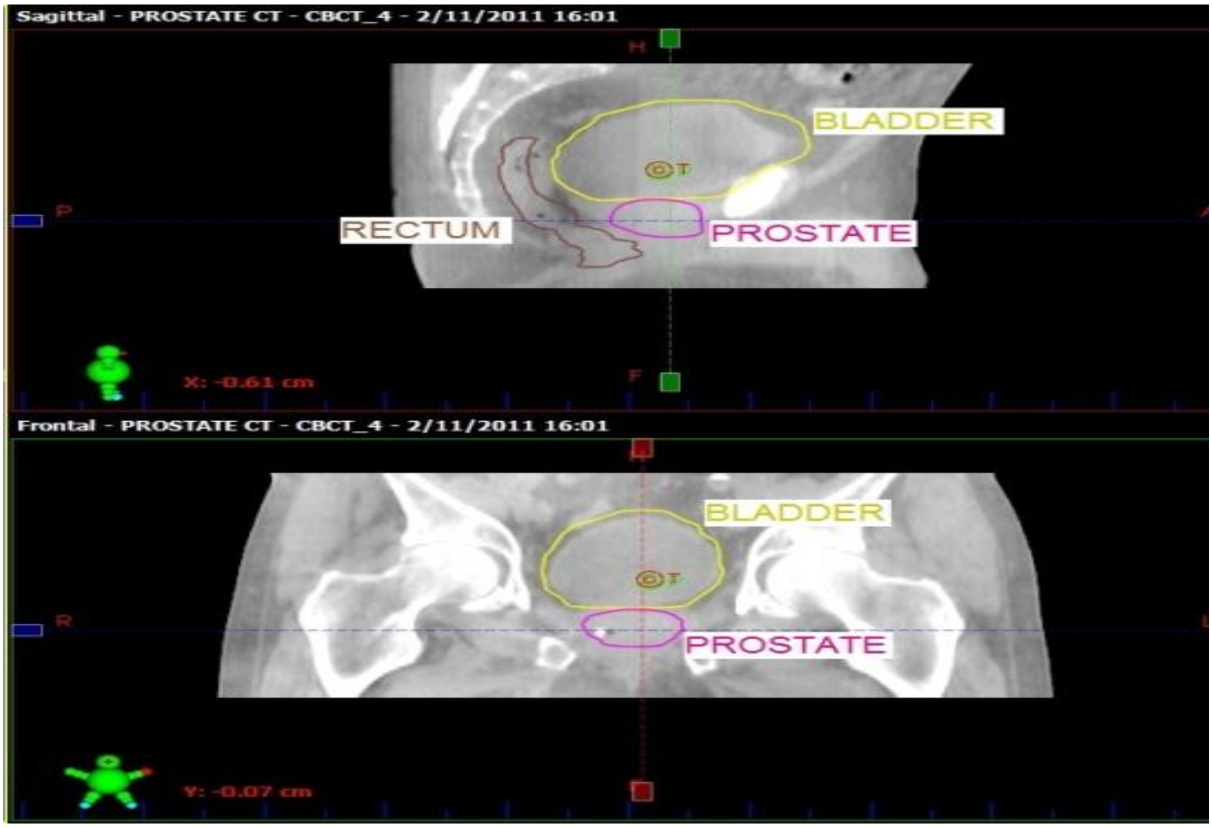

Achieving an empty rectum for prostate radiotherapy.

A randomised controlled trial comparing two laxation regimens for patients receiving radiotherapy to the prostate in rural Australia.

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Abbreviations

Central West Cancer Care Centre – CWCCC
Cone Beam Computed Tomography – CBCT
External Beam Radiation Therapy – EBRT
Generalised Estimating Equation - GEE
National Health and Medical Research Council – NHMRC

Abstract

Aim

To determine if, in addition to a low gas diet, a bulking laxative combined with a probiotic supplement are more effective than an osmotic laxative, at reducing rectal gas for patients receiving radiotherapy for prostate cancer.

Methods

Seventeen patients were randomly assigned into either an intervention group (n=8) instructed to take a bulking laxative, a probiotic and a low gas diet and a standard care group (n=9) instructed to take an osmotic laxative with a low gas diet.

Rectal gas ratings were determined from cone-beam computed tomography scans collected throughout treatment. Dietary and laxative compliance, bowel habits, fibre and fluid intakes were determined from food diaries.

Results

The odds of a higher rectal gas rating were increased for the bulking/probiotic group compared with the odds in the osmotic laxative group (OR 3.2, 95% CI 1.77-5.78, $p<0.001$). Average fibre intake was significantly higher in the bulking laxative group ($p = 0.036$), but not a contributing factor to the higher rectal gas levels (OR 1.001, 95% CI 0.92 - 1.09).

Conclusion

This study is the first to compare two different laxatives on their effect on achieving lower rectal gas ratings for prostate radiation treatment. The osmotic laxative was more effective at achieving lower rectal gas ratings.

Implications

This study informs clinical practice in the Australian and international setting on the differences in the two types of commonly used laxatives in their ability to reduce gas levels and achieve bowel evacuation during radiotherapy to the prostate.

Keywords

Prostatic neoplasms, radiotherapy, empty rectum, low gas diet, probiotics

Executive Summary

Background

During radiation therapy, changes in dimensions of the rectum are known to affect the position of the prostate which may result in the prostate receiving a lower than desired dose of radiation (Lips, 2011; McNair, 2011). Current practice is for the patient to have an empty rectum and a full bladder for daily treatment (Lips, 2011; Bayles, 2016; McNair, 2011). Achievement of an empty rectum is recognised as a limitation of treatment with factors influencing rectal fullness and gas being complex and varying for each individual (Lips, 2011; McNair, 2011). In practice this increases patient anxiety and when coupled with stressors associated with travelling for and receiving treatment, impacts on the patient journey and experience. In addition to this staff report increased work load in counselling the patient around these issues. On occasions, enemas are used to empty the rectum placing additional burden on the patient and cost to the health service. If this fails to adequately empty the bowels the patient does not receive the planned daily radiation dose extending the course of their treatment.

Methods

A randomised controlled trial was conducted at the Central West Cancer Care Centre (CWCCC) from June to December 2016. A total of 17 patients participated. Eight were randomised into a bulking laxative, low gas diet and probiotic arm and nine into an osmotic laxative and low gas diet arm. Cone Beam Computed Tomography (CBCT) scans were collected as part of standard practice and these were used to determine rectal gas levels. Food and bowel habit diaries were completed by participants at four different time points.

Results

Results indicate that for participants in the bulking laxative and probiotic group the odds of experiencing high (poorer) rectal gas ratings were 3.2 times greater than the odds in the osmotic laxative group (OR 3.20, 95% CI 1.77-5.78, $p<0.001$). Average fibre intake was significantly higher in the bulking laxative group due to the additional fibre from the laxative ($t = 2.31$, $df = 15$ and $p = 0.036$). However, higher fibre intakes were not a contributing factor to the higher rectal gas levels (OR 1.001, 95% CI 0.92 - 1.09). Seventy six percent of patients travelled to the CWCCC for treatment.

Conclusion

This study has demonstrated that an osmotic laxative is more effective than a bulking laxative/probiotic at achieving low rectal gas levels during treatment and supports current practice at the CWCCC. Although rectal gas levels were lower in the osmotic laxative group, the participants' levels were not always optimal and were above recommended treatment thresholds, on these occasions patients were asked to empty their bowels before treatment could proceed.

Implications

- Rectal gas levels can impact on prostate positioning and affect the radiation dose delivered. Bowel preparation is an important component to achieving an empty rectum.
- This study informs clinical practice by identifying the best laxative to achieve an empty rectum and prevent rectal gas during treatment.
- Use of an osmotic laxative resulted in lower levels of gas being present in the rectum. This limits stress and anxiety for patients, limits use of enemas and need for staff counselling, and prevents an extended course of treatment due to inadequate rectal emptying.
- This study informs clinical practice in the Australian and international setting on the differences in the two types of commonly used laxatives in their ability to reduce gas levels.

Recommendations

- Continue to use Movicol together with the low gas diet as the standard bowel preparation for patients undergoing external beam radiotherapy treatment (EBRT) to the prostate
- Continue to involve dietetic staff in the education and support of patients before and during treatment
- Patients undergoing treatment should be encouraged to consume adequate amounts of fibre in line with the National Health and Medical Research Council (NHMRC) guidelines of 30 grams per day
- Patients should continue to avoid foods known to have high levels of fermentable (gas forming) carbohydrates
- Further research is required to determine the effect of long term use of osmotic laxatives during treatment, the role of probiotics in reducing rectal gas in this setting and the role of stress and travelling for daily treatment on bowel habits.

Introduction

Dietary factors including fibre and fluid intake and consumption of gas forming foods can impact on rectal volume. During radiation therapy to the prostate, high levels of faecal matter and gas in the rectum increase the risk of the prostate moving and receiving a lower than desired radiation dose (Lips, 2011; McNair, 2011). This also increases the amount of radiation received by the rectum increasing gastric toxicities and unwanted side effects for the patient (McNair, 2011; Bayles, 2016). To minimise gastric toxicities, current recommendations are for the patient to have an empty rectum and a full bladder for daily treatment (Lips, 2011; Bayles, 2016; McNair, 2011). At the Central West Cancer Care Centre (CWCCC), based in Orange NSW, the current bowel preparation protocol involves patients taking an osmotic laxative (Movicol® half strength) daily and following a low gas diet. The patient is required to follow this protocol whilst receiving active treatment over eight weeks. However, over the five years that this protocol has been in use, achieving empty rectums has been difficult and many patients complain that the Movicol causes increased gas. Anecdotally, this has been reported to increase patient anxiety, increase staff work load in counselling the patient, increase use of enemas to achieve an empty rectum and delay patient treatment times.

There is limited published research as to the most effective way to achieve an empty rectum for prostate treatment (Bayles, 2016; McNair 2014). Many studies have a small sample size and there is currently no literature comparing laxatives which are used in standard practice both internationally and in Australia, to assess effectiveness and superiority. Osmotic and bulking laxatives are currently being used to promote bowel emptying in Radiation Oncology treatment centres across NSW and use of these is reported internationally in the literature (Lips, 2011; Bayles, 2016; McNair, 2011, Oates, 2014). There is emerging research around the role of probiotics in improving the health of gut microbiota, but only one study has looked at the use of probiotics in reducing rectal gas for patients receiving radiation therapy for prostate cancer, results showed a decrease in gas production, however the sample size was too small to show statistical significance (Ki, 2013).

It is envisaged that results from this study can improve the journey for rural patients undergoing radiation therapy to the prostate. This study aims to explore the difference in two laxation regimens: an osmotic laxative with a low gas diet (standard care) compared to a bulking laxative with the addition of an eleven strain probiotic with a low gas diet, in order to achieve an empty rectum for prostate radiotherapy. It is hypothesised that the bulking laxative and probiotic arm will achieve lower rectal volumes and gas levels, higher fibre intakes and fewer episodes of diarrhoea than the osmotic laxative arm. This would achieve appropriate rectal volumes and improve patient acceptability of the laxative regimen used for treatment.

Literature Review

Prostate cancer is the most commonly diagnosed cancer among males. It is estimated that 16,665 males will be diagnosed with prostate cancer in 2017, accounting for 22% of all new male Australian cancer diagnosis. Prostate cancer is the 3rd most common cause of cancer deaths in Australia and is the 2nd most common cause of cancer deaths among males in Australia. (Aust. Government, 2017). During radiation therapy, changes in dimensions of the rectum are known to affect the position of the prostate (Lips, 2011; McNair, 2011). External beam radiotherapy treatment (EBRT) for prostate cancer is typically delivered in a conventional dose of 78 gray. The introduction of intensity-modulated radiotherapy has enabled dose escalation to take place through increased accuracy with the ability to visualise prostate movement (Bayles, 2016). The prostate and seminal vesicles are positioned close to the mid rectum and so the positioning of the prostate may change during the delivery of irradiation on any given day (intrafraction prostate motion) due to moving gas pockets and faecal matter inside of the rectum (Bayles, 2016; Nichol, 2009). Variable rectal filling continues to be a hindrance to further reducing radiation treatment margins in order to prevent gastric toxicities. At the CWCCC routine Cone Beam Computed Tomography (CBCT) scans are conducted during treatment. If positioning of the prostate is affected by faecal matter or gas in the rectum the patient fails the CBCT scan and is asked to empty the bowel before treatment is delivered. Reproducing the position of the prostate for irradiation is essential to achieve adequate dose delivery, improve local tumour control, reduce toxicity to surrounding organs and to minimise treatment related side effects (Lips, 2011; McNair, 2011; Bayles, 2016).

Different approaches to achieve an empty rectum for treatment have been reported in the literature including dietary modification, use of laxatives, manual evacuation and the use of rectal balloons. However there remains a lack of prospective, adequately powered randomized controlled trials that have been designed to identify if any one intervention can result in a consistently empty rectum (McNair, 2014). The types of laxatives used in the studies also vary. Some studies compared an osmotic laxative to no intervention while others compared a bulking laxative to no intervention (Smitsman, 2008; Darud 2010; Oats, 2014). In the context of current practice in Australia, there is no consistency between treatment centres in the type of laxatives used. In a comparative assessment conducted by the CWCCC in 2011, the types of laxatives used varied and included osmotic agents such as magnesium tablets or Movicol and bulking agents such as Metamucil, Benefibre or Fybogel. These laxatives were used in conjunction with a low gas diet. The effectiveness of these interventions was not addressed at this time.

The use of a low gas diet to reduce rectal gas has been explored in a number of studies. However detail regarding compliance to the diet is absent in the majority of these studies, making it difficult to determine the relevance of reported findings (Lips, 2011; McNair 2011; Nichol, 2009; Smitsman, 2008; Yahya 2013). A low gas diets contains minimal amounts of foods that are fermented by gut microbiota or those which stimulate and irritate the large bowel. These include cruciferous vegetables, legumes, garlic, onions, spicy foods, eggs, beer, large amounts of caffeine and carbonated beverages (Smitsman, 2008). Results from the study conducted by Smitsman and colleagues (2008) showed that diet alone was insufficient to prevent short term movement of the prostate, while the study conducted by McNair and colleagues (2011) demonstrated that the regularity of rectal filling was not improved with the use of dietary advice in this regard. The theory of restricting fermentable substrates in the diet during radiation treatment to the prostate is feasible, however the effect of this on the health of gut microbiota has not been reported and further research is required to determine its impact during the treatment period.

The potential risk in altering an individual's diet, particularly decreasing foods which provide a source of fibre, may result in altered bowel habits including constipation. Therefore caution must be taken to ensure adequate fibre is still maintained when making recommendations for a low gas diet in this population. In the study conducted by McNair (2011), fibre was limited to eighteen grams per day and patients were advised to avoided fermentable carbohydrates in the diet. The Nutrient Reference Values for Australia and New Zealand (NHMRC 2006) recommend fibre intakes of thirty grams fibre per day for adult males aged fifty one and over. As fibre plays a significant role in increasing stool bulk and reducing colonic transit time (Escott Stump, 2012), restricting its intake to levels lower than current recommendations may result in decreasing stool bulk and ineffectual emptying of the rectum. The risk of constipation increases with age, with the existence of factors such as reduced fluid intake, low fibre intake, reduced mobility, depression, anxiety and certain medications resulting in slow colonic transit, low stool output and reduced bowel movement frequency (Leung, 2011). The incidence of prostate cancer in Australia is highest amongst males between the ages of 65-69 years (Aust. Government, 2017). As constipation risk increases with age ensuring adequate dietary fibre and fluid intake while undergoing radiation treatment to the prostate is an important consideration when attempting to achieve an empty rectum for treatment.

In a small Australian study of 11 participants, Oates et al (2013) demonstrated that recording of a food diary during prostrate radiation treatment is feasible, with a median of 100% compliance with recording the diet diary (Oates, 2013). Mean (SD) fibre intake for the group was 21.5 grams per day (± 5.5) and fluid intake 2.2 litres per day (± 0.733), but the effect of the fibre and diet on prostate motion and rectal volume was not assessed (Oates, 2013). In a second study conducted by McNair (2011), participants were instructed to restrict fibre intake to 18 grams per day. The average fibre intakes reported by the group ranged from 10.3 - 21.2 grams per day, with results showing that regularity of rectal filling was not improved by this dietary regimen.

Approximately 75% of flatus is derived from colonic bacterial fermentation of ingested nutrients, with the remainder from ingested air and back-diffusion of gases across the intestinal lumen. On average individuals pass approximately 13-21 gas passages per day (Greenberger, 2016). Diet accounts for most of the variation in flatus production and commonly considered first line therapy in an attempt to reduce excessive gas (Lovino, 2014). However differences in colonic microbiota and motility may also play a role (Greenberger, 2016). Azpiroz et al. (2014) demonstrated that dietary restriction of non-absorbable, fermentable residues reduced the substrates available for gas production by colonic microbiota and reduced the subjective perception of functional gas production. However, removal of these substrates did not reduce stool frequency or consistency but may alter the composition of gut microbiota by the negative selection of species dependant on these substrates (Azpiroz, 2014).

Non dietary strategies that are reported to reduce or remove excessive gas vary considerably (Bayle, 2016). It has been demonstrated that mild physical activity and being in an upright position accelerates gas transit and reduces bloating and distention (Harder, 2003). Promoting gentle exercise in prostate cancer patients to expel excessive gas is a common recommendation within treatment facilities. Commonly used over-the-counter drugs include peppermint oil which acts as an antispasmodic or simethicone and charcoal acting as gas reducing agents. Studies have shown that peppermint oil provides benefit in relieving symptoms of irritable bowel syndrome and abdominal pain, however its effect on bloating is still under discussion (Iovino, 2014). There is no consistent evidence to support the use of gas-reducing substances such as charcoal or simethicone, with mixed results reported (Greenberger, 2016; Azpiroz, 2010). However, use of these products occurs within the CWCCC in an attempt to reduce rectal gas during radiation therapy. Anecdotally patients who use this during treatment at the CWCCC report reductions in gas levels.

The microbiota in the gastrointestinal tract is comprised of both beneficial and pathogenic microorganisms (Mombelli, 2000). The homeostasis of these microorganisms can be disturbed when there is an increase in pathogenic bacteria during antibiotic treatment, after some surgery and radiation procedures, and in some disease situations (WHO, 2002). Probiotics are live microorganisms that when administered in adequate amounts confer a health benefit on the host (Timko, 2010). The use of probiotics may assist in improving gut microbiota and in reducing rectal gas. In particular *Bifidobacteria* has been shown to reduce gas and bloating in Irritable Bowel Syndrome and to assist in the management of colitis following viral or bacterial infection (WHO, 2002).

Radical radiation therapy to pelvic cancers carries a risk of complications to normal tissues around the tumour, and the use of probiotic agents may modulate intestinal inflammation through altering the composition and metabolic functioning of indigenous gut flora (Timko, 2010). A study that used the probiotic *Lactobicillis acidophilus* during prostate radiotherapy to reduce rectal gas showed a reduction in volume and percentage change in rectal volume (Ki, 2013). However there was no laxative used in this study and the use of probiotics combined with a laxative during radiation therapy to the prostate has previously not been reported in the literature. In addition to this the optimal dose and its effect on gut microbiota during radiation therapy has yet to be clearly established (McNair, 2014).

Rural patients are often required to travel and reside away from home whilst receiving treatment which can impact on emotional and financial stressors for the individual (Mercuri, 2005; Martin-McDonald, 2003). The average distance travelled by patients receiving treatment at the CWCCC is 210km, this is a well above distances travelled by patients in metropolitan areas and is above the NSW Health goal for 95% of the population to reside within 100 kilometres of a radiation centre. (Butler, 2014) As experienced at the CWCCC this coupled with the stress and anxiety of achieving an empty rectum for daily treatment can impact on the patients experience within the treatment facility.

Study Aim

To determine if, in addition to a low gas diet, a bulking laxative combined with a probiotic supplement are more effective than an osmotic laxative, at reducing rectal gas for patients receiving radiotherapy for prostate cancer. The hypothesis is that a bulking agent and probiotic will be more effective than standard treatment of an osmotic laxative at the CWCCC at reducing rectal gas during radiation therapy treatment to the prostate.

Objectives

To conduct a randomised trial comparing the effectiveness of two types of laxation regimens in their ability to reduce rectal gas during prostate radiation therapy. The primary objectives are:

1. To determine if there is a difference in median rectal gas rating on presentation across the Cone Beam Computed Tomography (CBCT) scans conducted during treatment between the bulking laxative with probiotic and osmotic laxative treatment arms
2. To determine if there is a difference in the proportion of rectum ‘fails’ and gas ‘fails’ between the bulking laxative with probiotic and osmotic laxative treatment arms

The secondary objectives are

1. To determine if there is a difference in average rectal volume at the radiation planning appointment between the bulking laxative with probiotic and osmotic laxative treatment arms
2. To determine if there is a difference in treatment related toxicities, specifically diarrhoea, between the bulking laxative with probiotic and osmotic laxative treatment arms
3. To assess patient compliance to the low gas diet, laxative and probiotic regimen

Methods

Study Design

A prospective single blinded randomised trial was conducted. Patients were randomly allocated into one of two groups using a computer generated number table. Group one received Osmotic laxative Movicol half strength® (Macrogol 3350 6.563 grams, providing half the standard daily dose) with a low gas diet. Group two received Metamucil ® (psyllium) providing the equivalent of 10 grams soluble fibre per day, Nutralife Probiotic 50 Billion strain®, an 11 strain probiotic, containing *Lactobacillus acidophilus, Bifidobacterium animalis spp. lactis, HOWARU Bifidobacterium, Bifidobacterium breve and longum, Lactobicillus casei, paracasei subsp, plantarum, salivarius spp, rhamnosus and delbrueckii ssp bulgaricus* and a low gas diet.

Ethics

Ethics was approved by the Greater Western Human Research Ethics Committee, project number HREC/15/GWAHS/120.

Eligibility criteria

Inclusion criteria: Adult patients fifty years of age or older undergoing external bean radiotherapy (EBRT) at the CWCCC, 2 to the intact prostate, using fiducial markers for position verification.

Exclusion criteria: Severe constipation defined as less than 3 bowel movements per week spanning over several months, abdominal disease (Crohn's disease, ulcerative colitis, irritable bowel syndrome), history of extensive abdominal surgery, patients using digoxin or salicylates and individuals whose primary language is other than English.

Research Population

The research was conducted at the CWCCC located at Orange Health Service, Forest Road Orange NSW 2800.

Patients who received radiation therapy to an intact prostate where fiducial markers were inserted for position verification were approached to participate in the study. Fiducial markers were inserted by an urologist as per standard practice in all patients receiving radiation therapy to an intact prostate.

Allocation Procedure

A clinician, with no involvement in the trial, created a Microsoft Excel computer spread sheet to randomise numbers one to twenty to either of the two intervention groups. Envelopes were then prepared in a numerical order. The computer generated randomisation instruction on which intervention the patient received was enclosed in the opaque numbered envelope and sealed with the appropriate numbers written on the front of the envelope.

A dietitian not involved in the trial assigned the envelopes in numerical sequence to the patients as they consented to partake in the study. This informed the Dietitian on what laxative to educate the patient on using and if to include the use of a probiotic into the education session. The dietitian then recorded the patient's allocation on the master list and this information was kept in a locked cupboard to blind this information from the lead researcher.

Recruitment and consent

Patients who attend the CWCCC for treatment present from a broad geographical area, covering all of the Western New South Wales Local Health District. The radiation oncologists conduct their assessments in clinics in Orange, Dubbo and Bathurst. This geographic range limited the opportunities for the lead researcher to be present at all assessments in order to introduce the research project and obtain consent in a face-to-face setting. The lead researcher contacted the patients via telephone once they had consented to radiation treatment and prior to the insertion of the fiducial gold markers by the urologist. During this phone contact the patient's eligibility for the study was assessed and the research project was introduced to the patient. The patient and their family member also had the opportunity to ask questions regarding the research during this phone call. All screened patients were then provided with a copy of the participant information sheet and written consent form via mail (appendix 1). This included a reply paid envelope for the patient to return completed consent forms. Patients were contacted one week after the information was posted to answer any further questions and to determine if the patient had consented to participate in the study.

If the patient declined to participate or withdrew from the study and/or not to have their data used as part of the study normal treatment procedures followed. The patient was assured that there were no impacts on their treatment or future health care and they were not disadvantaged in any way, with their radiotherapy continuing as normal. These patients were educated by the dietitian as per current procedure to follow the usual treatment protocol (Movicol® and the low gas diet).

After consent was received by return mail the patient was allocated into a treatment arm as per the allocation procedure and contacted by a dietitian not involved in the study to discuss dietary and laxative requirements for their radiotherapy planning session and treatment schedule. Participants who were allocated the probiotics had the shelf stable product sent in the mail.

Interventions

All patients were treated with radiotherapy as per standard practice under the care of the treating radiation oncologist being 78 gray delivered in two fractions per gray (39 treatments in total). The patients were required to follow the diet and laxative regimen for two weeks prior to their radiotherapy planning session and for the eight week duration of their treatment.

Both groups received dietetic assessment and education as per standard current practice before they attend the CWCCC for their radiation planning session. This was provided by an oncology dietitian who was not involved in the study but who was familiar with the dietary protocol for this patient group. Dietetic assessment involved the dietitian collecting information on current medications, current bowel habits, current dietary intake, height and weight. The patient was educated on dietary changes required to be compliant with a low gas diet (appendix 2) and when to commence taking the laxative with or without the probiotic agent. This information was recorded in the patient's clinical records as per current practice. As per standard practice the patient was provided with sufficient information to be able to alter their diet in the home setting. Food was not supplied to the patients during the course of the study.

Current practice at the CWCCC is for the patient to purchase their own laxatives for use prior to radiation planning and during treatment and therefore patients who participated in the trial continued to purchase their own laxatives (either the Movicol® half strength or Metamucil®) for use during the study. As the probiotics are not routinely prescribed for use during treatment, these were provided to the patients in the bulking laxative arm for use during the study.

The study participants received weekly nutrition reviews during which compliance to the diet was evaluated. Ongoing monitoring of bowel habits occurred as per the initial assessment and according to usual practice. Prior to attending the radiotherapy planning appointment and during weeks one, four and seven of treatment, the patients were asked to complete a three day food and bowel habit diary (appendix 3) on three consecutive days. This was used to determine fibre and fluid intakes and to assess compliance to the low gas diet. The food and bowel habit diary also contained a section for the patient to record information on daily bowel habits during the three days, including bowel frequency (number of motions), stool type according to the Bristol Stool 7-Form Scale, laxative use and use of anti-diarrhoeal medication.

As per usual practice the patients had CBCT images of the pelvis taken during treatment. This occurred at the radiation planning session, daily in the first week of treatment and once a week for the remainder of their treatment. This provided a minimum of 12 CBCT scans in total over the course of the patient's treatment. If however, a patient experienced difficulty achieving an empty rectum and was deemed to 'fail' due to excessive gas or matter in the bowel an additional scan/s would be collected until the bowel was considered empty enough to treat. Thus, for a 'poorer' bowel preparation regimen, there would be more scans collected across the course of treatment to ensure rectal volume did not exceed treatment thresholds. These scans were used to measure rectal volumes (cm^3) and gas levels (scale of 1-5) in the bowel.

<u>Data collection</u>

Demographics: The baseline characteristics collected included: age (years), weight (kilograms), height (centimetres), body mass index (BMI), Gleason score (2-10), insertion of rectal Space Oar, place of usual residence, travel required for treatment, and whether or not the patient was residing away from their usual residence during treatment. This information was gathered from the patient notes and documented in an Excel spread sheet.

Food and Bowel Habit Diaries: Completed foods diaries with the allocated participant number as the only identifier on the document, were entered by the principal investigator into Food Works Professional, version 8, to assess the diet for intake of fibre (grams) and fluid (litres). Nutrition and Dietetic students from the Charles Sturt University, who had been trained in using Food Works for this project, assisted with entering and analysing nutrition data at different time points of the project if they were attending the CWCCC for dietetic placement.

Compliance to the low gas diet was determined by using a high gas food checklist (based on foods to be avoided) from the completed food diaries. If the patient had consumed a gas forming food they were ticked off as being non-compliant. Similarly if no gas forming foods were consumed they were marked as being compliant. Compliance to the use of the prescribed laxative and probiotics was assessed during the weekly nutrition reviews and was documented by each participant when completing the three day food diary. If Degas was used during the study period this was also recorded on the food diary.

Bowel habits were defined as - 'constipation days' (where the frequency of bowel movements equals zero) and 'diarrhoea days' (where the frequency of bowel movements was greater than three motions per day of an unformed stool identified as Bristol Stool Type 6-7 watery, no solid pieces and/or use of anti-diarrhoeal medication was noted).

Cone-beam Computed Tomography (CBCT) Scans: CBCT scans were recorded in the patient's records over the course of their treatment. The scans were de- identified and assessed by the lead researcher who was blinded to the randomisation assignment. Data were recorded on Excel spread sheets which were developed by the lead researcher.

Rectal gas was estimated by viewing the CBCT scan in the mid-sagittal plane and using a semi quantitative scale of 1-5. This represented (1) no gas present, (2) gas occupying 5% to less than 25%, (3) 25% to less than 50%, (4) 50% to less than 75% and (5) 75% to less than 100% of the rectum. This approach to measuring rectal gas has previously been described (McNair, 2011).

The number of times a patient had a 'failed rectum' or 'failed gas' (faecal and gas levels too high to proceed for treatment) documented in the medical notes was recorded.

<u>Study Outcomes</u>

Primary outcome:

1. Differences in rectal gas measurements between the two treatment arms - Rectal gas will be estimated by viewing the CBCT scan in the mid-sagittal plane upon presentation for treatment
2. A difference in the number of rectum and gas fails between the two treatment arms - This is shown by the proportion of patients who fail Cone-beam Computed Tomography (CBCT) scan due to the rectum being outside of the acceptable treatment tolerance threshold due to excessive gas and or faeces.

Secondary outcomes:

1. The proportion of patients with symptoms of diarrhoea requiring the cessation of laxatives
2. The proportion of patients who complete the food diaries and adhere to the low gas diet
3. The proportion of patients who achieve adequate fibre and fluid intakes
4. The proportion of patients who adhere to the laxative and probiotic prescription

<u>Statistical Analysis</u>

Sample size: Patients were analysed according to the intention to treat principle. A priori effect size calculation was limited by the absence of published studies comparing two different laxatives in their effects on achieving an empty rectum. Previous studies compared use of a laxative to no intervention (Oates, 2013; Lips, 2012; Smitsman 2008). Sample size for this study was calculated setting power at 80%, alpha (p-value) at 0.05, with a primary outcome of rectal gas ratings (1-5 ordinal scale), using a Mann-Whitney U z test to detect significant difference between two arms, with a minimum 12 scans per patient. Ten patients per arm (i.e. 120 scans per arm), would be sufficient to detect an effect size of 0.38 (small to medium effect size). However, 34 patients in each arm would provide 408 scans per arm, which would be close to the required sample size required for a small effect size.

Demographics: Differences in baseline characteristics of the two groups were examined using Chi-Square tests for categoricall variables (and reporting the Fisher's Exact Test p value where cell sizes were small) and the independent samples t-test for continuous data. Due to the small sample size (< 20 subjects), deviation from the normal distribution for continuous data was not determined for the cohort.

Food diaries: Frequency analysis was carried out to obtain the median number of days recorded in the diet diary. Mean (plus or minus standard deviation (SD)) of the daily intake of fibre and fluids was assessed. Differences between the two groups on average fibre or fluid intake during each of the four recording weeks, and for all diaries combined, were analysed using independent samples t-tests. The total fibre (grams) and fluid (litres) intake consumed over the three days for each food diary was used for the analysis. For missing data mean imputation was used, determined by estimating the average fibre and fluid intake of each participant prior to the occurrence of the missing data. This approach was deemed to be more appropriate than a mean group imputation as fibre and fluid intakes varied greatly between the groups.

Bowel habits: Completed Bristol Stool Charts, frequency and type of bowel habit were assessed. For number of bowel openings reported, the average across the three days of each food diary was compared across the four time points, between the two groups using a repeated measures analysis of variance (ANOVA). The non-parametric Friedman's test was used to assess differences in the ordinal Bristol Stool Chart ratings over time, within each of the groups separately.

Rectal volume: Differences in observed rectal volume (m^3) at radiation planning between the osmotic and the bulking laxative/probiotic groups was tested using independent samples t- tests.

Rectal gas rating: A Chi-Square test and ordinal logistic generalised estimated equation (GEE) regression models were used to identify if there was a difference in rectal gas ratings between the two groups. Chi-Square analysis was used to determine if there was an association between group and gas rating. Use of the GEE allowed for covariates (number of scans and fibre intake) to be added into the model, this provided an estimate of the effect in the form of an odds ratio (OR) and 95% confidence interval (CI) for each potential predictor variable entered into the equation. The difference in the total number of scans per group was assessed using the independent samples t-test to determine if all collected CBCT scans could be used in the GEE analysis. This analysis was conducted to ensure that there was no in-balance in scan number between the intervention groups due to poor bowel preparation. The proportion of gas and rectum failures between the groups was analysed using Mann-Whitney U test.

All analysis was conducted using appropriate statistical software (IBM SPSS version 24) and the p value of significance set at 0.05.

Results

A total of 29 patients were screened and 17 patients agreed to participate in the trial. Recruitment and data collection occurred between June and December 2016. Of these 17 patients, eight were randomised into the bulking laxative/probiotic arm and nine into the osmotic arm. Over the six month period a total of 433 initial presentation scans were analysed; 180 from the osmotic laxative group and 253 from the bulking laxative/probiotic group. Patient participation and flow are depicted in a CONSORT (Consolidated Standards or Reporting Trials) diagram (see Figure 1.)

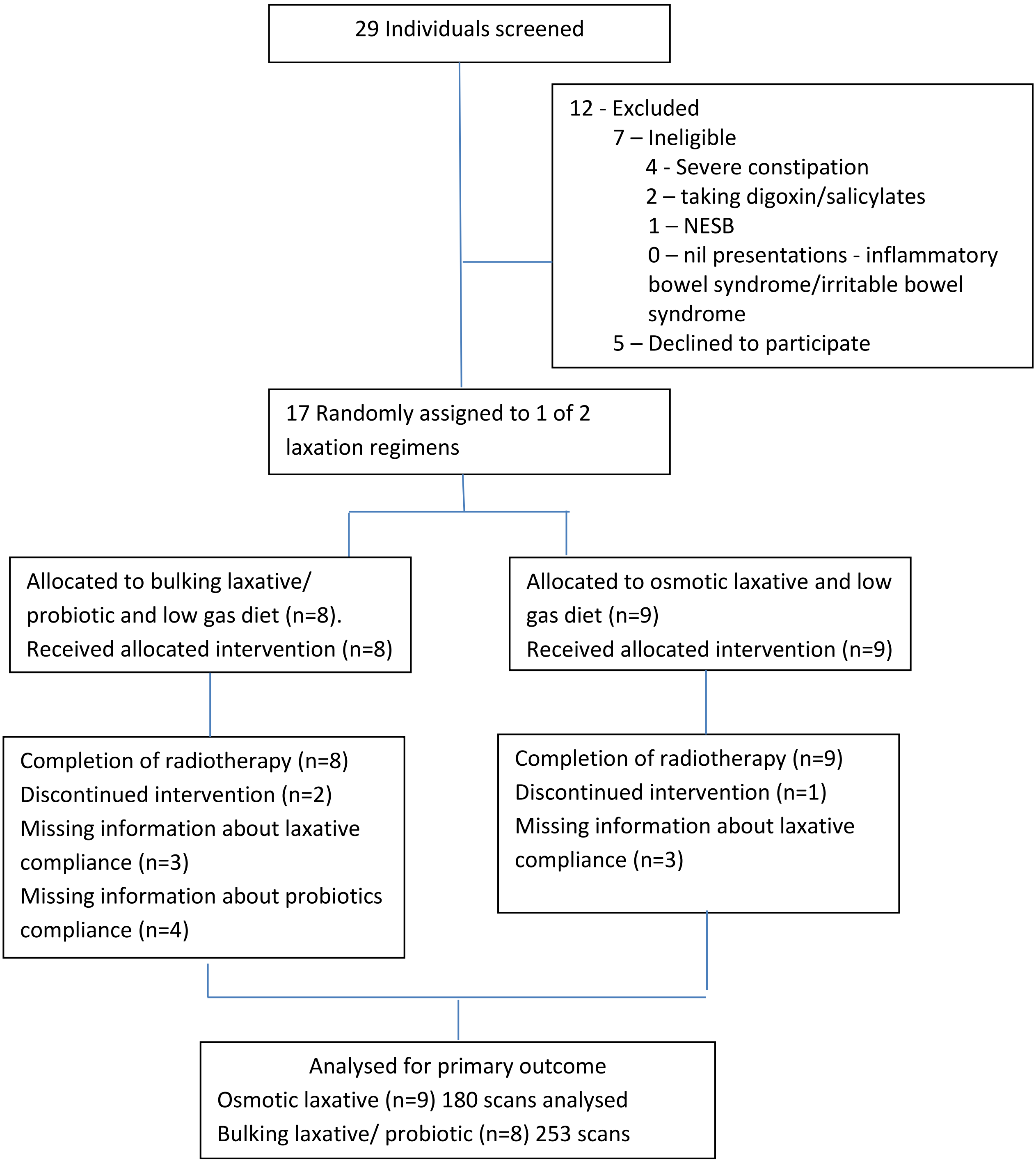


Fig 1. Flowchart of the study design of a randomised controlled trial comparing two laxation regimens for patients receiving radiotherapy to the prostate

<u>Demographics</u>

Demographic characteristics of the cohort can be found in Table 1. The mean age (SD) of the group was 74.6 (±5) years. There were no statistically significant differences seen between the demographics of the two groups.

Table 1. Demographic characteristics between the two treatment arms.

	TOTAL	Bulking laxative/ Probiotic	Osmotic laxative	
n	17	8	9	p value
Age, yrs, mean (SD)	74.6 (5.0)	75.8 (2.1)	73.6 (6.6)	0.386
BMI, kg/m^2, mean (SD)	29.8 (5.4)	28.3 (4.9)	31.0 (5.7)	0.298
Gleason score, mean (SD)	7 (2)	7 (2)	8 (2)	0.917
Travelled for treatment, % (n)	35 (6)	38 (3)	33 (3)	FET > 0.99
Living away from home for treatment, % (n)	41 (7)	63 (5)	22 (2)	FET 0.153
Space Oar, % (n)	65 (11)	63 (5)	67 (6)	FET > 0.99

Footnote. SD, Standard Deviation. FET, Fisher's Exact Test. n, number

<u>Food diary analysis outcomes</u>

Fourteen out of the 17 participants completed the four food diaries throughout the course of their treatment. Three food diaries from two participants were unable to be retrieved after being returned to nursing staff, and one patient completed only one out of four food diaries.

Average fibre intake was significantly higher in the bulking laxative group (t = 2.31, df = 15 and p = 0.036). The mean (SD) were 27.3 grams (± 6.9) for the bulking laxative/probiotic group and 19.8 grams (± 6.5) for the osmotic laxative group. Table 2 outlines the fibre and fluid intakes (average total intake over the three days of each food diary) of the groups. There was a statistically significant difference in fibre intake between the two groups during the pre-planning and the first treatment week diaries, and a significant difference in fluid intake during pre-planning, with the bulking laxative/probiotic group having a greater intake in each instance.

Two participants reported consuming gas forming foods in food diaries one and three and one participant reported to consume gas forming foods in food diaries two and four. The reported gas forming foods consumed included eggs (n=2), coffee intake greater than four cups per day (n=2), curry (n=1) and cruciferous vegetables (n=1)

Table 2. Differences in fibre and fluid intakes between the two treatment arms.

	TOTAL	Bulking laxative / Probiotic	Osmotic laxative	
n	17	8	9	p value
Fibre (grams), mean (SD)				
Food and stool diary pre planning	76 (27)	93 (19)	61 (24)	0.009
Food and stool diary Week 1	72 (28)	86 (31)	59 (18)	0.039
Food and stool diary Week 4	65 (25)	73 (27)	59 (22)	0.256
Food and stool diary Week 7	67 (23)	76 (17)	59 (26)	0.142
Fluid (litres), mean (SD)				
Food and stool diary pre planning	6.1 (2.1)	7.1 (2.1)	5.0 (1.7)	0.048
Food and stool diary Week 1	5.8 (2.2)	6.0 (2.4)	5.6 (2.1)	0.721
Food and stool diary Week 4	5.7 (2.8)	6.5 (2.9)	5.2 (2.6)	0.377
Food and stool diary Week 7	6.1 (2.4)	7.2 (2.3)	5.6 (2.4)	0.249

Bristol Stool Chart outcomes

The median Bristol Stool Chart rating for each of the groups over the four food diaries was five (interquartile range [IQR 2]) for the osmotic laxative group and four (IQR 1) for the bulking laxative/probiotic group. There was no statistical difference between the two groups (p=0.080). When both groups were compared at each time point, there was a statistically significant difference in Bristol Stool Chart rating in the pre-planning food diary with patients in the osmotic laxative group reporting looser stools than the bulking laxative group (p=0.018). This trend of looser stools continued for the osmotic laxative group with the median Bristol Stool Chart rating of stool type 5 being reported throughout treatment. The bulking laxative group reported experiencing looser stools towards the end of treatment compared to earlier in treatment, though this trend over time within the group was not significant. Table three outlines the differences in Bristol Stool rating between the two groups.

Stool Frequency outcomes

There was no statistically significant difference in the number of bowel openings per day between the two groups. There was no overall effect of time on bowel openings (F (3, 13) =1.73, p = 0.211), nor was there a group by time interaction (F (3, 13) = 0.30, p = 0.823). Thus the groups did not differ significantly by how they changed over time. Table 3 outlines the average bowel openings between the two groups.

Diarrhoea and Constipation

At the radiation planning appointment, no constipation or diarrhoea was reported in either group.
Only one individual reported constipation during the study (food diary week one and four). This patient was in the bulking laxative group and required use of an enema to achieve a bowel movement. Diarrhoea was only reported during week seven of treatment (food diary week seven) by one patient from each of the two intervention groups (although data were missing for n = 3 for the Metamucil/probiotic group). The use of Degas was reported by one patient who was in the bulking laxative group.

Table 3. Differences in Bristol Stool Chart and number of bowel openings between the two groups.

n	**TOTAL** 17	**Bulking laxative/ Probiotic** 8	**Osmotic laxative** 9	**p value**
Bristol stool score pre-intervention, median (IQR)	4 (1)	3.5 (2)	4 (1)	0.343
Bristol stool, median (IQR)				
Food and stool diary pre planning	4 (1)	4 (0)	5 (2)	0.018
Food and stool diary week 1	5 (2)	4 (2)	5 (2)	0.070
Food and stool diary week 4	5 (2)	4 (2)	5 (3)	0.487
Food and stool diary week 7	5 (2)	4.5 (2)	5 (2)	0.363
Average bowel openings, mean (SD)				
Food and stool diary pre planning	1.4 (0.4)	1.4 (0.4)	1.3 (0.5)	0.709
Food and stool diary week 1	1.5 (0.5)	1.5 (0.5)	1.5 (0.6)	0.827
Food and stool diary week 4	1.7 (0.6)	1.6 (0.6)	1.7 (0.6)	0.745
Food and stool diary week 7	1.8 (0.9)	2.0 (1.2)	1.7 (0.4)	0.616

Note, higher Bristol Stool Chart ratings indicate looser stools

Compliance to Laxative and Probiotic Prescription

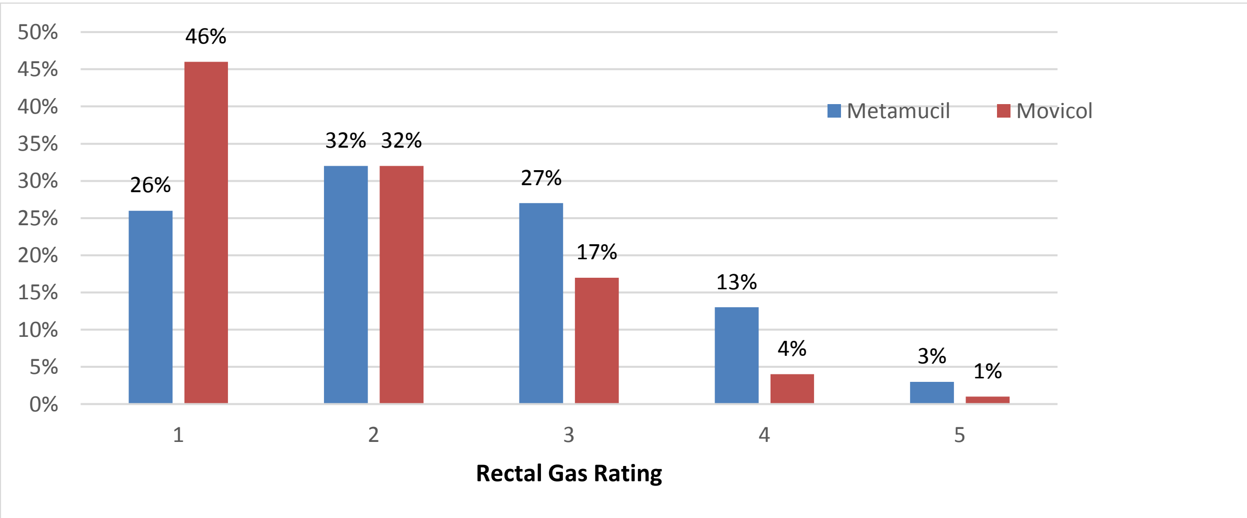
Compliance between the two groups did not vary significantly with 86% (65/76 recordings) of the bulking laxative group indicating they had taken their daily laxative and 88% (94/107 recordings) of the osmotic laxative group indicating compliance. It must be noted that three of the eight food diaries for the bulking laxative group were not included in the analysis. Compliance to daily use of the probiotic was reported at 68% for the bulking laxative group, however, data for three individuals were missing. Of the 96 recordings collected 65 individuals indicated they had taken the prescribed dose.

Cone Beam Computed Tomography Scans

No difference in rectal volume was seen across the two treatment arms on the radiation planning CBCT scans (p= 0.777). The mean (SD) rectal volume for the entire sample (n=17) was 77.6cm^3 (± 31.6). Rectal volume for the bulking laxative group was 80.1cm^3 (±29.8) and for the osmotic laxative group was 75.7cm^3 (±34.8).

Rectal gas ratings

The number of initial presentation scans per participant ranged from 12 to 40 (not including the planning scan). Chi square analysis demonstrated that participants in the bulking laxative group had a statistically significant higher proportion of scans which received a gas rating of three or above (poorer gas ratings) compared to those in the osmotic laxative group (43% versus 22% respectively, p<0.001, see Figure 2). The median (IQR) gas rating for each treatment arm was 2 (1). Figure 2 demonstrates the percentage of scans within each rectal gas rating, for each treatment arm.



Footnote, rectal gas ratings: (1) no gas present, (2) gas occupying 5% to less than 25%, (3) 25% to less than 50%, (4) 50% to less than 75% and (5) 75% to less than 100% of the rectum

Figure 2. Percentage of scans per treatment group based on rectal gas rating.

The number of scans per group did not differ significantly (p=0.054) (n=180 osmotic laxative and n=253 bulking laxative group), thus the total number of scans collected (n=433) was used in the GEE. Results showed that the odds of a higher (poorer) gas rating were increased for the bulking laxative group (OR = 3.20, 95% CI 1.77-5.78, p<0.001). When the average fibre intake across the four food diaries was input into the GEE as a covariate, the model remained significant and intervention group remained a significant predictor (OR 3.15, 95% CI 1.35-7.36, p = 0.008). When fibre intakes were ran as a single variable in the GEE it was not a significant predictor of gas rating (OR 1.001, 95% CI 0.92 - 1.09).

The median (IQR) proportion of scans rated as gas fails was higher in the bulking laxative group 2.9% (11%) compared to the osmotic laxative group 1.5% (9%) but there was no significant difference between the two groups (p=0.284). There was no differences between the groups in the median (IQR) number of rectum fails; bulking laxative group (IQR) 0.1% (5%), osmotic laxative group 0% (5%) (p=0.835). Figure 3 demonstrates the number of gas and rectum fails per participant.

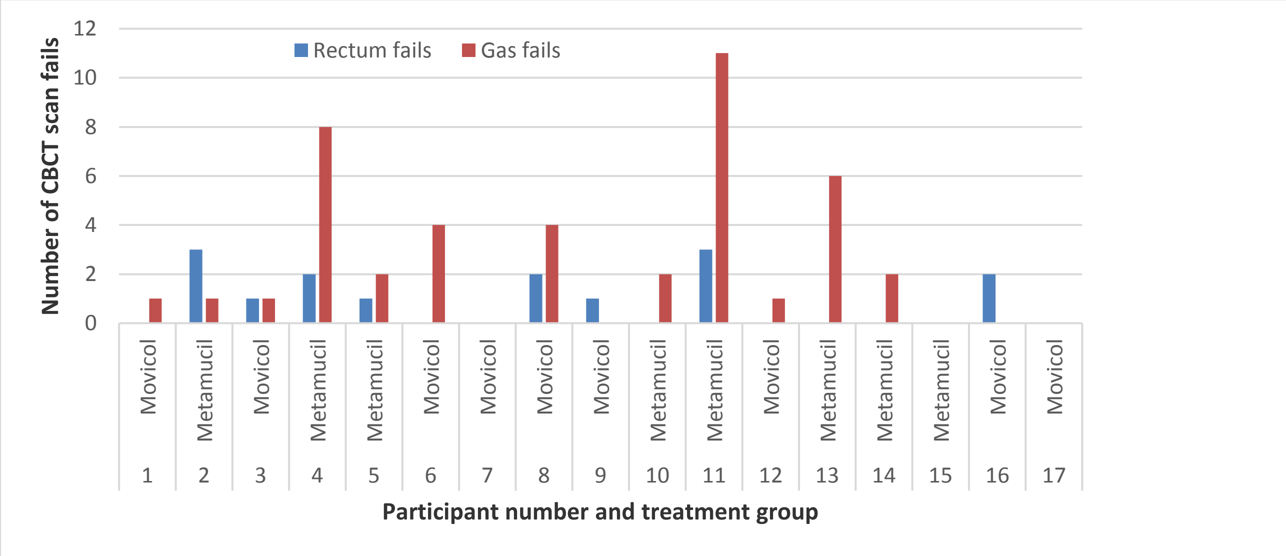


Figure 3. Number of gas and rectum fails per participant.

Discussion

To the author's knowledge, this is the first randomised controlled trial looking specifically at the effect of two different laxation regimens on rectal gas levels in men with prostate cancer undergoing EBRT to the prostate. The results of this study indicate that there is a significant benefit in the use of an osmotic laxative to reduce rectal gas ratings. This has been demonstrated by the outcome achieved with the odds of a high gas rating in the bulking laxative/probiotic group being 3.2 times greater than the odds of a high gas rating in the osmotic laxative group. Achieving a lower rectal gas rating ensure adequate radiation dose delivery to the prostate while minimising treatment related side effects (Lips, 2011; McNair, 2011).

Comparison of the findings of this study with previous research is limited as previous published literature compares a laxative and dietary regimen to no intervention. A study conducted by Smitsman and colleagues demonstrated a significant reduction in gas pockets when patients were placed on a low gas diet with an osmotic laxative (Smitsman, 2008). Darud and colleagues found that use of a low fibre diet and an osmotic laxative resulted in a trend for prostate motion to decrease (Darud, 2010). In another study using a low gas diet and a bulking laxative (10 grams psyllium per day) a reduction in rectal volume and variability of prostate movement was demonstrated (Oats, 2014). The results from this study indicate that the osmotic laxative in conjunction with a low gas diet is superior to a bulking laxative and a low gas diet in reducing rectal gas for treatment and further adds to the existing literature base.

The two laxatives used for this study vary in their modes of action in facilitating rectal evacuation. The osmotic laxative Movicol®, acts by attracting water osmotically into the large intestine with the resulting bulk stimulating peristalsis. Although osmotic laxatives have the potential to cause flatulence and diarrhoea (Yakabowich, 1990) when used in a lower dose in the form of Movicol half strength® such as in this study, the occurrence of gas was statistically lower compared to the bulking laxative. In addition to this there was a trend towards fewer CBCT scan fails for participants in the osmotic laxative group with participants achieving a successful bowel evacuation before treatment and lower amounts of gas evident on the collected scans.

The bulk-forming laxative Metamucil®, by comparison, acts by retaining water so the stool remains soft and large which stimulates peristalsis. Psyllium, the main component in Metamucil® and is only partially fermented and retains its water-holding gelled structure throughout the large bowel. This can minimise fermentation by gut microbiota and reduces bowel gas (McRorie, 2015). Results from this study however, have demonstrated that participants in the bulking laxative group experienced more occasions where they were unsuccessful in achieving a bowel evacuation before treatment ("failed rectum" and "failed gas") and had statistically higher gas rating levels compared to the osmotic laxative group. This suggests that the level of fermentation of the psyllium by an individual's gut microbiota is high enough to impact on gas levels in the rectum and prostate positioning. Despite the concurrent addition of beneficial probiotics, it is predicted that the difference between groups would have been higher without probiotic supplementation, given their known desirable effect on microbiota.

The NHMRC recommend a total fluid intake is 3.4 litres per day, which includes 2.6 litres drinking fluid (NHMRC, 2006). The average total fluid intake in the bulking laxative group was 2-2.4 litres per day and in the osmotic laxative group 1.6-1.8 litres per day. Intakes were likely to be higher in the bulking laxative group as 600 millilitres of water is required to be consumed with the Metamucil® compared to only 125ml with the Movicol®. However, some drinking fluids were likely to have been omitted from the food diary with the most frequent omission noted by the author being the water required for daily bladder preparation for treatment. It is also possible that males undergoing EBRT for prostate cancer may reduce fluid intake due to urinary frequency and retention toxicities associated with the cancer and treatment (Oates, 2011).

Participants in the bulking laxative/probiotic group achieved close to the recommend 30 grams of fibre per day set by the NHMRC (NHMRC, 2006). Participants in this group consumed on average 27.3 grams per day while the osmotic laxative group consumed on average 19.8 grams per day. The addition of nine grams of fibre per day from the Metamucil® is a likely contributor to the difference in fibre intakes between the two groups. The anticipated effect of higher fibre intakes in promoting a bowel evacuation prior to daily radiation treatment did not result in a favourable outcome for the bulking laxative group, with participants having higher gas ratings on CBCT scans and trending towards more gas and rectum fails. In a study conducted by McNair and colleagues rectal gas was the only factor to correlate with rectal distension, but this was not associated with a change in fibre intake. Fibre intakes in this study ranged from 11-20 grams per day, lower than levels achieved in the present study (McNair, 2011). These results are similar to those found in the present study with fibre not being a predictor of higher rectal gas levels. However, the bulking laxative group achieved a higher intake of fibre (25-30 grams per day) in line with the NHMRC guidelines which ensures adequate fibre intakes are achieved during treatment (NHMRC, 2006).

When assessing the regularity of the stools during the course of treatment the groups did not differ significantly over time and there was no statistically significant difference in median Bristol Stool rating over time (when considering the whole sample, n=17). The change in reported stool type from 4 to 5 in the osmotic laxative group indicates the osmotic laxative altered the consistency of the stool with this being statistically significant in the pre planning food diary. Diarrhoea was only reported in week seven by one participant in the osmotic laxative group and no constipation was reported within the group. The alteration in stool consistency in the osmotic laxative group was advantageous in promoting successful daily bowel evacuations prior to treatment with stools being softer and easy to pass. The reported change in consistency did not impact on participants with number of bowel openings per day and diarrhoea not significantly changing over time for the osmotic laxative group.

In comparison the median Bristol Stool Chart rating for the bulking laxative group was 4 (normal consistency) and this rating was consistent throughout the duration of treatment. Only one participant reported experiencing diarrhoea in the week seven food diary and one participant reported constipation in the week one and four food diaries. Reported average fibre and fluid intake by this participant was 20.22 grams and 1.54 litres respectively. The exact cause of the constipation is unknown as fibre and fluid intakes were adequate to promote a bowel motion. The use of enemas at the CWCCC is infrequent within the treatment setting and is generally used as a last resort to assist patients achieve an empty rectum for treatment. Constipation reduces gut transit and prolongs fermentation of fermentable carbohydrates, which may contribute to increased gas production in the large bowel. Preventing its occurrence during radiation treatment is essential (Azpiroz, 2010).

Compliance to the low gas diet was high amongst all participants with only five episodes of high gas food consumption being documented over the study period. When consumption of high gas foods were recorded, the frequency of consumption (aside from the coffee) was only once during the three day food diary. Recording of data was high among the group (94% n=16) with only one participant refusing to complete the diary. This result is similar to that of two previous studies who had 100% compliance rates with recording of a daily diet diary during treatment (Oates, 2013; McNair, 2011).

The impact of the probiotic agent used is difficult to determine. From the results obtained the levels of gas in the bulking laxative group were significantly higher most likely due to the increased availability of fermentable carbohydrates from the Metamucil®. Thus in this study the probiotics did not assist in reducing rectal gas as previously hypothesised. The gut microbiota profile can rapidly adapt depending on the substrates consumed in the diet (Wu, 2011). For example, regular consumption of a substrate which is known to cause flatulence in an individual will result in the proliferation of the microbiota that metabolise the substrate. Over time, consistent intake of this substrate that will result in decreased levels of gas (Azpiroz, 2014; Claesson, 2013). In the present study the psyllium in the Metamucil® was the additional fermentable carbohydrate, however the levels of gas production did not reduce over eight week treatment time frame in the bulking laxative group. This suggests that it may take considerable time for gut microbiota levels to increase to a substantial level to make a significant difference to rectal gas levels. In addition to this, the composition of intraluminal flora is highly individual, which explains the variation in gas production in different subjects (Furne, 1996). In a study conducted by Furne and colleagues the flatus levels of 25 healthy subjects were measured over a one week period. Participants then consumed Lactulose® (10 grams per day) for a week with results showing a significant increase in flatus frequency ($p<0.001$). However, some subjects consistently passed gas more often than others, demonstrating differences in the ability of gut microbiota to produce gas from a given quantity of fermentable carbohydrate (Furne, 1996).

A study conducted by Bouhnik and colleagues explored the effect of Movicol® and Lactulose® on gut microbiota (Bouhnik, 2004). In this study, patients diagnosed with chronic constipation were randomly assigned to either the Movicol® or the Lactulose® treatment arm and were prescribed a standard dose for a 28 day period. Results showed that there was a statistically significant decrease in the short chain fatty acids butyrate and acetate and a decrease in faecal bacterial mass after 28 days of taking Movicol®. This was compared to the Lactulose® which was shown to act as a pre biotic providing a fuel substrate for the colonic bacteria, significantly increasing levels of *bifidobacteria* and *β-galactosidase* activity (Bouhnik, 2004). Given this finding, and that patients take the laxative Movicol® as standard treatment for approximately 12 weeks while receiving EBRT to the prostate, the addition of a probiotic may be warranted in this patient group. The use of probiotics during EBRT to the prostate may assist in maintaining and improving the robustness of the gut microbiota. However, this is an emerging area of research and further study is warranted to determine its use in this clinical setting.

A high proportion of patients (76%) receiving treatment resided outside of the Orange area, with 41 per cent of patients living away from home to receive treatment and 35 per cent of patients travelling daily. For those individuals the distance travelled for radiation will remain an issue, as accommodation, fuel and time away from family and work will be costly and with increased stress and anxiety associated with this (Mercuri, 2005; Martin-McDonald, 2003). For these patients the change in routine may have an impact on their bowel habits, although this was not assessed in detail during this study. If optimal bowel preparation can be identified and this reduces the number of failed treatments, then those who do travel will be less inconvenienced. Daily treatment for prostate patients is scheduled in the morning (with the aim to treat with an empty bowel) as the majority of patients achieve early morning bowel evacuations. For those who travel, which was up to one to two hours one way, this may result in a change to their toileting routine and so making it difficult to empty bowels before treatment.

Strengths and Limitations

To the best of the author's knowledge, this is the first study to compare the two most common types of laxatives used within the Australian context to achieve an empty rectum for prostate radiation therapy. The study was conducted in a rural location which provided a snap shot of the demographics of the patients being treated and their dietary habits. The study used a randomised design and protocols from the CONSORT statement were used to maximise the credibility of the study (CONSORT Group). In addition, enough data was collected (participants and scans) to achieve sufficient power to detect a small to medium effect size in difference of rectal gas ratings between groups.

Due to time and resource constraints this study has several limitations. The method of analysis to determine rectal gas levels was subjective in nature. Objectively measuring rectal volumes using available computer software would provide more robust data but this was beyond the scope of this study. In addition to this there was limited capacity to test external validity of the rectal gas ratings collected from the CBCT scans. The food diaries only provided a 12 day snap shot of fibre and fluid intakes and bowel habits of participants. Having patients' complete daily food and bowel habit diaries during treatment would provide a more comprehensive data set, but would be a burden on the participants and most likely result in lower compliance with the diaries. Mean imputation was used to account for the missing data from the food diaries and final totals reported may not be reflective of actual intakes. Finally, the inclusion of the probiotic in only the bulking laxative arm makes it difficult to definitively determine if the bulking laxative was the cause of the higher rectal gas ratings. However, all evidence suggest probiotics lower gas levels so this is not likely to have a causative effect.

Conclusion

This study has demonstrated that an osmotic laxative is more effective than a bulking laxative and probiotic at achieving low rectal gas levels during treatment. The hypothesis that a bulking laxative and a probiotic being more effective at reducing rectal gas during treatment was not supported in this study. However results provide evidence to support current practice at the CWCCC. Although rectal gas levels were lower in the osmotic laxative group, at times gas levels were above recommended thresholds and not suitable for treatment. As per previous experiences at the CWCCC daily use of Movicol® does not result in trouble free bowel preparation. Understanding the physiology behind gut functioning to determine factors influencing rectal fullness and rectal gas is complex and when taking into consideration that every individual has their own unique gut microbiota, the determining factors on an individual level may vary considerably. Further research could determine other factors in addition to the use of laxatives and probiotics that may play a role in achieving an empty rectum during EBRT to the prostate.

Recommendations

Given the major findings of this study, it is recommended that the organisation:

- Continue to use Movicol® and the low gas diet as the standard bowel preparation for patients undergoing EBRT to the prostate
- Continue to involve dietetic staff in the education and support of patients before and during treatment
- Patients undergoing treatment should be encouraged to consume adequate amounts of fibre in line with the NHMRC guidelines of 30 grams per day, aiming for higher intakes from non-fermentable carbohydrates
- Patients should continue to avoid foods known to have high levels of fermentable carbohydrates
- Dissemination of these results beyond the health service to inform practice nationally and globally

Suggestions for further research:

- Additional research is required to explore the role of probiotics during EBRT to the prostate.
- Further research is required to determine the effect of long term use of Movicol® on gut microbiota and the role that probiotics may play in maintaining levels during treatment
- Ongoing research is required to understand the physiology behind gut functioning taking into consideration gut microbiota and how this influences rectal fullness and rectal gas levels
- Evaluate the impact on stress and bowel habits that travelling and living away from home has on patients while receiving active treatment
- Objective measurements on the collected CBCT could occur to provide additional rigour to the study results
- Conducting the study again to include a larger sample size to see if a trend towards lower scan fail can be substantiated

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Appendix One: Participant information and consent forms

PARTICIPANT INFORMATION SHEET

Achieving an Empty Rectum for Prostate Radiation Therapy

Invitation
You are invited to participate in a research study into the use of laxatives in achieving an empty bowel for radiation therapy to the prostate.

The study is being conducted by Nicole Weston, Senior Oncology Dietitian, Central West Cancer Care Centre, Orange Health Service.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. 'What is the purpose of this study?'

The purpose is to investigate whether Metamucil and a probiotic (good bowel bacteria) are more effective than Movicol at emptying the bowel while receiving daily radiation therapy to the prostate. It is hoped that results from this study will identify the most effective way to ensure an empty bowel while receiving treatment.

2. 'Why have I been invited to participate in this study?'
You are invited to participate in this study because you are about to undergo radiation therapy for prostate cancer.

3. 'What does this study involve?'
If you agree to participate in this study, you will be asked to sign the attached Consent Form.

You will then be randomly assigned into one of two groups. One group will be prescribed Movicol half strength and a low gas diet, which is the current prescription at the Central West Cancer Care Centre. The other group will be prescribed Metamucil, Nutralife Probiotic (to promote good bowel bacteria and reduce bowel gas) and a low gas diet. The treatment being investigated in this study (Metamucil and probiotic) differs from the standard treatment offered in this institution (Movicol). Metamucil is used at other treatment centers around Australia for bowel emptying for prostate cancer, however these two approaches used to empty the bowels have never been compared. The use of probiotics has been described in other studies, but has not been used locally.

Sometimes researchers don't know the best way of treating patients with a particular condition so comparisons need to be made between different treatments. To do this, study participants are put into groups and given different treatments, and the results are compared to see whether one treatment is better. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the doctor nor the study participant can decide which treatment the participant receives.

As per standard practice at the Central West Cancer Care Centre you will be contacted by phone by a Dietitian approximately two weeks prior to attending for your radiation planning session. During this phone consultation the laxative you are to take and if you will be prescribed the probiotic will be discussed. In addition to this the Dietitian will ask you for information on what you normally eat, any current medical conditions and medications prescribed and your current bowel habits. The Dietitian will then provide tailored information on what foods to consume or avoid while following the low gas diet and will post to you written information on the low gas diet for your reference during treatment. You will be required to commence taking the laxative with or without the probiotic and commence the low gas diet one week before attending for your prostate radiation planning session.

If you are allocated the probiotic to take during the course of the study this will be supplied to you at no cost and mailed to you after the phone consultation with the Dietitian. The laxatives are to be purchased by you for the course of your treatment and this is in line with current practice at the Central West Cancer Care Centre.

You will be asked to complete the 3 day food and bowel habit diary at four different time points during the course of your treatment, specifically in the week leading up to your radiation planning day, and in weeks one, four and seven of your treatment. This will involve writing down all of the food and fluid that you consume over the course of the three days. The diaries will be used to determine fibre and fluid intakes and compliance to the low gas diet.

An appointment with the dietitian will be scheduled for you for your radiation planning session and weekly during your treatment. At these appointments the Dietitian will ask you about your diet, current bowel habits, use of the laxatives and use of the probiotic if you have been assigned to this group. You will be able to ask the Dietitian about any concerns or issues that you are having with the diet, laxatives or with your bowels. This is offered as per standard practice while receiving treatment to the prostate. The Dietitian will collect your completed food and bowel habit diaries at your planning appointment and at your week one, four and seven appointments.

At your radiation planning day the Radiation Therapists will take a Cone-beam Computed Tomography (CBCT) scan as part of their usual practice. These are used to assess the size and shape of the bowel and the presence of any gas or faecal material. As part of usual practice the CBCT scans are also taken routinely daily during the first week of your treatment and then once a week for the remainder of your treatment. A total of 12 CBCT images will be recorded in your medical records. These images will be used in the study to assess the volume of the bowel and the amount of gas/faecal matter present in the bowel and will help us to determine which laxative is most effective at emptying the bowel for treatment.

Your personal medical records will be accessed to obtain information regarding your age, weight, height, tumour stage, tumour grade, rural location, travel required for treatment and if you are residing away from your usual residence during treatment.

This study will be conducted over ten months. In addition, the researchers would like to have access to your medical record to obtain information relevant to the study.

Figure 1. Flow chart of study design

The Dietitian will make contact two weeks before attending for your radiation planning session, to discuss diet and laxative use

↓

One week before your radiation planning day – Commence using the laxative and low gas diet and complete the 3 day food and bowel habits diary

↓

Attend the Central West Cancer Care Centre for radiation planning. CBCT scan to be taken. Hand in completed food and bowel habit diary

Approximately a 3 week gap ↓

Commence radiation treatment. CBCT scans to be taken daily during the first week of treatment. Complete a 3 day food and bowel habit diary and hand into Dietitian at review appointment.

↓

CBCT scans collected weekly in addition to weekly nutrition support as per standard practice during treatment.

↓

Additional 3 day food and bowel habits diary completed in weeks 4 and 7 of treatment. Completed diaries to be collected by the Dietitian at the review appointments

4. 'Are there risks to me in taking part in this study?'
All medical procedures - whether for diagnosis or treatment, routine or experimental - involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study.

The known risks of this study include:

- The inconvenience of giving up time to participate in the research project particularly the time required to complete the food and bowel habits diary.

5. 'What happens if I suffer injury or complications as a result of the study?'
If you suffer any injuries or complications as a result of this study, you should contact Nicole Weston at 63697360 as soon as possible, who will assist you in arranging appropriate medical treatment.
In some circumstances you may have a right to take legal action to obtain compensation for injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by the product under investigation

in the study, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor).

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can *receive* medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

6. 'Will I benefit from the study?'
This study aims to further medical knowledge and may improve future treatment for patients having radiation therapy for prostate cancer; however it may not directly benefit you.

7. 'How is this study being paid for?'
The study is being *sponsored* by the Health Education Training Institute, who are providing protected research hours for the lead researcher to conduct the study. Funding for the probiotic is being sought by internal funding from the Orange Health Service. There are no conflicts of interest that any investigators may have.

All of the money being paid by the sponsor to run the trial will be deposited into an account managed by Orange Health Service. No money is paid directly to individual researchers.

8. 'Will taking part in this study cost me anything, and will I be paid?
Participation in this study will not cost you anything, nor will you be paid.

9. 'What if I don't want to take part in this study?'
Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

10. 'What if I participate and want to withdraw later?'
New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. If you decide to withdraw, it will not affect the treatment you receive then or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

In withdrawing from the study you will cease completing the 3 day food and bowel habits diary but will still be required to take a laxative and follow the low gas diet to achieve an empty bowel for treatment. Current practice at the Central West Cancer Care Centre is for patients to use Movicol half strength daily during treatment.

If you decide to withdraw from the study, we will not collect any more information from you. Please let us know at the time when you withdraw what you would like us to do with the information we have collected about you up to that point. If you wish your information will be removed from our study records and will not be included in the study results, up to the point that we have analysed and published the results.

11. 'How will my confidentiality be protected?'

Of the people treating you, only Nicole Weston and the Dietitians and Nursing staff involved in your care will know whether or not you are participating in this study.

Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers named above will have access to your details and results that will be held securely at the Central West Cancer Care Centre.

13. 'What happens with the results?'
This study if being completed as part of the Rural Research Capacity Building Program and the researcher is required to submit a final report back to the Health Education and Training Institute at the end of the program. This report will be displayed on their public website. It is also envisaged to offer the findings for publication in a peer reviewed journal and to present at nutrition and radiation oncology conferences.

Results of the study will be provided to you, if you wish. You can indicate if you would like to receive a copy of the study results when you sign the consent form.

14. 'What happens to my treatment when the study is finished?'
At the completion of your radiation treatment the use of the laxative and the probiotic can cease.

15. 'What should I do if I want to discuss this study further before I decide?'
When you have read this information, Nicole Weston will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact her on 63697360.

16. 'Who should I contact if I have concerns about the conduct of this study?'
This study has been approved by The Greater Western Human Research Ethics Committee (HREC). Any person with concerns or complaints about the conduct of this study should contact Executive Officer of Greater Western HREC. You should contact them on 63305941 and quote AU/1/BA92220

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

PARTICIPANT CONSENT FORM

Achieving an Empty Rectum for Prostate Radiation Therapy

I have read the attached Participant Information Form on the above named research study, and understand the purpose and procedures described within it.

I have been made aware of any known or expected inconvenience, risk, discomfort or potential side effect and of their implications as far as they are currently known by the researchers.

I understand that my participation in this study will allow the researchers to *have* access to my medical records, and I agree to this. I understand that my medical records will remain confidential.

I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this study and understand that I can withdraw at any time.

I understand that I will be given a signed copy of this document to keep.

Would you like to receive feedback about the overall results of this study?
YES ☐ NO ☐

If you answered **YES**, please indicate your preferred form of feedback and address:

☐ Postal: ____

☐ Email:____

Participant's name (please print): ………………………………………………………………

Signature: ………………………………………………….. Date: ………………………………

Please return this completed form in the envelope provided at your earliest convenience.

Appendix Two: Low gas diet information

Prostate Treatment Diet Guidelines		
Food Group	**Choose**	**Avoid**
Beverages 1.5 – 2 L per day	All fluids except the ones listed to avoid <u>Keep your fluids up.</u> Try to drink 8 cups of fluid per day, this will help with your bladder filling. Water, juice, cordial and milk are suitable choices	Carbonated beverages such as soft drink, beer and mineral water. Limit coffee to less than 4 cups per day and tea to less than 6 cups per day
Breads and Cereals (4+ serves) 1 serve = 1 slice bread <u>OR</u> 1 cup cereal <u>OR</u> 1 cup cooked pasta or rice	Most cereals are suitable • Wholemeal bread, toast or rolls • Crackers and biscuits made from white or wholemeal flour including Sao's, Jatz, Milk arrowroot, Lattice • English muffins, plain pancakes, bagels • Plain cakes and cookies • Rice and Pasta	Muesli and cereals with nuts, dried fruit, coconut and seeds.
Fruit (2 serves) 1 serve = 1 medium piece <u>OR</u> 2 small pieces <u>OR</u> 1 cup tin fruit	All fruit except the ones listed to avoid e.g. – banana, apple, orange, peach, pear, mango, kiwi fruit, strawberries, blueberries, rockmelon, watermelon, pineapple etc.	Prunes/plums – limit to 1-2 per day Cherries – limit to 6-8 per day Dried fruit – limit to a small handful (golf ball size) per day
Vegetables (5 serves) 1 serve = ½ cup cooked vegetables OR 1 cup salad vegetables	All other vegetables except those listed to avoid e.g.- potato, pumpkin, sweet potato, carrot, peas, beans, corn, asparagus, choko, squash, lettuce, tomato, cucumber, avocado, beetroot etc.	Onion, garlic, leek, spring onions cabbage, cauliflower, broccoli, brussel sprouts, legumes such as baked beans, soya beans, lentils, split peas, barley and soup mix
Meat and Alternatives	All lean meats are suitable including beef, lamb, pork, chicken, fish and seafood	Processed meats such as spicy sausages, salami, chorizo, hot dogs and pepperoni Nuts – limit to a small handful (golf ball size) per day Eggs
Dairy	All dairy foods are suitable	
Miscellaneous	Spreads such as vegemite, jam, honey and smooth peanut butter	Soups containing any ingredient listed above under avoid category. Chilli, spicy foods and curries. Products such as cough syrups, lozenges and medications containing sorbitol or mannitol represented on the ingredients list by the number 420 or 421

Appendix 3: Food Diary

Diary instructions

Use these diary sheets to record (1) your food intake and (2) your bowel habits each day while you are undergoing radiation treatment. Please include your food intake and bowel habits on the weekends.

At the top of the page, NUMBER EACH DAY consecutively, starting from WHEN YOU BEGAN THE DIET. Alongside, record the day of the week and the date.

For example, if you started your diet on Monday the 1st of February 2016:

Day of diet ___1___ Day of the week __Monday______ Date __1 February 2016_____

In the INTAKE column, record:

- the time of your meals and snacks.
- which foods and drinks you had including the quantity e.g. ½ cup, 1 cup, small handful.
- vitamin & mineral supplements.
- any medication/s taken.

For example

INTAKE Food, drinks, vitamins, medicines
Breakfast 7am 2 weetbix with ½ cup of milk + 1 x banana + 1 piece of toast with jam and butter and 1 cup tea Diabetes and blood pressure medication
Lunch 12.30pm 1 sandwich with ham +tomato, cheese, lettuce and chutney + 1 cup juice and 2 scotch finger biscuits.

In the BOWEL HABITS column, answer the questions by ticking the relevant box and record the number of bowel motions you experienced that day

- **Laxative use**: Please indicate whether or not you took the prescribed laxative by ticking the relevant box (yes or no).
- **Probiotic use**: Please indicate whether or not you took the prescribed probiotic by ticking the relevant box (yes or no).

Day of Diet ______ Day of the week ______________ Date ___________________

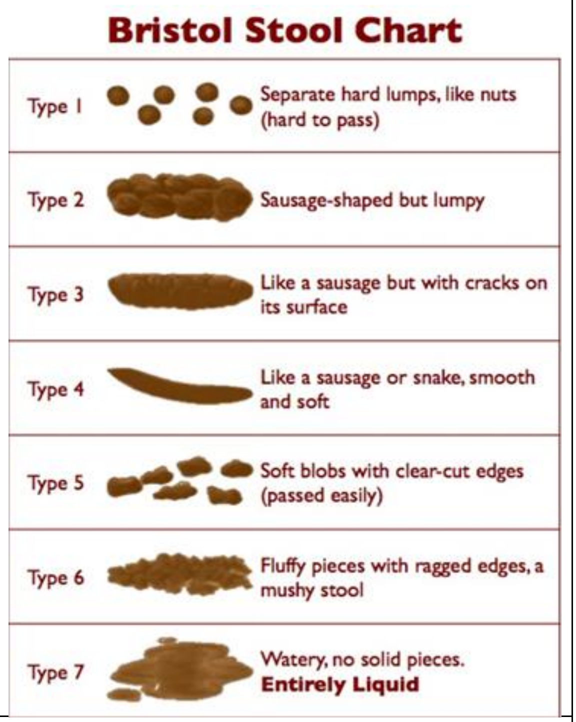
<table>
<tr><td>INTAKE
Food, drinks, vitamins, medicines</td><td>BOWEL HABITS</td></tr>
<tr><td>Breakfast</td><td>Have you opened your bowels today?

Yes ☐

No ☐</td></tr>
<tr><td>Morning tea</td><td rowspan="2">If you have opened your bowels today, how many times? (put 0 here if you have NOT opened your bowels)

____

If you have opened your bowels today, how would you describe your bowel motion? Please circle the number next to the description that most closely matches your bowel motion:



</td></tr>
<tr><td>Lunch</td></tr>
<tr><td>Afternoon tea</td><td></td></tr>
</table>

	Have you taken your laxative today? Yes ☐ No ☐
Dinner	Have taken any anti diarrhoea medication today (e.g. Gastrostop or Imodium)? Yes ☐ No ☐
Supper	Have you taken your probiotic today? Yes ☐ No ☐