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研究成果の刊行に関する一覧表

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Ⅲ. 研究成果の刊行物・別冊

Int J Clin Oncol (2009) 14:416–420
DOI 10.1007/s10147-009-0892-5

ORIGINAL ARTICLE

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Current therapeutic strategies for anal squamous cell carcinoma in Japan

Received: December 25, 2008 / Accepted: March 8, 2009

Abstract
Background. In Western countries, chemoradiotherapy (CRT) is well established as the standard therapy for stages II/III anal squamous cell carcinoma (ASCC). In Japan, the therapeutic modalities for and outcomes of this disease have not been clarified because ASCC is quite rare. The Colorectal Cancer Study Group of the Japan Clinical Oncology Group (JCOG-CCSG) conducted a survey to determine the current therapeutic strategies for ASCC in Japan.

Methods. In July 2006, a questionnaire was sent to 49 institutions affiliated with the JCOG-CCSG to gather information on numbers of cases, therapeutic modalities, and outcomes. The target subjects were patients with stages II/III ASCC, diagnosed from January 2000 to December 2004, who were 20–80 years of age with normal major organ function and no severe complications.

Results. Replies were received from 40 institutions. A total of 59 patients satisfied the subject criteria. Detailed information was obtained for 55 subjects; 25 (45%) had stage II ASCC and 30 (55%) had stage III ASCC. CRT was performed in 25 patients (45%); surgery in 17 (31%); surgery combined with radiotherapy (RT), chemotherapy, or CRT in 8 (15%); and RT in 5 (9%). Complete response rate in CRT was 80% (20/25). The 3-year progression-free survival rates for all subjects and for CRT-only subjects were 67% and 77%, respectively.

Conclusion. From 2000 to 2004, only 59 patients with ASCC were identified in the JCOG-CCSG survey and about half of them underwent CRT.

Key words Anal cancer · Squamous cell carcinoma · Chemoradiotherapy

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Introduction

The definition of anal cancer is anal canal cancer arising in the anal canal from the upper margin of the puborectalis muscle attachment site to the margin of the anus and cancer of the perianal skin adjacent to the anal verge. According to reports published in various Western countries, anal cancer accounts for approximately 2% of all cancers.[1] The histological types vary widely and include adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, basaloid carcinoma, malignant melanoma, and sarcoma.

While precise details on the incidence of anal cancer in Japan are unknown, a population survey report in 2003 published by the Japanese Ministry of Health, Labour and Welfare stated that 261 patients had died of anal cancer

accounting for 0.67% of all deaths caused by colorectal cancers. According to a survey involving 73 medical facilities conducted by the Japanese Society for Cancer of the Colon and Rectum (JSCCR), with an average follow-up period of 17.2 years.[2] there were a total of 1540 malignant anal tumors; 226 (14.7%) of these cases were squamous cell carcinomas and 24 (1.6%) were basaloid epithelial cancer. Although anal cancer is a relatively rare disease in the United States, there were 4660 patients (approximately 2 per 100000) in 2006.[1] The number of cases had doubled in 30 years and is expected to increase in the future.[3,4] Based on the current situation in Western countries, the incidence of anal cancer is also expected to rise in Japan. It is reported that the high incidence is associated with female gender, infection with human papillomavirus (HPV), lifetime number of sexual partners, genital warts, cigarette smoking, receptive anal intercourse, and infection with human immunodeficiency virus (HIV).[5]

Until the 1980s, surgery was the standard therapy for anal squamous cell carcinoma (ASCC) in Western countries.[6,7] Chemoradiotherapy (CRT) then replaced surgery as the standard treatment for stages II/III ASCC localized in the pelvis. The most important advantage of CRT is that the function of the anus can be preserved, but salvage surgery can also be safely performed if any cancer remains or if there is local recurrence after CRT. The majority of recurrences after CRT are local; the incidence of distal metastasis is relatively low, at 10%–17%, so salvage surgery can be performed for local recurrences as well. The results of retrospective studies of CRT have indicated comparable or better outcomes when it is compared to surgery.[8–11] Although there are no prospective studies comparing CRT and surgery to date, CRT is now considered the standard therapy for stages II/III ASCC in Western countries.

There are only a few published reports on ASCC in Japan because the disease is quite rare in this country; it is not clear what types of treatment are performed or how effective each treatment is against ASCC. Consequently, the Colorectal Cancer Study Group of the Japan Clinical Oncology Group (JCOG-CCSG) decided to conduct a survey on stages II/III ASCC in order to determine the current therapeutic strategies in Japan.

Methods

In May 2006, questionnaires were sent to 49 institutions affiliated with the JCOG-CCSG.

Questionnaire

Question 1. – Which option best describes the treatment of stages II/III ASCC at your institution as of May 2006:
(a) Surgery (alone or with preoperative/postoperative radiotherapy [RT], chemotherapy [CTx], or CRT
(b) RT (with surgery if cancer remains);
(c) CRT (with surgery if cancer remains) or
(d) Other (specify)?

Question 2. – During the 5-year period from January 2000 through December 2004, how many patients satisfied all of the following conditions: stages II/III ASCC; age between 20 and 80 years; performance status 0/1 with major organ function (GOT/GPT ≤100 IU/I, creatinine ≤1.5 mg/dl); and no severe complications?
Question 3. – Please provide the following details for each of the patients identified in question 2:
Start of initial therapy – age, gender, stage, and therapy (surgery, RT, CRT or other).
Initial therapy effectiveness (complete response [CR], partial response [PR], no change [NC], progressive disease [PD], or not evaluated [NE]).
Confirmation date of progression/recurrence, last known date of survival, and/or date of death.
Cause of death (primary disease, another disease, therapy-related death, other, and unknown).
Question 3 Definitions of terms. – Staging was defined according to the sixth edition of the cancer staging manual of the American Joint Committee on Cancer. Therapeutic effectiveness was determined by each attending physician.

Statistical analysis

Progression-free survival (PFS) was the length of time from the start of therapy to the confirmation date of progression/recurrence or death. Overall survival (OS) was the length of time from the start of therapy to the date of death. If the survival status of a patient was unknown, the last known date of survival was used. PFS and OS were determined using the Kaplan-Meier method, and statistical analyses were performed using Dr. SPSS II 11.0.1J (SPSS Japan, Tokyo, Japan).

Results

Replies were obtained from 40 of the 49 affiliated institutions (response rate, 82%) between May and September 2006.

Question 1

In the treatment of stage II ASCC, CRT was selected at 28 institutions (70%), surgery at 8 (20%) and other types of treatment at 4 (10%). As for the treatment of stage III ASCC, CRT was select at 27 institutions (67%), surgery at 9 (23%) and other types of treatment at 4 (10%).

Questions 2 and 3

Patient/Subject background information

During the 5-year period from January 2000 to December 2004, a total of 59 patients satisfied the subject criteria

Table 1. Patient characteristics

All patients	59
Patients with detailed information	55
Age, years; median (range)	66 (33–80)
Gender	
Male	9
Female	46
cT	
1	3
2	30
3	12
4	7
Unknown	3
cN	
1	25
2	5
3	16
Unknown	9
cStage[a]	
II	25
IIIA	5
IIIB	25
Treatment modality	
Chemoradiotherapy	25
Surgery	17
Surgery + alpha[b]	8
Radiotherapy	5

[a] Staging was defined according to the sixth edition of the cancer staging manual of the American Joint Committee on Cancer
[b] Surgery with chemotherapy, surgery with radiotherapy, or surgery with chemoradiotherapy

previously indicated in question 2. Detailed information was obtained for 55 subjects, as patient data were unavailable from 1 of the 40 responding institutions. The backgrounds of the 55 patients are summarized in Table 1. The median age was 66 years (range, 33–80 years) and 12 subjects were older than 76 years of age. There were nine men and 46 women, and the breakdown of stage II, IIIA, and IIIB subjects was 25, 5, and 25 patients, respectively.

Therapeutic modalities and results

The therapeutic details are also shown in Table 1. CRT was performed in 25 (45%) subjects; surgery alone in 17 (31%) subjects; surgery and either RT, CTx, or CRT in 8 (15%) subjects; and RT alone in 5 (9%) subjects. Of the CRT regimens, 5-fluorouracil (5-FU) and cisplatin (CDDP; FP) was the most common regimen, used for 16 subjects; followed by 5-FU plus mitomycin C (MMC) and other regimens, used for 5 and 4 subjects, respectively (Table 2). The median dose of RT for CRT was 60 Gy (range, 36–70 Gy).

The complete response rate for CRT was 80% (20/25). With a median follow-up period of 2.7 years, the 3-year PFS and OS rates for all the 55 subjects were 67% and 91%, respectively; for the 25 CRT-only subjects the rates were 77% and 95%, and for the 17 surgery-only subjects the rates were 73 and 3%.

Table 2. Chemotherapy regimens used in the 25 patients who received chemoradiotherapy

FP	16
5-FU+MMC	5
5-FU	3
5-FU+NDP	1

FP, 5-fluouracil (FU) + cisplatin; MMC, mitomycin C; NDP, nedaplatin

Discussion

In our JCOG-CCSG survey, only 59 patients diagnosed with stages II/III ASCC met the subject criteria during the 5-year period in question, which means an average of fewer than 12 such patients per year in our group. Our data were collected from a retrospective survey and a limited number of institutions. This survey revealed that ASCC is quite rare in Japan. In Western countries, the incidence of ASCC has doubled in the past 30 years, from 1 to 2 per 100 000; therefore, the incidence of ASCC is expected to increase in Japan as well.

According to a survey conducted by the JSCCR in 2003, the percentage of ASCC patients who underwent surgery was 89% before 1989, 65% from 1990 to 1994, and 49% after 1995. In the present JCOG-CCSG survey, 52% (14/27) of the patients from 2000 to 2002, and 39% (11/28) of the patients from 2003 to 2004 underwent surgery. In addition, 20% of the responding institutions identified surgery as their main therapeutic modality as of May 2006. Based on these results, the proportion of patients who have undergone surgery has decreased gradually.

Recently, instead of surgery, about 70% of the institutions surveyed in the present study selected CRT as the treatment best suited to stages II/III ASCC. We think this is because some studies showing the effectiveness of CRT were published from Western countries. We summarize the phase III trials in Table 3.[12–15] Based on these phase III trials, combination therapy with 5-FU, MMC, and RT is considered to be the standard therapy for stages II/III ASCC in Western countries.

When compared to CDDP, the incidence of hemotoxicity is higher for MMC. Because the results of FP and RT combination therapy appeared so promising[10,16,17] until the interim results of the Radiation Therapy Oncology Group (RTOG)-9811 trial were published, FP and RT combination therapy was one of the recommended options in the practice guidelines published by the National Comprehensive Cancer Network (NCCN). Consequently, CDDP has often been used in clinical settings. In the present JCOG-CCSG study, FP was used in 16 of the 25 patients (64%) who received CRT and was the most common agent used in CRT.

In our present survey, the 3-year OS rate was considerably higher than that reported previously. We think this is due to the relatively short follow-up period, with the median follow-up period being only 2.7 years. If the follow-up period had been longer, the 3-year OS rate may have been

Table 3. Summary of phase III trials for locally advanced anal cancer

	No. of patients	Chemotherapy	RT	OS	*P* value	DFS	*P* value	LCR	*P* value	CFS	*P* value
EORTC[12]	52	None	45 Gy	56%[a]	–	58%[a]	0.05	50%[a]	0.02	40%[a]	0.002
	51	5-FU+MMC	+15–20 Gy	56%[a]		63%[a]		68%[a]		70%[a]	
ACT I[13]	279	None	45 Gy	58%[b]	0.25	–		39%[b]	<0.01	–	
	283	5-FU+MMC	+15–25 Gy	65%[b]		–		61%[b]		–	
RTOG-8704[14]	145	5-FU	45 Gy+9 Gy	67%[c]	0.31	51%[c]	<0.01	66%[c]	<0.01	59%[c]	0.01
	146	5-FU+MMC		76%[c]		73%[c]		84%[c]		71%[c]	
RTOG-9811[15]	322	5-FU+MMC	45 Gy/25 Fr	84%[b]	0.13	68%[b]	0.33	75%[b]	0.19	90%[b]	0.04
	312	5-FU+CDDP	+10–14Gy	76%[b]		62%[b]		69%[b]		83%[b]	

EORTC, European Organization for Research and Treatment of Cancer; ACT, Anal Cancer Trial; RTOG, Radiation Therapy Oncology Group; CDDP, cisplatin; RT, radiotherapy; OS, overall survival; DFS, disease-free survival; LR, local-regional control; CFS, colostomy-free survival
[a] 5 Years
[b] 3 Years
[c] 4 Years

lower, because our 3-year PFS rate was about the same as that previously reported in other studies.

In conclusion, even though our study was conducted retrospectively and some results are still preliminary in nature, this survey is important because only a limited amount of information on this subject has previously been reported in Japan. Although CRT was not the standard therapy for stages II/III ASCC in Japan from 2000 to 2004, a consensus now appears to be growing and the JCOG-CCSG intends to conduct a clinical trial in the near future on a new combination CRT regimen for the express purpose of establishing a new standard that is more effective than the current therapy.

Conflict of interest statement

No author has any conflict of interest.

Acknowledgments Responding institutions and their respective persons-in-charge were: Sapporo-Kosei General Hospital, Yukifumi Kondo; Iwate Medical University Hospital, Kouki Ohtsuka; Miyagi Cancer Center, Kenichi Shiiba; Yamagata Prefecture Central Hospital, Toshihiko Sato; Ibaraki Prefectural Central Hospital, Fuyo Yoshimi; Tochigi Cancer Center, Kenjiro Kotake; Gunma Prefectural Cancer Center, Toshio Sawada; National Defence Medical College, Hidetaka Mochizuki; Saitama Medical Center Jichi Medical University, Fumio Konishi; National Cancer Center Hospital East, Norio Saito; National Cancer Center Hospital, Yoshihiro Moriya; Kyorin University Hospital, Tadahiko Masaki; Tokyo Medical University Hospital, Tatsuya Aoki; Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Keiichi Takahashi; Keio University Hospital, Hirotoshi Hasegawa; Tokyo Medical and Dental University, Sugihara Kenichi; Toho University Ohashi Medical Center, Yoshinobu Sumiyama; Kitasato University East Hospital, Takeo Sato; Kanagawa Cancer Center, Makoto Akaike; Showa University Northern Yokohama Hospital, Shinei Kudo; Ishikawa Prefectural Central Hospital, Tetsuji Yamada; Nagano Municipal Hospital, Yasuhiro Munakata; Shizuoka Cancer Center, Yamaguchi Shigeski; Aichi Cancer Center Hospital, Tomoyuki Kato; Fujita Health University, Koutaro Maeda; National Hospital Organization Kyoto Medical Center, Kinya Koizumi; Osaka University, Morito Monden; Osaka Medical Center for Cancer and Cardiovascular Diseases, Masayuki Ohue; Osaka City General Hospital, Masayuki Higashino; Osaka Medical College, Masahiko Tanigawa; Sakai Municipal Hospital, Mutsumi Fukunaga; Minoo Municipal Hospital, Takashi Kato; Kansai Rosai Hospital, Shu Okamura; Okayama Saiseikai General Hospital, Hideyuki Kimura; Hiroshima University, Masazumi Okajima; Hiroshima Municipal Hospital, Norihisa Takakura; Shikoku Cancer Center, Minoru Tanada; Kurume University, Kazuo Shirouzu; and Oita University, Seigo Kitano.

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Jpn J Clin Oncol 2009;39(6)406–409
doi:10.1093/jjco/hyp035

Clinical Trial Note

A Randomized Phase II/III Trial Comparing Hepatectomy Followed by mFOLFOX6 with Hepatectomy Alone as Treatment for Liver Metastasis from Colorectal Cancer: Japan Clinical Oncology Group Study JCOG0603

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Received October 22, 2008; accepted March 15, 2009; published online April 23, 2009

A randomized controlled trial is being conducted in Japan to compare hepatectomy alone with hepatectomy followed by adjuvant chemotherapy as treatment in patients with curatively resected liver metastases from colorectal cancer to improve survival with intensive chemotherapy. Between 42 and 70 days after liver resection, patients are randomly assigned to either hepatectomy alone or hepatectomy followed by 12 cycles of modified FOLFOX6 (mFOLFOX6) regimen. A total of 300 patients (including 78 patients in Phase II) will be accrued from 38 institutions within 3 years. The primary endpoint is treatment compliance at nine courses of mFOLFOX6 regimen in Phase II and disease-free survival in Phase III. The secondary endpoints are overall survival, incidence of adverse events and patterns of recurrence.

Key words: colorectal cancer – liver metastases – randomized controlled trial – mFOLFOX6

INTRODUCTION

Approximately one-third of patients survive for 5 years following curative resection of hepatic metastases from colorectal cancer (1,2), and the proportion of hepatectomy-related death is as low as 1–2% (3–5). These observations strongly support the view that hepatectomy seems to be the most effective therapy for treating hepatic metastases from colorectal cancer, due to the potential for long-term survival that is not possible with other treatment modalities. However, a hepatectomy alone does not always provide a complete cure. Most recurrences occur in liver, lung or both within the first 2 years after hepatectomy. Adjuvant chemotherapy may reduce the risk of recurrence and improve long-term survival, but administering systemic agents to the patients with resectable hepatic metastases in the clinical practice is not universal. In their EORTC40983 trial, Nordlinger et al. (6) identified a prominent need for a well-conducted randomized trial to compare hepatectomy alone with combined hepatectomy and chemotherapy treatment in patients with resectable colorectal liver metastases. However, we question the strategy to give pre-operative chemotherapy to patients with resectable colorectal liver metastases, as this postponed a possible curative treatment. Patients who receive pre-operative chemotherapy often have a higher risk toward

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post-operative complications. Theoretically, post-operative chemotherapy should be effective toward microscopic residual disease in the remnant liver or body. Until the report of the AURC 9002 trial by Portier et al. (7), there was no clear evidence from a randomized trial demonstrating that post-operative chemotherapy, either systemic or by hepatic arterial infusion, was more beneficial than hepatectomy alone. In the 10 years needed to complete accrual for this trial, however, the original question became outdated due to the availability of more effective chemotherapy regimens containing potentially more active agents such as oxaliplatin, irinotecan, bevacizumab or cetuximab. It is therefore still unclear whether combined treatment with post-operative chemotherapy is better than hepatectomy alone in patients with resectable liver metastases from colorectal cancer.

The rationale for choosing FOLFOX regimen as the treatment arm in this trial is based on the results of the previous studies for Stage III patients and unresectable Stage IV patients. Oxaliplatin-based therapy is also a standard first-line treatment for advanced or metastatic unresectable colorectal cancer. We chose the modified FOLFOX6 (mFOLFOX6) regimen for the study, since it is the most convenient of the FOLFOX regimens and can be administered on an outpatient basis. In Japan, however, oxaliplatin was approved in April 2005, and we set a Phase II part in this trial to confirm the feasibility of mFOLFOX6 regimen in the Japanese population with resected liver metastases from colorectal cancer.

Accordingly, we have started a Phase II/III randomized controlled trial to evaluate mFOLFOX6 as post-operative chemotherapy for patients with curatively resected liver metastases from colorectal cancer.

The study protocol was designed by the Colorectal Cancer Study Group (CCSG) of the Japan Clinical Oncology Group (JCOG) and was approved by the Protocol Review Committee of JCOG on 15 February 2007. This trial was registered at the UMIN Clinical Trials Registry as UMIN000000653 (http://www.umin.ac.jp/ctr/index.htm) and was activated on 16 April 2007.

STUDY PROTOCOL

Purpose

The aim of this study is to demonstrate the feasibility (Phase II) and the superiority of disease-free survival (Phase III) of systemic intravenous post-operative chemotherapy with mFOLFOX6 compared with hepatectomy alone in patients with curatively resected liver metastases from colorectal cancer.

Study Setting

The study was a multi-institutional prospective randomized Phase II/III trial, where participating institutions include 38 specialized centers as on 4 September 2008.

Resources

The study was supported by Health and Labour Sciences Research Grants for Clinical Cancer Research (h16-032 and h19-024) and Grants-in-Aid for Cancer Research (17S-3, 17S-5, 20S-3 and 20S-6), from the Ministry of Health, Labour and Welfare, Japan.

Endpoints

The primary endpoint in the Phase II part is treatment compliance at nine courses after beginning mFOLFOX6 [bolus and infusion fluorouracil (FU) and leucovorin (LV) with oxaliplatin] in all eligible patients. Treatment compliance at nine courses is defined as the proportion of patients in whom oxaliplatin is administered nine courses or more according to the protocol. The primary endpoint in the Phase III part is disease-free survival which is defined as days from randomization to first evidence of recurrence, secondary cancer or death from any cause, and it was censored at the latest day when the patient was alive without any evidence of recurrence or secondary cancer.

Secondary endpoints are overall survival, incidence of adverse events defined by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and patterns of recurrence after liver resection.

Eligibility Criteria

Primary tumors are staged according to the sixth edition of the tumor-nodes-metastasis classification system of the Union Internationale Contre le Cancer (UICC).

Inclusion Criteria

Prior to enrollment in the study, patients must fulfill all of the following criteria: the resected liver specimen consists of histologically proven adenocarcinoma of the colorectum. Potentially curative R0 resection was performed for both primary tumor and liver metastasis. In metachronous cases, the liver metastasis should be the first and the only recurrence. No extrahepatic metastasis or recurrence on chest and abdominal CT or MRI within 4 weeks before enrollment. No prior chemotherapy with oxaliplatin. No other chemotherapy or radiotherapy within 3 months before enrollment. No prior radiofrequency ablation or cryotherapy for liver metastasis. Time since their hepatectomy is between 42 and 70 days. Age is between 20 and 75 years old. European Cooperative Oncology Group (ECOG) performance status is 0–1. There are sufficient organ functions. Completed written informed consent from patient is obtained.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) synchronous or metachronous multiple cancer,

(ii) women during pregnancy or breast-feeding, (iii) psychosis, (iv) systemic steroids medication, (v) continuous use of flucytosine, phenytoin or warfarin potassium, (vi) insulin-dependent or poorly controlled diabetes mellitus and (vii) diarrhea or peripheral neuropathy greater than Grade 1.

Randomization

After the confirmation of the inclusion and exclusion criteria by telephone or fax to the JCOG Data Center, the patients are randomized to either hepatectomy alone arm or post-operative chemotherapy arm. The minimization method is used for randomization balancing the arms according to the state of liver metastases (synchronous/metachronous), the number of liver metastases (three or less/four or more), the largest size of liver metastases ($<5/\geq 5$ cm) and the number of metastatic lymph nodes in the primary lesion (three or less/four or more/unknown), and institution.

Treatment Methods

In hepatectomy alone arm, the patients are observed without any treatment until recurrence. In post-operative chemotherapy arm, the treatment schedule is summarized in Fig. 1. Chemotherapy with mFOLFOX6 is initiated between 56 and 84 days following liver surgery. Chemotherapy consists of an intravenous injection of oxaliplatin 85 mg/m^2 with L-LV 200 mg/m^2 over 2 h followed by 5-FU 400 mg/m^2 bolus and 2400 mg/m^2 continuous infusion over 48 h. This cycle is repeated every 2 weeks for 12 courses until disease progression or unacceptable toxicity.

Follow-up

Patient follow-up will be performed every 2 months for the first year, then every 4 months until the third year and every 6 months until the fifth year. Follow-up includes a clinical examination, analysis of tumor marker levels and thoracoabdominal computed tomography. Physicians will decide whether or not to treat recurrences, including administration of second-line chemotherapy.

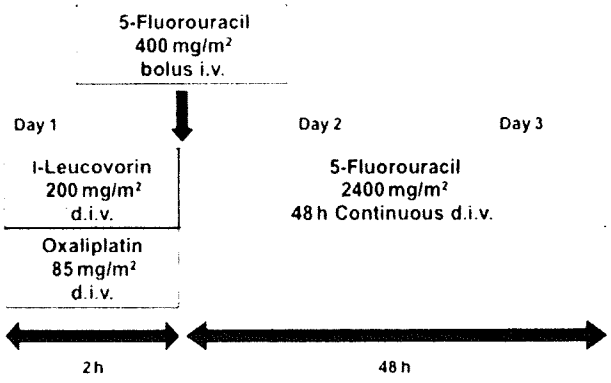

Figure 1. Treatment schedule in post-operative chemotherapy arm.

Study Design and Statistical Method

The Phase II part of this trial is designed to evaluate the feasibility of the post-operative chemotherapy with mFOLFOX6. If the treatment compliance at nine courses of post-operative chemotherapy arm is high as expected in the Phase II part, the registration is continued for the Phase III part. In the Phase II part, the sample size was 78 cases, with 39 cases per arm, provided 90% power under the hypothesis of treatment compliance at nine courses as the expected value of 70% and the threshold value of 50% using one-sided testing at a 10% significance level. Randomization is also performed in the Phase II part, but any tests to compare two arms directly in terms of efficacy endpoints are not planned in the Phase II part.

The Phase III part of this trial is designed to confirm the superiority in terms of disease-free survival of hepatectomy followed by mFOLFOX6 to hepatectomy alone. The hypothesis of the Phase III part is the 5-year disease-free survival of post-operative chemotherapy arm is greater than that (25%) obtained by hepatectomy alone arm by 12%. If a statistically significant improvement in 5-year disease-free survival is demonstrated, post-operative chemotherapy followed by hepatectomy will be the new standard treatment. According to that, the planned sample size in the Phase III part including the cases registered in the Phase II part is 300 cases, 150 cases per arm, and 233 events are expected with 3 years of accrual and 5 years of follow-up.

This ensures at least 80% power with a one-sided α of 5%.

Interim Analysis and Monitoring

An interim analysis is not planned in the Phase II part, and three interim analyses are planned in the Phase III part: the first at the time two-thirds of the total patients are registered, the second just after the completion of registration and the third at the time of 3-year follow-up. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis reports and consider whether it is necessary to stop the trial prematurely. In-house interim monitoring will be performed by the Data Center to evaluate and improve the study progress and quality. Monitoring reports will be submitted to and reviewed by the DSMC and the CCSG every 6 months.

Participating Institutions (from North to South)

Sapporo-Kosei General Hospital, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Ibaraki Prefectural Central Hospital, Tochigi Cancer Center, Gunma Prefectural Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, National Cancer Center Hospital, Keio University Hospital, Tokyo

Medical and Dental Hospital, Kitasato University East Hospital, Kanagawa Cancer Center, Kitasato University Hospital, Showa University Northern Yokohama Hospital, Yokohama City University Medical Center, Niigata Cancer Center Hospital, Ishikawa Prefectural Central Hospital, Nagano Municipal Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Fujita Health University Hospital, Kyoto Medical Center, Osaka University Hospital, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka National Hospital, Sakai Municipal Hospital, Minoh City Hospital, Suita Municipal Hospital, Kansai Rousai Hospital, Hyogo College of Medicine Hospital, Okayama Saiseikai General Hospital, Hiroshima University Hospital, Hiroshima City Hospital, Shikoku Cancer Center, Kurume University Hospital and Oita University Hospital.

Funding

Ministry of Health, Labour and Welfare, Japan.

Conflict of interest statement

None declared.

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ORIGINAL CONTRIBUTION

Outcomes of Surgery Alone for Lower Rectal Cancer With and Without Pelvic Sidewall Dissection

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PURPOSE: The goal of this retrospective multicenter study was to investigate the efficacy of pelvic sidewall dissection for lower rectal cancer.

METHODS: Data from 1,272 consecutive patients who underwent total mesorectal excision for lower rectal cancer in 12 institutions from 1991 through 1998 were reviewed. The rates of local recurrence and survival in patients with pelvic sidewall dissection were compared with those without pelvic sidewall dissection. Logistic regression analysis was used to determine independent risk factors for lymph node metastasis and local recurrence, and the Cox proportional hazards model was used to determine independent prognostic factors.

RESULTS: Of the 1,272 patients, 784 underwent pelvic sidewall dissection. Among them, 117 patients (14.9 percent) had lateral pelvic lymph node metastasis. Risk factors for lateral pelvic lymph node metastasis included female gender, tumor not well-differentiated adenocarcinoma, and perirectal lymph node metastasis. Lateral pelvic and perirectal lymph node metastases were independent risk factors for local recurrence. The Cox proportional hazard model showed age, grade of histology, invasion depth of the tumor, perirectal lymph node metastasis, and lateral pelvic lymph node metastasis to be independent prognostic factors. No significant differences between patients with and those without pelvic sidewall dissection were seen regarding rates of local recurrence (10.5 percent *vs.* 7.4 percent) or five-year overall survival (75.8 percent *vs.* 79.5 percent). Although the proportion of patients with advanced stages of disease was greater in patients who had pelvic sidewall dissection, no differences between the two groups were seen in local recurrence even when tumor category was taken into account. However, lack of pelvic sidewall dissection was a predictor of poor prognosis.

CONCLUSIONS: Although pelvic sidewall dissection does not appear to confer overall benefits regarding local recurrence or survival, the effectiveness of pelvic sidewall dissection in specific patient groups remains uncertain. A randomized controlled study is necessary to clarify this issue.

KEY WORDS: Rectal cancer; Lateral pelvic lymph node; Pelvic sidewall dissection; Local recurrence; Prognosis.

Colorectal cancer is the third most common cause of cancer-related death in the United States and Japan.[1] It is well known that, because of its high rate of local recurrence, rectal cancer is associated with a worse prognosis than colon cancer. Various therapies for rectal cancer have been developed since Miles described a method for systematic resection in 1908.[2] In the United States, aortopelvic lymphadenectomy was performed as extended lymph node dissection in the 1950s.[3] However, the effectiveness of lateral pelvic lymph node dissection was not accepted in Western countries. Stearns and Deddish[4] reported that extended lymphadenectomy

Study Group for Rectal Cancer Surgery of the Japanese Society for Cancer of the Colon and Rectum.

Read at the meeting of The American Society of Colon and Rectal Surgeons, Boston, Massachusetts, June 7 to 11, 2008.

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Dis Colon Rectum 2009; 52: 567–576
DOI: 10.1007/DCR.0b013e3181a1d994