ORIGINAL ARTICLE

Taylor&Francis healthsciences

Evaluation of Objective Measures of Smoking Status

A Prospective Clinical Study in a Group of Head and Neck Cancer Patients Treated with Radiotherapy

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Acta Oncologica Vol. 42, No. 2, pp. 154–159, 2003

The present study was undertaken to evaluate objective measures of the smoking status of head and neck cancer patients during the course of radiotherapy. This was done by conducting a weekly structured interview, and measurement of carbon monoxide in expired air and of serum concentration of cotinine, the major metabolite of nicotine. These methods were tested prospectively in a series of 20 patients with head and neck cancer treated with radiotherapy. The results showed significant differences in the levels of end-expired carbon monoxide as well as serum cotinine among the different self-reported smoking groups. Combining the two objective measures and the interview data, the study revealed that up to 50% of self-reported non-smokers were in fact smoking actively. Measurement of end-expired carbon monoxide levels was found to be a precise indicator of smoking in the hours preceding measurement. Serum cotinine was a valuable measure of true smoking status. Assuming that this assay reflects the true smoking status, sensitivity, specificity and positive predictive value of self-reporting in this patient population was 79%, 80%, and 92%, respectively. In research aiming to investigate possible relations between smoking and radiotherapy, it is recommended that patients' smoking status be evaluated objectively as a supplement to self-reporting, at least in the head and neck cancer patients.

Received 11 September 2002
Accepted 21 January 2003

A major proportion of head and neck cancer (HNC) patients present a history of former or current heavy smoking. The role of tobacco smoking as an etiologic factor in the development of this cancer type is well established (1). The negative implications of smoking on the outcome of radiotherapy has been addressed in a few prospective studies, but only by using a questionnaire to evaluate patients' consumption of tobacco (2–4). As self-reported smoking habit has repeatedly been shown to be inaccurate (5–7), the application of more objective methods would be relevant and several validated methods exist, but have not yet been applied in this setting. The aim of this study was to evaluate the value of measuring smoking status objectively.

MATERIAL AND METHODS

Twenty-six consecutive HNC patients referred for curative radiotherapy were invited to enrol in the study and 20 chose to participate. The participant group consisted of 20 male patients with a median age of 66 years (range 46–80) (Table 1). Ten patients had laryngeal tumours, 2 had hypopharyngeal tumours, 4 had oropharyngeal tumours, 3 had tumours of the oral cavity and one patient had nasopharyngeal tumour(s). All the tumours were squamous cell carcinomas. With the exception of two female patients who refused to participate, no significant demographic or other differences between participants and non-participants were recorded.

After giving their informed consent, the participants provided a detailed smoking history to the principal investigator, face-to-face, assessing the daily use of tobacco- and nicotine substitution products, as well as being measured on the Fagerstrøm nicotine dependency scale (8). The following parameters were recorded: year when smoking started, year and date when smoking stopped, number of cigarettes or equivalent units per day, use of nicotine replacement. Based on this information, patients were divided into five groups: 1) Long-term quitters including former and never smokers; 2) recent quitters who admitted to having quit smoking *less than 1 month* prior to the inclusion interview; 3) recent quitters using any kind of nicotine substitution products; 4) moderate smo-

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DOI: 10.1080/02841860310005020

Table 1

Summary of the individual patient data

No.	Sex	Age	Tumor Site	Cigarettes/ day	Smoker group	Fagertrøm score	End-tidal CO median (range), ppm	Cotinine: max score (all measurements)*
1	M	69	Larynx	40	Heavy smoker	6	21 (16–31)	6 (6-6-6-6-6-6)
2	M	80	Oropharynx	3	Moderate smoker	4	NA	6 (5-6-6-3-5)
3	M	66	Oropharynx	0	Recent quitter+NS	2	2.5 (2–4)	5 (5-5-5-5)
4	M	70	Oral cavity	0	Recent quitter	2	5 (2–6)	5 (5-5-5-5-5)
5	M	69	Larynx	0	Recent quitter	3	2 (1–2)	1 (1-1-1-1-1-1)
6	M	71	Larynx	0	Recent quitter+NS	2	2.5 (2–3)	4 (2-3-3-3-4)
7	M	46	Nasopharynx	0	Recent quitter	0	2 (2–4)	1 (1-1-1-1-1-1)
8	M	74	Larynx	15	Moderate smoker	3	13 (9–15)	6 (6-6-6-6-6)
9	M	74	Hypopharynx	15	Moderate smoker	2	NA	6 (1-6-6-5-4)
10	M	63	Oropharynx	0	Long-term quitter	0	3 (2–3)	1 (1-1-1-1-1)
11	M	78	Oral cavity	0	Long-term quitter	0	2 (2–3)	1 (1-1-1-1-1-1)
12	M	75	Larynx	4	Moderate smoker	2	3 (3–4)	4 (2-2-3-4-3-3-3)
13	M	59	Larynx	5	Moderate smoker	2	12 (8–16)	6 (5-5-5-5-6)
14	M	61	Larynx	40	Heavy smoker	4	15 (14–16)	6 (6-6-5)
15	M	58	Hypopharynx	3	Moderate smoker	4	10 (6–14)	5 (5-5-4-5-5)
16	M	64	Larynx	18	Moderate smoker	4	14 (11–18)	6 (6-6-6-6-6-6-6)
17	M	55	Oropharynx	10	Moderate smoker	6	18 (2–26)	6 (6-6-5-6-5-4)
18	M	66	Larynx	2/week	Moderate smoker	2	3 (2–6)	2 (1-1-1-2-2-2)
19	M	48	Larynx	0	Long-term quitter	0	6 (5–9)	5 (5-5-5-5-5-5)
20	M	60	Oral cavity	15	Moderate smoker	6	18 (11–27)	6 (6-5-5)

* [cotinine] classified as 1 = < 10 ng/mL; 2 = 10–24 ng/mL; 3 = 25–49 ng/mL; 4 = 50–99 ng/mL; 5 = 100–249 ng/mL; 6 = 250+ ng/mL.

kers; and 5) heavy smokers, smoking < 20, ≥ 20 cigarettes (or other tobacco product) per day, respectively.

The smoking status of the patients was recorded and measured weekly during the 5 to 6-week treatment course and 2 months after treatment by three methods: a) self-report, b) carbon monoxide in the expired air, c) serum cotinine blood samples. The weekly interviews and subsequent objective tests were carried out by the same investigator throughout the study period.

Self-report

The subjective smoking status was obtained through a structured interview—similar to the initial interview—assessing the daily use of tobacco- and nicotine substitution products.

Carbon monoxide in expired air

As end-tidal air represents alveolar air and equilibrium exists between the blood and the alveoli, an estimate of the alveolar fraction of CO as well as blood concentration of carboxyhemoglobin can be obtained by measuring the end-tidal fraction of carbon monoxide (Fig. 1). All three parameters are indicators of smoking status, since smoking is the only major source of environmental CO. The measurement was performed using the EC50 Micro Smokerlyzer® (Bedfont Scientific Ltd.). This portable apparatus measures the end-tidal CO electrochemically, with a reported precision of $< 2\%$. The Micro Smokerlyzer requires calibration every 6 months with a 50 parts per million CO gas standard, which comes with the apparatus. After 15 s of breath holding, the test subject slowly exhales fully into a mouthpiece, and the result is immediately readable from an inbuilt LCD display. Patients underwent this procedure weekly immediately after the interview, either shortly before or after the radiotherapy treatment. This study used a cut-off-value of 10 ppm to discriminate smokers from non-smokers. This value is also programmed into the Smokerlyzer and equals that recommended by several other investigators (9–11). In the measurement of end-tidal CO it is important to bear in mind that the T1/2 of carboxyhemoglobin and hence alveolar fraction of CO is 2–4 h (10, 11). With a tobacco smoke-free interval greater than 8 h, a non-smoker fraction of less than 10 ppm was expected, larger values indicating recent smoking.

Serum concentration of cotinine

Cotinine is the primary metabolite of nicotine, but has a longer T1/2 (approximately 15 h), which makes it possible to detect any smoking several days prior to serum sampling. Any use of nicotine substitution products (patch, chewing-gum, nasal spray) will thoroughly bias the estimation of true smoking status using serum cotinine. In the current series, serum was obtained weekly for analysis. A commercially available ELISA kit (Cozart Bioscience Ltd., UK) was used. In this competitive assay, cotinine from the patient sample competed with enzyme-conjugated cotinine for binding to the anti-cotinine antibody coat of the wells. After 30 min of incubation, the wells were washed four times before a substrate for bound enzyme conjugate was added. After 30 min of further incubation the reaction was

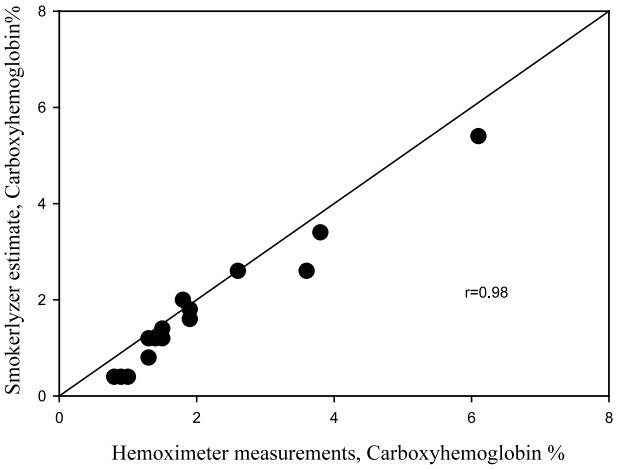

Fig. 1. Relationship between the estimated carboxyhemoglobin (%) from the Smokerlyzer and the carboxyhemoglobin (%) measured by the ABL700 hemoxymeter. Data from 15 tests in 15 patients. The correlation was highly significant ($r = 0.98$, $p < 0.0001$).

stopped and the absorbance read at 450 nm. In this study an automatic plate reader, Ceres 900® (Bio-Tek Instruments Incorporated), was used. Cut-off levels of 10 and 50 ng/mL serum used for dividing the measured values of samples into low, intermediate and high cotinine concentration groups correspond to the expected levels for non-smokers, light smokers and smokers, respectively. These levels are recommended by the kit manufacturer and equal those used by several other investigators (9, 12–14).

Statistics

Only descriptive statistics were used. Averages of values measured in various groups were compared using Student's *t*-test with a significance level of 5%. Calculations were performed using the SPSS 10.0 software package.

RESULTS

Self-report

Based on the first interview, which included a comprehensive smoking history, patients were divided into the five smoking status groups (Table 1). Twelve of the 20 patients (60%) admitted to smoking. Most of these participants (10/12) were moderate smokers; two were heavy smokers. The group of recent quitters comprised 25% (5/20), while 15% (3/20) reported being long-term quitters. All participants remained in the same self-reported group throughout the subsequent treatment period.

Carbon monoxide in expired air

The 20 patients had CO measurements done weekly during the 5 weeks' treatment and at the 2-month follow-up. A total of 108 measurements were obtained in 20 patients. Of these, 11 (10%) were excluded due to insufficient compliance with the sampling technique, mostly because radiation-induced mucositis made forced breath holding difficult. The average value for each patient was calculated from the available measurements. For each self-reported group, the mean of the average end-tidal CO was as follows: 3.9 ppm in long-term quitters; 2.6 ppm in recent quitters; 2.7 ppm in recent quitters using nicotine substitution; 11.0 ppm in moderate smokers; and 20.3 ppm in heavy smokers. There were no significant differences between the three quitter groups, while the moderate smoker and heavy smoker groups differed significantly from these three groups as well as from each other ($p < 0.05$). Prior to sampling, patients were asked to give the time since their last smoke, a factor that is important due to the short halftime of carboxyhemoglobin. The values in Table 2 show the ability of the Smokerlyzer assay to detect recent smoking. Measurements were expected to be in the smoker class if the test subject reported smoking within the last 8 h prior to sampling. The sensitivity was 95% (36/38), specificity 98% (58/59) and the predictive value of a positive reading 97% (36/37) regarding the ability of the Smokerlyzer to identify smoking within the hours preceding the measurement. We observed four situations where the readings indicated smoking despite the patients' a priori statement of being abstainers. In three of these cases the patients subsequently remembered (or admitted) that they had been smoking within 8 h of being tested. The table is corrected for theses cases of recall bias. The resulting agreement between self-reporting and classification by the Smokerlyzer is thus very high, with sensitivity, specificity and positive predictive values all above 95%.

Serum cotinine

A total of 104 serum samples were available for analysis. The measured values were divided into three categories of low, intermediate and high concentration of cotinine. For each patient, the highest measured value during the test period was used as the final indicator of objective smoking status. The distribution is presented in Table 3. This table shows that, in the groups with actively smoking patients, all but one patient were correctly scored as smokers. The one patient with a negative serum cotinine classification stated smoking only two cigarettes per week, and always at the weekend. As sampling was carried out on Wednesdays it seems, with a halftime of 15 h, reasonable to expect the concentration for this particular smoker to fall to the measured non-smoker level. In the 'recent quitter with nicotine substitution' group, all four samples taken from the one patient were in the high range, as expected. In the 'recent quitter' group, two of the four patients were caught with high serum cotinine values. Similarly, in the 'long-term quitter' group one of the three patients was found to have at least one high value. Interestingly, none of these three patients had, on any encounter, produced Smokerlyzer

Table 2

The ability of the Smokerlyzer assay to detect recent smoking. Measurements were expected to be in the smoker class if the test subject reported smoking within the last 8 h prior to sampling. Values are number of samples taken in 20 patients (average 5 tests per patient)

	Measured value		Total
	Smoker level ≥ 10 ppm	Non-smoker level < 10 ppm	
Expected group			
Smoker	36	2	38
Non-smoker	1	58	59
Total	37	60	97

readings indicating recent smoking. Assuming that the cotinine assay reflects the true smoking status, the sensitivity, specificity and positive predictive value of self-reporting in this patient population was 79% (49–95%), 80% (28–99%) and 92% (62–100%), respectively (numbers in parentheses indicate 95% confidence intervals).

At the 2-months' follow-up all patients were given the interpretation of their sample values, and were asked for their current smoking status. The distribution of smoking habits revealed a back-to-baseline status, with the exception of one of the recent quitters who was still not smoking. The deceptive patients were confronted with the discrepancy. The patient in the 'recent quitter with nicotine substitution' group declined to smoke while undergoing therapy, while the three 'discrepants' in the other groups all admitted smoking during the treatment period, although never on the day when they knew that they were going to use the Smokerlyzer.

DISCUSSION

In this prospective study, a major fraction of 20 consecutive head and neck cancer patients were smokers. The group of recent quitters, 25% in all in this population, was also substantial. This can be seen as an effect of repeated recommendations to the patients from all health personnel to quit smoking. Nicotine replacement in the form of patches is offered free to patients while undergoing radiotherapy, but only a minority of patients trying to quit smoking chose to take up this offer.

The wide variation in the Smokerlyzer measurements was expected because smoking is the only major external source of CO. The relatively short halftime of the alveolar fraction of CO is also likely to be the explanation for the wide range of values obtained within groups, especially in the group of moderate smokers where the reported consumption of cigarettes varied from 2 per week to 18 a day. The data confirm that the Smokerlyzer is a valuable tool in the screening of smoking within the hours previous to sampling, but sensitive to longer periods of smoking abstinence. The Smokerlyzer is an effective tool in 'quit smoking' programs, where the immediate and symbolic diode readout (red, yellow, green light) gives strong reinforcement and motivation.

The analysis of serum cotinine was useful in detecting smoking within a few days prior to sampling. The high values measured in the 'recent quitter with nicotine substitution' group stressed the importance of obtaining information on the use of nicotine substitution or smoke-free tobacco, since smoking status cannot be determined by serum cotinine in these patients.

The combined use of a questionnaire, Smokerlyzer and serum cotinine allows a detailed and more objective picture of the 'true' smoking status of a patient. The follow-up results two months after radiotherapy, where all patients were told the interpretation of their sample values, proved that 3 out of 4 quitters with high serum cotinine levels admitted smoking in the treatment period, although never on the day that they knew they were going to use the Smokerlyzer! This risk of inducing active deception from the patient side is the largest disadvantage of the Smokerlyzer, as mentioned by Whittet et al. (15). Other investigators have also found that self-reporting in a substantial fraction of smokers, especially those trying to stop, is

Table 3

Cross-tabulation of self-reported versus objective classification of smoking status based on serial weekly measurements of serum cotinine concentrations taken during a course of radiotherapy. A total of 104 samples were taken in 20 patients (average 5 samples per patient). Classification was based on highest serum cotinine measurement in each individual. Values marked with an asterisk indicate patients where the observed (measured) and expected (self-reported) classification did not correspond

Serum cotinine		Self-reported smoking status					
Group	ng/mL	Heavy smoker	Moderate smoker	Recent quitter with nicotine substitution	Recent quitter	Long-term quitter	Total
Low	< 10	0	1*	0	2	2	5
Intermediate	< 50	0	2	0	0	0	3
High	> 50	2	7	1	2*	1*	12
Total		2	10	1	4	3	20

Table 4

Recommendations for monitoring smoking status in clinical trials

1. Structured interview	Gives basic information on smoking history. Can identify long-term quitters—defined as abstinence for more than, e.g., 3 months before diagnosis of cancer—and never-smokers. These two groups of patients do not need to have further testing done. Others, especially recent quitters, should be monitored objectively.
2. Serum cotinine	Detects any smoking in the days prior to serum sampling and yields a reliable classification of patients in smokers and non-smokers, except in patients on nicotine replacement, or using other smokeless tobacco products.
3. Carboxyhemoglobin	Detects smoking in the hours prior to sampling. Blood sampling method relevant especially in protocols where 'effective' hemoglobin is recorded. Smokerlyzer testing is easy and cheap, can also be used to give positive reinforcement in quit-smoking programs.

unreliable (5–7). This may be a special problem in head and neck cancer patients, of whom a major proportion are former or present alcoholics—persons who are used to lying about their habits.

From the current study it seems that the sensitivity, specificity and positive predictive value of self-reporting in this head and neck cancer patient population is 80–90%. In research aiming to investigate possible relations between smoking and radiotherapy, we recommend that patients' smoking status should be evaluated objectively as a supplement to self-reporting, at least in the group of head and neck cancer patients. A program for smoking evaluation should contain the elements listed in Table 4. A short structured interview can be useful to detect non-smokers and long-term quitters. Long-term quitters and non-smokers need no further monitoring. The present data suggest that self-reporting from recent quitters (less than one month as used in this series) is unreliable and these patients should be monitored objectively. For safety reasons, we therefore recommend using a cut-off of at least 3 months. Serum cotinine evaluation is a valid and high-precision, long-term measure for describing smoking status in the days prior to serum sampling, and gives a better classification of patients in smokers and non-smokers. The measurement is simple, can be done retrospectively and centrally on stored blood samples, but cannot be interpreted in patients using nicotine substitution or smoke-free tobacco. The measurement of carboxyhemoglobin by Smokerlyzer or by blood samples can determine smoking in the hours prior to sampling. This procedure is reliable and the blood gas analysis is especially valuable if hemoglobin, and effective hemoglobin, is a relevant parameter in the clinical protocol. An example of such a situation is the estimation of the effective oxygen unloading capacity (16). The Smokerlyzer procedure itself can influence patients' smoking habits by motivating them to stop, and it is important to realize that patients can cheat by not smoking on the day of measurement.

In conclusion, this study demonstrates that application of objective estimators of smoking status in head and neck cancer patients is possible and provides a more accurate description than self-reporting. This is especially true in the group of self-reported recent quitters, a group likely to comprise a substantial fraction of patients in a setting where smoking cessation is repeatedly advised. Application of these objective methods in order to more accurately reveal possible relations between smoking and the effect of radiotherapy in terms of morbidity, locoregional control and survival is encouraged.

ACKNOWLEDGEMENTS

This work was funded by a grant awarded to Jonas Hald by the Danish Cancer Society, Clinical Research Unit, Aarhus, Denmark. Jonas Hald carried out the experimental work as a part of his diploma study at the University of Aarhus.

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