

A mixed methods pilot and feasibility open trial of internet-delivered cognitive behaviour therapy (*iCanADAPT Advanced*) for people with advanced cancer with depression and/or anxiety

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ABSTRACT

Purpose: Evaluate the feasibility, acceptability and potential efficacy of a form of online therapy for clinical depression and/or anxiety in people living with advanced cancer.

Methods: A single-arm open trial of a six-lesson clinician-supervised, internet-delivered cognitive behavioural therapy (iCBT) transdiagnostic intervention (*iCanADAPT Advanced*) was undertaken. Qualitative (semi-structured telephone interview conducted at 3-months) and quantitative data (questionnaires collected at pre-, post-, and 3-month follow-up) were analysed.

Results: 27 participants partook (26 women, 56% breast cancer, mean age 56yo; average number of mental health diagnoses 1.8, with majority (81%) meeting criteria for generalised anxiety disorder). **Feasibility** - Unanticipated numbers (48%) of participants had physical health deterioration (cancer progression or death). iCBT had high adherence overall (completion rates: 37% did 6 lessons; 70% did 4 lessons) but adherence was higher for those whose cancer remained stable (completion rates: 43% did 6 lessons; 85% did 4 lessons). **Acceptability** - the intervention was acceptable to the majority of participants, with high treatment satisfaction. Advisory data was achieved regarding future versions. **Potential efficacy** - regardless of physical health status, participants who completed the iCBT showed a significant decrease over time in anxiety and depression symptoms.

Conclusions: Online therapies may be useful in assisting those living with advanced cancer dealing with clinical depression and anxiety disorders. The specific modality of clinician supervised iCBT has significant potential to be a suitable modality of online therapy.

1. Introduction

A diagnosis of advanced cancer means that treatment is unlikely to result in cure, with the goal of treatment focused on managing and reducing the impact of symptoms on quality of life and slowing further progression (N. C. I., 2020). This wide-ranging term includes people at different stages of disease including *a*) those facing a de-novo metastatic (or newly recurrent) advanced cancer diagnosis, *b*) those living with advanced cancer as a chronic illness (NCCN, 2018), and *c*) those entering the final stages of life (palliative and/or terminal care). Ideally,

people at each stage of treatment should be able to access holistic care addressing physical, psychological, social and spiritual aspects as required (Excellence, 2004). However, a 2018 systematic review of 50 studies reconfirmed earlier work (Harrison et al., 2009) showing that there are many unmet needs in those living with advanced cancer, including in domains such as “psychological, physical, and healthcare service and information” (Wang et al., 2018).

Most psychosocial interventions for those with advanced cancer are delivered in a face-to-face setting (individual or group) which is advantageous for some but also has barriers for broader dissemination

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including a lack of suitably trained clinicians, high cost and low accessibility (Andrews, 2011; Greer et al., 2017). In 2012 Leykin et al. called for research into internet interventions for those living with a cancer diagnosis as they “*have the potential to fill an important gap in quality cancer care by augmenting limited available mental health services*” (Leykin et al., 2012). The authors noted such interventions may need to target specific (cancer) diagnoses and/or specific stages of the illness.

Internet interventions are operationalized and delivered via the internet with the goal of symptom improvement (Ritterband et al., 2003) and they additionally have benefits such as the ability to be tailored to the user population and enable access to large numbers. Internet intervention research in cancer care started over a decade ago and by 2015 a systematic review (McAlpine et al., 2015) into online interventions found 14 studies addressing a wide range of issues from quality of life, to cancer symptomatology (e.g. pain) to distress; however, all focused on the unmet needs of cancer survivors. The term cancer survivor hereon in is used to indicate cancer survivors of early stage i.e., potentially curable disease (Feuerstein, 2007). Cancer survivorship research into internet interventions has helped with *universal* issues such as empowering self-management (Duffecy et al., 2013; Hernandez Silva et al., 2019) and targeting the *physical* health sequelae of cancer (e.g. fatigue (Abrahams et al., 2017), cognitive concerns (Eysenbach, 2001)). Similarly, an increase in research into online interventions addressing the *psychological* aspects of cancer survivorship has occurred. By 2020, a systematic review identified 33 publications relating to internet interventions for cancer-related distress (Willems et al., 2020), and another 2019 systematic review identified four such interventions addressing the fear of cancer recurrence (Tauber et al., 2019) with further randomized controlled trials (RCTs) into insomnia (Zachariae et al., 2018) and clinical depression and/or anxiety in cancer survivors (Murphy et al., 2020). The explosion of research into online interventions relating to cancer survivorship is not mirrored for those living with advanced cancer.

In the advanced cancer context, a 2019 systematic review of psychosocial interventions between 2007 and 2016 for adults with advanced cancer (Teo et al., 2019) identified 68 RCTs of which six had some form of an online component. Three of these were feasibility studies and five focused on a single cancer type. Of the six identified online interventions: two focus on improving support (Vilhauer et al., 2010; Harris, 2017), two aim to facilitate better communication (Porter et al., 2017; Meropol et al., 2013), and the final two aim to improve coping skills (Cheung et al., 2017; Yanez et al., 2015). A 2018 systematic review of psychotherapeutic interventions for women with metastatic breast cancer (Beatty et al., 2018) identified 15 RCTs that addressed distress, coping and pain but noted that “*no studies of Web-based interventions have been published*”. There is limited further research of internet interventions in advanced cancer since those systematic reviews with the exception of trials into symptoms management (Nipp et al., 2019; Nipp et al., 2020; Basch et al., 2016) and a RCT of a CBT-app versus control for the management of anxiety in those with advanced cancer (Greer et al., 2017; Greer et al., 2019), the results of which will be discussed below. It is in this environment that the following open study evaluating an internet intervention in people with advanced cancer with a clinical range psychological disorder is described.

1.1. A novel internet intervention for depression and anxiety

Our group wished to develop an online intervention to improve the quality of life of people living with advanced cancer who had a clinical range depressive and/or anxiety disorder. A review of 24 studies summarized rates of clinical depression at 9.6% and clinical anxiety at 9.8% in those with advanced cancer without a significant difference between palliative and non-palliative settings (Mitchell et al., 2011). Many psychotherapeutic modalities are used to assist those living with advanced cancer in managing depression and/or anxiety (Watson and Kissane, 2011) and recent meta-analyses showed that psychotherapy overall

produced a *moderate decrease in depression* (Okuyama et al., 2017) and a *small effect on anxiety* (Sanjida et al., 2018) with both reviews noting that those with the more severe symptoms benefit most from an intervention. The modalities of therapy include, among others, structured therapies such as cognitive behavioural therapy (CBT) and meaning centered therapies, and both groups of therapies can be delivered face-to-face in an individual or group format.

We investigated CBT for several reasons. *First*, prior reviews identified that face-to-face CBT (individual (Moorey et al., 2009, Anderson et al., 2008) and group (Edelman et al., 1999)) provided some benefit in assisting those living with advanced cancer by decreasing depressive and anxiety symptoms (Greer et al., 2010; Moorey et al., 2009; Horne and Watson, 2011). *Second*, it lends itself well to the online format by being self-paced, modular and reproducible (Andersson, 2018), and internet-delivered CBT (iCBT) is backed by nearly 20 years of research (Andersson et al., 2016). *Third*, focus groups with cancer patients reviewing a prototype iCBT intervention for clinical range depression and/or anxiety found it to be acceptable. Participants advocated for a tailored course for those with advanced cancer to address their specific needs (Karageorge et al., 2017).

Some recent reservation about the role of CBT in managing depression in advanced cancer has emerged since a recent RCT (CanTALK) (Serfaty et al., 2019) of face-to-face CBT versus treatment-as-usual did not show a statistical benefit for the treatment of depression in advanced cancer. This is in contrast to recent RCT findings of Greer et al. regarding their mobile application CBT (CBT-app) versus a control of generic health education (similar number of sessions, delivered via an app). While mean changes did not differ between study groups for any outcome, both arms improved post intervention. The authors noted that “*the health education program was an active control that effectively improved outcomes*” and that a stratified subgroup analysis showed that in participants with severe baseline anxiety symptoms, the CBT-app group had a significant improvement in anxiety symptoms.

Both of these recent trials targeted a single disorder, whereas our intervention adopts a transdiagnostic approach targeting both depression and anxiety simultaneously (Clark, 2009). Transdiagnostic CBT uses “*universally applied therapeutic principles, empirically based modular strategies, and targeting shared mechanisms across classes of disorders*” (Sauer-Zavala et al., 2017) and this approach was chosen as a) many people living with advanced cancer have symptoms of both depression and anxiety (Cheung et al., 2009; Bender et al., 2005) b) cancer patient focus groups confirmed this was acceptable (Karageorge et al., 2017) c) transdiagnostic iCBT is effective in community samples (Newby et al., 2016; Pasarelu et al., 2017) and cancer survivors (Murphy et al., 2020; Dirkse et al., 2019).

1.2. The intervention

We developed a transdiagnostic iCBT program tailored to the specific needs of people with advanced cancer with clinical depressive and/or anxiety disorders, called “*iCanADAPT Advanced*”. The iCBT intervention includes general and cancer-specific CBT skills and was based around a previously developed evidence-based transdiagnostic program (Newby et al., 2013). It was iteratively developed by an expert panel including consumers, psycho-oncologists and psychiatrists with expertise in online therapeutic delivery, and consisted of a self-managed, 12-week, online 6 lesson program. An overview of the content is presented in Fig. 1 and an outline of the four components (lesson, lesson summary, additional information and the audio-visual component). Participants were encouraged to complete a lesson a fortnight, with a lock out period of at least five days between lessons. Further specifics of lesson completion and the level of communication and monitoring are outlined in Online Supplemental Material 1 (*Summary of running the iCanADAPT Advanced trial including Semi-structured telephone interview*).

The aim of this open trial was to determine the feasibility of *iCanADAPT Advanced* (including identification, recruitment and retention

An overview of the six lessons

General information

Introductory video. Basic sleep hygiene. Brief introduction to mindfulness. Finding cancer information and support.

Lesson 1 – Learning about Depression & Anxiety

Psycho-education about depression and anxiety, including their prevalence in cancer, psycho-education about the CBT cycle and the flight or fight response. Introduction to rumination and worry and good sleep hygiene. Skills of relaxation and progressive muscle relaxation. Goal setting introduced.

Lesson 2 – Adjusting to Change

Assessment of one's personal values and goals. Overview of adjusting to physical change and the need to pace physical activity. Examples of physical health symptoms exacerbating emotional health problems. The use of CBT to tackle the impact of physical health (and/or treatment) symptoms on emotional wellbeing. Activity and physical symptom monitoring diary.

Lesson 3 – Identifying and Tackling Thoughts

Key cognitive therapy skills including cognitive monitoring, recognising distorted cognitive styles, and later cognitive restructuring. Examples of each skill in use. Use of benefit finding and shifting attention from rumination and worry including examples of worry-free zones. Related worksheets.

Lesson 4 – Tackling Unhelpful Behaviours

Key behavioural activation skills including tackling the low activity cycle, daily activity scheduling and the role of physical activity. Additional skills relating to structured problem solving and assertive communication skills. List of pleasant activities and resource on 'scanxiety'.

Lesson 5 – Facing your fears

Introduction to avoidance and the rationale for combatting avoidance using graded exposure and exposure stepladders. Examples of confronting avoidance (both in cancer management and communication settings) are intertwined. Exposure stepladders and behavioural experiment sheets are provided.

Lesson 6 – Maintaining your skills

Identifying problems and related solution. Relapse prevention planning and an overview of the skills learned. Production of a relapse prevention plan.

Fig. 1. An overview of the six lessons.

of participants, and iCBT completion), acceptability (including perceived skill-development, feedback, and side-effects), and potential efficacy in reducing main targeted symptoms (depression and anxiety) and general distress levels, and improving physical, social, and emotional functioning. Finally, we wished to identify possible modifications needed for a subsequent randomized controlled trial. Mixed quantitative and qualitative methods were used as described next.

2. Methods

2.1. Participants

Eligibility criteria for inclusion were: *oncological* - any cancer type, advanced stage disease (similar to the NCI definition (NCI, 2020), self-report of current or past metastatic spread, with clarification on clinical interview that the cancer is unlikely to be cured or controlled with treatment), cancer diagnosis > 6 weeks prior (to exclude initial distress); *psychological* - met diagnostic criteria of at least one Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 disorder on clinical interview using the Anxiety Disorders Interview Schedule for DSM-5 (ADIS) for Major Depressive Disorder (MDE), Generalised Anxiety Disorder (GAD), Panic Disorder, Agoraphobia and/or Adjustment Disorder, no active suicidality; *general* – adult, fluent English, resident in Australia, access to a computer/printer, provision of name, phone number and

address, provision of name and details of general practitioner.

Exclusion criteria were: *oncological* – currently hospitalized, primary brain cancer (due to potential pre-existing cognitive changes), Eastern Cooperative Oncology Group (ECOG) performance status of >2; *psychological* – active alcohol misuse (as per Alcohol Use Disorders Identification Test Consumption (AUDIT-C) questions and clinical interview), undergoing recent/current CBT, current/ past diagnosis of schizophrenia or bipolar disorder, currently taking antipsychotic medications, frequent suicidality (indicated by a score of >2 on item 9 Beck Depression Inventory-II (BDI-II)).

2.2. Design and procedures

A pre-post open trial of iCBT over 12 weeks was conducted. Patients self-referred to the trial across 2017. Local hospital recruitment via posters and staff education was supplemented by Facebook advertising and approaching a state-wide cancer research database (www.register4.org.au). Applicants were screened via an online questionnaire and required a minimum Hospital Anxiety and Depression Scale (HADS)-Total score of ≥ 6 (identified as suitable for screening in a cancer population) (Mitchell et al., 2010; Singer et al., 2009) to proceed to telephone interview to assess eligibility.

On confirmation of eligibility, participants were given a link to the online *iCanADAPT Advanced* site which linked them to an online

research portal (virtualclinic.org.au) where electronic informed consent was obtained. They then completed baseline data collection and commenced the therapeutic intervention. Each participant completed the same measures four times, at pre-intervention (i.e. baseline), mid-point, post-intervention and 3-month follow-up. A semi-structured qualitative phone interview was undertaken at the 3-month follow-up.

2.3. Assessments

Feasibility was assessed for by identification of appropriate participants, determination of eligibility, recruitment, and retention rates. Acceptability was assessed via communication from participants across the trial, the qualitative phone interview (see interview schedule in Online Supplemental Material 1 (*Summary of running the iCanADAPT Advanced trial including Semi-structured telephone interview*)) and completion post-intervention of the Treatment Credibility/ Expectancy Questionnaire (CEQ) (Deville and Borkovec, 2000). Potential efficacy was assessed by reviewing longitudinal quantitative data from the: *i*) Hospital Anxiety and Depression Scale Total Score (HADS-T) and two subscales, Anxiety (HADS-A) and Depression (HADS-D), *ii*) Kessler-10 Psychological Distress Scale (K10) and, *iii*) Functional Assessment of Cancer Therapy-General Version (FACT-G QOL) with four subscales, Physical well-being (PWB), Social well-being (SWB), Emotional well-being (EWB) and Functional well-being (FWB). Participants additionally completed a Kessler-10 (K-10) Psychological Distress Scale before each lesson to monitor progress and distress levels.

2.4. Sample size

The planned sample size was 30 allowing for attrition. This study will inform the sample size for any future RCT (Leon et al., 2011).

2.5. Data and statistical analysis

Qualitative data were analysed using Framework Analysis (Gale et al., 2013). Within group effect sizes (Hedges *g*) were calculated to measure effect size for the pre to post-intervention change on all outcome measures for the overall group. Upon identification of two subgroups (described below i.e. cancer remaining stable versus cancer progressing), exploratory quantitative analysis was undertaken with significance testing of group differences on demographic data and pre-intervention measurements conducted using independent sample *t*-test and χ^2 for categorical data. Significant effects were followed up with pairwise comparisons comparing mean baseline to mean post-intervention (or follow-up) scores.

2.6. Ethics and registration

Prospectively registration on the Australian New Zealand Clinical Trials Registry: ACTRN12616001645448 (www.anzctr.org.au). Ethical approval via the National Human Research Ethics Committees (HREC), Australia.

3. Results

3.1. Participant flow

Participants came from each of the three recruitment strategies, with 15 (56%) coming through Facebook, and equal numbers from local recruitment and the research database ($n = 6$, 22% each). Fig. 2 outlines participant adherence. The vast majority ($n = 53$, 96%) of applicants proceeded to telephone interview to determine eligibility; 31 (58%) of those were found eligible and given access to the iCBT intervention. Four participants later formally withdrew. The 27 participants completed an average of 4.1 lessons per participant. Seven (26%) participants completed none, one or two lessons, while 16 (59%) completed five or

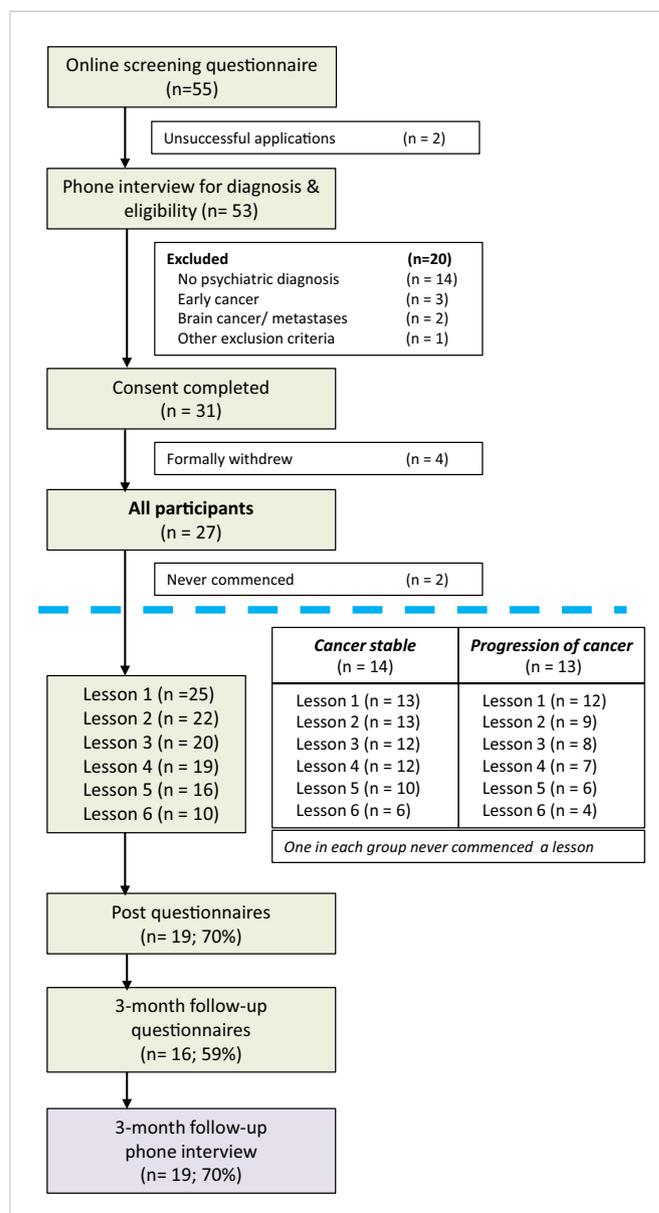


Fig. 2. Participant recruitment and adherence.

six lessons. More participants completed the qualitative phone interview ($n = 19$, 70%) than the online questionnaires ($n = 16$, 59%) at the 3-month follow-up assessment.

3.2. Emergence of two groups (Cancer stable and Progression of cancer)

Patients could volunteer to inform the research group of any new matters including physical health concerns via email or completion of a lesson. Two groups, unexpectedly, emerged across the study. At different time-points a group of participants informed the researchers that they experienced disease progression i.e. the participant themselves, or their family member, reported that the cancer “continued to grow or spread” (N. C. I., 2020) i.e. the “Progression” group. The research team became aware of at least one confirmed death via contact from a family member. If no information regarding cancer status occurred throughout the trial, then the participant was considered to have stable cancer illness “Stable” group. Of 27 participants, 13 had Progression and 14 were Stable. The Progression and Stable subgroups averaged 3.2 and 4.9 lessons, respectively. The Stable subgroup adherence was 10/14

(71%) completing 5-6 of the lessons, versus 6/13 (46%) for the *Progression* subgroup (see Fig. 2). At the three-month follow-up, some participants in the *Progression* subgroup chose to undertake only the phone interview, reporting physical/ emotional symptoms (fatigue, poor concentration etc.) as reasons for non-completion of the online

questionnaires.

3.3. Demographics, clinical characteristics and baseline measures

Table 1 outlines Demographics, Clinical Characteristics and Baseline

Table 1
Demographics, characteristics and baseline measures.

	N = 27	%
Demographics		
Female	26	96
<i>Marital status</i>		
Married/De-Facto	20	74
Other	7	26
<i>Education</i>		
High-school/certificate	13	48
≥University degree	14	52
<i>Employment</i>		
Paid work	11	41
Unemployed	3	11
Retired	8	30
Disability support	5	19
Australian born	19	70
Living rural	10	37
Have children	25	93
<i>Heard about trial</i>		
Facebook/online	15	56
Word of mouth/local	6	22
Research database	6	22
<i>Age, years</i>		
Mean	56.04	
SD	10.12	
Cancer factors		
<i>Time since metastatic cancer diagnosis (de novo or recurrence)</i>		
<1 year	9	35
1–5 years	12	45
>5 years	6	19
<i>Breast vs non breast cancer</i>		
Breast cancer	15	56
Non breast cancer	12	44
<i>De novo vs recurrent metastatic disease</i>		
De novo	14	52
Recurrent	13	48
Cancer treatments (past/present)		
Surgery	19	70
Chemotherapy	26	96
Radiotherapy	17	63
Hormonal therapy	15	56
Mental health factors		
	N = 27	%
<i>DSM diagnosis</i>		
Major depressive disorder	16	59
Generalised anxiety disorder	22	81
Panic disorder	4	15
Agoraphobia	6	22
Depression/anxiety before cancer	16	59
<i>Mental health treatments (past/present)</i>		
Antidepressant medications	15	56
Exposure to non-CBT therapy	21	78
Baseline measures (pre-questionnaires)		
	Overall	
	M	SD
HADS-Total	19.20	6.18
HADS-Anxiety subscale	10.92	3.19
HADS-Depression subscale	8.28	4.30
K-10	26.76	6.56
FACT-G (+positive scales)	52.52	12.99

HADS - Hospital Anxiety and Depression Scale.

K-10 - Kessler-10 Psychological Distress Scale.

FACT-G - Functional Assessment of Cancer Therapy – General.

+ = positive scale.

measures. All of the participants except one were female, and the mean age was 56 years. Most participants had breast cancer ($n = 15$, 56%) and were 1-5 years post diagnosis ($n = 12$, 45%). The remaining participants reported cancer diagnoses of gynecological ($n = 5$), gastrointestinal ($n = 3$), lung ($n = 2$), haematological malignancy ($n = 1$) and carcinoma of unknown origin ($n = 1$). The most common DSM-5 diagnosis was generalised anxiety disorder (GAD) ($n = 22$; 81%) and the average number of mental health diagnoses was 1.8 (range 1-3).

Overall the baseline HADS-Total mean 19.20 ($SD = 6.18$) was high, as compared to a non-clinical Australian community sample mean 9.82 ($SD = 5.98$) (Crawford et al., 2001). Similarly, the mean scores of the two HADS subscales were higher than measures from a German cancer clinic screening study i.e. HADS-Anxiety subscale mean 10.92 ($SD = 3.19$) is higher than a) general population 4.74 ($SD = 3.26$), b) cancer patient (all stages) mean 7.19 ($SD = 4.15$), c) stage 4 cancer patient female mean 8.3 ($SD = 4.5$). HADS-Depression subscale mean 8.28 ($SD = 4.30$) versus a) general population 4.68 ($SD = 3.83$), b) cancer patient cohort (all stages) mean 6.44 ($SD = 4.45$), c) stage 4 cancer patient female mean 7.6 ($SD = 5.1$) (Hinz et al., 2010). The K-10 mean scores (26.76 ($SD = 6.56$)) were high, as compared to Australian community samples K-10 mean scores of people a) without any a physical/ mental disorder 13.2 ($SD = 0.1$), b) with any physical health condition 15.0 ($SD = 0.1$), c) with an anxiety disorder 19.8 ($SD = 0.3$), d) with an affective disorder 23.2 ($SD = 0.5$) (Slade et al., 2011). And lastly, the FACT-G Total (52.5 $SD = 13$) was lower than normative reference of a) the general American population 80.1 ($SD = 18.1$) b) a large heterogeneous sample of adult cancer patients 80.9 ($SD = 17.0$) (Brucker et al., 2005).

There were no statistically significant demographic and/or clinical characteristics that distinguished the *Stable* and *Progression* subgroups at baseline (see Supplement 2). At baseline the *Progression* subgroup reported a lower quality of life versus the *Stable* Group (FACT-G Total (*Stable* = 57.14 ($SD = 7.78$) versus *Progression* = 46.64 ($SD = 16.1$), $p = 0.042$).

3.4. Qualitative results on intervention acceptability

The data from both the phone interviews and communication from participants across the running of the trial are presented following framework analysis in Table 2 *Acceptability of the intervention*. Five overarching themes are related to: *i*) Aspects regarding the current online delivery, identifying advantages (e.g. accessible, privacy) and problems (e.g. memory and concentration problems). *ii*) Suggestions regarding any future delivery of such an intervention. Within this theme, most participants requested more time and to have more relevant patient stories. However, there were mixed views on the inclusion of existential material (i.e., end-of-life/ spiritual aspects) in any future version with nine participants seeing this as a positive future development, six being neutral or unsure on the matter, with four seeing such an addition as negative. *iii*) Validation of CBT skills, including psycho-education *iv*) Positive behaviour changes, including accessing help and improved engagement *v*) Generation of negative emotional states, with some participants continuing and some stopping the intervention. Overall, many participants noted utility of skills gained, reported positive behaviour changes, and valued internet delivery. However, some found the intervention upsetting, too pressured, and that symptoms interfered with the required concentration.

3.5. Treatment satisfaction

Following completion of the online intervention, participants rated an average positive satisfaction level of 4.3 ($n = 19$, range 3-5) on the 5-point Likert rating scale to the question "Overall, how satisfied are you with the Program?" (Devilley and Borkovec, 2000). Satisfaction scores were similar in each group (*Stable* (4.3, range 4-5) and *Progression* (4.4, range 3-5).

Table 2
Acceptability of the intervention.

Aspects of intervention	Participant statements
Aspects regarding the current online delivery	
Benefits of internet modality	
Own pace	"... do it on my own... whenever suited".
Can revisit	"Living rural and no support groups... It was somewhere to go to get help".
Privacy	"... go back and look at the different activities and lessons".
Ease of use	"... good to be able to be online and not have to talk to anybody".
Problems with internet modality	
Chemo-brain	"... read things a couple of times (sometimes) because my brain is a bit dulled". Later "(physically) unwell and I felt bad, but it was hard to concentrate".
Cancer progression	"... printed copies... some of the drugs I am on effect my memory".
Medication	
Comic format	
Pros	"I'm quite a visual person so the illustrations were good".
Cons	"Despite me moaning about the cartoons, I thought it was very easy to follow... and I thought it was pretty good".
Aspects regarding any future delivery (possible change)	
Timing between lessons	
Need more time	
Overall 48% (10/21)	"I didn't have enough time... it would be nice if there was that bit longer".
Stable 50% (6/12)	"A little bit longer... the pressure.... having a negative effect ... I wanted to finish it".
Progression 44% (4/9)	
Number of characters	
Positive regard	"The woman with breast cancer was really appropriate... I could recognise it very easily".
Understand limitations	"I don't think it is necessary to change the characters as I understood from the narrative of the characters the point that was being made and was happy to take what I needed".
Need more characters	"... would be nice to have another example ... someone living with metastatic cancer for a number of years".
Stable 58% (7/12)	"... third person to cover singles... couples without the children and/or families".
Progression 22% (2/9)	
Possible inclusion of existential themes (end-of-life/spiritual)	
Positive (9)	"... very important... would be appropriate"
Neutral (6)	"very few opportunities to put it out in open".
Negative (4)	"It would depend on how much in depth you want to go with it" "so that no-one was turned away".
	"Too much to deal with"
Validation of CBT skills	
Core CBT	
Education & normalisation	
	"I didn't realise I was anxious... showed me I am not alone... more accepting of myself".
	"There were people outside of my four walls who understood what it's like to be this way and that there are answers".
Relaxation & meditation	
	"I am sleeping better. When I do wake... and start worrying about things I focus on deep breathing and most often I go straight back to sleep. Very happy...".
	"... breathing exercises helpful. Did it on the bus on the way to the Ca"
Cognitive skills including thought challenging	
	"... most like the analysing your thoughts"
	"put yourself in front of a judge".
	"By using the proformas to write down my feelings and behaviours ... helped me to understand my feelings and work through the negative thoughts".
Behavioural skills including planning, pacing & activation	
	"Boom and bust cycle... program is giving me permission to tackle this which is somehow very important".
	"Exercise definitely helps lift me".
Tailored CBT	

(continued on next page)

Table 2 (continued)

Aspects of intervention	Participant statements
Scanxiety	"I liked the lesson on scan anxiety as I suffer from this quite badly". "... did also help reduce the anxiety when it came to scans".
Tailoring to (advanced) cancer	<i>"It wasn't just mental health, it knew that you had cancer".</i> <i>"... like(d) reading of someone else going through similar experiences to my own, because there are a lot of people that have early breast cancer and I find ... my experience is completely different".</i>
Positive behaviour changes Accessing face-to-face counseling 6 participants	"I saw a psychologist yesterday", attributes this positively to the course "Doing it, I then decided that I would go to a counsellor", wished to talk to someone about "mortality issues". <i>"I have contacted a (palliative care) counsellor which I believe is a forward step. I was trying to do it all alone".</i>
Improved engagement with clinicians and family 8 participants 3: regarding health care 5: regarding family	"It made me a little bit more assertive... if I was feeling they weren't helping me, I would explain why I needed it". <i>"I'm less nervous about ringing up (health professionals). Coughing up blood in the past I would have just kept quiet... allowed me to ring the nurse practitioner". "I'm not as embarrassed".</i>
Generation of negative emotions	
Negative emotions, continued with intervention 6 participants 1: regarding health care 3: regarding family 2: guilt/burden	<i>"I found myself feeling very anxious when I read Chris's section because it reflected some of what I was feeling".</i> <i>"at times it was hard to continue because it brought up issues I hadn't been aware of, but in the long run I needed to know so I could deal with them" "(confronting) in a good way because it made me aware of how I was feeling and I was unaware of it prior to that, like it actually triggered me, and I got upset".</i>
Negative emotions, ceased accessing the intervention 3 participants 1: anxiety 1: confronting 1: guilt	Ceased after Lesson 2 - "I have become a little more anxious as I focus on the materials". Ceased after Lesson 2 "I'm finding the ideas challenging" Later "I felt very guilty... so I just avoided it..."

Quotes in plain text:- cancer remained stable; Quotes in **bold italics**: cancer progressed.

3.6. Pre- to post-intervention outcome measures and effect sizes

Table 3 presents the means at baseline (pre) and post-intervention, and effect sizes for total scores on each of the outcome measures. In relation to the key outcome, depressive and anxious symptoms, in the overall group there was a large and significant within-group reduction between pre (baseline) and post-intervention for HADS-T ($g = 1.84$), with similar large and significant within-group reductions for both subscales (HADS-A $g = 2.12$; HADS-D $g = 1.14$). For the other measures, in the overall group there were large and significant within-group reductions for Total scores (K-10, $g = 1.57$; FACT-G Total, $g = -1.38$).

Supplement 3 gives results of each of the measures' pre-post total scores for the subgroups, *Stable* ($n = 12$) and *Progression* ($n = 7$). The emergence of the subgroups was unplanned and so the quantitative results are exploratory: for the key-outcome, HADS-Total, a pre-post reduction was seen in both subgroups.

Table 3

Changes from baseline (pre) to post-intervention and 3-month follow-up (3mfu).

Baseline (pre-) to post (n = 19)	Pre-intervention		Post-intervention		Pre-post paired t-test		
	Mean	SD	Mean	SD	t	p-value	g
HADS-total	18.95	6.15	10.53	5.41	5.66	0.000	1.84
HADS-Anxiety subscale	11.21	3.08	6.53	3.08	6.53	0.000	2.12
HADS-Depression subscale	7.74	4.36	4.00	3.96	3.52	0.002	1.14
K-10	26.21	6.87	17.26	5.66	4.85	0.000	1.57
FACT-G (+positive scales)	53.21	13.74	69.74	17.16	-4.25	0.000	-1.38

Baseline (pre) to 3-month follow-up (n = 16)	Pre-intervention		3mfu		Pre-3mfu paired t-test		
	Mean	SD	Mean	SD	t	p-value	g
HADS-total	17.94	5.58	10.69	4.82	5.70	0.000	2.02
HADS-Anxiety subscale	10.50	2.85	6.75	2.77	5.08	0.000	1.79
HADS-Depression subscale	7.44	3.84	3.94	2.79	4.91	0.000	1.74
K-10	25.88	6.23	17.69	3.53	5.75	0.000	2.03
FACT-G (+positive scales)	55.19	9.34	71.31	15.27	-4.99	0.000	-1.76

HADS - Hospital Anxiety and Depression Scale.

K-10 - Kessler-10 Psychological Distress Scale.

FACT-G - Functional Assessment of Cancer Therapy - General * positive scale. + = positive scale.

3.7. Pre-intervention (baseline) to 3-month follow-up outcome measures and effect sizes

Table 3 presents the means at baseline (pre) and 3-month-follow-up and effect sizes. Completed data sets for the overall group comprised $n = 16$. In relation to depression and anxiety, for the total group there was a large and significant within-group reduction between baseline and 3-month-follow-up for HADS-T ($g = 2.02$), with similar within-group reductions for both subscales (HADS-A $g = 1.79$; HADS-D $g = 1.74$). For the overall group there remained a large and significant within-group reduction for Total scores on each of the other measures (K-10, $g = 2.03$; FACT-G Total, $g = -1.76$).

Supplement 3 shows further data for the *Stable* ($n = 12$) and *Progression* ($n = 4$) subgroups. On exploratory analysis, there was a pre-post reduction for both the *Stable* subgroup and for the *Progression* subgroup.

3.8. Clinician time spent contacting participants

The clinician spent on average a total of 70 min ($SD = 30$) across the trial per participant on email and telephone contact (*Stable* = 64 min, $SD = 25$; *Progression* = 71 min, $SD = 34$). Clinician contact included personalised emails at set points to each participant (e.g., after lesson 1 & 2) and also replying to clinical queries. It did not include time spent setting up the automated prefilled emails nor the technical troubleshooting. Online Supplemental 1 (*Summary of running the iCanADAPT Advanced trial including Semi-structured telephone interview*) further outlines the timing and nature of the clinician contact.

4. Discussion

This is the first trial of an internet intervention, in this case internet delivered cognitive behavioural therapy (iCBT), for clinical depression and/or anxiety in those with advanced cancer. It adds to the emerging

literature base into the role of internet interventions in addressing the unmet psychosocial needs for those living with advanced cancer. The open trial demonstrated the feasibility of the online intervention with no major barriers to recruitment and participants engaging well in the trial. This is in keeping with two recent studies of women with metastatic breast cancer showing firstly, high rates of internet use (Kemp et al., 2019) and secondly, increasing comfort in accessing online support (Kemp et al., 2018). The rates of progression of cancer were unexpected and may be accounted for by the heterogeneous mix of cancer types. While five-year cancer survival rates are improving overall there is a huge variation according to cancer type and stage (Welfare, 2019). No clinical baseline factors were identified that would predict progression and none of the participants on eligibility criteria were considered in a terminal phase of illness. Progression of disease was similarly reported as an influential factor in earlier trials for advanced cancer (e.g. group CBT for women with Stage IV breast cancer (Edelman et al., 1999)), and similarly in a recent study of 28 participants with various advanced cancer diagnoses who also noted progression and a death in a short time frame (Wells-Di Gregorio et al., 2019). This was not noted however in a recent trial of a cognitive behaviour stress management intervention delivered via a tablet (Yanez et al., 2015) in a group of patients with prostate cancer (Stage III and IV only), again indicating that the specifics of the cancer diagnosis and stage are important.

Many participants engaged with the intervention without any concerns. Participants who had a progression of disease completed fewer lessons than their counterparts with stable disease. The trial identified that some participants had difficulties (e.g. memory problems and fatigue) that interfered with using an online intervention. This makes clinical sense given the multitude of sequelae caused by cancer and its treatments. These findings need to be considered when developing any future online interventions for those with advanced cancer. Future internet interventions may wish to divide the mental burden and time needed at each key skills, even if this means increasing the number of lessons; similarly, they may wish to allow participants to choose when to access the next lesson i.e., allow participants to select their own timings that go parallel to physical health treatment schedules. This trial also allows the calculating of participant numbers for future trials; such future trials will gain further information on the most helpful aspects of the intervention in this particular population.

The *qualitative* data for iCBT obtained in this specific group of advanced cancer patients was favourable and the data obtained can be supplemented by the growing qualitative literature base in the general adult population (Patel et al., 2020). Side-effects of CBT are increasingly being recognised (Schermuly-Haupt et al., 2018) and future trials should plan to formally capture their nature and frequency. However, the benefits seen in the *quantitative* measures are promising and the observed benefit persisted at the 3-month follow-up. Both sets of results show that transdiagnostic iCBT as a specific online intervention modality for the treatment of clinical depression and/or anxiety in future trials of internet interventions is reasonable. The general positive direction on all measures is in keeping with the changes seen in a RCT of transdiagnostic iCBT in cancer survivors with clinical depression and/or anxiety (Murphy et al., 2020). Moreover, the sample was more anxious than depressed with nearly all participants meeting the criteria for at least one anxiety disorder; this may be why the results are more in line with the recent randomized trial results of CBT-app for anxiety in advanced cancer (Greer et al., 2019) showing that both CBT and psychoeducation provided benefit, rather than the results of face-to-face CBT for depression in advanced cancer (Serfaty et al., 2019) which did not find a significant benefit for CBT over usual care. More in keeping with the transdiagnostic approach of this trial, a recent randomized trial ($n = 28$) evaluated a three-session face-to-face CBT-ACT (acceptance-based cognitive behavioural - acceptance and commitment therapy) intervention versus waitlist. The intervention targeted a cluster of symptoms (worry-insomnia-depression-fatigue); results showed that a brief psychosocial intervention in people with advanced cancer was

feasible and had preliminary efficacy (Wells-Di Gregorio et al., 2019).

The authors are similarly aware of increasing interest in non-structured therapies (such as dignity therapy (Li et al., 2019)) for managing depressive and anxious symptomatology in those with advanced cancer. However, there are barriers in transforming many of the meaning-centred therapies into an online intervention. Less than half of the participants in this study were open to discussions of existential matters which is at the core of some therapies. For example, dignity therapy was first conceived to assist those facing existential distress matters, in terminally ill inpatients and those receiving home-based palliative care services (Chochinov et al., 2005). Another therapy modality that can improve quality of life of those living with advanced cancer is group Supportive Expressive Therapy (Kissane et al., 2007; Spiegel et al., 2007); however, this does not easily translate to an online format.

Any future trial in the advanced cancer population may wish to continue to have clinician support as the satisfaction rates achieved were high with this model; this is in keeping with a recent systematic review found that guidance can be a favourable feature of internet interventions (Baumeister et al., 2014). Internet interventions are still novel in this population and so we would recommend that future studies make formal *direct* enquiries about participant physical health status at specific points (e.g., ask every month about concentration/ memory problem, and ask whether the participant had any changes to their physical health treatments etc.). This would allow future studies to better identify and/or address barriers to engagement. A limitation of our study was that we relied on participants volunteering physical and/or cognitive concerns in an *indirect* manner across the study; with a solitary direct enquiry at the 3-month follow-up about obstacles. A further limitation of this study is that it was an open trial, with no control group, and a small sample size, and so over-valuation of the results is unwise.

Given the findings of this study, and that CBT translates well into an online format, and that other therapeutic modalities may not suit such an online approach, a randomized controlled trial of transdiagnostic iCBT may be reasonable in this population in order to evaluate evidence-based methods of improving peoples living with advanced cancer with an online intervention.

4.1. Conclusion

This study can inform future research and practice in e-mental health for people living with advanced cancer. The scalability of internet delivered psychotherapies, including iCBT, can ensure increased access to evidence-based therapy for many more cancer patients. This open trial shows that clinician supervised iCBT is feasible and acceptable for the management of clinical range depression and/or anxiety in those living with advanced cancer. However further development and research is warranted to better conceptualise the best methods of delivery in this clinical context.

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Declaration of competing interest

The authors declare no conflicts of interest. The views expressed herein are those of the authors and are not necessarily those of the Cancer Institute NSW.

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