unable to take serial measurements of self-rated health, which may confer more information than a single point measurement as we have done.

In conclusion, job status, additional earnings, and the ability to perform everyday duties were significantly associated with self-rated health status. A strong family relationship and adherence to a traditional lifestyle are still preserved in Uzbekistan. Substantial financial support is necessary for older people, and personal care is also essential. Thus, creating a healthful atmosphere for the elderly with provisions of a necessary support system at the individual and family level can prepare the Uzbek community to face upcoming challenges with elderly health-related issues in Uzbekistan. The findings of the present study can help in this process by highlighting the most important areas to protect elderly health and to promote quality of life for the elderly.

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ORIGINAL PAPER

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THE IMPACT OF MATERNAL OBESITY ON MOTHER AND NEONATAL HEALTH: STUDY IN A TERTIARY HOSPITAL OF ASTANA, KAZAKHSTAN

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ABSTRACT

This study was aimed to investigate the impact of maternal obesity on mothers and their neonatal health. Our study population consisted of 157 women with completed singleton pregnancies, which included both obese (Body mass index, BMI≥30) and non-obese women (BMI<30). Data were collected from case histories, and ante- and postnatal records at the tertiary hospital in Astana, Kazakhstan between January and February of 2008. Associations between pregnancy and delivery-related complications, outcomes, and maternal obesity were estimated as odds ratios (ORs) and 95% confidence intervals (CIs) using a logistic regression model. Women aged 30 years or more were at higher risk of obesity (OR=3.1, 95% CI=0.8–11.6) than women less than 30 years old. Multiparous women were also at higher risk of obesity (OR=4.1, 95% CI=0.9–19.6) than primiparous ones. Obese women were also more likely to have longer hospital stays of more than 10 days (OR=2.2, 95% CI=0.8–6.2), and were more prone to eclampsia/pre-eclampsia (OR=24.7, 95% CI=2.2–44.8), cesarean sections (OR=2.1, 95% CI=0.7–6.2), and abnormal labor (OR=8.1, 95% CI=1.0–63.8) compared to non-obese women. Neonatal complications such as pneumonia (OR=3.4, 95% CI=0.6–20.2) and fetal macrosomia (OR=2.2, 95% CI=0.6–8.0) were also more common among babies born to obese mothers. Congenital baby birth defects were strongly associated with maternal obesity (P=0.016). We concluded that maternal obesity is associated with increased risks of both maternal and neonatal complications, and that such risks increase with advanced age and parity of the mother. Hence, medical practices must take these complications into account by ensuring an adaptable and early management in order to improve mothers and their neonatal health.

Key Words: BMI, Maternal obesity, Pregnancy and neonatal complications, Kazakhstan

INTRODUCTION

The World Health Organization (WHO) defines obesity as an abnormal or excessive fat accumulation that presents a risk to health, using the body mass index (BMI) ≥30 as a crude estimate.[1)] Obesity contributes to significant morbidity and mortality worldwide from several

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diseases, including heart disease, diabetes and cancer.[2] There are approximately 350 million obese people in the world. Overall, about 2.5 million deaths are attributed to it.[3] The WHO characterizes obesity as a pandemic issue, with a higher prevalence in females, especially those of child-bearing age, than in males.[4]

Obesity has emerged as a major health problem in both developed and developing countries. The Third National Health and Nutrition Examination Survey conducted in the USA showed that among American women aged 25 and above, 28% were overweight and 28% were obese.[5] A study conducted in England showed that 18% of adult women suffered from obesity.[6] A study in the United Arab Emirates determined that 40% of married women were obese.[7] Over the last several years the rising rate of obesity has become a major public health concern not only in the West but also among Asian populations.[8] In 1990, a study in Kazakhstan enrolling 25,107 subjects older than 15 years revealed an excessive BMI in 36.1%, among whom obesity was diagnosed in 23.7%.[9] The obesity incidence was increasing with age and was negatively associated with the level of physical activity.[9]

Pregnancy complications in obese women were identified as early as 1945.[10] Complications of obesity seriously affect the obstetric outcome of such women, endangering both maternal and fetal health and well-being. Chinese researchers estimate that increasing BMI is associated with increased risks of adverse obstetric outcomes, such as pre-eclampsia, gestational diabetes, and preterm delivery among Chinese.[11] Since then, a number of studies have reported a clear association between maternal obesity and adverse pregnancy and neonatal outcomes. In particular, obesity in pregnancy is associated with a high rate of preeclampsia, pregnancy-induced hypertension, gestational diabetes, abnormal labor, cesarean section, fetal macrosomia, lower respiratory tract infections, and infant birth defects.[2,12-15]

In Kazakhstan, obesity and its effects on pregnancy and the newborn have not been carefully studied, with only a few studies reporting on it. A report by Kadyrova *et al.* found that the incidence of arterial hypertension, coronary heart disease and chronic diseases of the biliary tracts were, respectively 5, 4, and 3-fold higher in obese subjects than in those with a normal BMI.[9] There has been a gross insufficiency of information concerning obesity and its effects on pregnant women and neonatal health in Kazakhstan, which has warranted special attention. To our knowledge, ours was the first study on the effects of maternal obesity on pregnancy and neonatal outcomes carried out in that country. The aims of this study were to investigate the impact of maternal obesity on mothers and their neonatal health, and to evaluate the associations among maternal obesity and pregnancy complications, delivery outcomes, and neonatal complications.

MATERIALS AND METHODS

Our study is a retrospective cohort analysis. Initially, data collection was targeted on the records of 171 women at the tertiary hospital, Astana, Kazakhstan, between January and February of 2008. Only women with a singleton pregnancy booked on or before 20 completed weeks of gestation, and who gave birth at 24 or more completed weeks of gestation, were included in the statistical analysis. A total of 14 women were excluded from further study, 7 of whom had incomplete antenatal records and another 7 who gave birth to twins. The final study population consisted of 157 women with completed singleton pregnancies. Data were derived using a checklist from case histories and, ante- and postnatal records, which contained age, weight, height, previous obstetric history, and a variety of items concerning pregnancy, delivery and neonatal periods. The anonymity of each respondent's identity was strictly observed at all phases of analysis and reporting, hence ethical clearance was exempted. However, prior permission from

the hospital authority was given to collect data from their patient registry.

BMI calculation and grouping

BMI was calculated as the ratio of weight (kg) divided by height (m^2). Women were divided into four groups according to the WHO's classification: underweight, BMI<18.50; normal range, BMI 18.50–24.99; overweight, BMI 25.00–29.99; and obese, BMI≥30.00.[11] However, a statistical comparison was carried over between two groups: "obese" and "non-obese," which later consisted of a combined three BMI groups (underweight, normal weight, and overweight).

Outcome measures

The incidence of complications during pregnancy, delivery, and neonatal periods were evaluated for non-obese and obese groups. A case history, ante- and postnatal records of the mother and her children up to 28 days after delivery were made available from the patient registry. Pregnancy complications included the following: pre-eclampsia and/or eclampsia, amniotic fluid disorders (oligohydramnios and polyhydramnios), and placental insufficiency. Delivery complications included premature rupture of a membrane, and abnormal labor which refers to a condition that deviates from what most women undergoing spontaneous vaginal delivery experience.[16] Delivery outcomes included vaginal delivery and/or a cesarean section. Newborn complications studied were: intrauterine growth retardation, cerebral ischemia, pneumonia, birth defects, and fetal macrosomia (a fetal birth weight above 4,000 grams regardless of gestational age).[17] Since this study was carried out in a tertiary hospital, a specialist obstetrician and a specialist pediatrician were responsible for diagnosing maternal and neonatal complications.

Statistical analyses

Statistical analyses were conducted using the Statistical Package for Social Science, version 16.0 (SPSS, Chicago, Ill, USA). Continuous variables were presented as the mean and standard deviation (SD) for normally distributed data, and as median and the interquartile range (IQR) for non-normal data. Categorical data were presented as the frequency and percentage. Associations between maternal and neonatal complications involving the obesity of women were measured using a logistic regression model, and were estimated as odds ratios (ORs) and 95% confidence intervals (CIs). ORs were adjusted for age at delivery, parity, and length of a hospital stay. A Chi- square test was applied to compare categorical variables, and a two-tailed *P*-value less than 0.05 was regarded as statistically significant.

RESULTS

One hundred and fifty-seven pregnant women between 19 and 45 years of age who had a singleton delivery were included in this study. Among them, 84.8% were Kazakhs and 94.2% were from urban areas. The mean (±SD) age of the respondents was 30.5 (±5.5) years. The distribution of BMI was as follows: underweight 25 (15.9%), normal weight 101 (64.3%), overweight 14 (8.9%), and obese 17 (10.8%), whereas 52 (33.1%) pregnant women had suffered from some sort of pregnancy-related complications, 46 (29.3%) had experienced complications during delivery, while 66 (42.0%) of pregnant women required a cesarean section to deliver the baby. Nevertheless, almost a quarter (26.8%) of the newborn babies had some complications during birth. Maternal characteristics and outcomes are summarized in Table 1.

Table 1 Maternal characteristics and outcomes

Characteristics	Number	Percentage
Age at delivery (years)		
19–24	25	15.9
25–29	44	28.0
30–34	47	29.9
≥35	41	26.1
Mean=30.5 SD=5.5 Minimum=19 Maximum=45		
Nationality		
Kazakh	145	84.8
Other	26	15.2
Residence		
Urban	161	94.2
Rural	10	5.8
Profession		
Housewife	76	48.4
Clerk	65	41.4
Worker	12	7.6
Student	4	2.5
Parity		
Primipara	63	40.1
Multipara	94	59.9
BMI[a]		
Underweight	25	15.9
Normal	101	64.3
Overweight	14	8.9
Obesity	17	10.8
Pregnancy complications		
Yes	52	33.1
No	105	66.9
Delivery complications		
Yes	46	29.3
No	111	70.7
Delivery outcomes		
Vaginal delivery	91	58.0
Cesarean section	66	42.0
Hospital stay (days)		
<11	77	49.0
≥11	80	51.0
Median=11.0 IQR[b]=6–14 Minimum=2 Maximum=47		
Neonatal complications		
Yes	42	26.8
No	115	73.2

[a]BMI: body mass index. BMI was classified into following groups: underweight, BMI <18.50; normal range, BMI 18.50–24.99; overweight, BMI 25.00–29.99, and obesity, BMI ≥30.00.[11] [b]Interquartile range

Table 2 shows that among newborns, the male:female ratio was 54.8:45.2. About 131 (83.4%) newborns were delivered at the normal weight of 2,500–4,000 gms. However, 8 (5.1%) were low birth-weight babies with weights of <2,500 gms, and 18 (11.5%) of newborns were macrosomic with birth weights over 4,000 gms. Whereas 13 (8.3%) of the neonates were delivered before full term (i.e. 37 weeks), the median (IQR) period of gestation was 38.0 (37.0–39.0) weeks, ranging from 27 to 42 weeks.

Table 2 Neonatal characteristics

Characteristics	Male		Female		Total	
	N	(%)	N	(%)	N	(%)
Total	86	(54.8)	71	(45.2)	157	(100.0)
Birth weight (in grams)[a]						
<2,500	6	(75.0)	2	(25.0)	8	(5.1)
2,500–4,000	65	(49.6)	66	(50.4)	131	(83.4)
>4,000	15	(83.3)	3	(16.7)	18	(11.5)
Gestational age (in weeks)						
<37	10	(76.9)	3	(23.1)	13	(8.3)
37–42	76	(52.8)	68	(47.2)	144	(91.7)
Median=38.0 IQR[b]=37–39 Minimum=27 Maximum=42						

[a]Birth weight <2500 grams was classified as low birth weight (LBW),[41] and >4000 grams as fetal macrosomia regardless of gestational age,[17] [b]Interquartile range

Table 3 demonstrates that elderly and multiparous women were more likely to be obese than young and primiparous women with ORs of 3.1 (95% CI=0.8–11.6, *P*=0.090) and 4.1 (95% CI=0.9–19.6, *P*=0.075), respectively. Obese women also tended to show an increased tendency towards a longer hospital stay of more than 10 days (OR=2.2, 95% CI=0.8–6.2, *P*=0.135).

Table 3 Association of age, parity, and hospital stay with maternal obesity

Characteristics	Obese[a]		Non-obese[b]		OR[c]	95% CI[d]	*P* value
	N	(%)	N	(%)			
Total	17	(100.0)	140	(100.0)			
Age at delivery (years)							
<30	3	(17.6)	66	(47.1)	1	Reference	
≥30	14	(82.4)	74	(52.9)	3.1	0.8–11.6	0.090
Parity							
Primipara	2	(11.8)	61	(43.6)	1	Reference	
Multipara	15	(88.2)	79	(56.4)	4.1	0.9–19.6	0.075
Hospital stay (days)							
<11	7	(41.2)	70	(50.0)	1	Reference	
≥11	10	(58.8)	70	(50.0)	2.2	0.8–6.2	0.135

[a]Obese means women with BMI≥30.0, [b]Non-obese means women with BMI<30.0; [c]OR: Odds ratio; ORs were adjusted for parity in age group, and for age in parity and hospital stay; [d]CI: Confidence interval

Associations among pregnancy, delivery, and neonatal complications with maternal obesity are illustrated in Table 4. A statistically significant difference between the compared groups was observed in the prevalence of eclampsia/pre-eclampsia (P=0.010). Obese groups of women com-

Table 4 Associations of pregnancy, delivery, and neonatal complications with maternal obesity

Characteristics	Obese[a]	Non-obese[b]	OR[c]	95% CI[d]	P value
	N (%)	N (%)			
Pregnancy complications					
No	7 (41.2)	98 (70.0)	1	Reference	
Yes	10 (58.8)	42 (30.0)	3.6	1.2–10.6	0.040
Eclampsia/pre-eclampsia					
No	14 (82.4)	136 (97.1)	1	Reference	
Yes	3 (17.6)	4 (2.9)	24.7	2.2–44.8	0.010
Amniotic fluid disorders					
No	14 (82.4)	122 (87.1)	1	Reference	
Yes	3 (17.6)	18 (12.9)	1.7	0.4–7.1	0.449
Placental insufficiency					
No	11 (64.7)	112 (80.0)	1	Reference	
Yes	6 (35.3)	28 (20.0)	2.2	0.7–6.8	0.171
Delivery complications					
No	14 (82.4)	97 (69.3)	1	Reference	
Yes	3 (17.6)	43 (30.7)	0.6	0.2–2.3	0.460
Premature rupture of membrane					
No	16 (94.1)	106 (75.7)	1	Reference	
Yes	1 (5.9)	34 (24.3)	0.2	0.02–1.6	0.129
Abnormal labor[e]					
No	15 (88.2)	134 (95.7)	1	Reference	
Yes	2 (11.8)	6 (4.3)	8.1	1.0–63.8	0.056
Delivery outcomes					
Vaginal delivery	7 (41.2)	84 (60.0)	1	Reference	
Cesarean section	10 (58.8)	56 (40.0)	2.1	0.7–6.2	0.164
Neonatal complications					
No	10 (58.8)	105 (75.0)	1	Reference	
Yes	7 (41.2)	35 (25.0)	2.3	0.8–6.9	0.131
Fetal macrosomia[f]					
No	13 (76.5)	126 (90.0)	1	Reference	
Yes	4 (23.5)	14 (10.0)	2.2	0.6–8.0	0.244
Intrauterine growth retardation					
No	16 (94.1)	134 (95.7)	1	Reference	
Yes	1 (5.9)	6 (4.3)	1.5	0.1–15.1	0.738
Cerebral ischemia					
No	14 (82.4)	128 (91.4)	1	Reference	
Yes	3 (17.6)	12 (8.6)	2.0	0.5–8.8	0.345
Pneumonia					
No	15 (88.2)	135 (96.4)	1	Reference	
Yes	2 (11.8)	5 (3.6)	3.4	0.6–20.2	0.180
Birth defect					
No	14 (82.4)	136 (97.1)	1	Reference	
Yes	3 (17.6)	4 (2.9)	8.8	1.5–50.1	0.016

[a]Obese means women with BMI≥30.0, [b]Non-obese means women with BMI<30.0; [c]OR: odds ratio; ORs were adjusted for age of mother at delivery and parity; [d]CI: confidence interval; [e]abnormal labor refers to a process that deviates from what most women undergoing spontaneous vaginal delivery experience,[16] [f]birth weight >4000 grams as fetal macrosomia regardless of gestational age[17]

pared to non-obese groups displayed a substantially increased risk for eclampsia/pre-eclampsia, but a relatively lower risk for amniotic fluid disorders and placental insufficiency. In contrast to women from the non-obese group, obese women were more likely to require a cesarean section (OR=2.1, 95% CI=0.7–6.2, P=0.164). In particular, obese women were more likely to undergo abnormal labor (OR=8.1, 95% CI=1.0–63.8, P=0.056). Baby birth defects were strongly associated with maternal obesity (P=0.016), with the ORs for obese women being greater than those for the non-obese group (OR=8.8, 95% CI=1.5–50.1). Obese women tended to exhibit an increased risk of fetal macrosomia (OR=2.2, 95% CI=0.6–8.0, P=0.244), pneumonia (OR=3.4, 95% CI=0.6–20.2, P=0.180), cerebral ischemia (OR=2.0, 95% CI=0.5–8.8, P=0.345), and intrauterine growth retardation (OR=1.5, 95% CI=0.1–15.1, P=0.738) than those in the non-obese group.

DISCUSSION

We identified several factors related to pregnancy, delivery, and neonatal complications which were more prevalent among obese mothers and their children than among their non-obese counterparts. This study indicated that an increasing BMI was associated with a heightened risk of maternal and neonatal complications. Compared to women from a non-obese group, obese women were found to run a higher risk of eclampsia/pre-eclampsia, placental insufficiency, and abnormal labor. As for delivery outcomes, obese women were more likely to require a cesarean section, while their newborns ran a higher risk of cerebral ischemia, pneumonia, and birth defects. Overall, our conclusions were in agreement with many previous studies.[18,19]

Our findings that higher BMIs (obesity) are common among older mothers raises the possibility that increasing maternal and fetal complications have also been reported by several other studies.[11,12,20,21] Leung *et al.* in their study reported a stronger impact of high BMIs on adverse obstetric outcomes, and they suggested using a lower cut-off for BMIs to preserve maternal and child health.[11] Wolfe in his study "High prepregnancy body-mass index – a maternal-fetal risk factor," recognized higher BMIs as a risk factor for both mothers and their newborns.[19] In our study, multiparous women had higher BMIs than primiparous woman, which may be related with their tendency to gain weight with each pregnancy.[21,22]

The risk of pre-eclampsia has been positively associated with a raised BMI. In Kazakhstan, gestosis, which includes eclampsia/pre-eclampsia, took second place among the several causes of maternal mortality.[23] We discovered a 25-times higher risk of pre-eclampsia in obese compared to non-obese women, and similar findings have been reported in China, Australia, and Scotland.[11,12,24,25] In addition to increasing BMIs, the sedentary lifestyle of Kazakh women and their dietary habits may add a heightened risk to developing pre-eclampsia.

Obesity-induced complications of pregnancy, such as preeclampsia and/or eclampsia, fetal macrosomia, low birth weight, etc. further complicate delivery outcomes. Very often an elective termination of pregnancy in the form of a cesarean section is needed to save both the mother and her newborn. We found that cesarean deliveries were two-times more prevalent among obese mothers than those who were non-obese. Several other studies cited reports similar to ours.[2,11,14,15,23,26-31]

Concerning fetal risks, our data indicate that obese women were more likely to have macrosomic babies. Although genetic, racial, and ethnic factors play a role in macrosomia,[32] the risk is relatively low among Asian women. Parental height and weight may also influence the birth weights of children. Obesity has been associated with elevated insulin resistance and high levels of insulin in the fetus, even in the absence of maternal diabetes.[33] Although no conclusive risk factors for macrosomia could certainly be identified so far, much about birth weight variations

has remained unexplained; however, macrosomia has reportedly been associated with neonatal morbidity, injury and cesarean sections.[34] Despite the relatively small number of observations, this study has observed elevated risks for birth defects in neonates among obese compared with non-obese women (OR=8.8, 95% CI=1.5–50.1, *P*=0.016), a finding that was again in agreement with previous reports.[35-40] Our findings that pneumonia was 3 times more common among children of obese mothers was also supported by the findings of other researchers.[13]

Our study had several limitations worthy of mention. We collected data from a relatively small sample of women which may pose a threat to the generalization of our findings. We could not address some other underlying reasons of pregnancy and neonatal health-related issues such as compromised immunity arising out of malnutrition, diabetes, HIV/AIDS etc. in mothers. Finally, we followed mothers and neonates only until they were hospitalized. We could not follow-up for an entire neonatal period, which may have resulted in underestimation of some actual neonatal ailments. Despite these limitations, we consider our findings provide an important source of information for policy makers as well as future researchers in this field.

In conclusion, the results of our study indicated higher risks of maternal (pregnancy and delivery related) and neonatal (congenital and perinatal) complications among obese mothers than those among the non-obese. The major maternal obesity-associated risks were pregnancy and delivery-related complications, including eclampsia/pre-eclampsia, abnormal labor, and birth defects of neonates. Thus, medical practice must take these complications into account by ensuring adaptable and early management to improve both maternal and neonatal health.

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ORIGINAL ARTICLE

Combination chemotherapy with S-1 plus cisplatin for gastric cancer that recurs after adjuvant chemotherapy with S-1: multi-institutional retrospective analysis

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Abstract
Background It is unclear whether S-1 plus cisplatin is effective for patients with recurrent gastric cancer after adjuvant S-1 chemotherapy.
Methods We retrospectively evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant S-1 chemotherapy.
Results In the 52 patients evaluated, the median duration of adjuvant S-1 chemotherapy was 8.1 months, and the median recurrence-free interval (RFI) since the last administration of adjuvant S-1 was 6.4 months. Among the 36 patients with measurable lesions, 7 achieved a complete or partial response, and 13 were evaluated as having stable

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disease, for an overall response rate of 19.4% and a disease control rate of 55.6%. For all patients, the median progression-free survival (PFS) was 4.8 months, and the median overall survival (OS) was 12.2 months. Compared with patients with an RFI of <6 months ($n = 25$), patients with an RFI of ≥6 months ($n = 27$) had a significantly higher response rate (5.0 vs. 37.5%, respectively), longer PFS (2.3 vs. 6.2 months, respectively), and longer overall survival (7.3 vs. 16.6 months, respectively). According to a multivariate Cox model including performance status (PS) and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS and OS.
Conclusions S-1 plus cisplatin is effective for patients with gastric cancer that recurs after adjuvant S-1 chemotherapy, especially for those with an RFI of ≥6 months.

Keywords Adjuvant chemotherapy · Gastric cancer · Recurrence · S-1

Introduction

Gastric cancer is the fourth most common malignancy in the world (988,602 cases in 2008, 7.8% of total malignancy cases) and the second leading cause of cancer death (737,419 deaths, 9.7% of total) [1]. The prognosis of patients with advanced or recurrent gastric cancer remains poor; chemotherapy confers only a minimal survival advantage, with a median survival of approximately 1 year. The most commonly used regimens are combination chemotherapy consisting of a fluoropyrimidine [5-fluorouracil (5-FU) or oral fluoropyrimidine] plus a platinum agent with or without docetaxel or anthracyclines [2–6].

S-1 is an oral anticancer drug composed of the 5-FU prodrug tegafur and two 5-FU modulators; it has achieved high response rates in patients with gastric cancer in phase II studies [7, 8]. In the Japan Clinical Oncology Group (JCOG) 9912 trial, which compared S-1, cisplatin plus irinotecan, and 5-FU, S-1 demonstrated non-inferiority compared to 5-FU [9]. In another phase III trial that compared S-1 alone to S-1 plus cisplatin (SPIRITS trial), S-1 plus cisplatin showed a significantly higher response rate (54 vs. 31%), longer progression-free survival (PFS; 6.0 vs. 4.0 months), and longer overall survival (OS; 13 vs. 11 months) [4]. Also, in a large, non-Japanese, phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial), S-1 plus cisplatin was associated with fewer toxic effects and demonstrated non-inferiority compared with 5-FU plus cisplatin by exploratory analysis [6]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent gastric cancer.

In addition, the ACTS-GC trial has demonstrated that S-1 is also effective as adjuvant chemotherapy for Japanese patients who have undergone curative gastrectomy for locally advanced gastric cancer [10]. However, approximately 30% of patients still develop recurrence after curative resection followed by adjuvant S-1 [10]. As few patients who received adjuvant chemotherapy were included in the phase III trials described above [4, 7, 9], it is unclear whether patients who develop recurrence after adjuvant S-1 could achieve efficacy with S-1 plus cisplatin similar to that achieved in patients without adjuvant chemotherapy. To address this issue, we conducted the following multi-institutional retrospective analysis.

Patients and methods

Patients

This retrospective study was designed to evaluate the efficacy of first-line chemotherapy with S-1 plus cisplatin for recurrence in patients with gastric cancer who had undergone curative gastrectomy followed by adjuvant S-1 chemotherapy. Patients with histopathologically proven recurrent gastric adenocarcinoma after gastrectomy and lymph node dissection with no residual tumor were eligible for analysis. Additional eligibility criteria were: (1) previous adjuvant S-1 chemotherapy at a planned standard dose and schedule (80 mg/m^2 for 28 consecutive days followed by a 14-day rest; 42-day cycles to be repeated for 1 year); (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (3) adequate bone marrow, hepatic, and renal function to be treated with S-1 plus cisplatin; (4) evaluable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1); and (5) treated with a standard regimen of S-1 plus cisplatin (S-1 80 mg/m^2 for 21 consecutive days followed by a 14-day rest; cisplatin 60 mg/m^2 intravenous infusion on day 8; 35-day cycles to be repeated) [4]. Written informed consent for treatment was obtained from each patient prior to treatment initiation. The Institutional Review Board of each participating center approved the study.

Evaluation of treatment and statistical analysis

The tumor response was assessed objectively according to RECIST ver. 1.1, and the best overall response was recorded as the antitumor effect for that patient. The disease control rate (DCR) represented the percentage of patients with a complete response (CR), partial response (PR), or stable disease (SD). PFS was measured from the date of initiation of S-1 plus cisplatin to the date of progressive disease or death from any cause. Time to treatment failure

(TTF) was measured from the date of initiation of S-1 plus cisplatin to the date of last administration of S-1. OS was estimated from the date of initiation of S-1 plus cisplatin to the date of death or last follow-up visit, using the Kaplan–Meier method. The interval from the last administration of adjuvant S-1 to recurrence was defined as the recurrence-free interval (RFI).

The Cox proportional hazards model was used to estimate the impact of the RFI on TTF, PFS, and OS, with adjustment for other factors that were shown to be significant with a univariate log-rank test. *P* values for testing differences between proportions and response rates were calculated with χ^2 tests for homogeneity or for trend, or with Fisher's exact test. Results were considered to be statistically significant when the *P* value was <0.05. All reported *P* values are two-sided. In particular, we compared the response rate, DCR, time to progression (TTP), PFS, and OS between patients with RFIs of ≥6 and <6 months, because several clinical trials in the first-line setting set this interval of ≥6 months as an inclusion criterion [5, 9, 11].

Results

Patient characteristics

A total of 406 patients with recurrent gastric cancer after adjuvant S-1 chemotherapy had received chemotherapy at 18 institutions until October 2010. Among them, 57 patients (14.0%) had received S-1 plus cisplatin as first-line chemotherapy for recurrence. After the exclusion of 5 patients (1 patient with a non-evaluable lesion and 4 patients with insufficient data), 52 patients were included in the final

Table 1 Patient characteristics

Characteristic	All (n = 52)	RFI <6 months (n = 25)	RFI ≥6 months (n = 27)	*P* value
Age, years				
Median (range)	61 (32–77)	59 (32–77)	62 (32–77)	
Gender, *n* (%)				
Male	30 (58)	15 (60)	15 (56)	0.75
Female	22 (42)	10 (40)	12 (44)	
ECOG PS at recurrence, *n* (%)				
0	32 (62)	11 (44)	21 (78)	*0.012*
1	20 (38)	14 (56)	6 (22)	
Histological type[a], *n* (%)				
wel or mod	27 (52)	10 (40)	17 (63)	0.1
por or sig	24 (46)	15 (60)	9 (33)	
Other	1 (2)	–	1 (4)	
Pathological stage[a], *n* (%)				
Stage I or II	8 (15)	4 (16)	4 (15)	0.57
Stage IIIA	17 (33)	6 (24)	11 (41)	
Stage IIIB	15 (29)	8 (32)	7 (26)	
Stage IV	12 (23)	7 (28)	5 (19)	
Site of recurrence, *n* (%)				
Peritoneum	21 (40)	7 (28)	14 (52)	0.08
Lymph node	25 (48)	13 (52)	12 (44)	0.59
Liver	14 (27)	10 (40)	4 (15)	*0.041*
Lung	4 (8)	3 (12)	1 (4)	0.262
Bone	6 (12)	1 (4)	5 (19)	0.102
Local	2 (4)	1 (4)	1 (4)	0.96
Number of recurrence sites, *n* (%)				
1	38 (73)	18 (72)	20 (74)	0.87
2 or more	14 (27)	7 (28)	7 (26)	

P values shown in italics indicate significant differences

RFI Recurrence-free interval, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group, *wel* well-differentiated adenocarcinoma, *mod* moderately differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring-cell-like carcinoma

[a] According to the Japanese classification

analysis (Table 1). The median duration of adjuvant S-1 chemotherapy was 8.1 months (range 0.7–37.4 months), and the median RFI since the last administration of adjuvant S-1 was 6.4 months (range 0–81.3 months). Thirty of the 52 patients (57.7%) completed the planned duration of adjuvant S-1 therapy. In contrast, 14 patients discontinued S-1 due to disease recurrence, and 8 patients stopped therapy due to toxicity or patient refusal. Other than PS and liver metastasis, characteristics did not differ significantly between patients with an RFI of ≥6 months ($n = 27$) and those with an RFI of <6 months ($n = 25$) (Table 1).

Treatment results and efficacy

The median TTF was 4.1 months (95% confidence interval [CI] 2.5–5.1 months), with a median duration of follow-up of 32 months. Forty-four patients discontinued S-1 plus cisplatin due to disease progression ($n = 40$, 90.9%) or toxicity ($n = 4$, 9.1%). Of the 36 patients with measurable lesions, 7 achieved a CR ($n = 3$) or a PR ($n = 4$), and 13 were evaluated as having SD, for an overall response rate of 19.4% (95% CI 7.0–37.0%) and a DCR of 55.6% (95% CI 38.1–72.1%). The median PFS was 4.8 months (95% CI 3.9–6.2 months), and the median OS of all patients was 12.2 months (95% CI 10.2–16.6 months) (Fig. 1). Of the 44 patients who had discontinued S-1 plus cisplatin, 31 (70.4%) received second-line or third-line chemotherapy, including taxanes ($n = 25$) or irinotecan ($n = 17$).

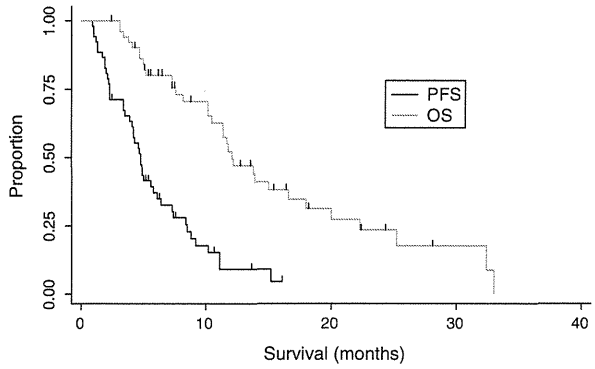

Fig. 1 Progression-free survival (*PFS*) and overall survival (*OS*) in all patients. The median PFS was 4.8 months (95% confidence interval [CI] 3.9–6.2 months), and the median OS was 12.2 months (95% CI 10.2–16.6 months). *PFS* progression-free survival, *OS* overall survival

Significance of the RFI

The response rate was significantly better in patients with an RFI of ≥6 months (37.5%; 95% CI 14–61%) than that in patients with an RFI of <6 months (5.0%; 95% CI 0–15%, $P = 0.014$, Table 2). In addition, compared with patients with an RFI of <6 months, patients with an RFI of ≥6 months had a significantly longer TTF (2.5 vs. 5.1 months, respectively, $P = 0.025$), longer PFS (2.3 vs. 6.2 months, respectively, $P < 0.001$, Fig. 2), and longer OS (7.3 vs. 16.6 months, respectively, $P = 0.003$, Fig. 2). According to a multivariate Cox model including PS and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS (hazard ratio [HR] 0.35, 95% CI 0.16–0.77, $P = 0.009$) and OS (HR 0.21, 95% CI 0.08–0.54, $P = 0.001$), although the association with TTF was not significant (HR 0.55, 95% CI 0.27–1.12, $P = 0.1$). When we divided the patients into two groups based on an RFI of 12 months, no significant difference between the groups was found in response rate, TTP, PFS, or OS.

Discussion

In the ACTS-GC study, adjuvant S-1 chemotherapy significantly improved the survival of patients who had undergone curative gastrectomy for locally advanced gastric cancer [10]. On the other hand, several small studies have suggested that patients with recurrence after adjuvant S-1 were refractory to S-1-containing regimens or had a worse prognosis compared with that of patients without adjuvant chemotherapy [12–14]. Although these reports never precluded the use of adjuvant S-1 chemotherapy, they raised the issue of how to treat recurrent disease after adjuvant S-1.

In the present retrospective study, we evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant chemotherapy with S-1. The response rate of 19.4% and PFS of 4.8 months were

Table 2 Objective response rates in patients with measurable lesions

	n	CR	PR	SD	PD	NE	ORR (%)	95% CI (%)
All	36	3	4	13	14	2	18.8	7–32
RFI <6 months	20	0	1	6	13	0	5.0	0–15
RFI ≥6 months	16	3	3	7	1	2	37.5	14–61

CR Complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate, *CI* confidence interval

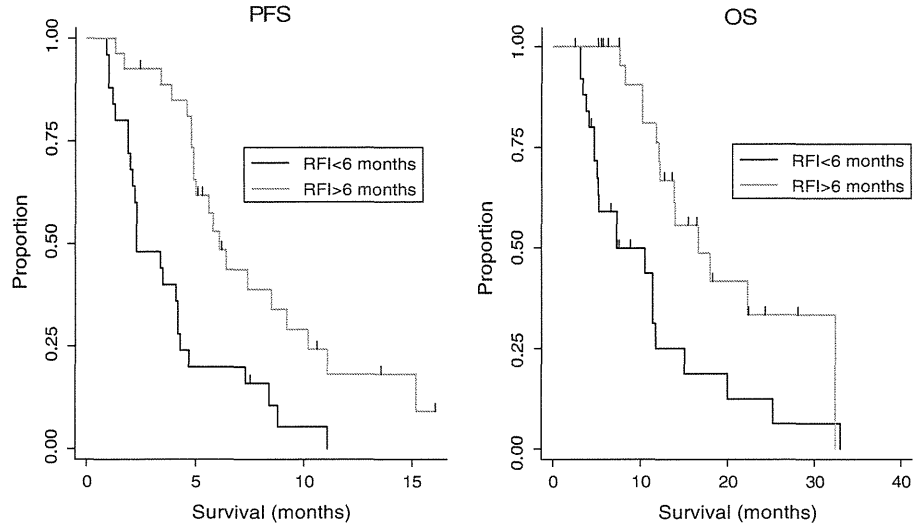

Fig. 2 Progression-free survival (*PFS*) and overall survival (*OS*) according to the length of the recurrence-free interval (*RFI*). Patients with an RFI of ≥6 months had a significantly longer median PFS (6.2 vs. 2.3 months, $P < 0.001$) and OS (16.6 vs. 7.3 months, $P = 0.003$) than patients with an RFI of <6 months. *RFI* recurrence-free interval, PFS progression-free survival, OS overall survival

relatively worse compared with those in the SPIRITS study [4]. However, our results also suggested that patients with an RFI of ≥6 months who received S-1 plus cisplatin had a significantly better response rate, longer PFS, and longer OS compared to patients with an RFI of <6 months. The efficacy of S-1 plus cisplatin for patients with an RFI of ≥6 months in this study was almost compatible with that of patients in the SPIRITS trial in terms of PFS and OS, although these results should be interpreted cautiously due to the heterogeneity of the characteristics of the patients in the two studies. Although no prospective study has evaluated any chemotherapy specifically for patients who have failed adjuvant S-1, Kang and colleagues [15] conducted a phase II study of capecitabine plus cisplatin for 32 patients with gastric cancer that recurred after adjuvant chemotherapy with doxifluridine or 5-FU-containing regimens. They reported a response rate of 28% and a median TTP of 5.8 months, and concluded that capecitabine plus cisplatin was effective as first-line treatment in patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant chemotherapy. In their report, the response rates (21 vs. 39%, $P = 0.427$), TTF (8.3 vs. 5.4 months, $P = 0.072$), and OS (14.1 vs. 9.3 months, $P = 0.075$) tended to be better in patients with an RFI of >6 months ($n = 13$) than in patients with an RFI of ≤6 months ($n = 19$), although the differences did not reach statistical significance [15]. These results were also consistent with those of previous studies in patients with other types of cancer, which suggested the importance of the RFI or treatment-free interval as a predictive marker of responsiveness to similar types of chemotherapy after recurrence [16–18]. Additionally, in the present study, the RFI cut-off value of 6 months was better than that of 12 months for predicting better outcomes and this finding may support the use of the conventional exclusion criteria in clinical trials in the first-line setting, which excluded patients who experienced disease recurrence within 6 months after the last adjuvant chemotherapy [5, 9, 11]. Therefore, selected patients with an RFI of ≥6 months with sufficient organ function may be adequately treated as chemo-naïve patients with standard chemotherapies such as S-1 plus cisplatin.

In contrast to the results for patients with an RFI of ≥6 months, the response rate in patients with an RFI of <6 months in the present study seemed to be worse than that of commonly used second-line chemotherapy regimens such as irinotecan and taxane combinations, which have a reported response rate of approximately 20% for patients with gastric cancer who received prior chemotherapy with fluoropyrimidines alone [18–23]. Based on these results, it may be suggested that the evaluation of chemotherapy regimens other than S-1 plus cisplatin might be warranted for the initial treatment of gastric cancer recurrence after adjuvant S-1. The response rate of 5.0% in our subset of patients with an RFI of <6 months was also lower than that reported previously by Kang et al. for capecitabine plus cisplatin after adjuvant chemotherapy (21%) [15]. The exact reasons for this difference are unknown. One possible reason is that Kang and colleagues did not use the same fluoropyrimidine (capecitabine after doxifluridine or 5-FU), and this choice might have contributed to a higher response in regard to early recurrence, although rechallenge with different types of fluoropyrimidine after the failure of another drug is still controversial in several types of cancer [24–28]. Second, the planned dose intensity of cisplatin as another key drug for gastric cancer was higher in their capecitabine plus cisplatin regimen (60 mg/m^2 every 3 weeks) [15] than that in the S-1 plus cisplatin regimen (60 mg/m^2 every 5 weeks). The efficacy of capecitabine plus cisplatin compared with other

chemotherapy (irinotecan, taxane or irinotecan plus cisplatin) for recurrence after adjuvant S-1 should be evaluated in future clinical trials.

It is important to note the limitations of the present study. First, it was retrospective, and treatment after recurrence was selected by each physician individually. Considering the low proportion of patients who received S-1 plus cisplatin after recurrence (14.0%), the selected population may have been biased toward patients with good performance status (PS) and low tumor burden. Second, toxicity was not evaluated in this study, although the proportion of patients who discontinued S-1 plus cisplatin due to toxicity was low. Third, human epidermal growth factor receptor 2 (HER2) status was not evaluated. Trastuzumab, a humanized monoclonal antibody against HER2, has recently been shown to improve the prognosis of HER2-positive advanced gastric cancer [29], and the HER2 status of all gastric cancer types should be evaluated, even in this setting of recurrent disease. Fourth, the moderate sample size in a single-country study is another limitation; therefore, it would be better to validate the significance of the RFI after adjuvant failure on the PFS in other cohorts as well.

In conclusion, this is the first report to have evaluated the efficacy of chemotherapy with S-1 plus cisplatin in patients with gastric cancer that recurred after adjuvant chemotherapy with S-1. S-1 plus cisplatin was effective in such patients, especially in those with an RFI of $\geq$6 months. Further well-defined, prospective trials in this important patient population are required to identify optimal treatment regimens.

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EDITORIAL

Geographic difference in advanced gastric cancer prevalence and chemotherapy treatment results: could it really be an independent prognostic factor?

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Although quite a few reports of retrospective studies have been published, definitive evidence for the source of the disparities between East and West associated with gastric cancer chemotherapy, safety, and efficacy has not been shown to date. In order to shed light on these long-lasting discussions, Hsu et al. [1] have accumulated published information from 25 randomized clinical trials and investigated geographic differences in the safety and efficacy of systemic chemotherapy for advanced gastric carcinoma.

According to their meta-analysis and meta-regression analysis, patients in Asian trials have an 8.2% lower incidence of grade 3–4 neutropenia and a 2.1% lower incidence of grade 3–4 diarrhea than patients in non-Asian trials. It is true that most gastric cancer oncologists and investigators have been realizing that there might be several factors favoring Asian patients. In colon cancer clinical trials using a fluorinated pyrimidine as the key drug, Haller et al. [2] reported more grade 3–4 adverse events and discontinuation of the treatment in United States patients compared with non-United States patients. Focusing on East Asia and the United States, grade 3–4 gastrointestinal toxicity was significantly higher (hazard ratio 3.62, 95% confidence interval 2.11–6.20, $p < 0.01$) in the United States. This disparity in the tolerability profiles of fluorinated pyrimidines could be explained as arising from: (1) genetic polymorphisms of genes involved in fluorinated pyrimidine metabolism, (2) differences in dietary folate intake, and (3) cultural differences in patients' behavior in using an oral self-administered drug. Moreover, Ajani et al., according to the result of their phase I study of the oral fluorinated pyrimidine S-1, plus cisplatin, have postulated that the efficacy of the CYP26 enzyme is higher in whites than in Asians [3]. They presume that this difference causes the conversion of ftorafur to active fluorouracil (FU) to occur at a faster rate, achieving a higher AUC of FU in whites than in Asians. From these results, the S-1 dose was reduced from 80 mg/m^2 in a Japanese study to 50 mg/m^2 in a global trial. Also, in a genomic analysis of the UGT1A1 enzyme, which is responsible for the glucuronization and detoxification of SN-38, the active metabolite of irinotecan, the UGT1A1*28 polymorphism was detected to differ between Caucasians and Asians [4]. A Japanese study has also demonstrated that the UGT1A1*6 polymorphism, rather than the UGT1A1*28 polymorphism, is a potential predictor of toxicity caused by irinotecan in Japanese patients [5]. All these complicated findings and assumptions have now alerted clinicians on the need to establish optimal regimens of various chemotherapeutic agents for diverse cancer populations.

Another finding from Hsu et al. [5] is that the frequent use of second-line chemotherapy was commonly observed in Asian trials, and this was assumed to lead to a better overall survival in Asian patients, whereas progression-free survival (PFS) is better in Western trials. This difference could be explained simply by the fact that two- to three-drug combination regimens are common as first-line chemotherapy in Western trials. In such cases, first-line chemotherapy might be able to show a better response and better PFS than the mono- or two-drug combination therapies routinely used in Asia. After the failure of first-line chemotherapy that has exhausted all promising

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