No.	PFS(day)	OS (day)	Pre-vaccination			Post-vaccination		
			WBC(/mm^3)	Lymphocyte (%)	Lymphocyte (/mm^3)	WBC(/mm^3)	Lymphocyte (%)	Lymphocyte (/mm^3)
1	36	36	7300	7	511	5300	10.5	557
2	26	108	7400	13	962	7900	8	632
3	31	31	7800	11	858	16200	10.5	1701
4	223	283	5100	21	1071	5200	10.5	546
5	24	128	2400	25.5	612	4200	10.8	454
6	26	40	4500	16.5	743	8000	4.1	328
7	55	155	4000	25	1000	6400	18.3	1171
8	56	145	4500	33	1485	14100	16	2256
9	>1219	>1219	2500	44.5	1113	3600	33	1188
10	27	142	2300	29.5	679	5800	11.5	667
11	112	225	2600	9	234	2200	11.5	253
12	32	32	4500	30	1350	2400	10.7	257
13	57	97	7100	15.5	1101	9100	10.5	956
14	169	220	2300	27	621	4100	19.5	800
15	24	44	8500	9.5	808	13300	4.8	638
16	28	182	4800	27	1296	6400	19.3	1235
17	169	309	6200	26.5	1643	7900	17.5	1383
18	93	93	4200	28	1176	6600	18.6	1228
19	57	105	10200	20.5	2091	28700	9	2583
20	169	332	10100	34	3434	7600	19.5	1482
21	56	249	6000	27.5	1650	9600	8	768
22	89	89	7000	11.5	805	5200	20	1040
23	148	148	7900	20	1580	11200	19	2128
24	415	495	3800	16	608	5600	17.8	997
25	11	11	7600	21.5	1634	7400	20.5	1517
26	112	207	6600	24	1584	7500	21.5	1613
27	115	317	2900	23.5	682	4000	25.5	1020
28	69	69	9000	26.5	2385	11200	7.5	840
29	52	388	4000	26	1040	5600	24.6	1378
30	56	69	4800	26.5	1272	8900	7.1	632
31	56	82	6800	33	2244	8300	19.5	1619

*Clinical response was evaluated one month after vaccination. PD, Progressive disease; SD, Stable disease; CR, Complete response; OR, Objective response.
**Best CTL response after vaccination. CTL responses were evaluated and classified based on the algorithm as described in Methods.
N.T. (Not Tested); CTL response was not tested in the samples in which PD was observed within one course of the treatment.
N.A. (Not Analyzed); CTL response was not analyzed because of the poor viability during the *in vitro* stimulation.

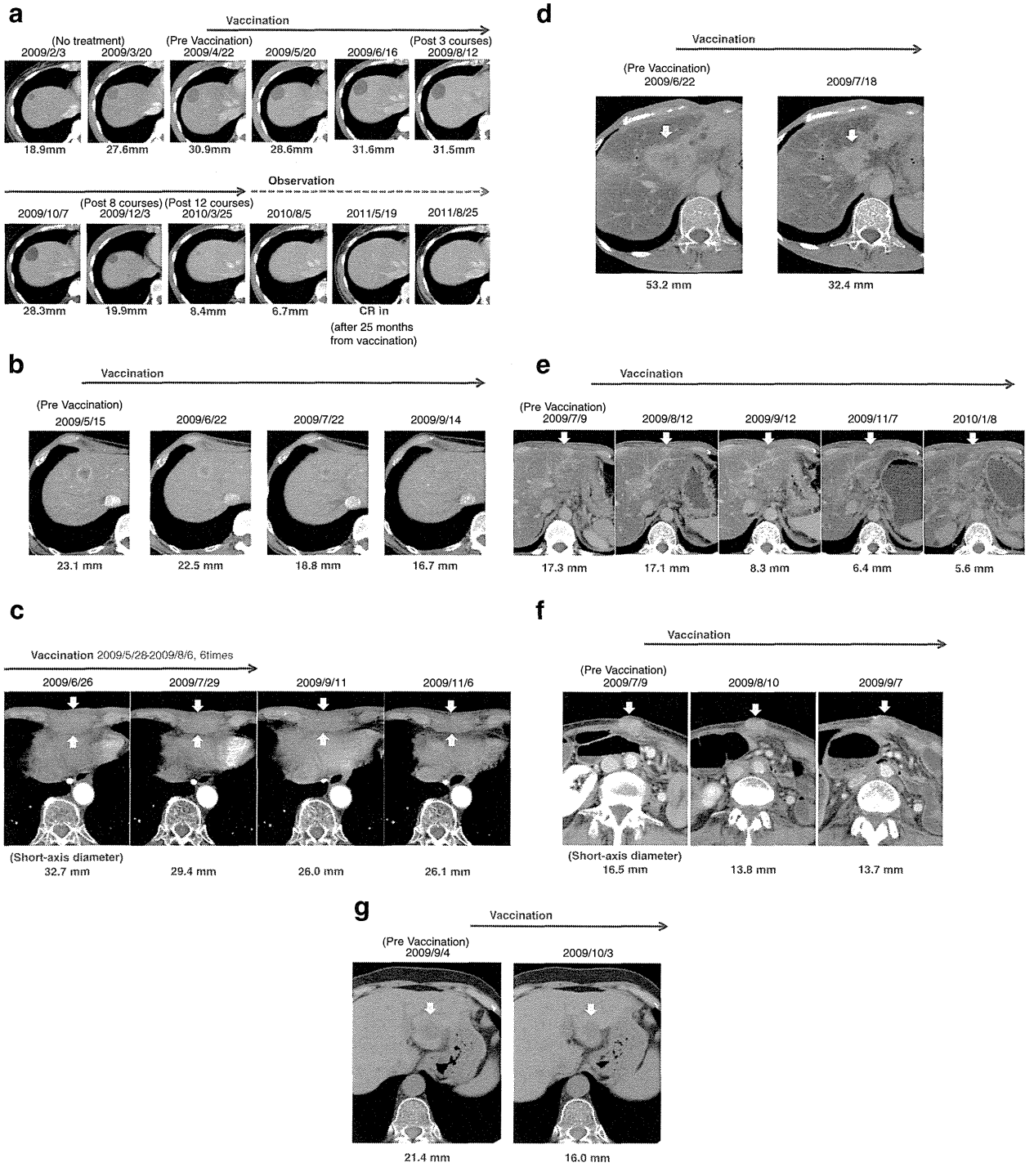

Figure 1 CT images of the target lesions showing objective tumor response. Representative CT images of the target lesions were shown, such as liver metastasis in case 9 **(a)**, liver metastasis in case 14 **(b)**, bone metastasis in xiphoid process in case 24 **(c)**, liver metastasis in case 22 **(d)**, liver metastasis in case 27 **(e)**, peritoneal metastasis in case 28 **(f)**, and liver metastasis in case 31 **(g)**. Arrow head indicates the target lesion.

CTL response and injection site reactions

We expected that the number of CTL responded to KIF20A peptide may be associated with the efficacy of the vaccine treatment. Therefore, CTL response was measured by ELISPOT assay in 29 patients who received the vaccination at least one cycle (Table 2). Among them, CTL responses in 24 patients were comparable in pre- and post-vaccination. In 16 patients out of 23 (70%), the

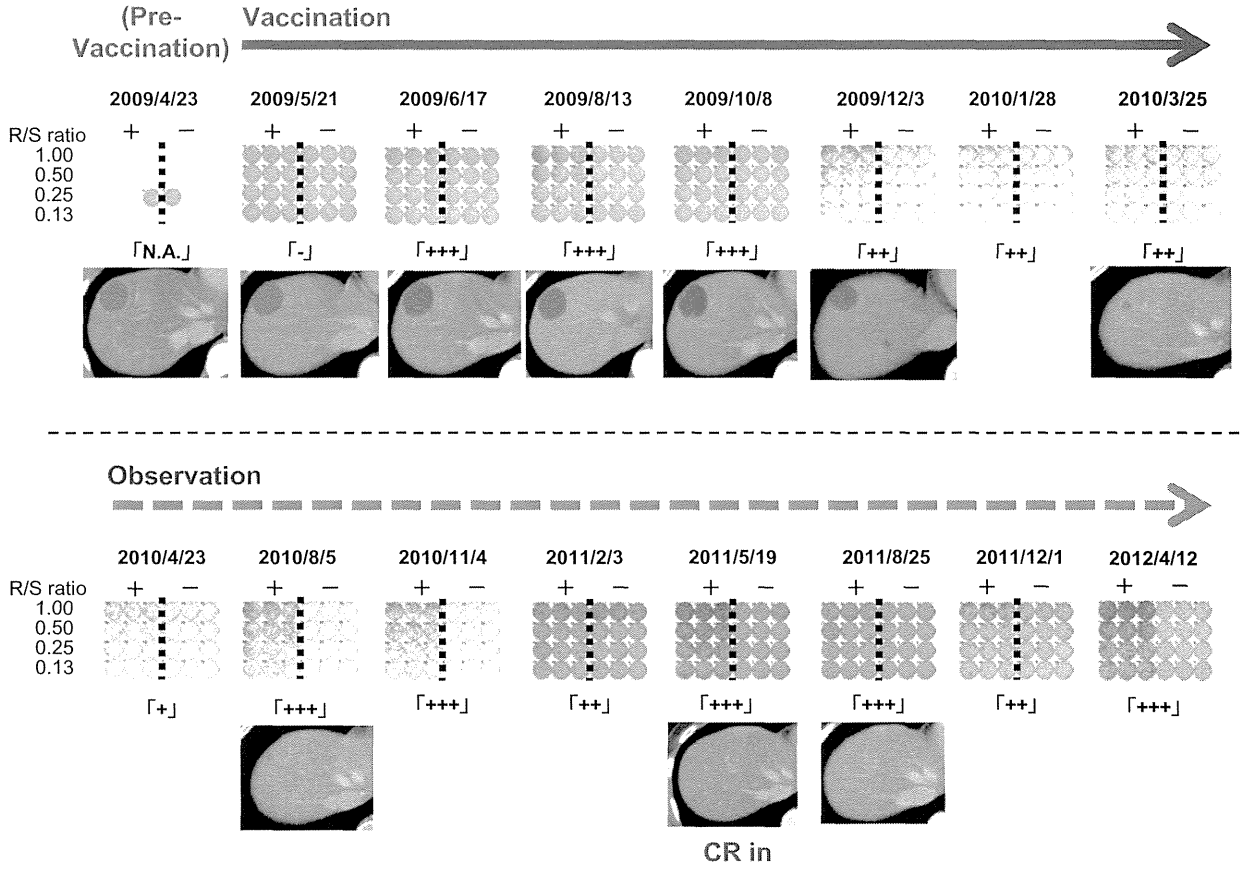

Figure 2 Peptide specific CTL response in case 9. Strong CTL responses specific to KIF20A-66 peptide were obtained at the time of 2 months after vaccination. The responses were kept strong positive during 2 years of the observation period. The number of the spots specific to peptide was calculated by subtracting the spot number in control wells from that in peptide-pulsed TISI cells.

intensity of CTL response was increased (Table 2), determined by the algorithm flow chart [25]. Of note, strong CTL response specific to KIF20A-66 was observed two months after the start of the vaccination in the patient of case 9, who achieved CR. This response kept strong for one year, and it was detectable even 2 years after the drug was discontinued (Figure 2). A flow cytometry assay demonstrated that the number of KIF20A-66 specific TCR in CD8-positive T cells was consistent with the grades classified according to our algorithm flow chart [25] (Figure 3a), compared to the negative control stain utilizing HIV-dextramer (Figure 3b). Also, injection site reactions were observed in 23 patients. MST of the patients with positive skin reaction was 182 days, while that of the patients with negative reaction was 42 days (Figure 5). These results demonstrate that CTL response and ISRs could be employed as biological markers to rapidly diagnose the efficacy of the peptide vaccination. Consistent with these results, when the 29 patients were classified into two groups in regard to the content ratio of lymphocyte (more than 16% (n = 23) vs. less than 16% (n = 6)), the group with higher number of lymphocyte yielded better prognosis with statistical significance (p = 0.0296). This result suggests that the number of lymphocyte is positively associated with the survival of the patients.

Discussion

Currently, there is no therapeutic strategy effective for the patients, whose pancreatic cancer is refractory to gemcitabine and TS-1. Combination therapy utilizing a couple of cytotoxic agents with gemcitabine has been investigated, but it has been failed to prove their clinical benefit so far [6-15]. We conducted an expression screening of proteins that were highly up-regulated in tumor cells, and not in normal cells, as a candidate of the target to develop novel anti-cancer drugs [20]. We successfully identified a member of kinesin super family protein 20A (KIF20A). Subsequently, we established an epitope peptide that were likely to be presented as an antigen in a HLA-A*2402- or HLA-A*0201-restricted manner [23,24,27]. In this report, we demonstrated that the KIF20A-derived peptide could improve the prognosis of the patients with advanced pancreatic cancer, suggesting that the KIF20A peptide vaccination is a promising approach as cancer immunotherapy.

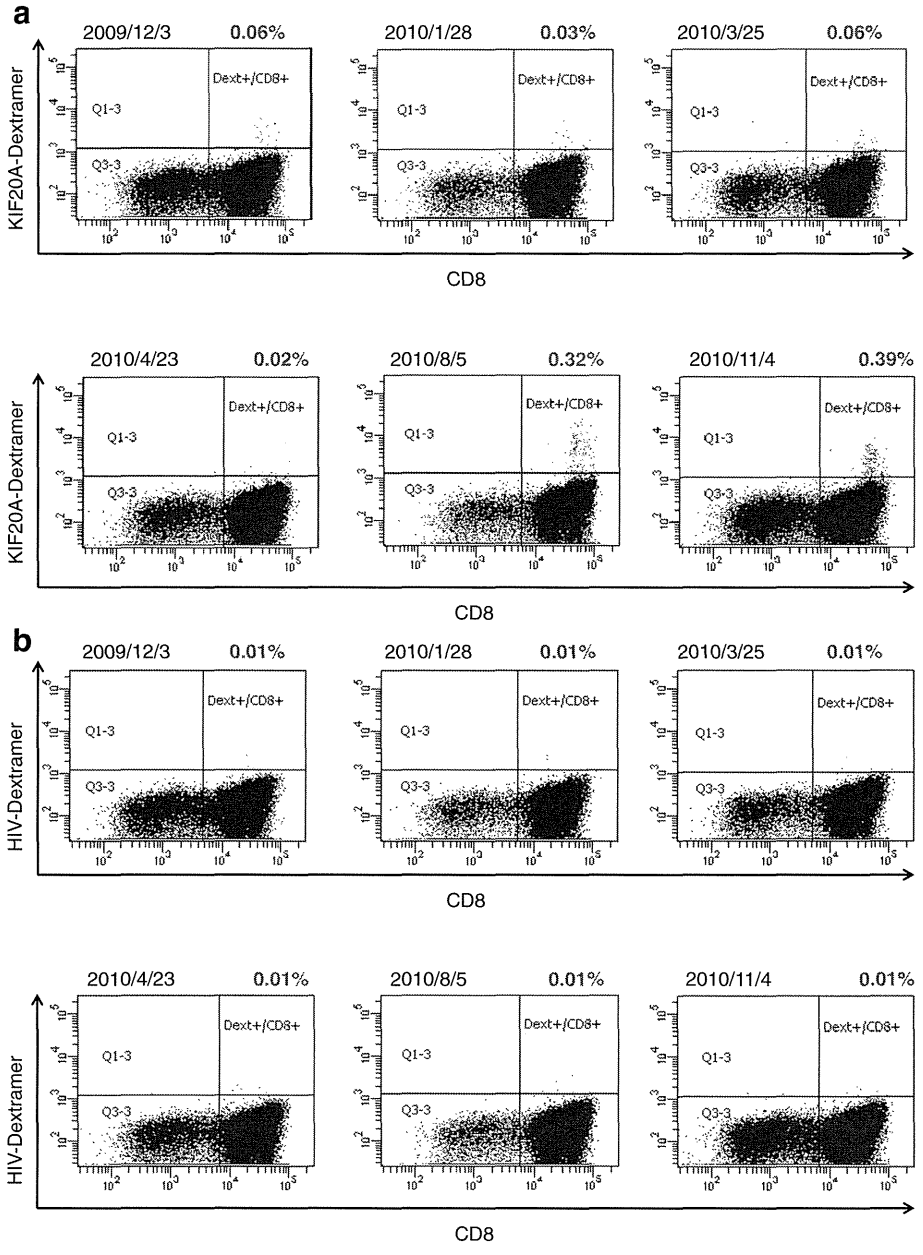

Figure 3 Flow cytometry analysis of KIF20A-66 specific TCR expression in $CD8^+$ cells in case 9. Cells were stained with either KIF20A-dextramer **(a)** or HIV-dextramer **(b)** after IVS as described in Methods section. The content rates of KIF20A-dextramer positive or HIV-dextramer positive cells (red dots) in $CD3^+$ $CD4^-$ $CD8^+$ cells are shown above panels in red.

In this clinical trial, we evaluated the safety and efficacy of KIF20A-66 peptide vaccine monotherapy for the patients with HLA-A*2402. This vaccine was well tolerated in the doses of 1.0 mg and 3.0 mg/body, although we do not exclude the possibility of two adverse events related to vaccination. The MST of 31 patients was 142 days in this phase I/II trial, indicating that vaccine treatment utilizing KIF20A-66 peptide provides survival benefit. Therefore, we concluded that the peptide vaccination improved overall survival period of the patients with advanced pancreatic cancer, who were resistant to chemotherapy. A placebo-controlled clinical trial should be required to further establish this peptide vaccine as a standard immunotherapy against pancreatic cancer.

We realized, during the course of peptide vaccination, that an induction of peptide-specific CTL and positive skin reaction were observed in the majority of the patients. We assure that these reactions could be employed as biomarkers of preferable clinical responses. Therefore, the number of CTL induced by peptide injection and the skin reaction at an injection site were analyzed. As we expected,

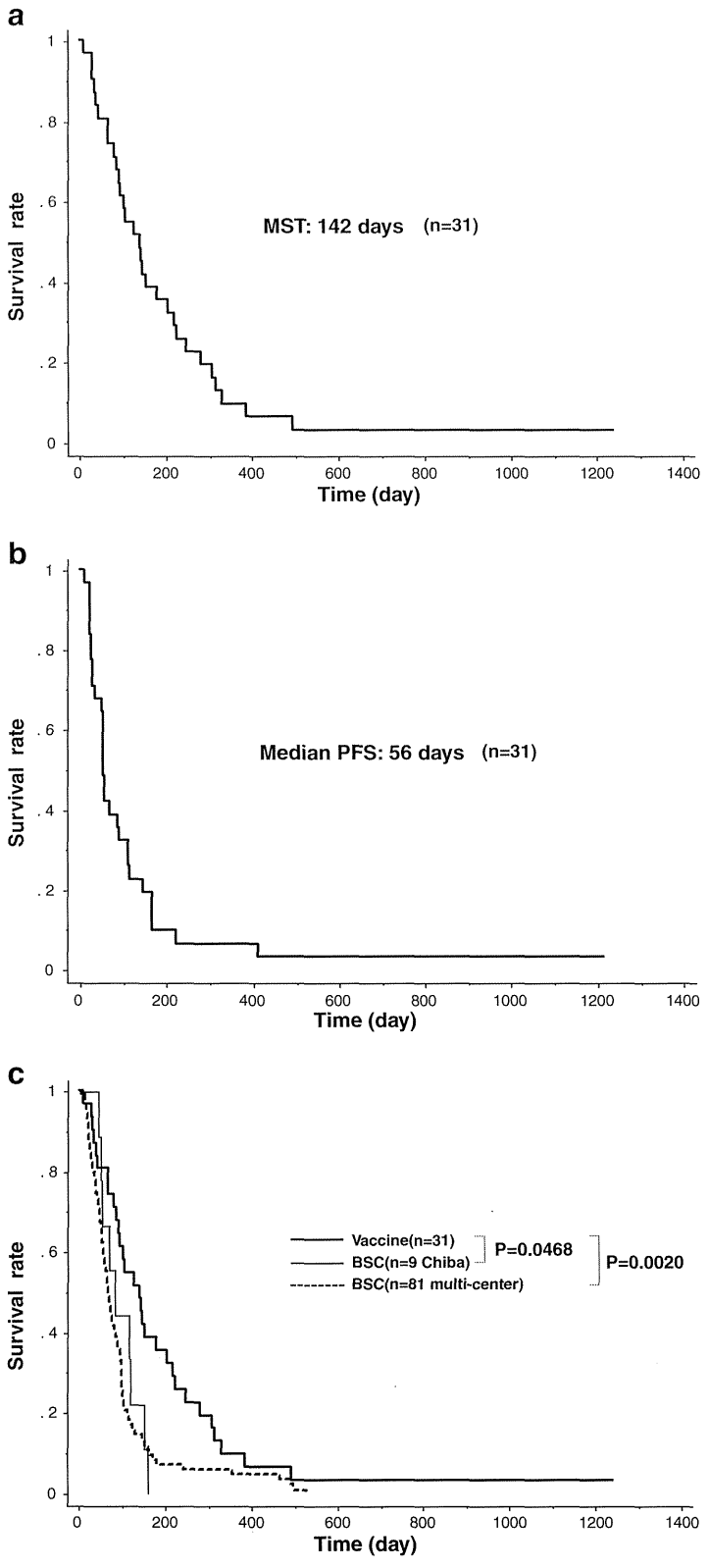

Figure 4 (See legend on next page.)

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Figure 4 Overall survival and progression free survival in phase I/II trial. Overall survival of the patients was shown in Kaplan-Meier plots (n = 31) **(a)**. MST of the patients with peptide vaccine was 142 days. PFS of the patients with peptide vaccine was 56 days **(b)**. In comparison with the control patients who were treated with best supportive care in Chiba Tokushukai Hospital (n = 9), overall survival of the patients with the KIF20A-peptide vaccination was fairly improved (p = 0.0468, MST: 142 vs. 83 days). In comparison with the BSC patients (n = 81), overall survival of the vaccinated patients in Chiba Tokushukai Hospital was significantly improved (p = 0.0020, MST: 142 vs. 63 days) **(c)**.

high level of CTL response specific to KIF20A-66 peptide resulted in CR in case 9. The liver metastasis continuously shrunk even after the peptide vaccination was discontinued (Figure 1a), and there was no sign of recurrence or metastasis at the time of 40 months after the vaccination started. Since biopsy of the tumor lesion was not performed during or after the vaccination, there is no information regarding the tumor infiltrating lymphocyte (TIL). This example indicates that positive correlation between tumor shrinkage and immunological reactions is of clinically interest (Figure 2). On the other hand, there is no CTL induction detected in Case No. 4, 27, and 28, while objective shrinkages were observed in these patients during the course of treatment. Since the number of CTL is usually low in peripheral blood, the CTL induction is measured after the stimulation utilizing respective peptide and IL-2 to yield higher detection limit. Despite this procedure, it is assumed that the intensity of CTL induction and the efficacy of vaccine treatment are not necessarily correlated according to a linear function, possibly due to the high expression levels of MHC Class I and/or targeted antigen KIF20A in tumor cells. Therefore, development of sensitive and reliable methods to detect CTL is required to evaluate the results of peptide vaccine treatment in the patients.

The US FDA published the guidance for the therapeutic cancer vaccine [28], describing that it is hard to expect clinical benefit of the vaccine treatment for the patients after multiple chemotherapy regimens due to very poor immune status. However, unlike many trials tested so far utilizing other peptide vaccines, this clinical study was quite successful. Our results clearly demonstrate that therapeutic cancer vaccination is still a promising approach for advanced pancreatic cancer after the failure of standard chemotherapy. In general, patients with relapsed or recurrent metastatic disease receive multiple treatments for their cancer. These therapies may be detrimental to the immune system, and adequate time is required for the cancer vaccine to elicit a detectable immune response. Given such therapeutic conditions affect the results of peptide vaccination, the use of adjuvant setting and the cohort study during an early treatment of the vaccine may be necessary to better understand a cause-and-result relationship of cancer immunotherapy. Furthermore, it is important to develop the peptides with the higher immunogenicity against active oncoproteins. Indeed, we have examined several peptides derived from a variety of cancer-testis antigens that have the oncogenic activity, including KIF20A, DEPDC1, MPHOSPH1, URLC10(LY6K),TTK, KOC1(IMP3),

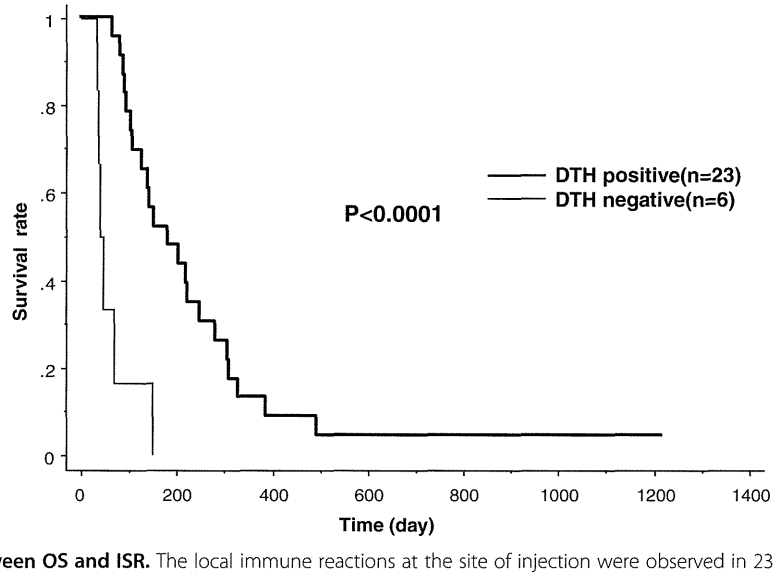

Figure 5 Correlation between OS and ISR. The local immune reactions at the site of injection were observed in 23 patients. MST of the patients who had injection site reaction was 182 days, while MST of the patients without such reaction (n = 6) was 42 days (p < 0.0001).

CDCA1, RNF43, and TOMM34 [16,17,20,22-25,27,29]. We propose that the trial of the cocktail vaccine of these high immunogenic peptides including KIF20A-66 will provide with better treatment and cure for cancer.

Abbreviations

HLA: Human leukocyte antigen; CR: Complete response; SD: Stable disease; PD: Progressive disease; MST: Median survival time; CTL: Cytotoxic T lymphocyte; 5-FU: 5-fluorouracil; ECOG: Eastern cooperative oncology group; RECIST: Response evaluation criteria in solid tumors; OS: Overall survival; PFS: Progression free survival; ISRs: Injection site reactions; IFA: Incomplete freund's adjuvant; ELISPOT: Enzyme-linked immunospot; PBMC: Peripheral blood mononuclear cell; IFN: Interferon; CIC: Cancer immunotherapy consortium; SAE: Severe adverse event; PR: Partial response; TIL: Tumor infiltrating lymphocyte.

Competing interests

The authors declare that they have no financial competing interest.

Authors' contribution

SA designed, performed, and evaluated clinical study. KT participated as the main coordinator and investigator regarding the immunological data analysis and evaluation. KY, HM, and HY analyzed control studies in their hospitals. SA wrote the manuscript. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Impact of anticancer treatment on recurrent obstruction in covered metallic stents for malignant biliary obstruction

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Abstract
Background In patients with unresectable malignant biliary obstruction (MBO), anticancer treatment is often administered. The impact of anticancer treatment on recurrent biliary obstruction in covered self-expandable metallic stents (SEMS) has not been fully elucidated.
Methods Data on 279 patients enrolled in a multicenter prospective cohort study of two different covered SEMS for distal MBO, WATCH study (141 partially covered WallFlex stents and 138 partially covered Wallstents) were retrospectively analyzed. The rates and causes of recurrent biliary obstruction (stent occlusion or migration) were compared between anticancer treatment group ($n = 173$) and best supportive care alone (BSC) group ($n = 106$). Cumulative time and prognostic factors for recurrent biliary obstruction were analyzed, using a proportional hazards model with death without recurrent biliary obstruction as a competing risk.
Results The overall rate (43 vs. 25 %, $P = 0.002$) and the cumulative incidence (16.1 vs. 8.2, 27.9 vs. 18.9 and 44.1 vs.

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26.6 % at 3, 6 and 12 months, $P = 0.030$ by Gray's test) of recurrent biliary obstruction were significantly higher in anticancer treatment group compared with BSC group. The multivariate analysis revealed anticancer treatment [subdistribution hazard ratio (SHR) 1.93, $P = 0.007$) as well as the use of a partially covered WallFlex stent (SHR 0.65, $P = 0.049$) as prognostic factors.

Conclusions Anticancer treatment was a risk factor for recurrent biliary obstruction in covered SEMS for distal MBO. The superiority of a partially covered WallFlex stent was again confirmed in this competing risk analysis; UMIN-CTR: UMIN000002293.

Keywords Chemotherapy · Competing risk analysis · Covered metallic stents · Obstructive jaundice

Introduction

Endoscopic biliary stenting [1, 2] is an established palliation for malignant biliary obstruction. Self-expandable metallic stents (SEMSs) were proved to have longer stent patency than plastic stents [3–5]. Covered SEMSs were developed to prevent stent occlusion by tumor ingrowth [6–9], which is the major problem with uncovered SEMSs. However, two randomized controlled trials (RCTs) failed to demonstrate better stent patency due to stent migration in covered SEMSs [10, 11]. Recently, we reported the superiority of a newly developed a partially covered WallFlex stent over a partially covered Wallstent in a multicenter prospective study, the WATCH study [12]. A partially covered WallFlex stent with low axial force and anti-migration system [13, 14] demonstrated less stent migration and longer time to recurrent biliary obstruction.

Recent development of chemotherapy in pancreatic cancer [15, 16] or biliary tract cancer has improved the prognosis, even in patients with distant metastasis. While better local tumor control by anticancer treatment can prevent tumor ingrowth or overgrowth and improve stent patency [17], tumor volume reduction may theoretically increase stent migration due to the resolution of the stricture. In addition, adverse events such as neutropenia can potentially increase cholangitis and/or sludge formation. We previously reported the safety and efficacy of SEMSs in patients with advanced pancreatic cancer receiving gemcitabine [18]. Though a Cox hazard regression analysis [19] was used to adjust the differences in patient characteristics, i.e., performance status (PS) and disease stage, the influence of different survival between patients receiving chemotherapy or best supportive care (BSC) alone, which can potentially affect the analysis of stent outcomes [20], has not been fully elucidated. Generally, conventional methods such as Kaplan–Meier method with the log-rank test and Cox proportional hazard model overestimate a cumulative incidence of recurrent biliary obstruction in the presence of a competing risk, death without recurrent biliary occlusion in this setting. Therefore, the comparison of stent outcomes between patients receiving anticancer treatment versus BSC alone can be biased if death without stent occlusion is not taking into account because of different prognosis in these two groups.

Here we conducted a retrospective analysis of 279 patients with distal malignant biliary obstruction enrolled in WATCH study [12] to clarify the impact of anticancer treatment on recurrent biliary obstruction using a competing risk analysis [21, 22].

Patients and methods

Study design

This is a retrospective analysis of WATCH study, a previously reported multicenter prospective consecutive study with a historical cohort in patients with distal malignant biliary obstruction [12]. A total of 279 patients were included in the study; 141 patients received a partially covered WallFlex stent between April 2009 and March 2010, and 138 patients received a partially covered Wallstent between May 2001 and Jan 2007.

Definitions of complications

Recurrent biliary obstruction was diagnosed if patients have recurrent jaundice with evidence of elevated bilirubin

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along with biliary dilation on CT, MRI or US. When recurrent biliary obstruction was suspected, reintervention was performed to confirm the biliary obstruction and its cause, unless patients were at terminal stage of the disease and could not tolerate the procedure. Recurrent biliary obstruction was defined as stent occlusion or migration. Death without recurrent biliary obstruction was defined as patients' death before any recurrent biliary obstruction was observed.

Study outcomes and statistics

The rates and causes of recurrent biliary obstruction were compared between patients receiving anticancer treatment (anticancer treatment group) and patients receiving no anticancer treatment (BSC group). Cumulative time to recurrent biliary obstruction was first calculated by the Kaplan–Meier method [23] and compared by the log-rank test [24]. Then, it was re-calculated treating death without recurrent biliary obstruction as a competing risk and compared by the Gray's test [21].

Univariate and multivariate analyses of prognostic factors for recurrent biliary obstruction were performed using a proportional hazards model proposed by Fine and Gray [22], with death without recurrent biliary obstruction as a competing risk. We included age (≥70 vs. <70), gender (male vs. female), WHO PS (0 vs. ≥1), primary cancer (pancreatic cancer vs. others), anticancer treatment (yes vs. no), tumor size (≥30 vs. <30 mm), stricture length (≥20 vs. <20 mm), stent length (80 vs. ≤60 mm), liver metastasis (yes vs. no), ascites (yes vs. no), duodenal invasion (yes vs. no), prior drainage (yes vs. no), location of distal stent end (duodenum vs. bile duct), stent type (a partially covered WallFlex stent vs. a partially covered Wallstent) into the model. Age, tumor size and stricture length were divided into two groups by the median value. In the competing risk analysis, death without recurrent biliary obstruction was considered as a competing risk and subdistribution hazard ratios (SHRs), with 95 % confidence intervals (CIs) calculated. Factors with $P < 0.20$ by univariate analysis were considered to be potential risk factors for recurrent biliary obstruction and were further analyzed in a multivariate analysis.

Either the chi square or Fisher's exact test was used to compare the categorical variables, and Student's *t*-test or Wilcoxon nonparametric test was used to compare continuous variables. A P value <0.05 was considered statistically significant. All analyses were performed using R software, version 2.14.0 (R Development Core Team: http://www.r-project.org). We used the *cmprsk* package for a competing risk analysis in R produced by Gray. All authors had access to the study data and had reviewed and approved the final manuscript.

Results

Patients

All 279 patients enrolled in WATCH study [12] were included in this retrospective analysis. Patient characteristics are shown in Table 1. Anticancer treatment was administered in 173 patients; chemotherapy alone in 154 (gemcitabine monotherapy in 120, S-1 monotherapy in 12, gemcitabine and S-1 combination therapy in 17 and others in 5), radiation therapy alone in 5, and chemoradiation therapy in 14. Between anticancer treatment group and BSC group, there were significant differences in age, PS and primary tumor. Stent type or length was similar between two groups. Median survival time by Kaplan–Meier method was 251 [interquartile range (IQR) 150–441] days in anticancer treatment group and 170 (IQR 73–301) days in BSC group ($P = 0.001$).

Recurrent biliary obstruction and stent-related complications

The incidences of recurrent biliary obstruction and stent-related complications are shown in Table 2. The overall rate of recurrent biliary obstruction was significantly higher in anticancer treatment group (43 %) compared with BSC group (25 %). Median time to recurrent biliary obstruction in those patients with recurrent obstruction was 126 (range 7–556) days in anticancer treatment group and 125 (range 3–385) days in BSC group ($P = 0.578$). Among recurrent biliary obstruction, the rate of stent migration was significantly higher in the anticancer treatment group (16 vs. 7 %, $P = 0.038$). Median time to stent migration was 84 (range 7–426) days in anticancer treatment group and 116 (range 4–281) days in BSC group ($P = 0.240$). The rate of pancreatitis or cholecystitis was similar between two groups.

Risk factors for recurrent biliary obstruction

Cumulative time to recurrent biliary obstruction was calculated with two different methods. Median cumulative time to recurrent biliary obstruction by the Kaplan–Meier method was 291 (IQR 250–373) days in anticancer treatment group and 378 (IQR 281 to unknown) days in BSC group ($P = 0.415$ by the log-rank test, Fig. 1). When death without recurrent biliary obstruction was treated as a competing risk, cumulative incidence of recurrent biliary obstruction was significantly higher in anticancer treatment group compared with BSC group ($P = 0.030$ by Gray's test, Fig. 2). Cumulative incidence of recurrent obstruction at 3, 6 and 12 months was 16.1 versus 8.2 %, 27.9 versus

Table 1 Patient characteristics

	Anticancer treatment (n = 173)	BSC (n = 106)	P value
Age (years)	69 (41–90)	77 (32–99)	<0.001
Male/female	106 (61 %)/67 (39 %)	60 (57 %)/46 (43 %)	0.454
WHO PS, 0/1/2–	75 (43 %)/65 (38 %)/33 (19 %)	17 (16 %)/26 (25 %)/63 (59 %)	<0.001
Primary tumor			<0.001
Pancreatic cancer	138 (80 %)	59 (56 %)	
Bile duct cancer	18 (10 %)	22 (21 %)	
Gallbladder cancer	4 (2 %)	3 (3 %)	
Others	13 (8 %)	22 (21 %)	
Tumor size	30 (10–115)	31 (10–70)	0.334
Stricture length	20 (5–65)	20 (8–55)	0.790
Liver metastasis	49 (28 %)	31 (29 %)	0.892
Ascites	20 (12 %)	18 (17 %)	0.212
Duodenal invasion	42 (24 %)	35 (34 %)	0.099
Stent type, WallFlex/Wallstent	92 (53 %)/81 (47 %)	49 (46 %)/57 (54 %)	0.270
Stent length (40/60/80 mm)	44 (25 %)/124 (72 %)/5 (3 %)	27 (25 %)/74 (70 %)/5 (5 %)	0.745
Distal end, duodenum/bile duct	168 (97 %)/5 (3 %)	100 (94 %)/6 (6 %)	0.342

PS performance status

The numbers are expressed in either median (range) or n (%)

Table 2 Recurrent biliary obstruction and complications

	Anticancer treatment (n = 173)	BSC (n = 106)	P value
Recurrent biliary obstruction	74 (43 %)	26 (25 %)	0.002
Stent occlusion	46 (27 %)	19 (18 %)	0.109
Biliary sludge	24 (14 %)	9 (8 %)	
Food impaction	11 (6 %)	4 (4 %)	
Tumor overgrowth	7 (4 %)	6 (6 %)	
Hemobilia	1 (1 %)	0	
Unknown	3 (2 %)	0	
Stent migration	28 (16 %)	7 (7 %)	0.038
Cholecystitis	15 (9 %)	8 (8 %)	0.825
Pancreatitis	7 (4 %)	5 (5 %)	0.770

The numbers are expressed in n (%)

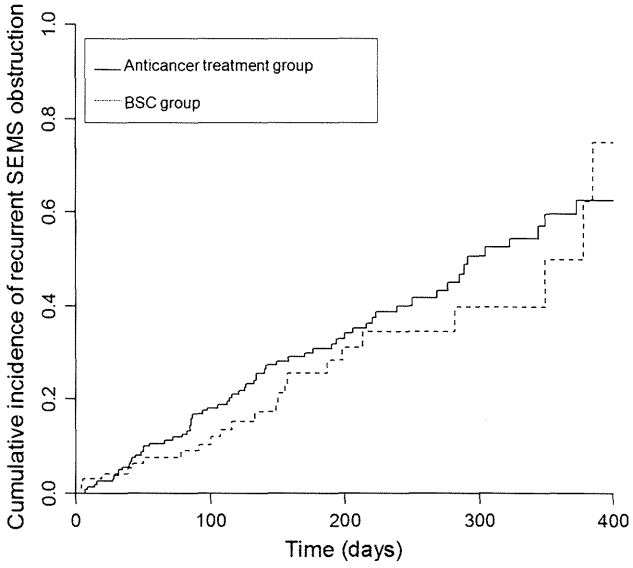

Fig. 1 Cumulative incidence of recurrent biliary obstruction in anticancer treatment and BSC groups by the Kaplan–Meier method

18.9 % and 44.1 versus 26.6 % in anticancer treatment group versus BSC group.

Cumulative recurrent biliary obstruction in partially covered WallFlex stents and partially covered Wallstents is shown in Fig. 3. Partially covered WallFlex stents showed longer time to recurrent biliary obstruction in a competing risk analysis, which was in line with results of the original analysis using the Kaplan–Meier method [12].

Univariate and multivariate analyses of prognostic factors for recurrent biliary obstruction were performed using a proportional hazard regression model by Fine and Gray [22], treating death without recurrent biliary obstruction as a competing risk (Table 3). The multivariate analysis revealed BSC group as well as the use of a partially covered WallFlex stent as prognostic factors for longer time to recurrent biliary obstructions. The SHRs of anticancer treatment and a partially covered WallFlex stent were 1.93 (95 % CI 1.20–3.10, P = 0.007) and 0.65 (95 % CI 0.42–1.00, P = 0.049).

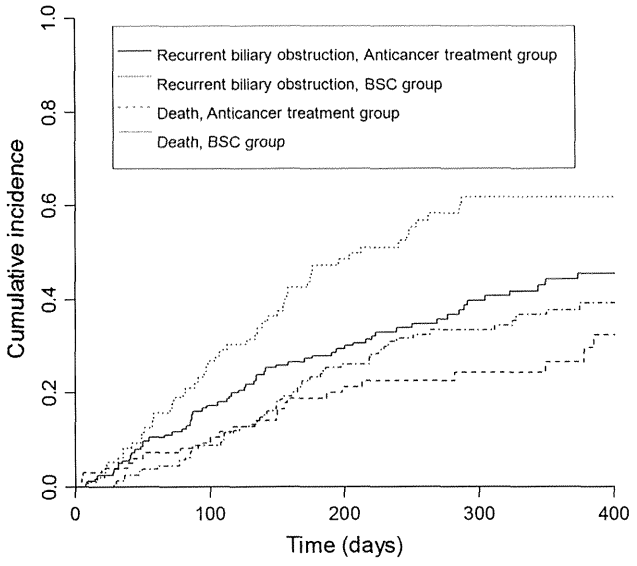

Fig. 2 Cumulative incidence of recurrent biliary obstruction and death in anticancer treatment and BSC groups, using a competing risk analysis. Death without recurrent obstruction was treated as a competing risk

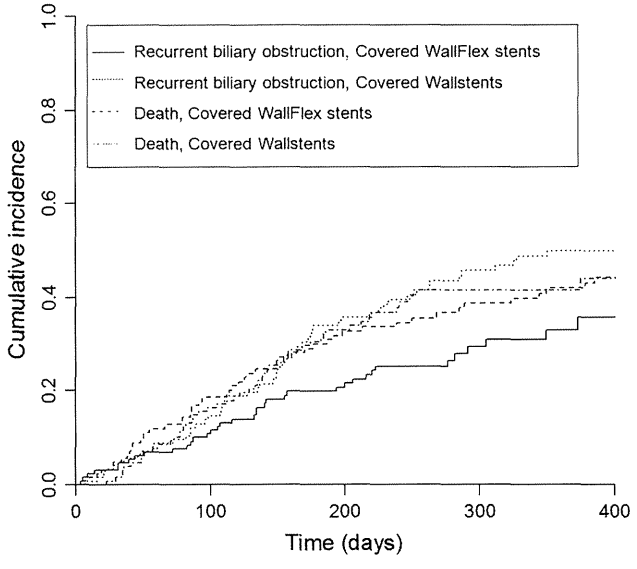

Fig. 3 Cumulative incidence of recurrent biliary obstruction and death in covered WallFlex stents and covered Wallstents, using a competing risk analysis. Death without recurrent obstruction was treated as a competing risk

Discussion

In this retrospective analysis of 279 patients with distal malignant biliary obstruction receiving a partially covered WallFlex stent or a partially covered Wallstent enrolled in the WATCH study [12], anticancer treatment was a significant risk factor for recurrent biliary obstruction only when survival difference was accounted for using a competing risk analysis. A partially covered WallFlex stent was proved to be superior to a partially covered Wallstent in this analysis as previously reported [12].

Safety and efficacy of biliary stenting have been reported in patients receiving chemotherapy [17, 18, 25, 26]. The conventional Kaplan–Meier analysis [23] or Cox regression analysis [19] was used and differences in survival were not accounted for in these studies. In these analyses, death without biliary event is usually treated as non-informative censoring, and given the possible overestimation of biliary events in BSC group with poor prognosis using that non-informative censoring, it is possible that the negative impact of anticancer treatment in patients with better survival was relatively underestimated. Therefore, we introduced a competing risk analysis [21, 22] to adjust the differences in survival between two groups. In this analysis, death without recurrent biliary obstruction was considered as a competing risk. In the conventional Kaplan–Meier analysis, anticancer treatment did not appear to affect time to recurrent biliary obstruction, but a competing risk analysis showed anticancer treatment was a significant risk factor for recurrent biliary obstruction both in univariate and multivariate analyses.

The incidences of recurrent biliary obstruction (43 vs. 25 %), especially stent migration (16 vs. 7 %), were significantly higher in the anticancer treatment group, but we can argue that the anticancer treatment group developed biliary events because of their longer survival. However, time to recurrent biliary obstruction or stent migration in patients with recurrent biliary event was similar between anticancer treatment group and BSC group. In addition, the cumulative time to recurrent biliary obstruction was shorter in patients with anticancer treatment, only when death without recurrent obstruction was treated as a competing risk. These results support the hypothesis that anticancer treatment per se, rather than longer survival in the anticancer treatment group, was a risk factor for recurrent biliary obstruction.

There are a few possible causes of shorter cumulative time to recurrent biliary obstruction in patients with anticancer treatment. Chemotherapy is reported to be a risk factor for stent migration of SEMS placement for gastric outlet obstruction [27, 28] due to reduced tumor burden. Similarly, higher migration rate in anticancer treatment group in this study might be caused by local tumor burden reduction, though no data was available about relations between local tumor response and stent migration. Meanwhile, neutropenia induced by anticancer treatment can lead to cholangitis or sludge formation due to bacterial overgrowth. Local tumor control by radiation therapy was reported to prevent tumor ingrowth and to provide longer stent patency in uncovered SEMSs [29], but in this study all patients received covered SEMSs, and tumor ingrowth was successfully prevented by the covering membrane

Table 3 Univariate and multivariate analyses of risk factors for recurrent biliary obstruction using a proportional hazard model by Fine and Gray [22]

	Univariate		Multivariate	
	SHR (95 % CI)	*P* value	SHR (95 % CI)	*P* value
Age ≥70	0.88 (0.59–1.32)	0.542		
Male	0.90 (0.60–1.35)	0.619		
WHO PS 0	0.87 (0.57–1.31)	0.503		
Primary tumor, pancreas	1.00 (0.65–1.54)	0.990		
Primary tumor ≥30 mm	0.73 (049–1.08)	0.116	0.79 (0.52–1.20)	0.270
Liver metastasis	0.68 (0.42–1.11)	0.126	0.66 (0.41–1.07)	0.094
Ascites	0.40 (0.17–0.94)	0.036	0.49 (0.20–1.17)	0.110
Duodenal invasion	0.92 (0.56–1.50)	0.733		
Anticancer treatment	1.79 (1.13–2.86)	0.014	1.93 (1.20–3.10)	0.007
Stricture length ≥20 mm	0.87 (0.58–1.31)	0.508		
Stent length 8 cm	1.44 (0.92–2.23)	0.112	1.29 (0.81–2.06)	0.280
Prior drainage	0.99 (0.61–1.61)	0.975		
Stent end in duodenum	1.01 (0.41–2.50)	0.982		
WallFlex stent	0.67 (0.45–1.01)	0.056	0.65 (0.42–1.00)	0.049

SHR subdistribution hazard ratio, *CI* confidence interval, *PS* performance status

even in patients without anticancer treatment. To draw a more solid conclusion, further studies are needed which focus on local tumor response or neutropenia and recurrent biliary obstruction.

The better outcome of a partially covered WallFlex stent than that of a partially covered Wallstent needs some comments. We reported longer time to recurrent biliary obstruction and less stent migration with a partially covered WallFlex stent because of the low AF profile and antimigration system [12]. The significantly better outcomes of a partially covered WallFlex stent were also confirmed even after the introduction of competing risk analysis. Similar results were obtained in two different analyses because there were no significant differences in survival between patients who received a partially covered WallFlex stent or Wallstent placement.

There are limitations in this study. First, this is a retrospective analysis of previously reported prospective study. There are imbalances between patients with and without anticancer treatment. In addition, various types of cancer were included and pancreatic cancer and bile duct cancer might behave differently in terms of biliary stenting. Though multivariate analyses were performed, it is impossible to avoid bias completely, due to the retrospective nature of our study. However, a prospective study randomizing patients to chemotherapy or BSC is clinically and ethically impossible. Since the survival benefit of anticancer treatment has been established in patients with malignant biliary obstruction, anticancer treatment should be given in eligible patients despite the increased risk of recurrent biliary obstruction. Second, data on adverse events including neutropenia by anticancer treatment were not collected and the influence of neutropenia could not be evaluated. Therefore, the cause of increased recurrent biliary obstruction in patients with anticancer treatment was unclear. There are also possibilities that patients with anticancer treatment had clinical visits with shorter intervals and biliary events might be overdiagnosed.

In conclusion, the use of anticancer treatment was a risk factor for recurrent biliary obstruction in patients with distal malignant biliary obstruction who underwent covered SEMS placement. For better management of malignant biliary obstruction in patients receiving anticancer treatment, further evaluation of subgroups at high risk for recurrent biliary obstruction is necessary. And improvement of covered SEMSs such as antimigration system is also essential, given the high rate of stent migration in anticancer treatment group.

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

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Comparison of partially covered nitinol stents with partially covered stainless stents as a historical control in a multicenter study of distal malignant biliary obstruction: the WATCH study

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Background: Covered self-expandable metal stents (CSEMSs) were developed to prevent tumor ingrowth, but stent migration is one of the problems with CSEMSs.

Objective: To evaluate a new, commercially available CSEMS with flared ends and low axial force compared with a commercially available CSEMS without the anti-migration system and high axial force.

Design: Multicenter, prospective study with a historical cohort.

Setting: Twenty Japanese referral centers.

Patients: This study involved patients with unresectable distal malignant biliary obstruction.

Intervention: Placement of a new, commercially available, partially covered SEMS.

Main Outcome Measurements: Recurrent biliary obstruction rate, time to recurrent biliary obstruction, stent-related complications, survival.

Results: Between April 2009 and March 2010, 141 patients underwent partially covered nitinol stent placement, and between May 2001 and January 2007, 138 patients underwent placement of partially covered stainless stents as a historical control. The silicone cover of the partially covered nitinol stents prevented tumor ingrowth. There were no significant differences in survival (229 vs 219 days; $P = .250$) or the rate of recurrent biliary obstruction (33% vs 38%; $P = .385$) between partially covered nitinol stents and partially covered stainless stents. Stent migration was less frequent (8% vs 17%; $P = .019$), and time to recurrent biliary obstruction was significantly longer (373 vs 285 days; $P = .007$) with partially covered nitinol stents. Stent removal was successful in 26 of 27 patients (96%).

Limitations: Nonrandomized, controlled trial.

Conclusion: Partially covered nitinol stents with an anti-migration system and less axial force demonstrated longer time to recurrent biliary obstruction with no tumor ingrowth and less stent migration. (Clinical trial registration number: UMIN000002293.) (Gastrointest Endosc 2012;76:84-92.)

Abbreviations: CI, confidence interval; HR, hazard ratio; EST, endoscopic sphincterotomy; SEMS, self-expandable metal stent; CSEMS, covered SEMS; PTBD, percutaneous transhepatic biliary drainage.

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Endoscopic stent placement is the treatment of choice for palliation of distal malignant biliary obstruction.[1,2] Self-expandable metal stents (SEMSs) are now widely used because of their longer patency compared with plastic stents,[3,4] but a problem with SEMSs is stent occlusion by tumor ingrowth through the stent mesh. Covered SEMSs (CSEMS) have been developed to prevent tumor ingrowth.[5-7]

In one randomized, controlled trial, hand-crafted polyurethane-covered Diamond stents (Boston Scientific Corp, Natick, Mass) showed longer patency than uncovered Diamond stents, with a minimal increase in complications.[8] Then, CSEMSs came to be commercially available, and partially covered stainless Wallstents (Boston Scientific) are one of the most widely used CSEMSs. Partially covered Wallstents demonstrated long stent patency with a low occlusion rate, but the rate of complications other than stent occlusion was relatively high.[9,10] The superiority of partially covered Wallstents to uncovered Wallstents was not demonstrated in two comparative studies[11,12] and one subsequent randomized, controlled trial.[13] The incidence of stent migration of partially covered Wallstents was high in these studies. Stent migration is one of the complications encountered with CSEMSs because they are not embedded in the bile duct. Migration may be related to conformability in the bile duct and may be influenced by axial force. Axial force is the recovery force that leads to a SEMS straightening after being bent, and partially covered Wallstents characteristically have high axial force.[14] With high axial force, the bile duct tends to kink at the proximal edge of the straightening stent,[10] which causes sludge formation or cholangitis. SEMSs with high axial force do not fit well in the curved bile duct, which also increases the risk of stent migration.

The WallFlex Biliary RX Partially Covered Stent (partially covered WallFlex stents; Boston Scientific) is a new nitinol CSEMS with flared ends and low axial force to prevent migration and kinking of the bile duct. We conducted this multicenter prospective study, entitled the WATCH study, by using a partially covered, nitinol WallFlex stent, with a partially covered, stainless Wallstent as a historical control.

Take-home Message

- Silicone cover of partially covered WallFlex stents prevented tumor ingrowth in patients with distal malignant biliary obstruction.
- Covered self-expandable metal stents with an anti-migration system and less axial force can demonstrate better clinical outcomes with less stent migration. Prevention of biliary sludge formation might be the next key to longer stent patency in covered self-expandable metal stents.

PATIENTS AND METHODS

Study design

This was a multicenter, prospective, consecutive study in 20 referral centers in Japan with a historical control. Inclusion criteria were unresectable distal (≥2 cm distal to the biliary hilum) malignant biliary obstruction and obtained written informed consent. Exclusion criteria were (1) contraindication to endoscopic procedures, (2) WHO performance status 3 or greater, (3) massive ascites, (4) intestinal obstruction distal to the ampulla, (5) prior biliary SEMS placement, and (6) inability to obtain written informed consent. The study was approved by the institutional review boards at each center, and written informed consent was obtained from each patient. Diagnoses of malignancy were based on clinical, laboratory, radiologic, and pathologic findings. Disease stages were based on the findings of CT and EUS. Prior drainage by a plastic stent, a nasobiliary drainage tube, or a percutaneous transhepatic biliary drainage tube was allowed if it was used as a bridge to SEMS placement until malignancy and unresectability were confirmed. All patients underwent placement of a partially covered WallFlex stent, and the results were compared with a historical control of 138 consecutive patients who underwent placement of a partially covered Wallstent between May 2001 and January 2007 at the University of Tokyo Hospital and 3 affiliated hospitals.

The characteristics of partially covered WallFlex stents and partially covered Wallstents (Fig. 1) are summarized in Table 1. Axial force and radial force were measured with the methods described in the previous report—axial force at 20-mm distance from the bending point and radial force at 4-mm diameter.[14] Both partially covered WallFlex stents and Wallstents have 5-mm uncovered portions at both ends, but WallFlex stents have flared and looped ends. In the distal end of partially covered WallFlex stents, there is a retrieval loop for stent removal or repositioning. The axial force of partially covered WallFlex stents made of nitinol wire is lower than that of partially covered Wallstents.

Covered WallFlex insertion

All WallFlex stents were inserted at ERCP. Sphincterotomy was performed before stent insertion in all patients. After cholangiography to evaluate the biliary stricture, the 8.5F delivery system was inserted into the bile duct over the guidewire. All stents were 10 mm in diameter. The length of the stent (40 mm, 60 mm, and 80 mm) was determined at the discretion of each endoscopist.

Data collection

All data regarding partially covered WallFlex stents were prospectively collected on a Web-based database. Data before stent insertion included patient age, sex, and performance status; history of a cholecystectomy or the presence of cholelithiasis; primary tumor type, size, and stage; biliary stricture location and length; presence of tumor involvement to the orifice of the cystic duct; use of

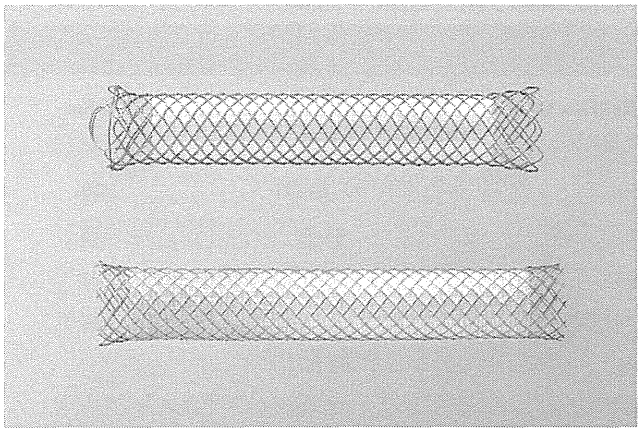

Figure 1. A partially covered WallFlex stent (*top*) and a partially covered Wallstent (*bottom*).

TABLE 1. Characteristics of partially covered WallFlex stents and partially covered Wallstents

	Partially covered WallFlex stent	Partially covered Wallstent
Design	Braided	Braided
Wire	Platinum-cored nitinol	Tantalum-cored Elgiloy
Cover membrane	Silicone	Silicone
Stent edge	Flared and looped	Non-flared and sharp
Radial force (N)	4.70	3.41
Axial force (N)	0.65	0.95

N, newton.

anti-cancer therapy; and blood work-up (liver function test, tumor marker). Tumor involvement to the orifice of the cystic duct was assessed by using cholangiography, intraductal US, EUS, CT, and/or MRCP. Follow-up data included survival, stent occlusion, or stent-related complications.

Follow-up and definition of complications

Patients were seen at the clinic, and clinical signs and symptoms as well as biochemical parameters of liver function were followed at least monthly until patient death or September 2010. Data were collected by telephone interview when patients could not visit the clinic. Stent occlusion was diagnosed if patients had recurrent jaundice with evidence of elevated bilirubin levels along with biliary dilation on CT, magnetic resonance imaging, or US. When stent occlusion was suspected, reintervention was performed to confirm the biliary obstruction and its cause unless patients were at a terminal stage of the disease and could not tolerate the procedure. Patients with fever along with elevated liver enzyme levels but without bilirubin level elevation were diagnosed as having cholangitis without stent occlusion.

Study outcomes and statistics

The primary endpoint was time to recurrent biliary obstruction, and the secondary endpoints were stent occlusion rate, overall survival, stent-related complication rate, and stent removal. Either the chi-square or Fisher exact test was used to compare the categorical variables, and a *t* test or Wilcoxon nonparametric test was used to compare continuous variables. A P value $< .05$ was considered statistically significant. Overall survival was calculated from the time of stent placement to the date of death or the last follow-up, and patients were censored if they were not dead. Time to recurrent biliary obstruction was calculated from the time of stent placement to the date of recurrent biliary obstruction or the last follow-up, and patients were included if stent occlusion was not observed. Overall survival and time to recurrent obstruction were estimated with the Kaplan-Meier method and compared by using the log-rank test. The Cox proportional hazards model was used to estimate hazard ratios (HR) of prognostic factors for recurrent biliary obstruction. We included age, sex, primary cancer (pancreatic cancer vs others), performance status, anti-cancer treatment, tumor size, stricture length, liver metastasis, ascites, prior stent placement, location of distal stent end (duodenum vs bile duct), and stent type (WallFlex vs Wallstent) into the model.

RESULTS

Patients

A total of 141 patients were included in 20 referral centers between April 2009 and March 2010. The patient characteristics are shown in Table 2. Pancreatic cancer was the primary disease in 104 patients (74%). Prior biliary drainage was performed in 95 patients (67%), with the use of plastic stents in 65 patients (46%), endoscopic nasobiliary drainage in 21 patients (15%), and percutaneous transhepatic biliary drainage in 9 patients (6%). A partially covered WallFlex stent was placed after a median period of 16 days. All patients underwent placement of one partially covered WallFlex stent, and stent length was 80 mm in 31 patients (22%), 60 mm in 107 patients (76%), and 40 mm in 3 patients (2%). The distal end of the stents was located in the duodenum in 139 patients (99%). Previous cholecystectomy had been performed in 9 patients (6%). Tumor involvement to the orifice of the cystic duct was observed in 32 patients (23%). A total of 92 patients (65%) received anti-cancer treatment, 82 patients (58%) had chemotherapy alone, and 10 patients (7%) had radiation plus chemotherapy.

TABLE 2. Patient characteristics

	Partially covered WallFlex stent	Partially covered Wallstent	*P* value
No. of patients	141	138	
Age, median (range), y	72 (32-99)	79 (38-90)	.330
Sex, male/female, no.	82/59	84/54	.715
WHO performance status (0/1/2), no.	60/37/44	32/54/52	.002
Primary tumor, no. (%)			.228
Pancreatic cancer	104 (74)	93 (67)	
Bile duct cancer	15 (11)	25 (18)	
Gallbladder cancer	5 (4)	2 (1)	
Other	17 (12)	18 (13)	
Tumor size, median (range), mm	31 (10-100)	30 (10-115)	.288
Length of stricture, median (range), mm	20 (5-65)	20 (10-60)	.299
Distant metastasis, no. (%)	56 (40)	54 (39)	
Liver metastasis, no. (%)	39 (28)	41 (30)	.791
Ascites, no. (%)	22 (16)	16 (12)	.384
Pathologic confirmation of malignancy, no. (%)	116 (82)	94 (68)	.008
Anti-cancer treatment, no. (%)	92 (65)	81 (59)	.270

Stent placement, follow-up, and survival

Stent placement was successful in all 141 patients. The median follow-up period was 196 days (range 8-498). Two patients (1%) were lost to follow-up within 6 months of stent placement. Cumulative median survival was 229 days. The Kaplan-Meier curve for overall survival is shown in Figure 2. Median survival was 306 days in 92 patients receiving anti-cancer treatment and 135 days in patients without anti-cancer treatment ($P < .001$).

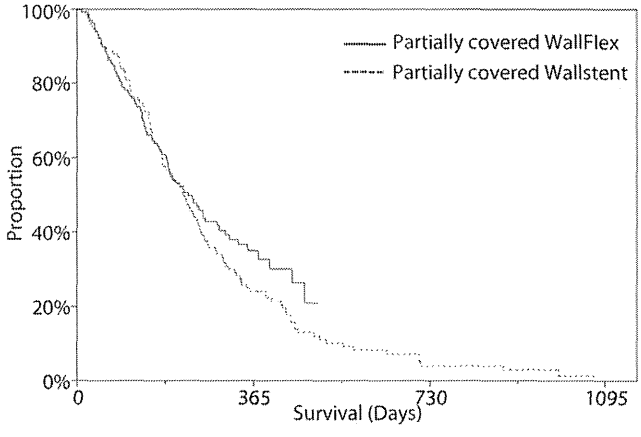

Figure 2. Kaplan-Meier curves of survival in partially covered WallFlex stents and partially covered Wallstents: median survival times were 229 and 219 days, respectively ($P = .250$).

Recurrent biliary obstruction

The causes of recurrent biliary obstruction are shown in Table 3. The rate of recurrent biliary obstruction was 26% (36/141 patients). The major cause of stent occlusion was sludge (18/36 patients), and there was no stent occlusion by tumor ingrowth. Stent migration was observed in 11 patients (8%), and stents migrated distally in 8 patients and proximally in 3 patients. The Kaplan-Meier curve for time to recurrent biliary obstruction is shown in Figure 3. The median time to recurrent biliary obstruction was 373 days (interquartile range 216 days to unknown) and stent patency rates at 6 months and 1 year were 78% and 54%, respectively. Neither the rate of recurrent biliary obstruction (36% vs 28%; $P = .448$) nor time to recurrent biliary obstruction (373 vs 436 days; $P = .406$) differed among patients who underwent biliary drainage before WallFlex stent placement and patients who underwent primary WallFlex stent placement. There were no significant differences in the rate of stent migration (10% vs 4%; $P = .329$) among patients with and without anti-cancer treatment.

Other stent-related complications

Cholecystitis developed in 14 patients (10%) after a median of 20 (range 1-404) days after stent insertion and was treated endoscopically in 3 patients and percutaneously in 11 patients (aspiration in 6 patients and drainage

TABLE 3. Recurrent biliary obstruction

	Partially covered WallFlex stent	Partially covered Wallstent	*P* value
Time to recurrent biliary obstruction,* median (interquartile range), d	373 (216)†	285 (125-385)	.007
Rate of recurrent biliary obstruction, no. (%)	47 (33)	53 (38)	.385
Stent occlusion, no. (%)	36 (26)	29 (21)	.398
Biliary sludge	18 (13)	15 (11)	
Food impaction	9 (6)	6 (4)	
Tumor overgrowth	5 (4)	8 (6)	
Tumor ingrowth	0	0	
Hemobilia	1 (1)	0	
Unknown	3 (2)	0	
Stent migration, no. (%)	11 (8)	24 (17)	.019

*Time to recurrent biliary obstruction was calculated by using the Kaplan-Meier method.
†Upper interquartile range was not calculable.

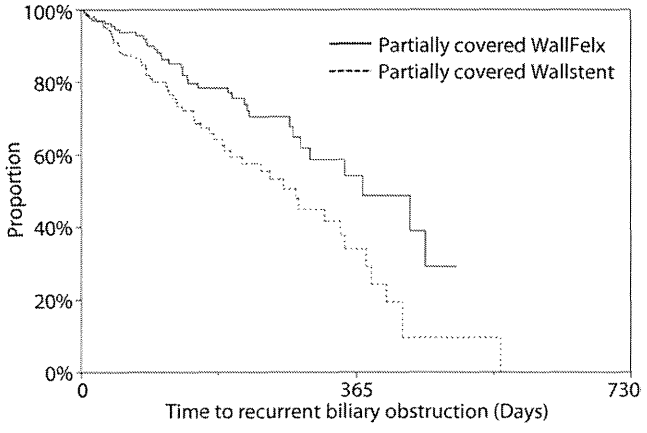

Figure 3. Kaplan-Meier curves of time to recurrent biliary obstruction in partially covered WallFlex stents and partially covered Wallstents: median time to recurrent biliary obstruction was 373 days and 285 days, respectively (P = .007).

tube placement in 5 patients). Involvement to the orifice of the cystic duct was observed in 7 of 14 patients, and gallbladder stones were seen in 4 of 14 patients. The rate of cholecystitis in patients with gallbladder in situ was 22% (7/32) with orifice of the cystic duct involvement and 7% (7/100) without orifice of the cystic duct involvement (P = .041).

Pancreatitis developed in 8 patients (6%). Pancreatitis was mild in 5 patients and moderate in 3 patients, based on consensus criteria.[15] The primary causes of biliary obstruction in 8 patients with pancreatitis after SEMS placement were pancreatic cancer in 3, bile duct cancer in 2, and cancer metastatic to lymph nodes in 3 patients. The rates of pancreatitis were 3% in pancreatic cancer and 14% in non-pancreatic cancer (P = .029). Cholangitis without stent occlusion was observed in 8 patients (6%). Cholangitis resolved by antibiotic treatment. Other complications included liver abscess, GI perforation, deep vein thrombosis, and pseudomembranous colitis.

Stent removal

Stent removal was attempted in 27 patients (19%) because of stent occlusion (n = 11), cholangitis (n = 5), stent migration (n = 4), pancreatitis (n = 3), cholecystitis (n = 2), and other causes (n = 2). The median duration from stent placement to removal was 108 days (range 3-373 days). Stent removal was successful in 26 of 27 patients (96%). Stents were removed with snares in 17 patients, with biopsy forceps in 5 patients, and with a combination of biopsy forceps and snares in 4 patients. The retrieval loop at the distal stent edge was used in 6 patients. In 1 patient with stent occlusion by hemobilia after 216 days from stent placement, stent removal was aborted because of massive bleeding during the procedure.

Comparison with partially covered Wallstents

A total of 138 consecutive patients who underwent placement of partially covered Wallstents between May 2001 and May 2005 at the University of Tokyo Hospital and 3 affiliated hospitals[16] were included as a historical control. The patient characteristics were similar except for better performance status and higher pathologic confirmation of disease in the partially covered WallFlex stent group (Table 2). Prior biliary drainage was performed in 122 patients (88%), and a partially covered Wallstent was placed after a median of 14 days. Nine patients underwent Wallstent placement at percutaneous transhepatic biliary drainage (PTBD). Overall survival was 219 days in the partially covered Wallstent group, compared with 229