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CRANBERRY CAPSULES

The efficacy of cranberry capsules in the management
of acute radiation cystitis in men with prostate cancer

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ABSTRACT

Background: Acute radiation-induced cystitis is a common side effect of radiation therapy (RT) to the pelvis, with up to 40-50% of prostate cancer patients suffering from cystitis to some extent. Acute symptoms can occur within weeks of radiation treatment and include urinary urgency, frequency, dysuria, and hematuria. Currently there is no effective treatment for radiation cystitis. Here, in a double-blinded pilot study, we investigated the effect of standardised cranberry capsules on the extent of radiation-induced cystitis, and how this impacts on quality of life in prostate cancer patients.

Methodology: A total of 41 men receiving RT for prostate cancer at the Southern Blood and Cancer Center (SBCC) in Dunedin participated in this trial, which opened in May 2012. The men took one capsule a day during breakfast from their first day of treatment until two weeks after completion of treatment. This took place regardless of which arm they were randomised to. Cranberry capsules contained 72mg of proanthocyanidins (PACs) each and were indistinguishable from placebo capsules. Patients, clinicians and research assistants were blinded to the content of the capsules. Severity of cystitis was assessed using a modified urinary domain of the Expanded Prostate Cancer Index Composite (EPIC) scale. Items included severity of symptoms (pain, blood in urine, leakage, urinary frequency in day and night) use of pads and symptomatic relief (URAL), as well as the effect of these symptoms on daily life.

Results: This thesis analysed the results of the first 10 cranberry and 10 control patients who presented with low baseline EPIC scores. The results showed that cranberry capsules seem to decrease certain aspects of radiation cystitis both with regard to physical symptoms and the effect on quality of life. However results in this small cohort did not generally reach statistical significance and limitations of the trial methodology have been recognised.

Limitations: Prostate cancer can lead to cystitis-like symptoms, it was therefore expected some men would present with low EPIC scores in some measures but that randomisation would evenly divide participants. However unblinding of the first 20 patients showed this was not the case and baseline scores were not evenly distributed over the cranberry and control arms, possibly due to low patient numbers. As such an uneven distribution had the potential to confound the results; we replaced five datasets from men with very high baseline scores with those from men with no or very low baseline scores.

At the time of the trial men receiving prostate RT at the SBCC were encouraged to drink at least two litres of fluid per day, mostly consisting of water to reduce the volume of bladder in the radiation field and thus reduce cystitis symptoms. However, during this trial we found that this resulted in overhydration in some men, overstretching their bladder wall and increasing urinary side effects. This was especially true for older men who were used to a very low fluid intake prior to treatment. Due to this excessive hydration in some men it was sometimes difficult to identify what was causing urinary symptoms. Fluid intake guidelines at the SBCC have since been revised as a result of this trial and the last 20 men to enter the study (not analysed in this thesis) were given new hydration advice.

Trial participants received the Southern Blood and Cancer Center routine standard of care, which included the use of URAL sachets for symptomatic relief. At the start of the study it was not appreciated how freely URAL is prescribed in Dunedin by nurses and radiation therapists, sometimes at the slightest change in urinary symptoms. URAL masks the symptoms of cystitis and therefore it is possible that 'over prescribing' of URAL in the current trial, masked whether cranberry capsules were more effective than placebo capsules in preventing radiation cystitis.

Finally, based on the literature, the Urinary Domain of EPIC seemed most suitable to measure physical symptoms and the effect on quality of life (QoL). The Urinary Domain of EPIC was tested in this pilot study to see how useful it would be as a measure of radiation cystitis in prostate cancer patients in New Zealand. The scale is subjective and therefore it is important questions are phrased to be interpreted similarly by all participants. However, as discussed in this thesis, it became apparent that several of the items were quite ambiguous and therefore left open to interpretation.

Conclusion: In light of the limitations of this trial and the positive trends in the results, further investigation is warranted. Future research should focus particularly on establishing consistent hydration levels, regulating the use of symptomatic relief and developing improved methods for assessing the level of acute radiation cystitis.

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LIST OF ABBREVIATIONS

AUASI: American Urological Association Symptom Index Score

BPH: Benign Prostatic Hyperplasia

CBCT: Cone Beam Computed Tomography

CT: Computed Tomography

CTC: Common Toxicity Criteria

DNA: Deoxyribonucleic acid

DVH: Dose Volume Histograms

EORTC: European Organisation for Research and Treatment of Cancer

EPIC: Expanded Prostate Cancer Index

IGIMRT: Image Guided Intensity Modulated Radiation Therapy

IMRT: Intensity Modulated Radiation Therapy

IPSS: International Prostate Symptom Score

ISS: Incontinence Symptom Severity Index

LINAC: Linear accelerator

UOW: University of Otago, Wellington

RT: Radiation therapy

RTOG: Radiation Therapy Oncology Group

SBCC: Southern Blood and Cancer Center

QoL: Quality of life

1 CHAPTER 1: INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy in men in New Zealand, with more than 2900 new cases reported annually (1). The main treatment options for prostate cancer are radiation therapy (RT), surgery and hormone therapy. RT uses ionizing radiation in the form of high-energy photons (x-rays and gamma rays), or through charged particle beams (protons and electrons) (2) to kill cells by producing free radicals that generate DNA damage (3,4). RT can be delivered from both external and internal sources. External beam radiation therapy in New Zealand is delivered by a linear accelerator (LINAC). Brachytherapy is RT delivered by radioactive isotopes close to or inside organs that have been infiltrated by tumor (5).

Although ionizing radiation affects both cancer cells and normal cells, RT is delivered in such a way that it delivers a lethal dose to the tumor whilst minimising the dose to the surrounding normal tissues (6). Healthy cells contain more anti-oxidants that neutralise free radicals and therefore sustain less DNA damage than many cancer cells (7,8). In addition, normal cells are generally better at repairing DNA than cancer cells (8). However, unavoidable irradiation of normal tissues close to the treatment target does result in acute and chronic side effects which can significantly impact on a patient's quality of life (6,9).

For men receiving RT for prostate cancer, partial irradiation of the urinary bladder is common and unavoidable. As a result, 40-50% of these men will experience some degree of acute radiation cystitis during their treatment (10,11). Cystitis can develop as early as two weeks into a seven and a half week treatment regime and usually presents as urinary frequency, nocturia, urgency, leakage or occasionally hematuria (9). The presence and extent of side effects depends on patient and treatment related factors, however for some men, side effects can severely compromise their quality of life during treatment (12).

To date, there is no effective preventative treatment for radiation-induced cystitis. Clinical practice is generally based on historical and anecdotal evidence and considerable variation in care exist between radiation therapy centers world-wide (9). Recently, antioxidants such as proanthocyanidins (PACs) found in cranberry berries (13,14) have been shown to have radical

scavenging properties and may protect the bladder lining from radiation damage, reducing the development and severity of acute radiation cystitis (15–18).

This thesis reports on the effect of cranberry capsules on the severity of radiation-cystitis in the first 20 men receiving radiation therapy for prostate cancer, as part of a larger 40 patient trial in Dunedin Hospital.

1.1 STRUCTURE AND FUNCTION OF THE URINARY BLADDER

The urinary bladder is a hollow muscular organ which functions as a temporary storage unit for urine produced by the kidneys (19). The urinary bladder lies anterior to the rectum and posterior to the pubis symphysis.

Structure

The bladder wall is made up of several layers: a muscularis layer, lamina propria and urothelium, which borders the bladder lumen (Figure 1.1) (20).

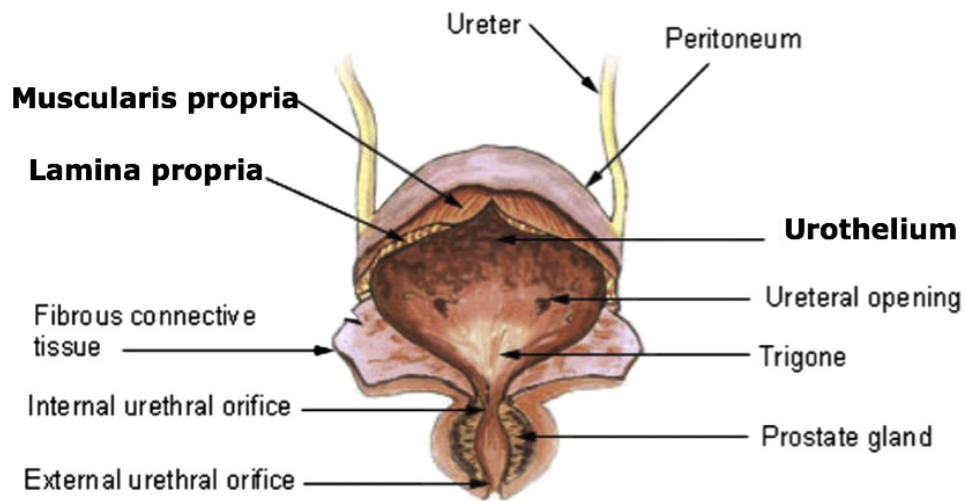


Figure 1.1 Illustration showing the components and tissue layers of the adult male urinary bladder (21).

The muscularis propria consists of bundles of smooth muscle fibre that form the detrusor muscle responsible for bladder voidance. The lamina propria consists of loose connective tissue with a small amount of smooth muscle fibers and connects the inner and outer layers.

The innermost layer is the urothelium. The urothelium is a unique type of epithelium that can alter urine composition and respond to pressure changes via activation of the autonomic nervous system. It is a transitional epithelium made up of three distinct cell types (22). A single layer of small stem cells sits immediately above the connective tissue and capillary bed (23). The stem cells turn over slowly with a half-life of 3 to 6 months and differentiate into intermediate cells, which then form the much larger hexagonal umbrella cells that abut the lumen (Figure 1.2) (22).

The apical surface of umbrella cells is covered in scalloped-shaped plaques divided by microplicae. Under the microscope, this surface membrane appears pleated into ridges with tight intercellular junctions formed between umbrella cells (Figure 1.2). The composition of the umbrella cells makes it impermeable to water, ions, solutes and macromolecules in the urine (22,23).

The urothelium is covered in a thick layer of mucus (9). This forms a highly hydrated layer between urinary irritants and the urothelium, and prevents bacteria from binding to the epithelial surface (24,25).

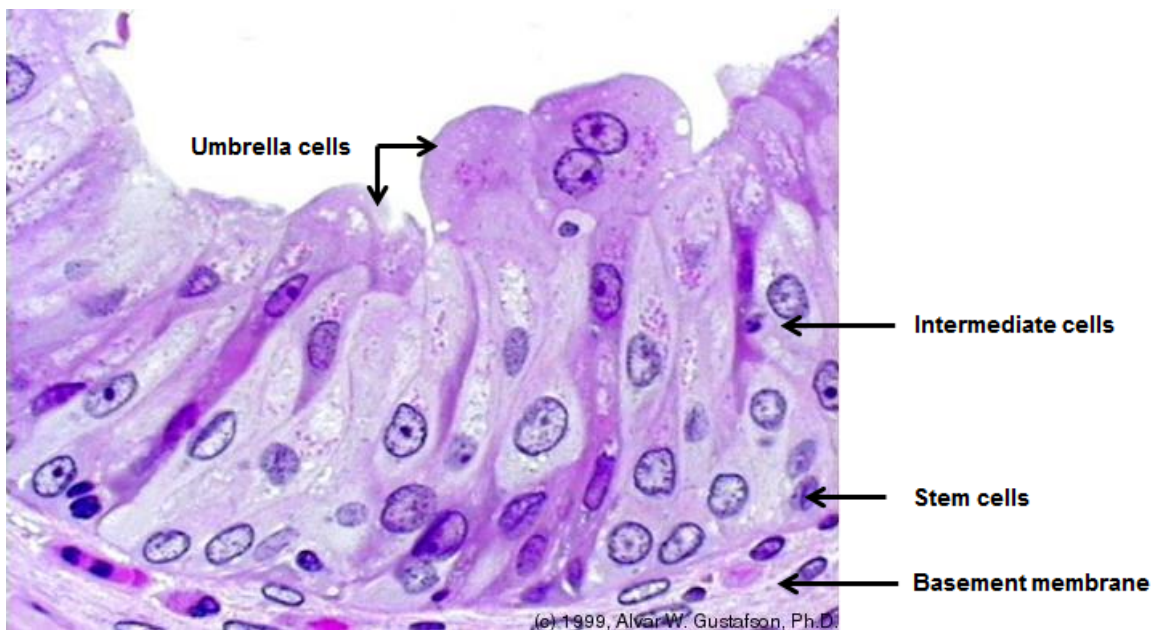


Figure 1.2 Section through the urothelium; a pseudo-stratified epithelium with all cells touching the basement membrane, but not all cell reaching the free surface. When relaxed (in a non-expanded bladder) the umbrella cells (often with two nuclei) have the characteristic dome-shaped appearance (26).

Function

The empty bladder has a pyramid appearance and sits entirely in the pelvic cavity. As urine from the kidneys accumulates in the bladder, it expands and extends superiorly into the abdominal cavity (19).

Once the bladder reaches full capacity a message is sent to the brain via the parasympathetic autonomic nervous system, whilst voiding of the bladder is under voluntary control. With the cognitive decision to void the bladder the voluntarily external urinary sphincter relaxes, the bladder neck opens, and the detrusor muscle contracts forcing urine into the urethra until emptying is achieved (20). If urination is inconvenient the internal and external sphincters remain closed. The bladder slowly relaxes until a repeat message is fired. This process continues until emptying and thus pressure within the bladder returns to baseline.

Regulation of normal bladder function relies on its interaction with complex neural control system in the brain and spinal cord as the bladder constantly responds to a variable volume of urine and changes in hydrostatic pressure (22).

Geometrically, the bladders' spherical shape provides a minimal surface area to urine volume ratio, desirable to achieve less movement of substances between urine and blood (23). On a mechanical level, the empty urothelium is folded into many rugae, which unfold, as filling occurs. Finally, to accommodate volume changes on a cellular level, the urothelium is able to transition in shape, structure and function. Uroplakin proteins allow the umbrella cells to transform without losing their structural integrity. The urothelium thins as the cuboidal shaped cells of the empty bladder are stretched laterally to become flat and squamous (23,27). However, when the urothelium loses its integrity, urinary irritants can enter the underlying layers, causing inflammation and symptoms of cystitis (23).

1.2 RADIATION DAMAGE

Ionising radiation transfers energy to the cells it interacts with and causes either direct or indirect damage to its macromolecules (28). At a molecular level direct damage is caused by ionization, while indirect damage is caused by the generation of highly unstable oxygen free radicals, produced through radiolysis of water (5). These interact with other macromolecules in cells causing damage to proteins, lipids and DNA. Double stranded DNA breaks are the most

likely cause of cell death by ionizing radiation (5). The urinary bladder as a whole is classified as a radiosensitive organ with different radiation tolerances for each of the cell types. Radiation damage in one portion of the bladder influences not only the damaged area, but can also affect the functioning of an undamaged area nearby. There is limited data on bladder tolerances, which makes modeling the effect of radiation on the whole organ challenging.

1.2.1 Acute Radiation Cystitis

Radiation damage can cause early or late effects in tissues, depending on the type of tissue affected. Acute radiation damage is the result of direct cellular damage to tissues that exhibit a fast turnover rate and contain a large number of stem cells that repopulate the damaged area relatively quickly. These effects commonly occur two weeks into treatment and resolve 4-5 weeks after completion of treatment (5).

Each cell type has an inherent radiosensitivity, dependent on its intrinsic ability to neutralize free radicals and repair the damage sustained. However, other factors also affect radiosensitivity, including the level of oxygenation and the cell cycle phase at the time of radiation (5). Rapidly proliferating cells such as the epithelial cells lining the bladder show the results of radiation damage very soon after radiation therapy treatment has started, causing acute radiation cystitis.

Damage to the urothelium is caused by a cascade of reactions starting with a loss in selective permeability of external and internal membranes, resulting in intracellular edema, membrane rupture and rapid cell death. Desquamation of the umbrella cells, production of pro-inflammatory proteins, and breakdown of the mucin layer ultimately compromises the barrier function of the urothelium (6). The cascade continues with progressive degenerative changes, tissue breakdown, superficial ulceration and mucosal hemorrhages.

Increased permeability of the capillaries in the submucosa leads to tissue edema and damages the muscularis and sub-mucosal layers (29). Secondary inflammation is caused by the seepage of urinary irritants through the weakened urothelial barrier. As these tissues swell, the bladder wall becomes thicker, the detrusor muscle loses flexibility and cannot contract as normal (27). The extent of acute damage depends on a range of radiobiological factors including dose, fractionation, length of treatment, and concomitant treatments (9).

1.2.2 Symptoms of Radiation-Induced Cystitis

The symptoms of radiation cystitis are similar to those of interstitial or bacterial cystitis and include a reduced capacity to store urine, frequency, nocturia, hematuria, urgency, and pain (25). Patients with severe radiation cystitis can experience significant pain or frequent bladder contractions and urinary incontinence, starting two to three weeks after the commencement of radiation treatment. According to Meerleer and Vakaet (2004), approximately 40 percent of men having IMRT treatment for prostate cancer can expect to experience these acute toxicities of grade two or more during their RT (11). The majority of these early changes will resolve several weeks after completion of radiation treatment (25).

Symptoms that stem from muscular damage largely relate to difficulty with urine storage, (frequency, urgency and nocturia) and difficulty during voiding (hesitancy, weak urine stream and intermittent stream). Other symptoms include dysuria (pain during urination), hematuria (blood in the urine) or urinary incontinence (2). These symptoms along with the impact they have on an individual's quality of life can vary significantly.

Symptoms relating to urinary storage dysfunction are considered to have the greatest impact on everyday activities and QoL (30). Frequency is defined as clinically severe when an individual urinates more than once every two hours. Urinary urgency is a rapid and compelling urge to urinate. It is usually seen as significant when a sudden onset in the need to urinate cannot be held off for more than 10 minutes. Frequency and urgency are significant because they can cause isolation and lifestyle changes as individuals make decisions around their activities based on their immediate access to bathroom facilities (30). Nocturia is defined as excessive urination at night; some literature suggests this is getting up more than once a night (31). In the clinical setting this may be merely a consequence of excessive fluid intake rather than a side effect from radiation therapy (27). This definition of nocturia does not incorporate whether or not it is perceived as a bother. This makes it difficult to determine in practice, a level of nocturia that is 'too frequent'. It is important however, that decisions around management are based on each individual and the impact that cystitis symptoms have on their QoL (32).

Symptoms relating to urinary voiding include urinary hesitancy, which is defined as a reduced force of stream at the beginning of micturition. In men with benign prostate hyperplasia, enlargement of the prostate gland can lead to urethral obstruction and restricted urine output

(30). This can also occur with prostate enlargement and inflammation from pelvic RT. Voiding dysfunction is likely linked to inflammation and loss of contractibility of the detrusor muscle, which is key in the process of urination (27). These symptoms are most troublesome when they result in post-void residual volumes, when a certain amount of urine remains in the bladder immediately after voiding (31). A bladder remaining partially full after voiding has decreased capacity, which contributes to frequency.

Dysuria is a burning sensation or pain felt upon urination (31). The burning feeling may be caused by urinary irritants reaching the sensory nerves in the deeper tissues of the urethra (9). Overstimulation of messages from the bladder wall also intensify feelings of lower abdominal pain and can be linked back to a rise in urinary frequency and urgency (33).

Hematuria is a symptom of very severe radiation induced cystitis, and a rare event in current practice (25). Blood in the urine is a consequence of dilation and rupture of capillaries or ulceration of the bladder wall, usually in the lower triangular (trigone) region of the bladder (27).

1.2.3 Late Radiation Cystitis

Late or chronic radiation-induced side effects present several months after completion of treatment. Late reactions are caused by damage to connective tissues, which have a slow turnover rate and poor repair abilities. Although damaged by radiation exposure, the effects are not seen until the cell attempts to divide, a few months to years after treatment has been completed (6).

Late bladder reactions are caused by a reduction in urothelial basal progenitor cells and vascular changes (6,34). Loss of structural integrity in capillary system leads to vascular changes to the epithelium. This results in a varying degree of atrophy, fibrosis, ulceration, fistula formation and necrosis (25). Due to poor regenerative capacities of these tissues, permanent changes to the barrier of the urothelium can cause permanent problems with urine leakage into the tissues and inflammation. In the connective tissue and muscle layer fibrosis occurs as a result of a lack of tissue repair. It presents as a reduction in bladder capacity and loss of function (25,27).

1.3 ASSESSMENT OF ACUTE BLADDER TOXICITIES

1.3.1 RTOG/EORTC measure

The Radiation Therapy Oncology Group (RTOG) developed a series of toxicity criteria in the early 1980's. This was in response to a lack of consistency in clinical research for reporting and defining radiation related toxicities (35). The modified scale published in 1995 by RTOG and the European Organisation for Research and Treatment of Cancer (EORTC) has been the most extensively used classification for acute toxicities in clinical research since its publication. This scale classifies acute bladder toxicity into 4 grades as shown in Table 1.1 (36).

Table 1.1 RTOG/EORTC classification of acute radiation cystitis (36).

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No change	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring intervention	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic.	Frequency with urgency and nocturia hourly or more frequently /dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic. Gross hematuria with/without clot passage	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis.

1.3.2 Common Toxicity Criteria

The National Cancer Institute developed the Common Toxicity Criteria (CTC) measure. The CTC provides a robust classification of adverse bladder symptoms as a result of pelvic radiation therapy (Table 1.2). This scale is more comprehensive and deals more specifically with particular 'adverse events' rather than grouping all symptoms together. This is useful in determining what specific symptoms have occurred and which have been most problematic for the patient (35).

Table 1.2 CTC for Acute Toxicities of radiation cystitis (35)

Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Bladder Spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmodics	severe symptoms requiring narcotic	n/a
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	n/a
Hematuria	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation or transfusion	open surgery or necrosis or deep bladder ulceration
Incontinence	none	with coughing, sneezing, etc	spontaneous, some control	no control (in the absence of fistula)	n/a
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase >2 x normal but <hourly	hourly or more with urgency, or requiring catheter	n/a
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period for <6 weeks.	requiring frequent in/out catheterization (>4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture
Urine colour	normal	asymptomatic change in urine color			

1.3.3 Expanded Prostate Cancer Index Composite

The RTOG/EORTG and the CTC both classify symptoms but not their impact on health-related quality of life (QoL). Other measures that specifically assess urinary symptom and function in prostate cancer patients include the American Urological Association Symptom Index Score (AUASI), also known as the International Prostate Symptom Score (IPSS) questionnaire (37), the University of California-Los Angeles Prostate Cancer Index (UCLA-PCI) (38), and the Incontinence Symptom Severity Index (ISS) (39). These scales all focus on function and symptom assessment with little or no evaluation how this affects QoL.

Modern refinement in primary treatments such as radical prostatectomy, external beam radiation therapy, together with an increasingly early detection of prostate cancer have increased the number of patients surviving for longer periods of time (12). This makes QoL during and after treatments a pivotal component in a patients' choice of primary therapy (38,40). It is therefore important to view the patient holistically and include a patient perspective in evaluating interventions for side effects. QoL questionnaires help to better understand the impact of different symptoms associated with cystitis on day to day life and therefore help to inform best management for individual patients (41).

The Expanded Prostate Cancer Index (EPIC) is a measurement tool that incorporates both an assessment of urinary function and its effect on QoL. The Expanded Prostate Cancer Index Composite (EPIC) is a 50 item patient self-administered instrument with domain specific assessment of urinary, bowel, sexual and hormonal symptoms. This instrument is a robust and validated tool for assessing the effect of modern prostate cancer treatments on patient quality of life (40).

Testing of the EPIC measure showed good test retest reliability and good internal consistency across all of the four domains and summary scores ($r > 0.8$ and cronbach's alpha > 0.82) and has good validity against other quality of life questionnaires and domain specific instruments (40,42,43). The four domains of this scale have been validated separately and therefore can be used independently of each other (40).

The Urinary Domain of EPIC contains 12 items that are scored using a Likert-like scale. Raw scores are converted to percentage scores using specially designed macros in the statistical software package, SAS. Unfortunately we did not have access to these and therefore analysed

only the raw scores of the 12 items. This is a limitation of the study design, as the raw scores have not been externally validated. We wanted to assess both QoL and physical symptoms of cranberry and placebo capsules on radiation cystitis. Therefore in this pilot study, we use the raw scores of the EPIC items as opposed to other validated scales that only assessed physical symptoms.

1.3.4 Objective Measures for Radiation Cystitis

In current practice, the assessment of radiation induced urinary side effects is largely subjective through patient self-reporting tools such as those described above. Although these provide information on how symptoms are felt and perceived by a patient they are subject to a degree of interpretation, as each patient will experience the same clinical effects from treatment differently. Although subjective assessments measures describe a patient's perception, there is a need for the development of objective measures to assess bladder wall injury after radiation therapy. The ability to measure accurately the histopathological changes will assist in identifying the objective benefit of an intervention, clarify the relationship linking radiation therapy dose and the degree of urinary dysfunction and provide evidence based dose constraints for planning radiation treatments (biodosimetry).

With respect to interstitial cystitis, which is another type of non-infectious cystitis, research has highlighted a link between symptoms of urinary toxicity and objective measures such as uroflowmetry and urinary biomarkers (24).

Uroflowmetry

Uroflowmetry is a noninvasive and reasonably inexpensive urodynamic assessment measure of the lower urinary tract. It measures the flow rate of the urinary stream during voiding as volume per unit time in milliliters per second, (ml/s), and provides objective and quantitative information on both voiding and storage as part of physiological functioning (44). Uroflowmetry is particularly valuable to monitor changes in individuals over time and therefore could be very useful in bladder toxicity studies (45).

Urine Biomarkers

The implementation of biomarkers into clinical practice is in its infancy (46). It is a complex multi-step process, complicated by the need for individual biomarker assessment for each site

and type of tissue damage (47). Ideally, future clinical trials will use biomarkers to predict severity for radiation induced tissue damage and provide an objective measure for comparing treatments and interventions (47).

1.4 MANAGEMENT OF RADIATION CYSTITIS

To date, there is no effective standard prevention or treatment for acute radiation-induced cystitis. Clinical data on acute radiation cystitis symptoms are generally subjective and as a result are difficult to analyse. Practice is generally based on historical and anecdotal evidence with treatment generally geared toward symptomatic relief (9).

URAL is the current first line standard of care for symptomatic relief at the Southern Blood and Cancer Center. URAL is made up of citric acid anhydrous 0.72g; tartaric acid 0.89g; sodium bicarbonate 1.76g; sodium citrate anhydrous 0.63g per 4g sachet. It acts as a urinary alkalizer to reduce bladder acidity and improve the symptoms of acute radiation cystitis, particularly pain, burning, frequency and nocturia. Other medications used to alleviate symptoms can cause adverse effect and are less commonly used at the Southern Blood and Cancer Centre (48,49). These include, oral phenazopyridine hydrochloride can act as a topical analgesic inside the bladder, oxybutynin chloride is a smooth muscle relaxant which helps relieve symptoms of urgency and frequency cause by idiopathic detrusor instability (49,50), and finally terazosin Hydrochloride (Hytrin) and other alpha-1-selective adrenoreceptor blocking agents can improve urodynamics of men with symptoms of over activity and bladder outlet obstruction (48,50).

The position of the bladder directly above and in front of the prostate inevitably results in partial irradiation during prostate cancer treatment. With dose escalation well established in modern IMRT treatments, the extent of unintentional bladder irradiation is important to consider. A full bladder during treatment can help to push the bladder and small bowel out of the treatment field aiming to minimise acute bladder toxicity (51,52). Treatment with a full bladder is therefore standard protocol in the Southern Blood and Cancer Center. Daily bladder variation has been shown to have only a small effect on prostate motion. This is compared with the rectum volume, where filling and emptying of gas and matter have a major influence on the prostate position (51,52).

1.4.1 Cranberries and Radiation Cystitis

Cranberries (*Vaccinium macrocarpon*) have been used for urinary problems for several decades (53). Despite this long history, gaps in evidence-based research exist in the clinical application of cranberries, especially in relation to radiation-induced cystitis.

Cranberries have been thought to decrease the incidence of repeated urinary tract infections in young women by inhibiting colonization on the bladder wall by the gram negative bacterium, *Escherichia coli* (54). While this trial was ongoing an updated Cochrane review has suggested that the efficacy of cranberry juice for preventing UTIs is less than previously indicated (53). More well designed double blinded RTCs with standardised cranberry capsules or tablets are needed to validate previous findings. In regard to the use of cranberries for radiation cystitis, there are only three studies (summarised in Table 1.3) that have reported on the effects of cranberries for radiation cystitis with mixed results.

Campbell et al, (2003) compared cranberry and apple juice for prevention of radiation cystitis (7). Patients consumed 118ml pre-packaged juice cartons 3 times per day, were asked not to drink additional fruit juices but otherwise eat a normal diet. Cystitis was scored using a modified International Prostate Symptom Score (IPSS) with the maximum scores and maximum change from baseline scores reported. Men with high IPSS baseline scores were included in the study with groups stratified to baseline IPSS < 6 or \geq 7. There was no significant difference between study arms, however trends showed fewer symptoms in participants on cranberry juice. Unfortunately there was no assessment on quality of life, and the sealed envelope randomisation system was acknowledged as being suboptimal. The authors also highlighted concerns with the test retest reliability of the scale, as IPSS is designed for singular use to assess obstructive symptoms of BPH. In this study participants completed the questionnaire up to 18 times, twice a week during RT and for two weeks after completing treatment.

Cowan et al, (2011) used cranberry juice in a placebo-controlled, double blind trial of 128 patients treated with radiation therapy for pelvic cancer (6). The placebo drink was developed to taste and smell like cranberry juice. It is not mentioned if blinding success was tested. As cranberry juice is readily available the true taste and smell may be familiar and identifiable to participants. Juice preparation was non-standardised and no details were given on dose or PAC content, although the fully compliant patients took at least 16L during their time on the trial.

Exclusion criteria included a baseline urinary CTC of grade one or higher or a urinary tract infection present at baseline. The vulnerability of this study population to pre-treatment urinary complications due to disease characteristics resulted in almost half (44%) of potential participants excluded because of baseline CTC scores. Enrolment was much slower than anticipated, and this, along with low compliance due to poor palatability of the cranberry juice undermined the powering of the study. The authors reported results for both the intention to treat cohort (n=128) and the fully compliant population (n=32) but results did not reach statistical significance and were therefore regarded as inconclusive.

Concluding from these studies, cranberry juice does not seem a good way to test the effects of cranberry products. The lack of standardisation of content and volume, lack of blinding and difficulties in compliance testing are limitations of these studies. Along with this, large volumes of cranberry juice can cause diarrhea and is unsuitable for diabetics due to high sugar content. Using standardised cranberry capsules in combination with placebo capsules instead of juice, addresses some of these limitations. The third study conducted by Bonetta and Pierro (2012) assessed the effect of standardised cranberry tablets on the incidence of urinary tract infections (UTIs) and urinary symptoms during IMRT prostate radiotherapy (8). Capsules contained 200mgs of cranberry extract with 60mg of this made up of proanthocyanidins. This study reported cranberry tablets reduced urinary tract infections and improved urinary symptoms compared to control patients who did not get any intervention at all. However results must be considered with respect to the limitations. The study was not blinded, non-randomised and provided no information on how the groups were stratified. Baseline scores were not obtained as patients were reported not to have symptoms of cystitis at the time of enrolment. There was also no follow up after treatment completion which is noteworthy, as radiation reactions tend to peak shortly after completing radiation therapy. Finally, limited information was given on statistical calculations used.

Table 1.3 Summary of studies investigating cranberry to reduce symptoms of radiation induced cystitis

Reference		Campbell et al. 2003 - Canada	Cowan et al. 2011 – Scotland	Bonetta and Pierro, 2012 – Italy
Participants	<i>n</i>	112 Males	128 Males/Females	370 Males
	Primary site	Prostate/Prostate + Seminal vesicles	Cervix + Bladder	Prostate/Prostate + Nodes/Prostate Bed
Participants	Dose	64 to 70Gy	50 to 52Gy	66.7 to 73.66Gy
	Technique	Conformal RT – four field	---	IMRT
	Recruitment	---	March 2003 –June 2006	July 2007- Sept 2010
Study design	Design	Open label RTC	Double blind RTC	Non-blind, Non-randomised
	Intervention	118ml 3x daily (354ml) of 27% cranberry juice cocktail versus 118 3x daily (354ml) apple juice, cranberry juice supplied by ocean spray cranberries	Cranberry juice 2x daily (morning and night) versus similar control juice consumed 2x daily. Cranberry juice supplied by ocean spray cranberries	200mg standardised cranberry capsules (30% PACs) taken daily without food vs no treatment
	Measurement	Self administered modified IPSS questionnaire completed 2x weekly during RT+ two weeks after	CTC questionnaire completed once weekly with nurse during RT + two weeks after treatment	Assessed once weekly during RT only for lower urinary tract infection and self-reported bladder symptoms (Boyersky scale)
	Baseline	Groups stratified for baseline IPSS scores of <6 or ≥ 7	Excluded if CTC ≥ 1 or urinary tract infection at baseline	No patients reported to have cystitis symptoms at baseline
Results		No significant different in levels of urinary symptoms between the two study arms	Grade 3 cystitis was higher in the placebo arm however this was not statistically significant	Cranberry patients compared to controls had a significant decrease in UTI incidence and cystitis symptoms (frequency, nocturia, urgency, urine flow)

Possible Mode of Action

We can only speculate about the mechanism by which cranberry capsules may reduce radiation-induced cystitis. Based on the current literature this maybe achieved through protection of the internal lining of the urinary bladder by decreasing inflammation(27). Radiation causes damage to cellular and nuclear membranes, causing intracellular swelling followed by membrane rupture and cell death (55). Desquamation of the umbrella cells and breakdown of the mucin layer compromises the barrier function allowing urinary irritants to leak into the tissues below, causing chronic inflammation (6). Cranberries were shown to prevent urinary tract infections in young females by adhering to the fimbriae of uropathogenic bacteria (particularly *E. coli*). This blocks adhering of bacteria to the urothelium and prevents mucosal infection (54,56,57).

Because radiation damage is mediated by the production of free radicals, cranberries have been thought to prevent or minimise radiation damage by scavenging free radicals. Cranberries are rich in polyphenols, including flavenoids, anthocyanins and proanthocyanidins. These compounds are well known for their strong anti-oxidant properties (58–62). However, the bioavailability of anthocyanins and proanthocyanidins is very poor (<1-5% of ingested dose) in both rats (63) and humans (64–66). This demonstrates that cranberry products are unlikely to affect radiation cystitis through their radical scavenging abilities. Perhaps anthocyanins and proanthocyanidins in the bladder decrease radiation-induced inflammation in the submucosa by affecting cell signaling pathways in immune cells, responsible for inflammation. In support of this hypothesis, anthocyanins from cranberries were shown to inhibit activation of the NFkB signaling pathway of monocytes of healthy volunteers, dampening their pro-inflammatory response (67).

1.5 AIMS AND OBJECTIVES OF THE CURRENT STUDY

Prostate cancer is the most common diagnosed malignancy in men in New Zealand, with more than 2900 new cases reported annually (1). Treatment options include radiation therapy which leads to partial irradiation of the urinary bladder, resulting in acute radiation cystitis with urinary symptoms such as frequency, urgency, hematuria and nocturia (9). By treatment completion between 40-50% of men receiving radiation treatment for prostate cancer will experience some degree of cystitis (10,11). Lack of standard management highlights a need for research into different preventative and treatment options. PACs found in cranberries may protect the bladder lining from radiation damage, reducing the onset and extent of acute radiation cystitis.

Aim

This thesis aims to investigate efficacy of standardized cranberry capsules compared with placebo capsules on the severity of radiation cystitis, and how this impacts on the quality of life of men receiving external beam radiation for prostate cancer.

Hypothesis

That cranberry capsules containing 72mg of PACs are superior to placebo control capsules in decreasing the severity of acute radiation cystitis in men who receive radiation for prostate cancer.

Specific Objectives

The aim will be addressed by determining if,

- Cranberry capsules reduce the severity of cystitis during RT
- Cranberry capsules decrease URAL usage during RT

Endpoints

- Severity of cystitis, using the modified validated Urinary Domain of the EPIC measure (Appendix A).
- URAL usage

2 CHAPTER 2: METHODOLOGY

The current trial was a randomised double blinded placebo controlled trial comparing the effect of cranberry capsules to placebo capsules on the severity of radiation-cystitis in men receiving RT for prostate cancer at Dunedin Hospital. Cystitis is assessed using a modified Urinary Domain of the EPIC scale (Appendix A). This honours thesis reports on the first 20 patients available for analysis as part of a larger 41 patient trial. If taking cranberry capsules results in a clinically significant decrease (p -value < 0.05) in outcome measures, the trial results will be used to calculate participant numbers to adequately power a larger national trial.

Ethical approval was gained from the Upper South Island Regional Ethics Committee (Protocol number URA/11/08/038) and the trial was registered in the Australian New Zealand Clinical Trials Registry: ACTRN12611000887976. The trial opened for recruitment in April 2012.

2.1 PARTICIPANTS

Eligibility/Exclusion criteria

Men receiving image guided Intensity Modulated Radiation Therapy (IGIMRT) to their prostate, prostate and regional lymph nodes or prostate bed at the Southern Blood and Cancer Center were eligible to enter the study. Men were excluded if they had received previous RT to the pelvis, had metastatic disease, an allergy to cranberries or a history of kidney stones. Although case reports indicated a possible interaction between cranberry juice and warfarin, three recent studies have demonstrated that warfarin pharmacokinetics were not affected by a moderate consumption of cranberry juice (68–70). However, we did exclude patients who were on warfarin from participation.

Sample Size

The sample size of 41 men was based on the number of patients likely to participate in the trial in one year. Unblinding and interim analysis was scheduled after 20 patients had completed the trial in order to allow for thesis analysis and write up.

Description of Radiation Therapy Treatment

Men receiving treatment to the prostate or prostate bed were prescribed a dose of 74Gy in 37 fractions or 64Gy in 32 fractions respectively. All patients received 6MV photon beam Intensity Modulated Radiation Therapy (IMRT) with a consistent planning technique. Treatment was delivered in the supine position in seven fields (prostate or prostate bed), 12 fields (prostate and regional lymph nodes) or six fields (pre existing metal hip). Men were instructed to have a full bladder and empty bowels for their CT scan and then each day for treatment. To achieve this, men emptied their bladder and bowels an hour before treatment then consumed two or three cups of water and held this until after CT or treatment. Daily Cone Beam CT scans were performed to assess prostate position and bowel and bladder status as per standard department protocol.

Randomisation

Randomisation was carried out by the Principle Investigator, Dr. Paries Herst from the Department of Radiation Therapy, University of Otago, Wellington (UOW), who had no patient contact and was not involved in data collection. Bottles containing cranberry or placebo capsules were allocated a number between 1 and 40 using computer-generated random numbers (provided by the UOW biostatistician Dr James Stanley). Each participant was given a numbered bottle by the research radiation therapist (honours student), corresponding to his place of enrolment (patient 01 was given bottle 01 etc.).

Blinding

Capsules were indistinguishable in taste, colour and smell ensuring patients, clinicians and research assistants were blinded with respect to the content of the capsules. Unblinding occurred after 20 participants had completed the trial to allow data analysis for this thesis.

Adverse Reactions

If a patient experienced an unexpected severe side effect, he left the trial at that point and his data set was deleted from the database. The cranberry capsules were anticipated to be well tolerated by patients as these cranberry capsules are freely available as “over-the counter” nutritional supplements.

Participant Received Routine Care

Study participants received standard department care and advice with regard to their treatment, side effects, hydration and side effect interventions such as taking URAL sachets when cystitis symptoms were present. As well as meeting with the research radiation therapist (RT) twice a week, they continued to be seen in the weekly patient on treatment review clinic.

2.2 PROCEDURE

The New Zealand Company Creative Energy LTD provided the standardized cranberry and placebo capsules free of charge. The company provided 20 unmarked bottles with 70 cranberries capsules (containing 72mg Proanthocyanidins or PACs each) and 20 unmarked bottles with 70 placebo capsules containing colloidal silica, magnesium stearate, cellulose and gelatin. The cranberry and placebo capsules were indistinguishable from each other.

Participant role

All patients followed the same study regime shown in Figure 2.1

1. Participants were given the supply of capsules on their first day of treatment and took one capsule a day during breakfast and continued for two weeks post treatment (nine weeks prostate bed, ten weeks prostate and prostate nodes).
2. Participants were specifically told not to consume any foods, drinks or supplements containing berries including cranberries, blueberries, blackberries and blackcurrants and were to limit consumption of red grapes and red wine (1 glass/night).
3. Participants met with the research assistant twice a week to fill in EPIC forms.

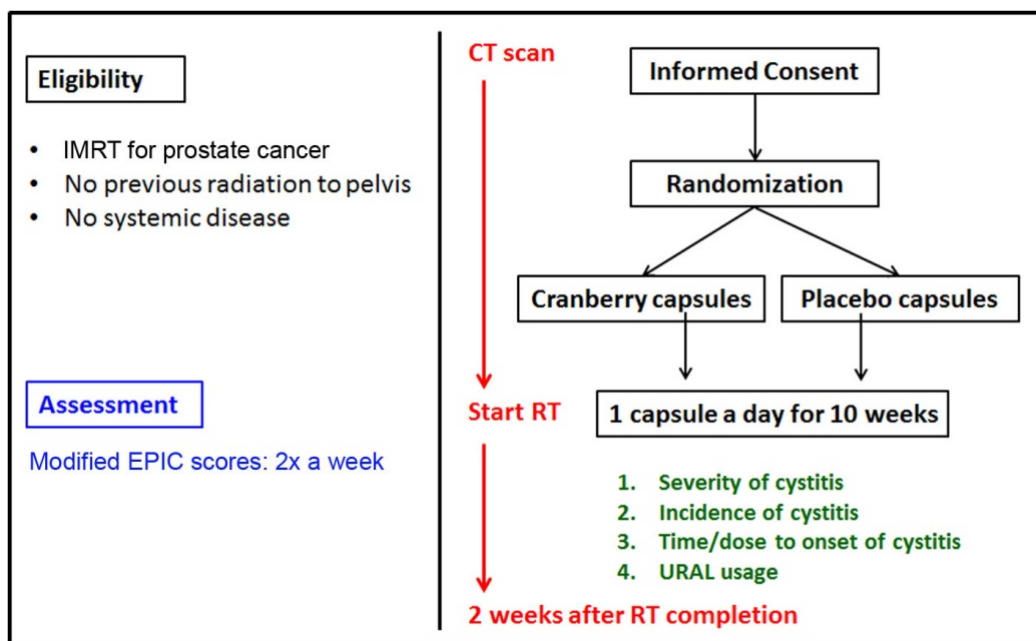


Figure 2.1 Schematic diagram of study regime

Information about the trial

The research assistant identified eligible patients when they were booked for their planning CT scan. The first introduction to the trial was given on the day of the planning CT scan. To ensure consistency and build initial rapport the research RT met with most of the patients. If this was not possible the men were given the trial participant sheet (Appendix B) by CT staff and asked for verbal consent to be phoned by the research assistant who would then give more trial information over the phone. At the time of CT men were also given verbal and written information about coming for treatment and possible side effects with reference to the department prostate or prostate bed treatment booklet.

Informed Consent/Randomisation

On the first day of treatment (approximately four weeks after CT) patients met with the research RT and were given the opportunity to ask any questions they may have had about the trial. If they elected to participate, they gave written informed consent before randomisation (Appendix C). The intervention started from the patients' first day of treatment.

2.2.1 Assessments

Patient Demographics

Initial profiling of participants information was gathered by the research assistant, from clinical notes or through consultation with participants.

Modified Expanded Prostate Index (EPIC)

The Urinary Domain of the EPIC patient assessment tool was modified to fit the context of this trial (Appendix A). A question on URAL usage was added, as this is the current standard care for acute radiation induced cystitis at Dunedin Hospital. As the questionnaire was to be completed twice weekly, the words "in the past four weeks" were substituted for "in the past week" and the words "rarely or never" were replaced with "never". It is not considered these minor changes would threaten the validity of the scale in assessing urinary function and its effect on quality of life.

Baseline scores were obtained on the patients first day of treatment. Men then filled in the modified EPIC questionnaire with the research RT twice a week while in the department for

daily RT, and once a week over the phone during the two weeks post treatment. The EPIC measure took less than five minutes to fill in and clinic appointments took between five and 20minutes.

Exit Questionnaire

At the conclusion of the trial, men were asked to complete an exit questionnaire asking them about their feelings with regard to trial participation, the positive and negative aspects and areas for future improvement. Men had the option of completing it with the research assistant through discussion or filling it in independently and were provided with a pre-paid envelope.

Dose Volume Histograms

Dose volume histograms (DVH) were obtained in trial patients using the planning software Xio. Participant anatomy was contoured using the 3D helical planning CT scan. Information on the bladder volume (cc) was provided along with an overview of the maximum, minimum and average bladder dose across the IMRT dosimetry plan.

2.2.2 Data Collection, Entry and Analysis

EPIC scores and participant characteristics were entered into Excel work sheets (Microsoft v 2010; Redmond Campus, Redmond, Washington, USA), which were used to calculate averages, standard deviations and standard errors as reported in the results section. Unpaired two-tailed student t tests were used to generate p values to assess the statistical significance of any differences between cranberry and placebo arms, with $p < 0.05$ being statistically significant.

2.2.3 Funding

The capsules were provided free of charge by the New Zealand Company Creative Energy LTD. The University of Otago, Wellington, paid the salary of Dr. Patries Herst (PI) and the Southern District Health Board paid the full salary of Noelle Bennett (Charge Radiation Therapist) and four days a week for Katelin Hamilton (Research Radiation Therapist and honours student). A University of Otago Research Grant also provided funding for Katelin Hamilton to work on this project one day a week for a year.

3 CHAPTER 3: RESULTS

A total of 20 men yielded complete data for analysis for this honours thesis; ten men had been assigned to the cranberry arm and ten men to the placebo arm. This part of the thesis describes the results of these 20 men with respect to demographics, flow through the trial and cystitis symptoms.

Eligible participants for this trial were enrolled between 07 May 2012 and 11 February 2013. Randomisation of the first 20 participants yielded a full data set of ten cranberry participants and ten placebo participants. However, data from two control participants had to be removed due to non-compliance. PT3 took several glasses of cranberry juice on a daily bases, even though he was told specifically not to do so and PT20 kept forgetting to take his capsules. The next two data sets that were randomized were therefore added, leaving datasets from eleven cranberry and nine controls.

3.1 BASELINE EPIC SCORES

Because prostate cancer can lead to cystitis like symptoms, it was expected that some of the men would present with low EPIC scores (of 1 or 2) in some of the measures. As this trial set out to measure the effect of cranberries on radiation-cystitis, it was always our assumption that averaging the increase in EPIC scores would negate this issue. And indeed, it was noticed that there was a substantial range in baseline EPIC scores for some of the measures. However it was anticipated that randomisation would evenly divide those with high baseline scores over the two arms of the trial. We therefore did not have high baseline EPIC scores as an exclusion criterion in this trial.

Surprisingly, un-blinding of the first 20 men showed that baseline EPIC scores varied significantly between individuals and that this was not evenly spread between treatment and control arms. To determine the effect of any intervention on radiation cystitis, the intervention should be tested on men that do have cystitis like symptoms at the start of radiation treatment. It can be argued that the pathophysiology of pre-radiation cystitis and radiation cystitis are different. As this trial investigated radiation cystitis specifically, all data from men who presented with an EPIC score of 2 or more at baseline were removed. This resulted in ten

cranberry participants (one participant removed due to high baseline scores) and five control participants (four participants removed due to high baseline scores). In order to perform a more balanced thesis analysis, data sets from the next five patients randomised to the control arm were added to make up a total of ten cranberry patients and ten control patients for thesis analysis.

All 34 men undergoing IMRT treatment for prostate cancer met the eligibility criteria and were invited to participate. Of these, seven men declined participation; three men did not want to forgo cranberry juice or berries, one man did not want to be blinded to what arm he was on and the remaining three men gave no reason for declining to participate. To summarise, a total of 20 men yielded a complete data set for analysis for this thesis.

Recruitment and patient flow through the trial

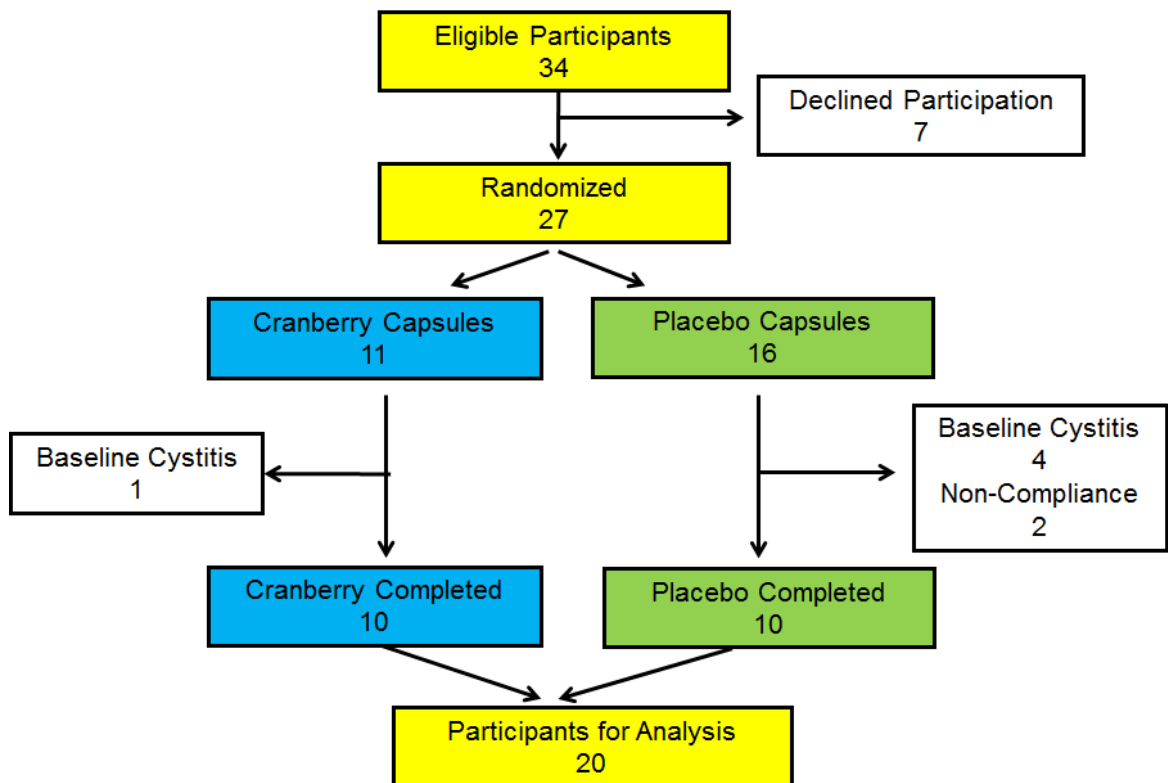


Figure 3.1 Flow of all participant through the trial (CONSORT Diagram)

3.2 PATIENT DEMOGRAPHIC CHARACTERISTICS

Table 3.1 Baseline demographics and clinical characteristics for each cohort

Characteristics	Cranberry Arm (n=10)	Placebo Arm (n=10)	Total (n=20)
Personal Construct			
Age	66 (52-81)	68 (55-76)	67 (52-81)
Ethnicity			
NZ European	10 (100%)	8 (80%)	18 (90%)
Maori/NZ European	0 (0%)	2 (20%)	2 (10%)
Smoker			
Never	9 (90%)	7 (70%)	16 (80%)
Past/Current	1 (10%)	3 (30%)	4 (20%)
Alcohol			
≤ 1 standard drink/week	6 (60%)	7 (70%)	15 (75%)
≥ 1 standard drink/week	4 (40%)	3 (30%)	5 (25%)
Treatment Construct			
Treatment Site n (%)			
Prostate 74Gy/37#	6 (60%)	4 (40%)	10 (50%)
Prostate Nodes 74Gy/37#	3 (30%)	5 (50%)	8 (40%)
Prostate Bed 64Gy/32#	1 (10%)	1 (10%)	2 (10%)
Adjuvant Hormones Therapy	5(50%)	8 (80%)	13(65%)
Alpha-1 Blockers n	4 (40%)	1 (10%)	5(25%)
Planning Construct DVH			
Mean dose ± SD (Gy)	36.9 ± 13.4	38.67 ± 12.5	38.2±12.9
Minimum dose ± SD (Gy)	6.7 ± 9.3	8.6 ± 7.6	7.6 ± 8.3
Maximum dose ± SD (Gy)	77.3 ± 3.8	78.0 ± 3.9	77.6±3.8
Total bladder volume (cc)	275.2 ± 93.9	312.3 ± 200	293.8 ± 153.2

3.3 AVERAGE EPIC SCORES

The EPIC score provides information about several symptoms commonly associated with cystitis and the bother these symptoms caused the patient. This directly relates to their health related quality of life (40).

3.3.1 Effect of Cranberry Capsules on the Severity of Physical Symptoms of Radiation Cystitis

The physical symptoms of radiation cystitis are presented in Table 3.2 and Figure 3.2. Although cranberry capsules seemed to decrease some of the cystitis measures, in particular leakage/dribbling, this was not statistically significant in this small cohort (p=0.14:Table 3.2).

Table 3.2 Comparison of average EPIC scores for the effect of cranberry capsules on the physical symptoms of cystitis

Physical Symptoms	Cranberries		Placebo		t-test
	Ave	± SEM	Ave	± SEM	p Values
Pain/burning	0.28	0.17	0.54	0.19	0.31
Blood in urine	0.09	0.09	0.08	0.08	0.89
Leakage/dribbling	0.14	0.09	0.48	0.20	0.14
Urinary control	0.19	0.10	0.14	0.08	0.71
Pads usage	0.15	0.15	0.03	0.03	0.45
URAL usage	1.09	0.55	1.59	0.42	0.48

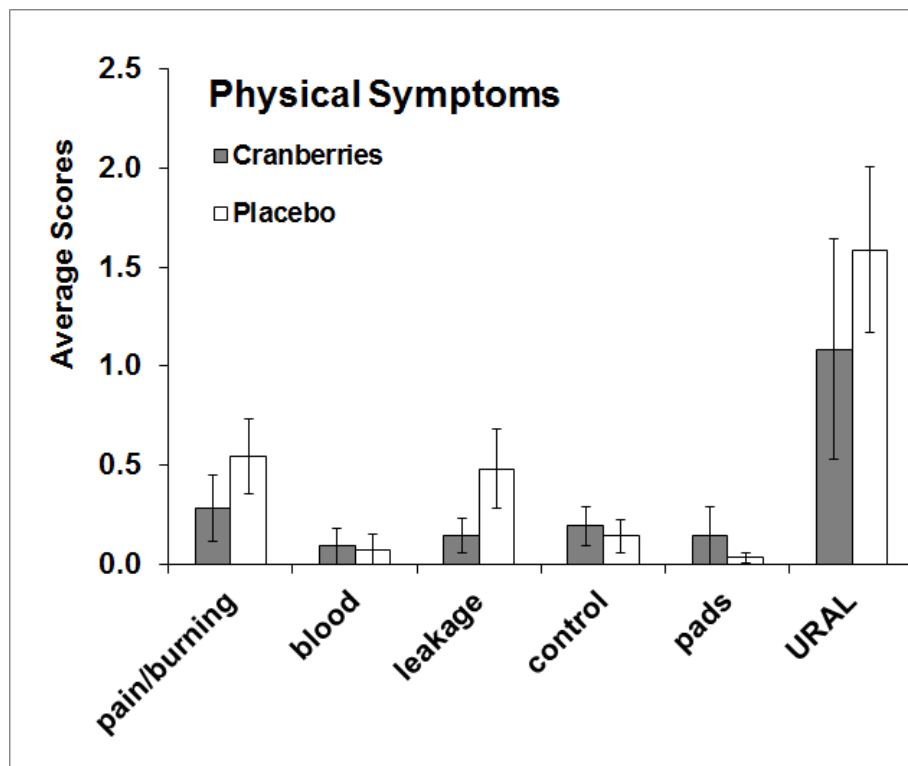


Figure 3.2 Comparison of average EPIC scores for the effect of cranberry capsules on the physical symptoms of cystitis

3.3.2 Effect of Cranberry Capsules on Quality of Life

With respect to the effect on quality of life, the cranberry capsules seemed to decrease night frequency (nocturia) (Figure 3.3) and this was statistically significant in this cohort (p=0.04: Table 3.3). Cranberry capsules also seemed to allow for a stronger flow and completely empty bladders, with p values approaching statistical significance (p=0.09: Table 3.3).

Table 3.3 Comparison of average EPIC scores for the effect of cranberry capsules on quality of life

Effect on QoL	Cranberries		Placebo		t-test
	Ave	SEM	Ave	SEM	p Values
Pain/burning	0.14	0.08	0.38	0.17	0.22
Blood in urine	0.06	0.04	0.03	0.02	0.55
Leakage/dribbling	0.17	0.09	0.30	0.13	0.43
Weak stream/incomplete emptying	0.42	0.14	0.81	0.17	0.09
Day frequency	0.81	0.24	0.87	0.17	0.85
Night frequency	0.69	0.27	1.50	0.25	0.04*
Overall effect	0.39	0.17	0.76	0.27	0.26

*Statistically significant

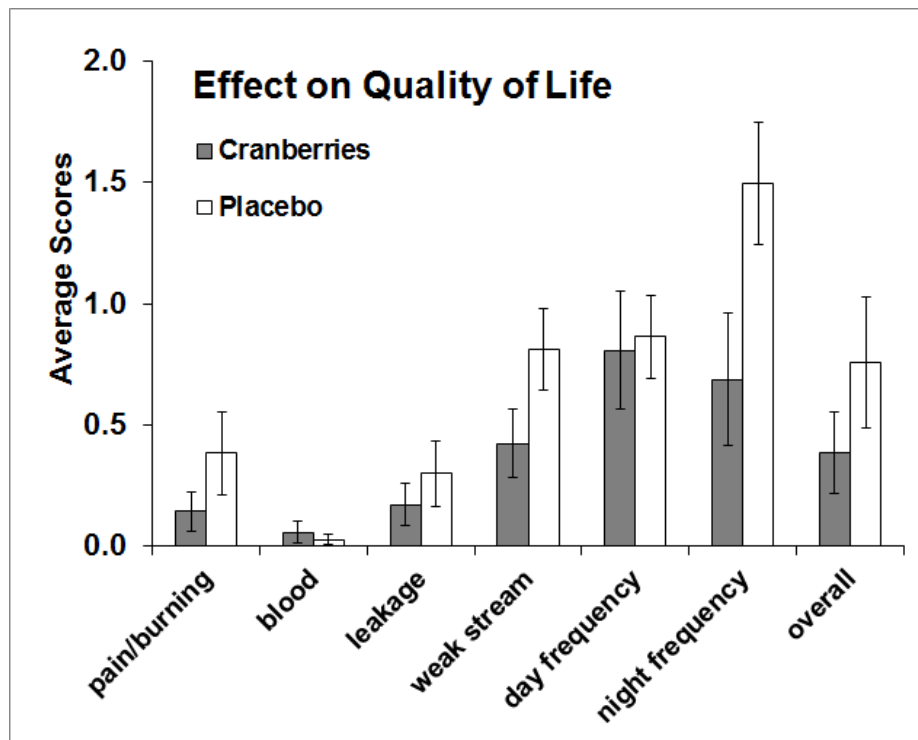


Figure 3.3 Comparison of average EPIC scores for the effect of cranberry capsules on quality of life

3.4 EXIT QUESTIONNAIRES

At trial completion men were asked to fill in an exit questionnaire (Appendix E) to highlight their opinion of positive and negative aspects of their involvement in the trial with both yes/no and open questions. A total of 17 out of 20 men completed the questionnaire. All of the men responded that taking part in the trial was a positive experience for them. Men were also asked if 'based on your experience with this trial, would you take part in other trials where appropriate', to which 16 out of 17 responded yes. The one participant who said no, commented 'I have had my run'. In general, the feedback to the open questions was brief. Some men requested to fill in the exit questionnaire with the research RT and this seemed to yield more in-depth feedback. The exit questionnaire was valuable as an avenue for men to comment on their experience. However, for this group it provided little additional information to discussions in clinic over the 10 weeks with the research RT.

4 CHAPTER 4: DISCUSSION

Acute radiation-cystitis occurs in 40-50% of men receiving radiation therapy for prostate cancer (10,11). There is currently no treatment that prevents or decreases the extent of radiation cystitis. Because there seems to be some evidence that cranberry products may reduce the severity of radiation cystitis (54,71) we conducted a small pilot study (n= 41) to determine whether cranberry capsules were superior to placebo capsules in decreasing the severity of cystitis. This thesis analyses the results of the first 20 compliant prostate cancer patients (10 on the cranberry arm and 10 on the placebo arm) who presented with low baseline cystitis scores.

This part of the thesis will discuss the results in light of the limitations inherent in the design of this pilot study and make suggestions for further clinical studies into the use of cranberry capsules for radiation cystitis.

4.1 PATIENT DEMOGRAPHICS

4.1.1 *Personal Construct*

The patients' personal construct refers to factors related to them as an individual, such as age, ethnicity or life style, that may influence their susceptibility to developing side effects from radiation treatment. Limited documentation makes it difficult to fully evaluate the impact of personal predictive factors on levels of cystitis. Patients demographics (Table 3.1) have been reported to allow for comparison of future research and where relevant between study arms.

Age: Older patients are traditionally thought to suffer worse side effects from radiotherapy as older tissues may have a slower rate of healing (72). However for pelvic irradiation this concept is not well supported and in otherwise healthy individuals chronological age does not affect the extent of acute side effects (73,74). The mean age of cranberry participants was 66 years ranging from 52 to 81 years, which was similar for the placebo participants with a mean age of 68 years ranging from 55 to 76 years.

Ethnicity: 18 out of the 20 participants identified themselves as New Zealand European. Two participants in the placebo group identified as being both New Zealand European and Maori.

Lifestyle: Smoking is thought to increase a number of early and late reactions for specific organs and sites (72,75,76). In this setting current literature suggests smoking during radiotherapy treatment is not likely to affect cystitis severity (74). One participant within the placebo arm described themselves as a current smoker and two as past smokers. None of the cranberry participants were current smokers and one was a past smoker.

Alcohol consumption during RT can intensify side effects to the bladder. Alcohol is very acidic which will increase the acidity in the urine and consequently irritate the bladder wall, especially when this is already compromised by RT. Alcohol also acts as a bladder stimulant and diuretic, which can contribute to the feelings of urgency. Alcohol consumption was similar in both study arms. Sixty percent of men allocated cranberry and seventy percent of men allocated placebo reported an alcohol intake between zero and one standard drink per week while on treatment. One participant in the placebo arm reported consuming more than 10 standard drinks per week.

4.1.2 Treatment Construct

Treatment site: The radiation dose and the size of the volume irradiated can influence side effects. Included in this study were men receiving treatment to their prostate, prostate plus nodes and prostate bed. These three sites, although similar, have slightly different fractionation schedule and treated area. The total dose given to the prostate bed was 64Gy in 32 fractions, and to the prostate or prostate node 74Gy in 37 fractions. The PTV volume for treatment to the prostate and nodes extends more superior compared to the other two sites. It is difficult to know if treatment site affects the bladder dose or bladder volume irradiated and consequently if this affected cystitis levels in this cohort. In other research, dose escalation of 10Gy has not been shown to increase urinary side effects (77).

Table 4.1 presents the average and maximum bladder dose from participants planning dose volume histograms (DVH) categorized by treatment site. This suggests a difference in bladder dose between treatment sites cannot be ruled out. Data must be considered in light of the low patient numbers for some sites and limitations of the DVH discussed below. Six (60%) cranberry participants received prostate only treatment, three (30%) received treatment to prostate and pelvic lymph nodes and one (10%) received treatment to his prostate bed. This was comparable to placebo participants with four (40%) receiving prostate only treatment, five (50%) prostate and pelvic lymph nodes and one (10%) prostate bed.

Table 4.1 Planning DVH values showing mean and max dose by treatment site (Total N=20)

Treatment Site	Prostate	Prostate/Nodes	Prostate Bed
Mean Dose \pm SD (Gy)	78.6 \pm 1.2	79.2 \pm 0.7	67 \pm 0.1
Maximum Dose \pm SD (Gy)	32.9 \pm 14.0	4.80 \pm 3.5	30.4 \pm 14.9

Adjuvant Hormones: Adjuvant hormone therapy (HT) is unlikely to affect cystitis scores as it decreases the levels of circulating testosterone and this should not affect functioning of the bladder. However an association cannot be ruled out as some studies have reported a link between hormone therapy and acute gastrointestinal-urinary toxicity. Unfortunately these studies were not specifically designed to investigate hormone therapy and therefore important information is missing from the methodology and no firm conclusions can be drawn (74,78). Lucrin or Zoladex was given to 65% of study participants. There was a higher proportion in the placebo than cranberry group with eight men (80%) compared to five men (50%) respectively.

Alpha 1 Blockers: Four (40%) of men in the cranberry arm were taking alpha-1 blockers before commencing treatment and continued on these throughout treatment. Three men were taking Doxazosin Mesylate (Cardura) and one Terazosin (Hytrin). In the placebo arm one participant started Terazosin mid way though his treatment due to symptoms of an overactive bladder. An overactive bladder presents as an involuntary contraction of the bladder during filling that cannot be voluntarily suppressed by the individual. This can lead to urinary urgency, frequency and nocturia, symptoms also seen from radiation cystitis. Although alpha-1 blockers do not directly affect radiation-induced cystitis, their use may mask the effects of cranberry capsules.

4.1.3 Planning Construct

Dose Volume Histogram: DVH data specific to the urinary bladder varied significantly across all participants. Bladder volume ranged from 150.16cc to 717.34cc, maximum dose to the bladder from 67Gy to 80Gy and mean dose from 14Gy to 52Gy.

A full bladder for treatment has historically been thought desirable to push the bladder superiorly and out of the treatment field, theoretically decreasing the level of acute and chronic cystitis (79). Therefore a participant with a very full bladder should experience less cystitis due to a decrease in irradiated bladder volume. Similarly, a lower maximum and mean dose should correlate with less severe cystitis because of a decrease in radiation damage.

The DVH results reported here are taken from the pretreatment CT scan and although they can be used as an indicator it is difficult to estimate the actual dose delivered to the bladder on a daily basis. The effects of setup variability, daily bladder filling and internal organ motion during treatment have not been taken into account and therefore could lead to over or underestimation of the actual dose to the bladder (80). The DVH limitations have made it difficult to compare the dose and bladder volumes received by the participants.

Accurate data on bladder filling throughout the participants course of treatment would have been particularly useful for this study. This is in light of the unexpected increase in side effects observed in some men who appeared to be over-hydrated and consequently over-stretched their bladders. This will be discussed under paragraph 4.4.1 in more detail.

With the standard use of daily CBCT for prostate positioning in many RT departments, bladder-filling information is readily available; however collating this is more challenging. Future studies should endeavor to adapt practical methods to utilise this valuable information.

4.2 METHODOLOGY

Participant numbers

For this pilot trial we aimed to enroll only 41 patients (20 on cranberry arm and 20 on the placebo control arm), which would see enrollment completed within a one year time period. Initially we were going to analyse a full set of data from the first 20 patients, however, non-compliance and high baseline scores meant extra data sets needed to be added. Two control participants were removed due to non-compliance and the next two data sets randomised (one cranberry and one placebo) were added. This left datasets from eleven cranberry and nine controls. After this, data from one cranberry patient and four control patients was discarded due to high baseline scores, which left a total of five placebo patients and ten control patients. To achieve a more balanced analysis with ten patients in each arm, all with similar level of baseline cystitis scores we added the data sets of an extra five patients who were randomised to the control arm. This was the final group used for thesis analysis.

Because this is a pilot study with relatively low patient numbers we did not expect statistically significant results. However with this trial we hoped to detect a small difference in outcome measures between the cranberry and control groups. This would give the basis for calculating

participant numbers necessary to adequately power a larger trial to determine whether such differences would be statistically significant and clinically relevant. Even in this small cohort we found a statistically significant reduction in pain for men on the cranberry arm.

Randomisation and blinding

We decided on a randomised double-blinded placebo controlled methodology with men receiving unmarked bottles with cranberry capsules and placebo capsules that were indistinguishable from each other. This circumvented the possibly confounding issues of participant and researcher bias and is therefore a strength of this trial.

4.2.1 Modified EPIC scores

Based on the literature, the Urinary Domain of EPIC seemed most suitable to our study, as we were interested both in the physical symptoms along with their effect on QoL. However, we analysed only the raw scores of the 12 items of the Urinary Domain of EPIC. We believed that the raw scores themselves were a good way to determine the effect of cranberry and placebo capsules on radiation cystitis in this pilot study. We wanted to trial the Urinary Domain of EPIC in this pilot study to see how useful it would be as a measure of radiation cystitis in prostate cancer patients in New Zealand. The different items of EPIC are subjective. Therefore it is important that each of the items is phrased in a way that is interpreted similarly by men of different ages, ethnic and socio-economic backgrounds. During this study we found that the phrasing of several items were open to interpretation.

The EPIC questionnaire was created from a development cohort of prostate cancer patients and an expert panel, including urologic oncologists, radiation oncologists, survey researchers and prostate cancer nurses (12). Nevertheless no justification was given to the phrasing of the questions. The EPIC questionnaire has been used in previous studies, although no one has commented on the specific questions (41,43).

Appendix G proposes a new questionnaire for assessing radiation-induced cystitis in an attempt to resolve the issues we faced with EPIC. Developed by members of the research team, most questions are based on elements of EPIC that we considered worked well. Some additional questions are based on recurrent themes identified during this trial. Areas of EPIC we considered could be improved will be discussed in more detail below. This new scoring measure is a proposal and has not been tested in the clinical setting.

Severity of Pain and Burning

The EPIC measure asks how often pain or burning was experienced but did not assess its severity. Therefore participants could score the same for different symptom severities. For example participants number six and nine experienced mild burning more than once a day and therefore scored a four on the EPIC scale. In comparison participants one, 15 and 21 experienced severe burning that caused considerable discomfort, more than once a day and also scored a four.

The RTOG and CTC scales for acute bladder toxicities include such an assessment on the severity of pain but do not assess the affect of pain on QoL. The RTOG scale, measures this in regard to the type of pain relief required. No intervention, local anesthetic and regular narcotics for grades one, two and three respective (36). The CTC scale measures if dysuria is relieved by an intervention. Grade one; no intervention required, grade two; symptoms relieved with therapy, grade three, symptoms not relieved with therapy (35). There is no validated scale that incorporates an assessment of both the severity of pain and burning, and the effect of this on the participants QoL. The proposed scale (Appendix G) attempts to address this by using separate questions to evaluate the frequency, severity and affect of pain and burning on QoL.

The interpretation of leaking or post micturition dribble

This question was open to interpretation, as many men did not understand the difference between leaking and dribbling. Most men and particularly older men, experience some dribbling after urination and this question only gave a few options to select from.

No assessment of urgency

Through discussion, urgency arose as a significant bother to many participants to the extent that men reported making lifestyle adjustments to deal with these symptoms though EPIC did not measure this specifically. For example,

“One thing I have got to know about Dunedin while being here is where every toilet is within the CBD, because I can’t hold on anymore” PT1.

“ If I am going out walking with our walking group and I know there are going to be women, I go to the toilet before I leave and then don’t drink water till I get back home. That way I’m not darting off

behind every tree. But if I'm going by my self or with my wife, I'll usually drink quite a bit along the way." PT26

Pads or Liners

The number of pads used did not correlate with the severity of cystitis symptoms, however, it provided a means of opening discussion about the role of pads and their usage. This helped break down some of the stigmatism surrounding them although understandably, in general men were very against using pads. Only two men used pads during or after their treatment. One man started using them after a discussion with the research RT when filling in his first EPIC form and another used them from week nine onwards as a security measure after experiencing leakage in public.

Influence of the support person

Men filled in the EPIC questionnaire independently although many men had a support person who either accompanied them on their first day or accompanied them to most or all clinic appointments. Sometimes a support person, particularly if this was a wife or a daughter, would chip in if she felt "her" man was not answering honestly or correctly. It is uncertain what influence this may have on the EPIC scores as sometimes these same men attended some appointments alone. The original description of the EPIC measure strongly recommends to let the men fill in the questionnaires by themselves, to avoid this sort of problem (40).

Frequency of measuring EPIC scores

The original EPIC form was designed to assess QoL before, during and after prostate cancer treatment and was not specifically intended for repeated use over a short time frame (40). Participants in the current study completed the EPIC questionnaire twice weekly while undergoing RT. Score repeatability of some of the items was not always strong as some participants tried and failed to recall earlier scores.

"I'm not sure if I am filling this in correctly today as I don't remember what I put in last time" PT18.

Another issue was that some participants would become too familiar with the questions and were careless when filling in the forms. These problems were managed by reassuring participants it was a snap shot of how they had been feeling over the past few days and by questioning participants about scores that did not align with their verbal account of symptoms.

It was also noted that some men tended to focus on the day or night before, rather than what their symptoms had been over the last few days. This observation was supported by one patient stating if he had a one off symptom and then did not experience it again for a few days he would score a zero on the EPIC form indicating he had not experiencing that symptom at all.

Previous studies have reported EPIC was well suited to assess urinary complications in men with prostate cancer. In comparison to our study, questionnaires were administered either once or every one to three months (12,43). Hedgepeth et al (2009) for example compared EPIC, the Incontinence Symptom Index and Sexual Health Inventory to measure functional outcomes after prostatectomy. Questionnaires were administered preoperatively, postoperatively and then at three, six, nine and 12 months. Results showed good over all correlations with the urinary and sexual domain scores. This suggests EPIC may be more suitable in studies over a longer course of time where the forms are completed less frequently (43).

Questioning regarding URAL usage

When starting the trial, men were given the original EPIC form that included a question on URAL intake (Appendix A). Men inquired as to what this was and the research assistant explained it. After the first 18 men finished the trial it was noticed this increased awareness made some men more eager to be given URAL before it was necessary. This may have contributed to an over prescription of URAL. Therefore, for all consecutive men enrolled, this question was removed from the questionnaire until after they had started taking Ural (Appendix B).

More sensitive Likert scales for measuring radiation induced cystitis

When scoring symptoms using the EPIC score men had five options they could select, which differed for each question. It was noted that particularly the QoL measures might benefit from including more options. The current scales used to score the measures lacked the sensitivity to pick up small changes. Sensitivity is important to document small changes in urinary function over time. Because the highest possible score was “big problem”, this meant that if a participant scored “big problem” one week and symptoms increased the week after, he would again score “big problem” despite progression of his symptoms. As discussed, the RTOG and CTC scales are also used to evaluate acute bladder toxicities in clinical research. Comparably to EPIC they include five scoring categories. These scales are broad and provide general

information on patients' symptoms rather than the small changes over time which we were interested in (35,36). The new proposed scale (Appendix G) attempts to improve sensitivity by providing more choice, such as the seven-point Likert scale used for appropriate questions.

Scoring during follow up phone call

Follow up phone calls were made by the research assistant to all men after they finished radiation therapy treatment. It became clear early on in the trial that the way in which the questions were asked verbally affected the scores allocated to that item. This was particularly important in the QoL section. Sometimes scores did not align with their verbal account and their score for similar symptoms in previous weeks (symptoms either less or more). Men would say there symptom was 'just a small problem', whether it seemed to be a very small problem, a small problem or a moderate problem. This was managed by getting men to say the corresponding number to the score, but this would be improved by the use of a more sensitive Likert scale where men could decide where their symptoms fell within a range. Another solution would be to have men fill in the EPIC questionnaire themselves while on the phone and post it back to the department.

4.3 INTERPRETATION OF EPIC RESULTS

4.3.1 Average EPIC scores

Severity of radiation-cystitis

The primary objective of this pilot study was to see whether cranberry capsules decreased the severity of radiation cystitis compared with placebo capsules.

Regarding the physical symptoms, cranberry capsules seem to be most beneficial for controlling leakage and dribbling of urine even though this was not statistically significant. With respect to the effect on quality of life, cranberry capsules decreased nocturia in this cohort ($p=0.04$) and allowed for a stronger flow and better bladder emptying ($p=0.09$).

Bonetta and Pirro (2012) assessed the effect of cranberry capsules on urinary symptoms during IMRT prostate radiotherapy in 370 patients who did not present with baseline cystitis (8). This Italian trial reported that cranberry capsules significantly reduced symptoms of radiation cystitis with a 23% decrease in nocturia and urgency ($p<0.001$), a 7.5% improvement in urinary

flow and slight improvement in urinary frequency and dysuria ($p=0.066$). The trends of our results relating to urinary symptoms were consistent with those of Bonetta and Pirro.

4.3.2 Adverse Events

Cranberry and placebo capsules were tolerated well by men in the trial. None of the participants experienced an adverse event that required withdrawal from the study. One participant reported he felt nauseous after taking the capsule but also reported this had occurred in the past when taking pills that were difficult to swallow. To help with this he made sure he took the capsule with a large glass of water and food. A number of participants also noted they found the capsules very large and difficult to swallow. This could be resolved in future trials by having two smaller capsules.

4.3.3 Follow up

All men were phoned at home once a week for two weeks after finishing treatment to fill in the EPIC questionnaire. As it turned out these phone calls were very valuable for the men. During radiation treatment they were in a bubble of care being seen every day by staff on the treatment machine, once a week in the prostate review clinic and if problems arose they could be seen any time during the nurse/RT clinic.

Once treatment is completed all this attention stopped, patients went back home and tried to adjust to normal life again without the support of the health care team. Side effects from radiation can peak one to two weeks post treatment. Although men were told they could phone if they have any problems, they rarely did so because they did not want to be a bother and therefore battled on until symptoms resolved. An example of this is participant 21. He was phoned one-week post treatment and reported significant nocturia and burning upon urination. He was having two URAL sachets per day at that time and was advised to increase this. When phoned back the next day his symptoms were improved and he was much happier. We found these post-treatment phone calls can be of substantial benefit to patients whilst having little impact on the workflow of the day. All calls were made in down time and generally only took between five and ten minutes.

4.3.4 Compliance

Initially, participants were given the capsules all at once; however, this made it very difficult to assess if participants were taking the one capsule each day. Several participants had a few capsules left over at the end of the trial. It was unclear at which point they had been non-compliant. Partway through the trial participants were given capsules in a two-week supply in an attempt to improve compliance and monitoring of this. Those men who had capsules left at the end of the two weeks received extra encouragement and strategies to help them remember to take the capsules. Compliance is important in this study to fully assess the affect of cranberry capsules on radiation-induced cystitis. This is a placebo controlled study therefore if men on the cranberry arm were non compliance in taking the capsules it may under power the results. Compliance could be improved in future studies by using blister packs labeled with each day of the week printed on them. This would not only allow for improved monitoring of compliance but also encourage men to remember to take the capsules.

4.3.5 Exit Questionnaire

The exit questionnaire provided an avenue for men to comment on their experience. For this group it provided little additional information to the discussions in clinic over the 10 weeks with the research RT. In general the men were happy being a part of the trial and had minimal comments about improving future research.

It seems written exit questionnaire was not the most appropriate for this male cohort and in the future it may be more beneficial for the research assistant to verbally discuss how men found trial participation in a semi-structured format. All men could also be given an anonymous comments card in their introduction packet to continue to provide a path for feedback they may feel uncomfortable discussing with the research RT.

4.4 POSSIBLE CONFOUNDERS

Although the trial was double blinded which avoided patient and researcher bias, particularly important when the measures used are subjective and open to interpretation, there were still a number of important factors we did not account for in this trial and which may have affected the results.

4.4.1 Hydration

Hydration levels have proven to be a very important consideration during this trial and this needs to be addressed in any future cystitis trials. At the beginning of the trial, men were encouraged to drink at least 2 liters of fluid consisting of mostly water, regardless of their pre-treatment fluid intake. Daily Cone Beam CT also meant the bladder was evaluated on a daily bases and feedback was given if the bladder was not considered full enough compared to CT. As a result some men felt extreme pressure to do a 'good job' and became very anxious if they struggled to increase their fluids and achieve a full bladder for treatment. We observed that this hydration regimen was too much for some men and as a consequence over-hydration seemed to increase symptoms. Overstretching of the bladder wall increases urothelial permeability and therefore may contribute to cystitis severity particularly for urinary urgency and frequency (81). We observed this was especially true for older men who were use to a very low fluid intake prior to treatment.

Participant 6 was in his early 70's and had been a sheep farmer all his life. His pre-treatment fluid intake consisted of a few cups of tea and coffee per day, and he found it difficult to drink the required 2L. He said when he was younger the culture was that a hard worker didn't stop for a drink of water, and this is what he had continued with through his life. Coming for treatment meant a significant increase in his water consumption. Early in his treatment he reported bothersome symptoms of frequency and nocturia. These side effects could have been due to radiation cystitis or the result of an overstretched bladder and therefore it is impossible to determine the actual cause of his symptoms.

Over-hydration also seemed to increase side effects for participant 15. This man was in his mid 60's, was very fit and physically active and was staying away from home while receiving treatment. His pre-treatment fluid intake was reasonable at around 1.5L per day with the majority of this water. At baseline he scored zero for all EPIC questions however under a week later his scores had increased significantly (Table 4.1). Radiation cystitis is unlikely to occur so early in treatment. He had increased his fluid intake to approximately 2.5-3L of water per day in an effort to reduce treatment side effects and was encouraged to continue with this by the oncology nurse in clinic. He reported that he had made no other changes. He was clear of a urinary infection and had never experienced these effects in the past. At the end of week two he was prescribed URAL and this seemed to help. He continued taking this for the remainder of

his treatment despite feeling improvements, as he was concerned his symptoms would return if he stopped.

During a discussion around week four he reported that not only had he been drinking 2.5-3L of water per day, he was also drinking many more cups of tea and coffee than he would at home as he had been visiting with friends more often. In addition he was also having large portions of soup for lunch and sometimes for dinner as his wife had been making soups at the weekend for him to take to Dunedin as they were easy to heat and kept well.

Obviously the fluid intake of participant 15 was far above his normal fluid intake and would have contributed to the side effects he experienced so early into his radiation treatment. He was very determined to 'do everything right' and as encouraged by the departmental information booklet, radiation therapists and nursing staff he considered a high fluid intake was key to helping this. After a few weeks with the introduction of URAL and a reduction in overall fluid intake he seemed more comfortable and side effects dropped and then remained consistently low throughout the remainder of his treatment.

As an outcome of this trial, the fluid intake guidelines at the SBCC have been revised. The last 20 men to enter the study were advised to increase fluid intake from their normal intake but to drink an amount that they felt comfortable with. Men were directed to start this from their CT scan (approximately one month prior to treatment) to give their bodies time to adjust and allow for better identification for what was causing urinary symptoms when men started treatment. Men were still given hydration advice and strategies to ensure a full bladder for treatment but the focus of this was relaxed. As a result men seemed less stressed, happier and more relaxed during treatment. This new hydration protocol also seemed to correspond with a drop in cystitis severity with men in the second half of the study (not analysed in this thesis) reporting lower EPIC scores, even though this was not statistically significant in the 40 patient cohort. The effect of different hydration regimes will be discussed in detail in the manuscript describing the results for the entire cohort.

4.4.2 URAL usage

Men participating in the trial received routine standard of care for those having prostate cancer treatment at the Southern Blood and Cancer Center. This included the use of URAL sachets for symptomatic relief. We hypothesized that men taking cranberry capsules would

require fewer URAL sachets during treatment. At the start of the study it was not appreciated how freely URAL is prescribed in Dunedin by nurses and radiation therapists in the patient on treatment clinic. URAL lowers the acidity of the urine and is considered not harmful with a base ingredient of baking soda. As a result of this some men were prescribed URAL at the slightest change in their urinary symptoms. Sometimes this was within the first or second week of treatment and therefore not likely a cause of radiation treatment but rather related to other factors such as hydration levels or anxiety as discussed previously. Once started on URAL, men generally continued on this for the remainder of their treatment.

URAL masks the symptoms of cystitis. Therefore in the current trial it is possible that 'over prescribing' of URAL, masked whether cranberry was more effective than placebo in preventing radiation cystitis. To better control for this in future trials, patients should be given symptomatic relief only when their symptoms reach a predefined threshold, for example a three or a four on the EPIC scale.

4.4.3 Other possible confounders

Anxiety

Anxiety can manifest itself through a range of symptoms, including sleeping difficulties, urinary frequency and urinary urgency (82). As such anxiety is likely to affect the severity of at least some of the cystitis measures.

Radiation induced side effects generally peak towards the end of a patient's treatment. Surprisingly, some participants scored their highest EPIC score at baseline. A possible explanation could be the timing of the baseline score coinciding with patients' often-heightened anxiety at the start of treatment. Although temporary, a significant life style adjustment takes place and a six to seven week time frame can initially seem very daunting, especially for those not residing in Dunedin. The Southern Blood and Cancer Center services a wide geographical area and many patients travel several hours from home to attend their appointments or must find accommodation in Dunedin. As discussed earlier men having treatment for prostate cancer are also required to have empty bowels and a full bladder for treatment. This is often hardest and most stressful at the beginning of treatment as men work out their routines to achieve this. Once men were settled into treatment they appeared less distressed and anxiety levels generally fell. In some patients this also corresponded with a fall

in their EPIC scores. To account for this, baseline scores were reviewed for all participants. Scores higher at baseline than throughout treatment, were replaced by scores obtained at the start of week two and therefore provided a more representative baseline.

Urinary specific medication

As trial participants received the Dunedin Radiation Oncology standard of care this allowed them to continue or start taking prescribed medications. Hytrin (Terazosin) and Cardura (Doxazosin Mesylate) are alpha-1-selective adrenoceptor blocking agents that help to improve the urodynamics for men with chronic bladder outlet obstruction such as Benign Prostate Hyperplasia (BPH) or as a result of radiation therapy (48). Some participants were taking these before starting treatment, some had increases in dose made during treatment and some men were prescribed these medications part way through. Hytrin or Cardura do not affect cystitis itself but may have an effect on symptoms similar to cystitis such as frequency, nocturia and flow, not dissimilar to URAL. This may have influenced the scores men recorded on the EPIC questionnaire and therefore influenced the results of the current trial. In future trials participants who are taking alpha-1-selective adrenoceptor blocking agents need to be excluded from participation for these reasons.

Timing of cranberry administration

In the current trial all patients were told to take one capsule in the morning with breakfast regardless of their appointment time. With respect to timing of taking the capsules, pharmacokinetic studies have shown that a single dose of elderberry extract (64) and cranberry juice (65,66) produced maximum anthocyanin levels in urine 3-6 hours after consumption (65,66), indicating that breakfast would be the best time to take the capsules. Therefore, the timing of cranberry administration is worthwhile considering in future trials.

4.5 RECOMMENDATIONS FOR FUTURE RESEARCH

1. *Hydration*: Establishing a consistent hydration level for each patient is extremely important for future research in this field. Increases in hydration must be tailored to each individual patient taking into account their past and current fluid intake along with their activities, the climate and what is realistically achievable for them. Men should increase their fluid in the weeks prior to starting treatment and continue with this during treatment. This would allow their bodies time to adjust to the extra fluid and improve accuracy of the baseline score due to consistent hydration.
2. *Symptomatic Relief*: URAL masks the symptoms of cystitis and therefore may mask whether cranberry is more effective than placebo in preventing radiation cystitis. Future trials must control for this. Patients could be given symptomatic relief only when their symptoms reach a predefined threshold, for example a three or a four on the EPIC scale. It is important a consistent threshold is agreed upon and adhered to by all staff members or departments dealing with trial participants.
3. *Scoring*: Subjective measures for assessing radiation cystitis must be phrased in a way that promotes similar interpretation by men of different ages, ethnic and socio-economic backgrounds. Furthermore it must be sensitive enough to pick up small changes as cystitis symptoms often up build gradually. The current study demonstrated that some items of the EPIC questionnaire could be modified to better meet these criteria. We developed a new questionnaire (Appendix G), in an attempt to resolve the issues we faced with EPIC. Most questions are based on elements of EPIC that we considered worked well. Some additional questions are based on recurrent themes identified during discussions with men in this trial.

In the proposed questionnaire, physical symptoms and quality of life questions have been integrated for each urinary problem rather than being dealt with in separate sections of symptoms and bother. This may make it easier for the men to fill out independently. Careful consideration has been given to the way in which the questions are asked in an effort to decrease ambiguity and therefore improve consistency in the answers. For example question four is very descriptive with quantifiable time frames and feelings that should not require additional explanation.

This new scoring measure is a proposal and has not been tested in the clinical setting. Therefore to be used in future research it would require both initial testing in small groups of participants and then validated in a larger population against other cystitis measures.

4. *Urinary Diary:* Rigour could be added to questionnaires such as EPIC with the use of a daily urinary diary. Men could record the number of times they needed to get up in the night to urinate, how many URAL sachets or pads they used and anything significant they wished to comment on for that day. This diary could be brought along to clinic appointments for discussion and to assist men when filling in the EPIC scores. Identifying ways to reduce subjectivity and add rigour to study measures should be fundamental in the design of future research. The feasibility of a urinary diary (Appendix F) was briefly assessed and discussed with a few men enrolled at the end of the trial. These men found the diary quick and easy to complete, reporting they felt happy to take the time to complete it each day in support of the study. These forms helped to frame discussion during the clinics and also provided a visual aid that seemed to help men identify why symptoms on particular days had been better or worse than others.
5. *Baseline scores:* This study highlighted the importance of recording baseline scores. To ensure a true baseline cystitis score, multiple baseline scores could be obtained and averaged, for example the week before starting treatment, the first day and during the first week of treatment. As the pathophysiology of baseline cystitis may be different for radiation cystitis it is important to consider how this is dealt with in future research. In a large trial this could be addressed by stratifying men according to high or low baseline scores or have high baseline scores as an exclusion criterion.
6. *Compliance:* Attempts should be made to improve the ability to monitor compliance. Patients could be given blister packs with a corresponding day of the week. This may help patients remember to take their capsule and may help the research team monitor if or when capsules were missed.

7. *Evaluating bladder dose and volume irradiated:* Future research should consider identifying ways to more accurately evaluate the dose-volume effect to the bladder and how this corresponds to cystitis. This information could help when analysing the level of cystitis between participants, treatment groups and other studies. In this study DVH were derived from participants planning CT scan, the daily variation in bladder filling means doses although providing an indication may not be an accurate representation of what actually happened on treatment. This could be addressed by developing methods to utilise data already available from patients daily CBCT scan.

8. *Study design:*

- a. In the current study, men receiving treatment to their prostate, prostate and nodes and prostate bed were all eligible to enter the study. It is unclear what influence treatment site may have on cystitis levels. Future studies could stratify for treatment site.
- b. Future research could attempt to incorporate objective measures of cystitis into the study design. Measures adapted would be based on the nature of the design however consideration should be given to uroflowmetry, post-void residual measurements, biosimetry and urine markers (44,64,66,83). Reduced flow and feelings of incomplete emptying can be symptoms of cystitis therefore uroflowmetry and post void residual measurements used alongside questioners may increase strength of the results.
- c. As a result of the subjective nature of measurements in this type of research, establishing the placebo effect is an important consideration. One method to accurately test this is to include a third study arm as a 'pure control' group who receives neither the cranberry or placebo capsules.

4.6 CONCLUSIONS

Partial irradiation of the urinary bladder is common in men receiving EBRT for prostate cancer. As a result, 40-50% of men experience acute radiation cystitis during their treatment. The presence and extent of side effects depends on patient and treatment related factors and symptoms could include urinary frequency, nocturia, urgency, leakage or occasionally hematuria. To date, there is no effective preventative treatment for radiation-induced cystitis with treatment generally geared toward symptomatic relief. Despite an established history for the use of cranberries for urinary problems, there are gaps in evidence-based research, especially for radiation-induced cystitis.

The aim of this thesis was to determine the effect of cranberry and placebo capsules on 1] the severity of urinary symptoms and 2] the effect of these symptoms on QoL. To investigate this, we conducted a double blind RTC with 41 men receiving treatment for prostate cancer at the Southern Blood and Cancer Center. This BRT(honours) thesis analyses the results of the first 20 compliant participants who had no high baseline scores. It was hypothesized that cranberry capsules would decrease RT induced cystitis symptoms and improve quality of life.

Careful consideration was given to trial methodology. There are limitations inherent in the design that were not foreseen at the beginning. Initially the highly validated Urinary Domain of EPIC seemed suitable to measure cystitis and quality of life though it later became apparent that several of the items did not perform as intended. Over-hydration and excessive use of symptomatic relief (URAL) were also problems faced during this trial, highlighting a need to ensure participants receive consistent advice by all members of the health care team involved in their care. This will become even more important in large trials based over multiple centers.

In conclusion, there is some evidence to suggest cranberry capsules may reduce the severity of certain aspects of radiation-induced cystitis, such as pain. This indicates further investigation is warranted. Future trials must attempt to address the limitations brought to light as a result of this pilot study.

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Modified Expanded Prostate Cancer Index Composite (EPIC) Measure

Name:

Date:

In the last week:

1. How often have you had pain or burning when you pass urine?

0 never 1 once 2 more than once 3 about once a day 4 more than once a day

2. How often have you noticed blood in your urine?

0 never 1 about once a week 2 more than once a week 3 about once a day 4 more than once a day

3. How much URAL have you taken to help with your cystitis symptoms?

0 none 1 3 per day 2 4 per day 3 6 per day 4 8 per day

4. How often have you leaked urine?

0 never 1 about once a week 2 more than once a week 3 about once a day 4 more than once a day

5. Which of the following best describes your urinary control?

0 total control 1 occasional dribbling 2 frequent dribbling 3 no control whatsoever

6. How many pads or liners per day did you use to control leakage?

0 no pads 1 1 pad 2 2 pads 3 3 or more pads

APPENDIX A: Modified EPIC Questioner (with Ural question)

In the last week:

7. How big a problem if any has each of the following been for you?

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big problem
A. Pain or burning when you pass urine	0	1	2	3	4
B. Weak urine stream or incomplete emptying	0	1	2	3	4
C. Need to pass urine frequently during the day	0	1	2	3	4
D. Waking up in the night to pass urine	0	1	2	3	4
E. Blood in your urine	0	1	2	3	4
F. Leaking or dribbling urine	0	1	2	3	4
G. Overall, how big a problem has your urinary function been for you	0	1	2	3	4

8. Is there anything else you would like to tell us about?

Modified Expanded Prostate Cancer Index Composite (EPIC) Measure

Name:

Date:

In the last week:

1. How often have you had pain or burning when you pass urine?

0 never

1 once

2 more than once

3 about once a day

4 more than once a day

2. How often have you noticed blood in your urine?

0 never

1 about once a week

2 more than once a week

3 about once a day

4 more than once a day

4. How often have you leaked urine?

0 never

1 about once a week

2 more than once a week

3 about once a day

4 more than once a day

5. Which of the following best describes your urinary control?

0 total control

1 occasional dribbling

2 frequent dribbling

3 no control whatsoever

6. How many pads or liners per day did you use to control leakage?

0 no pads

1 1 pad

2 2 pads

3 3 or more pads

APPENDIX A: Modified EPIC Questioner (with no Ural question)

In the last week:

7. How big a problem if any has each of the following been for you?

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big problem
A. Pain or burning when you pass urine	0	1	2	3	4
B. Weak urine stream or incomplete emptying	0	1	2	3	4
C. Need to pass urine frequently during the day	0	1	2	3	4
D. Waking up in the night to pass urine	0	1	2	3	4
E. Blood in your urine	0	1	2	3	4
F. Leaking or dribbling urine	0	1	2	3	4
G. Overall, how big a problem has your urinary function been for you	0	1	2	3	4

8. Is there anything else you would like to tell us about?



March, 2012

University of Otago, Wellington

Cranberry Capsules for Radiation Cystitis

Participant Information Sheet

You are invited to take part in a clinical trial which is looking into the effect of cranberry capsules on the severity and incidence of cystitis experienced by men having radiation therapy for prostate cancer. All participation in this research is completely voluntary. If you do decide to take part, you are free to withdraw from the study or decline to answer any particular question at any time. Please discuss your participation in this trial with friends, family and whanau and take your time to decide whether you wish to take part in this study.

1. Why are you doing this study?

Radiation therapy for prostate cancer aims to kill cancer cells in the prostate. However the bladder can also be affected by this treatment, resulting in cystitis (inflammation of the bladder). The symptoms of cystitis include the need to pass urine more often and more urgently - during the day as well as during the night - a burning sensation whilst passing urine and loss of bladder control (dribbling). In very severe cases, blood can appear in the urine. There is currently no worldwide standard treatment for radiation cystitis, but both cranberry juice and cranberry capsules have been found to be beneficial for other causes of bladder irritation. Over the last year, a number of the men receiving prostate treatment in the Dunedin radiation therapy department have been taking cranberry capsules during their treatment. They have reported that this seems to make the cystitis better. We want to see if this apparent benefit is correct, and whether cranberry capsules with a standardised amount of cranberry powder can help to minimise the symptoms of cystitis.

This study compares the effect of cranberry capsules with placebo control capsules on the severity and incidence of cystitis in men, receiving radiation therapy for prostate cancer.

2. What does my participation in the study involve?

A. Randomization

Once you have been accepted into the trial you will be randomly placed in either the cranberry arm or in the control arm. Randomisation is done using a computer programme and cannot be influenced by the oncologist, the research assistant or yourself. You will not know which arm you have been placed in and neither will your doctor or the research assistant.

Why randomization?

Generally people feel better when they get capsules that they think will make them better, even if these are fake capsules. This is called the “placebo effect”. In this trial we give people in the control arm placebo (fake) capsules to measure this placebo effect. We give people in the cranberry arm the real cranberry capsules to measure the real effect of cranberries over and above the placebo effect. Randomisation is much more effective if the participants, their clinicians and their radiation therapists do not know whether they are taking cranberry capsules or placebo capsules. This is called blinding the trial.

B. Protocol

- Regardless of the arm you are placed in, you will be given a bottle containing 70 capsules.
- You need to take 1 capsule each day at breakfast time from the day you start radiation treatment until you have used up all the capsules (10 weeks later).
- You may take ural sachets if you need them.
- You are not allowed to take foods, drinks or supplements containing any type of berries and you will need to limit your consumption of grapes and wine.

C. Assessment

You will be asked to fill in a questionnaire before you start radiation treatment and then every week for 10 weeks. The questionnaire should take no more than 15 minutes to fill in and will ask you to comment on your urinary habits of the previous week, including frequency, urgency and discomfort.

3. Are there any risks to me if I participate in this study?

Cranberry capsules are a nutritional supplement which are available in pharmacies, health shops and supermarkets. They are very unlikely to cause any side effects. However, in the unlikely event of an adverse reaction to either the cranberry or the placebo capsules, you will be advised to stop using the capsules.

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to

APPENDIX B: Participant Information Sheet

be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

4. Are there any costs involved if I participate in this study?

No, there are no costs involved in this study for you. You will be supplied with the capsules free of charge.

5. What will you do with the information?

The information from all participants will be kept completely confidential and participant files will be stored at the University of Otago, Wellington, in a locked steel filing cabinet in the office of the Principal Investigator, Dr Ptries Herst, for at least 10 years, after which time the files will be destroyed. Only the official investigators of this study will have access to this information.

When the study is completed we will collate and analyse the information from all the participants of the study. This will tell us whether the cranberry capsules are better than placebo capsules in decreasing the severity and incidence of radiation cystitis. If this is the case, we want to do a larger trial, and we would like to incorporate the data from this trial into this larger future study. We hope that this will lead to a standardised treatment for radiation cystitis in NZ.

Reporting

- We will report on the results of this study in scientific reports and publications.
- You will be informed of the results of the study by a letter from the Principal Investigator, Dr Ptries Herst

NO material will be published which can identify you personally.

6. Does the study have ethical approval?

Yes, the study has ethical approval from the Upper South A Regional Ethics Committee.

7. Do I have to participate in this study?

No, there is absolutely no requirement to participate in the study.

8. Can I withdraw from the study if I change my mind?

If you do agree to take part, you are free to withdraw from the study at anytime without having to give a reason and this will in no way affect your future health care. If you wish to withdraw please contact the clinical research supervisor and advise her that you have decided to withdraw so that all

APPENDIX B: Participant Information Sheet

information and data that have been collected about you will be entirely deleted from the database.

9. What if I have more questions or concerns about this study?

If you have any questions or concerns about your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Local (03) 479 0265; Telephone: (NZ wide) 0800 555 050; Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT); Email (NZ wide): advocacy@hdc.org.nz. If there is a specific Māori issue/concern please contact Linda Grennell at 0800 37 77 661

If you have any questions or concerns about your urinary symptoms or any other aspects of this study, at any time, please call the clinical research supervisor, Noelle Bennett (telephone 03-4747047).



Te Whare Wānanga o Ōtago

September, 2011

University of Otago, Wellington

Cranberry Capsules for Radiation Cystitis

Informed Consent

This form is to obtain your agreement to participate in our study which intends to find out whether cranberry capsules decrease the severity and incidence of cystitis caused by radiation therapy.

REQUEST FOR INTERPRETER

English	I wish to have an interpreter	Yes	No
Deaf	NZ Sign Language interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero	Ae	Kao
Cook Island	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Samoaan	Ou te mana'o ia i ai se fa'amatala upu	loe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania kin a gagana o na motu o te Pahefika	loe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

Informed Consent

- I have read and I understand the information sheet dated September 2011 for volunteers taking part in the study designed to investigate whether cranberry capsules decrease the extent of radiation cystitis.
- I have had the opportunity to discuss this study with whanau and friends. I am satisfied with the answers I have been given.
- I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time, and that this will in no way affect my future health care.
- I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.
- I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.
- I have had time to consider whether to take part in the study.
- I know who to contact if I have any side effects from the study.
- I know who to contact if I have any questions about the medication used in this study or about the study in general.

I would like to participate in this research study and I give consent to participating in the study assessment which includes:

- Filling in a questionnaire about any urinary symptoms I may have before I start radiation treatment and once a week for ten weeks after that.
- The use of my information as part of a future larger trial. Yes/No

I consider my ethnicity to be:

- New Zealand European
- Māori
- Samoan
- Cook Islands Maori
- Tongan
- Niuean
- Chinese
- Indian
- Other (such as Dutch, Japanese, Tokelauan). Please state.

APPENDIX C: Consent Form

I, (*full name*) hereby consent to take part in this study.

Date:

Signature:

Full names of researchers:

Contact phone number for researchers:

Project explained by:

Treating physician:

Signature:

Date:

APPENDIX D: Excel Scoring Sheet

Patient number		Baseline	Week 1	Week 2	Week 2	Week 3	Week 3	Week 4	Week 4	Week 5	Week 5	Week 6	Week 6	Week 7	Week 7	Week 8	Week 8	Week 9	Week 10
Question																			
1	How often have you had pain or burning with urination?		Thur	Mon	Thur	Mon	Thur	Mon	Thur	Mon	Thur	Mon	Thur	Mon	Thur	Mon	Thur	Thur	Thur
2	How often have you urinated blood?																		
3	How much URAL have you taken help with your cystitis symptoms?																		
4	How often have you leaked urine?																		
5	Which of the following best describes your urinary control?																		
6	How many pads or liners did you use to control leakage How big a problem if any has each of the following been for you?																		
7	A. Pain or burning when you pass urine B. Weak urine stream or incomplete emptying C. Need to pass urine frequently during the day D. Waking up in the night to pass urine E. Blood in you urine F. Leaking and dribbling urine G. Overall, how big a problem has your urinary function been for you																		
Comments																			

Cranberry Trial Exit Questionnaire

1. Was taking part in this trial a positive experience for you?

Yes/No

Please comment in the box below:

2. Taking part in a blinded randomized trial meant that you did not know whether you were given cranberry capsules or placebo capsules. How did you feel about that?

Please comment in the box below:

APPENDIX E: Exit Questionnaire

3. Based on your experience with this trial, would you take part in other clinical trials when appropriate?

Yes/No

Please comment in the box below:

4. Is there anything we could do to make this a better experience for you?
Yes/No

Please comment in the box:

5. Would you like the results of this trial sent to you?
Yes/No

Thank you for your participation in this trial. This valuable research would not be possible without your help.

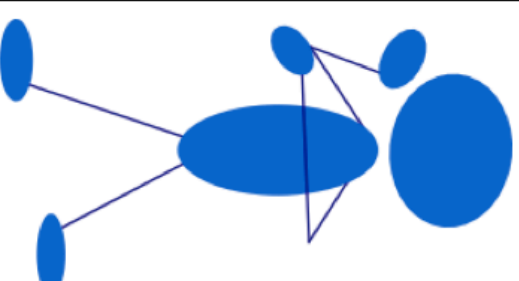
Best of wishes for the future.

Cranberry Study – Daily Diary

Name: _____

Please fill in each day over the next week and bring back to your next Monday appointment.

Week 1	How often did you get up in the night to pass urine?	How many sachets have you taken today?	Any comments about how things have been for you today?
Date:			
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			



Cranberry Study

Urinary Symptom Questionnaire

Name: _____ Date: _____

These questions are designed to capture a snap shot of your urinary symptoms during the past week.

1. In the past week have you experienced any burning when passing urine? Yes/No

*If you **did** experienced burning...*

A. How often did you experience that burning?									
<input type="checkbox"/> 1	once	<input type="checkbox"/> 2	more than once	<input type="checkbox"/> 3	about once a day	<input type="checkbox"/> 4	more than once a day		
B. How severe would you describe the burning? (Please circle)									
Very mild	1	2	3	4	5	6	7	Extremely painful	
C. How much of a problem, if any, was this for you? (Please circle)									
No problem at all	1	2	3	4	5	6	7	A huge problem	

2. Over the last week how often during the <u>day</u> did you needed to empty your bladder?									
<input type="checkbox"/> 1	Once or twice								
<input type="checkbox"/> 2	Every 2-3 hours								
<input type="checkbox"/> 3	Every hour								
<input type="checkbox"/> 4	Every half hour or less								
B. How much of a problem, if any, was this for you? (Please circle)									
No problem at all	1	2	3	4	5	6	7	A huge problem	
3. Over the last week how often during the <u>night</u> did you needed to empty your bladder?									

APPENDIX G: Proposed Urinary Symptom Questionnaire

<input type="checkbox"/> 1	Once							
<input type="checkbox"/> 2	Twice							
<input type="checkbox"/> 3	More than twice							
B. How much of a problem, if any, was this for you? (Please circle)								
No problem at all	1	2	3	4	5	6	7	A huge problem

4. Over the last week, which of the following statements best describes your urinary control <u>before</u> emptying your bladder?								
<input type="checkbox"/> 1	Good control, I could easily hold on as long as I needed to							
<input type="checkbox"/> 2	I could hold on but needed to find a toilet within 30 min once I was aware I needed to go							
<input type="checkbox"/> 3	I could hold on however needed to find a toilet within 10-15min once I was aware I needed to go							
<input type="checkbox"/> 4	I experienced leakage once or twice because I couldn't make it to the toilet in time							
<input type="checkbox"/> 5	I experienced leakage quite often because I couldn't make it to the toilet in time							
B. How much of a problem, if any, was this for you? (Please circle)								
No problem at all	1	2	3	4	5	6	7	A huge problem
If leakage did occur how much urine did you lose?								
A very small amount	1	2	3	4	5	6	7	A lot

5. Over the last week, which of the following statements best describes your urinary control <u>immediately after</u> emptying your bladder?								
<input type="checkbox"/> 1	Good control or a 'normal' amount of dribbling							
<input type="checkbox"/> 2	Occasional dribbling							
<input type="checkbox"/> 3	Frequent dribbling							
<input type="checkbox"/> 4	No control at all							
B. How much of a problem, if any, was this for you? (Please circle)								
No problem at all	1	2	3	4	5	6	7	A huge problem

APPENDIX G: Proposed Urinary Symptom Questionnaire

6. Over the last week how would you score your urinary flow? *(Please circle)*

Very strong 1 2 3 4 5 6 7 Very weak

B. How much of a problem, if any, was this for you? *(Please circle)*

No problem at all 1 2 3 4 5 6 7 A huge problem

7. How many URAL sachets have you taken each day to help with your urinary symptoms?

1 One a day

2 Two or

3 Three a day

4 Four a day

5 Five or six a day

6 Seven or eight a day

8. Overall how much of a problem, if any, has your urinary function been for you? *(Please circle)*

No problem at all 1 2 3 4 5 6 7 A huge problem

Is there anything else you would like to mention?

