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ORIGINAL REPORT

Cost-Utility of Stepped Care Targeting Psychological Distress in Patients With Head and Neck or Lung Cancer

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ABSTRACT

Purpose

A stepped care (SC) program in which an effective yet least resource-intensive treatment is delivered to patients first and followed, when necessary, by more resource-intensive treatments was found to be effective in improving distress levels of patients with head and neck cancer or lung cancer. Information on the value of this program for its cost is now called for. Therefore, this study aimed to assess the cost-utility of the SC program compared with care-as-usual (CAU) in patients with head and neck cancer or lung cancer who have psychological distress.

Patients and Methods

In total, 156 patients were randomly assigned to SC or CAU. Intervention costs, direct medical costs, direct nonmedical costs, productivity losses, and health-related quality-of-life data during the intervention or control period and 12 months of follow-up were calculated by using Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry, Productivity and Disease Questionnaire, and EuroQol-5 Dimension measures and data from the hospital information system. The SC program's value for the cost 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% CI, –€8,158 to –€190) lower, and mean number of QALYs was 0.116 (95% CI, 0.005 to 0.227) higher in the intervention group compared with the control group. The intervention group had a probability of 96% that cumulative QALYs were higher and cumulative costs were lower than in the control group. Four additional analyses were conducted to assess the robustness of this finding, and they found that the intervention group had a probability of 84% to 98% that cumulative QALYs were higher and a probability of 91% to 99% that costs were lower than in the control group.

Conclusion

SC is highly likely to be cost-effective; the number of QALYs was higher and cumulative costs were lower for SC compared with CAU.

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INTRODUCTION

Recent reviews on the cost-effectiveness and cost-utility of psychosocial care in patients with cancer in general found that psychosocial care is likely to be cost-effective at potentially acceptable willingness-to-pay thresholds.[1,2] However, more research is warranted because economic evaluations are scarce, and heterogeneity among studies hampers comparison of the findings. In addition, there have not been any studies specifically targeted to novel psychosocial care programs such as stepped care (SC). To overcome barriers to the use of psychosocial care for patients with cancer, an SC program targeting psychological distress in those patients has been developed, and it consists of four steps: (1) watchful waiting for 2 weeks, (2) guided self-help, (3) face-to-face problem-solving therapy, and (4) specialized psychological interventions (eg, cognitive behavioral therapy) and/or psychotropic medication.[3] Patients proceed to the next step only when symptoms of distress do not resolve.

Recently, this SC program was found to have beneficial effects on distress compared with

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

PATIENTS AND 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 randomized controlled trial on the efficacy of an SC program for patients with HNC or LC who had symptoms of psychological distress, a Hospital Anxiety and Depression Scale (HADS) distress score $>$ 14, or an anxiety or depression score $>$ 7. The study was approved by the Medical Ethics Committee of VU Medical Center and conducted according to the principles of the Declaration of Helsinki.

Randomization and Treatment Allocation

Patients who met the eligibility criteria and signed informed consent were randomly assigned to the intervention group that was given SC or to the control group that was given CAU (Fig 1). The SC program consisted of four steps: (1) watchful waiting, (2) guided self-help via the Internet or a 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 for anxiety/depression score remained above 7) proceeded to a more intensive step. More information is provided in the Data Supplement.[3]

Outcome Measures

Cost and clinical end point data were collected at baseline (t0), immediately after the intervention or control period (t1), and at 3, 6, 9, and 12 months after t1. The economic evaluation was conducted from a societal perspective and included intervention costs, direct medical costs (cost of health care use and medication), direct nonmedical costs (cost of support groups, informal care, traveling to health services, and parking), and indirect nonmedical costs (loss of productivity from paid work). Intervention costs were calculated by using a bottom-up approach. Mean costs per patient in the intervention group were €318 (range, €24 to €9,043; Table 1).

The Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry (TiC-P)[15] was used to measure the use of health care facilities (eg, number of visits to the general practitioner) and other facilities (eg, time spent in self-help groups or informal care) in the past 4 weeks and medication used (antidepressants, analgesics, and sedatives) in the past 2 weeks. In addition, data on health care use within the hospital (visits to the medical specialist, day treatment, and hospital admission) was collected by using the hospital information system. Direct medical and direct nonmedical costs of support groups and informal care were calculated by multiplying resource use by the integral cost price.[16] Direct nonmedical costs of traveling to health services and parking were calculated by multiplying unit resource use by average distance to the location times the price per kilometer. All prices were adjusted to 2011 prices by 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 performed paid work (presenteeism) in the past 4 weeks. Losses as a result of 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 to 10 points). Indirect nonmedical costs from paid work were calculated by multiplying productivity losses by age- and sex-specific costs[16] using the human capital approach. The EuroQol-5 Dimension (EQ-5D) instrument was used to measure health-related quality of life. The EQ-5D utility score was obtained by using the Dutch index tariff.[18]

Statistical Analyses

All analyses were performed by using SPSS version 20 (IBM, Armonk, NY) and STATA version 12.1 (STATA, College Station, TX). Descriptive statistics, χ^2 tests, and independent t tests were used to describe and compare baseline characteristics among different groups.

To provide information on types of costs included in the analyses and their relative importance (their contribution to the mean total costs per group) at various time points, data for 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) were used. Data for complete cases were also used to provide information on the mean utility scores per group at the different time points.

To assess the value of SC for its cost compared with CAU, a base case intention-to-treat cost-utility analysis was performed at first that included all 156 randomly assigned patients and imputed any missing data. Consequently, to assess the robustness of this finding, four additional analyses were performed: (1) an analysis in which we adjusted the base case analysis by using multivariable regression analyses for variables at baseline found to have a major influence (a change of $\geq$ 20%) on incremental costs (European Organisation for Research and Treatment of Cancer [EORTC] social functioning and total costs at baseline) and incremental effects (HADS for depression at baseline), (2) an analysis excluding patients from the base case analysis who died during the study, (3) an analysis in which data were imputed for patients who died during the study as though they were still alive, and (4) 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 by using multiple imputation (predictive mean matching) by chained equations. Data were thus imputed only for those time points that were missing. Linear and logistic regression analyses were performed to investigate which variables (sociodemographic, clinical, HADS total, HADS for depression, HADS for anxiety, and EORTC global quality of life) were associated with missing data, observed costs, or EQ-5D utility scores. Variables associated with missing data (sex 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 that differed at baseline (alcohol dependency, HADS-D, EORTC Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] social functioning, and EORTC module for head and neck cancer [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 10 analyses were pooled by 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 by using the TiC-P and PRODISQ between t0 and t1 were calculated 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 randomly assigned to the intervention group, the costs as measured by

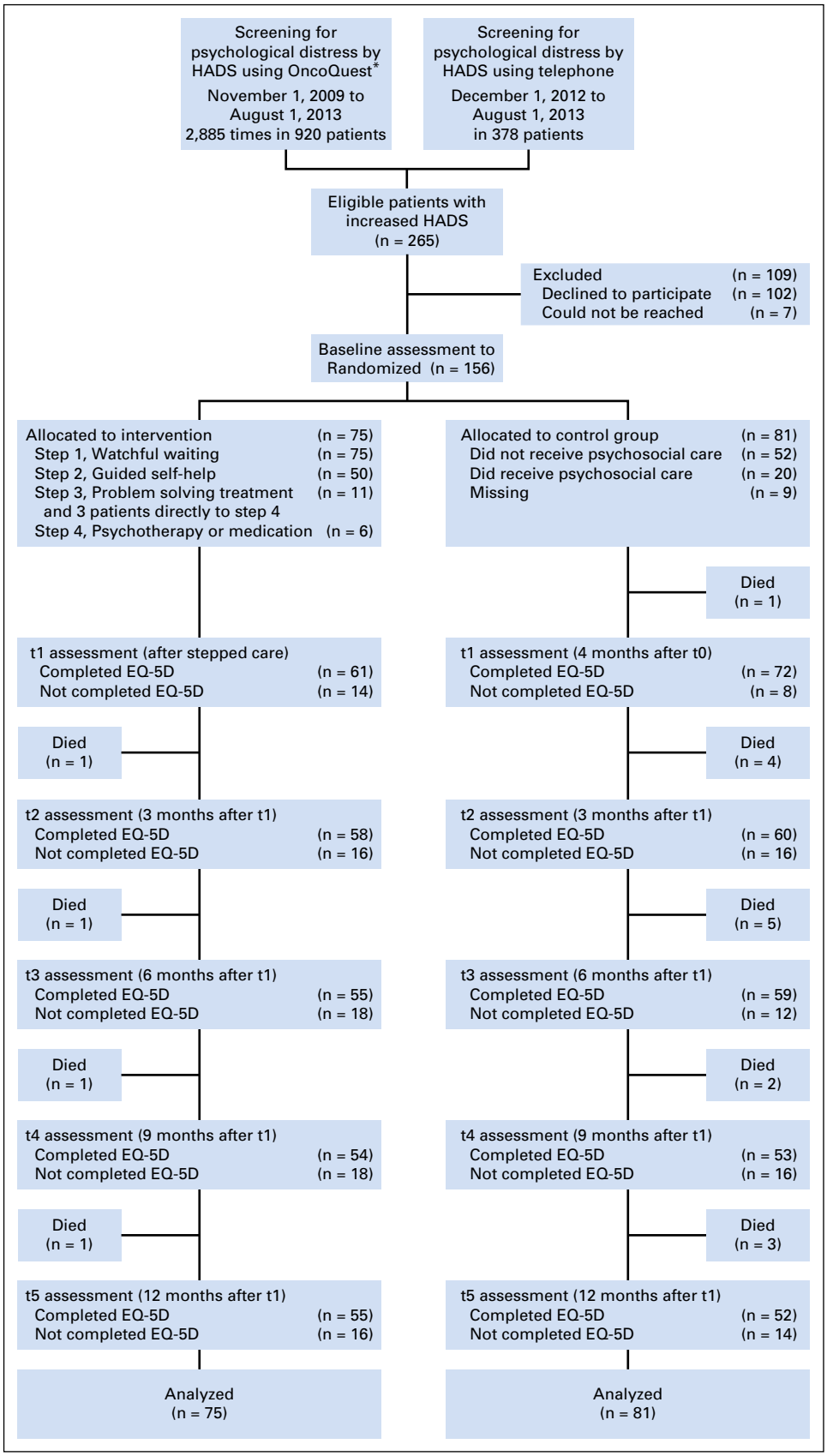

Fig 1 CONSORT flow diagram. (*) At the Department of Otolaryngology–Head and Neck surgery, and at the Department of Pulmonary Diseases of VU Medical Center in Amsterdam, Netherlands. EQ-5D, EuroQol-5 Dimension instrument; HADS, Hospital Anxiety and Depression Scale.

Table 1 Description of Health Care Use Within the Stepped Care Program

Steps	Cost (€)
Screening	
Screening for distress	7.97
Consultation with a nurse for 15 minutes	7.97
Step 1: Watchful waiting	
Monitoring distress with HADS assessment	7.97
Step 2: Guided self-help	
Self-help Internet tool or booklet	39.00
Feedback from a nurse by e-mail or telephone (in 1 hour total)	31.88
Monitoring distress with HADS assessment	7.97
Step 3: Face-to-face problem-solving therapy	
Five sessions of problem-solving therapy with a nurse	151.42
Monitoring distress with HADS assessment	7.97
Step 4: Specialized psychological interventions and/or psychotropic medication	
Costs were calculated per person individually because type of treatment and number of sessions or duration of treatment differed.	Differed

Abbreviation: HADS, Hospital Anxiety and Depression Scale.

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 group patients were calculated by summing costs per step. Mean costs per step per 4 weeks were calculated for all patients who participated in step 4, for patients who participated in step 3 but not in step 4, for patients who participated in step 2 but not in steps 3 or 4, and for patients who participated in step 1 but not in steps 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 by using the TiC-P and PRODISQ for both groups were calculated by using linear interpolation. Total cumulative costs per patient were calculated by summing cumulative costs measured by using the TiC-P and PRODISQ with intervention costs and costs measured by 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 by using linear interpolation.

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

RESULTS

In total, 75 patients were randomly assigned to the intervention group and 81 patients to the control group. Table 2 summarizes the baseline characteristics of both groups and compares patients with complete data with patients who did not have complete data. During the study, four (5.3%) of 75 patients in the intervention group versus 15 (18.5%) of 81 patients in the control group died (P = .012).

Direct and Indirect Medical and Productivity Costs

The mean costs for 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 4 weeks before baseline measurement, no statistically significant differences in costs were found between the two groups (P = .17), although there were large absolute differences. Mean total costs at baseline in the intervention group were €660 (standard deviation, €1,150) compared with €1,087 (standard deviation, €1,958) in the control group.

Health-Related Quality of Life

Table 4 presents the mean EQ-5D utility score for patients with complete data. At baseline, a statistically nonsignificant difference in EQ-5D utility score of .08 was found in favor of the intervention group (P = .12), which exceeded the subjectively appreciable difference of .07 reported in Walters et al.[19]

Cost-Utility Analyses

Results of the different cost-utility analyses are presented in Table 5 and Figure 2. In the base case analysis, mean costs in the intervention group were statistically significantly 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 with the control group (incremental effects were .116). Of the bootstrapped cost-utility pairs, 96% fell into the southeast quadrant, representing the probability that SC is more effective and less costly compared with CAU.

To assess the robustness of this finding, four additional analyses were performed as presented in Table 5. In these additional analyses, the intervention group had a probability of 84% to 98% that cumulative QALYs were higher and a probability of 91% to 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%).

DISCUSSION

This study investigated the cost-utility of an SC program targeting psychological distress in patients with HNC or LC compared with CAU. In the base case analysis, the number of QALYs was statistically significantly higher and cumulative costs were statistically significantly lower in the intervention group compared with the control group. The probability that cumulative QALYs were higher and costs were lower was 96%, indicating that SC is highly likely to be cost-effective compared with 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 that had a major impact on incremental costs or incremental effects. After correction, incremental costs and QALYs decreased to a statistically nonsignificant difference; however, the intervention group still had a probability of 93% that cumulative QALYs were higher and a probability of 89% that they were less costly than the control group.

In addition, we investigated the influence of the lower mortality rate in the intervention compared with the control group (5.3% *v* 18.5%). A debate is ongoing concerning the influence of psychosocial care on survival in patients with cancer; some authors suggest that psychosocial care may improve survival,[20-22] although

Table 2. Baseline Characteristics

Characteristic	Total Group (N = 156)	Intervention			Control			Significance Level			
		Total (n = 75)	Complete Cases* (n = 47)	Incomplete Cases† (n = 28)	Total (n = 81)	Complete Cases* (n = 56)	Incomplete Cases† (n = 25)	Intervention *v* Control Total	Intervention Complete *v* Incomplete Cases	Control Complete *v* Incomplete Cases	Intervention Complete *v* Control Complete Cases
Mean age (SD)	62.0 (9.4)	62.5 (8.7)	62.8 (8.2)	62.1 (9.5)	61.6 (10.0)	63.3 (9.6)	57.7 (10.0)	.538	.752	.019	.755
Sex (%)								.663	.028	.168	.254
Male	60.9	62.7	53.2	78.6	59.3	64.3	48.0				
Female	39.1	37.3	46.8	21.4	40.7	35.7	52.0				
Marital status (%)								.297	.537	.599	.355
Married/living with partner	67.9	72.0	74.5	67.9	64.2	66.1	60.0				
Unmarried/divorced/ widowed	32.1	28.0	25.5	32.1	35.8	33.9	40.0				
Work situation (%)								.979	.411	.372	.990
Paid job	30.8	30.7	34.0	25.0	30.9	33.9	24.0				
No paid job/retired	69.2	69.3	66.0	75.0	69.1	66.1	76.0				
Tumor location (%)								.176	.615	.643	.189
Lip/oral cavity/oropharynx	48.7	40.0	42.6	35.7	56.8	58.9	52.0				
Hypopharynx/larynx	25.6	28.0	23.4	35.7	23.5	25.0	20.0				
Other head and neck cancers	19.9	25.3	25.5	25.0	14.8	12.5	20.0				
Lung	5.8	6.7	8.5	3.6	4.9	3.6	8.0				
Tumor stage (%)								.146	.434	.813	.069
I	25.0	22.7	19.1	28.6	27.2	28.6	24.0				
II	16.0	20.0	23.4	14.3	12.3	12.5	12.0				
III	18.6	16.0	19.1	10.7	21.0	17.9	28.0				
IV	34.0	30.7	25.5	39.3	37.0	39.3	32.0				
Unknown	6.4	10.7	12.8	7.1	2.5	1.8	4.0				
Months since treatment (%)								.527	.626	.445	.725
< 7	35.9	38.7	38.3	39.3	33.3	35.7	28.0				
7-12	16.7	13.3	10.6	17.9	19.8	16.1	28.0				
> 12	47.4	48.0	51.1	42.9	46.9	48.2	44.0				
Treatment (%)								.430	.034	.839	.694
Single treatment	48.7	52.0	42.6	67.9	45.7	46.4	44.0				
Surgery	22.4	17.3	12.8	25.0	27.2	28.6	24.0				
Radiotherapy	26.3	34.7	29.8	42.9	18.5	17.9	20.0				
Combination treatment	51.3	48.0	57.4	32.1	54.3	53.6	56.0				
Chemoradiation‡	17.3	8.0	10.6	3.6	25.9	23.2	32.0				
Surgery and radiotherapy	26.3	33.3	36.2	28.6	19.8	21.4	16.0				
Surgery and chemoradiation§	5.1	5.3	8.5	0.0	4.9	3.6	8.0				
Surgery and chemotherapy¶	2.6	1.3	2.1	0.0	3.7	5.4	0.0				
Anxiety or depressive disorder (%)								.278	.636	.053	.733
Yes	22.4	18.7	17.0	21.4	25.9	19.6	40.0				
No	77.6	81.3	83.0	78.6	74.1	80.4	60.0				

(continued on following page)

Table 2. Baseline Characteristics (continued)

Characteristic	Total Group (N = 156)	Intervention			Control			Significance Level			
		Total (n = 75)	Complete Cases* (n = 47)	Incomplete Cases† (n = 28)	Total (n = 81)	Complete Cases* (n = 56)	Incomplete Cases† (n = 25)	Intervention *v* Control Total	Intervention Complete *v* Incomplete Cases	Control Complete *v* Incomplete Cases	Intervention Complete *v* Control Complete Cases
Nicotine dependence (%)								.678	.322	.396	.636
Yes	17.3	16.0	12.8	21.4	18.5	16.1	24.0				
No	82.7	84.0	87.2	78.6	81.5	83.9	76.0				
Alcohol dependence (%)								.030	.022	.238	.825
Yes	8.3	13.3	6.4	25.0	3.7	5.4	0				
No	91.7	86.7	93.6	75.0	96.3	94.6	100				
Mean HADS anxiety (SD)	9.5 (3.5)	9.3 (3.6)	9.2 (3.6)	9.6 (3.6)	9.6 (3.4)	9.3 (3.1)	10.2 (4.0)	.643	.676	.263	.869
Mean HADS depression (SD)	8.9 (3.8)	8.2 (3.7)	7.9 (3.6)	8.6 (3.7)	9.5 (3.8)	9.1 (3.6)	10.3 (4.1)	.029	.472	.181	.103
Mean HADS total (SD)	18.3 (5.4)	17.5 (5.2)	17.1 (4.9)	18.1 (5.6)	19.1 (5.6)	18.4 (4.6)	20.6 (7.2)	.071	.423	.185	.174
EORTC global quality of life	58.0 (19.8)	59.2 (20.1)	59.0 (19.0)	59.6 (22.3)	56.8 (19.6)	58.3 (21.1)	52.9 (15.2)	.441	.915	.266	.859
Mean EQ-5D utility score (SD)	0.63 (0.27)	0.66 (0.24)	0.68 (0.22)	.60 (.28)	.60 (.29)	.60 (.30)	.58 (.28)	.179	.178	.755	.115
Mean total costs in € (SD)	886 (1,614)	790 (1,443)	660 (1,150)	1,046 (1,895)	974 (1,762)	1,087 (1,958)	671 (1,060)	.491	.290	.238	.173

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol-5 Dimension; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation.
*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.
†Incomplete cases are patients who did not complete one or more of the baseline or follow-up measurements.
‡Cisplatin was given in 21 patients, and cetuximab was given in five patients; data were missing in one patient.
§Cisplatin was given in all eight patients.
¶Cisplatin was given in two patients, and erlotinib was given in one patient; data were missing in one patient.

Table 3. Mean Costs Per Time Point for Complete Cases

Variable	Reference Price Per Unit (€)	Intervention Group (n = 47)														Control Group (n = 56)													
		t0 (baseline)		t1		t2		t3		t4		t5		t0-t5		t0 (baseline)		t1		t2		t3		t4		t5		t0-t5	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Direct medical costs*		189	303	203	230	176	222	186	240	148	169	116	170			315	581	260	479	280	518	226	414	199	459	190	747		
General practitioner	29	26	49	20	27	23	37	17	31	22	35	17	29			24	32	27	46	23	34	20	35	20	29	18	29		
Company doctor	65	11	34	11	25	12	29	7	24	3	13	3	13			20	72	6	19	2	17	6	36	3	15	1	9		
Social worker																													
Company	68	1	10	1	10	—		—		—		—				1	9	—		—		—		1	9	—			
General	68	10	32	4	17	3	20	7	35	6	28	1	10			6	27	4	20	5	36	—		7	34	—			
Physiotherapist	38	65	193	58	100	46	99	52	117	31	72	40	92			45	88	45	93	50	105	39	89	28	65	21	76		
Dietitian	28	12	24	7	19	8	22	8	20	4	12	2	10			7	15	4	13	8	20	3	10	2	7	2	6		
Psychological help																													
Private practice	81	—		12	38	3	17	3	17	2	12	12	38			—		—		16	89	—		4	32	4	24		
Outpatient	179	19	107	19	77	15	63	30	120	15	63	4	26			13	67	6	48	6	48	13	96	—		—			
Addiction	179	—		15	104	19	107	—		—		—				—		—		—		32	239	—		—			
Mental hospital	181	—		15	63	4	26	4	26	4	26	4	26			—		13	97	—		3	24	13	58	3	24		
General hospital specialist	67	26	100	24	49	16	42	19	39	20	39	16	40			37	66	36	96	18	45	29	67	20	56	42	6		
Priest	122	—		—		3	18	3	18	3	18	—				13	69	4	23	2	16	—		—		—			
Housecleaning	25	11	59	14	62	19	79	32	102	38	112	18	56			42	128	25	67	46	112	30	77	21	67	67	9		
Personal care	46	—		—		—		—		—		—				67	364	65	324	99	385	51	237	25	172	46	6		
Visiting nurse	68	7	41	1	10	4	17	3	20	1	10	—				40	210	24	182	5	36	—		55	366	727	97		
Other direct medical costs																													
Medication*	0.19-7.58 per DDD	19	33	17	30	17	28	17	29	12	21	12	25			19	50	14	44	19	59	16	56	12	37	22	70		
Specialist†	130													1,104	936													1,088	780
Day treatment†	252													27	94													27	115
Hospitalization†	576 or 2,184 (IC)													441	1,774													1,882	5,193
Direct nonmedical costs*		80	177	34	83	79	230	60	158	49	146	47	129			184	463	51	161	64	163	56	137	78	281	78	263		
Support groups	12.80-57.50	34	138	4	14	18	54	37	150	16	55	28	124			30	93	7	31	24	87	8	40	7	33	45	229		
Informal care	12.80	41	123	24	80	57	223	19	59	30	137	16	47			149	459	40	159	43	127	43	127	68	280	31	107		
Transportation and parking costs	0.20/km; 3.00 parking	4	8	6	7	4	6	4	6	3	4	3	4			5	7	4	9	3	7	5	13	3	7	2	4		
Indirect nonmedical costs‡		372	1,127	264	914	205	582	172	747	124	422	37	179			569	1,530	305	1,104	333	1,027	151	427	158	722	130	478		
Absenteeism paid work	8.97-40.32/h	339	1,128	149	482	169	503	145	593	96	405	16	93			509	1,448	237	1,046	162	728	49	198	65	484	15	116		
Presenteeism paid work	8.97-40.32/h	33	117	115	681	36	170	27	165	28	140	21	92			61	214	68	335	170	500	103	365	94	275	115	461		

NOTE. 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.
Abbreviations: DDD, defined daily dose; IC, intensive care; SD, standard deviation; t1, assessment after 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.

*Measured by using the Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry over the past 4 weeks.

†Measured by using the VU Medical Center hospital information system over the entire study period.

‡Measured by using the Productivity and Disease Questionnaire over the past 4 weeks.

Table 4 Mean EQ-5D Utility Score Per Time Point for Complete Cases

Time Point	Intervention Group (n = 47)		Control Group (n = 56)	
	Mean	SD	Mean	SD
Baseline T1	.68	.22	.60	.30
t1	.74	.20	.65	.30
t2 (3 months after t1)	.77	.19	.65	.30
t3 (6 months after t1)	.75	.20	.61	.32
t4 (9 months after t1)	.74	.24	.61	.35
t5 (12 months after t1)	.73	.22	.60	.36

NOTE. 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. t1, assessment after the intervention (intervention group) or 4 months after baseline (control group).
Abbreviation: EQ-5D, EuroQol-5 Dimension.

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, because the higher mortality rate in the control group would have resulted in lower mean QALYs and was expected to influence mean total costs. Therefore, two additional analyses were performed: one analysis in which all patients who died were excluded and one analysis in which for all patients who died, 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 statistically nonsignificant difference. However, the intervention group still had a probability of 84% to 90% that cumulative QALYs were higher than in the control group and a probability of 96% to 99% that the intervention was less costly. This indicates that when SC does not influence survival, it is still likely to be cost-effective.

Our findings are in agreement with those from one previous study that targeted patients with cancer who had increased levels of distress.[26] All other previous studies targeting patients with cancer who had increased levels of distress reported an improvement in QALYs, although at higher costs.[27-29] This difference in cost-benefit may be a result of the design of SC in which intervention patients are first provided with watchful waiting (recovery rate, 28%), followed by guided self-help when they do not spontaneously recover after 2 weeks (recovery rate, 34%).[4] When the patient had still not recovered after guided self-help, more resource-intensive care was provided, although in the previous studies, all patients in the intervention group 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, and it incorporated productivity losses and direct nonmedical costs such as informal care costs. Previous studies found that being distressed was associated with unemployment in survivors of mixed cancer types[30] and that higher levels of depression were associated with unemployment as a result of loss of job, sick leave, or early retirement after treatment for HNC.[31] In another study of employment and return to work among patients with HNC, an association between anxiety and return to work was reported, although no association with distress or depression was found.[32] Our efficacy study showed that SC was beneficial in improving level of distress,[4] which may have had a beneficial effect on productivity losses in the intervention group compared with the control group. We conducted an additional analysis in which we excluded productivity losses; indeed, the analysis showed that the cost difference between the two groups was reduced by €1,062. However, even without productivity losses, SC had a probability of 97% to be more effective and less costly.

Some potential limitations were evident in this study. One potential limitation is that several assumptions were made regarding resource use and EQ-5D utility scores for data that were missing. First, missing total costs or utility scores per time point per treatment were imputed using multiple imputation techniques. Second, linear interpolation between time points was used. Both assumptions may not necessarily reflect reality, however, because the same assumptions were made for both groups, this was not expected 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] The small sample size of 156 patients is another limitation of this study. Although bootstrapping was

Table 5 Results of the Different Cost-Utility Analyses

Analysis and Group	No. of Patients	Costs (€)		QALY		Incremental Costs		Incremental Effects	
		Mean	SEM	Mean	SEM	€	95% CI	QALY	95% CI
Base case						−3,950	−8,158 to −190*	.116	.005 to .227*
Intervention	75	9,761	1,041	.884	.039				
Control	81	13,711	1,828	.768	.040				
Adjusted for several variables at baseline						−2,499	−6,082 to 630	.076	−.032 to .184
Intervention	75	NA		NA					
Control	81	NA		NA					
Excluding patients who died during the study						−3,939	−8,722 to 229	.052	−.053 to .156
Intervention	71	9,934	1,088	.911	.037				
Control	66	13,874	2,080	.859	.038				
With imputed data for patients who died during the study						−4,692	−8,898 to −889*	.059	−.035 to .153
Intervention	75	9,887	1,035	.908	.035				
Control	81	14,579	1,848	.849	.033				
Without productivity losses						−2,888	−5,630 to −424*	.118	.009 to .227*
Intervention	75	6,287	677	.885	.039				
Control	81	9,175	1,161	.767	.040				

Abbreviations: NA, not applicable; QALY, quality-adjusted life year.
*Significant difference between the two groups ($P < .05$).

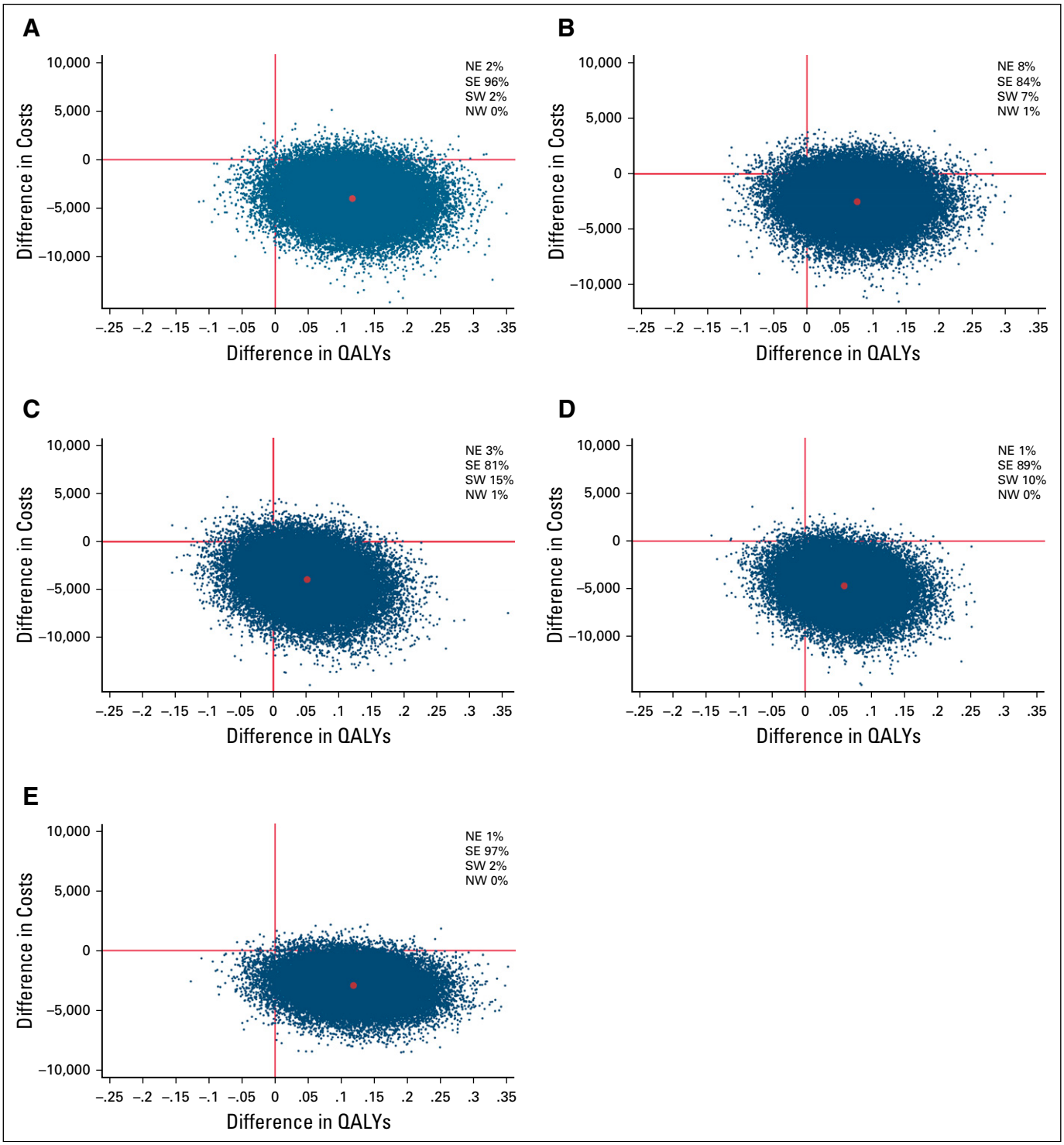

Fig 2 Cost-utility plane of (A) the base case analysis (B) adjusted for social functioning and total costs at baseline (costs) and Hospital Anxiety and Depression Scale (effects), (C) without patients who died during the study, (D) with imputed data for patients who died during the study, and (E) with productivity losses not included. QALYs, quality-adjusted life years. The percentages indicate the percentage of bootstrap replications in a certain quadrant.

performed, which supported the finding that SC 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 SC in subgroups of the investigated population, such as in patients with and without a diagnosis of major depression disorder or anxiety disorder.

Further research should investigate whether findings are replicable in other groups of patients with cancer. Further research should also be performed on optimal implementation of SC in routine cancer care, which may potentially differ between different health care systems (eg, the Netherlands compared with the United States). The Reach, Efficacy, Adoption, Implementation, and

Maintenance framework can be used to evaluate the different steps involved in optimal implementation and maintenance of SC.[33]

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

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Cost-Utility of Stepped Care Targeting Psychological Distress in Patients With Head and Neck or Lung Cancer

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