Final Report for non interventional study - EUPAS8748

"Smoking cessation by combined medication and counseling in lung cancer patients: effectiveness in a high prevalence real life setting"

German title:

„Multimodale Tabakentwöhnung mit pharmakologischer Unterstützung bei Patienten mit Lungenkarzinom – Effektivität im klinischen Alltag eines Lungenkrebszentrums."

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Background and rationale for the study

Quitting is important in diagnosed lung cancer

Smoking is a strong risk factor for lung cancer and lung cancer has the highest incidence of all cancers in industrialized countries. The positive National Lung Screening Trial using low dose CT published in 2011 will further the awareness of this still difficult to treat but common disease. In current European lung cancer trials about 30-50% of the patients smoke at the time of diagnosis [1,2]. In our lung cancer center smoking prevalence at the time of diagnosis is about 40%. Smoking prevalence is also high among patients with other smoking related malignancy such as head and neck, esophageal, bladder, kidney as well as breast cancer.

Smoking cessation is not only paramount in the prevention but also in the treatment of lung cancer. Generally long-term survival in lung cancer is negatively influence by persistent smoking [3]. The clear benefits of quitting smoking have been described in lung cancer patients treated by different modalities: In a large database of thoracic surgeons perioperative morbidity and mortality was mitigated by preoperative cessation albeit no optimal period of smoking cessation was identifiable [4]. In a Brazilian retrospective study smoking was associated with reduced activity of chemotherapy [5]. Similar results were described in patients undergoing chemo-radiotherapy [6]. Furthermore quitting smoking in lung cancer improves quality of life [7] and performance status [8].

Physicians are reluctant to advise lung cancer patients to quit smoking

The majority of patients who receive a lung cancer diagnosis report that they want to quit smoking, but most are unable to do so [9]. Those who continue smoking after a lung cancer diagnosis are a challenging population with a long smoking history, high nicotine dependence, and low confidence to quit. Furthermore, very little clinical data is available concerning smoking cessation in lung cancer. Sanderson et al. compared smoking lung cancer patients with normal smokers [10]. The six-month success rate was 22% in the lung cancer patients which is comparable to normal smokers if corrected for confounders [10]. A study reporting that a nurse-managed intervention is feasible included only 15 patients [11]. In another study including 28 patients more than 90% of the patients who resumed smoking did so within the first week of discharge [12]. Only one small (n=49 patients) randomized controlled study used varenicline as an aid to smoking cessation in lung cancer patients. Participants were also exposed to intensive counseling with a median of nine sessions. The 12 week abstinence rate was 34%

in the varenicline group and 14% in the controls (p = 0.18) [13]. Of note the smoking prevalence of lung cancer patient in this US study was 17% and thus considerable lower than the current German experience. Accordingly the number of patients investigated was small with only 16 patients receiving the intended varenicline course [13].

While even a brief advice delivered by a physician has a small but significant effect on cessation rates [14], success rates can be significantly enhanced by more intense counseling and use of pharmacotherapy [15]. The technique of motivational interviewing is especially effective [16]. Concerning hospitalized patients a meta-analysis which mainly evaluated patients with cardiovascular disease, demonstrated that high-intensity behavioral interventions (preferable with pharmacologic therapy) that begin during a hospital stay promote smoking cessation [17].

Given the limited clinical experience published so far, it is understandable - although unfortunate - that most physicians are reluctant to offer advice on smoking cessation to their patients despite clear recommendations in recent lung cancer guidelines [18]. Arguments commonly raised by physicians in this context are: Smoking cessation does not work in these highly addicted patients; patients should not be bothered by a cumbersome smoking cessation intervention; cessation medication might be problematic due to co-morbidities, and prognosis is poor anyway. On the other hand, expensive therapy with common side-effects and limited effectiveness is well accepted in the treatment of lung cancer.

Smoking cessation encompassing pharmacotherapy is efficient and safe

A Cochrane meta-analysis clearly indicated that Nicotine replacement therapy (NRT) helps smokers to quit [19]. A total of 105 placebo-controlled, randomized trials of NRT found an odds ratio of 1.8 (95% CI 1.7–1.9) in favor of NRT versus placebo. In COPD patients smoking cessation encompassing NRT has been reported to improve outcome [20]. Absolute contraindications for NRT as an adjunct to professional smoking cessation do not exist. Specifically, NRT has been shown to be safe in patients with coronary heart disease and other cardiovascular diseases [21]. Of note in epidemiologic studies with long follow up there is no indication that NRT is carcinogenic [22].

Varenicline has demonstrated good efficacy versus placebo in a number of RCTs. According to a recent network meta-analysis varenicline is the most effective pharmacotherapy for smoking cessation with a 2.4 fold increase as compared with pharmacologically unassisted quit attempts [15,23]. Varenicline is especially effective in difficult to treat cohorts such as COPD or psychotic patients [15,24,25].

Concerning safety a meta-analysis showed no evidence of increased incidence of cardiovascular morbidity or mortality [26]. Recent analyses of large datasets from clinical trials including psychiatric disease such as schizophrenia have not shown that varenicline is any more associated with depression or suicidality than other treatments for smoking cessation [15,27]. It must be kept in mind however, that smoking cessation per se inflicts a plethora of symptoms among which depression is common. For discussion of safety aspects please see also “Ethical issues” below.

Study rationale and the need for a trial

Considering the above-mentioned evidence there is an unmet need to substantiate that smoking cessation is feasible among lung cancer patients. It is crucial to determine whether a comprehensive smoking cessation program delivered directly following the diagnosis of lung cancer can be implemented. Specifically the effectiveness and safety of pharmacologic treatment, especially varenicline needs to be established in this context.

Thus a real-life study addressing a comprehensive smoking cessation intervention in newly diagnosed lung cancer patients is feasible and urgently needed.

Methods:

This is a monocenter, 12-week, prospective, observational, non-comparative trial performed at a large University lung cancer center. The primary objective was the abstinence rate at week 12 based on biochemical verification (CO-Hb ≤ 2,0% and/or exhaleted CO >8 ppb). Secondary endpoints were the abstinence rate at week 26, quality of life and abstinence phenomena.
Quality of life and abstinence phenomena were measured via standardized questionnaires using HADS-Depression Score, EORTC-QLQ C30 Core-Questionnaire [28] including lung specific QLQ-LC13 and EQ-5D VAS, and the latest version of the Mood and physical symptoms scale (MPSS) [29].
Patients were enrolled after verified diagnosis of lung cancer.

Inclusion criteria were as follows:

- Newly diagnosed lung cancer of all stages within 14 day of study enrollment
- Active smoking or smoking up to 4 weeks before study enrollment
- Age > 18 years

Exclusion criteria was severity of the disease with prognosis less than a few weeks, if foreseeable at time of enrollment.

The study was done in accordance to good clinical practice standards (GCP). It was approved by local ethics committee. All patients provided written informed consent before study enrollment.

After enrollment each patient received a counseling of at least 30 min in smoking cessation which was done by trained doctors. The counseling was based on a motivational interview. It also included advices for further strategies to stay abstinent.
After that patients had to choose whether they wanted additional medication to support further abstinence or not.
Medication offered was nicotine replacement therapy in form of patches and/or nicotine gums/ lozenges according to their daily amount of cigarettes or varenicline.
Each patient was given written instructions on how to use the medication within the next 12 weeks. Medication was given for free to the patients.

CO-Measurement was done using a Senko BMC 2000 device for measurement of CO-concentration in exhaled air. CO-Hb was measured via capillary blood gas analysis using a Roche cobas system. A CO concentration > 8 ppm and/ or a CO-Hb concentration > 2% was defined as cigarette smoking.

		Study entry	Week 6	Week 12	Week 26
Informed consent	X				
Medical history/ physical examination	X				
In-/ exclusion criteria	X				
FTCD (Fagerstroem Test)		X		X	
Vital signs	X	X		X	
Motivational interview		X			
Optional pharmacological treatment		X	X	X	
CO-concentration	X	X		X	X
HADS (depression)		X	X	X	
MPSS (withdrawal symptoms)		X	X	X	
Side effects			X	X	
ECOG	X	X		X	
EORTC-QLQ C30/ QLQ-LC 13/ EQ-5D VAS	X	X		X	

Table 1 Timetable of study

Results:

The study run from April 2015 up to June 2018. Baseline characteristics of study population are shown in table 2. Of 80 patients enrolled, 39 decided for an additional nicotine replacement therapy, 35 for varenicline, whereas six patients choose counseling without medication.

	NRT[1] (n=39)	**Vareniclin (n=35)**	**NM[2] (n=6)**	**Total (n=80)**
Sex				
Female	11 (13,8%)	11 (13,8%)	2 (2,5%)	24 (30%)
Male	28 (35%)	24 (30%)	4 (5%)	56 (70%)
Age (years)	62,9 (+/- 8,4)	62,6 (+/- 7,8)	59,5 (+/- 4,9)	62,6 (+/- 7,9)
BMI (kg/m²)	25,9 (+/- 4,8)	25,2 (+/- 4,8)	24,8 (+/- 5,3)	25,5 (+/- 4,8)
Score of Fagerstroem Test	4,7 (+/- 2,2) (13 missings)	4,9 (+/- 2,4) (2 missings)	4 (+/- 1,4) (4 missings)	4,8 (+/- 2,3)
PackYears	41,92 (+/- 18)	49,58 (+/- 27,51)	36,9 (+/- 9,6)	44,9 (+/- 22,5)
At least one attempt in smoking cessation	18 (22,5%)	18 (22,5%)	1 (1,3%)	37 (46,3%)
Current smoking at study entry	26 (32,5%)	31 (38,8%)	1 (1,3%)	58 (72,5%)
Quit smoking within 4 weeks before study entry	13 (16,3%)	4 (5%)	5 (6,3%)	22 (27,5%)
ECOG**				
0	7 (17,9%)	7 (20%)	2 (33,3%)	16 (20%)
1	25 (64,1%)	25 (71,4%)	2 (33,3%)	52 (65%)
2	1 (15,4%)	0	0	1
Lung-Cancer Stage				
NSCLC I-II	7	6	1	14 (17.5%)
NSCLC III-IV	17	20	2	39 (49%)
SCLC	15	9	3	27 (34%)
Lung-Cancer Therapy				
Surgery	10	5	1	16
Chemotherapy or radiochemotherapy	29	29	5	63
Radiotherapy	0	1	0	1

Table 2: Baseline Characteristics: 1 NRT = nicotine replacement therapy, 2 NM = no medication. ** no data available for 11 patients

Of 80 patients enrolled into the study 49% percent had stage III or IV non small cell lung cancer and 34% had small cell lung cancer. Thus, mortality during study period was high (13 patients died (8 within the first 3 months): ten due to worsening of lung cancer, one due to myocardial infarction, one due to renal failure, one patient committed suicide after receiving the message of cancer progress). Four patients were lost to follow up and 7 patients withdraw their consent, one patient was diagnosed as non small cell lung cancer and received nicotine replacement therapy. A few day later diagnosis was changed to urothelial cancer and the patient was closed out. Some patients responded to a call for visit 4 but not for visit 3. Thus, there was only data of 58 patients after 12 weeks and of 52 patients at week 24. Patients who withdraw their consent or were lost to follow up were counted as smokers according to the intention to treat protocol. Patients who died during the study period were censored.

Abstinence rate

Overall verified tobacco abstinence at week 12 was 37,5 percent, and 32,8 percent at week 24 respectively. Abstinence rate according to medical treatment is shown in table 3.

	Week 12			**Week 24**		
	Smoker	*Non-smoker*	*Total*	*Smoker*	*Non-smoker*	*Total*
NRT[1]	27 (71,1%)	11 (28,9%)	38 (52,8%)	25 (69,4%)	11 (30,6%)	36 (53,7%)
Varenicline	16 (55,2%)	13 (44,8%)	29 (40,3%)	18 (66,7%)	9 (33,3%)	27 (40,3%)
NM[2]	2 (40%)	3 (60%)	5 (6,9%)	2 (50%)	2 (50%)	4 (6%)
Total	*45 (62,5%)*	*27 (37,5%)*	*72 (100%)*	*45 (67,2%)*	*22 (32,8%)*	*67 (100%)*

Table 3: Rate of verified tobacco abstinence at week 12 and week 24. *1 NRT = nicotine replacement therapy, 2 NM = no medication*

Abstinence phenomena

Abstinence phenomena were measured via the latest version of the Mood and Physical Symptom Scale Questionnaire (MPSS) [29,30].
Total MPSS-Score for the treatment groups are shown in table 4. There was no increase in Total-MPSS-Score during treatment period. There was a significant difference in withdrawal symptoms between patients in the no medication group and patients in NRT or varenicline group. Patients in the no medication group showed less withdrawal symptoms then others right from the beginning up to week 12. There were no significant differences in abstinence phenomena between NRT- and varenicline-group, as shown in table 5.

	Therapy	N	Miss	Mean	STD	Mean (95%LCL)	Mean (95%UCL)
Day 1	NRT	37	2	1.832	0.496	1.666	1.997
	Varenicline	35	0	1.963	0.524	1.783	2.143
	NM	6	0	1.389	0.390	0.980	1.798
	Total	78	2	1.857	0.519	1.740	1.974
Week 6	NRT	33	6	1.750	0.617	1.532	1.969
	Varenicline	28	7	1.706	0.566	1.486	1.925
	NM	4	2	1.063	0.356	0.496	1.629
	Total	65	15	1.689	0.598	1.540	1.837
Week 12	NRT	23	16	1.609	0.460	1.410	1.807
	Varenicline	24	11	1.785	0.572	1.544	2.026
	NM	5	1	1.165	0.401	0.667	1.663
	Total	52	28	1.647	0.532	1.499	1.796

Table 4: Mean Total MPSS during treatment period. NRT = Nicotine replacement therapy. NM = no medication. Miss = Missings. STD = standard deviation.

	Therapy	Method	t Value	DF	Mean	LCL	UCL	p-Value
Day 1	NRT vs. Vareniclin	Pooled	-1.09	70	-0.13	-0.37	0.11	0.2793
Day 1	NRT vs. NM	Pooled	2.08	41	0.44	0.01	0.87	*0.0441*
Day 1	Vareniclin vs. NM	Pooled	2.55	39	0.57	0.12	1.03	*0.0147*
Week 6	NRT vs. Vareniclin	Pooled	0.29	59	0.04	-0.26	0.35	0.7712
Week 6	NRT vs. NM	Pooled	2.17	35	0.69	0.04	1.33	*0.0369*
Week 6	Varenicline vs. NM	Pooled	2.19	30	0.64	0.04	1.24	*0.0362*
Week 12	NRT vs. Varenicline	Pooled	-1.16	45	-0.18	-0.48	0.13	0.2512
Week 12	NRT vs. NM	Pooled	1.99	26	0.44	-0.01	0.90	0.0569
Week 12	Varenicline vs. NM	Pooled	2.29	27	0.62	0.07	1.17	*0.0298*

Table 5: Comparison of Mean Total MPSS during treatment period. NRT = Nicotine replacement therapy. NM = no medication.

Quality of life

Quality of life was assessed using the Hospital Anxiety and Depression Scale (HADS) [31]. As an additional tool for oncological patients EOC QLQ C30 and the lung specific EOC QLQ LC5 Questionnaire as well as EQ-5D VAS was used at the beginning and week 12 [28].
Total HADS-Score for the each treatment group is shown in table 6. There was no increase in Total-HADS-Score during treatment period. There was a tendency to a significant difference in symptoms between patients in the no medication group and patients in NRT or varenicline group at week 6 and week 12. Medication (table 7).

	Treatment-Group	N	Missings	Mean	STD	Mean (95%LCL)	Mean (95%UCL)
Day 1	NRT	36	3	12.8	5.8	10.8	14.7
	Varenicline	35	0	14.3	7.5	11.7	16.8
	NM	6	0	11.8	7.2	4.3	19.4
	Total	77	3	13.4	6.7	11.8	14.9
Week 6	NRT	33	6	12.5	6.1	10.3	14.7
	Varenicline	28	7	12.6	6.2	10.2	15.1
	NM	4	2	7.3	5.6	-1.6	16.1
	Total	65	15	12.2	6.2	10.7	13.8
Week 12	NRT	23	16	12.9	6.2	10.2	15.5
	Varenicline	23	12	14.0	7.8	10.7	17.4
	NM	5	1	6.6	6.9	-2.0	15.2
	Total	51	29	12.8	7.2	10.8	14.8

Table 6: Mean Total HADS during treatment period. NRT = Nicotine replacement therapy. NM = no medication. STD = standard deviation.

Visite	Contrast	Method	t Value	DF	Mean	LCL	UCL	p-Value
Day 1	NRT vs. Varenicline	Pooled	-0.95	69	-1.51	-4.68	1.67	0.3471
Day 1	NRT vs. NM	Pooled	0.35	40	0.92	-4.43	6.26	0.7306
Day 1	Varenicline vs. NM	Pooled	0.73	39	2.42	-4.27	9.12	0.4683
Week 6	NRT vs. Varenicline	Pooled	-0.10	59	-0.16	-3.33	3.02	0.9210
Week 6	NRT vs. NM	Pooled	1.62	35	5.23	-1.32	11.79	0.1138
Week 6	Varenicline vs. NM	Pooled	1.64	30	5.39	-1.32	12.11	0.1114
Week 12	NRT vs. Varenicline	Pooled	-0.57	44	-1.17	-5.35	3.01	0.5743
Week 12	NRT vs. NM	Pooled	2.01	26	6.27	-0.13	12.67	0.0544
Week 12	Varenicline vs. NM	Pooled	1.97	26	7.44	-0.33	15.21	0.0597

Table 7: Comparison of Mean Total HADS during treatment period. NRT = Nicotine replacement therapy. NM = no medication

Results of EQ 5D VAS, EO QLQ C30 and EO LC5 items are shown in table 8 to 20. Due to mass of data, we only report sub items of EO QLQ C30 of interest during smoking cessation: global health status, cognitive- and emotional functioning, nausea and vomiting, fatigue and insomnia.

EQ 5D VAS

There are no significant differences among the groups at study entry and at week 12.

	Treatment	N	NMiss	Mean	STD	Mean (95%LCL)	Mean (95%UCL)
Day 1	NRT	37	2	58.1	21.7	50.9	65.4
	Varenicline	35	0	52.3	21.6	44.9	59.8
	NM	5	1	42.0	26.4	9.3	74.7
	Total	77	3	54.5	22.1	49.4	59.5
Week 12	NRT	23	16	51.8	20.0	43.2	60.5
	Varenicline	24	11	54.7	19.3	46.5	62.8
	NM	5	1	63.0	14.0	45.7	80.3
	Total	52	28	54.2	19.1	48.9	59.5

Table 8: Mean EQ 5D VAS on day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication. NMiss = number of missings. STD = standard deviation.

Visite	Treatment	Method	t Value	DF	Mean	LCL	UCL	p-Value
Day 1	NRT vs. Varenicline	Pooled	1.13	70	5.79	-4.39	15.98	0.2606
Day 1	NRT vs. NM	Pooled	1.52	40	16.14	-5.28	37.55	0.1357
Day 1	Varenicline vs. NM	Pooled	0.98	38	10.34	-11.07	31.76	0.3344
Week 12	NRT vs. Varenicline	Pooled	-0.50	45	-2.84	-14.38	8.69	0.6223
Week 12	NRT vs. NM	Pooled	-1.18	26	-11.17	-30.63	8.28	0.2484
Week 12	Vareniclin vs. NM	Pooled	-0.91	27	-8.33	-27.08	10.42	0.3699

Table 9: Comparison of EQ 5D VAS on day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication

EORTC-QLQ C 30 3.0 global health

There is a significant difference among the score between NRT and varenicline group at study entry.

	Treatment	N	NMiss	Mean	STD	Mean (95%LCL)	Mean (95%UCL)
Day 1	NRT	36	3	52.8	24.0	44.7	60.9
	Varenicline	35	0	47.9	25.3	39.2	56.5
	NM	6	0	29.2	39.4	-12.1	70.5
	Total	77	3	48.7	26.3	42.7	54.7
Week 12	NRT	23	16	40.6	19.5	32.1	49.0
	Varenicline	24	11	50.0	17.4	42.7	57.3
	NM	5	1	55.0	18.3	32.3	77.7
	Total	52	28	46.3	18.8	41.1	51.6

Table 10: Mean EORTC-QLQ C30 3.0 sub item *global health status* at day 1 and week 12. NRT = Nicotine replacement therapy. NMiss = number of missings. NM = no medication. STD = standard deviation.

	Treatment	Method	t Value	DF	Mean	LCL	UCL	p-Value
Day 1	NRT vs. Varenicline	Pooled	0.84	69	4.92	-6.74	16.58	0.4029
Day 1	NRT vs. NM	Pooled	2.03	40	23.61	0.08	47.14	0.0492
Day 1	Varenicline vs. NM	Pooled	1.54	39	18.69	-5.87	43.25	0.1318
Week 12	NRT vs. Varenicline	Pooled	-1.75	45	-9.42	-20.26	1.42	0.0870
Week 12	NRT vs. NM	Pooled	-1.51	26	-14.42	-34.02	5.18	0.1425
Week 12	Vareniclin vs. NM	Pooled	-0.58	27	-5.00	-22.66	12.66	0.5661

Table 10: Comparison of Mean EORTC-QLQ C30 3.0 sub item g*lobal health status* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication

EORTC-QLQ C 30 3.0 emotional functioning

There is an increase in EORTC-QLQ C 30 score among patients of NM group. There are no significant differences among the groups at study entry and at week 12.

	Treatment	N	NMiss	Mean	STD	Mean (95%LCL)	Mean (95%UCL)
Day 1	NRT	37	2	66.9	23.0	59.2	74.6
	Varenicline	35	0	56.8	26.2	47.8	65.8
	NM	6	0	54.2	25.1	27.8	80.5
	Total	77	3	61.4	24.9	55.8	67.0
Week 12	NRT	23	16	62.3	22.6	52.5	72.1
	Varenicline	24	11	68.7	22.6	59.2	78.3
	NM	5	1	83.3	28.9	47.5	119.2
	Total	52	28	67.3	23.5	60.8	73.9

Table 11: Mean EORTC-QLQ C30 3.0 sub item *emotional functioning* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication. NMiss = number of missings. STD = standard deviation.

	Treatment	Method	t Value	DF	Mean	LCL	UCL	p-Value
Day 1	NRT vs. Varenicline	Pooled	1.74	70	10.07	-1.50	21.64	0.0871
Day 1	NRT vs. NM	Pooled	1.24	41	12.73	-7.99	33.44	0.2218
Day 1	Varenicline vs. NM	Pooled	0.23	39	2.66	-20.60	25.92	0.8184
Week 12	NRT vs. Varenicline	Pooled	-0.98	45	-6.43	-19.70	6.84	0.3341
Week 12	NRT vs. NM	Pooled	-1.80	26	-21.01	-45.02	2.99	0.0836
Week 12	Vareniclin vs. NM	Pooled	1.74	70	10.07	-1.50	21.64	0.0871

Table 12: Comparison of Mean EORTC-QLQ C30 3.0 sub item *emotional functioning* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication

EORTC-QLQ C 30 3.0 cognitive functioning

There is an increase in EORTC-QLQ C 30 score among patients of NM group. There are no significant differences among the groups at study entry and at week 12.

	Treatment	N	NMiss	Mean	STD	Mean (95%LCL)	Mean (95%UCL)
Day 1	NRT	37	2	81.1	18.1	75.1	87.1
	Varenicline	35	0	78.1	24.5	69.7	86.5
	NM	6	0	69.4	26.7	41.4	97.5
	Total	78	2	78.8	21.8	73.9	83.8
Week 12	NRT	23	16	80.4	19.2	72.1	88.8
	Varenicline	24	11	78.5	21.1	69.6	87.4
	NM	5	1	96.7	7.5	87.4	105.9
	Total	52	28	81.1	19.8	75.6	86.6

Table 13: Mean EORTC-QLQ C30 3.0 sub item *cognitive functioning* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication. STD = standard deviation.

	Treatment	Method	t Value	DF	Mean	LCL	UCL	p-Value
Day 1	NRT vs. Varenicline	Pooled	0.59	70	2.99	-7.10	13.07	0.5567
Day 1	NRT vs. NM	Pooled	1.37	41	11.64	-5.55	28.82	0.1788
Day 1	Varenicline vs. NM	Pooled	0.79	39	8.65	-13.52	30.82	0.4347
Week 12	NRT vs. Varenicline	Pooled	0.33	45	1.96	-9.92	13.85	0.7410
Week 12	NRT vs. NM	Pooled	-1.83	26	-16.23	-34.42	1.96	0.0781
Week 12	Vareniclin vs. NM	Pooled	-1.88	27	-18.19	-38.07	1.69	0.0712

Table 14: Comparison of Mean EORTC-QLQ C30 3.0 sub item *cognitive functioning* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication

EORTC-QLQ C 30 3.0 fatigue

There is a decrease in EORTC-QLQ C 30 score among patients of NM group, and an increase among patients receiving NRT. There is a significant difference among the NRT and NM group at study entry, with patients of NRT having less symptoms.

	Treatment	N	NMiss	Mean	STD	Mean (95%LCL)	Mean (95%UCL)
Day 1	NRT	37	2	35.4	23.7	27.5	43.3
	Varenicline	35	0	40.6	28.8	30.8	50.5
	NM	6	0	61.1	33.5	25.9	96.3
	Total	78	2	39.7	27.3	33.6	45.9
Week 12	NRT	23	16	50.2	25.5	39.2	61.3
	Varenicline	24	11	47.2	24.1	37.0	57.4
	NM	5	1	44.4	30.4	6.7	82.2
	Total	52	28	48.3	24.9	41.4	55.2

Table 15: Mean EORTC-QLQ C30 3.0 sub item *fatigue* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication. NMiss = number of missings. STD = standard deviation.

	Treatment	Method	t Value	DF	Mean	LCL	UCL	p-Value
Day 1	NRT vs. Varenicline	Pooled	-0.84	70	-5.20	-17.56	7.16	0.4043
Day 1	NRT vs. NM	Pooled	-2.32	41	-25.68	-47.98	-3.37	0.0251
Day 1	Varenicline vs. NM	Pooled	-1.58	39	-20.48	-46.77	5.82	0.1233
Week 12	NRT vs. Varenicline	Pooled	0.42	45	3.02	-11.56	17.60	0.6785
Week 12	NRT vs. NM	Pooled	0.45	26	5.80	-20.88	32.48	0.6589
Week 12	Vareniclin vs. NM	Pooled	0.22	27	2.78	-22.61	28.16	0.8240

Table 16: Comparison of Mean EORTC-QLQ C30 3.0 sub item *fatigue* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication

EORTC-QLQ C 30 3.0 nausea and vomiting

There are no significant differences among the groups at study entry and at week 12.

	Treatment	N	NMiss	Mean	STD	Mean (95%LCL)	Mean (95%UCL)
Day 1	NRT	37	2	5.9	11.3	2.1	9.6
	Varenicline	35	0	6.7	16.8	0.9	12.4
	NM	6	0	2.8	6.8	-4.4	9.9
	Total	78	2	6.0	13.7	2.9	9.1
Week 12	NRT	23	16	24.6	27.5	12.8	36.5
	Varenicline	24	11	22.9	27.7	11.2	34.6
	NM	5	1	10.0	22.4	-17.8	37.8
	Total	52	28	22.4	27.0	14.9	30.0

Table 17: Mean EORTC-QLQ C30 3.0 sub item *nausea and vomiting* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication. NMiss = number of missings. STD = standard deviation.

	Treatment	Method	t Value	DF	Mean	LCL	UCL	p-Value
Day 1	NRT vs. Varenicline	Pooled	-0.24	59.054	-0.81	-7.58	5.96	0.8115
Day 1	NRT vs. NM	Pooled	0.65	41	3.08	-6.53	12.69	0.5215
Day 1	Varenicline vs. NM	Pooled	0.56	39	3.89	-10.27	18.05	0.5817
Week 12	NRT vs. Varenicline	Pooled	0.21	45	1.72	-14.50	17.94	0.8317
Week 12	NRT vs. NM	Pooled	1.11	26	14.64	-12.49	41.76	0.2775
Week 12	Vareniclin vs. NM	Pooled	0.97	27	12.92	-14.31	40.14	0.3390

Table 18: Comparison of Mean EORTC-QLQ C30 3.0 sub item *nausea and vomiting* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication

EORTC-QLQ C 30 3.0 insomnia

There are no significant differences among the groups at study entry and at week 12.

	Treatment	N	NMiss	Mean	STD	Mean (95%LCL)	Mean (95%UCL)
Day 1	NRT	36	3	30.6	33.2	19.3	41.8
	Varenicline	34	1	44.1	36.4	31.4	56.8
	NM	6	0	50.0	40.8	7.2	92.8
	Total	76	4	38.2	35.6	30.0	46.3
Week 12	NRT	23	16	40.6	36.2	24.9	56.2
	Varenicline	24	11	43.1	31.8	29.6	56.5
	NM	5	1	13.3	29.8	-23.7	50.4
	Total	52	28	39.1	34.1	29.6	48.6

Table 19: Mean EORTC-QLQ C30 3.0 sub item *insomnia* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication. NMiss = number of missings. STD = standard deviation.

	Treatment	Method	t Value	DF	Mean	LCL	UCL	p-Value
Day 1	NRT vs. Varenicline	Pooled	-1.63	68	-13.56	-30.18	3.05	0.1080
Day 1	NRT vs. NM	Pooled	-1.29	40	-19.44	-49.98	11.09	0.2054
Day 1	Varenicline vs. NM	Pooled	-0.36	38	-5.88	-39.09	27.33	0.7219
Week 12	NRT vs. Varenicline	Pooled	-0.25	45	-2.48	-22.47	17.52	0.8042
Week 12	NRT vs. NM	Pooled	1.57	26	27.25	-8.53	63.02	0.1296
Week 12	Vareniclin vs. NM	Pooled	1.92	27	29.72	-2.08	61.53	0.0658

Table 20: Comparison of Mean EORTC-QLQ C30 3.0 sub item *insomnia* at day 1 and week 12. NRT = Nicotine replacement therapy. NM = no medication

Side effects

Each patient was asked if side effects of medication occurred at visit 2 (week 6) and visit 3 (week 12). Hospitalization due to lung cancer therapy or lung cancer therapy complications was not considered as adverse event as predefined in the study protocol.

Nicotine replacement therapy
Patients receiving nicotine replacement therapy were, amongst others, especially asked about skin irritation, flu like symptoms and coughing due to the therapy at visit 2 and 3. Furthermore there were asked about neurological symptoms, cardiovascular and endocrinological symptoms.
None of the 39 patients receiving nicotine replacement therapy reported any of these symptoms at visit 2 and visit 3, respectively.
One patient suffered a myocardial infarction four weeks after visit 3 and died of cardiogenic shock two days later. At that time the patient had already stopped nicotine replacement therapy.

Varenicline
Patients who received varenicline were, amongst others, especially asked about psychological effects as abnormal dreams, insomnia, anxiety, hallucinations and others. Furthermore, there were asked about gastrointestinal side effects such as sickness, vomiting, obstipation and of cardiovascular side effects.
Six patients reported about sickness at week 6, in 3 of them there was additional vomiting. All patients stopped varenicline by themselves without further symptoms. One patient switched to nicotine replacement therapy. Of note all patients reporting sickness received chemotherapy or radio chemotherapy, respectively.
When comparing EORTC QLQ C30 sub item Nausea and vomiting there was no difference at week 12 between treatment groups (table 18).

In one patient a transient ischemic attack led to a hospitalization after approx..10 days of taking varenicline. Patient reported about a transient hemiparesis on the left side. Symptoms dissolved within hours. There was an ischemic insult in patients` history. The same patient reported about mild hallucinations after increasing varenicline dose to 1 mg twice daily. As the patient was further interested in pharmacological support, dosage was reduced but symptoms reoccurred and the patient switched to a nicotine replacement therapy by herself.

One patient receiving varenicline, who stopped the medication due to sickness after 4 weeks suffered a renal failure about 3 weeks later due to chemotherapy-associated diarrhea. The patient finally died due to renal failure.

One patient receiving varenicline committed suicide after receiving the message of progress of lung cancer. The patient was a hunter. He received only one package of varenicline, which was taken up to 4 weeks before the suicide. The patient never received a further package of varenicline. To the best of our knowledge, there was no hint for any influence of the medication to his decision.

Discussion

This prospective study evaluated the effectiveness of a comprehensive smoking cessation therapy in smokers with newly diagnosed lung cancer. Achieved smoking abstinence rate was 37,5% after 12 and 32,8% after 24 weeks and thus comparable to results in other patient groups or even healthy subjects [24,32,33]. However, it should be kept in mind, that comparison between different studies is difficult because of varieties in the intensity of the cessation intervention.
There is only limited evidence on smoking cessation in lung cancer patients. Previous studies were retrospective [12] and included only a limited number of patients (15 to 49) [15] [16] [17]. Of note side effects of pharmacotherapy were not systematically evaluated. Thus a recent Cochrane review stated insufficient evidence for smoking cessation in patients with lung cancer mainly due to the limited number of patients with lung cancer included and the uncontrolled design [34].

Smoking abstinence was higher in the varenicline group as compared to the nicotine replacement group, but the study was not designed to show differences between different forms of treatment. In a general smoking cessation population varenicline is known to be more effective as compared to nicotine replacement therapy [23,33].

Most of the patients choose an additional pharmacological therapy after counseling for smoking cessation. Only six Patients decided against a medication. Among these most already stopped smoking within the 4 weeks before enrollment into the study and the score of the Fagerstroem-Test was lower than in the other patients indicating lesser nicotine addiction. Thus our study revealed that intense cessation counseling during hospitalization for diagnoses and treatment of lung cancer leads to a high proportion of patients using pharmacotherapy as an aid for smoking cessation. This is relevant, since pharmacotherapy increases the success rate by the factor of about two [35].

Side effects of medication are important when treating lung cancer patients with a high symptom burden and a limited prognosis. The side effects observed in the present study were keeping within the previously published data. There were no side effects reported in patients using nicotine replacement therapy. Sickness after taking varenicline was reported by six patients. Of note, all of these patients received chemotherapy or radiochemotherapy, respectively. There was no difference in the sub item nausea and vomiting in EO QLQ C30 questionnaire between the different treatment groups. Thus, the study revealed no novel side effects in the cohort of patients with live limiting disease often undergoing systemic therapy including chemotherapy and immunotherapy.

As the study was including patients with all lung cancer stages among them many patients with advanced disease, most patients died due to progression of lung cancer. Accordingly, mortality was high during the study period.

Symptoms of nicotine withdrawal were lowest in patients who did not opt for additional pharmacological treatment. This might be explained by the low rate of active smokers in this group at study entry as discussed above. Correspondingly the abstinence rate was highest (60% of all patients were non-smokers at week 12) in this group. The significant difference of nicotine withdrawal symptoms at week 12 between patients receiving NRT or varenicline and patients without medication might also be explained by the disparity of the groups at baseline. Furthermore, the small number of patients in this group hampers interpretation of the data.

A limitation of the present study is that not all smokers were included in the study since some patients were reluctant to be included in the study. Furthermore, the lack of randomization precludes any formal comparison between the different pharmacologic treatments. A strength of the study is the comprehensive evaluation of the patients and the prospective design reflecting a real life setting in a large, tertiary lung cancer center.

In conclusion, our results indicate that smoking cessation is feasible in patients with newly diagnosed lung cancer. The observed cessation rate is comparable to other patient cohorts or healthy subjects. Furthermore, pharmacotherapy using nicotine replacement therapy or varenicline in addition to tumor therapy often including chemotherapy was save and did not show novel side effects in this seriously ill patients. Given the known positive effects of smoking cessation in lung cancer patients, smoking cessation should be integral part of lung cancer treatment.

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