Gynecologic Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

OVPSYCH2: A randomized controlled trial of psychological support versus standard of care following chemotherapy for ovarian cancer

E. Frangou [a,b], G. Bertelli [c], S. Love [a,b], M.J. Mackean [d], R.M. Glasspool [e], C. Fotopoulou [f], A. Cook [g], S. Nicum [h], R. Lord [i], M. Ferguson [j], R.L. Roux [h], M. Martinez [f], C. Butcher [k], N. Hulbert-Williams [l], L. Howells [m], S.P. Blagden [h,*]

[a] Centre for Statistics and Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[b] MRC Clinical Trials Unit at UCL, London, UK
[c] Sussex Cancer Centre, Brighton, UK
[d] Edinburgh Cancer Centre Western General Hospital, Edinburgh, UK
[e] Beatson West of Scotland Cancer Centre, Glasgow, UK
[f] Ovarian Cancer Action Research Centre, Hammersmith Hospital, Imperial College London, London, UK
[g] Gloucester Oncology Centre, Cheltenham, UK
[h] Churchill Hospital, University of Oxford, Oxford, UK
[i] Clatterbridge Cancer Centre, Wirral, UK
[j] Ninewells Hospital, Dundee, UK
[k] Oncology Clinical Trials Office (OCTO), University of Oxford, Oxford, UK
[l] School of Psychology, University of Chester, UK
[m] Research Team, Maggie's Centres, London, UK

HIGHLIGHTS

- After chemotherapy, most ovarian cancer patients depression symptoms.
- Most have significant fear of progression.
- While depression symptoms improve rapidly, fear of progression worsens.
- Fear of progression responds to cognitive behavioural therapy-based support.
- Routine and regular psychological support should be offered post chemotherapy.

ARTICLE INFO

Article history:
Received 21 January 2021
Accepted 22 May 2021
Available online xxxx

Keywords:
Ovarian cancer
Quality of life
Clinical trial
Fear of relapse
Fear of progression

ABSTRACT

Background. Fear of disease progression (FOP) is a rational concern for women with Ovarian Cancer (OC) and depression is also common. To date there have been no randomized trials assessing the impact of psychological intervention on depression and FOP in this patient group.

Patients and methods. Patients with primary or recurrent OC who had recently completed chemotherapy were eligible if they scored between 5 and 19 on the PHQ-9 depression and were randomized 1:1 to Intervention (3 standardized CBT-based sessions in the 6–12 weeks post-chemotherapy) or Control (standard of care). PHQ-9, FOP-Q-SF, EORTC QLQ C30 and OV28 questionnaires were then completed every 3 months for up to 2 years. The primary endpoint was change in PHQ-9 at 3 months. Secondary endpoints were change in other scores at 3 months and all scores at later timepoints.

Results. 182 patients registered; 107 were randomized; 54 to Intervention and 53 to Control; mean age 59 years; 75 (70%) had completed chemotherapy for primary and 32 (30%) for relapsed OC and 67 patients completed both baseline and 3-month questionnaires. Improvement in PHQ-9 was observed for patients in both study arms at three months compared to baseline but there was no significant difference in change between Intervention and Control. A significant improvement on FOP-Q-SF scores was seen in the Intervention arm, whereas for those in the Control arm FOP-Q-SF scores deteriorated at 3 months (intervention effect = −4.4 (−7.57, −1.22), *p*-value = 0.008).

* Corresponding author at: Department of Oncology, Churchill Hospital, University of Oxford, Oxford, UK.
E-mail address: sarah.blagden@oncology.ox.ac.uk (S.P. Blagden).

https://doi.org/10.1016/j.ygyno.2021.05.024

Conclusions. CBT-based psychological support provided after chemotherapy did not significantly alter the spontaneously improving trajectory of depression scores at three months but caused a significant improvement in FOP. Our findings call for the routine implementation of FOP support for ovarian cancer patients.

1. Background

Despite studies demonstrating significant psychological distress in ovarian cancer (OC) patients, many UK centres do not routinely provide post-treatment psychological support [1,2]. This is predominantly due to financial constraints as well as a lack of robust (randomized) evidential research to identify the interventions that confer greatest survivorship benefit. Further evidence is needed, for example, to clarify whether support should be focused on depression, anxiety or fear of relapse, and of which underlying psychological models should be chosen to inform intervention content [3,4]. Unfortunately, the low prioritization of survivorship research makes randomized studies challenging to conduct in this subject area [5]. Having previously identified a high level of self-reported depression in OC patients [6], we decided to prospectively evaluate a Cognitive Behavioural Therapy (CBT)-based survivorship intervention first in a pilot study (OVPSYCH) to define the research questions, trial methodology and intervention [7] followed by a randomized study (OVPSYCH2) conducted across multiple UK centres. Our decision to pursue CBT as the underlying therapeutic framework was based upon promising findings from small-scale trials [8] and subsequently reinforced by other positive studies using CBT in similar patient groups [9]. The overarching aim of OVPSYCH2 was to assess the impact of three CBT-based sessions on the wellbeing of patients with mild, moderate or moderately-severe depression delivered within 3 months of completing chemotherapy for primary or relapsed OC. Those in the control arm received no intervention unless it was specifically requested, as was standard-of-care in these centres at the time. The primary endpoint was change in PHQ-9 depression score at 3 months following randomization compared to baseline. Secondary endpoints assessed the impact of the intervention on other Quality of Life (QOL) scores measured at follow-up visits for up to 24 months. Importantly, having found in our pilot study that patients had low levels of generalised anxiety but specific worries and concerns around fear of relapse (also known as Fear of Progression, FOP), we included assessment of FOP using the FOP-Q-SF questionnaire in addition to the other questionnaires.

2. Patients and methods

Women ≥18 years of age with a diagnosis of primary or relapsed epithelial ovarian, peritoneal or fallopian tube cancer (collectively termed "ovarian cancer" or OC) were eligible for OVPSYCH2. Other inclusion criteria included a life expectancy of at least 12 weeks, Eastern Cooperative Oncology Group (ECOG) performance status 0–3 and the ability to independently consent and complete written questionnaires. Patients were required to have completed chemotherapy within 6 weeks of registration; those receiving maintenance targeted therapies (such as bevacizumab or olaparib) following chemotherapy were also eligible. Patients with evidence of intercurrent illness, actively recurring OC or currently receiving psychological counselling or therapy at the time of enrolment were excluded. All patients provided written informed consent. The study protocol was reviewed and approved by the Westminster Research Ethics Committee (REC number 13/LO/1375). The protocol was approved by Institutional Review Boards within each Centre. The study was performed in accordance with Good Clinical Practice guidelines and the principles of the 1964 Declaration of Helsinki.

2.1. Study design

This prospective, randomized controlled trial was conducted at ten UK Cancer Centres (Cheltenham, Dundee, Edinburgh, Glasgow, Kings Mill, Liverpool, London (Hammersmith), Nottingham, Oxford and Swansea) and their associated Maggie's Centres. Patients were given information about OVPSYCH2 by research staff during their penultimate or final cycle of chemotherapy for primary or relapsed OC. They were subsequently invited to consent at their first post-chemotherapy follow-up appointment (usually 3 weeks later). Once they had consented, patients completed a baseline PHQ-9 depression questionnaire to screen them for eligibility; paper questionnaires were used for this and subsequent visits and were collected by research staff. Those scoring 5–19 (indicating mild, moderate or moderately severe depression) on their PHQ-9 score were randomized 1:1 to either intervention or standard of care (no intervention). Those randomized to intervention received it at their local Maggie's Centre. Patients were not paid to participate but travel expenses were refunded on request. The primary study objective was to assess the short-term impact of the psychological intervention on depression by comparing change in mean PHQ-9 scores from baseline to 3-month follow-up between the two arms. Secondary endpoints were change in mean PHQ-9 scores at 6, 12, 15, 18 and 24 months and other QOL measures using the FOP-Q-SF, EORTC-OV28 and C30 questionnaires at 3, 6, 12, 15, 18 and 24 months compared to baseline. The study design is summarised in Fig. 1.

2.1.1. Randomization

Patients were allocated 1:1 to either the standard of care or intervention arm through stratified block randomized assignment. Randomization for all sites was conducted blind by the trial co-ordination team at Hammersmith Hospital. The stratification factors were OC (primary, relapsed) and PHQ-9 at baseline (mild, moderate or moderately-severe). The PHQ-9 score ranges from 0 to 27 and correlate with levels of depression; scores 0–4 with normal, 5–9 with mild depression, 10–14 moderate depression, 15–19 moderate severe depression and scores >20 signifying severe depression [10]. Patients with scores ≥20 on the baseline PHQ-9 questionnaire were excluded from randomization and referred for immediate psychological or psychiatric intervention. Patients without depression, defined as a baseline score of 0–4, were also excluded from randomization as they were considered unlikely to benefit from the psychological intervention.

2.1.2. Sample size

Initial calculations indicated that a sample size of 63 women per treatment arm (total $N = 126$ participants) was required to detect a between-group difference of 3 in mean PHQ-9 scores from baseline to three-month follow-up, assuming a pooled standard deviation of 6, based on a two-sided 5% significance and with at least 80% power. However, following data published by Hinz et al., [11] the sample size calculations and standard deviation in the control arm was updated to 4.27 whilst the standard deviation (SD) in the treatment arm was set at 6. A sample size of at least 49 women per treatment arm (total of 98 participants) was then required to detect a between-group difference of 3 points in PHQ-9 scores from baseline to month 3, based on a two-sided 5% significance and with at least 80% power.

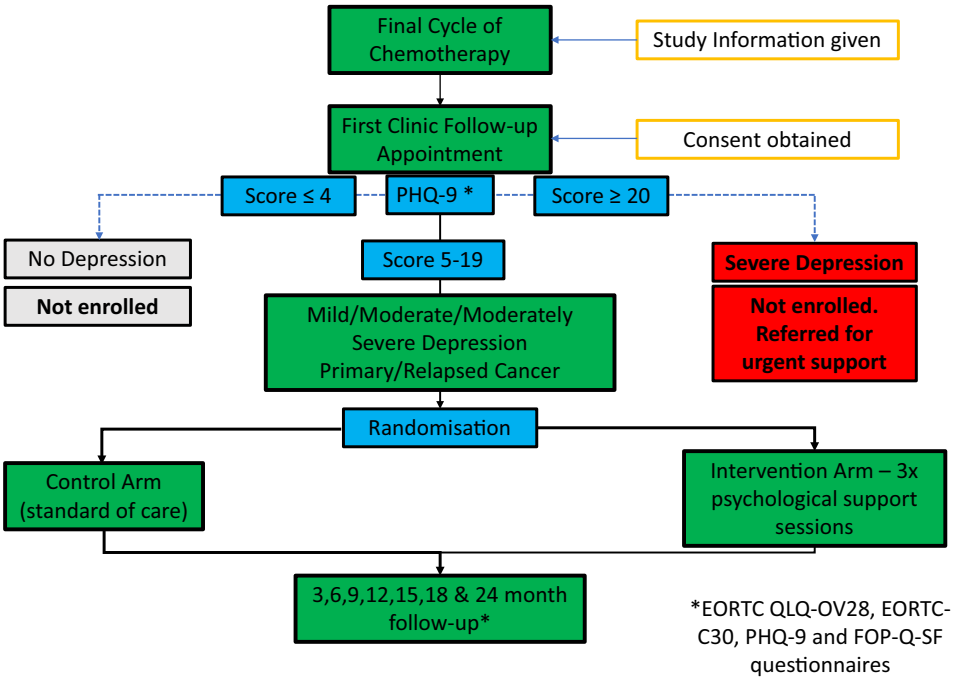


Fig. 1. Study Schema. A flow diagram of the OVPSYCH2 study.

2.1.3. Study procedures

In addition to PHQ-9 score, patients were asked to complete three other QOL questionnaires: 1) the Short-form Fear of Progression Scale (FOP-Q-SF) [12], 2) the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 [13] and 3) the EORTC Ovarian Cancer-specific (EORTC-QLQ-OV28) questionnaire [14]. The four questionnaires were given to patients at baseline and at 3, 6, 12, 15, 18 and 24-month follow up visits. The decision to screen and stratify by PHQ-9 score came from the pilot study in which patients were screened using both PHQ-9 and the Generalised Anxiety Disorder (GAD-7) questionnaires. Both were developed by psychiatrists as sensitive and reliable tools for detecting depression and anxiety respectively. We found that most patients with mild, moderate, or moderately-severe depression, corresponding to a PHQ-9 score ≥ 4 also had positive GAD-7 scores, but none had positive GAD-7 and negative PHQ-9 measures [7]. We concluded that the PHQ-9 was a better stratifier of emotional distress than GAD-7 in this patient group.

The 12-item FOP-Q-SF Fear of Progression Questionnaire is a shorter form of the original 43-item Fear of Progression Questionnaire [12]. Items are scored on a five-point Likert scale, ranging from 1 ("never") to 5 ("very often") and the score has been validated in clinical studies of patients with cancer and other chronic diseases [12,15,16]. Scores range from 12 to 60 with 34 or above indicating a dysfunctional level of FOP. Change of at least 3.1 mean score points has previously been validated as being clinically significant in a cancer study [16].

Those randomized to the intervention group received CBT-based support (the OVPSYCH intervention) during a 3-month period between first and subsequent follow-up appointments. Those allocated to the control group received standard supportive care but did not attend OVPSYCH intervention sessions. Additional psychological support was given to all patients who requested it or if it was deemed clinically necessary, regardless of their randomization status or PHQ-9 score.

At each visit, the study team recorded if participants had started anti-depressant, anxiolytic or antipsychotic medication, or had received additional counselling or psychological therapy from another source since their previous visit. An event reporting system was used to record any hospital admissions or adverse events that arose and could have been study related. The study was open to recruitment between November 2013 and January 2018.

2.1.4. Study intervention

The OVPSYCH psychological intervention consisted of three 90-min face to face sessions delivered 1:1 by a doctoral-level clinical or counselling psychologist at the patient's nearest Maggie's Centre using validated psychological techniques [2,4]. The sessions primarily incorporated Cognitive Behavioural Therapy (CBT) which is currently the gold-standard intervention for cancer-related distress [4], as well as elements of both mindfulness and Acceptance and Commitment Therapy (ACT) which have established acceptability in this patient group [17]. To ensure consistency and reproducibility across the centres, psychologists were provided with a manual outlining the standardized session content. The content was designed to be broad, encourage resilience, facilitate the development of coping strategies and the management of cancer-related emotional distress. Patients were encouraged to describe their experiences and feelings and were given the opportunity to shape the agenda of the meetings around particular topics (such as insomnia, living with uncertainty or worries of burdening their families). They were taught models of distress and how to manage strong moods like anxiety, FOP, stress, depression and anger. The program concluded by focusing on broader wellbeing issues identified as important such as sex, relationships, diet and managing day-to-day life. Where possible, sessions were scheduled fortnightly to allow time for tailored 'homework' exercises such as adopting specific coping skills.

2.2. Data collection and study outcomes

2.2.1. Statistical analysis

A final statistical analysis plan was approved prior to any analyses being performed. Patient characteristics as well as baseline and follow-up QOL scores were presented using means (standard deviation) for continuous variables and frequencies (percentage) for categorical variables.

The primary analysis was based on the modified intention to treat population. All available data contributed to the analysis; no data imputation was performed. This consisted of all patients who completed the

PHQ-9 both at baseline and month 3, irrespective of completing some or all of the study interventions. The primary outcome of mean change in PHQ-9 scores from baseline to 3 months, between treatment groups, was analysed using analysis of covariance (ANCOVA). The regression model used the PHQ-9 score at month 3 as the dependent variable while the independent variables comprised of the PHQ-9 score at baseline, age, stratification factors (primary/relapsed EOC and depression category) and treatment arm. Any departure from normality was assessed visually and via the Shapiro–Wilk test. Results were presented as regression coefficients with 95% confidence intervals and associated *p*-values. The analysis of the secondary outcomes at three months followed the same procedure as for the primary outcome. Each subscale of the QLQ-OV28 and QLQ-C30 was analysed and reported separately. Mean scores, along with associated standard deviations, were reported for all questionnaires across the different time points. Multilevel mixed-effects linear regression models were fitted to the available data of each outcome, to explore change trajectories beyond 3 months. The fixed effects part of each model included the same variables as in the primary analysis; participant number was the random effect. Treatment effect alongside the corresponding 95% C.I. and *p*-value are reported.

3. Results

A total of 182 patients were enrolled into the study of whom 75 were excluded, 73 with PHQ-9 < 4 and 2 with PHQ-9 > 20 (see CONSORT diagram Fig. 2). The remaining 107 patients had PHQ-9 scores between 5 and 20 and a mean score of 10.2 (SD = 4.3) indicating moderate depression. Patients were randomized, 54 to intervention and 53 to control. Of note, two patients were randomized in error with PHQ-9 score > 20, one to each arm, and remained in the study. Table 1 summarises baseline patient characteristics that were well-balanced between the two arms. Stage at original diagnosis was collected retrospectively from medical records and returned in 82% of the randomized patients and was also well-balanced. Questionnaire completion was good at baseline (between 80% and 95% completion across the different questionnaires) and month 3 (between 76% and 97% across questionnaires) but deteriorated during the study as patients either developed recurrent/progressive disease, or withdrew. Twenty-two withdrawals occurred, 12 from the control arm and 10 from the intervention arm but the data from withdrawers was included in the analysis. Reasons for withdrawing from trial was recorded for 13 (59%) patients and varied from switching

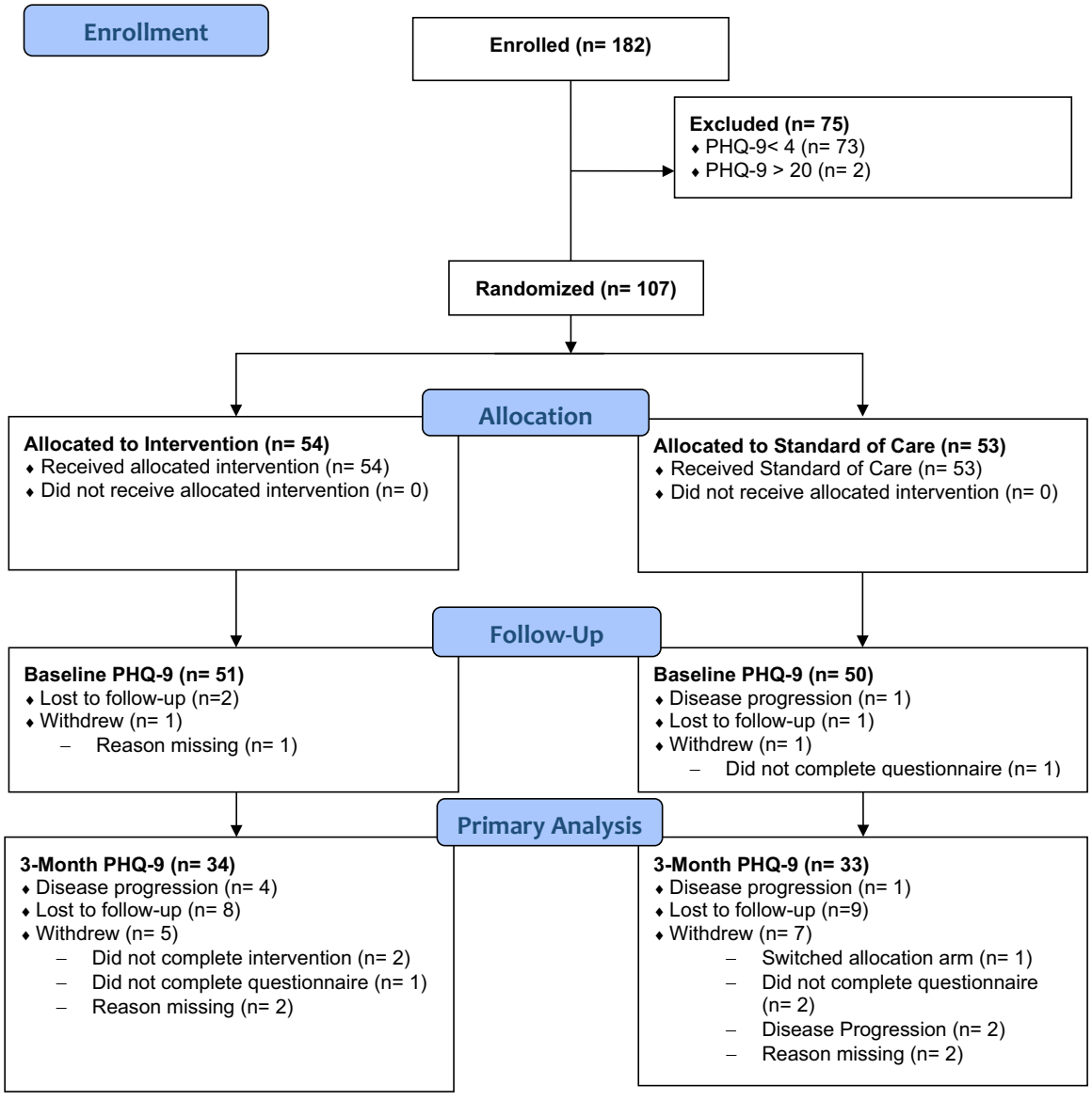


Fig. 2. Consort Flow Chart showing numbers enrolled, randomized and follow-up during OVPSYCH2.

Table 1
Characteristics of patients enrolled into OVPSYCH2.

Variable at Baseline	Standard of Care (Control) $N = 53$	Intervention $N = 54$	Total $N = 107$
Age, Mean (SD)	**60.9 (10.2)**	**58.1 (9.46)**	**59.5 (9.88)**
PHQ9, Mean (SD)	**10.4 (4.25)**	**9.98 (4.4)**	**10.2 (4.31)**
PHQ9 categories			
Minimal/Normal[a]	0	1 (2%)	1 (1%)
Mild	25 (47%)	24 (44%)	49 (46%)
Moderate/Moderately Severe	24 (45%)	25 (46%)	49 (46%)
Severe[a]	1 (2%)	1 (2%)	2 (2%)
Missing	3 (6%)	3 (6%)	6 (6%)
Stage at diagnosis			
I	8 (15%)	12 (22%)	20 (19%)
II	0	3 (6%)	3 (3%)
III	20 (38%)	22 (41%)	44 (40%)
IV	11 (21%)	10 (19%)	21 (20%)
Missing	14 (26%)	7 (13%)	19 (18%)
Primary/relapsed EOC			
Primary	37 (70%)	38 (70%)	75 (70%)
Relapsed	16 (30%)	16 (30%)	32 (30%)
Maintenance therapy			
No	32 (60%)	34 (63%)	66 (62%)
Yes	2 (4%)	2 (4%)	4 (4%)
Missing	19 (36%)	18 (33%)	37 (35%)

[a] These patients were randomized in error to the study despite having PHQ-9 scores of <4 or >20.

to active intervention ($n = 1$), non-completion of intervention ($n = 3$) and non-completion of follow-up questionnaires ($n = 9$).

3.1. Additional treatments and adverse events

Amongst the 107 patients randomized, 22 (20%) reported receiving additional psychological support during the study: 16 in the interventional arm and 6 in the standard of care arm: 2 (9%) with anti-depressants, 11 (50%) with counselling, 4 (18%) with a psychological therapy, 1 (5%) with a combination of both anti-depressants and counselling, 4 (18%) with a combination of psychological therapy and counselling. Of note, at the 3-month visit, 10 patients in the intervention arm were continuing to receive psychological intervention and 6 in the control arm had commenced a psychological intervention external to the trial. No adverse events relating to study procedures were reported. Disease progression was recorded in 24 participants: 13 in the control arm and 11 in the intervention arm. There were 23 deaths reported in study patients (7 in the control arm, 16 in the intervention arm) within two years of enrolment, in all cases due to underlying cancer.

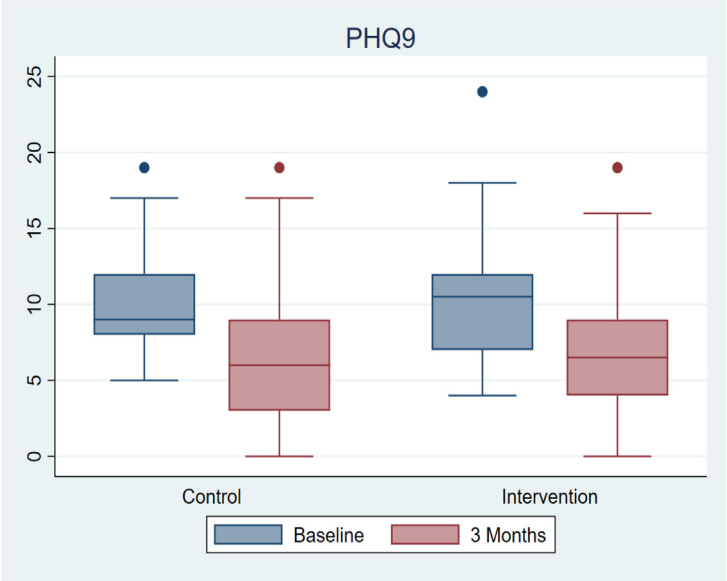
3.2. Outcomes

The primary outcome of change in PHQ-9 was compared between the control and intervention arms. The mean (SD) PHQ-9 scores at baseline were 9.97 (95% Confidence Interval (C·I) 3.62) vs 10.29 (4.64) in the control and intervention arms respectively while at 3 months the scores were 6.85 (5.06) vs 7.21 (4.97) respectively, reducing the sample mean from the 'moderate' to 'mild' PHQ-9 category (Fig. 3). Three-month mean PHQ-9 improved in both arms; by 3.12 points in control and 3.08 points in the intervention arm. The resulting ANCOVA treatment effect coefficient was not statistically significant (0.016, (95% C.I. -2.28, 2.32) p-value = 0.989). Thus, the expected primary endpoint of mean improvement of at least 3 points in PHQ-9 score was successfully met in the intervention arm but did not differ from the (similar) improvement in PHQ-9 score observed in the control arm. This indicates depression symptoms improved following chemotherapy regardless of intervention. Similarly, we did not observe a statistically significant treatment effect on depression over time (0.28, (85% C.I. -1.03, 1.60) p-value = 0.672). Fig. 4 and Tables 2 and 3 summarise the mean (SD) of secondary outcomes FOP-Q-SF, EORTC QLQ-OV28 and C30, at baseline and 3 months across the two treatment arms. The majority showed no statistically significant difference at 3 months or later time points. The exception were the mean FOP scores which measured 34.6 (SD = 8.9) in the control group, and 33.7 (SD = 8.6) in the intervention group at baseline. The score worsened by 0.33 points in the standard-of-care arm but improved by −3.74 points in the intervention arm where it fell to 30.0 (SD = 9.0), with a significant difference in treatment effect between the two arms of −4.4 points [95% CI: (−7.57, −1.22), p value = 0.008]. This indicates that fear of progression was improved by the intervention; crucially the intervention group remained below the cut-off score for dysfunctional fear of progression, whilst the control group remained in this problematic score range. Across all patients in the intervention arm, there was no sustained treatment effect beyond 3 months (−1.41 (95% C.I. -4.70, 1.88) p-value = 0.401. However, amongst those who scored ≥34 on the FOP score at baseline, there was a longer-term improvement in FOP score to 6 months, p-value = 0.006. Results of the mixed effects models fitted to the subscales of EORTC QLQ-OV28 and C30 can be found in the Appendix.

3.3. Discussion

Our study demonstrated that, consistent with findings from others [18], over 50% of ovarian cancer patients have symptoms of depression on completion of chemotherapy for primary or relapsed disease. Interestingly we observed that these symptoms spontaneously improved in the 3 months after chemotherapy and were not influenced by the OVPSYCH CBT-based intervention. The majority of secondary endpoints in the study such as other QOL subscores also improved following treatment in both study arms.

These findings could indicate that depression is a result of the impact of cancer and its treatment and resolves over time as natural psychological adjustments and adaptations occur. Alternatively, they could suggest that depression is a toxicity caused by chemotherapy itself and resolves with other treatment-related side effects. The latter hypothesis is supported by research in mice which displayed signs of depression after treatment with cancer chemotherapy [19,20]. It is perhaps hazardous to assume the improvement trajectory we observed in this study occurs in all ovarian cancer patients. Patients who participated in OVPSYCH2 self-selected by agreeing to enrol and, furthermore, were screened by their baseline PHQ-9 scores. Although there was no apparent difference in levels of depression between the newly diagnosed and relapsed patients, the inclusion of both in this study may have had a dilutive effect on the outcomes. Either way, our findings reinforce the need for more research into psychological interventions during earlier treatment phases and which, if any, anti-depressant options are effective – and acceptable to patients – during this acute post-chemotherapy period. OVPSYCH2 also demonstrates the importance of conducting randomized studies in the post-chemotherapy phase to prevent the erroneous attribution of a non-randomized intervention to any improvements in depression symptoms. Fear of Progression or "Damocles syndrome" is defined as fear, worry or concerns about cancer returning or progressing and is experienced at high levels in an estimated 50% of cancer patients [21,22]. While a realistic understanding of prognosis is important for OC patients, debilitating levels of fear can impair daily activities and lead to longstanding anxiety, depression and post-traumatic stress disorder [21–24]. Although FOP was previously thought to be anxiety-related, it is now considered a separate, concrete and rational concern for patients; instruments designed to detect anxiety or depression show inconsistent correlation with FOP scores [21]. Previous studies have disputed the time of onset of FOP, from early after diagnosis to later during cancer recovery [21] and interventional studies in breast, melanoma and colorectal cancer have tested the impact of psychological interventions on FOP identified during the later stages of recovery rather than the acute post-



Endpoint	Mean (SD)	
	Control	Intervention
Number[1]	33	34
Baseline PHQ-9 Score (95% CI)	9.97 (3.62)	10.29 (4.64)
3 Month PHQ-9 Score (95% CI)	6.85 (5.06)	7.21 (4.97)
T-test P-value[2]	0.0008	0.0005
Treatment Effect (95% CI), p-value[3]	0.016 (-2.28, 2.32), 0.989	

[1]67 patients completed baseline and 3 month questionnaires

[2]t-test p-value testing difference between 3 month and baseline scores within each group

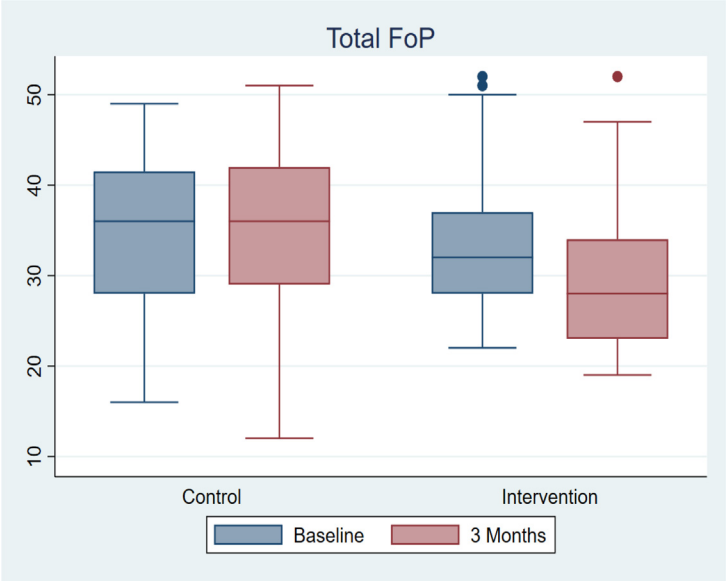
[3]Treatment effect, 95% confidence interval and p-value based on ANCOVA model

Fig. 3. Change in PHQ-9 scores. Boxplots represent total PHQ-9 scores by arm, at baseline and 3 months. The mean (SD) are presented in the table; the *p*-value is based on a two-sided 95% *t*-test and the treatment effect is based on the fitted ANCOVA model. Lower scores indicate decreasing depression severity.

chemotherapy window. Although FOP has been identified as an area of unmet need in ovarian cancer, no dedicated intervention studies have yet been performed in this patient group [25,26]. Scores designed to measure FOP include the Worry of Cancer Scale (WOC) [27], Concerns About Recurrence Scale (CARS) [28], Fear of Cancer Recurrence Inventory (FCRI) [29] and FOP-Q-SF [12]. The FOP-Q-SF score has been validated in cancer patients; scores of 34 or over indicate "dysfunctional" levels of FOP associated with psychological distress that negatively impacts daily life. This is in contrast to "mobilizing" levels of FOP seen in those patients with lower scores who may utilize effective coping strategies or seek out available resources [16,30]. We found baseline FOP-Q-SF scores were high amongst patients in both arms of the study (34.6 (SD = 8.8) in the standard arm, 33.7 (SD = 8.6) in the intervention arm) indicating borderline dysfunctional levels of fear immediately following chemotherapy. We observed no correlation between FOP-Q-SF and EORTC QOL scores or the PHQ-9 depression questionnaire; and whilst the PHQ-9 improved in the 3 months after chemotherapy, the FOP-Q-SF worsened in the control arm to a peak of 51 points.

The OVPSYCH intervention significantly improved mean FOP at 3 months. It is likely this is attributable to its CBT-aspect which, in other studies, has been shown to be effective [31]. However, in OVPSYCH2 the benefit was lost after 6 months suggesting the intervention delivered in its current form of three concentrated sessions did not make a lasting impact. It is important to note that the study was not originally designed around FOP and, by selecting patients by their PHQ-9 score and including primary and recurrent OC, we may have excluded some with significant FOP or diluted the true impact of the intervention [32]. The outcome of ongoing studies utilising the iConquerFear programme to overcome FOP will be important in determining whether web-based self-management is as effective as psychologist-led interventions, or if a mixed model is preferred [33]. The OVPSYCH intervention is relatively brief in comparison to other CBT trials and there might be a dosage effect that is worth exploring in future studies; perhaps with the addition of telephone check-in between sessions, or a booster session some weeks later to enhance the duration of efficacy.

The study had a number of weaknesses. As with many QOL trials, recruitment was slow and questionnaire completion poorly maintained over time which hindered our original aim of recruiting 63 patients into each study arm and the resulting statistical power of the endpoints. Reasons for poor recruitment included the perceived stigma of engaging



Endpoint	Mean (SD)	
	Control	Intervention
Number[1]	24	27
Baseline total FOP	34.63 (8.80)	33.74 (8.63)
3 Month total FOP	34.96 (9.10)	30.00 (9.00)
T-test P-value[2]	0.7845	0.0012
Treatment Effect (95% C.I), p-value[3]	-4.39 (-7.57,-1.22), p-value = 0.008	

[1] 51 patients completed baseline and 3 month FOP-Q-SF questionnaires

[2] t-test p-value testing difference between 3 month and baseline scores within each group

[3] Treatment effect based on ANCOVA

Fig. 4. Change in Fear of Progression (FOP) Scores. Boxplots represent the total FOP scores by study arm, at baseline and 3 months. The mean (SD) are presented in the table, the p-value is based on a two-sided 95% t-test and the treatment effect is based on the fitted ANCOVA model. Lower scores indicate decreasing fear of progression.

in a study that addressed mental health concerns, a common feature of survivorship trials that was also reported by participants in the pilot OVPSYCH trial [7,34], the low clinical priority of the study in trial centres and a lack of sufficient funding to institute site-level oversight. This also meant the data return at time points beyond 6 months was too poor to address many of the secondary endpoints. There was an imbalance with greater additional interventions (such as counselling or anti-depressants) sought by patients in the intervention compared to control arm; a factor that could have contributed to the larger overall reduction in FOP observed in this group. Alternatively it could represent greater motivation by patients to seek additional support conducive with lowered levels of fear. The FOP-Q-SF questionnaire, originally developed

Table 2
Mean SD of QLQ-OV28. QLQ-OV28 consists of three functional scales and five symptom scales. Scores range from 0 to 100 points. Each subscale is analysed separately, p-values are based on a two-sided 95% t-test; higher function scores indicate better function, and higher symptom scores indicate higher symptomatology.

Mean (SD)	Control			Intervention		
OV28 Scale	N	Baseline	3 months	N	Baseline	3 months
Functional Scales						
Body image	32	45.83 (37.39)	57.29 (32.22)	35	47.62 (34.33)	64.76 (34.01)
Sexuality	27	73.46 (27.64)	80.25 (26.57)	34	90.44 (14.81)	87.01 (19.05)
Attitude to disease/treatment	32	36.46 (26.66)	42.71 (25.73)	35	35.56 (22.68)	45.24 (28.14)
Symptom Scales						
Abdominal/GI symptoms	35	27.80 (16.34)	25.92 (21.44)	36	31.75 (22.54)	23.94 (21.58)
Peripheral neuropathy	35	41.59 (31.12)	32.70 (25.98)	36	50.93 (32.46)	33.95 (30.62)
Hormonal/menopausal symptoms	35	41.43 (36.46)	30.00 (34.49)	36	35.19 (36.03)	37.50 (36.60)
Other chemotherapy side-effects	35	37.14 (19.35)	30.38 (19.01)	36	38.56 (20.36)	26.48 (19.83)
Hair loss	35	43.33 (39.85)	19.52 (34.65)	36	46.76 (39.80)	10.19 (26.21)

Table 3
Mean SD of QLQ-C30 scores. QLQ-C30 consists of five functional scales, three symptom scales: a global health status, QOL scale and six single symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All of the scales and single-item measures range from 0 to 100. Each subscale is analysed separately, p-values are based on a two-sided 95% t-test; a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status (QOL) represents a high QOL, but a high score for a symptom scale item represents a high level of symptomatology / problems.

Mean (SD)	Control			Intervention		
C30 Scale	N	Baseline	3 Months	N	Baseline	3 Months
Global health status/QoL	31	54.84 (18.98)	63.98 (22.91)	37	53.83 (16.85)	61.71 (19.39)
Functional Scales						
Physical functioning	35	66.05 (19.84)	72.00 (23.03)	37	62.21 (22.36)	67.57 (22.29)
Role functioning	35	54.76 (29.86)	69.52 (34.65)	37	54.05 (27.61)	71.17 (30.84)
Emotional functioning	31	58.15 (22.24)	63.71 (21.89)	37	54.95 (25.79)	62.39 (27.54)
Cognitive functioning	31	67.20 (29.02)	74.19 (21.01)	37	55.86 (28.11)	65.77 (26.92)
Social functioning	31	52.69 (33.91)	68.28 (28.33)	37	50.45 (33.21)	66.67 (30.68)
Symptom scales						
Fatigue	35	47.94 (22.18)	38.41 (27.82)	37	54.35 (24.54)	48.05 (26.06)
Nausea and vomiting	35	10.48 (15.70)	10.00 (18.17)	37	8.11 (15.02)	7.66 (13.38)
Pain	35	31.90 (26.62)	30.95 (33.61)	37	34.23 (30.42)	30.18 (26.30)
Dyspnea	35	36.19 (30.65)	29.52 (32.11)	37	29.73 (32.19)	31.53 (34.20)
Insomnia	34	49.02 (35.99)	41.18 (34.87)	37	55.86 (34.30)	40.54 (35.25)
Appetite loss	35	23.81 (31.90)	23.81 (33.89)	37	20.72 (31.77)	13.51 (24.16)
Constipation	35	23.81 (28.66)	20.00 (32.54)	37	19.82 (28.82)	20.72 (25.28)
Diarrhea	31	10.75 (23.39)	11.83 (23.65)	37	13.51 (22.85)	9.91 (22.03)
Financial difficulties	31	23.66 (31.26)	20.43 (29.41)	37	36.04 (39.58)	34.23 (41.19)

for breast cancer, is an imperfect tool for measuring FOP in OC as it contains questions around work and family life that may not be relevant for the typically older OC patient. Although routine psychological support was not standard of care for cancer patients at the time of the study, the immediate referral of patients with high PHQ-9 scores was an important safety measure. However, the PHQ-9 includes a question that specifically addresses suicidal ideation but is underweighted in the overall score. We would therefore recommend using a score such as the PHQ-2 when screening patients for depression in this population [35].

Notwithstanding these limitations, OVPSYCH2 is the first study to assess the benefit of an intervention on FOP in the post-chemotherapy window and highlights the rapid acceleration of fear in the 3–6 months following treatment. We recognise this as a teachable moment, wherein an early psychological intervention can have immediate impact on reducing the debilitating fear that affects many OC patients once they complete chemotherapy and try to return to a normal life. A trial utilizing the core features of the OVPSYCH intervention, particularly its introduction in the immediate post-chemotherapy phase, and comparing the short and long-term impact of face-to-face and online interventions would be a fruitful avenue for future research.

4. Conclusions

In OVPSYCH2 we showed that 58% patients with ovarian cancer exhibit symptoms of depression on completion of chemotherapy, whether for upfront or recurrent disease. These symptoms improve spontaneously on a trajectory that is not significantly altered by a CBT-based psychological intervention. This may be because patients learn to naturally adjust to the challenges of post-chemotherapy life and depression symptoms dissolve. Alternatively, these data might indicate that the onset of depression is chemotherapy-induced and resolves at the same rate as other chemotherapy side effects such as neuropathy and fatigue. We found that 47% patients had dysfunctional levels of fear of progression (FOP) at study entry; this worsened over time amongst those receiving standard-of-care but was temporarily but significantly improved for those in the intervention arm who received three sessions of CBT-based psychological support.

We propose that Fear of Progression is routinely assessed using tools such as the FOP-Q-SF questionnaire or an equivalent tailored more specifically to ovarian cancer patients. We show that a focused support intervention given soon after completing chemotherapy is effective at delaying the emergence of FOP. Although the intervention was delivered by psychologists in OVPSYCH2, a modified version of this intervention could be administered by trained members of any healthcare team or provided online [36,37]. To provide a more lasting effect, we propose support is provided at intervals throughout the patients' cancer journey to maximize their chances of living unencumbered by intrusive and debilitating fear of progression, regardless of future prognosis.

Funding

This work was supported by Imperial Health NHS Charity, Ovarian Cancer Action and the National Institute for Health Research (NIHR).

CRediT authorship contribution statement

E. Frangou: Data curation, Formal analysis, Software, Writing - original draft, Writing - review & editing. **G. Bertelli**: Investigation, Supervision, Writing - review & editing. **S. Love**: Data curation, Formal analysis, Software, Writing - review & editing. **M.J. Mackean**: Investigation, Supervision, Writing - review & editing. **R.M. Glasspool**: Investigation, Supervision, Writing - review & editing. **C. Fotopoulou**: Investigation, Supervision, Writing - review & editing. **A. Cook**: Investigation, Supervision, Writing - review & editing. **S. Nicum**: Investigation, Supervision, Writing - review & editing. **R. Lord**: Investigation, Supervision, Writing - review & editing. **M. Ferguson**: Investigation, Supervision, Writing - review & editing. **R.L. Roux**: Investigation, Writing - review & editing. **M. Martinez**: Conceptualization, Data curation, Writing - review & editing. **C. Butcher**: Data curation, Software, Writing - review & editing. **N. Hulbert-Williams**: Conceptualization, Supervision, Writing - review & editing. **L. Howells**: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing - review & editing. **S.P. Blagden**: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Acknowledgements

We acknowledge the support of Ovarian Cancer Action and the National Institute for Health Research (NIHR). We thank Professor Robert Leonard and the Maggie's Research Group for their support with the design and conduct of the study and the UK Maggie's Centres for providing the psychological intervention arm of this study. We are grateful to the University of Oxford's OCTO for providing data collection and analysis and to the members of the Trial Management Committee.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.05.024.

References

[1] S. Watts, P. Prescott, J. Mason, N. McLeod, G. Lewith, Depression and anxiety in ovarian cancer: a systematic review and meta-analysis of prevalence rates, BMJ Open 5 (11) (2015), e007618, https://doi.org/10.1136/bmjopen-2015-007618.
[2] I. Teo, A. Krishnan, G.L. Lee, Psychosocial interventions for advanced cancer patients: a systematic review, Psycho-Oncology 28 (2019) 1394–1407, https://doi.org/10.1002/pon.5103.
[3] K. McCarter, B. Britton, A.L. Baker, S.A. Halpin, A.K. Beck, G. Carter, et al., Interventions to improve screening and appropriate referral of patients with cancer for psychosocial distress: systematic review, BMJ Open 8 (1) (2018), e017959, https://doi.org/10.1136/bmjopen-2017-017959.
[4] N.J. Hulbert-Williams, L. Beatty, H.M. Dhillon, Psychological support for patients with cancer: evidence review and suggestions for future directions, Curr. Opin. Support Palliat Care 12 (3) (2018) 276–292, https://doi.org/10.1097/SPC.0000000000000360.
[5] G. Rodin, From evidence to implementation: the global challenge for psychosocial oncology, Psychooncology 27 (10) (2018) 2310–2316, https://doi.org/10.1002/pon.4837.
[6] C. Stavraka, A. Ford, S. Ghaem-Maghami, T. Crook, R. Agarwal, H. Gabra, S. Blagden, A study of symptoms described by ovarian cancer survivors, Gynecol. Oncol. 125 (1) (2012) 59–64, https://doi.org/10.1016/j.ygyno.2011.12.421.
[7] L. Howells, N.J. Hulbert-Williams, S.P. Blagden, New challenges in psycho-oncology: using drug development methodology to improve survivorship and supportive care intervention trials, Psychooncology 28 (7) (2019) 1362–1366, https://doi.org/10.1002/pon.5100.
[8] A.D. Rost, K. Wilson, E. Buchanan, M.J. Hildebrandt, D. Mutch, Improving psychological adjustment among late-stage ovarian cancer patients: examining the role of avoidance in treatment, Cogn. Behav. Pract. 19 (4) (2012) 508–517, https://doi.org/10.1016/j.cbpra.2012.01.003.
[9] S.L. Manne, S.M. Virtue, M. Ozga, D. Kashy, C. Heckman, D. Kissane, et al., A comparison of two psychological interventions for newly-diagnosed gynecological cancer patients, Gynecol. Oncol. 144 (2) (2017) 354–362, https://doi.org/10.1016/j.ygyno.2016.11.025.
[10] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (9) (2001) 606–613, https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
[11] A. Hinz, A. Mehnert, R.D. Kocalevent, E. Brähler, T. Forkmann, S. Singer, et al., Assessment of depression severity with the PHQ-9 in cancer patients and in the general population, BMC Psychiatry 16 (2016) 22, https://doi.org/10.1186/s12888-016-0728-6.
[12] A. Mehnert, P. Herschbach, P. Berg, G. Henrich, U. Koch, Progredienzangst bei Brustkrebspatientinnen–Validierung der Kurzform des Progredienzangstfragebogens PA-F-KF [Fear of progression in breast cancer patients-validation of the short form of the Fear of Progression Questionnaire (FoP-Q-SF)], Z. Psychosom. Med. Psychother. 52 (3) (2006) 274–288, https://doi.org/10.13109/zptm.2006.52.3.274.
[13] N.K. Aaronson, S. Ahmedzai, B. Bergman, M. Bullinger, A. Cull, N.J. Duez, et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology, J. Natl. Cancer Inst. 85 (5) (1993) 365–376, https://doi.org/10.1093/jnci/85.5.365.
[14] E. Greimel, A. Bottomley, A. Cull, A.C. Waldenstrom, J. Arraras, L. Chauvenet, Et al; EORTC quality of life group and the quality of life unit. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer, Eur. J. Cancer 39 (10) (2003) 1402–1408, https://doi.org/10.1016/s0959-8049(03)00307-1.
[15] P. Herschbach, P. Berg, A. Dankert, G. Duran, U. Engst-Hastreiter, S. Waadt, M. Keller, R. Ukat, G. Henrich, Fear of progression in chronic diseases: psychometric properties of the fear of progression questionnaire, J. Psychosom. Res. 58 (6) (2005) 505–511, https://doi.org/10.1016/j.jpsychores.2005.02.007.
[16] S. Sarkar, A. Scherwath, L. Schirmer, F. Schulz-Kindermann, K. Neumann, M. Kruse, et al., Fear of recurrence and its impact on quality of life in patients with hematological cancers in the course of allogeneic hematopoietic SCT, Bone Marrow Transplant. 49 (9) (2014) 1217–1222, https://doi.org/10.1038/bmt.2014.139.
[17] N.J. Hulbert-Williams, L. Storey, K. Wilson, Psychological interventions for patients with cancer: psychological flexibility and the potential utility of acceptance and commitment therapy, Euro J. Cancer Care 24 (1) (2015) 15–27, https://doi.org/10.1111/ecc.12223.
[18] H. Liu, L. Yang, Dynamic change of depression and anxiety after chemotherapy among patients with ovarian cancer, Medicine (Baltimore) 98 (31) (2019), e16620, https://doi.org/10.1097/MD.0000000000016620.
[19] W. Toma, S.L. Kyte, D. Bagdas, Y. Alkhlaif, S.D. Alsharari, A.H. Lichtman, et al., Effects of paclitaxel on the development of neuropathy and affective behaviors in the mouse, Neuropharmacology 117 (2017) 305–315, https://doi.org/10.1016/j.neuropharm.2017.02.020.
[20] M. Egeland, C. Guinaudie, A. Du Preez, K. Musaelyan, P.A. Zunszain, C. Fernandes, et al., Depletion of adult neurogenesis using the chemotherapy drug temozolomide in mice induces behavioural and biological changes relevant to depression, Transl. Psychiatry 7 (4) (2017), e1101, https://doi.org/10.1038/tp.2017.68.
[21] P. Herschbach, A. Dinkel, Fear of progression, Recent Results Cancer Res. 197 (2014) 11–29, https://doi.org/10.1007/978-3-642-40187-9_2.
[22] S. Simard, J. Savard, H. Ivers, Fear of cancer recurrence: specific profiles and nature of intrusive thoughts, J. Cancer Surviv. 4 (4) (2010) 361–371, https://doi.org/10.1007/s11764-010-0136-8.
[23] E.K. Black, C.A. White, Fear of recurrence, sense of coherence and posttraumatic stress disorder in haematological cancer survivors, Psychooncology 14 (6) (2005) 510–515, https://doi.org/10.1002/pon.894.
[24] M.H. van den Beuken-van Everdingen, M.L. Peters, J.M. de Rijke, H.C. Schouten, M. van Kleef, J. Patijn, Concerns of former breast cancer patients about disease recurrence: a validation and prevalence study, Psychooncology. 17 (11) (2008) 1137–1145, https://doi.org/10.1002/pon.1340.
[25] M. Ozga, C. Aghajanian, S. Myers-Virtue, G. McDonnell, S. Jhanwar, S. Hichenberg, et al., A systematic review of ovarian cancer and fear of recurrence, Palliat Support Care 13 (6) (2015) 1771–1780, https://doi.org/10.1017/S1478951515000127.
[26] S.B. Myers, S.L. Manne, D.W. Kissane, M. Ozga, D.A. Kashy, S. Rubin, et al., Social-cognitive processes associated with fear of recurrence among women newly diagnosed with gynecological cancers, Gynecol. Oncol. 128 (1) (2013) 120–127, https://doi.org/10.1016/j.ygyno.2012.10.014.
[27] J.A. Custers, S.W. van den Berg, H.W. van Laarhoven, E.M. Bleiker, M.F. Gielissen, J.B. Prins, The cancer worry scale: detecting fear of recurrence in breast cancer survivors, Cancer Nurs. 37 (1) (2014) E44–E50, https://doi.org/10.1097/NCC.0b013e3182813a17.
[28] S.M. Vickberg, The concerns about recurrence scale (CARS): a systematic measure of women's fears about the possibility of breast cancer recurrence, Ann. Behav. Med. 25 (1) (2003) 16–24, https://doi.org/10.1207/S15324796ABM2501_03.
[29] S. Simard, J. Savard, Fear of Cancer recurrence inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence, Support Care Cancer 17 (3) (2009) 241–251, https://doi.org/10.1007/s00520-008-0444-y.
[30] P. Herschbach, P. Berg, S. Waadt, G. Duran, U. Engst-Hastreiter, G. Henrich, et al., Group psychotherapy of dysfunctional fear of progression in patients with chronic arthritis or cancer, Psychother. Psychosom. 79 (1) (2010) 31–38, https://doi.org/10.1159/000254903.
[31] N.M. Tauber, M.S. O'Toole, A. Dinkel, J. Galica, G. Humphris, S. Lebel, et al., Effect of psychological intervention on fear of Cancer recurrence: a systematic review and meta-analysis, J. Clin. Oncol. 37 (31) (2019) 2899–2915, https://doi.org/10.1200/JCO.19.00572.
[32] E.J. Shim, Y.W. Shin, D.Y. Oh, B.J. Hahm, Increased fear of progression in cancer patients with recurrence, Gen. Hosp. Psychiatry 32 (2) (2010) 169–175, https://doi.org/10.1016/j.genhosppsych.2009.11.017.
[33] A.B. Smith, A. Bamgboje-Ayodele, P. Butow, B. Klein, J. Turner, L. Sharpe, J. Fardell, L. Beatty, A. Pearce, B. Thewes, Beith J; iConquerFear community advisory group, Girgis a. development and usability evaluation of an online self-management intervention for fear of cancer recurrence (iConquerFear), Psychooncology. 29 (1) (2020 Jan) 98–106, https://doi.org/10.1002/pon.5218.
[34] A.K. Matthews, P.W. Corrigan, J.L. Rutherford, Mental illness stigma as a barrier to psychosocial services for cancer patients, J. Natl. Compr. Cancer Netw. 1 (3) (2003) 375–379, https://doi.org/10.6004/jnccn.2003.0032.
[35] K. Kroenke, R.L. Spitzer, J.B. Williams, The patient health questionnaire-2: validity of a two-item depression screener, Med. Care 41 (11) (2003) 1284–1292, https://doi.org/10.1097/01.MLR.0000093487.78664.3C.
[36] A.B. Smith, Integrating fear of cancer recurrence screening into routine care: opportunities and challenges, Psychooncology (2020 Sep 25)https://doi.org/10.1002/pon.5558 (Epub ahead of print).
[37] B. Mutsaers, N. Rutkowski, G. Jones, J. Lamarche, S. Lebel, Assessing and managing patient fear of cancer recurrence, Can. Fam. Physician 66 (9) (2020) 672–67332933983.