BMJ Open

Benefits of cardiac coherence combined with medical hypnosis on preoperative anxiety before cancer surgery: the COHEC II study trial protocol

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To cite: Amraoui J, Bordenave L, Leclerc G, *et al*. Benefits of cardiac coherence combined with medical hypnosis on preoperative anxiety before cancer surgery: the COHEC II study trial protocol. *BMJ Open* 2023;**13**:e072215. doi:10.1136/bmjopen-2023-072215

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-072215).

Received 26 January 2023
Accepted 29 November 2023

Check for updates

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ABSTRACT

Introduction Preoperative anxiety is a frequent problem that can lead to complications both during anaesthesia and in the postoperative period, especially in oncology. Studies have shown that it can be managed using non-pharmacological approaches, but few works have evaluated psychoeducational programmes. The aim of the COHErence Cardiaque (COHEC) II Study is to evaluate the combination of medical hypnosis (MH) and cardiac coherence (CC) training to manage preoperative anxiety in patients with cancer.

Methods and analysis COHEC II is an ongoing multicentre randomised clinical trial carried out in three French comprehensive cancer centres. In total, 296 patients who will undergo surgery for cancer will be recruited during 18 months and will be randomised in the control arm or the intervention arm. Patients in the intervention arm will follow a daily programme that combines MH and CC, starting 7 days before surgery. The control arm will receive the standard treatment to manage preoperative anxiety. The primary endpoint is the anxiety level on surgery day, measured using a Visual Analogue Scale. Secondary endpoints are patient adherence to the programme, satisfaction and postsurgery recovery quality.

Ethics and dissemination The study protocol was approved by the French Ethics Committee (Comité de Protection des Personnes EST-II) on 24 November 2021 and will be carried out following the good practice guidelines and the Declaration of Helsinki. Results will be published in peer-reviewed journals and presented at conferences.

Trial registration number NCT05197972.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is one of the first controlled, large-scale, multicentre, randomised trials to assess medical hypnosis combined with cardiac coherence to manage preoperative anxiety, especially in patients with cancer.
⇒ This approach will offer to patients undergoing surgery free and non-pharmacological techniques that they can use independently throughout the entire care process.
⇒ A previous study showed the feasibility of this approach and the present study may also provide updated information on the incidence of anxiety in surgical oncology.
⇒ The results of the study could change the day-to-day management of patients in surgical oncology by offering specific treatments to patients with high anxiety levels, especially before undergoing surgery.
⇒ A selection bias may occur if many patients with very high (fear of information overload) or very low anxiety level (intervention programme deemed unnecessary by them) refuse to participate.

INTRODUCTION

Preoperative anxiety is a common problem in patients undergoing surgery.[1 2] Its prevalence varies widely among studies and populations, ranging from 40% to 60% in children and up to 80% in adults. Preoperative anxiety is more frequent in patients with cancer, preoperative pain, psychiatric disorders and depressive symptoms or in women.[3–6]

Different approaches can be proposed to patients to manage anxiety. The standard treatment is the administration of a short-acting anxiolytic on the morning of surgery.[7–11] However, its use has become more complex due to changes in clinical practice, including the implementation of the Enhanced Recovery After Surgery programme and the development of outpatient surgery.[7 8] In addition, a growing number of studies have highlighted potential side effects.[12] For example, Maurice-Szamburski *et al* showed that systematic premedication with anxiolytics may be associated with delayed extubation and memory and cognitive impairment in some patients.[12] Therefore, new approaches have been developed, including non-pharmacological interventions.[3] Several studies on medical hypnosis (MH) before surgery found that MH significantly reduces pain, improves recovery and

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decreases treatment duration and negative effects.[13] In their meta-analysis, Montgomery *et al* confirmed that MH reduces pain, anxiety and psychological and physical distress in patients undergoing surgery.[13] Music therapy also can reduce anxiety and improve depression scores and patient satisfaction.[14–17] Similarly, techniques based on personalised videos or handheld games seem to reduce preoperative anxiety in children, although more investigations are needed.[18] Combinations of different approaches also have been successfully tested. Touil *et al* showed that virtual reality, combining music and MH, can reduce preoperative anxiety in patients undergoing locoregional anaesthesia.[19] However, we observed that some patients are no longer receptive to these techniques when they arrive in the operating theatre, especially those with the highest anxiety levels. Alternatives are needed for such patients. Gade *et al* evaluated cognitive behavioural therapy for the management of preoperative anxiety and showed that it significantly reduces patient anxiety and improves patient satisfaction.[20] However, it requires long-term supervised practice, which is not compatible with surgical oncology.

McEwen *et al* thoroughly described the physiopathology of anxiety that involves complex interactions between different structures of the central nervous system (CNS), including the limbic system, the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal axis.[21] The limbic system interacts with the brainstem, the hypothalamus and the prefrontal cortex through various mediators, such as steroids, norepinephrine, serotonin, gamma-aminobutyric acid and brain peptides. In stress conditions, these mediators, which are mainly controlled by the ANS, modify the synaptic activity, resulting in structural and functional changes in the neural architecture. Other physiological systems, such as the metabolic and the immune systems, also are modulated in response to stress conditions.[21]

To overcome anxiety, we propose an innovative approach that associates cardiac coherence (CC) and MH to regulate the CNS, particularly the ANS. CC is a breathing technique in which the respiratory frequency is controlled to regulate the ANS. By controlling their inspiratory and expiratory times, patients can achieve an optimal balance between the sympathetic and parasympathetic systems to reach a state of well-being and relaxation.[22 23] MH has multiple effects on the CNS and modifies the interbrain connectivity of several cerebral regions to facilitate the disconnection of critical consciousness. Consequently, patients become less aware of their environment and focus on their feelings and emotions.[24 25] MH effects are also mediated by psychological and cognitive factors. Montgomery *et al* showed that expectations of positive responses to MH were associated with a reduction in postoperative emotional distress in patients undergoing breast surgery.[26]

We hypothesised that patients will benefit from a preoperative programme (called 'COHErence Cardiaque' (COHEC)) that combines CC and MH and that is started several days before surgery. On surgery day, patients can use these techniques to manage anxiety. Our recent feasibility study (NCT03981731) in 53 patients gave encouraging results on the COHEC programme: 79.1% (95% CI: 64.0% to 90.0%) of adherence in the per-protocol population and >80% of satisfaction. We now propose to evaluate the COHEC programme in a randomised multicentre trial. The primary outcome will be the anxiety level on surgery day. The main secondary outcomes will be the anxiety level changes between inclusion and surgery, patient satisfaction and postsurgery recovery quality.

METHODS

Aims, study design and settings

Primary objective

The primary objective of the COHEC II study is to evaluate the efficacy of a psychoeducational programme that combines CC and MH, implemented several days before cancer surgery, for managing preoperative anxiety in patients with cancer.

Secondary objectives

Secondary objectives include:

- Patient adherence to the COHEC programme schedule.
- Anxiety level and causes (anaesthesia, surgery, risk of surgery delay due to COVID-19, fear of the unknown or of the cancer) at the pre-anaesthesia consultation.
- Change in anxiety level between the pre-anaesthesia consultation and the day of surgery.
- Anxiety frequency and level in patients undergoing surgery for cancer and identification of the profile of patients who are the most likely to experience anxiety on surgery day.
- Effects of the COHEC programme on the patients' use of anxiolytics before surgery.
- Benefits of the COHEC programme on the hospital stay length according to the surgical type and magnitude.
- Effect of the COHEC programme on the amounts of hypnotic and opioid administered during anaesthesia induction.
- Effect of the COHEC programme on adverse events (pain, fatigue, agitation, nausea and vomiting).
- Assessment of the patients' perioperative experience, recovery and satisfaction.
- Assessment of chronic postoperative pain.

Study design and settings

The COHEC II study is a prospective, multicentre, randomised trial carried out in three French comprehensive cancer centres: Montpellier Cancer Institute, Montpellier; Claudius Régaud Institute, Toulouse; and Gustave Roussy Institute, Villejuif. The study is open for recruitment since April 2022, and should be completed in 21 months (18 months for patient recruitment and

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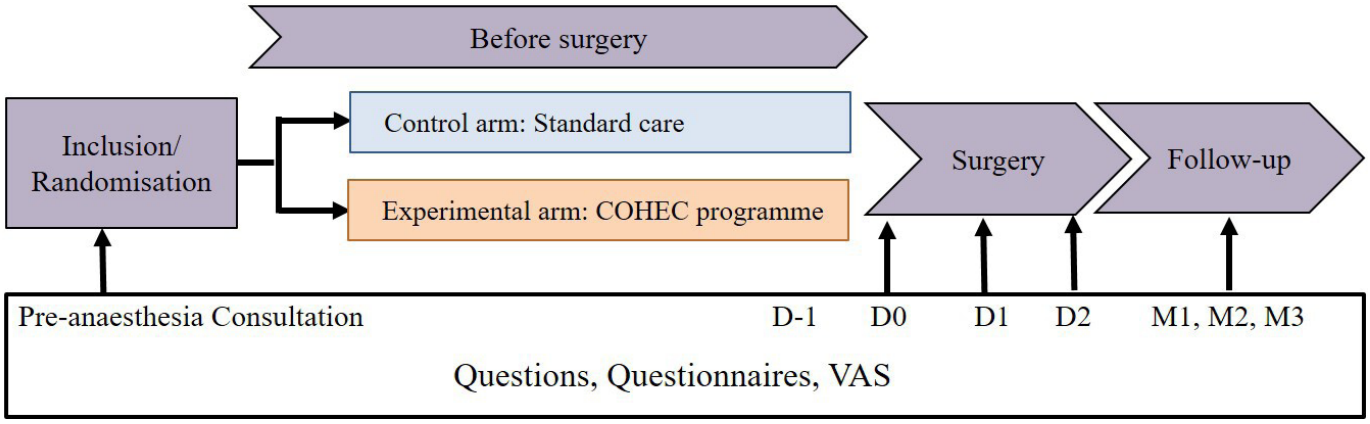

Figure 1 Schematic diagram of the study. COHEC, COHErence Cardiaque; D0, day of surgery; D–1, 1 day before surgery; D1 and D2, 1 and 2 days after surgery; M1–3, month 1 to 3 after surgery; VAS, Visual Analogue Scale.

3 months for the follow-up). The study will include 296 patients undergoing surgery for cancer.

Patients will be included during the pre-anaesthesia consultation at least 7 days before the planned surgery. Eligible patients who agree to participate will sign an informed consent form before enrolment. They will be randomised in the intervention arm (COHEC programme) or the control arm (standard care). The COHEC programme is initiated at least 7 days before surgery and continues daily until surgery day (D0) (see figure 1 for the study timeline). Table 1 summarises the data collection schedule.

Participants

Sample size

We hypothesised that the intervention would have a positive effect on preoperative anxiety compared with standard care, with a reduction of the Visual Analogue Scale (VAS) scores for anxiety (score ranging from 0 to 100, 0=no anxiety). Sample size was calculated based on an

Table 1 Data collection schedule

	Pre-anaesthesia consultation	D–15 to D–2	D–1	D0	D1	D2	M1–M3
Baseline participants' characteristics*	✓						
CC and MH sessions†		✓	✓	✓			
ASA Score	✓						
Apfel Score‡	✓						
GAD-7	✓						
APAIS	✓						
EVAN-G						✓	
QoR-15					✓		
ISI Scale	✓		✓		✓		
VAS for anxiety causes§	✓						
VAS for anxiety, pain and fatigue	✓			✓¶	✓		✓
VAS for satisfaction					✓		

*Includes demographic (age, sex), socioeconomic and clinical data (medical history, anxiolytic and depressant intake).
†For the intervention arm only, sessions recorded with the Exolis e-health application.
‡Identification of patients at high risk of postoperative nausea and vomiting.
§Each potential cause of anxiety (ie, anaesthesia, surgery, risk of surgery delay due to COVID-19, fear of the unknown or of the cancer disease) is assessed with a dedicated VAS.
¶Assessed three times: just before surgery, in the PACU and 3 hours after discharge from the PACU.
APAIS, Amsterdam Preoperative Anxiety and Information Scale; ASA, American Society of Anesthesiologists; CC, cardiac coherence; D0, surgery day; D1 and D2, days 1 and 2 after surgery; D–15 to D–1, from day 15 to day 1 before surgery; EVAN-G, Evaluation du Vécu de l'ANesthésie Générale (French questionnaire to assess perioperative satisfaction concerning anaesthesia); GAD-7, Generalised Anxiety Disorder-7 items; ISI, Insomnia Severity Index; MH, medical hypnosis; M1–M3, months 1–3 after surgery; PACU, post-anaesthesia care unit; QoR-15, Quality of Recovery-15 items; VAS, Visual Analogue Scale.

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expected difference of at least 10 points in the mean VAS Score of preoperative anxiety between arms, according to the results of the HYPNOSEIN study and the study by Kain *et al*.[27 28] Assuming a mean VAS-anxiety score of 40 in the control arm, this would correspond to a reduction of at least 25% in the intervention arm. With 90% power (β=0.10), a two-sided α risk of 0.05 and assuming a SD of 25, 133 patients per arm are required to detect such a difference.[29] Considering 10% of patients as non-evaluable, a total sample size of 296 is required (148 patients per arm). Sample size was calculated based on a comparison of mean values using the Student's t-test and the Sample Size Tables for Clinical Studies software.[30]

Inclusion criteria

Patient who meet all the following criteria are included:

- Patients older than 18 years of age.
- Patients undergoing surgery for suspected or declared cancer, as inpatients or outpatients.
- Patients undergoing surgery that requires general anaesthesia, with or without associated locoregional anaesthesia.
- Patients with a smartphone, tablet or computer and who are willing to install and use a digital health software application.
- Patients enrolled at least 7 days before surgery.
- Patients who signed the informed consent form.
- Patients covered by the French social security system.

Exclusion criteria

Exclusion criteria are:

- Patients undergoing emergency, plastic (eg, lipomodelling) or prophylactic surgery (no suspected or confirmed cancer).
- Patients with bradycardia (<50 beats/min), whether treated or not with β-blockers.
- Patients with severe heart failure.
- Patients with uncontrolled chronic pain for more than 3 months and treated with morphine derivatives.
- Patients with unstable epilepsy or respiratory pathology with resting dyspnoea.
- Patients already using relaxation techniques such as yoga, hypnosis, sophrology, meditation, music therapy and virtual reality.
- Patients with medical (eg, neurological, psychiatric) or psychological conditions that could prevent participation in the study.
- Patients who are deaf without hearing aids.
- Patients under legal protection (eg, guardianship, curatorship).

Randomisation

Patients who meet the eligibility criteria and sign the informed consent form will be randomly assigned to the intervention (COHEC programme) or the control arm (standard care) in a 1:1 ratio. The randomisation procedure uses a randomised design and is stratified by centre and patient anxiety level at inclusion, assessed with the VAS-anxiety (VAS<40, between 40 and 60 or ≥60 out of 100). Patients are not blinded to the randomisation.

COHEC programme

The COHEC psychoeducational programme combines MH and CC approaches. First, patients are asked to follow a daily programme with both techniques at home. Patients are trained by the investigator at inclusion. A booklet is also provided by the investigator to help patients in their daily CC practice. This programme must be followed for at least 7 consecutive days and up to 15 days using the Exolis e-health application (HOPPEN Society, Cesson-Sevigné, France). Then, patients can use MH and CC to manage anxiety on surgery.

MH intervention

Two scripts of standardised MH practice, based on the Ericksonian approach, were developed by a research team member (JA, an anaesthesiologist with expertise in MH) and reviewed by an independent panel of experts and a patient committee. The two scripts (sessions) were recorded with a female voice over a very discreet musical background (piano or flute). The first session is based on calm breathing. Patients are encouraged to focus on their breathing for 8 min by visualising the transport of oxygen bubbles throughout the body. In the second session, patients are invited to imagine themselves in a safe place. This session lasts 15 min. Both sessions are available on the application. During the training period, each patient can choose between these MH sessions. The calm breathing session is used for 3 min during the preoxygenation phase before anaesthesia on surgery day.

CC intervention

CC sessions are based on a breathing approach, called the '365 method'.[31–35] At least three times per day (in the morning, before meals and at the day end), patients are invited to practise a breathing technique consisting of 6 breaths/min for 5 min. Each breathing cycle consists of 5 s of inhalation and 5 s of exhalation. Patients inhale through the nostrils while the abdomen expands. They exhale through the mouth while the abdomen flattens. The application provides a support video (a bubble that rises and falls as the breathing cycle progresses) that can be used to perform the breathing technique.

Procedure

Pre-anaesthesia consultation

At inclusion, after signing the informed consent form, all patients will undergo a 30–45 min individual interview. The investigator will explain the care process before, during and after surgery, including the anaesthesia modalities, and will record the baseline patient characteristics. The investigator will give information on the study in function of the arm in which the patient is randomised and also a video of the operating theatre and the link to the cancer centre website. Additional information on the COHEC programme and a training are provided to patients in the intervention arm.

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All patients must install an application to fill in the study questionnaires. This application will also be used to record the patients' adherence to the COHEC programme, to send reminders (SMS) and to provide audio and video support for the MH and CC sessions to the patients in the intervention arm.

All patients will receive a prescription for a short-acting anxiolytic (oxazepam 10 mg) that they can take on the morning of surgery, if necessary. Alternatively, patients can take their usual medication, if similar.

COHEC programme

Patients in the intervention arm must follow the COHEC programme via the application for at least 7 days, and up to 15 days before surgery, as detailed in the 'COHEC programme' section. Patients should do at least three CC sessions and one MH session per day. The control arm will not receive any treatment.

Surgery day

All patients will receive the standard care on the morning of surgery, according to each cancer centre practice. Patients in the intervention arm will perform the COHEC programme before arriving in the operating theatre, as they would normally do at home. In the operating room, the anaesthesiologist will perform a 3 min preoxygenation session, during which patients in the intervention arm will be invited to use the CC breathing technique while listening to the calm breathing MH session. The control arm receives only standard preoxygenation. Then, anaesthesia induction is performed according to each cancer centre practice and good practice guidelines. The anaesthetic protocol will be chosen by the anaesthesiologist in function of the type of surgery and complexity. Usually, it includes hypnotics (propofol), opioids (sufentanil) and muscle relaxants (cisatracurium besilate, rocuronium bromide). Other molecules may be used depending on the surgery (eg, lidocaine, ketamine, clonidine, magnesium). Patients' anxiety is assessed on arrival in the surgery theatre reception area, in the post-anaesthesia care unit (PACU) and 3 hours after discharge from the PACU (+3 hours). The monitoring protocol is left to medical staff's discretion.

Outcome measures

Primary outcome measures

The primary endpoint is the anxiety level at D0 on arrival in the operating theatre, using a VAS-anxiety (score ranging from 0 to 100).

Secondary outcome measures

Adherence to the COHEC programme is defined as the completion of at least 2/3 of the proposed MH and CC sessions per day for at least 5 days. VAS (score from 0 to 100, 0=no problem) will be used to evaluate outcomes related to patient anxiety, fatigue, satisfaction, pain and chronic pain.[36] A specific VAS (score from 0 to 100, 0=not present) will be used to assess each potential cause of anxiety: anaesthesia, surgery, risk of surgery delay due to COVID-19, fear of the unknown and fear of the cancer disease. The anxiety level and profile will also be assessed with the Amsterdam Preoperative Anxiety and Information Scale and the Generalised Anxiety Disorder-7 items Scale.[37 38] The Insomnia Severity Index-7 items (score from 0 to 28, 0=no sleep problem) will be used to assess sleep quality.[39] The quality of recovery from anaesthesia and surgery will be assessed with the Quality of Recovery-15 Questionnaire.[40] The anaesthesia experience will be assessed using the 'Evaluation du Vécu de l'Anesthésie Générale' Questionnaire (French questionnaire to assess the perioperative experience concerning anaesthesia).[41] Table 1 shows when each scale and questionnaire will be completed by the patients.

To determine patients' intake of anxiolytics before surgery, the names and doses of each drug will be recorded in both arms. The use of propofol and morphine derivatives during anaesthesia induction, the names and doses of all drugs used in the perioperative period will be reported by the medical staff. The occurrence and management of adverse events (eg, pain, nausea, vomiting) will be reported by the medical staff as well as the hospital stay length.

Data collected

Baseline patient characteristics include demographic (age, sex), socioeconomic and clinical data (medical history including previous surgery, anxiolytic and depressant intakes) and also use of relaxation techniques, tobacco/alcohol/illegal substance consumption, anxiety-depressive disorder and American Society of Anaesthesiologists and Apfel risk scores.[42]

Other data related to preoperative use of anxiolytics (anxiolytics, antidepressants and opioids), doses of hypnotics and opioids used for anaesthesia induction, surgical procedure magnitude (minor/intermediate/major), surgery type, other information related to anaesthesia and surgery, adverse events (eg, surgical site pain, nausea, vomiting), postoperative mobilisation and feeding will be collected.

Data collection and management

Adherence to CC and MH sessions and their duration will be automatically collected via the application. Participants will use the application to complete the different VAS, questionnaires and answer questions throughout the study. Anxiety before randomisation will be assessed by the investigator using VAS-anxiety. At D0, before surgery and in the PACU, a medical staff member not involved in the study and blinded to the randomisation will assess the patients' anxiety using the same VAS. At +3 hours, patients will complete the VAS Questionnaire on their own, with the help of a nurse blinded to the randomisation, if needed. In hospital, and in the event of application failure, paper forms of the questionnaires will be used and the score recorded on the Exolis digital platform.

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Data not collected via the application are recorded using an electronic case report form (eCRF) in the Ennov Clinical software. Data from the eCRF and the application will be merged at the study end and uploaded into a database for analysis. The Montpellier Cancer Institute Biometrics Unit is responsible for data management and analysis. Consent forms will be kept at the centre where the patient is enrolled. All data sent by the centres to the sponsor will be deidentified. Data and sign consent forms will be kept for at least 15 years.

Statistical analysis

A detailed statistical analysis plan will be drafted before the database is locked for the final analysis. Analyses will be performed according to the intention-to-treat principle. In case of a significant difference between the intention-to-treat and per-protocol populations, a per-protocol analysis will also be performed. All tests will be two-tailed and p-values<0.05 will be considered statistically significant.

All VAS scores, including the anxiety level at D0 just before surgery (primary endpoint), will be treated as continuous variables. The Student's t-test will be used to compare the mean VAS scores for preoperative anxiety (primary endpoint) between arms. The effect size will be calculated to characterise the magnitude of the difference. An additional analysis will be performed to adjust for potential confounders, such as use of premedication.

For descriptive analyses, categorical variables will be summarised as number of observations and percentages and continuous variables as medians and ranges. Comparisons between arms will be performed using the χ^2 or Fisher's exact test (for expected frequencies<5) for categorical variables and the Student's t-test or Mann-Whitney-Wilcoxon test for continuous variables. Adherence to the COHEC programme (intervention arm) will be presented with its 95% CI. The mean VAS scores for anxiety and causes of anxiety at the pre-anaesthesia consultation will be presented with their 95% CI (CI for means); the VAS-anxiety score at the pre-anaesthesia consultation will be compared between arms using the above-mentioned test for continuous variables. Changes in VAS-anxiety score between the pre-anaesthesia consultation and surgery will be evaluated in the whole population and in each arm using the Wilcoxon matched pairs signed-rank test. The percentage of patients, in the whole sample and in each arm, with a monitoring or blunting coping style will be presented. A logistic regression adjusted for arm and baseline variables will be used to identify the patient profiles associated with high preoperative anxiety levels.

Patient and public involvement

The patient committee for cancer clinical research of 'La Ligue contre le Cancer' was consulted concerning the study synopsis, the informed consent form and information document. Participants will have access to the study results on request. Participants in the control arm will be offered the COHEC programme at the study end.

ETHICS AND DISSEMINATION

This research will be conducted in accordance with the French Public Health Code, the Good Clinical Practice and the Declaration of Helsinki. This study has been registered on clinicaltrial.gov (NCT05197972). It has been approved by the local ethics committee (Comité de Protection des Personnes EST-II, accepted on 24 November 2021) and the 'Agence nationale de sécurité du médicament et des produits de santé' (French National Agency Authority for the Safety of Health Products) has been informed (6 January 2022). The patient committee for cancer clinical research of 'La Ligue contre le Cancer' has been consulted concerning the study synopsis, the informed consent form and the information document.

The investigator will inform all patients about the study objectives and procedures before enrolment. The informed consent form will be signed by all patients before the study start. Patients may withdraw from the study at any time, for any reason, without any consequence or prejudice on their treatment.

In the event of a substantial protocol change, a request will be submitted to the ethics committee for approval. Once approved, the amended version will be sent to all investigators.

On study completion, participants will have access to the results on request. Results will be published in peer-reviewed journals and presented at national and international conferences. Participants in the control arm will have access to the COHEC programme at the study end.

DISCUSSION

In this study, we propose to evaluate a psychoeducational programme (COHEC) that combines MH and CC to help patients undergoing surgery for cancer to cope with anxiety. MH is a successful technique for managing anxiety in patients.[3] However, to our knowledge, the association of MH with a breathing technique, such as CC, has never been evaluated. We hypothesise that by combining MH and CC, their effects on the CNS and ANS will be potentiated and anxiety management will be improved.[24 25] This approach, based on the regulation of the pathophysiological mechanisms of anxiety, is innovative. Indeed, for the first time, it associates MH and CC, it is implemented before surgery and can be used independently by the patient on surgery day. In addition, unlike standard treatments, MH and CC are free, readily available and non-pharmacological techniques. First, patients become familiar with the COHEC programme through home practice using an e-health application. This will allow patients to use the programme independently on surgery day. The COHEC programme could help patients to manage anxiety not only on the day of surgery but also throughout the entire care process (eg, biopsies, CT and

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MRI scans). Moreover, the short duration of the home practice to become familiar with the programme allows proposing this tool to patients undergoing surgery in short term, which is often the case in oncology. This tool could also reduce the use of drugs, including anxiolytics, before surgery and of anaesthetic drugs during surgery. This could limit the side effects often observed with pharmaceutical approaches. The main limitation of the study is linked to the anxiety profile of the patients who accept to participate in the study. Indeed, the results could be biased if the most and least anxious refuse to participate. To limit this, patients will be randomised at inclusion according to their anxiety level, assessed with VAS-anxiety.

CONCLUSION

Preoperative anxiety is a common unpleasant experience that significantly affects patients undergoing surgery for cancer. The results of this study will provide information on the efficacy of the COHEC programme to manage anxiety, its benefits in terms of anxiolytic and anaesthetic drug consumption and patient well-being. This study will also provide insights into the frequency and levels of anxiety in patients with cancer undergoing surgery and will help to identify patients who are the most likely to be anxious on the surgery day in order to personalise their management. We hope that this programme will provide a new tool for patients to reduce anxiety and control over their feelings and emotions.

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Acknowledgements The authors thank the patient committee for cancer clinical research of 'La Ligue contre le Cancer' for their feedback, comments and suggestions on the study synopsis, informed consent form and information document. The authors also thank Dr Fanny Salasc of the Montpellier Cancer Institute for providing medical writing and editorial support and Dr Elisabetta Andermarcher for editing the manuscript.

Contributors All authors designed the study and/or recruited the patients. CT and MJ were responsible for the methodological and statistical design of the study. JA and CT drafted the manuscript. CF is the project manager responsible for the study. All the authors have read and approved the final manuscript.

Funding This work was supported by the French Ministry of Health (grant PHRCI-20-021).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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