Does Patient-reported Dyspnea Reflect Thoracic Disease Characteristics in Patients with Incurable Cancer?

CARSTEN NIEDER[1,2], THOMAS A. KÄMPE[1] and KIRSTEN ENGLJÄHRINGER[1]

[1]Department of Oncology and Palliative Medicine, Nordland Hospital Trust, Bodø, Norway;
[2]Department of Clinical Medicine, Faculty of Health Sciences,
UiT – The Artic University of Norway, Tromsø, Norway

Abstract. *Background/Aim: A considerable proportion of patients with incurable cancer experience dyspnea. This study evaluates associations between the feeling of dyspnea, as quantified by radiotherapy patients scoring their symptoms before palliative treatment with the Edmonton symptom assessment system (ESAS), and potential underlying causes. Patients and Methods: Retrospective comparison of the incidence of different parameters that could cause a feeling of dyspnea in two groups, patients with no or minimal dyspnea (ESAS score 0-2) and those with dyspnea scores >2. Results: The mean dyspnea score of all 102 patients was 2.6. Dyspnea scores >2 were present in 68% of patients with lung cancer, 50% of those with breast cancer, 39% of those with prostate cancer and 26% of those with other tumors (p=0.025). Dyspnea scores >2 were also present in 69% of patients with pleural effusion (vs. 40% in patients without pleural effusion), p=0.031. Among patients treated with palliative thoracic radiotherapy, 71% had dyspnea scores >2 (40% if other targets were irradiated), p=0.041. In 13% of patients, anemia and pulmonary comorbidity were the most likely explanation for dyspnea. In 29% the feeling of dyspnea could not be related to objective findings. Conclusion: In the majority of patients, the feeling of dyspnea was associated with the presence of thoracic metastases with or without pleural effusion from extrathoracic primary tumors or with a lung cancer diagnosis. A substantial proportion of patients reported dyspnea that could be related neither to cancer burden nor comorbidity.*

Correspondence to: Carsten Nieder, Department of Oncology and Palliative Medicine, Nordland Hospital Trust, 8092 Bodø, Norway. Tel: +47 75578449, Fax: +47 75534975, e-mail: carsten.nieder@nlsh.no

Most patients with incurable cancer experience clinical symptoms and worse quality of life than the general population (1, 2). Symptom control is an important aim of palliative treatment and can be achieved, *e.g.*, with radiotherapy and supportive measures. The Edmonton symptom assessment system (ESAS) is a short, one-sheet questionnaire addressing major symptoms and wellbeing on a numeric scale of 0-10 (3), which can easily be integrated into routine workflow in oncology departments (4-6). Dyspnea is among the symptoms on the questionnaire and may be caused by different underlying diagnoses, including but not limited to cardiac and pulmonary comorbidity, anemia, thoracic primary tumors and thoracic metastases. Previous research has shown that cancer patients who reported higher feelings of dyspnea on the ESAS tool were more likely to report feelings of depression (7). These patients also more often reported higher feelings of anxiety. A different study has shown that shortness of breath increased in severity over time, particularly in the month before death (8). More than one third of the cohort reported moderate to severe scores (*i.e.*, 3 to 10) for most ESAS symptoms in the last month of life. The purpose of the present study was to assess associations between the feeling of dyspnea and different patient-, comorbidity- and cancer-related characteristics that may explain the presence of dyspnea in patients with incurable cancer managed at a dedicated palliative radiotherapy facility, which routinely screens all patients with the ESAS tool.

Patients and Methods

We performed a retrospective chart review in 102 unselected, consecutive in- and out-patients who received palliative radiotherapy at a single study site during the time period 2013-2015. In 2013, the facility's pre-treatment work-up changed towards routine inclusion of the ESAS tool, administered by a registered oncology nurse immediately before physician consultation, blood drawing and imaging for treatment planning, *i.e.* approximately one week before radiotherapy. The treating physician recorded the patients' medical history and ECOG performance status (PS).

Comorbidity was retrospectively scored by use of the Charlson comorbidity index (CCI), a validated and widely used tool (9). All medical records were available in the hospital's electronic patient record (EPR) system (DIPS®, DIPS ASA, Bodø, Norway). Statistical analysis was performed with IBM SPSS Statistics 22. We analyzed two different subgroups, patients with no or minimal dyspnea, corresponding to an ESAS score of 0-2, and those with moderate or severe dyspnea, score 3-10. The incidence of different parameters that could cause a feeling of dyspnea was assessed and compared between the two groups with the chi-square test (when appropriate Fisher exact probability test or *t*-test). A *p*-value ≤0.05 was considered statistically significant. Two-tailed tests were performed. Ethical approval was not required for this study in accordance with the national and institutional guidelines.

Results

The median age was 70 years, range=49-91 years. As displayed in Figure 1, no dyspnea was more common than severe dyspnea. The mean score was 2.6. As shown in Table I, 27% of the patients had a lung cancer diagnosis and the same percentage had parenchymal lung metastases. Fifteen percent had pleural effusion with or without pleural metastases. Nineteen percent were active smokers. Of all baseline characteristics mentioned in this section and Table I only three were significantly associated with the dichotomized dyspnea item. Dyspnea scores >2 were present in 68% of patients with lung cancer, 50% of those with breast cancer, 39% of those with prostate cancer and 26% of those with other tumors (Table II). Dyspnea scores >2 were also present in 69% of patients with pleural effusion (40% in patients without pleural effusion). Among patients treated with thoracic radiotherapy, 71% had dyspnea scores >2 (40% if other targets were irradiated). Age, performance status and smoking were not significantly associated with dyspnea scores. The same holds true for comorbidity (mean CCI 2.7 and 2.8 in the two groups, respectively).

In all 45 patients with dyspnea scores >2 a comprehensive EPR review was performed in order to identify the most likely explanation. In 13 cases (29%) dyspnea seemed to be caused by primary lung cancer or mesothelioma without thoracic metastases. In 8 cases (18%) primary lung cancer with thoracic metastases was present. In 5 cases (11%) the reason seemed to be thoracic metastases with or without pleural effusion from extrathoracic primary tumors. In one and 5 cases (2 and 11%), respectively, anemia and pulmonary comorbidity were judged to be responsible for dyspnea. In the remaining 13 patients (29%) the feeling of dyspnea could not be related to objective findings.

Discussion

In the present study the question "does patient-reported dyspnea reflect thoracic disease characteristics in patients with incurable cancer?" was addressed. One-hundred and

Table I. *Baseline characteristics before palliative radiotherapy.*

Characteristic	No	%
ECOG performance status		
0	15	15
1	23	23
2	34	33
≥3	30	29
Gender		
Male	75	74
Female	27	26
Primary tumor site		
Prostate	31	30
Breast	12	12
Lung (small cell)	2	2
Lung (non-small cell)	26	25
Colorectal	5	5
Bladder	5	5
Malignant melanoma	4	4
Kidney	4	4
Multiple myeloma	3	3
Other	10	10
RT target types[1]		
Bone metastases	63	62
Brain metastases	13	13
Lymph node metastases	6	6
Lung or thorax	14	14
Prostate	4	4
Others	15	15
Patients without metastatic disease	10	10
One organ system with metastases	41	40
Two organ systems with metastases	32	31
>2 organ systems with metastases	19	19
Parenchymal lung metastases		
No	74	73
Yes	28	27
Pleura effusion		
No	86	85
Yes	16	15
Systemic cancer treatment		
No	49	48
Before RT	53	52
Systemic steroids[2]		
No	41	40
Before RT	60	59
Charlson comorbidity index[3]		
0-2	57	56
>2	45	44
Smoking status[2]		
No	52	51
Active	19	19
Former smoker	25	25
Serum hemoglobin[2]		
Normal	49	48
Below ILN	27	26
Blood transfusion (RBC)		
Not given	89	88
Given	13	13
Mean time from first cancer diagnosis to RT	53 months	
Mean time from first metastasis (if any) to RT	27 months	

RT: Radiotherapy; ILN: institutional limit of normal; RBC: red blood cells. [1]more than one could be present in the same patient; [2]missing information in some cases; [3]excluding currently treated cancer.
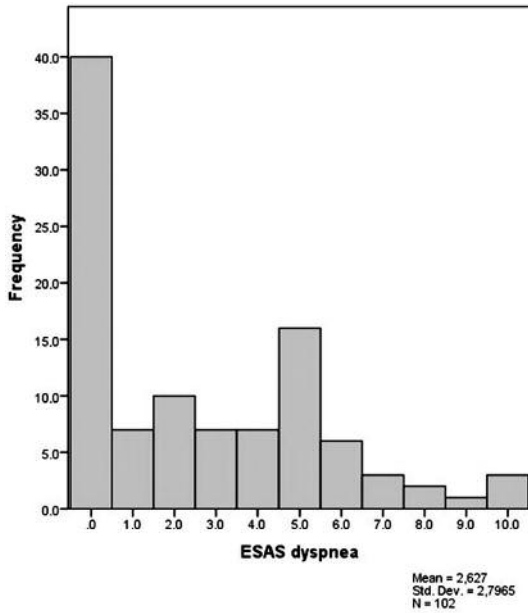
Figure 1. *Frequency table showing the number of patients with different ESAS dyspnea scores (0= no dyspnea, 10= worst dyspnea).*

Table II. *Association between ESAS dyspnea severity and different patient characteristics.*

	Score 0-2, n=57	Score >2, n=45	*p*-Value
Parameter			
Lung cancer	9	19	
Breast cancer	6	6	
Prostate cancer	19	12	
Others	23	8	0.025
Pleura effusion	5	11	
No pleura effusion	52	34	0.031
Thoracic radiotherapy	4	10	
No thoracic radiotherapy	53	35	0.041

two patients treated with palliative radiotherapy scored their symptoms including the feeling of dyspnea with the ESAS tool at the time of treatment planning. Objective lung function tests or oxygenation measurements were not available. The patients were not selected for particular primary tumor types or treatment indications and are thus representative of daily clinical practice in palliative radiotherapy facilities such as ours. As one might expect intuitively, many patients treated with palliative thoracic radiotherapy (71%) reported dyspnea scores >2. We decided to dichotomize our study population by score 0-2 *vs*. >2 because this resulted in reasonably balanced group size and thereby improved statistical power, compared to, *e.g*., a cut-off of 4 or 5. Palliative radiotherapy is a well-established, widely used means of providing symptom improvement, *e.g*., of dyspnea, pain and cough, and, in selected patients with less advanced disease, increased overall survival (10-14). This treatment is often associated with improved quality of life and functional independence and should be combined with other, *e.g*., drug-based supportive measures (15).

When interpreting our results, the following drawbacks must be taken into account. In retrospective studies, selection bias and incomplete recording of data might complicate the analyses and their interpretation. With a median age of 70 years, our study group was comprised of many elderly and geriatric patients. This resulted in a high proportion of patients with comorbidity. We found that dyspnea scores >2 were significantly more common in patients with lung cancer and

those with pleural effusion. However, other baseline characteristics were not associated with this endpoint. A detailed chart review revealed that dyspnea scores >2 were likely caused by comorbidity or anemia in 13% of the patients reporting this degree of dyspnea. In 29% the feeling of dyspnea could not be related to objective findings or diagnoses.

In a large Canadian study of administrative healthcare data more than half of ambulatory cancer patients reported dyspnea (use of ESAS) (16). Lung cancer patients had the worst burden of symptoms. Reddy et al. analyzed 70 patients with dyspnea referred to a palliative care service (17). Forty-four percent had a lung cancer diagnosis. Dyspnea intensity significantly interfered with activities (general activity, *p*=0.01, mood, *p*=0.02, walking ability, *p*=0.04, normal work *p*=0.04, and enjoyment of life, *p*=0.01). Interestingly, ESAS dyspnea was associated with forced expiratory volume (*p*=0.004). A different study included 299 patients with an average age of 62 years hospitalized at MD Anderson Cancer Center (37% with lung cancer) (18). In 125 patients (42%) parenchymal lung metastases were present and in 166 pleural effusion (56%). Twenty-nine had COPD (10%). The median intensity of patients' dyspnea on a numeric rating scale at the time of assessment was 3. Median ESAS shortness of breath was 5. Many patients (152, 51%) used oxygen *via* nasal cannula. Respiratory rate and oxygen saturation did not have any significant correlation with patients' expression of dyspnea. Compared to our patients, this cohort was comprised of hospitalized patients only and thus reported a larger burden of dyspnea. The authors also evaluated the Respiratory Distress Observation Scale (RDOS). The median RDOS rating was 2/16 and the number of potential causes for respiratory distress was 3, with pleural effusion (n=166, 56%), pneumonia (n=144, 48%), and lung metastasis (n=125, 42%) being the most common. In line with our study, lung metastasis and pleural effusion were scored in a present/absent format, not taking into account the potential impact of differences in size or volume.

Conclusion

In the majority of patients, the feeling of dyspnea was associated with the presence of thoracic metastases with or without pleural effusion from extrathoracic primary tumors or with a lung cancer diagnosis. However, a substantial proportion of patients reported dyspnea that could be related neither to cancer burden nor comorbidity. Further studies are needed to elucidate the underlying causes and whether or not typical palliative interventions including radiotherapy are effective in this particular subgroup.

Conflicts of Interest

The Authors declare that they have no competing interests.

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