Review

Determinants of health-related quality of life in patients with small cell lung cancer: a systematic PubMed review and meta-analysis

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Abstract: *Objective* — Symptoms of small cell lung cancer (SCLC), along with the side-effects of treatment interventions (e.g. nausea and vomiting due to cytotoxic drugs), are supposed to influence negatively the health-related quality of life (HRQoL) of the patients. An understanding of the determinants of SCLC patients' HRQoL could help health professionals in clinical decision making, screening and prediction of health outcomes. *The aim* of this review was to identify the health-related quality of life determining factors of patients with SCLC.

Methods — A literature review in the PubMed database was conducted in relation to the clinical and sociodemographic determinants of SCLC patients' HRQoL. The extraction and evaluation of the studies was carried out, according to preset criteria, by two reviewers who worked independently.

Results — Thirty-three publications were detected four of which met the inclusion criteria. The majority of the included studies were randomized trials. By the multivariate statistical analysis it was detected that negative influence on SCLC patients' HRQoL had the female gender (Wald Chi-Square=7.86, p=0.005), the quite a bit or very much tiredness (χ^2=28.54, p<0.001), the walking difficulty (χ^2=31.80, p<0.001) and the presence of dyspnea (χ^2=47.52, p<0.001).

Conclusions — Health professionals could pay more attention to the management of cancer-related fatigue and dyspnea as well as to the enhancement of patients' mobility through low-impact exercise programs or appropriate assistive devices.

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Introduction

Thirteen to fifteen percent of all lung cancer cases worldwide, are of small cell type (small cell lung cancers, SCLCs) with the median survival time, without any treatment, to be between two and four months [1, 2]. SCLC, like the non-small lung cancers, is strongly associated with tobacco smoking [2, 3]. The decrease of tobacco use in recent years led to a respective decrease of the overall incidence of the disease. However, because of the last decades tobacco use expanding among women, the incidence of SCLC in this subgroup has been increased [4, 5].

Symptoms of SCLC, along with the side-effects of treatment interventions (e.g. nausea and vomiting due to cytotoxic drugs), are supposed to influence negatively the health-related quality of life (HRQoL) of the patients [6-8].

The HRQoL concept was developed for meeting the need of measuring the subjective perception of a person's health. The World Health Organization (WHO), in 1948, influenced by the opinions of Sigerist [9, 10] defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [9, 11]. This evolvement emerged the need of measuring the physical, mental and social well-being, concepts which are related to the subjective perception of the individual and are beyond, and many times superior, than the measuring ability of the biomedical indicators. For fulfilling the above need the concept of Health-Related Quality of Life was developed [12].

The HRQoL of SCLC patients has not been well investigated yet [8]. An understanding of the determinants of SCLC patients' HRQoL could help health professionals in clinical decision making, screening and prediction of health outcomes.

The aim of this review was to identify the health-related quality of life determining factors of patients with small cell lung cancer.

Material and Methods

Search Strategy

This review was conducted by searching in the electronic database PubMed for the period 1991 to June 2015. PubMed is considered the optimal tool in health sciences electronic research [13].

Table 1. Summary of the studies included in the review

Study	Country	Sample	Research design	Measurement instrument
Bergman et al. [6]	Sweden	62 patients with SCLC undergoing chemotherapy	Randomized trial	SIP, HAD
Hürny et al. [7]	Switzerland	127 patients with SCLC undergoing chemotherapy	Randomized trial	EORTC QL questionnaire, Bf-S well-being scale, LASA general well-being scale
Chen et al. [8]	China	223 patients with SCLC	Analytical, retrospective, case-control	LCSS, LASA, ECOG-PS, Appetite change since diagnosis item
Wolfson et al. [14]	USA	265 patients with LD SCLC undergoing radiation therapy	Randomized trial	QLQ-C30, BN20

SIP, sickness impact profile; HAD, hospital anxiety and depression scale; QLQ-C30, european organization for research and treatment of cancer (EORTC) quality of life questionnaire; Bf-S, befindlichkeits-skala; LASA, linear-analogue self-assessment scale; LCSS, lung cancer symptom scale; ECOG-PS, eastern cooperative oncology group performance status; BN20, brain cancer module 20.
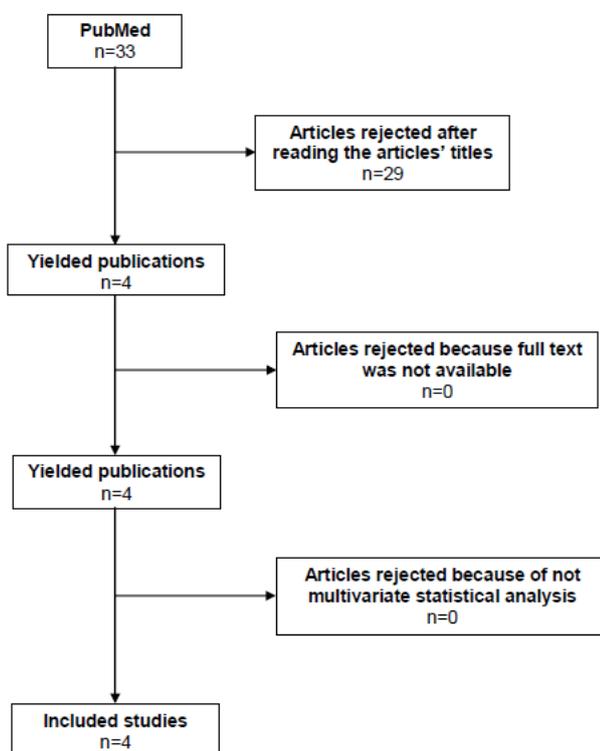

Figure 1. Flow chart – Review process

The literature search was performed using the following string of terms: (((("small cell"[Title] OR "oat cell"[Title] OR "small-cell"[Title] OR "oat-cell"[Title])) AND ("lung cancer"[Title] OR "carcinoma"[Title])) AND "quality of life"[Title]) AND ("multivariate"[Title/Abstract] OR "multivariable"[Title/Abstract] OR "regression"[Title/Abstract] OR "ANOVA"[Title/Abstract]). The terms "multivariate", "multivariable", "regression" and "ANOVA" were used, with respect to the "Title/Abstract" search criterion, for identifying studies with multivariate analysis.

Eligibility Criteria

The selection of the studies conducted by two reviewers working independently (A. Kossioris, T. Karousi). Firstly, the articles which yielded through the literature search were evaluated, through reading of the articles' titles, and the related to the purpose of the review primary studies were chosen. Afterwards, at the second phase of the selection process, a review of the full text of the publications was taken place (*Figure* 1).

For including a study in the review, the following criteria were set:

- Articles written in English language.
- Reference population: Persons with SCLC or LD SCLC.
- Outcome: The health-related quality of life measured by a reliable and valid instrument.
- Determinants: Factors concerning the health-related quality of life.
- Statistical analysis: Articles with multivariate analysis and
- Articles published in peer reviewed journals.

Data Extraction

The data which retrieved from the studies included in the review, came along after consensus of reviewers. The name of the study first author, measurement instrument, sample size, research design, gender, educational level, marital status, fatigue presence or absence, coughing presence or absence, walking capacity, awareness of drive to breath (increased or decreased drive), working status and smoking status were summarized (*Tables* 1 and 2).

Data Analysis

The Likelihood Ratio Chi-Square test was used for assessing the value of performing a diagnostic test and evaluate the goodness of fit of our model (χ^2=221.249, p<0.001). The dependent variable of the linear model was the quality of life measurements mean score which was extracted of each study separately and is calculated massively.

Results

After the selection process (*Figure* 1) four studies were included in the review, three randomized trials and one of analytic, retrospective, case-control research design.

The studies of Bergman et al. [6] from Sweden, Hürny et al. [7] from Switzerland and Wolfson et al. [14] from the USA were the randomized trials, while the study of Chen et al. [8] from China was of the analytical, retrospective, case-control design (*Table* 1).

By the multivariate statistical analysis it was detected that more positive impact on SCLC patients' HRQoL had the high school, and below, level of education (Wald Chi-Square=10.10, p=0.001), the substantial presence of coughing (quite a bit or very much) (χ^2=80.86, p<0.001) and the smoking habit (χ^2=12.29, p<0.001).

Table 2. Descriptive table of patients' characteristics

Variables		N	Percentage
Gender	Male	300	55.2
	Female	206	37.9
	Missing values	37	6.8
	Total	543	100
Educational level	< high school	21	3.9
	> high school	35	6.4
	Missing values	487	89.7
	Total	543	100
Marital status	Married	36	6.6
	Single	23	4.2
	Missing values	484	89.1
	Total	543	100
Fatigue	Quite a bit or very much	371	68.3
	Not at all or a little	172	31.7
	Total	543	100
Coughing	Quite a bit or very much	379	69.8
	Not at all or a little	164	30
	Total	543	100
Walk difficulty	Yes	230	42.4
	No	313	57.6
	Total	543	100
Dyspnea	Yes	364	67.0
	No	179	33.0
	Total	543	100
Work	Light work	378	69.6
	Unable to work and worse	165	30.4
	Total	543	100
Smoking status	Never smoker	69	12.7
	Former smoker	160	29.5
	Current smoker	118	21.7
	Missing values	196	36.1
	Total	543	100

Table 3. SCLC patients' HRQoL determining factors

	Factors	B	Wald Chi-Square	P value
Gender	Male	-0.18	5.21	0.022
	Female	-0.23	7.86	0.005
Educational level	< high school	0.80	10.09	<0.001
	> high school	0.72	10.32	<0.001
Marital status	Married	0.034	0.02	0.890
	Single	0.032	0.02	0.880
Fatigue	Quite a bit or very much	-0.34	28.54	<0.001
Coughing	Quite a bit or very much	0.56	80.86	<0.001
Walk difficulty	Yes	-0.32	31.80	<0.001
Dyspnea	Yes	-0.43	47.52	<0.001
Work	Light work	0.01	0.02	0.900
Smoking status	Never smoker	-0.7	1.24	0.270
	Former smoker	0.18	4.44	0.035
	Current smoker	0.20	12.29	<0.001

On the other hand, negative influence on SCLC patients' HRQoL had the female gender (χ^2=7.86, p=0.005), the quite a bit or very much tiredness (χ^2=28.54, p<0.001), the walking difficulty (χ^2=31,80, p<0,001) and the presence of dyspnea (χ^2=47.52, p<0.001) (*Tables* 2 and 3).

Discussion

Symptoms of SCLC, in company with the side-effects of the cytotoxic medications, are supposed to affects negatively the HRQoL of the patients [6-8]. An understanding of the determining factors of SCLC patients' HRQoL could guide health professionals in clinical decision making, screening and prognosis of health outcomes.

The most significant finding of this review, was the fact that dyspnea influences negatively the HRQoL. Dyspnea is a common symptom among lung cancer patients [15, 16]. According to the study done by Smith et al. [17], patients with high dyspnea scores had lower QoL (p=0.040). Additionally, the cross-sectional study of Sarna et al. demonstrated that dyspnea induces risk for decreased physical and social aspects of QoL [18].

In regard to the educational level, it was found that the high school, and below, level of education had more positive impact on HRQoL (B=0.795). This finding is, generally, in contrast with the literature. A Spanish study done by Regidor et al. [19] showed that perceived health status diminishes with decreasing educational level, with the exception of women with secondary education who had a higher mean scoring than women with higher education on diverse health dimensions. Furthermore, concordantly to Mielck et al. [20], low educational status groups are encountered with a double burden. Nevertheless, the outlandish finding of our study could be justified by the many missing values of the massive sample (n=487).

From the statistical analysis, it was detected that the quite a bit or very much coughing had affirmative effect on HRQoL. This finding is in contrast with the literature [21], in which coughing is considered an afflicting factor for life's quality. However, this could be explained from the symptoms characteristics of the Chen et al. study [8], the main research from which the coughing data were retrieved. Chen et al. [8] found that the lowest coughing mean score (66.4) took place in the fourth follow-up year. Furthermore, in the same study [8] appears to be a proneness that as the years pass, the coughing scores decreases.

As for the smoking status, it was discovered that smoking habit has positive impact on HRQoL. This finding is also contradictory with the literature [22-26]. Smoking has been repeatedly associated with lower QoL. Nonetheless, this discrepancy could be explained by the fact that there were many missing values in the review sample (n=196).

In relation to the gender, the female gender had negative effect on HRQoL. This detection is in agreement with the study of Pud et al. [27] in which female cancer patients reported significantly lower psychological dimension of QoL than their male counterparts (p=0.009).

With regard to fatigue presence or absence, the quite a bit or very much tiredness was detected to be adversely associated with HRQoL. This finding is concordant with the literature [28, 29]. Fatigue has been acknowledged as a common and distressing symptom in cancer.

With respect to walking capacity, walking difficulty had negative impact on HRQoL. This detection is consonant to the recent study of Bindawas et al. [30] in which increased lower extremity performance was associated with slower rates of decrease in participants' physical and mental HRQoL.

As for the awareness of drive to breath, it was detected that the presence of dyspnea had adverse influence on HRQoL. The

aforementioned finding is in agreement with the study done by Smith et al. [17] in which patients with high dyspnea scores had lower QoL (p=0.040) such as with the study of Gupta et al. [31] which demonstrated that every ten unit increase in dyspnea score was statistically significantly associated with 0.81, 0.16, 0.47, and 0.47 unit decline in Ferrans and Powers [32] Quality of Life Index (QLI).

Conclusion

Health professionals could pay more attention to the management of cancer-related fatigue and dyspnea as well as to the enhancement of patients' mobility through low-impact exercise programs or appropriate assistive devices.

Conflict of Interest

The authors declare that there are no conflicts of interest. The review was self-funding.

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