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Assessment of Palliative Care in Lung Cancer in Turkey

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Keywords

Lung cancer · Palliation · Palliative treatment · Symptoms · Treatment

Abstract

Objective: To investigate the symptoms of lung cancer in Turkey and to evaluate approaches to alleviate these symptoms. **Subjects and Methods:** This study included 1,245 lung cancer patients from 26 centers in Turkey. Demographic characteristics as well as information regarding the disease and treatments were obtained from medical records and patient interviews. Symptoms were evaluated using the Edmonton Symptom Assessment Scale (ESAS) and were graded on a scale between 0 and 10 points. Data were compared using the χ^2 , Student *t*, and Mann-Whitney U tests. Potential predictors of symptoms were analyzed using logistic regres-

sion analysis. **Results:** The most common symptom was tiredness ($n = 1,002$; 82.1%), followed by dyspnea ($n = 845$; 69.3%), appetite loss ($n = 801$; 65.7%), pain ($n = 798$; 65.4%), drowsiness ($n = 742$; 60.8%), anxiety ($n = 704$; 57.7%), depression ($n = 623$; 51.1%), and nausea ($n = 557$; 45.5%). Of the 1,245 patients, 590 (48.4%) had difficulty in initiating or maintaining sleep. The symptoms were more severe in stages III and IV. Logistic regression analysis indicated a clear association between demographic characteristics and symptom distress, as well as between symptom distress (except nausea) and well-being. Overall, 804 (65.4%) patients used analgesics, 630 (51.5%) received treatment for dyspnea, 242 (19.8%) used enteral/parenteral nutrition, 132 (10.8%) used appetite stimulants, and 129 (10.6%) used anxiolytics/anti-depressants. Of the 799 patients who received analgesics, 173 (21.7%) reported that their symptoms were under control, and also those on other various treatment modalities

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(dyspnea: 78/627 [12.4%], appetite stimulant: 25/132 [18.9%], and anxiolytics/antidepressants: 25/129 [19.4%]) reported that their symptoms were controlled. **Conclusion:** In this study, the symptoms progressed and became more severe in the advanced stages of lung cancer, and palliative treatment was insufficient in most of the patients in Turkey.

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Introduction

Lung cancer is a highly mortal disease with poor survival rates. Patients with lung cancer suffer many limitations due to symptoms related to the disease and its treatment [1]. Most patients with lung cancer are symptomatic at presentation, and most of them experience multiple symptoms, including dyspnea, pain, fatigue, anorexia, nausea, anxiety, and depression, especially in the advanced stages [1].

Lung cancer symptoms are known to cause secondary effects on the emotional, social, physical, and spiritual well-being of patients [2]. Because there is a close relationship between the symptoms, quality of life, and survival, early implementation of palliative care has been reported to improve a patient's quality of life, symptom burden, and even survival [3]. However, in clinical practice, the importance of symptoms and palliative care is often neglected by physicians, and is generally not considered in the disease's management [4].

The goal of palliative care is to provide relief from pain and other distressing symptoms in order to give patients and their families the best possible quality of life, regardless of disease stage or need for other therapies [5]. Common pulmonary symptoms of lung cancer that require palliative therapy include those caused by the cancer itself, i.e., dyspnea, wheezing, cough, hemoptysis, and chest pain; locoregional metastases within the thorax, i.e., superior vena cava syndrome, pleural effusions, etc.; or by distant metastases, i.e., bone and brain [1]. Hence, this study, which was conducted in Turkey, aimed to investigate the symptoms of lung cancer and its treatment, as well as to evaluate approaches for palliating those symptoms.

Subjects and Methods

Following approval from the Ethics Committee of Karadeniz Technical University Faculty of Medicine, this multicenter and prospective study was performed at 26 centers in Turkey from March 2014 to September 2014. During the study period, all lung

Table 1. Characteristics of disease and treatment options in patients with lung cancer

	n (%)
Histopathologic diagnosis (n = 1,245)	
Squamous cell carcinoma	489 (39.3)
Adenocarcinoma	369 (29.6)
Small-cell lung carcinoma	237 (19.0)
NSCLC-not otherwise specified	127 (10.2)
Others	23 (1.8)
Stage of disease (n = 1,202)	
Stage I	78 (6.5)
Stage II	121 (10.1)
Stage III	332 (27.6)
Stage IV	671 (55.8)
Metastases	
Bones (n = 663)	291 (43.9)
Brain (n = 667)	154 (23.1)
Liver (n = 665)	134 (20.2)
Adrenal glands (n = 664)	116 (17.5)
Other (n = 718)	151 (20.0)
Treatment options ¹ (n = 1,159)	
Chemotherapy	532 (45.9)
Chemo-radiotherapy	327 (28.2)
Surgery	213 (18.4)
Radiotherapy	87 (7.5)

¹ First-line treatment options that have been delivered or are currently being delivered.

cancer patients (both old and newly diagnosed for any stage) who presented at the hospital were included in the study if they agreed to participate and signed informed consent.

Demographic characteristics and disease and treatment variables were collected for each patient by physicians using a standard questionnaire, which was completed during face-to-face interviews, and hospital records. The symptoms at the time of data collection were recorded and graded using the Edmonton Symptom Assessment Scale (ESAS). The ESAS symptom scores were categorized by severity as follows: none = 0; mild = 1–3; moderate = 4–6; and severe = 7–10. The ESAS is a patient-reported validated tool for assessment of symptoms and its validity and reliability of ESAS for use in a Turkish population were established by Yesilbalkan et al. [3, 6]. The ESAS was supplemented with a question regarding whether or not the patient had difficulty initiating or maintaining sleep: "Do you frequently have difficulty in falling asleep at night or waking up frequently during the night or getting back to sleep after waking during the night?"

Data analysis (regarding the demographic characteristics, symptoms, and the potential predictors of symptoms) were performed using SPSS software (Version 13.01; SPSS Inc., Chicago, IL, USA). The χ^2 test was used to compare categorical variables. The parametric Student *t* test was used for comparing mean or median values of normally distributed data, and the nonparamet-

Table 2. Distribution of symptoms according to severity and disease stage in patients with lung cancer

Symptoms	Stage	Symptom severity				Total	p
		no symptom n (%)	mild n (%)	moderate n (%)	severe n (%)		
Pain	1-2	79 (39.7)	68 (34.2)	31 (15.6)	21 (10.6)	1,186	<0.0001
	3-4	327 (33.1)	246 (24.9)	216 (21.9)	198 (20.1)		
Tiredness	1-2	48 (24.1)	69 (34.7)	51 (25.6)	31 (15.6)	1,186	<0.0001
	3-4	166 (16.8)	201 (20.4)	252 (25.5)	368 (37.3)		
Drowsiness	1-2	90 (45.2)	66 (33.2)	26 (13.1)	17 (8.5)	1,187	<0.0001
	3-4	375 (38.0)	242 (24.5)	162 (14.6)	209 (21.2)		
Nausea	1-2	115 (57.5)	48 (24.0)	30 (15.0)	7 (3.5)	1,189	0.018
	3-4	529 (53.5)	210 (21.2)	145 (14.7)	105 (10.6)		
Lack of appetite	1-2	95 (47.0)	50 (24.8)	38 (18.8)	19 (9.4)	1,191	<0.0001
	3-4	319 (32.3)	177 (17.9)	199 (20.1)	294 (29.7)		
Shortness of breath	1-2	51 (25.6)	78 (39.2)	48 (24.1)	22 (11.1)	1,185	<0.0001
	3-4	313 (31.7)	231 (23.4)	202 (20.5)	240 (24.3)		
Depression	1-2	112 (56.3)	55 (27.6)	16 (8.0)	16 (8.0)	1,185	<0.0001
	3-4	468 (47.5)	200 (20.3)	163 (16.5)	155 (15.7)		
Anxiety	1-2	98 (49.2)	55 (27.6)	26 (13.1)	20 (10.1)	1,186	0.002
	3-4	404 (40.9)	218 (22.1)	170 (17.2)	195 (19.8)		
Well-being	1-2	71 (45.3)	63 (37.3)	39 (6.7)	25 (10.7)	1,185	<0.0001
	3-4	261 (38.6)	219 (21.9)	251 (25.9)	256 (13.6)		

ric Mann-Whitney U test was used to compare data that was not normally distributed. Factors that were potential predictors of symptoms (age, gender, body weight, disease stage, comorbidities, weight loss, histology [small-/non-small-cell lung cancer], metastasis, and time since diagnosis) were analyzed using logistic regression, as were symptoms that were the potential predictors of lack of well-being (pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, and anxiety). Multivariate logistic regression analysis was used as a stepwise descending method from predictive factors with a significance ≤ 0.05 in the univariate analysis.

Results

A total of 1,245 lung cancer patients (1,104 [88.7%] males; 141 [11.3%] females) participated in the study. However, the number of patients included in analyses was variable because of some missing data. Of the 1,202 patients, 671 (55.8%) had stage IV disease and the most frequent histologic type was squamous cell cancer (Table 1). The mean age of the patients was 61.8 ± 9.4 years. The ESAS revealed that 1,085/1,216 (89.2%) of the patients had more than one symptom, and tiredness 1,002/1,220 (82.1%) was the most common symptom. There was a gradual increase in severity of symptoms based on the disease stages (Table 2). Patients with stages III and IV disease had more symptoms, and those with

earlier stages had higher levels of well-being (Table 2). Of the patients, 590/1,218 (48.4%) had difficulty initiating or maintaining sleep, and this was more common in the advanced stages (509/980 [51.9%] vs. 63/200 [31.5%], $p < 0.0001$). Six hundred eleven (49.3%) patients had unintended weight loss of at least 5 kg, while 164 (13.2%) patients gained weight during the treatment period. Weight loss was also more significant in the advanced stages (517/1,002 [51.6%] vs. 75/199 [37.7%], $p < 0.001$).

Logistic regression analysis indicated a clear association between demographic characteristics (age, gender, comorbidities, body weight, weight loss, disease stage, metastasis, and time since diagnosis) and symptom distress (Table 3). There was also a significant association between the symptom distress (except nausea) and well-being (Table 4).

Palliation of Symptoms

Dyspnea

Overall, 51.5% of the patients (630/1,223) received treatment for dyspnea (Table 5). Of the 1,223 patients who received treatment for dyspnea, 78 (12.4%) had resolution of dyspnea; while the remaining 549 (87.6%) did not. On the other hand, 256 patients with mild/moderate dyspnea and 37 with severe dyspnea (total 293: 34.8%) received no palliative therapy for their dyspnea.

Table 3. Multivariate logistic regression analysis of demographic parameters predicting symptoms in lung cancer

Variables ¹	OR	95% CI	<i>p</i>	Variables ¹	OR	95% CI	<i>p</i>
Pain				Shortness of breath			
Gender (female)	1.402	0.929–2.115	0.107	Age	1.005	0.991–1.019	0.502
Body weight	0.987	0.977–0.996	0.007	Body weight	0.984	0.975–0.993	0.001
Disease stage	0.944	0.735–1.213	0.653	Comorbidity	1.903	1.462–2.477	<0.001
Weight loss	1.023	1.007–1.040	0.005	Depression			
Metastasis	1.727	1.102–2.708	0.017	Gender (female)	1.777	1.210–2.610	0.003
TST	0.986	0.977–0.994	0.001	Body weight	0.988	0.979–0.997	0.010
Tiredness				Disease stage	1.065	0.826–1.374	0.626
Body weight	0.982	0.971–0.993	0.002	Comorbidity	1.421	1.116–1.809	0.004
Disease stage	1.130	0.861–1.484	0.378	Weight loss	1.042	1.021–1.063	<0.0001
Weight loss	1.031	1.002–1.060	0.037	Metastasis	1.353	0.863–2.119	0.187
Metastasis	1.537	0.914–2.587	0.105	TST	0.988	0.979–0.997	0.009
Drowsiness				Anxiety			
Age	1.010	0.996–1.024	0.152	Age	1.010	0.996–1.023	0.167
Body weight	0.997	0.987–1.006	0.524	Gender (female)	1.791	1.195–2.684	0.005
Disease stage	1.032	0.803–1.326	0.807	Body weight	0.991	0.982–1.001	0.071
Comorbidity	1.264	0.979–1.632	0.072	Disease stage	1.088	0.846–1.401	0.511
Weight loss	1.044	1.021–1.067	<0.0001	Comorbidity	1.238	0.961–1.594	0.098
Metastasis	1.640	1.048–2.567	0.031	Weight loss	1.040	1.018–1.062	<0.0001
TST	0.990	0.987–0.998	0.020	Metastasis	1.328	0.848–2.079	0.215
Nausea				TST	0.992	0.983–1.001	0.077
Age	0.985	0.972–0.997	0.017	Poor well-being			
Body weight	0.991	0.982–1.000	0.057	Age	1.028	1.013–1.044	<0.0001
Disease stage	1.020	0.790–1.317	0.881	Body weight	0.981	0.971–0.991	<0.0001
Weight loss	1.030	1.011–1.050	0.002	Disease stage	0.998	0.770–1.294	0.990
Metastasis	1.276	0.814–2.001	0.289	Comorbidity	1.198	0.903–1.590	0.211
TST	0.986	0.977–0.995	0.004	Weight loss	1.049	1.022–1.077	<0.0001
Lack of appetite				Metastasis	2.168	1.349–3.484	0.001
Age	1.008	0.993–1.022	0.314	TST	0.991	0.982–1.000	0.044
Body weight	0.970	0.960–0.980	<0.001	Awakening			
Disease stage	1.172	0.903–1.520	0.234	Gender (female)	1.361	0.936–1.979	0.107
Comorbidity	1.463	1.114–1.921	0.006	Disease stage	1.403	1.080–1.822	0.011
Weight loss	1.046	1.022–1.072	<0.001	Comorbidity	1.406	1.107–1.785	0.005
Metastasis	1.477	0.924–2.361	0.103	Weight loss	1.027	1.008–1.046	0.004
TST	0.987	0.972–0.991	<0.001	Metastasis	1.291	0.822–2.027	0.267

TST, time since diagnosis. ¹ Only variables derived from predictive factors with a significance ≤ 0.05 in the univariate analysis were included.

Pain

Overall, of 1,229 patients, 804 (65.4%) used analgesics (Table 5). Nonnarcotic and narcotic analgesic use alone or in combined forms were detected in 693 (86.2%) and 320 (39.8%) patients using analgesics ($n = 804$), respectively. Among the entire study population, these rates were 56.4% (693/1,229) and 26.0% (320/1,229), respectively. Only 173 (21.7%) of the patients receiving analge-

sics reported complete pain relief; 626 (78.3%) patients reported continuing pain despite analgesic use. In contrast, 171 (21.5%) patients reported no analgesic use despite having pain (147 with mild/moderate pain, 24 with severe pain). Two hundred ninety-one (43.9%) patients had metastases to bone, and of these only 135 (39.6%) were treated with bisphosphonates and 88 (30.2%) were treated with palliative radiation.

Table 4. Multivariate logistic regression analysis of symptoms predicting well-being in patients with lung cancer

Symptoms	Poor well-being		<i>p</i>
	OR	95% CI	
Pain	2.287	1.619–3.231	<0.0001
Tiredness	1.738	1.141–2.648	0.010
Drowsiness	2.020	1.419–2.875	<0.0001
Nausea	0.975	0.646–1.472	0.905
Lack of appetite	3.675	2.543–5.312	<0.0001
Shortness of breath	1.842	1.293–2.624	0.001
Depression	2.848	1.723–4.708	<0.0001
Anxiety	4.281	2.717–6.745	<0.0001

Enteral/Parenteral Nutrition, Appetite Stimulant, and Vitamin Use

Two hundred forty-two patients (out of 1,222; 19.8%) received enteral or parenteral nutrition; this was more prevalent in advanced stages than in those with stages I and II (21.4 vs. 10.0%, respectively, $p < 0.001$). The reasons that patients used nutritional products were difficulty swallowing (35/221, 15.8%), cachexia (85/221, 38.5%), and other causes (101/221, 45.7%). The nutritional support was given via an oral route in 192/239 patients (80.3%), via nasogastric tube in 10/239 patients (4.2%), via percutaneous endoscopic gastrostomy in 2/239 patients (0.8%), and via parenteral route in 35/239 patients (14.6%).

Of 1,224 patients, 132 (10.8%) were using appetite stimulants, and use was more frequent in patients at advanced stages (12.3 vs. 4.5%, $p < 0.001$). Of these, 93 (70.4%) used megestrol acetate, 29 (22.0%) used cyproheptadine, 2 (5.4%) used a combination of these drugs, and 8 (6.1%) used other medications. Overall, 81/1,041 (6.6%) reported vitamin use, and 238/1,227 patients (19.4%) reported the use of blood products including whole blood, erythrocyte suspension, plasma, etc.

Of the patients with appetite loss, 107/792 (13.4%) were using appetite stimulants (79 megestrol acetate, 21 cyproheptadine, 9 a combination of drugs, and 5 other drugs). Twenty-five patients (18.9%) using an appetite stimulant reported no appetite loss. Similarly, 77/602 (12.8%) of the patients with weight loss were using an appetite stimulant (55 megestrol acetate, 17 cyproheptadine, 1 combination, 2 other). Again 38/454 (8.4%) of the patients with no weight loss and 17/163 (10.4%) of the patients with weight gain were using appetite stimulants.

Table 5. Palliative treatment options in patients with lung cancer

	Patients receiving palliative treatment, <i>n</i> (%)	All patients, <i>n</i> (%)
Treatment of dyspnea (51.5%, 630/1,223)		
Bronchodilator	562/624 (90.1)	562/1217 (46.2)
Home oxygen	177/619 (28.6)	177/1212 (14.6)
Nebulizer	175/617 (28.4)	175/1210 (14.5)
Palliative radiotherapy	55/613 (9.0)	55/1206 (4.6)
Thoracentesis	43/613 (7.0)	43/1206 (3.6)
NIMV	18/610 (2.9)	18/1210 (1.5)
Endobronchial treatment/stenting		
	12/614 (2.0)	12/1207 (1.0)
Pleurodesis		
	11/613 (1.8)	11/1206 (1.0)
Analgesic use (65.4%, 804/1,229)		
Paracetamol/ NSAID	476/804 (59.2)	476/1224 (38.9)
Tramadol	46/804 (5.7)	46/1215 (3.8)
Fentanyl	36/804 (4.5)	36/1214 (2.9)
Morphine	3/804 (0.4)	3/1211 (0.2)
NSAIDs+tramadol	73/804 (9.1)	73/1212 (6.0)
NSAIDs+fentanyl	59/804 (7.3)	59/1211 (4.9)
NSAIDs+tramadol+fentanyl	46/804 (5.7)	46/1211 (3.8)
Other combinations	62/804 (7.7)	62/1211 (5.2)

NIMV, noninvasive mechanical ventilation; NSAID, nonsteroidal anti-inflammatory drug.

Anxiolytic/Antidepressant Drugs and Sleeping Pills

One hundred twenty-nine patients (129/1,222, 10.6%) received anxiolytic/antidepressant treatment. Of these patients, 104 (80.6%) had only depression or anxiety, while 25 (19.4%) did not report having depression or anxiety. One hundred four patients (104/1,221, 8.5%) used sleeping pills and 84 of these patients (80.8%) had complained of difficulty with sleep.

Discussion

In the current study, more than 85% of the lung cancer patients experienced multiple symptoms (ranging from mild to severe) regardless of their disease stage. Symptoms were more severe in the advanced stages than in stages I–II of the disease; the most common symptom was tiredness, followed by shortness of breath, loss of appetite, pain, drowsiness, anxiety, depression, and nausea. The finding that tiredness was the most common symptom of lung cancer was consistent with previous studies [4, 7]. Equally, the findings that age, gender, comorbidities, body weight, weight loss, disease stage, me-

tastasis, and time since diagnosis were independent predictors of lung cancer symptoms are similar to demographic features including age, gender, disease stage, treatment type, comorbidities, income, and weight loss that had been reported to be associated with symptom distress [8–10].

The finding in the current study that symptom distress was an independent predictor of well-being, except for nausea, was consistent with that of Lien et al. [11], who reported that the number of symptoms was negatively correlated with emotional distress and sense of well-being. Anxiety was the symptom that was most significantly associated with poor well-being. Smalbrugge et al. [12] also showed that presence of depression and/or anxiety has a clinically significant negative impact on well-being.

Our results indicate that there are a significant number of unmet needs reported by patients with lung cancer. Most patients in our study reported continuing symptoms, and a significant number of patients with dyspnea and pain reported that they were not receiving treatment. Similar to our results, some studies reported that lung cancer patients with high symptom scores were not undergoing any treatment [7, 9]. Several studies have also shown that there is a high prevalence of uncontrolled symptoms in patients with advanced lung cancer [7, 13, 14].

Dyspnea is common in patients with lung cancer; it may develop due to malignant airway obstruction, lymphangitic spread, radiation or drug-induced pneumonitis, pleural effusion, accompanying chronic obstructive pulmonary disease, etc. Patient discomfort may be alleviated by radiotherapy, endobronchial treatment/stent placement, and thoracentesis, or pleurodesis for pleural effusion. In the present study, the rates of palliative radiotherapy, thoracentesis, endobronchial treatment/stent placement, and pleurodesis were 4.6, 3.6, 1.0, and 1.0%, respectively; these results were comparable to those of the LUCEOR study [5]. However, home oxygen use and bronchodilator use in the current study were higher; we believe that those high percentages reflect the rate of comorbid chronic obstructive pulmonary disease patients, since 1/4 to 1/2 of lung cancer patients are reported to have chronic obstructive pulmonary disease [15].

In the present study, at least 50% of all patients were using nonnarcotic analgesics either alone or in combination with narcotic analgesics. Narcotic analgesic use (26.0%) was similar to that in studies by Lester et al. [5] and Di Maio et al. [14] (19.2 and 23%, respectively); however, nonnarcotic analgesic use in the current study (56.4%) was higher than their results (30 and 13.7%, respectively). Compared to our current data and that from

previous studies, a study from Greece reported higher use of narcotic and nonnarcotic analgesics (80.6 and 64.2%, respectively) in cancer patients [16]. In the current study, 30.2% of the patients underwent palliative radiotherapy for bone metastasis, which is similar to a report by Alexopoulos et al. [16]. Skeletal metastatic disease is the main cause of pain and the gold standard treatment for pain due to bone metastases is radiotherapy [17]. Bisphosphonates also play an important role in the treatment of bone metastasis; however, bisphosphonate use in the current study was lower than in the studies by Lester et al. [5] and Alexopoulos et al. [16].

The rates for nutritional support in the current study is in accordance with several studies reporting variable rates between 1.1 and 42.9% [5, 18]; however, the use of appetite stimulants (e.g., megestrol acetate and cyproheptadine) was lower than the percentages of patients with weight loss and appetite loss. Appetite stimulants may be effective alternatives in cancer patients suffering from anorexia/cachexia syndrome, but their effect on weight gain is controversial [19–22]. The use of blood products, including whole blood, erythrocyte, plasma, etc., was quite common in our patients. Erythrocyte and platelet use was reported as 9.1% in the LUCEOR study [5]. While 3.2% of the patients in that study reported using erythropoiesis-stimulating agents, they were not used at all in the current study.

The ratio of anxiety and depression in our study (~50%) was comparable to previously reported data [23]. Similar to Salvo et al. [23] we found that female patients were more likely to report higher levels of anxiety and depression. Again, 48.4% of our patients had sleep problems, which is similar to Chen et al. [24] and Gooneratne et al. [25]. Sleep quality is associated with the distressing symptoms of lung cancer, and studies have shown a clear correlation between sleep quality and fatigue [24, 26], pain [27], and dyspnea and cough [28]. Despite the high rates of depression and anxiety in our patients, only 10.6% were using anxiolytic/antidepressant treatment. While approximately half of our patients had sleep disturbances, only 8.5% were using sleeping pills. In contrast to our current study, Farriols et al. [28] reported that 84% of patients were using benzodiazepines and 27.1% were using antidepressants, in a general cancer population.

The most important limitation of this study was that data collection was focused on the perceived burden of symptoms at a single time point. It is important to acknowledge that the results presented herein reflect only one point of a patient's life, and do not reflect symptoms during the entire disease duration.

Conclusion

In this study the prevalence of symptoms was higher and most severe in patients in the advanced stages of the lung cancer than the other stages. Palliative treatment of symptoms was mostly inadequate, and large number of patients continued to suffer from uncontrolled symptoms and unmet needs. Because well-being was clearly

associated with the distress from the symptoms, controlling these symptoms is important in patients with cancer. Hence, we recommend that patients undergo regular symptom assessment in order to achieve this, and treatment should be provided according to the published guidelines. Furthermore, both physician and patient education as well as more effective future therapeutic options are essential.

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