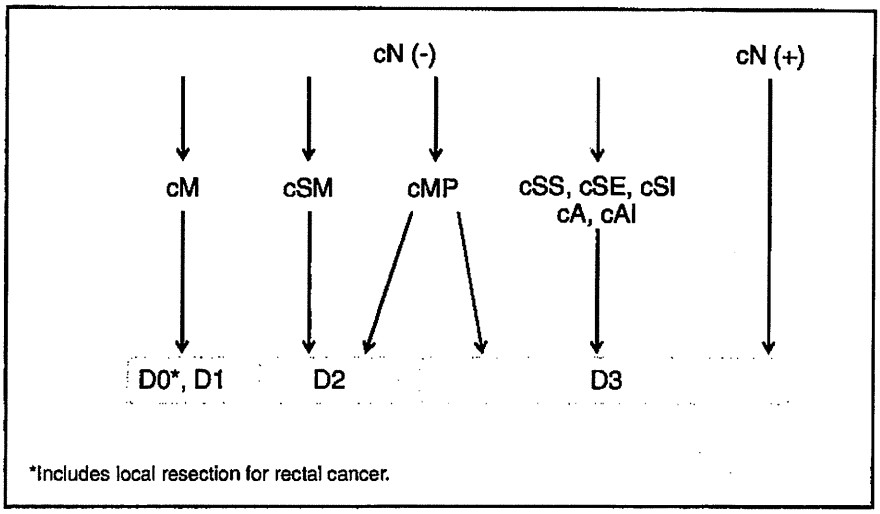


Fig. 2 Surgical treatment strategies for stage 0 to stage III colorectal cancer

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)

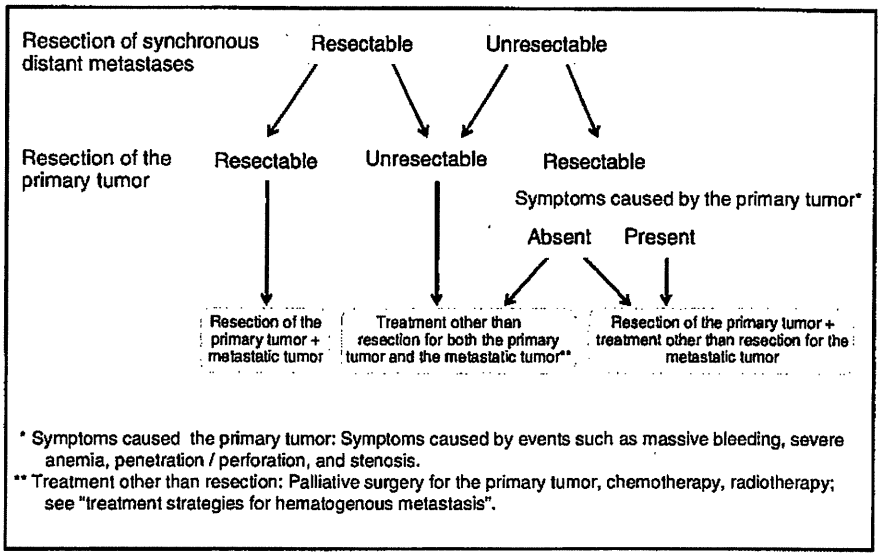


Fig. 3 Treatment strategies for stage IV colorectal cancer

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).

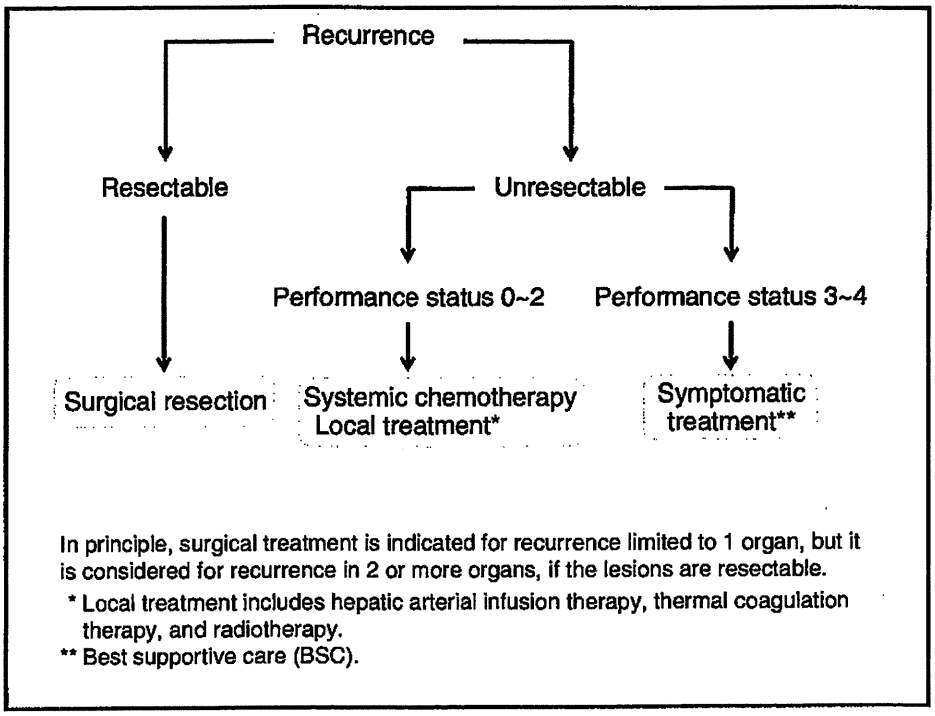


Fig. 4 Treatment strategies for recurrent colorectal cancer

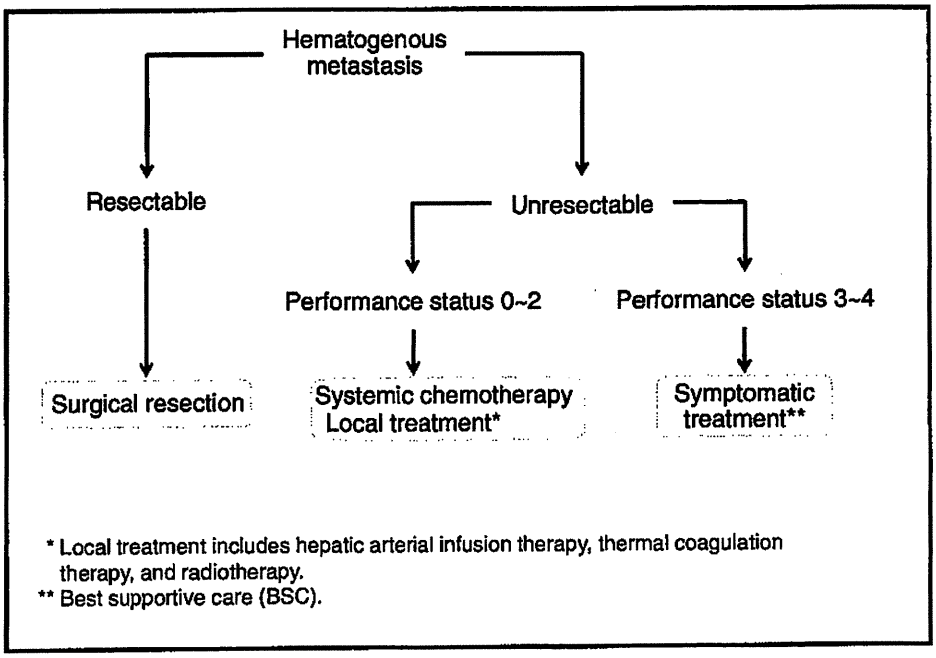


Fig. 5 Treatment strategies for hematogenous metastases

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.

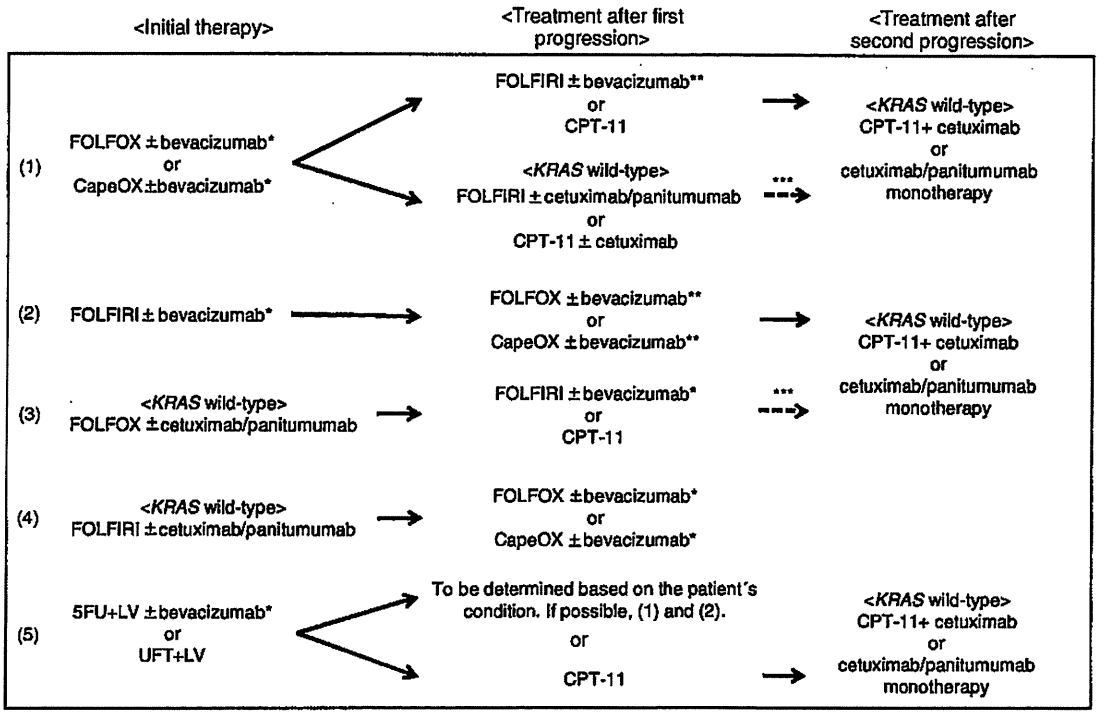
Comments

- 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.

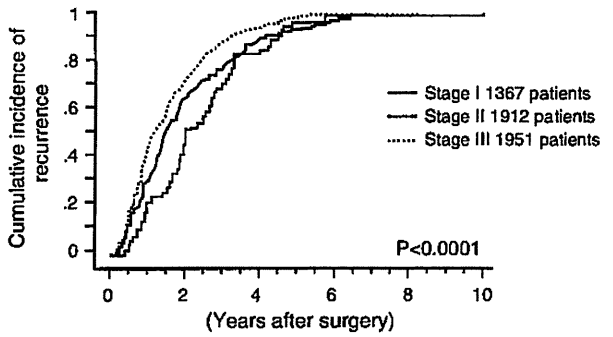


Fig. 8 Graph of the cumulative incidence of recurrence according to stage. (Project study by the JSCCR: patients in years 1991–1996)

- 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)

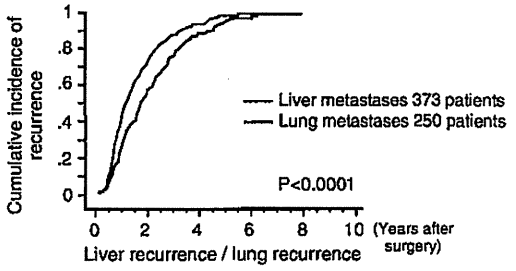
1. Stage I

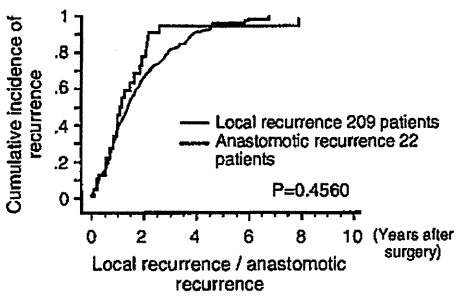
- The recurrence rate of pSM cancer was approximately 1% in both colon cancer and rectal cancer.
- The overall recurrence rate of pMP cancer was 6.4%, and it was 5.0% in colon cancer and 8.3% in rectal cancer.
- Two-thirds of the recurrences were detected within 3 years after surgery, and the overall 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)





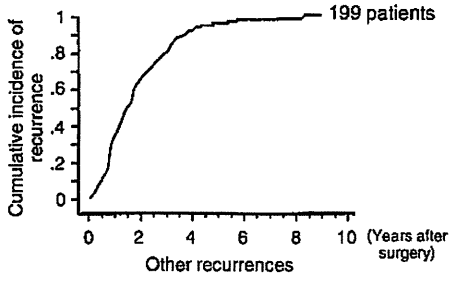


Table 7 Recurrence rate after curative resection of colorectal cancer according to stage and cumulative incidence of recurrence according to the number of years after surgery

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

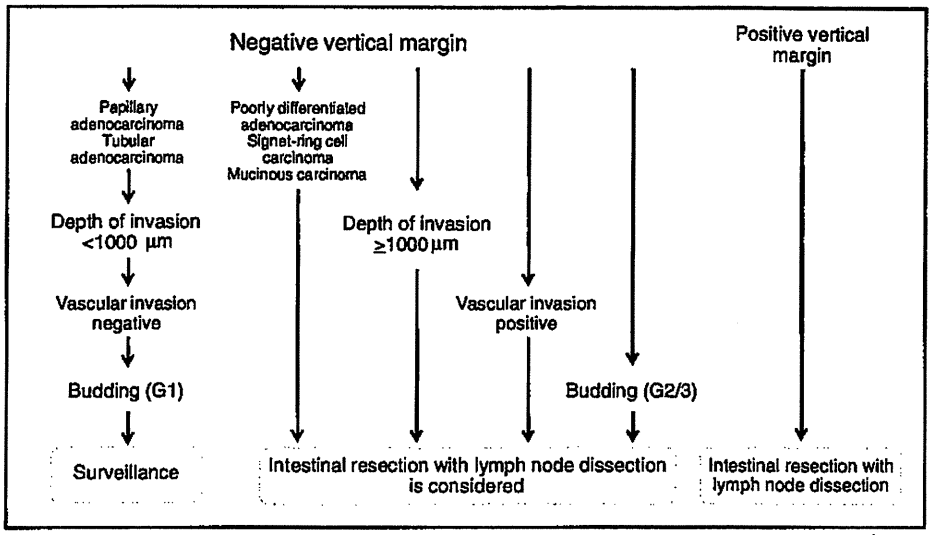


Fig. 10 Treatment strategies for pSM cancer after endoscopic resection

[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

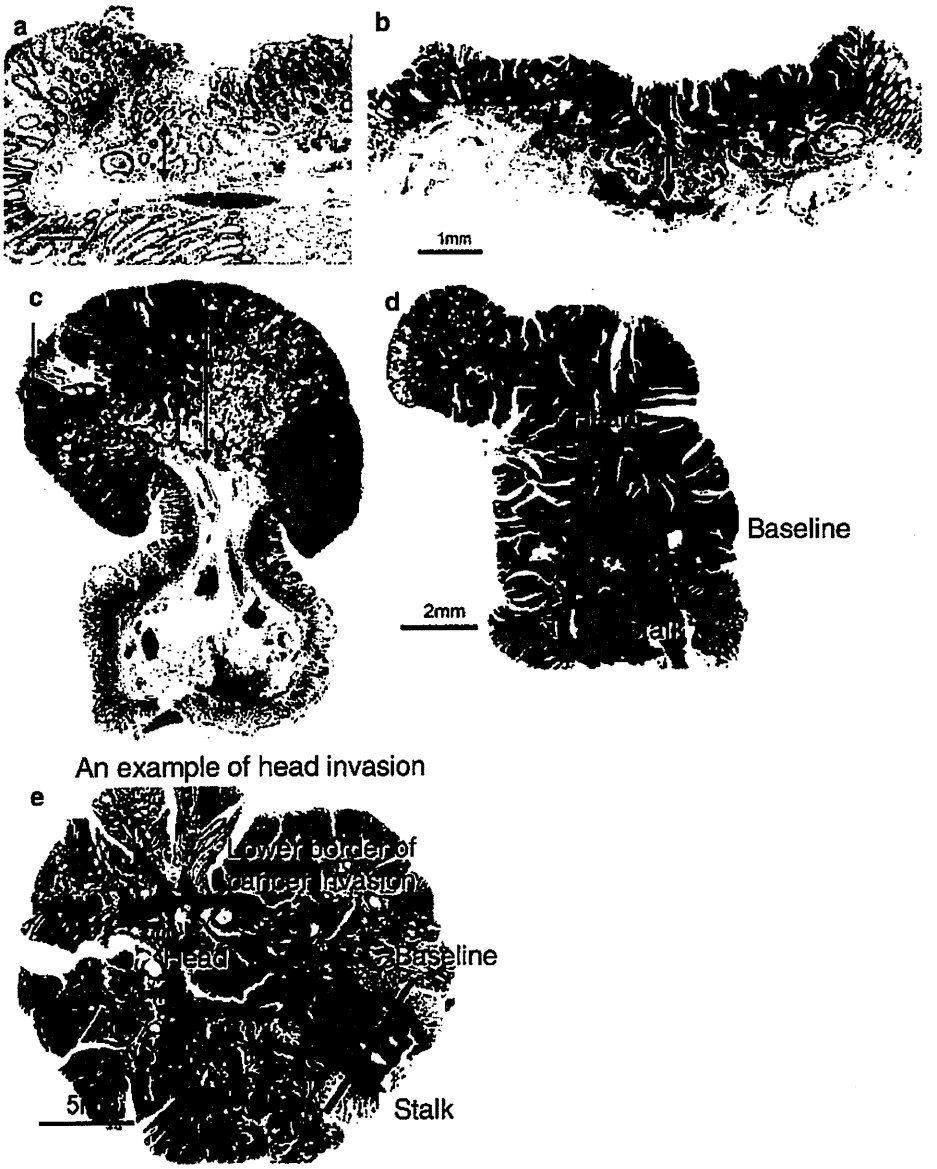


Fig. 11 Method for measuring depth of SM invasion. **a** When it is possible to identify or estimate the location of the muscularis mucosae, depth of SM invasion is measured from the lower border of the muscularis mucosae. **b, c** When it is not possible to identify or estimate the location of the muscularis 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

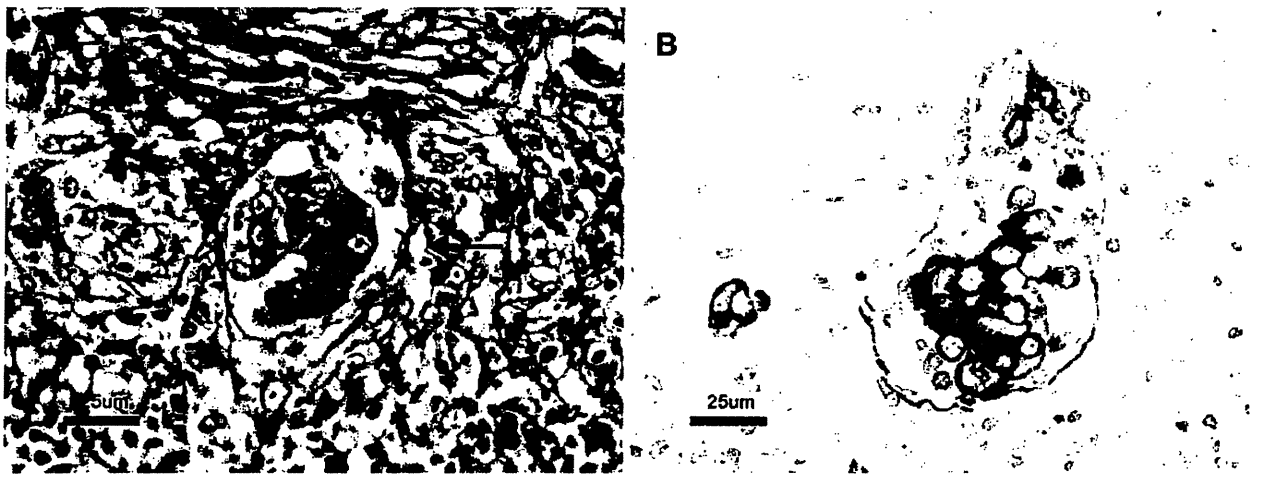


Fig. 13 Lymphatic invasion (*arrow* in a). **a** A cancer cell nest is visible in the interstitial space. **b** Double staining for cytokeratin and D2-40. Cancer cells are stained *brown*, and the lymphatic endothelium is stained *purplish red*

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.

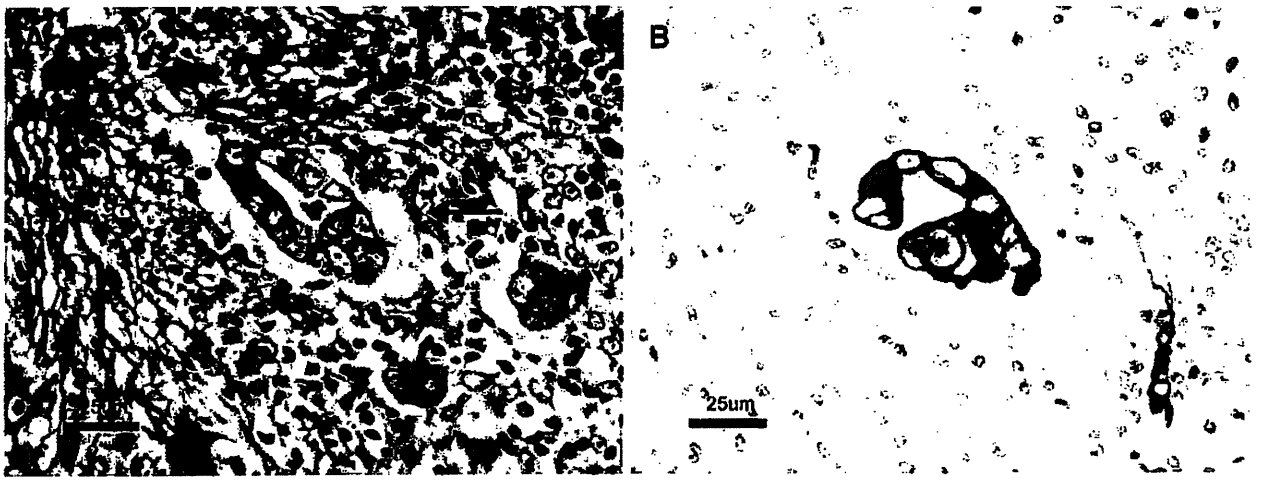


Fig. 14 Space formed by artifacts during preparation of the specimen (*arrow* in a). a A cancer cell nest is visible in the interstitial space. b Double staining for cytokeratin and D2-40. The interstitial space is D2-40-negative

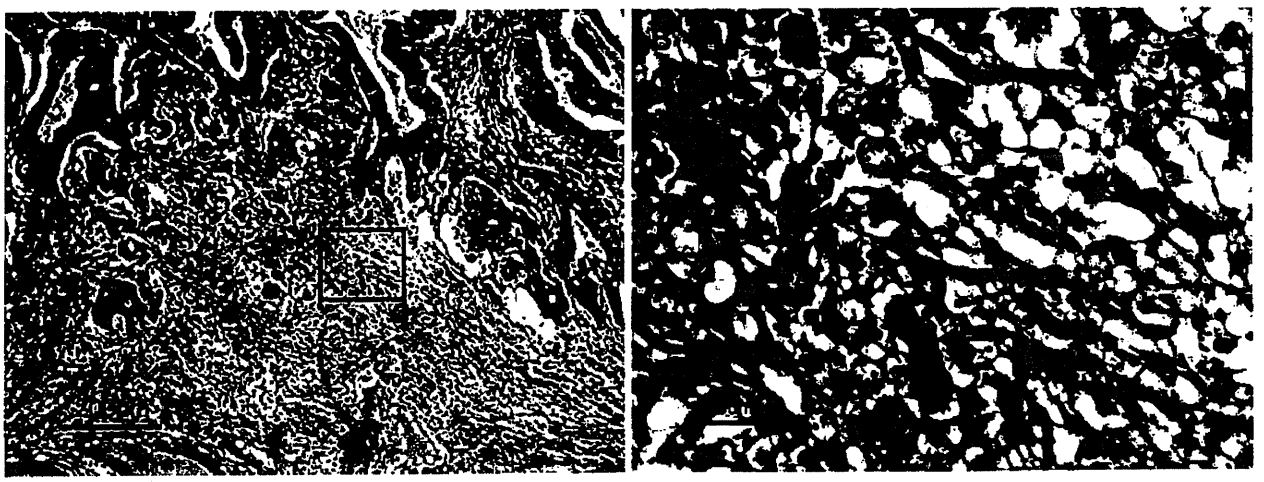


Fig. 15 Budding (*arrows* in b). a A cancer cell nest consisting of 1 or less than 5 cells that has infiltrated the interstitium at the invasive margin of the cancer is seen. b is the square area in a

Table 11 Depth of invasion of sm cancer and lymph node metastasis (modified from [80])

sm invasion distance (μm)	Pedunculated		Nonpedunculated	
	Number of lesions	*n* (+) (%)	Number of lesions	*n* (+) (%)
Head invasion	53	3 (5.7)		
$0 < X < 500$	10	0 (0)	65	0 (0)
$500 \leq X < 1{,}000$	7	0 (0)	58	0 (0)
$1{,}000 \leq X < 1{,}500$	11	1 (9.1)	52	6 (11.5)
$1{,}500 \leq X < 2{,}000$	7	1 (14.3)	82	10 (12.2)
$2{,}000 \leq X < 2{,}500$	10	1 (10.0)	84	13 (15.5)
$2{,}500 \leq X < 3{,}000$	4	0 (0)	71	8 (11.3)
$3{,}000 \leq X < 3{,}500$	9	2 (22.2)	72	5 (6.9)
$3{,}500 \leq X$	30	2 (6.7)	240	35 (14.6)

The lymph node metastasis rate of patients with a depth of invasion of 1,000 μm or above was 12.5%

All 3 lymph node metastasis-positive patients with head invasion were ly positive

Side Memo 1

- Method for measuring depth of SM invasion (Fig. 11):

- 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 of the lesion, regardless of the macroscopic type.
- When it is not possible to identify or estimate the location of the muscularis mucosae, the depth of SM invasion is measured from the surface of the lesion. The phrase "possible to identify or to estimate" means that there is no "deformity" (i.e., disarray, dissection, rupture, fragmentation, etc.) of the muscularis mucosae as a result of SM invasion. If a deformed muscularis mucosa is used as the baseline of the measurement, the depth of SM invasion may be underestimated. Although judging whether there is a "deformity" is not always straightforward, if a desmoplastic reaction is present around the muscularis mucosae, it is assumed to be "deformed."
- For pedunculated lesions with a 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 (the boundary between the tumor area and the non-tumor area in the mucosa). Invasion by pedunculated lesions that is limited to within the head is defined as "head invasion."

- Method for assessing vascular invasion (Figs. 12, 13, 14):

- Attention to arteries is a key factor in assessing venous invasion. Venous invasion is highly likely when a circular, semicircular, or oblong cancer cell nest with regular margins is located in the vicinity of an artery and distant from the main lesion. If such a cancer cell nest is surrounded by venous wall structures (such as internal elastic membrane or perivascular smooth muscle), it can be concluded to represent venous invasion. However, the venous wall structures are often displaced or obliterated by the cancer cell nest, and it is difficult to recognize in hematoxylin and eosin stained sections.
- The presence of cancer cells and cancer cell nests in the interstitial space suggests lymphatic invasion. A space filled with lymph and lymphocytes is especially likely to be a lymph vessel. When endothelial cells are identified around the space, the space can be concluded to represent a lymph vessel. However, it is often difficult to identify endothelial cells in specimens stained with hematoxylin and eosin, and spaces may be artifacts created during the process of preparing the specimen.
- As stated above, evaluation of vascular invasion, which is an important indicator for determining treatment strategies for SM cancer, is often difficult in hematoxylin and eosin stained specimens. Special staining methods are useful for evaluating vascular invasion, such as elastica van Gieson staining or Victoria blue staining for venous invasion, and D2-40 immunostaining for lymphatic invasion.

- Method for assessing tumor budding (Fig. 15):

[Definition of tumor budding] [79]

A cancer cell nest consisting of 1 or less than 5 cells that infiltrates the interstitium at the invasive margin of the cancer.

[Grade of budding]

After selecting one field where budding is the most intensive, the number of buddings is counted in a field measuring 0.785 mm^2 observed through a 20× objective lens (WHK 10× ocular lens). Depending on the number of buddings, the grade of budding is defined as follows:

Grade 1: 0–4
Grade 2: 5–9
Grade 3: 10 or more

- The lymph node metastasis rate associated with grade 2/3 tumors is significantly higher than that associated with grade 1 tumors. A multi-center study conducted by the Budding Investigation Project Committee (2005–) of the JSCCR in which grade 1 was defined as "low grade" and grade 2/3 as "high grade" showed that high grade is an independent predictor of lymph node metastasis.

CQ-3: Laparoscopic surgery for colorectal cancer

Recommendation: Category B

- Since laparoscopic surgery requires surgical skills that are different from those required for open abdominal surgery, and an understanding of regional anatomy is essential for laparoscopic surgery, the indication criteria should be determined depending on the skills of the surgical team.

Laparoscopic surgery is suitable for D2, D1 or D0 resection of colon and RS cancer, and is well indicated for the treatment of cStage 0 to cStage I disease. Because laparoscopic colectomy with D3 dissection is difficult, whether it is indicated for patients with cStage II to cStage III

disease should be determined after carefully considering the skills of the surgical team. Laparoscopic surgery is also difficult in patients with transverse colon cancer, in severely obese patients, and in patients with severe adhesions. The efficacy and safety of laparoscopic surgery for rectal cancer has not been sufficiently established.

CQ-4: Resection of the primary tumor in patients with unresectable distant metastases

Recommendation: Category B

- The initial resection of the primary tumor should be determined based on the performance status of each patient, such as the symptoms caused by the primary tumor, the status of distant metastases, and the patient's general condition. Resection of the primary tumor is often desirable when a patient has symptoms caused by the primary tumor that cannot be well controlled by other therapies, if the patient is sufficiently able to tolerate surgery, and the resection can be accomplished with acceptable morbidity.

CQ-5: Resection of peritoneal metastases (carcinomatous peritonitis)

Recommendation: Category C

- If patients with localized peritoneal dissemination (P1, P2) have no other unresectable distant metastases and resection will not result in excessive invasion, it is preferable to resect the disseminated tumors at the same time as the resection of the primary tumor.

CQ-6: Surgical treatment for local recurrence of rectal cancer

Recommendation: Category B

- Resection should be considered for local recurrence of rectal cancer when R0 resection is considered possible.

CQ-7: Resection in patients with liver and lung metastases

Recommendation: Category C

- The efficacy of resection in patients who have liver and lung metastases at the same time has been shown, and thus resection should be considered for patients with resectable liver and lung metastases.

However, there are insufficient data to determine the indication criteria for surgery. It is necessary to obtain informed consent after informing the patient of the rather low cure rate and the absence of outcome predictors.

CQ-8: Adjuvant chemotherapy after curative resection of liver metastases

Recommendation: Category B

- The efficacy of adjuvant chemotherapy after hepatectomy has not been established. It is desirable to investigate its efficacy in clinical trials.

CQ-9: Preoperative chemotherapy for resectable liver metastases

Recommendation: Category B

- The safety of preoperative chemotherapy for resectable liver metastases has not been established. It should be evaluated in properly designed clinical trials.

CQ-10: Chemotherapy for unresectable liver metastases

Recommendation: Category B

- Hepatectomy should be considered for liver metastases that have become resectable after successful chemotherapy.

No clear difference has been observed between hepatic arterial infusion therapy and systemic chemotherapy in terms of the prolongation of survival time of patients with unresectable liver metastases.

CQ-11: Postoperative adjuvant chemotherapy and age

Recommendation: Category A

- Even in patients 70 years old or older, postoperative adjuvant chemotherapy can be performed if their PS is good, if the function of major organs is adequate, and if there are no complications that may be a risk for performing chemotherapy.

CQ-12: Postoperative adjuvant chemotherapy for stage II colorectal cancer

Recommendation: Category A

- The usefulness of postoperative adjuvant chemotherapy for stage II colorectal cancer has not been proven, and it is not appropriate to routinely administer adjuvant chemotherapy to all patients with stage II colorectal cancer.