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Cost-utility of stepped care targeting psychological distress in head and neck cancer and lung cancer patients

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ABSTRACT

Background. A stepped care program in which effective yet least resource-intensive treatment is delivered to patients first, followed by, when necessary, more resource-intensive treatments was found to be effective in improving distress levels of head and neck cancer (HNC) and lung cancer (LC) patients. Information on this program's value for money is now called for.

Purpose. To assess the cost-utility of the stepped care program compared to care-as-usual (CAU) in HNC and LC patients with psychological distress.

Methods. In total 156 patients were randomized to stepped care or CAU. Intervention costs, direct medical costs, direct non-medical costs, productivity losses and health-related quality of life data during the intervention or control period and 12 months follow-up were calculated using TIC-P, PRODISQ and EQ-5D measures and data from the hospital information system. The stepped care program's value for money was investigated by comparing mean cumulative costs and quality-adjusted life years (QALYs).

Results. After imputation of missing data, mean cumulative costs were €-3,950 [95% confidence interval (CI): €-8,158 to €-190] lower and mean number of QALYs were 0.116 [95%CI: 0.005 – 0.227] higher in the intervention compared to the control group. The intervention group had a probability of 96% that cumulative QALYs were higher and cumulative costs were lower than the control group. Four additional analyses which were conducted to assess the robustness of this finding found that the intervention group had a probability of 84% - 98% that cumulative QALYs were higher and a probability of 91% - 99% to be less costly than the control group.

Conclusion. Stepped care is highly likely to be cost-effective; the number of QALYs were higher and cumulative costs were lower compared to CAU.

INTRODUCTION

Recent reviews on the cost-effectiveness and cost-utility of psychosocial care in cancer patients in general found that psychosocial care is likely to be cost-effective at potentially acceptable willingness-to-pay thresholds[1,2]. More research is, however, warranted, since economic evaluations are scarce and heterogeneity among studies hampers comparison of findings. Also no study specifically targeted novel psychosocial care programs as stepped care. To overcome barriers to usage of psychosocial cancer care, a stepped care program targeting psychological distress in cancer patients has been developed consisting of four steps: 1. watchful waiting for two weeks, 2. guided self-help, 3. face-to-face problem-solving therapy, and 4. specialized psychological interventions (e.g., cognitive behavioral therapy) and/or psychotropic medication[3]. Patients proceed to the next step only when symptoms of distress do not resolve.

Recently, this stepped care program was found to have beneficial effects on distress compared to care-as-usual (CAU) in head and neck cancer (HNC) and lung cancer (LC) patients[4]. HNC and LC patients were targeted, since they are seldom involved in randomized controlled trials (RCTs) of psychosocial care, despite a high prevalence of depression[5]. Previous economic evaluation studies of stepped care programs targeting primary care patients[6-9], older patients[10,11], patients with diabetes[12,13], or patients with acute coronary syndrome[14] with psychological distress, have found that, except for one study[10], the stepped care program improved quality-adjusted life years (QALYs) or depression-free days compared to control care, albeit in most studies[6,7,9,11,13] at higher costs. However, no such economic evaluation on stepped care has been performed in cancer patients yet. This study therefore assessed the cost-utility of a stepped care program targeting psychological distress in HNC and LC patients compared to CAU.

METHODS

Study design and population

Detailed information on the study design and population can be found in previous publications[3,4]. In short, this cost-utility analysis was conducted alongside a prospective RCT on the efficacy of a stepped care program for HNC and LC patients with symptoms of psychological distress (Hospital Anxiety and Depression Scale (HADS) distress score > 14 or anxiety or depression score > 7). The study was approved by the Medical Ethics

Committee of VU University Medical Center and conducted according to the principles of the Declaration of Helsinki. The trial has been registered in the Netherlands Trial Register (NTR1868).

Randomization and treatment allocation

Patients who met the eligibility criteria and signed informed consent were randomized to the intervention group providing stepped care or the control group providing CAU (Figure 1). The stepped care program consisted of four steps: 1. watchful waiting, 2. guided self-help via the internet or booklet, 3. face-to-face problem-solving therapy, and 4. specialized psychological interventions and/or psychotropic medication. Patients who did not recover after a treatment step (HADS anxiety/depression score remained above 7), proceeded to a more intensive step. More information is provided in the protocol[3].

Outcome measures

Cost and clinical endpoint data were collected at baseline (t0), immediately after the intervention or control period indicated as t1, and 3, 6, 9 and 12 months after t1. The economic evaluation was conducted from a societal perspective and included intervention costs, direct medical costs (costs of healthcare utilization and medication), direct non-medical costs (costs of support groups, informal care, travelling to health services and parking), and indirect non-medical costs (productivity losses from paid work). Intervention costs were calculated using a bottom-up approach. Mean costs per patient in the intervention group were €318 (range: €24 to €9,043) (see Table 1).

The Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry (TIC-P)[15] was used to measure utilization of healthcare facilities (e.g., number of visits to the general practitioner) and other facilities (e.g., time spent in self-help groups or informal care) in the past four weeks and medication used (antidepressants, analgesic, and sedative) in the past two weeks. In addition, healthcare utilization within the hospital (visits to the medical specialist, day treatment, and hospital admission) was collected using the hospital information system. Direct medical and direct non-medical costs of support groups and informal care were calculated by multiplying resource use by the integral cost price[16]. Direct non-medical costs of travelling to health services and parking were calculated by multiplying unit resource use by average distance to the location times the price per km. All prices were adjusted to 2011 prices using the consumer price index. The Productivity and Disease Questionnaire (PRODISQ)[17] was used to measure productivity losses through absence from paid work (absenteeism) or reduced quantity or quality of

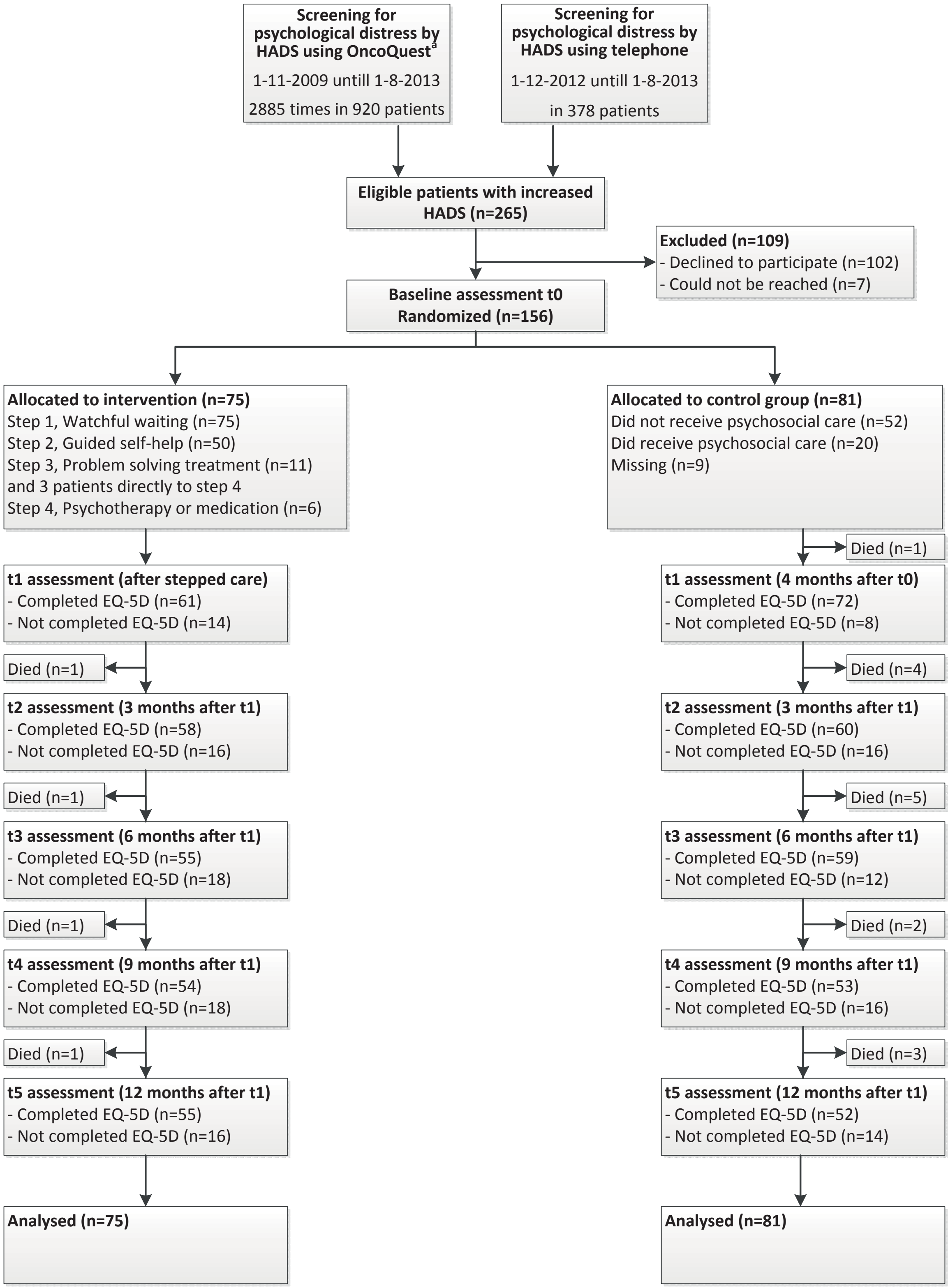

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Figure 1: CONSORT flow diagram

performed paid work (presenteeism) in the past four weeks. Losses due to presenteeism were calculated by multiplying the days of less productivity at work by the estimated amount of lost quantity or quality of performed work (ranging from 0 - 10). Indirect non-medical costs from paid work were calculated by multiplying productivity losses by respectively age- and gender-specific costs[16] using the human capital approach.

The EuroQol-5 dimensions (EQ-5D) was used to measure health-related quality of life. The EQ-5D utility score was obtained using the Dutch index tariff[18].

Table 1. Description of healthcare utilization within the stepped care program

Description of healthcare utilization within the stepped care program	Costs (€)
Screening	
- Screening for distress	7.97
- Consultation by a nurse for 15 minutes	7.97
Step 1 watchful waiting	
- Monitoring distress by HADS assessment	7.97
Step 2 guided self-help	
- Self-help internet tool or booklet	39.00
- Feedback by e-mail or telephone from a nurse (in total one hour)	31.88
- Monitoring distress by HADS assessment	7.97
Step 3 face-to-face problem-solving therapy	
- Five-sessions of problem-solving therapy by a nurse	151.42
- Monitoring distress by HADS assessment	7.97
Step 4 specialized psychological interventions and/or psychotropic medication	
- Costs were calculated per person individually since type of treatment and number of sessions or duration of treatment differed.	Differed

Abbreviations: HADS, Hospital Anxiety and Depression Scale.

Statistical analyses

All analyses were performed using the IBM Statistical Package for the Social Science (SPSS) version 20 (IBM Corp., Armonk, NY USA) and STATA version 12.1. Descriptive statistics, chi-squared tests and independent t-test were used to describe and compare baseline characteristics between different groups.

To provide information on type of costs included in the analyses and its relative importance (its contribution to the mean total costs per group) at various time points, data of complete cases (patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died) was used. Data of complete cases was also used to provide information on the mean utility scores per group at the different time points.

To assess the value for money of stepped care compared to CAU, at first a base case intention-to-treat cost-utility analysis was performed including all 156 randomized patients and imputing any missing data. Consequently, to assess the robustness of this finding four additional analyses were performed (a) an analysis in which we adjusted the base case analysis using multivariate regression analyses for variables at baseline found to have a major influence (a change of ≥ 20%) on incremental costs (EORTC social functioning and total costs at baseline) and incremental effects (HADS depression at baseline); (b) an analysis excluding patients from the base case analysis who died during the study; (c) an analysis in which data was imputed for patients who died during the study as though they are still alive; and (d) an analysis in which productivity losses were excluded.

All cost-utility analyses were performed in agreement with the intention-to-treat principle. Missing data were imputed as total costs or utility score per time point per treatment arm separately using multiple imputation (predictive mean matching) by chained equations. Data were thus only imputed for those time points that were missing. Linear and logistic regression analyses were performed to investigate which variables (socio-demographic, clinical, HADS-total, HADS-D, HADS-A, and EORTC global quality of life) were associated with missing data, observed costs or EQ-5D utility scores. Variables associated with missing data (gender and HADS-total), observed costs (work situation, EORTC global quality of life, and marital status) or utility scores (HADS-total, EORTC global quality of life score, tumor stage, tumor location, and years of education) and variables which differed at baseline (alcohol dependency, HADS-D, EORTC QLQ-C30 social functioning, and EORTC QLQ-H&N35 social contact and sexuality) were included in the multiple imputation model. Ten imputed data sets were created and analyzed separately. Results of the ten analyses were pooled using Rubin's (1987) rules.

To perform incremental cost-utility analyses, the cumulative costs and number of QALYs per patient per treatment group were calculated. For patients in the control group cumulative costs as measured using the TIC-P and PRODISQ between t0 and t1 were calculated

Table 2. Baseline characteristics

		Total group	Intervention		
		Total	Total	Complete cases[1]	Non-complete cases[2]
		n = 156	n = 75	n = 47	n = 28
Mean age (SD)		62.0 (9.4)	62.5 (8.7)	62.8 (8.2)	62.1 (9.5)
Gender (%)					
-	Male	60.9%	62.7%	53.2%	78.6%
-	Female	39.1%	37.3%	46.8%	21.4%
Marital status (%)					
-	Married/living with partner	67.9%	72.0%	74.5%	67.9%
-	Unmarried/divorced/widowed	32.1%	28.0%	25.5%	32.1%
Work situation (%)					
-	Paid job	30.8%	30.7%	34.0%	25.0%
-	No paid job/ retired	69.2%	69.3%	66.0%	75.0%
Tumor location (%)					
-	Lip/oral cavity/oropharynx	48.7%	40.0%	42.6%	35.7%
-	Hypopharynx/larynx	25.6%	28.0%	23.4%	35.7%
-	Other head and neck cancers	19.9%	25.3%	25.5%	25.0%
-	Lung	5.8%	6.7%	8.5%	3.6%
Tumor stage (%)					
-	I	25.0%	22.7%	19.1%	28.6%
-	II	16.0%	20.0%	23.4%	14.3%
-	III	18.6%	16.0%	19.1%	10.7%
-	IV	34.0%	30.7%	25.5%	39.3%
-	Unknown	6.4%	10.7%	12.8%	7.1%
Time since treatment (%)					
-	< 7 months	35.9%	38.7%	38.3%	39.3%
-	7-12 months	16.7%	13.3%	10.6%	17.9%
-	> 12 months	47.4%	48.0%	51.1%	42.9%
Treatment (%)					
-	Single treatment	48.7%	52.0%%	42.6%	67.9%
	Surgery	22.4%	17.3%	12.8%	25.0%
	Radiotherapy	26.3%	34.7%	29.8%	42.9%
-	Combination treatment	51.3%	48.0%	57.4%	32.1%

Control			Significance level			
Total n = 81	Complete cases[1] n = 56	Non-complete cases[2] n = 25	Intervention total vs. control total	Intervention complete vs. non-complete cases	Control complete vs. non-complete cases	Intervention complete vs. control complete cases
61.6 (10.0)	63.3 (9.6)	57.7 (10.0)	0.538	0.752	0.019	0.755
			0.663	0.028	0.168	0.254
59.3%	64.3%	48.0%				
40.7%	35.7%	52.0%				
			0.297	0.537	0.599	0.355
64.2%	66.1%	60.0%				
35.8%	33.9%	40.0%				
			0.979	0.411	0.372	0.990
30.9%	33.9%	24.0%				
69.1%	66.1%	76.0%				
			0.176	0.615	0.643	0.189
56.8%	58.9%	52.0%				
23.5%	25.0%	20.0%				
14.8%	12.5%	20.0%				
4.9%	3.6%	8.0%				
			0.146	0.434	0.813	0.069
27.2%	28.6%	24.0%				
12.3%	12.5%	12.0%				
21.0%	17.9%	28.0%				
37.0%	39.3%	32.0%				
2.5%	1.8%	4.0%				
			0.527	0.626	0.445	0.725
33.3%	35.7%	28.0%				
19.8%	16.1%	28.0%				
46.9%	48.2%	44.0%				
			0.430	0.034	0.839	0.694
45.7%	46.4%	44.0%				
27.2%	28.6%	24.0%				
18.5%	17.9%	20.0%				
54.3%	53.6%	56.0%				

Table 2. Baseline characteristics

	Total group	Intervention		
	Total	Total	Complete cases[1]	Non-complete cases[2]
	n = 156	n = 75	n = 47	n = 28
Chemoradiation[3]	17.3%	8.0%	10.6%	3.6%
Surgery and radiotherapy	26.3%	33.3%	36.2%	28.6%
Surgery and chemoradiation[4]	5.1%	5.3%	8.5%	0.0%
Surgery and chemotherapy[5]	2.6%	1.3%	2.1%	0.0%
Anxiety or depressive disorder (%)				
- Yes	22.4%	18.7%	17.0%	21.4%
- No	77.6%	81.3%	83.0%	78.6%
Nicotine dependence (%)				
- Yes	17.3%	16.0%	12.8%	21.4%
- No	82.7%	84.0%	87.2%	78.6%
Alcohol dependence (%)				
- Yes	8.3%	13.3%	6.4%	25.0%
- No	91.7%	86.7%	93.6%	75.0%
Mean HADS anxiety (SD)	9.5 (3.5)	9.3 (3.6)	9.2 (3.6)	9.6 (3.6)
Mean HADS depression (SD)	8.9 (3.8)	8.2 (3.7)	7.9 (3.6)	8.6 (3.7)
Mean HADS total (SD)	18.3 (5.4)	17.5 (5.2)	17.1 (4.9)	18.1 (5.6)
EORTC global quality of life (SD)	58.0 (19.8)	59.2 (20.1)	59.0 (19.0)	59.6 (22.3)
Mean EQ-5D utility score (SD)	0.63 (0.27)	0.66 (0.24)	0.68 (0.22)	0.60 (0.28)
Mean total costs in € (SD)	886 (1614)	790 (1443)	660 (1150)	1046 (1895)

Abbreviations: SD, Standard deviation.
[1] Complete cases are patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died. Non-complete cases are patients who did not complete one or more of the baseline or follow-up measurements.

Control			Significance level			
Total n = 81	Complete cases[1] n = 56	Non-complete cases[2] n = 25	Intervention total vs. control total	Intervention complete vs. non- complete cases	Control complete vs. non-complete cases	Intervention complete vs. control complete cases
25.9%	23.2%	32.0%				
19.8%	21.4%	16.0%				
4.9%	3.6%	8.0%				
3.7%	5.4%	0.0%				
			0.278	0.636	0.053	0.733
25.9%	19.6%	40.0%				
74.1%	80.4%	60.0%				
			0.678	0.322	0.396	0.636
18.5%	16.1%	24.0%				
81.5%	83.9%	76.0%				
			0.030	0.022	0.238	0.825
3.7%	5.4%	0%				
96.3%	94.6%	100%				
9.6 (3.4)	9.3 (3.1)	10.2 (4.0)	0.643	0.676	0.263	0.869
9.5 (3.8)	9.1 (3.6)	10.3 (4.1)	0.029	0.472	0.181	0.103
19.1 (5.6)	18.4 (4.6)	20.6 (7.2)	0.071	0.423	0.185	0.174
56.8 (19.6)	58.3 (21.1)	52.9 (15.2)	0.441	0.915	0.266	0.859
0.60 (0.29)	0.60 (0.30)	0.58 (0.28)	0.179	0.178	0.755	0.115
974 (1762)	1087 (1958)	671 (1060)	0.491	0.290	0.238	0.173

[3] Cisplatin was given in 21 patients, Cetuximab in five patients and in one patient cytostatics was missing. [4] Cisplatin was given in all 8 patients, [5] Cisplatin was given in two patients, Erlotinib was given in one patient and in one patient cytostatics was missing.

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Table 3. Mean costs per time point of complete cases[1]

		Intervention group (n = 47)				
	Reference price per unit (€)	Baseline (t0)	t1	t2	t3	t4
Direct medical costs[2]		189 (303)	203 (230)	176 (222)	186 (240)	148 (169)
General practitioner	29	26 (49)	20 (27)	23 (37)	17 (31)	22 (35)
Company doctor	65	11 (34)	11 (25)	12 (29)	7 (24)	3 (13)
Social worker (company)	68	1 (10)	1 (10)	-	-	-
Social worker (general)	68	10 (32)	4 (17)	3 (20)	7 (35)	6 (28)
Physiotherapist	38	65 (193)	58 (100)	46 (99)	52 (117)	31 (72)
Dietitian	28	12 (24)	7 (19)	8 (22)	8 (20)	4 (12)
Psychological help (private practice)	81	-	12 (38)	3 (17)	3 (17)	2 (12)
Psychological help (out-patient)	179	19 (107)	19 (77)	15 (63)	30 (120)	15 (63)
Psychological help (addiction)	179	-	15 (104)	19 (107)	-	-
Psychological help (mental hospital)	181	-	15 (63)	4 (26)	4 (26)	4 (26)
Specialist (general hospital)	67	26 (100)	24 (49)	16 (42)	19 (39)	20 (39)
Priest	122	-	-	3 (18)	3 (18)	3 (18)
House cleaning	25	11 (59)	14 (62)	19 (79)	32 (102)	38 (112)
Personal care	46	-	-	-	-	-
Visiting nurse	68	7 (41)	1 (10)	4 (17)	3 (20)	1 (10)
Other direct medical costs						
Medication[2]	0.19 – 7.58 per DDD	19 (33)	17 (30)	17 (28)	17 (29)	12 (21)
Specialist[3]	130					
Day treatment[3]	252					
Hospitalization[3]	576 or 2184 (IC)					
Direct non-medical costs[2]		80 (177)	34 (83)	79 (230)	60 (158)	49 (146)
Support groups	12.80 – 57.50	34 (138)	4 (14)	18 (54)	37 (150)	16 (55)
Informal care	12.80	41 (123)	24 (80)	57 (223)	19 (59)	30 (137)
Transport and parking costs	0.20 per km / 3.00 parking	4 (8)	6 (7)	4 (6)	4 (6)	3 (4)
Indirect non-medical costs[4]		372 (1127)	264 (914)	205 (582)	172 (747)	124 (422)
Absenteeism paid work	8.97 – 40.32 per h	339 (1128)	149 (482)	169 (503)	145 (593)	96 (405)
Presenteeism paid work	8.97 – 40.32 per h	33 (117)	115 (681)	36 (170)	27 (165)	28 (140)

Abbreviations: DDD, defined daily dose; IC, intensive care; t1: assessment post-intervention (intervention group) or 4 months after baseline (control group); t2: 3 months after t1, t3: 6 months after t1, t4: 9 months after t1; t5: 12 months after t1.

		Control group (n = 56)						
t5	t0 - t5	Baseline (t0)	t1	t2	t3	t4	t5	t0 – t5
116 (170)		315 (581)	260 (479)	280 (518)	226 (414)	199 (459)	190 (747)	
17 (29)		24 (32)	27 (46)	23 (34)	20 (35)	20 (29)	18 (29)	
3 (13)		20 (72)	6 (19)	2 (17)	6 (36)	3 (15)	1 (9)	
-		1 (9)	-	-	-	1 (9)	-	
1 (10)		6 (27)	4 (20)	5 (36)	-	7 (34)	-	
40 (92)		45 (88)	45 (93)	50 (105)	39 (89)	28 (65)	21 (76)	
2 (10)		7 (15)	4 (13)	8 (20)	3 (10)	2 (7)	2 (6)	
12 (38)		-	-	16 (89)	-	4 (32)	4 (24)	
4 (26)		13 (67)	6 (48)	6 (48)	13 (96)	-	-	
-		-	-	-	32 (239)	-	-	
4 (26)		-	13 (97)	-	3 (24)	13 (58)	3 (24)	
16 (40)		37 (66)	36 (96)	18 (45)	29 (67)	20 (56)	42 (6)	
-		13 (69)	4 (23)	2 (16)	-	-	-	
18 (56)		42 (128)	25 (67)	46 (112)	30 (77)	21 (67)	67 (9)	
-		67 (364)	65 (324)	99 (385)	51 (237)	25 (172)	46 (6)	
-		40 (210)	24 (182)	5 (36)	-	55 (366)	727 (97)	
12 (25)		19 (50)	14 (44)	19 (59)	16 (56)	12 (37)	22 (70)	
	1104 (936)							1088 (780)
	27 (94)							27 (115)
	441 (1774)							1882 (5193)
47 (129)		184 (463)	51 (161)	64 (163)	56 (137)	78 (281)	78 (263)	
28 (124)		30 (93)	7 (31)	24 (87)	8 (40)	7 (33)	45 (229)	
16 (47)		149 (459)	40 (159)	43 (127)	43 (127)	68 (280)	31 (107)	
3 (4)		5 (7)	4 (9)	3 (7)	5 (13)	3 (7)	2 (4)	
37 (179)		569 (1530)	305 (1104)	333 (1027)	151 (427)	158 (722)	130 (478)	
16 (93)		509 (1448)	237 (1046)	162 (728)	49 (198)	65 (484)	15 (116)	
21 (92)		61 (214)	68 (335)	170 (500)	103 (365)	94 (275)	115 (461)	

[1] Complete cases are patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died. [2] Measured using the TIC-P over the past four weeks. [3] Measured using the VUmc hospital information system over the entire study period. [4] Measured using the PRODISQ over the past four weeks.

by multiplying the mean costs at time point t1 by the corresponding time period (time between t0 and t1). Unlike patients in the control group, for patients randomized to the intervention group, the costs as measured using the TIC-P and PRODISQ at t1 were not expected to be generalizable to the entire intervention period (a patient was expected to have different costs during step 4 than during step 1). Therefore, cumulative costs between t0 and t1 for intervention patients were calculated by summing costs per step. Mean costs per step per 4 weeks were calculated for all patients who 1) participated in step 4, 2) participated in step 3 but not in step 4, 3) participated in step 2 but not in step 3 or 4, and 4) patients who participated in step 1 but not in step 2, 3 or 4. Subsequently, cumulative costs per patient were calculated by multiplying mean cumulative costs per step per 4 weeks by the time a patient participated in the particular step. Costs between t1 and t5 as measured using the TIC-P and PRODISQ for both groups were calculated using linear interpolation. Total cumulative costs per patient were calculated by summing cumulative costs measured using the TIC-P and PRODISQ with intervention costs and costs measured using the hospital information system. The number of QALYs per patient was calculated by multiplying the EQ-5D utility score by the appropriate time period it accounts for using linear interpolation.

An incremental cost-utility ratio (ICUR) was calculated to obtain the costs per gained QALY by dividing the incremental costs by the incremental effects using the following formula (mean $\text{Costs}_{\text{intervention}}$ – mean $\text{Costs}_{\text{control}}$) / (mean $\text{QALYs}_{\text{intervention}}$ – mean $\text{QALYs}_{\text{control}}$). The uncertainty surrounding the ICUR were assessed using bootstrapping with 5,000 replications and projected on a cost-utility plane.

RESULTS

In total, 75 patients were randomized to the intervention group and 81 patients to the control group. Table 2 summarizes the baseline characteristics of both groups and compared patients with complete data with patients without complete data. During the study, 4/75 (5.3%) patients in the intervention group vs. 15/81 (18.5%) patients in the control group died ($p = 0.012$).

Direct and indirect medical costs and productivity costs

The mean costs of patients with complete data (patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died) per time point per group are presented in Table 3. In the four weeks prior to baseline, no statistically significant differences in costs were found between the two groups (p = 0.17), although there were large absolute differences. Mean total costs at baseline in the intervention group were €660 (standard deviation (SD) = 1,150) compared to €1,087 (SD = 1,958) in the control group.

Health-related quality of life

In Table 4 the mean EQ-5D utility score of patients with complete data are presented. At baseline, a non-statistically significant difference in EQ-5D utility score of 0.08 was found in favor of the intervention group (p = 0.12), which exceeded the subjectively appreciable difference of 0.07 reported in Walters et al.[19].

Table 4. Mean EQ-5D utility score per time point of complete cases[1]

Time point	Intervention group (n = 47)	Control group (n = 56)
Baseline	0.68 (0.22)	0.60 (0.30)
t1	0.74 (0.20)	0.65 (0.30)
t2 (3 months after t1)	0.77 (0.19)	0.65 (0.30)
t3 (6 months after t1)	0.75 (0.20)	0.61 (0.32)
t4 (9 months after t1)	0.74 (0.24)	0.61 (0.35)
t5 (12 months after t1)	0.73 (0.22)	0.60 (0.36)

t1: assessment post-intervention (intervention group) or 4 months after baseline (control group)
[1] Complete cases are patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died.

Cost-utility analyses

Results of the different cost-utility analyses are presented in Table 5 and Figures 2 - 6. In the base case analysis, mean costs in the intervention group were statistically significant lower than mean costs in the control group (incremental costs were €-3,950). Besides, QALYs gained were statistically significantly higher in the intervention group compared to the control group (incremental effects were 0.116). Of the bootstrapped cost-utility pairs, 96% fell into the south-east quadrant, representing the probability that stepped care is more effective and less costly compared to CAU.

To assess the robustness of this finding, four additional analyses were performed as

Table 5. Results of the different cost-utility analyses

	Costs (€) Mean (SEM)	**QALYs** Mean (SEM)	**Incremental costs** € [95% CI]	**Incremental effects** QALYs [95% CI]
Base case analysis			-3,950 [-8,158 to -190]*	0.116 [0.005 to 0.227]*
- Intervention group (n = 75)	9,761 (1,041)	0.884 (0.039)		
- Control group (n = 81)	13,711 (1,828)	0.768 (0.040)		
Analysis adjusted for several variables at baseline			-2,499 [-6,082 to 630]	0.076 [-0.032 to 0.184]
- Intervention group (n = 75)	Not applicable	Not applicable		
- Control group (n = 81)	Not applicable	Not applicable		
Analysis excluding patients who died during the study			-3,939 [-8,722 to 229]	0.052 [-0.053 to 0.156]
- Intervention group (n = 71)	9,934 (1,088)	0.911 (0.037)		
- Control group (n = 66)	13,874 (2,080)	0.859 (0.038)		
Analysis with imputed data for patients who died during the study			-4,692 [-8,898 to -889]*	0.059 [-0.035 to 0.153]
- Intervention group (n = 75)	9,887 (1,035)	0.908 (0.035)		
- Control group (n = 81)	14,579 (1,848)	0.849 (0.033)		
Analysis without productivity losses			-2,888 [-5,630 to -424]*	0.118 [0.009 to 0.227]*
- Intervention group (n = 75)	6,287 (677)	0.885 (0.039)		
- Control group (n = 81)	9,175 (1,161)	0.767 (0.040)		

Abbreviations: QALYs, quality-adjusted life years; CI, confidence interval
*, significant difference between the two groups ($p < 0.05$)

presented in Table 5. In these additional analyses, the intervention group had a probability of 84% - 98% that cumulative QALYs were higher and a probability of 91% - 99% to be less costly than the control group. The analysis that showed the lowest probability of being more effective and less costly was the analysis in which patients who died during the study were excluded (probability of 81%).

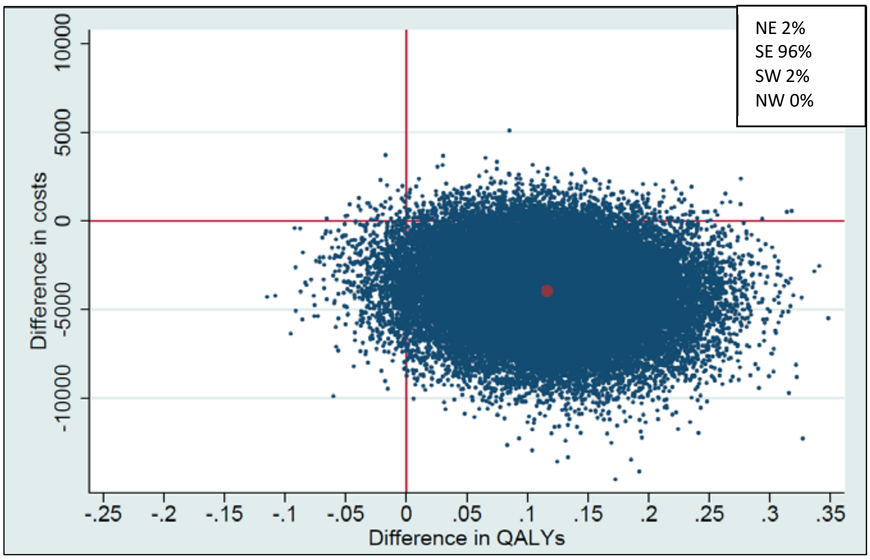

Figure 2. Cost-utility plane of the base case analysis

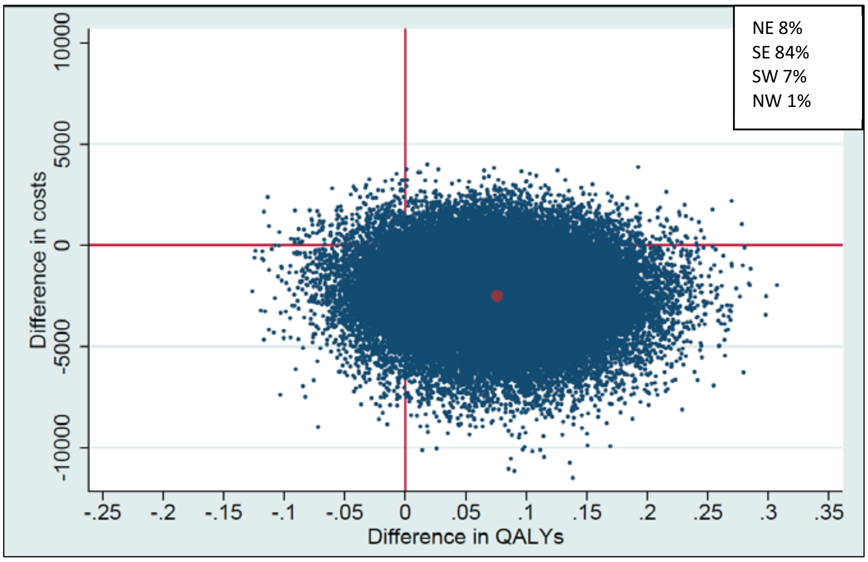

Figure 3. Cost-utility plane of the base case analysis adjusted for social functioning and total costs at baseline (costs) and HADS depression (effects)

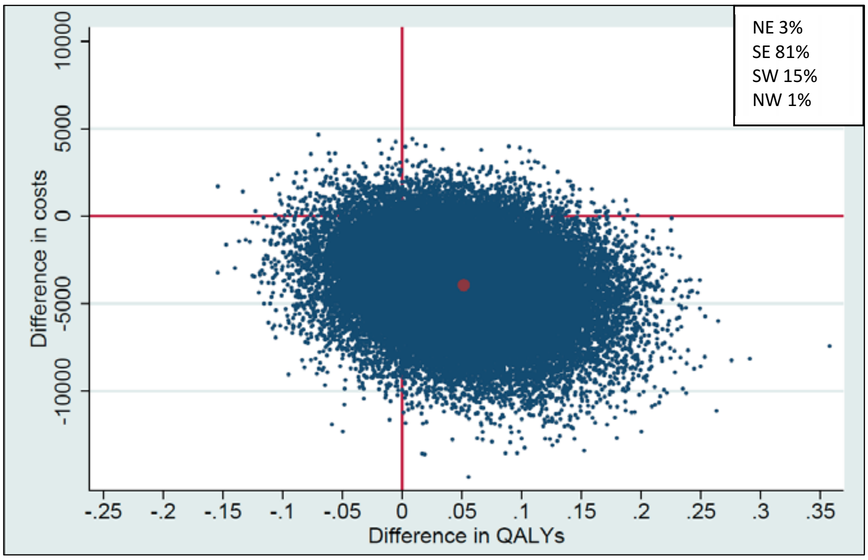

Figure 4. Cost-utility plane of the base case analysis without patients who deceased during the study

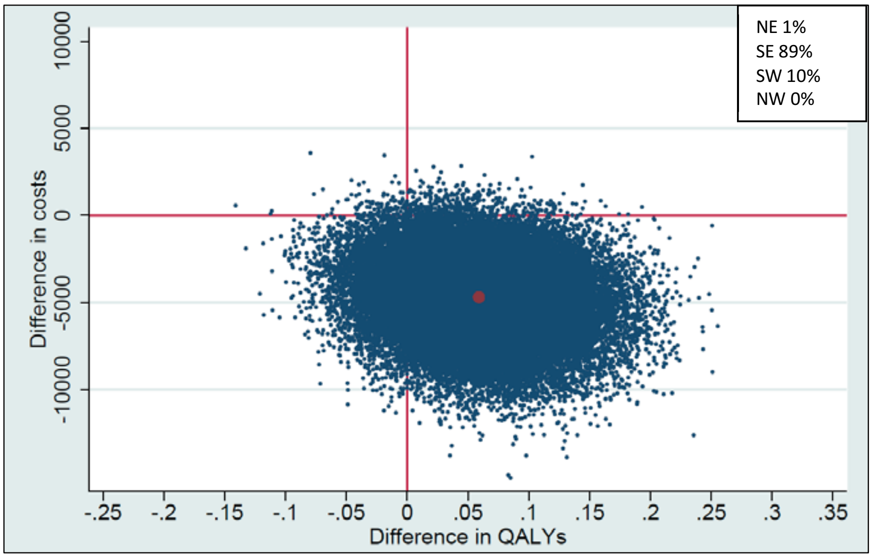

Figure 5. Cost-utility plane of the analysis with imputed data for patients who deceased during the study

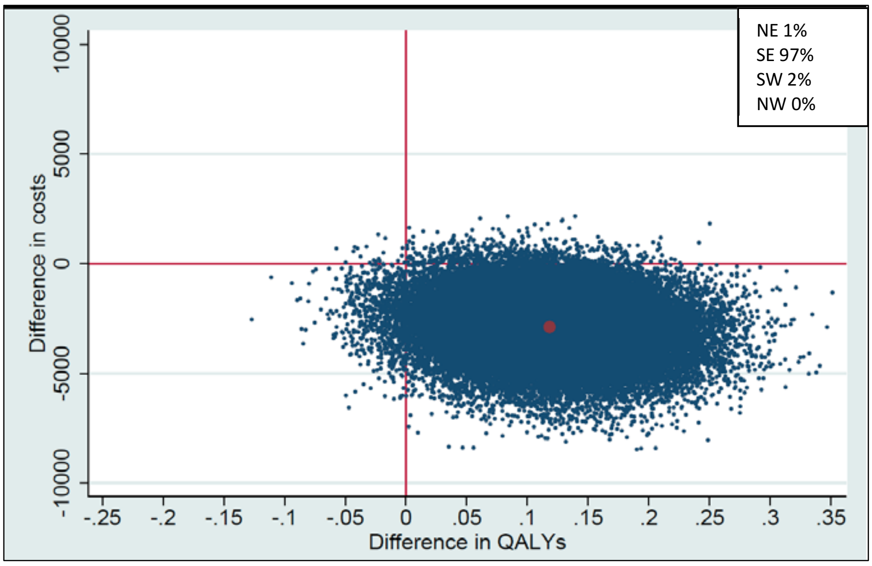

Figure 6. Cost-utility plane of the analysis in which productivity losses are not included

DISCUSSION

This study investigated the cost-utility of a stepped care program targeting psychological distress in HNC and LC patients compared to CAU. In the base case analysis, the number of QALYs were statistically significantly higher and cumulative costs were statistically significantly lower in the intervention group compared to the control group. The probability that cumulative QALYs were higher and costs were lower was 96%, indicating that stepped care is highly likely to be cost-effective compared to CAU.

Several additional analyses were performed to assess the robustness of this finding. In one analysis we adjusted for variables that differed at baseline between the two groups and had a major impact on incremental costs or incremental effects. After correction, incremental costs and QALYs decreased to a non-statistically significant difference, however, the intervention group still had a probability of 93% that cumulative QALYs were higher and a probability of 89% to be less costly than the control group.

In addition, we investigated the influence of the lower mortality rate in the intervention compared to the control group (5.3% vs. 18.5%). A debate is ongoing concerning the influence of psychosocial care on survival in cancer patients, with some authors suggesting that psychosocial care may improve survival[20-22], while others argue against such an effect[23-25]. If we assume that psychosocial care does not improve survival, our cost-utility estimate may be biased, as the higher mortality rate in the control group will have resulted in lower mean QALYs and is expected to influence mean total costs. Therefore, two additional analyses were performed: one analysis in which all died patients were excluded and one analysis in which for all died patients cost and utility data were imputed as though they were still alive. In both analyses incremental costs between the two groups changed somewhat, while the incremental QALYs decreased to a non-statistically significant difference. However, the intervention group still had a probability of 84% - 90% that cumulative QALYs were higher than in the control group and a probability of 96% - 99% that it was less costly. This indicates that when stepped care does not influence survival, it is still likely to be cost-effective.

Our findings are in agreement with one previous study that targeted cancer patients with increased levels of distress[26]. All other previous studies targeting cancer patients with increased levels of distress reported an improvement in QALYs, although, at higher costs[27-29]. This difference in cost benefit may be due to the design of stepped care in which intervention patients are first provided with watchful waiting (recovery rate 28%), followed by guided self-help when not spontaneously recovered after two weeks (recovery rate 34%)[4]. When still not recovered after guided self-help more resource-intensive care was provided, while in the previous studies all intervention patients received relatively more resource-intensive care[26-29]

Another explanation for the difference in cost benefit may be that unlike previous studies[26-29], our study was conducted from a societal perspective, incorporating productivity losses and direct non-medical costs such as informal care costs. Previous studies found that being distressed was associated with unemployment in mixed cancer survivors[30] and that higher levels of depression were associated with unemployment due to loss of job, sick leave or early retirement after cancer treatment for HNC[31]. In another study on employment and return to work among HNC patients, an association between anxiety and return to work was reported, while no such association with distress or depression was found[32]. Our efficacy study showed that stepped care was beneficial in improving level of distress[4], which may have had a beneficial effect on productivity losses in the intervention group compared to the control group. We conducted an additional analysis in which we excluded productivity losses, which showed indeed that the cost difference between the two groups reduced with €1,062. However, even without productivity losses, stepped care had a probability of 97% to be more effective and less costly.

Some potential limitations were evident in this study. A potential limitation is that a number of assumptions were made regarding resource utilization and EQ-5D utility scores for data that were missing. Firstly, missing total costs or utility scores per time point per treatment were imputed using multiple imputation techniques. Secondly, linear interpolation between time points was used. Both assumptions may not necessarily reflect reality, however, since the same assumptions were made for both groups, this was expected not to have influenced our findings. Another potential limitation is that productivity losses were calculated using the human capital approach instead of the recommended friction cost approach[16]. Also, the small sample size of 156 patients is a limitation of this study. Although bootstrapping was performed which supported the finding that stepped care is likely to be more effective and less costly than CAU, it also showed that there is considerable uncertainty. More research is therefore needed on the cost-utility of stepped care in subgroups of the investigated population, such as patients with and without a diagnosis of major depression disorder or anxiety disorder.

In addition, further research should investigate whether findings are replicable in other cancer patient groups. Also, further research should be performed on optimal implementation of stepped care in routine cancer care, which may potentially differ between different health care systems (e.g., the Netherlands compared to The United States). The RE-AIM framework (Reach, Efficacy, Adoption, Implementation, and Maintenance) can be used to evaluate the different steps involved in optimal implementation and maintenance of stepped care[33].

In conclusion, since in the base case analysis the number of QALYs were statistically significantly higher and cumulative costs were statistically significantly lower in the intervention group compared to the control group, supportive care is highly likely to be dominant (more effective and less costly) compared to CAU. After adjustment for differences at baseline, after taking into account differences in mortality rate and after excluding productivity losses, number of QALYs and cumulative costs mostly decreased to a non-statistically significant difference. However, the intervention group still had a probability of 84% - 98% that cumulative QALYs were higher and a probability of 91% - 99% to be less costly than the control group, supporting the finding that stepped care is likely to be cost-effective. In combination with findings on the efficacy of stepped care[4], stepped care is expected to be beneficial in routine HNC and LC care practice. Further research in needed on the optimal implementation of this stepped care program in clinical practice.

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