Cryotherapy of the Prostate: Assessment of and Correlation between Iceballs Thermal Properties and Quality of Life after Salvage Treatment

By

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I would like to dedicate this work to Lanja and Bana.
Abstract

Introduction

Cryotherapy is being used increasingly as a minimally invasive treatment option to treat salvage cases of prostate cancer after radiation therapy has failed. The technique of cryotherapy includes freezing the prostate by a number of iceballs created by cryoprobes. The process is monitored by thermosensors and transrectal ultrasound scan. There is little agreement in the literature on the iceball characteristics; hence, variations of the technique of cryotherapy exist among clinicians particularly as to the positioning of the cryoprobes and thermosensors.

The current salvage therapies for prostate cancer have comparable early oncological outcome, and all have some adverse effects. Patients choosing treatment with different modalities tend to experience different morbidities, the significance of which may be subjective to each patient. Hence, the impact on quality of life is an important tool in assessing treatment outcome.

In this dissertation, the factors determining the characteristics of the iceballs formed during cryotherapy have been investigated in an in vitro model; aiming to help clinicians to increase the safety and efficacy of the procedure.

The impact of cryotherapy on quality of life has also been assessed using several validated instruments.

We assessed the correlation between the iceball temperature profile and the impact on quality of life of patients after salvage cryotherapy of the prostate in an aim to reduce the impact of salvage cryotherapy on the quality of life of patients.

Material and Methods

The thermal properties of three different probes (3.4mm and 2.4mm diameter cryoprobes produced by Endocare™ and the 1.47mm diameter cryoneedles produced by the Seednet™) were compared in vitro. The temperatures of several points within the iceball created within bovine muscle were measured using thermosensors. The effects of changing the freezing gas flow rate from 100% to 20% on the properties of the resultant iceball were also investigated.

The impact of salvage cryotherapy on quality of life was investigated using a prospective study design and a number of validated questionnaires including: EROTC QLQ-C30, EROTC PR-25, IPSS and IIIE.

The lowest temperatures at the apex of the prostate, at the external urethral sphincter area and at the Denonvillier's fascia (between prostate and rectum) during salvage cryotherapy were obtained, and correlated to the changes in the global health, urinary problem domains, urinary incontinence question, IPSS and quality of life question of the IPSS at 6 weeks post cryotherapy.
Results

1. There was a significant difference between the thermal properties of the iceballs (p <0.05). The 2.4 mm diameter probes produced an iceball with the highest ablative ratio (percentage of lethal iceball/ total iceball volume) and the least non-lethal ice thickness (the outer zone of the iceball where temperature ranges between 0° and 40°C). The 3.4mm diameter probes produced an iceball, which had larger dimensions than the 2.4mm probes, but had a statistically significant lower ablative ratio (p<0.001).

The most important feature of the 1.47mm diameter cryoneedles was that they produced a small iceball with statistically significant short lethal ice (p<0.001) compared to both Endocare™ cryoprobes, and with smaller ablative ratio (P<0.001) compared to the 2.4mm diameter cryoprobes.

Reduction of the gas flow rate to 20% resulted in a decrease in the lethal iceball dimensions, cooling rates and the ablative ratios for all the iceballs which was more pronounced when using the 1.47 cryoneedles.

2. The quality of life study is ongoing and preliminary results are presented. The trend suggested worsening (of "a little" clinical significance) of the global health score temporarily for 3 months after cryotherapy. Urinary problems worsened until 9 months after cryosurgery at which time it became of no clinical significance. There were no clinically significant changes in sexual activity and function after salvage cryosurgery, as the majority (86%) were considered impotent before cryotherapy.

3. The study is ongoing and preliminary results showed no correlation exists between the lowest iceball temperature at the apex of the prostate, the external urethral sphincter or the Denonvillier’s fascia and the impact on the quality of life of patients after salvage cryotherapy.

Conclusions

There are differences between the iceball thermal properties of the different freezing probes, and the 2.4mm diameter probes appear to be superior to the other probes.

Conclusions cannot be drawn on the quality of life study, but the trends suggest that the changes in quality of life and symptoms, except for incontinence, are limited to 6-9 months post-operatively on average.

The lack of correlation between the lowest iceball temperatures and the quality of life should be interpreted with caution due to the small number of patients assessed in this study to date.
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Abbreviations

3D-CRT= Three-Dimensional Conformal Radiotherapy
ANOVA= Analysis of Variance
ASTRO= American Society for Therapeutic Radiology and Oncology
BPH= Benign Prostatic Hyperplasia
CT= Computerised Tomography
CV= Coefficient of Variation
DFR= Disease-Free Rate
DRE= Digital Rectal Examination
EBRT= External Beam Radiotherapy
ED= Erectile Dysfunction
ED-EQoL= Erectile Dysfunction Effect on Quality of Life
EORTC= European Organization for Research and Treatment of Cancer
EPC= Early Prostate Cancer
ERSPC= European Randomised study of Screening for Prostate Cancer
FACT= Functional Assessment of Cancer Therapies
FAIT-U= Functional Assessment of Incontinence Therapy-Urinary
HDR= High-Dose Rate
HIFU= High-Intensity Focused Ultrasound Scan
HQoL= Health-Related Quality of Life
IPSS= International Prostate Symptom Score
IIEF= International Index of Erectile Function
IIF= Intracellular Ice Formation
J -T= Joule-Thompson
IMRT= Intensity Modulated Radiotherapy
LH-RH= Luteinizing Hormone–Releasing Hormone
LSD= Least Significant Difference
LUTS= Lower Urinary Tract Symptoms
MRI= Magnetic Resonance Imaging
PR25= Prostate 25
PSA= Prostate Specific Antigen
PSM= Positive Surgical Margin
QLQ-C30= Quality of Life Questionnaire C30.
RALRP= Robotically Assisted Laparoscopic Radical Prostatectomy
RCT= Randomised Control Trial
RITA= Radiofrequency Interstitial Tumour Ablation
RT= Radiotherapy
RTOG= Radiation Therapy Oncology Group
SD= Standard Deviation
SSQ= Subjective Significance Questionnaire
TNM= Tumour Node Metastasis
TPSM= Taunton Psychosocial Morbidity
TRUS=Transrectal Ultrasound Scan
TURP= Transurethral Resection of Prostate
UCLA-PCI= University of California Los Angeles-Prostate Cancer Index
Chapter 1
Introduction
1.1 Prostate Cancer Epidemiology

Incidence

Prostate cancer is the most common cancer in men in western countries and is the second most common cause of cancer death (Moul et al, 2003).

In 2000, the number of new cases of prostate cancer was estimated at 513,000 worldwide (Gronberg, 2003). This accounts for 9.7% of all cancers in men (15.3% in developed countries and 4.3% in developing countries).

The incidence of prostate cancer varies worldwide. United States, Canada, Australia and Scandinavia have the highest rates, with lower rates being found in China, India, Japan and Singapore (Gronberg, 2003; Quinn and Babb, 2002a). These differences may be caused by one or a combination of factors, including genetic vulnerability, unknown environmental factors or differences in healthcare and cancer registration (Gronberg, 2003).

In the United States, prostate cancer accounts for 33% of all newly diagnosed malignancies among men (reviewed by Crawford, 2003). According to the American Cancer Society, there were an estimated 220,900 men diagnosed with prostate cancer in 2003 and 28,900 men died from it, making it the second most common cause of cancer death in men.
In England and Wales, prostate cancer is the second most common cancer in men with 19,300 men diagnosed with prostate cancer in 1997 (Quinn and Babb, 2002b).

The incidence of prostate cancer has changed over the last 30 years (figure 1.1). The age-specific incidence rates increased gradually between the early 1970s and the late 1980s in the USA. The apparent increase in the incidence of prostate cancer in the 1970s and 1980s have partly been attributed to the increased use of TURP for treating BPH, which resulted in the incidental detection of preclinical cases to approximately 10% of patients (reviewed by Quinn and Babb, 2002a). Between 1986 and 1992, the age-adjusted incidence increased from 91.4 to 190.4 per 100,000 men (Stephenson, 2002). The apparent rapid rise in the incidence may have occurred due to increased detection of prostate cancer by the use of PSA and improved ultrasound-guided biopsy techniques. The peak incidence in 1992 was followed by a sharp fall in 1994 and then stabilised at a new post-peak level through 1997, which is higher than the incidence before the PSA era. The decline in the incidence from 1992 to 1995 may be the result of a cull phenomenon whereby repeat screening in a relatively cancer-depleted population resulted in lower cancer case yields (Stephenson et al, 1996).

In addition to the changing incidence of prostate cancer, the advent of PSA testing brought several changes to the patterns of clinical presentation and treatment for prostate cancer. These include earlier disease stage at
diagnosis and greater rates of treatment with curative intend by radical prostatectomy or radiation therapy (reviewed by Mettlin et al, 1998).

In England and Wales, the incidence rates were 2 to 3 times lower than in the USA (Quinn and Babb, 2002b); however, similar to USA, there was a steady increase in the incidence rates in all age groups during the 1970s and 1980s (figure 1.1). The sharp rise in the incidence rates due to the use of PSA began later in England and Wales than in USA (Quinn and Babb, 2002b). The all-ages directly age-standardized incidence in England and Wales increased from 29 to 59 per 100 000 between 1971 and 1993 (Majeed et al, 2000).

Mortality

In contrast to the wide variation in the incidence of prostate cancer worldwide, there has been relatively little variation in mortality (Quinn and Babb, 2002a). The highest mortality rates are reported for the Caribbean and Scandinavia and the lowest in China and Japan, India and Singapore (reviewed by Crawford, 2003; Quinn and Babb, 2002a). Despite differences in prostate cancer mortality, there were large increases in mortality rates in virtually all the countries between the 1970's and early 1990's (reviewed by Quinn and Babb, 2002a). In USA, Canada, England, France and Austria, a decline in mortality was observed in the late 1990s.

In the USA, age-adjusted prostate cancer mortality rates rose gradually from 21.7 to 26.7 deaths per 100,000 men between 1973 and 1991 (figure 1.1). Mortality rates seemed to flatten in the early 1990s and then steadily declined
through 1997 to equal the rate observed in the 1970s (Stephenson, 2002). The reasons for this decline is not clear but could have been contributed by a number of factors including better diagnostic methods with TRUS guided biopsy coupled with wide use of PSA leading to earlier detection, and improvement in curative treatments (reviewed by Roberts et al, 1999). Data suggest that most of the decline in mortality is explained by reductions in mortalities in men with distant-stage disease rather than from localised prostate cancer. However, the duration of follow-up in these studies is too short to detect changes in localised prostate cancer mortality since the use of PSA testing (Stephenson, 2002).

In England and Wales, the annual number of deaths from prostate cancer has increased by 113% between 1971 and 1998, from 4027 to 8570 (Majeed et al, 2000). In 2000, 8300 men died from prostate cancer accounting for 12% of all cancer deaths and just over 3% of all deaths in men (Quinn and Babb, 2002b). There was a little change in prostate cancer mortality in the 1970s (figure 1.1). Death rates began to increase from the 1980's to peak in 1995 (age-standardised death rate of 30 per 100,000). Death from prostate cancer declined in the subsequent 3 years to reach 27 per 100,000 in 1998 (an overall increase of 38% between 1971 and 1998) (Majeed et al, 2000).
Figure 1.1. The age standardised incidence of (red) and mortality from (blue) prostate cancer in England and Wales (solid line) and USA (dashed line), 1971-1999 (Quinn and Babb, 2002a).

**Staging and Prognosis**

Prostate cancer may either be confined to the prostate (so called localised or early prostate cancer), locally advanced (with local infiltration), or advanced where there has been metastasis to other sites including lymph node or bones. Early prostate cancer is the commonest comprising 65.5% of cancers detected in the UK, locally advanced disease making up 22.1% of cases and 12.4% with advanced disease (baus.org.uk, 2005).

Prostate cancer progresses either through local infiltration resulting in invasion of adjacent structures including urethra, bladder, ureter or rectum, or by metastasis commonly to bone. Prognosis depends on the stage of the disease and the potential for the cancer to progress.
In the UK, prostate cancer is commonly staged according to the TNM 2002 staging classification (Green, 2002) which uses clinical examination and imaging to determine the extent of the cancer (table 1.1). Potential for cancer to progress has been shown to be associated with several microscopic features of the tumour. These features include: tumour grade (Gleason score); perineural invasion and the presence of high grade Prostatic Intraepithelial Neoplasm (DeMarzo A.M. et al, 2003; McNeal et al, 1986; Whitmore, 1984).

Gleason grade ranges from 1 to 5 depending on the degree of differentiation of the tumour (grade 1 for well differentiated and grade 5 for undifferentiated). Because prostate cancer is commonly heterogeneous and multifocal, it is more useful to consider more than one area of the prostate. Therefore, Gleason score or sum is widely used to determine the grade of the cancer where the two areas which make up most of the cancer are added together. The Gleason score is commonly expressed as the two Gleason grades added together. The first grade is the most commonly seen grade, while the second grade is the second most commonly seen grade (Pan et al. 2000). Therefore, although both 3+4 and 4+3 result in a Gleason score of 7, the latter is more aggressive.

Using a combination of PSA, Gleason score and clinical staging (T), three risk groups (low, intermediate and high) for prostate cancer have been established by a number of institutes to help predict outcome after treatment for early prostate cancer. Commonly used classifications include the Seattle risk score (Blasko et al, 2000), Mount Sinai risk score (Lee et al, 2002) and D'Amico risk score (D'Amico et al, 1998).
<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tx</strong> Primary tumor cannot be evaluated</td>
<td><strong>Nx</strong> Regional lymph nodes cannot be evaluated</td>
<td><strong>Mx</strong> Distant metastasis cannot be evaluated</td>
</tr>
<tr>
<td><strong>T0</strong> No evidence of tumor</td>
<td><strong>N0</strong> No spread to the regional lymph nodes</td>
<td><strong>M0</strong> No distant metastasis</td>
</tr>
<tr>
<td><strong>T1</strong> Tumor not apparent clinically or with imaging</td>
<td><strong>N1</strong> Spread to the regional lymph nodes</td>
<td><strong>M1</strong> Distant Metastasis</td>
</tr>
<tr>
<td><strong>T1a</strong> Found in &lt;5% of TURP chips</td>
<td></td>
<td><strong>M1a</strong> Metastasis to lymph nodes beyond the regional ones</td>
</tr>
<tr>
<td><strong>T1b</strong> Found &gt;5% of TURP chips</td>
<td></td>
<td><strong>M1b</strong> Metastasis to bone</td>
</tr>
<tr>
<td><strong>T1c</strong> Found on needle biopsy</td>
<td></td>
<td><strong>M1c</strong> Metastasis to other sites (regardless of bony involvement)</td>
</tr>
<tr>
<td><strong>T2</strong> Tumor can be felt on examination, but has not spread outside the prostate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T2a</strong> Tumour involves &lt; ½ of one prostate lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T2b</strong> Tumour involves &gt; ½ of one prostate lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T2c</strong> Tumour involves both lobes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T3</strong> Tumor has spread through the prostatic capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T3a</strong> Extracapsular extension on one or both sides</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T3b</strong> Tumor has invades one or both seminal vesicles</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T4</strong> Tumour invades adjacent structures: bladder neck, external sphincter, rectum and levator muscles.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.1. TNM 2002 staging classification for prostate cancer.
1.2 Treatment Options for Early Prostate Cancer

There are several treatment options for early prostate cancer (table 1.2). However, there is a lack of prospective randomised trials (RCT) directly comparing outcomes following these treatments. Only one RCT has been published (Bill-Axelson et al, 2005) in which 695 patients were randomised to watchful waiting versus radical prostatectomy. After a median follow up of 8.2 years, 177 patients in the watchful waiting arm received hormonal treatment compared to 110 in the radical prostatectomy arm. The results were in favour of radical prostatectomy with prostate cancer-specific mortality, overall mortality and the risk of metastasis and progression being reduced by 5.3%, 5%, 10.2% and 25.1% respectively compared to watchful waiting patients.

Comparison of the available retrospective data is difficult due to the differences in the definitions used for disease recurrence for various local treatment options. However, it is generally agreed that cohort and institutional series have suggested equivalent efficacy of radical prostatectomy, three-dimensional conformal EBRT and brachytherapy in the treatment of early prostate cancer (Kupelian et al, 2004; Potters et al, 2002).

Selection of treatment options depends on many factors including the patient's age, race, cancer risk group, comorbidities, patients choice and his doctors' advice (Kane et al, 2003). Urologists commonly prefer surgery whilst oncologists favour radiation therapy (Fowler, Jr. et al, 2000). It is possible that future decision making may depend on the degree of impact of treatment on
quality of life. Discussion of all treatment options is beyond the scope of this dissertation.

1 Active Surveillance
2 Radical Prostatectomy
   i) Open (Retropubic/ Perineal)
   ii) Laparoscopic
   iii) Robotic
3 Radiation Therapy
   i) External Beam Radiotherapy
   ii) Brachytherapy
4 Cryosurgery
5 High Intensity Focused Ultrasound
6 Hormonal Therapy: usually in combination with other therapies, either:
   i) Before (neoadjuvant)
   ii) Immediately after (adjuvant).
7 Emerging / Rarely Used Treatments
   i) Photodynamic Therapy
   ii) Microwave
   iii) Radiofrequency
   iv) Particle Beam Radiation Therapy

Table 1.2 Treatment options for early prostate cancer.
1.2.1 Radiation Therapy

Radiation can either be delivered with external beam (external beam radiation therapy or EBRT) or interstitially (also known as brachytherapy or seed implant therapy).

1.2.1.1 External Beam Radiation Therapy (EBRT)

This is widely accepted as a curative treatment choice for localised prostate cancer. The concept of this therapy is that the delivered radiation dose should be lethal to the tumour, whilst safe to the adjacent organs (e.g. bladder and rectum) to avoid toxicity.

Recent technological advances in radiation treatment planning and delivery has resulted in the development and implementation of sophisticated techniques including three-dimensional conformal radiotherapy (3D-CRT) and, more recently, intensity modulated radiotherapy (IMRT).

a. Conventional EBRT

The technique of conventional EBRT delivery involves patient immobilization, radiographic simulation (to define the anatomical landmarks) and treatment planning aiming to encompass the prostate with a 2-3cm margin.

Radiation is typically delivered as an out-patient procedure in 2 Gy fractions for 5 days a week over 5-7 weeks.
Several retrospective long-term follow-up series of conventional EBRT are available. Most of these patients were non-surgical candidates, poorly selected, and referred for radiation therapy during the pre-PSA era.

Zietman et al (1995) reviewed 1044 men with T1-T4NxM0 prostate cancer treated with conventional ERBT between 1977 and 1991. After a median follow-up of 49 months, 40% and 18% of T1-2 and T3-4 patients were biochemically disease free respectively, where failure was defined as a serum PSA ≥ 1ng/ml 2 or more years after treatment.

In a shorter follow-up study, Preston et al (1999) reviewed 371 prostate cancer patients who had EBRT with a mean follow-up of 40.2 months. The overall 5-year disease-free survival was 55.3%.

Radiation induced rectal and genitourinary toxicities are frequently graded according to increasing severity from mild (grade 1) to severe (grade 4). The most frequently used grade scales are the Radiation Therapy Oncology Group (RTOG) scale for acute toxicity and the RTOG/ EORTC (the European organization for research and treatment of cancer) scale for late toxicity (Cox et al, 1995).

Zurlo et al (2002) reported the acute toxicity of 405 prostate cancer patients treated with conventional EBRT in the EORTC trial 22863. The incidence of ≥ grade 2 acute genitourinary and lower gastrointestinal toxicities were 31.6% and 24.9% respectively. The late toxicity of the same trial was reported by
Ataman et al (2004) which showed that 22.8% of the patients had ≥ grade 2 urinary and intestinal complications.

b. Conformal Radiotherapy (3D-CRT)

During the past decade, the increased availability of CT scanners and the development of sophisticated three-dimensional (3D) planning and delivery systems have made the clinical use of 3D-CRT possible. This allows more precise delivery of higher doses of external beam radiation to the prostate with steep drop-off of the dose to the adjacent normal organs.

Long-term results are awaited; however, there is good evidence from intermediate follow-up studies to support the use of 3D-CRT.

Zelefsky et al (2001) reviewed 1100 patients who were treated with 3D-CRT. The 5-year actuarial recurrence-free survival for patients treated with <70.2 Gy was 77%, 50% and 21% for favourable, intermediate and unfavourable prognostic features respectively. For those patients treated with 75.6-86.4 Gy, the corresponding 5-year actuarial PSA recurrence-free survival rates were 90%, 70% and 47%.

The advantage of 3D-CRT is the ability to escalate the radiation dose delivered to the prostate without increasing complications. However, Pollack et al (2002) found that the benefit of dose escalation was only noted in patients with unfavourable prognostic features (PSA > 10 ng/ml). They randomised 301 men with T1-T3 prostate cancer to receive 70 Gy
(conventional ERBT) or 78 Gy (3D-CRT). At 6-years, a significant difference in biochemical-free rates (43% vs 62%) was observed only in the unfavourable cancer patients in favour of the 3D-CRT arm.

Storey et al (2000) randomised 189 patients to receive either conventional ERBT (70 Gy) or 3D-CRT (78Gy). There were no statistical differences in early or late toxicities between the two groups.

Michalski et al (2005) analysed the toxicities of 218 patients treated with 3D-CRT (78 Gy) in a phase I-II RTOG (Radiation Oncology Group) 9406 trial. They concluded that only 2% and 4% developed late bowel and bladder grade 3 toxicities respectively and no patients had grade 4 toxicity.

c. Intensity Modulated Radiotherapy (IMRT)

A refinement of the 3D-CRT is the intensity modulated radiotherapy (IMRT) which involves the use of multiple small, non-uniform radiation beams of various intensities directed toward the target. One of the main advantages is the flexibility of devising a desired dose distribution of any 3D shape to match the clinical target. Thus, the desired dose to the tumour can be optimised, while the doses to various adjacent critical organs can be selectively minimised to reduce toxicity. However, long-term risks of larger volumes of normal tissue receiving low doses of radiation are unknown.

Another potential of IMRT is the ability to escalate radiation dose to other targets including pelvic lymph nodes.
Short-term data suggest that IMRT is comparable to 3D-CRT in terms of PSA outcome without increasing toxicity. Zelefsky et al (2002) followed a series of 772 patients for a median of 24 months. The 3-year actuarial PSA recurrence-free rates were 93%, 84% and 81% in patients with low, medium and high-risk features. The incidences of acute grade 2 rectal and genitourinary toxicities were 4% and 28% respectively. The corresponding figures of late toxicities were 1.5% and 9.5% respectively.

De Meerleer et al (2004) reported 114 patients treated with a IMRT (mean does of 77 Gy). Grade 2 acute gastrointestinal and genitourinary toxicity was observed in 29% and 36% of patients respectively. The corresponding figures for grade 3 complications were 0% and 7% respectively.

1.2.1.2 Brachytherapy

'Brachy' comes from the Greek meaning 'close' and as such the name is apt in describing targeted radiation therapy using radioactive seeds where high dose of radiation is delivered to a focused area of the prostate. Modern brachytherapy was born in the 1980's following the development of the transrectal ultrasound scan (TRUS).

The technique involves TRUS imaging of the prostate, seed configuration measurement, loading needles with the seeds and finally insertion of the needles into pre-determined positions under TRUS guidance where the seeds are implanted. Postoperative CT scan are performed at either day 1 or 1
month from the implant to assess the quality of implant, allowing correction of poor positioning.

The choice of the radioactive isotope for the implant is controversial. Iodine-125 ($^{125}$I) has a half-life of 60 days compared to 17 days for Palladium-103 ($^{103}$Pd). Urologists have commonly used $^{125}$I for slower growing tumours and $^{103}$Pd for faster growing tumours (reviewed by Mangar et al, 2005). However, clinical data has shown no differences between the two isotopes in terms of cancer control (Cha et al, 1999).

The minimum prescribed dose to the prostate gland is 145Gy using Iodine-125 implants with approximately 50% of the gland receiving 150% of the dose (i.e. 217Gy). The implants are arranged to allow relative sparing of the prostatic urethra to minimize urinary toxicity.

Results of brachytherapy suggest that it is a feasible treatment option for localised prostate cancer particularly in patients with low and intermediate – risk disease.

Potters et al (2005) reviewed 1449 patients with 12-years biochemical disease-free rates for low, medium and high-risk prostate cancer patients were 91%, 80% and 66% respectively using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of biochemical failure (3 successive PSA rises).
In the UK, Joseph et al (2004) presented their series of 667 patients treated with I\textsuperscript{125} which were comparable with most USA series. After a mean follow-up of 8.2 years, the biochemical recurrence-free rates were 84.3%, 73.9% and 52.6% for low, Intermediate and high-risk prostate cancer patients.

Side effects of brachytherapy are predominantly urinary, though rectal toxicity and erectile dysfunction are also known risks. Most patients experience a temporary worsening of urinary function with increased irritative and obstructive symptoms which tend to improve after 2-3 months (Henderson et al, 2004). Toxicities include: acute urinary retention (2-22%), Incontinence <1% and proctitis 4-11% (Blasko et al, 2000; Henderson et al, 2004; Merrick et al, 2003; Terk et al, 1998).

A wide range of erectile dysfunction rate has been reported after brachytherapy (6% to 90%). This is likely due to differences in follow-up, mode of data collection, patient selection and use of neoadjuvant androgen deprivation and EBRT(reviewed by Langley and Laing, 2004; Merrick et al, 2003).
1.2.2 Cryosurgery

The word "cryo" comes from the Greek word "Kruos" for cold. Cryosurgery, also known as cryotherapy or cryoablation is a technique in which freezing is used to destroy undesirable tissues.

1.2.2.1 History and Development of Cryosurgery

The first physician to use cold or congelation to treat cancers was Dr James Arnott (figure 1.2) from Brighton (1797-1883), UK (Arnott J., 1850). He used a mixture of saline and ice applied to advanced breast and cervical cancer to reduce pain, discharge and haemorrhage.

Fig. 1.2. Dr James Arnott
In 1877 Cailletet of France and Pictet of Switzerland began developing adiabatic expansion systems for cooling gases. This led to liquefaction of oxygen, air and nitrogen. In 1895, Linde of Germany and Hampson of UK began using throttle expansion or the so called the Joule-Thompson effect which will be explained later (1.2.2.3) that enabled the production of continuous operating air liquefiers.

Liquid nitrogen became commercially available in 1940's, and was used clinically in 1950's by Allington of Oakland, California (Allington, 1950) but only to treat superficial skin conditions as delivery systems for deeper tissues were not available.

One of the most important steps in the history of cryosurgery was the development of the closed liquid nitrogen system in 1961 by a neurosurgeon, Irving Cooper and an engineer, Arnold Lee (Cooper I.S. and Lee A.St.J., 1961). They designed a cannula capable of delivering liquid nitrogen to deep tissue, which was essentially the model from which future liquid nitrogen probes were manufactured.

In 1964, Maurice J Gonder from New York and colleagues began experimenting on canine prostate (Gonder et al, 1964) using liquid nitrogen. Two years later, the same group published the first report of prostate cryosurgery in 50 patients with BPH and prostate cancer (Gonder et al, 1966; Soanes and Gonder, 1969). The prostate was frozen using a single 26 Fr diameter liquid nitrogen probe, only the tip of which was cooled (-160°C). The
probe was placed urethrally and the freezing process was continuously monitored by a single thermocouple positioned between the rectal wall and the prostate and by regular digital examination. Freezing was stopped when the thermocouple temperature reached 0°C or if any fixation of the rectal mucosa was felt. Although they achieved sufficient outcome in terms of BPH symptoms and cancer control, complications were significant. These included urethral sloughing of necrotic tissue which required removal, frequent infections such as epididymitis, prolonged catheterization and incontinence. Despite technical modifications of cryosurgery including open perineal (Flocks et al, 1972) and percutaneous transperineal (Megalli et al, 1974) approaches, complications remained a problem as surgeons were still unable to precisely place the cryoprobes or monitor the freezing process. Therefore, urologists lost interest in cryosurgery in the 1980’s.

Another significant landmark in the development of modern cryosurgery which led to the revival of interest was the development of real-time trans-rectal ultrasound scan monitoring by Onik et al (1993). This enabled surgeons to accurately place the cryoprobes and continuously visualise iceball progression. At the same time, a multi-probe liquid nitrogen system (Accuprobe™) was introduced (figure 1.3a). This allowed a synergistically uniform and effective distribution of lethal low temperature throughout the iceball. In addition, it permitted some flexibility to the surgeon.

In the 1990’s, cryosurgery developed rapidly. Lee et al (1994) described the use of transperineal thermocouple probes placed at specific points providing real-time temperature information of the iceball, sphincter and rectal wall.
A year later, a double-lumen urethral warming catheter was developed (Cohen et al, 1995) in order to preserve the urethral mucosa. These developments facilitated more effective tumour destruction and significantly reduced complications including incontinence, urethral sloughing and rectourethral fistula.

In 1996, Endocare, Inc., Irvine, CA. introduced the multiple-port high-pressure gas system (Cryocare™) which later became more known as the second generation system (figure 1.3b). The system utilizes the Joule-Thompson effect, which will be discussed later in the chapter (1.2.2.3), using pressurised argon gas for freezing and helium for active thawing. The system is compact, responds rapidly to user input and able to create an iceball faster with steeper internal temperature gradients than the liquid nitrogen systems (Rewcastle et al, 1999a).

In the late 1990's, Galil Medical, Inc., Plymouth Meeting, PA introduced the third generation (SeedNet™) system (figure 1.3c) using ultra-thin 17-gauge needle probes aiming to produce higher resolution freezing and more uniform coverage of the prostate; however more needles are required to freeze the entire prostate (Han et al, 2003).

In 2003, Endocare introduced the fourth generation (Cryocare™ CS) system with (figure 1.3d) integrated biplaner ultrasound which allows intra-operative real-time planning. This new system is designed to simplify the procedure and allow more flexibility.
Figure 1.3. Cryosurgery systems. The Accuprobe™ system (a), the Cryocare™ (b), the Seednet™ (c) and the Cryocare CS™ (d).
1.2.2.2 Equipment for Cryosurgery

a. Transrectal Ultrasound Systems

Biplanar TRUS allows for viewing the prostate and monitoring the progression of the iceball both in transverse and longitudinal views. The leading edge of the iceball appears as a bright line as the sound waves reflect off the frozen/unfrozen interface (figure 1.4). The tissue behind the iceball edge is concealed in the acoustic shadow; therefore, TRUS cannot monitor beyond the anterior boundary of the iceball.

Figure 1.4. TRUS view of the iceball during prostate cryosurgery. The tissue behind the iceball edge is concealed (appears dark).
b. Freezing Probes

Double-lumen cryoprobes are used, where high-pressure gas is delivered via a thin central tube to the tip of the probe. The gas is then released to the expansion chamber where it expands rapidly as its pressure decreases to room temperature (15 pounds per square inch or psi). The expanded gas is then circulated back to the cryogenic unit through the outer lumen of the cryoprobe and the supply hose where it is vented into the room (figure 1.5). This sudden change of gas pressure results in temperature change via the Joule-Thompson (J-T) effect. High-pressure argon gas (300 bar) is used for freezing as its temperature decreases to -186°C while helium is used for thawing (+67°C) according to the J-T effect. The shaft and base of the probe is insulated with an air chamber to protect perineal tissue from freezing. The Cryocare™ system uses 3.4mm or 2.4mm diameter probes, while the Seednet™ system utilizes smaller diameter (1.47mm) cryoneedles.

![Figure 1.5. Diagram of the tip of a Joule-Thompson type freezing probe](image)
c. Urethral Warming Device
This consists of a closed double-lumen catheter made of polyethylene membrane, through which heated saline (38-40°C) is continuously circulated by a special pump.

d. Thermosensors
To monitor the iceball temperature, 1.5mm diameter probes with T-type 0.07mm diameter copper/constantan alloy thermocouple wire are used.

e. Cryogenic Systems
Two cryosurgical systems are available for prostate cancer treatment. The Cryocare™ system (Endocare Inc, Irvine, CA) allows the use of up to 8 freezing probes and 8 thermosensors. The system enables the user to control the rate of cooling by changing the rate of freezing gas flow rate between 5 to 100% in 5% increments. Endocare produced a newer generation (Cryocare™ CS) system which has a biplaner ultrasound built in.
The Seednet™ system (Galil Medical, Plymouth, Meeting, PA) allows the use of up to 30 cryoneedles and 5 thermosensors. The users can change the gas flow rate between 20 to 100% in 20% increments.
1.2.2.3 The Joule-Thompson Effect

The Joule-Thompson effect is a process in which high-pressure gas changes temperature when expands adiabatically; argon cools to -186°C while helium warms to +67°C.

For a fixed pressure, a gas has a Joule-Thompson inversion temperature which determines if the gas cools down or warms up upon expansion. The value of this temperature is -233°C for helium and +450°C for argon. Therefore, at room temperature helium results in warming while argon causes cooling on expansion.

The reason of this difference is explained by the difference in the intermolecular forces of each gas. In any gas, there are attractive and repulsive forces present between the molecules or atoms. When a system goes to a more stable state, it gives off energy; the process is exothermic, whereas if a system goes to a less stable state, energy must come from somewhere for the process to occur. In the process of gas expansion, this energy is in the form of heat.

In the case of argon gas, the attractive forces predominate, upon expansion, a larger average separation of molecules leads to a less stable state, and energy in the form of heat must be taken from the surroundings, hence cooling is observed upon expansion. When helium is used, heating is observed upon expansion as the repulsive forces predominate, and a greater separation of molecules results in a more stable state, releasing energy in the form of heat.
1.2.2.4 Cryobiology

The destructive effect of freezing on tissues can be due to many mechanisms: direct cellular injury, vascular injury, increased apoptosis and a possible immunogenic effect.

a. Direct Cellular Injury

There are 2 biophysical changes in water that occur in cells during freezing that have been linked to direct cell injury. As the temperature falls to less than 0°C, water crystallizes and ice starts to form. This first occurs in the extracellular spaces creating an extracellular hyperosmotic environment. This in turn withdraws water from the cells causing cellular dehydration. The resulting high concentration of intracellular solute has been hypothesised to cause cellular injury by damaging vital enzymes and destabilization of the cell membrane through increased protease activity and lipid peroxidation respectively (reviewed by Hoffmann and Bischof, 2002). Effective cellular dehydration occurs predominantly between 0°C and -20°C and with relatively low cooling rates when the cells have sufficient time to dehydrate completely.

The second biophysical response is intracellular ice formation (IIF), which occurs when the temperature drops below -40°C (Theodorescu, 2004). IIF is more efficient when the cooling rate is rapid, not allowing sufficient time for water to leave cells which keeps their solute freezing point higher. The ice crystals are purported to cause injury to the organelles and membranes and regarded more lethal than extracellular ice, although the precise mechanism
whereby IIF destroys cells is still debated (reviewed by Hoffmann and Bischof, 2002).

During thawing, ice crystals fuse to form larger crystals (a process called recrystallization) which can disrupt the cell membrane and causes additional cell damage. As the ice melts, the extracellular environment becomes hypotonic, and water enters the damaged cells which subsequently increases cell volume leading to cell membrane rupture (Theodorescu, 2004).

b. Vascular Injury

The initial response to the cooling of tissue is vasoconstriction, a decrease in the flow of blood and eventually the circulation ceases with freezing. During thawing, the circulation returns with vasodilatation. This hyperaemic response is brief and associated with increased vascular permeability leading to tissue oedema.

Cryotherapy has also shown to cause endothelial damage which results in a further increase in capillary wall permeability and oedema, platelet aggregation, and microthrombus formation resulting in stagnation of the circulation (Han et al. 2004). The loss of blood supply deprives all cells of any possibility of survival and results in tissue necrosis.

c. Apoptosis

Apoptosis is a form of cell death designed to eliminate unwanted cells through activation of a coordinated, internally programmed series of events. Biochemical features of apoptotic cells include protein cleavage, protein cross-linking and DNA breakdown. Apoptosis may happen in normal tissues
such as endometrial cell breakdown during the menstrual cycle, and also occurs in pathological conditions including cancers, cytotoxic chemotherapy, heat injury and irradiation. Apoptosis is also seen after tissue freezing predominantly in the peripheral zone of the cryogenic lesion where the temperature was not sufficiently cold to kill all the cells (Hollister et al, 1998). Studies have shown apoptosis occurs at temperatures between 6°C and -10°C (reviewed by Hoffmann and Bischof, 2002), and that cells were susceptible to entering the apoptotic state up to eight hours after re-warming (reviewed by Baust and Gage, 2005).

Most of the studies examining the role of apoptosis in cold and freezing injury have been in vitro, and the effect of apoptosis in vivo is still unclear.

d. Immunogenic Effect

Soanes et al (1970) have suggested a possibility of an “immuno-cryothermic response” following a spontaneous regression of metastatic lesions in two men after cryotherapy for primary prostate cancer. According to this hypothesis, after cryosurgery, the immune system of the host is sensitized to the tissue destroyed by the cryosurgery. Any tissue remaining undamaged by the freezing insult is destroyed by the immune system during the time after cryosurgery.

Since then many investigators have examined the role of cryo-immunological response in animals, however, their results were inconsistent. While several studies showed immunogenic response, many showed little or no response and others have shown that cryosurgery increases tumour growth and metastasis (reviewed by Hoffmann et al, 2001).
The role and mechanism of cryo-immunological stimulation in still unclear, and is currently under investigation.

1.2.2.5 Parameters of Cryosurgical Injury

Studies have shown that the degree of cryosurgical injury is a function of five different parameters: end tissue temperature, cooling rate, duration of freezing, thawing rate and number of freeze-thaw cycles.

a. End Tissue Temperature

The temperature range over which cells die is -5° to -50°C (reviewed by Gage and Baust, 1998). Extensive tissue damage occurs at -20°C to -30°C, but cell destruction is uncertain or incomplete. As explained before, IIIF, which is more effective, occurs commonly in temperatures below -40°C. Therefore, temperatures between -40°C and -50°C are essential to ensure complete damage of all cancer cells.

b. Cooling Rate

The cooling rate should be as fast as possible to increase the potential to produce the more effective IIIF. Studies have shown that IIIF occurs over a wide range of temperatures, i.e. at cooling rates from 20–50 C/min, and in tightly packed cells even a slower cooling rate may produce intracellular ice (reviewed by Gage and Baust, 1998). From these variances, the cooling rate appears to be less critical to cell injury than other factors. In cryosurgery, rapid freezing of the order of 50°C per minute or more occurs only close to a cryosurgical probe. The further away from the probe, the lower
is the cooling rate. At about 1 cm from the probe, the cooling rate may only be 10–20°C/min, where there is no IIF. However, experimental work in this area supports the view that cooling rate is not the primary factor in determining cell survival.

c. Duration of Freezing

Increasing the duration of freezing can allow the intracellular space to equilibrate with the extracellular space, thereby increasing cellular dehydration. Holding longer at subzero temperatures can also increase the amount of IIF. Increasing hold time may also allow recrystallization, whereby smaller ice crystals fuse to form larger ice crystals. (reviewed by Hoffmann and Bischof, 2002). It has been recommended that the prostate should be held in the frozen state for 5 minutes, although the optimum duration of freezing is not well defined (Baust and Gage, 2005).

d. Thawing Rate

The rate of thawing should be as slow as practical, and is best done by allowing the tissues to thaw passively with no assistance by heating. The longer the duration of the thaw, the greater the damage to the cells because of solute effects, ice-crystal restructuring (recrystallization), prolonged oxidative stress and growth of ice crystals (Schmidt et al., 1998). The large ice crystals that form during ‘warming’ recrystallization create shearing forces which disrupt the tissues.
e. Number of Freeze-Thaw Cycles

Repeating the freeze cycle produces faster cooling and more extensive tissue destruction. It has been shown that repetition of freeze cycle increases tissue necrosis to include about 80% of the previously frozen volume (Dilley et al., 1993). This means, in the prostate, the border of tissue destruction moves closer to the outer limit of the frozen volume, permitting a closer approach to the margins of the gland without endangering the rectum. Therefore, repetition of the freeze-thaw cycle is thought to be critical in the treatment of prostate cancer.

1.2.2.6 The Cryogenic Lesion

This is characterized by a central uniform coagulation necrosis surrounded by a peripheral zone in which only partial cell death has occurred. This tissue change develops several days after freezing. Soon after thawing, the tissue appears congested and hyperaemtic, and becomes oedematous. The extent of necrosis becomes evident in about 2 days. In the central zone, near the cryoprobe/cryoneedle, cell death is uniform, but in the border zone at the periphery of the previously frozen tissue, where the tissue temperature was 0°C to -20°C, some cells survive, other cells are dead, and others are in the balance between life and death. Apoptotic cells are seen in this peripheral zone. The process of wound repair begins in the peripheral zone in the areas in contact with viable tissue. Inflammatory cells infiltrate and new blood vessels may grow into the injured tissue. Over the following weeks or even months, the dead tissue is slowly replaced by fibroblasts and new collagen formation. The end result is a contracted healed area.
1.2.2.7 Technique of Modern Cryosurgery

Patients undergo bowel preparation the night before the operation with a phosphate enema. Under general or spinal anaesthesia, the patient is placed in extended lithotomy position. A brachytherapy-type template, stabilised with a stepper, is placed in front of the perineum. A biplaner TRUS probe is used to image the prostate and measure its dimensions. Guided by the TRUS, the freezing probes are then placed (figure 1.6), the number of which depends on the volume of the prostate and the type of the probe used. Typically 6 freezing probes are used (2 anterior and 4 posterior) for the Cryocare™ system probes (2.4mm or 3.4mm diameter) (figure 1.7a). The recommended maximum distance between 2 adjacent probes ranges between 18 to <30mm, and probes should not be placed more than 10mm from the prostatic capsule. (Donnelly and Saliken, 2002; Lee et al, 1999). However, if the Seednet™ system is used, then more cryoneedles are required. Commonly 12-15 cryoneedles are used divided into 3 to 4 rows with needles placed not more than 10mm apart and within 5-7mm of the capsule (Zisman et al, 2001) (figure 1.7b).

Depending on the surgeon's preference, up to 5 thermosensors are then placed at the level of external urethral sphincter, right and left neurovascular bundles, Denonvillier's fascia and either at the apex or the middle of the prostate.

Once the probes are all in place, a flexible cystoscopy is performed to ensure that none of the probes has been placed accidently through the urethra. A guidewire is then placed through the cystoscope and into the bladder, followed by insertion of a urethral warming catheter over the guidewire.
Freezing is then commenced by running argon gas starting in the anterior probes followed by the posterior group to maintain TRUS visibility throughout the procedure. Freezing is stopped when the temperature of the neurovascular bundles and the apical thermosensors reach -40°C or when the temperatures of the Denonvillier's fascia or the external sphincter is approaching 0°C or when the edge of the iceball becomes close to the rectal wall indicated by TRUS picture. Both cryosurgical systems have incorporated treatment software which enables surgeons to pre-set endpoint temperatures of thermosensors and freezing stops automatically when the temperatures are reached. Commonly, the iceball is allowed to thaw passively; however, helium has also been used to facilitate thawing.

Double freeze-thaw cycles are used for effective freezing. The urethral warming catheter is then left for 5-20 minutes after completion to minimize the risk of urethral sloughing (Fahmy and Bissada, 2003; Han and Belldegrun, 2004).

A urethral catheter is left for between 3 days to 3 weeks postoperatively.

In a long prostate, a "pull back" technique is performed where the freezing probes are pulled back by few millimetres and then freezing is repeated to cover the apex of the prostate. When the Cryocare™ probe is used, "pull back" is rarely performed due to longer iceball; however for the Seednet™ cryoneedles, the recommended prostate length at which "pull back" is performed varies between different surgeons ranging from 26 to 35mm (Witzsch et al, 2005; Zisman et al, 2001).
Figure 1.6. View of the perineum showing both the template and TRUS probe on the stepper and the first cryoneedle is already placed in the prostate.

Figure 1.7. Configuration of the cryoprobes in Cryocare™ system (a) and the Seednet™ system (b).
1.2.2.8 Anatomical Considerations of the Prostate During Cryosurgery

The prostate is often described as an ovoid or chestnut-shaped gland with an approximate length of 3cm and width of 4cm in a normal man. However, it is commonly larger in older men due to benign prostatic enlargement. The prostate has an anterior, posterior and lateral surfaces, with a narrow apex inferiorly and a wide base superiorly (figure 1.8).

The base of the prostate is adjacent to the base of the bladder, while the apex is closely related to the external urethral sphincter. During cryosurgery if the iceball extends below the apex, it could damage the sphincter resulting in incontinence. Therefore, during the procedure, a thermosensor is placed at the external urethral sphincter region as explained before (1.2.2.7); when the temperature reaches 0°C, freezing is terminated to avoid damage.

Anteriorly the dorsal vein complex separates the anterior wall of the prostate from the symphysis pubis. This vein complex may act as a heat source during freezing which may prolong the freezing process anteriorly. Osteitis pubis has been reported from iceball extension to the pubic bone (Seigne et al, 1996).

The prostate is closely related to the rectum posteriorly, only separated by the Denonvillier's fascia which is a strong collagenous fascia enriched with elastic fibres and smooth muscles. During the procedure, the iceball must not be allowed to reach to and damage the rectum, hence, resulting in recto-urethral fistula formation. The surgeon monitors the iceball progression with TRUS and a thermosensor at the Denonvillier's fascia (as described in 1.2.2.7).
Laterally, the prostate is embraced by the levator ani muscle, and on the posterior-lateral surface of the prostate, the neurovascular bundle run on each side. This contains the cavernosal nerves which are responsible for achieving erection. During cryosurgery, the iceball is allowed to extend to and freeze the neurovascular bundles (-40°C) as described before (1.2.2.7) as it is a common site for micro-metastasis to occur. Hence, erectile dysfunction is a common complication after cryosurgery.
Figure 1.8. Sagittal (a) and cross (b) sections of the male pelvis through the middle of the prostate demonstrating the anatomical relationships of the prostate.
1.2.2.9 Technical Considerations of Prostate Cryosurgery

Prostates larger than 50cc are difficult to freeze effectively due to pubic arch interference and such patients may benefit from 3 month neoadjuvant androgen deprivation to reduce the target volume (Connolly et al, 1997).

Patients with a prior history of TURP are at higher risk of sloughing and urinary retention; hence, cryotherapy is best avoided in this group of patients especially when the TURP defect is large on the TRUS picture (Lam and Belldegrun, 2004).

There is a relative contraindication for cryotherapy in patients with significant symptoms of obstruction prior to treatment due to high risk of developing urinary retention after cryotherapy. (Lam and Belldegrun, 2004)

Patients with a history of abdominoperineal resection for rectal cancer, rectal stenosis or other major rectal pathology that preclude the use of TRUS are also not eligible for cryosurgery (Lam and Belldegrun, 2004).

1.2.2.10 Results of Prostate Cryosurgery

Short to medium-term results of recent studies of prostate cryosurgery are available. Derrick et al (2005) reviewed 230 patients (low-risk 34.7%, intermediate-risk 38% and high-risk 21.1%). After a mean follow-up of 62 months, 64% of the patients were biochemically disease-free (PSA <0.5 ng/ml).
Bahn et al (2002) published their series of 590 patients, of which, 53.7% had high-risk disease, 30.3% had intermediate-risk and 15.9% were with low-risk disease. Using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition for biochemical failure (3 consecutive PSA rises), the 7-years actuarial biochemical disease-free rate were 92%, 89% and 89% for the low, intermediate and high-risk groups respectively.

Jones el al. (2008) published the largest series of 1198 patients from the COLD (Cryo On-Line Data) registry which is the largest multi-centre database for cryotherapy patients. The overall 5-year biochemical-free survival rate (ASTRO) was 77.1%.

Short-term results of the Seednet™ system were published from more than one centre. In a multi-institutional study, Han et al (2003) presented a total of 106 patients treated with cryotherapy, 89 of which were for primary disease. At 12 months, 66/89 (74%) were biochemically disease-free using PSA value of >0.4 ng/ml for failure.

Gowardhan et al. (2007) followed up 49 patients for a mean of 19.16 months after primary cryotherapy using the Seednet™ system. At 1 year, they achieved 59% biochemical disease-free rate using a PSA cut-off of 0.5 ng/ml to define biochemical failure.

Complications following cryosurgery have declined significantly with advancement of technology and modification of technique (Beerlage et al,
Impotence is the commonest complication of cryosurgery with the majority of the studies reporting a greater than 70% impotence rate, although, late recovery has been reported (Rees et al, 2004; Robinson et al, 2002). Recent series have reported rates of incontinence and recto-urethral fistula as between 1.3 -7.5% and 0 - 0.5% respectively (reviewed by Han and Belldegrun, 2004).

Urethral sloughing which may present with irritative or obstructive lower urinary tract symptoms, pyuria and possibly urinary retention has commonly been reported as occurring between 9-10% (reviewed by Rees et al, 2004). The incidence of prolonged perineal pain ranges from 0.4% to 12% (reviewed by Rees et al, 2004). The origin of the pain is not clear and may be multifactorial including ischaemia of the rectal wall, extravasation of urine into the periprostatic tissue and freezing of the local tissue (Ahmed and Davies, 2005).
1.3 Prostate Cancer Recurrence after Radiation Therapy

As discussed earlier in the chapter (1.2.1), and despite advancements in the delivery of radiation therapy, a number of interventions still fail.

The aetiology of prostate cancer cell resistance to ionising radiation remains unclear. Theories of tumour resistance to radiotherapy include ineffective cell kill, pre-existing radio-resistant clones, inadequate tumour localization and de novo tumour development (Schellhammer et al, 1991).

For patients who have not received neoadjuvant androgen suppression therapy, serum PSA declines slowly after completion of RT. The time to nadir has been shown to be inversely proportional to disease-free survival. The median time to nadir in patients who remain free from failure is 22 to 33 months.

Several different definitions of biochemical failure have been used previously, which has led to difficulties in deciding if or when a biochemical failure has occurred in an individual patient, and has also made it difficult for physicians and increasingly well-informed patients to interpret reported experiences.

At the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Conference (ASTRO, 1997), a standardized definition of biochemical failure after Radiotherapy has been developed. The new definition defined biochemical failure as three consecutive increases in PSA
after achieving a nadir, recommending that the PSA determinations be 3 to 4 months apart in the first 2 years after radiation and every 6 months thereafter. The requirement for three readings and the temporal spacing between the readings are necessary to avoid overcalling failure due to "PSA bounce", which is a transient PSA rise (usually < 3 ng/ml) during follow-up and occurs typically between 12-30 months in up to one third of the patients (ASTRO, 1997; Merrick et al, 2002).

Recurrent disease after radiotherapy is typically a higher grade than the primary cancer in the majority of cases (Wheeler et al, 1993). This is thought to be due to time-dependent tumour progression, new tumour development or radiation-induced transformation (Wheeler et al, 1993).

Untreated local recurrence will usually result in the development of distant metastasis and ultimately death with a median survival of only 30 months (Hanks et al, 1989).

**Treatment Options for Locally Recurrent Prostate Cancer after Radiation Failure**

Historically, hormonal therapy was the main treatment option to control the disease in these men; however, early detection of recurrence, using PSA measurement, will render some of the patients suitable candidates for salvage treatment with curative intent. Selection criteria for salvage treatment include positive histological finding of localised disease recurrence with no evidence of metastasis on staging imaging (Bone and MRI scans). Salvage treatment options include: radical prostatectomy, cryotherapy, brachytherapy and HIFU.
a. Salvage Radical Prostatectomy

Operating in a previously irradiated field is challenging due the associated vasculitis, fibrosis and loss of tissue plane, resulting in significant complications (see below).

Several groups reported the outcome of salvage radical prostatectomy in terms of oncological outcome and complications (reviewed by Ahmed et al, 2005; Sokoloff, M. H. et al 2008). The rates of biochemical disease-free rate ranged between 23-55%. They showed that men with positive surgical margins (15.3% - 70%) and seminal vesicles involvement (40 - 50%) had higher biochemical failure rates.

A number of prognostic factors have been found to predict improved outcome after salvage radical prostatectomy including pre-radiation and pre-operative localised clinical stage (Gheiler et al, 1998), pre-operative PSA < 10ng/ml (Rogers et al, 1995), Gleason score < 7 and aneuploid tumour cells (Cheng et al, 1998). Bladder neck invasion has been found to correlate with poor biochemical outcome (Rogers et al, 1995).

Complications after salvage radical prostatectomy were common including incontinence 10-58%, impotence 100%, rectal injury 0-10% and bladder neck contracture in 11-29 % (reviewed by Ahmed et al 2005; Sokoloff, M. H. et al 2008).
The mean blood loss following salvage prostatectomy ranges from 1000 to 1650ml per patient. Amling et al (1999) reported that 43% of their patients required transfusion post-operatively.

b. Salvage Cryotherapy

In addition to the technical aspects described for primary cryotherapy which was discussed earlier in the chapter (1.2.2.9), there are a few technical aspects that need to be addressed in relation to salvage cryotherapy. Complications associated with salvage cryotherapy are higher than for primary intervention (Bales et al, 1995; Pisters et al, 1997). This is thought to be due to poor vascular circulation in the surrounding tissues limiting healing abilities post radiotherapy (Shinohara and Carroll, 2002). Therefore, freezing must be stopped once the leading edge of the iceball has reached the capsule of the prostate (Katz and Ghafar, 2002). If the target temperature of -40 °C is not achieved then an additional freeze/thaw cycle can be performed (Wong et al, 1997). Some surgeons inject 30-50 ml of sterile saline into the Denonvillier's fascia in order to separate the rectum and prostate and hence facilitate more adequate freezing posteriorly (Donnelly and Saliken, 2002). Other surgeons have found that 3 months androgen deprivation pre-operatively can increase the distance between the anterior rectal wall and the posterior prostatic capsule by few millimetres (Shinohara and Carroll, 2002) in addition to the overall reduction in prostate size.

In patients who had undergone brachytherapy, the seeds can mimic the cryoprobe ultrasonically. Therefore in this group of patients probe placing is
more challenging. Using TRUS in the longitudinal view could help to differentiate between the seeds and the probes (Katz and Ghafar, 2002).

In our experience, patients with histological recurrence grade of Gleason score 8-10 are at high risk of pelvic lymph node involvement; therefore, pelvic lymph node biopsy is performed (via mini laparotomy or laparoscopy) before the cryotherapy in those group of patients. Patients with lymph node involvement are not suitable for salvage cryotherapy.

Lastly during insertion of the cryoprobe (particularly the 17 gauge needle) resistance might be encountered due to fibrosis (Ahmed et al, 2005).

Recent studies reported comparable cancer survival rates to salvage radical prostatectomy with intermediate-term biochemical disease -free rates ranging between 34-77% (reviewed by Ahmed et al, 2005; Ismail et al. 2007; Pister et al. 2008). However, they reported significantly lower complication rates than salvage radical prostatectomy (excluding potency) with incontinence rates 6.3-13.8% and recto-urethral fistula 0-3.4%. Erectile dysfunction is common after salvage cryotherapy, ranging between 62.2% and 100% (reviewed by Ahmed et al, 2005; Ismail et al. 2007; Pister et al. 2008). However, it is difficult to assess the true incidence of impotence due to salvage cryosurgery as several patients already have sexual impairment prior to the operation particularly in men on hormonal therapy.
Positive predictors of biochemical control include pre-operative PSA<10ng/ml, Gleason score of ≤ 8 and postoperative PSA nadir of ≤ 0.5 ng/ml (Chin et al, 2003; Greene et al, 1998; Pisters et al, 1999).

c. Salvage Brachytherapy
Additional radiotherapy is unlikely to be effective in tumours that have already demonstrated radiation resistance, and it has been associated with substantial additional risks (Cumes et al, 1981; Wallner et al, 1990). However, two small series reported five-year biochemical disease-free rates of 34% and 53% (Beyer, 1999; Grado et al, 1999). Complications included incontinence 24%; lower urinary tract symptoms requiring TURP in 14%; rectal ulcer 4%, and 2% of patients had colostomy due to rectal bleeding. Larger and longer follow-up studies are required to draw conclusions on the efficacy and safety of salvage brachytherapy.

d. Salvage High-Intensity Focused Ultrasound (HIFU) Therapy
The principle of HIFU involves focusing high-energy ultrasonic waves emitted from a transducer into a small region of the prostate, which results in a sharp focal temperature rise to 70° -100°C within a few seconds leading to protein denaturation and eventually coagulative necrosis (Colombel et al, 2004). The procedure is performed under general or spinal anaesthetic. The ultrasound probe is placed transrectally inside a balloon-shape latex cooling device containing degassed coupling liquid to keep the temperature of the rectal wall below 37°C throughout the procedure.
Using the imaging mode, the boundaries of the treatment area and the position of the rectum are first defined. The distance between the rectal mucosa and the posterior prostatic capsule is also measured. Once the data have been entered, the computer places the firing head in the target region and treatment proceeds automatically. A beam of focused ultrasound waves is emitted from the transducer intermittently for 3-5 seconds followed by 5-6 seconds gap, during which the transducer changes position. The shot creates an elliptical-shape elementary lesion which measures approximately 2mm in thickness and 10-18mm in length. The treatment continues layer by layer until the whole area is covered.

The role of HIFU as salvage therapy for localised recurrence of prostate cancer after radiotherapy has been studied in two short-term reports.

Mallick et al (2006) reported on 50 patients treated with salvage HIFU with a median follow-up of 16 months. At 12 months, 54% of the patients remained biochemically disease-free. Complications included: incontinence 10%, impotence 47% and none had recto-urethral fistula.

Murat et al (2006) treated 118 patients with HIFU after failing radiotherapy with mean follow-up of 16.4 months. After HIFU, 84% had negative prostate biopsy and 62% had PSA nadir <0.5 ng/ml within 4 months. Survival free rates were 58%, 44% and 14% for patients with pre-operative Gleason scores of ≤6, 7 and ≥8 respectively. Adverse events included recto-urethral fistula in 3%, incontinence in 28% and bladder neck stricture in 10%.
In a recently published study, Zacharakis et al. (2008) followed up 31 patients for a mean of 7.4 months after salvage HIFU. Overall, 22 of the patients (71%) had no evidence of disease at the last follow-up. Complication rates included urethral stricture (36%), incontinence (7%) and recto-urethra fistula (7%).

These results suggest that HIFU provided a high local control rate, but longer follow-up is required to determine efficacy. Complications rates were not insignificant.
1.4 Thermal Properties of the Freezing Probes and their Iceballs

Although the development of Trans Rectal Ultrasound Scan (TRUS) monitoring has resulted in the rejuvenation of prostate cryosurgery, it does have its own limitations. As previously described in this chapter (1.2.2.5), not all the cells frozen by the cryoprobes subsequently die. Experiments have shown that to kill prostate cancer cells effectively, it is necessary to freeze the prostate twice to a temperature of -40°C or below (Larson et al, 2000; Tatsutani et al, 1996). Therefore, the inner zone of the iceball, where the temperature is £ -40°C is considered the lethal zone of the iceball (also called zone of complete necrosis). Clinically, it is important to ensure that the entire prostate is within the lethal zone (Ellis, 2002). This necessarily means that the outer non lethal zone will extend beyond the prostate. Although this zone is not entirely lethal to cancer cells, it has been shown that damage of normal tissue can still occur (Larson et al, 2000; Tatsutani et al, 1996). Damage to the external urethral sphincter and the rectum may be caused during prostate freezing, hence, it has been recommended that, in these regions, temperatures should not drop below 0°C (Ellis, 2002). We can conclude from this, that the thinner the outer zone is, the less risk of complications. In experimental studies, the ablative ratio (the volume of the lethal zone ice divided by the total iceball volume) was introduced to objectively quantify and compare the killing efficiency of iceballs (Rewcastle et al, 1999b). Hence, a higher value of the ablative ratio implies more effective killing with less collateral tissue damage.
For the reasons mentioned above, information about temperature distribution within the iceball is important. One limitation of ultrasound is that it does not provide information on the temperature within the iceball. Another problem is that almost all the ultrasound waves reflect off the interface between the frozen and unfrozen tissue (Onik et al, 1988), therefore, the surgeon becomes blind to any structure behind the iceball (see page 23). In addition, as the ultrasound signals strike the curved edge of the iceball obliquely on the lateral surfaces, the sound wave not only reflects but also refracts away from the edge of the iceball (a phenomenon called “critical angle shadowing”). This results in the iceball appearing to be significantly larger on the ultrasound image than its true size (Wong et al, 1997). Therefore, TRUS alone is not sufficient to monitor the progression of the iceball. This was verified in clinical studies by Grampsas et al (1995), who performed radical prostatectomy after cryosurgery. They showed that the zone of necrosis of the excised prostate is much smaller than predicted by per-operative TRUS. In another study, Steed and colleagues (1997) were able to demonstrate that operators made significant mistakes in predicting the subzero temperatures at the neurovascular bundle region by TRUS alone.

Thermocouple probes were introduced (Lee et al, 1994) to measure the real time temperatures of the Denonvillier’s fascia, external sphincter and both neurovascular bundles. This ensured adequate freezing of the prostate and at the same time a significant reduction in complication rates (Wong et al, 1997). Despite these advantages, thermocouples have not yet been unanimously accepted as part of the standard procedure (Rewcastle et al, 1999a). This may be explained by the fact that temperature mapping using thermocouples
is prone to considerable error (Rewcastle et al, 2001). The operator must guess the location of the lethal temperature isotherm given knowledge of the iceball boundary provided by TRUS image, the cryoprobe location and temperature reading of the thermocouple. In addition, thermocouples only assess temperatures where the sensing tips are placed; therefore, inaccurate readings can occur with misplacement, displacement or migration of the thermocouple. Furthermore, the current systems allow using up to 5 or 6 thermocouples at a time, limiting temperature monitoring to a few individual locations within the iceball. Lee et al (1999) performed cryosurgery on 81 men using 6-8 cryoprobes and double freeze-thaw cycle. Despite using 5 thermosensors, sextant biopsy at 6 months showed that 47% of the patients had residual epithelial acini.

There are two available prostate cryosurgery systems available. The Cryocare™ system (Endocare Inc., Irvine, CA), which has two types of probes: the Cryo-40 (3.4mm diameter) and the thinner less invasive Cryo-44 (2.4mm diameter). Surgeons can adjust the speed of the freezing by changing the rate of argon gas flow from a maximum of 100% flow to a minimum of 5% flow. The second system (Seednet™) produced by (Galil Medical Inc, Plymouth Meeting, PA) uses smaller cryo-needles (1.47mm diameter), with the gas flow ranging between 100% and 20%.
In-vitro Models to Predict and Optimise Temperature Distribution around Cryoprobes

Several in-vitro models for thermal prediction around a single and multiple probes have been developed based on a finite difference formulation of bio-heat transfer equation (reviewed by Rewcastle et al, 2001). The type of the probe assessed was either the outdated liquid nitrogen probe or the 3.4mm diameter probe. The majority of these models have not been validated (reviewed by Rewcastle et al, 2001). Rewcastle et al (1998) developed a computer model to provide a time-dependant simulation of the three-dimensional thermal distribution within a homogenous tissue iceball surrounding a single 3.4mm diameter probe. They used the thermal properties of water assuming their close proximity with those of soft tissue. They also assumed that the thermal properties remain constant and only changes below freezing point. They compared the temperature predictions with experimental data using seven thermosensors. These experiments were carried out in 1.4% gelatine solution at a temperature of 1.5°C. This model predicted temperatures with ± 4.3°C accuracy. The same group developed a second model to predict thermal distribution around 1, 3 and 5 cryoprobes configurations (Rewcastle et al, 2001). They validated the model by comparing temperature predictions with a limited number of thermosensors readings within iceballs in experimental studies carried out in similar conditions to the first model. All the predictions were accurate; however, one of the drawbacks of these experiments was that the room-temperature gelatine media has different thermal properties to the prostate as will be explained later in the chapter.
The model of Budman and colleagues (1986) has not made accurate predictions at a distance more than 2mm from the probe surface. Hong et al (1994) calculated temperatures within an iceball given the probe temperature and the location of the iceball interface as determined with MRI. When they validated their results using experiments measuring a single point temperature close to the shaft of the probe, they predicted temperatures within 5°C accuracy. Gilbert et al (1997) determined the temperature distribution around a single liquid nitrogen probe placed in live rabbit liver using MRI. They compared the estimated temperatures with measured temperatures in only two regions of the iceball using thermocouples. The differences were within ± 1°C. Mala et al (2001) estimated the temperature distribution around a single 3.2mm in diameter probe placed in a live pig liver using MRI. They validated their work by measuring the temperature of a single point within the iceball. They concluded that the median distance between the estimated and the measured temperature location was ±0.7mm.

Several groups have created multiple cryoprobe heat transfer models for use with optimization algorithm for cryosurgery planning. Jankun et al (1999) developed three-dimensional multiple probe algorithm called CryoSim which accurately predicted the location of a single probe iceball edge as verified by ultrasound. No comparisons for the temperature distribution within the iceball were made. In 2003, a newer, faster and more accurate version of the software CryoSim was developed by the same group (Wojtowicz et al, 2003), however, it was not validated.
Baissalov et al (2000) presented a three-dimensional model for optimizing multiprobe prostate cryosurgery. A comparison of the predicted 0° C isotherm with the actual iceball boundary imaged by CT demonstrated a difference of ±2 mm. No validation of the predicted temperature within the iceball was made.

**In-vitro Assessment of the Temperature Distribution around Cryoprobes**

A number of *in vitro* experiments were carried out to assess the thermal profile and size of the iceball of the liquid nitrogen probe (Chang et al, 1994; Lam et al, 1998; Popken et al, 2000; Saliken et al, 1995). The freezing media used were gelatine and *ex vivo* pig liver. Although there were discrepancies in the results between authors, perhaps due to different experimental conditions or the inconsistency in the freezing capacity of the liquid nitrogen probe which was observed by many urologists (Saliken et al, 2002), there was a common observation of differences in the characteristics of the iceball produced in gel and the liver tissue. The iceball in gel was larger and with a lower core temperature.

To date, there has been only one published study assessing the Cryocare™ machine probe. Hewitt et al (1997) compared the iceball of the 3.4mm cryoprobe (Cryo-40) with the liquid nitrogen probe using both fresh sheep liver at room temperature and warm water. Their conclusions were that the Cryocare™ system was faster than the liquid nitrogen system, but produced a smaller iceball in the water bath.
Discrepancies exist between the iceball and lethal zone (temperature < -40°C) dimensions of the currently used cryoprobes. Table 1.4 illustrate the dimensions as quoted by the manufacturers (Endocare, 2005; oncura.com, 2005). This is based on experiments carried out in gelatine medium; using a single probe.

Theodorescu (2004) suggested that the maximum diameter of the iceball and lethal zone of a single 3.4mm cryoprobes was 40 and 20mm respectively. Zisman et al (2001) explained the technique of prostate cryosurgery using the 1.47mm cryoneedles based on iceball radius of 13mm at 10 minutes of freezing. All these different measurement were based on single probe iceballs. However, as described previously (1.2.2.7), the technique of modern prostate cryosurgery involves freezing the prostate with a minimum of 6 cryoprobes with a maximum distance between two adjacent probes of no more than 18mm for the Cryocare™ probes and 10 mm for the Seednet™ needles. Experiments have shown that the temperature distribution and cooling rate are different between single and multiple probe configurations. Saliken et al (1995) demonstrated that the iceball temperature is much colder and with faster cooling rate at a point between two cryoprobes than at any point on the same radius around a single probe. Therefore, all the studies that examine the dimensions of the iceball formed by a single cryoprobe are not applicable to clinical situation.
Manufacturer | Cryoneedle (1.47mm diameter) Seednet™ system | Cryo-44 (2.4mm diameter) Cryocare™ system | Cryo-40 (3.4mm diameter) Cryocare™ system
---|---|---|---
Galil Medical® | 18 x 27 (8 X 17) | 42 x 61 (20 X 35) | 43 x 67 (20 X 48)
Endocare® | n/a | 40 X 59 (19 X 38) | 40 X 64 (19 X 43)

n/a: not available

Table 1.4 Diameter x length in mm of the iceballs and (lethal zones) according to manufacturers. Galil Medical® is the producer of the Seednet™ system and Endocare® produces the Cryocare™ system (Endocare, 2005; oncura.com, 2005). Oncura used to have the ownership rights of the Seednet™ system before Galil Medical®.

In-vivo assessment of the probes is not possible since it requires a large number of tests, each involves accurate placement of a number of cryoprobes and thermosensors. In our study, we investigated iceballs of multiple probes in a medium that is closer to the clinically relevant tissue than gelatine. The choice and condition of the medium used will be discussed later in chapter 2 (2.1.3).

**Hypothesis**

The properties of the iceballs formed using different cryoprobes and conditions of cooling may have a clinically significant impact on the efficacy of cryosurgery.
1.5 Quality of Life in Early Prostate Cancer

Contemporary interpretations of health-related quality of life (HQoL) are based on the 1948's World Health Organisation's definition of health as not merely the absence of disease, but a state of physical, emotional and social well-being. It includes the burden associated with specific complications, any impact on normal function or social roles, and a composite of other psychosocial domains.

Men with early prostate cancer are generally asymptomatic at the time of diagnosis, and treatment-related complications, such as changes in sexual, bowel, and urinary functions, are especially troublesome for this group (Litwin et al, 1999; Lubeck et al, 1997). Crawford et al (1997) reported in a survey the treatment goals of 1000 prostate cancer patients. Approximately 45% of the patients' goal was to preserve quality of life; 29% of the men's aim was to extend life and only 13% to delay progression.

HQoL is measured by self-administered instruments or questionnaires. Interviewer assistance may be required in answering the questions; however, it must be from a neutral third party. It has been shown that physicians typically underestimate the impact of treatment on quality of life impairment, perhaps because their queries are not sensitive enough or because patients tend to understate their quality of life impairment when speaking directly with physicians (da Silva et al, 1996; Litwin et al, 1998). Therefore, questionnaire studies of morbidities are more valuable in measuring patient's treatment experience.
In clinical practice, questionnaires are unlikely to be used routinely due to time restrictions. However, in a research setting they are useful tools to improve medical care through several ways including: improving patient's education and information feedback; facilitating medical decision-making; assessing the overall treatment efficacy and safety; and determining whether the goals of treatment have been met.

The selection of a questionnaire has a significant impact on the ability of a study to answer a research question. HQoL instruments must be shown to have the following properties (Higginson and Carr, 2003):

1. Reliability: is the measure reproducible?
2. Validity: does the instrument measure the attribute it is intended to measure?
3. Responsiveness: is the measure sensitive to changes over time?
4. Appropriateness: are the measure's length, format and language appropriate?
5. Interpretability: do the results from using the measure have clinical relevance?

Researcher must be pragmatic in the selection of HQoL instruments. While longer instrument may provide a richer database, fatigue may limit the ability of patients to provide useful information, a phenomenon called "response burden".
It is also preferable to collect HQoL data prospectively including baseline information to avoid recall bias and the disadvantages of retrospective symptomatic recall (Chouinard and Walter, 1995; Emberton et al, 1995).

Repeated administration of questionnaires in a longitudinal study design is necessary to reveal any time-dependant evolution of symptoms (Talcott et al, 1997). Cross-sectional studies, where instruments are administered once at variable time after treatment, rely on direct comparisons between appropriate groups. It is less accurate as late toxicity following prostate cancer treatment may occur, which can be overlooked.

1.5.1 Early Prostate Cancer Assessment Instruments

A number of validated questionnaires are used in research to assess HQoL in early prostate cancer. They can be general HQoL, cancer specific or prostate cancer specific quality of life.

General HQoL instruments address the component of overall well-being including physical, emotional and social functioning. Example of a commonly used instrument is the RAND Short Form 36 (SF36), which is regarded as the "gold standard". It has 36 items and takes less than 10 minute to complete.

Cancer specific quality of life instruments assess the impact of cancer on patients' routine activities. The European Organisation for Research and
Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ –C30) is a widely used instrument in oncological trials, and well-validated in most European languages. Another example is Functional Assessment of Cancer Therapies- General (FACT-G) which has 28 items and usually coupled with FACT- Prostate (FACT-P).

Commonly used prostate cancer specific questionnaires include FACT-P which is used in combination with FACT-G. EORTC-PR-25 is a more comprehensive questionnaire (25 items) which assesses erectile dysfunction (ED), bowel, urinary and toxicity from androgen deprivation. It is a new questionnaire, often paired with EORTC QLQ –C30, but still awaiting the publication of validation studies. The University of California Los Angeles- Prostate Cancer Index (UCLA-PCI), commonly used with SF36, is a well validated and comprehensive instrument which measures urinary, sexual and bowel function and bother. However, it does not assess irritative lower urinary tract symptoms (LUTS).

Two further well-validated instruments are commonly used to assess symptom index. The International Prostate Symptom Score (IPSS) which is a familiar index of LUTS, but it does not assess incontinence, haematuria or dysuria. The International Index of Erectile Function (IIEF) is a comprehensive fifteen items questionnaire measuring ED; however, it does not assess the effect of ED on HQoL.
The current salvage therapies have comparable early oncological outcome and all have some adverse effects on either urinary, sexual and bowel function. Patients choosing treatment with different modalities tend to experience different morbidities, the significance of which may be subjective to each patient. The currently published studies of HQoL after salvage treatments are limited to one longitudinal study assessing quality of life following salvage cryotherapy and two cross-sectional studies comparing salvage treatment with other therapies.

Robinson et al. (2006) assessed quality of life in 46 men treated with salvage cryotherapy of the prostate following EBRT failure. Patients were invited to complete the EORTC QLQ-C30 and UCLA-PCI questionnaires pre-operatively and at 6 weeks, 3, 6, 12, 18 and 24 months follow-up. There was a temporary worsening of all the domain and subscale scores, which returned to baseline levels at 24 month, with the exception of urinary and sexual function scores. At 24 months, 29% of the patients reported urinary bother as a "moderate to big" problem, and 56% reported sexual bother as a "moderate to big" problem.

Tefilli et al (1998) compared HQoL of 44 men after salvage radical prostatectomy with 24 men who had salvage EBRT after radical prostatectomy. Questionnaires FACT-G and FACT-P were mailed to patients at variable follow-up length (mean 36.1 - 37.2 months). In addition, they used
the Functional Assessment of Incontinence Therapy-Urinary (FAIT-U) instrument to assess incontinence. The only statistical differences between the two groups, in favour of salvage ERBT, were the physical well-being and urinary continence.

Anastasiadis et al (2003) compared HQoL of 89 men with primary prostate cryosurgery with 42 men after salvage cryosurgery for radiation failure recurrence. The study design was cross-sectional, patients were asked to complete, at least 6 months post-operatively, the EORTC QLQ-C30 and a prostate-specific supplementary instrument, which has been validated in a single institution. The time interval between surgery and completion of questionnaire was significantly different between the two groups (25.6 vs. 11.4 months for primary and salvage groups respectively). The overall HQoL scores were high in both groups, with the primary group faring significantly better in the physical and social functioning domains compared to the salvage patients. The most prominent and significance prostate-specific symptom was sexual dysfunction, which was equal between the two groups. Urinary symptoms domain was significantly worse in the salvage group.
1.6 The Impact of Iceball Temperature on HQoL during Salvage Cryotherapy

Temperature of \(\leq -40^\circ C\) is required to ensure effective ablation of the prostate, whereas incomplete tissue damage occurs at temperatures between 0 and \(-40^\circ C\) (Tatsutani et al. 1996). During prostate cryosurgery, the lethal zone of the iceball (\(\leq -40^\circ C\)) is allowed to cover the entire prostate. Hence, the outer non-lethal ice zone (0 to \(-40^\circ C\)) extends beyond the prostate which may potentially damage the external urethral sphincter, cavernosal nerves (neurovascular bundles) and Denonvillier’s fascia resulting in urinary, sexual and bowel problems respectively. The severity of tissue damage is related to the iceball temperature; the lower the temperature, the more extensive is the tissue damage (Larson et al, 2000), and hence, a higher risk of co-morbidities and perhaps greater impact on HQoL.

The impact of the iceball temperature at the external urethral sphincter, neurovascular bundles or Denonvillier’s fascia during cryosurgery on the quality of life of the patients has not been studied before.

In our study we will assess the impact of the temperature the external urethral sphincter, the apex of the prostate which is closely related to the external urethral sphincter and Denonvillier’s fascia on HQoL of patients.

The majority of the patients have erectile dysfunction prior to the procedure, which will be demonstrated later, hence it will difficult to assess the effect of iceball temperature at the neurovascular bundles on sexual function.

If we could demonstrate that the temperature of the iceball has an impact on HQoL, and if we could also demonstrate, in the \textit{in-vitro} iceball study, that different cryoprobes and conditions of cooling have an impact on the iceball
thermal properties then we may be able to reduce the impact on HQoL of patients by using different freezing probes or by modifying the technique of procedure.

**Hypothesis**

Treatment variables during salvage cryotherapy can affect quality of life.
1.7 The Specific Objectives of the Research

1. To assess the thermal distribution, and compare the dimensions of the total iceball and kill zone using 1.47mm cryoneedles, with 2.4 and 3.4mm cryoprobes in vitro.

2. To measure and compare the thicknesses of the non-lethal ice zone from the side and the top of the iceball.

3. To measure and compare the distance between cryoprobe and the -40°C isotherm (lethal ice thickness from the side of the freezing probe) which indicates the distance at which the cryoprobe should be placed away from the prostatic capsule.

4. To calculate and compare the thickness of lethal ice below the tips of the cryoprobes. This would indicate how far to place the cryoprobes from the base of the prostate.

5. To analyse and compare the cooling rate in the centre of the iceballs of the three different cryoprobes.

6. To estimate and compare the "kill" efficiency of the iceballs by measuring the ablative ratio.

7. To study the effect of slowing the argon gas flow from 100% to 20% on the above mentioned parameters

8. To assess the HQoL changes after salvage cryotherapy for radiation failure prostate cancer recurrence.

9. To assess the correlation between HQoL of the patients and the iceball temperature at the external urethral sphincter and Denonvillier's fascia during salvage cryosurgery.
Chapter 2
Material and Methods
2.1 *In-vitro* Assessment of Three Different Cryoprobes used for Prostate Cryosurgery

2.1.1 Instruments

1. Cryosurgery machines:
   
   I. **Cryocare™** (Endocare Inc., 201 Technology Drive, Irvine, CA 92618, USA)
   
   II. **Seednet™** (Galil Medical Inc, 401 Plymouth Road, Suite 130 Plymouth Meeting, PA 19462-1645, USA)

2. Probes (figure 2.1) (all probes are marked at 5mm interval from the tip):
   
   a. **Cryo – 44** (2.4mm diameter)
   
   b. **Cryo – 40** (3.4mm diameter)
   
   c. **Cryoneedles** (1.47mm diameter)

3. Thermosensor probes, each contains:

   T-type 0.07mm diameter copper/constantan alloy thermocouple wire (OMEGA Engineering Inc., One Omega Drive, Stamford, Conn 06907-0047, USA) with the following features:

   - Operating temperature range: -200°C to + 250°C
   - Time response: 0.22 seconds.
• All thermosensors were calibrated with Fluke® 714 thermocouple calibrator (Fluke Corp., 6920 Seaway Blvd., Everett, WA 98203, USA) at +50, 0 and -50°C achieving accuracy of ± 1°C.

• Thermocouple probe diameter: 1.5mm.

4. Travel Logger Thermacq data acquisition box (Dianachart Inc., Rockaway, NJ) connected to Compaq laptop (dv5000z). Insta-Trend (Dianachart Inc., Rockaway, NJ) software was used to digitally display the temperatures.

5. Sony digital camera (Cybershot DSC-V1) mounted on a tripod.

6. Four polyvinyl chlorine templates measuring 110mm X 70mm with a thickness of 20mm. Further details will be discussed later (2.1.6)

7. Plastic container with internal dimensions of 150mm (W) X 90mm (D) x 100mm (H) for the water bath used to place freezing medium.

8. Argon and helium gas cylinders (Messer Group GmbH, Otto-Volger-Straße 3c, Sulzbach, D-65843, Germany) with connecting tubes and pressure gauges:
I. Argon 5.0 F50 300 bar (used for freezing) with the following specifications:

- Ar > 99.999 vol %
- O2 < 2 vol ppm (parts per million)
- N2 < 5 vol ppm
- H2O < 3 vol ppm
- THC < 0.1 vol ppm
- CO2 < 0.1 vol ppm

Cylinder size: F50
Valve connection: NEVOC CEN 30
Filling pressure: 300 bar
Content: 15.3 m3

II. Helium 5.0 F50 300 bar (for thawing with the Cryocare™ machine) with the following specifications:

- He > 99.999 vol %
- O2 < 1 vol ppm
- N2 < 4 vol ppm
- H2O < 3 vol ppm
- THC < 0.5 vol ppm
- Ne < 1 vol ppm

Cylinder size: F50
Valve connection: NEVOC CEN 30
Filling pressure: 300 bar
Content: 13.2 m3

III. Helium 5.0 L50 200 bar (for thawing with the Seednet™ machine) with the following specifications:

- He > 99.999 vol %
- O2 < 1 vol ppm
- N2 < 4 vol ppm
- H2O < 3 vol ppm
- THC < 0.5 vol ppm
- Ne < 1 vol ppm

Cylinder size: L50
Valve connection: BS 341 no.3
Filling pressure: 200 bar
Content: 9.1 m3
10. *Ex vivo* bovine (cow) skeletal thigh muscle as the freezing medium.

11. Special jig to hold the probes, thermosensors and the water bath (figure 2.2).
Figure 2.1. The freezing probes:
a. Cryo – 44 (2.4mm diameter)
b. Cryo – 40 (3.4mm diameter)
c. Cryoneedles (1.47mm diameter)
Figure 2.2. Special jig holding the probes and thermosensors
2.1.2 Setup of the Experiments

The argon and helium gas cylinders were connected to the cryomachine. The probes, held by the special jig, were placed into the freezing media in the water bath using special templates. The templates were used to place the cryoprobes and thermosensors in specific locations; this will be discussed later in this chapter (2.1.6). The cryoprobes were connected to the cryomachine. The thermosensors were connected to the cryomachine and to the Travel Logger Thermacq data acquisition box which was subsequently connected to the Compaq laptop. The Sony digital camera, mounted on the tripod, was placed in front of the laptop and cryomachine screens (figure 2.3).
Figure 2.3. Setup (a) and schematic plan from the top (b) of the experiments. The helium and argon gas cylinders connected to the cryomachine. On the left side of the table, the Travel Logger Thermacq data acquisition box and the Compaq laptop are placed. The water bath, special holding jig and probes are seen on the right side of the table. A digital camera was mounted on the tripod.
2.1.3 The Freezing Medium

Initially we intended to use animal prostate as the freezing medium. However, the bovine prostate does not have a solid-structure prostate and porcine prostate consist of two narrow cylindrical structures. Therefore, they were not suitable for our experiments. We reviewed the thermal properties (thermal conductivity and specific heat capacity) of various materials (Duck, 1990; Jankun et al, 1999). From table 2.1, it is obvious that cow skeletal muscle has thermal properties most similar to human prostate. Therefore, beef was used as the freezing media in all our experiments.

<table>
<thead>
<tr>
<th>Material</th>
<th>Thermal conductivity ($k$) ($W \ m^{-1} K^{-1}$)</th>
<th>Specific heat capacity ($c$) ($J \ g^{-1} K^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Prostate</td>
<td>0.45</td>
<td>3.52</td>
</tr>
<tr>
<td>Cow skeletal muscle</td>
<td>0.434 - 0.467</td>
<td>3.43 - 3.81</td>
</tr>
<tr>
<td>Pig skeletal muscle</td>
<td>0.43 - 0.51</td>
<td>3.72, 3.87</td>
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<td>Cow liver</td>
<td>0.488</td>
<td>3.37</td>
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<tr>
<td>Pig liver</td>
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<td>3.51</td>
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<tr>
<td>Water (20°C)</td>
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<tr>
<td>Water (40°C)</td>
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<td>4.17</td>
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<td>2% Gelatine (20°C)</td>
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</tbody>
</table>

Table 2.1. Thermal properties of various medium
2.1.4 Freezing Probes Configurations

In the operative setting, the anterior (anterior to the urethra) group of cryoprobes is important as it sets the pace of formation and dimensions of the entire iceball and is responsible for freezing the entire width of the prostate (Zippe, 1996). Therefore, we have designed our experiments to simulate the arrangements of the anterior probes. As discussed in chapter 1 (1.2.2.7), for the Cryocare™ system, 2 probes are regularly used to freeze the anterior prostate (figure 2.4 a). The recommended distance between the two probes has varied between surgeons, although, the commonly used distance is a maximum of 18mm. Therefore, we assessed each of the Cryocare™ probes (Cryo -40 and Cryo- 44) in a two probe configuration, using 18mm as the distance between the probes. For the more widely used Cryo-44 probe, we have carried out an additional experiment by reducing the distance between the two probes to 15mm, and assess the effect on all the parameters. We also explained in chapter 1 (1.2.2.7) that in the Seednet™ system, the recommended distance between two adjacent cryoneedles (probes) should be 10mm. The number of the probes used in the anterior group varies according to the size of the prostate, but commonly 8 probes are used (2 rows X4 probes) to freeze the anterior prostate as shown in figure 2.4 b. Therefore, we used this configuration in assessing the Seednet™ cryoneedles.
Figure 2.4. Diagram of the prostate showing the arrangement of the cryoprobes of the Cryocare™ system (a) and the Seednet™ system (b).
2.1.5 Experiments

We performed 4 experiments. In each experiment, several tests were carried out to measure the temperature of the iceball using a number of thermosensors:

1. Two cryo-44 (2.4mm diameter) probes, 18mm apart.
2. Two cryo-44 (2.4mm diameter) probes, 15mm apart.
3. Two cryo-40 (3.4mm diameter) probes, 18mm apart.
4. Eight Cryoneedles (1.47mm diameter) in a two rows X four probes

Before carrying out the experiments, we performed three freezing tests in water for 10 minutes, evaluating the shape and size of the iceballs to assist in determining the configuration of the thermosensors later on during the experiments. The first test was carried out on single probes using the 2.4mm and the 3.4mm probes with 100% gas flow rate (figure 2.5) in 20°C water. This showed that the 3-dimension shape of the 2.4mm probe was more or less a lemon-shape, while the 3.4mm is more like tear-drop. The iceball of the 2.4mm probe was smaller than the 3.4mm probe with maximum dimensions (diameter X length) of 26.5 X 48.2mm and 27 X 53.1mm respectively. The second test was carried out on two 3.4mm probes (18mm apart) with 100% gas flow rate in 20°C water (figure 2.6). The two iceball fused in the middle after 6 minutes. The maximum width and length was 45 X 55.1mm respectively. The last test was performed on eight 1.47mm probes (2 rows X 4 probes) with 20% gas flow rate in 20°C water (figure 2.7). The iceball
started fusing after 5 minutes, and at 10 minutes the maximum length and width measured 17.5 and 42.1 mm respectively.

Figure 2.5. Iceballs of the 2.4 mm (a) and the 3.4 mm (b) probes with 100% gas flow rate in water at 20°C.
Figure 2.6. Iceball of two 3.4mm probes (18mm apart) with 100% gas flow rate in 20°C water.

Figure 2.7. Iceball of eight 1.47mm cryoneedles with 20% gas flow rate in 20°C water.
2.1.6 Templates

The templates were designed to allow the placement of the thermosensors in parallel to the freezing probes measuring the temperature between and around the probes. Each thermosensor has a unique identifying number. In experiments 1-3 (figure 2.8 to 2.10), sixteen thermosensors were used, divided into two groups: the first group (thermosensor 1-9) which were placed between the cryoprobes, were used to estimated the depth of the iceball. Group two (thermosensor 10-16) were placed on the outside of cryoprobe number 1 and they were used to assessed the width of the iceball. The method for calculating the width and depth of the iceball will be explained later in this chapter (2.1.12). In experiment 4 (figure 2.11), because of the larger number of cryoprobes, twenty six thermosensors were used.

The thickness of the template is 20mm; probe channels diameters were made only 0.1mm larger than the corresponding probes to prevent unnecessary shakes and probe misplacement.
1. Template 1 (for experiment 1): Two 2.4mm probes, 18mm apart (Figure 2.8). The distances between each thermosensor and the cryoprobes are displayed in table 2.2

![Diagram of template 1](image)

Figure 2.8. Diagram of template 1

<table>
<thead>
<tr>
<th>Thermosensor</th>
<th>Cryoprobe 1</th>
<th>Cryoprobe 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>10.2</td>
<td>10.2</td>
</tr>
<tr>
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<td>18.5</td>
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<tr>
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<td>7</td>
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<td>8</td>
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<td>20.9</td>
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<tr>
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<td>17.6</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>20.6</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.2. The distances (mm) between each thermosensor and the cryoprobes of template 1
2. Template 2 (for experiment 2): Two 2.4mm probes, 15mm apart (figure 2.9). Table 2.3 demonstrates the distances between each thermosensor and the cryoprobes.

![Diagram of template 2](image)

**Figure 2.9. Diagram of template 2**

<table>
<thead>
<tr>
<th>Thermosensor</th>
<th>Cryoprobe 1</th>
<th>Cryoprobe 2</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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<td>-</td>
</tr>
<tr>
<td>15</td>
<td>20.6</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2.3. The distances (mm) between each thermosensor and the cryoprobes of template 2.**
3. Template 3 (for experiment 3): Two 3.4mm probes, 18mm apart (figure 2.10). The distances between each thermosensor and the cryoprobes are shown in table 2.4.

![Diagram of template 3](image)

**Fig 2.10. Diagram of template 3**

<table>
<thead>
<tr>
<th>Thermosensor</th>
<th>Cryoprobe 1</th>
<th>Cryoprobe 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>9</td>
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<tr>
<td>2</td>
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<td>10.2</td>
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<td>17.6</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>20.6</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2.4. The distances (mm) between each thermosensor and the cryoprobes of template 3.**
4. Template 4 (for experiment 4): Eight 1.47mm probe in a two row X four probes (figure 2.11).

![Diagram of template 4](image)

Fig 2.11. Diagram of template 4. The distances between two adjacent thermosensors or a thermosensor and cryoprobe is 5mm horizontally or vertically and 7.1mm diagonally.
2.1.7 Temperature Measurement

The thermosensors were connected to:

- The cryomachine using the standard thermocouple ports and the cryoprobe thermocouple ports of the cryoprobe™ system (maximum 13 thermocouples)
- The Thermoacq data acquisition box connected to the laptop (maximum 4 thermocouples).

The thermal distribution of the iceball was assessed by measuring the temperatures of several horizontal slices (5mm apart). The thermal mapping of each slice was assessed using a number of thermosensors as follows:

- Experiments 1 - 3: 15 thermosensors were required.
- Experiment 4: 26 and 17 thermosensors were required during the 100% and 20% gas flow tests respectively.

Since the setup only allowed measuring the temperature of up to 17 thermosensors at a time, each run of experiment four had to be carried out twice to cover the 26 points.

The temperature sensitive region of the thermosensor is located in the distal 5mm of the probe. We decided to consider the middle point of this region (i.e. 2.5mm from the tip) as the reference point for temperature measurement. The thermosensor probes were marked at 5mm intervals from this reference point.
2.1.8 The Experiment

The following steps were followed in each experiment:

1. The beef was cut into cubes with dimensions of approximately 80mm X 80mm X 100mm. The cube was placed in water at a temperature of 50°C for 20 minutes to increase the temperature, and once the temperature of the muscle reached between 30-38°C, it was placed in the plastic container on its square surface. To help maintain the temperature, the container was filled with water at 40°C up to the upper level of the cube. Then, the appropriate template was placed on the container (above the cube) and secured in place using 2 strips of adhesive tape. Since the height of the cube equals the internal height of the container (100mm), there was no gap between the template and the cube of muscle.

2. Through the template, the freezing probes were placed 70mm deep into the muscle. This was to ensure that the entire iceball was contained with a minimum of 10-15mm margin of the cube of muscle throughout the experiments, as the initial experiments in water (2.1.5) suggested that the maximum height of the iceball is not more than 55mm.

3. For the first test, all the thermosensors were inserted into the muscle at the same level as the level of the cryoprobes tips (figure 2.12).
4. The temperatures of thermosensors (digitally displayed on the screens of the cryomachine and the Compaq laptop) were recorded by taking a digital picture of the screens (figure 2.13). They represent pre-freeze or 0 time temperatures. An 8X5cm white card displaying the details of the test was also included in each picture throughout the tests. The temperatures displayed on the captured pictures were manually entered and stored into Microsoft Excel database. To minimize errors in this process, random figures were double checked personally and by one of my colleagues.

5. Freezing commenced by running the argon gas on full flow (100%) through the cryoprobes and pictures of the screens were taken at 2, 5, 7 and 10 minutes of freezing as determined by the timer displayed on the cryomachines screens.

6. Once the last picture was taken, freezing was stopped and the iceball was thawed by running helium gas. Then all the probes were removed, the muscle cube was discarded.

7. Using a new muscle cube, steps 1-6 were repeated for the second test except step 3. On this occasion the thermosensors were placed 5mm above the cryoprobes tips. In test 3, the thermosensors were placed at 10mm above the tip levels and we continued to measure the temperatures of all the levels above the tips of the cryoprobes until ice disappears (when all the thermosensors readings remain above 0°C at
ten minutes of freezing). Using the same principle, temperature measurement of the levels below the cryoprobes tips was carried out. This completes the thermal mapping of the entire iceball.

8. All the tests were repeated but using a lower gas flow (step 5) of 20%.

After completing all four experiments, they were repeated twice more for verification. The gas cylinders were replaced each time the pressure dropped to the lowest acceptable level (220 bar) according to the manufacturer guidelines.

In summary (figure 2.14), each of the four experiment tests repeated three times. In each experiment, the temperature distribution of the iceball was assessed in two situations: using 100% and 20% gas flows.
Figure 2.12. Freezing and thermosensor probes are placed inside the beef cube in the water bath using a special template. Two strips of adhesive tape were then used to secure a template in place.

Figure 2.13. Photograph of the temperature monitoring screens of the cryomachine and the Compaq laptop taken before freezing. The white card displays the details of the experiment (2.4mm probe, 18mm apart, 100% gas flow, level 7 and first freeze)
Figure 2.14. Summary of the experiments and tests
* Test were done in two stage (due to limitation of thermosensors numbers) to assess 11 levels
2.1.9 Thermal Mapping

In each test, the probe type and freezing condition is the same. Therefore, if we divide each template into two equal virtual halves horizontally or vertically, as seen in figure 2.15, we assumed that the temperature distribution of each half mirrors the opposite one.

Figure 2.15. Diagram of one of the templates divided in half horizontally (a) and vertically (b) by imaginary lines.
Based on this, we mapped the thermal distribution of each level of the iceball using the mean temperatures at 10 minutes of freezing as follows:

1. Using Microsoft PowerPoint, the diagram of the template was placed on a 1X1 mm grid.

2. The ice-water interface temperature was considered to be 0°C.

3. When the mean temperature of a thermosensor is 0°C at 10 minutes, then the edge of the iceball passes through the centre of that thermosensor at that point.

4. More commonly, the 0°C lies between 2 adjacent thermosensors and the position of the iceball edge was estimated as follow:
   
   a. We divided the two probe temperature gradient by the distance between the two probes in millimetres. This yields the temperature gradient per 1 millimetre at this point.
   
   b. The lower temperature of the two thermosensors (closer to the centre of the iceball) is then divided by the 1mm temperature gradient (ignoring the negative sign). This represents the distance (mm) at which the 0°C lies outside the centre of the cooler thermosensor (the most peripheral thermosensor of the iceball). An example is shown (figure 2.16):

As we assumed, the temperature of the thermosensor marked with yellow equals thermosensor number 9, and will be called 9 in this example.

The temperature gradient between thermosensor 4 & 9 equals 11.3 - (-7.3) =18.6. The distance between 4 & 9 is:
Therefore, the 1mm temperature gradient between 4 & 9 is: $18.6 + 5 = 3.72$

The lower temperature thermosensor is number 4, hence the distance between the iceball edge and thermosensor 4 is: $7.3 + 3.72 = 1.96$mm. Knowing that each square on the grid represents 1mm, the position of the iceball edge was marked.

**Figure 2.16.** Mean temperatures and thermal mapping of a single level of an iceball at 10 minutes of freezing
5. All the 0°C points were placed on the grid. By joining all the points together, we drew the iceball border at one specific level.

6. The same principle was used to graph the ≤ -20°C and the ≤ -40°C isotherm within the iceball. The only modification was in step 4b, where -20 and -40 were subtracted from the lower temperature respectively before dividing it by the 1mm gradient.

7. The 1mm temperature gradient could not be accurately measured beyond the most peripheral thermosensor using our method. In very few occasions when the iceball extended beyond thermosensor 9, we estimated the temperature gradient using the gradient between 4 & 9.

8. The method, described above, measuring the distance between the 0°C and the -40°C isotherms and the adjacent thermosensor has become the basis for iceball and lethal zone dimensions measurement (as will be described later in this chapter).

The thermal distribution of the entire iceball was obtained by combining the entire cross-sectional levels together as illustrated in figure 2.17.
Figure 2.17. Illustration of a 3-dimensional reconstruction of the thermal distribution of all the horizontal levels providing a model of the thermal mapping of the entire iceball.
2.1.10 Longitudinal Views

1. Experiments 1 - 3: two views were created for each experiment:

   a. View 1: created by a plane through the cryoprobes, dividing the iceball into two equal halves, showing the width (W) and the length (L) of the iceball (figure 2.18).

   ![Figure 2.18. Illustration of the longitudinal view 1 of experiments 1-3 iceballs showing the iceball plane (a) and dimensions [Width (W) and Length (L)] (b)
b. View 2: created by a plane halfway between the cryoprobes, dividing the iceball into two equal halves, showing the length (L) and depth (D) of the iceball (figure 2.19).

Figure 2.19. Illustration of the longitudinal view 2 of experiments 1-3 iceballs showing the iceball plane (a) and dimensions [Depth (D) and Length (L)] (b)
2. **Experiment 4**: two views were created.

a. **View 1**: created by a plane between the two rows, dividing the iceball into two equal halves, showing the width (W) and the length (L) (figure 2.20).

![Diagram of Experiment 4 view 1](image)

Figure 2.20. Illustration of the longitudinal view 1 of experiment 4 iceball showing the iceball plane (a) and dimensions [Width (W) and Length (L)] (b)
b. View 2: created by a plane passes through the middle of both rows, dividing the iceball into two equal halves, revealing the depth (D) of the iceball (figure 2.21).

Figure 2.21. Illustration of the longitudinal view 2 of experiment 4 iceball showing the iceball plane (a) and dimensions [Depth (D) and Length (L)] (b)
2.1.11 Determination of the Level of Maximum Iceball width and Depth

The temperatures of all the horizontal levels of the four experiments were recorded and a thermal map of each level was created from the 10 minutes mean temperatures as described before (2.1.9). From these thermal maps, the horizontal levels at which the maximum dimensions (widths and depths) of the iceballs occurred were determined. From the horizontal thermal map, longitudinal views were created for all the iceballs as explained before in the chapter (2.1.10). The maximum dimensions levels could also be concluded from these views.
2.1.12 Measuring the Maximum Dimensions of the Iceball

a. Width

The maximum width of the iceball at this level was measured at the maximum dimension level as follows:

1. Experiments 1 – 3 (figure 2.22):

Figure 2.22. An example of the thermal distribution of a single iceball level of experiments 1-3. The width \( W = a + b + c \)
• Width (W) = a + b + c

• (a) equals the distance between thermosensor (12) (in this example) and cryoprobe (1) (this distance is known as discussed before in 2.1.6) + the distance between the edge of the iceball and thermosensor (12) (can be calculated as described before in (2.1.9) point 4.

• (b) is the distance between the cryoprobes which is known.

• (a) was assumed to equal (c) (as explained before in 2.1.9). Therefore, Width (W) = (2 X a) + b

• Using the same rules, the width of the lethal zone (≤ -40°C or the purple colour) was measured.
2. **Experiment 4 (figure 2.23):**

![Diagram of thermal distribution of an iceball level of experiment 4.](image)

Figure 2.23. An example of the thermal distribution of a single iceball level of experiment 4. The width \(W= a+b+c\)

The same principle of previous experiments was used to measure \(W\), knowing the distance between 2 adjacent thermosensors is 5mm.
b. Depth

Depths of the lethal and total ice (figure 2.24) were measured across the centre of the iceball, at the maximum dimension level in similar way to the width. However, the distance between 2 adjacent thermosensors was 5 mm in all experiments.

In experiments 1 and 3 at 100% gas flow and experiment 2, the edge of the iceball (0°C isotherm) extended just beyond thermosensor 9. Hence, the 1 mm temperature gradient and subsequently the distance between iceball edge and thermosensor 9 could not be precisely calculated. In these situations, we estimated the distance between the edge of the iceball and thermosensor 9 using the 1 mm temperature gradient between thermosensor 4 and 9. All the lethal zones remained within the thermosensor coverage area.

Figure 2.24. An example of the thermal distribution of a single iceball level of experiments 1-3. The depth (D) = a+b+c
c. Length

The length (L) demonstrated in the longitudinal views, was calculated by measuring the length of the longitudinal axis passing through the centre of the iceball:

1. Experiments 1-3 (figure 2.25)

The centre of the iceball is located at thermosensor number 1.

![Figure 2.25](image)

Figure 2.25. An example of the longitudinal view thermal distribution of experiments 1-3 iceball. Length (L) = a + b + c

- Iceball length equals a + b + c.
- b equals to the number of levels X 5mm. a & c are the distances between the upper and lower edges of the iceball and the first and the last horizontal levels within the iceball respectively at thermosensor 1. These distances are located in a similar way as described in thermal mapping point 4.
2. **Experiment 4**

Similar principle was used in this as for the other experiments, however, the centre of the iceball passed through thermosensor number (4) instead.
2.1.13 Anterior Prostate Dimensions

As explained previously in the chapter (2.1.4), we have assessed and compared the iceballs and the lethal zones of the anterior group of probes. In order to assess the adequacy of these dimensions, we have compared the iceball dimensions with dimensions of the anterior part of 40 patients' prostate that underwent cryosurgery of the prostate following radiotherapy failure. These dimensions, which will be presented in the next chapter (3.1.4), were measured as illustrated in figure 2.26 using TRUS. The measurements were then compared with corresponding iceball and lethal zone dimensions.

Figure 2.26. Diagram (top) and ultrasound (bottom) pictures of the prostate demonstrating the dimensions of the anterior part of the prostate. In the cross-sectional view (a), the depth (D) represented the distance between the anterior prostatic capsule and the urethra. The width (W) was the distance between the sides of the prostate at the mid point of the depth. In the side view (b), the length (L) measured from the distance between the base and apex of the prostate.
2.1.14 The Distance between the Cryoprobe and the Edge of the Lethal Zone

The length between the centre of the cryoprobe and the edge of the lethal zone (figure 2.27) determines the maximum distance at which cryoprobes can be placed away from the edge of the capsule. This distance was assessed at the maximum iceball dimensions level using the principles of measurement method described before in this chapter (2.1.12).

Figure 2.27. Illustration of the longitudinal view of the iceball. The red arrow represents the distance between the cryoprobe and the edge of the lethal zone.
2.1.15 The Thickness of the Non-Lethal Ice Zone

The outer zone of the iceball, where the temperature ranges between 0 and 
-39.9°C, is considered the non-lethal zone. We have measured the thickness 
of this zone using the same principles as described before (2.1.12) in three 
places (Fig. 2.28)

Figure 2.28. Illustration of the longitudinal views of the iceball. Arrow number 1 stands for 
the thickness of the non-lethal zone on the side of the iceball across the width. Arrow 2 
represents the non-lethal zone thickness across the depth of the iceball. Both 1 and 2 
were measured at the maximum dimensions level. Arrow 3 represents the non-lethal 
zone thickness at the top of the iceball, midway between the cryoprobes.
2.1.16 The Length of the Lethal Iceball below the Tip of the Cryoprobes

This length was measured through the central longitudinal axis of the iceball using the same principle described before in the chapter (figure 2.29).

Figure 2.29. Illustration of the longitudinal view of the iceball. The arrow represents the length of the lethal ice below the level of cryoprobes tips.
2.1.17 Cooling Rate

Although the cooling rate does not appear to be a critical factor for cell injury, as explained in chapter 1 (1.2.2.5), it is still a valuable tool to compare the efficiency of iceball formation. The cooling rate of each iceball was measured in the centre of the iceball (corresponding to thermosensors 1 for experiments 1-3 and 4 for experiment 4 at the maximum dimensions (width and depth) horizontal level. We have compared the cooling rates (degree/minute) of the first 5 minutes of freezing by using the 0-5 minutes temperatures gradients.

2.1.18 Ablative Ratio

This is a tool used to quantify the efficiency of iceball and is estimated by dividing the lethal zone volume by the total iceball volume (Rewcastle et al, 1999b). The higher the value of the ablative ratio, the more effective the killing and the less collateral damage is likely to occur.

There is no validated formula which can used to measure the volume of the iceball or the lethal zones since they both have irregular shapes. In our experiments, the iceballs were intended to cover half of the prostate in the majority of the cases and from examining longitudinal views of the iceballs and the shape of the iceball in water, there were similarities between the shape of the iceball and the prostate. Based on these factors, we have used the same prostate volume measurement formula to assess the volume of the total iceball and lethal zones. In clinical practice, several methods have been described to measure the prostate volume using TRUS. The step-section
planimetry method is regarded the most accurate (Terris and Stamey, 1991). In this method, the prostate is divided into several sections; the volume is measured by taking the sum of the prostate sections surface areas multiplied by the inter-section interval. This method is time consuming, and requires operator experience and cumbersome equipment; therefore, it is not commonly used in clinical practice (Littrup et al, 1991). We did not consider using this method in our study because it relies on outlining the boundary of the iceball to measure the surface area at each section, which we were unable to achieve accurately using our methodology. TRUS could have been used to assess the boundaries of the total iceball but not the lethal zone.

Several formulas have been examined to measure prostate volume using TRUS (Aarnink et al, 1996; Eri et al, 2002; Littrup et al, 1991; Terris and Stamey, 1991) including:

1. Prolate ellipsoid: volume= (width X depth X length) X \( \frac{1}{6} \) (most commonly used in clinical practice).
2. Spherical: volume= (diameters)\(^3\) X \( \frac{1}{6} \)
3. Prolate spheroid: volume= (major axis)\(^2\) X (minor axis) X \( \frac{1}{6} \)
4. Spheroid: volume= \([(length + width + length)/3]\(^3\) X \( \frac{1}{6} \)
5. Quick spheroid: Volume= \([(length + width)/2]\(^3\) X \( \frac{1}{6} \)

Although the prolate ellipsoid formula is probably the most commonly used in practice, it has been challenged and shown to be less accurate than the prolate spheroid and the spheroid formulas (Aarnink et al, 1996; Terris and Stamey, 1991). However, it was believed that the inaccuracies are caused by errors in the measurement of primarily the length and then transverse...
diameter (Terris and Stamey, 1991; Yip et al, 1991). Nathan et al (1996) concluded that these errors resulted from operators' failure to locate the maximum diameters image for each dimension on the TRUS. When the measurements are accurately taken, then prostate volumes calculated from prolate ellipsoid formula correlate better with the step planimetry technique than other methods (Dahnert, 1992; Nathan et al, 1996). Therefore, we have used the prolate ellipsoid formula to estimate the volumes of the iceball and lethal zone for each experiment.

2.1.19 Statistical Analysis

Data are expressed as means (standard deviation). For each parameter at 100% gas flow, comparisons were made between the means of the four experiments using the one way analysis of variance (ANOVA) with 95% confidence intervals to determine if there was a significant difference between the means. If differences were present, then we used the Least Significant Difference (LSD) (as the pos hoc test) to compare the means against each other. Comparisons were also made between the means of the 100% and 20% gas flow parameters using independent samples t-test. We considered a P value of ≤ 0.05 to be significant for all the statistical tests.

We also measured the coefficient of variation (CV) within each experiment and between the experiments for all the data. It was measured by dividing the standard deviation to the mean, and was presented as percentage. The CV provides a relative measure of data dispersion compared to the mean, with the smaller the CV value, the less scattered the data is around the mean.
2.2 Treatment Protocol for Salvage Cryotherapy

The technique of and technical considerations during primary and salvage cryotherapy have been described before (1.2.2.7, 1.2.2.9 and 1.3.). The protocol for salvage cryotherapy is summarised in figure 2.30.

All patients were thoroughly assessed with history, clinical examination and transrectal ultrasound scan. Prostate biopsy was performed on all patients; patients with positive histology were investigated with pelvic MRI and bone scan. Pelvic lymph nodes biopsy was performed if the lymph nodes were enlarged on MRI scan and/or when the prostate biopsy Gleason was =>8. Patients were suitable if the prostate biopsy was positive for recurrence, MRI indicated disease stage <T3b (no seminal vesicles involvement), negative bone scan and no pelvic lymph nodes involvement. Previous history of TURP was considered a contraindication for cryotherapy if they had a large residual TURP defect on TRUS. Cytoreductive androgen deprivation was given to patients with prostate volume larger than 40cc. Following cryotherapy, ciprofloxacin was prescribed for 1 week, an indwelling urethral catheter was used for 2 weeks and patients were prescribed alpha-blockers for 4 week. Patients with rising PSA after salvage cryotherapy underwent a repeat prostate biopsy which if positive underwent repeat cryotherapy. If the biopsy showed no evidence of residual malignant tissue, patients were treated with androgen deprivation.
Figure 2.30. Summary of treatment protocol of salvage cryotherapy

Three consecutive PSA rises after radiation therapy

Assessment:
Prostate biopsy
Pelvic MRI
Bone scan
Prostate volume (TRUS)

Pelvic lymph nodes biopsy (selected cases)

Suitable

Yes

Androgen deprivation (Selected cases)

Cryotherapy

Repeat prostate biopsy (Patients with rising PSA)

Positive

Repeat Cryotherapy

No

Androgen deprivation

Negative

Androgen deprivation
2.3 HQoL Study Design and Questionnaires Selection

The study was intended to assess HQoL changes after salvage cryotherapy for recurrent prostate cancer post-radiation therapy using a number of questionnaires in a longitudinal study design.

2.3.1 Study Design

A prospective longitudinal study collecting data to measure various outcomes to assess the impact of salvage cryotherapy on men with locally recurrent prostate cancer and their partners. Figure 2.31 summarises the study design.

![Study Design Diagram]

Figure 2.31. Summary of HQoL Study Design
2.3.2 Study Population

Men who were suitable for and choose salvage cryotherapy (1.2.2.9 and 1.3), with or without partners, were invited to take part in the study. Patients were excluded from the study if: they received androgen deprivation therapy before cryotherapy only, received androgen deprivation after cryotherapy only, and patients who had repeat cryotherapy. All patients were recruited from 2 centres in Guildford, Surrey (one surgeon): The Royal Surrey County Hospital, Egerton Road, GU2 7XX (NHS) and The Mount Alvernia Hospital, 46 Harvey Road, GU1 3LX. (private).

Patients were excluded from the study if they failed to complete their baseline questionnaire after a reminder.

2.3.3 Questionnaires

A series of questionnaires (summarised in table 2.5) were used to assess various aspects of HQoL and symptoms following salvage cryotherapy. These were combined with a further questionnaire collecting data on concurrent treatment for erectile dysfunction, urinary retention and health services usage. The questionnaire booklet is reproduced in appendices B and C.
<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Items</th>
<th>Assesses</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ C30</td>
<td>Cancer specific QoL</td>
<td>30</td>
<td>Cancer specific QoL</td>
<td>Well validated and widely used in oncological trials</td>
</tr>
<tr>
<td>(Aaronson et al, 1993)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC PR-25</td>
<td>Prostate cancer specific QoL</td>
<td>25</td>
<td>ED, bowel, urinary and toxicity from androgen deprivation</td>
<td>Comprehensive, suitable for localised and metastatic prostate cancer. Awaiting full validation.</td>
</tr>
<tr>
<td>(Aaronson and Van Andel, 2001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIEF</td>
<td>Symptom index</td>
<td>15</td>
<td>ED</td>
<td>Well validated</td>
</tr>
<tr>
<td>(Cappelleri et al, 1999)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPSS</td>
<td>Symptom index</td>
<td>8</td>
<td>LUTS</td>
<td>Well validated and familiar</td>
</tr>
<tr>
<td>(Barry and O’Leary, 1995)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPSM</td>
<td>Paired patient and partner</td>
<td>10</td>
<td>Cancer distress and social impact</td>
<td>Validated and previously used in UK prostate cancer trials</td>
</tr>
<tr>
<td>(Cliff and MacDonagh, 2000a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED-EQoL</td>
<td>Symptom specific QoL</td>
<td>15</td>
<td>Impact of ED on QoL</td>
<td>Validated specific measure</td>
</tr>
<tr>
<td>(Meyer et al, 2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.5. Questionnaires used in the health related quality of life study. European Organization for research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Quality of Life (QoL), EORTC Prostate-25 (EORTC PR-25), Erectile Dysfunction (ED), International Index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS), Lower Urinary Tract Symptoms (LUTS), Taunton Psychosocial Morbidity questionnaire (TPSM), Erectile Dysfunction Effect on Quality of Life questionnaire (ED-EQoL).
2.3.4 Questionnaires Administration

All questionnaires, except the IIEF and ED-EQoL, were administered prior to operation (baseline) and at 6 weeks, 3, 6, 9, 12, 18, and 24 months post-operatively. The IIEF and ED-EQoL questionnaires (assessing sexuality) were administered less frequently at baseline and at 6, 12, 18 and 24 months post-operatively to reduce “burden response” where fatigue from completing lengthy questionnaires may limit the ability of patients to provide useful information. The arrangement of administering sexuality questionnaires 6 monthly was based on observations from the ongoing trial of quality of life assessment following early prostate cancer treatment where no significant changes in sexuality were observed in 3 months period (personal communication Prof. S. E. Langley). The baseline questionnaires (before cryotherapy) were handed to patients after obtaining consent. The post-operative questionnaires were mailed to the patients, with a stamped addressed return envelope, 1 week prior to the due date. The TPSM partners’ questionnaires were sent in a separate envelope.
2.3.5 Scoring of Questionnaires

EORTC QLQ C30 version 3.0

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items (table 2.6).

<table>
<thead>
<tr>
<th>Scale</th>
<th>Number of items</th>
<th>Item range*</th>
<th>Version 3.0 Item numbers</th>
<th>Function scales</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global health status / QoL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global health status/QoL</td>
<td>QL2</td>
<td>2</td>
<td>6</td>
<td>29,30</td>
</tr>
<tr>
<td><strong>Functional scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>PF2</td>
<td>5</td>
<td>3</td>
<td>1 to 5</td>
</tr>
<tr>
<td>Role functioning</td>
<td>RF2</td>
<td>2</td>
<td>3</td>
<td>6, 7</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>EF</td>
<td>4</td>
<td>3</td>
<td>21 to 24</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>CF</td>
<td>2</td>
<td>3</td>
<td>20, 25</td>
</tr>
<tr>
<td>Social functioning</td>
<td>SF</td>
<td>2</td>
<td>3</td>
<td>26, 27</td>
</tr>
<tr>
<td><strong>Symptoms scales / items</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>FA</td>
<td>3</td>
<td>3</td>
<td>10, 12, 18</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>NV</td>
<td>2</td>
<td>3</td>
<td>14, 15</td>
</tr>
<tr>
<td>Pain</td>
<td>PA</td>
<td>2</td>
<td>3</td>
<td>9, 19</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>DY</td>
<td>1</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>SL</td>
<td>1</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>AP</td>
<td>1</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Constipation</td>
<td>CO</td>
<td>1</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>DI</td>
<td>1</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>FI</td>
<td>1</td>
<td>3</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 2.6. Scoring the EORTC QLQ-C30 version 3.0
* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high
QoL, but a high score for a symptom scale / item represents a high level of symptoms / problems.

The principle for scoring these scales which is described in the EORTC QLQ C-30 manual is the same in all cases (Fayers et al, 2001):

1. Estimate the average of the items that contribute to the scale; this is the raw score.
2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

In practical terms, if items $l_1, l_2, ... l_n$ are included in a scale, the procedure is as follows:

1. $\text{Raw Score} = RS = (l_1 + l_2 + l_n)n$

2. Linear transformation: apply the linear transformation to 0-100 to obtain the score $S$,

For the Functional scales:

$$S = 1 - \frac{(RS - 1)}{\text{range}}$$
For the **Symptom scales** / **items** and **Global health status** / **QoL**:

\[ S = \{(RS - 1) \text{ range}\} \times 100 \]

<table>
<thead>
<tr>
<th>Examples:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emotional functioning</strong></td>
</tr>
<tr>
<td>RawScore = ((Q_{21} + Q_{23} + Q_{24} + Q_{25})/4)</td>
</tr>
<tr>
<td>EF Score = ([1 - (\text{RawScore} - 1)/3] \times 100)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
</tr>
<tr>
<td>RawScore = ((Q_{10} + Q_{12} + Q_{18})/3)</td>
</tr>
<tr>
<td>FA Score = ([{(\text{RawScore} - 1)/3} \times 100)</td>
</tr>
</tbody>
</table>

These algorithms have been included in a program produced by Fayers et al (2001) to process the EORTC QLQ C-30 raw data into symptom scales using the SPSS statistical package.

The clinical significance of QLQ-C30 score changes was assessed by Osoba et al (1998) using the **Subjective Significance Questionnaire** (SSQ). The SSQ asks patients about **perceived changes** in physical, emotional, and social functioning and in global QoL, using a 7-point scale ranging from 'much worse' over 'no change' to 'much better'. Patients who reported 'a little' change for better or worse on a particular scale (function or symptom) had QLQ-C30 changes about 5 to 10%. Those reporting 'moderate' change had changed about 10 to 20%, and 'very much' change corresponded to a change > 20%.
EORTC PR-25

Full validation of the PR-25 is still ongoing. Factor analysis, discriminant validity and test-retest reliability have been assessed and published in a summary form indicating all were satisfactory (Aaronson and Van Andel, 2001). The PR25 has been used in HQoL studies published in international journals (Davison and Goldenberg, 2003; Lintz et al, 2003). The EORTC has provided a tentative scoring system for the questionnaire, unlike the QLQ C-30. Formal scoring manual may become available in the near future. The current available scoring system divides the questionnaire into 5 separate multi-items scale as shown in table 2.7.

<table>
<thead>
<tr>
<th>Symptom scales / items</th>
<th>Scale</th>
<th>Number of items</th>
<th>Item range</th>
<th>PR25 Item numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Problems</td>
<td>UR</td>
<td>8</td>
<td>3</td>
<td>1 to 7 and 9</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>UI</td>
<td>1</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Bowel Symptoms</td>
<td>BS</td>
<td>4</td>
<td>3</td>
<td>10 to 13</td>
</tr>
<tr>
<td>Treatment Symptoms</td>
<td>TS</td>
<td>6</td>
<td>3</td>
<td>14 to 19</td>
</tr>
<tr>
<td>Sexual Activity</td>
<td>SA</td>
<td>2</td>
<td>3</td>
<td>20, 21</td>
</tr>
<tr>
<td>Sexual Functioning</td>
<td>SF</td>
<td>4</td>
<td>3</td>
<td>22 to 25</td>
</tr>
</tbody>
</table>

Table 2.7. Scoring the EORTC PR-25

It is assumed that items 1 to 9, excluding 8, forms a multi-item scale assessing urinary function. Item 8 is for patients using an incontinence device, hence not relevant to all patients.

Items 10 to 13 and 14 to 19 are assumed to represent multi-item scales addressing bowel function and treatment-related symptoms respectively.
The scoring of the multi-scale and individual items (1 to 19) is such that the higher scores represent the more problems/symptoms.

It is hypothesised that two scales assess sexual function: the first scale comprises of items 20 and 21 is for all patients and the second scale comprises items 22 to 25 which is conditional for sexually active patients only. The scoring of the sexual function scales is such that the higher the score represent the higher (better) sexual functioning.

**International Prostate Symptom Score (IPSS)**

The IPSS is a well-validated 7-item instrument to assess LUTS, excluding incontinence (Barry et al, 1992). Each of the 7 items has six possible answers; items 1 to 6 answers range from “not at all” scoring 0 to “almost always” scoring 5. While the seventh item, which addresses nocturia, score ranges from 0 for “none” to 5 for “5 times or more”. The total IPSS score ranges between 0 and 35; patients scoring 0 to 7 are mildly symptomatic, those who scores 8 to 19 have moderate symptoms and a score of => 20 indicates severe LUTS. IPSS scores will be expressed as a continuous variable and changes of more than 3 points considered clinically significant (Barry and O'Leary, 1995).
International Index of Erectile Function (IIEF)

The IIEF is self-administered tool to assess ED in both clinical and research setting (Rosen et al, 1997). It has 5 multi-item domains with a total of 15 items; each item has either 5 or 6 possible answers (table 2.8).

<table>
<thead>
<tr>
<th>Domain</th>
<th>Items</th>
<th>Score range</th>
<th>Minimum score</th>
<th>Maximum score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile Function (EF)</td>
<td>1,2,3,4,5,15</td>
<td>0 (or 1) -5</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Orgasmic Function (OF)</td>
<td>9,10</td>
<td>0-5</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Sexual Desire (SD)</td>
<td>11,12</td>
<td>1-5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Intercourse Satisfaction</td>
<td>6,7,8</td>
<td>0-5</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Overall Satisfaction (OS)</td>
<td>13,14</td>
<td>1-5</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2.8. The IIEF questionnaire domain scoring

An abridged five-item version (IIEF-5) was developed to identify the presence and severity of ED. This comprises of items 2, 4, 5, 7 and 15 of the original IIEF. Both versions have been extensively validated in heterosexual patients (Rosen et al, 1997; Rosen et al, 1999). The scoring of IIEF-5 ranges between 1 and 25 (the lower the score the more significant ED), based on which, five severity classes of ED has been developed as demonstrated in table 2.9 (Rosen et al, 1999). The table suggests that a change in the score of 4 points would be clinically significant, and men are considered potent if they score ≥ 12. The scores of IIEF were expressed either as mean scores or percentage of each severity class of ED.
<table>
<thead>
<tr>
<th>ED severity</th>
<th>IIEF-5 score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>22-25</td>
</tr>
<tr>
<td>Mild ED</td>
<td>17-21</td>
</tr>
<tr>
<td>Mild-Moderate ED</td>
<td>12-16</td>
</tr>
<tr>
<td>Moderate ED</td>
<td>8-11</td>
</tr>
<tr>
<td>Severe ED</td>
<td>1-7</td>
</tr>
</tbody>
</table>

Table 2.9. Severity classes of ED according to IIEF-5 score.

Taunton Psychosocial Morbidity Questionnaire (TPSM)

This questionnaire assesses psychological morbidity in patients with prostate cancer and in their partners. It comprises of 2 multi-item scales and five single items (Cliff and MacDonagh, 2000a). The scoring of each subscale or item, which is demonstrated in table 2.10, will be expressed as a continuous variable. The higher the score the more is the distress or worry. The primary end point of interest is the general cancer distress subscale for both patients and partners. Cliff and MacDonagh (2000b) defined the mean differences of the items and scales scores between morbid and non morbid patients (shown in table 2.10) after comparing the scores with the Hospital Anxiety and Depression Scale. They also concluded that people with scores of \( \geq 4 \) on the general cancer distress subscale can be classified as morbid.
<table>
<thead>
<tr>
<th>Scales/Items</th>
<th>Score range</th>
<th>Mean score difference between morbid and not morbid</th>
</tr>
</thead>
<tbody>
<tr>
<td>General cancer distress</td>
<td>0 – 12</td>
<td>3.7</td>
</tr>
<tr>
<td>Fear of diagnosis</td>
<td>0 – 4</td>
<td></td>
</tr>
<tr>
<td>Future worries</td>
<td>0 – 4</td>
<td></td>
</tr>
<tr>
<td>Emotional distress</td>
<td>0 – 4</td>
<td></td>
</tr>
<tr>
<td>Social Subscales</td>
<td>0 – 8</td>
<td>2.3</td>
</tr>
<tr>
<td>Social functioning</td>
<td>0 – 4</td>
<td></td>
</tr>
<tr>
<td>Role functioning</td>
<td>0 – 4</td>
<td></td>
</tr>
<tr>
<td>Items</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worry from pain</td>
<td>0 – 4</td>
<td>0.7</td>
</tr>
<tr>
<td>Worry from urinary symptoms</td>
<td>0 – 4</td>
<td>0.9</td>
</tr>
<tr>
<td>Worry from physical limitation</td>
<td>0 – 4</td>
<td>0.6</td>
</tr>
<tr>
<td>Worry from treatment</td>
<td>0 – 4</td>
<td>0.9</td>
</tr>
<tr>
<td>Worry from sex</td>
<td>0 – 4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Table 2.10. Score range and the mean scoring difference between morbid and non morbid patients of the Taunton Psychosocial Morbidity questionnaire domains

**Erectile Dysfunction Effect on Quality of Life (ED-EQoL)**

This is a validated questionnaire which comprises 15 questions (items), each scoring between 0 and 4. The scoring of the ED-EQoL, which represents the total of the 15 items scores, is such that the higher the score the more effect on QoL. Based on this, three groups of patients have been identified: men with ED-EQoL total score < 15 have mild impact of ED on QoL; score 15-29 represents a moderate effect on QoL and scores >30 represent severe effect on QoL (MacDonagh et al, 2002; MacDonagh et al, 2004).
2.3.6 Statistical Analysis

A power calculation (table 2.11) was determined by comparing baseline and follow-up data from the first 10 patients using paired t-test with p-value of <0.05 to determine significance and allowing 80% power. The comparison was based on the most important and sensitive domains of well validated questionnaires which are the global health status domain of the EORTC QLQ-C30 and the IPSS. Although the IIEF-5 is well validated, it was not used in power calculations as the number of patients who are expected to be potent at baseline was small. From the first 10 patients' data, only one patient had IIEF-5 score of ≥12 (potent), therefore in order to assess the impact of salvage cryotherapy on the potent men, significant number of men is required to achieve the required 18 potent men (table 2.11). This will significantly over-power and delay the study with a huge increase in the workload of data collection and cost.

We aimed to assess the outcome by comparing follow-up with baseline data using paired t-test using p-value of 0.05 to determine significance. The study is currently ongoing; therefore, we present preliminary results without statistical analysis as recruitment is incomplete.
<table>
<thead>
<tr>
<th>Name</th>
<th>Key endpoint</th>
<th>Minimum clinically significant change in score</th>
<th>Estimated mean difference</th>
<th>Estimated SD of difference</th>
<th>Number of patients required to achieve 80% power</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30</td>
<td>Global HQoL</td>
<td>5 - 10% = little</td>
<td>5</td>
<td>17</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 - 20% = moderate</td>
<td>10</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;20% = very much</td>
<td>20</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>EORTC PR-25</td>
<td>Urinary problem</td>
<td>Unknown but likely to be similar to QLQ-C30</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>IIEF</td>
<td>Change in IIEF-5</td>
<td>4 points</td>
<td>4</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>IPSS</td>
<td>Change in symptoms scale</td>
<td>4 points</td>
<td>4</td>
<td>7.7</td>
<td>29</td>
</tr>
<tr>
<td>TPSM</td>
<td>General cancer distress</td>
<td>Unknown. Mean score difference between morbid and non morbid ranges between 0.6 to 3.7</td>
<td>1</td>
<td>2.0</td>
<td>32</td>
</tr>
<tr>
<td>ED-EQoL</td>
<td>ED QoL</td>
<td>Unknown</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.11. Quality of life instruments, key endpoints and power calculations measured based on the first 10 patients data.
2.4 The Impact of Iceball Temperature on HQoL during Salvage Cryotherapy

Operative data were collected from patients taking part in the HQoL study. The lowest temperature measured by the thermosensors at the external urethral sphincter, the apex of the prostate and the Denonvillier's fascia were recorded.

The following HQoL domains/items were assessed: global health status domain of the EORTC QLQ C30 questionnaire; urinary problem scale and urinary incontinence question of the EORTC PR25; IPSS and the quality of life question of the IPSS questionnaire. The differences between the 6 week and the baseline scores of these domains/items were calculated to measure the impact on HQoL.

2.4.1 Statistical Analysis

Two-tailed bivariate correlation test with Spearman correlation coefficient was used to compare the lowest temperature at each point with the baseline - 6weeks differences in the HQoL domains/items scores. P-value of ≤0.05 was used to consider significance.
Chapter 3
Results
3.1 *In-vitro* Assessment of Three Different Cryoprobes Used for Prostate Cryosurgery

Temperatures of all the horizontal slices of the four experiments were recorded and thermal mapping of each level was created from the 10 minutes mean temperatures (appendix A). Maximum dimension (widths and depths) levels of the iceballs (Table 3.1) were determined as discussed in chapter 2 (2.1.11). This showed that for the 2.4mm and 3.4mm diameter probes, the maximum iceball dimensions level was 10-15 mm above the tip of the probes (level 8 & 9); however it was only 5mm above the tip of the 1.47mm diameter probe.

From the horizontal levels thermal mapping, longitudinal views were created (figures 3.1 to 3.8) for all the iceballs as described before in the chapter 2 (2.1.10). None of the thermosensor temperatures in experiment 4 iceball reached -40 C° or below at 20% gas flow rate, hence, the iceball was considered to be devoid of a lethal zone. Therefore, we considered the measurements to equal zero in calculating the maximum iceball dimensions. However, when measuring the non-lethal ice thicknesses and the lethal ice thickness below the tips of the probes, we regarded the measurements “Not Applicable” (n/a) rather than zero to avoid the wrong impression that lethal ice is present, and in this situation, statistical tests were not carried out.
<table>
<thead>
<tr>
<th>Experiments</th>
<th>100% gas flow</th>
<th>20% gas flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2.4mm, 18mm apart)</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>2 (2.4mm, 15mm apart)</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>3 (3.4mm, 18mm apart)</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>4 (1.47mm, 10mm apart)</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 3.1. The corresponding levels at which maximum dimensions (width and depth) of the iceballs of each experiment took place.
Figure 3.1. Real-size longitudinal thermal mapping views of experiment 1 iceball at 100% gas flow.

- 0 to -19.9°C zone
- -20 to -39.9°C zone
- ≤ -40°C zone
Figure 3.2. Real-size longitudinal thermal mapping views of experiment 1 iceball using 20% gas flow.
Figure 3.3. Real-size longitudinal thermal mapping views of experiment 2 iceball using 100% gas flow.

- 0 to -19.9°C zone
- -20 to -39.9°C zone
- ≤ -40°C zone
Figure 3.4. Real-size longitudinal thermal mapping views of experiment 2 iceball using 20% gas flow.

- 0 to -19.9°C zone
- -20 to -39.9°C zone
- ≤ -40°C zone
Figure 3.5. Real-size longitudinal thermal mapping views of experiment 3 iceball using 100% gas flow.

- 0 to -19.9°C zone
- -20 to -39.9°C zone
- ≤ -40°C zone
Figure 3.6. Real-size longitudinal thermal mapping views of experiment 3 iceball using 20% gas flow.
Figure 3.7. Real-size longitudinal thermal mapping views of experiment 4 iceball using 100% gas flow.
Figure 3.8. Real-size longitudinal thermal mapping views of experiment 4 iceball using 20% gas flow.
3.1.1 Maximum Width of the Iceballs and Lethal Zones

The means and standard deviations of the maximum iceball and lethal zone widths were measured (table 3.2). Comparing the 100% and the 20% iceballs, in experiment 1, reducing the freezing rate to 20% resulted in a significant decrease in the width of the kill zone. This reduction was not observed in the total iceball width. No significant width reductions were found in experiment 2 for both the total and kill zone. However, in experiment 3, the reduction in the freezing rate resulted in iceballs and kill zones that had significantly less width. A more pronounced width reduction was noted in experiment 4.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Total iceball width (mm)</th>
<th>Sig.</th>
<th>Kill zone width (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100% gas flow</td>
<td>20% gas flow</td>
<td></td>
<td>100% gas flow</td>
</tr>
<tr>
<td>1</td>
<td>50.04 (0.71)</td>
<td>50.49 (1.43)</td>
<td></td>
<td>37.23 (0.62)</td>
</tr>
<tr>
<td>2</td>
<td>49.59 (1.95)</td>
<td>48.16 (0.66)</td>
<td></td>
<td>34.33 (0.52)</td>
</tr>
<tr>
<td>3</td>
<td>52.93 (0.23)</td>
<td>48.19 (0.9)</td>
<td>$\dagger$</td>
<td>38.01 (1.28)</td>
</tr>
<tr>
<td>4</td>
<td>57.96 (2.07)</td>
<td>38.44 (1.52)</td>
<td>$\dagger$</td>
<td>39.38 (2.36)</td>
</tr>
</tbody>
</table>

$\dagger$ Significant at p value of 0.01
$\dagger$ Significant at p value of 0.001

Table 3.2. Means (standard deviation) of the maximum width of the total iceball and the kill zone at 100% and 20% gas flow rates. Each experiment was performed three times. Comparisons were made between the means of the 100% and the 20% widths for each experiment for both the total ice and kill zone widths using independent samples t-test.
Using one way analysis of variance (ANOVA) to compare the kill zone widths between the experiments iceballs at 100% gas flow rate, there was a significant difference ($p = 0.013$). Post hoc analysis between the four groups (LSD) (Table 3.3) showed that experiment 2 produced significantly smaller kill zone width than all the other experiments. The width of kill zone 4 was larger than the other iceballs; however, the difference was only significant with iceball 2. There were no significant differences between iceball 1 and 3.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>+2.9</td>
<td>*</td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-0.77</td>
<td></td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>-2.15</td>
<td></td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>-3.67</td>
<td>*</td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>-5.05</td>
<td>¶</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>-1.37</td>
<td></td>
</tr>
</tbody>
</table>

* Significant at $p$ value of 0.05  
¶ Significant at $p$ value of 0.01

Table 3.3. The mean difference in mm of the kill zone width between each experiment at 100% gas flow rate using the Least Significant Difference (LSD) test. The negative sign (-) indicates smaller while the positive sign (+) indicates larger.

The differences were also significant comparing the total ice widths at 100% gas flow using one way ANOVA ($p < 0.001$). Post hoc analysis (LSD) (Table 3.4) confirmed that iceball 4 was significantly wider than the other iceballs. The difference between iceballs 1 and 2 was not significant; however, both had significantly smaller total widths than iceball 3.
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>+0.45</td>
<td></td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-2.88</td>
<td>*</td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>-7.91</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>-3.33</td>
<td>*</td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>-8.36</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>-5.03</td>
<td>¶</td>
</tr>
</tbody>
</table>

* Significant at p value of 0.05  
¶ Significant at p value of 0.01  
§ Significant at p value of 0.001

Table 3.4. The mean difference in mm of the total iceball width between each experiment at 100% gas flow rate using the Least Significant Difference (LSD) test. The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
3.1.2 Maximum Depth of the Iceballs and Lethal Zones

The means and standard deviations of the maximum total iceball and lethal zone depths were measured (table 3.5). By reducing the freezing rate to 20%, the depths have reduced significantly for all the iceballs except the total iceball depth in experiment 2, where the depth reduction was not significant. The total iceball depth reduction in experiment 4 was the most significant.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Total iceball depth (mm)</th>
<th>Sig.</th>
<th>Kill zone depth (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100% gas flow</td>
<td>20% gas flow</td>
<td></td>
<td>100% gas flow</td>
</tr>
<tr>
<td>1</td>
<td>43.69 (2.14)</td>
<td>37.61 (1.04)</td>
<td>$</td>
<td>23.54 (0.75)</td>
</tr>
<tr>
<td>2</td>
<td>44.65 (2.94)</td>
<td>41.89 (0.62)</td>
<td>$</td>
<td>24.09 (1.13)</td>
</tr>
<tr>
<td>3</td>
<td>45.02 (1.14)</td>
<td>37.33 (0.56)</td>
<td>$</td>
<td>23.53 (0.9)</td>
</tr>
<tr>
<td>4</td>
<td>38.29 (0.37)</td>
<td>23.57 (2.05)</td>
<td>$</td>
<td>24.26 (0.86)</td>
</tr>
</tbody>
</table>

Table 3.5. Means (standard deviation) of the maximum depth of the total iceball and the kill zone at 100% and 20% gas flow rates. Each experiment was performed three times. Comparisons were made between the means of the 100% and the 20% depths for each experiment for both the total ice and kill zone widths using independent samples t-test.

There were no significant differences ($p = 0.699$) between the kill zone depths of the iceballs at 100% gas flow rate using one way ANOVA. However, the differences were significant for the total ice depth ($p= 0.009$). Post hoc analysis between the four groups using the LSD (Table 3.6) showed that only experiment 4 was significantly different (smaller total iceball depth) from the other iceballs.
Table 3.6. The mean difference in mm of the total iceball depth between each experiment at 100% gas flow rate using the Least Significant Difference (LSD) test. The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
3.1.3 Maximum Length of the Iceballs and Lethal Zones

The means and standard deviations of the maximum total iceball and lethal zone lengths were measured (table 3.7). When reducing the gas flow, the length of all the iceballs and the lethal zones has decreased, although the reduction was not statistically significant for the total iceball in experiment 1. The largest length reduction was noted in the total length of iceball 4.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Total iceball length (mm)</th>
<th>Sig.</th>
<th>Kill zone length (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100% gas flow</td>
<td>20% gas flow</td>
<td></td>
<td>100% gas flow</td>
</tr>
<tr>
<td>1</td>
<td>50.33 (0.38)</td>
<td>49.07 (0.35)</td>
<td>*</td>
<td>35.71 (0.62)</td>
</tr>
<tr>
<td>2</td>
<td>52.56 (0.49)</td>
<td>50.57 (1.59)</td>
<td>*</td>
<td>39.3 (0.7)</td>
</tr>
<tr>
<td>3</td>
<td>59.39 (1.41)</td>
<td>52.88 (1.96)</td>
<td>§</td>
<td>37.58 (0.63)</td>
</tr>
<tr>
<td>4</td>
<td>42.66 (0.31)</td>
<td>23.27 (0.37)</td>
<td>§</td>
<td>22.62 (0.48)</td>
</tr>
</tbody>
</table>

* Significant at p value of 0.05
§ Significant at p value of 0.001

Table 3.7. Means (standard deviation) of the maximum length of the total iceball and the kill zone at 100% and 20% gas flow rates. Each experiment was performed three times. Comparisons were made between the means of the 100% and the 20% lengths for each experiment for both the total ice and kill zone widths using independent samples t-test.

One way ANOVA showed significant differences in both the kill zones (p=<0.001) and the total iceballs length (p=<0.001) between the experiments iceballs at 100% gas flow rate. LSD (Tables 3.8 and 3.9) showed that the differences were significant for all the experiment. The tables showed that iceball 4 had the lowest lethal zone and total iceball lengths by big margins. On the other hand, iceball 2 had the largest kill zone length, but not the total...
length as we would have expected. Instead, iceball 3 had the highest total
iceball length.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>-3.59</td>
<td>$§$</td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-1.87</td>
<td>$¶$</td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>+13.09</td>
<td>$§$</td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>+1.72</td>
<td>$¶$</td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>+16.68</td>
<td>$§$</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>+14.96</td>
<td>$§$</td>
</tr>
</tbody>
</table>

$¶$ Significant at p value of 0.01
$§$ Significant at p value of 0.001

Table 3.8. The mean difference in mm of the lethal zone length between each experiment at 100% gas flow rate using the Least Significant Difference (LSD). The negative sign (-) indicates smaller while the positive sign (+) indicates larger.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>-2.23</td>
<td>$¶$</td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-9.06</td>
<td>$§$</td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>+7.67</td>
<td>$§$</td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>-6.83</td>
<td>$§$</td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>+9.9</td>
<td>$§$</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>+16.73</td>
<td>$§$</td>
</tr>
</tbody>
</table>

$¶$ Significant at p value of 0.01
$§$ Significant at p value of 0.001

Table 3.9. The mean difference in mm of the total iceball length between each experiment at 100% gas flow rate using the Least Significant Difference (LSD). The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
3.1.4 Anterior Prostate Dimensions

The mean (SD) dimensions of the anterior part of the 40 prostates, which were measured using TRUS as described in chapter 2 (2.1.13) were as follows:

1. Width (W): 31.23 (4.43) mm
2. Depth (D): 17.18 (2.62) mm
3. Length (L): 35.21 (5.8) mm

3.1.5 The Distance between the Cryoprobe and the Edge of the Lethal Zone

The distance between the centre of the cryoprobe and the lethal zone edge for each iceball was measured (table 3.10). Reducing the freezing rate to 20% resulted in a significant reduction in the distance in experiment 1 and 3. Comparisons were not made between experiment 4 iceballs due to the lack of lethal ice when freezing at 20% gas flow.
Table 3.10. Means (standard deviation) of the distance in mm between the cryoprobe and the edge of the lethal zone at the maximum dimension level of the iceball. Each experiment was performed three times. Comparisons were made between the means of the 100% and the 20% distances for each experiment using independent samples t-test. Iceball 4 at 20% freeze rate did not have lethal ice.

<table>
<thead>
<tr>
<th>Experiments</th>
<th>100% gas flow</th>
<th>20% gas flow</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.81 (0.31)</td>
<td>9.17 (0.56)</td>
<td>§</td>
</tr>
<tr>
<td>2</td>
<td>10.84 (0.25)</td>
<td>10.28 (0.32)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11.74 (0.16)</td>
<td>9.79 (0.12)</td>
<td>§</td>
</tr>
<tr>
<td>4</td>
<td>3.28 (0.96)</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

§ Significant at p value of 0.001
n/a: not applicable

There was a significant difference (p = <0.001) using the one way ANOVA to compare the means of the distances between the iceballs at 100% gas flow rate. LSD (Table 3.11) test showed that the differences between experiment 1, 2 and 3 iceballs were not statistically significant, all of which had significantly longer distance than iceball 4.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>-0.33</td>
<td></td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-0.93</td>
<td></td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>+7.53</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>-0.9</td>
<td></td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>+7.56</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>+8.46</td>
<td>§</td>
</tr>
</tbody>
</table>

§ Significant at p value of 0.001

Table 3.11. The mean difference in mm of the cryoprobe-lethal ice distance between each experiment at 100% gas flow rate using the Least Significant Difference (LSD). The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
3.1.6 The Thickness of the Non-Lethal Ice Zone

The thickness of this zone was measured in three places:

1. **The side of the iceball across the width**

   The means and standard deviations of the non-lethal zone thickness across the width were measured (table 3.12). The thickness has significantly increased only in iceball 1 when the freezing rate was reduced to 20%. Comparison was not made in experiment 4 due to the lack of lethal ice when freezing at 20% gas flow.

   ![Table 3.12](image)

<table>
<thead>
<tr>
<th>Experiments</th>
<th>100% gas flow</th>
<th>20% gas flow</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.4 (0.24)</td>
<td>8.27 (0.44)</td>
<td><img src="image" alt="" /></td>
</tr>
<tr>
<td>2</td>
<td>7.63 (0.81)</td>
<td>7.47 (0.67)</td>
<td><img src="image" alt="" /></td>
</tr>
<tr>
<td>3</td>
<td>7.46 (0.8)</td>
<td>6.9 (0.38)</td>
<td><img src="image" alt="" /></td>
</tr>
<tr>
<td>4</td>
<td>9.28 (0.5)</td>
<td>n/a</td>
<td><img src="image" alt="" /></td>
</tr>
</tbody>
</table>

   ![](image)

   Significance at p value of 0.01
   n/a: not applicable

   Table 3.12. Means in mm (standard deviation) of the thickness of the non-lethal ice zone on the side of the iceball across the width at 100% and 20% gas flow rates. Each experiment was performed three times. Comparisons were made between the means of the 100% and the 20% thicknesses for each experiment using independent samples t-test. Iceball 4 at 20% freeze rate did not have lethal ice.
Comparing the means at 100% gas flow, there was a significant difference [one way ANOVA (p=0.002)]. Iceball 4 had, statistically, the largest thickness compared to the other iceballs (table 3.13) and iceball 1 had the shortest distance, however, the difference was not statistically significant compared to experiment 3.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>-1.22</td>
<td>*</td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-1.05</td>
<td></td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>-2.88</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>+0.17</td>
<td></td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>-1.65</td>
<td>¶</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>-1.82</td>
<td>*</td>
</tr>
</tbody>
</table>

* Significant at p value of 0.05
¶ Significant at p value of 0.01
§ Significant at p value of 0.001

Table 3.13. The mean difference in mm of the non-lethal ice distance across the width between each experiment at 100% gas flow rate using the Least Significant Difference (LSD). The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
2. The side of the iceball across the depth.

The means and standard deviations of the non-lethal zone thickness across the depth were measured (table 3.14). There were no significant differences between the thicknesses of the non-lethal ice across the depth in experiment 1-3 when reducing the freezing rate. Comparison was not made between the 100% and 20% experiment 4 iceballs, as the iceball at 20% gas flow did not have lethal zone.

<table>
<thead>
<tr>
<th>Experiments</th>
<th>100% gas flow</th>
<th>20% gas flow</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.07 (0.87)</td>
<td>9.49 (0.71)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10.28 (1.28)</td>
<td>10.08 (0.42)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10.74 (0.43)</td>
<td>10.35 (0.21)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7.01 (0.44)</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.14. Means in mm (standard deviation) of the thickness of the non-lethal ice zone on the side of the iceball across the depth at 100% and 20% gas flow rates. Each experiment was performed three times. Comparisons were made between the means of the 100% and the 20% thicknesses for each experiment using independent samples t-test. The differences were not significant. Iceball 4 at 20% freeze rate did not have lethal ice.
Comparisons between the 100% gas flow iceballs suggested significant differences [one way ANOVA (p=0.002)] which, according to table 3.15, was due to shorter thickness of iceball 4 only.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-0.67</td>
<td></td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>+3.06</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>-0.46</td>
<td></td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>+3.27</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>+3.73</td>
<td>§</td>
</tr>
</tbody>
</table>

†† Significant at p value of 0.01
§ Significant at p value of 0.001

Table 3.15. The mean difference in mm of the non-lethal ice distance across the depth between each experiment at 100% gas flow rate using the Least Significant Difference (LSD). The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
3. **The top of the iceball**

The means and standard deviations of the non-lethal zone thickness from the top of the iceball were measured (table 3.16). Changing the freezing rate has not shown to cause significant differences between the iceballs in experiment 1-3. Experiment 4 iceball did not have lethal zones when frozen at 20% gas flow rate; hence, comparison was not made with 100% iceball.

<table>
<thead>
<tr>
<th>Experiments</th>
<th>100% gas flow</th>
<th>20% gas flow</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.83 (0.96)</td>
<td>7.41 (1.75)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7.26 (1.2)</td>
<td>9.76 (1.41)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>13.34 (1.83)</td>
<td>12.06 (0.88)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11.34 (0.65)</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

n/a: not applicable

Table 3.16. Means in mm (standard deviation) of the thickness of the non-lethal ice zone from the top of the iceball at 100% and 20% gas flow rates. Each experiment was performed three times. Comparisons were made between the means of the 100% and the 20% thicknesses for each experiment using independent samples t-test. The differences were not significant. Iceball 4 at 20% freeze rate did not have lethal ice.
The one way ANOVA comparing the means at 100% gas flow showed that there was a significant difference between the iceballs \((p<=0.001)\). The post hoc test (table 3.17) concluded that the difference was not significant between iceball 1 and 2, both of which had significantly shorter non-lethal ice than iceball 3 and 4. Although Iceball 4 had longer non-lethal than iceball 3, it was not statistically significant.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>-0.42</td>
<td></td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-6.5</td>
<td>$\S$</td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>-4.5</td>
<td>$\Dagger$</td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>-6.08</td>
<td>$\S$</td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>-4.08</td>
<td>$\Dagger$</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>+2</td>
<td></td>
</tr>
</tbody>
</table>

$\S$ Significant at \(p\) value of 0.01

$\Dagger$ Significant at \(p\) value of 0.001

Table 3.17. The mean difference in mm of the non-lethal ice distance from the top of the iceball between each experiment at 100% gas flow rate using the Least Significant Difference (LSD). The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
3.1.7 The Length of the Lethal Iceball below the Tips of the Cryoprobes

The means and standard deviations of length of the lethal iceball below the tips of the cryoprobes were measured (table 3.18). No significant differences were observed between the 100% and the 20% gas flow experiments. No comparison was made between experiment 4 iceballs due to the lack of lethal ice when frozen at 20% flow rate.

<table>
<thead>
<tr>
<th>Experiments</th>
<th>100% gas flow</th>
<th>20% gas flow</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.72 (1.44)</td>
<td>0.21 (0.89)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.6 (0.28)</td>
<td>1.58 (1.37)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.53 (0.08)</td>
<td>3.15 (0.31)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.14 (0.31)</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.18. Means in mm (standard deviation) of the length of the lethal ice below the cryoprobes tips at 100% and 20% gas flow rates. Each experiment was performed three times. Comparisons were made between the means of the 100% and the 20% thicknesses for each experiment using independent samples t-test. The differences were not significant. Iceball 4 at 20% freeze rate did not have lethal ice.
The differences between the means of the four iceballs at 100% gas flow (table 3.19) were significant [one way ANOVA (p= 0.012)]. This was exclusively due to the significantly shorter lethal ice of experiment 1. There were no significant differences between the other iceballs.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>-1.88</td>
<td>*</td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-2.81</td>
<td>‖</td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>-2.42</td>
<td>‖</td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>-0.92</td>
<td></td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>-0.54</td>
<td></td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>+0.38</td>
<td></td>
</tr>
</tbody>
</table>

* Significant at p value of 0.05
‖ Significant at p value of 0.01

Table 3.19. The mean difference in mm of the lethal ice lengths below the tips of the cryoprobes between each experiment at 100% gas flow rate using the Least Significant Difference (LSD). The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
3.1.8 The Cooling Rate

Thermal records in the centre of the iceball at the maximum dimension levels at 0, 2, 5, 7 and 10 minutes of freezing were plotted (figure 3.9). The means and standard deviation of the 0-5 minutes cooling rates (table 3.20) were calculated as described in chapter 2 (2.1.17). By reducing the freezing rate to 20%, the 0-5 minutes cooling rate declined significantly in all the experiments.

<table>
<thead>
<tr>
<th>Experiments</th>
<th>0-5 min cooling rate (°C/min)</th>
<th>100% gas flow</th>
<th>20% gas flow</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.54 (0.71)</td>
<td>16.2 (1.49)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22.56 (1.55)</td>
<td>18.8 (1.17)</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20.64 (0.8)</td>
<td>16.28 (1.34)</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>19.7 (0.58)</td>
<td>8.03 (0.29)</td>
<td>§</td>
<td></td>
</tr>
</tbody>
</table>

* Significant at p value of 0.05
§ Significant at p value of 0.001

Table 3.20. Means (standard deviation) of the 0-5 minutes cooling rates in the centre of the iceball at the maximum dimension levels at 100% and 20% gas flow rates. Each experiment was performed three times. Comparisons were made between the means of the 100% and the 20% thicknesses for each experiment using independent samples t-test.
Figure 3.9. Temperature measurements in the centre of the iceball at the maximum dimensions horizontal level at 100% and 20% gas flow rate. Each experiment was repeated three times.
One way ANOVA suggested that the differences between the cooling rates of the four iceballs at 100% gas flow were significant \((p=0.004)\). Further analysis using the LSD test (table 3.21) showed that iceball 2 had the fastest cooling, while iceball 1 had the lowest cooling rate, although it did not differ significantly from iceball 4.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>-4.02</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>-2.1</td>
<td>*</td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>-1.16</td>
<td></td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>+1.92</td>
<td></td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>+2.86</td>
<td>¶</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>+0.93</td>
<td></td>
</tr>
</tbody>
</table>

* Significant at \(p\) value of 0.05
¶ Significant at \(p\) value of 0.01
§ Significant at \(p\) value of 0.001

Table 3.21. The mean difference of the 0-5 minute cooling rates in degree C/min between each experiment at 100% gas flow rate using the Least Significant Difference (LSD). The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
3.1.9 The Ablative Ratio

This ratio was estimated by dividing the kill zone by the total iceball volume.

Comparisons of the means of the ratios between the 100% and the 20% gas flow using the independent samples t-test were made (table 3.22). This showed that the ablative ratios decreased significantly by reducing the freezing rate for all the iceballs except in experiment 2, where the changes were marginal.

<table>
<thead>
<tr>
<th>Exp.</th>
<th>100% gas flow</th>
<th>20% gas flow</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total ice volume (cc)</td>
<td>Kill zone volume (cc)</td>
<td>Ablative ratio (%)</td>
</tr>
<tr>
<td>1</td>
<td>57.68 (3.91)</td>
<td>16.4 (0.92)</td>
<td>28.45 (0.37)</td>
</tr>
<tr>
<td>2</td>
<td>60.92 (3.56)</td>
<td>17.02 (1.22)</td>
<td>27.93 (0.42)</td>
</tr>
<tr>
<td>3</td>
<td>74.12 (1.55)</td>
<td>17.61 (1.13)</td>
<td>23.75 (1.2)</td>
</tr>
<tr>
<td>4</td>
<td>49.59 (2.11)</td>
<td>11.33 (1.04)</td>
<td>22.81 (1.11)</td>
</tr>
</tbody>
</table>

§ Significant at p value of 0.001

Table 3.22. Means (standard deviation) of the total iceball and the kill zone volumes. The ablative ratio is the ratio of the kill zone / total iceball volumes. Each experiment was performed three times. Comparisons were made between the ablative ratios of the 100% and 20% for each experiment using independent samples t-test.
The differences between the 100% iceballs ablative ratios were significant [one way ANOVA (p<0.001)]. Post hoc test (LSD) between the four groups (table 3.23) concluded that there were insignificant differences between iceballs 1 and 2, both of which had significantly larger ablative ratio than 3 and 4. Iceball 4 had smaller ablative ratio than iceball 3, but was not statistically significant.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (mm)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1 vs. 2</td>
<td>+0.52</td>
<td></td>
</tr>
<tr>
<td>Experiment 1 vs. 3</td>
<td>+4.7</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 1 vs. 4</td>
<td>+5.64</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 2 vs. 3</td>
<td>+4.17</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 2 vs. 4</td>
<td>+5.11</td>
<td>§</td>
</tr>
<tr>
<td>Experiment 3 vs. 4</td>
<td>+0.94</td>
<td></td>
</tr>
</tbody>
</table>

§ Significant at p value of 0.001

Table 3.23. The mean difference of the ablative ratio between each experiment at 100% gas flow rate using the Least Significant Difference (LSD). The negative sign (-) indicates smaller while the positive sign (+) indicates larger.
3.1.10 The Coefficient of Variance (CV)

Table 3.24 summarises the CV for the data within each experiment and between all the experiments. The CV for the data between the experiments has always been larger than the CV within experiments. The CV for the lethal ice width, depth and length between the experiments at 20% gas flow rate were significantly large due to the lack of lethal ice in experiment 4.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>100% gas flow</th>
<th>20% gas flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Between</td>
<td>Within</td>
</tr>
<tr>
<td></td>
<td>experiments</td>
<td>experiments</td>
</tr>
<tr>
<td>Iceball width</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ice</td>
<td>0.84%</td>
<td>0.04%</td>
</tr>
<tr>
<td>Lethal ice</td>
<td>0.37%</td>
<td>0.05%</td>
</tr>
<tr>
<td>Iceball depth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ice</td>
<td>0.69%</td>
<td>0.09%</td>
</tr>
<tr>
<td>Lethal ice</td>
<td>0.02%</td>
<td>0.04%</td>
</tr>
<tr>
<td>Iceball length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ice</td>
<td>2.79%</td>
<td>0.01%</td>
</tr>
<tr>
<td>Lethal ice</td>
<td>5.13%</td>
<td>0.01%</td>
</tr>
<tr>
<td>Probe-lethal zone edge distance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ice</td>
<td>5.87%</td>
<td>0.04%</td>
</tr>
<tr>
<td>Lethal ice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-lethal ice thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Across width</td>
<td>0.55%</td>
<td>0.04%</td>
</tr>
<tr>
<td>Across depth</td>
<td>0.91%</td>
<td>0.07%</td>
</tr>
<tr>
<td>At the top</td>
<td>3.11%</td>
<td>0.16%</td>
</tr>
<tr>
<td>Lethal ice below tip of probes</td>
<td>1.86%</td>
<td>0.26%</td>
</tr>
<tr>
<td>0-5 cooling rate</td>
<td>0.43%</td>
<td>0.04%</td>
</tr>
<tr>
<td>Ablative ratio</td>
<td>0.96%</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

* CV was measured between experiments 1 to 3 due to lack of lethal ice in experiment 4.

Table 3.24 Coefficient of variance (%) for the data within each experiment and between the experiments for all the parameters at 100% and 20% gas flow rates. The smaller the CV value, the less dispersed is the data around the mean.
3.2 Health Related Quality of Life of Salvage Cryotherapy on Patients with Localised Prostate Cancer Recurrence after Radiation Failure

A total of 47 patients have been recruited to date, 12 of whom have not received androgen deprivation, while the remaining 35 patients received androgen deprivation from before cryotherapy and during follow-up. The recruitment is ongoing and the results are preliminary.

3.2.1 Cancer Specific Quality of Life (EORTC QLQ-C30)

The mean baseline and up to 12 months follow-up scores are summarised in table 3.25. The scores suggest that the majority of the domains have deteriorated temporarily within 6 weeks to 3 months after cryotherapy. This included: global health, physical function, role function, cognitive function, social function, fatigue, nausea and vomiting, pain, loss of appetite, diarrhoea and financial problems. Emotional function, social function and insomnia have been noted to improve after 9 months. All the mean score changes do not exceed 10% from the baseline score, hence; represent only "a little change" in quality of life measured as assessed by Osoba et al (1998). The trend of changes in the global health domain score, which is illustrated in figure 3.10, shows a "little" deterioration and seems to return to pre-treatment level at 9 months.
Figure 3.10. Box and whisker plot of the global health domain of the QLQ C-30 before and after cryotherapy for the whole group. The higher the score represents the better outcome.
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3.2.2 Prostate Cancer Specific Quality of Life (PR-25)

The preliminary results of the PR25 is summarised in table 3.26.

EORTC PR25 – Urinary Problems

The trend of changes in the mean scores of the urinary problems domain is illustrated in figure 3.11. The clinical significance of the changes in the mean scores has not been assessed before, but likely to be similar to that of the QLQ- C30 questionnaire due to the similarity in the structure of the questionnaires. The clinical significance for the changes in the score of the QLQ- C30 questionnaire was assessed by Osoba et al (1998)(see page 123). The urinary problems worsen "moderately" at 6 weeks follow-up, but then gradually improved to become "clinically insignificant" at 9 months.

Figure 3.11. Box and whisker plot of the urinary problems domain of the EORTC PR25 before and after cryotherapy for the whole group. The higher the score represents the worse outcome. Patient no. 18 had consistently the worst score (pre- and post-cryotherapy).
EORTC PR25 – Urinary Incontinence Aid Bother and Urinary Incontinence

Urinary Incontinence Aid Bother (question 8) is relevant to patients with incontinence, therefore, closely related to question 6 of the PR25 questionnaire which assesses urinary incontinence. Question 6 is an important outcome measure, and also included in the Urinary Problems domain described (table 3.26). We have reported the raw scores of both question 6 (figure 3.12) and question 8 (figure 3.13).

The trends in incontinence score (figure 3.12) suggested that incontinence increased after salvage cryotherapy, the majority were regarded as "A little". Urinary aid bother has worsened following salvage cryosurgery. However, surprisingly, the percentage of patients who responded to the urinary aid bother question, i.e. considering themselves incontinent, has not changed after cryotherapy (figure 3.13 and table 3.26).
Figure 3.12. Urinary incontinence (question 6 of PR25) at baseline and post cryotherapy.

Figure 3.13. Urinary incontinence aid bother (question 8 of PR25) at baseline and post cryotherapy.
EORTC PR25 – Bowel Problems

This domain assesses abdominal bloating, faecal incontinence, pre-rectal bleeding and limitation due to bowel symptoms. The trend of this domain scores were heterogeneous and seemed not to change with time (figure 3.14 and table 3.26).

Figure 3.14. Box and whisker plot of the bowel problems domain of the EORTC PR25 before and after cryotherapy for the whole group. The higher the score represents the worse outcome.
EORTC PR25 – Treatment Symptoms

This domain assesses a variety of symptoms including hot flushes, nipple and breast soreness, ankle swelling, weight changes and loss of masculinity.

The scales data, which is summarised in table 3.26 and figure 3.15, showed no changes of clinical significance after cryosurgery. There were differences observed at baseline between hormone naïve and patients received androgen deprivation, in favour of the former group (figure 3.16). However, from 9 months follow-up, the two groups became comparable. This should be interpreted with caution as the number of patients in each group was uneven.

Figure 3.15. Box and whisker plot of the treatment symptoms domain of the EORTC PR25 before and after cryotherapy for the whole group. The higher the score represents the worse outcome.
Figure 3.16. Box and whisker plot of the treatment symptoms domain of the EORTC PR25 before and after cryotherapy by treatment group. The higher the score represents the worse outcome.
EORTC PR25 – Sexual Activity and Sexual Function

The scaled scores of sexual activity are presented in figure 3.17 and table 3.26. This showed no overall clinically significant changes in the sexual activity after cryotherapy. Comparing hormone naïve and hormone treated patients, there no significant difference at the baseline trend (table 3.26 and figure 3.18). The only clinically significant changes after cryosurgery was observed in the hormone naïve group at 6 weeks which showed “a little” changes in sexual activity. However, these scores should be interpreted with caution due to the small number and disparity in the number of patients between the two groups.

The sexual function domain questions are relevant to sexually active patients, and only small number answered them (table 3.26 and figure 3.19). The overall scores were heterogeneous, but there was a trend of higher sexual function in the hormone naïve group (table 3.26).
Figure 3.17. Box and whisker plot of the sexual activity domain of the EORTC PR25 before and after cryotherapy for the whole group. The higher the score represents the better outcome.
Figure 3.18. Box and whisker plot of the sexual activity domain of the EORTC PR25 before and after cryotherapy by treatment group. The higher the score represents the better outcome.
Figure 3.19. Box and whisker plot of the sexual function domain of the EORTC PR25 before and after cryotherapy for the sexually active patients only. The higher the score represents the better outcome.
<table>
<thead>
<tr>
<th></th>
<th>Urinary Problems</th>
<th>Urinary Incontinence Aid Bother*</th>
<th>Bowel Problems</th>
<th>Treatment Symptoms</th>
<th>Sexual Activity</th>
<th>Sexual Function†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline n= 47</td>
<td>20.9 (16.2)</td>
<td>12.5 (24.)</td>
<td>6.9 (8.5)</td>
<td>11.7 (10.0)</td>
<td>25.9 (30.5)</td>
<td>13.0 (11.8)</td>
</tr>
<tr>
<td>6 Weeks n=41</td>
<td>35.8 (21.1)</td>
<td>38.9 (25.1)</td>
<td>8.7 (14.4)</td>
<td>12.6 (11.7)</td>
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Table 3.26. EORTC PR25 mean scores out of 100 (standard deviation). For urinary problems, urinary incontinence aid bother, bowel problems and treatment symptoms domains: the higher the score represents the worse the outcome. While for sexual activity and function: the higher the score represents the better the outcomes.

* This question is relevant to patients with incontinence only. The number (n) of the patients responded to this question is shown separately in each cell.

† This question is relevant to sexually active patients. The number (n) of the patients responded to this question is shown separately in each cell.
3.2.3 The International Index of Erectile Function (IIEF-5)

The IIEF-5 scores were compatible with the sexual activity domain scores of the EORTC PR-25. The mean scores at baseline, 6 months and 12 months are demonstrated in figures 3.20, 3.21 and table 3.27. The trend showed that the only 6 patients (14%) were considered potent at baseline (IIEF-5 score ≥12). Only one patient remained potent after cryotherapy. There was a trend towards higher IIEF score at baseline in the hormone naïve compared to the hormone treated group as demonstrated in figure 3.22 and table 3.27; however, no differences were noted at follow-up.

![Box and whisker plot of the International Index of Erectile Function-5 (IIEF-5) before and after cryotherapy for the whole group. The higher the score represents the better outcome.](image)

Figure 3.20. Box and whisker plot of the International Index of Erectile Function-5 (IIEF-5) before and after cryotherapy for the whole group. The higher the score represents the better outcome.
Figure 3.21. IIEF-5 at baseline and post cryotherapy for the whole group.

Figure 3.22. Box and whisker plot of the IIEF-5 score before and after cryotherapy by treatment group. The higher the score represents the better outcome.
3.2.4 International Prostate Symptom Score (IPSS)

The scores are presented in figure 3.23 and table 3.27. The only clinically significant (=> 4 points) worsening occurred at 6 weeks follow-up. This is in agreement with urinary problems domain scores of the EORTC PR-25 described earlier (3.2.2). The scores of quality of life due to urinary symptoms are presented in table 3.26 and figure 3.24 which suggested a temporary deterioration at 6 weeks follow-up. From 3 months after cryosurgery, the scores became parallel to the baseline score.

![Figure 3.23. Box and whisker plot of the International Prostate Symptom Score before and after cryotherapy for the whole group. The higher the score represents the better outcome.](image)

Figure 3.23. Box and whisker plot of the International Prostate Symptom Score before and after cryotherapy for the whole group. The higher the score represents the better outcome.
3.2.5 Erectile Dysfunction Effect on Quality of Life (ED-EQoL)

This question is relevant only to patients considering themselves to have ED. The baseline, 6 months and 12 months means scores are presented in figures 3.25 and 3.26, and table 3.27. At baseline, 63% of the patients considered that their erectile dysfunction have mild effect on QoL. This became worse at 6 months with 48% of the patients considering that their erectile dysfunction to have moderate to severe effect on QoL; however it improved back to baseline level by 12 months.
Figure 3.25. Box and whisker plot of the Erectile Dysfunction Effect on Quality of Life (ED-EQoL) before and after cryotherapy for the whole group. The higher the score represents the more severe effect of ED on QoL.

Figure 3.26. ED-EQoL at baseline and post cryotherapy for the whole group.
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<th>QoL</th>
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<td>9.5 (6.9)</td>
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<tr>
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<td>-</td>
<td>11.0 (8.1)</td>
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Table 3.27. International Index of Erectile Function -5 (IIEF-5), Erectile Dysfunction Effect on Quality of Life (ED-EQoL), International Prostate Symptoms Score mean and IPSS Quality of Life (QoL) (standard deviation). IIEF-5 score 1-25, with higher score represents better outcome. The QD-EQoL score 0 to 60, with score <15 considered mild, 15-29 moderate and ≥ 30 severe effect of ED on QoL. The IPSS score 0-35, with higher the score represents worse outcome. IPSS QoL score 0-6, the higher the score corresponds to worse outcome.

* This question is relevant for men who have ED only. The number of the patients who responded is displayed in each cell.
3.2.6 Taunton Psychosocial Morbidity Questionnaire (TPSM)

The mean scores of TPSM for patients with partners and their partners are presented in table 3.28. For the patients, the scales of the treatment and general cancer distress domains showed a gradual improvement post cryosurgery. Distress from pain, urinary symptoms, physical and social limitations showed a temporary worsening after cryosurgery for 3-6 months before returning to pre-cryosurgery scores. Worry for sexual function has not changed after cryosurgery.

The severity of worry due to treatment, pain, social limitation and general cancer distress were more problematic in the partners than the patients at baseline. Partners had less distress from sexual function at baseline compared to the patients. The magnitude and timescale of the scores changes of the partners were similar to those of the patients themselves.
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Table 3.28. Taunton Psychosocial Morbidity Questionnaire (TPSM) mean scores (standard deviation) for patients with partners and their partners. The higher the score the more is the distress or worry.
3.3 The Impact of Iceball Temperature on HQoL following Salvage Cryotherapy

Comparisons were made between the lowest temperatures at the apex of the prostate, the external urethral sphincter and the Denonvillier’s fascia during salvage cryosurgery and the 6weeks -baseline differences in the HQoL domains/items scores. To date, temperature data were available for 14 patients (table 3.29). The table also shows that some patients did not in fact get adequate cryotherapy as the temperature at the apical region of the prostate failed to reach subzero.

There was no significant correlation between the lowest temperature at the apex of the prostate, the external urethral sphincter or the Denonvillier’s fascia and the impact on the HQoL domains/ items at 6 weeks (table 3.30).
Table 3.29. Demographics and the lowest temperature measured at the apex of the prostate, the external urethral sphincter and the Denonvillier's fascia during cryosurgery in degrees centigrade, and the 6 weeks -baseline differences between Global Health (GH) domain of the EORTC QLQ-C30 questionnaire, the urinary problems (UP) domain and urinary incontinence (UI) item of the EORTC PR25 questionnaire, the IPSS and the quality of life question (QoL) of the IPSS for 14 patients.

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<th>GH score differences</th>
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<td>-1</td>
<td>-6</td>
<td>-1</td>
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<td>20.2</td>
<td>7.9</td>
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<td>-16.67</td>
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Table 3.30. P-value for the correlation between the lowest temperatures measured at the apex of the prostate, the external urethral sphincter and the Denonvillier's fascia and the 6 weeks -baseline differences between Global Health (GH) domain of the EORTC QLQ-C30 questionnaire, the urinary problems (UP) domain and urinary incontinence (UI) item of the EORTC PR25 questionnaire, the IPSS and quality of life question (QoL) of the IPSS.

<table>
<thead>
<tr>
<th></th>
<th>GH score differences</th>
<th>UP score differences</th>
<th>UI score differences</th>
<th>IPSS score differences</th>
<th>QoL question of the IPSS score differences</th>
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<tbody>
<tr>
<td>Lowest temperature at the apex of the prostate</td>
<td>0.068</td>
<td>0.409</td>
<td>0.79</td>
<td>0.739</td>
<td>0.825</td>
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<td>Lowest temperature at the external urethral sphincter</td>
<td>0.716</td>
<td>0.799</td>
<td>0.543</td>
<td>0.971</td>
<td>0.63</td>
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<tr>
<td>Lowest temperature at the Denonvillier's fascia</td>
<td>0.352</td>
<td>0.435</td>
<td>0.864</td>
<td>0.253</td>
<td>0.094</td>
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Chapter 4
Discussions and Conclusions
4.1 *In-vitro* Assessment of Three Different Cryoprobes Used for Prostate Cryosurgery

In our study, we have carried out four *in vitro* experiments to analyse and compare the dimensions of the lethal, non lethal and total iceballs, ablative ratio and the cooling rate of iceballs produced by three different cryoprobes. We have also assessed the effect of reducing the cooling rate on these parameters by decreasing the rate of the freezing gas flow to 20%. The probes were tested in configurations similar to the anterior probes arrangement during clinical situations. We assessed the 2.4mm and the 3.4mm diameter probes, each in two probe model placed 18mm apart. This was repeated but with reducing the distance between the probes to 15mm. We did not investigate the effect of increasing the distance between the probes. The fourth experiment was carried out on the 1.47mm diameter probes. We used 8 probes divided into two rows kept at 10mm apart. To date, there is no published data on similar experiments. We did not assess the effect of changing the distances between the 3.4mm and 1.47mm probes.

From our study, it is not possible to suggest a complete protocol for prostate cryosurgery as we did not examine the posterior cryoprobes; in addition, prostate size and shape varies widely amongst patients.

The maximum width mean (SD) of lethal zone of the 2.4mm probes 18mm apart at 100% gas flow rate was 37.23mm (0.62). This appeared to be adequate to cover the width of the majority of anterior part of the prostate of the 40 patients, which measured 31.23mm (SD 4.43), treated at the Royal
Surrey county Hospital. The lethal ice zone width has decreased by approximately 3 mm when the distance between the 2 probes was reduced to 15 mm. This indicates that the thickness of the lethal ice outside the probes did not change, and this was demonstrated when we measured the lethal ice thickness. However, we could not explain the lack of comparable reduction in the total iceball width. The 3.4 mm probe did not add any significant lethal ice width. The lethal iceball width of the 1.47 mm cryoneedles at 100% gas flow rate was the largest, measuring 39.38 mm (SD 2.36). In this experiment, the cryoneedles were arranged in 2 rows of 4 needles each, and the distance between 2 adjacent needles was 10 mm. Therefore, the length of each row of cryoneedles equalled 30 mm. Hence, we concluded that there is little lethal ice created outside the cryoneedles, and this will be discussed later in the chapter.

No differences were observed between the lethal ice depths of the four iceballs when frozen at 100% gas flow rate. We expected to witness a significant increase in the lethal ice depth when we reduced the distance between the 2.4 mm cryoprobes by 3 mm in experiment 2; however, the increase was not statistically significant.

The means of the lethal ice depths ranged between 23.53 – 24.26 mm. This is adequate to cover the anterior prostate depths of our 40 patients, which had a mean measurement of 17.18 mm.

Measuring the total ice depths at 100% gas flow, we noticed that they were statistically comparable, except in the 1.47 mm cryoneedles, which was
significantly shorter. This indicated that for a similar lethal ice depth, the
1.47mm cryoneedles had less non-lethal ice. This was confirmed when we
compared the non-lethal ice thickness across the depth, which will be
discussed later.

Unlike the depth, the length of the lethal ice zone increased significantly when
the distance between the two 2.4mm probes was reduced by approximately
3mm (from a mean of 35.71mm to 39.3mm). The mean (SD) length of the 40
anterior prostates lengths was 35.2 (5.8). We concluded that when placing
2.4mm probes 18mm and 15mm apart, the lethal ice covered the length of the
prostate in approximately half and less than 75% of our patients respectively.

The most significant difference was noted in the 1.47mm cryoneedles, which
produced significantly short lethal ice [mean (SD) of 22.62mm (0.48)]. All of
the 40 prostate we measured had prostate length of more than 23mm;
therefore, this iceball is inadequate to freeze the apical region (see figure 2.4)
of our patients' prostates. In clinical situations, when it is felt the prostate
gland is longer than the iceball, a "pull back" technique is applied as
discussed in chapter 1 (1.3.4.7). In this technique, the freezing probes are
pulled back by few millimetres after the first freeze, ensuring iceball coverage
of the apical region in the second freeze. However, the prostate length at
which the "pull back" technique is applied varies amongst urologists.

Lam et al (2004) and Fahmy and Bissada (2003) suggested to perform "pull
back" when the prostate length is greater than 27mm using the Seednet™
cryoneedles. Zisman et al (2001) recommended similar prostate length,
However, they considered the lethal ice to be ≤ -20° C instead of ≤ -40° C. Witzch et al. (2005) performed cryosurgery on 80 patients using between 9 – 17 cryoneedles (Seednet™). They performed “pull back” for prostates longer than 35mm.

Lee et al (1999) did not specify the length of the prostate; they pulled back the posterior probes by 1cm if they believed that apical kill was not achieved using the 3.4mm Cryocare™ probes. Rewcastle et al (1998) have developed a computer model to predict thermal distribution around 3.4mm cryoprobe. From the 10 minute isotherm graph, the maximum lethal ice length (≤-40°C) could be estimated between 26-27mm only. However, the model was based on single probe using the thermal properties of water. To date, there are no published reports on the 2.4mm Cryocare™ probes.

The distance between the centre of the freezing probe and the -40° isotherm reflects the maximum distance at which the freezing probes should be placed away from the prostatic capsule during the procedure. This distance was almost equal statistically between the 3 iceballs of Cryocare™ probes when frozen at 100% gas flow rate with a mean distance ranging between 10.81 – 11.74mm. However, for the Seednet™ cryoneedles, the distance between the freezing probe and the-40° isotherm was only 3.28mm (SD 0.96).

Larson et al (2000) performed prostate cryosurgery on 6 patients scheduled for radical prostatectomy using a single 3.4mm cryoprobe to determine the critical lethal temperature and its location within the iceball. They observed
that temperatures of $\leq -41.4^\circ C$ were required to cause prostatic necrosis after two freeze cycles of 7.5 to 10 minutes of freezing on full gas flow. Using thermosensors, they concluded that the radius of the zone of necrosis was 6mm. When using single freeze, temperatures of $\leq -61.7^\circ C$ were required to produce necrosis, which was located at 4.1 mm radius. These measurements are less than our experiment. One hypothesis to explain this dissimilarity is the difference in the number of probes used (one vs. two) and the effect of prostate perfusion in vivo which will discussed later in the chapter. Rewcastle and colleague's (1998) computer model (based on water thermal properties) isotherm graphs estimated the radius of the $-40^\circ C$ isotherm to be approximately 5-6mm using a single 3.4mm probe after 10 minutes of freezing. In another study, the same group (Rewcastle et al, 1999a) have estimated that the $-40^\circ C$ isotherm is located 8.6 mm from a single 3.4 cryoprobe surface based on theoretical thermal gradient about an infinitely long cryoprobe with surface temperature of $-186^\circ C$.

Clinically, it has been recommended that 3.4mm cryoprobes to be placed within 10mm of the prostate margin (Donnelly and Saliken, 2002; Lee et al, 1999). Zisman et al (2001) believed that the $-20^\circ C$ isotherm is located at a radius of 10mm of a single cryoneedle iceball after 10 minutes of freezing. They, together with Fahmy and Bissada (2003), have suggested to place the posterior group of the Seednet™ cryoneedles 5-7mm from the prostatic capsule.
Although the non-lethal ice zone does not eradicate prostate cancer cells effectively, it can cause tissue damage (Larson et al, 2000) to the rectum and urethra. Therefore, the thinner the non-lethal ice thickness, the less risk of collateral damage. Larson et al (2000) have observed that the critical temperature for tissue damage ranged between -38.5°C to -20.7°C (mean -29.6°C) after a double freezing cycle. This was located 1.5 mm outside the critical lethal temperature of -41.4°C. We have measured and compared the thickness of non-lethal ice (from the 0°C to -40°C) in three places as an indicator for the risk of collateral tissue damage.

The thickness of the non-lethal iceball at 100% gas flow was measured and compared between the iceballs. The cryoneedles' iceball had the highest non-lethal ice thickness when measured across the width of the iceball, but the least non-lethal ice thickness across the depth. The differences in the non-lethal ice across the width may have little clinical implications as the lethal ice is normally allowed to encompass the neurovascular bundles during freezing (see 1.2.2.7); hence the incidence of impotence is high after cryosurgery. Across the depth, the prostate is bounded by the pubic bone anteriorly and the Denonvillier's fascia posteriorly. Cases of osteitis pubis due to iceball extension have been reported (Connolly et al, 1996), while the rate of rectourethral fistula, which results from iceball extension to the rectum during salvage cryosurgery, ranges between 0-3.4%. Therefore, we may conclude that the Seednet™ cryoneedles may have less risk of osteitis and rectourethral fistula. However, this should be interpreted with caution particularly, the risk of rectal damage because – as explained in chapter 1 (1.2.2.7) - four
probes are commonly used in the posterior group rather than two (as used in our experiments) in the Cryocare™ system, therefore, comparisons may not be accurate.

The thickness of the non-lethal ice at the top was largest in the 3.4mm cryoprobe and the 1.47mm cryoneedles measuring 13.34 mm (SD 1.83) and 11.34 mm (SD 0.65) respectively compared to the 2.4mm probe's iceballs which was approximately half these thicknesses. The clinical impact is that the top of the iceball corresponds to the apical region of the prostate which is close to the external urethral sphincter; therefore, we concluded that the risk of sphincter damage and incontinence is less when using the 2.4mm cryoprobess.

Lam and colleagues (2004) suggested to extend the iceball 2 to 4mm beyond the apex of the prostate when using the 1.47mm cryoneedles. If this indicates the distance between the edge of the iceball and the -40°C isotherm, then it is significantly shorter than our experimental measurements.

Rewcastle and colleagues' (1998) computer model’s graph at 10 minutes predicted that the thickness of the 0°C to -40°C zone is approximately 9-10mm at the top of an iceball created by a single 3.4mm cryoprobe. This is less than our experiments perhaps due to the fact that Rewcastle’s simulation was based on a single probe and using water thermal properties. However, using the same computer model, the non-lethal zone thickness across the side of a single 3.4mm cryoprobe's iceball was comparable to our experimental measurements across the width (measuring between 7-8mm).
Theodorescu (2004) showed, that the thickness of the 0°C to -40°C zone is 4mm for an iceball created by 3 Seednet™ cryoneedles arranged in a triangular fashion.

The thickness of the lethal ice below the tips of the cryoprobe indicate how close to place the cryoprobe from the base of the prostate (see figure 2.4). We have concluded that there is very little lethal ice below the cryoprobe tips in experiment 1 (2.4mm probe, 18mm apart) regardless of the gas flow rate. In fact, on two occasions, no lethal ice could be measured beyond the cryoprobe tips. Therefore, in clinical situations, these probes should be placed deep in until they reach the base of the prostate.

In experiment 2, when we reduced the distance between the probes to 15mm, there was approximately 2mm more lethal ice below the cryoprobe tips. This was expected as we have previously concluded that after reducing the distance between the cryoprobe tips, the entire length of the lethal ice increased by approximately 4mm. There was approximately 3mm lethal ice below the 3.4mm and the 1.47mm probes tips at 100 gas flow rates.

We have not measured the thickness of non-lethal ice below the cryoprobe tips as no bladder damage has been previously reported. We hypothesised that this could be from the large heat sink effect of the urinary bladder which would be full of urine that is maintained warm by the urethral warming catheter during the procedure as described in chapter 1 (1.2.2.7). Zippe (1996) suggested that the iceball does not extend 5mm below the tip of liquid
nitrogen probes due to the heat sink effect of the bladder. Such effect on the argon-based probes has not been assessed previously or during our experiments.

The computer model graph of Rewcastle et al (1998) suggested that approximately 10mm of ice is present below the tip of a single 3.4mm probe, 3mm of which is lethal.

Clinically, Lee et al (1999) advocated that the tips of the two posterio-lateral probes should extend through the posterior capsule using the 3.4mm Cryocare™ probe. Zisman et al (2001) explained their operative technique was based on the fact that the 1.47mm cryoneedles produces ice 5mm beyond the tip.

We have assessed the effect of reducing the argon gas flow rate from 100% to 20% on all the measurements. The most significant difference was observed in the 1.47mm cryoneedles as the iceball failed to produce any lethal ice when frozen at 20%. Lethal iceball dimensions have also reduced in the first three experiments, more pronouncedly in experiment 3. Therefore, we can conclude that freezing using 20% gas flow is not as efficient as 100% gas flow rate particularly when using the Seednet™ system. The effect of reducing the gas flow rate on the non-lethal ice thickness and lethal ice thickness below cryoprobe tips was minimal.

We have measured and compared the 0-5 minutes cooling rates in the centre of the iceball at the maximum dimension level of the 4 experiments at 100% and 20% gas flow rates. Although, statistically, experiment two's iceball had
the fastest cooling rate, the differences were too small and there is no
evidence to suggest any clinical significance. The most significant difference
was noted between the 100% and 20% gas flow rates in experiment 4.
Tatsutani et al (1996) have experimented on a prostate adenocarcinoma cell
line (ND-1). These cells were frozen at 1, 5 and 25 °C/min cooling rates. They
concluded that there was a little difference in terms of cell destruction
between the 1 and 5°C/min cooling rates, while, the 25°C/min cooling rate
was significantly more lethal. Bischof et al (1997) carried out similar
experiments on the AT-1 rat prostate tumour at cellular and tissue level. They
concluded that there were little differences (in terms of cell viability) between
different cooling rates (ranging from 5 to 50 °C/min) when the cells or tissue
were frozen to -40°C.

Although measurement of the ablative ratios was based on assumptions as
described before in chapter 2 (2.1.18), it has value when comparing the
iceballs. In addition, we observed that the value of the ablative ratio was
consistent with the other measured parameters, adding to its validity.
The highest ablative ratio was observed in the 2.4mm cryoprobe regardless
whether they were 18 or 15mm apart. The smallest ratio was seen in the
Seednet™ system iceball, with only 22.81% of the iceball was lethal when
frozen at 100%. This is probably owing to the short length of the iceball and
the fact that the lethal ice length was approximately only half the total iceball
length. The lethal ice length of the 2.4mm probe's iceball was in the region of
2/3 of the total iceball length.
The ablative ratio of the 3.4mm cryoprobe did not differ significantly from the Seednet™ iceball measuring 23.75%. This is perhaps due to the increase in non lethal ice at the top of the iceball. There were statistically significant reductions in all the ablative ratios when the gas flow rates were reduced to 20%.

Limitations of the Study

1. *In vivo* assessment of the iceballs is the most accurate way to compare different cryoprobes, but for reasons explained earlier in chapter 1 (1.4), it is not possible to precisely map the temperature of the iceballs *in vivo* during prostate cryosurgery. We anticipate that the iceball will be smaller *in vivo* due tissue perfusion. Bhattacharya and Mahajan (2003) concluded that sheep gelatine and cow liver's thermal conductivity increases with increasing temperature. They also demonstrated that thermal conductivities of various organs of a living pig were higher compared to the reported *in vitro* values. These differences were different between different organs, and were directly dependant on tissue perfusion. Prostate perfusion varies greatly according to the volume of the prostate; patient's age; PSA value; history of prostate irradiation and hormonal therapy (reviewed by Vulpen et al, 2002). Therefore, it is not possible to standardize *in vivo* thermal conductivity of the prostate. In addition to the increase in the metabolic heat generation, blood flow through big vessels (e.g. neurovascular bundles) act as a "heat sink" which may further reduce the iceball size and the cooling rate. Therefore,
despite the similarities between thermal properties of the prostate and the freezing medium (bovine muscle), differences between the iceballs' properties are expected. However, the four experiments were conducted in similar conditions; consequently, comparisons between the four iceballs are still valuable.

2. The configuration of the probes used in the experiments was similar to the configuration of the probes responsible for freezing the anterior part of the prostate. However, we have not assessed the effect of the posterior probes' iceball which fuses with anterior iceball during the later part of the freezing phase. We have also not assessed the heat sink effects of the urethral warming catheter and the neurovascular bundles in the middle and on each side of the iceball respectively.

Conclusions

We have compared the properties of the iceballs formed using three different types of freezing probes under similar conditions in vitro. We have also assessed the effect of reducing the rate of the freezing gas flow from 100% to 20% on the iceball properties. The 2.4 mm diameter probes produced an iceball with the highest ablativ ratio and the least non-lethal ice thickness. When the probes are place at 18mm apart; they should be inserted deep into the prostate until they reach the base as there was a little lethal ice below the tips of the probes. Reduction of the distance between the probes to 15mm resulted in an increase in the
length of lethal ice at the expense of the width. Hence, if the shape of the prostate is relatively narrow and long, the distance between the probes can be reduced.

Although the more invasive 3.4mm diameter probes produced a larger iceball it had a lower ablative ratio than that produced by the 2.4mm probe, perhaps due to significant volume of non-lethal ice at the top. Therefore, the 3.4mm diameter probes are potentially associated with higher risk of external urethral sphincter damage and incontinence.

The most important feature of the 1.47mm diameter cryoneedles was that they produced significantly short lethal ice which was inadequate to cover the length of the entire 40 patient's prostate treated with cryosurgery in our centre. Therefore, a "pull back" technique is required in almost every patients unless the prostate length is less than 23mm. The iceball had the lowest ablative ratio and the cryoneedles should be placed very close to the prostatic capsule.

Reduction of the freezing gas flow rate to 20% resulted in decrease in lethal iceball dimensions, cooling rates and the ablative ratios for all the iceballs. However, the most significant changes were observed in the 1.47mm cryoneedles (Seednet) as it failed to produce lethal ice at 20% gas flow rates. Therefore, we recommend that if possible, freezing should be performed at the highest gas flow rate especially when using the 1.47mm cryoneedles.
4.2 Health Related Quality of Life of Salvage Cryotherapy on Patients with Localised Prostate Cancer Recurrence after Radiation Failure

Recommendations are currently lacking regarding which specific questionnaires are preferable for assessment of QoL after treatment for early prostate cancer as a primary or salvage modality. It is likely that EORTC QLQ C30 and PR25 will continue to be used in European countries due to its availability/fields testing in several European languages, although the full validation of PR25 is still ongoing.

The results were presented using the scales of various questionnaires. Individual key items were also presented separately as a percentage of patients with moderate or severe symptoms to add more value to the PR25 questionnaire, as it is still awaiting complete validation. It may also be easier for clinicians to interpret the answers to single questions than understand the complexities of a multi-scale structure.

The results should be interpreted with caution due to the small number of recruited patients to date, particularly at 6 months follow-up, which was due to an administration error resulting in a group of patients missing their questionnaires. Direct comparisons between hormone treated and hormone naïve patients could not be done accurately due to the small and uneven numbers of patients in both groups.
From the trend of the changes in the data, it seems that the impact of salvage cryotherapy on global health is temporary and lasting less than 9 months, indicating that patients do not regard salvage cryotherapy to have long-term harmful effects. However, more patients, longer follow-up and comparison with other salvage therapies are required.

There is a trend for "a little" improvement in insomnia from 3 months follow-up which could be due to less nocturia. At 6 weeks follow-up, 50% of the patients reported that urinating at night disturbed their sleep by "quite a bit" or "very much" compared to only 15% at 3 month.

The data of the IPSS scores suggest that deterioration in urinary symptoms is of clinical significance for less than 3 months post-operatively. The changes from 3-12 months were not clinically significant. More detailed assessment with EORTC-PR25 questionnaire suggests that initial worsening in urinary symptoms becomes none clinically significant from 9 months onwards. However, more patients are required to confirm these findings.

Urinary incontinence seems to increase after salvage cryotherapy. At 6 weeks follow-up, 21.9% of the patients reported "quite a bit" or "very much" incontinence compared to 4.3% pre-operatively. Although the incontinence rate falls to affect 13.1% of the patients at three months it rises to 26.3% at 12 months. The reason for this late rise is unclear; one explanation is that many of the patients with the longest period of follow-up underwent surgery in the early part of the operator's learning curve when imprecise placement of the
probes might have damaged the external sphincter. However, more data are required to confirm this suggestion. 12 patients responded to the urinary incontinence "aid bother". Only 3 responded in the category "quite a bit". One was incontinent before the operation.

The majority (41 out of 47) of the patients were impotent before the salvage cryosurgery (IIEF-5 <12). One of the factors which could influence this is that approximately 75% of the patients were on hormonal treatment. However, it is worth mentioning that 3 out of the 6 potent patients before the operation were on hormonal treatment, but the number is small to achieve conclusions. Both the IIEF-5 and the PR-25 sexual function questions and sexual activity suggest that salvage cryotherapy does not cause sexual impairment of clinical significance, which is in contrast to previously reported cross-sectional data (Anastasiadis et al, 2003). The reason for this discrepancy is the small number of potent patients in our series and the lack of published longitudinal data especially in men with concomitant hormonal treatment. It is worth mentioning that out of the six potent patients before cryosurgery, only one remains potent, hence, we anticipate that with more data, salvage cryosurgery will be confirmed as a causal factor in the development of ED.

Patients' treatment worry and general cancer distress have shown trends of improvement after salvage cryotherapy. This is in parallel with improvement in emotional functioning of the EORTC QLQ-C30 questionnaire. It is interesting that the partners showed a similar pattern of changes but to a greater degree intensity. Remarkably, the only area where patients are more worried than
their partners is the impairment of sexual function. However the trends of the EDQoL scores suggest that in the long run ED does not in fact affect quality of life in the majority of patients. This may be partly due to small number of potent patients at baseline, and also patients’ expectations of high incidence of ED after salvage cryotherapy.

Our preliminary results of the HQoL assessment were comparable to the results of Robinson et al. (2006) who assessed HQoL two years after salvage cryotherapy using EORTC QLQ-C30 and UCLA-PCI questionnaires. Out of the 46 patients recruited in their study, 13 were on hormonal therapy prior to cryosurgery. There was a temporary worsening of all the domain and subscale scores, which returned to baseline levels, with the exception of urinary and sexual function which remained impaired.

Limitations of the Study

1. This study is at present immature in terms of recruitment and follow-up.

2. The majority of the patients (75%) were hormonally treated which may result in significant confounding due to possible side effects including hot flushes, loss of libido and sexual function, asthenia and breast pain (Iversen et al, 2000; Sieber et al, 2004).

We plan to address this by increasing recruitment of hormone naïve patients to achieve statistical power.
Conclusions

Although the study is still immature; the preliminary data suggest that deterioration in general health is limited to a period of less than 9 months. Incontinence seems to increase; however, this still compares favourably with other salvage modalities (reviewed by Ahmed et al, 2005). Sexual activity and function were difficult to assess due to the small number (19%) of sexually active men at baseline.

4.3. The Impact of Iceball Temperature on HQoL during Salvage Cryotherapy

We assessed the correlation between the temperatures at the apex of the prostate, the external urethral sphincter and at the Denonvillier's fascia during cryosurgery and the impact on HQoL following salvage cryotherapy. If we proof that such a correlation exists, then we may be able to reduce the impact on HQoL after salvage cryotherapy by choosing different freezing probes or by modifying the technique. During cryosurgery, non-lethal ice may reach the external urethral sphincter or the Denonvillier's fascia (see 1.2.2.7) resulting in urinary incontinence or recto-urethral fistula respectively, with the lower temperatures, the more risk of collateral damages (Larson et al. 2000). Urinary and bowel related side-effects of prostate cancer treatment have a negative impact on HQoL (Helgason et al. 1998). Therefore, we anticipated that patients with lower temperature at the external urethral sphincter or
Denonvillier's fascia would sustain more tissue damage, and hence, more co-morbidities and worst impact on HQoL.

In our study, we could not demonstrate such a correlation between lowest iceball temperatures and HQoL impact; however, this should be interpreted with caution due to the small number of patients included in the study. We anticipate that with more data, it may be possible to demonstrate that a correlation between the lowest temperature at the external urethral sphincter or Denonvillier's fascia and HQoL impact exists.
Chapter 5
Appendices
Appendix A

Thermal Map of Horizontal Slices of the Four Iceballs Created from the 10 Minutes Mean Temperatures

Temperature mapping of experiment 1 iceball horizontal slices (level 3-6) at 100% freezing rate after 10 minutes of freezing

Temperature zones:  
- 0° to -19.9°  
- -20° to -39.9°  
- ≥ -40°
Temperature mapping of experiment 1 iceball horizontal slices (level 7-12) at 100% freezing rate after 10 minutes of freezing

Temperature zones:

- □ 0° to -19.9°
- □ -20° to -39.9°
- □ ≥ -40°

Levels:
- Level 7: 20 mm above tip level
- Level 8: 15 mm above tip level
- Level 9: 10 mm above tip level
- Level 10: 5 mm above tip level
- Level 11: Tip level
- Level 12: 5 mm below tip level
Temperature mapping of experiment 1 iceball horizontal levels (level 3-8) at 20% freezing rate after 10 minutes of freezing

Temperature zones:

- 0° to -19.9°
- -20° to -39.9°
- ≥ -40°
Temperature mapping of experiment 1 iceball horizontal levels (level 9-12) at 20% freezing rate after 10 minutes of freezing

Temperature zones: 

- □ 0° to -19.9°
- -20° to -39.9°
- ≥ -40°
Temperature mapping of experiment 2 iceball horizontal levels (level 3-8) at 100% freezing rate after 10 minutes of freezing

Temperature zones:

- □ 0° to -19.9°
- -20° to -39.9°
- ≥ -40°
Temperature mapping of experiment 2 iceball horizontal levels (level 9-12) at 100% freezing rate after 10 minutes of freezing

Temperature zones:  
□ 0° to -19.9°  
-20° to -39.9°  
≥ -40°
Temperature mapping of experiment 2 iceball horizontal levels (level 3-8) at 20% freezing rate after 10 minutes of freezing

Level 3
40 mm above tip level

Level 4
35 mm above tip level

Level 5
30 mm above tip level

Level 6
25 mm above tip level

Level 7
20 mm above tip level

Level 8
15 mm above tip level

Temperature zones: □ 0° to -19.9°  □ -20° to -39.9°  □ ≥ -40°
Temperature mapping of experiment 2 iceball horizontal levels (level 9-12) at 20% freezing rate after 10 minutes of freezing

Temperature zones:

- 0° to -19.9°
- -20° to -39.9°
- ≥ -40°
Temperature mapping of experiment 3 iceball horizontal levels (level 2-7) at 100% freezing rate after 10 minutes of freezing

Temperature zones: □ 0° to -19.9°  □ -20° to -39.9°  □ ≥ -40°
Temperature mapping of experiment 3 iceball horizontal levels (level 8-13) at 100% freezing rate after 10 minutes of freezing

Temperature zones:  

- 0° to -19.9°  
- -20° to -39.9°  
- ≥ -40°
Temperature mapping of experiment 3 iceball horizontal levels (level 3-8) at 20% freezing rate after 10 minutes of freezing

Temperature zones: □ 0° to -19.9° □ -20° to -39.9° □ ≥ -40°
Temperature mapping of experiment 3 iceball horizontal levels (level 9-13) at 20% freezing rate after 10 minutes of freezing

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<th>Level</th>
<th>Distance from Tip</th>
<th>Temperature Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>10 mm above tip level</td>
<td>-20° to -39.9°</td>
</tr>
<tr>
<td>10</td>
<td>5 mm above tip level</td>
<td>-40°</td>
</tr>
<tr>
<td>11</td>
<td>Tip level</td>
<td>-20° to -39.9°</td>
</tr>
<tr>
<td>12</td>
<td>5 mm below tip level</td>
<td>-40°</td>
</tr>
<tr>
<td>13</td>
<td>10 mm below tip level</td>
<td>-20° to -39.9°</td>
</tr>
</tbody>
</table>

Temperature zones: 
- 0° to -19.9°
- -20° to -39.9°
- ≥ -40°
Temperature mapping of experiment 4 iceball horizontal levels (level 6-11) at 100% freezing rate after 10 minutes of freezing.

Temperature zones:  □ 0° to -19.9°  □ -20° to -39.9°  □ ≥ -40°
Temperature mapping of experiment 4 iceball horizontal levels (level 12-13) at 100% freezing rate after 10 minutes of freezing

Temperature zones:  
- □ 0° to -19.9°  
- □ -20° to -39.9°  
- □ ≥ -40°
Temperature mapping of experiment 4 iceball horizontal levels (level 8-11) at 20% freezing rate after 10 minutes of freezing

Temperature zones:  

- 0° to -19.9°  
- -20° to -39.9°
Appendix B

Patients Questionnaire Booklet

General Health Questionnaire (EORTC QLQ C30 v3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Today's date (Day, Month, Year): ____________ ____________

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you need to stay in bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you had vomiting?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

16. Have you been constipated? 1  2  3  4
17. Have you had diarrhoea? 1  2  3  4
18. Were you tired? 1  2  3  4
19. Did pain interfere with your daily activities? 1  2  3  4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? 1  2  3  4
21. Did you feel tense? 1  2  3  4
22. Did you worry? 1  2  3  4
23. Did you feel irritable? 1  2  3  4
24. Did you feel depressed? 1  2  3  4
25. Have you had difficulty remembering things? 1  2  3  4
26. Has your physical condition or medical treatment interfered with your family life? 1  2  3  4
27. Has your physical condition or medical treatment interfered with your social activities? 1  2  3  4
28. Has your physical condition or medical treatment caused you financial difficulties? 1  2  3  4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?
   1  2  3  4  5  6  7
   Very poor Excellent

30. How would you rate your overall quality of life during the past week?
   1  2  3  4  5  6  7
   Very poor Excellent

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Specific Symptoms Related to Prostate Problems (EORTC QLQ - PR25)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

<table>
<thead>
<tr>
<th>Question</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Have you had to urinate frequently during the day?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32. Have you had to urinate frequently at night?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35. Have you had difficulty going out of the house because you needed to be close to a toilet?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36. Have you had any unintentional release (leakage) of urine?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37. Did you have pain when you urinated?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38. Has wearing an incontinence aid been a problem for you?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39. Have your daily activities been limited by your urinary problems?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40. Have your daily activities been limited by your bowel problems?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41. Have you had any unintentional release (leakage) of stools?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42. Have you had blood in your stools?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43. Did you have a bloated feeling in your abdomen?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44. Did you have hot flushes?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please answer the following questions

During the past week

<table>
<thead>
<tr>
<th>Question</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>39. Have your daily activities been limited by your urinary problems?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40. Have your daily activities been limited by your bowel problems?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41. Have you had any unintentional release (leakage) of stools?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42. Have you had blood in your stools?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43. Did you have a bloated feeling in your abdomen?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44. Did you have hot flushes?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
During the last 4 weeks...

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>45. Have you had sore or enlarged nipples or breasts?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Have you had swelling in your legs or ankles?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. Has weight loss been a problem for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Has weight gain been a problem for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Have you felt less masculine as a result of your illness or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50. To what extent were you interested in sex?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>51. To what extent were you sexually active (with or without intercourse)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>52. To what extent was sex enjoyable for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>53. Did you have difficulty getting or maintaining an erection?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>54. Did you have ejaculation problems (eg dry ejaculation)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>55. Have you felt uncomfortable about being sexually intimate?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
**International Index of Erectile Function (IIEF)**

These questions ask about the effects your erection problems have had on your sex life **over the past 4 weeks**. Please answer the following questions as honestly and clearly as possible. In answering these questions, the following definitions apply:

- **Sexual activity** includes intercourse, caressing, foreplay and masturbation
- **Sexual intercourse** is defined as vaginal penetration of the partner (you entered your partner)
- **Sexual stimulation** includes situations like foreplay with a partner, looking at pictures, etc
- **Ejaculate**: the ejection of semen from the penis (or the feeling of this)

1. **Over the past 4 weeks**, how often were you able to get an erection during sexual activity?

   Please tick one box only

   - □ No sexual activity 0
   - □ Almost always or always 5
   - □ Most Times (much more than half the time) 4
   - □ Sometimes (about half the time) 3
   - □ A few times (much less than half the time) 2
   - □ Almost never or never 1

2. **Over the past 4 weeks**, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?

   Please tick one box only

   - □ No sexual stimulation 0
   - □ Almost always or always 5
   - □ Most Times (much more than half the time) 4
   - □ Sometimes (about half the time) 3
   - □ A few times (much less than half the time) 2
   - □ Almost never or never 1
The next three questions will ask about the erections you may have had during sexual intercourse.

3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

Please tick one box only

☐ Did not attempt intercourse 0
☐ Almost always or always 5
☐ Most times (much more than half the time) 4
☐ Some times (about half the time) 3
☐ A few times (much less than half the time) 2
☐ Almost never or never 1

4. Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

Please tick one box only

☐ Did not attempt intercourse 0
☐ Almost always or always 5
☐ Most times (much more than half the time) 4
☐ Sometimes (about half the time) 3
☐ A few times (much less than half the time) 2
☐ Almost never or never 1

5. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Please tick one box only

☐ Did not attempt intercourse 0
☐ Extremely difficult 1
☐ Very difficult 2
☐ Difficult 3
☐ Slightly difficult 4
☐ Not difficult 5
6. **Over the past 4 weeks** how many times have you attempted sexual intercourse?

*Please tick one box only*

- No attempts 0
- 1-2 attempts 1
- 3-4 attempts 2
- 5-6 attempts 3
- 7-10 attempts 4
- 11+ attempts 5

7. **Over the past 4 weeks**, when you attempted sexual intercourse how often was it satisfactory for you?

*Please tick one box only*

- Did not attempt intercourse 0
- Almost always or always 5
- Most times (much more than half the time) 4
- Sometimes (about half the time) 3
- A few times (much less than half the time) 2
- Almost never or never 1

8. **Over the past 4 weeks**, how much have you enjoyed sexual intercourse?

*Please tick one box only*

- No intercourse 0
- Very highly enjoyable 5
- Highly enjoyable 4
- Fairly enjoyable 3
- Not very enjoyable 2
- No enjoyment 1
9. **Over the past 4 weeks**, when you had sexual stimulation or intercourse how often did you ejaculate?

*Please tick one box only*

- No sexual stimulation/intercourse 0
- Almost always or always 5
- Most times (much more than half the time) 4
- Sometimes (about half the time) 3
- A few times (much less than half the time) 2
- Almost never or never 1

10. **Over the past 4 weeks**, when you had sexual stimulation or intercourse how often did you have the feeling of orgasm (with or without ejaculation)?

*Please tick one box only*

- No sexual stimulation/intercourse 0
- Almost always or always 5
- Most times (much more than half the time) 4
- Sometimes (about half the time) 3
- A few times (much less than half the time) 2
- Almost never or never 1

The next two questions ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (for example masturbation or intercourse), thinking about having sex, or feeling frustrated due to lack of sex.

11. **Over the past 4 weeks** how often have you felt sexual desire?

*Please tick one box only*

- Almost always or always 5
- Most times (much more than half the time) 4
- Sometimes (about half the time) 3
- A few times (much less than half the time) 2
- Almost never or never 1
12. **Over the past 4 weeks** how would you rate your level of sexual desire?

*Please tick one box only*

- Very high 5
- High 4
- Moderate 3
- Low 2
- Very low or none at all 1

13. **Over the past 4 weeks** how satisfied have you been with your overall sex life?

*Please tick one box only*

- Very satisfied 5
- Moderately satisfied 4
- About equally satisfied and dissatisfied 3
- Moderately dissatisfied 2
- Very dissatisfied 1

14. **Over the past 4 weeks** how satisfied have you been with your sexual relationship with your partner?

*Please tick one box only*

- Very satisfied 5
- Moderately satisfied 4
- About equally satisfied and dissatisfied 3
- Moderately dissatisfied 2
- Very dissatisfied 1

15. **Over the past 4 weeks** how do you rate your confidence that you can get and keep your erection?

*Please tick one box only*

- Very High 5
- High 4
- Moderate 3
- Low 2
- Very low 1

Thank you for completing this questionnaire.
**Supplementary Questionnaire**

We need to know to what extent your treatment affects the amount of time and help you require from the local health services and from your family or friends.

The questions below should be answered in relation to those services you have required since the last questionnaire and are to do with all those services which relate to the treatment you are having within this study. If you have not previously completed a questionnaire then please complete this section for the past 3-months.

<table>
<thead>
<tr>
<th>Since the last assessment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you been to your own doctor for any reason?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>Number of times ____</td>
<td></td>
</tr>
<tr>
<td>2. Has your own doctor visited you at home for any reason?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>Number of times ____</td>
<td></td>
</tr>
<tr>
<td>3. Have you visited your nurse or surgery/health clinic for any reason?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>Number of times ____</td>
<td></td>
</tr>
<tr>
<td>4. Has the nurse visited you at home for any reason?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>Number of times ____</td>
<td></td>
</tr>
<tr>
<td>5. Have you required any help from social services/any voluntary group?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>Number of times ____</td>
<td></td>
</tr>
<tr>
<td>6. Have your family or friends taken time from work to help you at any time?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>Number of times ____</td>
<td></td>
</tr>
<tr>
<td>7. Have you needed to pass a catheter at home since being treated?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>If so for how many weeks did treatment continue?</td>
<td>____ Weeks</td>
</tr>
<tr>
<td>8. Are you currently receiving any treatment for problems in getting or maintaining erections of the penis?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>If so for how long have you been receiving such treatment?</td>
<td></td>
</tr>
<tr>
<td>What is the name of the treatment (eg Viagra™ you are receiving?)</td>
<td></td>
</tr>
</tbody>
</table>
International Prostate Symptom Score (IPSS)

Please complete this form which you may have seen previously in clinic, it relates to your current ease of urination. Please ring the closest answer to how you have felt over the last month. Thank you.

<table>
<thead>
<tr>
<th>Date:</th>
<th>Not at all</th>
<th>Less than 1 time in 5</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>More than half the time</th>
<th>Almost always</th>
<th>Your score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Incomplete emptying</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2 Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you had to urinate again less than two hours after you finished urinating?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3 Intermittency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you found you had stopped and started again several times when you urinated?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4 Urgency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you found it difficult to postpone urination?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>5 Weak Stream</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you had a weak urinary stream?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6 Straining</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how often have you had to push or strain to begin urination?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>7 Nocturia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Total IPSS Score

Quality of Life due to Urinary Symptoms

<table>
<thead>
<tr>
<th>Delighted</th>
<th>Pleased</th>
<th>Mostly satisfied</th>
<th>Mixed</th>
<th>Mostly satisfied &amp; dissatisfied</th>
<th>Mostly dissatisfied</th>
<th>Unhappy</th>
<th>Terrible</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

233
Patient’s Questionnaire (TPSM)

These questions attempt to measure some of the effects of your prostate cancer upon you. We will ask your partner to complete a similar questionnaire (if you have one). Please read each question carefully and answer by ticking the appropriate box. Answer according to how you are feeling at the moment.

- Are you worried or concerned about the fact that you have cancer?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

- Are you worried or concerned about what might happen in the future?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

* Are you having any difficulty in coping with your feelings or emotions resulting from your cancer?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

* Your day to day activities might include chores around the house, going shopping or your job. Do you find yourself restricted in these sort of activities, because of your cancer?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

* Your social life might include seeing friends, going for day trips and your hobbies. Has your social life become restricted, for whatever reason, as a result of your cancer?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)
From now on, first answer YES or NO, then answer the second part of the question only if asked to do so.

- **Are you receiving any treatment for your cancer?**
  □ Yes □ No

  **IF YOU ANSWERED YES,** how much does the treatment worry you?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

  **IF YOU ANSWERED NO,** how much does this worry you?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

- **Do you have any pain?**
  □ Yes □ No

  **IF YOU ANSWERED YES,** how much does this pain worry you?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

- **Do you have any urinary problems?**
  □ Yes □ No

  **IF YOU ANSWERED YES,** how much does these problems worry you?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

* Do you have difficulty doing the things that you used to be able to do, as a result of your cancer?
  □ Yes □ No

  **IF YOU ANSWERED YES,** how much does this worry you?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

- **Has your sex life been changed by your cancer diagnosis or treatment?**
  □ Yes □ No

  **IF YOU ANSWERED YES,** how much does this worry you?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)
Quality of Life Questionnaire (ED-QoL)

This questionnaire only applies to men who have problems getting an erection. If you never have problems getting an erection DO NOT complete this questionnaire.

This questionnaire asks for your views about your erectile problem. Please read each item and place a tick in the box opposite the reply which comes closest to how you feel.

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Somewhat</th>
<th>Quite a lot</th>
<th>A great deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. As a result of your erectile difficulties, do you blame yourself for being unable to satisfy your partner?</td>
<td>☐ o</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>A little</td>
<td>Somewhat</td>
<td>Quite a lot</td>
<td>A great deal</td>
</tr>
<tr>
<td>2. Does your inability to produce an erection with your partner make you feel guilty?</td>
<td>☐ o</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>A little</td>
<td>Somewhat</td>
<td>Quite a lot</td>
<td>A great deal</td>
</tr>
<tr>
<td>3. Do you feel less desirable as a result of your erectile difficulties?</td>
<td>☐ o</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>A little</td>
<td>Somewhat</td>
<td>Quite a lot</td>
<td>A great deal</td>
</tr>
<tr>
<td>4. Do you feel hurt by your partner's response to your erectile difficulties?</td>
<td>☐ o</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>A little</td>
<td>Somewhat</td>
<td>Quite a lot</td>
<td>A great deal</td>
</tr>
<tr>
<td>5. Does the fact that you are unable to produce an erection make you feel less of a man?</td>
<td>☐ o</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>A little</td>
<td>Somewhat</td>
<td>Quite a lot</td>
<td>A great deal</td>
</tr>
<tr>
<td>6. Do you feel angry or bitter that you cannot produce an erection?</td>
<td>☐ o</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>A little</td>
<td>Somewhat</td>
<td>Quite a lot</td>
<td>A great deal</td>
</tr>
<tr>
<td>7. Do you feel a failure because of your erectile difficulties?</td>
<td>☐ o</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>A little</td>
<td>Somewhat</td>
<td>Quite a lot</td>
<td>A great deal</td>
</tr>
</tbody>
</table>
Please read each item and place a tick in the box opposite the reply which comes closest to how you feel.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Somewhat</th>
<th>Quite a lot</th>
<th>A great deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Does your partner feel let down by your inability to produce an erection?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>9. Are you worried that your erectile problems have affected the closeness between you and your partner?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>10. Does your erectile failure make you worry about how your life will develop in the future?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>11. Is your sense of identity altered by your lack of erectile function?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>12. Are you preoccupied by your erection problems?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>13. Do you feel sad or tearful as a result of your erectile difficulties?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>14. Do you feel that other people are happier than you are because they are sexually fulfilled?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
<tr>
<td>15. Is your self esteem damaged by your erectile problems?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
</tr>
</tbody>
</table>

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Appendix C

Partner's Questionnaire

These questions attempt to measure some of the effects of your partner's prostate cancer upon you. Please read each question carefully and answer by ticking the appropriate box and answer according to how you are feeling at the moment.

- Are you worried or concerned about the fact that your partner has cancer?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

- Are you worried or concerned about what might happen in the future?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

* Are you having any difficulty in coping with your feelings or emotions resulting from your partner's cancer?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

* Your day to day activities might include chores around the house, going shopping or your job. Do you find yourself restricted in these sort of activities, because of your partner's cancer?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

* Your social life might include seeing friends, going for day trips and your hobbies. Has your social life become restricted, for whatever reason, as a result of your partner's cancer?
  □ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)
From now on, first answer YES or NO, then answer the second part of the question only if asked to do so.

• Is your partner receiving any treatment for his cancer?
  □ Yes □ No

IF YOU ANSWERED YES, how much does the treatment worry you?
□ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

IF YOU ANSWERED NO, how much does this worry you?
□ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

• Does your partner have any pain?
□ Yes □ No

IF YOU ANSWERED YES, how much does this pain worry you?
□ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

• Does your partner have any urinary problems?
□ Yes □ No

IF YOU ANSWERED YES, how much do these problems worry you?
□ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

* Does your partner have difficulty doing the things that he used to be able to do, as a result of his cancer?
□ Yes □ No

IF YOU ANSWERED YES, how much does this worry you?
□ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)

• Has your sex life been changed by your partner’s cancer diagnosis or treatment?
□ Yes □ No

IF YOU ANSWERED YES, how much does this worry you?
□ Not at all (0) □ A little (1) □ Somewhat (2) □ Quite a lot (3) □ A great deal (4)
Appendix D

Publications

Articles Published in peer-reviewed journal

Ismail M, Ahmed S, Kastner C and Davies J.

Ahmed S and Swinn M.

Ahmed L, Ahmed S and Davies J.

Ahmed S, Lindsey B, Davies J.

Ahmed S and Davies J.

Ahmed S, Lindsey B and Davies J.

Book chapter

Ahmed S.

Article Submitted to peer-reviewed journal

Ahmed S, Davies J and Chinn D.
Cryosurgery of the Prostate: Comparison of the Thermal Properties of Three Different Freezing Probes Iceball. *Submitted to Cryobiology.*
References


Endocare. (2005). The right cryoprobe for the right procedure. Endocare (pamphlet no. PM - 3432 05/05).


McNeal, J.E. et al. (1986). Patterns of progression in prostate cancer. Lancet 1, 60-63.


