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.

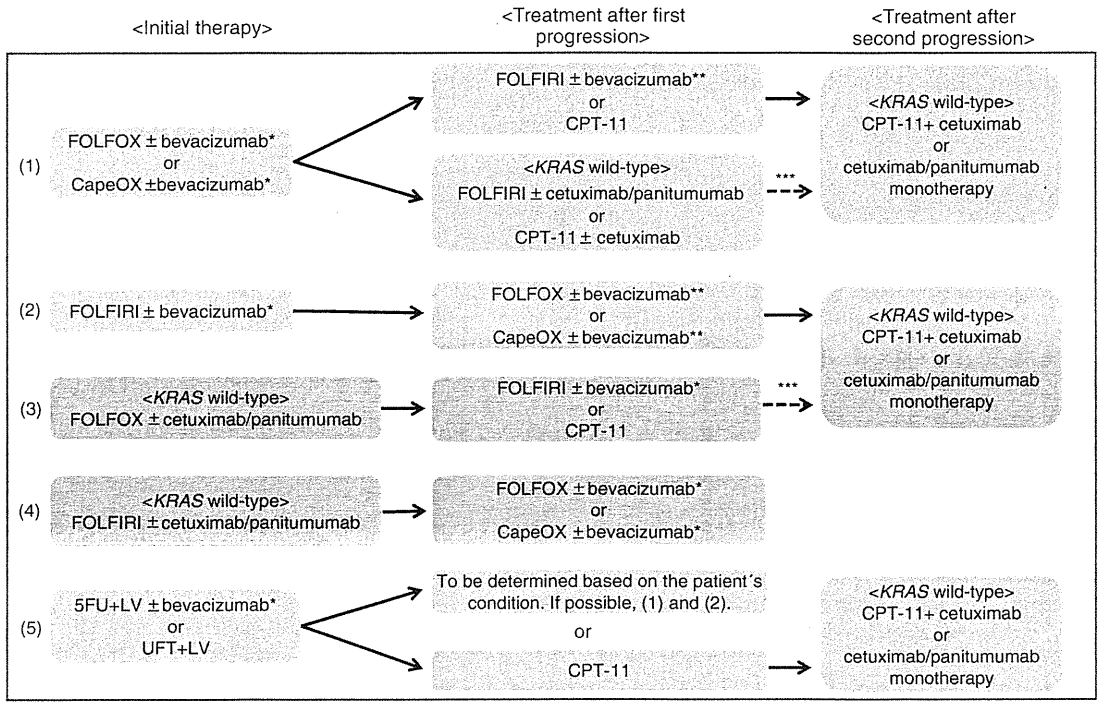
Comments

- 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."

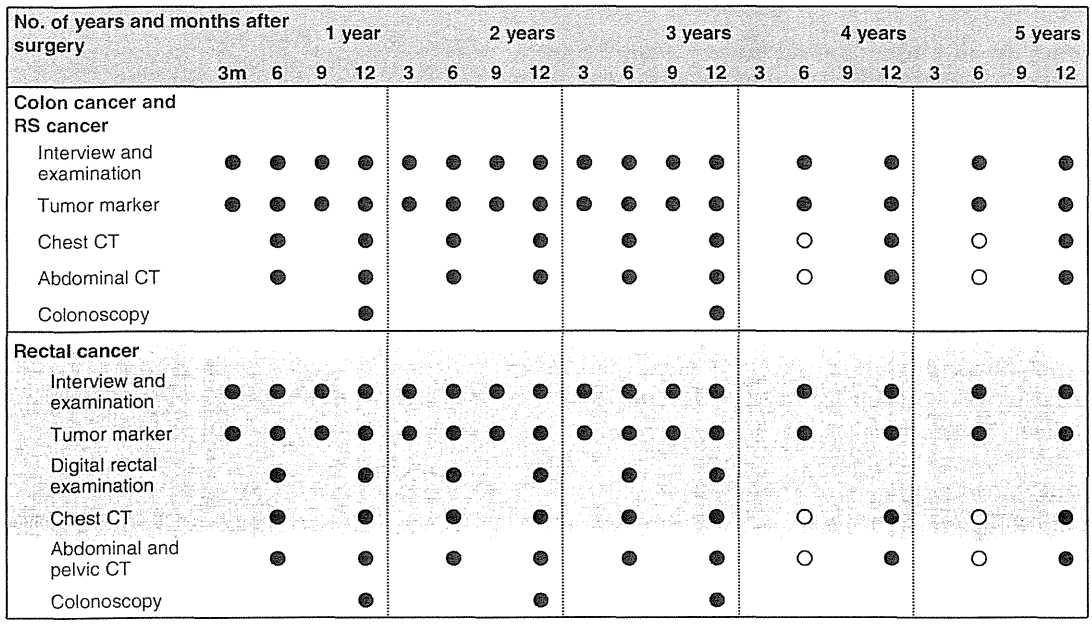
[Dose and fractionation]

- 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,



●: 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 reηcurrences 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.

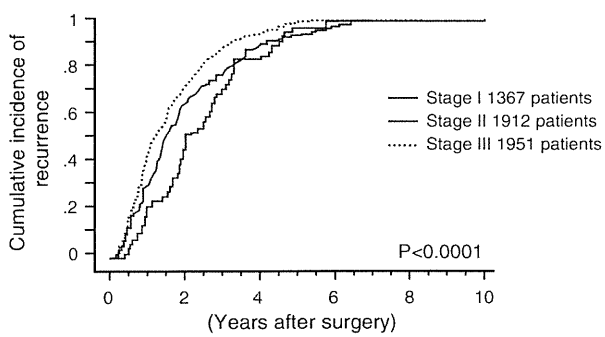


Fig. 8 Graph of the cumulative incidence of recurrence according to stage. (Project study by the JSCCR: patients in years 1991–1996)

- 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)

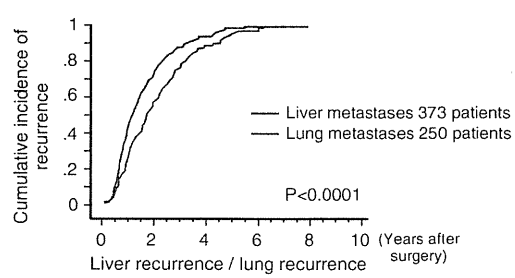
1. Stage I

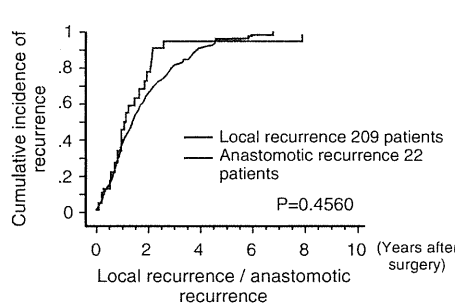
- The recurrence rate of pSM cancer was approximately 1% in both colon cancer and rectal cancer.
- The overall recurrence rate of pMP cancer was 6.4%, and it was 5.0% in colon cancer and 8.3% in rectal cancer.
- Two-thirds of the recurrences were detected within 3 years after surgery, and the overall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





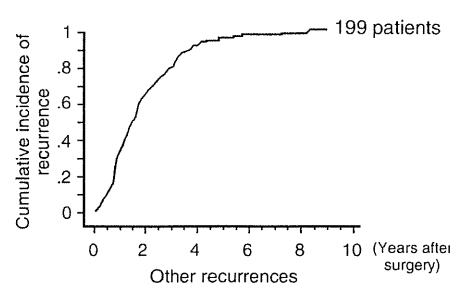


Table 7 Recurrence rate after curative resection of colorectal cancer according to stage and cumulative incidence of recurrence according to the number of years after surgery

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

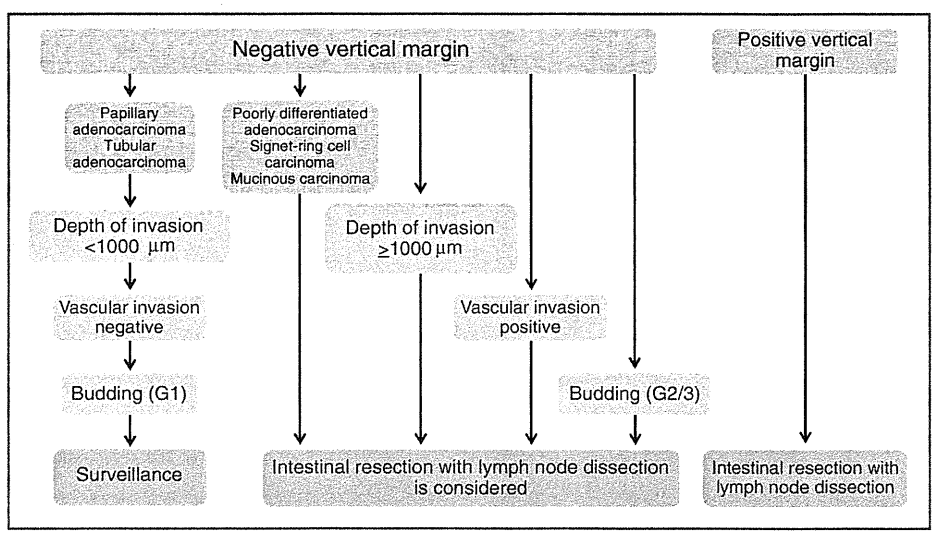


Fig. 10 Treatment strategies for pSM cancer after endoscopic resection

[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

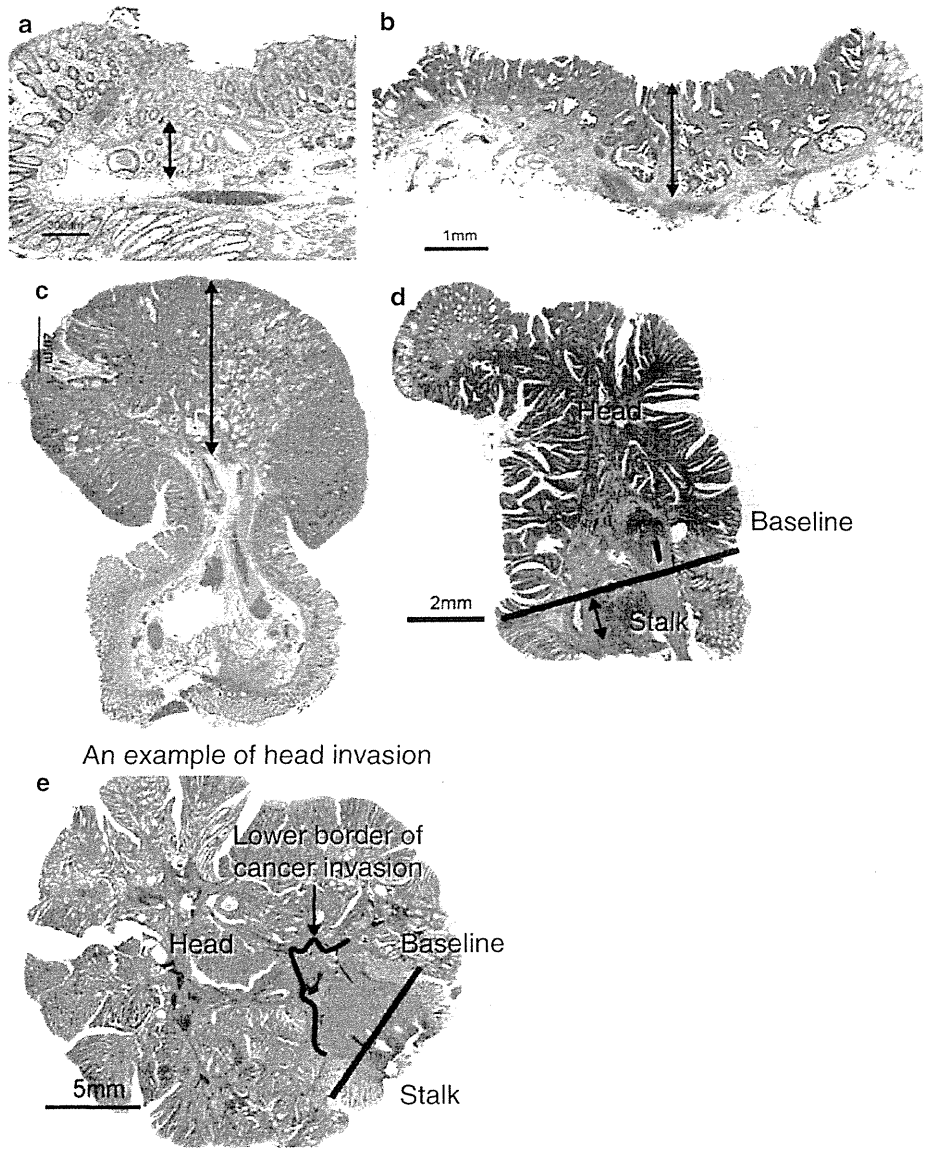


Fig. 11 Method for measuring depth of SM invasion. **a** When it is possible to identify or estimate the location of the muscularis mucosae, depth of SM invasion is measured from the lower border of the muscularis mucosae. **b**, **c** When it is not possible to identify or estimate the location of the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

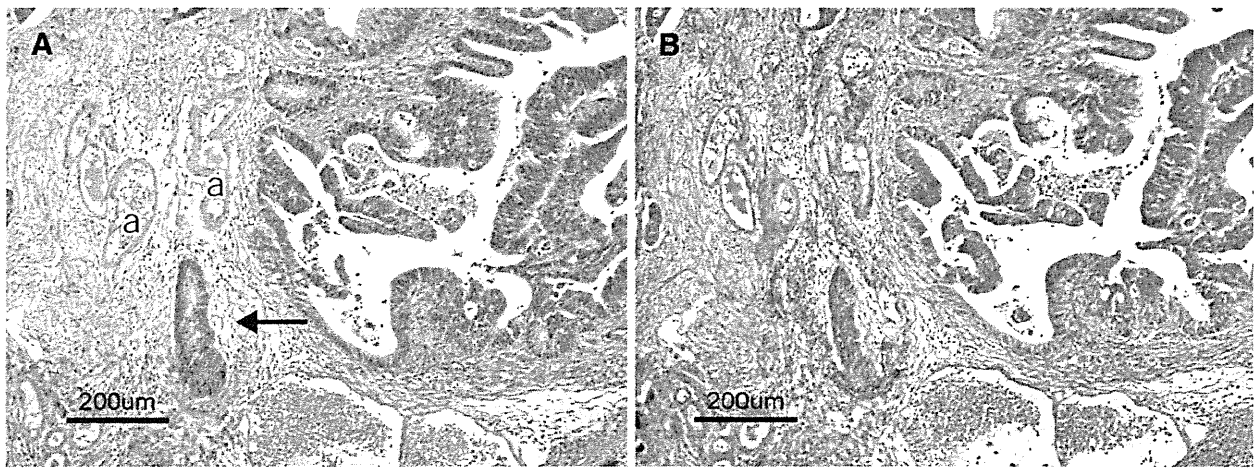


Fig. 12 Venous invasion (*arrow* in **a**). **a** Located in the vicinity of an artery (*a*). **b** Elastic fibers in the vein wall have been highlighted by Victoria blue staining

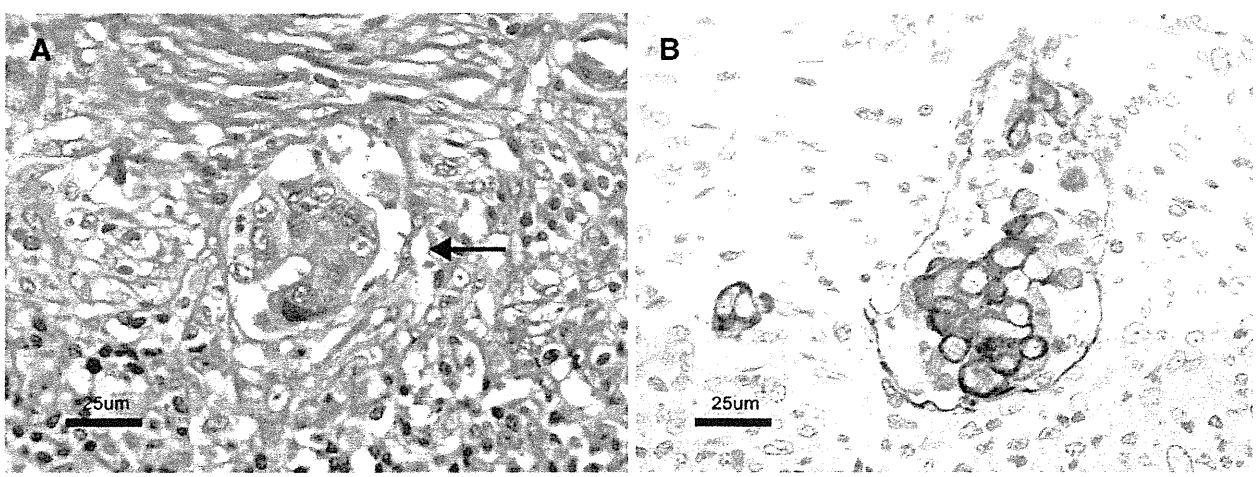


Fig. 13 Lymphatic invasion (*arrow* in **a**). **a** A cancer cell nest is visible in the interstitial space. **b** Double staining for cytokeratin and D2-40. Cancer cells are stained *brown*, and the lymphatic endothelium is stained *purplish red*

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.

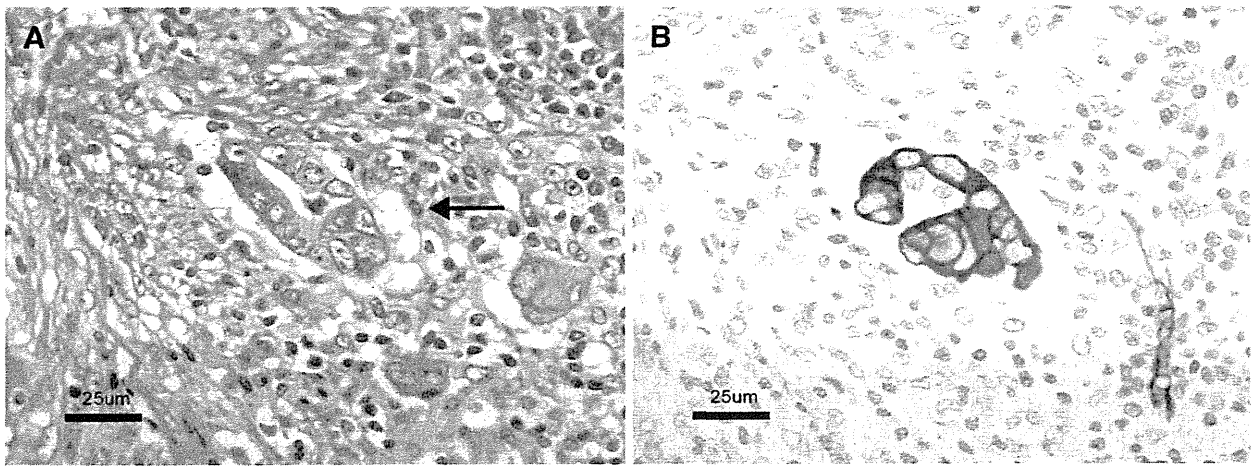


Fig. 14 Space formed by artifacts during preparation of the specimen (*arrow* in **a**). **a** A cancer cell nest is visible in the interstitial space. **b** Double staining for cytokeratin and D2-40. The interstitial space is D2-40-negative

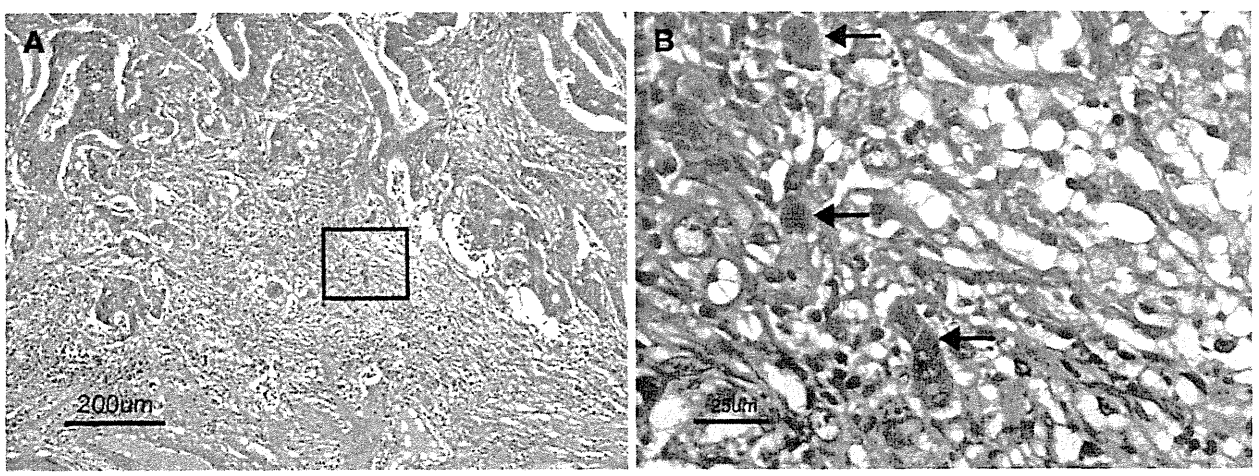


Fig. 15 Budding (*arrows* in **b**). **a** A cancer cell nest consisting of 1 or less than 5 cells that has infiltrated the interstitium at the invasive margin of the cancer is seen. **b** is the square area in **a**

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.

CQ-13: Duration of postoperative adjuvant chemotherapy

Recommendation: Category A

- Although no definitive conclusion regarding the duration of postoperative adjuvant chemotherapy has been reached, the current standard duration of treatment by 5-FU-based adjuvant chemotherapy is 6 months.

CQ-14: Oxaliplatin (L-OHP) in postoperative adjuvant chemotherapy

Recommendation: Category A

- In August 2009, L-OHP was approved for postoperative adjuvant chemotherapy in Japan. When selecting target patients, the indication should be determined after obtaining sufficient informed consent regarding adverse events and medical care costs as well as the expected additional benefit in terms of survival time.

CQ-15: Molecular target drugs for secondary treatment

Recommendation: Category B

- It is desirable to use bevacizumab as secondary treatment in patients who can be treated with bevacizumab and have not received it as primary treatment. There is no clear evidence supporting the optimal dose in this situation (5 or 10 mg/kg) [44, 49].

CQ-16: KRAS gene mutations and anti-EGFR antibody drugs

Recommendation: Category A

- The usefulness of anti-EGFR antibody drugs has been reported in metastatic colorectal cancer without KRAS gene mutations [38–41, 47, 53, 55, 85–90].

Side Memo 2

- Anti-EGFR antibody drugs and EGFR immunostaining

Since most clinical research on cetuximab has been conducted on EGFR-positive patients, insurance coverage is limited to EGFR-positive patients. On the other hand, most clinical research on panitumumab has also been conducted on EGFR-positive patients, and evidence in regard to EGFR-negative patients is insufficient, but insurance coverage has been restricted to EGFR-positive patients. A recent report showed that there is no relationship between the effect of anti-EGFR antibody drugs and the level of EGFR expression assessed by immunostaining [91].

- CPT-11 and UGT1A1 genetic polymorphism

SN-38 is an active metabolite of CPT-11 and the UGT1A1 gene encodes an intrahepatic metabolizing enzyme which converts the active form SN-38 to the inactive form SN-38 G. In patients who are double heterozygotes for *6 and *28 or homozygotes for *6 or *28 of the UGT1A1 gene, the glucuronic acid conjugation capacity of UGT1A1 is known to be decreased and the metabolism of SN-38 to be delayed, and serious adverse drug reactions such as neutropenia may occur as a result. It is especially desirable to test for a UGT1A1 genetic polymorphism before administering CPT-11 to patients with a high serum bilirubin level, elderly patients, patients whose general condition is poor (e.g., PS2), and patients in whom severe toxicity (especially neutropenia) developed after the last administration of CPT-11. On the other hand, because CPT-11 toxicity cannot be predicted with certainty on the basis of the presence of a UGT1A1 genetic polymorphism alone, it is essential to monitor the patient's general condition during treatment and manage adverse drug reactions carefully regardless of whether a genetic polymorphism is detected.

CQ-17: Significance of preoperative chemoradiotherapy for rectal cancer

Recommendation: Category C

- Preoperative chemoradiotherapy is standard treatment for rectal cancer in Europe and the United States. However, there is insufficient evidence in support of its efficacy and safety in Japan, and it needs to be evaluated in properly designed clinical trials.

CQ-18: Chemoradiotherapy for unresectable locally advanced and locally recurrent rectal cancer

Recommendation: Category C

- The indication for chemoradiotherapy aiming at complete cure by R0 resection will also be considered for locally advanced or locally recurrent, unresectable rectal cancer.

CQ-19: Significance of surveillance after surgery of colorectal cancer

19A: Diagnosis of recurrence
Recommendation: Category A

- Early detection of recurrence has been shown to contribute to an improvement in outcome, and

postoperative surveillance examinations should be performed regularly. However, an optimal surveillance protocol incorporating the health economical point of view has not been sufficiently established.

19B: Multiple cancer
Recommendation: Category B

- With the exception of hereditary colorectal cancer, a past medical history of colorectal cancer has not been demonstrated to be a risk factor for the development of cancer in other organs, and it is unnecessary to incorporate special surveillance for multiple cancer into the surveillance performed after curative surgery for colorectal cancer.

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ORIGINAL REPORT

Optimal Colorectal Cancer Staging Criteria in TNM Classification

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ABSTRACT

Purpose
Histologic components of the TNM classification system have been repeatedly revised since the fifth edition (TNM5). TNM classification revisions provide different criteria for categorizing tumor nodules without residual lymph node structure (ND). However, there are few systematic evaluations regarding the effectiveness of these revisions.

Patients and Methods
A multicenter pathologic review for ND in colorectal cancer (CRC) was performed. Tumor staging defined by TNM5, sixth edition (TNM6), and seventh edition (TNM7) were compared on the basis of Akaike information criterion (AIC) and Harrell's concordance index (c-index). Moreover, TNM7's prognostic value was compared between the original ND and modified criteria, which considered all regional NDs as lymph node metastasis (LNM) irrespective of the original structure.

Results
In 1,716 treated patients with CRC (1994 to 1998), tumor stages (I/II/III) exhibited better prognoses in TNM7 (AIC, 3055.1; c-index, 0.7215) than in TNM6 (AIC, 3063.7; c-index, 0.7149), but not better than in TNM5 (AIC, 3051.6; c-index, 0.7240). Comparing the original TNM7 and modified criteria, 4.2% of patients were classified in different N stages (N0/N1/N2a/N2b); both AIC and the c-index were superior in the modified criteria (AIC, 3029.40; c-index, 0.7271) compared with the original criteria (AIC, 3040.58; c-index, 0.7230). Modified criteria were also associated with improved prognostic power of tumor stages (I/IIA/IIB/IIC/IIIA/IIIB/IIIC). These results were similar in another cohort of 2,242 treated patients with CRC (1999 to 2003).

Conclusion
The prognostic value of TNM7 is better than that of TNM6; however, improvement over TNM5 is insignificant. By considering all regional NDs as LNM irrespective of their morphology, TNM classification can be simplified and its prognostic value improved.

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INTRODUCTION

The TNM classification system provides accurate prognostic information and helps plan proper treatment for patients with malignant tumors. The tumor (T) and lymph node (N) factors of the TNM classification have been significantly revised twice since the publication of the fifth edition (TNM5) in 1995.[1] These revisions were based on changes in tumor nodule treatment without the accompanying histologic evidence regarding residual lymph node structure in the nodule (ND; Table 1). Specifically, a histologic criterion in the TNM staging system was used to categorize ND into T or N: the size rule in TNM5[1] and contour rule in the sixth edition (TNM6).[2] In the seventh edition (TNM7), ND was not considered a T component.[3] TNM7 provides a specific N1c category for ND with irregular-contour characteristics that are not considered lymph nodes completely infiltrated by malignant cells.

These revised editions of TNM classification are not used in every country; TNM5 is still predominantly used in Western countries, including the United Kingdom, the Netherlands, Belgium, and Denmark,[4] whereas in Japan, none of the newly revised TNM criteria regarding ND were adopted in the national cancer staging manual edited by the Japanese Society for Cancer of the Colon and Rectum (JSCCR).[5] This discrepancy is because scientific evidence has not satisfactorily justified the use of these criteria in cancer staging.

Table 1. Definition and Categorization of Tumor Nodules in the Original and Modified TNM Classification Systems

TNM Edition	Location of ND Counted As a Staging Factor	T Factor	N Factor
TNM5	Pericolorectal area	ND ≤ 3 mm	ND > 3 mm (= counted as LNM)
TNM6	Pericolorectal area	I-ND	S-ND (= counted as LNM)
TNM7	UICC: pericolorectal area AJCC: (1) pericolorectal area AJCC: (2) adjacent mesentery away from the leading edge of the tumor	—	(1) ND considered to be a totally replaced lymph node (generally having a smooth contour; = counted as LNM) (2) other ND (= categorized as N1c)
Modified	Regional area of the tumor	—	All ND (= counted as LNM)

Abbreviations: AJCC, American Joint Committee on Cancer; I-ND, irregular-contour ND; LNM, lymph node metastasis; ND, tumor nodules without histologic evidence of residual lymph node structure; S-ND, smooth-contour ND; UICC, International Union Against Cancer.

In addition, a retrospective single-institution study indicated that the best predictive prognostic model for survival outcome was obtained by including all tumor nodules except intravascular deposits in the N stage.[6] On the basis of this research, JSCCR has projected a multicenter study to establish the optimal definition and ND categorization that should be adopted in a staging manual. Two multicenter clinicopathologic databases focusing on colorectal cancer (CRC) were developed, which included detailed information on ND obtained by reviewing all pathologic specimens made in routine practice.[7,8] As previously reported, statistical analyses of these cohorts showed that the impact on survival and recurrence of ND in the regional lymph node area was similar to that of metastatic lymph nodes.[7] Considering ND as a metastatic lymph node in the tumor stage, while disregarding its size and shape, enhanced the prognostic power of the Japanese N staging system, which varies according to the location and the number of involved nodes.[8]

Few carefully designed multicenter studies[9] have compared each TNM edition to determine which revision has the greatest usefulness for therapeutic decision making in CRC treatments. To establish robust evidence-based tumor classification principles, the existing TNM staging systems should be studied using a scientific process to clarify and remove any existing problems.[4,10-13] In the present study, we compared each edition of the TNM staging using the previously mentioned multicenter databases. We then attempted to clarify whether TNM classification could be improved by modifying the definition and categorization of ND in CRC.

PATIENTS AND METHODS

Patients

Two databases with stage I to III CRC cases were established in this multicenter study for optimally categorizing tumor nodules without histologic evidence of residual lymph node in the tumor stage (as projected by JSCCR). The first cohort involved 1,716 patients (1,031 men, 685 women; average age, 64 years; range, 20 to 95 years) who underwent curative surgery between 1994 and 1998 at 11 separate institutions. The patients were followed up for at least 5 years or until death. A total of 1,192 patients had colon or rectosigmoid cancer, and 524 patients had rectal cancer. No patients received preoperative chemotherapy or radiotherapy. Regarding postoperative adjuvant therapy, 578 patients received chemotherapy; most (467 patients) received oral anticancer drugs such as tegafur plus uracil, 5′-deoxy-5-fluorouridine, carmofur, fluorouracil, or tegafur. Adjuvant therapy was not administered in 578 patients, and little information about postoperative treatment could be obtained from 560 patients. The average follow-up of 1,310 survivors was 93 months (range, 61 to 140 months).

To validate results of the first cohort, 2,242 patients with stage I to III disease (1,345 men, 897 women; average age, 65 years; range, 17 to 96 years) who underwent curative surgery between 1999 and 2003 in nine separate institutions were enrolled as the second cohort. A total of 1,635 patients had colon or rectosigmoid cancer, and 607 patients had rectal cancer. No patients received any preoperative therapy. Postoperative adjuvant chemotherapy was administered to 703 patients; 1,518 patients received no adjuvant therapy. No information on postoperative therapy could be obtained for 21 patients. Regarding the type of adjuvant therapy administered, oral anticancer drugs were the most common (550 patients), followed by intravenous chemotherapy using agents such as fluorouracil/leucovorin (129 patients). The average follow-up period for 1,788 survivors was 68 months (range, 1 to 123 months).

Histologic Examination for ND

ND was defined as all types of isolated extramural tumor nodule without lymphocyte aggregates that were considered a part of a lymph node (LN). Cancer foci mostly confined to the vascular or perineural spaces were not regarded as ND. ND was classified into smooth-contour nodules (S-ND) and irregular-contour nodules (I-ND; Fig 1).

The method of identifying ND was reported previously.[7,8] Briefly, adipose tissues attached to the bowel and pathologic specimens postoperatively collected and submitted for pathologic examination of lymph node metastasis (LNM) were retrospectively examined at each institution (Fig 1). Detailed information of cancer lesions with discontinuous spread was collected by categorizing them into LNM, ND, and isolated foci of vascular/perineural invasion.

Interobserver Agreement

To determine the reproducibility of the various N staging systems incorporating NDs, we evaluated 47 consecutive patients with CRC that had been confirmed pathologically to be accompanied by one or more NDs. All patients had undergone surgery at the National Defense Medical College Hospital, Japan, between March 2009 and July 2011. Three independent observers (H.U., K.I., and H.S.) evaluated a total of 107 NDs observed in this series (range, one to nine per patient) to evaluate reproducibility.

Statistical Analyses

Statistical analyses were performed using the SPSS software package (SPSS, Chicago, IL) and STATA/SE 10 (StataCorp, College Station, TX). Prognostic stratification of the N- and T-staging systems was evaluated by the Akaike information criterion (AIC)[14] and Harrell's concordance index (c-index).[15] AIC was analyzed in a Cox proportional hazards regression model to identify ND categorization, as it accounted for the N- and T-staging systems with the highest ability of discrimination for survival outcome. The optimum model, the simplest effective model with the smallest information loss when predicting the outcome, gives the lowest AIC value. Harrell's c-index was also calculated as a measure of predictive accuracy of survival outcome; a c-index of 0.5 indicates accuracy similar to random guessing, and that of 1.0 indicates 100% predictive accuracy. To assess interobserver agreement in judging discontinuous spread lesions as N-stage factors, the Fleiss κ value was calculated to evaluate variability.

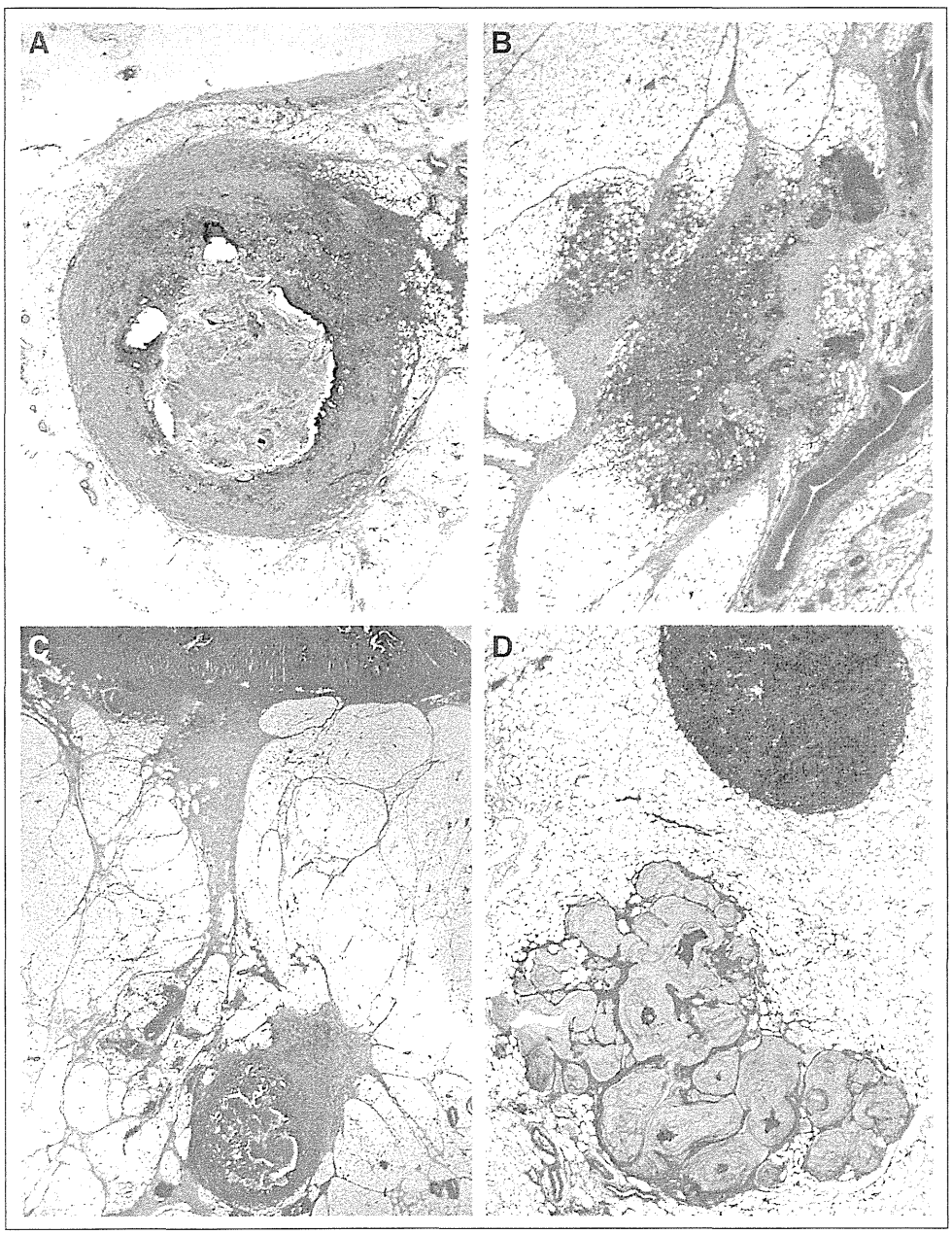

Fig 1. Tumor nodules without residual lymph node structure (ND) in colorectal cancer. ND were classified into (A) smooth-contour nodules (orignal magnification ×2) and (B) irregular-contour nodules (original magnification: ×2). (C) Extramural fatty tissue attached to primary tumors (original magnification: ×1.25) was examined for the detection of ND. Isolated tumor lesions located in the extramural fatty tissue were regarded as ND in T1 or T2 tumors. For T3 or T4 tumor, isolated cancer lesions located ≥ 5 mm from the leading edge of the extramural part of the primary tumor (or from the lower edge of the muscularis propria, when the glass slide did not contain the extramural part of the tumor to be regarded as a standard of measurement) were regarded as ND. (D) Histologic specimens submitted as lymph nodes for pathologic investigation were also examined (original magnification: ×4). All tumor nodules in a lymph node specimen were regarded as ND; however, with regard to lymph node specimens containing positive lymph nodes, extracapsular spread lesions from metastatic lymph nodes and tumor deposits adjacent to metastatic lymph nodes presumed to be associated with lymph node metastasis were not regarded as ND.

RESULTS

Incidence of ND

In the first cohort, ND was observed in 275 patients (16.0%). Among 540 foci of ND that were observed in this cohort, 234 (43.3%) were considered as S-ND and 306 (56.7%) as I-ND. In the second cohort, 334 patients (14.9%) exhibited ND. Specifically, among the detected 727 foci of ND, 240 (33.0%) were considered as S-ND and 487 (67.0%) as I-ND.

Distribution of ND was quite similar between the first and second cohorts (Fig 2). The majority of the observed ND was in the pericolic/perirectal area. The incidence of ND in this area was significantly higher in rectal cancer than in colon cancer in both the first ($P < .001$) and second cohorts ($P < .001$). Although ND was quite rare (0% to 0.4% in both cohorts) in the main lymph node area, in CRC, ND occurred at a higher rate in the intermediate (1.9% to 2.4%) and lateral pelvic areas (1.5% to 1.6%).

Comparison of Staging Systems in TNM5, TNM6, and TNM7

In Table 2, we list stage migration resulting from subsequent changes in definitions of TNM in a total of 3,958 patients by combing the first and second cohorts. The method of categorization of ND in tumor staging has a stronger impact on N staging than T staging.