Optimization of treatment strategies and prognostication for patients with esophageal cancer

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CHAPTER 6

Patients with esophageal cancer report elevated distress and problems yet do not have an explicit wish for referral prior to receiving their medical treatment plan

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ABSTRACT

Objective: This study aims to identify esophageal cancer patients' level of distress, type of problems, and wish for referral prior to treatment. To identify the clinical relevance of esophageal cancer patients' level of distress and type of problems, we build models to predict elevated distress, wish for referral, and overall survival.

Methods: We implemented the Distress Thermometer (DT) and Problem List (PL) in daily clinical practice. A score of ≥5 on the DT reflected elevated distress. We first created an initial model including predictors based on the literature. We then added predictors to the initial model to create an extended model based on the sample data. We used the 'least absolute shrinkage and selection operator' (LASSO) to define our final model.

Results: We obtained data from 187 patients (47.9%, of 390 eligible esophageal cancer patients) which were similar to non-respondents in their demographic and clinical characteristics. One-hundred-thirteen (60%) patients reported elevated distress. The five most frequently reported problems were: eating, tension, weight change, fatigue, and pain. Most patients did not have a wish for referral. Predictors for elevated distress were: being female, total number of practical, emotional, and physical problems, pain, and fatigue. For referral, we identified age, the total number of emotional problems, the level of distress, and fear. The level of distress added prognostic information in a model to predict overall survival.

Conclusions: Esophageal cancer patients report elevated distress and a myriad of problems yet do not have an explicit wish for referral prior to receiving their medical treatment plan.

BACKGROUND

Esophageal cancer is one of the ten most common cancers worldwide. Moreover, its incidence is increasing rapidly [1]. At presentation, only a third of esophageal cancer patients are diagnosed with localized disease and may be eligible for potentially curative treatment [2-4]. Prognosis after such treatment is poor, with five-year survival rates rarely exceeding 50% [5;6]. In addition, many patients experience a clinically relevant and long-lasting deterioration in health-related quality of life (HRQL)[7]. Hence, being diagnosed with esophageal cancer is a life-changing and distressful event.

Distress is defined as a multifactorial experience and may reflect physical, social, and emotional concerns[8]. Chronic and untreated, distress or any of its associated problems such as depression can result in poorer adherence to treatment [9;10], satisfaction with care [9;11], quality of life [9;12;13], and even survival [14;15]. Despite recommendations from government and guideline developers, hospitals may not screen all of their cancer patients for distress [8;16-18]. As a result, oncologists may not be aware of the additional support needed by cancer patients to cope with their problems.

A method to improve the detection of distress is to systematically screen cancer patients [19;20], thus enabling the identification of patients in need of more extensive evaluation [8;21]. To successfully implement such screening in clinical practice, there is a need for rapid, valid, and easy-to-use instruments [22;23]. American, Canadian, and Dutch clinical guidelines recommend the use of the Distress Thermometer (DT) and Problem list (PL) to identify the level and nature of patients' distress, and their wish for referral [8;18;24;25]. However, to the best or our knowledge, no such information is yet available for esophageal cancer patients.

Therefore, this study aims to identify esophageal cancer patients' level of distress, type of problems, and wish for referral prior to treatment. To identify the clinical relevance of each reported problem, we build prediction models for patients' elevated level of distress and wish for referral. To explore further the clinical relevance of elevated distress, we build a prediction model for overall survival.

METHODS

The Medical Ethics Committee of the AMC exempted this study from formal approval.

Study sample

Patients included in this study represent patients with a suspected diagnosis of esophageal cancer who are referred by their general practitioner.

Study procedure

The Distress Thermometer/Problem List was implemented in daily clinical practice from July 2010 to December 2012 at the Gastro-Intestinal Oncology Diagnostic Center (GIOCA) of the Academic Medical Center (AMC), Amsterdam, The Netherlands, a tertiary referral centre for gastro–esophageal cancer. Patients can be referred to GIOCA if they are suspected of having gastrointestinal cancer. Approximately one week prior to their first visit, patients received an information letter, their appointment card, and the DT/PL [8]. At the day of their visit, patients were approached in the waiting room by a specialized nurse to collect the DT/PL. Patients who had not received the package or completed the questionnaire were invited to complete the DT/PL in the waiting room prior to their first visit [8;16]. Hence, most, if not all, patients who filled out the DT/PL knew that they had esophageal cancer, yet were unaware of their treatment intent (i.e., curative, palliative). This information was to be distributed at the end of the day when all test results had been gathered and discussed in the multidisciplinary team meeting. The minority of patients referred to GIOCA were patients looking for a second opinion regarding their diagnosis and or treatment plan.

Distress Thermometer and Problem List

The DT/PL was presented together on a single short questionnaire of one page. First, patients were instructed to circle the number (ranging from 0 [no distress] to 10 [extreme distress]) that best described the overall level of distress they experienced in the past week (including today). Patients were requested to take into account all physical, emotional, social, and practical aspects that could lead to distress. Patients who circled a five or more showed 'elevated' distress [24]. Then, patients had to indicate if ('yes', 'no') they experienced practical (7 items), family/social (3 items), emotional (10 items), religious/spiritual (2 items), or physical (25 items) problems. Finally, patients could indicate ('yes', 'maybe', 'no') whether they wanted to be referred to a professional.

Statistical analysis

All analyses conducted in this study represent secondary analyses on previously collected and electronically stored data of patients with a confirmed diagnosis of esophageal cancer. Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS) version 19.0 and R 3.0.2.

Selection bias

We compared respondents and non-respondents on demographic and clinical characteristics). We additionally compared the DT/PL scores of patients who had filled out the questionnaire prior to the consultation to those of patients who completed these at the clinic. Comparisons were made by use of sensitivity analyses and significance testing (independent samples T-test, Mann-Whitney U, Chi^2, and Kaplan Meier's log rank test).

Missing data

Based on the frequency distributions and associations between variables we assumed that the data were missing at random and thus could be substituted by multiple imputation [26]. The imputation models were determined by a prediction matrix and 'predictive mean matching'[27] to ascertain convergence and plausible imputations. In the end, we created 10 datasets [28] and compared the results obtained from multiple imputation to results obtained by complete case analysis. Results obtained by multiple imputations were either combined using Rubin's Rules, robust methods (e.g., the median and range to report pooled model performance across 10 imputation sets)[29], or the majority method (e.g., predictors selected in ≥5 imputation sets were included)[30].

Problem clusters

Since problems that tend to systematically cluster together may be of prognostic value we also explored the presence and clinical relevance of problem clusters [31]. In summary, we used the results from oblique factor analysis[32] and Cronbach's α to select clusters[33;34]. Patients were assigned cluster membership if they experienced all the problems in a cluster [35]. Patients could belong to more than one cluster.

Identifying predictors

To identify predictors for elevated distress, wish for referral and overall survival, we followed a multi-step approach. We first created an initial model including predictors based on the literature [36]. For the elevated distress and referral model, we used generalized linear models with a logit link function to estimate the probability of elevated distress (<5 vs. ≥5) and patient's wish for referral (yes/maybe vs. no). For overall survival (i.e., death by any cause), we used a Cox regression model and defined the time to event as the time from first appointment to death, or last follow-up (December 13th 2013). To assess the proportionality of hazards assumption, we added a time-dependent covariate with log(time) and examined Schoenfeld residuals[37]. To create an extended model we added predictors to the initial model. We only added problems which occurred in ≥5% of our patients to limit the possibility of convergence failure of the statistical model.

To select potential predictive problems, we used four different selection methods: (1) univariate analyses (P≤0.10 significant) followed by simultaneously entry into multivariate analyses, (2) backward selection using 2000 bootstrap resamples, (3) Bayesian Model Averaging (BMA), and (4) the 'least absolute shrinkage and selection operator'(LASSO) [38]. To be included in the 'extended model', predictors had to be deemed important by at least three methods, of which inclusion by LASSO was mandatory. We then applied LASSO to define our final model [38]. Because of multiple imputation, we applied the analyses separately to each of the 10 imputed datasets.

Transformations

For continuous predictors, we applied winsorization to limit the influence of outliers, and tested various transformations to assess the assumption of non-linearity. Because of the limited events per variable, we did not include any interaction terms [26]. We added multivariable fractional polynomials to transform the predictors and account for potential non-linearity [39]. For simplicity, and to maximize power, we only considered FP1 transformations [30]. Since transformations could differ across imputed datasets, we used the set of transformations selected in ≥5 imputed datasets to determine the final model.

Performance

Overall performance was evaluated by Nagelkerke's R2 and the scaled Brier score. Both measures express the explained variance on a scale of 0-100% Discrimination, which is the ability of the model to discriminate between patients with and patients without the outcome, was estimated using the concordance (c) statistic [26]. The c-statistic is identical to the area under the receiver operating characteristic (ROC) curve (AUC) for binary outcomes [26]. A model is considered strong when the c-statistic exceeds 0.8.[40]. The scaled Brier is more sensitive to the inclusion of new predictors then the c-statistic [41]. Calibration, which is the agreement between observed and predicted outcomes, was measured by use of the calibration intercept and slope. Perfect calibration is marked by an intercept of 0 and a slope of 1[26]. To determine how a model would hypothetically perform in a new sample (i.e. internal validation) we created 500-2000 bootstrap samples [26;42]. Unless otherwise stated, a p-value ≤0.05 was considered statistically significant.

RESULTS

Study sample

We included 187 esophageal cancer patients (47.9% of 390 eligible esophageal cancer patients) of which 135 were male (72%) (Table 1). The mean age was 66 (SD=10). Most

patients were diagnosed with adeno-carcinoma (n=135, 72%) at the lower part of the esophagus (n=150, 80%). Treatment was mostly with curative intent (n=148, 79%). Median survival was 796 days. Respondents and non-respondents had similar demographic and clinical characteristics (Table 1).

Table 1: Comparison of respondents vs. non-respondents

Characteristic	Respondents (N=187)	Non-respondents (N=203)	p-value
Age *(mean, SD)*	65.75 (10)	64.64 (11.7)	0.328
Sex			0.733
Male	135 (72%)	150 (74%)	
Female	52 (28%)	53 (26%)	
WHO			0.610
0	71 (38%)	66 (33%)	
1/2/3	53 (24%)	57 (24%)	
Missing	63 (33%)	80 (39%)	
Charlson Index			0.220
Low	99 (53%)	121 (60%)	
Medium/High/Very high	88 (47%)	82 (40%)	
BMI *(median, IQR)*	25.3 (5.3)	24.7 (5.1)	0.898
Histology			0.677
Adeno	135 (72%)	138 (68%)	
Squamous Cell	47 (25%)	56 (28%)	
Other	0 (0%)	1 (0%)	
Missing	5 (3%)	8 (4%)	
Tumor location			0.278
Upper third	14 (7%)	9 (4%)	
Middle third	19 (10%)	28 (14%)	
Lower third / GEJ	150 (80%)	159 (78%)	
Missing	4 (2%)	7 (4%)	
TNM stage - clinical			1.000
Stage I-II	47 (25%)	49 (24%)	
Stage III-IV	128 (68%)	137 (68%)	
Missing	12 (7%)	17 (8%)	
cN			0.729
Yes	131 (70%)	140 (69%)	
No	53 (28%)	51(25%)	
Missing	3 (2%)	12 (6%)	
Treatment			0.178
Curative intent	148 (79%)	145 (71%)	
Palliative / no treatment	36 (19%)	50 (25%)	
Missing	3 (2%)	8 (4%)	

Table 1: Continued

Characteristic	Respondents (N=187)	Non-respondents (N=203)	p-value
Surgery			0.348
Yes	113 (60%)	111 (55%)	
No	70 (37%)	84 (45)	
Missing	4 (2%)	8 (4%)	
Neo-adjuvant treatment[a]			0.256
Yes	106 (94%)	101 (91%)	
No	7 (6%)	10 (9%)	
Missing	4 (2%)	8 (4%)	
ASA[a]			0.602
1	18 (16%)	20 (18%)	
2	66 (58%)	72 (65%)	
3	29 (26%)	19 (17%)	
Mandard[b]			0.116
1	23 (22%)	17 (17%)	
2	17 (16%)	9 (9%)	
3	27 (25%)	36 (36%)	
4	19 (18%)	25 (24%)	
5	4 (4%)	7 (7%)	
Missing	16 (15%)	7 (7%)	
Morbidity grade (Clavien-Dindo)[a]			0.557
No complications	41 (36%)	48 (43%)	
1	12 (11%)	7 (6%)	
2	24 (21%)	24 (22%)	
3	7 (6%)	9 (8%)	
4	20 (18%)	20 (18%)	
5	9 (8%)	3 (3%)	
Radicality of Resection[a]			0.507
R0	107 (95%)	104 (94%)	
R1 / R2	6 (5%)	7 (6%)	
Death			0.543
Yes	94 (50%)	95 (47%)	
No	93 (50%)	108 (53%)	
Survival[c] *(median, 95% CI)*	796 (565 - 1026)	854 (690 - 1017)	0.845

SD= standard deviation, IQR= interquartile range, WHO = World Health Organization, BMI = body mass index, GEJ = gastro-esophageal junction, cN = clinically derived lymph node status, ASA= American Society for Anaesthesiologists, R0 = radical resection, no cancerous cells seen microscopically, CI= confidence interval

[a] Only applicable to patients who had received surgery

[b] Only applicable to patients who had received neo-adjuvant treatment

[c] Survival time in days

Missing data

Missing data on the DT/PL ranged from 10% to 21% per item. Results obtained from multiple imputation showed comparable results with complete case analysis. Patients who had filled out the DT/PL prior to the consultation reported similar levels of distress and type of problems, and had similar demographic and clinical characteristics, compared to patients who had filled out the DT/PL at the clinic

Distress, problems, problem clusters & wish for referral

The median (i.q.r.) thermometer score was 5 (3 - 7) (Figure 1). We identified 113 (60%) patients with elevated distress. The ten most frequently reported problems were: eating (n=140,75%), tension (n=114, 61%), weight change (n=109, 58%), fatigue (n=82,44%), pain (n=71,38%), fear (n=68,36%), physical fitness (n=67,36%), sleep (n=63,34%), emotional control (n=56,30%), and depression (n=52, 28%) (Figure 2). We identified three problem clusters: eating/weight change (n=99, 53%), fatigue/physical fitness (n=63, 34%), and fear/tension (n=58, 31%). Of 187 patients, 24 (13%) wanted to be referred, 66 (35%) maybe wanted to be referred, and 97 (52%) did not want to be referred to a professional.

Figure 1: Level of distress (frequency) prior to esophageal cancer treatment

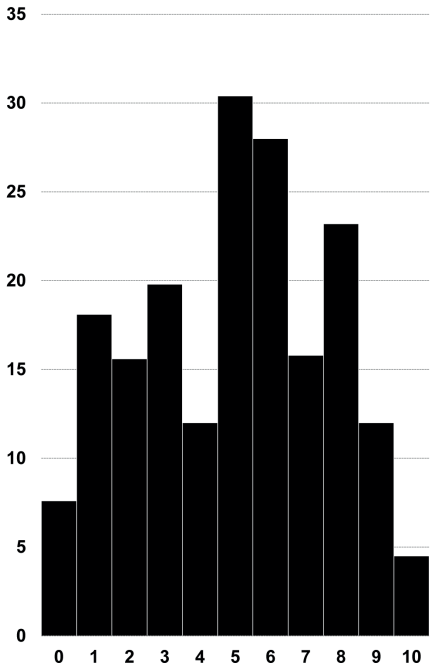
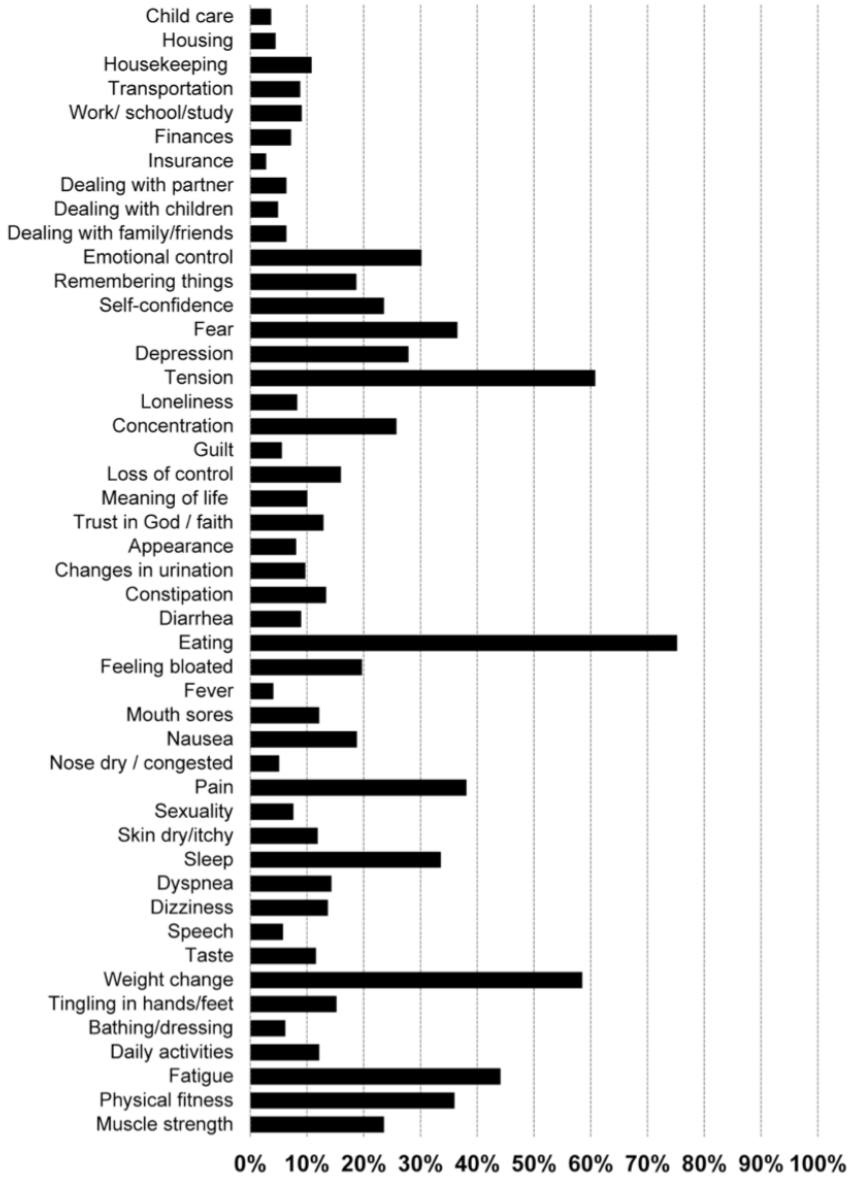


Figure 2: Problems experienced prior to esophageal cancer treatment



Predictors of elevated distress

For the extended model, we confirmed the possible predictive role of 'pain' and added the three problem clusters. Adding and transforming predictors did not increase the performance of the models, and the initial model performed best. The final model (Table 2) included: female gender (OR=1.63), the total number of practical (OR=0.41), emotional (OR=1.40), and physical problems (OR=1.54), pain (OR=3.37), and fatigue (OR=0.63). After internal validation, this model explained half of the observed variance (R^2 = 50% [42% - 55%], scaled Brier = 40% [34% - 45%]), and showed excellent discrimination (0.88 [0.86 - 0.89]) and good calibration (intercept = 0.00 [-0.07 - 0.02], slope = 0.99 [0.92 - 1.40]) (Table 2).

Predictors of wish for referral

For the extended model, we selected fear. Adding, but not transforming the predictors, increased the performance of the model. The final model (Table 2) included: age (OR=0.98), the total number of emotional problems (OR=1.21), the level of distress (OR=1.04), and fear (OR=1.69). After internal validation, this model explained a small amount of the observed variance (R^2 = 14% [9% - 18%], scaled Brier = 11%[7% - 14%]) , showed reasonable discrimination (0.70 [0.68 - 0.73]) and reasonable calibration (intercept = 0.00 [-0.01 - 0.05], slope = 0.95 [0.89 - 1.76]).

Predictors of overall survival

For the extended model, we added the problems 'constipation', 'sexuality', and 'weight change' as additional predictors. Adding predictors, but not transformations, increased the performance of the model. The final model (Table 2) included: palliative treatment (**HR=4.90**), clinically determined lymph node status (HR=1.57), Charlson index = medium/high/very high (**HR=1.28**), daily activities (**HR=1.82**), level of distress (**HR=0.94**), constipation (**HR=1.97**), sexuality (**HR=2.20**), cluster eating/weight change (**HR=2.20**), cluster fear/tension (**HR=0.68**), and the cluster fatigue/physical ability (**HR=1.21**) (Table 4). After internal validation, the final model explained 29% (26% - 30%) of the observed variance, and showed reasonable discrimination (0.74 [0.73 - 0.76]).

Table 2: Selected predictors of elevated distress, wish for referral, and overall survival in 187 esophageal cancer patients prior to treatment.

	Elevated distress[a] (# = 110 - 115)		**Wish for referral[d] (# = 88 - 91)**		**Overal Survival[e] (# deaths = 94)**	
	Selected predictors	**OR[b]**	**Selected predictors**	**OR[b]**	**Selected predictors**	**HR[b]**
	Sex	1.63	Age	0.98	Palliative treatment	4.90
	Total practical problems	0.41[c]	Total emotional problems	1.21[c]	Cn	1.57
	Total emotional problems	1.40[c]	Level of distress	1.04[c]	Charlson score[f]	1.28
	Total physical problems	1.54[c]	Fear	1.69	Daily activities	1.82
	Pain	3.59			Level of distress	0.94[c]
	Fatigue	0.63			Constipation	1.97
					Sexuality	2.20
					Cluster eating / weight change	2.20
					Cluster fear / tension	0.68
					Cluster fatigue / physical fitness	1.21
Model performance	Apparent *Internal validation[g]*		Apparent *Internal validation[g]*		Apparent *Internal validation[g]*	
R^2	53% (46% - 56%) *50% (42% - 55%)*		15% (13% - 19%) *14% (9 % - 18%)*		32% (30% - 33%) *29% (26% - 30%)*	
C-statistic	0.88 (0.86 - 0.89) *0.87 (0.85 - 0.89)*		0.71 (0.69 - 0.73) *0.70 (0.68 - 0.73)*		0.72 (0.74 - 0.76) *0.74 (0.73 - 0.76)*	
Brier scaled	43% (38% - 46%) *40% (34% - 45%)*		12% (10% - 15%) *11 % (7% - 14%)*		N/A	
Calibration intercept	-0.01 (-0.1 - 0.01) *0.00 (-0.07 - 0.02)*		0.00 (0.01 - 0.05) *-0.01 (-0.01 - 0.03)*		N/A	
Calibration slope	1.06 (1.02 - 1.25) *0.99 (0.92 - 1.40)*		1.05 (1.02 - 1.47) *0.95 (0.89 - 1.76)*		N/A	

OR= odds ratio, N/A= not applicable, HR= hazard ration, Cn= clinically determined lymph node status

[a] Odds ratios, model fit, and model performance based on initial model, winsorization, and the least absolute shrinkage and selection operator (LASSO)

[b] Since the LASSO does not provide estimates of the standard error it is not feasible to compute confidence intervals for the odds or hazard ratio.

[c] Winsorized

[d] Odds ratios, model fit, and model performance based on extended model, winsorization, and LASSO

[e] Hazard ratios, model fit, and model performance based on extended model, winsorization, and LASSO

[f] Medium/High/Very high vs. low score

[g] Estimates provided by combining the results of 100 bootstrap samples across 10 imputed datasets

CONCLUSIONS

Our results show that, prior to receiving the medical treatment plan, the majority of esophageal cancer patient's show elevated distress and report a myriad of problems, yet do not wish to be referred to a professional to discuss their distress or problems. These results are similar to the findings of another Dutch study including a different cancer sample [24].

Many esophageal cancer patients reported emotional and physical problems prior to treatment. This is a likely a result of patients knowing their diagnosis but not their medical treatment plan (i.e. curative or palliative). Despite their predictive importance, there is little detailed information available on the emotional problems experienced by esophageal cancer patients prior to treatment [31]. To the contrary, most studies conclude that patients' 'emotional functioning' is not greatly affected by treatment and might even improve over time [43]. However, a recent population-based survey looking more closely at the specific emotional consequences of esophageal cancer treatment reveals that many patients do report tension, worry, irritation, and depressed mood six months after surgery [44]. Although the physical consequences of surgery are well known, it is very likely that patients experience a least as many emotional as physical problems, despite receiving a 'successful' treatment.

These findings warrant the systematic and longitudinal use of a screening instrument to identify and monitor the specific (emotional) problems of each patient. This should be supplemented with qualitative work to obtain more in-depth knowledge on how patients experience the diagnostic, treatment, and post-treatment phase. Combined, such data could be used by oncologists, or nurses, to create patient profiles and better prepare, and guide, their consultation. Ideally, this information would also be used to monitor and, if need be, change patient management.

Despite the high level of distress and many problems experienced, most esophageal cancer patients did not have an explicit wish for referral to a professional and expressed doubt. One likely explanation is that patients would likely be focused on getting a medical treatment plan, rather than considering if they wanted psychosocial referral. Furthermore, it is likely that the high levels of distress, emotional problems, tension and fear experienced at that moment can only be 'treated' by receiving a positive message. As such, patients might not directly see the value of being referred, which could explain

the large number of 'maybe' and 'no' reported. However, in the absence of more robust quantitative (and qualitative) data, we are not exactly sure why patients did not express an explicit wish for referral.

Since it is difficult to *a priori* determine patients' wish for referral, and many patients report doubts, oncologists might explicitly ask about the possible wish for referral during the consultation. Ideally, this enquiry should be conducted prior to and following the discussion of the medical treatment plan, and on a continuous basis following each assessment. As a result, oncologists are likely to obtain a more detailed view of the needs of their patient. In addition, patients will be able to provide an answer that is less hindered by immediate other priorities and the anxiety and uncertainty experienced during the diagnostic phase. Patients who report fear and or high levels of emotional problems on the screening instrument should receive additional attention and more thorough enquiries, especially in the absence of a wish for referral.

We were unable to attribute a strong prognostic role for level of distress, or confirm any prognostic role for the cluster pain/fatigue. Possible explanations may be related to the differences in the cancer sample included, specific construct of distress investigated (e.g., depression), type of questionnaire used, and statistical analyses applied. However, we did verify the prognostic role of patients' physical functioning by using 'daily activities' as a proxy. In addition, we showed that obtaining knowledge about constipation, sexuality, weight change, eating, fear, tension, fatigue, and physical fitness, increases our ability to predict patients' overall survival. Nevertheless, the discriminative power of our final model was reasonable at best. Hence, the additional value of the DT/PL alongside established clinical variables to predict the overall survival of esophageal cancer patients deserves further study.

This study has several limitations. First, the timing of assessment for enquiring about patients' wish for referral limited the usefulness of the results obtained. By asking patients during their diagnostic phase, but prior to receiving their medical treatment plan, most patients may have likely had other priorities than whether they will need to be referred to psychosocial care. As such, their answers may not reflect their 'true' wish. Ideally, such an assessment should be conducted once the uncertainty and anxiety of the treatment plan is reduced. Second, our study sample was small due to a low response rate and we did not obtain reasons for missing data. Third, by primarily looking at problems rather than additional socio-demographic (e.g., education) and personality factors (e.g., coping) we

may have missed potential important predictors for patients' wish for referral. Fourth, the majority method applied may not result in optimal predictor selection [45]. Fifth, using predictive mean matching to impute missing data may not have yielded the most optimal imputation model [46]. Sixth, we did not ask patients which professional they would like to be referred too. Seventh, our findings are not directly comparable to studies using the widely used cut-off ≥4. However, we explicitly chose a cut-off of ≥5, since this was the cut-off identified in a validation study of the DT/PL conducted in the Netherlands in a heterogeneous cancer population. Since our study was conducted in the Netherlands, we automatically assumed this to be the correct cut-off score to use. Finally, since we did not externally validate the final models it is possible that their 'true' performance is substantially less. For instance, compared to literature, our study sample comprised of a much larger percentage of that were deemed eligible for treatment with curative intent.

The strengths of this study are the inclusion of a large number of problems and clinical variables, extensive and iterative analyses conducted to test the representativeness of our study sample and select potential predictors for elevated distress, wish for referral, and overall survival. In addition, by using multiple imputation, we maximized the statistical power of our sample.

To better support patients, oncologists should systematically screen patients for distress, problems, and their wish for referral in the diagnostic, treatment, and post-treatment phase. Such extensive screening should be used to guide consultations and support patient management.

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