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## Original research article

# Prospective evaluation of anxiety, depression and quality of life in medically inoperable early stage non-small cell lung cancer patients treated with stereotactic ablative radiotherapy



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## ABSTRACT

**Aim:** The aim of this prospective study was to evaluate the level of anxiety, depression, and quality of life (QoL) in medically inoperable patients with early stage non-small cell lung cancer (NSCLC) treated with stereotactic ablative radiotherapy (SABR).

**Background:** Prolonged survival is equally important as maintaining high QoL and good psychological functioning during the treatment of lung cancer. Nowadays available SABR has markedly changed clinical care and outcomes in the group of medically inoperable patients. To our knowledge, analysis of QoL and psychological state has not been performed in Polish patients with early NSCLC treated with SABR.

**Materials and methods:** Research group consisted of medically inoperable, early NSCLC (T1-2aN0M0) patients qualified to SABR. Patients were asked to complete Polish versions of the European Organization for Research and Treatment of Cancer Quality of Life – Core Questionnaire (EORTC QLQ-C30) with the Lung Cancer Questionnaire (LC13) and Hospital Anxiety and Depression Scale (HAD). These questionnaires were repeated 2 weeks and then 3 months after treatment completion.

**Results:** We enrolled 51 patients who met the inclusion criteria. SABR did not deteriorate QoL and psychological functioning. On the contrary, clinically meaningful improvement was observed in emotional functioning, level of insomnia, anxiety and depression. Significantly worse improvement was shown in patients with chronic obstructive pulmonary disease (COPD).

**Conclusions:** Our results confirm that SABR is well tolerated and does not have a deleterious effect on QoL and psychological state. Results of our study indicate the importance of additional psychological care in the group of patients with COPD.

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## 1. Background

Lung cancer is considered to be a lifestyle disease, unfortunately with extremely poor prognosis. Radical surgical treatment has been regarded the first choice treatment in early stage of non-small cell lung cancer (NSCLC) for many years. In fact, lobectomy with lymphadenectomy has been the only potentially curable method.<sup>1</sup> Unfortunately, this approach puts patients at high risk of severe toxicity. Due to the global aging of the population, about 20% of all stage I NSCLC patients are medically ineligible for surgery.<sup>2,3</sup> Increased risk of treatment-related complications is unacceptable in this group of older patients with multiple comorbidities. Instead, the best supportive care (BSC) has been the only treatment option, because it does not negatively impact the patients' quality of life (QoL). Unfortunately, BSC does not prolong survival. In the past few years stereotactic ablative radiotherapy technique (SABR) has evolved as a consequence of radiobiological concept of higher efficacy of extremely hypofractionated radiotherapy in many tumors, including lung cancer.<sup>4–6</sup> Phase II multicenter clinical trials addressed to medically inoperable patients with early stage NSCLC showed 90% of 3-year cancer specific survival and above 60% of 3-year OS.<sup>7,8</sup> SABR has a low toxicity rate and seems to be well tolerated.<sup>9,10</sup>

Prolonged survival is equally important as maintaining high quality of life and good psychological functioning during the last years. QoL of lung cancer patients depends on several factors related to the neoplastic disease as well as other concomitant diseases and treatment characteristics.<sup>11</sup> Among many available questionnaires, the European Organization for Research and Treatment of Cancer Quality of Life – Core Questionnaire (EORTC QLQ-C30) with the Lung Cancer questionnaire (QLQ LC13) was found to be well developed, reliable, and validated.<sup>12</sup> Psychological problems are more difficult to assess. A very good tool like Hospital Anxiety and Depression Scale questionnaire (HAD Scale, reserved for psychologists, allows accurate evaluation of psychological functioning.<sup>13</sup>

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## 2. Aim

The aim of our study was to prospectively assess the level of anxiety and depression, and QoL in medically inoperable patients with early stage NSCLC treated with the stereotactic ablative radiotherapy technique.

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## 3. Materials and methods

### 3.1. Patients

Recruited patients received information about the project before any treatment procedures. Only those were eligible who provided written informed consent for participation in the study.

Research group consisted of medically inoperable, early stage NSCLC patients qualified to SABR in the Department of Clinical Oncology and Radiotherapy, University Clinical Centre in Gdansk by the local multidisciplinary tumor board. Inclusion criteria were: at least 18 years of age, cytopathological

or histopathological proof of NSCLC, PET/CT-confirmed early (T1-T2aN0M0) stage of the disease, cognitive status sufficient to understand and complete questionnaires.

Exclusion criteria included other synchronic malignancy, stage IV chronic obstructive pulmonary disease, severe asthma, other ongoing or a history of previous anti-cancer treatment (chemotherapy, radiotherapy, small molecule therapy, immunotherapy), active infection or inflammation, cognitive impairment.

### 3.2. Research methods

Study protocol and procedures were approved by the local bioethical committee and conducted in accordance with the 1964 Helsinki Declaration and its subsequent amendments. After providing a written informed consent included patients were asked to complete a baseline assessment using Polish versions of validated questionnaires EORTC QLQ-LC30, QLQ LC13 and HAD scale. The same questionnaires were repeated 2 weeks after accrual and then 3 months after treatment completion. Functional and cognitive status, symptoms, psychological distress, and overall QoL were assessed three times. The timeframes were selected based on the expected incidence of acute treatment-related toxicities. At the time of study, the medical staff, other than the treating physician, assisted patients with poor eyesight or those who did not understand questions. EORTC QLQ-C30, QLQ-LC13 and HAD scale questionnaires were evaluated with the support of psychologist.

Medical chart audits were conducted to obtain key demographics, clinical and system resource use characteristics.

### 3.3. Questionnaires

#### 3.3.1. EORTC QLQ-C30

This questionnaire is composed of multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), global health and quality of life scales and several single items assessing the most common symptoms of cancer patients (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea).<sup>14</sup>

#### 3.3.2. EORTC QLQ-LC13

This is a supplementary questionnaire dedicated for lung cancer patients. It contains 13 parameters defining characteristic lung cancer associated symptoms as cough, hemoptysis, dyspnea, pain, treatment related side-effects as hair loss, neuropathy, sore mouth and dysphagia.<sup>15,16</sup>

Hospital Anxiety and Depression (HAD) scale is dedicated to measure anxiety and depression in patients with somatic disease. The questionnaire contains 14 parameters for self-assessment.<sup>17</sup>

### 3.4. Raw results calculation

In accordance with EORTC recommended algorithm, data were converted to linear parameters in the range from 0 and 100. Score between 60 and 100 was considered as high level of

functioning fields or described a high level of reported symptoms severity.

The results of a standard HAD scale algorithm were grouped in 2 categories – anxiety and depression, separately with the score between 0 and 21.

### 3.5. Statistical analysis

Statistical analysis was performed using STATISTICA 12 software (StatSoft Polska). After determining normality of data distribution with the Shapiro–Wilk test, the Friedman ANOVA test with the Kendall coefficient of concordance was calculated for dependent variables. Furthermore, the Spearman rang test was performed to find significant correlations, *p* value less than 0.05 was considered significant.

## 4. Results

Between October 2013 and July 2015, 51 patients with inoperable early stage NSCLC qualified to SABR were enrolled into the study. Baseline characteristics of the patients are presented in Table 1.

All three assessments were performed in 42 (83%) patients. In 49 cases (96%), only two sets of questionnaires were completed. 2 patients refused further observation early after enrollment and were censored for statistical analysis.

SABR did not deteriorate QoL and psychological functioning. On the contrary, significant improvement was observed in many of the analyzed components of QoL, and HAD scale. However, some parameters of QLQ C30 and LC13 questionnaires had changed more significantly than others. Statistically significant 7% gain in physical functioning, almost 10% gain in emotional functioning or 16% decreased severity of insomnia 3 month after treatment should be highlighted. Moreover, we did not observe exacerbation of respiratory system syndromes, such as dyspnea, cough or hemoptysis. The intensity of anxiety and depression also reduced significantly,

especially 3 months after radiotherapy. Detailed results are presented in Table 2.

Gross Tumor Volume (GTV), Planned Target Volume (PTV), T stage, smoking, treatment schedule, or other baseline characteristics had no impact on anxiety, depression and QoL. However, significant differences were observed between patients with or without chronic obstructive pulmonary disease (COPD). Significantly greater improvement in global health, emotional functioning, insomnia and, especially, anxiety and depression after SABR was observed in patients without COPD (Fig. 1).

Global health, physical functioning, emotional functioning and the level of insomnia significantly correlated with anxiety ( $r = -0.5, p < 0.001$ ;  $r = -0.42, p < 0.01$ ;  $r = -0.75, p < 0.001$ ;  $r = 0.35, p < 0.01$ , respectively) and depression ( $r = -0.5, p < 0.001$ ;  $r = -0.23, p = 0.006$ ;  $r = -0.49, p < 0.001$ ;  $r = 0.30, p = 0.003$ , respectively).

## 5. Discussion

It is widely known that treatment-related toxicity may significantly deteriorate the patients' performance status and even decrease the overall survival. That is why the best supportive care has been the only treatment offered to many older patients with medically inoperable early stage NSCLC for many years. Nowadays available SABR has markedly changed clinical care and patient's outcomes.<sup>18</sup> However, the issue of Quality of Life and psychological functioning has been poorly investigated.<sup>19</sup> The results of phase II studies on SABR in early stage NSCLC proved feasibility and a good tolerance profile of this method.<sup>9,10</sup> Previously published results of two studies conducted by Lagerwaard et al. and Widder et al. did not show any SABR effect on QoL.<sup>20,21</sup> To our knowledge, such analysis has not been performed in Polish patients. Answering these questions is extremely important because an expensive therapy potentially deteriorating QoL in older population with severe comorbidities should not be implemented.

Findings from our study confirm previous reports that SABR is well tolerated and does not have a deleterious effect on QoL. Our results also showed that SABR does not have a negative impact on anxiety and depression after treatment. To our knowledge, such correlation has not been assessed so far.

Among numerous changes of parameters, clinically meaningful (>7%) improvement was observed only in two domains: emotional functioning and level of insomnia.<sup>22–24</sup> However, the lack of QoL deterioration, is of utmost importance, especially when compared to other methods of oncological treatment. Moreover, the analysis of the HAD Scale showed the enhancement of psychical outcome. It seems that observed reduction of anxiety and depression may be a significant cause of QoL parameters improvement, more than the reduction of symptoms level.

Cancer diagnosis is a well-known, important factor of high risk of anxiety and depression in patients. Other important factors include stage of the disease and severity of symptoms may impact psychological state.<sup>25,26</sup> Early stage NSCLC is usually asymptomatic, and its diagnosis is incidental. Nonetheless, primary physicians and family caregivers often have to face the problem of anxiety and depression in

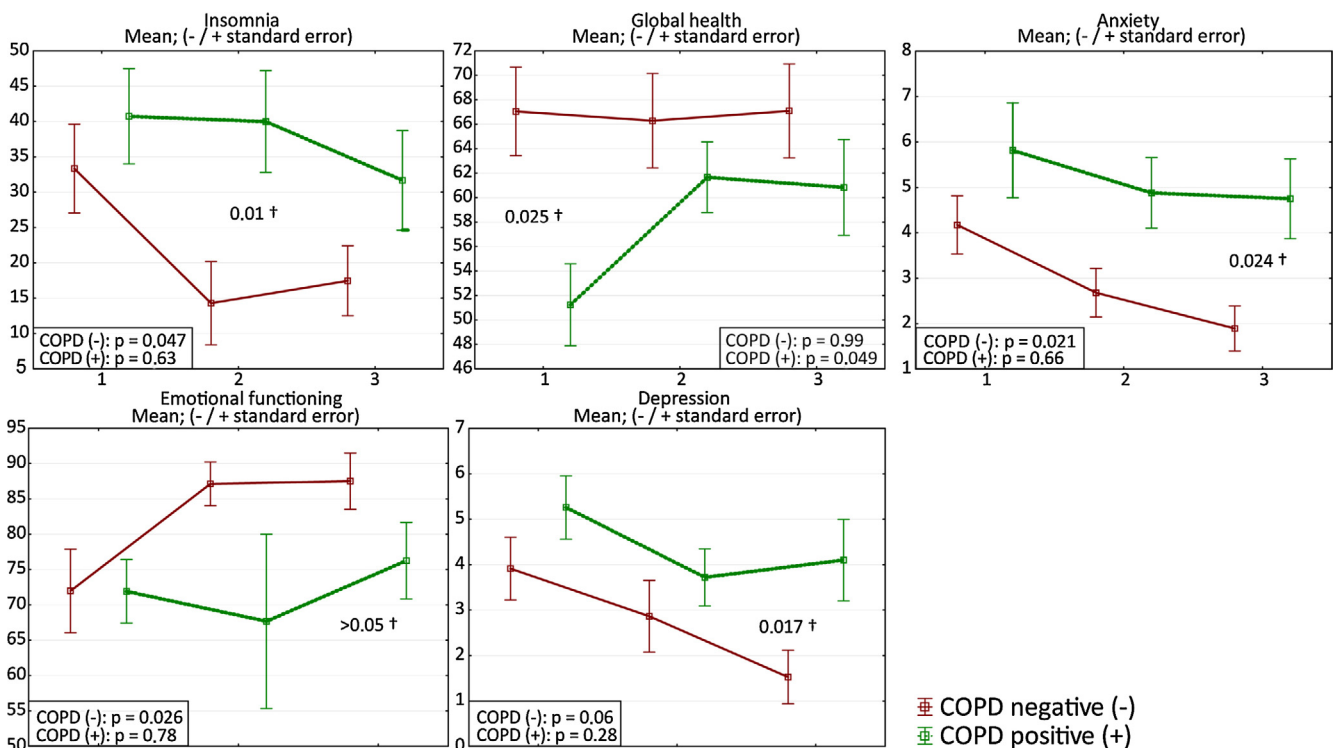
**Table 1 – Baseline characteristics of the patients.**

Median age (min–max)	74 y (58–88)
Sex	
Female	17
Male	34
T value	
T1	30 (59%)
T2a	21 (41%)
Tumor histology (NSCLC)	
Adenocarcinoma	19 (37%)
Squamous	15 (30%)
Other	13 (25%)
Radiological diagnosis	4 (8%)
COPD status	
Yes	27 (53%)
No	24 (47%)
Median PTV volume	37.8 cm <sup>3</sup>
Median GTV volume	10.2 cm <sup>3</sup>
Smoking status	
Never smokers	8 (16%)
Ex-smoker	34 (67%)
Current smoker	9 (17%)

**Table 2 – Changes of QoL, anxiety and depression parameters level (median %, in brackets standard deviation). Friedman (X<sup>2</sup>) ANOVA test used for statistical analysis.**

	Before SABR	2 w. after	14 w. after	p value	Change
<b>QLQ-C30</b>					
Global health	58.5 (18.9)	63 (17)	64 (17.5)	<b>0.025</b>	↑
Physical functioning	66 (21.5)	70.2 (19.6)	73 (16.9)	<b>0.032</b>	↑
Role functioning	84 (27.1)	87.2 (21.8)	86.3 (25)	0.82	-
Emotional functioning	73.7 (24.8)	78.9 (50)	82.7 (21)	<b>0.0003</b>	↑
Cognitive functioning	80.7 (22.7)	82.9 (22.7)	84.6 (20.3)	0.14	-
Social functioning	79.9 (21)	83.3 (19.9)	85 (18)	0.15	-
Fatigue	32 (28.9)	31.1 (25.6)	25.3 (18.9)	0.49	-
Nausea	1.3 (4.5)	2.5 (6.1)	0.8 (3.7)	0.23	-
Pain	23.1 (26)	17.9 (24.3)	15.8 (20.9)	0.18	-
Dyspnea	33.3 (32.4)	29.1 (28.8)	28.2 (25.9)	0.27	-
Insomnia	40.2 (33.5)	26.5 (33.5)	23.9 (28.5)	<b>0.003</b>	↓
Appetite loss	18.8 (26.3)	18.8 (30)	11.1 (20.7)	0.03	-
Constipation	27.3 (33.2)	19.6 (30.2)	12.9 (23.7)	<b>0.002</b>	↓
Diarrhea	1.7 (7.4)	1.7 (7.4)	2.5 (8.9)	0.71	-
Financial problems	17.1 (26)	14.5 (22.7)	14.5 (18.4)	0.91	-
<b>QLQ-LC13</b>					
Dyspnea	37.0 (25)	33.0 (25)	32.0 (23.2)	<b>0.027</b>	-/↓
Coughing	35.8 (27.6)	37.0 (29.1)	29.1 (24.1)	0.19	-
Hemoptysis	0.8 (5.2)	1.6 (7.3)	0.0 (NA)	NA	-
Sore mouth	5.8 (19.1)	5.8 (17)	0.0 (NA)	0.06	-
Dysphagia	8.3 (19.6)	7.5 (22)	6.7 (21)	0.25	-
Neuropathy	24.1 (29)	20.1 (29)	23.3 (26)	0.50	-
Alopecia	15.8 (30.1)	5.8 (21.2)	7.5 (20.6)	0.06	-
Pain in chest	19.1 (26.3)	15.0 (22.6)	15.0 (16.7)	0.41	-
Pain arm	24.2 (30.1)	14.2 (22.5)	14.2 (22.5)	<b>0.02</b>	-/↓
Pain in other	23.3 (31.3)	21.7 (24.5)	15.9 (26.1)	0.19	-
<b>HAD-S</b>					
Anxiety	4.8 (4.5)	3.6 (3.5)	3.3 (3.4)	<b>0.0063</b>	↓
Depression	4.5 (3.7)	3.0 (3.4)	2.84 (3.6)	<b>0.0016</b>	↓

Bold values indicate statistically significant changes at p < 0.05.



**Fig. 1 – Differences in variation of QoL, anxiety and depression parameters after SABR in patients with or without COPD. All three checkpoints of follow-up have been shown. †p value, of significant differences between COPD(+) vs. COPD(-) (U-test). p values for parameter variation (X<sup>2</sup> ANOVA).**

those patients.<sup>27,28</sup> Especially, patients with a higher level of anxiety have higher expectations toward medical staff and need more psychological assistance during radiotherapy.<sup>29</sup> In this group, there is a hypothetical risk of poor compliance during treatment and afterwards. Standard treatment including surgery and radiotherapy usually induces unpleasant adverse events, sometimes life-threatening, which may have an influence on QoL, and patient's mental status.<sup>21,30</sup> Our study has shown that offering radical yet very well tolerated treatment like SABR helps to control malignant disease and additionally positively impacts QoL. Patients feel partially relieved from distress, which was demonstrated by a decreased level of anxiety and depression compared to the pre-treatment status. Interestingly, QoL improvement in a subgroup of patients with severe COPD was lower than in non-COPD subgroup. Moreover, the pre-treatment level of QoL, anxiety and depression in this subgroup was also worse. This finding supports previously published data showing that severity of disease symptoms should be regarded as an important risk factor for anxiety and depression.<sup>25,26</sup>

## 6. Conclusions

We suggest that patients with COPD should be subject to additional psychological care. However, due to the small sample of study group, this conclusion should not be considered as definitive. Further instigation of this issue is warranted.

To our knowledge, this is the first prospective study evaluating the level of anxiety, depression and QoL in patients with early stage NSCLC treated with definitive SABR. Encouraging results confirm clinical and mental benefit of SABR in this population.

## Conflict of interest

None declared.

## Financial disclosure

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