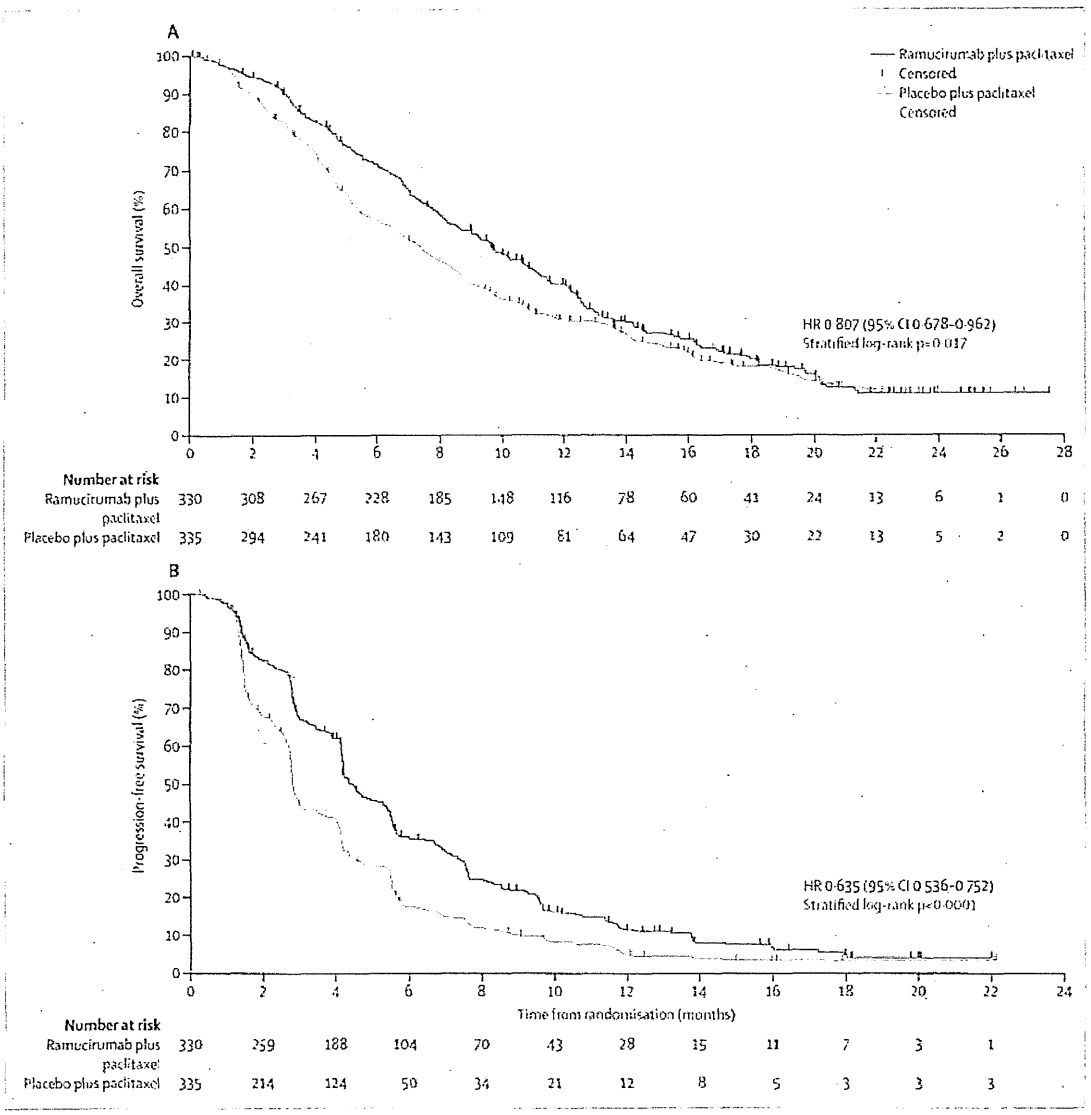

Figure 2: Kaplan-Meier curves of overall survival (A) and progression-free survival (B)
HR=hazard ratio.

We did a multivariate analysis using the stepwise Cox model with inclusion of all prespecified factors, and identified seven significant independent predictors for improved survival: region 3, ECOG performance status 0, weight loss of less 10%, up to two metastatic sites, absence of ascites, well or moderately differentiated tumour, and previous gastrectomy. After adjustment for these factors, the HR for overall survival with ramucirumab plus paclitaxel compared with placebo plus paclitaxel was 0·745 (95% CI 0·626–0·888 (p=0·0010; appendix). ECOG performance status, region, and presence of ascites were the strongest predictors for survival (appendix). Slight imbalances in ECOG performance status and ascites between the treatment groups (table 1 and appendix) might have contributed to the difference between the adjusted and unadjusted estimates.

Median progression-free survival with ramucirumab plus paclitaxel was significantly longer than with placebo plus paclitaxel (4·4 months [95% CI 4·2–5·3] *vs* 2·9 months [2·8–3·0]; stratified HR 0·635, [95% CI 0·536–0·752]; p<0·0001; figure 2B). 6-month progression-free survival was 36% (95% CI 31–41) in the ramucirumab plus paclitaxel group and 17% (13–22) in the placebo plus paclitaxel group; 9-month progression-free survival was 22% (95% CI 17–27) and 10% (7–14; figure 2B). Progression-free survival for the ramucirumab plus paclitaxel was

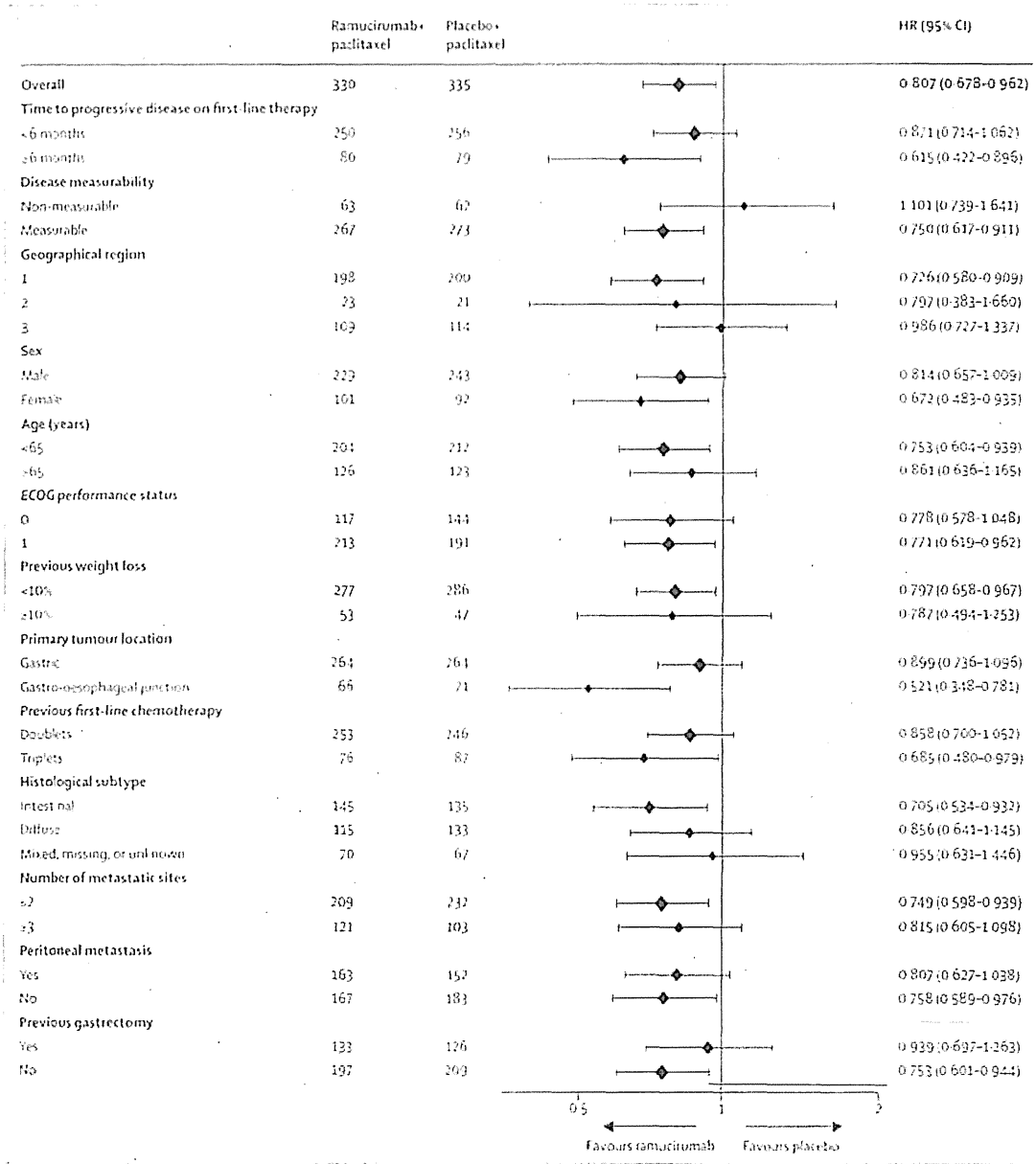

Figure 3: **Forest plot for subgroup univariate analyses of overall survival**
Data are stratified HR (95% CI). The size of the diamonds is proportional to the size of the subgroup. Geographic regions are defined as region 1: Europe, Israel, Australia, and the USA; region 2: Argentina, Brazil, Chile, and Mexico; and region 3: Japan, South Korea, Hong Kong, Singapore, and Taiwan. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio.

longer than for the placebo plus paclitaxel group in most subgroups (figure 4). Progression-free survival was significantly increased in the ramucirumab plus paclitaxel group compared with the placebo plus paclitaxel group after adjustment for significant baseline factors (adjusted HR 0·599; [95% CI 0·506–0·708]; p<0·0001; appendix).

A significantly greater proportion of patients achieved an objective response in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (92 [28%, 95% CI 23–33] of 330 *vs* 54 [16%, 13–20] of 335, respectively; p=0·0001, table 2). A significantly greater proportion of patients also achieved disease control in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (264 [80%, 95% CI 75–84] *vs* 213 [64%, 58–69], respectively; p<0·0001). The median duration of response was longer in the ramucirumab

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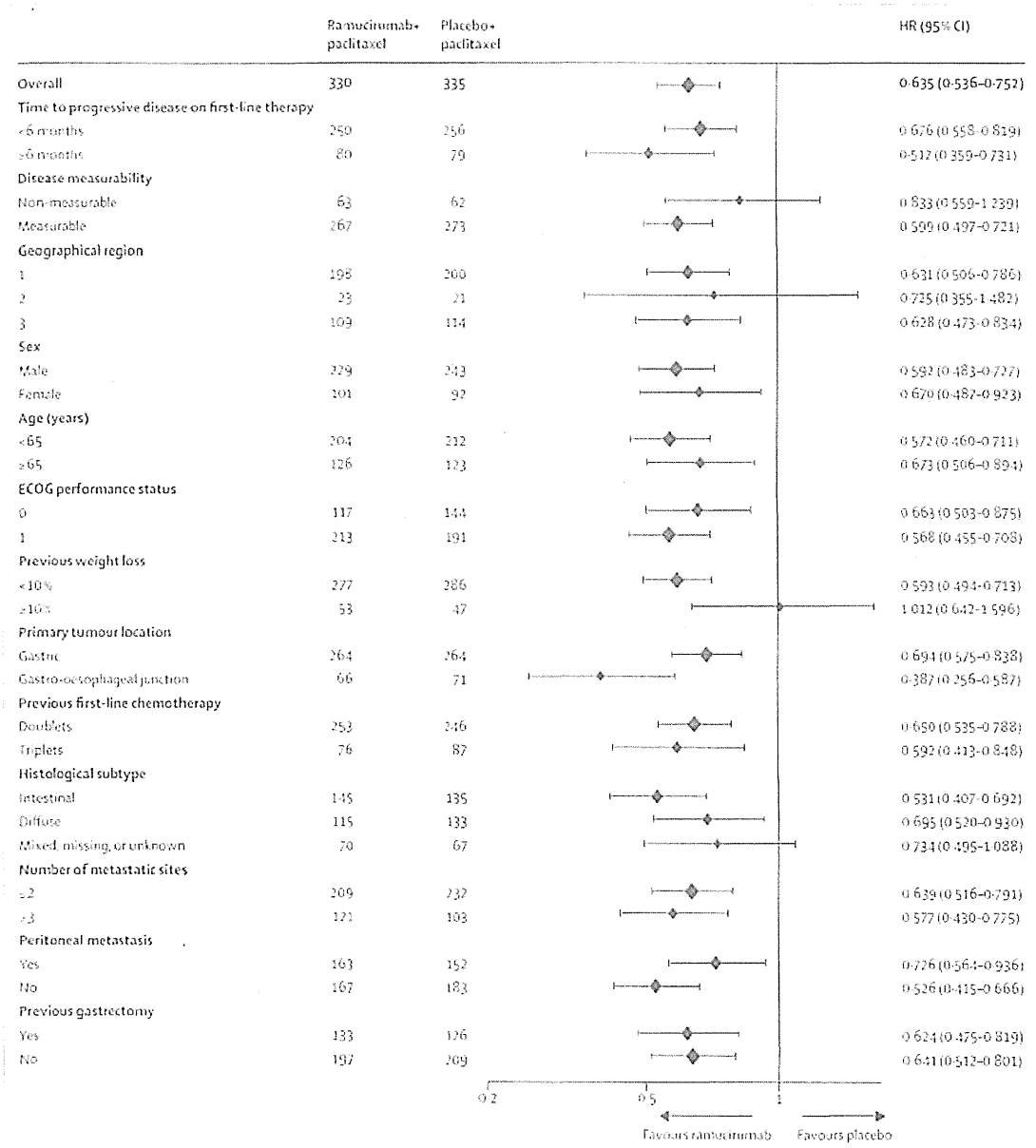

Figure 4: **Forest plots for subgroup univariate analyses of progression-free survival**
Data are stratified HR (95% CI). The size of the diamonds is proportional to the size of the subgroup. Geographic regions are defined as region 1: Europe, Israel, Australia, and the USA; region 2: Argentina, Brazil, Chile, and Mexico; and region 3: Japan, South Korea, Hong Kong, Singapore, and Taiwan. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio.

plus paclitaxel group than in the placebo plus paclitaxel group (4·4 months [IQR 2·8–7·5], *vs* 2·8 months [1·4–4·4], respectively).

Table 3 summarises overall survival, progression-free survival, and the proportion of patients achieving an objective response by geographic regions, comparing Asian with non-Asian patients. Overall survival in the ramucirumab plus paclitaxel group compared with placebo plus paclitaxel was not significantly increased for patients in region 3 compared with those in regions 1 and 2.

Baseline and end-of-treatment results for global quality of life from the QLQ-C30 and index scores from the EQ-5D-3L were similar in the treatment groups (table 4). Further details for quality of life will be published separately.

	Ramucirumab plus paclitaxel (N=330)	Placebo plus paclitaxel (N=335)
Best overall response		
Complete response	2 (<1%)	1 (<1%)
Partial response	90 (27%)	53 (16%)
Stable disease	172 (52%)	159 (47%)
Progressive disease	43 (13%)	83 (25%)
Not evaluable or not assessed	23 (7%)	39 (12%)

Data are number (%) or number (%; 95% CI), unless otherwise indicated

Table 2: Best overall response

	Ramucirumab plus paclitaxel	Placebo plus paclitaxel	Hazard ratio (95% CI)	Odds ratio (95% CI)
Median overall survival				
Regions 1 (n=398) and 2 (n=44)	8·5 months (7·4–9·8)	5·9 months (5·2–7·1)	0·732 (0·591–0·907)	
Region 3 (n=223)	12·1 months (10·0–13·3)	10·5 months (7·8–14·1)	0·986 (0·727–1·337)	
Median progression-free survival				
Region 1 (n=398) and 2 (n=44)	4·2 months (3·9–4·9)	2·9 months (2·6–3·5)	0·639 (0·518–0·788)	
Region 3 (n=223)	5·5 months (4·2–5·7)	2·8 months (2·8–4·1)	0·628 (0·473–0·834)	
Proportion of patients achieving an objective response				
Regions 1 (n=398) and 2 (n=44)	55 (25%)	31 (14%)		2·087 (1·278–3·409)
Region 3 (n=223)	37 (34%)	23 (20%)		2·235 (1·177–4·244)

Data are median (95% CI) or number (%), unless otherwise indicated. Region 1=Europe, Israel, Australia, USA. Region 2=Argentina, Brazil, Chile, and Mexico. A pooled analysis is presented for regions 1 and 2 because of the similarity of the patient populations in these two regions and the small sample size in region 2. Region 3=Japan, South Korea, Hong Kong, Singapore, and Taiwan.

Table 3: Efficacy by geographic region

	Ramucirumab plus paclitaxel (n=330)	Placebo plus paclitaxel (n=335)
EORTC QLQ-C30		
Patients completing baseline QLQ-C30	322 (98%)	328 (98%)
Baseline global quality-of-life score*	61·5 (22·0)	58·0 (22·0)
Patients completing baseline plus post-baseline QLQ-C30	287 (87%)	273 (81%)
Patients completing end-of-treatment QLQ-C30	211 (64%)	204 (61%)
End-of-treatment global quality-of-life score*	49·0 (23·0)	48·3 (23·9)
EQ-5D		
Patients completing baseline EQ-5D	323 (98%)	328 (98%)
Baseline index score†	0·75 (0·22)	0·75 (0·24)
Patients completing baseline plus post-baseline EQ-5D	287 (87%)	274 (82%)
Patients completing end-of-treatment EQ-5D	211 (64%)	206 (61%)
End-of-treatment index score†	0·61 (0·32)	0·60 (0·35)

Data are number (%) or mean (SD). EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality-of-life questionnaire. EQ-5D=EuroQol five-dimension health questionnaire. *Based on a 100-point scale, with a higher score representing better quality of life. †Based on a −0·59 to 1 scale, with 1 representing perfect health.

Table 4: Quality of life QLQ-C30 and EQ-5D mean scores at baseline and end of treatment

Median duration of treatment with ramucirumab was 18·0 weeks (IQR 10·0–31·1) in the ramucirumab plus paclitaxel group, and 12·0 weeks (6·4–20·0) with placebo in the placebo plus paclitaxel group. Median relative dose intensity of ramucirumab was similar to placebo (99% [IQR 94–101] *vs* 100% [97–101]) and was similar for paclitaxel in both groups (88% [IQR 72–97] *vs* 93% [85–99]). Dose reductions of ramucirumab occurred in 16 (5%) of 327 patients in the ramucirumab plus paclitaxel group, and of placebo in three (<1%) of 329 patients in the placebo plus paclitaxel group. Paclitaxel dose reductions occurred in 78 (24%) patients in the ramucirumab plus paclitaxel group, and in 24 (7%) patients in the placebo plus paclitaxel group. Median cumulative doses and number of infusions are provided in the appendix.

Disease progression was the most common reason for treatment discontinuation in both treatment groups (236 [72%] of 330 in the ramucirumab plus paclitaxel group *vs* 255 [76%] of 335 in the placebo plus paclitaxel group); 39 (12%) and 38 (11%) patients, respectively, discontinued treatment because of adverse events (appendix). One patient (who was randomly assigned to placebo but received ramucirumab) was unmasked to the investigator before surgery because of the occurrence of serious adverse events (sepsis and intestinal occlusion). After the discontinuation of study drug, the number of patients receiving systemic anti-neoplastic treatment was similar in both groups (appendix). Of note, a higher percentage of patients in region 3 received treatment after discontinuation of the study drug than in regions 1 or 2 (appendix).

Nine randomly assigned patients did not receive study medication and were excluded from the safety analyses (figure 1). Hence, 656 patients were included in the safety analyses. The patient who was randomly assigned to the placebo plus paclitaxel group but erroneously received ramucirumab instead of placebo discontinued treatment after one infusion. This patient is included in the intention-to-treat population (as randomly assigned) in the placebo plus paclitaxel group and is included in the safety population (as treated) in the ramucirumab plus paclitaxel group. Consequently, the safety population consisted of 327 patients in the ramucirumab plus paclitaxel group and 329 patients in the placebo plus paclitaxel group.

The incidence of grade 3 or 4 adverse events was higher in the ramucirumab plus paclitaxel group, including grade 3 or 4 neutropenia, leucopenia, and grade 3 hypertension, abdominal pain, and fatigue (table 5). All grade 3–5 adverse events are listed in the appendix. Although the incidence of grade 3 or 4 neutropenia was higher in the ramucirumab plus paclitaxel group, the incidence of grade 3 or greater febrile neutropenia was similar in both groups (ten [3%] *vs* eight [2%]). Neuropathy, of all grades, was more common in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (table 5), and was associated with a higher cumulative paclitaxel dose (appendix).

	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Any patients with a treatment-emergent adverse event	57 (17%)	155 (47%)	73 (22%)	39 (12%)	116 (35%)	128 (39%)	27 (8%)	51 (16%)
Non-haematological adverse events								
Fatigue*	147 (45%)	39 (12%)	0	0	126 (38%)	18 (5%)	0	0
Neuropathy*	123 (38%)	27 (8%)	0	0	104 (32%)	15 (5%)	0	0
Decreased appetite	121 (37%)	10 (3%)	0	0	92 (28%)	13 (4%)	0	0
Abdominal pain*	98 (30%)	20 (6%)	0	0	87 (26%)	10 (3%)	1 (<1%)	0
Nausea	109 (33%)	5 (2%)	1 (<1%)	0	100 (30%)	8 (2%)	0	0
Alopecia	107 (33%)	0	0	0	126 (38%)	1 (<1%)	0	0
Diarrhoea	94 (29%)	12 (4%)	0	0	71 (22%)	4 (1%)	1 (<1%)	0
Epistaxis	100 (31%)	0	0	0	23 (7%)	0	0	0
Vomiting	78 (24%)	9 (3%)	1 (<1%)	0	56 (17%)	12 (4%)	0	0
Peripheral oedema	77 (24%)	5 (2%)	0	0	43 (13%)	2 (<1%)	0	0
Hypertension	32 (10%)	46 (14%)	0	0	8 (2%)	8 (2%)	0	0
Constipation	70 (21%)	0	0	0	69 (21%)	2 (<1%)	0	0
Stomatitis	62 (19%)	2 (<1%)	0	0	22 (7%)	2 (<1%)	0	0
Pyrexia	56 (17%)	3 (<1%)	0	0	36 (11%)	1 (<1%)	0	0
Proteinuria	50 (15%)	4 (1%)	0	0	20 (6%)	0	0	0
Malignant neoplasm progression	5 (2%)	16 (5%)	4 (1%)	27 (8%)	1 (<1%)	24 (7%)	1 (<1%)	34 (10%)
Weight decreased	39 (12%)	6 (2%)	0	0	45 (14%)	4 (1%)	0	0
Dyspnoea	34 (10%)	8 (2%)	0	0	29 (9%)	2 (<1%)	0	0
Rash*	42 (13%)	0	0	0	31 (9%)	0	0	0
Cough	40 (12%)	0	0	0	25 (8%)	0	0	0
Back pain	35 (11%)	4 (1%)	0	0	35 (11%)	5 (2%)	0	0
Hypoalbuminaemia*	32 (10%)	4 (1%)	0	0	13 (4%)	2 (<1%)	0	1 (<1%)
Myalgia	34 (10%)	0	0	0	32 (10%)	1 (<1%)	0	0
Ascites	21 (6%)	11 (3%)	1 (<1%)	0	14 (4%)	13 (4%)	0	0
Headache	32 (10%)	0	0	0	21 (6%)	1 (<1%)	0	0
Haematological adverse events								
Neutropenia*	45 (14%)	71 (22%)	62 (19%)	0	40 (12%)	51 (16%)	11 (3%)	0
Anaemia*	84 (26%)	30 (9%)	0	0	85 (26%)	31 (9%)	3 (<1%)	0
Leucopenia*	54 (17%)	52 (16%)	5 (2%)	0	47 (14%)	19 (6%)	3 (<1%)	0
Thrombocytopenia*	38 (12%)	5 (2%)	0	0	14 (4%)	6 (2%)	0	0

Data are number (%), unless otherwise stated. *Consolidated adverse event category comprising synonymous MEdDRA preferred terms.

Table 5: **Treatment-emergent adverse events occurring in at least 10% of patients on ramucirumab plus paclitaxel, irrespective of causality**

Grade 3 adverse events that were potentially associated with the VEGF pathway—and thus were of special interest—that were more common in the ramucirumab plus paclitaxel group included hypertension, proteinuria, and bleeding or haemorrhage (table 6). The incidences of grade 4 and 5 adverse events of special interest were low in both groups, with no grade 4 or 5 hypertension, a similar incidence of gastrointestinal haemorrhage, and a higher incidence of gastrointestinal perforation in the ramucirumab plus paclitaxel group than the placebo plus paclitaxel group (table 6).

Similar numbers of patients had at least one serious adverse event (153 [47%] of 327 in the ramucirumab plus paclitaxel group *vs* 139 [42%] of 329 in the placebo plus paclitaxel group), or treatment-emergent adverse event leading to death (39 [12%] *vs* 51 [16%], respectively). Six (2%) patients in the ramucirumab plus paclitaxel group had adverse events leading to death with a causal relation to any study drug, which were septic shock; malabsorption; gastrointestinal haemorrhage; death of unknown origin; pulmonary embolism; and sepsis. Five (2%) patients in the placebo plus paclitaxel group had adverse events leading to death with a causal relation to any study drug, which were acute renal failure; cardiac failure; febrile neutropenia, septic shock, and pulmonary embolism; pulmonary embolism; and cerebral haemorrhage.

Serum samples for detection of anti-ramucirumab antibodies were available for 320 (98%) of 327 patients receiving ramucirumab plus paclitaxel and 323 (98%) of 329 patients receiving placebo plus paclitaxel. Five (2%) patients receiving ramucirumab plus paclitaxel and one

	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Bleeding or haemorrhage	123 (38%)	12 (4%)	1 (<1%)	1 (<1%)	51 (16%)	4 (1%)	2 (<1%)	2 (<1%)
Proteinuria	51 (16%)	4 (1%)	0	0	20 (6%)	0	0	0
Liver injury or failure	39 (12%)	12 (4%)	3 (<1%)	0	28 (9%)	11 (3%)	2 (<1%)	0
Hypertension	34 (10%)	48 (15%)	0	0	10 (3%)	9 (3%)	0	0
Gastrointestinal haemorrhage†	21 (6%)	10 (3%)	1 (<1%)	1 (<1%)	15 (5%)	3 (<1%)	1 (<1%)	1 (<1%)
Infusion-related reaction	17 (5%)	2 (<1%)	0	0	12 (4%)	0	0	0
Renal failure	16 (5%)	4 (1%)	2 (<1%)	0	11 (3%)	0	1 (<1%)	2 (<1%)
Congestive heart failure	6 (2%)	2 (<1%)	0	0	2 (<1%)	1 (<1%)	0	1 (<1%)
Venous thromboembolic events	5 (2%)	7 (2%)	0	1 (<1%)	7 (2%)	8 (2%)	1 (<1%)	2 (<1%)
Arterial thromboembolic events	3 (<1%)	1 (<1%)	2 (<1%)	0	2 (<1%)	2 (<1%)	0	1 (<1%)
Gastrointestinal perforation	0	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0

*Pooled adverse-event terms. †Events pooled as gastrointestinal haemorrhage are also pooled as bleeding or haemorrhage.

Table 6: Adverse events of special interest*

(<1%) patient receiving placebo plus paclitaxel had a positive response. No patients developed neutralising antibodies.

Discussion

Ramucirumab plus paclitaxel significantly increased overall survival compared with placebo plus paclitaxel in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma that had progressed after first-line chemotherapy. Patients treated with ramucirumab plus paclitaxel also had significantly longer progression-free survival, and a higher proportion of patients achieving an overall response and disease control than did those treated with placebo plus paclitaxel. Increased proportions of patients achieving an overall response has been noted previously in trials of anti-angiogenic drugs in combination with chemotherapy, especially when there seems to be an improvement in survival.[35] Results of a preplanned subgroup analysis showed a difference in treatment effect for ramucirumab plus paclitaxel on survival between non-Asian (region 1 and 2) and Asian (region 3) regions. We could speculate that the higher use of post-study discontinuation treatment in Asia (almost 70%) than in the non-Asian regions (almost 40%) attenuated the survival benefit in this region.

Fatigue, diarrhoea, and abdominal pain were some of the most frequently reported non-haematological

Panel: Research in context

Systematic review

We searched PubMed and the abstracts from major oncology congresses (American Society of Clinical Oncology [ASCO] Annual Meeting and ASCO Gastrointestinal Cancers Symposium, European Society for Medical Oncology [ESMO] Annual Meeting and ESMO World Congress on Gastrointestinal Cancer, International Society of Gastrointestinal Oncology Conference, American Association for Cancer Research-National Cancer Institute-European Organisation for Research and Treatment of Cancer Congress, and European Multidisciplinary Cancer Congress). We used MeSH and full-text search terms for gastric and gastro-oesophageal junction cancer and molecular targeted therapies, limiting our results to English-language articles published in the past 4 years; the last search was done on Dec 31, 2013. For PubMed, the search terms were ("molecular targeted therapy") or ("molecular" and "targeted") and ("therapy" or "therapies") and ("gastric neoplasms" or "gastric cancer") or ("gastric" and "cancer") or ("gastroesophageal neoplasms" or "gastroesophageal cancer") or ("gastroesophageal" and "cancer") and ("2009/01/01"and "2013/11/13"). For conferences, the search terms were "metastatic gastric cancer" or "advanced gastric cancer," manually limited to abstracts on targeted therapies or phase 3 studies. We identified several potential targeted agents (monoclonal antibodies or small-molecule tyrosine-kinase inhibitors) that are being investigated either in synergy with, or instead of, established treatments, including inhibitors of growth factors and their receptors (VEGF, EGFR, insulin-like growth factor, HER2, C-MET), MEK inhibitors, and agents targeting hedgehog protein. We used information from the abstracts and ClinicalTrials.gov to identify the latest stage of clinical developments of these agents in gastric and gastro-oesophageal junction cancer. We have limited our discussion to the agents we believe are most promising and relevant to the patient population on the basis of clinical trial efficacy.

Interpretation

Various oncogenic signalling processes have been implicated in gastric cancer. Findings with the monoclonal antibodies trastuzumab and ramucirumab suggest that the HER2 and VEGF signalling pathways might be valid targets for therapy for gastric cancer. RAINBOW shows that, in patients with progressive gastric or gastro-oesophageal adenocarcinoma after standard first-line therapy, ramucirumab in combination with paclitaxel can significantly increase overall survival compared with placebo plus paclitaxel. Together with an earlier phase 3 trial of single-agent ramucirumab in second-line advanced gastric cancer,[35] the results of these studies support the role of a VEGF receptor-targeted therapy and maybe the addition of a new agent to the treatments and standard of care in this patient population.

toxicities in both groups, and were more common in the ramucirumab plus paclitaxel group than the placebo plus paclitaxel group. These events are common in patients with gastric cancer; incidences reported in our trial are in the range of what was previously reported in large phase 3 gastric cancer trials.[9,26,28] Peripheral neuropathy, a typical side-effect of taxanes, was more common in the ramucirumab plus paclitaxel group and, as expected, was associated with a higher cumulative paclitaxel dose. Neutropenia was one of the most frequently reported haematological toxicities in both groups, and had a similar incidence to that reported in other trials of the same paclitaxel dose and schedule.[12,13,17,29] Although severe neutropenia was more frequently reported for ramucirumab plus paclitaxel, the incidence of febrile neutropenia was low and similar in the groups. As expected, hypertension, proteinuria, bleeding (mainly grade 1 or 2 epistaxis), and gastrointestinal perforations, adverse events associated with most anti-angiogenic treatments, were more common in the ramucirumab plus paclitaxel group. Grade 3 hypertension was controlled with antihypertensive medication; grade 4 or greater hypertension was not noted in this study. The incidences of grade 3 bleeding (mainly grade 3 gastrointestinal haemorrhage) and grade 3 proteinuria were higher in the ramucirumab plus paclitaxel group (table 6). However, nephrotic syndrome was not reported, and grade 4 or 5 bleeding events occurred with a similar incidence in both groups. Grade 3 or greater gastrointestinal perforation was reported only in the ramucirumab plus paclitaxel group (four patients, including one death). Importantly, the overall higher rate of grade 3 or 4 adverse events in the ramucirumab plus paclitaxel group did not result in a higher number of patients discontinuing, or a higher number of deaths, than in the placebo plus paclitaxel group. We also showed that quality of life was maintained during treatment with ramucirumab.

To our knowledge, RAINBOW is the largest trial in second-line gastric cancer, and the first report of a survival benefit with a VEGFR-2 targeted antibody in combination with chemotherapy. REGARD, a randomised phase 3 trial that compared ramucirumab as a single agent with best supportive care, showed a significant median survival benefit of 1·4 months, favouring ramucirumab treatment (median survival 5·2 months [IQR 2·3–9·9]) versus best supportive care (3·8 months [IQR 1·7–7·1]).[10] Other recently published randomised second-line gastric cancer trials showed an increase in median survival of about 1·5 months with single-agent chemotherapy (docetaxel or irinotecan) relative to supportive care.[4,5] By contrast, a trial of everolimus versus placebo in the second-line setting did not significantly extend overall survival,[27] and trials of anti-EGFR therapy in the first-line setting adding panitumumab[30] or cetuximab[31] to chemotherapy have also not significantly extended overall survival or progression-free survival, respectively.

The increased overall survival for patients treated with ramucirumab plus paclitaxel compared with placebo plus paclitaxel can be regarded as clinically meaningful in this population. In RAINBOW, the median overall survival in patients from Asia (region 3, most from Japan) was longer than in patients from regions 1 and 2, independent of treatment. In a study by Hironaka and colleagues,[5] patients receiving paclitaxel had a similar median overall survival as patients from Asia in our trial (about 10 months). Likewise, the median overall survival in patients receiving irinotecan or docetaxel in non-Asian studies, and in the non-Asian population receiving placebo plus paclitaxel in our trial (regions 1 and 2) was similar (about 4–5 months).[4,5] Together, these findings might explain the higher median overall survival in the placebo plus paclitaxel group than that in previously reported trials in entirely western populations.

Since RAINBOW showed that second-line therapy can significantly improve survival of patients with advanced gastric cancer, ramucirumab plus paclitaxel could be regarded as a new standard second-line treatment for advanced gastric cancer. Our findings, combined with those of the REGARD trial,[10] validate the role of VEGFR-2 signalling as an important therapeutic target in advanced gastric and gastro-oesophageal junction adenocarcinoma (panel). Analyses are ongoing to identify potential predictive biomarkers for ramucirumab.

Contributors

JDS, ME, PR, DC, AO, and HW conceived and designed the study. HW, EVC, S-CO, GB, YS, SH, NS, OL, T-YK, DC, AO, PR, YK, JA, DF, and KM gathered the data. JDS, ME, RC, KC, AO, and HW analysed and interpreted the data. All authors were involved in the drafting, review, and approval of the manuscript and the decision to submit for publication.

Declaration of interests

HW reports honoraria for lectures and advisory boards. EVC reports grants from Eli Lilly and Company during the conduct of the study, and grants from Eli Lilly outside of the submitted work paid to the University of Leuven. YS reports grants from Eli Lilly and Company during the conduct of the study; grants and personal fees from Taiho; grants and personal fees from Chugai; grants and personal fees from Yakult; grants and personal fees from Pfizer; grants from Sanofi; grants from Novartis; personal fees from Bayer; personal fees from Bristol-Myers Squibb; personal fees from Merck Serono outside of the submitted work. SH reports personal fees and non-financial support from Eli Lilly Japan during the conduct of the study. DC reports grants from Roche; grants from Amgen; grants from Celgene; grants from Sanofi; grants from Merck Serono; grants from Novartis; and grants from AstraZeneca outside of the submitted work. PR reports grants and personal fees from Eli Lilly and Company during the conduct of the study; grants from Bayer; grants and personal fees from Sanofi; personal fees from Merck Serono; personal fees from Ipsen; and grants from Novartis outside the submitted work. AO reports personal fees from Taiho; personal fees from Daiichi Sankyo; personal fees from Chugai-Roche; personal fees from Merck Serono; personal fees from Novartis; personal fees from Eisai; and personal fees from Takeda outside the submitted work. YK reports personal fees from Eli Lilly Japan during the conduct of the study and personal fees from Eli Lilly Japan outside of the submitted work. ME, RC, and KC are employees of Eli Lilly and Company. DF reports non-financial support from Eli Lilly and Company during the conduct of the study; personal fees from Eli Lilly and Company outside of the submitted work; and is currently an employee of Eli Lilly and Company. JDS was an employee of the sponsor during the design, conduct, and analysis of the study. The other authors declare no competing interests.

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HOW TO DO IT

Simultaneous resection of colorectal cancer and liver metastases in the right lobe using pure laparoscopic surgery

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Abstract It is now common to resect colorectal cancer by laparoscopic surgery. Hepatectomy has become a standard treatment for patients with colorectal cancer with resectable liver metastases. The resection of liver tumors can now be done partly by laparoscopic surgery. However, metastatic tumors in the right lobe are often difficult to resect laparoscopically. Furthermore, simultaneous resection of the colorectum and liver may also be difficult. In this study, we evaluated a new method to resect both colorectal cancer and liver metastases in the right lobe by laparoscopic surgery. Two cases are presented that underwent total laparoscopic resection of a right lobe tumor, associated with laparoscopic colorectal resection. The metastatic tumor in the right lobe was first resected in the left hemi-prone position. Then, the colorectal cancer was resected in the lithotomy position. The method for resecting the right lobe liver tumor and colorectal cancer was safe and feasible. The mean duration of surgery was 443.5 min, and the mean blood loss was 158 mL. The postoperative course was uneventful. In selected patients, laparoscopic hepatectomy for right lobe synchronous metastatic tumors can be safely performed simultaneously with colorectal surgery.

Keywords Laparoscopic surgery · Simultaneous resection · Hepatectomy · Colectomy · Left semi-prone position

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Introduction

Colorectal cancer is a major problem worldwide. More than 1 million people develop colorectal cancer and approximately half a million people die every year of the disease [1]. It has been reported that about 50 % of patients develop liver metastases during the natural course of colorectal cancer. It has also been reported that in patients with liver metastasis, 15–50 % have synchronous disease [2–5]. Hepatic resection is recommended in the National Comprehensive Cancer Network (NCCN) Guidelines if the primary tumor can be controlled. In selected patients, it has been reported that a simultaneous resection of primary colorectal tumor and liver metastases can be safely performed [6, 7].

Currently, laparoscopic surgery for colorectal cancer has been shown to have the same outcome as open surgery [8]. The advantages of laparoscopic surgery are its small incision and lower invasion compared with open surgery. Further, under laparoscopic surgery, the enlarged view helps the operator to find the vessels easily, so the operation can be performed compactly and more precisely.

The Clinical Outcomes of Surgical Therapy (COST) study group has reported that laparoscopic surgery is an acceptable alternative approach to open surgery for colon cancer [8]. In that study, the recurrence rate, overall survival and rate of complications were similar in the laparoscopic and open colectomy groups. Lacy et al. [9] have also reported a clinical study comparing open and laparoscopic colectomy, and concluded that laparoscopic colectomy benefits patients with cancer more than open surgery does.

Laparoscopic surgery can now be performed safely even for liver resection. The first laparoscopic liver resection was reported in 1992 [10]. After that report, many studies

have shown that laparoscopic hepatectomy, including larger resection of three or more segments, can be safely performed [11–13].

Despite increasing laparoscopic indications for both colorectal and liver resection, laparoscopic combined procedures for primary colorectal cancer with synchronous liver metastases have rarely been performed. Furthermore, metastatic tumors in the right lobe are difficult to resect because of anatomical difficulties. In this report, we describe a method that can be used to perform simultaneous resection of colon cancer and liver metastases in the right lobe using pure laparoscopic surgery.

Surgical techniques

During our procedure, the liver metastases were resected before the primary colorectal cancer. The patient was placed in the left hemi-prone position, then four 12-mm trocars were placed on the right upper abdomen (Fig. 1a; sites A–C) and on the navel (Site D). One 5-mm trocar was placed between the navel and rib (Site E). A representative picture of the placement of trocars is shown in Fig. 1c.

The locations of the metastases were identified by ultrasonography (ALOKA α-10). The Glisson sheath was taped, and a Pringle maneuver using a Nelaton tube was performed. Then, resection of the metastatic tumor was performed laparoscopically using an ENSEAL device (Johnson and Johnson). The liver specimens were moved into a bag (End-Catch II) placed in the peritoneal cavity. The patient was then changed to the lithotomy position.

A further four trocars were added for colectomy (Fig. 1b, 5 mm: Sites F–H and 12 mm: Site I). The trocar at the navel (Site D) was used for the camera. The total number of trocars used for this procedure was therefore nine. The fat tissues and lymph nodes were dissected at the level of the inferior mesenteric artery (D3). The sigmoid and superior rectal arteries were clipped and cut, then the inferior mesenteric vein was also ligated and cut at the same level. The left colic artery was preserved. Tumor-specific mesorectal excision (TSME) was then performed, and the rectum, including the tumor, was resected with a linear stapler. The incision on the navel was extended to 4 cm, and the liver specimen and rectum were extracted from the peritoneal cavity.

The rectum was cut at 5 cm on the oral side of the tumor. A low anterior resection with D3 lymph node dissection was performed. The anvil head of a stapling instrument was introduced into the colon, and the body of the instrument was inserted into the rectum through the anus. An end-to-end colorectal anastomosis was created with the usual double stapling technique. Two 19 Fr drains were inserted into the pelvic cavity and the liver resected surface. The trocars were withdrawn, and all of the incisions were closed.

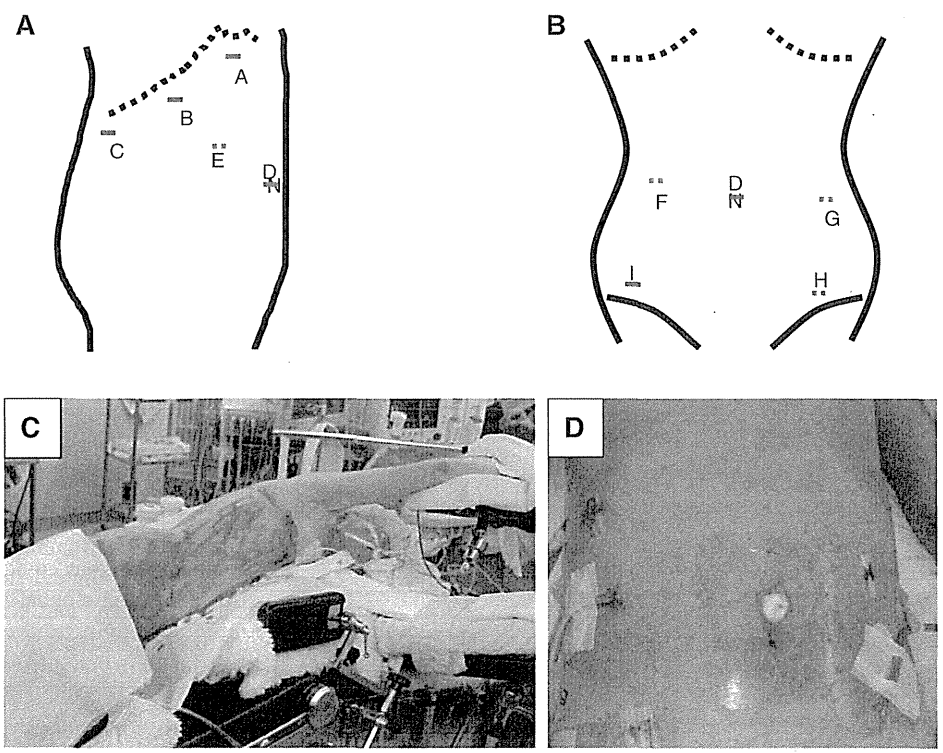

Fig. 1 The trocar sites used for the simultaneous resection of colon cancer and liver metastases in the right lobe under laparoscopic surgery. **a** The trocar sites for the left hemi-prone position. The *solid lines* indicate the 12-mm trocar and *dotted lines* indicate the 5-mm trocars. Sites *A–C* were inserted under the right rib. Site *D* was used for the camera. Site *E* was used to retain the liver. **b** The trocar sites for colectomy or resection of the metastatic tumor in the *left* lobe. Sites *F–I* were used for colectomy. **c** A representative photograph of the *left* hemi-prone position

Results

Case 1

An 83-year-old female presented with hemorrhagic stool. Colonoscopy revealed two tumors in the sigmoid colon and rectum (Fig. 2a). A tumor biopsy showed well-differentiated adenocarcinoma. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 15-mm tumor on the inferior subsegment of the posterior segment (S6) of the liver (Fig. 2b). The serum levels of carcinoembryonic antigen and cancer antigen 19-9 were normal.

Although she was elderly, the patient's general condition was good. Simultaneous laparoscopic resection was therefore attempted by the liver and gastrointestinal teams. The S6 liver tumor was first resected with the patient in the left hemi-prone position, and then low anterior resection was performed for rectal cancer.

The duration of surgery was 416 min, and the estimated blood loss was 15 mL. The postoperative course was uneventful, and the patient was discharged on day 10.

Case 2

An 81-year-old male presented to a nearby hospital with abdominal pain and nausea. He was diagnosed with ileus that was caused by sigmoid colon cancer (Fig. 3a). A transverse colostomy was created. He was referred to our hospital for treatment of the sigmoid colon cancer. A precise workup revealed a 25-mm metastatic tumor in the superior subsegment of the anterior segment (S8) of the liver (Fig. 3b). This patient was also elderly, and his general condition was good. As simultaneous resection was considered possible, laparoscopic resection was attempted by the same team as in Case 1. An intraoperative image is shown in Fig. 4. The patient was also noted to have a gallstone; therefore, cholecystectomy was added to the procedure. We performed a functional end-to-end anastomosis to resect the sigmoid colon cancer. After cancer resection, insertion holes were made on the oral and anal sides of the colon. A linear stapler (Endo GIA Ultra; Covidien) was inserted into the hole, and an anastomosis was created. The inserted hole was closed with the stapler. Although the colostomy was created before surgery, it did not interfere with the procedure.

The duration of surgery was 471 min and estimated blood loss was 300 mL. The postoperative course was uneventful. The patient was discharged on day 10. Three months after laparoscopic surgery, the colostomy was closed.

For these two cases, the mean duration of surgery was 443.5 min and mean blood loss was 158 mL.

Discussion

In this report, we described a procedure for laparoscopic surgery for the simultaneous resection of the liver and colorectum. The incision of the navel was extended to remove the resected specimen (liver metastases and colorectal cancer). We designated this procedure as a pure laparoscopic surgery, because the large incision was only created to remove the specimen and was not required to perform the operation.

Several previous reports have described the simultaneous resection of colon cancer and liver metastases under laparoscopic surgery. The liver resection has often been carried out using hybrid techniques, such as hand-assisted

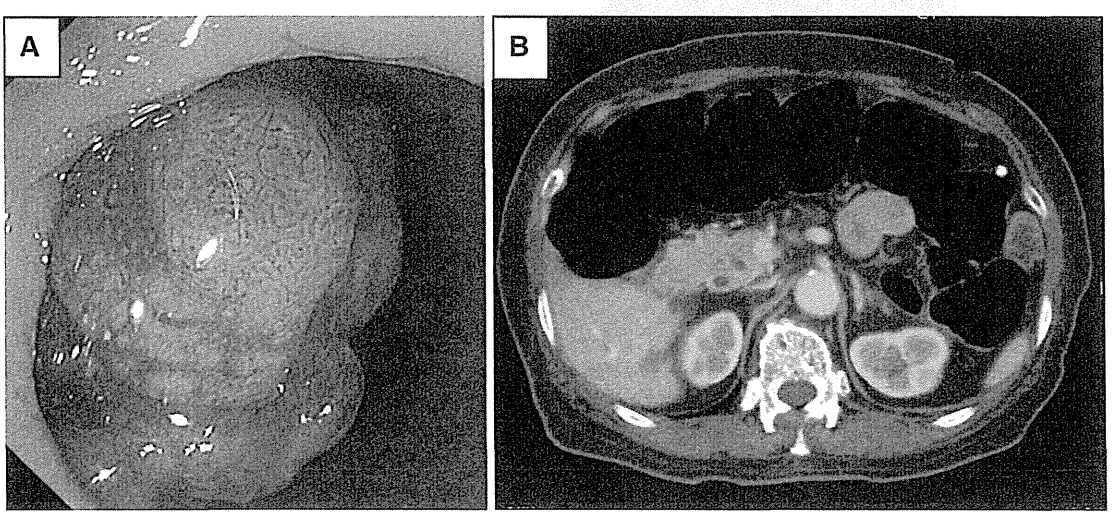

Fig. 2 The colonoscopy and CT for Case 1. **a** Colonoscopy revealed a rectal tumor. **b** The CT scan showed a metastatic tumor in S6 of the liver

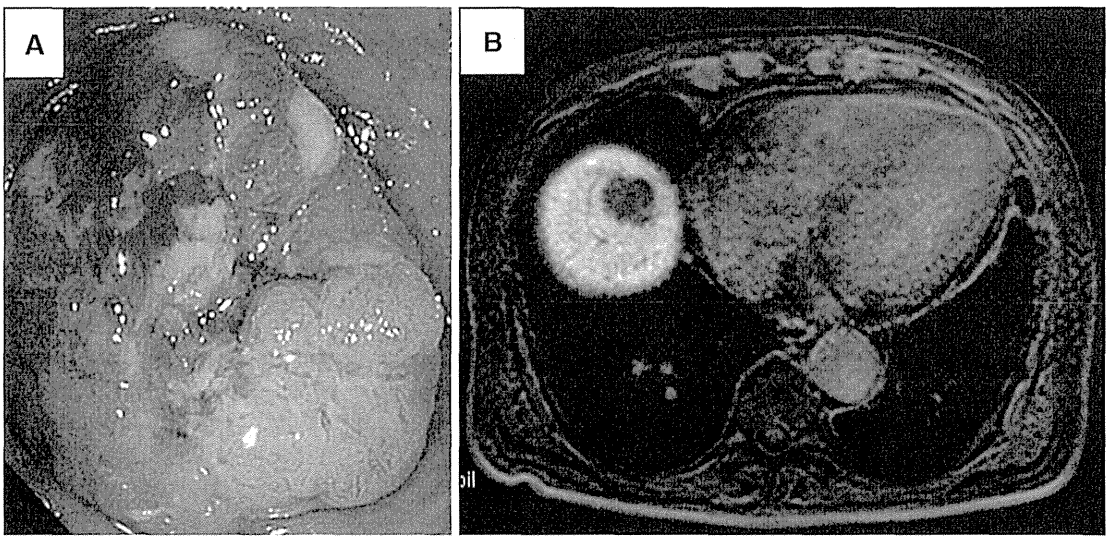

Fig. 3 The colonoscopy and MRI for Case 2. **a** Colonoscopy revealed a sigmoid colon tumor that completely obstructed the colon. **b** MRI showed a metastatic tumor in S8 of the liver

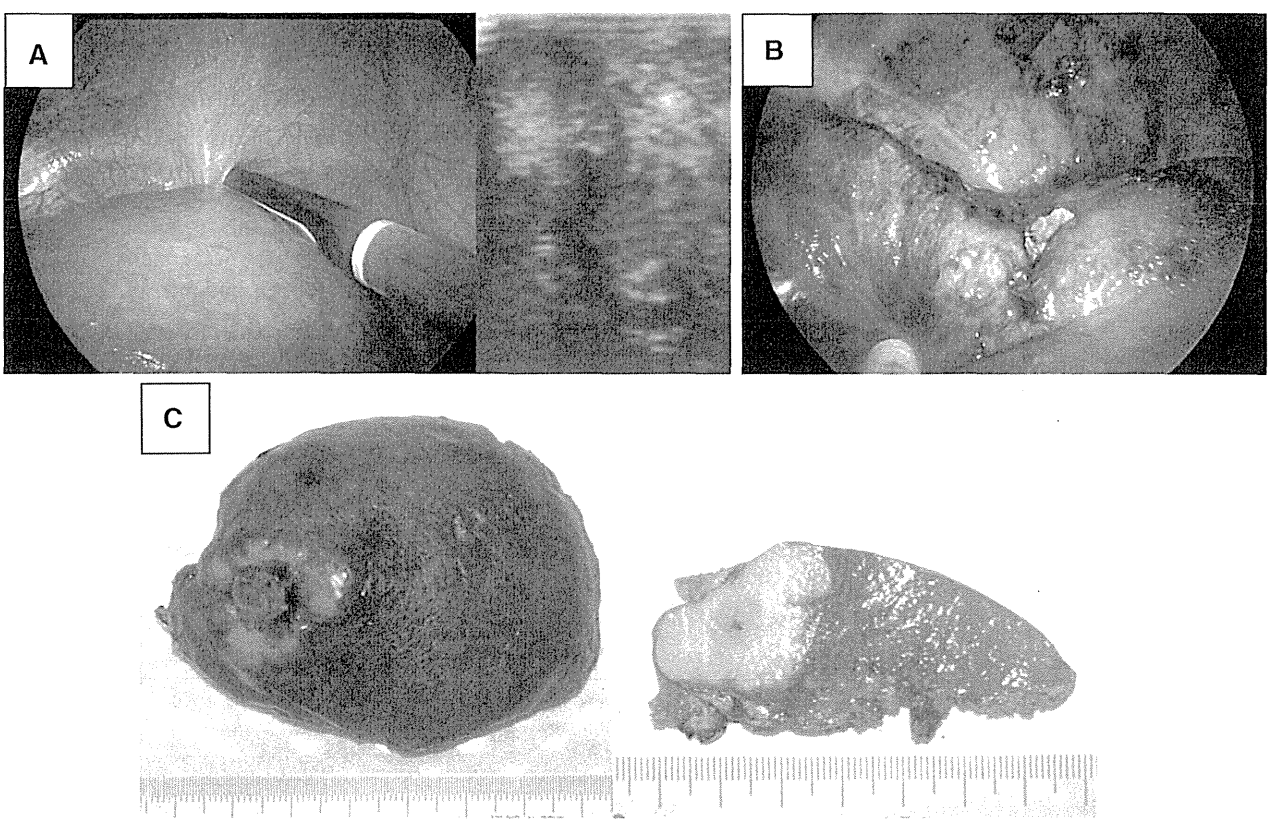

Fig. 4 An intraoperative image of the liver metastasis and the resected specimen from Case 2. **a** An intraoperative image of the liver metastasis in S8. An adhesion was observed. **b** An image obtained after resection of the liver metastasis. The resected surface was covered with a Neo-veil. **c** The resected specimen of the liver metastasis. The size was 34 × 22 mm, and the weight was 50 g

[14] or laparoscopically assisted [15] methods. However, pure laparoscopic procedures for simultaneous resection have been reported since 2011.

Nguyen et al. [16] have reported a multi-institutional and international study on minimally invasive liver resection for metastatic colorectal cancer. They concluded that

liver resection for metastatic tumors is safe, feasible and oncologically comparable to open liver resection for both minor and major resections. Our study demonstrated that metastatic liver tumors can be resected synchronously or metachronously.

For synchronous resection, Fahy et al. [17] have reviewed the safety and oncological outcomes compared with staged resection. They reported that simultaneous resection is both feasible and safe when the hepatic resection is limited to three or fewer segments.

Laparoscopic simultaneous resection has also been described in some recent reports. Kim et al. [15] reported laparoscopically assisted combined colon and liver resection in 2008. In their study, ten patients with primary colorectal cancer and synchronous liver metastases underwent laparoscopically assisted combined resection, and there was no surgical mortality and only one case of major morbidity. They concluded that this procedure is feasible and safe. Recently, Spampinato et al. [18] experienced five cases with one-stage, total laparoscopic major hepatectomy and colorectal resection. They reported that, even with major hepatectomy, a total laparoscopic approach is a feasible and safe option to treat primary colorectal neoplasms with synchronous liver metastasis. A laparoscopic approach to resect primary colorectal cancer and liver metastasis simultaneously is therefore reasonable for selected patients.

Nevertheless, liver metastasis in the right lobe, especially in S6–S8, is difficult to resect with a pure laparoscopic method. Therefore, we developed a new method employing a left hemi-prone position hepatectomy combined with laparoscopic colorectal surgery. We herein described two cases that underwent simultaneous resection of colorectal cancer and liver metastasis in the right lobe using this procedure. Our procedure includes new steps to complete the pure laparoscopic procedures for metastases in the right lobe. First, resection of the liver metastases was preceded by the resection of the colorectal cancer. Performing the operation in this order enabled us to take all the specimens (liver metastases and colorectal cancer) out from the peritoneal cavity at the same time after colectomy. Second, we used the left hemi-prone position for metastasis resection. By adopting this position, the metastatic tumor could be observed in front of the field, and its resection was simplified. The metastatic tumor cannot be observed with the patient in the supine position, because it would be a dorsal lesion. Finally, the colectomy was performed with the patient in the lithotomy position. The same trocars used for resecting the liver metastasis were used as much as possible for the second procedure.

With our procedure, the metastases in the right lobe of the liver could be resected simultaneously under pure laparoscopic surgery. Pure laparoscopic simultaneous resection of colorectal cancer and liver metastases therefore represents a choice for multidisciplinary treatment.

Conflict of interest The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

The early discontinuation of adjuvant hormone therapy is associated with a poor prognosis in Japanese breast cancer patients

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Abstract
Purpose It is important for patients to complete the planned hormone therapy to reduce both the recurrence and mortality rates of hormone receptor-positive breast cancer. We investigated the rates and factors related to the early discontinuation of adjuvant hormone therapy at our institution.
Methods We identified 145 females prescribed adjuvant hormone therapy who were followed up for longer than 5 years. The rate of completing the planned hormone therapy and factors related to early discontinuation were examined. The relapse-free survival rate was examined between the completion group and the discontinuation group.
Results The completion rate was 90.6 %. The primary reason for discontinuing hormone therapy within 5 years was side effects, such as arthritic pain. The primary factor related to early discontinuation was a significantly younger age. The relapse-free survival rate was significantly lower in the discontinuation group ($p = 0.025$).
Conclusions More than 90 % of the patients completed the planned adjuvant hormone therapy, and early discontinuation was related to a shorter RFS. To improve the rate of the successful completion of adjuvant hormone therapy, it is important to provide supportive care to reduce the occurrence of side effects and to care for young females with a desire to become pregnant.

Keywords Adherence · Early discontinuation · Adjuvant hormone therapy · Side effect

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Introduction

Treatment with postoperative hormone therapy reduces the recurrence and mortality of early hormone receptor (HR)-positive breast cancer in both pre- and postmenopausal females [1]. Oral hormone therapies include selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs), which are typically prescribed for 5 years or longer. Among premenopausal females with postoperative HR-positive early breast cancer, treatment with tamoxifen (TAM) improves the disease-free survival compared with that observed in patients receiving no adjuvant treatment [2]. In addition, inhibiting the ovarian function with LHRH agonists has been proven to reduce the recurrence rate of breast cancer [3]. A meta-analysis of randomized trials of TAM in patients with early breast cancer demonstrated significant 15-year risk reductions in cancer recurrence and mortality [4]. In the ATLAS (Adjuvant Tamoxifen: Longer Against Shorter trial), 10 years of TAM treatment was found to be related to a superior prognosis compared to that observed following 5 years of treatment [5]. Among postmenopausal females, treatment with AIs improved the disease-free survival compared with that achieved with TAM [6, 7]. For perimenopausal females, switching adjuvant hormone therapy from TAM to AIs is thus considered to be an effective treatment strategy [8–10].

The lack of adherence to prescribed medications is a well-known problem in the medical literature [11]. Many patients fail to fill the initial prescription (noninitiation), take the drug on a daily basis as prescribed (nonadherence) or continue long-term treatment with the drug (early discontinuation) [11]. Among patients receiving adjuvant hormone therapy, 32 % discontinue therapy by 4.5 years, and of those who continue, only 72 % are fully adherent [12]. The adherence and discontinuation of SERMs and AIs are related to higher recurrence rates and worse survival in many studies [13, 14]. The discontinuation rate for TAM and AIs is approximately 7–10 % per year [13, 15–21]. In clinical trials, 8–28 % of patients do not complete the treatment as recommended [6, 22, 23]. Moreover, reports have indicated that the rate of completing the recommended hormone therapy ranges from only 10–50 % due to failure to take the correct dose at the prescribed frequency or due to the discontinuation of therapy in both clinical trials and the clinical practice setting [18, 24–28]. A consistent finding in the literature is that treatment side effects are strongly associated with adherence to or continuation with adjuvant therapy [29]. With regard to the factors predicting the adherence to hormone therapy regimens, Hershman et al. [14] reported that Asian race, being married and a longer prescription refill interval are associated with higher rates of completion of therapy.

Although there have been many reports regarding adherence to and/or the completion of hormone therapy in European countries and the United States, no studies of Japanese breast cancer patients have so far been reported. It is important to verify whether the same factors identified in these studies apply to the Japanese breast cancer patients [30].

In the current study, we investigated the rates of completion and factors related to the early discontinuation of adjuvant hormone therapy and compared the prognoses between the completion group and the discontinuation group among Japanese breast cancer patients.

Patients and methods

Patient selection and study design

This study was a retrospective observational study. Among the patients who underwent curative surgery at the Department of Surgery and Science, Kyushu University Hospital between 2002 and 2006, we selected 263 patients with breast cancer of stage I–III according to the UICC TNM classification. Written informed consent regarding data acquisition was obtained from all patients before surgery. The rate of and reason for discontinuing adjuvant hormone therapy and the relationships between these factors and the prognosis were investigated by reviewing the patients' medical records. The medical records contained information regarding the status of recurrence, date of last follow-up, time after surgery and clinical characteristics, such as the stage, type of operation, history of cancer therapy, nuclear grade and the expression of hormone receptors (HRs) [the estrogen receptor (ER) and progesterone receptor (PR)] and the HER2 status.

Evaluation of the ER, PR and HER2 status

The ER, PR and HER2 status was evaluated as described previously [31]. The ER and PR were considered to be positive if ≥ 1 % of the nuclei of the tumors were stained during IHC. The tumors were considered to be HER2-positive if they were scored as either 3+ on IHC or 2+ on IHC with HER2 amplification (ratio > 2.0) based on fluorescence in situ hybridization.

Statistical analysis

The survival analyses were performed using the Kaplan–Meier method, and differences between the groups with regard to the survival and relapse-free survival times were evaluated using the log-rank test. All of the analyses were conducted using the JMP version 9 software program (SAS Institute Inc., Cary, NC). Differences were considered to be significant at values of $p < 0.05$.

Results

Rate of and reason(s) for discontinuing adjuvant hormone therapy

We identified 263 females diagnosed with stage I–III breast cancer who had undergone surgery between January 1, 2002 and December 31, 2006 in our department. One hundred and seventy-seven patients were diagnosed with HR-positive breast cancer, while the remaining 86 patients were diagnosed with HR-negative breast cancer. Among the HR-positive patients, 171 were treated with adjuvant hormone therapy. SERMs and AIs were prescribed to 103 (71 %) and 42 (29 %) patients at the start of adjuvant therapy, respectively.

Among these patients, 26 were excluded from the study due to failure to participate in follow-up as a result of transferring to another hospital or ending hospital visits with no contact (Fig. 1). One hundred and forty-five patients who were followed up for longer than 5 years were included in the analysis. Seventeen patients who experienced relapse within 5 years changed therapies.

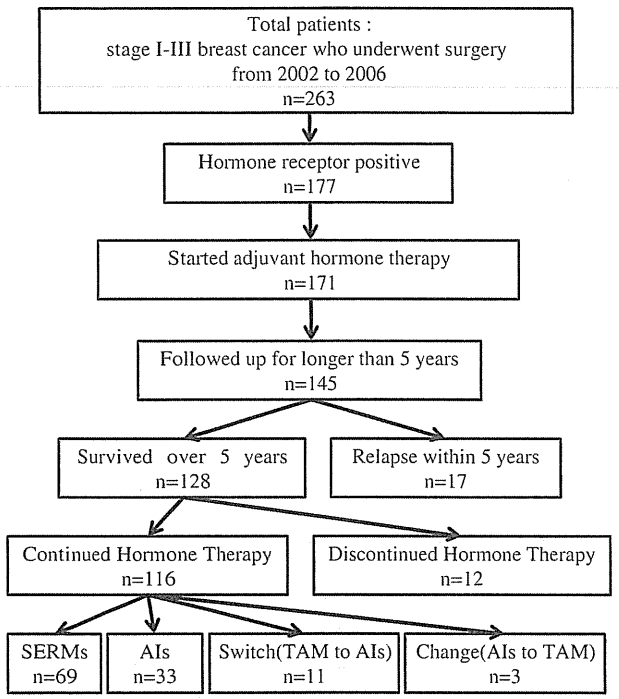

Fig. 1 A schematic diagram of the patients evaluated in this study. Among the 145 patients followed up for longer than 5 years, 128 survived longer than 5 years without relapse. A total of 116 patients continued hormone therapy for 5 years, while 12 patients discontinued therapy. In the continuation group, 69 patients were treated with SERMs, 22 patients were treated with AIs, 11 patients were switched from TAM to an AI and three patients were switched from an AI to TAM

The rate of completing the planned hormone therapy and the factors related to the early discontinuation of hormone therapy were examined among the 128 patients who survived longer than 5 years without relapse. Twelve (9.4 %) patients discontinued and 116 (90.6 %) patients completed the planned hormone therapy. In the completion group, SERMs and AIs were administered to 69 (59.4 %) and 33 (28.4 %) of the patients for 5 years, respectively. In addition, 11 (9.4 %) perimenopausal patients switched from TAM to AI after menopause. There was a change from an AI to TAM in three (2.6 %) cases due to the development of arthritic pain (Fig. 1).

In the discontinuation group, the reasons for discontinuing hormone therapy within 5 years included side effects, such as arthritic pain, in five (41.7 %) cases, a desire to become pregnant in two (16.7 %) cases, dependence on Qigong in one (8.3 %) case and no specific reason in four (33.3 %) cases (Table 1). We found that females younger than 40 years of age discontinued adjuvant hormone therapy significantly more frequently than did older patients (Table 2). Two of the four patients under age 40 (50 %) wished to become pregnant.

Table 1 The reasons for the discontinuation of hormone therapy

Reason	Number (%)
Side effect	5 (41.7)
Arthritic pain	2 (16.7)
Headache	1 (8.3)
Endometrial hypertrophy	1 (8.3)
Atypical genital bleeding	1 (8.3)
Desire to be pregnant	2 (16.7)
Taking Qigong	1 (8.3)
No specific reason	4 (33.3)

Relationship between the discontinuation of adjuvant hormone therapy and the prognosis

We classified the patients into two groups: the continuation group and the discontinuation group. We analyzed the overall survival (OS) and relapse-free survival (RFS) rates between the two groups. There were no significant differences in the OS between the two groups. However, the RFS rate was significantly lower in the discontinuation group ($p = 0.025$) (Fig. 2).

Discussion

To the best of our knowledge, this is the first report regarding the completion and discontinuation of adjuvant hormone therapy in Japanese breast cancer patients. With regard to breast cancer therapy, both surgery and adjuvant therapy are important factors associated with improvements in the survival rate. The mortality rate has been improved with the administration of hormone therapy to patients with HR-positive breast cancer [1]. Currently, cancer research is focused on discovering and proving the efficacy of new interventions to reduce cancer mortality. However, these treatments are meaningless if the patient does not take the medication as planned.

In previous clinical trials, the rate of completing hormone therapy among ER-positive breast cancer patients has been reported to be 8–28 % [6, 22, 23, 32]. On the other hand, in clinical practice, the discontinuation rate has been reported to be 31–73 % [33]. The low completion rate is considered to be largely due to differences in provider support, that is, who is responsible for providing cancer follow-up care [33]. The Behavioral Risk Factor Surveillance System demonstrated that only 20 % of all cancer survivors continue to see an oncologist or cancer specialist as their primary provider for cancer follow-up care. Compared with primary care physicians (PCPs),

Table 2 The clinicopathological features of the completion and the discontinuation groups

Factors	Completion group ($n = 116$)	Discontinuation group ($n = 12$)	p value
Age (years)			
<40	7	4	0.001
>40	109	8	
T			
1.2	96	10	0.959
3.4	20	2	
N			
Negative	83	10	0.383
Positive	33	2	
NG			
1	73	8	0.833
2	26	3	
3	17	1	
Ly			
Negative	88	9	0.947
Positive	28	3	
Unknown	1	0	
v			
Negative	113	12	0.645
Positive	2	0	
Unknown	1	0	
Surgery			
Mastectomy	57	8	0.247
Lumpectomy	59	4	
ER			
Negative	2	0	0.646
Positive	114	12	
PR			
Negative	23	2	0.792
Positive	93	10	
HER2			
Negative	49	7	0.321
Positive	64	5	
Unknown	3	0	
Chemotherapy			
+	28	2	0.56
−	88	10	
Radiation			
+	54	5	0.746
−	62	7	

oncologists are less likely to believe that PCPs have the skills to conduct appropriate testing to detect breast cancer recurrence (59 vs. 23 %, $p < 0.001$) or provide care for the late effects of breast cancer (75 vs. 38 %, $p < 0.001$)[34].

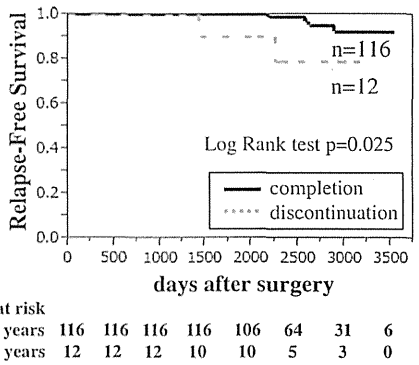

Fig. 2 Kaplan–Meier curves comparing the RFS rates in the continuation and discontinuation groups. The continuation group exhibited a significantly better prognosis than the discontinuation group

In this study, it was difficult to evaluate the precise level of adherence to the hormone therapy regimen in each patient based on a review of the medical records. Therefore, only the rate of completion or early discontinuation was evaluated in this study. There is little knowledge regarding the factors related to adherence. Smoking, the breast cancer risk, extremes of age, a non-white ethnicity, the socioeconomic status and the level of education are all associated with the adherence to TAM treatment as adjuvant therapy [35]. Another report showed that a younger or older age, the use of lumpectomy or unknown surgery and the presence of additional comorbid conditions are associated with the discontinuation of hormone therapy. On the other hand, an Asian/Pacific Islander ethnicity, being married, an earlier age at diagnosis, prior receipt of adjuvant chemotherapy, receipt of adjuvant radiation therapy and a longer prescription refill interval have been found to be associated with the completion of 4.5 years of hormonal therapy [12]. Similar phenomena have been observed for other oral medications, such as Gleevec, used to treat gastrointestinal stromal tumors or chronic myelogenous leukemia [36, 37].

The side effects are strongly associated with the adherence to adjuvant therapy, and reducing and controlling side effects are one way to increase the adherence rate. In a survey of 622 postmenopausal females, 30 % of the patients discontinued hormone therapy, and the rate of discontinuation related to side effects was reported to be very high (84 %) [38]. In the present study, side effects, such as arthritic pain, were also a major factor associated with the discontinuation of hormone therapy (41.7 %). In addition, the younger females exhibited early discontinuation of adjuvant hormone therapy significantly more often in our study. Half of these patients discontinued treatment because they wished to become pregnant. Identifying and reducing the reasons for nonadherence and discontinuation

of oral hormone medications can increase adherence and the completion rate, and ultimately improve the outcomes. Therefore, clinicians must address side effects.

Figure 2 shows the importance of the effects of hormone therapy on late relapse. The EBCTCG (Early Breast Cancer Trialists' Collaborative Group) showed that the risk reduction effect of endocrine therapy was seen even 15 years after the initiation of TAM in estrogen receptor-positive breast cancer [4]. This is considered to be a carryover effect. It is thought that this carryover effect was reduced in the discontinuation group compared to the completion group in this study.

In conclusion, we demonstrated that, in Japan, the rate of completing adjuvant hormone therapy in HR-positive breast cancer patients is higher than that reported in other countries. Side effects and a younger age were the major factors associated with early discontinuation, while early discontinuation was significantly associated with a shorter RFS. Therefore, we emphasize that controlling side effects and caring for young females are important for helping patients to continue and complete their planned adjuvant hormone therapy.

Conflict of interest There are no conflicts of interest to declare.

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ORIGINAL ARTICLE

Gender differences in prognosis after esophagectomy for esophageal cancer

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Abstract
Purpose The purpose of this study was to clarify the gender differences in the prognosis, as well as mortality and morbidity, of patients who have undergone esophagectomy for esophageal cancer.
Methods The clinical results of esophagectomy were compared between 975 male and 156 female patients with esophageal cancer.
Results The male to female ratios of cervical and thoracic esophageal cancer were 1.87 and 7.38, respectively ($P < 0.01$). The incidence of preoperative comorbidities was 32.4 and 17.4 %, respectively, and the rates of both tobacco and alcohol abuse were significantly lower in the females than in the males. The mortality rate was lower in the females (3.8 %) than in the males (5.7 %), although the differences were not significant. The overall survival was significantly better in the female than in the male patients ($P = 0.039$). The 5- and 10-year overall survival rates were 32.6 and 20.5 % in the males and 39.5 and 32.5 % in the females, respectively. A multivariate analysis revealed gender to be an independent prognostic factor. However, no significant differences were recognized in disease-specific survival.
Conclusions These results suggest that the prognosis of females with esophageal cancer is better than that of males after esophagectomy, most likely due to multiple clinical factors, such as a more favorable lifestyle and general status.

Keywords Esophageal cancer · Female · Gender · Prognosis

Introduction

Esophageal cancer is a biologically and clinically aggressive cancer with a high incidence of node and organ metastasis. The prognosis of patients with esophageal cancer is generally poor [1–3]. The morbidity and mortality in addition to the prognosis observed after esophagectomy have recently been greatly improved; however, esophagectomy continues to be considered highly invasive [4, 5]. Esophageal cancer predominantly develops in males [6], and the male to female ratio is approximately 6.5 to 1 in Japan [7]. Both experimental [8, 9] and clinical studies [10, 11] have suggested that this discrepancy is due to an advantage among females in recovery of the immune function following surgical damage, such as trauma or infection. However, the gender differences in mortality and morbidity following esophageal resection have not yet been adequately studied.

In terms of gender differences in prognosis, many authors have reported better prognoses after esophagectomy in female patients than in male patients [4, 12–20]. The existence of sex hormone receptors is reported to be a possible reason for the gender difference in prognosis [21, 22]. However, thus far, no studies have examined gender differences following esophagectomy using an analysis of a large number of patients (i.e. >1,000 patients) at a single institution. It is, therefore, unclear whether the prognosis in females is truly superior to that of males. Furthermore,

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