AIIHPC
All Ireland Institute of Hospice and Palliative Care

Project Title: High C-Reactive Protein as a Predictor of Specialist Palliative Care Needs
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Keywords: C-reactive protein, quality of life, symptoms, cancer
Duration of Project (mths): 35

SECTION 2: Project Summary

Complete description of project using the headings Background, Methods, Results and Conclusions. (3000 words max)

Background:

Early specialist palliative care in cancer is associated with better patient outcomes. A comprehensive assessment is recommended to identify people with specialist palliative care (SPC) needs. This may not be possible in a busy Oncology outpatient setting. "Red flags" to identify people at risk of high symptom burden and poor quality of life (QoL) could prompt a detailed assessment and early SPC referral.

Inflammation may be one such "red flag". Inflammation is the body's response to many challenges, including infection and illness. Although we know that inflammation is often seen in cancer, this link is still not well understood. Inflammation in cancer is associated with increased symptoms and poor QoL (Laird 2013). Inflammation is also associated with abnormalities in skeletal muscle in cancer (Malietzis 2016). C-reactive Protein is the most commonly used blood test to measure inflammation (Ryan 2015). Abnormal skeletal muscle may also be seen as a manifestation of inflammation and can be measured on Computerised Tomography scan (CT). CT imaging and blood tests are a standard part of the cancer diagnostic process. Thus information on skeletal muscle change and inflammation could be easily accessed, without any additional burden to the patient.

If a high C-reactive Protein and abnormal skeletal muscle were shown to predict symptoms and quality of life in cancer, they could potentially be used as a prompt for detailed holistic assessment and SPC referral. This study set out to determine whether this is possible.

Primary objective

Determine feasibility of study design.

Secondary objectives

1. Describe prevalence of high C-Reactive Protein and poor quality skeletal muscle, symptom burden and poor QoL in newly diagnosed advanced cancer

2. Assess if objective markers of inflammation (as measured by C-reactive Protein and radiologically-assessed body composition) can predict subjective outcomes (symptoms and quality of life (QoL)) in people with newly diagnosed advanced cancer.

Methods

This was a prospective observational feasibility study, which recruited consecutive participants with cancer, prior to treatment. Most recent C-reactive Protein level at time of enrolment was recorded. Diagnostic Computerised Tomography (CT) was reviewed to assess skeletal muscle, using specialised software (Slice-O-Matic (Tomovision, Canada). Symptom burden and QoL and performance status were assessed with validated tools (The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC QLQ-C30)) at study enrolment and after six to eight weeks. Eastern Cooperative Oncology Group Scale of Performance Status (ECOG) was noted (Oken 1982). Follow-up questionnaires were completed in person or over the telephone, depending on patient preference.

As a feasibility study, there was periodic review of study progress after 8 weeks of recruitment. At each review, the study protocol was modified and ethical amendment sought, as summarised in Figure 1 below. Challenges identified at each point are addressed in the results section.

Data analysis was conducted using Microsoft Excel. EORTC-QLQ C30 scores are reported as a summary score, which summarises the symptom and functional scales components of the questionnaire; this approach is recommended by the EORTC Quality of Life Group (Giesinger 2016). The EORTC-QLQ C30 global quality of life subscale of is also reported. Both are reported as 0-100, with 0 worst and 100 best.

Change in score over time was analysed as little change if 5-10% change in score, moderate if 10-20% change and very much change if >20% change as per EORTC guidance (Fayers 2001).

Results

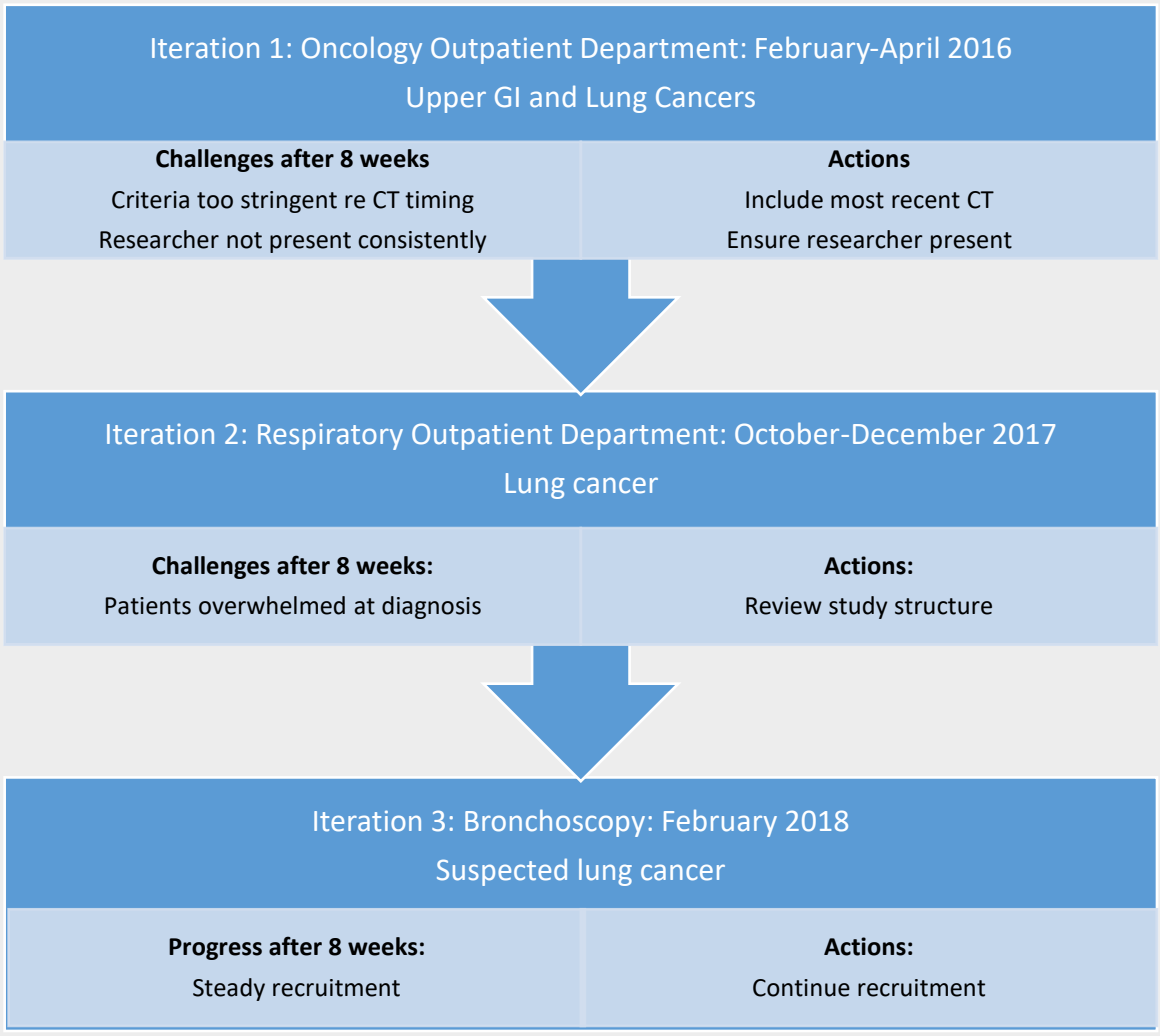

Figure 1: Summary of Study Iterations with Key Challenges and Actions

Recruitment

3 iterations of this study were conducted, summarised in Figure 1.

Iteration 1: Medical Oncology clinic, St James's Hospital

15 potentially eligible patients, no patients recruited after 8 weeks.

Feasibility issues encountered

- Inclusion criteria too restrictive regarding dates of CT (last one month)
- Requirement for researcher to be in clinic at all times, conflict with clinical and academic duties
- Busy and long day for patients attending OPD, often seeing 4 healthcare professionals in a row

Action

- Amendment to ethical approval obtained: change to "most recent CT"
- Plan to restart study on return from maternity leave in summer 2017

Iteration 2: Recruitment in Oncology clinic no longer possible as another study recruiting there

- Alternative site identified: St James's Hospital Rapid Access Lung Cancer Assessment clinic
- Feasibility issues encountered
  - Recruitment slow
    - 4 eligible patients identified by clinicians
    - 2 agreed to take part, 2 declined
    - 1 later withdrew before starting study
    - 1 unable to participate due to illness
  - Discussion with clinical team: difficulty identified for clinical team in proposing study to patients at time of diagnosis due to patient distress
- Action
  - Review of study design underway in consultation with clinical team
  - Plan to identify and recruit eligible participants at bronchoscopy and follow up after diagnosis
  - Amendment to ethical approval sought

Iteration 3: Bronchoscopy suite, St James's Hospital

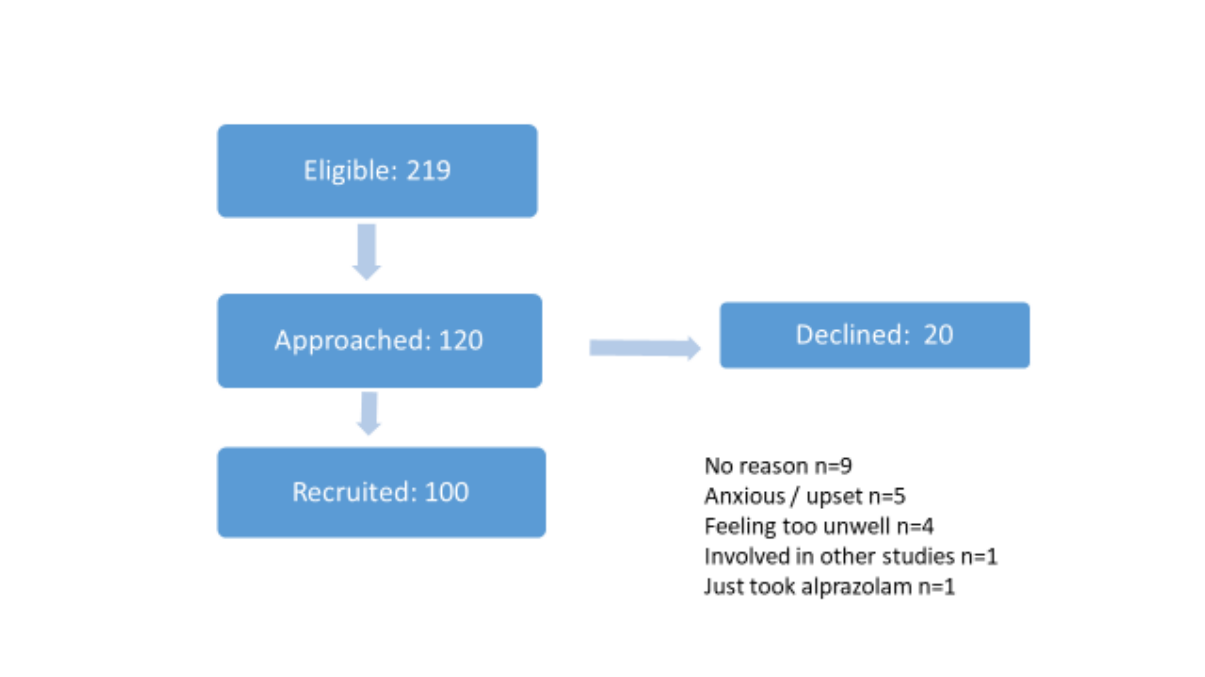

Figure 2: Summary of recruitment process (Iteration 3)

Over a period of 8 months (February to October 2018), 100 people were recruited. 35 had inoperable lung cancer, as shown in Figure 3 overleaf. This report will focus on the inoperable cohort.

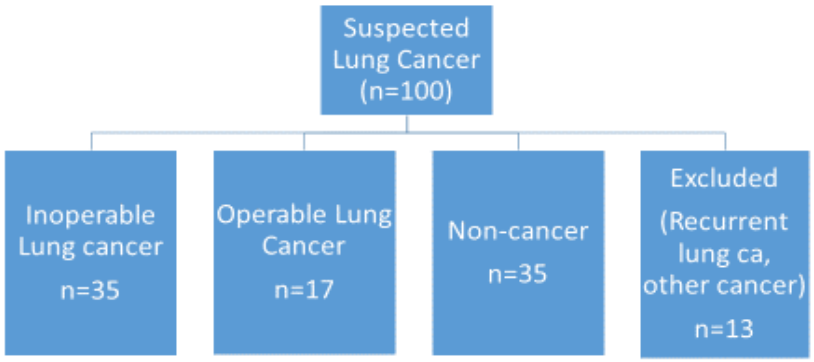

Figure 3: Breakdown of Recruited Patients

Attrition Rate

8 patients did not complete the study. 4 had died, 2 requested to withdraw from the study, 1 was too unwell and 1 was lost to follow-up.

Follow-up was delayed beyond 8 weeks for n=21 people, most commonly due to ongoing investigations, being too unwell or difficulty contacting the participant.

Complete datasets

Complete data (CT, C-Reactive Protein, baseline and follow-up questionnaires) complete were available for 16 patients.

Demographics (n=35 recruited patients)

Median age was 68 (range 52 – 88). 19 were female, 16 male. All were of white ethnicity. 18 were current smokers, 13 ex-smokers, 2 non-smokers; data on smoking status was missing for 2. Median ECOG performance status was 1 (range 0-3).

Quality of life scores

Median QoL score on day 1 was 55 (range 0-100). Median QoL score on day 2 was 67 (range 25-100).

Change in quality of life score on follow-up assessment

8 had moderately better / very much better scores, 6 people had moderately / very much worse scores and 7 had little change.

Symptom and function score (summary EORTC QLQ-C30)

Median summary score on day 1 was 76 (range 52-97). Median summary score on day 2 was 76 (range 40-97).

Change in symptom and function score on follow-up assessment

12 had little or no change in their symptom and function score, 6 had moderately better / very much better scores and 2 had very much worse scores.

C-Reactive Protein

Median C-Reactive Protein was 7.3mg/L (range 0.9-66).

Body composition

24 of 35 had abnormal skeletal muscle at initial assessment.

Relationship between C-Reactive Protein and body composition and change in QoL

There was no significant association found between C-Reactive Protein and skeletal muscle and change in QoL or summary symptom / function score.

Discussion

The first 2 iterations of the study identified a number of barriers to recruitment. These were a mixture of study design (inclusion criteria), practical realities (busy Oncology OPD, another study starting recruitment in the same clinic), other researcher commitments and possible gatekeeping by the clinical team. Difficulties with recruitment in palliative care research are common (Jordhoy 1999).

The third iteration of the study recruited successfully. However, attrition was a significant problem, with almost a quarter of participants not completing the study. Attrition is known to be a challenge in longitudinal studies in palliative care (Shipman 2008). This study was devised taking into account the recommended ways to overcome attrition (short duration of study, simple methodology) (Aktas 2011) and having assessments at times convenient to participants (Shipman 2008). This may explain why attrition was less than in other longitudinal studies of QoL or symptoms, where reported attrition ranged from 33% at 5 weeks in one study (Perez Cruz 2017) to over 50% at 3 weeks in another (Stromgren 2005).

Follow-up assessment was delayed in a majority of participants. While some had ongoing investigations and thus no clear diagnosis or treatment plan at time of planned follow-up, others were too unwell and requested delaying the second assessment. It was often difficult to contact participants; several noted that they were frequently out of the house at medical appointments while many more reported not answering calls if they did not recognise the phone number.

This work has highlighted several remaining feasibility issues. As discussed above, attrition with resulting incomplete data would be a major barrier to the conduct of a larger scale study. Furthermore, the study design results in a heterogeneous study cohort. While it was valuable for the researcher to include people with operable cancer and non-cancer controls (as a PhD student, this simply created 3 parallel studies for her overall thesis), this model would be inefficient in a larger scale study. Even among the inoperable cohort, there is heterogeneity in treatments planned – some were to have chemotherapy, some radiotherapy, and some best supportive care. Such heterogeneity could confound results of a full-scale study to the point of making the study invalid, unless sufficiently large numbers were recruited to account for this. In turn, a very large sample size would increase the time taken to complete the study, based on recruitment and retention findings from this work.

There was no clear pattern in QoL and symptom scores in this study. While some had deteriorated from initial assessment to follow-up, many other participants reported unchanged or improved scores. This may reflect the short timeframe of the study, improved symptom management once the diagnosis of cancer was confirmed, early responses to treatment or simply be an artefact of the small numbers in the study. While a pilot or feasibility study is never powered to detect significant differences (Jones 2017), objective measures of inflammation did not appear to be linked to QoL and symptom scores in this cohort. Although this is clearly not definitive, neither does it support the idea of using these measures as predictors of palliative care need.

A strength of this study was the development and maintenance of a good working relationship with the clinical teams; this may be key to recruitment (Aktas 2011). Moreover, in this study, discussion of the recruitment challenges with the clinical team informed the changes in study design, which finally led to successful recruitment.

Ultimately, this study demonstrates the value of a feasibility study – to highlight which issues can be addressed and which remain, as well as giving an indication of likely recruitment rates in an eventual full scale trial. This helps to ensure scarce resources and patient time are used efficiently (Hagen 2011). Hagen et al argue (Hagen 2011) argue that feasibility should be formally assessed for most studies conducted in palliative care.

Hagen et al (Hagen 2011) advocate for the use of a kinesthetic learning model in feasibility studies. They explain this as an iterative process where learning from one cycle of the study feeds into the next cycle and the study changes based on the emerging experience. The idea of an iterative process during research is already accepted, for example in the development and evaluation of complex interventions. This iterative process was key to the conduct of this study. Interim review of study progress allowed for changes to be made in time to inform the next iteration, rather than at the study's end.

Conclusion

Recruitment to a study assessing C-Reactive Protein and abnormal skeletal muscle as possible predictors of poor QoL and high symptom burden was feasible. However, feasibility issues are apparent, most notably attrition and a heterogeneous cohort. Objective measures of inflammation did not appear to be linked to QoL and symptom scores in this cohort. This work utilised an iterative process to identify and

address barriers to the successful conduct of the study. The study demonstrates the value of a feasibility study in palliative care research.

Lay description of completed project (500 words max)
*Please include an **up-to-date** description of your research in lay terms.*

Background

Inflammation is the body's response to many challenges, including infection and illness. Although we know that inflammation is often seen in cancer, this link is still not well understood. Recent studies suggest that inflammation may be related to symptoms and quality of life. It is also thought that inflammation can affect the muscle in your body. Early research has shown that people with high levels of inflammation may have less muscle than people with little inflammation. It also appears that the muscle may have more fat inside in the muscle than usual.

A blood test known as C-reactive Protein is often used to measure inflammation in the body. Changes in the muscle of the body can be measured on a Computerised Tomography scan (CT scan).

In the future, if C-Reactive Protein and changes on CT scan could be used to predict who will develop symptoms or have poor quality of life, the healthcare team could act early to treat or perhaps even prevent these problems.

Aim

This was a feasibility study – that means the main aim of the study is to see if this type of study can work. It could then lead on to other bigger studies in the future. A feasibility study can also give an idea of how many people would be needed in a bigger study. Researchers also hoped to see if commonly used blood tests and scans could be used to predict which people are likely to develop symptoms or have poor quality of life during treatment.

Study

People with recently diagnosed inoperable lung cancer were asked to take part in the study, while they were attending hospital for a test called bronchoscopy. They were asked to complete a questionnaire about their symptoms and quality of life.

6 - 8 weeks later, the person was asked the same questions about symptoms and quality of life.

Researchers looked at the person's most recent C-Reactive Protein blood test and CT scan. They looked at these results to see if there was any link between people with high levels of C-Reactive Protein / changes in the muscle in the body and poor quality of life / lots of symptoms.

Because the researchers wanted to find out if this study could be run as a larger study in the future and wanted to find out the best way to set up the study, they paused after the first 8 weeks of the study, reviewed what progress they had made and made changes to the study if it was not going well.

Results

This study proved challenging. Researchers had to make changes to the study twice before they found a set-up that worked well to get patients involved with the study. Even then, they identified a number of problems that would mean this study would be unlikely to work on a larger scale. Also, there was a wide range of C-Reactive Protein levels and amount of muscle in people's bodies and researchers did not see any link with quality of life or symptoms. This study has given some useful information though. This study has also shown how important it is to do a feasibility study before a bigger study. It means that another researcher thinking of studying this question or other similar questions would know what doesn't work, as well as what does. Learning from others experience is an important part of planning better studies in the future and better studies lead to better patient care.

References (2000 words max)

1. Aktas A, Walsh D. 2011. Methodological challenges in supportive and palliative care cancer research. *Semin Oncol* 38: 460-466
2. Fayers, P, Aaronson, NK, Bjordal, K, Groenvold, M, Curran, D & Bottomley, A 2001, *EORTC QLQ-C30 Scoring Manual*. 3rd edn, European Organisation for Research and Treatment of Cancer, Brussels.
3. Giesinger JM[1], Kieffer JM[1], Fayers PM[2], Groenvold M[3], Petersen MA[4], Scott NW[5], Sprangers MA[6], Velikova G[7], Aaronson NK[8]; EORTC Quality of Life Group. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol. 2016 Jan;69:79-88. doi: 10.1016/j.jclinepi.2015.08.007. Epub 2015 Sep 28

4. Neil A. Hagen, Patricia D. Biondo, PhD[a,] Penny M.A. Brasher, PhD[c,] Carla R. Stiles, BN[a,] Formal Feasibility Studies in Palliative Care: Why They Are Important and How to Conduct Them. JPSM August 2011Volume 42, Issue 2, Pages 278–289
5. Jordhøy MS[1], Kaasa S, Fayers P, Ovreness T, Underland G, Ahlner-Elmqvist M. Challenges in palliative care research; recruitment, attrition and compliance: experience from a randomized controlled trial. Palliat Med. 1999 Jul;13(4):299-310.
6. Laird BJ, McMillan DC, Fayers P, Fearon K, Kaasa S, Fallon MT, Klepstad P.The systemic inflammatory response and its relationship to pain and other symptoms in advanced cancer. Oncologist 2013;18(9):1050-5. doi: 10.1634/theoncologist.2013-0120. Epub 2013 Aug 21.
7. Malietzis G, Johns N, Al-Hassi HO, Knight SC, Kennedy RH, Fearon KC, et al. Low Muscularity and Myosteatosis Is Related to the Host Systemic Inflammatory Response in Patients Undergoing Surgery for Colorectal Cancer. Annals of Surgery. 2016;263(2):320-5.
8. NIHR National Institute for Health Research https://www.journalslibrary.nihr.ac.uk/information-for-authors/pilot-and-feasibility-studies/. Accessed 5th September 2019.
9. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5 (6):649-655
10. Perez-Cruz PE[1], Shamieh O[2], Paiva CE[3], Kwon JH[4], Muckaden MA[5], Bruera E[6], Hui D[7].Factors Associated with Attrition in a Multicenter Longitudinal Observational Study of Patients with Advanced Cancer. J Pain Symptom Manage. 2018 Mar;55(3):938-945. doi: 10.1016/j.jpainsymman.2017.11.009. Epub 2017 Nov 16.
11. Ryan AM, Cushen S, Ni Bhuachalla E, Dwyer F, Power DG. The Role of Inflammatory Biomarkers in the Assessment of Nutritional Status and Disease States. Topics in Clinical Nutrition. 2015;30(1):3-15.
12. Shipman C, Hotopf M, Richardson A, Murray S, Koffman K et al. 2008. The views of patients with cancer regarding participation in serial questionnaire studies. *Palliative Medicine* 22: 913-920
13. Strömgren AS[1], Sjogren P, Goldschmidt D, Petersen MA, Pedersen L, Hoermann L, Groenvold M.A longitudinal study of palliative care: patient-evaluated outcome and impact of attrition. Cancer. 2005 Apr 15;103(8):1747-55.