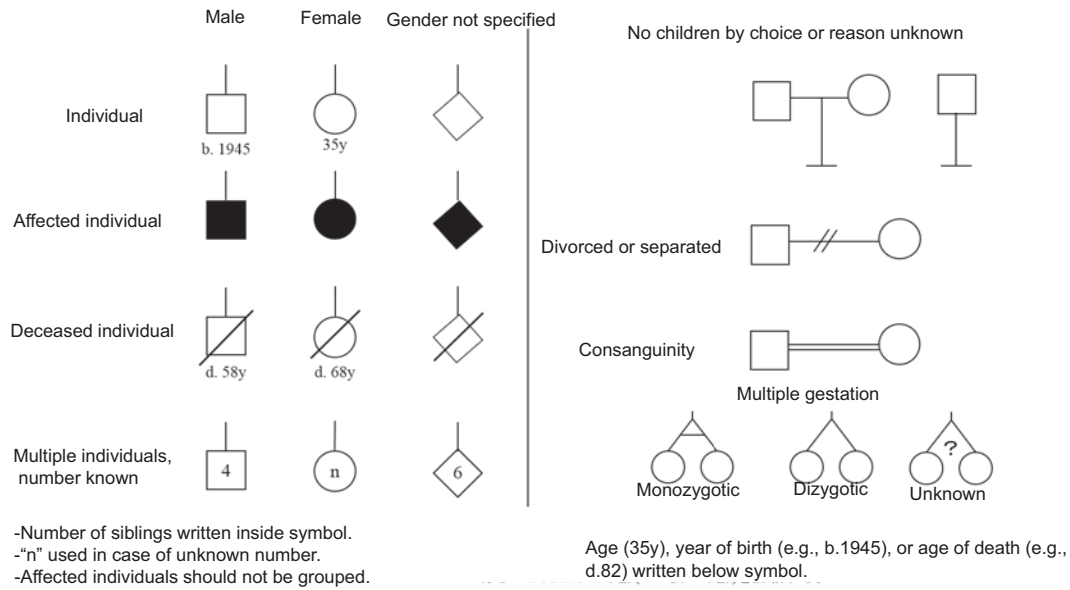
Genomic reference sequence: g.

Coding DNA reference sequence#: c.

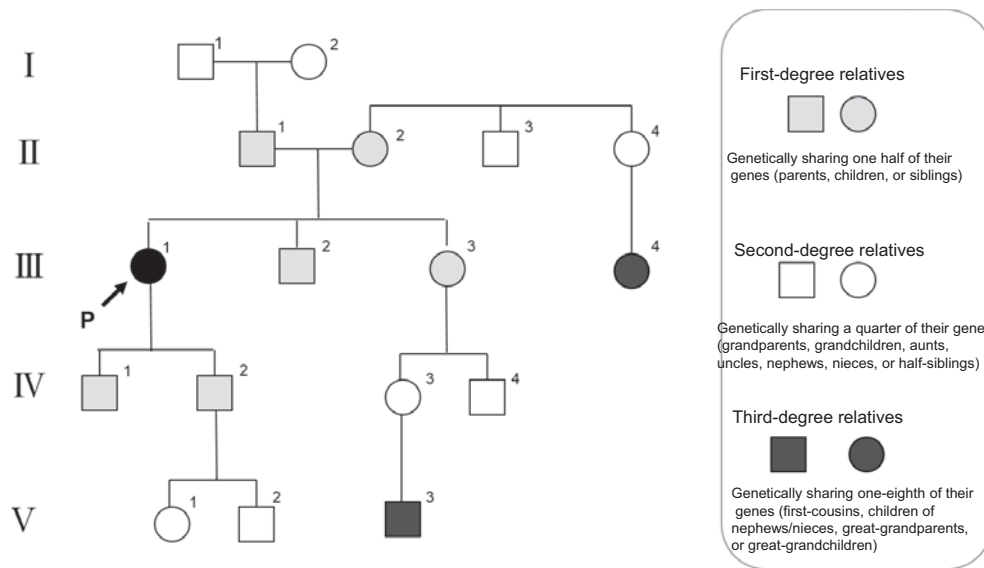
RNA reference sequence: r.

Protein reference sequence: p.

#Coding DNA sequence is a DNA sequence between the start and stop codons that serves as a template for the synthesis of mRNA, which is translated into protein.



Appendix Figure 1. Symbols for family pedigrees.



Appendix Figure 2. The first-, second-, or third-degree relatives of the proband.

2. Locations of variants

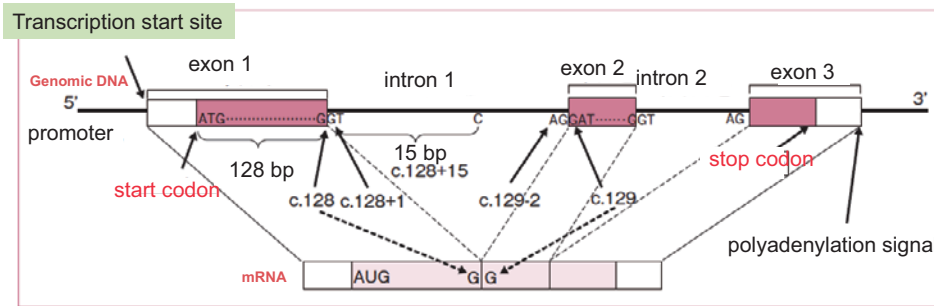
(1) Changes at the genomic DNA level should be indicated by “g,” and the first nucleotide of the reference genome sequence should be numbered 1.

(2) Changes at the coding DNA level should be indicated by “c.,” and the A of the start codon ATG (translation start point) should be numbered 1 (in Appendix Figure 3, the last nucleotide of exon 1 is the 128th nucleotide from the A of the start codon ATG, and should be indicated as c. 128). Because coding DNA sequences are translated into proteins and contain no introns, when a nucleotide position in an intron is shown, the nucleotide number counted from an adjacent

cent exon should be indicated using “+” or “-.” For example, in Appendix Figure 3, the 15th nucleotide from the start of intron 1 should be indicated as “c. 128 + 15,” and the second nucleotide upstream of the start of exon 2 (c. 129) should be indicated as “c. 129 - 2.”

(3) Changes at the RNA level should be indicated by “r,” in accordance with the method for describing the changes at DNA level.

(4) Changes at the protein level should be indicated by “p.,” and the translation initiation methionine should be numbered 1. Both three-letter and one-letter amino acid codes can be used.



Appendix Figure 3. The gene structure and variant nomenclature.

3. Types of changes and their descriptions

(1) Changes at the DNA level should be described as follows. Substitution: >; deletion: del; insertion: ins; deletion-insertion: delins; duplication: dup; inversion: inv; conversion: con.

(2) For changes at the protein level, ">" is not used in the case of substitution, but the original and changed amino acids are shown before and after the amino acid position (number), respectively. Other changes, such as deletion (del), insertion (ins), deletion-insertion (delins), duplication (dup), inversion (inv) and conversion (con) are described in a similar manner to those at the DNA level.

In general, changes are commonly described at the coding DNA (c.) or protein (p.) level.

Specific examples are given below.

Example 1) Missense mutation

● c. 146T > A (p. Val49Glu)

The T nucleotide at the 146th position from the A of the start codon ATG is substituted with an A. This is associated with change of the 49th amino acid from valine (Val) to glutamic acid (Glu).

Example 2) Nonsense mutation

● c. 184C > T (p. Glu62Ter or p. Glu62*)

The C nucleotide at the 184th position is substituted with a T. This is associated with the 62nd codon becoming a stop codon, resulting in a stop of protein biosynthesis.

Example 3) Duplication and its associated frame-shift mutation

● c. 175dupA (p. Ile59Asnfs*20)

The A nucleotide at the 175th position is duplicated and the 176th nucleotide becomes A with the shift in the codon reading frame (this shift of the reading frame is called frame shift and designated as "fs"). This is associated with change of the 59th amino acid from isoleucine (Ile) to asparagine (Asn), and furthermore, with the 20th codon from this site becoming a stop codon (fs*20), resulting in the termination of protein biosynthesis.

Example 4) Deletion and its associated frame-shift mutation

● c. 3927_3931delAAAGA (p. Glu1309Aspfs*4)

The nucleotides the 3927th to 3931th position, AAAGA,

are deleted. This is associated with change of the 1309th amino acid from glutamic acid (Glu) to aspartic acid (Asp) and the 4th codon from this site becoming a stop codon (fs*4).

Example 5) A mutation in an intron

● c. 792 + 1G > A

The G nucleotide at the first position following the last (792nd) of the exon is substituted with an A. This is speculated to be associated with abnormal splicing.

Example 6) Exon deletion

● c. 458-?_627 +?del

At least one exon (DNA sequence from C. 458 to C. 627) is deleted (unknown nucleotides in the deleted intron region are indicated by "?").

In addition, to assess whether the variant obtained causes disease or not, registration of the variant in databases such as InSiGHT (<http://insight-group.org/variants/database/>) and ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>) should be checked, and a comprehensive assessment based on the results is sometimes required.

It cannot be necessarily said that variants listed in databases cause disease, and careful management is required. Variants are usually classified into 5 categories according to whether they can potentially be associated with disease or not (Attachment Table 1).

Attachment

I. Familial adenomatous polyposis

Familial adenomatous polyposis in Japan: Data from the JSCCR "A retrospective multicenter study of familial adenomatous polyposis" (n = 303) (Attachment Table 1-5)

II. Lynch syndrome

Germline mutations in Lynch syndrome in Japan: Data from the JSCCR "Registration and genetic analysis of HNPCC (secondary study)" (Attachment Table 6)

[Translated from Japanese²³⁵) to English with a permission from the publisher of the original version]

Conflicts of Interest

Kei Muro received lecture fees from Chugai, Takeda, and Eli Lilly and research fundings from MSD, Daiichi Sankyo,

Attachment Table 1. Number of Colorectal Cancers According to the Phenotype of Familial Adenomatous Polyposis.

Number of colorectal cancers	Profuse type	Sparse type	AFAP	Total
1	18 (62.1%)	50 (73.5%)	15 (83.3%)	83 (72.2%)
2	4 (13.8%)	13 (19.1%)	3 (16.7%)	20 (17.4%)
3	6 (20.7%)	3 (4.4%)	0 (0.0%)	9 (7.8%)
4	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.9%)
5	1 (3.4%)	1 (1.5%)	0 (0.0%)	2 (1.7%)

AFAP: attenuated FAP

Attachment Table 2. Stage of Colorectal Cancer According to the Phenotype of Familial Adenomatous Polyposis.

Stage*	Profuse type	Sparse type	AFAP	Total
Stage I	8 (27.6%)	18 (26.9%)	5 (27.8%)	31 (27.2%)
Stage II	4 (13.8%)	14 (20.9%)	6 (33.3%)	24 (21.1%)
Stage III a	5 (17.2%)	14 (20.9%)	2 (11.1%)	21 (18.4%)
Stage III b	8 (27.6%)	7 (10.4%)	3 (16.7%)	18 (15.8%)
Stage IV	4 (13.8%)	14 (20.9%)	2 (11.1%)	20 (17.5%)

*: according to the classification proposed by JSSCR

Attachment Table 3. Cumulative Incidence of Development of Colorectal Cancer and Duodenal Adenoma.

Age (Years)	Colorectal cancer			Duodenal cancer		
	Profuse type	Sparse type	AFAP	Profuse type	Sparse type	AFAP
20	0%	1.1%	0%	1.3%	1.1%	0%
30	21.4%	9.6%	13.1%	7.8%	8.4%	5.8%
40	47.7%	41.1%	20.4%	32.4%	28.4%	18.4%
50	68.3%	54.8%	31.1%	52.1%	38.3%	23.5%
60	-	80.2%	55.3%	71.3%	48.9%	23.5%

Attachment Table 4. Cumulative Risk of Development of Desmoid Tumors after Colorectal Resection.

	1y	2y	3y	4y	5y
Cumulative risk (%)	5.20%	10.20%	11.90%	12.90%	13.40%

Attachment Table 5. Postoperative Complications after Restorative Proctocolectomy+Heal-Pouch Anal Anastomosis.

	Conventional open surgery	Stapled anastomosis	Hand-sewn anastomosis
Intestinal obstruction	6.5%	8.1%	5.7%
Anastomotic leakage	0%	0%	0.9%
Anastomotic stricture	3.4%	0%	5.7%
Intra-abdominal abscess	3.5%	0%	4.0%
Wound infection	2.2%	0%	4.0%
Dysuria	1.3%	0%	1.1%
Erectile dysfunction	0%	0%	1.5%
Ejaculatory dysfunction	12.5%	4.3%	4.7%

Attachment Table 6. Germline Mutations in Lynch Syndrome in Japan: Data from the JSCCR “Registration and Genetic Analysis of HNPCC (Secondary Study) ”.

Mismatch repair gene	Type of mutation	Regions (Sites) of mutation	Germline nucleotide change
<i>MLH1</i>	Substitution	Exon1	c.37G>T (p.E13*)
		Exon2	c.122A>G (p.D41G)
		Exon2	c.199G>A (p.G67R)
		Intron2, splice acceptor site	c.208-2A>G (aberrant splicing)
		Exon8	c.677G>A (p.R226Q, aberrant splicing)
		Intron9, splice donor site	c.790+5G>T (aberrant splicing)
		Intron9, splice donor site	c.790+1G>A (aberrant splicing)
		Exon13	c.1459C>T (p.R487*)
		Intron13, splice donor site	c.1558+1G>A (aberrant splicing)
		Exon15	c.1731G>A (aberrant splicing)
	Intron15, splice donor site	c.1731+5zG>A (aberrant splicing)	
	Exon19	c.2250C>G (p.Y750*)	
	Deletion	Intron2, splice donor site	c.207+1_c.207+2delGT (aberrant splicing)
		Exon3	c.209_211delAAG (aberrant splicing)
		Exon4	c.319_320delAT (p.I107Kfs*14)
		Exon6	c.472delA (p.N158Tfs*2)
		Exon6	c.523delA (p.I176Ffs*26)
		Intron6, splice donor site	c.545+3delAC (aberrant splicing)
		Exon16	c.1846_1848delAAG (p.K616del)
Insertion	Exon5	c.440_441insT (p.T148Dfs*24)	
	Exon15	c.1672_1673insAACT (p.F560Tfs*8)	
	Exon19	c.2198_2199insTT (p.T735Sfs*49)	
Deletion/insertion	Exon12	c.1039-4215_c.1409+2347del6933ins101 (exon12 deletion)	
Duplication	Exon6	c.464dupT (p.Y157Lfs*15)	
	Intron9, splice donor site	c.790+2dupT (aberrant splicing)	
	Exon12-13	c.1039-?_1558+? (exon12-13 duplication)	
<i>MSH2</i>	Substitution	Intron1, splice donor site	c.211+1G>C (aberrant splicing)
		Intron5, splice donor site	c.942+3A>T (aberrant splicing)
		Exon7	c.1165C>T (p.R389*)
		Exon7	c.1204C>T (p.Q402*)
		Exon7	c.1225C>T (p.Q409*)
		Exon7	c.1255C>T (p.Q419*)
		Intron9, splice acceptor site	c.1511-1G>A (aberrant splicing)
		Intron10, splice donor site	c.1661+1G>A (aberrant splicing)
		Exon12	c.1861C>T (p.R621*)
		Exon12	c.1865C>T (p.P622L)
	Exon12	c.1915C>T (p.H639Y, aberrant splicing)	
	Exon14	c.2455A>T (p.K819*)	
	Exon15	c.2563C>T (p.Q855*)	
	Deletion	Exon2	c.274_276delCTT (p.L92del)
		Exon7	c.1226_1227delAG (p.Q409Rfs*7)
Exon11		c.1705_1706delGA (p.E569Ifs*2)	
Exon11		c.1744delG (p.V582Sfs*8)	
Exon13		c.2031_2032delAT (p.I679Sfs*19)	
Exon14		c.2309delT (p.I770Mfs*42)	
Exon1		c.1-7550_c211+2019del9780 (exon1 deletion)	
Deletion/insertion	Exon1-6	c.1-19640_c1076+10104del42982 (exon1-6 deletion)	
	Exon6-7	c.943-596_c1276+12033del126275 (exon6-7 deletion)	
Duplication	Exon14	c.2300_2303delCAGAINSATATATAT (p.S767Yfs*20)	
	Exon5-6	c.793-455_c1076+5894dup8510 (exon5-6 duplication)	
	Exon7	c.1077-10584_c1276+207dup10991 (exon7 duplication)	
	Exon2 Exon13	Exon2 duplication Exon13 duplication	
<i>MSH6</i>	Duplication	Exon5	c.3261dupC (p.F1088Lfs*5)
		Exon5	c.3403dupC (p.N1136Lfs*31)

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