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Fear of cancer recurrence in peritoneal malignancy patients following complete cytoreductive surgery (CCRS) and hyperthermic intraperitoneal chemotherapy (HIPEC): an observational study protocol

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ABSTRACT

Introduction Fear of cancer recurrence (FCR) is correlated with higher depression levels, worse quality of life and increased utilisation of healthcare services. There is no research on FCR in peritoneal malignancy (PM) patients—a rare type of abdominal cancer. This study aims to explore the prevalence, trajectory, demographic and clinical characteristics that are associated with FCR and its relationship with quality of life in PM patients.

Methods and analysis This is a cross-sectional study. Validated measures will be used to collect data on the levels of FCR (Fear of Cancer Recurrence Inventory-Short Form) and quality of life (36-Item Short-Form Health Survey) of PM patients who have had surgery in the last 5 years at the Peritoneal Malignancy Institute in Basingstoke Hospital (minimum N=260). Descriptive statistics, Pearson χ^2 tests and correlational tests will be used to analyse the data.

Ethics and dissemination Ethical approval was obtained from the HRA and Health and Care Research Wales (HCRW). The results of this study will be shared with the participants of this study, presented at conferences and PM patients' days in the form of presentations or posters, and published in a scientific journal.

Discussion The results of this exploratory study will be used to inform a multicentre observational study to explore the effect of FCR on PM patients' mental health (depression and anxiety), quality of life and healthcare utilisation which will inform a multicentre randomised controlled trial to assess the effectiveness of using evidenced-based interventions to lower FCR in PM patients.

Strengths and limitations of this study

- This is the first study to assess levels of fear of cancer recurrence (FCR) and its relation to quality of life in peritoneal malignancy (PM) patients using a cross-sectional study design.
- This study will collect cross-sectional data from PM patients in five different groups depending on time since treatment (up to 5 years postsurgery) which will allow for a preliminary exploration of FCR over time post-treatment.
- The study uses self-report measures to measure FCR and quality of life which may pose a risk of cognitive bias and may result in a recruitment bias as those with high FCR are more likely to decline to avoid the topic.

INTRODUCTION

Peritoneal malignancy (PM) is a common clinical problem. It may be metastatic from gastrointestinal tract cancers or rarely may arise as a primary neoplasm of the peritoneum, usually malignant mesothelioma.[1 2] At the Peritoneal Malignancy Institute (PMI), Basingstoke the main types of PM treated are pseudomyxoma peritonei (PMP), colorectal peritoneal metastases (CPM) and peritoneal mesothelioma. PMP is a syndrome of mucinous intra-abdominal neoplasia that usually arises from a primary mucinous tumour of the appendix.[3 4] Colorectal cancer is a common primary site of PM.[5 6] Histologically it is generally adenocarcinoma and may be mucinous or non-mucinous.[5 6] Primary peritoneal malignant mesothelioma is rare and is associated with asbestos exposure.[7] Selected PM patients undergo a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).[8] The outcome of the surgery is considered complete if all PM nodules larger than 2.5 mm are removed.[8] Unfortunately, studies have shown that PM can recur even after having complete CRS.[9] Still, there is

no study on the fear of cancer recurrence (FCR) in PM patients.

FCR is defined as 'fear or worry that cancer will return, progress, or metastasis'.[10] Patients with cancer report FCR as their number one unmet need.[11 12] It is harder to adjust to than the initial diagnosis.[13] Patients with higher FCR report lower quality of life up to 6 years post-treatment,[10] worsened relationships, difficulties at work and mental health problems such as anxiety, post-traumatic stress and depression.[10] Even though FCR is a common reaction to cancer, it can become chronic and disabling in up to 70% of patients.[10] A study on FCR among patients with colorectal cancer found that 4%–85% of them struggle with FCR, and 38% struggle with clinical/high FCR.[14] A study on FCR in patients with breast cancer found that 70% of their participants (N=218) struggled with clinical/high FCR.[11] FCR does not subside with time.[10 15] High FCR levels are correlated with an increase in healthcare cost because patients with high FCR are more likely to seek medical services for reassurance or may avoid follow-up out of fear and thus requiring more invasive treatments that could be avoided.[11] A survey with oncology health professionals found that 31% of doctors spent more than a quarter of their follow-up time addressing FCR concerns.[11]

Evidence shows that uncertainty is positively correlated with FCR levels.[15] A qualitative study that explored the experiences of PM patients found 'uncertainty' to be one of the main themes reported by patients.[16] We hypothesise that the rare nature of the disease and the uncertainty around it increases PM patients' risk of developing FCR. PM patients in the UK report relying solely on the few PM specialists available (two centres in the UK) and online groups for support because of the limited knowledge available around PM in other services.[16] For PM patients, high levels of FCR combined with limited resources to seek support might result in an increase in pressure and demand on already strained services. For those reasons, along with the negative impact of FCR on patients' mental health and quality of life, it is important to address FCR in PM patients. This study aims to assess the prevalence and trajectory of FCR, and its relationship to a number of demographic and clinical characteristics and quality of life.

Aim

The primary outcome of this study is:

- Assess the severity levels of FCR in PM patients who have had surgery in the past 5 years, its trajectory over time, and its relationship with quality of life in PM patients postsurgery.

The secondary outcomes of this study are:

- Assess the characteristics that affect FCR in PM patients (age, gender, income, education, ethnicity, relationship status, whether they have any dependents, disease type (PMP, CPM or peritoneal mesothelioma), time since treatment (complete cytoreductive surgery (CCRS) and HIPEC), disease grade, mental health history and mental health history at time of surgery (diagnosis and prescriptions of psychotropic medications).
- Inform a multicentre observational study to explore the effect of FCR on PM patients' mental health (depression and anxiety), quality of life and healthcare utilisation to inform a multicentre randomised controlled trial to assess the effectiveness of using evidenced-based interventions to lower FCR in PM patients.

METHODS

Study design

This is an exploratory cross-sectional study.

Patient and public involvement

This protocol was shared with the patient and public involvement (PPI) group during its development to ensure the engagement of PM patients in the design process of this study. The protocol was edited based on the feedback from PM patients in the PPI group.

Participants

PM patients who had a complete CRS and HIPEC (surgery) in the last 5 years at the PMI in Basingstoke Hospital will be invited to take part in this study.

Inclusion and exclusion criteria

Inclusion criteria: PM patients who had a complete CRS and HIPEC (surgery) in the last 5 years at the PMI in Basingstoke Hospital. Exclusion criteria: below the age of 18, disease recurrence and any cognitive or language difficulties that may affect results. Participants who have also had other malignancies that they were treated for (cancer free at the time of the study) will not be excluded from this study.

Material

- Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF) will be used to measure FCR. The FCRI-SF is a 9 item Likert scale that was derived from the 42-item FCRI.[17] It is used to measure FCR by assessing the presence and severity of FCR related intrusive thoughts in patients with cancer.[17] Scores range from 0 to 36, with higher scores indicating higher levels of FCR.[17] Thirteen is the scale's suggested cut-off point as it has shown optimal sensitivity (88%) and specificity (75%) compared with the other previously used cut-off points (>16 and >22) in screening for clinical/severe FCR—which is associated with impaired physical, emotional, cognitive and social functioning.[18 19] The FCRI-SF has a strong internal consistency (α=0.95), temporal stability (r=0.89) and construct validity.[20]
- The 36-Item Short-Form Health Survey (SF-36) will be used to assess participants' quality of life. The SF-36 is a self-administered health survey that is used to assess patients' quality of life.[21] The SF-36 contains eight domains: physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general

health (5 items), vitality (4 items), social functioning (2 items), role-emotional (3 items) and mental health (5 items).[22] All items relate to the 4 weeks preceding the questionnaire's completion.[23] The SF-36 has two component summary scores: (1) Physical Component Summary which encompasses physical function, role physical and bodily pain, and (2) Mental Component Summary which encompasses social function, role emotional and mental health.[23] Total scores range from 0 to 100 with higher scores indicating a better quality of life.[21]

- Clinical and demographic characteristics will be collected to assess the relationship between them and FCR. Participants will be asked about their age, gender, income, education, ethnicity, relationship status, whether they have any dependents, disease type (PMP, CPM or peritoneal mesothelioma), time since treatment (CCRS and HIPEC), disease grade, mental health history and mental health history at the time of surgery (diagnosis and prescriptions of psychotropic medications).

Procedure

The research and data coordinator will generate a report of all the patients who have had a complete CRS and HIPEC in the last 5 years at the PMI in Basingstoke Hospital, and meet the inclusion and exclusion criteria from the hospital's database. The generated report will be ordered based on patients' surgery date and will be divided into five lists as such:

List 1	List 2	List 3	List 4	List 5
Patients who had CCRS and HIPEC in the last 0–1 year	Patients who had CCRS and HIPEC in the last 1–2 years	Patients who had CCRS and HIPEC in the last 2–3 years	Patients who had CCRS and HIPEC in the last 3–4 years	Patients who had CCRS and HIPEC in the last 4–5 years

The first 52 patients of every list will be invited to participate in this study. This will be done to ensure that participants' sample sizes are comparable over time to investigate the trajectory of FCR in the 5 years post-treatment. A copy of the participant information sheet along with a letter that explains the reason why these patients are receiving this invitation will be mailed to all potential participants. The letter will also inform participants that they will receive a call within 1–2 weeks' time from the research assistant at the PMI in Basingstoke Hospital to answer any questions they have and ask for their consent to participate. The letter will also include an email and a phone number to contact if they would prefer not to be contacted about this study. On the day of the call, the research assistant will explain the study and what it involves, answer any questions that potential participants have, and ask if they want to participate in the study (verbal consent). Participants who consent to participate will be asked whether they would like to receive the questionnaires via mail or email. Participants who choose mail will be sent an envelope that contains the participant information sheet, FCRI-SF, SF-36, demographic and clinical questions, and a prepaid return envelope. Those patients will be asked to kindly return the completed questionnaires within 2 weeks from receiving them. The research assistant will call these patients after a week of sending the questionnaires to ensure that they have received them, ask if they have any questions, and remind them to send the completed questionnaires within 2 weeks from receiving them. Participants who choose email will be emailed a link using Microsoft Forms (per the Trust's data security regulations) that contains the participant information sheet, FCRI-SF, SF-36, and the demographic and clinical questions, and asked to complete the questionnaires within 2 weeks of receiving them. Participants who receive the questionnaires by email will be sent an email 1 week later to ask if they have any questions and remind them to send the completed questionnaires in the following week. Even though it may be more accurate to collect the clinical data such as disease type and grade from the hospital's database rather than the patients themselves, for the purposes of the study (measuring FCR) it is more important what participants know/believe about their disease that is, if a patient has a high-grade disease but is unaware of it that will not affect their 'fear' of cancer recurrence. All collected data will be stored on an encrypted excel spreadsheet on a National Health Service (NHS) computer and in a folder in the PMI Research room at Hampshire Hospitals NHS Foundation Trust in a locked metal cabinet only accessible by the study team.

We are currently in the process of recruiting and collecting data for this study. Recruitment and data collection for this study started on 4 October 2021. We estimate that it will take 2–3 months to complete the data collection process and 3–4 months to analyse the data, write the paper and submit it for publication. In total, we expect this study to take up to 7 months to complete.

Sample size and statistics

To the authors' knowledge, there is no previous study on FCR among PM patients, hence, there is a known effect size to be used to calculate the sample size. For this reason, a standardised Cohen's d=0.25 was used to detect a medium to large effect size.[24]

To detect an effect |p| of 0.25 (Cohen's d) with 80% power in a one-way between subjects Analysis of Varaince (ANOVA) (α=0.05), the required sample is 52 participants in each group (total=260). Sample size was calculated with R V.3.6.3 program (R Foundation for Statistical Computing, Vienna, Austria).

Categorical variable will be outlined with frequencies and percentages and continuous data with mean and SD. Analysis of categorical data will be performed using the Pearson χ^2 test or Fisher's exact test where appropriate. A p value of less than 0.05 is considered statistically significant. A line graph using group mean scores will be used to plot the trajectory of FCR and quality of life over time.

Correlation tests will be conducted to explore the relationship between FCR and quality of life. Data will be analysed using SPSS V.26 (IBM).

ETHICS AND DISSEMINATION

Ethical approval was obtained from the HRA and Health and Care Research Wales (HCRW) (IRAS ID: 295431). Below are the main ethical considerations of this study:

- Participants with language and/or cognitive difficulties who are unable to complete the questionnaires without assistance will be excluded from this study. This will be done because PM patients are dispersed all over the UK as it is a specialist service. Thus, it will be logistically difficult to arrange for translators to support these participants. We are also aware that participants might be uncomfortable answering these questions (sensitive topic) in front of translators, which might cause participants discomfort and affect results.
- Participants will be given the option to choose whether they would like to receive the questionnaires by mail or email. This is done to accommodate all age groups and different levels of technical skills.
- All data (mail and online) will not include any identifying information, to protect patients' confidentiality.
- Participants will be informed in the participant information sheet that the questions will address their thoughts around the disease and its recurrence, and their quality of life both mental and physical, and that these questions might cause some distress. Participants will also be informed that they can withdraw from the study at any point and that that will not affect their rights or any future treatment. They will also be encouraged to contact the research assistant if completing the questionnaires causes them any distress. If they do so, the research assistant—in discussion with them and with their permission—will refer them to their local General Practitioner and/or other emotional support services in their area.
- All data and information collected during this study will be considered and treated as confidential by the study team.
- The results of this study will be shared with the study's participants, presented at conferences and PM patients' days in the form of presentations or posters, and published in a scientific journal.

DISCUSSION

According to Butow *et al*: 'FCR is a critical target for optimal survivorship care'.[25] We hypothesise that the limited knowledge and uncertainty around PM increases the risk of FCR in this population. This study will explore the prevalence, trajectory and potential risk factors of FCR in PM patients and its relationship to quality of life. The results of this study will inform a multicentre study to explore the effect of FCR on PM patients' mental health (depression and anxiety), quality of life and healthcare utilisation which will inform a multicentre randomised controlled trial to assess the effectiveness of using evidenced-based interventions to lower FCR in PM patients.

One of the limitations of this study is that it is a cross-sectional study; thus, no causal relationships can be drawn from the results. Another limitation is the use of self-report measures to collect FCR and quality of life data increases the risk of cognitive bias and recollection distortion which might affect results. There might also be a selection bias in the recruitment process as those who suffer from FCR are more likely to avoid participating in a study about FCR. Even though all participants will be cancer free—to the best of their knowledge—at the time of the study (inclusion criteria), some participants might have had other malignancies in the past. Participants will be asked to focus on their PM experience when answering the questions however that might still affect results and pose a limitation for this study. This study is assessing the trajectory of FCR over time using a cross-sectional design (comparing different patients over time) thus individual differences may affect results (confounding variables).

The results of this exploratory cross-sectional study will be used to inform a multicentre study to explore the effect of FCR on PM patients' mental health (depression and anxiety), quality of life and healthcare utilisation. The results of both studies will then be used to conduct a multicentre randomised controlled trial to assess the effectiveness of using evidenced-based psychological interventions with high-risk patients on decreasing FCR levels and improving PM patients' quality of life.

The measure used is a self-report measure that poses risks of cognitive bias and recollection distortion

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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 Consent obtained directly from patient(s).

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