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A feasibility study of relaxation therapy plus autohypnotherapy training (HYPREL) for patients with thoracic cancer undergoing radiotherapy.

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SUMMARY

As radical thoracic radiotherapy becomes more sophisticated, it is becoming increasingly important to minimise and regularise respiratory and other movement during radiotherapy planning (CT simulation) and treatment. Procedure-related anxiety, pain and other psychological factors may affect respiratory parameters in a time-dependant manner, resulting in sub-optimal planning and radiotherapy.

The aims of this study, therefore, were (a) to develop a psychological intervention that would minimise respiratory changes associated with procedure-related anxiety during radiotherapy planning and radiotherapy, and to test the acceptability and feasibility of the intervention, and (b) to carry out a preliminary evaluation of the effects of the intervention on respiration and quality of life during planning and radiotherapy.

Thirty-one patients were randomised to the experimental intervention (HYPREL - relaxation, autohypnotherapy and exposure *in vivo*) or to standard support (SIS) in the Oncology Health Centre (control). The primary outcome, respiratory amplitude during radiotherapy planning, was assessed objectively and repeatedly using the Varian RPM system. Secondary respiratory outcomes - amplitude variability, frequency, and frequency variability - were also assessed during radiotherapy planning. In addition, respiratory parameters were assessed repeatedly during the course of radiotherapy, and quality of life was assessed on six occasions during the study using standardised psychometric measures.

At baseline, the two groups did not differ significantly on any of the clinical or sociodemographic variables. However, patients subsequently randomised to SIS showed greater variability in respiration frequency ($p=0.026$), and patients randomised to HYPREL scored significantly higher on the Functional Assessment of Cancer Therapy (Physical) scale, indicating fewer physical symptoms/greater physical wellbeing: otherwise, the two groups did not differ at baseline ($p=0.040$). Also, patients randomised to SIS showed a trend towards higher hypnotic susceptibility ($p=0.057$).

Compared to patients in the control group, patients randomised to HYPREL had a lower mean amplitude of respiration during radiotherapy planning ($p=0.059$). There were no

significant differences in amplitude variability, respiration frequency, or frequency variability. The two groups did not differ on any of the respiratory or quality of life parameters during the course of radiotherapy. Levels of anxiety and depression were very low in both groups throughout the study.

This pilot study has demonstrated that HYPREL is an acceptable intervention for patients undergoing radiotherapy to the chest wall, and, in line with the initial hypothesis, there is some evidence that HYPREL reduces the amplitude of respiration during radiotherapy planning, thereby potentially minimising unnecessary radiotherapy-induced damage to tissue surrounding the tumour.

In conclusion, the data from this preliminary study show that the intervention is feasible, and provides the justification for a larger, adequately powered, randomised controlled trial in a centre where there is CT planning and radiotherapy time and facilities dedicated to the study.

BACKGROUND

Recent advances in technology have allowed oncologists to deliver increasingly precise radiotherapy treatments to tumours while sparing surrounding normal tissues from the damaging effects of high doses. Three-dimensional conformal radiotherapy is planned using a CT scanner to design a 3-D shape which conforms to the tumour and which represents the volume to be treated. Using this approach, an arbitrary margin of normal tissue must be added to the tumour volume to ensure that the tumour is within the treatment field at all times during radiotherapy (Senan *et al*, 2004). When thoracic and breast cancers are treated, movement of the tumour and/or healthy tissue with respiration must be taken into account, making precise radiotherapy, and sparing healthy tissue, a difficult challenge.

Lung tumours move with respiration, particularly in the cranio-caudal direction, with estimates of maximal excursions ranging from 2 to 5 cm (Chen *et al*, 2001). Tumours move with respiration in a manner which is not reliably predicted by their size or their position within the lung though smaller tumours which are not attached to other structures and which are situated in the lower lobes tend to show the greatest motion with respiration (Mechalakos *et al*, 2004). Attempts to correlate the motion of lung cancers with the external motion of the chest or abdomen have shown tumour behaviour which varies greatly not only between subjects but also within individual subjects over the period of measurement (Hoisak *et al*, 2004). Studies of chest wall and abdominal motion in healthy volunteers have revealed that periods of quiet breathing are frequently interrupted by transient episodes of unstable breathing motion (Ozhasoglu and Murphy, 2002).

Radiotherapy to the breast or chest is carried out using external beam radiotherapy. Because the chest and breasts move with respiration, this means the region to be treated also moves with respiration. As lung tissue is at risk of damage from the effects of radiation, the volume irradiated should be kept to a minimum. Through reducing the amplitude and frequency of respiration, it may be possible to reduce the volume of lung irradiated.

It is well known that respiratory parameters can be significantly affected by psychological factors. For example, hyperventilation commonly occurs during panic attacks, and lesser levels of anxiety may cause increased respiratory frequency as well as thoracic (as opposed to

diaphragmatic) breathing. In the context of radiotherapy, patients may be anxious about planning (simulation CT scan), exposure to radiation and, more generally, the unfamiliar environment of the planning and radiotherapy suites. The greater the extent to which respiratory movement during planning simulates respiration during radiotherapy, the more valid the results of CT simulation are likely to be. As patients become increasingly familiar with radiotherapy (procedures, environment, staff), anxiety is likely to habituate, resulting in normalisation of breathing, and consequent reduction in the validity of the original CT simulation.

During radiotherapy itself, several strategies have been developed in an attempt to attenuate respiration-induced tumour motion. The simplest approach is to limit tumour motion by active or passive breath holding techniques, and treating only when the tumour is expected to be stationary (Rosenzweig *et al*, 2000; Stromberg *et al*, 2000). However, breath-holding techniques are difficult for patients whose breathing is already compromised and active breathing control involves the discomfort of being attached to a spirometer device.

Respiratory gating is an alternative to breath-holding and involves synchronising the radiotherapy beam exposure to those parts of the breathing cycle where tumour motion is minimal (Keal *et al*, 2006). Using this technique, the shortest overall treatment time is achieved by treating throughout the respiratory cycle and the smallest treatment volume achieved by exposures only when the tumour is immobile at the end of a respiratory cycle. Respiratory-gated radiotherapy thus requires that breathing motion is assessed at the time of the radiotherapy planning CT to assess the phase of respiration which will give the best compromise between treated volume and overall treatment time.

As the breathing pattern can vary greatly in the time it takes to deliver an exposure of radiotherapy and from day to day, some centres have developed methods of breathing training to improve reproducibility. Techniques which use visual feedback have proved useful in regularising the amplitude of breathing at the cost of some variation in frequency whereas those using audio cues resulted in reproducible frequency but variation in amplitude (Kini *et al*, 2003) Ultimately, the success of respiratory gating requires that the tumour moves in a measurable and predictable fashion with respiration and that this is maintained

throughout the course of radiotherapy. Without some form of image guided control it is impossible to ensure accuracy of such techniques on a day to day basis.

Real time tumour tracking systems have been developed whereby the radiation field is continuously adapted to follow the tumour and/or radiation is only delivered when the tumour is within a certain predefined field (Jiang, 2006; Xing *et al*, 2006). These techniques can be combined with respiratory gating technology, but real time tracking requires either a surgically implanted tumour marker or high doses of radiation for fluoroscopic monitoring.

In addition to improving various aspects of coping, treatment compliance and quality of life in patients with cancer (Walker, 1992; Owens and Walker, in press), relaxation and hypnotherapeutically-based interventions have been used to minimise anxiety, including procedure-related anxiety. In addition to being associated with feelings of calmness and confidence, relaxation therapy is associated with a number of physiological changes, including breathing changes that could be beneficial in terms of producing predictable, regular and gentle breathing. Hypnotherapy is thought to intensify the relaxation response and reduce pre-treatment anxiety (Heap and Aravind, 2002; Walker *et al*, 1988; Walker; 1992; Walker *et al*, 2011). However, these interventions have not previously been developed to optimise the benefits of the above developments in conformal thoracic radiotherapy.

In recent years, technology has become available to measure chest movement during radiotherapy and this can be used to assess the effect of relaxation and hypnotherapy on chest wall motion. For example, the RPM (Real Time Position Management System) system available from Varian Oncology Systems can be used to measure movement of the chest wall during radiotherapy (Palo Alto, CA 94304) (Kini *et al*, 2003). Because it is non-invasive, it cannot directly measure tumour motion. However, it does allow the frequency and amplitude of chest wall motion during radiotherapy to be compared between patients who have been taught relaxation techniques and a control group.

AIMS

The aims of this study, therefore, were (a) to develop a psychological intervention that would

minimise respiratory changes associated with procedure-related anxiety during radiotherapy planning and radiotherapy, and to test the acceptability and feasibility of the intervention, and (b) to carry out a preliminary evaluation of the effects of the intervention on respiration and quality of life during planning and radiotherapy.

METHODS

(1) Patient eligibility

Patients were eligible for the study if they (a) had lung cancer, breast cancer or oesophageal cancer; (b) were scheduled to have 15-20 fractions of radical radiotherapy to the thorax or breast; (c) were aged at least 18 years: (d) had an ECOG performance status of 0-1; (e) were able to complete questionnaires, and (f) were able and willing to give written informed consent.

They were excluded if they were unable to lie supine for medical reasons or had a history of functional psychosis, the latter being a relative contra-indication to hypnotherapy (Walker *et al*, 2007).

(2) Study design

This was a phase two, pragmatic, randomised trial. Patients were recruited from the Department of Oncology, Hull and East Yorkshire Hospitals NHS Trust[1]. Eligible patients referred to the clinical oncology department at Princess Royal Hospital were identified by their clinical oncology consultant or specialist registrar. These patients were invited, at their convenience, to an appointment with one of the clinical psychologists who gave a full verbal explanation and a patient information sheet, and obtained consent according to the Centre of Research: Ethical Campaign (COREC) guidelines.

[1] When the study commenced, the outpatient clinics and the radiotherapy department were located at the Princess Royal Hospital, Saltshouse Rd, East Hull. In October 2009, the clinics and the Radiotherapy Department were relocated to the newly built Queen's Centre for Oncology and Haematology at Castle Hill Hospital, Cottingham.

Patients were randomised either to self initiated support (SIS) from behavioural oncology nurses within the Oncology Health Service (control intervention) (Sharp *et al*, 2009; Walker *et al*, 2003; Walker *et al*, 2009) or to a similar level of support plus training in relaxation and auto-hypnotherapy (HYPREL).

Various parameters of quality of life were assessed immediately before and after the baseline respiration assessment (Assessment 1 – day 1), immediately before and after CT planning (Assessment 2 – day 15), immediately before and after the first fraction of radiotherapy (Assessment 3 day 28), immediately before and after 10 fractions of radiotherapy (Assessment 4 – day 42[2]), immediately before and after the final fraction of radiotherapy (Assessment 5 - day 49 or 56 [depending on whether patients received 15 or 20 fractions of radiotherapy]), and 4 weeks after the final fraction of radiotherapy (Assessment 6 – day 77 or 84).

To correspond with the quality of life assessments, respiratory movement was assessed at baseline (in the CT radiotherapy planning suite), during CT planning, and during the first, tenth and final fractions of radiotherapy.

The primary outcome was respiratory amplitude during radiotherapy planning. Secondary respiratory outcomes - amplitude variability, frequency, and frequency variability - were also assessed during radiotherapy planning. In addition, respiratory parameters and quality of life were assessed at the time-points indicated above.

(3) Interventions

(a) Control intervention (SIS)

All patients had full access to the facilities in the Oncology Health Service (OHS) and could access the "drop-in" service at any time: appointments were not required. Further details of the service have been previously documented (e.g. House of Commons, 2004; Sharp *et al,*

[2] Radiotherapy was administered five times per week and hence the gap between the first and 10 cycle was 14 days.

2009a; Sharp *et al*, 2009b; Walker *et al*, 2003).

(b) HYPREL

In addition to full access to the facilities of the OHS, patients randomised to HYPREL received a standardised, protocolised intervention. This consisted of training in progressive muscular relaxation and cue-controlled relaxation (Hutchings *et al*, 1980) and hypnotherapy consisting of training in autohypnosis (Spiegel eye roll technique, anchoring); rehearsal *in imagno*, and ego strengthening (Heap and Aravind, 2002)). We used a standard audio recording developed from those used in our previous studies of patients with breast cancer (Eremin *et al*, 2009; Walker *et al*. 1999), patients with lymphoma (Ratcliffe *et al*. 1995), and healthy volunteers (Johnson *et al*. 1996). Following randomization to HYPREL, patients were asked to practice with the recording at least once daily until the completion of radiotherapy (e.g., Walker *et al*, 1999).

HYPREL patients also received four sessions of protocolised live hypnotherapy. The first two sessions were carried out in the Oncology Health Centre following recruitment and before CT treatment planning. The third session was carried out in the CT planning suite (rehearsal *in vivo*) before CT planning. Session 4 was a "booster session and was carried out in the Oncology Health Centre after the 10^{th} session of radiotherapy. These sessions were all carried out by one of three qualified clinical psychologists.

(4) Trial outcomes

(a) Assessment of movement

During radiotherapy, the frequency and amplitude of chest wall movement was measured using the Varian RPM system (Kini *et al*, 2003). This is an established system with an integrated software package for data retrieval and processing. It involves no direct patient contact. An infra-red camera is used to track a pair of reflective markers that are mounted on the front face of a small box which is placed on the patient's chest. Apart from the placement of this box, the use of this equipment has no impact on the standard treatment.

The motion of these markers acts as a surrogate for that of the chest itself and is used to measure its amplitude and frequency. The regularity of the breathing cycle of each patient was characterised by the mean and standard deviation of measurements made during each of the sessions. Details of calibration and assessment of accuracy were carried out (Appendix One). A total uncertainty of 0.47±0.06mm SD over the range of measurements was determined.

(b) Psychological assessments

In order to obtain preliminary information about the psychological effects of the intervention, the following measures were used:

Mood Rating Scale (Walker *et al*, 1999). This is a brief scale based on the factor-analytically derived dimensions of the bipolar Profile of Mood States. It measures 6 components of mental state, including relaxation. One version, 7-day, assesses these components with reference to the previous 7 days. The "now" version measures these components at the present time.

Brief State Anxiety Inventory (BSAI) (Marteau and Becker, 1992). This is a 6-item measure of state anxiety suitable for assessing procedure-related anxiety.

Functional Assessment of Cancer Therapy (FACT) (Cella *et al*, 1993). This is a widely used, reliable, valid measure of cancer-related quality of life, with subscales for emotional, social, physical and functional wellbeing.

Hospital Anxiety and Depression Scale (HADS) (Zigmund and Snaith, 1983). This 14-item scale measures the prevalence of probable clinically significant anxiety and depression.

*Patient Satisfaction Questionnaire (*PSQ). This satisfaction questionnaire has been used in our previous studies (e.g. Walker *et al*, 1999). The first five items use a 4 point Likert scale ranging from very dissatisfied (1) to very satisfied (4) and the final item assessing global self-rated quality of life is a 5-point scale (where 5 is best).

In addition, the *Creative Imagination Scale* (CIS) (Wilson and Barber, 1978) was used to compare the hypnotic responsiveness of the two groups at baseline. To standardise

administration, a CD recording was used.

The *Structured Clinical Interview for Diagnosis* (SCID) was used at baseline to assess current and past psychiatric disorders (APA, 2000).

The psychological assessment schedule is shown in Figure One below.

Figure One

Pre-Randomisation	Before planning and before 1st, 10th and final fractions of radio-therapy.	After planning and after 1st, 10th and final fractions of radio-therapy.	Follow-up (4 weeks post final RT)
FACT-G			FACT-G
HADS			HADS
MRS (7-day version)	MRS (Now version)	MRS (Now version)	MRS (7-day version)
BSAI	BSAI	BSAI	CMQ
CIS			PSQ
SCID			

(5) Statistical and ethical aspects

Patients were randomised using a permuted blocks design (Altman, 1991). The use of the remote randomisation service at the Institute of Rehabilitation, Kingston upon Hull, ensured immediate and unbiased allocation of individual patients.

Because this was a feasibility study aiming to provide initial evidence of acceptability and effectiveness, the target sample size was approximately 30 (2 groups of 15).

Two-sided significance tests were used to analyze outcomes by intention-to-treat. The two groups were compared statistically using Pearson's chi-squared (categorical data) and Fisher's

one-way analysis of variance (interval data). Data were analysed in the Clinical Trials Section, Institute of Rehabilitation, University of Hull.

Standard radiotherapy treatment protocols were used and all patients were able to access the full range of services in the Oncology Health Centre.

The trial was conducted according to the most recent revision of the Declaration of Helsinki.

RESULTS

In total, 52 patients were identified initially as being suitable for the study. Of these, nine were excluded because of logistical problems in carrying out the baseline assessment before radiotherapy planning took place, eight declined entry because of the time commitment, two did not wish to attend the Oncology Health Centre, one turned out not to have breast or lung cancer, and one was profoundly deaf. Thirty-one patients, therefore, were randomized (16 to HYPREL and 15 to SIS).

Assessment One (baseline characteristics)

Twenty-six (84%) patients had breast cancer, 4 (13%) had lung cancer and 1 (3%) had oesophageal cancer. Twenty-nine patients (94%) were female and the mean age of the cohort was 60.19 years (standard deviation 12.37). Twenty-three (74%) were married or cohabiting, 4 (13%) were widowed, 2 (7%) were separated or divorced, and 2 (7%) were single. Ten (32%) had attended college or university. Three patients (10%) had a current psychiatric disorder as assessed by the SCID (two had major depression and one had an adjustment disorder), and two (6%) had a previous history (one Generalised Anxiety Disorder and one Agoraphobia without panic). Similarly, according to the HADS, three (10%) were clinically anxious and none was clinically depressed (the three anxious patients were all subsequently randomised to HYPREL). The detailed baseline clinical, sociodemographic, psychological and respiratory status of the patients who were randomised

is shown in Table One (categorical data) and Table Two (interval data).

Table One: Assessment One - Baseline Characteristics of the two groups (categorical variables)

	Hypnotherapy		**Self Initiated Support**		**Total**		Pearson Chi-Square	P value
	Number	%	Number	%	Number	%		
Location of cancer							0.969	0.616
Oesophageal	1	6.3	0	0	1	3.2		
Lung	2	13	2	13.3	4	13		
Breast	13	81.3	13	87	26	84		
Gender							0.002	0.962
Male	1	6.3	1	7	2	7		
Female	15	94	14	93	29	94		
Education							2.387	0.303
School	11	69	8	53.3	19	61.3		
College	4	25	3	20	5	16.1		
University	1	6.3	4	27	5	16.1		
Employment status							0.301	0.860
Working	7	44	7	47	14	45		
Retired	7	44	7	47	14	45		
Homemaker	2	13	1	7	3	10		
Marital status							6.027	0.197
Single	0	0	2	13	2	7		
Married	10	63	9	60	19	61.3		
Separated/Divorced	0	0	2	13.3	2	7		
Widowed	3	19	1	7	4	13		
Cohabiting	3	19	1	7	4	13		
Psychiatric diagnosis							2.971	0.563
Negative	13	81.3	13	87	26	84		
Major Depression (current)	1	6.3	1	7	2	7		
Generalised anxiety disorder (previous)	1	6.3	0	0	1	3.2		
Adjustment disorder (current)	1	6.3	0	0	1	3.2		
Agoraphobia with Panic Disorder (previous)	0	0	1	7	1	3.2		

*Ethnicity: all patients were white

At baseline, patients subsequently randomised to SIS showed greater variability in respiration frequency ($p=0.026$), and patients subsequently randomised to HYPREL scored significantly higher on the Functional Assessment of Cancer Therapy (Physical) scale ($p=0.040$), indicating fewer physical symptoms/greater physical wellbeing. Also, patients randomised to SIS showed a trend towards higher hypnotic susceptibility ($p=0.057$). Otherwise, the two

groups did not differ significantly at baseline on any of the clinical, sociodemographic, respiratory, psychological and psychiatric parameters.

Table Two: Assessment One - Baseline Characteristics of the two groups (ordinal variables)

	Hypnotherapy		**Self Initiated Support**		**Total**			
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	F ratio	P value
Age	61.63	14.30	58.67	10.21	60.19	12.37	0.434	0.515
Respiration (N=28)								
Amplitude	0.539	0.217	0.671	0.341	0.601	0.284	1.535	0.226
Amplitude variability	0.110	0.829	0.135	0.101	0.121	0.090	0.504	0.484
Frequency	4.300	1.121	4.669	0.967	4.472	1.050	0.840	0.368
Frequency variability	0.515	0.198	0.762	0.346	0.630	0.299	5.562	0.026
FACT-G (N=31)								
Physical	20.56	5.06	23.93	3.45	22.19	4.61	4.631	0.040
Social/Family	22.75	5.23	24.33	3.02	23.52	4.31	1.046	0.315
Emotional	18.63	4.33	20.20	3.32	19.39	3.90	1.277	0.268
Functional	20.25	5.85	21.13	5.77	20.68	5.73	0.179	0.675
Total	82.31	16.34	88.60	11.52	85.35	14.34	1.514	0.228
CIS Total	18.25	11.96	25.27	6.95	21.65	10.34	3.914	0.057
HADS (N=31)								
Anxiety	5.56	4.35	3.33	2.82	4.48	3.80	2.823	0.104
Depression	3.67	2.75	2.53	3.04	3.13	2.91	1.230	0.277
Total	9.31	6.81	5.87	5.67	7.65	6.42	2.328	0.138
MRS (N=31)								
Relaxation	96.19	45.61	96.60	45.74	96.39	44.91	0.001	0.138
Happiness	95.75	41.69	101.87	33.43	98.71	37.42	0.201	0.657
Energy	53.88	39.57	61.60	38.01	57.61	38.37	0.306	0.584
Clear-headedness	110.31	40.70	127.27	21.17	118.52	33.34	2.074	0.161
Easy-goingness	90.06	39.32	102.47	49.59	96.06	44.27	0.600	0.445
Confidence	98.56	37.25	114.07	36.18	106.06	36.97	1.379	0.250
Total	544.75	152.56	629.80	171.27	585.90	164.90	2.137	0.154
BSAI (N=31)	9.88	3.61	9.07	2.84	9.48	3.23	0.475	0.496

Assessment Two (CT radiotherapy planning)

Table Three shows the respiratory and psychosocial data for the two groups at Assessment Two (CT radiotherapy planning). Twenty-seven patients (14 patients randomised to SIS and 13 patients randomised to HYPREL) had complete respiratory data. In accordance with our hypothesis, the respiratory amplitude of patients randomised to HYPREL was lower than those in the comparison group and this almost reached statistical significance

(p=0.059). Amplitude variability, respiratory frequency and respiratory variability were similar in the two groups.

As far as psychosocial variables were concerned, there were no significant differences between the groups on any of the measures. Twenty-nine patients completed the pre-planning and 30 the post-planning questionnaires.

Table Three: Assessment Two (CT radiotherapy planning)

	Hypnotherapy		**Self Initiated Support**		**Total**			
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	F ratio	p value
Respiration (N=27)								
Amplitude	0.407	0.215	0.633	0.355	0.524	0.313	3.905	0.059
Amplitude variability	0.092	0.073	0.129	0.092	0.111	0.084	1.288	0.267
Frequency	4.446	0.938	4.400	0.691	4.422	0.803	0.022	0.884
Frequency variability	0.632	0.282	0.701	0.328	0.668	0.303	0.347	0.561
Pre- MRS (N=29)								
Relaxation	115.93	33.33	102.29	40.55	109.34	36.97	0.986	0.329
Happiness	113.60	34.00	98.29	30.99	106.21	32.94	1.599	0.217
Energy	71.73	31.43	58.36	29.37	65.28	30.67	1.397	0.248
Clear-headedness	123.47	38.67	121.64	29.70	122.59	34.03	0.020	0.888
Easy-goingness	123.47	30.30	110.29	40.72	117.10	35.69	0.987	0.329
Confidence	107.60	30.29	97.50	49.05	102.72	40.03	0.452	0.507
Total	655.80	128.58	588.36	106.65	623.24	121.34	2.344	0.137
Pre-BSAI (N=29)	9.80	3.53	9.57	2.62	9.69	3.07	0.039	0.845
Post- MRS (N=30)								
Relaxation	101.50	44.26	109.00	43.72	105.00	43.41	0.217	0.645
Happiness	115.81	32.10	102.86	33.67	109.77	32.93	1.162	0.290
Energy	72.63	39.94	71.14	32.01	71.93	34.71	0.013	0.910
Clear-headedness	124.94	27.65	130.93	22.88	127.73	25.29	0.411	0.527
Easy-goingness	113.31	42.38	102.86	42.43	108.43	42.00	0.454	0.506
Confidence	106.63	39.91	117.64	36.15	111.77	37.96	0.621	0.437
Total	634.81	158.62	634.43	121.03	634.63	139.93	0.000	0.994
Post-BSAI (N=30)	9.44	3.27	10.07	3.58	9.73	3.37	0.257	0.616

Assessment Three (first fraction of radiotherapy)

There were no significant between-group differences in any of the movement or

psychosocial parameters (Table Four). Complete respiratory data were available for 25 patients (12 patients randomised to SIS and 13 patients randomised to HYPREL) and complete questionnaire data for 30 patients.

Table Four: Assessment 3 (first fraction of radiotherapy)

	Hypnotherapy		**Self Initiated Support**		**Total**			
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	F ratio	p value
Respiration (N=25)								
Amplitude	0.507	0.241	0.684	0.372	0.592	0.317	2.024	0.168
Amplitude variability	0.099	0.065	0.120	0.073	0.109	0.068	0.600	0.446
Frequency	4.082	0.946	4.303	0.635	4.188	0.803	0.462	0.503
Frequency variability	0.564	0.218	0.666	0.390	0.613	0.310	0.668	0.422
Pre- MRS (N=30)								
Relaxation	75.63	42.86	77.57	36.27	76.53	39.26	0.018	0.895
Happiness	108.25	29.15	97.07	30.48	103.03	29.80	1.052	0.314
Energy	75.31	36.01	58.71	29.86	67.57	33.78	1.856	0.184
Clear-headedness	108.13	44.33	123.43	23.08	115.27	36.28	1.345	0.256
Easy-goingness	103.00	4.60	103.07	33.08	103.03	36.65	0.000	0.996
Confidence	103.50	32.16	107.64	32.27	105.43	31.72	0.124	0.728
Total	573.81	133.06	574.93	113.11	574.33	122.03	0.001	0.981
Pre-BSAI (N=30)	10.94	3.11	11.21	3.04	11.07	3.03	0.060	0.808
Post- MRS (N=30)								
Relaxation	105.94	40.87	111.29	39.71	108.43	39.73	0.131	0.720
Happiness	101.06	32.95	104.71	32.63	102.77	32.29	0.093	0.763
Energy	78.31	29.29	60.21	23.21	69.87	27.74	3.445	0.074
Clear-headedness	109.25	49.26	122.00	33.59	115.20	42.46	0.666	0.422
Easy-goingness	114.88	35.26	119.43	24.88	117.00	30.43	0.0162	0.690
Confidence	115.44	39.33	118.79	38.66	117.00	38.38	0.055	0.816
Total	624.88	154.60	636.43	118.72	630.27	136.81	0.052	0.822
Post-BSAI (N=30)	9.50	3.12	9.14	2.48	9.33	2.80	0.118	0.734

Assessment Four (tenth fraction of radiotherapy)

There were no significant between group differences in any of the movement or psychosocial parameters. Complete respiratory data were available for 18 patients (9 patients randomised to SIS and 9 patients randomised to HYPREL), and complete questionnaire data for 28 patients (Table Five).

Table Five: Assessment 4 (tenth fraction of radiotherapy)

	Hypnotherapy		**Self Initiated Support**		**Total**			
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	F ratio	p value
Respiration (N=18)								
Amplitude	0.535	0.322	0.719	0.435	0.627	0.383	1.031	0.325
Amplitude variability	0.111	0.096	0.107	0.081	0.1096	0.086	0.012	0.915
Frequency	3.965	0.966	4.516	0.530	4.240	0.973	1.485	0.241
Frequency variability	0.577	0.300	0.713	0.444	0.645	0.375	0.582	0.457
Pre- MRS (N=28)								
Relaxation	120.14	28.66	106.57	42.28	113.36	36.11	0.988	0.329
Happiness	111.86	38.62	96.57	32.21	104.21	35.75	1.293	0.266
Energy	51.93	31.16	63.39	34.52	57.59	32.73	0.866	0.361
Clear-headedness	132.50	23.15	128.50	24.15	130.50	23.30	0.200	0.658
Easy-goingness	101.21	41.45	112.57	37.38	106.89	39.16	0.580	0.453
Confidence	115.21	25.04	117.29	41.77	116.25	33.81	0.025	0.875
Total	632.86	138.96	620.64	165.60	626.75	149.87	0.045	0.834
Pre-BSAI (N=28)	9.36	3.20	9.71	3.41	9.55	3.29	0.079	0.780
Post- MRS (N=28)								
Relaxation	120.00	42.34	109.07	37.79	114.54	39.77	0.519	0.478
Happiness	119.00	29.41	102.36	32.15	110.68	31.40	2.042	0.165
Energy	41.50	18.65	58.36	25.75	49.93	23.67	3.936	0.058
Clear-headedness	124.00	30.31	121.00	32.43	122.50	30.83	0.064	0.802
Easy-goingness	116.43	27.85	117.08	26.12	116.74	25.51	0.004	0.951
Confidence	106.86	40.14	115.50	39.94	111.18	39.53	0.326	0.573
Total	627.79	114.70	615.00	168.19	621.39	141.20	0.055	0.816
Post-BSAI (N=28)	8.79	4.53	9.57	3.03	9.18	3.80	0.291	0.594

Assessment Five (final fraction of radiotherapy)

There were no significant between-group differences in any of the movement or psychosocial parameters. Complete respiratory data were available for 18 patients (11 patients randomised to SIS and 7 patients randomised to HYPREL). Pre-radiotherapy questionnaire data was available for 27 patients and post radiotherapy questionnaire data for 29 patients (Table Six).

Twenty-eight (90%) of the 31 patients had 15 fractions of radiotherapy.

Table Six: Assessment 5 (final fraction of radiotherapy)

	Hypnotherapy		**Self Initiated Support**		**Total**			
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	F ratio	p value
Respiration (N=18)								
Amplitude	0.478	0.191	0.639	0.330	0.576	0.289	1.353	0.261
Amplitude variability	0.068	0.041	0.093	0.066	0.084	0.058	0.820	0.379
Frequency	4.163	0.192	4.157	0.853	4.159	0.850	0.000	0.988
Frequency variability	0.422	0.192	0.571	0.270	0.513	0.248	1.602	0.224
Pre- MRS (N=27)								
Relaxation	118.57	30.93	116.00	34.98	117.33	32.32	0.041	0841
Happiness	115.43	28.22	107.92	30.60	111.81	29.06	0.440	0.513
Energy	52.64	45.33	47.46	30.92	50.15	38.42	0.118	0.734
Clear-headedness	122.71	35.56	124.46	34.08	123.56	34.19	0.017	0.897
Easy-goingness	115.00	31.11	114.00	36.96	114.52	33.39	0.006	0.940
Confidence	123.79	25.39	119.31	36.64	121.63	30.77	0.138	0.713
Total	648.14	128.34	629.15	172.31	639.00	148.43	0.107	0.747
Pre-BSAI (N=27)	8.57	2.38	9.38	3.18	8.96	2.77	0.573	0.456
Post- MRS (N=29)								
Relaxation	130.00	31.30	114.77	40.29	123.17	35.77	1.315	0.262
Happiness	124.69	30.71	112.62	43.25	119.28	36.67	0.771	0.388
Energy	71.50	46.94	54.77	36.15	64.00	42.57	1.113	0.301
Clear-headedness	128.81	27.20	116.69	35.04	123.38	30.98	1.101	0.303
Easy-goingness	124.81	23.04	115.69	37.56	120.72	30.17	0.647	0.428
Confidence	131.44	22.81	121.69	37.63	127.01	30.16	0.742	0.397
Total	711.25	109.88	636.62	194.63	677.79	155.34	1.697	0.204
Post-BSAI (N=29)	7.69	2.52	9.31	4.40	8.41	3.52	1.549	0.224

Assessment Six (4 weeks post radiotherapy follow-up)

There were no significant between-group differences in any of the psychosocial parameters. Twenty nine patients completed the HADS and FACT-G and 28 completed the MRS and PSQ (Table Seven). According to the HADS, three (10%) were clinically anxious and one (3%) was clinically depressed (all in the HYPREL group).

Table Seven: Assessment 6 (Follow-up)

	Hypnotherapy		**Self Initiated Support**		**Total**			
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	F ratio	p value
FACT-G (N=29)								
Physical	20.27	5.98	23.57	4.33	21.86	5.42	2.669	0.102
Social/Family	22.13	5.55	22.86	2.77	22.48	4.38	0.192	0.665
Emotional	17.53	5.97	19.71	4.39	18.59	5.29	1.239	0.275
Functional	20.33	5.38	20.07	6.20	20.21	5.68	0.015	0.904
Total	80.27	19.10	86.21	12.42	83.14	16.23	0.927	0.333
HADS (N=29)								
Anxiety	6.73	4.56	4.36	2.62	5.59	3.88	2.904	0.100
Depression	4.07	4.32	2.50	2.36	3.31	3.61	1.385	0.249
Total	10.80	8.28	6.86	4.35	8.90	6.86	2.320	0.124
MRS (N=28)								
Relaxation	112.33	42.74	103.46	41.97	108.21	41.84	0.305	0.588
Happiness	109.13	45.73	113.15	38.70	111.00	41.89	0.062	0.805
Energy	46.73	42.03	47.23	29.36	46.96	36.04	0.001	0.972
Clear-headedness	103.13	44.28	123.08	35.32	112.39	40.91	1.698	0.202
Easy-goingness	99.20	42.73	112.62	42.72	105.43	4.48	0.687	0.415
Confidence	103.13	45.15	106.08	44.79	104.50	44.17	0.030	0.864
Total	573.67	198.55	605.62	155.43	588.50	177.32	0.220	0.643
PSQ (N=28)								
Relationship with hospital doctors	3.60	0.51	3.71	0.47	3.66	0.48	0.395	0.535
Relationship with GP	3.46	0.66	3.60	0.52	3.52	0.59	0.298	0.591
Relationship with OHC	3.73	0.46	3.93	0.27	3.83	0.38	1.930	0.176
Treatment received since diagnosis	3.73	0.46	3.85	0.38	3.79	0.42	6.498	0.487
Help given from radiotherapy staff	3.64	0.50	3.86	0.36	3.75	0.44	1.696	0.204
Quality of life	4.13	1.41	3.93	1.07	4.03	1.24	0.192	0.665

DISCUSSION

The first aim of the study was to develop a brief psychological intervention that would be feasible and acceptable to patients undergoing thoracic radiotherapy. A four-session standardised programme incorporating elements of progressive muscular relaxation, cue controlled relaxation, rehearsal *in imaguo*, ego strengthening and training in auto-hypnotic induction was developed successfully for live therapy as well as for home practice using an audio recording. Of 52 patients initially identified as suitable for the study, eight declined because of the time commitment and two did not wish to attend the Oncology Health

Centre, thereby giving an acceptability rate of 81%.

From the point of view of the therapists (clinical psychologists), the intervention proved entirely feasible; no particular problems were encountered using the protocol, and no adverse reactions were observed. Although formal records of home practice were not kept, most patients said that they practiced regularly and enjoyed the programme. Some also reported that their general coping had improved also. Levels of satisfaction with treatment, and with the Oncology Health Centre, as assessed by the PSQ were very high in both groups (Table Seven).

The second aim of the study was to carry out a preliminary evaluation of the effects of the intervention on respiration and quality of life during planning and radiotherapy. The main finding is that patients randomised to HYPREL tended to show less variability in amplitude during the radiotherapy planning CT scan ($p=0.059$). Reduced variability in respiratory amplitude should have permitted more efficient radiotherapy planning. In addition, if reduced amplitude of respiratory motion correlates with reduced tumour movement, techniques such as those used by the HYPREL group might be useful as an adjunct to respiratory gating to allow the treatment of a smaller volume of normal tissue while still adequately encompassing the tumour. This is therefore an encouraging finding. It should be noted that this reduction in amplitude was not associated with an increase in respiratory frequency or frequency variability, and the higher variability in respiration rate in the SIS group at baseline was no longer apparent at radiotherapy planning.

It is tempting to assume that the reduced variability in respiratory amplitude was associated with reduced procedure-related anxiety or more general distress. However, examination of the MRS and BSAI data, both immediately before and immediately after, radiotherapy planning do not show a significant between-group difference for any variable, although it should be noted that anticipatory anxiety was low in both groups. For example, the overall pre-planning mean score of 9.69 is lower than we obtained in a national mammography study where women scored 11.3 before receiving an X-ray (Hutton *et al*, 2011).

No significant intervention effects on respiration, or quality of life, were observed during

radiotherapy, and this is, at first sight, surprising, given that radiotherapy is known to cause anxiety and that relaxation-based interventions have been shown to reduce anxiety in women undergoing radiotherapy (Bridge *et al*, 1988). A number of factors may have contributed to this. First, for practical reasons to do in part with scheduling radiotherapy sessions (see below), the number of patients for whom respiration data were available reduced as the study progressed (baseline - N=28; radiotherapy planning - N=27, first fraction of radiotherapy - N=25, tenth fraction - N=18; and final fraction - N=18), thereby reducing statistical power. Statistical power was reduced further at Assessment Five, where the two groups were unbalanced (11 patients randomised to SIS and 7 patients randomised to HYPREL). Second, our cohort as a whole had a very low incidence of psychiatric morbidity throughout the trial. For example, using a cut-off score of 10 on the HADS, at baseline 3 (9%) were clinically anxious, and 0 (0%) were clinically depressed; at the final follow up, 3 (9%) were clinically anxious, and 1 (3%) was clinically depressed. Crawford *et al* (2001) administered the HADS to a non-clinical sample, broadly representative of the general adult UK population (N = 1792) in terms of the distributions of age, gender and occupational status. They found that 12.6% scored above this cut-off for anxiety and 3.6% scored above this for depression, which is a higher point prevalence of morbidity than we observed in our population either at baseline or at the final assessment. Finally, in order to assess baseline respiration, patients in both groups had to be assessed in the radiotherapy planning suite, thereby possibly decreasing their anxiety during radiotherapy planning because of the well known effects of *in vivo* exposure.

Three statistically significant between-group differences occurred by chance, that is they were obtained at baseline before randomization. At baseline, patients subsequently randomised to SIS showed greater variability in respiration frequency, and patients subsequently randomised to HYPREL scored significantly higher on the Functional Assessment of Cancer Therapy (Physical) scale, indicating fewer physical symptoms/greater physical wellbeing. Also, patients randomised to SIS showed a trend towards higher hypnotic susceptibility (p=0.057). Although there are no obvious reasons to suggest that these differences influenced the trial outcome, the size of the study precluded the use of statistical adjustment, for example by using analysis of covariance, which would have allowed these baseline differences to be taken into account in the analysis.

Although the study was successful in achieving its objectives, it should be noted that a number of practical difficulties were encountered and these should be addressed if the intervention is to be evaluated definitively in a fully powered randomised controlled trial. First, in clinical practice, the aim is to provide the patient with the best possible streamlined service. This may involve taking advantage of planning slots which become available at short notice, thereby making it difficult to carry out baseline and other assessments according to the research protocol. Second, although there were no difficulties in obtaining almost complete psychosocial data (see completion data in Tables Two – Seven), the same was not true of the respiration data. As indicated above, for practical reasons to do in part with scheduling radiotherapy, the number of patients for whom respiration data were available reduced as the study progressed. Also, although the plan was to assess respiration over 40 breathing cycles per session, this did not always prove possible. Although the mean number of breaths recorded per session was 36, with a standard deviation of 15, the range was 14-79. In a busy NHS radiotherapy department, with limited staff and facilities and 10 minute slots, scheduling sessions when staff and facilities are available to do the respiration measurements can be problematic in the absence of dedicated staff and facilities.

In conclusion, a feasible psychological intervention and protocol have been developed for use in patients undergoing thoracic radiotherapy. Initial evaluation has found the intervention to be widely acceptable and free from adverse effects. Preliminary evaluation suggests that it may reduce respiratory amplitude variability during radiotherapy planning and this may be beneficial in terms of optimisation of planning.

We have reported data which can now be used to inform the sample size calculations for a full-scale, properly powered, randomised trial (Vickers and Altman, 2001). We have also identified issues that would need to be addressed in order to ensure that such a trial reached a satisfactory and definitive conclusion.

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Appendix One

Varian RPM - Uncertainty in Measurement

Andrew Greenhalgh
Radiation Physicist

Summary

The RPM system vertical displacement measurement was tested using the 2-marker block at various positions to check that RPM measurements were accurate and repeatable. Plastic Water (PW) was used to position the block at different heights above the couch. RPM measurements were found to have a combined uncertainty of ±0.5mm for the range of measures made.

Introduction

The Varian RPM system is designed for use on CT and Linacs for respiratory gating of patient radiotherapy treatments. It uses a simple system of an infrared camera and LED array, and a patient-mounted plastic block with two reflective dot markers. The system monitors the real-time vertical position of the marker block during the patient's breathing cycle and calculates displacement based on the number of pixels between the two dots on the image which are a known distance apart (3±0.1cm).

A brief investigation into the accuracy of this calculation was carried out in order to validate the system for measuring relative vertical position over a range of feasible marker block locations during patient measurements. It was hoped that this would show that there was no need for a calibration check before each individual patient measurement. A desirable level of uncertainty in relative vertical distance is ±0.5mm, but ±1mm would be acceptable.

The camera in CT is couch mounted, so the couch vertical movement could not be utilised for displacement, the supplied respiratory motion phantom from Varian is not suitable for calibration measurements as it only produces a fixed amplitude sine wave, so a different method was required to achieve known vertical displacements. Sheets of CIRS Plastic Water (PW) are used in the department and come in a range of thicknesses from 1mm-50mm with uncertainty in thickness measured in department as ±0.01mm. This represents a simple and accurate method of achieving vertical displacement of the 2-marker block.

Method

The camera and marker block were set up, so that the block was in line with the F3 couch marker (130cm between block and camera) and elevated by 15cm PW in the centre of the couch with the camera angled and focused so that the marker dots were visible towards the bottom-centre of the screen to allow space to further elevate the marker without needing to readjust the camera. The RPM system was then used to track the marker as PW was added underneath, increasing height by 1mm, 2mm, 5mm and 10mm PW. These were repeated ten times to obtain a measure of consistency. Care was taken so that the marker blocks position laterally and longitudinally was as consistent as possible. The camera was not adjusted throughout all these measurements.

The data files were then exported and opened with a Matlab program which allowed display and analysis of the traces so that vertical displacement, relative to baseline 15cm, could be measured and compared to Plastic Water thickness.

Results

	Baseline	0.1cm	0.2cm	0.5cm	1cm
Mean RPM Output (cm)	-0.681	-0.591	-0.485	-0.168	0.345
Relative to Baseline (cm)	0.000	0.090	0.196	0.513	1.026
95% CI	0.031	0.035	0.032	0.022	0.036

Table 1

The first row of Table 1 shows the mean RPM output values at each height as obtained from the raw RPM data file using the Matlab program. The second row shows these values offset, so that the baseline is zero and the other heights are relative to this. The third row shows the 95% confidence intervals (CI), calculated as 2*SD (standard deviation) of the ten repeated measures at each height. These results were then analysed in order to calculate total uncertainty in measurement for each displacement, shown in Table 2 below. Error in RPM Output is the percentage difference between the Mean RPM Output and the actual PW thickness. Uncertainty in Baseline and Measure Point are both derived from the 95% CI and take account of the inter-measurement variability of RPM output. Uncertainty in PW thickness as stated before is ±0.01mm. These errors are all expressed as percentages of the measurement and added in quadrature to determine the total percentage uncertainty. This is then multiplied by the displacement to obtain the Total Uncertainty (cm).

Displacement (cm)	Error in RPM Output (%)	Uncertainty in Baseline (%)	Uncertainty in Measure Point (%)	Uncertainty in PW thickness (%)	Total Uncertainty (%)	Total Uncertainty (cm)
0.1	0.1	0.31	0.35	0.01	0.48	0.048
0.2	0.002	0.155	0.16	0.005	0.22	0.045
0.5	0.026	0.062	0.044	0.002	0.08	0.040
1	0.026	0.031	0.036	0.001	0.05	0.054
					Mean Total Uncertainty (cm)	0.047
					SD Total Uncertainty (cm)	0.006

Table 2

Conclusion

Following error analysis of 10 repeated increments of 1, 2, 5 and 10 mm at 15cm above couch at the F3 couch marker; a total uncertainty of 0.47±0.06mm SD over this range of measurements was determined. There is no reason to suspect that this uncertainty would increase at larger displacements, so a figure of ±0.5mm is a reasonable uncertainty to quote with displacement measurements made using the RPM system over the clinically significant range.