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.

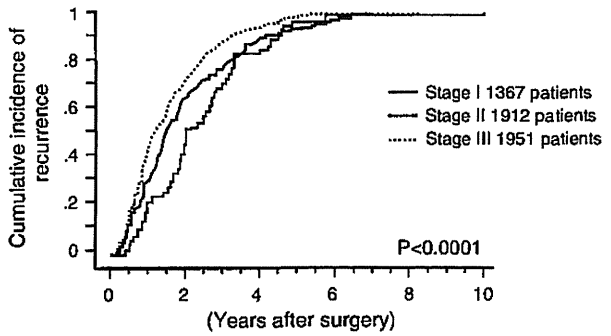


Fig. 8 Graph of the cumulative incidence of recurrence according to stage. (Project study by the JSCCR: patients in years 1991–1996)

- 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)

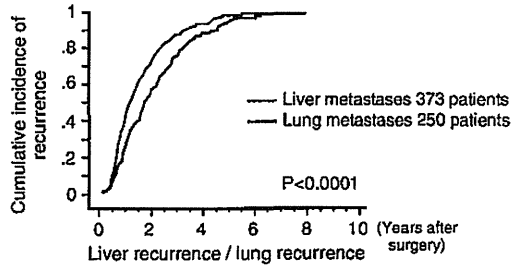
1. Stage I

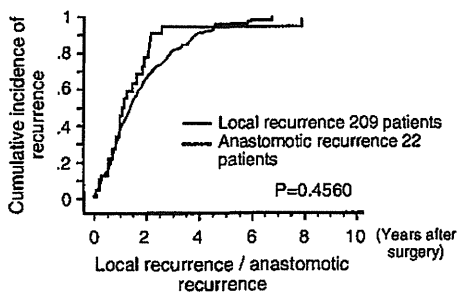
- The recurrence rate of pSM cancer was approximately 1% in both colon cancer and rectal cancer.
- The overall recurrence rate of pMP cancer was 6.4%, and it was 5.0% in colon cancer and 8.3% in rectal cancer.
- Two-thirds of the recurrences were detected within 3 years after surgery, and the overall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





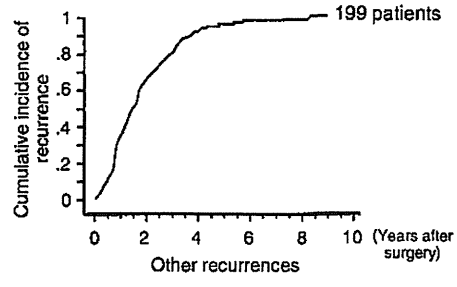


Table 7 Recurrence rate after curative resection of colorectal cancer according to stage and cumulative incidence of recurrence according to the number of years after surgery

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

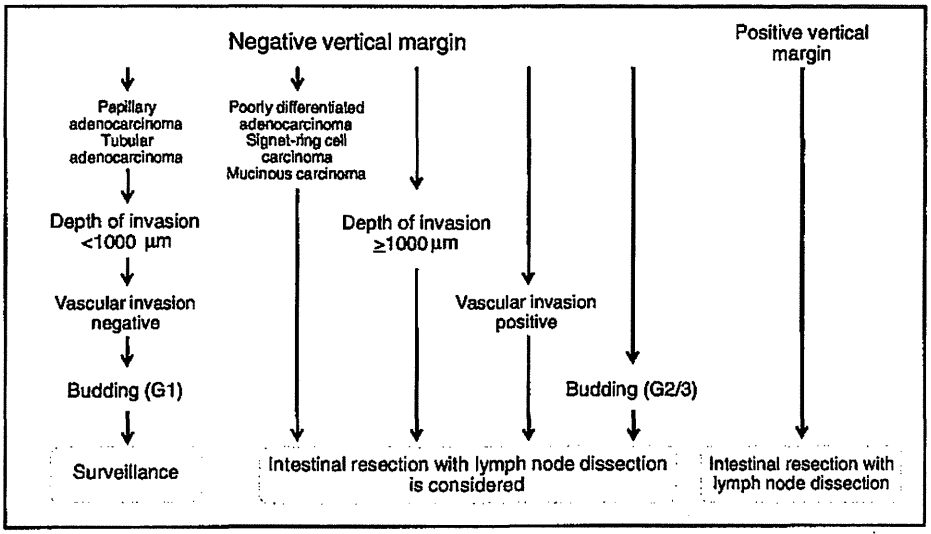


Fig. 10 Treatment strategies for pSM cancer after endoscopic resection

[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

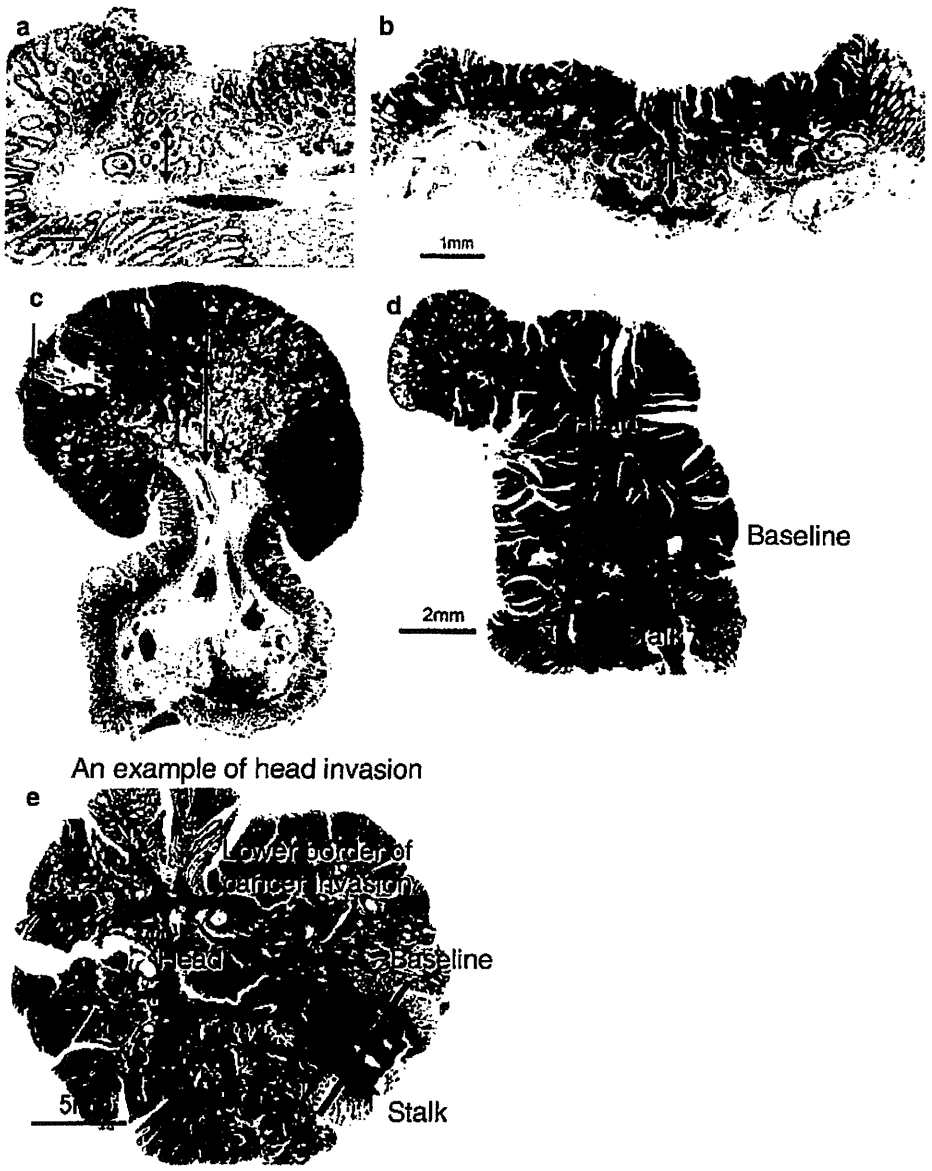


Fig. 11 Method for measuring depth of SM invasion. **a** When it is possible to identify or estimate the location of the muscularis mucosae, depth of SM invasion is measured from the lower border of the muscularis mucosae. **b, c** When it is not possible to identify or estimate the location of the muscularis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

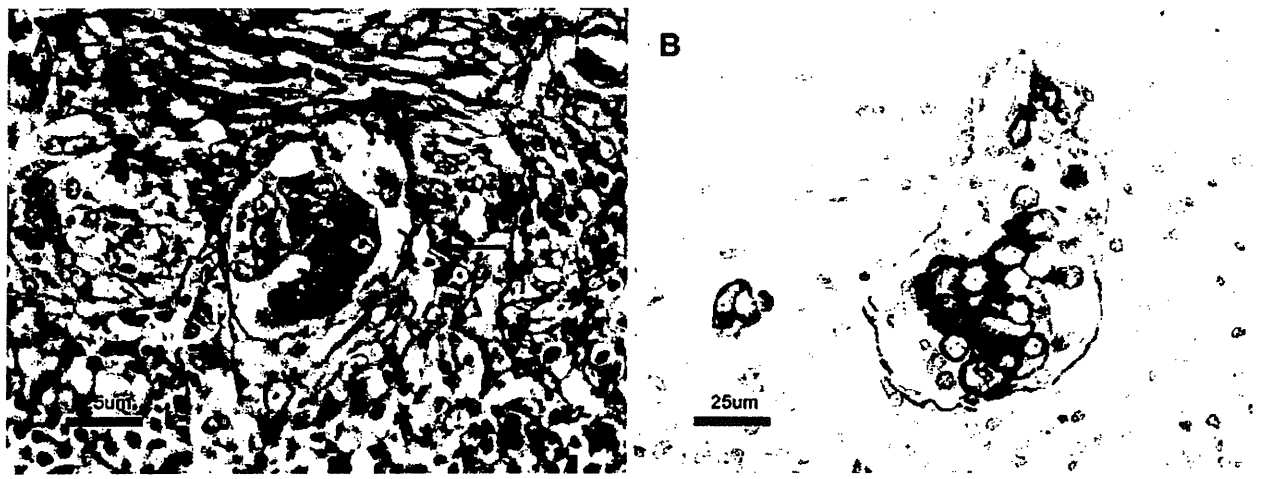


Fig. 13 Lymphatic invasion (*arrow* in a). **a** A cancer cell nest is visible in the interstitial space. **b** Double staining for cytokeratin and D2-40. Cancer cells are stained *brown*, and the lymphatic endothelium is stained *purplish red*

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.

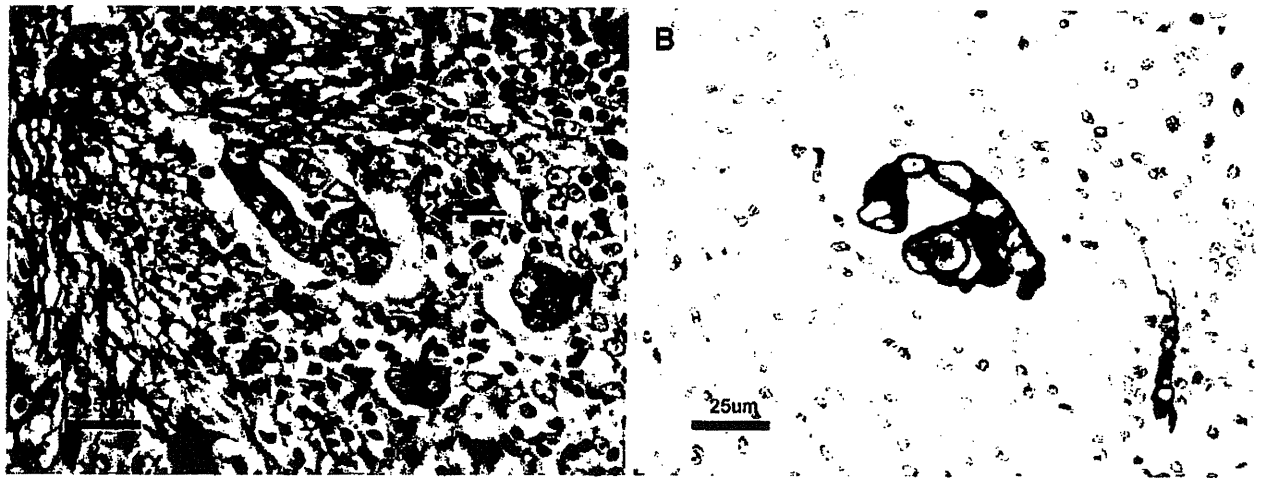


Fig. 14 Space formed by artifacts during preparation of the specimen (*arrow* in **a**). **a** A cancer cell nest is visible in the interstitial space. **b** Double staining for cytokeratin and D2-40. The interstitial space is D2-40-negative

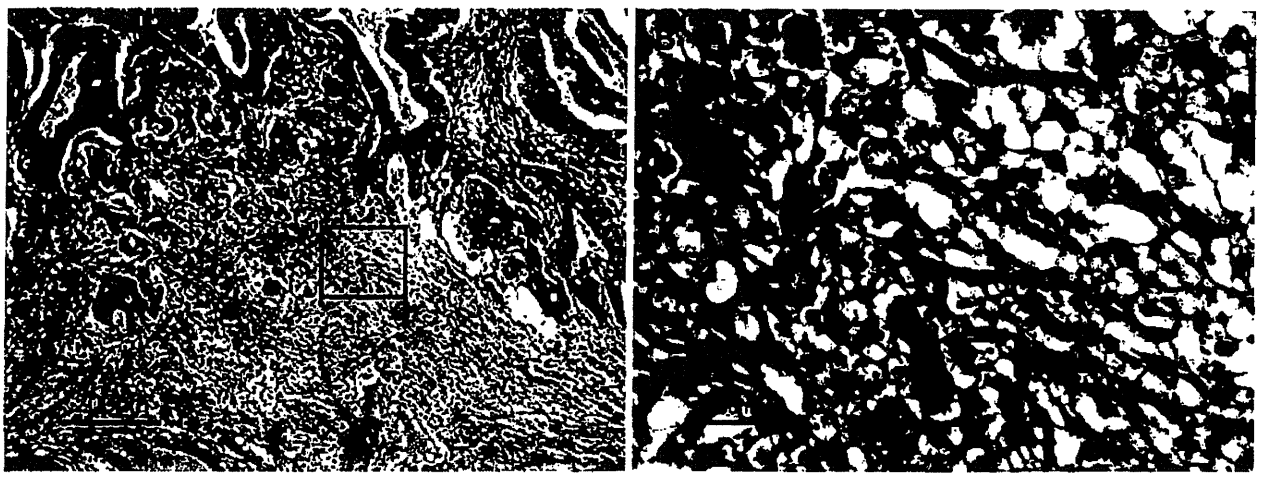


Fig. 15 Budding (*arrows* in **b**). **a** A cancer cell nest consisting of 1 or less than 5 cells that has infiltrated the interstitium at the invasive margin of the cancer is seen. **b** is the square area in **a**

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.

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.

References

1. Japanese Society for Cancer of the Colon and Rectum (2010) JSCCR guidelines 2010 for the treatment of colorectal cancer. Kanehara & Co., Ltd., Tokyo
2. Kudo S (1993) Endoscopic mucosal resection of flat and depressed early colorectal cancer. Endoscopy 25:455–461
3. Tanaka S, Oka S, Chayama K (2008) Colorectal endoscopic submucosal dissection (ESD): the present status and future perspective including its differentiation from endoscopic mucosal resection (EMR). J Gastroenterol 43:641–651
4. Japanese Society for Cancer of the Colon and Rectum (2010) Multi-Institutional Registry of Large Bowel Cancer in Japan. Cases treated in 1995–1998 [vols. 17 (1999), 18 (2000), 21 (2001), 24 (2003)]. Japanese Society for Cancer of the Colon and Rectum, Tokyo
5. Heald RJ, Husband EM, Ryall RD (1982) The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? Br J Surg 69:613–616
6. MacFarlane JK, Ryall RD, Heald RJ (1993) Mesorectal excision for rectal cancer. Lancet 341:457–460
7. Enker WE, Thaler HT, Cranor ML et al (1995) Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg 181:335–346
8. Lowry AC, Simmang CL, Boulos P et al (2001) Consensus statement of definitions for anorectal physiology and rectal cancer. Dis Colon Rectum 44:915–919
9. Sugihara K, Kobayashi H, Kato T et al (2006) Indiçation and benefit of pelvic sidewall dissection for rectal cancer. Dis Colon Rectum 49:1663–1672
10. Japanese Society for Cancer of the Colon and Rectum (1998) General rules for clinical and pathological studies on cancer of the colon, rectum and anus, 6th edn. Kanehara & Co., Ltd., Tokyo
11. Mentges B, Buess G, Schafer D et al (1996) Local therapy of rectal tumors. Dis Colon Rectum 39:886–892
12. Murata S, Moriya Y, Akasu T et al (1998) Resection of both hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 83:1086–1093
13. Robinson BJ, Rice TW, Strong SA et al (1999) Is resection of pulmonary and hepatic metastases warranted in patients with colorectal cancer? J Thorac Cardiovasc Surg 117:66–76
14. Lambert LA, Colacchio TA, Barth RJ Jr (2000) Interval hepatic resection of colorectal metastases improves patient selection. Arch Surg 135:473–479
15. Kobayashi K, Kawamura M, Ishihara T (1999) Surgical treatment for both pulmonary and hepatic metastases from colorectal cancer. J Thorac Cardiovasc Surg 118:1090–1096
16. Regnard JF, Grunenwald D, Spaggiari L et al (1998) Surgical treatment for hepatic and pulmonary metastases from colorectal cancers. Ann Thorac Surg 66:214–218
17. Patchell RA, Tibbs PA, Walsh JW et al (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322:494–500
18. National Institute of Health Consensus Conference (1990) Adjuvant therapy for patients with colon and rectal cancer. JAMA 264:1444–1450
19. Benson AB 3rd, Schrag D, Somerfield MR et al (2004) American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 22:3408
20. Van Cutsem E, Oliveira J, ESMO Guidelines Working Group (2008) Colon cancer: ESMO clinical recommendations for diagnosis, adjuvant treatment and follow-up. Ann Oncol 19(Suppl 2):ii29–ii30
21. André T, Boni C, Mounedji-Boudiaf L et al, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343–2351
22. Kuebler JP, Wieand HS, O'Connell MJ et al (2007) Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 25:2198–2204
23. André T, Boni C, Navarro M et al (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 27:3109–3116
24. Wolmark N, Wieand S, Kuebler PJ et al (2008) A phase III trial comparing FULV to FULV+oxaliplatin in stage II or III carcinoma of the colon: survival results of NSABP Protocol C-07. Proc Am Soc Clin Oncol 26 (Abstr LBA4005)
25. Haller D, Tabernero J, Maroun J et al (2009) First efficacy findings from a randomized phase III trial of capecitabine + oxaliplatin vs. bolus 5-FU/LV for stage III colon cancer (NO16968/XELOXA study). In: Proc ECCO 15–34th ESMO Congr, Berlin, Germany, 20–24 Sept 2009, Abstr 5LBA
26. Haller DG, Catalano PJ, Macdonald JS et al (2005) Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol 23:8671–8678
27. Scheithauer W, Rosen H, Kornek GV et al (1993) Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. Br Med J 306:752–755
28. Simmonds PC (2000) Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. Br Med J 321:531–535
29. Cunningham D, Pyrhonen S, James RD et al (1998) Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413–1418
30. de Gramont A, Figer A, Seymour M et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947
31. Goldberg R, Sargent D, Morton R et al (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23–30
32. Saltz LB, Clarke S, Díaz-Rubio E et al (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 26:2013–2019

33. Cassidy J, Clarke S, Díaz-Rubio E et al (2008) Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 26:2006–2012
34. Tournigand C, André T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR Study. J Clin Oncol 22:229–237
35. Douillard JY, Cunningham D, Roth AD et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355:1041–1047
36. Fuchs CS, Marshall J, Mitchell E et al (2007) Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 25:4779–4786
37. Fuchs CS, Marshall J, Barrueco J et al (2008) Randomized, controlled trial of irinotecan plus infusional, bolus or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. J Clin Oncol 26:689–690
38. Bokemeyer C, Bondarenko I, Makhson A et al (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 27:663–671
39. Siena S, Cassidy J, Tabernero J et al (2010) Randomized phase III study of panitumumab (pmab) with FOLFOX4 compared to FOLFOX4 alone as first-line treatment (tx) for metastatic colorectal cancer (mCRC): PRIME trial. In: Proc 2010 ASCO Gastrointestinal Cancers Symp, Orlando, FL, USA, 22–24 Jan 2010, Abstr 283
40. Van Cutsem E, Köhne CH, Hitre E et al (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360:1408–1417
41. Kohne C, Mineur L, Greil R et al (2010) Primary analysis of a phase II study (20060314) combining first-line panitumumab (pmab) with FOLFIRI in the treatment of patients (pts) with metastatic colorectal cancer (mCRC). In: Proc 2010 ASCO Gastrointestinal Cancers Symp, Orlando, FL, USA, 22–24 Jan 2010, Abstr 414
42. Petrelli N, Herrera L, Rustum Y et al (1987) A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. J Clin Oncol 5:1559–1565
43. Hurwitz H, Fehrenbacher L, Hainsworth JD et al (2005) Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. J Clin Oncol 23:3502–3508
44. Kabbinavar F, Hurwitz HI, Fehrenbacher L et al (2003) Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 21:60–65
45. Shirao K, Hoff PM, Ohtsu A et al (2004) Comparison of the efficacy, toxicity, and pharmacokinetics of a uracil/tegafur (UFT) plus oral leucovorin (LV) regimen between Japanese and American patients with advanced colorectal cancer: joint United States and Japan study of UFT/LV. J Clin Oncol 22:3466–3474
46. Sobrero AF, Maurel J, Fehrenbacher L et al (2008) EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 26:2311–2319
47. Peeters M, Price TJ, Hotko YS et al (2010) Randomized phase III study of panitumumab (pmab) with FOLFIRI vs FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC): patient-reported outcomes (PRO). In: Proc 2010 ASCO Gastrointestinal Cancers Symp, Orlando, FL, USA, 22–24 Jan 2010, Abstr 282
48. Rothenberg ML, Oza AM, Bigelow RH et al (2003) Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol 21:2059–2069
49. Giantonio BJ, Catalano PJ, Meropol NJ et al (2007) Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 25:1539–1544
50. Rothenberg ML, Cox JV, Butts C et al (2008) Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Ann Oncol 19:1720–1726
51. Cunningham D, Humblet Y, Siena S et al (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351:337–345
52. Jonker DJ, O'Callaghan CJ, Karapetis CS et al (2007) Cetuximab for the treatment of colorectal cancer. N Engl J Med 357:2040–2048
53. Karapetis CS, Khambata-Ford S, Jonker DJ et al (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 359:1757–1765
54. Van Cutsem E, Peeters M, Siena S et al (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 25:1658–1664
55. Amado RG, Wolf M, Peeters M et al (2008) Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 26:1626–1634
56. Skibber JM, Hoff PM, Minsky BD et al (2001) Cancer of the rectum. In: Devita VT, Hellman S, Rosenberg SA (eds) Cancer: principles and practice of oncology, 6th edn. Lippincott, Williams and Wilkins, Philadelphia, pp 1271–1318
57. Swedish Rectal Cancer Trial (1997) Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 336:980–987
58. Camma C, Giunta M, Fiorica F et al (2000) Preoperative radiotherapy for resectable rectal cancer. A meta-analysis. J Am Med Assoc 284:1008–1015
59. Colorectal Cancer Collaborative Group (2001) Adjuvant radiotherapy for rectal cancer: a systematic overview of 22 randomised trials involving 8507 patients. Lancet 358:1291–1304
60. Kapiteijn E, Marijnen CA, Nagtegaal ID et al (2001) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345:638–646
61. Peeters KC, Marijnen CA, Nagtegaal ID et al (2007) The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 246:693–701
62. Marijnen CA, van de Velde CJ, Putter H et al (2005) Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 23:1847–1858
63. Peeters KC, van de Velde CJ, Leer JW et al (2005) Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients—a Dutch colorectal cancer group study. J Clin Oncol 23:6199–6206
64. Francois Y, Nemoz CJ, Baulieux J et al (1999) Influence of the interval between preoperative radiation therapy and surgery on

downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90–01 randomized trial. J Clin Oncol 17:2396–2402
65. Bosset JF, Collette L, Calais G et al, EORTC Radiotherapy Group Trial 22921 (2006) Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355:1114–1123
66. Gerard JP, Conroy T, Bonnetain F et al (2006) Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3–4 rectal cancers: results of FFCD 9203. J Clin Oncol 24:4620–4625
67. Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al (2006) Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 93:1215–1223
68. Sauer R, Becker H, Hohenberger W, German Rectal Cancer Study Group et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731–1740
69. WHO (1990) Cancer pain relief and palliative care (WHO Tech Rep Ser 804). WHO, Geneva, pp 21–22
70. Renehan AG, Egger M, Saunders MP et al (2002) Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trial. Br Med J 324:813–816
71. Figueredo A, Rumble RB, Maroun J et al (2003) Follow-up of patients with curatively resected colorectal cancer: a practice guideline. BMC Cancer 6:26
72. Renehan AG, Egger M, Saunders MP et al (2005) Mechanisms of improved survival from intensive followup in colorectal cancer: a hypothesis. Br J Cancer 92:430–433
73. Jeffery M, Hickey BE, Hider PN (2007) Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 24:CD002200
74. Tjandra JJ, Chan MK (2007) Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis Colon Rectum 50:1783–1799
75. Bruinvels D, Stiggelbout A, Kievit J et al (1994) Follow-up of patients with colorectal cancer. A meta-analysis. Ann Surg 219:174–182
76. Fleischer D, Goldberg S, Browning T et al (1989) Detection and surveillance of colorectal cancer. JAMA 261:580–585
77. Green RJ, Metlay JP, Propert K et al (2002) Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of Intergroup 0089. Ann Int Med 136:261–269
78. Berman J, Cheung R, Weiberg D (2000) Surveillance after colorectal cancer resection. Lancet 355:395–399
79. Ueno H, Mochizuki H, Hashiguchi Y et al (2004) Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 127:385–394
80. Kitajima K, Fujimori T, Fujii S et al (2004) Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol 39:534–543
81. Tanaka S, Haruma K, Oh-e H et al (2000) Conditions of curability after endoscopic resection for colorectal carcinoma with submucosally massive invasion. Oncol Rep 7:783–788
82. Japanese Society for Cancer of the Colon and Rectum (1980) General rules for clinical and pathological studies on cancer of the colon, rectum and anus, 2nd edn. Kanehara & Co., Ltd., Tokyo
83. Japanese Society for Cancer of the Colon and Rectum (1994) General rules for clinical and pathological studies on cancer of the colon, rectum and anus, 5th edn. Kanehara & Co., Ltd., Tokyo
84. Japanese Society for Cancer of the Colon and Rectum (2005) JSCCR guidelines 2005 for the treatment of colorectal cancer. Kanehara & Co., Ltd., Tokyo
85. Cappuzzo F, Finocchiaro G, Rossi E et al (2008) EGFR FISH assay predicts for response to cetuximab in chemotherapy refractory colorectal cancer patients. Ann Oncol 19:717–723
86. Lièvre A, Bachet JB, Boige V et al (2008) KRAS mutation as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 26:374–379
87. Lièvre A, Bachet JB, Corre DL et al (2006) KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 66:3992–3995
88. Khambata-Ford S, Garrett CR, Meropol NJ et al (2007) Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 25:3230–3237
89. de Reyniès A, Boige V, Milano G et al (2007) KRAS mutation signature in colorectal tumors significantly overlaps with the cetuximab response signature. J Clin Oncol 26:2228–2230
90. Di Fiore F, Blanchard F, Charbonnier F et al (2007) Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy. Br J Cancer 96:1166–1169
91. Wierzbicki R, Jonker DJ, Moore MJ et al (2009) A phase II, multicenter study of cetuximab monotherapy in patients with refractory, metastatic colorectal carcinoma with absent epidermal growth factor receptor immunostaining. Invest New Drugs 23:1803–1810

Invest New Drugs
DOI 10.1007/s10637-011-9779-1

PHASE II STUDIES

A multicenter phase II study of the stop-and-go modified FOLFOX6 with bevacizumab for first-line treatment of patients with metastatic colorectal cancer

Natsuko T. Okita · Taito Esaki · Eishi Baba · Daisuke Sakai · Shinya Tokunaga · Hiroya Takiuchi · Nobuyuki Mizunuma · Kengo Nagashima · Ken Kato

Received: 21 September 2011 / Accepted: 30 November 2011
© Springer Science+Business Media, LLC 2011

Summary Currently, no prospective data exists to support a "stop-and-go" modified FOLFOX6 regimen with bevacizumab in metastatic colorectal cancer (mCRC) patients. This study aimed to evaluate the efficacy and safety of this regimen in first-line mCRC patients. Eligible patients (age ≥20 years) had previously untreated mCRC; Eastern Cooperative Oncology Group performance status of 0–2; and adequate hematologic, hepatic, and renal function. The modified FOLFOX6 regimen and bevacizumab (5 mg/kg) was administered intravenously every 2 weeks. After 8 cycles, patients received maintenance therapy with simplified LV5FU2 and bevacizumab until completion of 8 cycles or disease progression. After maintenance therapy, patients received another 8 cycles of modified FOLFOX6 with bevacizumab until completion of 8 cycles or disease progression. We recruited 50 patients between August 2007 and January 2009. The overall response rate was 48% (80% confidence interval [CI]; 38.2–58) with outcomes as follows: complete response, n=1; partial response, n=23; stable disease, n=21; progression, n=1; and not evaluated, n=4. Median time to treatment failure was 7.7 months (80% CI: 6.2–8.0), and median progression-free survival was 12.8 months (80% CI: 10.8–14). Grade 3/4 toxicities included neutropenia (40%), nausea (4%), diarrhea (14%), thrombosis (4%), and hypertension (4%) et al. Grade 1, 2, or 3 peripheral neuropathy was reported in 38%, 40%, and 10% of patients, respectively. The stop-and-go modified FOLFOX6 and bevacizumab regimen is effective and well tolerated as first-line chemotherapy for mCRC patients.

Keywords Metastatic colorectal cancer · Stop and go · Modified FOLFOX6 · Bevacizumab

N. T. Okita (✉) · K. Kato
Gastrointestinal Oncology Division,
National Cancer Center Hospital,
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: natukot@gmail.com

T. Esaki
Gasrointestinal and Medical Oncology Division,
National Kyushu Cancer Center,
Fukuoka, Japan

E. Baba
Department of Medicine and Biosystemic Science,
Kyushu University Graduate School of Medical Sciences,
Fukuoka, Japan

D. Sakai
Department of Clinical Oncology,
Osaka Medical Center for Cancer and Cardiovascular Diseases,
Osaka, Japan

S. Tokunaga
Department of Clinical Oncology, Osaka City General Hospital,
Osaka, Japan

H. Takiuchi
Cancer Chemotherapy Center, Osaka Medical College Hospital,
Osaka, Japan

N. Mizunuma
Department of Medical Oncology, Cancer Institute Hospital
of Japanese Foundation for Cancer Research,
Tokyo, Japan

K. Nagashima
Faculty of Pharmaceutical Sciences, Josai University,
Saitama, Japan

Published online: 10 December 2011

Introduction

Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. Bevacizumab binds to VEGF and inhibits VEGF-receptor binding, thereby preventing the growth and maintenance of tumor blood vessels.

The addition of bevacizumab to a regimen consisting of bolus 5-fluorouracil (5-FU), leucovorin, and irinotecan (IFL) was shown to improve survival for first-line chemotherapy of metastatic colorectal cancer (mCRC) [1]. Second-line treatment with a regimen of oxaliplatin plus 5-FU/folinic acid (FOLFOX4) combined with bevacizumab was found to improve survival [2]. In the first-line setting, the addition of bevacizumab to oxaliplatin-based chemotherapy improved progression free survival (PFS) [3]. In that study, a large proportion of patients stopped treatment earlier than allowed by the study protocol.

FOLFOX4 often induces grade 3 neurotoxicity in previously untreated metastatic colorectal cancer patients [4]. In some case, neurotoxicity became the reason for discontinuation of oxaliplatin. Moreover, the symptom remains for several years after discontinuation of oxaliplatin [5]. There were some reports to prevent neurotoxicity of oxaliplatin [6, 7]. A stop-and-go strategy, stop oxaliplatin after a difined period of time and later reintroduction, can be an effective approach for avoiding severe neurotoxicity [8, 9]. On the other hand, modified FOLFOX6 with or without bevacizumab is effective, tolerable and less burdensome for patients as a first line treatment [10]. Therefore, in the present phase II study, we investigated the efficacy and tolerability of the stop-and-go strategy for therapy with mFOLFOX6 plus bevacizumab.

Materials and methods

This study was a multicenter, open-label, phase II study. Patients at least 20 years of age were eligible if they had: histologically-confirmed metastatic or recurrent colorectal cancer; provided written informed consent; not previously undergone chemotherapy; Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; adequate hematologic, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 [7]. Patients were excluded if they had brain metastasis, hypertension, proteinurea, hemorrhage, embolism, uncontrolled diabetes mellitus, heart disease, renal failure, liver failure, intestinal obstruction or active infection. The study protocol was approved by the institutional review boards of the participating institutions. This study was registered with UMIN-CTR (number: UMIN000001233). All costs of medical treatment (drugs and tests) were paid for by Japanese health insurance.

Treatment plan and evaluation

The modified FOLFOX6 regimen consisted of oxaliplatin (85 mg/m^2) on Day 1, given as a 2-hour infusion concurrent with *l*-leucovorin (200 mg/m^2), followed by 5-FU (400 mg/m^2 by injection and 2,400 mg/m^2 by continuous infusion for 46 h) [10]. Bevacizumab (5 mg/kg) was administered intravenously on day 1 before the modified FOLFOX6 regimen, and all therapies were administered every 2 weeks. After 8 cycles or until grade 3 neurotoxicity developed, patients received maintenance therapy other than oxaliplatin (simplified LV5FU2 and bevacizumab) until completion of 8 cycles or the incidence of disease progression. After maintenance therapy, patients received another 8 cycles of modified FOLFOX6 with bevacizumab until completion of 8 cycles or the incidence of disease progression. Prophylaxis of nausea and premedication for allergy after one allergic event were recommended. We did not use prophylaxis against neurotoxicity.

Tumor response was assessed according to RECIST criteria [11] every 8 weeks. Patients were re-evaluated over 4 weeks after initial documentation of complete response or partial response to confirm the assessment. Progression-free survival (PFS) was defined as the time from the date of registration to the first confirmation of disease progression, or death from any cause, and was censored at the last tumor assessment if a patient withdrew before progression. Overall survival (OS) was defined as the time from registration to any death. Time to treatment failure (TTF) was defined as the time from registration to discontinuation of the protocol treatment. Toxicity was assessed before each 2-week cycle using the Common Terminology Criteria for Adverse Events version 3.0 [12]. Clinical report forms were sent to data managers and monitored data was sent to a statistician. We shared our experience with toxicity evaluation in our prior studies [13, 14] and decided how to evaluate neurotoxicity before planning the protocol.

Statistics

The primary objective of the trial was to estimate the response rate for this treatment protocol. We calculated that with a sample size of 45 patients, assuming that the observed response rate was approximately 50% based on past studies, the half-width of the exact 80% binomial confidence interval would be approximately equal to 10.4%. In particular, for an observed response rate of 50%, the exact 80% binomial confidence interval was 38.4% to 59.4%. If the response rate is lower than 30%, the protocol treatment should not be applied in clinical practice. Assuming 5 ineligible cases, we calculated that we would need to enroll 50 patients.

The primary endpoint of this study, the response rate, was estimated, and the exact two-sided 80% confidence interval

Table 1 Patient characteristics (n=50)

Sex	
Male/Female	28 /22
Age	
Median (Range)	61 (37–75)
ECOG performance status	
0/1/2	34/16/0
Primary tumor site	
Colon/Rectum	32/18
Histology type	
Adeno/Muc/Sig	49/0/1
Metastatic site	
Liver/Lung/Lymph node/Other	34/28/22/14
Surgery	
Yes/No	41/9
Adjuvant chemotherapy	
Yes/No	8/42

was calculated. The secondary endpoints were TTF, PFS, OS, the incidence of adverse events and the incidence of grade 3 neurotoxicity. PFS, TTF and OS were estimated according to the Kaplan-Meier method. Median PFS, TTF and OS were estimated, and 80% confidence intervals were calculated with the use of the Greenwood formula. The cumulative incidence of grade 3 neurotoxicity was estimated using competing risk analysis [15], where death was considered the competing risk. Median follow-up was computed by the reverse Kaplan-Meier method [16]. The primary endpoint, TTF, PFS and OS were analyzed in the all eligible cases (all patients excluded ineligible patients). The incidence of adverse events and the incidence of grade 3 neurotoxicity were analyzed in the all treatment cases (all patients who were received one or more the protocol treatment). The FREQ procedure with binomial option (SAS software, version 9.2 (SAS Institute)) was used to analyze categorical data and the LIFETEST procedure was used to analyze time-to-event data.

Results

Patient characteristics

A total of 50 patients from 7 different Japanese hospitals were enrolled in this study from August 2007 to January 2009. All patients were included in the efficacy and safety analysis. Baseline characteristics are summarized in Table 1. Median age was 61 years (range: 37–75), 56% of the patients were men. The primary tumor was located in the colon in 32 patients (64%) and in the rectum in 18 patients (36%).

Efficacy

All 50 patients had measurable metastatic sites. The overall response rate was 48% (80% CI: 38.2, 58) with outcomes as follows: complete response, n=1; partial response, n=23; stable disease, n=21; progression, n=1; and not evaluated, n=4. The disease control rate was 90%. Two patients underwent curative surgery because of tumor shrinkage during protocol chemotherapy. After a median follow-up of 27.8 months, median TTF and PFS were 7.7 months (80% CI: 6.2, 8.0) and 12.8 months (80% CI: 10.8, 14.0), respectively (Fig. 1). At the data cut-off date, 24 patients had died, and median OS was 30.1 months (80% CI: 25.6, –).

Safety

Table 2 summarizes hematological and non–hematological toxicities. Grade 3–4 neutropenia was observed in 40% of patients, but no patient experienced Grade 3–4 febrile neutropenia. Grade 3–4 bevacizumab-associated adverse events

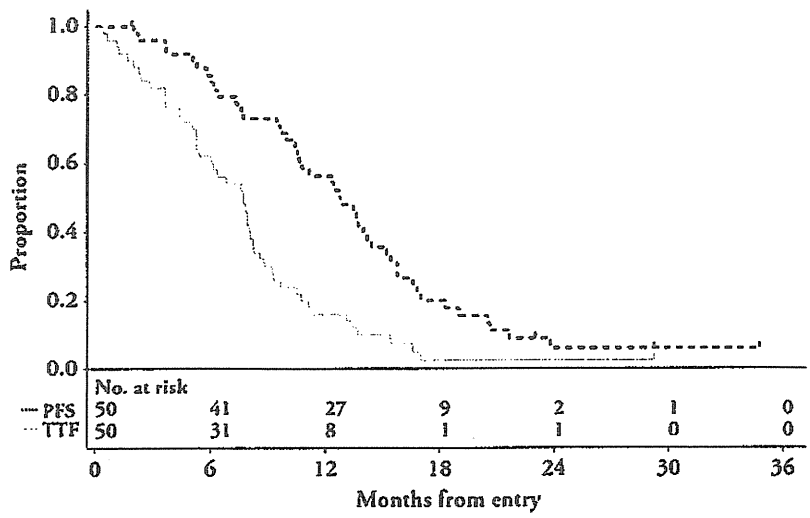


Fig. 1 The median time to treatment failure was 7.7 months (80% CI: 6.2, 8.0) and the median progression free survival time was 12.8 months (80% CI: 10.8, 14.0)

Table 2 Toxicity (n=50)

Adverse event CTC–AE v. 3.0	Grade1–2		Grade 3–4	
	No.	%	No.	%
Hematologic toxicity				
Neutropenia	24	48	20	40
Anemia	35	70	0	0
Thrombocytopenia	24	48	0	0
Bevacizumab-associated toxicity				
Thromboembolism	0	0	2	4
Hypertension	5	10	2	4
Protein urea	19	38	0	0
Bleeding	22	44	0	0
Delayed wound healing	3	6	0	0
Perforation –colon–	0	0	1	2
Non-hematologic toxicity				
Diarrhea	16	32	7	14
Sensory neurotoxicity	39	78	5	10
Nausea	34	68	2	4
Allergic reaction	9	18	0	0

were observed as follows: thrombosis 2/50, hypertension 2/50, and perforation of colon 1/50. There were no treatment-related deaths. Figure 2 shows cumulative proportion of grade 1–3 neurotoxicity. Grade 3 sensory neuropathy was observed in 5 (10%) patients during the protocol treatment. Four of five patients with Grade 3 sensory neuropathy recovered to Grade 0–2 after protocol treatment. Thirteen (26%) and fourteen (28%) patients withdrew from protocol treatment due to adverse events and doctor's decision, respectively. Protocol treatment was discontinued due to grade 2 neurotoxicity based on the doctors' decision in 7 patients, and 4 patients discontinued due to grade 3 neurotoxicity. Three patients were needed to have oxaliplatin reintroduction due to progression during maintenance and only one patient could be reintroduced.

Discontinuation during and after protocol treatment

All patients ended the protocol treatment at the data cutoff date (April 20, 2011). Fourteen (28%) patients received protocol re-introduction and only 6 patients completed 24 cycles of protocol treatment. Thirty-six patients were discontinued the protocol treatment before re-introduction because of early progression (5/36), toxicity (24/36), patients' refusal (4/36), or other reasons (3/36). The re-introduction rate in eligible patients was 53.8% (14 of 26 patients). As a post-therapy, patients received several treatments as follows: FOLFOX-based regimen, 22%; sLV5FU2-based regimen, 36%; irinotecan-based regimen, 22%; and other, 20%. Nine of twelve patients (75%) without reintroduction despite eligibility received the sLV5FU2-based regimen.

Discussion

The FOLFOX plus bevacizumab regimen is one of the standard chemotherapy for the first-line treatment of mCRC. However, oxaliplatin induces severe sensory neuropathy, and as result the stop-and-go strategy has been investigated in order to decrease toxicity. There are 2 major unresolved issues with the stop-and-go strategy: (1) whether "stop" has the same efficacy as the normal FOLFOX regimen; and (2) when is the optimal time to "go" (reintroduction)?

OPTIMOX1 [8] and OPTIMOX2 [17] studies have revealed that maintenance therapy without oxaliplatin is promising and that chemotherapy discontinuation is unfavorable. In order to increase dose intensity, a stop-and-go regimen of

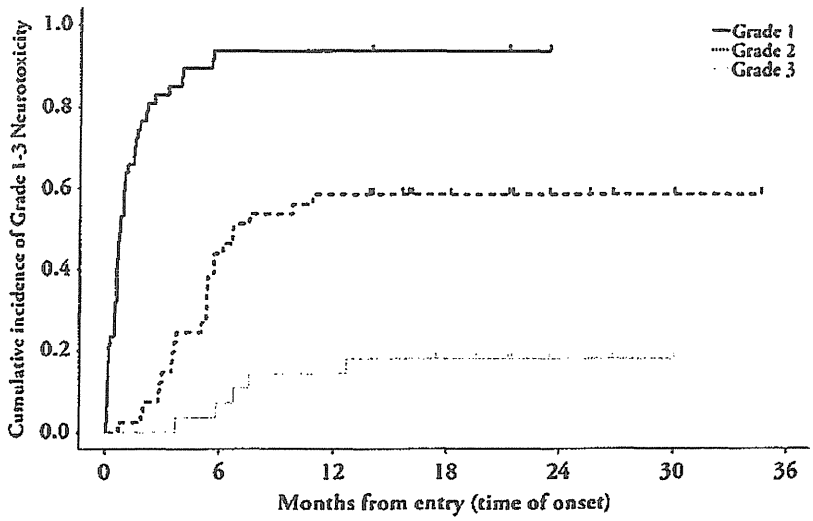


Fig. 2 Cumulative proportion of grade 1–3 neurotoxicity

OPTIMOX1 was investigated by using 6 cycles of FOLFOX7 (oxaliplatin 130 mg/m^2). On the other hand, bevacizumab added to FOLFOX4 (oxaliplatin 85 mg/m^2) in the first line study [3]. FOLFOX4 regimen requires two times hospital visit each cycle and modified FOLFOX6 (oxaliplatin 85 mg/m^2) plus bevacizumab is reported to be effective, tolerable, and less burdensome for patients as first-line treatment [10]. Thus, we added bevacizumab to mFOLFOX6 in this study. Because the dose intensity of mFOLFOX6 is lower than FOLFOX7, efficacy could be reduced if the mFOLFOX6 regimen were to be administered using a stop-and-go strategy.

Previous studies have revealed that the response rates for FOLFOX4 plus bevacizumab without a stop-and-go strategy were in the range of 45%~58.5% [3, 4, 8]. In our study, the response rate was 48% (80% CI: 28.2–56.8) as compared with the rate of 56% for stop-and-go mFOLFOX6 therapy reported in a previous retrospective study [18]. These results show that the early impact of stop-and-go mFOLFOX6 is comparable to treatment without "stop".

As for the ideal number of cycles of induction with FOLFOX, previous studies stopped at a total oxaliplatin dose of approximately 680–780 mg/m^2 [8, 9, 17–19]. The estimated incidence of grade 3 neurotoxicity was reported to be 10% after 9 cycles (oxaliplatin 765 mg/m^2) and 25% after 12 cycles (oxaliplatin 1,020 mg/m^2) [20]. In our schedule, oxaliplatin was stopped after reaching a dose of 680 mg/m^2. The total dose of oxaliplatin during the induction chemotherapy in our protocol is the same as in the CONcePT trial, investigated by using 8 cycles of modified FOLFOX7 (oxaliplatin 85 mg/m^2) [9]. Induction chemotherapy should result in a reasonably high response rate; we consider that rate to be roughly 50% and, therefore, conclude that our dosages were acceptable. Further studies are needed in order to determine the efficacy and safety of lower induction dose of oxaliplatin.

The re-introduction rate of 28% in our patients was lower than the rates of 40.1% [8] and 55.1% [17] reported in previous studies. We defined discontinuation of oxaliplatin as the time patients had grade3 neurotoxicity. But doctors and patients tended to avoid reintroduction if tumors were controlled and/or patients had sustained grade 2 neurotoxicity. Although the reintroduction rate was low, the median PFS was longer than in previous reports without bevacizumab [8, 17]. Most patients without reintroduction, for reasons other than progression, received a regimen of sLV5FU2 plus BV after protocol treatment. Bevacizumab containing intermittent oxaliplatin also revealed a long PFS (12.0 month) [9]. Bevacizumab could increase the probability of tumor control. Furthermore, all patients with grade 3 sensory neuropathy received sLV5FU2, with or without bevacizumab, after discontinuation of protocol treatment, and most of these patients recovered to grade 0–2 neurotoxicity. Consequently, our results suggest that reintroduction at the time of progression is preferable to reintroduction at the scheduled time.

It has been reported that oxaliplatin-related neurotoxicity can be treated with calcium plus magnesium [6] or pregabalin [7]. While these studies suggested that certain drugs were effective in minimizing oxaliplatin-related neurotoxicity, the impact of these drugs on survival was unclear. It remains to be determined whether drugs used to treat neurotoxicity have an acceptable risk-benefit balance in relation to oxaliplatin-based regimens for mCRC. Although our uncontrolled study data has limitations, the results indicate that the stop-and-go mFOLFOX6 plus BV regimen is an effective treatment modality for patients with mCRC.

Acknowledgements We thank Hiroshi Yoshida, Aasako Sakamoto and Makiko Shinogi for data collection, and Yushi Nagai and Michiyo Tada for data management. This work was supported by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan [grant number 20S-3].

Conflict of interest statements The authors declare that they have no conflict of interest.

References

1. Hurwitz H, Fehrenbacher L, Novotny W et al (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335–2342
2. Giantonio BJ, Catalano PJ, Meropol NJ et al (2007) Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 25:1539–1544
3. Saltz LB, Clarke S, Diaz-Rubio E et al (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 26:2013–2019
4. Goldberg RM, Sargent DJ, Morton RF et al (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23–30
5. Andre T, Boni C, Boudiaf LM et al (2004) Oxaliplatin, fluorouracil and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343–2351
6. Grothey A, Nikcevich DA, Sloan JA et al (2011) Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. J Clin Oncol 29:421–427
7. Saif MW, Syrigos K, Kaley K, Isufi (2010) Role of pregabalin in treatment of oxaliplatin-induced sensory neuropathy. Anticancer Res 30:2927–2934
8. Tournigand C, Cervantes A, Figer A et al (2006) OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer-a GERCOR study. J Clin Oncol 24:394–400
9. Grothey A, Hart LL, Rowland KM, et al. (2008) Intermittent oxaliplatin (oxali) administration and time-to-treatment-failure (TTF) in metastatic colorectal cancer (mCRC): Final results of the phase III CONcePT trial. J Clin Oncol 26S: Abstr 4010.

10. Hochster HS, Hart LL, Ramanathan RK et al (2008) Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE study. J Clin Oncol 26:3523–3529
11. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
12. National Cancer Institute-Common Toxicity Criteria. (NCI-CTC Version 3.0, March 31, 2003).
13. Kato K, Inaba Y, Tsuji Y et al (2011) A multicenter phase-II study of 5-FU, leucovorin and oxaliplatin (FOLFOX6) in patients with pretreated metastatic colorectal cancer. Jpn J Clin Oncol 41:63–68
14. Yasui H, Hamaguchi T, Shimada Y, et al. (2008) A multicenter phase-II study of 5-FU, leucovorin and oxaliplatin (FOLFOX6) in patients with previously untreated metastatic colorectal cancer. The 4th Annual Meeting of Japanese Society of Clinical Oncology P-183
15. Kalbfleisch JD, Prentice RL (2002) The statistical analysis of failure time data, 2nd edn. Wiley, Hoboken
16. Schemper M, Smith TL (1996) A note on quantifying follow-up in studies of failure time. Controlled Clinical Trials 17:343–346
17. Chibaudel B, Maindrault-Goebel F, Gerard Lled et al (2009) Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 study. J Clin Oncol 27:5727–5733
18. Vaidyanathan G, Groman A, Wilding G, Fakih MG (2010) Stop and go FOLFOX plus bevacizumab chemotherapy in the first-line treatment of metastatic colorectal cancer. Oncology 79:67–71
19. Hochster HS, Grothey A, Shpilsky A, Childs BH (2008) Effect of intravenous calcium and magnesium versus placebo on response to FOLFOX+bevacizumab in the CONcePT trial. J Clin Oncol (ASCO-GI 2008 Abstract No.280)
20. de Gramont A, Figer A, Seymour M et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947

British Journal of Cancer (2012) 106, 666–672
© 2012 Cancer Research UK All rights reserved 0007 – 0920/12
www.bjcancer.com

Clinical Studies

Phase I first-in-human study of TAK-285, a novel investigational dual HER2/EGFR inhibitor, in cancer patients

T Doi*[,1], H Takiuchi[2], A Ohtsu[1], N Fuse[1], M Goto[2], M Yoshida[2], N Dote[3], Y Kuze[3], F Jinno[3], M Fujimoto[4], T Takubo[5], N Nakayama[5] and R Tsutsumi[6]

[1]Division of Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan; [2]Cancer Chemotherapy Center, Osaka Medical College Hospital, 2-7 Daigakucho, Takatsuki, Osaka 569-8282, Japan; [3]Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan; [4]Clinical Data Science Division, Takeda Bio Development Center Limited, Sapia Tower, 1-7-12 Marunouchi, Chiyoda-ku, Tokyo 100-0005, Japan; [5]Preclinical and Clinical Pharmacology Division, Takeda Bio Development Center Limited, Sapia Tower, 1-7-12 Marunouchi, Chiyoda-ku, Tokyo 100-0005, Japan; [6]Clinical Development Division, Takeda Bio Development Center Limited, Sapia Tower, 1-7-12 Marunouchi, Chiyoda-ku, Tokyo 100-0005, Japan

BACKGROUND: This phase I first-in-human study was conducted in Japanese patients to investigate the safety, pharmacokinetics (PKs), and determine the maximum tolerated dose (MTD) of oral TAK-285, a novel dual erbB protein kinase inhibitor that specifically targets human epidermal growth factor receptor (EGFR) and HER2.

METHODS: The TAK-285 dose was escalated until MTD was determined. A second patient cohort received TAK-285 at the MTD for at least 4 weeks.

RESULTS: In all, 26 patients received TAK-285 at doses ranging from 50 to 400 mg once daily (q.d.) or twice daily (b.i.d.); 20 patients made up the dose escalation cohort and the remaining 6 patients were the repeated administration cohort. TAK-285 was well tolerated. Dose-limiting toxicities noted in two patients who received 400 mg b.i.d. were grade 3 increases in aminotransferases and grade 3 decreased appetite. Consequently, the MTD was determined to be 300 mg b.i.d. Absorption of TAK-285 was rapid after oral dosing, and plasma exposure at steady-state increased in a dose-proportional fashion for doses ranging from 50 to 300 mg b.i.d. A partial response was observed for one patient with parotid cancer who received 300 mg b.i.d.

CONCLUSION: The toxicity profile and PK properties of oral TAK-285 warrant further evaluation.

British Journal of Cancer (2012) **106,** 666–672. doi:10.1038/bjc.2011.590 www.bjcancer.com
Published online 12 January 2012
© 2012 Cancer Research UK

Keywords: first-in-human; phase I TAK-285; epidermal growth factor receptor; dual erbB protein kinase inhibitor family; receptor tyrosine kinase inhibitor

Dimerisation of the human epidermal growth factor receptor (EGFR) protein family members, including HER1/EGFR and HER2, activates intracellular kinase and initiates a phosphorylation cascade that, in tumour cells, results in enhanced cellular proliferation and survival. Especially in the case of dimers that contain HER2, such activation of signal transmission can be persistent and potent, and under these circumstances is associated with high cellular differentiation and abnormal growth (Reid *et al*, 2007).

Clinically, HER2 and EGFR overexpression and the associated increase in cellular signal transduction is a common feature of tumours such as breast cancer and gastric cancer, and is associated with aggressive disease (Yonemura *et al*, 1991; Salomon *et al*, 1995; Nicolini *et al*, 2006). The prognosis is worse for such patients than for non-overexpressing patients. This also applies to many other cancer types such as colon cancer, ovarian cancer and bladder cancer, and small molecular weight chemotherapeutic agents or antibodies that target EGFR and HER2 and inhibit their activity have been proven to be clinically effective in overexpressing cancers (Hynes and Lane, 2005; Shepherd *et al*, 2005; Thatcher *et al*, 2005; Moore *et al*, 2007; Mok *et al*, 2009).

TAK-285 is a novel low-molecular weight compound that was designed and synthesised by Takeda Pharmaceutical Company, Osaka, Japan and has been shown to selectively and potently inhibit HER2 and EGFR kinase activities. Biochemically, TAK-285 inhibits HER2 and EGFR phosphorylation, with 50% inhibition concentrations of 17 and 23 nmol l^{-1}, respectively (Aertgeerts *et al*, 2011).

The antitumour activity of TAK-285 was evaluated in several murine models employing HER2- or EGFR-overexpressing human tumour xenografts such as BT-474, 4-1 ST and A431. These studies revealed that orally administered TAK-285 effectively inhibited xenograft growth and this effect appeared to correlate with its ability to inhibit EGRF and HER2 (Iwahara *et al*, 2008). Additionally, in rodent and primate toxicity models, TAK-285 was well tolerated and induced toxicities observed with other compounds possessing a similar mechanism of action. TAK-285 also demonstrated potentially no exhibition of elevated cardiac risks whereas other tyrosine kinase inhibitors can elicit secondary effects including heart toxicity (Shell *et al*, 2008). In total, these non-clinical studies suggest that TAK-285 may possess exploitable

*Correspondence: Dr T Doi; E-mail: tdoi@east.ncc.go.jp
Received 2 September 2011; revised 1 December 2011; accepted 16 December 2011; published online 12 January 2012