Who Experiences Higher and Increasing Breathlessness In Advanced Cancer?

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Abstract

PURPOSE: Breathlessness is a major cause of suffering in advanced cancer. We aimed to determine the symptom trajectory in people with advanced cancer and to identify those at increased risk of experiencing higher or increasing breathlessness over time in advanced cancer.

PATIENTS AND METHODS: Analysis of the multinational, prospective, longitudinal European Palliative Care Cancer Symptom (EPCCS) study. We included adults with confirmed incurable cancer enrolled in palliative care, with prospective monthly assessments for up to six months, withdrawal or death, whichever came first. Symptom severity (0-10 numerical rating scales; NRS) was analyzed using multivariate random coefficients regression.

RESULTS: A total of 1,689 patients (50% women; mean age 65.7 ± [standard deviation; SD] 12.4 years) were included. Main diagnoses were digestive (31%), lung (20%), and breast (17%) cancers. During a median follow-up of 62 (interquartile range, 0 to 133) days, 65% were breathless at some point and 36% of all patients reported moderate/severe breathlessness. The group mean (1.6 points; SD, 2.4) was unchanged over time, but the severity varied markedly between patients and over time. Independent predictors for worse breathlessness were COPD, lung cancer, living alone, lung metastases, anxiety, pain, depression, and lower performance status. Predictors of worsening breathlessness over time were low performance status (p=0.039) and moderate to severe pain (p=0.012).

CONCLUSION: In the largest longitudinal clinical study to date in advanced cancer alone, breathlessness was frequent and associated with factors including respiratory disease, other concurrent unpleasant symptoms and impaired performance status. Increase in severity over time was predicted by performance status and pain.

Objectives

We aimed to determine:

1) the prevalence, severity, and variability of breathlessness;
2) predictors of higher breathlessness severity; and
3) predictors of increasing breathlessness severity over time in patients with advancing cancer.

The study protocol is registered with ClinicalTrials.gov (NCT01362816).

Material and Methods

Design: Observational longitudinal study.

Data source: The European Palliative Care Cancer Symptom (EPCCS) study of adults with incurable cancer at 30 palliative care centres across Europe, Australia and Canada (12 countries) between 12 Apr 2011 and 29 Oct 2013.

Inclusion criteria: age ≥18 years; advanced, incurable cancer confirmed through radiological, histological, cytological or operative evidence; enrolled in palliative care; written informed consent; and eligible for at least one follow-up assessment after inclusion.

Exclusion criteria: treated with curative intent; inability to comply with the study due to psychiatric disorders, severe cognitive impairment or language problems; imminent death; or inability to come for follow-up due to medical, social or geographical reasons.

Assessments: First clinical assessment (baseline) and then at each approximately monthly encounter for up to six months, death or study withdrawal, whichever came first.

Data were obtained on demographics; cancer diagnosis, stage and location of metastases; comorbidities; treatments; living situation; Karnofsky Performance Scale (KPS); severity of symptoms (Edmonton Symptom Assessment System [ESAS-r]) [27]; health related quality of life (EORTC-QLQ-PAL15 questionnaire); and whether patient or proxy report. Date of death was ascertained from each study centre six months after the last study inclusion.

Severity of symptoms (breathlessness; pain, anxiety; and depression) were scored on numerical rating scales (NRS) between 0 ("no") and 10 ("worst possible").

Statistical methods: Predictors of breathlessness were estimated using multivariate linear multilevel regression with random intercepts and slopes. Predictors of change in breathlessness over time were tested by adding a interaction term with time for each factor in the fully adjusted model.

Results

A total of 1,689 patients (50% women) from 12 countries were included. Mean age was 65.7 (standard deviation [SD], 12.4) years. The majority (81%) had metastatic solid cancer: gastro-intestinal (31%), lungs (20%), and breast (17%).

Follow-up was a median 62 (IQR, 0 to 133) days. The median number of breathlessness measurements was 3 (IQR, 1 to 5; range, 1 to 11) per patient; 72% had two or more measurements.

Breathlessness was prevalent; 65% of patients reported breathlessness (NRS > 0) at some point. The average breathlessness of 1.6 points remained relatively unchanged over time. However, individual trajectories varied, with 95% of changes being between -0.36 and 0.41 points per month.

Predictors of higher adjusted breathlessness (0-10 NRS)

	Overall		Between participants		Within participants	
Variable	**Coef.**	**95% CI**	**Coef.**	**95% CI**	**Coef.**	**95% to CI**
Study time (per 30 days)	**-0.01**	-0.03 to 0.02				
Age (per y)	**0.00**	-0.01 to 0.01				
Male gender	**0.12**	-0.07 to 0.32				
Lung cancer	**0.82**	0.58 to 1.06				
Lung metastasis	**0.49**	0.28 to 0.69				
COPD	**1.03**	0.70 to 1.37				
Anxiety (per 1 point)	**0.15**	0.12 to 0.18	**0.15**	0.09 to 0.21	**0.15**	0.12 to 0.18
Depression (per 1 point)	**0.07**	0.04 to 0.10	**0.04**	-0.02 to 0.10	**0.08**	0.05 to 0.11
Pain (per 1 point)	**0.13**	0.11 to 0.16	**0.17**	0.11 to 0.21	**0.12**	0.09 to 0.15
KPS (per 10 points)	**-0.02**	-0.02 to -0.02	**-0.02**	-0.03 to -0.02	**-0.01**	-0.02 to -0.01
Living alone	**0.76**	0.53 to 1.00				
Model intercept	**1.70**	1.00 to 2.40				

Change in breathlessness over time was predicted by pain severity (interaction term: 0.01; 95% CI, 0.00 to 0.03; p=0.012) and performance status (interaction term: 0.002; 95% CI, 0.000 to 0.003; p=0.039) adjusting for the other covariates. Patients with no or low pain scores had slightly decreasing breathlessness, whereas patients with higher pain severity experienced increasing breathlessness over time. The opposite pattern was seen for performance status.

Conclusion

Most patients with advanced cancer experience breathlessness with higher severity scores predicted by lung involvement, worse functional status, living alone, and the presence of concurrent unpleasant symptoms. Individual trajectories vary but worse pain and lower performance status are associated with increasing breathlessness over time.

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Conflicts of interest: None.

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