were observed, whereas those toxicities were infrequent (2.0%, 4.0%, respectively) in the S-1 arm. Common grade 1–4 adverse events were liver dysfunction (AST, ALT, ALP, and total bilirubin), fatigue, and anorexia in both arms, whereas grade 3 or 4 symptomatic toxicities were infrequent in both arms. One patient in the GS arm died as a result of pneumonitis 13 days after the last dose of the study drug (S-1), and another patient in the GS arm died from myocardial infarction the day after the last dose of the study drug (S-1), and these were judged to be TRD. Reported serious adverse events are: TRD in the above two patients and grade 4 hyponatremia in one patient (GS arm); grade 4 acute myocardial infarction in one patient (S-1 arm); and grade 4 AST elevation in one patient (S-1 arm).

Efficacy. At the data cut-off point, 74 (73.3%) deaths had been recorded. The median survival time of the patients assigned to the GS arm was 12.5 (95% confidence interval [CI], 9.0–15.4) months, whereas that of the patients assigned to the S-1 arm was 9.0 (95% CI, 7.3–12.7) months (hazard ratio, 0.859; 95% CI, 0.543–1.360; $P = 0.52$). One-year survival was 52.9% in the GS arm and 40.0% in the S-1 arm (Fig. 2). In the subgroup analysis, the survival of the patients with GB cancer tended to be worse than that of the patients with non-GB cancer in both arms. The survival of the patients with recurrent disease tended to be better than that for the patients with stage II/III or IV disease in both treatment arms (Table 3).

Median progression-free survival was 7.1 (95% CI, 5.7–8.6) months in the GS arm and 4.2 (95% CI, 2.5–5.0) months in the S-1 arm (Fig. 3; hazard ratio, 0.437; 95% CI, 0.286–0.669; $P < 0.0001$).

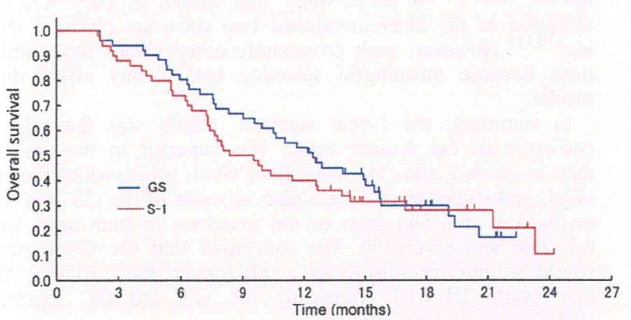

Fig. 2. Kaplan–Meier curves for overall survival in the randomized phase II study of gemcitabine plus S-1 combination therapy (GS) *versus* S-1 alone in patients with advanced biliary tract cancer.

Table 3. Median survival time by stratification factor in patients with advanced biliary tract cancer treated with gemcitabine plus S-1 combination therapy (GS) or S-1 alone

	GS	S-1	Total
Tumor site			
GB (n = 38)	11.7 (6.3–13.9)	6.5 (3.6–8.0)	7.9 (6.3–11.1)
Non-GB (n = 63)	15.0 (7.7–20.6)	14.3 (8.0–23.3)	15.0 (9.9–20.6)
Stage			
Stage II, III (n = 15)	13.0 (5.9–NE)	14.3 (2.1–NE)	13.9 (7.3–NE)
Stage IV (n = 61)	10.6 (6.3–15.4)	7.5 (5.6–10.0)	8.0 (6.9–10.6)
Recurrence (n = 25)	19.1 (7.6–NE)	17.0 (6.2–21.3)	17.0 (11.7–21.3)

Data are shown as the median (95% confidence interval). GB, gallbladder; NE, not estimable.

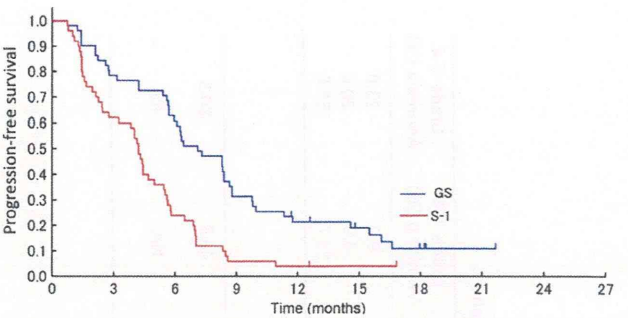

Fig. 3. Kaplan–Meier curves for progression-free survival in the randomized phase II study of gemcitabine plus S-1 combination therapy (GS) *versus* S-1 alone in patients with advanced biliary tract cancer.

Among the patients with measurable lesions, the response rates were 36.4% (16/44) in the GS arm and 17.4% (8/46) in the S-1 arm. The response rates for the patients with GB carcinomas were 12.5% (2/16) in the GS arm and 16.7% (3/18) in the S-1 arm. The response rates for patients with non-GB carcinomas were 50% (14/28) in the GS arm and 17.9% (5/28) in the S-1 arm.

Twenty-five patients (49%) in the GS arm received second-line chemotherapy containing S-1 monotherapy (seven patients), gemcitabine monotherapy (six patients), GC therapy (seven patients), and other regimen (five patients). In the S-1 arm, 39 (78%) patients received second-line chemotherapy containing gemcitabine monotherapy (33 patients), GC therapy (one patient), GS therapy (one patient) and other regimen (four patients).

Discussion

The aim of this randomized phase II trial was to select the test arm regimen for a subsequent phase III trial. The frequency of toxicity was expected to be higher in the GS arm than in the S-1 arm, but we expected that the frequency of serious adverse events would be almost equivalent. Therefore, we decided to select the more promising regimen based on efficacy, namely, 1-year survival, as long as the levels of severe toxicity did not differ markedly between the two arms. In this study, the GS arm showed a higher 1-year survival than the S-1 arm. Furthermore, other measures of efficacy in the GS arm, such as the response rate, overall survival, and progression-free survival, were also better than those obtained in the S-1 arm.

Although hematological toxicities tended to be more frequent in the GS arm than in the S-1 arm, most toxicities in both arms were tolerable and reversible. Serious adverse events occurred in 7.8% in the GS arm and in 6.0% in the S-1 arm, and two patients in the GS arm experienced TRDs. The frequency of serious adverse events was almost equivalent, as expected. However, these findings should be noted carefully in subsequent phase III trials.

In this study, we stratified the patients into those with GB cancer and those with other BTCs. Gallbladder cancer has been recognized to have a poorer survival outcome.[8,14–17] As shown in Table 3, the patients with GB cancer had a shorter survival than those with other BTCs, consistent with the findings of previous reports. Importantly, despite the dismal clinical outcomes of GB cancer patients, the median survival times of the patients with GB cancer was much better in the GS arm (11.7 months) than in the S-1 arm (6.5 months) in

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Table 4. Clinical trials of gemcitabine plus S-1 (GS) therapy or gemcitabine plus cisplatin (GC) combination therapy for patients with advanced biliary tract cancer

GS therapy	Gemcitabine (mg/m^2)	S-1 (mg/m^2/day)	Cycle (days)	No. of patients	RR (%)	Median PFS (TTP), months	Median OS (months)	Grade 3/4 Neutropenia (%)	Grade 1–4 Nausea (%)	Grade 1–4 Vomiting (%)	Grade 1–4 Anorexia (%)
Sasaki *et al.*	1000 (days 1, 15)	80 (days 1–14)	28	35	34	5.9	11.6	34.0	26.0	9.0	23.0
Kanai *et al.*	1000 (days 1, 8)	60 (days 1–14)	21	25	30	NA	12.7	56.0	20.0	4.0	28.0
Current study	1000 (days 1, 8)	60 (days 1–14)	21	51	36	7.1	12.5	60.8	35.3	13.7	51.0
GC therapy	**Gemcitabine (mg/m^2)**	**Cisplatin (mg/m^2)**									
BT22 (GC regimen)	1000 (days 1, 8)	25 (days 1, 8)	21	42	20	5.8	11.2	56.1	68.3	48.8	80.5
ABC-02 (GC regimen)	1000 (days 1, 8)	25 (days 1, 8)	21	204	26	8.0	11.7	25.3	NA	NA	NA

NA, not available; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression.

the present trial as well, concurring with previous reports.[8,14–17]

Another stratification factor used in this study was the clinical stage (II or III versus IV or recurrent). Locally advanced or metastatic cancer, the stratification factor used in the ABC-01 and ABC-02 studies,[7,18] has been shown to affect the OS of patients with advanced BTC.[19] However, there is no consensus as to whether recurrent disease should be classified as locally advanced disease or metastatic disease or should be an isolated disease entity. In this study, the patients with recurrent disease had more favorable overall survival than those with stage IV disease and even those with stage II /III. However, because of the limited number of patients in these subgroup analyses, the results should be viewed with caution.

When compared to the GC regimen (the current standard) in the BT22 study, the incidence of symptomatic gastrointestinal toxicities such as nausea (68.3% *vs* 35.3%), vomiting (48.8% *vs* 13.7%), and appetite loss (80.5% *vs* 51%) were lower for the GS regimen. Similar favorable gastrointestinal toxicity profiles were also observed in two previous phase II studies of GS regimens (Table 4), although the treatment schedule and dosage were different from those in the current study.[10,11] Additionally, although the GC regimen requires an infusion time including hydration before and after cisplatin administration (typically over 3 h), the GS regimen requires a 30-min infusion only for gemcitabine administration. Therefore, the GS regimen may be a more convenient regimen for patients, compared with the GC regimen. Additionally, the median survival (12.5 *vs* 11.2 months), progression-free survival (7.1 *vs* 5.8 months), and response rate (36.4% *vs* 19.5%) of the GS arm in the current study were better than those of the GC arm in the BT22 study, and similar efficacy was also observed in the abovementioned two previous phase II studies.[10,11] However, such cross-study comparisons have limitations because meaningful selection biases may affect those results.

In summary, the 1-year survival, which was the primary end-point of the present study, was superior in the GS arm than in the S-1 arm. The overall survival, progression-free survival, and response rate were also superior in the GS arm than in the S-1 arm, and most of the toxicities in both arms were tolerable and reversible. We concluded that the GS regimen would be more promising for a subsequent phase III trial. Our new phase III trial comparing the GS and GC regimens (JCOG1113) is now ongoing.

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Appendix I

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ORIGINAL ARTICLE

Survival prolongation after treatment failure of first-line chemotherapy in patients with advanced gastric cancer: combined analysis of the Japan Clinical Oncology Group Trials JCOG9205 and JCOG9912

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Abstract
Background Two randomized phase III trials of first-line chemotherapy for advanced gastric cancer (JCOG9205 and JCOG9912) conducted by the Japan Clinical Oncology Group used 5-fluorouracil continuous infusion (5-FUci) as the control arm. New active agents (e.g., S-1, irinotecan, and taxanes) were introduced as second-line chemotherapy in the late 1990s after JCOG9205. This combined analysis evaluated whether patients in the 5-FUci arm of JCOG9912 exhibited better survival after adjusting for baseline factors and also investigated the cause of survival prolongation.
Patients and methods The subjects were patients assigned to the 5-FUci arms who met the eligibility criteria of both JCOG9205 and JCOG9912. Overall survival (OS), time to treatment failure (TTF), and survival after treatment failure in the first-line chemotherapy (OS-TTF) were compared after adjusting baseline characteristics using the Cox proportional hazard model. Second-line chemotherapy details were also reviewed.
Results The combined analysis included 89 and 230 patients in JCOG9205 and JCOG9912, respectively. After adjusting baseline characteristics, TTF was similar between groups (HR 0.95; 95 % CI, 0.73–1.26). However, both OS (HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (HR, 0.76; 95 % CI, 0.57–1.01) were longer in JCOG9912. More patients in JCOG9912 received second-line chemotherapy (83 vs. 52 %) with new drugs (77 vs. 10 %) than in JCOG9205. OS-TTF was substantially prolonged in patients who received second-line chemotherapy (HR, 0.66; 95 % CI, 0.46–0.95).
Conclusion OS and OS-TTF were longer in JCOG9912 than JCOG9205. Second-line chemotherapy with new drugs is a potential reason for the observed prolongation of survival.

Keywords Gastric cancer · Post-treatment failure survival · Second-line chemotherapy

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Introduction

Although advanced gastric cancer (AGC) cannot be cured by systemic chemotherapy, some randomized controlled trials [1–3] and meta-analyses [4] demonstrate a survival benefit for first-line chemotherapy compared to best supportive care alone. The survival benefit attributable to second-line chemotherapy was unclear until recently [5]. However, two randomized trials comparing second-line chemotherapy and best supportive care have demonstrated the survival benefit of second-line chemotherapy [6, 7].

Two randomized phase III trials of first-line chemotherapy for AGC [i.e., Japan Clinical Oncology Group (JCOG) 9205 and JCOG9912] conducted by the JCOG involved 5-fluorouracil continuous infusion (5-FUci) as the control arm. In JCOG9205, a combination of 5-FU plus cisplatin did not confer a survival benefit over 5-FUci alone; 5-FUci was regarded as standard chemotherapy in the 1990s [8]. Thereafter, monotherapy with S-1 exhibited non-inferiority to 5-FUci in JCOG9912 in the 2000s [9]. When these two trials are compared directly, the survival of the 5-FUci arm in JCOG9912 is longer than that in JCOG9205 [median survival times: 7.1 months (95 % confidence interval (CI), 5.8–8.2) vs. 10.8 months (95 % CI, 8.9–12.0), respectively].

The periods of patient accrual for JCOG9205 and JCOG9912 were 1992–1997 and 2000–2006, respectively. In Japan, after some new active agents such as S-1, irinotecan, paclitaxel, and docetaxel were approved for AGC in the late 1990s [10–14], they have been used not only in first-line chemotherapy but in second-line chemotherapy as well. The proportions of patients in the 5-FUci arms in JCOG9205 and JCOG9912 who received second-line chemotherapy were 53 and 78 %, respectively. It is speculated that second-line chemotherapy might have contributed to the prolongation of overall survival (OS) in JCOG9912 compared to JCOG9205.

However, survival is possibly affected by other factors including baseline factors. Furthermore, the details of regimens employed as second-line chemotherapy have not been reviewed in either trial. Therefore, it is necessary to adjust the patient backgrounds of JCOG9205 and JCOG9912 to assess the influence of second-line chemotherapy on survival.

This combined analysis evaluated whether patients in the 5-FUci arm of JCOG9912 exhibited better survival even after adjusting the baseline factors of patients who met the common eligibility criteria. If survival prolongation was evident, we aimed to investigate the underlying causes of survival prolongation.

Patients and methods

Patient population

The subjects in this combined analysis were the patients assigned to the 5-FUci arms in JCOG9205 ($N = 105$) and JCOG9912 ($N = 234$). The subjects were selected according to the following eligibility criteria of common to both trials: histologically confirmed unresectable or recurrent gastric adenocarcinoma; adequate self-supported nutrition intake; age 20–75 years; ECOG performance status 0, 1, or 2; no history of chemotherapy or radiotherapy; preserved organ functions; and written informed consent. Patients with intestinal stenosis, who were eligible in JCOG9205 but not JCOG9912, and those with a history of adjuvant chemotherapy, who were eligible in JCOG9912 but not JCOG9205, were excluded from this study.

In both trials, the protocol treatment was continuous infusion of 5-FU (800 mg m^{-2} day^{-1}) from day 1 to 5 repeated every 4 weeks until progressive disease or unacceptable toxicity was observed. The tumor response was evaluated by computed tomography and endoscopy every 4 and 8 weeks in JCOG9205 and JCOG9912, respectively.

The study protocol of this ad hoc combined analysis was approved by the Protocol Review Committee of the JCOG as well as the institutional review boards at the institutions of the study chair and study coordinator in compliance with the Japanese Ethical Guidelines for Clinical Studies.

Statistical analysis

The study endpoints were OS, time to treatment failure (TTF), survival after treatment failure (OS-TTF), the proportions of patients who received second-line chemotherapy, and the type of treatment regimens of second-line chemotherapy.

OS was counted from the date of randomization to the date of death from any cause or was censored at the date of the last follow-up for surviving patients. TTF was defined as the period from the date of randomization to the date of off-treatment from any cause (e.g., death, documentation of disease progression, adverse event, or patient refusal) or was censored at the date of last follow-up for surviving patients on treatment. OS-TTF was calculated by subtracting TTF from OS in each patient or censored in case of survival. OS-TTF was counted as 0 if the protocol treatment (i.e., first-line chemotherapy) was terminated because of death. OS, TTF, and OS-TTF were compared between JCOG9205 and JCOG9912 using the Cox proportional hazard model after adjusting the following baseline factors: age (<65 vs. ≥ 65 years), sex (male vs. female), performance status (PS, 0–2), macroscopic type (0–5) [15], histological type (intestinal vs. diffuse) [16], prior gastrectomy (+ vs. −), target lesion (+ vs. −), peritoneal metastasis (+ vs. −), and number of metastatic sites (0–2). Prognostic factors for OS-TTF were also analyzed using the Cox proportional hazard model. For Cox regression analysis, all variables were treated as categorical variables.

OS, TTF, and OS-TTF were estimated using the Kaplan–Meier method. All analyses were carried out with SAS release 9.1 (SAS Institute, Cary, NC, USA).

Results

Patients

The study schema is shown in Fig. 1. There were 105 and 234 patients assigned to the 5-FUci arms in JCOG9205 and JCOG9912, respectively. Sixteen and 4 patients in JCOG9205 and JCOG9912 were excluded from this combined analysis because they did not meet the eligibility criteria or had missing data. Finally, 319 patients, 89 from JCOG9205 and 230 from JCOG9912, were included in the combined analysis.

The patients' baseline characteristics are shown in Table 1. JCOG9912 contained more patients ≥65 years old, with better PS, and fewer metastatic sites and fewer patients with peritoneal metastasis compared to JCOG9205. Thus, there appear to be substantial differences in patient background between JCOG9205 and JCOG9912.

Reasons for treatment failure and second-line chemotherapy

The reasons for treatment failure in both trials were similar: disease progression or death in 84 % (disease progression, 68; death, 7/89) and 86 % (disease progression, 197; death, 1/230) in JCOG9205 and JCOG9912, respectively.

Second-line chemotherapy is summarized in Table 2. A greater proportion of patients received second-line chemotherapy in JCOG9912 than JCOG9205 [83 % (190/230) vs. 52 % (46/89), respectively]. The drugs used in second-line chemotherapy largely differed between JCOG9205 and JCOG9912. In JCOG9912, regimens containing new-generation drugs (e.g., irinotecan, paclitaxel, docetaxel, and S-1) were used as second-line chemotherapy in 178/190 patients (94 %). On the other hand, only 9/46 (20 %) patients received new-generation drugs in JCOG9205.

OS and OS-TTF

TTF adjusted by the Cox model did not differ significantly between trials [adjusted hazard ratio (HR), 0.95; 95 % CI, 0.73–1.26]. However, both OS (adjusted HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (adjusted HR, 0.76; 95 % CI, 0.57–1.01) were longer in JCOG9912 (Fig. 2a–c).

Subgroup analyses by second-line chemotherapy are shown in Fig. 3. Among the patients with second-line chemotherapy, OS-TTF was remarkably longer in JCOG9912 than JCOG9205 (adjusted HR, 0.66; 95 % CI, 0.46–0.95). On the other hand, among the patients who did not receive second-line chemotherapy, OS-TTF was longer in JCOG9205 than JCOG9912 (adjusted HR, 1.37; 95 % CI, 0.74–2.53).

Multivariate analysis was performed to determine the prognostic factors for OS-TTF. PS ($p < 0.001$), gastrectomy ($p = 0.031$), peritoneal metastasis ($p = 0.015$), and number of metastatic sites ($p = 0.011$) were selected as the prognostic factors for OS-TTF (Table 3).

Discussion

Even after selecting patients on the basis of common eligibility criteria and adjusting baseline factors, the OS (adjusted HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (adjusted HR, 0.76; 95 % CI, 0.57–1.01) of the 5-FUci arm was longer in JCOG9912 than JCOG9205.

We tried to align the two groups as much as possible to maximize comparability. Only the patients from the 5-FUci

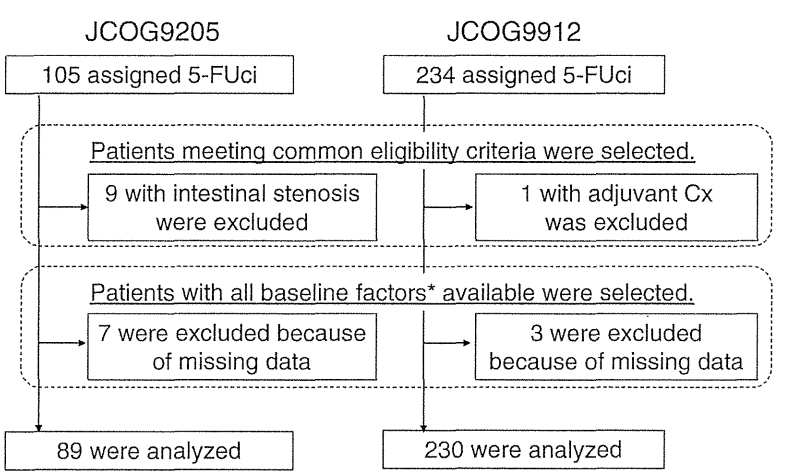

Fig. 1 Study profile. The baseline factors used in this study were age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and number of metastatic sites. *Cx* chemotherapy

Table 1 Patient characteristics

	JCOG9205		JCOG9912		*p* value[a]
No. of patients	89	%	230	%	
Age (years)					
Median (range)	63 (27–75)		63 (24–75)		0.4
<65	52	58	119	52	0.06
≥65	37	42	111	48	
Sex					
Male	63	71	172	75	0.48
Female	26	29	58	25	
PS[b]					
0	41	46	149	65	<.0001
1	33	37	78	34	
2	15	17	3	1	
Macroscopic type[c]					
0	0	0	5	2	0.75
1	5	6	8	4	
2	20	22	53	23	
3	45	51	120	52	
4	17	19	40	17	
5	2	2	4	2	
Histological type					
Intestinal	45	51	110	48	0.71
Diffuse	44	49	120	52	
Gastrectomy					
−	69	78	161	70	0.21
+	20	22	69	30	
Target lesions					
−	20	22	59	26	0.66
+	69	78	171	74	
Peritoneal metastasis					
−	76	85	143	62	<.0001
+	13	15	87	38	
Number of metastatic sites					
0	0	0	2	1	0.06
1	51	57	100	43	
≥2	38	43	128	56	

[a] All *p* values are two sided. The Wilcoxon rank-sum test was used to analyze continuous variables, and Fisher's exact test was used to analyze categorical data

[b] PS was evaluated at treatment initiation in JCOG9205 and at registration in JCOG9912

[c] Japanese Classification of Gastric Carcinoma

arms meeting the common eligibility criteria of both trials were analyzed, and baseline characteristics were adjusted in multivariate analysis. In addition, both trials were conducted by the same study group. The results show that TTF (adjusted HR, 0.95; 95 % CI, 0.73–1.26) and the reasons for treatment discontinuation did not differ between trials. This finding indicates that the impact of the first-line chemotherapy with 5-FUci on OS might be comparable between the two trials.

Table 2 Second-line chemotherapy

Second-line chemotherapy	JCOG9205		JCOG9912	
+	46	51.7 %	190	82.6 %
PTX, DTX, irinotecan, or S-1-containing regimen	9	10.1 %	178	77.4 %
PTX/DTX containing	2		60	
Irinotecan containing	6		100	
S-1 containing	1		29	
Other	37	41.6 %	12	5.2 %
5-FU/MTX	25		7	
5-FU/CDDP	6		0	
Other	6		5	
−	39	43.8 %	35	15.2 %
Unknown	4	4.5 %	5	2.2 %

PTX paclitaxel, *DTX* docetaxel, *CDDP* cisplatin, *MTX* methotrexate

To evaluate the effect of second-line chemotherapy, it would be ideal to estimate the time from the start of second-line chemotherapy to death. However, because we did not collect the start date of second-line chemotherapy in the case report form, we adopted OS-TTF as the endpoint. Survival post progression is another endpoint sometimes used to evaluate the effect of second-line chemotherapy. However, protocol treatment is sometimes terminated for reasons other than progression. Moreover, second-line chemotherapy is started before progression. Therefore, we considered OS-TTF to be a more suitable surrogate of the time from the start of second-line chemotherapy than survival post progression.

The present comparison between the two trials performed in different decades is considered to contain some bias. There have been many changes in patient management during this time, leading to better survival in the recent trial. Considering OS was longer in JCOG9912 than JCOG9205, even though TTF did not differ between trials, it can be speculated that patient management after treatment failure might have changed in the era of JCOG9912 compared to that of JCOG9205. One of the major changes that occurred was the availability of antitumor drugs in second-line chemotherapy. A greater proportion of patients received second-line chemotherapy in JCOG9912 than JCOG9205 (83 vs. 52 %, respectively) (Table 2). In particular, new-generation drugs (e.g., irinotecan, paclitaxel, docetaxel, and S-1) were used more frequently in JCOG9912 than JCOG9205 (77 vs. 10 %, respectively). Moreover, the improvements in OS and OS-TTF from JCOG9205 to JCOG9912 were only observed in the subset of patients who received second-line chemotherapy (HR, 0.66; 95 %

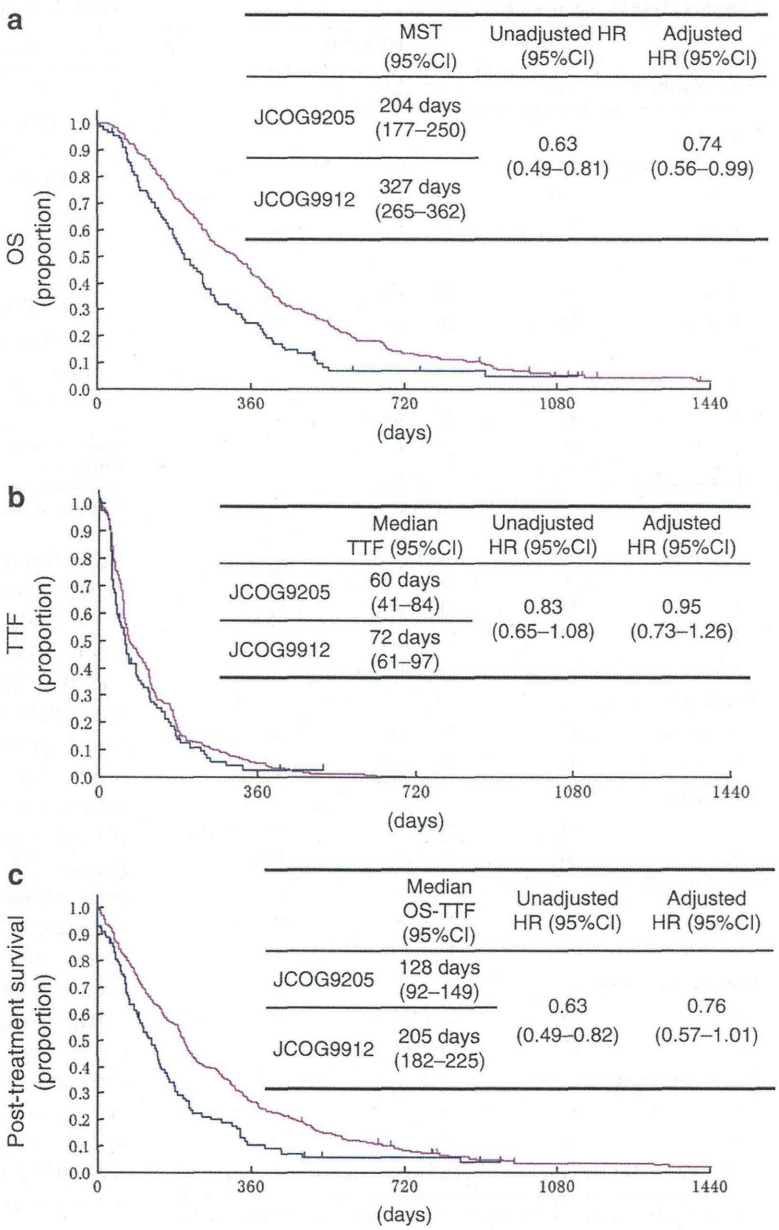

Fig. 2 Overall survival (OS) (**a**), time to treatment failure (TTF) (**b**), and OS-TTF (**c**). Seven patients and one patient in JCOG9205 and JCOG9912, respectively, who died during first-line chemotherapy, were considered to have events on day 0. Adjustment factors included patient age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and number of metastatic sites. *MST* median survival time, *OS* overall survival, *TTF* time to treatment failure

CI, 0.46–0.95) (Fig. 3). These results suggest second-line chemotherapy with new-generation drugs might have contributed to survival prolongation. Kawakami et al. [17] reported the post-progression survival (PPS) of AGC is significantly longer in trials published in 2006 or later than in those published before 2005 published trials (5.34 vs. 3.74 months, $p = 0.001$). The present results corroborate these previous results, further indicating the increasing availability of active drugs in subsequent therapies is a potential reason for the observed survival prolongation.

As mentioned in the Introduction, the survival benefit attributable to second-line chemotherapy was unclear until recently [5]. However, two randomized trials compared second-line chemotherapy and best supportive care in AGC (6, 7). The first trial compared best supportive care with irinotecan monotherapy [6]. Irinotecan-treated patients had significantly longer survival (median survival time, 4.0 vs. 2.4 months for patients receiving best supportive care alone; HR, 0.48; 95 % CI, 0.25–0.92). These results suggest second-line chemotherapy with irinotecan confers a survival benefit.

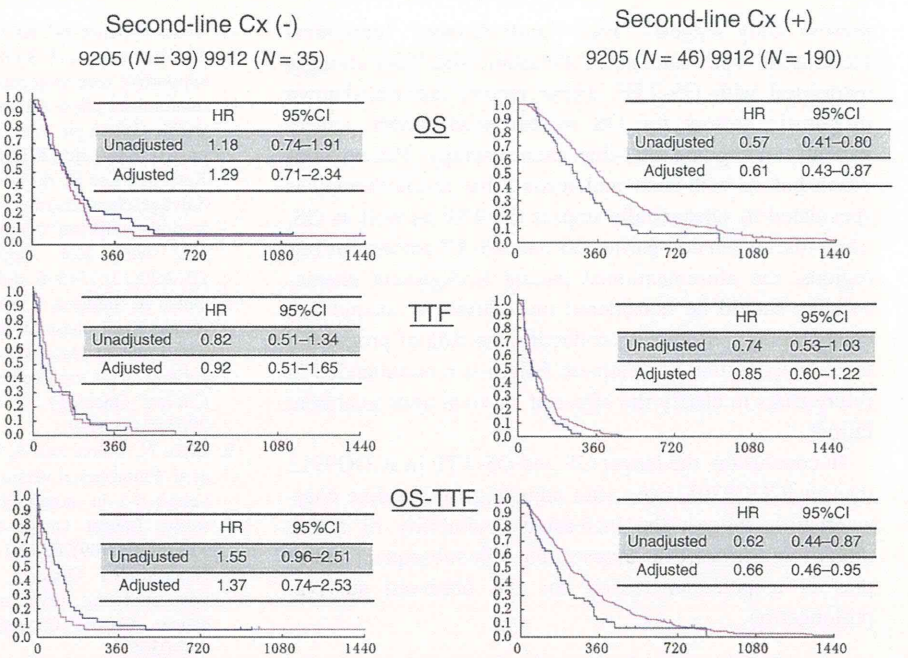

Fig. 3 Subgroup analyses according to the presence of second-line chemotherapy. Adjustment factors included age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and the number of metastatic sites. *Cx* chemotherapy, *MST* median survival time

Table 3 Mutivariate analysis of survival after treatment failure

	HR	95 % CI	*p* value
Trial			
JCOG9912 (vs. JCOG9205)	0.76	0.57–1.01	0.06
Age (years)			
≥65 (vs. ≤64)	1.04	0.82–1.31	0.77
Sex			
Male (vs. female)	0.84	0.63–1.10	0.20
Performance status (PS)			
PS1 (vs. 0)	1.51	1.17–1.95	<0.0001
PS2 (vs. 0)	3.67	2.11–6.37	
Macroscopic type			
1 (vs. 0)	0.61	0.20–1.85	0.63
2 (vs. 0)	0.53	0.21–1.37	
3 (vs. 0)	0.67	0.27–1.69	
4 (vs. 0)	0.61	0.23–1.64	
5 (vs. 0)	0.54	0.15–1.95	
Histological type			
Intestinal (vs. diffuse)	0.97	0.76–1.24	0.78
Gastrectomy			
+ (vs. −)	0.73	0.55–0.97	0.03
Target lesions			
+ (vs. −)	1.08	0.80–1.47	0.61
Peritoneal metastasis			
+ (vs. −)	0.70	0.52–0.93	0.01
Number of metastatic sites			
1 (vs. 0)	2.24	0.30–16.8	0.01
≥2 (vs. 0)	3.26	0.43–24.9	

However, the study was terminated early because of poor accrual. The second study, which compared treatment with irinotecan or docetaxel to best supportive care, also showed a survival benefit of second-line chemotherapy compared to best supportive care (median survival time, 5.3 vs. 3.8 months for patients receiving best supportive care alone; HR, 0.66; 95 % CI, 0.49–0.89) [7]. This result is currently the only evidence from a completed randomized trial justifying the use of second-line chemotherapy for AGC. Besides these two studies, the present results provide additional evidence supporting a survival benefit of second-line chemotherapy in AGC.

The present combined analysis has some limitations. There may be some other reasons for the prolongation of post-treatment failure survival in this analysis, including better general condition at treatment failure in JCOG9912, recent advances in supportive care, lead-time bias of diagnosis of metastasis, and unidentified baseline factors in first-line chemotherapy; however, these factors could not be adjusted in the analysis. In particular, prognostic factors at the failure of first-line chemotherapy that could strongly influence survival after treatment failure, such as PS, were not collected in either trial.

At present, regional differences in clinical outcomes between Asian and Western countries are major obstacles for conducting global trials for AGC [18]. Although better survival in Asian countries is considered to be mainly the result of a higher proportion of patients who receive second-line chemotherapy than in Western countries, the true reason for this difference remains unknown [19]. The

present study suggests "PS," "gastrectomy," "peritoneal metastasis," and "number of metastatic sites" are strongly associated with OS-TTF. These factors are well-known prognostic factors for OS in advanced gastric cancer patients undergoing first-line chemotherapy. Patient condition before both first- and second-line chemotherapy is speculated to substantially impact OS-TTF as well as OS. Therefore, when comparing OS and OS-TF among various regions, the aforementioned patient background characteristics should be considered in addition to second-line chemotherapy. Moreover, collecting the data of prognostic factors at the time of treatment failure is recommended in future trials to clarify the effect of survival after treatment failure.

In conclusion, the longer OS and OS-TTF in JCOG9912 than in JCOG9205, even after adjusting for baseline characteristics, suggest the increasing availability of active drugs (e.g., irinotecan, taxanes, etc.) in subsequent therapies is a potential reason for the observed survival prolongation.

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Conflict of interest The authors have declared no conflicts of interest.

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Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial

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Summary

Background Mesorectal excision is the international standard surgical procedure for lower rectal cancer. However, lateral pelvic lymph node metastasis occasionally occurs in patients with clinical stage II or stage III rectal cancer, and therefore mesorectal excision with lateral lymph node dissection is the standard procedure in Japan. We did a randomised controlled trial to confirm that the results of mesorectal excision alone are not inferior to those of mesorectal excision with lateral lymph node dissection.

Methods This study was undertaken at 33 major hospitals in Japan. Eligibility criteria included histologically proven rectal cancer of clinical stage II or stage III, with the main lesion located in the rectum with the lower margin below the peritoneal reflection, and no lateral pelvic lymph node enlargement. After surgeons had confirmed macroscopic R0 resection by mesorectal excision, patients were intraoperatively randomised to mesorectal excision alone or with lateral lymph node dissection. The groups were balanced by a minimisation method according to clinical N staging (N0 or N1, 2), sex, and institution. Allocated procedure was not masked to investigators or patients. This study is now in the follow-up stage. The primary endpoint is relapse-free survival and will be reported after the primary analysis planned for 2015. Here, we compare operation time, blood loss, postoperative morbidity (grade 3 or 4), and hospital mortality between the two groups. Analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00190541.

Findings 351 patients were randomly assigned to mesoretcal excision with lateral lymph node dissection and 350 to mesorectal excision alone, between June 11, 2003, and Aug 6, 2010. One patient in the mesorectal excision alone group underwent lateral lymph node dissection, but was analysed in their assigned group. Operation time was significantly longer in the mesorectal excision with lateral lymph node dissection group (median 360 min, IQR 296–429) than in the mesorectal excision alone group (254 min, 210–307, p<0·0001). Blood loss was significantly higher in the mesorectal excision with lateral lymph node dissection group (576 mL, IQR 352–900) than in the mesorectal excision alone group (337 mL, 170–566; p<0·0001). 26 (7%) patients in the mesorectal excision with lateral lymph node dissection group had lateral pelvic lymph node metastasis. Grade 3–4 postoperative complications occurred in 76 (22%) patients in the mesorectal excision with lateral lymph node dissection group and 56 (16%) patients in the mesorectal excision alone group. The most common grade 3 or 4 postoperative complication was anastomotic leakage (18 [6%] patients in the mesorectal excision with lateral lymph node dissection group *vs* 13 [5%] in the mesorectal excision alone group; p=0·46). One patient in the mesorectal excision with lateral lymph node dissection group died of anastomotic leakage followed by sepsis.

Interpretation Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than mesorectal excision alone. The primary analysis will help to show whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

Funding National Cancer Center, Ministry of Health, Labour and Welfare of Japan.

Introduction

Total mesorectal excision or mesorectal excision, in which at least a clear margin of 4 cm of the attached mesorectum distal to the tumour is resected, is the international standard surgical procedure for rectal cancer because it has a lower rate of associated local recurrence and higher rate of patient survival than conventional surgery.[1–3] However, metastasis to lateral pelvic lymph nodes occasionally occurs in patients with clinical stage II or stage III lower rectal cancer, the lower margin of which is located at or below the peritoneal reflection.

The incidence of lateral pelvic lymph node metastasis from lower rectal cancer is about 15%, and mesorectal excision with lateral lymph node dissection has been the

standard procedure for patients with lower rectal cancer in Japan[4-6] since it was introduced in the 1970s. Pelvic autonomic nerve-sparing lateral lymph node dissection has been developed and refined since in the mid-1980s.[7] If metastatic lymph node metastases are not dissected, local or systemic recurrence can develop.[8,9] However, the incidence of local recurrence in patients with rectal cancer who undergo total mesorectal excision or mesorectal excision without lateral lymph node dissection at major hospitals in Europe and North America is reported to be less than 10%.[10-13] Although this incidence is much the same as the rate for patients undergoing standard treatment in major hospitals in Japan,[4-6] comparison is difficult because of differences in the backgrounds of patients.

The difficulty of comparison between different procedures in distinct populations prompted us to assess the survival benefit, local control, operative complications, and sexual and urinary function of patients with rectal cancer undergoing mesorectal excision alone or with lateral lymph node dissection in a randomised controlled trial in major hospitals in Japan. The study aims to determine whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection in terms of efficacy. The primary analysis is planned for 2015, and this study is now in the follow-up stage. In this report, we present the data obtained so far for operation time, blood loss, and postoperative morbidity (grade 3 or 4) and mortality. Further analyses of urinary and sexual function are underway and will be reported at a later date.

Methods

Study design and participants

Preoperative inclusion criteria were histologically confirmed adenocarcinoma of clinical stage II or III (as determined by digital rectal examination, CT or MRI, and endoscopy); main lesion of tumour located in the rectum, with the lower tumour margin below peritoneal reflection; no extramesorectal lymph node enlargement (ie, lymph nodes with a short-axis diameter of less than 10 mm shown by CT scan or MRI is not regarded as lymph node enlargement); and no invasion to other organs. Eligible patients were aged between 20 and 75 years with performance status 0 or 1 and no history of chemotherapy, pelvic surgery, or radiation. Intraoperative inclusion criteria were completed mesorectal excision, confirmation that the main lesion of the tumour was located in the rectum, with the lower tumour margin below peritoneal reflection, and macroscopic R0 (ie, no residual tumour) after the mesorectal excision. Exclusion criteria were synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ or mucosal carcinoma, pregnancy or breastfeeding in women, or a psychological disorder or severe mental illness. Patients undergoing treatment with systemic steroids, or with a history of myocardial infarction or unstable angina pectoris within 6 months, or with severe pulmonary emphysema or pulmonary fibrosis were also excluded. The attending physician had the final decision for exclusion.

Clinical stage was based on the results of digital rectal examination, imaging (CT or MRI), and endoscopy. Clinical stage I rectal tumours and tumours in which the lower margin was located above the peritoneal reflection were not included, because the incidence of lateral pelvic lymph node metastasis in such cases is very low. If lateral pelvic lymph node enlargement was detected by CT or MRI with 5 mm thick sections and the short-axis diameter of the nodes exceeded 10 mm, which is the minimum measurable size in such sections, patients were not included in this study and underwent mesorectal excision with lateral lymph node dissection.

Only surgeons specialising in both procedures from 33 Japanese institutions (listed in the appendix) participated in the study. We obtained written informed consent from all patients before surgery and the protocol was approved by institutional review boards.

See Online for appendix

Randomisation and masking

Randomisation and data handling were done by the JCOG Data Center. After surgeons had confirmed macroscopic R0 resection (ie, no residual tumour) by mesorectal excision and macroscopic absence of lymph node metastasis in the lateral pelvic lymph area, patients were randomised intraoperatively to mesorectal excision alone or with lateral lymph node dissection by phone call to the JCOG Data Center. The groups were balanced by a minimisation method with biased-coin assignment according to clinical N staging by imaging (CT or MRI) and surgical exploration (N0 or N1, 2), sex, and institution. Allocated procedure was not masked to investigators or patients.

Procedures

Mesorectal excision was done by open surgery in accordance with reported methods.[1] Under direct vision with sharp dissection, the rectum was mobilised keeping the plane around the mesorectum, and the attached mesorectum with at least a 4 cm clearance margin distal to the tumour was resected. If the length of the attached mesorectum distal to the tumour was less than 4 cm, the mesorectum was totally resected. The inferior mesenteric artery was ligated at its root. If the blood supply to the distal colon was deemed inadequate as a result of this procedure, preservation of the left colonic artery after lymph node dissection at its root was allowed.

Lateral lymph node dissection was done in accordance with reported methods.[4,5,14] Lateral pelvic lymph nodes include the common iliac node, internal iliac node, external iliac node, obturator node, and middle sacral node. Because metastasis to the external iliac node and middle sacral node in the patients eligible for this study without clinical lateral pelvic lymph node metastasis is rare,[15] dissection of those nodes was not deemed necessary. The other lateral pelvic lymph nodes in the fatty and

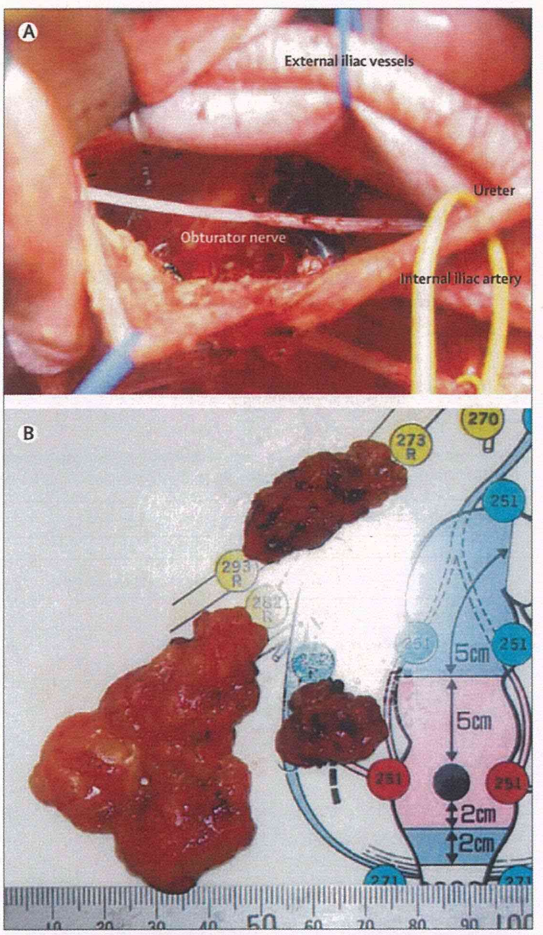

Figure 1: **Lateral lymph node dissection**
(A) The obturator fossa after lateral lymph node dissection, with the dissected fatty and connective tissues (right side). (B) Dissected fatty and connective tissues including lymph nodes.

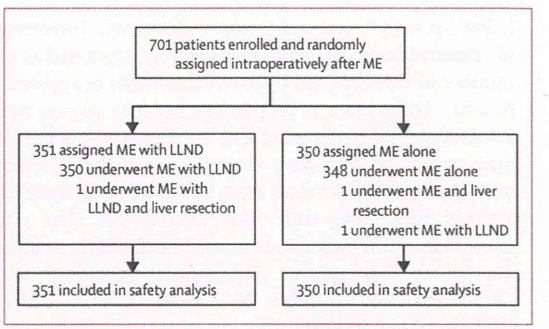

Figure 2: **Trial profile**
We did not collect data for the number of eligible patients before enrolment. ME=mesorectal excision. LLND=lateral lymph node dissection.

connective tissues outside the pelvic plexus, around the common, internal, and oburator fossa were dissected after mesorectal excision (figure 1). All the autonomic nerves were preserved because lymph node metastasis around these nerves is rare in patients without clinical lateral pelvic lymph node metastasis.

For surgical quality control and assurance, intraoperative photographs were taken. In the mesorectal excision alone group, five photos were taken: the site of inferior mesenteric artery ligation, the preserved right and left hypogastric nerves, and the anterior and posterior sides of the resected specimen. In the mesorectal excision with lateral lymph node dissection group, 11 photos were taken: the site of inferior mesenteric artery ligation, the preserved right and left hypogastric nerves, the right and left internal iliac artery, the right and left obturator fossa, the anterior and posterior sides of the resected specimen, and the right and left dissected fatty and connective tissues in the lateral pelvic lymph node area. These photographs were assessed and scored by the committee for quality control and assessment of surgery, and the surgical procedure was discussed and assured according to the score at meetings held twice a year.

Adjuvant chemotherapy with the Roswell Park regimen of intravenous fluorouracil (500 mg/m²) and L-leucovorin (250 mg/m²) was given to patients with pathological stage III tumours in both groups. Patients who were stage II did not receive adjuvant chemotherapy.[16] This regimen consisted of three courses of six doses of weekly chemotherapy followed by a 2-week rest. Adjuvant radiotherapy was not used.

Operative methods and pathology results were recorded according to the Japanese Classification of Colon and Rectal Carcinoma (sixth edition)[17] and TNM classification (fifth edition).[18] The primary endpoint was relapse-free survival, and the secondary endpoints were overall survival, local recurrence-free survival, incidence of adverse events, incidence of major adverse events, operation time, blood loss, and incidence of sexual and urinary dysfunction. Operation time, blood loss, and all postoperative morbidities during hospital stay were recorded prospectively on case report forms. Postoperative morbidity was described according to the National Cancer Institute-Common Toxicity Criteria version 2·0. Hospital mortality was defined as postoperative death from any cause within 30 days.

Statistical analysis

We originally estimated that 5-year relapse-free survival after mesorectal excision with lateral lymph node dissection and mesorectal excision alone would be 65%, and the initial sample size was 600 patients, which was determined with one-sided alpha of 0·05, a power of 0·75, and a non-inferiority margin for a hazard ratio (HR) of 1·34. However, we calculated the 5-year relapse-free survival for all randomised patients 5 years after the start of registration, and recorded that it was about 75%. Therefore, the sample size was increased to 700 patients to maintain the required statistical power. Planned accrual and

follow-up were 7 years and 5 years, respectively. Incidences of operative morbidity and mortality were expressed as the number of cases divided by the total number of registered patients. Differences in proportions between groups were assessed with Fisher's exact test. Differences in operation time and blood loss were compared with the Wilcoxon rank sum test. All p values were two-sided, and statistical analysis was done with SAS version 9·1. The data presented in this paper were as of June 12, 2011. Analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00190541, and UMIN-CTR, number C000000034.

Role of the funding source

The funding sources had no role in the design of the study, collection, analysis, interpretation of the data, writing of the report, or in the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the report for publication.

Results

701 patients were randomly assigned to the mesorectal excision alone group (n=350) or the mesorectal excision with lateral lymph node dissection group (n=351) between June 11, 2003, and Aug 6, 2010 (figure 2). All but three patients received the allocated surgery. Liver metastasis was identified after randomisation in one patient in each group and they underwent hepatic resection after rectal cancer surgery. Lateral lymph node metastasis was strongly suspected after randomisation in one patient allocated to the mesorectal excision alone group and the patient underwent lateral lymph node dissection. These three patients were eligible and included in this analysis. Two patients assigned to the mesorectal excision with lateral lymph node dissection group were found to have clinical stage I disease, despite being reported as clinical stage II or III at enrolment. Two other patients assigned to the same group had synchronous multiple cancers. Three patients (one in the mesorectal excision with lateral lymph node dissection group and two in the mesorectal excision alone group) were judged to have residual tumours before randomisation. We included these seven patients in this analysis, but their data will be excluded from the final survival analysis.

Table 1 shows the characteristics of all patients. Low anterior resection was done in 568 (81%) of 701 patients. Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than did mesorectal excision alone (table 2). Of the 26 patients in the mesorectal excision with lateral lymph node dissection group who had lateral pelvic lymph node metastasis, 11 (42%) were clinical stage II and 15 (58%) were clinical stage III. 19 (73%) had pathological mesorectal lymph node metastasis and seven (27%) had no pathological mesorectal lymph node metastasis. Although more common in the mesorectal excision with lateral lymph node dissection group than with mesorectal excision alone, differences between groups in grade 3 and 4 postoperative complications were not significant (table 3). Anastomotic leakage of all grades,

	ME with LLND (n=351)	ME (n=350)
Sex		
Male	236 (67%)	236 (67%)
Female	115 (33%)	114 (33%)
Age (years)		
Median (IQR)	61 (54-67)	62 (55-68)
Clinical stage		
II	188 (54%)	197 (56%)
III	163 (46%)	153 (44%)
Tumour location*		
Ra	81 (23%)	80 (23%)
Rb	270 (77%)	270 (77%)
Tumour distance from anal verge (cm)†		
Median (IQR)	5·0 (4·0–6·0)	5·0 (3·7–6·0)

ME=mesorectal excision. LLND=lateral lymph node dissection. *Ra=tumour centre located above the peritoneal reflection, Rb=tumour centre located below the peritoneal reflection. †Data for five patients are missing.

Table 1: **Characteristics of patients**

	ME with LLND (n=351)	ME (n=350)	p value*
Type of surgery			..
Low anterior resection	284 (81%)	284 (81%)	
Abdominoperineal resection	66 (19%)	64 (18%)	
Hartmann's procedure	1 (<1%)	2 (<1%)	
Time (min)			
Median (IQR)	360 (296–429)	254 (210–307)	<0·0001
Blood loss (mL)			
Median (IQR)	576 (352–900)	337 (170–566)	<0·0001
Lateral lymph node metastasis			
Number (%)	26 (7%)	..	..

ME=mesorectal excision. LLND=lateral lymph node dissection. *Wilcoxon rank sum test, two-sided.

Table 2: **Operative details**

	ME with LLND (n=351)	ME (n=350)	p value*
Any grade 3–4 complication†	76 (22%)	56 (16%)	0·07
Anastomotic leakage‡	18 (6%)	13 (5%)	0·46
Urinary retention	18 (5%)	10 (3%)	0·18
Infection with normal absolute neutrophil count	16 (5%)	17 (5%)	0·86
Haemorrhage with surgery	13 (4%)	5 (1%)	0·09
Wound infection	10 (3%)	8 (2%)	0·81
Pelvic abscess	6 (2%)	2 (<1%)	0·29
Bowel obstruction	4 (1%)	3 (<1%)	1·00
Other§	12 (3%)	9 (3%)	0·66

ME=mesorectal excision. LLND=lateral lymph node dissection. *Fisher's exact test, two-sided. †National Cancer Institute-Common Toxicity Criteria Version 2·0. ‡Denominator is patients with anastomosis (ME with LLND=284, ME=284). §Other=fever, melaena, fistula, thrombosis, urinary frequency.

Table 3: **Grade 3–4 postoperative morbidity**

which is the major complication after low anterior resection, occurred in 37 (13%) of 284 patients in the mesorectal excision alone group and 32 (11%) of 284 patients in the mesorectal excision with lateral lymph node dissection group (p=0·61). One patient in the mesorectal excision with lateral lymph node dissection group died of anastomotic leakage followed by sepsis. All other patients recovered from surgery and were discharged from hospital.

Discussion

As expected, mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than did mesorectal excision alone. Although the incidence of grade 3 or grade 4 complications was higher in the mesorectal excision with lateral lymph node dissection group than in the mesorectal excision alone group, these differences were not significant.

In previous reports, the mean difference in intraoperative blood loss between surgical procedures with and without lateral lymph node dissection was more than 500 mL.[19–22] Blood loss might have been less in our study because none of the eligible patients had clinical evidence of lateral pelvic lymph node metastasis. In these patients, lateral lymph node dissection is easier than it is in those with clinical evidence of such metastasis. Also, because expertise with the lateral lymph node procedure is improving, blood loss might have been minimised compared with earlier studies.

The median operation time needed for mesorectal excison with lateral lymph node dissection was longer than that for mesorectal excision alone. This result is attributable to the time needed for lateral lymph node dissection, which is a meticulous procedure, and confirms previous results with regard to the difference in operation time.[20–22]

The incidence of all grade 3 or 4 postoperative complications, apart from infection with a normal absolute neutrophil count, was higher in the mesorectal excision with lateral lymph node dissection group than in the mesorectal excision alone group, but differences were not significant. Results of a previous meta-analysis[19] comparing extended lymphadenectomy including lateral lymph node dissection and conventional surgery for rectal cancer showed that the incidence of perioperative morbidity was higher for extended lymphadenectomy than for conventional surgery. However, one of the major complications, anastomotic leakage of all grades, showed no difference in incidence between the groups. Although we did not collect data for defunctioning stoma, the incidences of anastomotic leakage of all grades in patients who underwent low anterior resection in the mesorectal excision with lateral lymph node dissection group and mesorectal excision alone group were much the same, which suggests that lateral lymph node dissection was not a highly invasive surgical procedure.

Only one patient died from sepsis after anastomotic leakage. The reported mortality after mesorectal excision for rectal cancer surgery in Europe and North America is 1–3%,[11–13,23] and that after mesorectal excision with lateral lymph node dissection in Japan is 1%,[19] which is in line with our results (panel). The low mortality in our study can be attributed to several factors. Only surgeons specialising in both mesorectal excision and lateral lymph node dissection participated in this trial. Second, only patients who were judged to be capable of tolerating lateral lymph node dissection were selected and only high-volume centres for cancer treatment were allowed to enrol patients by the Colorectal Cancer Study Group.

Neoadjuvant chemoradiotherapy for rectal cancer is used worldwide. However, patients undergoing such treatment were not included and adjuvant radiotherapy was not used in our study for two reasons. First, the effectiveness and safety of adjuvant or neoadjuvant chemoradiotherapy for rectal cancer had not been clearly shown when we designed the protocol of this study. Second, adjuvant radiotherapy is not commonly used in Japan because of the lower local recurrence rate and better prognosis for patients in Japan than for those in Europe and North America.

Kim and colleagues[8] showed that lateral pelvic lymph node metastasis is a major cause of local recurrence of rectal cancer. With serial sections from human fetuses and three-dimensional reconstruction, Kusters and colleagues[24] showed that tumour recurrence might arise from lateral pelvic lymph nodes. However, other reports from Europe and North America have not supported these results. Syk and colleagues[25] examined the pattern of local recurrence after total mesorectal excision and concluded that lateral pelvic lymph node metastases are not a major cause of local recurrence. The results of a Dutch trial of total mesorectal excision showed that the rate of lateral site

***Panel:* Research in context**

Systematic review

Total mesorectal excision or mesorectal excision is the international standard surgical procedure for lower rectal cancer.[1] However, lateral pelvic lymph node metastasis occasionally occurs in patients with clinical stage II or stage III rectal cancer, and therefore mesorectal excision with lateral lymph node dissection is the standard procedure in Japan. When metastatic lateral pelvic lymph nodes are not dissected, the patients can have local or systemic recurrence. Although we did not do a systematic search of published work before starting this trial, the reported incidence of local recurrence in rectal cancer patients undergoing mesorectal excision without lateral lymph node dissection at major hospitals in Europe and North America is less than 10%,[10–13] which is much the same as the incidence in patients who undergo mesorectal excision with lateral lymph node dissection at major hospitals in Japan.[4–6] Therefore, we did a randomised controlled trial to determine whether mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

Interpretation

7% of the patients with lower rectal cancer without lateral pelvic lymph node enlargement had lateral pelvic lymph node metastasis. Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than mesorectal excision alone. The primary analysis will help to determine whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

recurrence was only 3% in patients with lower rectal cancer, being much the same as results for patients who underwent lateral lymph node dissection at the National Cancer Center, Tokyo.[26] Analysis of the pattern of local recurrence in our study is very important, and should give a reliable indication of the incidence of lateral pelvic lymph node metastasis. The incidence of such metastasis was 7%, which was lower than the 15% reported in a retrospective multicentre study in Japan,[6] because only patients who had no clinical evidence of lateral pelvic lymph node enlargement were eligible for our study. This result shows that even in patients without clinically evident lateral pelvic lymph node metastasis, such metastasis is sometimes present pathologically.

Our patient population was defined as being lateral pelvic lymph node negative by CT or MRI. Nonetheless, the 7% of patients in the mesorectal excision with lateral lymph node dissection group were found to have lateral pelvic lymph node metastasis after lymph node dissection. Therefore, a similar proportion of patients undergoing mesorectal excision alone probably have such metastasis. If all patients with lateral pelvic lymph node metastasis have local or systemic recurrence, then the relapse rate will be about 7% higher in patients who undergo mesorectal excision alone than in those who also have lateral lymph node dissection. If the results for the primary analysis planned for 2015 show that the upper confidence limit of the HR is less than 1·34, which corresponds to an 8% difference in 5-year relapse-free survival between the groups, then the non-inferiority of mesorectal exicision alone will be confirmed in terms of outcome. If not, mesorectal excision with lateral lymph node dissection should be considered the standard surgical procedure for lower rectal cancer.

Contributors

SFujita, TA, NS, and YM contributed to study design. SFujita, TA, NS, YKi, YKa, MO, SFujii, MS, TY, and YM contributed to data collection, data analysis, and interpretation. JM contributed to statistical analyses. All the authors contributed to writing or review of the report and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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特集 治療効果の判定基準と臨床試験のendpoint

QOL
2）がん臨床試験における QOL評価の問題点*

福田治彦**

Key Words：quality of life(QOL), health-related quality of life(HRQOL), patient-reported outcome(PRO), clinical trials, oncology

QOL(キューオーエル)
測れるはずがないのに測れると一部の人が信じ，現実的な研究者を辟易させるもので，富山県などで出現すると蜃気楼とも呼ばれる．
［里見清一 著「誰も教えてくれなかった癌臨床試験の正しい解釈」中外医学社］

はじめに

がん診療・がん研究のコミュニティには，いわゆる“QOL(quality of life)調査肯定派”と“QOL調査否定派”がいる．どちらでもない人の中には“消極的肯定派(雷同派)”と“消極的否定派(懐疑派)”もいるだろう．筆者は里見氏と同じく“積極的否定派”である．

昨今，「がんの臨床試験においては，もはやQOL評価はde facto standard(やって当たり前)である」といったような声を耳にする．本当にそうだろうか？

がん専門医のバイブルといえるDeVitaの教科書[1]をみると「HRQOL(health-related quality of life)」の記載は全2,500ページのうち半ページ，PRO(patient-reported outcome)として約3ページである．がんに詳しい生物統計家として有名なPiantadosiの教科書「CLINICAL TRIALS」[2]では約600ページ中，PROとして1ページで「quality of life」という項立てすらない．現在筆者らが翻訳中のSWOGのClinical Trials in Oncology第3版[3]ではQOLは220ページのうち半ページ(18行)であり，SWOGではQOL調査をルーチンには組み込まない理由が書かれている．これら3冊あわせてもたかだか5ページなので読者にも是非読んでみて欲しいが，DeVitaに「今後PROの重要性は増すと期待される」という締めの一文はあるものの，「がんの臨床試験においてQOL評価は当たり前」といった記載は見当たらない．

このように，本稿ではQOL調査に否定的な見解を述べるが，その前提としてまず断っておきたいことは，「(診療や研究において)患者さんのQOLを大事にすること」と「患者自記式の“QOL調査”を行うこと」とは別物であるということである．「QOL調査を行うこと」は必ずしも「患者さんのQOLを大事にする」ことになるとは限らない．後述するようにQOL調査がかえって患者さんのQOLを損うこともあるし，QOL調査否定派の医者が患者さんのQOLを大事にしない医者であるわけでもない(筆者の知るQOL調査否定派/懐疑派の医師は皆，日々の診療において患者さんのQOLを大事にする優れた臨床医である)．

* Dark side of quality of life assessment in oncology clinical trials.

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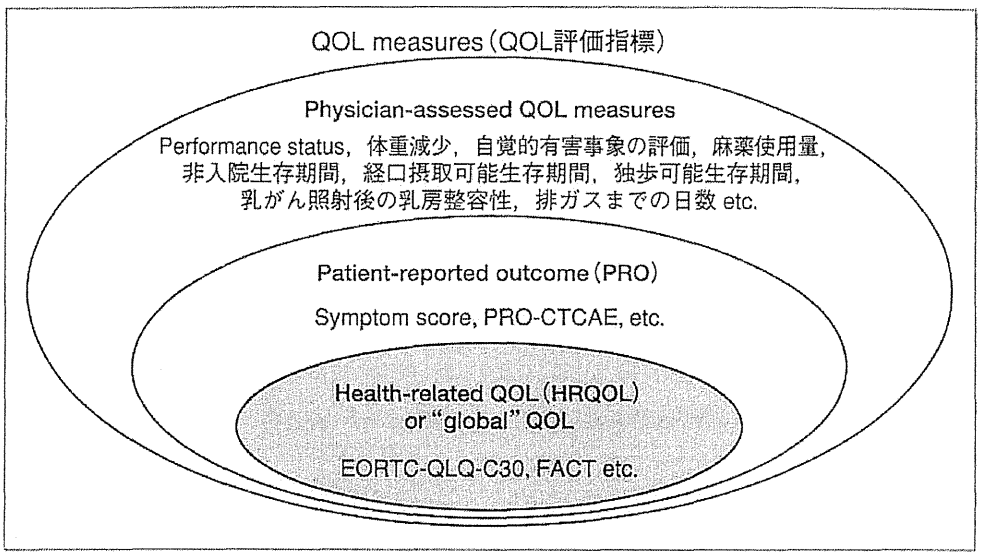

図1　QOL, PRO, HRQOLの関係

「QOL」が論じられるとき，常にこの「QOL」と「QOL調査」の（意図的もしくは無意識の）「混同」が背景にあり，「QOL調査」に対して否定的な意見を述べる者は「患者さんのQOLを大事にしない人間」かのように扱われるリスクを負う．そのためQOL否定派の意見は表に出にくく，QOL肯定派の言のみがさも大勢の世論かのように扱われるという構造的な「非対称性」が存在する．逆に言うと，（意図的か無意識かに依らず）「QOL調査が大事だ」と主張することで，周囲や社会に自分（たち）が「患者さんのQOLを大事にする（善い）人間である」と思わせることができるのである．それは一種の「欺瞞」ではないのだろうか？本稿が，世の中に瀰漫するこうした誤解を解く一助になることを期待する．

QOL（quality of life），HRQOL（health-related quality of life），PRO（patient reported outcome）の関係

「HRQOL」は「PRO」の一種とする考えが一般的である[1][4]．「QOL」を広くとらえた場合，ECOGやKarnofskyのperformance status（PS）等，医療従事者（health-care staff）が評価するスコアもQOL評価指標（QOL measures）に含まれる[4]ことから，これらの関係は図1のように整理できる．つまり，「QOL measures」は「physician（またはhealth-care staff）-assessed QOL measures」と「PRO」に分けられ，さらに「PRO」の一種として「HRQOL」があるという構造である．

筆者が責任者を務めるJCOG（Japan Clinical Oncology Group）データセンターでは，参加施設の担当医やCRC（clinical research coordinator）が記載する通常の症例報告用紙（case report form；CRF）で収集する有効性や安全性のデータと同様に，担当医やCRCが評価して記載するデータとしての「physician-assessed QOL measures」の開発に積極的に取り組んできた．JCOGデータセンターが考案したエンドポイントには「非入院生存期間（non-hospitalized survival time）」（生存期間－入院日数）や「経口摂取可能生存期間（ingestion-possible survival）」があるが，これらはPROよりハード（客観的）であり，かつデータ収集に患者さんの負担を伴わないことから，「QOLを評価したい」という研究者の要望に応じて筆者らが考案し，使用してきたエンドポイントである．こうしたハードなphysician-assessed QOL measuresはJCOGデータセンターとして今後も積極的に扱う．

また，QOL調査票は，日常診療の一環として，個々の患者さんに症状や日常生活の状況を記入してもらい，その時系列での変化を主治医が把握して治療の意思決定や生活指導に役立てるという使い方がされることがあるが[5]，筆者はそれについても否定的な見解は持っておらず，むし

ろそうした臨床医は応援したいと思っている．

以下，がんの臨床試験におけるHRQOLやPROに対する批判的吟味を試みよう．もう一つお断りしておくと，本稿での批判的見解はあくまでも筆者個人の見解であって，JCOGデータセンターの総意ではない．JCOGデータセンターにHRQOL賛成派はいないがPRO賛成派はいる．

HRQOLの臨床的な意味

われわれが，がん治療の臨床試験，特に(QOL評価が重要であるといわれる)第III相試験を行うのは，対象とする患者集団に対して，新しい試験治療が従来の標準治療に比べてよりよい治療かどうかを調べ，試験治療が優れていた場合に「従来の標準治療ではなく試験治療を第一選択とする(新たな標準治療とする)」という意思決定を行い，逆に試験治療が優れていなかった場合には「従来の標準治療が引き続き第一選択である」という意思決定を行うためである．つまりわれわれは，臨床試験の結果に基づいて「治療法の優劣」の意思決定を行う．HRQOLがこの意思決定に役立つのかどうかの吟味において，まずその「臨床的な意味」から問うことにしよう．

がんの標準治療を決める第III相試験では，通常は有効性のエンドポイントである生存期間(overall survival；OS)をprimary endpointとし，安全性のエンドポイントである有害事象(治療との因果関係を問わないあらゆる不都合な事象)や有害反応(治療との因果関係ありと判断される有害事象)をsecondary endpointとして，リスク/ベネフィットバランスの考察を行う．OSに対する代替性(surrogacy)が認められている場合(乳がんや大腸がんの術後補助療法)や，標準治療を決めることを目的としない場合(新薬の製造販売承認を目的とする場合など)には，無再発生存期間や無増悪生存期間をprimary endpointとすることもある．試験治療がOSで勝っていた場合，たとえば，「試験治療は標準治療に対して5年生存割合で10%(に相当する分だけ)上回っていた」時には，「治療を受ける患者さんが100人いるとすると，5年後に生存している人は従来の治療での30人に対して，新しい治療では40人と見込まれます」といった，患者さんにも具体的にイメージできる情報として説明することができる．毒性についても同様である．「(臨床的に最も重要とされた)grade 3以上の末梢神経障害が20% vs. 30%であった」という結果は，「日常生活に支障がある“しびれ”が100人中20人と30人でした」と，患者さんにも理解可能な情報に翻訳可能である．

一方，HRQOLではどうだろうか？「QOLスコアが標準治療30点，試験治療40点」であった場合，「患者さんが「生活の質」について付けた点数が標準治療の30点に対して試験治療では40点と勝っていました」といった説明しかできず，この説明を具体的なイメージをもって理解できる患者さんはおそらく存在しない．「治療に満足した人が，100人中30人と40人」という説明なら理解可能であろうが，それではウソになる(満足したかどうかを尋ねているわけではないため)．つまり，HRQOL評価の結果は「臨床的な意味」を持つ情報として提示することはできず，それは有効性や安全性のデータとともにリスク/ベネフィットの考察の俎上にあげることができないことを意味する．

また，この文脈で考えた場合，優越性試験と非劣性試験の違いも考慮する必要がある．「毒性が軽い」，「外来治療が可能」等のメリットが新治療にある場合，新治療は有効性(OS等)で勝らなくても，劣ってさえいなければ「よりよい治療」になりうると考えられることから，新治療が(通常OSで)標準治療に劣らないことを検証する非劣性試験(non-inferiority trial)が行われる．非劣性試験におけるリスク/ベネフィットバランスの考察は「有効性は劣らない」かつ「その他の要素で勝っている」のか否かの考察となり，毒性に加えて，もしくは毒性の代わりに「QOLスコアが上回る」を用いることは正当とされうるだろう．なぜなら「QOLスコアが何ポイント勝った」という説明は必要ではなく，「(延命効果は同等でしたが)患者さんが「生活の質」について付けた点数は，新治療が標準治療に勝っていました」という説明は多くの人になんとか理解可能と思われるからである．そして，もし，標準治療と試験治療が有効性でも同等で，(たまたま予想に反して)毒性でも同等という結果であった場合には，QOLスコアが優れた方をよりよい治療とすることは

許容されるだろう(次項で述べる比較可能性の問題は残るが)．ただし，それは有効性で非劣性，担当医評価の毒性でも差がないという限られた状況でのみ有用でありうるのであって，いわば“保険”のようなものである．限られた状況でのみ有用であるものに手間とリソース(および後述する「患者さんへの負担」)をかける価値があるかどうかは常に問われなければならないだろう．

一方，優越性試験(superiority trial)ではどうだろうか？ 試験治療がOSで有意に標準治療を上回った場合，試験治療の毒性が許容可能な範囲にあれば，QOLスコアの優劣がどうであったにせよ，「試験治療が新しい第一選択である」という意思決定は変わらない．逆に，試験治療がOSで勝らなかった場合には，QOLスコアがいくらよかったとしても「(毒性の強い)試験治療が新しい第一選択である」という意思決定にはならないだろう．すなわち，少なくともがんの標準治療を決める優越性の第III相試験において，QOLスコアは治療選択の意思決定に寄与しない．意思決定に寄与しないのであるから，その手間やリソースや患者さんの負担に見合わないとする方が自然な考えであろう．

この，「測っているものの臨床的な意味が説明できない」という問題は，「患者さん自身の評価による“中等度以上のしびれ”は○○治療の方が有意に軽かった」といった説明が可能であるPROによる毒性評価には当てはまらず，HRQOL特有の問題といえる．

情報バイアスと比較可能性

次は，「ちゃんと測れているか？」，すなわちバイアスと比較可能性についての吟味である．

世俗的な仮想例で恐縮だが，たとえば，自家用車の販売展示場で行う，試乗後に「乗り心地」を問うアンケートを考えよう．一つは「国産の軽自動車Jにご試乗いただきます」，もう一つは「欧州産の高級車Dにご試乗いただきます」としよう．価格はJが100万円，Dが400万円とし，試乗前に顧客に伝えられることとする．結果，「満足」と答えた人は，Dの40%に対してJが60%と上回っていたとしよう．この結果をもって「JはDより乗り心地がよい」ないしは「JはDより優れた車である」と結論してよいであろうか？多くの人の答えは「そんなわけないだろ？」であろう．

別の仮想例を考えよう．ある切除不能がんに対して，標準治療である「薬剤X+cisplatin」と，試験治療である「薬剤X+carboplatin」が非劣性試験デザインでランダム化比較されるとしよう．がん治療の臨床試験では，「cisplatinでは吐き気が強く出ること」と「carboplatinは吐き気が軽いこと」は，試験の意義(rationale)そのものにかかわる情報であるため患者さんへの説明文書には当然書かれなければならない．試験の結果，OSに関して「X+carboplatin」の非劣性が示され，嘔気・嘔吐を含む担当医評価による消化器毒性は期待どおり「X+carboplatin」が軽かった．QOLスコア(もしくはPROの消化器毒性grade)も「X+carboplatin」が有意に良好であった．これをもって「X+carboplatinは(QOLが)よりよい治療である」といえるであろうか？

ここで問題とすべきは，事前に与えられた情報による「情報バイアス」とそれによる「比較可能性」の損失である．車の例と同様に，「+cisplatin」と「+carboplatin」の比較には「比較可能性」が担保されているとはいえない．Jに試乗した顧客が「100万円にしては乗り心地がよい」，Dに試乗した顧客が「400万円にしてはたいしたことがない」と感じるのと同様，「吐き気」に関する事前情報は，患者さんのQOLスコアに影響を及ぼしうる．「吐き気が強い」という事前情報を与えられて「+cisplatin」の治療を受けた患者さんは，自分が「むかむか」を感じたときに「これはcisplatinのせいだ」と感じて低い点数をつけるかもしれないし，逆に「吐き気はほとんど出ない」と説明されて「+carboplatin」の治療を受けた患者さんは「むかむか」しても「治療のせいではないかもしれない．気のせいかもしれない」と考えて点数を低くつけないかもしれない．

全体のQOLスコアに大きく寄与しうる「吐き気」に関する「事前情報」によってQOLスコアは左右されうる．これは疫学でいう「情報バイアス(information bias)」の一種である．患者選択にまつわるバイアスである「選択バイアス(selection bias)」はランダム化により小さくすることがで