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Low anterior resection syndrome (LARS) in patients with epithelial ovarian cancer after primary debulking surgery

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HIGHLIGHTS

- LARS is a common and significant postoperative complication in ovarian cancer patients.
- The prevalence of major LARS - described to impair patient's quality of life - is almost 40%.
- LARS prevalence is stable irrespective of time interval between surgery and LARS evaluation.
- Multiple bowel anastomoses increase the risk for developing major LARS.

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ABSTRACT

Objective. To evaluate the prevalence of low anterior resection syndrome (LARS) in patients with debulking surgery for primary advanced epithelial ovarian cancer and to identify potential risk factors for development of LARS.

Methods. We reviewed data on 552 consecutive patients with primary epithelial ovarian cancer (EOC), who underwent upfront or interval cytoreductive surgery including low anterior resection at two different academic institutions (Kliniken-Essen-Mitte, Germany, and Medical University of Vienna, Austria). Intestinal dysfunction was assessed by the validated LARS-questionnaire via telephone call. We performed descriptive statistics and a binary logistic regression model to evaluate risk factors for LARS.

Results. In total, 341 patients were eligible and 206 (60.4%) were successfully contacted and provided complete information. Major LARS was observed in 78 (37.9%) patients, minor LARS in 44 (21.4%) patients, and no LARS in 84 (40.8%) patients. The prevalence rate of major LARS was not influenced by time interval between surgery and LARS assessment, type of cytoreductive surgery, and recurrent disease at the time of assessment. In multivariate analyses, number of anastomosis was independently associated with an increased risk for presence of major LARS (OR 3.76 [1.95–7.24]). In the present cohort, 25.2% patients had more than one bowel anastomosis.

Conclusions. LARS in general and major LARS in particular seem to be a frequent long-term complication after debulking surgery including low anterior resection in primary advanced EOC patients. Particularly EOC patients with more than one bowel anastomosis during surgery seem to be at an increased risk for major LARS.

1. Introduction

Epithelial ovarian cancer (EOC) accounts for 65,000 new diagnoses per year in Europe [1]. Lacking an efficient screening program, the majority of tumors are diagnosed in advanced stages [2]. Cytoreductive surgery aiming at complete tumor resection is an essential part of the

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treatment of EOC [3,4]. In order to achieve this surgical goal of no macroscopic residual disease, radical debulking surgery often includes both extensive upper abdominal surgery and bowel resections [5,6]. Anterior resection of the rectum, also known as low anterior resection, is frequently carried out in patients with advanced EOC and is sometimes accompanied by additional bowel resections [7]. Anastomotic leakage is the most significant short-term postoperative complication after bowel resection [7]. In contrast, low anterior resection syndrome (LARS) is a serious long-term complication observed in patients after low anterior resection [8,9]. LARS comprises a collection of intestinal dysfunction symptoms, such as diarrhea, fecal incontinence (gases or stool), increased bowel movements and frequencies of defecation, fecal urgency, constipation and incomplete emptying or accumulation of intestinal gases. Appearance, duration and severity of symptoms differ widely inter-individually [8,9].

Diagnosis of LARS is based on the LARS score, a validated questionnaire consisting of five questions and patients are classified in having "no LARS", "minor LARS" or "major LARS" (Table 1) [10–13]. Major LARS is reported to have a significant negative impact on patients' quality of life [12]. So far, evidence for LARS is exclusively based on studies for rectal cancer. In this group of patients, the prevalence of LARS is reported to range from 25 to 80% [8]. Neoadjuvant or adjuvant radiotherapy, postoperative chemotherapy, low anastomosis, total mesorectal excision, temporary colostomy and anastomotic complications have been discussed as potential risk factors for LARS in patients with rectal cancer [14–18].

Currently, no data on LARS in EOC patients is available. Thus, aim of the present study is to ascertain the prevalence and identify risk factors for LARS in EOC patients receiving upfront or interval debulking surgery including large bowel resection with low anterior resection.

2. Patients and methods

We reviewed all data on consecutive patients with primary EOC who underwent upfront or interval cytoreductive surgery at either the Medical University of Vienna (MUV; $n = 295$) or at the Kliniken Essen Mitte (KEM; $n = 919$) between 2011 and 2017 – in total 1214 patients. This exploratory analysis included only patients with primary advanced EOC and cytoreductive surgery including low anterior resection, no definite stoma, and no total colectomy were included ($n = 552$). Out of these, 190 (34.4%) patients were dead at the time of assessment and therefore not available for final analysis. As the present study was designed as a cross-sectional study, 341 (61.8%) patients (MUV = 72, KEM = 269) identified retrospectively from our tumor registries were prospectively contacted in March 2018 via telephone call to assess the LARS score. Finally, 206 (60.4%) patients (MUV = 46, KEM = 160) were successfully contacted, provided complete information regarding LARS, and were subsequently included in final analysis. The interview was conducted via telephone call by a standardized validated assessment comprising five question concerning symptoms of a potential LARS (Table 1). The LARS score is a validated score for postoperative long-term bowel complications after lower anterior bowel resection. The scoring system stratifies patients in three categories depending on the severity of bowel symptoms: 0–20 no LARS, 21–29 minor LARS, 30–42 major LARS [10]. Institutional review board approval was obtained from the Ethics Committee of the Medical University of Vienna (1201/2018).

Surgery in both institutions was performed by dedicated surgical teams specialized on gynaecologic oncology. Surgery had to be performed as primary debulking or interval debulking surgery and had to comprise low anterior bowel resection without terminal large bowel stoma. Typically, radical debulking surgery in the pelvis was performed as an "en-bloc resection" of uterus, bilateral salpingo-oophorectomy, low anterior bowel resection and removal of the whole pelvic peritoneum with end-end descendo-rectostomy. This "en-bloc resection" is performed as a nerve sparing procedure with preservation of the plexus hypogastricus inferior. Of note, "enhanced recovery after surgery" (ERAS), an evidence-based care improvement process for surgical patients was introduced in both institutions in October 2016. Patients received preoperative carbohydrate loading, perioperative antibiotic prophylaxis, early food uptake and early mobilisation on the first postoperative day [19]. Platinum based combination chemotherapy, mainly carboplatin and paclitaxel, with or without Bevacizumab was recommended stage adapted for neoadjuvant or adjuvant treatment [20].

Descriptive statistics such as mean, median, frequencies, and percentages were used to present patients' characteristics: prevalence (%) for categorical variables; median/range for metric variables without normal distribution; mean (standard deviation = SD) for metric variables with normal distribution. For univariate and multivariate analyses, LARS score was categorized according to a two-tier model with "no or minor LARS" and "major LARS". Univariate analyses were performed by chi-square tests providing odds ratios (OR) and 95% confidence intervals (95% CI). Binary logistic regression was used to calculate a multivariate model to identify risk factors for major LARS. Statistical analysis was performed using SPSS version 20.0 (IBM Corporation, New York, USA).

Table 1
Assessment form and interpretation for the low anterior resection (LARS) score.

Do you ever have occasions when you cannot control your flatus (wind)?	
☐ No, never	0
☐ Yes, less than once per week	4
☐ Yes, at least once per week	7
Do you ever have any accidental leakage of liquid stool?	
☐ No, never	0
☐ Yes, less than once per week	3
☐ Yes, at least once per week	3
How often do you open your bowels?	
☐ >7 times per day (24 h)	4
☐ 4–7 times per day (24 h)	2
☐ 1–3 times per day (24 h)	0
☐ Less than once per day (24 h)	5
Do you ever have to open your bowels again within one hour of the last bowel opening?	
☐ No, never	0
☐ Yes, less than once per week	9
☐ Yes, at least once per week	11
Do you ever have such strong urge to open your bowels that you have to rush to the toilet?	
☐ No, never	0
☐ Yes, less than once per week	11
☐ Yes, at least once per week	16
Total score:	
Interpretation:	
0–20:	**No LARS**
21–29:	**Minor LARS**
30–42:	**Major LARS**

3. Results

In the present study, 206 patients with primary advanced EOC and bowel resection containing at least a low anterior resection were included. Forty-six (22.3%) and 160 (77.7%) patients were enrolled at the Department of Gynecology and Gynecological Oncology at the Medical University of Vienna and Kliniken Essen Mitte, respectively. Patient's characteristics are shown in Table 2. One patient reported intestinal symptoms prior to oncological treatment due to her diagnosis of ulcerative colitis. Within this cohort, 175 (85.0%) patients had undergone primary debulking surgery and 31 (15.0%) patients had received neoadjuvant chemotherapy followed by interval debulking surgery. Overall, 164 (79.6%) patients had no macroscopic residual disease at the end of cytoreductive surgery. In addition to low anterior resection, 21.8% of patients had an additional resection of the large bowel, and

Table 2
Patients' characteristics of women with low anterior rectum resection at the time of debulking surgery for primary advanced epithelial ovarian cancer.

Variable	n (%)
N	206 (100%)
Age (yrs)	59 (11.9)[a]
Charlson Index	2 (1.8)[a]
ASA	
I	21 (10.2%)
II	156 (75.7%)
III	29 (14.1%)
ECOG	
0	197 (95.6%)
1	9 (4.4%)
BMI (kg/m^2)	24 (4.7)[a]
Albumin serum level	43.2 (5.7)[a]
Ascites	
≤500 ml	139 (67.5%)
>500 ml	67 (32.5%)
Tumor stage	
FIGO III	115 (55.8%)
FIGO IV	91 (44.2%)
Type of surgery	
PDS	175 (85.0%)
IDS	31 (15.0%)
Type of bowel surgery	
Low anterior resection (LAR) only	151 (73.3%)
LAR + large bowel	45 (21.8%)
LAR + small bowel	10 (4.9%)
Number of anastomosis	
1	154 (74.8%)
>1	52 (25.2%)
SCS	
≤11	128 (62.1%)
>11	78 (37.9%)
Residual disease	
Yes	42 (20.4%)
No	164 (79.6%)
Recurrence	
Yes	73 (35.4%)
No	133 (64.6%)
History of IBD	1 (0.5%)
LARS	
no LARS	84 (40.8%)
minor LARS	44 (21.4%)
major LARS	78 (37.9%)

ASA: American Society of Anesthesiologists Classification, ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, FIGO: Fédération Internationale de Gynécologie et d' Obstétrique, SCS: Surgical complexity score, PDS: primary debulking surgery; IDS: interval debulking surgery, IBD: Inflammatory Bowel Disease, LARS: Low Anterior Resection Syndrome.
[a] Mean (standard deviation).

4.9% an additional resection of the small bowel. The majority of patients had a single anastomosis ($n = 154$, 74.8%), 47 patients (22.8%) had two anastomosis, and five patients (2.4%) had three anastomosis. Seventy-three (35.4%) patients experienced disease recurrence before the assessment of LARS.

With respect to LARS, 78 (37.9%) patients had significant postoperative bowel problems resulting in a major LARS, 44 (21.4%) patients developed a minor LARS, and 84 (40.8%) patients had no long-term side effects after low anterior resection. We further aimed to describe major LARS in more detail and identify potential limitations in our cohort. The time interval between debulking surgery for primary advanced EOC and LARS assessment could potentially influence the prevalence of major LARS. In the present study, median time between surgery and assessment of LARS was 26 (2–84) months. After stratification for time interval between surgery and LARS assessment (<12 months vs 12-24 months vs 24-36 months vs 36-48 months vs >48 months) prevalence rates for major LARS ranged between 34.1% and 48.3% and no difference between time interval groups was observed (Fig. 1; $p = 0.29$). In addition, the prevalence of LARS was neither influenced by timing of cytoreductive surgery (primary debulking surgery vs. interval debulking surgery) nor did occurrence of recurrence disease show a significant impact ($p = 0.24$). Moreover, the introduction of another potential confounder, namely the initiation of the ERAS program did not influence the prevalence of major LARS significantly (before ERAS start 40.7% major LARS; after ERAS start 34.4% major LARS; $p = 0.38$). Presence of anastomotic leakage after cytoreductive surgery was also not associated with the prevalence of major LARS ($p = 0.55$). However, only five patients with anastomotic leakage were included in final analysis, as anastomotic leakage occurred only in 2.4% of patients in the present study cohort.

A major aim of the present study was to identify potential risk factors for the development of major LARS (Table 3). Patient's age and number of anastomosis were identified as a potential risk factor for major LARS in univariate analysis. Patient's age > 65 years was associated with a 54% risk reduction for major LARS (OR 0.46 [0.24–0.88]). Patients with more than one bowel anastomosis were almost four times more likely to develop major LARS (OR 3.76 [1.95–7.24]). In multivariate analyses, only number of anastomosis remained to be identified as an independent risk factor for major LARS (Table 4). Patients with more than one bowel anastomosis had a fourfold higher risk for major LARS compared to patients with one bowel anastomosis (HR 4.2 [1.97–8.96], $p = 0.005$). In multivariate analysis, following parameters were not associated with a higher risk for developing major LARS: patient's age > 65 years, Charlson Comorbidity Index ≥3, advanced tumor stage (FIGO IV), residual tumor after cytoreductive surgery, surgery complexity score > 11, timepoint of surgery after the introduction of the ERAS care program, and occurrence of anastomotic leakage.

4. Discussion

The present study is the first to evaluate the prevalence of LARS in patients with primary advanced ovarian cancer undergoing debulking surgery with low anterior resection. Major LARS was observed in 37.9% and minor LARS in 21.4% of the patients. Only 40.8% of patients had no long-term side effects after low anterior resection. Additionally, presence of multiple bowel anastomosis was ascertained as an independent risk factor for major LARS leading to an almost fourfold increased risk for the presence of major LARS.

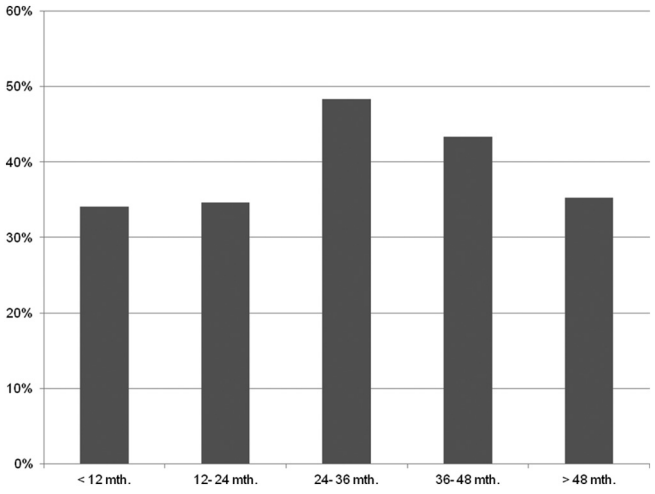

Fig. 1. Prevalence of major LARS (low anterior resection syndrome) broken down by time interval between debulking surgery for primary advanced epithelial ovarian cancer patients.

Table 3
Risk factors for minor and major low anterior resection syndrome (LARS) in patients with bowel resection at the time of primary debulking surgery for advanced epithelial ovarian cancer.

Variable	No or minor LARS n (%)	Major LARS n (%)	OR (95% CI)	P
N	128 (62.1)	78 (37.9)		
Age (yrs)			0.46 (0.24–0.88)	**0.02**
≤ 65	82 (56.9)	62 (43.1)		
> 65	46 (74.2)	16 (25.8)		
ERAS				
yes	61 (65.6)	32 (34.4)	0.76 (0.43–1.35)	0.38
No	67 (59.3)	46 (40.7)		
Charlson Index			0.66 (0.37–1.17)	0.2
≥3	64 (67.4)	31 (32.6)		
<3	64 (57.7)	47 (42.3)		
ECOG			0.45 (0.09–2.25)	0.48
0	121 (61.4)	76 (38.6)		
≥1	7 (77.8)	2 (22.2)		
BMI (kg/m^2)			1.19 (0.67–2.1)	0.56
≥25	53 (58.9)	37 (41.1)		
<25	70 (63.1)	41 (36.9)		
NACT			1.43 (0.66–3.09)	0.42
no	111 (63.4)	64 (36.6)		
yes	17 (54.8)	14 (45.2)		
Tumor stage			1.30 (0.74–2.3)	0.39
FIGO III	74 (65.5)	39 (34.5)		
FIGO IV	54 (59.3)	37 (40.7)		
No. of anastomosis			3.76 (1.95–7.24)	**0.001**
1	108 (70.1)	46 (29.9)		
≥1	20 (38.5)	32 (61.5)		
SCS			1.60 (0.90–2.87)	0.14
≤11	85 (66.4)	43 (33.6)		
>11	43 (55.1)	35 (44.9)		
Residual disease			0.89 (0.44–1.8)	0.86
0	101 (61.6)	63 (38.4)		
>0	27 (64.3)	15 (35.7)		
Anastomotic leakage				
Yes	2 (40.0)	3 (60.0)	2.52 (0.41–15.43)	0.37
No	126 (62.7)	75 (37.3)		
Recurrent disease			1.16 (0.64–2.09)	0.65
yes	47 (64.4)	26 (35.6)		
no	81 (60.9)	52 (39.1)		

ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, NACT: neoadjuvant chemotherapy, FIGO: Fédération Internationale de Gynécologie et d' Obstétrique, SCS: Surgical complexity score, OR (95% CI): Odds Ratio (95% Confidence Interval).

LARS is a term introduced by colorectal surgery to describe intestinal symptoms after low anterior resection. Based on data for LARS in rectal cancer, a clinically relevant prevalence of LARS in ovarian cancer had to be expected and could be demonstrated in the present study. In patients with rectal cancer the prevalence of major LARS has been described to vary between 25 and 80% [8]. However, the therapy approaches for patients with EOC and rectal cancer differ in terms of type of surgery and adjuvant or neoadjuvant treatment. In contrast to rectal cancer, "en-bloc resection" of female organs, including the pelvic peritoneum and rectosigmoid is performed in debulking surgery for ovarian cancer [21]. Therefore, it was not possible to simply extrapolate from previous studies in rectal cancer for our group of advanced EOC patients.

LARS does not only occur after debulking surgery. A recent Danish cross-sectional study investigated the prevalence of LARS in Danish women between 50 and 79 years. This group of women was randomly picked out of nationwide database without selection for diseases, comorbidities and medications. They observed a prevalence of 18.8% of major LARS in this group of women [22]. This allows to put our data into perspective. In comparison to this "baseline risk" of LARS in women between 50 and 79 years, patients in our study had a twofold risk for LARS after debulking surgery including bowel surgery for primary advanced EOC. The latter might be useful for counselling patients with planned debulking surgery. Interestingly, we found no difference with respect to upfront or interval debulking.

Another aim of this study was to identify potential risk factors for developing LARS in patients with EOC. Only more than one large bowel anastomosis could be identified as independent risk factor for LARS in our multivariate regression model. Multiple bowel anastomosis led to an almost fourfold higher risk for developing major LARS. Although confirming research data is lacking, this seems clinically quite plausible: a shortened large bowel caused by multiple bowel anastomosis might lead to a more liquid stool texture and in combination with a hyperactive postprandial response after low anterior resection could promote symptoms of the LARS- complex. In univariate analysis, younger patients had an increased risk for major LARS. Patients 65 years of age or older had a 54% risk reduction for major LARS. This finding is in line with other studies for LARS in rectal cancer [16,23,24] and could be explained by the increased risk for constipation in elderly people. The colonic dysmotility could be protective for major LARS [24,25]. In rectal cancer studies multiple factors have been shown to worsen intestinal function after low anterior resection, such as low anastomosis, radio- or chemotherapy, different types of reconstruction, anastomotic leakage, etc. [14–18] Nonetheless, patient's age was not confirmed as an independent risk factor for major LARS in multivariate regression analysis.

The prevalence of major LARS is particularly interesting, because it has a potential negative effect on quality of life [26]. Creating awareness for LARS in the group of clinicians operating on women with advanced EOC and taking care of them postoperatively might help to develop strategies to ameliorate this specific sequela. In oncological follow-up care, patients tend to underreport intestinal symptoms and doctors may not evaluate intestinal symptoms adequately. The main focus of gynecologic oncologist is the detection of tumor recurrence [27], however, evaluation of LARS according to the LARS score is easily applicable in clinical routine and takes just a few minutes. Once physicians in gynecologic oncology are aware of LARS and familiar with its assessment, evaluation, treatment, and ultimately improvement of patient's quality of life should be fairly simple.

Given the high prevalence of LARS after low anterior resection and the implication on patient's quality of life, the literature for preventive strategies and therapeutic options for LARS is very limited [15,28–30]. Based on data existing for patients with rectal cancer, preventive strategies include the avoidance of very low anastomosis close to the anal verge, total mesorectal excision, temporary colostomy and/or anastomotic complications [15]. Further data on ovarian cancer patients have to be awaited. Potential therapeutic options for patients diagnosed with LARS comprise medical treatment options (e.g. Loperamide Hydrochlorid, 5-HT$_3$ antagonists), local supportive strategies (e.g. transanal irrigation, pelvic floor rehabilitation), as well as surgical treatment options (e.g. sacral nerve stimulation) [28–30]. Of note, all of these modalities are based on individual physician's and patient's preference and severity of symptoms as none of these treatments has been evaluated in high-quality prospective studies.

Table 4
Multivariate binary logistic regression model to identify independent predictive factors for major low anterior resection syndrome (LARS) in patients with bowel resection at the time of debulking surgery for primary advanced epithelial ovarian cancer.

Variable	HR (95% CI)	P
Patient's age (decades)	0.96 (0.66–1.39)	0.83
Charlson Comorbidity Index (<3 vs. ≥3)	0.71 (0.32–1.54)	0.39
Tumor stage (FIGO ≤3 vs. FIGO IV)	1.14 (0.61–2.17)	0.68
Number of anastomosis (1 vs. ≥1)	4.2 (1.97–8.96)	**0.005**
Residual disease (0 vs. >0)	0.96 (0.78–1.73)	0.69
Surgical complexity score (≤11 vs. >11)	0.86 (0.41–1.81)	0.69

FIGO: Fédération Internationale de Gynécologie et d'Obstétrique, HR (95% CI): Hazard Ratio (95% Confidence Interval)

The present study has some limitations. Due to the retrospective cross-sectional study design LARS-scores are evaluated at different time intervals after surgery. This might cause a certain reporting and selection bias potentially influencing the observed LARS prevalence and severity rates. Nonetheless, in the present analysis we do not observe a signal, that prevalence of major LARS is changing because of different time intervals between date of surgery and assessment. Additionally, a recent study in rectal cancer patients demonstrates, that severity of LARS might vary within the first 12 months after surgery but thereafter persists on a constant level [24,31]. We are also not able to provide individual changes of LARS over time per patient to further evaluate the influence of each oncologic treatment modality (e.g. chemotherapy, bevacizumab) on LARS. In studies for rectal cancer patient's height of anastomosis is described to be a risk factor for developing LARS [28]. Due to the retrospective analysis, we are not able to evaluate this risk factor in our cohort adequately. Moreover, we were not able to directly assess "amount of colon removed", but indirectly ascertained it by number of large bowel anastomosis and type of large bowel resection. Number of large bowel anastomosis, i.e., a surrogate for a large amount of colon removed, was identified as the only independent risk factor for major LARS. Nonetheless, this is the first study to address this clinically relevant question in a very large cohort of patients retrieved from prospectively maintained databases of two high-volume gynecologic oncology centers and more studies should further elucidate this field.

To conclude, the prevalence of major LARS in patients with primary advanced EOC undergoing low anterior resection at time of debulking surgery was almost 40%. In indirect comparison with a nationwide Danish cross-sectional study this would translate into a twofold risk of major LARS after debulking surgery including low anterior resection. Multiple bowel anastomosis seems to almost quadruple the risk for major LARS. The rate of postoperative major LARS is particularly interesting, as major LARS has been described to significantly deteriorate quality of life in rectal cancer [26]. In comparison to other significant postoperative complications after bowel surgery, i.e. anastomotic leakage, LARS is not well studied in EOC patients. Therefore, education of gynecologic oncologist resulting in an increased awareness for LARS in EOC is of high clinical relevance. A prospective study evaluating LARS in the studied cohort including preoperative defecation problems and urinary incontinence is currently in development.

Author contribution

MK performed telephone calls, performed data retrieval, statistical analysis, wrote manuscript draft, revised final manuscript.

BA co-designed study, performed telephone calls, performed data retrieval, co-wrote manuscript draft, revised final manuscript.

CG designed study, coordinated study, statistical analysis, co-wrote manuscript draft, revised final manuscript.

SS co-designed study, performed telephone calls, performed data retrieval, revised final manuscript.

SR co-designed study, performed data retrieval, revised final manuscript.

PA co-designed study, performed data retrieval, revised final manuscript.

SP performed telephone calls, performed data retrieval, revised final manuscript.

MKW co-designed study, performed data retrieval, revised final manuscript.

FH co-designed study, performed data retrieval, revised final manuscript.

AS co-designed study, performed data retrieval, revised final manuscript.

FH co-designed study, performed data retrieval, revised final manuscript.

AR co-designed study, statistical analysis, revised final manuscript.

SP co-designed study, performed data retrieval, statistical analysis, revised final manuscript.

PH co-designed study, data monitoring, revised final manuscript.

AdB co-designed study, data monitoring, statistical analysis, co-wrote manuscript draft, revised final manuscript.

Declaration of Competing Interest

MK received non-financial support (e.g. travel grant) from Roche and PharmaMar.

BA received honoraria (e.g. lectures, advisory boards) from Roche, Amgen, Astra Zeneca, Tesaro, Clovis, Celgene, and non-financial support (e.g. travel grant) from Roche, PharmaMar, Tesaro outside the submitted work.

CG received honoraria for consultation from AstraZeneca, Celgene, MSD, PharmaMar, Roche, Tesaro, Vifor Pharma; honoraria as a speaker from Amgen, AstraZeneca, MSD, PharmaMar, Roche, Tesaro; direct research funding from Meda Pharma and Roche Diagnostics.

SS received honoraria from Astra Zeneca, Roche and Tesaro.

SR received honoraria from Medtronic and Takeda.

PA has nothing to disclose.

SP has nothing to disclose.

MKW has nothing to disclose.

FH has nothing to disclose.

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