The following are expected to be achieved with these Guidelines: (1) improved treatment of colorectal cancer in Japan; (2) improved results of such treatment; (3) reduced human and financial burdens; and (4) increased benefits for patients.

2. How to use these Guidelines

These Guidelines have been prepared by consensuses reached by the JSCCR Guideline Committee, based on a careful review of the evidence retrieved by literature searches and in view of the medical health insurance system and actual clinical practice settings in Japan, so these Guidelines can be used as a tool for treating colorectal cancer in actual clinical practice settings. More specifically, they can be used as a guide to obtaining informed consent from patients and choosing the method of treatment for each patient. However, these Guidelines provide only general recommendations for choosing treatment strategies for colorectal cancer, and they do not control or limit treatment strategies or treatment methods that are not described herein. These Guidelines can also be used as a document to explain the rationale for selecting treatment strategies and treatment methods that differ from those described in these Guidelines.

JSCCR is responsible for the statements in these Guidelines. However, the personnel directly in charge of treatment, not the JSCCR or the Guideline Committee, are responsible for the outcome of treatment.

3. Method used to prepare these Guidelines

(1) Classification of evidence

Levels of evidence were classified as "high-level evidence" or "low-level evidence" as follows:

[High-level evidence]

- Meta-analyses of systematic reviews/randomized controlled trials (RCTs),
- randomized controlled trials,
- nonrandomized controlled trials,
- cohort studies, case–control studies, and cross-sectional studies.

[Low-level evidence]

- Case series studies, case studies, expert opinions, and clinical experience.

(2) Clinical Questions and classification of recommendation categories

As a result of the discussions held by the Guideline Committee, controversial issues were selected as Clinical Questions (CQ), and recommendations were made.

Each recommendation in response to a CQ is accompanied by a classification of the evidence and a classification of recommendation categories based on the consensus reached by the Guideline Committee members. In determining the recommendation categories, in addition to an evaluation of the internal validity of the source of evidence for each recommendation, a comprehensive investigation of the internal validity, external validity, and clinical applicability of each recommendation was performed, considering the following points: (1) the treatment method has a clear scientific rationale and is the best treatment method conceivable; (2) the treatment method is as safe as possible, causes little invasion, and maintains physical function; (3) the treatment method is cost-effective and imposes the smallest financial burden on the patient; and (4) the treatment method is in line with the treatment methods used in actual clinical practice settings in Japan.

Recommendations with which all members of the Guideline Committee agreed were classified as category A or category B recommendations. Recommendations with which three or more members of the Committee disagreed were classified as category D recommendations, and all other recommendations were classified as category C recommendations. The category D recommendations are not included in these Guidelines.

Classification of recommendation categories:

- Category A: unanimous recommendations by the Guideline Committee based on high-level evidence
- Category B: unanimous recommendations by the Guideline Committee based on low-level evidence
- Category C: recommendations that were not agreed to completely by the members of the Guideline Committee, irrespective of the level of evidence
- Category D: recommendations that were not agreed to by three or more members of the Guideline Committee

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Table 1 Number of scientific articles retrieved and selected

	Number of articles retrieved		Number of articles selected		Number of articles retrieved manually
	PubMed	Ichushi	PubMed	Ichushi	
(1) Endoscopic treatment of colorectal cancer	283	214	10	8	8
(2) Treatment of stage 0 to stage III colorectal cancer	347	268	49	11	2
(3) Treatment of stage IV colorectal cancer	189	98	79	14	9
(4) Treatment of liver metastases of colorectal cancer	645	281	255	42	14
(5) Treatment of lung metastases of colorectal cancer	54	134	28	22	2
(6) Treatment of recurrent colorectal cancer	488	125	111	18	7
(7) Adjuvant chemotherapy for colorectal cancer	340	189	154	27	31
(8) Chemotherapy for unresectable colorectal cancer	472	66	234	41	121
(9) Adjuvant radiotherapy for colorectal cancer	398	61	86	6	15
(10) Palliative radiotherapy for colorectal cancer	704	31	107	6	17
(11) Palliative care for colorectal cancer	182	58	19	5	8
(12) Surveillance after surgery for colorectal cancer	1,203	1,213	249	37	13
Total	5,305	2,738	1,381	237	247

4. Literature search

Initially, the literature search was performed for the following 12 broad categories. Then, a further search was done as needed with additional search techniques.

(1) Endoscopic treatment of colorectal cancer
(2) Treatment of stage 0 to stage III colorectal cancer
(3) Treatment of stage IV colorectal cancer
(4) Treatment of liver metastases of colorectal cancer
(5) Treatment of lung metastases of colorectal cancer
(6) Treatment of recurrent colorectal cancer
(7) Adjuvant chemotherapy for colorectal cancer
(8) Chemotherapy for unresectable colorectal cancer
(9) Adjuvant radiotherapy for colorectal cancer
(10) Palliative radiotherapy for colorectal cancer
(11) Palliative care for colorectal cancer
(12) Surveillance after surgery for colorectal cancer

The PubMed and Ichushi-Web databases were selected for the search, and the English and Japanese literature was searched in both databases for the period from January 1983 to December 2007. The task of searching was shared by four members of the medical library; the four members created a search formula by discussion with the Committee members in charge of each item and collected literature during the search period (January 2008 to July 2008). For categories (7) and (8), however, April 2010 was set as the end of the search period. In addition, secondary documents such as UpToDate and literature collected by manual searching were added and critically examined as needed, and other documents such as minutes and guidelines were included as necessary. Of the 8,043 references identified as a result of the searches (5,305 in the PubMed database and 2,738 in the Ichushi-Web database), 1,618 references were retrieved and examined critically (Table 1).

5. Funding

Preparation of these Guidelines was funded by the JSCCR and the Health and Labour Sciences Research Fund (3rd Term Comprehensive 10-Year Strategy for Cancer Control Research Project).

6. Conflicts of interest

None of the members of the committee in charge of the preparation of these Guidelines has any conflict of interest with entities such as any specific profit or nonprofit organizations or any entities related to pharmaceutical or medical products, and the board of the JSCCR confirmed the self-reported absence of any conflicts of interest by the Guideline Committee members.

Treatment guidelines for colorectal cancer

Chapter 1: Treatment strategies for stage 0 to stage III colorectal cancer

1. Endoscopic treatment

General principles underlying the indications for endoscopic resection (Fig. 1)

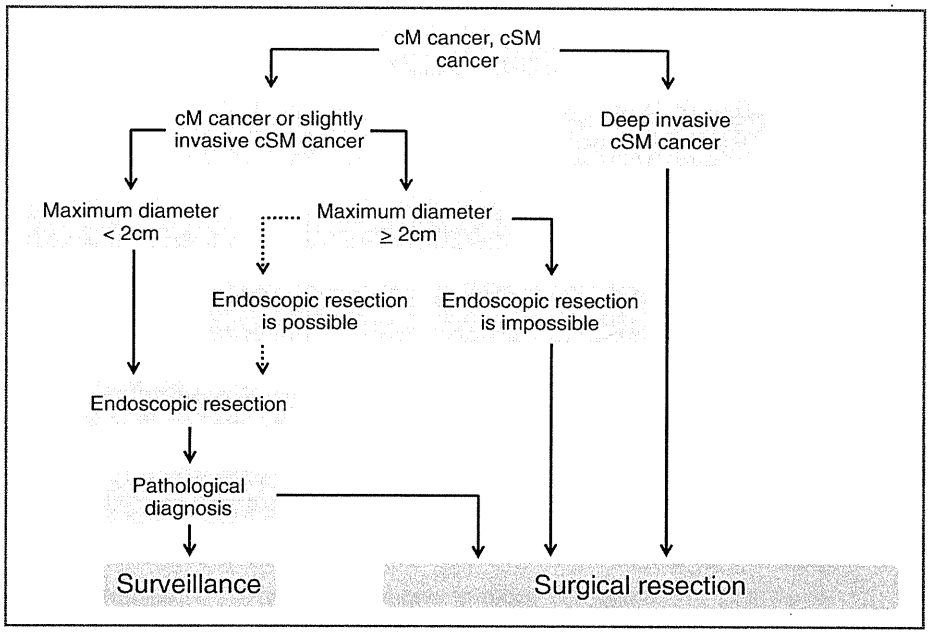


Fig. 1 Treatment strategies for cM cancer and cSM cancer

- There is little possibility of lymph node metastasis, and the size and location of the tumor make en bloc resection possible.

Indication criteria for endoscopic resection:

(1) Intramucosal carcinoma or carcinoma with slight submucosal invasion
(2) Maximum diameter <2 cm
(3) Any macroscopic type

- Endoscopic treatment is a method of endoscopically resecting lesions in the large bowel and of collecting the resected specimens.
- Endoscopic treatment methods consist of polypectomy,[1] endoscopic mucosal resection (EMR),[2] and endoscopic submucosal dissection (ESD).[3]
- In determining the indication for endoscopic treatment and the treatment method, information on the size, predicted depth of invasion, and morphology of the tumor is essential, and the histological type of the tumor should also be taken into consideration.

Comments

- Endoscopic resection is intended for both diagnosis and treatment. It consists of total excisional biopsy in which curability and the need for additional intestinal resection are assessed by histopathological examination of the resected specimens (CQ-1).
- En bloc resection is desirable for accurate diagnosis of the status of carcinoma invasion in the resection margin and the deepest area.
- 2 cm is the largest size of a tumor that can be easily resected en bloc by polypectomy or snare EMR [3] (CQ-2).
- Colorectal ESD has not become a common treatment method, because the technique is difficult and there is a high risk of complications (perforation) [3].
- EMRC (EMR using a cap) involves a high risk of perforation when used for colon lesions.
- If the preoperative diagnosis is intramucosal carcinoma, piecemeal resection can be performed. It should be noted, however, that piecemeal resection is associated with a high incomplete resection rate and a high local recurrence rate [3].

2. Surgical treatment (Fig. 2)

- The extent of lymph node dissection to be performed during colorectal cancer surgery is determined based on the preoperative clinical findings (c) or on the extent of

[1] In polypectomy, a snare is placed on the stalk of the lesion, and the lesion is electrocauterized using a high-frequency current. This method is mainly used for protruding lesions.

[2] In EMR, the lesion is elevated through the local injection of a liquid such as physiological saline into the submucosa, and the lesion is electrocauterized just as in polypectomy. This method comprises the snare method [2] and EMR using a cap (EMRC). It is mainly used for superficial tumors and large sessile lesions.

[3] In ESD, the lesion is elevated through the local injection of a liquid such as sodium hyaluronate solution into the submucosa of the perilesional area; then, circumferential incision of the mucosa surrounding the lesion and dissection of the submucosa are performed with a special knife [3]. ESD is mainly indicated for large tumors that cannot be resected by EMR.

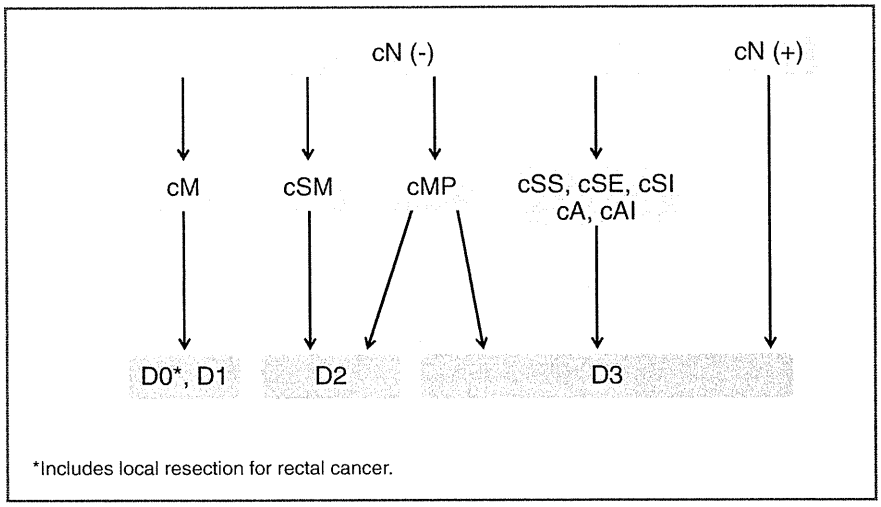


Fig. 2 Surgical treatment strategies for stage 0 to stage III colorectal cancer

lymph node metastasis and depth of wall invasion by the tumor observed intraoperatively (s).

- If lymph node metastasis is suspected based on the preoperative/intraoperative diagnostic findings, D3 dissection is performed.
- If no lymph node metastases are observed based on the preoperative/intraoperative diagnostic findings, lymph node dissection is performed based on the depth of wall invasion by the tumor [4].

(1) Lymph node dissection is unnecessary for M cancer (D0), because M cancer is not accompanied by lymph node metastasis; however, D1 dissection can be performed because the accuracy of the preoperative diagnosis of invasion depth may be insufficient.
(2) D2 dissection is necessary for SM cancer, because the incidence of lymph node metastasis is approximately 10% and because SM cancer is often accompanied by intermediate lymph node metastasis.
(3) Although there is insufficient evidence describing the area of dissection for MP cancer, at the very least D2 dissection is necessary. However, D3 dissection can be performed, because MP cancer is often accompanied by main lymph node metastases and because preoperative diagnosis of depth of invasion is not very accurate.

Surgical treatment of rectal cancer:

- The principle for proctectomy is TME (total mesorectal excision) or TSME (tumor-specific mesorectal excision) [5–8].

[Indications criteria for lateral lymph node dissection]

- Lateral lymph node dissection is indicated when the lower border of the tumor is located distal to the peritoneal reflection and has invaded beyond the muscularis propria [9].

[Local rectal resection]

- Local resection is indicated for cM cancer and cSM cancer (slight invasion) located distal to the second Houston valve (peritoneal reflection). Approaches for local resection are classified into transanal resection, transsphincter resection, and parasacral resection [10]. Transanal resection includes the conventional method in which the tumor is resected under direct vision and transanal endoscopic microsurgery (TEM) [11]. More proximal lesions can be resected by TEM than by the conventional method.

[Autonomic nerve-preserving surgery]

- The autonomic nervous system relating to surgery of rectal cancer consists of the lumbar splanchnic nerves, superior hypogastric plexus, hypogastric nerves, pelvic splanchnic nerves, and the pelvic plexus. Considering factors such as the degree of cancer progression and the presence or absence of macroscopic nerve invasion, preservation of autonomic nerves is attempted in order to preserve urinary and sexual functions as much as possible, provided that curability is unaffected.

Laparoscopic surgery:

- Transabdominal surgery consists of open abdominal surgery and laparoscopic surgery. The indications for laparoscopic surgery are determined by considering the surgeon's experience and skills as well as tumor factors, such as the location and degree of progression of the cancer, and patient factors, such as obesity and history of open abdominal surgery (CQ-3).

Table 2 Lateral lymph node dissection and lateral lymph node metastasis of rectal cancer

	No. of patients	No. of patients who underwent lateral lymph node dissection	Lateral lymph node dissection rate (%)	No. of patients with lateral lymph node metastasis	Lateral lymph node metastasis rate (% of all patients)	Lateral lymph node metastasis rate (% of patients who underwent lateral lymph node dissection)
RS						
sm	124	0	0	0	0.0	0.0
mp	127	6	4.7	0	0.0	0.0
ss/a_1	316	24	7.5	0	0.0	0.0
se/a_2	177	8	4.5	0	0.0	0.0
si/ai	32	14	43.8	1	3.1	7.1
Total	776	52	6.7	1	0.1	1.9
Ra						
sm	138	5	3.6	0	0.0	0.0
mp	149	18	12.1	0	0.0	0.0
ss/a_1	230	58	25.2	4	1.7	6.9
se/a_2	181	59	32.6	7	3.9	11.9
si/ai	15	8	53.3	0	0.0	0.0
Total	713	148	20.8	11	1.5	7.4
RaRb+Rb						
sm	234	37	15.8	2	0.9	5.4
mp	372	218	58.6	20	5.4	9.2
ss/a_1	350	230	65.7	28	7.7	12.2
se/a_2	412	319	77.4	75	18.0	23.5
si/ai	59	48	81.4	17	28.8	35.4
Total	1,427	852	59.7	142	9.8	16.7

Project study by the JSCCR: patients in years 1991–1998

Comments

[Lateral lymph node dissection]

- An analysis of 2916 cases of rectal cancer in the project study by the JSCCR showed that the lateral lymph node metastasis rate in patients whose lower tumor border was located distal to the peritoneal reflection and whose cancer had penetrated through the rectal wall was 20.1% (only patients who underwent lateral lymph node dissection) (Table 2). After performing lateral lymph node dissection for the indication mentioned above, the risk of intrapelvic recurrence decreased by 50%, and the 5-year survival rate improved by 8–9% [9].
- The lateral lymph node metastasis rate of patients whose lower tumor border was located distal to the peritoneal reflection and who had lymph node metastasis in the mesorectum was 27%.
- Urinary function and male sexual function may be impaired after lateral lymph node dissection, even if the autonomic nervous system is completely preserved.

[Aggregate data from the Colorectal Cancer Registry]

- The incidence of lymph node metastasis according to site and depth of invasion, curative resection rate, and 5-year survival rate is shown in Tables 3, 4, and 5 [4].
- The 5-year survival rates after curative resection of stage 0 to stage III colorectal cancer according to site were: all sites 81.3%; colon 83.7%, rectosigmoid 81.2%; Ra–Rb rectum 77.1%.

Chapter 2: Treatment strategies for stage IV colorectal cancer (Fig. 3)

- Stage IV colorectal cancer is associated with synchronous distant metastasis to any of the following organs: liver, lung, peritoneum, brain, distant lymph nodes, or other organs (e.g., bone, adrenal gland, spleen).
- If both the distant metastases and the primary tumor are resectable, curative resection of the primary tumor is performed, and resection of the distant metastases is considered.
- If the distant metastases are resectable but the primary tumor is unresectable, in principle, resection of the primary tumor and distant metastases is not performed, and another treatment method is selected.
- If the distant metastases are unresectable but the primary tumor is resectable, the indication for the resection of the primary tumor is determined, based on the clinical symptoms of the primary tumor and the impact on the prognosis (CQ-4).

Table 3 Incidence of lymph node metastasis according to primary site and depth of invasion

	No. of patients	Extent of lymph node metastasis detected histologically				
		n_0 (%)	n_1 (%)	n_2 (%)	n_3 (%)	n_4 (%)
All sites (C–P)						
sm	2,846	90.1	7.5	2.1	0.1	0.2
mp	3,402	77.0	17.2	4.8	0.7	0.3
ss/a_1	9,862	56.1	27.4	12.2	2.7	1.6
se/a_2	6,175	37.0	32.4	20.2	5.8	4.5
si/ai	1,294	44.0	25.2	15.7	7.6	7.6
Total	23,579	57.6	24.7	12.2	3.2	2.3
Colon (C–S)						
sm	1,757	90.9	6.9	1.9	0.1	0.2
mp	1,598	79.0	16.1	4.4	0.2	0.3
ss/a_1	6,428	57.7	25.8	1.2	2.8	1.4
se/a_2	3,547	38.0	31.7	20.1	5.8	4.4
si/ai	814	46.3	24.8	15.2	5.4	8.2
Total	14,144	58.6	23.8	12.2	3.1	2.3
Rectosigmoid (RS)						
sm	276	90.9	8.0	1.1	0	0
mp	388	78.9	16.2	4.4	0.3	0.3
ss/a_1	1,227	54.9	30.6	10.2	1.6	2.6
se/a_2	793	37.6	36.4	17.9	4.2	3.9
si/ai	134	44.8	28.4	14.2	4.5	8.2
Total	2,818	56.4	28.0	10.9	2.1	2.7
Rectum (Ra–Rb)						
sm	800	88.1	8.6	2.8	0.3	0.3
mp	1,377	74.3	19.0	5.1	1.5	0.2
ss/a_1	2,169	51.7	30.5	13.4	2.8	1.7
se/a_2	1,774	34.7	32.9	21.0	6.3	5.1
si/ai	322	37.6	26.1	17.7	13.7	5.0
Total	6,442	55.7	25.8	12.6	3.7	2.3
Anal canal (P)						
sm	13	84.6	7.7	7.7	0	0
mp	39	69.2	12.8	12.8	2.6	2.6
ss/a_1	38	65.8	18.4	13.2	2.6	0.0
se/a_2	61	42.6	8.2	32.8	14.8	1.6
si/ai	24	45.8	8.3	12.5	16.7	16.7
Total	175	57.1	11.4	19.4	8.6	3.4

National Registry of Patients with Cancer of the Colon and Rectum of the JSCCR: patients in fiscal years 1995–1998. Depth of invasion and the degree of lymph node metastasis were determined according to the rules set forth in the *Japanese Classification of Colorectal Carcinoma* (6th edition)

Comments

- The incidence of synchronous distant metastasis is shown in Table 6.
- Distant metastasis associated with peritoneal dissemination (CQ-5).

(1) Complete resection is desirable for P1.
(2) Complete resection is considered for P2 when easily resectable.
(3) The efficacy of resection of P3 has not been demonstrated.

Chapter 3: Treatment strategies for recurrent colorectal cancer (Fig. 4)

- The goal of treatment for recurrent colorectal cancer is to improve the prognosis and the patient's QOL.
- Treatment methods include surgery, systemic chemotherapy, arterial infusion chemotherapy, thermal coagulation therapy, and radiotherapy.
- An appropriate treatment method is selected with the informed consent of the patient in view of a variety of factors, such as the prognosis, complications, and QOL expected after treatment.

Table 4 Curative resection rate according to stage (lower rows: nos. of patients)

Stage	I	II	IIIa	IIIb	IV	All stages
All patients (C–P)	99.5%	97.0%	91.1%	79.7%	–	78.4%
	5,125	7,168	5,098	2,518	3,953	23,862
Colon (C–S)	99.7%	97.9%	92.2%	82.7%	–	78.1%
	2,838	4,609	2,924	1,436	2,567	14,374
Rectosigmoid (RS)	99.8%	96.2%	91.3%	82.2%	–	77.0%
	548	870	647	258	519	2,842
Rectum (Ra–Rb)	98.9%	95.5%	89.0%	74.7%	–	79.8%
	1,699	1,644	1,497	775	852	6,467
Anal canal (P)	100.0%	80.0%	80.0%	59.2%	–	72.1%
	40	45	30	49	15	179

National Registry of Patients with Cancer of the Colon and Rectum of the JSCCR: patients in fiscal years 1995–1998

Curative resection rate = number of patients with histological curability A cancer/total number of patients who underwent surgery

Staging was performed according to the rules set forth in the *Japanese Classification of Colorectal Carcinoma* (6th edition)

Table 5 Cumulative 5-year survival rate according to site (lower rows: nos. of patients)

Stage	0	I	II	IIIa	IIIb	IV	All stages
Cecum	90.2%	86.7%	81.4%	69.3%	59.5%	9.8%	63.7%
(C)	110	149	252	209	137	225	1,082
Ascending colon	96.3%	90.9%	83.7%	73.9%	57.3%	14.2%	68.3%
(A)	209	257	698	398	254	409	2,225
Transverse colon	94.5%	89.1%	82.6%	70.1%	60.1%	9.6%	67.8%
(T)	176	199	447	270	143	261	1,496
Descending colon	94.7%	90.3%	82.8%	70.9%	57.8%	18.5%	73.4%
(D)	129	151	267	152	67	115	881
Sigmoid colon	95.2%	91.4%	84.5%	81.4%	67.4%	16.6%	75.0%
(S)	559	1,149	1,373	879	394	781	5,135
Rectosigmoid	95.4%	94.6%	79.2%	71.2%	58.1%	11.6%	69.3%
(RS)	184	390	534	448	149	340	2,045
Upper rectum	94.2%	93.1%	77.7%	69.5%	53.7%	9.8%	68.8%
(Ra)	211	471	579	523	238	329	2,351
Lower rectum	92.2%	87.3%	75.2%	60.6%	43.7%	12.3%	66.9%
(Rb)	370	876	653	623	431	336	3,289
Anal canal	91.3%	92.2%	78.9%	43.7%	47.0%	10.2%	59.7%
(P)	12	31	36	32	33	24	168
Colon	94.8%	90.6%	83.6%	76.1%	62.1%	14.3%	71.4%
(C–S)	1,183	1,905	3,037	1,908	995	1,791	10,819
Rectum	92.9%	89.3%	76.4%	64.7%	47.1%	11.1%	67.7%
(Ra–Rb)	581	1,347	1,232	1,146	669	665	5,640
All sites	94.3%	90.6%	81.2%	71.4%	56.0%	13.2%	69.9%
(C–P)	1,960	3,673	4,839	3,534	1,846	2,820	18,672

National Registry of Patients with Cancer of the Colon and Rectum of the JSCCR: patients in fiscal years 1991–1994

Only adenocarcinomas (including mucinous carcinomas and signet-ring cell carcinomas) were counted

Survival rates were calculated by the life table method with death from any cause as an event

Lost to follow-up rate 2%; 5-year censoring rate 19%

Staging was performed according to the rules set forth in the *Japanese Classification of Colorectal Carcinoma* (6th edition)

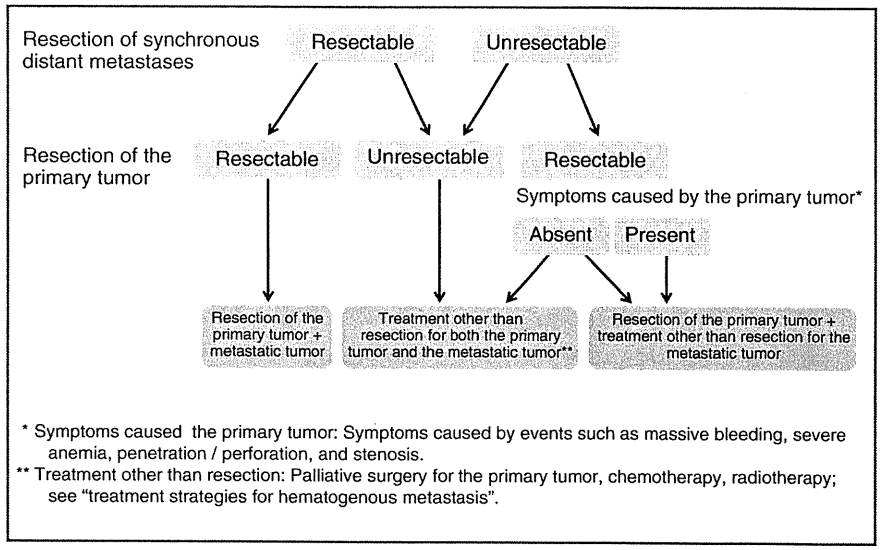


Fig. 3 Treatment strategies for stage IV colorectal cancer

Table 6 Incidence of synchronous distant metastasis of colorectal cancer

	Liver	Lung	Peritoneum	Other sites				
				Bone	Brain	Virchow	Other	Total
Colon cancer	11.4%	1.6%	6.4%	0.3%	0.1%	0.1%	0.4%	0.9%
No. of patients 15,528	1,777	242	993	44	9	19	64	136
Rectal cancer	9.5%	1.7%	3.0%	0.3%	0.1%	0.01%	0.5%	1.0%
No. of patients 10,563	1,002	180	314	36	8	1	57	102
Total no. of patients	10.7%	1.6%	5.0%	0.3%	0.1%	0.1%	0.5%	0.9%
26,091	2,779	422	1,307	80	17	20	121	238

National Registry of Patients with Cancer of the Colon and Rectum of the JSCCR: patients in fiscal years 1995–1998

- If recurrence is observed in a single organ and complete surgical resection of the recurrent tumor(s) is possible, resection is strongly considered.
- If recurrence is observed in more than a single organ, resection can be considered if the recurrent tumors in all of the organs are resectable [12, 13]; however, there is no consensus on the effects of treatment.
- Some authors believe that resection of liver or lung metastases should be performed only after a certain observation period to rule out occult metastases [14].
- Treatment methods for hematogenous metastases (see "Chapter 4: Treatment strategies for hematogenous metastases").
- Local recurrences of rectal cancer take the form of anastomotic recurrences and intrapelvic recurrences.

  (1) Resection is considered for resectable recurrences,
  (2) radiotherapy and systemic chemotherapy, either alone or in combination, are considered for unresectable recurrences.

Comments

[Local recurrence of rectal cancer]

- The extent of spread of the recurrent tumor is evaluated by diagnostic imaging, and resection is considered only for patients in whom complete resection can be expected, after taking into consideration such factors as the pattern of recurrence, symptoms, and physical findings (CQ-6).

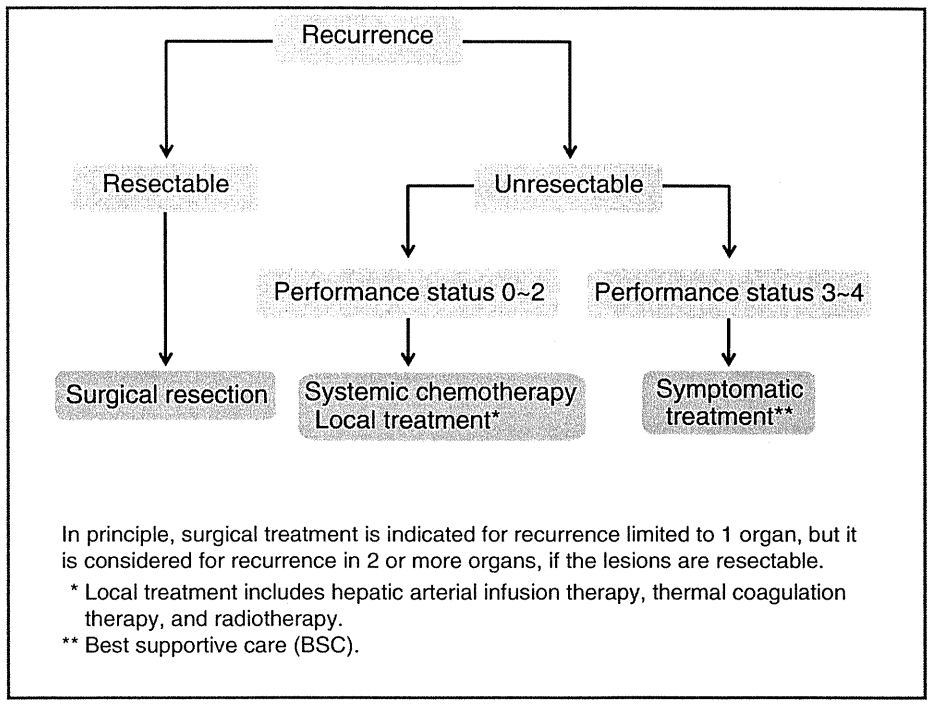


Fig. 4 Treatment strategies for recurrent colorectal cancer

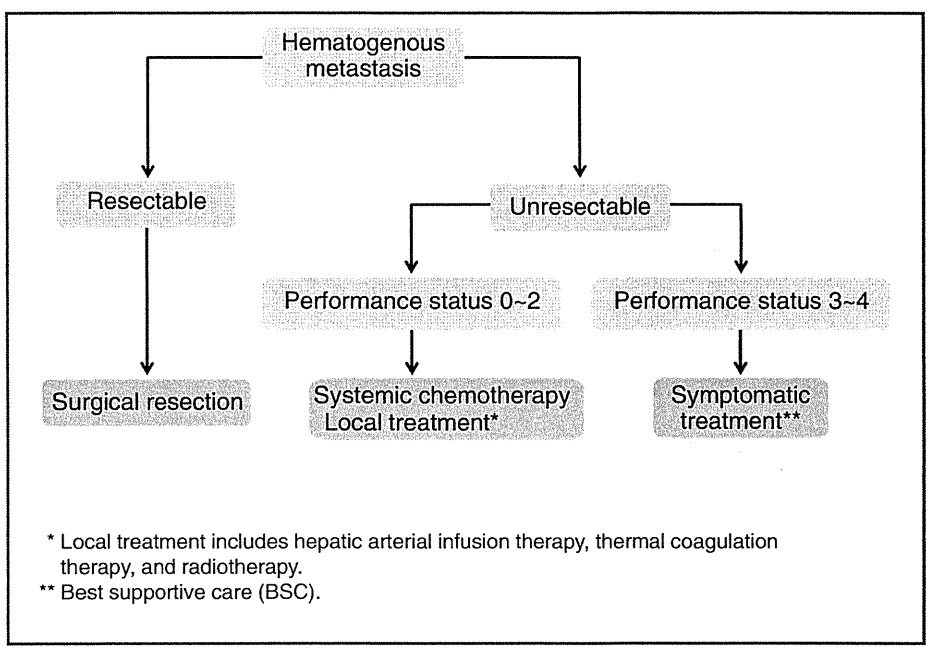


Fig. 5 Treatment strategies for hematogenous metastases

Chapter 4: Treatment strategies for hematogenous metastases (Fig. 5)

1. Treatment strategies for liver metastases

- Treatment of liver metastases is broadly divided into hepatectomy, systemic chemotherapy, hepatic arterial infusion therapy, and thermal coagulation therapy.
- Hepatectomy is recommended for liver metastases when curative resection is possible.
- Hepatectomy consists of systematic resection and partial (nonsystematic) resection.

Indication criteria for hepatectomy

(1) the patient is capable of tolerating surgery,
(2) the primary tumor has been controlled or can be controlled,

(3) the metastatic liver tumor can be completely resected,
(4) there are no extrahepatic metastases or they can be controlled,
(5) the function of the remaining liver will be adequate.

- Systemic chemotherapy and hepatic arterial infusion therapy, either alone or in combination, are considered for patients with unresectable liver metastases whose general condition can be maintained at a certain level or higher (PS 0 to PS 2).
- Thermal coagulation therapy consists of microwave coagulation therapy (MCT) and radiofrequency ablation (RFA).
- If the patient's general condition is poor (PS $\geq$ 3), best supportive care (BSC) is provided.

Comments
[Hepatectomy]

- There are reports showing the efficacy of hepatectomy in patients who have controllable extrahepatic metastases (mainly lung metastases) in addition to liver metastases [12, 13, 15, 16] (CQ-7).
- The efficacy of systemic chemotherapy and hepatic arterial infusion therapy after hepatectomy has not been established (CQ-8).
- The safety of preoperative chemotherapy for resectable liver metastases has not been established (CQ-9).

[Treatment methods other than resection]

- Systemic chemotherapy or hepatic arterial infusion therapy with anticancer drugs is performed alone or in combination for patients with unresectable liver metastases (CQ-10).

2. *Treatment strategies for lung metastases*

- Treatment of lung metastases consists of pulmonary resection and chemotherapy.
- Pulmonary resection is considered if the metastatic lung tumor is resectable.
- Pulmonary resection consists of systematic resection and partial (nonsystematic) resection.

Indication criteria for pulmonary resection
(1) The patient is capable of tolerating surgery,
(2) the primary tumor has been controlled or can be controlled,
(3) the metastatic lung tumor can be completely resected,
(4) there are no extrapulmonary metastases, or they can be controlled,
(5) the function of the remaining lung will be adequate.

- Systemic chemotherapy is considered for patients with unresectable lung metastases whose general condition can be maintained at a certain level or higher.
- Even if the patient cannot tolerate surgery, stereotactic radiotherapy is considered if the primary tumor and extrapulmonary metastases are controlled or can be controlled and the number of lung metastases is no more than three or four.
- If the patient's general condition is poor, appropriate BSC is provided.

3. *Treatment strategies for brain metastases*

- Brain metastases are often detected as a part of a systemic disease, and surgical therapy or radiotherapy is considered for lesions in which treatment can be expected to be effective.
- The optimal treatment method is selected after considering the patient's general condition and the status of other metastatic tumors, and evaluating the sizes and locations of metastatic tumors and the number of lesions.
- Radiotherapy is considered for patients with unresectable metastases.

[Surgical therapy]
Indications criteria for removal of brain metastases [17]

(1) The patient has a life expectancy of at least several months,
(2) resection will not cause significant neurologic symptoms,
(3) there are no metastases to other organs, or they can be controlled.

[Radiotherapy]

- The purpose of radiotherapy is to relieve symptoms, such as cranial nerve symptoms and intracranial hypertension symptoms, and to prolong survival time by reducing locoregional relapse.
- Whole-brain radiotherapy is considered for patients with multiple brain metastases and for patients with a solitary brain metastasis for which surgical resection is not indicated.
- Stereotactic irradiation is considered when the number of brain metastases is no more than three or four and the maximum diameter of each metastasis does not exceed 3 cm.

4. *Treatment strategies for hematogenous metastases to other organs*

- Resection is also considered for other hematogenous metastases, such as to the adrenal glands, skin, and

spleen, if they are resectable. However, patients with such metastases often have metastasis to more than one organ, and chemotherapy or radiotherapy is often indicated.

Chapter 5: Chemotherapy

- Chemotherapy consists of adjuvant chemotherapy to prevent postoperative recurrence and systemic chemotherapy to treat unresectable colorectal cancer.
- Commonly used anticancer drugs that have been approved for the indication of colorectal cancer and are covered by Japanese National Health Insurance are:

Oral drugs	5-FU, tegafur, UFT, doxifluridine (5′-DFUR), carmofur (HCFU), S-1, UFT + leucovorin (LV), capecitabine, etc.
Injection drugs	5-FU, mitomycin C, irinotecan (CPT-11), 5-FU + *l*-leucovorin (*l*-LV), oxaliplatin (L-OHP), bevacizumab, cetuximab, panitumumab, etc.

1. Adjuvant chemotherapy

- Postoperative adjuvant chemotherapy is systemic chemotherapy that is performed after surgery to prevent recurrence and improve the prognosis of patients who have undergone R0 resection [18].

General principles underlying the indications for systemic chemotherapy

(1) Stage III colorectal cancer (colon and rectal cancer) for which R0 resection has been performed
(2) The function of major organs is maintained

- Bone marrow: peripheral blood WBC count >4,000/mm^3; platelet count >100,000/mm^3.
- Liver function: total bilirubin <2.0 mg/dL; AST/ALT <100 IU/L.
- Renal function: serum creatinine concentration no higher than the upper limit of the normal at the institution.

(3) Performance status (PS) of 0 or 1 (CQ-11),
(4) the patient has recovered from postoperative complications, if any
(5) the patient has provided written informed consent,
(6) the patient has no serious complications (in particular: no intestinal obstruction, diarrhea, or fever).

- For patients who have stage II colorectal cancer with a high risk of recurrence, the indications for adjuvant chemotherapy are considered after obtaining informed consent [19, 20] (CQ-12).

Recommended therapies (listed in the order of the date of their coverage by Japanese National Health Insurance)

- 5-FU+*l*-LV
- UFT + LV
- Capecitabine
- FOLFOX4 or mFOLFOX6 (CQ-14)

Recommended administration period (CQ13)

- In principle, the administration period is 6 months.

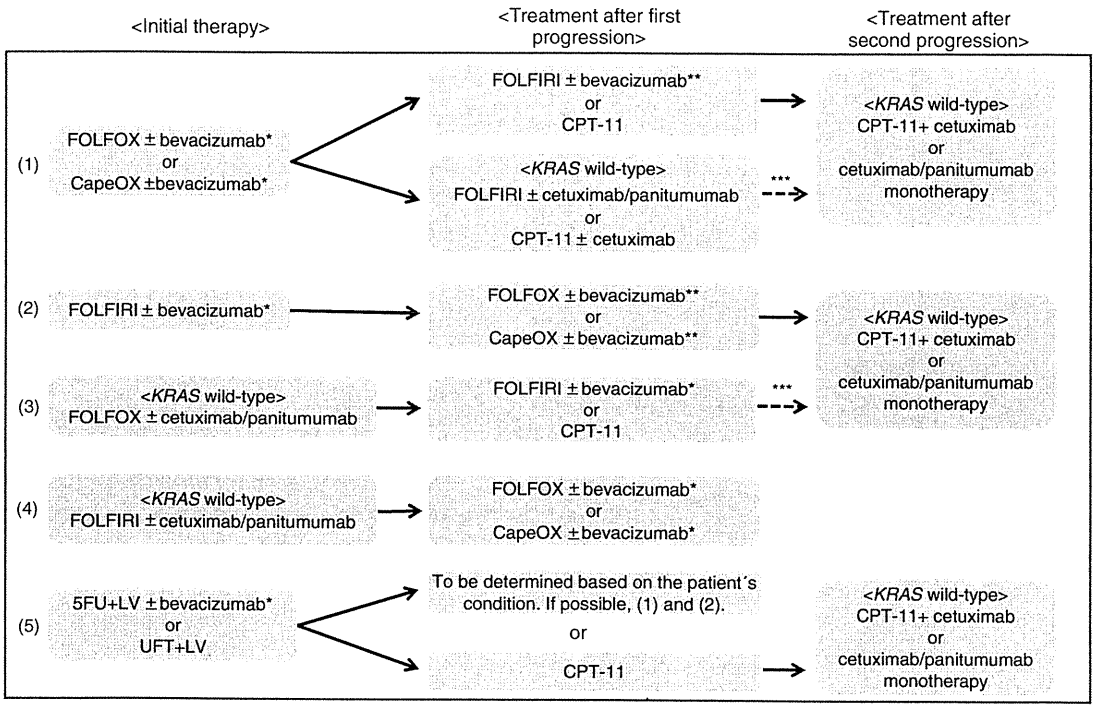
Comments

- Randomized controlled trials conducted in Europe and the United States have shown that the combination of intravenous infusion of 5-FU + LV and L-OHP (FOLFOX4 and FLOX) used as postoperative adjuvant chemotherapy for stage III colon cancer provides an additional benefit in terms of prevention of recurrence and survival time [21–24]. FOLFOX has also been approved in Japan for the postoperative adjuvant therapy of stage III colon cancer, and it became available in August 2009. Although combinations of oral anticancer drugs and L-OHP have been reported to be useful in Europe and the United States, as of July 2010 no such combinations had been approved in Japan [25] (CQ-14).

Note The Roswell Park Memorial Institute (RPMI) method of 5-FU + LV therapy as an adjuvant chemotherapy (drip infusion of *l*-LV 250 mg/m^2 administered for 2 h; intravenous infusion of 5-FU 500 mg/m^2 slowly administered within 3 min at 1 h after the start of administration of l-LV; once-weekly administration for 6 consecutive weeks followed by a 2-week rest period, 3 cycles every 8 weeks [26]).

2. Chemotherapy for unresectable colorectal cancer (Fig. 6)

- In the absence of chemotherapy, the median survival time (MST) of patients with unresectable colorectal cancer has been reported to be approximately 8 months. Although their MST has been extended to approximately 2 years as a result of recent chemotherapy, unresectable colorectal cancer is still difficult to cure.
- The purpose of chemotherapy is to prolong survival time and control symptoms by delaying tumor enlargement.
- Phase III clinical trials in PS 0 to PS 2 patients have shown significantly longer survival time in the chemotherapy



*: Administration of bevacizumab is recommended, but not when considered appropriate.
**: If bevacizumab was not administered as primary treatment, or if administration of bevacizumab was discontinued because of toxicity of CPT-11 and L-OHP even though the primary treatment was still effective, then, administration of bevacizumab is recommended as secondary treatment.
***: If anti-EGFR antibody drugs were not used in the secondary treatment.

Fig. 6 Chemotherapy for unresectable colorectal cancer

groups than in the best supportive care (BSC) groups that did not receive anticancer drugs [27–29].

- Unresectable colorectal cancer may become resectable after successful chemotherapy.

General principles underlying the indications for systemic chemotherapy

(1) The clinical diagnosis or histopathological diagnosis has been confirmed
(2) The metastatic or recurrent tumor can be confirmed by imaging
(3) Performance status (PS) is 0–2
(4) The function of major organs is maintained
   1. Bone marrow: peripheral blood WBC count >3,500/mm^3; platelet count >100,000/mm^3
   2. Liver function: total bilirubin <2.0 mg/dL; AST/ALT <100 IU/L
   3. Renal function: serum creatinine concentration no higher than the upper limit of the normal range at the institution
(5) The patient has provided written informed consent
(6) The patient has no serious complications (especially, no intestinal obstruction, diarrhea, or fever)

Initial therapy

- The following are regimens that have been shown to be useful in clinical trials and that are available as initial therapies covered by Japanese National Health Insurance.
- The usefulness of cetuximab and panitumumab has been demonstrated in KRAS wild-type tumors (CQ-16).

(1) FOLFOX[4] [30, 31] ± bevacizumab [32], CapeOX[5] ±bevacizumab [32, 33].
(2) FOLFIRI[6] [34, 35] ± bevacizumab [36, 37]
(3) FOLFOX ± cetuximab/panitumumab [38, 39]
(4) FOLFIRI ± cetuximab/panitumumab [40, 41]
(5) 5-FU + LV [42] ± bevacizumab [43, 44] or UFT + LV [45]

[4] FOLFOX is infusional 5-FU + LV + L-OHP.
[5] CapeOX is capecitabine + L-OHP.
[6] FOLFIRI is infusional 5-FU + LV + CPT-11.

Therapy after the first or second progression

- The following regimens are considered as chemotherapy for secondary or follow-up treatment (CQ-15).
- The usefulness of cetuximab and panitumumab has been demonstrated in KRAS wild-type tumors (CQ-16).

(a) For patients whose cancer has become resistant to a regimen that includes L-OHP:

(1) FOLFIRI [34] ± bevacizumab,
(2) FOLFIRI (or CPT-11 alone) ± cetuximab/panitumumab [46, 47].

(b) For patients whose cancer has become resistant to a regimen that includes CPT-11:

(1) FOLFOX [34, 48] ± bevacizumab [49], CapeOX^2 [50] ± bevacizumab,
(2) CPT-11 + cetuximab [51].

(c) For patients whose cancer has become resistant to a regimen that includes 5-FU, L-OHP, and CPT-11:

(1) CPT-11 + cetuximab [51],
(2) Cetuximab/panitumumab monotherapy [52–55].

Comments

- Careful attention must be paid when using CPT-11 to treat patients with constitutional jaundice, such as caused by Gilbert's syndrome, or to treat patients with high serum bilirubin values. Relationships between genetic polymorphisms of enzymes that metabolize CPT-11 and toxicity have been suggested (see "Side Memo 2").

Chapter 6: Radiotherapy

- Radiotherapy is used to treat patients with locally advanced rectal cancer, either as an adjuvant therapy after surgery to prevent recurrence, or before surgery to reduce tumor volume and preserve the anal sphincter, and also as palliative care to relieve the symptoms and prolong the survival times of patients with unresectable colorectal cancer who have symptomatic lesions.

1. Adjuvant radiotherapy

- Adjuvant radiotherapy is classified into three categories, according to the timing of surgery and radiation therapy: preoperative radiotherapy, intraoperative radiotherapy, and postoperative radiotherapy.
- The purpose of adjuvant radiotherapy is to improve the local control rate and the survival rate of rectal cancer patients. In addition the purpose of preoperative radiotherapy is to improve the anal sphincter preservation rate and resection rate.
- Preoperative radiotherapy is indicated for patients with T stage clinically diagnosed as "invasion depth cSS/cA or deeper or cN-positive;" postoperative radiotherapy is indicated for patients with T stage pathologically diagnosed after surgery as "invasion depth pSS/pA or deeper or pN-positive;" and intraoperative radiotherapy is indicated for surgical dissection plane positive (RM+) cancer or cancer with invasion close to the dissection plane (RM±).
- Radiotherapy is delivered with a linear accelerator, with electron beams being used for intraoperative radiotherapy and photon beams for external radiotherapy.

Comments

- Preoperative radiotherapy (CQ-17).

1. Preoperative radiotherapy has the following advantages: seeding during surgery can be prevented by inactivating lesions with irradiation; a high percentage of tumor cells are normo-oxic and radiosensitive, because blood flow to the tumor is maintained; the small bowel is not fixed within the pelvic cavity, thereby resulting in low radiation-induced delayed toxicity, which means less toxic than postoperative setting; improvements in the resection rate and anal sphincter preservation can be expected because of tumor size reduction [56].
2. Preoperative radiotherapy has the following disadvantages: early-stage patients may be subjected to overtreatment and postoperative complications may increase.
3. Twelve phase III clinical trials of preoperative radiotherapy (without chemotherapy) have been reported [56], and in 5 of the 12 trials the local control rate in the group that received preoperative radiotherapy was significantly higher than that in the surgery-alone group. However, an improvement in the survival rate was observed in only 1 trial [57].
4. Two meta-analyses of radiotherapy showed improvement in the local control rate and improvement in the survival rate in the groups that received doses of 30 Gy or more. However, there is controversy as to whether there is improvement in the survival rate [58, 59].
5. Trials of short-course radiotherapy with 5 Gy per fraction have been conducted, mainly in Europe [57, 60]. Because the late effects of radiation depend on the fraction size, long-term follow-up for late adverse effects, such as anal dysfunction and bowel dysfunction, is necessary.
6. In the Dutch CKVO 95-04 trial, which compared preoperative radiotherapy (25 Gy delivered in five

fractions in 1 week) + TME with TME alone to investigate the significance of adding short-course radiotherapy to TME, the 5-year local control rate was significantly higher in the combination therapy group but there was no significant difference between the two groups in the 5-year survival rate [60, 61]. The incidences of sexual dysfunction and bowel dysfunction were higher in the preoperative radiation combination therapy group than in the surgery-alone group [62, 63].

7. The effect of preoperative radiotherapy in reducing the size of the primary tumor may enable sphincter preservation. When the purpose of the preoperative radiotherapy is sphincter preservation, it is recommended to perform surgery after allowing an appropriate period for the tumor to decrease in size (6–8 weeks after the completion of radiotherapy) [64].
8. In Europe, three phase III clinical trials, including the EORTC trial, were performed to investigate the usefulness of adding chemotherapy to preoperative radiotherapy. The incidence of acute-phase adverse events was significantly higher in the preoperative chemoradiotherapy groups, but the pathologic complete response rates (pCR) were significantly higher than in the preoperative radiotherapy alone groups. In two trials (the exception being the short-course radiotherapy trial), the local recurrence rate was significantly lower in the preoperative chemoradiotherapy group, and there was no significant difference between the two groups in terms of sphincter preservation or survival rate [65–67].
9. In a phase III clinical trial that compared preoperative chemoradiotherapy and postoperative chemoradiotherapy, there was no significant difference in the 5-year survival rate, but the local recurrence rate and incidence of grade 3 or higher adverse events were significantly lower in the preoperative chemoradiotherapy group. Among the patients in whom abdominoperineal resection (APR) was considered necessary at the time of enrollment, the percentage of patients in whom sphincter preservation was possible was significantly higher in the preoperative chemoradiotherapy group [68].

2. Palliative radiotherapy

a. Intrapelvic lesions (CQ-18)

- The purpose of palliative radiotherapy for intrapelvic lesions is to relieve symptoms such as pain, hemorrhage, and bowel movement disorders caused by intrapelvic tumors.
- The target volume includes the tumor that is causing the symptoms.

[Dose and fractionation]

- A total dose of 45–50 Gy is administered in 1.8–2.0 Gy per fraction.
- Depending on the patient's general condition, such as performance status, and the severity of the symptoms, radiotherapy may be completed in a shorter term with a larger fraction size, for example 30 Gy in 10 fractions over 2 weeks.

b. Extrapelvic lesions

(1) Bone metastases

- The purpose of palliative radiotherapy for bone metastases is to achieve pain relief, prevent pathological fractures, and prevent and treat spinal cord paralysis.
- The target volume includes the metastatic bone lesions causing the symptoms.

[Dose and fractionation]

- Local field radiotherapy, such as 30 Gy in 10 fractions and 20 Gy in 5 fractions, is widely performed.

(2) Brain metastases

- See "Chapter 4: Treatment strategies for hematogenous metastases."

[Dose and fractionation]

- When whole brain radiotherapy is performed, 30 Gy in 10 fractions is the standard treatment. If long-term survival is expected, prolonged fractionated radiotherapy, such as 37.5 Gy in 15 fractions and 40 Gy in 20 fractions, is considered.
- When stereotactic radiosurgery is performed, a peripheral dose of 16–25 Gy is delivered in a single fraction.

Chapter 7: Palliative care

- Palliative care is a general term for palliative treatment of various mental and physical symptoms related to cancer.
- Palliative care extends from the time the diagnosis of cancer is made to the end stage, and the care provided should depend on the disease stage and symptoms.
- In principle, cancer treatment should be performed under conditions in which symptom relief is achieved [69], and palliative care should be started at the same time as surgical treatment and chemotherapy.
- Palliative care to improve the QOL of patients with end-stage colorectal cancer includes:

  (1) pain relief,
  (2) surgical treatment,

No. of years and months after surgery	1 year				2 years				3 years				4 years				5 years			
	3m	6	9	12	3	6	9	12	3	6	9	12	3	6	9	12	3	6	9	12
Colon cancer and RS cancer																				
Interview and examination	●	●	●	●	●	●	●	●	●	●	●	●		●		●		●		●
Tumor marker	●	●	●	●	●	●	●	●	●	●	●	●		●		●		●		●
Chest CT		●		●		●		●		●		●		○		●		○		●
Abdominal CT		●		●		●		●		●		●		○		●		○		●
Colonoscopy				●								●								
Rectal cancer																				
Interview and examination	●	●	●	●	●	●	●	●	●	●	●	●		●		●		●		●
Tumor marker	●	●	●	●	●	●	●	●	●	●	●	●		●		●		●		●
Digital rectal examination		●		●		●		●		●		●								
Chest CT		●		●		●		●		●		●		○		●		○		●
Abdominal and pelvic CT		●		●		●		●		●		●		○		●		○		●
Colonoscopy				●				●				●								

●: Performed for Stage I to Stage III colorectal cancer.
○: Performed for Stage III colorectal cancer. Can be omitted in Stage I and Stage II colorectal cancer.
Diagnostic imaging of the chest: CT is desirable, but plain chest X-ray is acceptable.
Diagnostic imaging of the abdomen: CT is desirable, but abdominal ultrasound is acceptable.

Fig. 7 An example of a surveillance schedule after curative resection of stage I to stage III colorectal cancer

(3) chemotherapy,
(4) radiotherapy,
(5) counseling for psychiatric symptoms.

Chapter 8: Surveillance after surgery for colorectal cancer

1. Surveillance for recurrence after curability A resection of colorectal cancer

- Surveillance is not required for stage 0 (pM cancer) if the resection margin is cancer-free. However, when evaluation of the resection margin is difficult, colonoscopy is performed 6 months to 1 year later to determine whether local recurrence is present.
- In principle, the duration of surveillance is 5 years after surgery, but the surveillance examinations are scheduled at shorter intervals during the first 3 years after surgery.
- It should be noted that there is a high incidence of lung metastasis and local recurrence after surgery for rectal cancer.
- As a general rule, the duration of surveillance for anastomotic recurrence is until 3 years after surgery.
- The following is an example of a surveillance schedule after curative resection of stage I to stage III colorectal cancer that was designed on the basis of the results of a retrospective investigation of factors such as the common sites and the incidence of recurrence and the efficacy of treatment (Fig. 7).

2. Surveillance after curability B resection of colorectal cancer and after resection of recurrent tumors

- The same surveillance method as for stage III colorectal cancer is used. It should be noted that recurrence and re-recurrence are common in organs that were previously operated on.

3. Surveillance of metachronous multiple cancer

- Colonoscopy is performed for surveillance of metachronous multicentric colorectal cancer.

Comments
[Aim of surveillance]

- The aim of surveillance is to improve the patient's prognosis by early detection and treatment of recurrences. Meta-analyses of RCTs conducted in Europe and the United States have shown that surveillance after curative surgical resection of colorectal cancer contributes to improving the resection rate of recurrent tumors and to improving the prognosis [70–74] (CQ-19).

[Recurrence rate, sites of recurrence, times of recurrence]

- The results of a review of the project study by the JSCCR are shown in Figs. 8, 9 and Tables 7, 8, 9, 10. The subjects were patients who underwent curative resection of colorectal cancer between 1991 and 1996 at the 14 institutions that participated in the project, and the follow-up period was 6–11 years.

(1) Times of the recurrences and sites of the recurrences (Fig. 9; Tables 7, 9, 10).

- More than 80% of the recurrences were detected within 3 years after surgery, and more than 95% of the recurrences were detected within 5 years after surgery.
- The overall incidence of recurrence more than 5 years after surgery was less than 1%.
- Among lung recurrences, 5% of recurrences were detected more than 5 years after surgery.

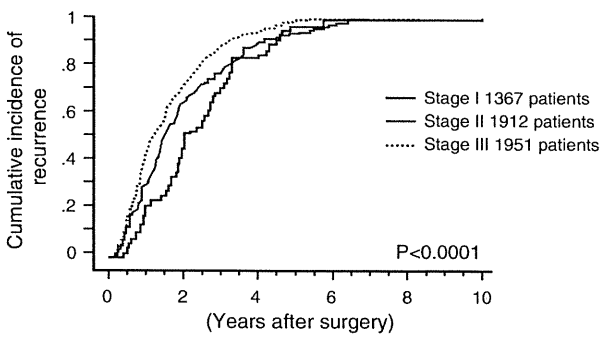


Fig. 8 Graph of the cumulative incidence of recurrence according to stage. (Project study by the JSCCR: patients in years 1991–1996)

- More than 95% of the anastomotic recurrences were detected within 3 years after surgery.
- Local recurrence and lung recurrence were more frequent in rectal cancer than in colon cancer.
- There have been reports regarding recurrences after curative resection in Europe and the United States showing that approximately 50% of the recurrences were detected within 1 year after surgery, that approximately 70% of the recurrences were detected within 2 years after surgery [75, 76]; and that in most patients the recurrences were detected within 5 years after surgery [76].

(2) Characteristics according to stage (Fig. 8; Tables 7, 8)

1. Stage I

- The recurrence rate of pSM cancer was approximately 1% in both colon cancer and rectal cancer.
- The overall recurrence rate of pMP cancer was 6.4%, and it was 5.0% in colon cancer and 8.3% in rectal cancer.
- Two-thirds of the recurrences were detected within 3 years after surgery, and the overall incidence of recurrence more than 5 years after surgery was less than 0.2% among all patients.

2. Stage II, Stage IIIa, and Stage IIIb

- The recurrence rate increased with the stage.
- 78–90% of recurrences were detected within 3 years after surgery, and the overall incidence of recurrence more than 5 years after surgery was less than 1% among all patients.

Fig. 9 Graphs of the cumulative incidence of recurrence according to the site of recurrence. (Project study by the JSCCR: patients in years 1991–1996)

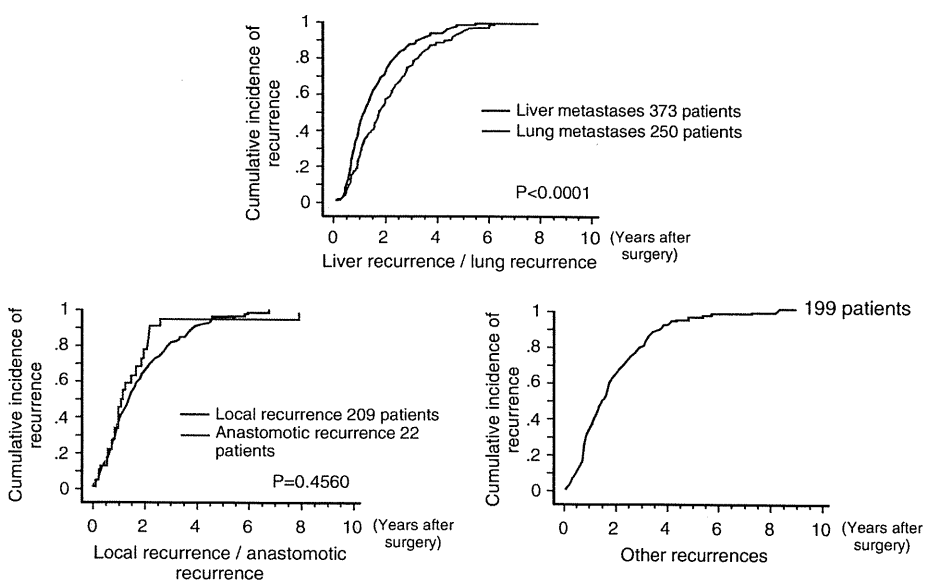


Table 7 Recurrence rate after curative resection of colorectal cancer according to stage and cumulative incidence of recurrence according to the number of years after surgery

Stage (no. of patients)	Recurrence rate (no. of patients with recurrence)	Cumulative incidence of recurrence according to the number of years after surgery (cumulative no. of patients with recurrence)			Percentage of patients experiencing recurrence more than 5 years after surgery among all patients (no. of patients)
		3 years	4 years	5 years	
I	3.7%	68.6%	82.4%	96.1%	0.15%
(1,367)	(51)	(35)	(42)	(49)	(2)
II	13.3%	76.9%	88.2%	92.9%	0.94%
(1,912)	(255)	(196)	(225)	(237)	(18)
III	30.8%	87.0%	93.8%	97.8%	0.67%
(1,957)	(600)	(522)	(563)	(587)	(13)
All	17.3%	83.2%	91.6%	96.4%	0.63%
(5,230)	(906)	(753)	(830)	(873)	(33)

Project study of the JSCCR: patients in years 1991–1996

Table 8 Recurrence rate of stage I colorectal cancer (RS cancer was counted as colon cancer)

Stage I	No. of patients	No. of patients with recurrence	Recurrence rate (%)	*p* value
Tumor location				
Colon	891	24	2.7	0.0056
Rectum	476	27	5.7	
Depth of tumor invasion				
SM	714	9	1.3	<0.0001
MP	653	42	6.4	
Tumor location and depth of tumor invasion				
Colon				
SM	528	7	1.3	0.0024
MP	363	17	4.7	
Rectum				
SM	186	2	1.1	0.0005
MP	290	25	8.6	

Project study of the JSCCR: patients in years 1991–1996

Table 9 Recurrence rate according to the site of the first recurrence after curative resection of colorectal cancer and cumulative incidence of recurrence according to the number of years after surgery

Site of first recurrence	Recurrence rate (no. of patients with recurrence (including overlaps)	Cumulative incidence of recurrence according to the number of years after surgery (cumulative no. of patients with recurrence)			Percentage of patients experiencing recurrence more than 5 years after surgery among all patients (no. of patients)
		3 years	4 years	5 years	
Liver	7.1% (373)	87.9% (328)	94.1% (351)	98.7% (368)	0.10% (5)
Lung	4.8% (250)	78.0% (195)	88.8% (222)	94.8% (237)	0.25% (13)
Local	4.0% (209)	80.9% (169)	90.4% (189)	96.2% (201)	0.15% (8)
Anastomotic	0.4% (22)	95.5% (21)	95.5% (21)	95.5% (21)	0.02% (1)
Other	3.8% (199)	79.4% (158)	91.0% (181)	95.5% (190)	0.17% (9)
All (5,230)	17.3% (906)				

Project study of the JSCCR: patients in years 1991–1996

Table 10 Comparison between the recurrence rates of colon cancer and rectal cancer according to the site of the first recurrence (RS cancer was counted as colon cancer)

Project study of the JSCCR: patients in years 1991–1996

Site of recurrence	Colon cancer (3,583 patients)	Rectal cancer (1,647 patients)	*p* value
Liver	7.0% (252)	7.3% (121)	NS
Lung	3.5% (126)	7.5% (124)	<0.0001
Local	1.8% (64)	8.8% (145)	0.0001
Anastomotic	0.3% (9)	0.8% (13)	0.0052
Other	3.6% (130)	4.2% (69)	NS
All	14.1% (506)	24.3% (400)	<0.0001

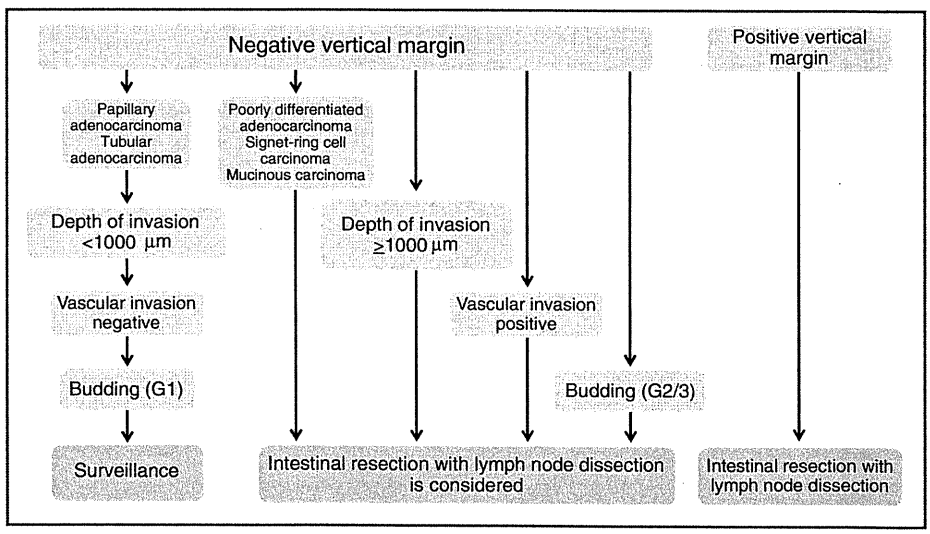


Fig. 10 Treatment strategies for pSM cancer after endoscopic resection

[Surveillance of metachronous multiple primary cancer]

- A past medical history of colorectal cancer, regardless of stage, is a risk factor for metachronous colorectal cancer [77].
- The recommended interval between colonoscopy ranged from 1 to 5 years, depending on the report [78].
- There was no evidence indicating the necessity of periodic detailed examinations for cancer in other organs (multiple cancer) after surgery for colorectal cancer (CQ-19).

Clinical questions

CQ-1: Indication criteria for additional treatment after endoscopic resection (Fig. 10)

Recommendation: Category B

- Surgical resection is preferable when the vertical margin is positive.
- If any of the following findings is observed during histological examination of the resected specimen, intestinal resection with lymph node dissection is considered as an additional treatment:

(1) Depth of SM invasion ≥1,000 μm,
(2) vascular invasion positive,
(3) poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma [79],
(4) Grade 2/3 budding at the site of deepest invasion [79].

Note:

- "Vertical margin-positive" means that carcinoma is exposed at the submucosal margin of the resected specimen.
- Depth of SM invasion is measured by the method described in "Side Memo 1" (Fig. 11).
- Vascular invasion consists of lymphatic and venous invasion (Figs. 12, 13, 14).
- The method for assessing budding is described in Fig. 15.

The principle for the treatment of pSM carcinomas, which are invasive carcinomas, is intestinal resection with lymph node dissection. However, some pSM carcinomas have a very low risk of metastasis, and the purpose of these

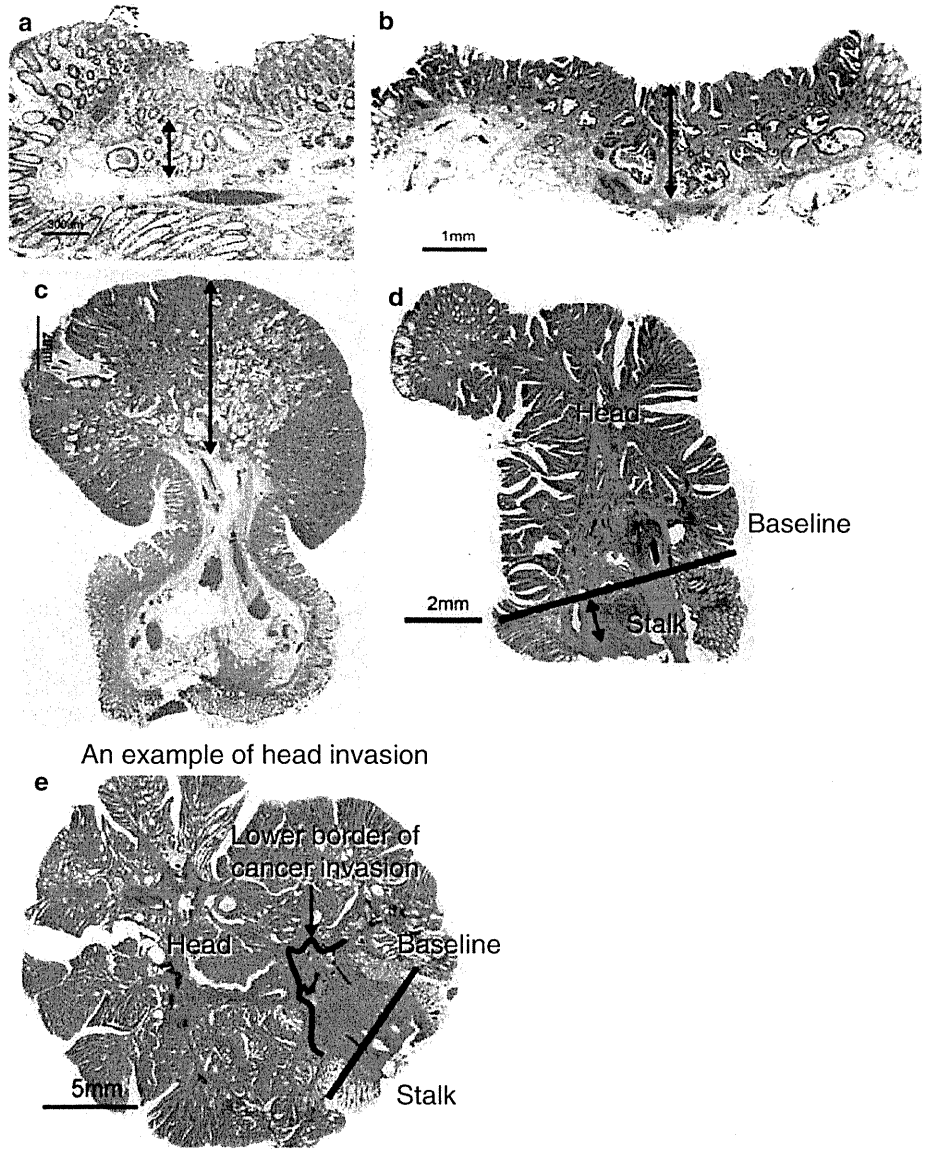


Fig. 11 Method for measuring depth of SM invasion. **a** When it is possible to identify or estimate the location of the muscularis mucosae, depth of SM invasion is measured from the lower border of the muscularis mucosae. **b**, **c** When it is not possible to identify or estimate the location of the muscularis mucosae, depth of SM invasion is measured from the surface layer of the muscularis mucosae. Sessile lesion (**b**), pedunculated lesion (**c**). **d** For pedunculated lesions with tangled muscularis mucosae, depth of SM invasion is measured as the distance between the point of deepest invasion and the reference line, which is defined as the boundary between the tumor head and the stalk. **e** Invasion by pedunculated lesions that is limited to within the head is defined as "head invasion."

criteria is to minimize the need for additional resections that eventually result in overtreatment of such patients. While no diagnostic methods make it possible to predict lymph node metastasis (pN) without fail, the degree of risk of metastasis can be used as a basis for determining whether or not to perform additional treatment.

Factors such as the depth of submucosal invasion (SM invasion depth) [80], histological type (such as poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous carcinoma [79]), the presence of a poorly differentiated area and muconodules at the site of deepest invasion, budding, and vascular invasion have been reported to be risk factors for regional lymph node metastasis by pSM carcinoma [79, 81].

The above criteria for determining whether additional treatment is indicated were prepared based on the following 3 criteria for performing additional intestinal resection of pSM carcinoma described in the *Japanese Classification of Colorectal Carcinoma* (2nd edition, 1980): (1) obvious intravascular carcinoma invasion; (2) poorly differentiated adenocarcinoma or undifferentiated carcinoma; (3) massive carcinoma invasion extending to the vicinity of the margin [82]. The description of "massive carcinoma invasion" in the 4th edition of the *Japanese Classification of Colorectal Carcinoma* was revised to the following more specific description in the 5th edition (1994): invasion deeper than "very shallow invasion" (e.g., invasion exceeding approximately 200 to 300 μm) [83].

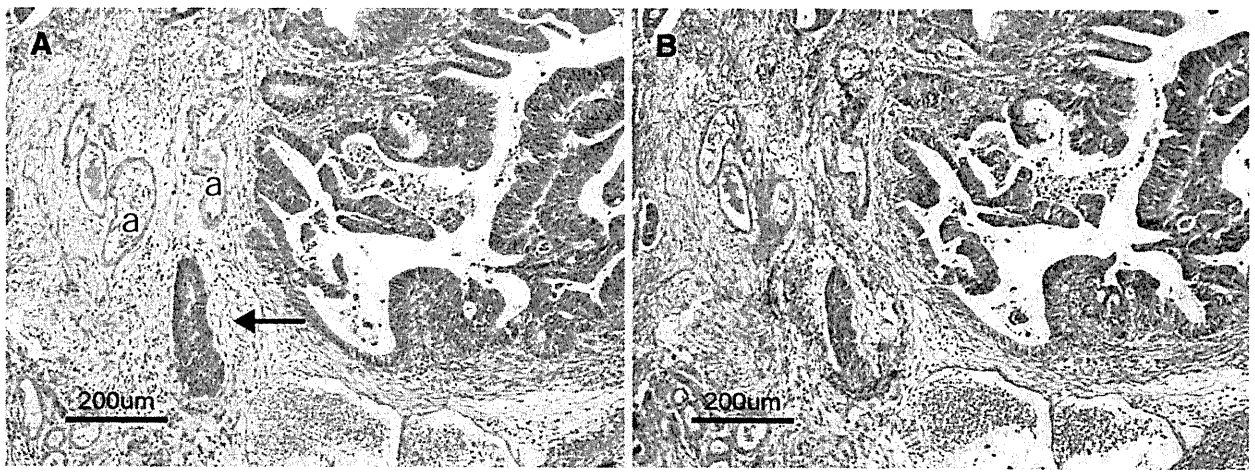


Fig. 12 Venous invasion (*arrow* in **a**). **a** Located in the vicinity of an artery (*a*). **b** Elastic fibers in the vein wall have been highlighted by Victoria blue staining

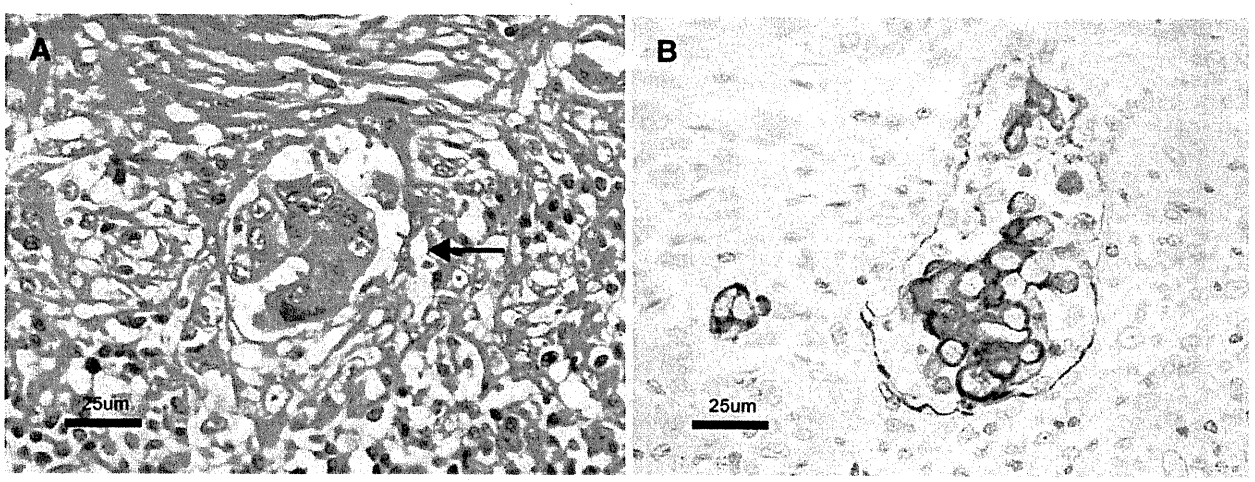


Fig. 13 Lymphatic invasion (*arrow* in **a**). **a** A cancer cell nest is visible in the interstitial space. **b** Double staining for cytokeratin and D2-40. Cancer cells are stained *brown*, and the lymphatic endothelium is stained *purplish red*

Subsequent case series studies in Japan have shown that "200–300 μm" can be extended to 1,000 μm [84]. According to the results of the project study by the JSCCR, the lymph node metastasis rate of colorectal carcinoma with an SM invasion depth of 1,000 μm or more was 12.5% (Table 11) [80, 84]. However, approximately 90% of patients with a depth of invasion of 1,000 μm or more did not have lymph node metastasis, and it is important to determine whether additional treatment is indicated after sufficiently considering other factors in addition to depth of SM invasion, such as whether other risk factors for lymph node metastasis are present, the physical and social background of the patient, and the patient's wishes. Because budding was demonstrated to be an important risk factor for lymph node metastases in the project study by the JSCCR, additional intestinal resection has been added to the list of factors that should be considered in this revised edition. None of the guidelines in other countries include depth of invasion or budding as criteria for additional treatment.

CQ-2: Endoscopic resection of cM carcinomas and cSM carcinomas with a maximum diameter of 2 cm or greater

Recommendation: Category B

- Accurate preoperative endoscopic diagnosis is essential, and whether resection by EMR, piecemeal EMR, or ESD is indicated is determined after taking the operator's skill in performing endoscopic resection into consideration.