Optimizing psychosocial support and symptom management for patients with advanced cancer

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CHAPTER 3

Screening and stepped care targeting psychological distress in patients with metastatic colorectal cancer: the TES cluster randomized trial

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Abstract

Background

Psychological distress occurs frequently in patients with cancer. This study evaluated the effectiveness of a screening and stepped care program (the TES program) in reducing psychological distress compared to usual care in patients with metastatic colorectal cancer (mCRC) starting with first line systemic palliative treatment.

Patients and methods

Patients with mCRC starting first line systemic palliative treatment were eligible. In this cluster randomized trial, 16 hospitals were assigned to the TES program or care as usual (CAU). Patients in the TES arm were screened for psychological distress with the Hospital Anxiety and Depression Scale (HADS) and Distress Thermometer/Problem List (at baseline, 10 and 18 weeks). Stepped care was offered to patients with distress or expressed needs, and consisted of watchful waiting, guided self-help, face-to-face problem-solving therapy, or referral to specialized mental health care. The primary outcome was change in psychological distress over time (HADS); secondary outcomes were quality of life (QOL), satisfaction with care, and recognition and referral of distressed patients by clinicians. Linear mixed models and effect sizes (ES) were used to evaluate differences.

Results

349 patients were randomized; 184 received the TES program and 165 CAU. In the TES arm, 60.3% of the patients screened positive for psychological distress; 26.1% of patients entered the stepped care program (14.7% only used watchful waiting, and 11.4% used at least one of the other treatment steps). There was no difference in change in psychological distress over time between the two treatment groups (ES=-0.16,95%CI=-0.35;0.03, p>0.05). The TES group reported higher satisfaction with the received treatment and better cognitive QOL (all p-values <0.05).

Conclusion

A combined screening and treatment program targeting psychological distress in patients with mCRC does not improve psychological distress. Our results suggest that enhanced evaluation of psychosocial concerns may improve aspects of patient's well-being.

Introduction

Cancer diagnosis and treatment are often associated with elevated levels of psychological distress[1]. Psychological distress ranges from normal feelings (e.g. vulnerability, sadness) to severe problems (e.g. major depressive disorder, anxiety disorder)[2], which may cause poorer quality of life (QOL), reduced adherence to treatment, and potentially a poorer prognosis[3-5]. Routine screening for distress is recommended by a number of major cancer organizations, with the assumption that identification of elevated levels of distress will result in increased uptake of psychosocial services and reduction in distress[2,6]. Multiple psychosocial interventions for patients with diagnosed distress have been shown to be effective[7,8], but so far, there is no conclusive evidence that the combination of screening and subsequent treatment for distress actually improves patient outcomes [Supplemental material, Review / Table 1]. It has been suggested that for screening programs to be effective, these should be designed to target and follow-up on patients' actual needs, in order to direct patients to appropriate psychosocial services[9,10]. In line with these suggestions, we developed the TES program. In the TES program, targeted selection (T), enhanced care (E), and referral to well-described effective interventions using a stepped care oriented approach (S) were combined to create optimal conditions for a screening and treatment program targeting psychological distress. The aim of this cluster randomized trial was to assess the effectiveness of the TES program to improve psychological distress compared with care as usual (CAU) in patients with metastatic colorectal cancer (mCRC) starting with first line systemic palliative treatment. Secondary aims were to assess effects of the TES program on QOL, patient satisfaction with the care offered, actual recognition and management of distressed patients by clinicians, and evaluation of the cost-effectiveness of the TES program in comparison with CAU.

Patients and methods

Study design and population

This study was a multicenter, cluster randomized trial (CRT), approved by the Medical Ethics Committee of VU University Medical Center and registered in the Netherlands Trial Register (NTR4034). An extensive description of the study protocol has been published previously[11]. All procedures were in accordance with the ethical standards of the Medical Ethics Committees and with the Helsinki Declaration.

Patients were recruited from the medical oncology departments of 16 participating hospitals in the

Netherlands between July 2013 and October 2016. Eligible patients had a diagnosis of metastatic colorectal cancer, were scheduled to start palliative treatment with first line chemotherapy, and had a life expectancy of more than three months. Exclusion criteria were age < 18 or > 85 years, insufficient command of the Dutch language, recent psychotherapy (in the past three months, at least one session every two weeks), and severe psychopathology (i.e. suffering from mental illnesses that require (acute) inpatient treatment). All patients provided informed consent.

Randomization and blinding

In this CRT, hospitals were selected as the unit of randomization to avoid contamination of treatment between groups. The randomization procedure was performed prior to patient recruitment by a blinded statistician. Blinding of patients, oncologists, nurses and psychologists was not possible due to the nature of the intervention. Statistical analyses were performed blindly.

TES program and CAU

A detailed description of the TES program can be found elsewhere[11]. In short, patients in the hospitals assigned to the TES arm were screened for psychological distress by a trained nurse/clinical nurse specialist before start of treatment (S0), and 10 (S10), and 18 (S18) weeks thereafter. Screening was performed using the Hospital Anxiety and Depression Scale (HADS)[12] and Distress Thermometer/Problem List (DT/PL)[13,14]. Scores of ≥13 on the HADS[12] or ≥5 on the DT[13] were seen as indicators for elevated psychological distress. After evaluating the distress scores together with the patient, the trained nurses offered treatment in the form of stepped care to patients scoring above the cut off scores of either one of the screening tools, and to patients expressing the need for receiving psychosocial care. The steps included: (1) watchful waiting; (2) a guided self-help program via the Internet or a booklet; (3) face-to-face problem solving treatment (PST) offered by a trained nurse; and (4) referral to specialized psychosocial services and/or psychotropic medication. In contrast, in the hospitals assigned to CAU, distress was identified by oncologists and nurses on an *ad hoc* basis only (when the patient expressed psychosocial concerns or the oncologists and nurses suspected psychosocial concerns). To these patients non-standardized regular care was delivered in the form of advice or referral to other services. Three hospitals assigned to CAU introduced screening for psychological distress. Contrary to the TES program, in

these hospitals screening was used as a stand-alone tool, without standardized follow-up and algorithms to guide triage (patients from these three hospitals were excluded in a sensitivity analysis; see below).

Outcomes

Outcome measures were collected at baseline (T0), shortly after start of treatment (T1), after 10 (T2), 24 (T3) and 48 (T4) weeks in both treatment arms. The primary outcome was the difference in course of distress measured with the HADS[15] between treatment arms over time. The HADS is a 14-item self-assessment scale for measuring distress. The HADS does not contain items which might also be symptoms of physical illness (such as loss of appetite) and has been widely used in research on cancer patients (e.g.[12,16]). The HADS total score ranges from 0-42. Secondary outcomes were differences in the course over time in QOL, assessed with the functioning scales and global score of the EORTC-QLQ-C30 version 3.0[17], patients' evaluation of psychosocial care assessed with the Client Satisfaction Questionnaire-8 (CSQ-8)[18], and actual recognition and referral related to psychological distress by clinicians in both treatment arms assessed by data extracted from medical records. The results on cost-effectiveness will be reported elsewhere.

Sample size

The sample size calculation was based on the effectiveness of screening and treatment *in all patients* in the TES group, including patients who were not offered or did not use stepped care after screening. The expected proportion of patients in the TES group treated for psychological distress was 33%[1], in whom an effect size (ES) of d=0.54 was expected[19]. The remaining 67% of patients without treatment had an expected ES of d=0. The overall expected ES was therefore d=0.18. To demonstrate this effect on the primary outcome measure (i.e. HADS) using a longitudinal design with four follow-up measurements, setting the within-subject correlation rho=0.3, alpha=0.05 (two-tailed), power (1-beta)=0.80, a total of *n*=302 patients was needed in each group. In a CRT, patients within a cluster (i.e. hospital) cannot be assumed to be independent. Assuming an intra cluster correlation of 0.005[20], a total of 715 patients was needed, i.e. 359 in each group.

Statistical analyses

Analyses were based on the intention-to-treat principle. Descriptive statistics were used to describe the baseline values of demographic and clinical variables in both arms. Linear mixed model (LMM) analyses were

conducted to evaluate the differences in psychological distress and secondary outcomes between the TES arm and CAU. Both discrete time models and linear time models were conducted. The LMM's considered three levels: measurements of individuals at the lowest level, individuals at the second level, and hospitals at the highest level. In the discrete time models, fixed effects were estimated for the four time indicators, for the four group by time two-way interaction terms, and for disease progression that we added as a covariate. In the linear time model, fixed effects were estimated for time, the group by time two-way interaction term, and for progression as a covariate. It should be noticed that no main effect for the group membership was estimated, thus correcting for baseline differences between the two intervention groups[21]. At the second level, error terms within persons were allowed to be correlated according to an unstructured covariance matrix, while at the highest level a random intercept for hospitals was used. Cohen's formula was used to calculate effect sizes from the estimated differences, using pooled (across intervention groups) pre-test standard deviations[22]. Since LMM analyses are able to handle missing observations due to dropout under the Missing At Random assumption, no additional actions were undertaken for handling missing data. A sensitivity analysis was performed excluding patients enrolled in the three hospitals assigned to CAU that offered routine screening for psychological distress. For all statistical analyses, *p*-values <0.05 were considered statistically significant. Data were analyzed using IBM SPSS statistics version 22.0 (IBM Corp., Armonk, NY) and Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

In-between futility analysis

During the recruitment period, the actual proportion of patients treated for psychological distress in the TES group appeared to be lower than expected. After recruitment of 321 patients, the observed proportion of patients receiving active treatment (not including watchful waiting) in the TES group was 8.7% (95% CI = 5.1%, 13.7%), instead of the initially expected proportion of 33%. The low uptake of active treatment resulted in a decrease of the expected ES. The unplanned futility analysis showed that with the planned number of 715 patients, the conditional power would be small (power = 0.11) (Supplemental material Table 2). The planned power of 0.80 would require recruitment of an unrealistic number of patients (*n*=33,318). To prevent burdening additional patients in palliative treatment, the Medical Ethics Committee recommended to close the study for further patient entry and to report on the results in the patients already included.

Study population

Sixteen departments of Medical Oncology consented to participate and were either allocated to the TES program (*n*=8) or CAU (*n*=8). No hospital dropped out during the study. The first patient was enrolled on July 29, 2013, the final assessment of the last patient was on October 20, 2017. Out of 393 patients meeting the inclusion criteria and willing to participate, 349 patients participated in the study, 184 in the TES arm, and 165 in the control arm receiving CAU (Figure 1, CONSORT diagram). During the study 98 patients died (47 patients (25.5%) in the TES group versus 51 patients (30.9%) in the CAU group (*p*=0.263)). After 48 weeks of follow-up (T4), 110 patients (59.8%) in the TES arm and 98 patients (59.4%) in the CAU arm completed the outcome assessment.

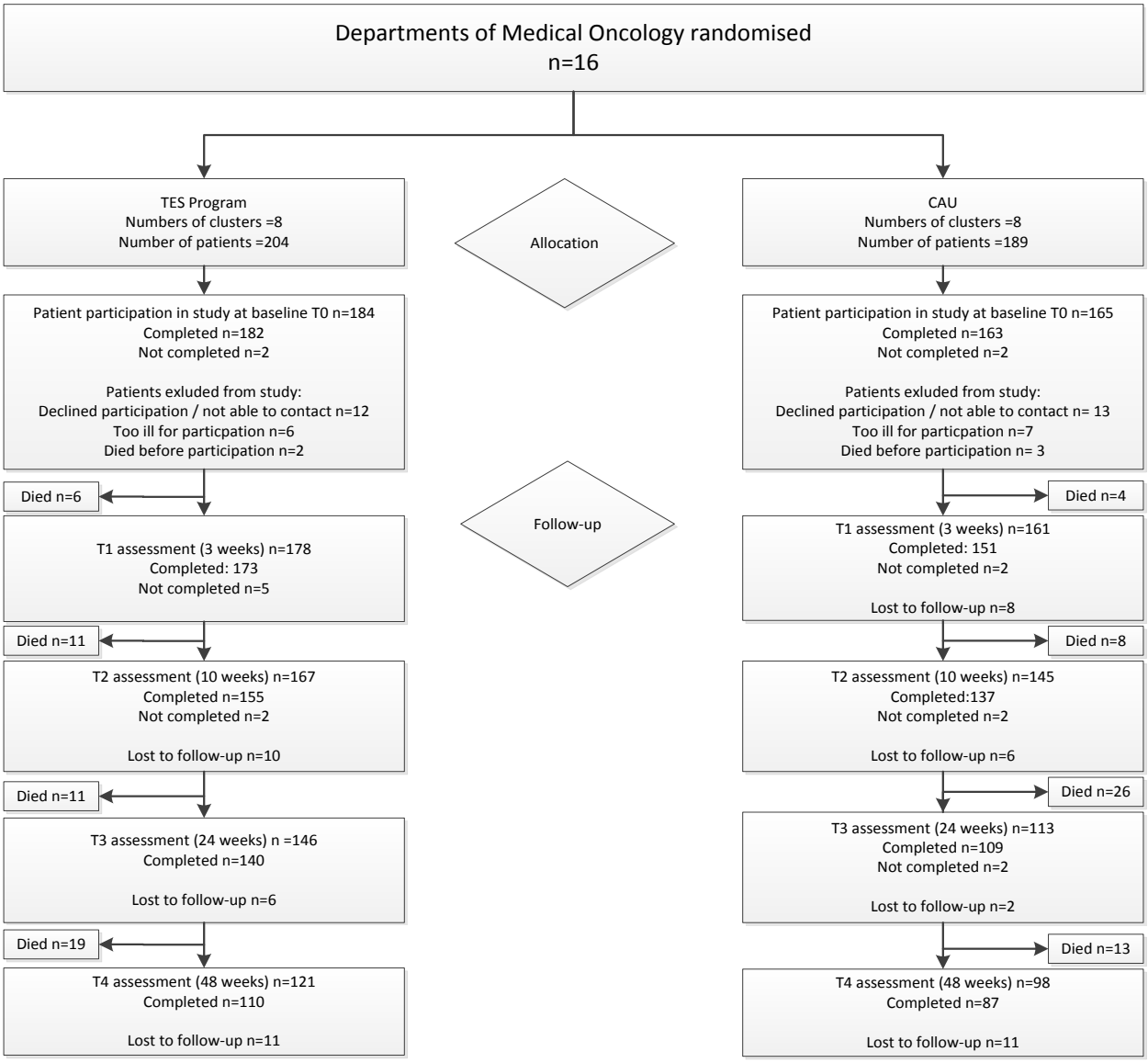


Figure 1 CONSORT Diagram: Study flow chart

At baseline, the TES and CAU groups were comparable regarding sociodemographic and most clinical characteristics (Table 1). Patients in the TES arm more often received prior treatments for their metastases (27.7%) than CAU patients (15.2%) and presented with peritoneal lesions more frequently (31.0% vs 20.0%) (Supplemental material S3). Mean HADS scores at baseline were lower in patients assigned to the TES arm than in patients assigned to the CAU arm. The EORTC QLQ-C30 at baseline showed better scores for role functioning and social functioning in the TES group. When comparing baseline characteristics of patients who completed the study and patients who dropped out before the last assessment, completers had better ECOG PS scores and were more often male (all *p*'s <0.05, data not shown).

Screening, enhanced care and use of stepped care in TES arm

According to protocol 552 screenings had to be performed and subsequently evaluated by clinical nurse specialists in the 184 patients enrolled in the TES arm (i.e. 3 screenings per patient). A total of 480 screenings and evaluations (87.0%) were accomplished in the 8 hospitals assigned to TES. Thirty five of the 72 screenings not accomplished were the result of patients that dropped out due to death or disease progression; the remaining 37 of 552 screenings were missed (6.7%) (Figure 2).

Out of 184 patients in the TES arm, 111 (60.3%) patients screened positive for elevated distress assessed by the HADS and/or the DT/PL on at least one of the screenings (i.e. S0, S10 and S18) (Figure 2). Forty six (25.0%) patients in the TES arm entered stepped care after screening. In addition, two patients without elevated distress scores entered after expressing the need for psychosocial care. Out of 184 patients in the TES arm, 27 (14.7%) only used watchful waiting, and 21 (11.4%) used at least one of the following steps. Overall, a total of 62 interventions were used by these 48 patients. Step 1 (watchful waiting) was used most frequently by 38 patients; of those, three patients chose to undergo watchful waiting for a second time. Two patients entered step 2 (self-help intervention); however, neither one of those two patients actually started this treatment due to disease progression. Step 3 (face-to-face PST) was provided to one patient. A total of 18 patients were referred to specialized psychosocial care (step 4)(Table 2).

Effectiveness of the TES program

Means and standard deviations (observed scores) of the HADS scores and secondary outcomes are summarized in Supplemental material S4. There was no evidence of an intervention effect on HADS scores at any time point

Table 1 Baseline characteristics of patients participating in the TES study			
	Total group (n=349) (n,%)	TES program (n=184)(n,%)	CAU (n=165)(n,%)
Age, years			
Mean age (SD)	66.1 (10.2)	66.25 (9.8)	65.84 (10.6)
Gender			
Male	224 (64.2)	113 (61.4)	111 (67.3)
Female	125 (35.8)	71 (38.6)	54 (32.3)
ECOG PS			
0	82 (23.5)	48 (26.1)	34 (20.6)
1	105 (30.1)	71 (28.6)	34 (20.6)
2	11 (3.2)	6 (3.3)	5 (3.0)
Missing	151 (43.3)	59 (32.1)	92 (55.8)
Primary tumor location			
Right-sided	107 (30.7)	62 (33.7)	45 (27.3)
Left-sided	239 (68.5)	121 (65.8)	118 (71.5)
Missing	3 (0.9)	1 (0.5)	2 (1.2)
Chemotherapy regimen			
Capecitabine	72 (20.6)	36 (19.6)	36 (21.8)
CAPOX	240 (68.8)	124 (67.4)	116 (70.3)
FOLFOX	24 (6.9)	17 (9.2)	7 (4.2)
Other	10 (2.9)	1 (0.5)	
Missing	3 (0.9)	1 (0.5)	2 (1.2)
Marital status			
Married/domestic partnership	256 (73.4)	133 (72.3)	123 (74.5)
Unmarried/divorced/widowed	89 (25.5)	49 (26.6)	40 (24.2)
Missing	4 (1.1)	2 (1.1)	2 (1.2)
Education			
Low	19 (5.4)	10 (5.4)	9 (5.5)
Middle	223 (63.9)	122 (66.3)	101 (61.2)
High	101 (28.9)	49 (26.6)	52 (31.5)
Missing	6 (1.7)	3 (1.6)	3 (1.8)
Currently working			
Yes	81 (23.2)	39 (21.2)	42 (24.5)
No/retired	264 (75.6)	143 (77.7)	121 (73.3)
Missing	4 (1.1)	2 (1.1)	2 (1.2)
Time from diagnosis primary tumor until start study			
<1.5 months	116 (33.2)	52 (28.3)	64 (38.8)
1.5-10 months	114 (32.9)	66 (35.9)	48 (29.1)
>10 months	116 (33.2)	65 (35.3)	51 (30.9)

Table 1 Baseline characteristics of patients participating in the TES study			*continued*
Missing	3 (0·9)	1 (0·5)	2 (1·2)
Distress HADS (SD)	9·52 (6·6)	8·8 (6·5)	10·3 (6·7)
Quality of life (QLQ-C30)			
Physical functioning	74.4 (20.6)	76.0 (20.9)	72.6 (20.2)
Role functioning	64.3 (30.7)	68.3 (28.9)	59.8 (32.0)
Emotional functioning	77.1 (18.9)	78.3 (18.1)	75.9 (19.8)
Cognitive functioning	88.9 (15.4)	89.8 (14.2)	88.0 (16.5)
Social functioning	76.2 (25.8)	79.3 (23.8)	72.8 (27.5)
Global QOL	63.0 (21.8)	64.9 (22.0)	60.9 (21.3)

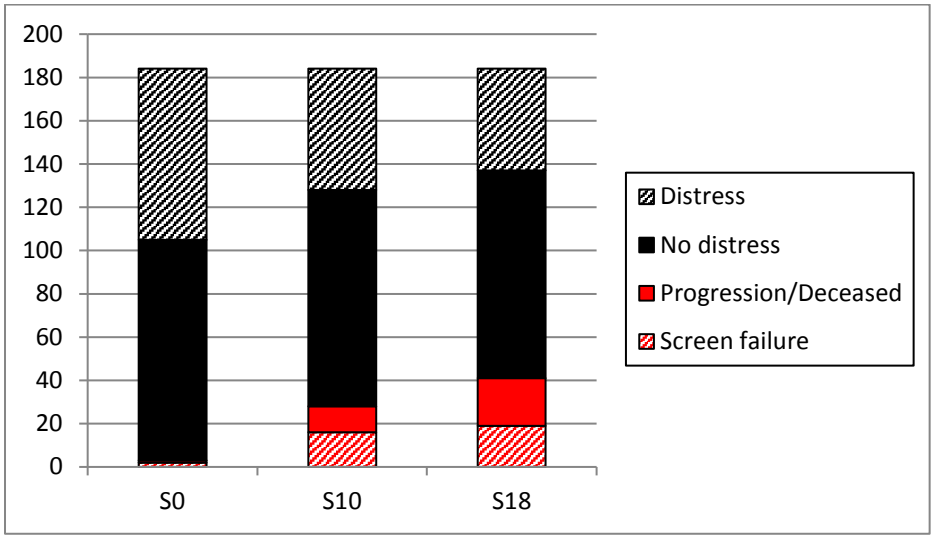


Figure 2 Distress screening with HADS and DT/PL in TES arm

Out of 184 patients in the TES arm, 111 (60.3%) patients screened positive for elevated distress assessed by the HADS and/or the DT/PL on at least one of the screenings (e.g. S0, S10 and S18). A total of 79 (42.9%), 56 (30.4%) and 47 (25.5%) out of 184 patients screened positive for elevated distress assessed by the HADS and/or the DT/PL at S0, S10 and S18, respectively. Out of 552 screenings planned, a total of 480 (87.0%) screenings were performed. 35 of the 72 screenings not executed, were the result of patients that dropped out due to death or disease progression, the remaining 37 of 552 screenings were missed (6.7%) (Figure 2).

Table 2 Stepped care in TES arm	TES arm (n=184)
	Patients using stepped care, n (%)
Watchful waiting	27 (14.7)
Active stepped care treatment	21 (11.4)
Self-help program	2 (1.1)
Problem solving treatment	1 (0.5)
Specialized psychosocial care	18 (9.8)
Total of patients using stepped care	48 (26.1)

(discrete time models, all *p*-values >0.05; effect sizes d ≤ 0.16) (Table 3, Figure 3). Similarly, the course of distress over time did not differ between patients in the TES and CAU arm (linear time model, *p*=0.093; effect size d = 0.16) (Table 3, Figure 4). For the course of secondary endpoints between groups over time, a positive effect on patient satisfaction (*p*=0.009) and cognitive functioning (*p*=0.003) was seen in the intervention arm (Table 3). Symptoms of distress were recognized by clinicians in 79 (42.9%) patients in the TES group and in 62 (37.6%) patients in the control group (*p*=0.309). Also no difference between groups was found regarding referral of distressed patients by clinicians (*p*=0.264), which was reported for 30 (16.3%) and 20 (12.1%) of patients in the TES and control group, respectively (Table 3, Supplemental material S4).

The sensitivity analysis conducted in 269 patients (i.e. excluding patients in the CAU arm from the three hospitals that provided screening) demonstrated the robustness of the primary findings. No evidence of an intervention effect on HADS scores at any time point (discrete time models, all *p*-values >0.05; effect sizes d ≤ 0.12), or on the course of distress over time (linear time model, *p*=0.479; effect size d = 0.08) was found (data not shown).

Discussion

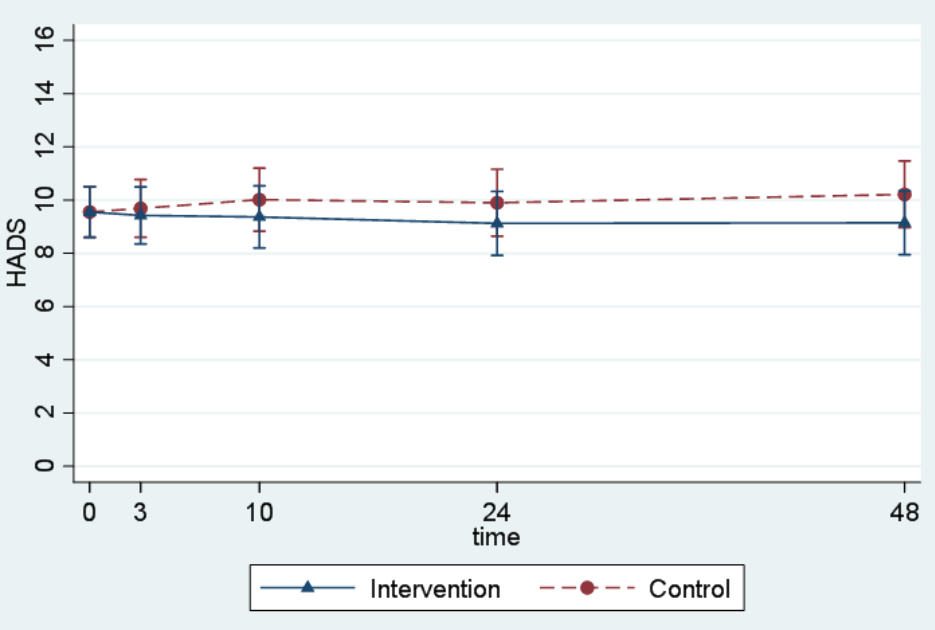
In this cluster randomized study, we found no evidence that a combined screening and treatment program targeting psychological distress in patients with mCRC improves psychological distress. The course of distress did not differ in patients assigned to the TES group compared to patients in the CAU group. Previous studies already revealed that screening for distress alone is not enough to improve distress[23] [Supplemental material: review, S1], but suggested that screening when followed-up with further assessment of specific needs and appropriate referral and treatment could lead to improvement in patient outcomes[9,10]. However, the results of the present study demonstrate that the combination of screening, triage and referral to appropriate services did not result in better distress outcomes. Therefore, there is no evidence to support implementation of screening for distress into routine cancer care, even when combined with triage and referral for treatment.

Table 3 Test statistics and effect sizes of the differences in primary and secondary outcomes between TES program and CAU arm, from LMM analyses

		Discrete time model			Linear time model		
Primary outcome		Test statistic	*p*-value	Effect size (*d*)[1)]	Test statistic	*p*-value	Effect size (*d*)[1)]
Distress	3 weeks	z=-0.54	0.590	-0.04			
(HADS)	10 weeks	z=-1.07	0.283	-0.10			
	24 weeks	z=-1.17	0.240	-0.12			
	48 weeks	z=-1.62	0.104	-0.16	z=-1.68	0.093	-0.16
Secondary outcomes							
Physical functioning	10 weeks	z=2.72	0.006	0.26			
(QLQ-C30)	24 weeks	z=0.28	0.779	0.03			
	48 weeks	z=1.39	0.164	0.17	z=1.27	0.204	0.15
Role functioning	10 weeks	z=0.94	0.345	0.10			
(QLQ-C30)	24 weeks	z=-0.22	0.826	-0.02			
	48 weeks	z=0.48	0.630	0.06	z=0.30	0.767	0.04
Emotional functioning	10 weeks	z=0.72	0.474	0.07			
(QLQ-C30)	24 weeks	z=1.02	0.306	0.12			
	48 weeks	z=1.35	0.178	0.17	z=1.36	0.175	0.17
Cognitive functioning	10 weeks	z=1.98	0.048	0.23			
(QLQ-C30)	24 weeks	z=2.61	0.009	0.34			
	48 weeks	z=2.09	0.037	0.31	z=2.58	0.010	0.37
Social functioning	10 weeks	z=1.33	0.182	0.13			
(QLQ-C30)	24 weeks	z=0.66	0.507	0.08			
	48 weeks	z=-0.40	0.689	-0.05	z=-0.51	0.613	-0.06
Global functioning	10 weeks	z=1.61	0.107	0.17			
(QLQ-C30)	24 weeks	z=-0.16	0.870	-0.02			
	48 weeks	z=1.74	0.083	0.21	z=1.44	0.149	0.17
Patient Satisfaction[2)]	24 weeks	z=0.89	0.371	0.08			
(CSQ-8)	48 weeks	z=2.98	0.003	0.31	z=2.99	0.003	0.31
Recognition distress by clinicians	79 (42.9%) vs 62 (37.6%)	z=-1.02	0.309	0.11			
Referral distress by clinicians	30 (16.3%) vs 20 (12.1%)	z=-1.12	0.264	0.12			

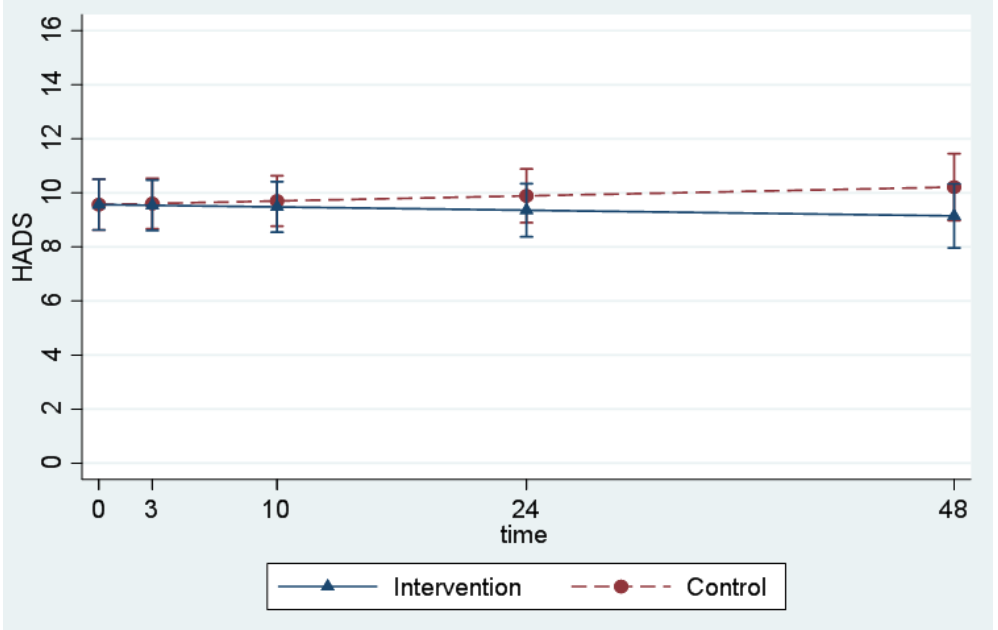
[1)] Effect size obtained by standardizing the group-by-time interaction term from the Linear Mixed Model using the pooled within group standard deviations [2)] Outcome variables were administered at 10 weeks, 24 weeks and 48 weeks only and corrected for differences at 10 weeks.

Figure 3 Predicted means of HADS score (with error bands) in the TES arm versus CAU arm from an LMM analysis using a discrete time model



Predicted means of HADS score (with error bands) in the TES group (Intervention = blue line) versus CAU arm (Control = red dotted line) over the different time points in weeks from an LMM analysis using a discrete time model. No differences in HADS score at the different time points between groups. HADS: Hospital Anxiety and Depression Scale. LMM: Linear Mixed Models.

Figure 4 Predicted course of HADS score (with error bands) in the TES arm versus CAU arm from an LMM analysis using a linear time model



Predicted means of HADS score (with error bands) in the TES group (Intervention = blue line) versus CAU arm (Control = red dotted line) over time in weeks from an LMM analysis using a linear time model. No differences in HADS score over time between groups. HADS: Hospital Anxiety and Depression Scale. LMM: Linear Mixed Models.

Psychological treatment in patients with cancer has been shown to effectively reduce psychological distress[7]. However, the present trial was not designed to study the effectiveness of psychological treatment per se; instead, the aim was to study the effectiveness of screening for psychological distress and offering treatment if indicated. The absence of effect of this combined approach is most likely the result of the low use of stepped care in the intervention group. In the TES arm, 26.1% of patients entered the stepped care program, with only 11.4% using genuine active treatment to address psychological distress, and 14.7% just using watchful waiting. The low uptake of care, despite a rather high rate of distressed patients, is consistent with findings in other studies showing low acceptance rates of psychological treatment ranging from 3-10%[24-26]. Empirical evidence is accumulating that an elevated level of distress does not equate the need for support[13,26]. Some patients needing psychological support show no signs of distress, while other patients with elevated levels of distress do not report unmet needs[27]. The results of our study further underscore these findings and challenge the assumption that screening for distress helps to ensure identification of patients in need of support[28]. Alternatively, developing valid indicators of the need for psychological treatment is an urgent research priority[26].

Patients assigned to the TES group reported higher satisfaction with care and better cognitive function as compared to patients assigned to the CAU group. Also, patients in the TES arm tended to have better QOL scores over time, compared with patients in the CAU group although not statistically significant. A plausible explanation is that enhanced discussion of psychosocial concerns by nurses and oncologists improves well-being in patients with mCRC. It has been previously suggested that, rather than implementing screening, patients could be simply asked whether they would like to discuss any psychosocial concerns with oncologic or psychosocial staff, regardless of their level of distress[29]. Indeed, patients' emotional well-being and QOL outcomes have been shown to improve after solely evaluating psychological issues with staff [30].

Limitations of this study include the following. The observed low use of the stepped care program led us to pursue the futility analysis, resulting in the halted recruitment for this study. The low uptake of psychological treatment, which is consistent with findings in other studies (see above), results in a small overall effect size of routine screening and subsequently offering treatment if indicated. The results of the present study demonstrate that only a very large trial would be sufficiently powered to detect the small overall effect size:

our data suggested that *n*=33,318 patients would be required to achieve the planned power of 0.80. One might question the clinical relevance of such a modest effect size of screening and subsequent treatment, even it would be statistically significant. Second, even though several studies have shown the HADS to be effective in detecting clinically significant elevations of distress in oncology populations[12], it was recently shown that a range of psychosocial concerns are not covered by the HADS, especially those expressed by young, male patients[31]. Yet, in the present study, the DT/PL was used in addition to the HADS; and trained nurses evaluated all screening results with patients, enabling them to identify additional patients in need of psychosocial care, not identified by the HADS or the DT/PL. Furthermore, 60% of patients in the TES arm were identified as being distressed, which is considerably higher than percentages reported in previous studies[13,32]. Our results illustrate that screening patients for distress at multiple time points increases the total number of identified distressed patients considerably. In addition, by combining two validated screening tools (i.e. HADS and DT/PL) we further increased the rate of identified distressed patients.

A strength was that this study was conducted in 16 oncology departments and a cluster random design was used, which minimized the risk of contamination. Further, we created optimal conditions for a standardized screening and referral program, with marked contrasts existing between the intervention and CAU arm. Our findings showed that 89% of planned screenings and evaluations were indeed performed, indicating successful intervention delivery in the TES arm[33]. The high protocol adherence enhanced the likelihood of finding differences in distress over time between the two arms. Three out of eight hospitals assigned to CAU offered routine screening for psychological distress (without standardized follow-up and algorithms to guide triage): the sensitivity analysis excluding patients enrolled in these hospitals yielded similar results as the primary analysis, thereby strengthening our conclusion and confirming its robustness. Another strength of this trial was the timing and the multiple time points of screening for distress (e.g., at start of treatment, after 10 and 18 weeks). Previous intervention studies offering screening and subsequent treatment were designed to screen and treat directly at diagnosis[25], or only once[34], while the importance of monitoring emotional problems and distress over time has been highlighted[35].

In conclusion, we found no evidence that screening and subsequent treatment for psychological distress improves psychological distress. Our findings, however, suggest that enhanced discussion of psychosocial concerns may improve aspects of patient's well-being.

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Supplemental material

Review: Evaluation of distress screening on psychological well-being

Aim

The objective of this review was to evaluate the effect of screening programs for psychological distress in patients with cancer on psychological well-being.

Methods

Search strategy

PubMed was searched with the terms “distress”, “screening”, “randomized trial”, and “cancer OR oncology” for English-language studies published from inception up to February 20, 2018. Manual searches were done on relevant systematic reviews[1-3].

Selection criteria and analyses of eligible studies

Eligible articles included English-language studies on patients with any type of cancer at any disease stage and treatment that reported original data. RCTs that compared outcomes of psychosocial well-being between patients who underwent screening for psychological distress and those who did not were included. Studies were excluded if the control group also received screening (even in absence of subsequent discussion or treatment).

Data collection and analysis

We extracted data on: design, setting and sample, screening and intervention, and effect on psychological well-being. Results of the trials were evaluated using the narrative synthesis approach.

Results

A total of 395 studies were retrieved from the search. Of those, 330 studies were excluded after title review; an additional 54 studies were excluded after abstract review. Eleven studies were selected for full text review, resulting in a total of 6 eligible randomized trials on the effect of screening for distress on psychological well-being[4-9]. Five studies were not included; in four of these the control group also received (minimal) screening[10-13], making it impossible to evaluate the effect of screening itself on psychological well-being; one study was excluded because it lacked an outcome measure of well-being[14].

Screening and intervention

Table 1 provides an overview of the characteristics and outcomes of the included RCTs. Five screening tools for measuring distress were used in the six studies: the distress thermometer[5,6,9], the general health questionnaire[7], the screening inventory of psychosocial problems[4], and the patient health questionnaire combined with the generalized anxiety screener[8]. A distress management plan was used in four out of six studies[5,7-9], in two studies, no standardized plan was available on how to handle on the basis of the screening results[4,6].

Effect of screening on psychological well-being

None of the included studies showed a screening effect on primary well-being outcomes. In one study however, screening and stepped care resulted in better referral to psychosocial services[8]; in Hollingworth et al. a subgroup analysis suggested that the DT&PL might be more effective in patients with better mood states at enrollment[6]; and in the trial of Braeken et al. post-hoc analyses revealed significant interactions of the intervention with early referral and improved QOL and anxiety, suggesting that earlier referral might influence short-term QOL and experienced anxiety in patients[4].

Conclusion

In this review, none of the six randomized trials evaluating distress screening found an effect on psychological well-being. Despite lack of supporting evidence several clinical recommendations have been made for screening for psychological distress to be part of standard cancer care[15,16]. It was stated by many of the included RCTs that future studies on screening programs should include distress as a patient outcome, use appropriate samples, include a detailed, theory-based distress management plan, offer staff training and track staff and patient use of subsequent interventions.

Supplementary Table 1 Characteristics and outcomes of included RCTs								
Reference	**Primary outcome**	**Secondary outcomes**	**Study design**	**Sample**	**Measures**	**Results**	**Conclusion**	**Comments**
Braeken et al. (2013)[4]	Distress	QOL	Cluster randomized trial at the level of radiotherapists, with two experimental and two control groups. Patients in the intervention groups were screened twice; before the first consultation and at the end of RT. Potential referral for psychosocial support was based on the scores of the SIPP in combination with the judgement concerning patient's needs. All patients had distress and QOL assessment at 3 and 12 months.	N=568, control n=300, intervention n=268. Patients with different types of cancer, no distant disease starting radiotherapy. Baseline distress on GHQ-12: 2.89 vs 3.16 in control vs intervention group respectively (p=0.53)	HADS, GHQ-12, EORTC-QLQ-C30 Screening tool: SIPP	No significant difference in distress between control vs. intervention group at 3 and 12 months, (*p*=0.19 and *p*=0.12, respectively) Distress on GHQ-12 at 3 months: 2.85 vs 2.74, at 12 months: 2.14 vs 1.96, in control vs intervention group, respectively.	No effect on psychosocial well-being.	An additional baseline assessment was conducted in one experimental and one control group to check for potential pre-measurement effect on the intervention outcomes.
Geerse et al. (2017)[5]	QOL	Distress, patient satisfaction	Intervention group: 5 screening moments, followed by face-to-face discussion with nurse and referral to patients with high scores or expressed need. All patients had QOL, distress and satisfaction assessment at 1, 7, 13 and 25 weeks after randomisation.	N=223; control n=113, Intervention n=110. Patients with newly diagosed stage Ib to IV or recurrent lung cancer. Baseline global QOL-score: 57.7 vs 59.2 in control vs intervention group.	EORTC-QLQ-C30, EQ-5D, HADS, PSQ-III Screening tool: DT/PL	No significant difference was found in the mean change global QOL-score (−2.4, 95% CI: 12.1–7.2; *p*= 0.61), nor in the other patient-reported outcomes.	No effect on psychosocial well-being.	A substantially higher dropout than originally anticipated led to conduction of an interim analyses. Based on the results of the interim analysis, study inclusion was stopped early at 223 patients since not even a trend towards a significant effect in primary outcome was found.
Hollingworth et al. (2013)[6]	Mood State	QOL, satisfaction with care, costs	Intervention group: patients completed assessment in a face-to-face meeting with radiographer/nurse where potential solutions were discussed including referrals during second week of treatment. Outcomes for all patients were collected at baseline and 1, 6, and 12 months.	N=220; control n=112, Intervention n=108. Patients with primary solid tumor diagnosis undergoing outpatient chemotherapy of radiation therapy.Mean total POMS score at baseline was 35 in both groups.	POMS, EORTC-QLQ-C30, EQ-5D. TPVCSQ. Screening tool: DT/PL	There was no evidence of an intervention effect on the total POMS score at 12 months or over the 12-month follow-up. The comparison total POMS scores at 12 months (estimate, −5.16; 95% CI, −10.36 to 0.04; *p*=0.052) provided weak evidence of higher (worse) POMS scores in the DT&PL	No effect on psychosocial well-being.	No formal triage criteria were implemented: the DT&PL was used as a needs assessment rather than a triage tool.

						group.		
Maunsell et al. (1996)[7]	Distress	QOL including depression, anxiety, physical health, return to usual activities, employment, marital satisfaction	Intervention group: 12 monthly telephone screenings: patients with high distress contacted by social worker within 2 weeks. All patients had telephone follow-up at baseline, at 3 and 12 months	N=250, control n=127, intervention n=123. Women newly diagnosed with first primary breast cancer, no distant disease. Baseline distress; mean PSI of 20.5	PSI, GHQ, LES, LWMAT, DIS, SSQ, employment. Screening tool: GHQ.	No significant difference in distress between intervention vs. control group (p=0.65) Distress changes: mean PSI, 20.4-13.5 in intervention group, 20.7-14.6 in control group. Distress level in both groups decreased over time (p=<0.001) .	No effect on psychosocial well-being.	All patients had brief psychosocial intervention from social worker at initial treatment; this may have obscured an effect of the intervention.
Singer et al. (2017)[8]	Referral to psychosocial services and distress	Uptake of outpatient care	Cluster-randomized trial at the level of wards, 7 in the control arm and 6 in the intervention arm. Intervention comprised screening for distress, consultation between doctor and patient about the patient's need for services, and provision of service. All patients had assessment of well-being at the beginning (t1) and the end (t2) of their hospital stay, and at 3 (t3) and 6 months (t4) after baseline.	N=1012, control n=570 (7 wards), intervention n=442 (6 wards). Patients treated for cancer in the wards. At t1 mean HADS distress scores were 10.2 in the control group and 11.4 in patients in the intervention group.	HADS, referral to psychosocial services, GHS. Screening tool: PHQ-9, GAS-7.	22% of the patients in the intervention group were referred to services and 3% with standard care odds ratio [OR] 10.0; p=<0.001). Well-being 6 months after baseline was 9.5 after stepped care (n=341) and 9.4 after standard care (n=234, β −0.3; p=0.71	No effect on psychosocial well-being.	
Van der Meulen et al. (2018)[9]	Depressive symptoms	QOL, worry of cancer	The intervention consisted of screening and nurse-guided follow-up lasting about 20 minutes three to four times during 12 months. All patients had assessments at baseline, at 6 and 12 months.	N=110, control n=57, intervention n=53. Patients with head and neck cancer. Baseline depressive scores were 12.4 in the control group and 11.8 in patients in the intervention group.	CES-D, EORTC QLQ-C30, EORTC QLQ-H&N35, Worry of cancer scale. Screening tool: DT/PL	Depressive symptoms, health-related quality of life, and worry of cancer were not significantly different in the two treatment groups.	No effect on psychosocial well-being.	Feasibility trial

CES-D, Center for Epidemiologic Studies-Depression scale; DIS, Diagnostic Interview Schedule; DT/PL, Distress Thermometer/Problem List; EQ-5D, EuroQol 5D; GAS, Generalized Anxiety Screener; GHQ-12, General Health Questionnaire 12; GHS, German Health Survey; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HADS, Hospital Anxiety and Depression Scale; H&N35, Head and Neck module; LES, Life Experiences Survey; LWMAT, Locke-Wallace Marital Adjustment Test; PHQ-9, Patient Health Questionnaire 9; POMS, Profile of Mood States; PSI, Psychiatric Symptom Index; PSQ-III, Patient Satisfaction Questionnaire III; QOL, Quality of Life; SIPP, Screening Inventory of Psychosocial Problems; SSQ, Social Support Questionnaire; TPVCSQ, Trent Patient Views of Cancer Services Questionnaire

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Supplemental Table 2 Conditional power and required number of patients to obtain a power of 0.80		
Proportion of patients receiving treatment for distress in TES program (q%)	Conditional power, with n = 715	N needed (experimental + control group) for power = 0.80
5%	0.06	251088
8.7% (a)	0.11	33318
10%	0.13	20716
13.7% (b)	0.21	7548
15%	0.24	5746
15.4% (c)	0.25	5318
20%	0.39	2552
25%	0.56	1432
33%	0.80	716
35%	0.84	640

(a) Observed proportion of patients treated for psychological distress
(b) The upper limit of the 95%CI of the observed proportion treated
(c) The upper limit of the 99%CI of the observed proportion treated

Supplemental Table 3 Mean observed scores for primary and secondary outcomes for the TES program arm at T0 (n=184), T3 (n=173), T10 (n=155), T24 (n=140) and T48 (n=110), and CAU arm at T0 (n=184), T3 (n=151), T10 (n=137), T24 (n=109) and T48 (n=87). Not corrected for clustering and baseline differences			
		TES program Mean (SD) (n, %)	CAU Mean (SD) (n,%)
Primary outcome			
Distress (HADS)	T0* T1 T2* T3* T4*	8.8 (6.5) 8.7 (6.2) 8.4 (6.6) 8.0 (6.9) 7.8 (6.0)	10.3 (6.7) 10.2 (7.0) 10.4 (7.6) 9.9 (7.2) 9.8 (7.3)
Secondary outcome			
Physical functioning (QLQ-C30)	T0 T2* T3 T4	76.0 (20.9) 75.3 (19.8) 73.5 (21.9) 76.7 (18.8)	72.6 (20.2) 67.1 (22.6) 71.9 (21.3) 71.9 (22.0)
Role functioning (QLQ-C30)	T0* T2* T3 T4	68.3 (28.9) 64.9 (30.5) 68.0 (29.6) 71.5 (27.1)	59.8 (32.0) 55.6 (30.5) 63.7 (28.4) 65.3 (31.5)
Emotional functioning (QLQ-C30)	T0 T2 T3 T4	78.3 (18.1) 81.8 (17.8) 80.6 (20.7) 83.8 (16.8)	75.9 (19.8) 79.3 (20.2) 77.7 (20.8) 80.2 (21.9)
Cognitive functioning (QLQ-C30)	T0 T2* T3* T4	89.8 (14.2) 86.3 (17.6) 86.9 (17.3) 87.0 (17.3)	88.0 (16.5) 81.6 (21.7) 81.3 (20.6) 82.8 (18.3)
Social functioning (QLQ-C30)	T0* T2* T3 T4	79.3 (23.8) 79.4 (22.4) 79.1 (24.7) 83.8 (21.0)	72.8 (27.5) 71.7 (28.0) 74.2 (25.7) 81.2 (24.4)
Global QOL (QLQ-C30)	T0 T2* T3 T4*	64.9 (22.0) 68.5 (21.5) 68.1 (21.3) 72.5 (16.8)	60.9 (21.3) 61.8 (22.6) 66.7 (20.4) 65.7 (22.3)
Patient Satisfaction (CSQ-8)	T2 T3 T4	25.5 (5.6) 25.7 (6.0) 26.2 (5.4)	25.0 (5.5) 25.2 (5.3) 25.0 (5.3)
Recognition distress by clinicians		79 (42.9%)	62 (37.6%)
Referral distress by clinicians		30 (16.3%)	20 (12.1%)