FUNCTIONAL AND STRUCTURAL CHANGES IN THE ANORECTUM FOLLOWING RADIOTHERAPY FOR UROLOGICAL MALIGNANCY

A thesis submitted to the University of London for the Degree of Doctor of Medicine

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ABSTRACT

FUNCTIONAL AND STRUCTURAL CHANGES IN THE ANORECTUM FOLLOWING RADIOTHERAPY FOR UROLOGICAL MALIGNANCY

Pelvic radiotherapy (RT) is a common treatment modality for bladder and prostate cancer. Current understanding of the effects of radiation on the anorectum is based on a limited number of studies with a paucity of prospective studies. The aetiology and extent of functional and structural anorectal injury remains unclear.

The first aim of this thesis was to use in-vivo techniques and computerised RT planning predictions to determine the dose of RT received by the anorectum. The second aim of this thesis was to prospectively measure the acute effects of RT on function and structure of the anorectum using a combination of interview, anorectal physiological investigations (ARP), endoanal ultrasonography and dynamic contrast enhanced MRI and to relate dose to the changes that occurred.

Thirty-two patients were recruited and 29 underwent investigations before and six weeks after radiotherapy. 18 patients underwent in-vivo dosimetry and ten patients were re-investigated six months after RT. Faecal urgency, frequency and incontinence were seen in 17(59%), 15(52%) and 9(31%) patients six weeks after RT and ARP demonstrated significantly decreased rectal sensation and rectal capacity suggesting a causative association. After RT, a reduction of 0.2mm in the thickness of the sub-epithelial layer of the anal canal on endoanal ultrasound and increased degree and rate of anal enhancement on dynamic contrast MRI (40%, 50% respectively) were seen. No functional anal canal disturbance was detected on ARP six weeks after RT. External sphincter function improved six months after RT demonstrating a degree of training of the external sphincter. Radiation doses to the anorectum were highly variable but could not be correlated with any of the functional or structural changes that were demonstrated in this study.

Conclusion

The functional disturbance experienced at this stage results mainly from rectal injury, though evidence for acute anal canal injury exits. Efforts to reduce symptoms should concentrate on rectal protection.

ACKNOWLEDGEMENTS

LIST OF ABBREVIATIONS

AAA	= Abdominal aortic aneurysm
AES	= Anal electrical sensitivity
AF	= Atrial fibrillation
ARP	= Anorectal physiology
CT	= Computerised tomography
CTV	= Clinical target volume
CRF	= Chronic renal failure
DNA	= Deoxyribose nucleic acid
DVH	= Dose volume histogram
EAS	= External anal sphincter
EORTC	= European Organisation for Research and Treatment of Cancer
3DCRT	=Three-dimensional conformal radiation therapy
GTV	= Gross Tumour Volume
Gy	= Gray
HT	= Hypertension
ICRU	= International committee of radiation units and measurements
IMRT	= Intensity-modulated radiation therapy
IAS	= Internal anal sphincter
LENT	= Late effects normal tissue task force
LINAC	= Linear accelerator
LM	= Longitudinal muscle
MI	= Myocardial Infarction
MRC	= Medical Research Council
MRI	= Magnetic Resonance Imaging
NIDDM	= Non insulin dependant diabetes mellitus
PTV	= Planning target volume
PR	= per rectum
PSA	= Prostatic specific antigen
PSI	= Pounds per square inch
RF	= Radio-frequency
ROI	= Region of interest
RT	= Radiotherapy

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RTOG	= Radiation Therapy Oncology Group
SOMA	= Subjective objective management analytic
TLD	= Thermo-luminescent dose-meter
TRUS	= Trans rectal ultrasound
TURBT	= Trans urethral resection of bladder tumour
TURP	= Trans urethral resection of prostate
UC	= Ulcerative colitis

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STATEMENT OF ORIGINALITY

The studies described and the analysis of the data in this thesis is the original work of the author. All studies took place at The Middlesex Hospital and were performed by the author with the following exceptions:

1. Some dosimetric data were collected in conjunction with Miss Ursula Johnson and Dr Derek D'Sousa, Medical Physicists, Department Of Medical Physics.

2. All anorectal physiological studies were performed in conjunction with Miss Elisa Wrightham, Clinical Scientist, Clinical Measurement Unit,

3. All endoanal ultrasound images were taken by Dr Chris Hare, Consultant Radiologist, Department Of Radiology

4. Some MRI data were analysed in conjunction with Dr Chis Hare, Consultant Radiologist, Department Of Radiology and Dr Andy Priest, MRI Medical Physicist, Department Of Medical Physics.

5. The statistical tests used in this thesis have been discussed at length with the statisticians of the Research & Development Department of the University College Hospital NHS Trust, and in particular with Dr Joseph Eliahoo. All statistical analysis was performed by the author using a combination of SPSS™ statistical software package and Microsoft Excel™.

No part of this work has been submitted to any other university for consideration of a higher degree.

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CHAPTER 1:

INTRODUCTION

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HISTORICAL REVIEW

1.1 BACKGROUND

Urological malignancies, particularly prostate and bladder cancer have shown a dramatic increase in incidence over the last two decades [Majeed and Burgess, 1994]. Pelvic radiotherapy (RT) is a common treatment modality for these malignancies, which is being increasingly adopted. Current knowledge of the effects of radiation on the anorectum is based on a limited number of studies. Variability in delivery techniques both currently and historically, combined with a paucity of prospective and randomised studies makes interpretation of the reported results difficult. This introduction aims to present the existing evidence and to identify those areas that require further work, some of which will be addressed in this thesis.

The use of radiation as a medical therapy is a relatively recent development. Wilhelm Röntgen discovered x-rays in 1895. The first therapeutic use for x-rays was reported in 1897 by a German surgeon called Wilhelm Freund. He used x-rays to induce regression of a hairy mole and presented his work to the Vienna Medical Society. In 1901 Pierre Curie deliberately used a radium tube to produce an ulcer on his arm and charted its progress and ultimate healing [Hall, 1993]. From these early beginnings the study of radiobiology and radio-therapeutics began. Modern external beam RT was born in the 1950's with the development of mega-voltage linear accelerators.

Radiation therapy now has a major role in the treatment of a number of malignancies arising in the pelvis. Carcinomas of the prostate, bladder, rectum and gynaecological malignancies are commonly treated with external beam RT.

Rectal injury after pelvic RT is well documented [Mathes and Alexander, 1996] and

minimizing the rectal dose is an important issue for the radiotherapist [Brizel, 1998].

Anal canal injury and subsequent dysfunction receives scant attention in the literature.

Treatment options following anorectal injury remain controversial.

1.2 RADIATION PHYSICS AND MECHANISMS OF RADIATION INJURY

Therapeutic radiation is known as ionising radiation due to its effects on cellular processes through the ionisation of intracellular molecules. This ionisation of intracellular molecules, in turn affects the processes of cell division. Ionising radiation may be classified as particulate radiation or electromagnetic radiation. Particulate radiation consists of subatomic particles including electrons, neutrons, protons and alpha particles. At present only electrons are used in radiotherapy and only for limited indications, usually skin lesions due to their poor penetration. Electromagnetic radiation refers to x-rays or gamma rays. These are physically identical but the two names are used to distinguish their means of production. Both can be described in terms of 'rays', or as individual packets of energy (photons). Gamma rays are produced from the decay of radioactive isotopes, whereas x-rays are usually produced artificially by accelerating electrons to a high energy and stopping them abruptly with a heavy metal target. Part or all of this kinetic energy is converted into x-rays. The energies required to produce x-rays capable of penetrating tissue are in the megavoltage (MV) range and are produced by machines known as a linear accelerators (LINACs). The higher the energy of the x-rays, the greater the degree of penetration into the body, and the less they interact with superficial tissues. In the treatment of urological tumours energies of greater than 8MV are required. This process is called teletherapy, but is most commonly referred to as external beam radiotherapy.

When x-rays collide with body tissues they produce fast electrons that ultimately cause biological damage. These fast electrons are produced as a result of three

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different absorption mechanisms that are largely dependent on the energy of the incident x-rays. Low energy x-rays (diagnostic x-rays) are absorbed by a process known as *the photoelectric effect*. The incident photon interacts with an inner orbital electron shell of an atom. The absorbed energy causes an electron (known as a fast electron) to be ejected from its orbit shell, which then goes on to ionise other atoms, breaking chemical bonds in cellular DNA. The x-rays most commonly used for radiotherapy are in the 1-10MV range. This energy of photon generally produces an absorption interaction known as the *Compton effect*. The effect is similar to the photoelectric effect, in that energy is given up resulting in release of a fast electron. However, the photon is not absorbed, but deflected from its original path and proceeds through the tissues resulting in further interactions and fast electron productions. At treatment energies in excess of 10MV *pair production* predominates. The incident photon interacts with the nucleus of the atom, giving up all its energy in the process. This results in production of a positron and a fast electron. The fast electron results in ionisation as before. The positron collides with adjacent electrons and is rapidly annihilated with the creation of two new photons both capable of causing subsequent ionisations.

The resultant biological damage produced by fast electrons occurs directly by ionisation and breaking of chemical bonds in cellular DNA and indirectly by interaction with biological molecules to produce free radicals. These free radicals, in particular hydroxyl, are highly reactive molecules, which can diffuse far enough to reach and damage cellular DNA. A single strand DNA break may be recognised and repaired using the complimentary strand as a template. When several ionisations occur in close proximity, a double strand DNA break may occur. This is an

irreparable lesion and the damage caused prevents normal mitosis from occurring, resulting in cell death during attempted division. Despite DNA damage most cells continue to carry out their other normal physiological functions until mitosis occurs[Tubiana M, 1999;Hall et al., 1988]. In early responding tissues such as skin, mucosal epithelium and bone marrow, radiotherapy damage is rapidly apparent, usually within the course of RT itself. Late responding tissues (e.g. neurological tissue) may not show the effects of RT for months or even years after treatment. This explains delayed RT damage in some tissues.

In the clinical setting radiation is usually delivered in 'fractions' of the total treatment dose over several weeks. This fractionation has a number of advantages, namely repopulation, repair, reassortment and reoxygenation. Fractionation allows rapidly proliferating normal tissues to recover cell mass between fractions (repopulation). Normal tissues that are dividing slowly are able to repair DNA damage more effectively than tumour (repair). Fractionation also allows more tumour cells to move out of the relatively protected S phase of the cell cycle into the G2 and M phases of the cell cycle making them vulnerable to radiation (reassortment). Finally, revascularisation of hypoxic areas in a tumour mass between fractions, results in their reoxygenation, enhancing their radiosensitivity [Mould RF, 1981];[Huddart RA, 1999].

1.3 RADIOTHERAPY TREATMENT PLANNING

The initial phase of radiotherapy is treatment planning. This involves patient position and immobilization, definition of treatment volumes, choice of technique and calculation of dose distribution. Dosimetry is the assessment of dose distribution.

1.3.1 Patient Position And Immobilization

Accurate patient set-up on the planning machine is achieved by aligning bony landmarks using wall-mounted lasers and then tattooing the patient at three sites. These tattoos are then aligned with wall-mounted lasers on the treatment machines to ensure patients are in an identical position for each fraction of RT once treatment begins. The patient is always planned and treated supine and with the bladder full for prostate cancer patients and empty for bladder cancer patients.

1.3.2 Definition Of Treatment Volumes

When delivering RT, parameters such as volume and dose have to be specified for the purposes of prescription, recording and reporting. This has been standardised by the International Committee of Radiation Units and Measurements –ICRU (1993) allowing international comparisons of various RT treatments. The report defines the Gross Tumour Volume (GTV), Clinical Target Volume (CTV) and Planning Target Volume (PTV). The GTV is the demonstrable macroscopic extent of the tumour. To encompass sub clinical or microscopic disease a margin is added to the GTV; this is the CTV. The PTV is a further margin added to the CTV to allow for internal organ movement and set-up error.

1.3.3 Localization Of The Target Volume

The target volume may be localized using plain x-rays on a machine called a simulator (conventional planning). Alternatively a dedicated spiral CT scanner with an integrated computer planning system (CT Planning) can be used. The area to be treated is scanned, in the case of prostate cancer from the sacro-iliac joints to the below the inferior pubic rami. The radiation oncologist then outlines the GTV and may also outline other areas of interest such as the rectum using dedicated planning software. The clinical target volume and planning target volume are then added. The increase in margin to allow for microscopic disease and internal movement are then added. An example of a planning CT (central slice) with the CTV and rectum outlined is shown in **Fig. 1.1**.
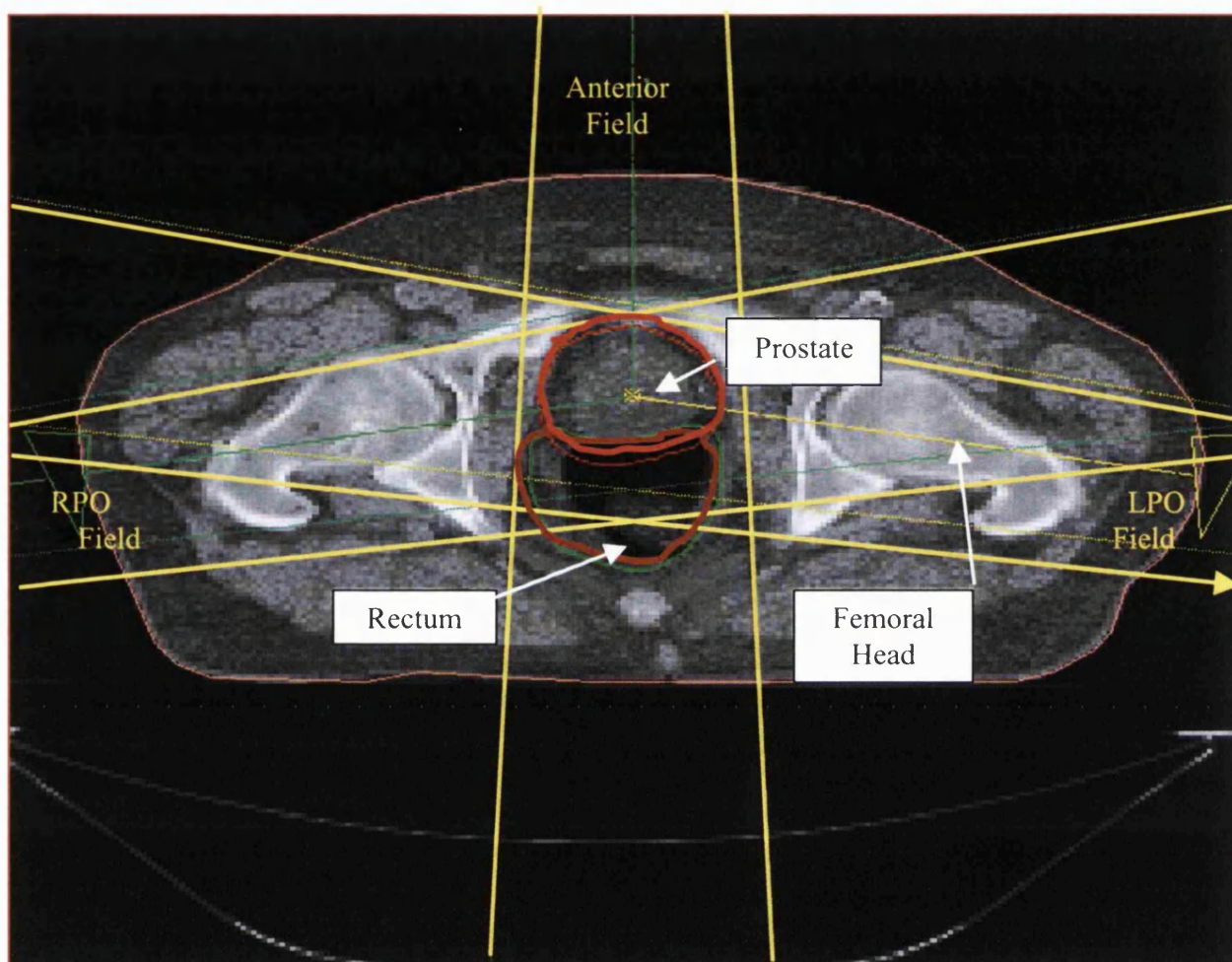
Fig. 1.1 Central Planning CT Slice (Prostatic Carcinoma)

KEY:

RPO = Right Posterior Oblique Field

LPO = Left Posterior Oblique Field

━━ = Planning Target Volume
━━ = Rectal Outline

1.3.4 Calculation Of Dose Distribution

The calculation of dose distribution is performed by medical physicists. The arrangement of the radiation fields and their relative contribution to the total dose, facilitated by a Treatment Planning System are determined and then the planning images are processed. A Treatment Planning System is a computer program to help calculate the expected doses at any given point in the pelvis accounting for changes in the energy of the radiation field as it passes through different structures such as bone and soft tissue as well as adjusting for complex photon interactions and scatter. Two Treatment Planning systems are referred to in this thesis. TARGET^{TM}, which is an older treatment planning system, utilises a two-dimensional calculation of dose based on measured beam data, and HELAX^{TM}, calculates dose using a sophisticated three-dimensional photon interaction model, which fully includes radiation scatter.

1.3.5 Dosimetry

Dosimetry is the quantitative measurement of radiation dose. This usually involves physical measurements although computerised simulations and dose predictions are frequently referred to as dosimetry. Dosimetry can be used as a form of quality control, which is usually performed by medical physicists. The LINACs themselves are frequently evaluated to ensure that they are accurately producing the expected doses of radiation. There are a number of devices used for assessing radiation dose. An ionisation chamber is considered the gold standard although a number of other electronic devices exist. Devices called thermo-luminescent dose-meters (TLDs), which are pieces of lithium fluoride, are frequently used. TLDs are exposed to radiation and then heated, which results in light being produced. The degree of luminescence is measured using photomultiplier tubes and is proportional to the

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amount of radiation received. Other devices such as radiation detecting diodes can also provide dosimetric data. Silicon diodes contain a sandwich of a second metal that acts as an electron donor or recipient. The disparity in electron number provides a potential difference across the diode. P type diodes are positive (less electrons) and N type are negative (more electrons). As photons of radiation collide with the diodes they result in ionisation and liberated electrons flow as current driven by the potential difference described above. This current flows to an electrometer and is registered as a count. The count is directly proportional to the number of photons hitting the diodes and hence the radiation dose. Diodes are in many ways superior to TLDs because, once calibrated, they can provide an immediate and continuous reading of dose.

Radiation doses to specific organs can be estimated from radiotherapy planning data. Presenting a dose to a specific organ (such as the rectum) in a clinically meaningful way can be achieved by using a dose volume histogram (DVH). The DVH plots the percentage volume of a specific organ against the percentage of the prescribed radiation dose received. The DVH has become accepted amongst radiotherapy oncologists as useful tool for treatment plan evaluation[Cheng and Das, 1999] and has more clinical relevance than a single dose at any given point, because the volume of an organ that is irradiated to a certain degree is displayed graphically.

Under some circumstances dosimetry is carried out *in-vivo*. This means that radiation doses are assessed during the actual treatment of a patient using TLDs or diodes. Most commonly a skin dose is measured, although dosimetry within body cavities is sometimes performed.

The SI unit of radiation dose is the Gray. One Gray is equal to one joule of energy absorbed per kilogram of mass. The magnitude of a Gray in clinical terms is realised from the following dose examples. A total body CT is a dose of about 0.01 Gray. Abortion would be considered if a foetus received a radiation dose of greater than 0.2 Gray. The tolerance dose of the rectum (rectal tolerance dose TD $^{5/5}$) is 45-50Gy, which is defined as the dose expected to result in a serious rectal complication in 5% of patients by 5 years.

1.4 THERAPIES FOR UROLOGICAL CANCER

1.4.1 Prostate Cancer

Prostate cancer is the second commonest cause of death from cancer in men and in 1998 was responsible for 8570 deaths in England and Wales [Majeed et al, 2000]. The directly age-standardized incidence (i.e. accounting for an increasing elderly population) has more than doubled in the last ten years with a corresponding increase in prostate cancer deaths. There has been no improvement in 5-year survival for cases diagnosed since 1985 when compared with preceding decades [Majeed et al., 2000]. It has been estimated that 30% of American men aged over 50 have histological evidence of prostate cancer [Whitmore et al.,1973]. However, the lifetime risk of developing clinically apparent disease is 10% with a 3% lifetime risk of mortality from prostate cancer.

Prostate cancer is an adenocarcinoma in more than 90% of cases and arises in the peripheral zone of the prostate in 75% of cases. In the early stages patients may be asymptomatic or have symptoms of urinary outflow obstruction as in benign prostatic hypertrophy. Asymptomatic patients can present either as an incidental finding following abnormal digital rectal examination or after prostatic specific antigen (PSA) measurement. Those patients with lower urinary tract symptoms may also have PSA estimation or prostatic cancer may be an incidental finding in the histological examination of the specimen following trans urethral resection of the prostate (TURP). In the late stages skeletal pain from bony metastases, nodal disease and obstructive renal failure are common presenting features.

Localised prostate cancer refers to disease confined within the capsule of the prostate without lymph node or metastatic spread. This equates to a TNM classification of T2 N0 M0 or less.

TNM Classification of Prostate Cancer

Primary tumour (T)

TX: Primary tumour cannot be assessed
T0:   No evidence of primary tumour
T1:   Clinically unapparent tumour not palpable nor visible by imaging
T1a: Tumour incidental histological finding in 5% or less of tissue resected
T1b: Tumour incidental histological finding in more than 5% of tissue resected
T1c: Tumour identified by needle biopsy
T2:   Tumour confined within prostate
T2a: Tumour involves 1 lobe
T2b: Tumour involves both lobes
T3:   Tumour extends through the prostatic capsule
T3a: Extra capsular extension
T3b: Tumour invades seminal vesicle(s)
T4:   Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

Regional lymph nodes (N)

Regional lymph nodes are the nodes of the true pelvis, are the pelvic nodes below the bifurcation of the common iliac arteries.
Distant lymph nodes are outside the confines of the true pelvis and their involvement constitutes distant metastasis.
NX: Regional lymph nodes cannot be assessed
N0:   No regional lymph node metastasis
N1:   Metastasis in regional lymph node or nodes

Distant metastasis (M)

MX: Distant metastasis cannot be assessed
M0:   No distant metastasis
M1:   Distant metastasis
M1a: Non regional lymph node(s)
M1b: Bone(s)
M1c: Other site(s)

The histopathological grading system for the TNM system is described below.

Histopathological grade (G)

GX: Grade cannot be assessed
G1:   Well differentiated (slight anaplasia)
G2:   Moderately differentiated (moderate anaplasia)
G3-4: Poorly differentiated or undifferentiated (marked anaplasia)

However, a different histopathological grading system is commonly adopted that has been shown to provide prognostic information. The Gleason system [Gleason DF et al., 1974] relies on the low-power microscopic appearance of the glandular architecture of the prostate. A primary grade (1-5) is assigned to the most commonly observed glandular architecture and a secondary grade (1-5) to the second most commonly occurring glandular architecture in the specimen. The Gleason score or Gleason sum is obtained by adding the primary and secondary grades thus Gleason sums range from 2 to 10. Well-differentiated tumours score 2-4, moderately differentiated score 5-6 and poorly differentiated score 8-10. Gleason score 7 have been grouped as both poorly and moderately differentiated. As the primary grade is the more important in terms of prognosis Gleason score 7 tends to be graded as 4+3 (worse prognosis) or 3+4 (better prognosis).

The treatment options are controversial as the natural history of the disease is not fully understood. Post mortem evidence shows early prostatic cancer is far more common than clinical prostatic cancer thus many men develop localised prostate cancer which never presents in their lifetime [Whitmore et al., 1973]. Localised prostate cancer is amenable to cure both with surgery or radical RT. However, both cause significant morbidity and which modality of treatment is the more appropriate in any given circumstance is debated. The alternative option of a watch and wait policy also has its

advocates. Based on the current evidence there is little to choose between these treatment options.

Radical prostatectomy has a ten-year survival of 90% and a disease-free survival of 75%, although long-term morbidity is significant [Wilt TJ et al., 1998]. Urinary incontinence rates after radical prostatectomy are acceptable; total urinary incontinence is rare (<3%) but stress incontinence may occur in up to 20% of patients. The return of urinary continence is gradual over the first year after surgery [Steiner MS et al., 1991]. Impotence rates may reach 50% [Moffat L., 2000], although nerve sparing prostatectomy when feasible has made the operation more acceptable [Wilt TJ et al., 1998]. Preservation of potency varies as a function of age. In men under the age of 60 reported rates of potency are 40-82% when both neurovascular bundles are preserved dropping to 20-60% if only one nerve is preserved. Recovery of sexual function also occurs in the first year [Walsh et al., 1994].

External beam RT offers a disease-specific survival of 76% at 10 years in T1 and T2 prostate cancer [Leibel SA et al., 1996]. In locally advanced disease local control and probably survival after radiotherapy is further improved with adjuvant androgen blockade [Mason MD et al., 2000]. Significant urinary disturbance following external beam RT for prostate cancer is uncommon [Hamilton et al., 2001]. Gastrointestinal complications following radiotherapy are common and are discussed in detail (1.5).

The watch and wait policy was reported in two studies involving untreated organ-confined prostate cancer. The 10-year survival was described as 85%, but patients with poorly differentiated cancers were excluded [Moffat L., 2000].

To determine the optimal approach for these patients a prospective randomised trial is required. The MRC randomised trial of radiotherapy versus surgery versus no immediate treatment in early prostate cancer (PR06) was discontinued in 1996 due to recruitment difficulties. There are two similar ongoing studies; The Prostate Cancer Intervention Versus Observation Trial (PIVOT) in North America and a smaller Swedish study, the results of which are keenly awaited [Wilt TJ et al., 1998]. With a lack of scientific evidence treatments tend to be offered based on the patient or the clinician's preference. Radiotherapy is traditionally offered to an older patient group, or those who are unwilling or deemed unfit to undergo major pelvic surgery. However, until more information becomes available the uncertainty about the best and most appropriate treatment modality remains.

1.4.2 Radiotherapy Techniques For Localised Prostate Cancer

RT for localised prostate cancer is most commonly delivered by external beam using a three-field technique, usually with an anterior and two lateral (or posterior oblique) beams. This provides the maximum dose to the target volume whilst allowing minimal doses to adjacent radiosensitive areas such as the rectum and the femoral heads [Dobbs J, 1985]. 64Gy given as 32 fractions of 2Gy over a six-week period is a typical treatment regime for localised prostate cancer - **Fig 1.2.**
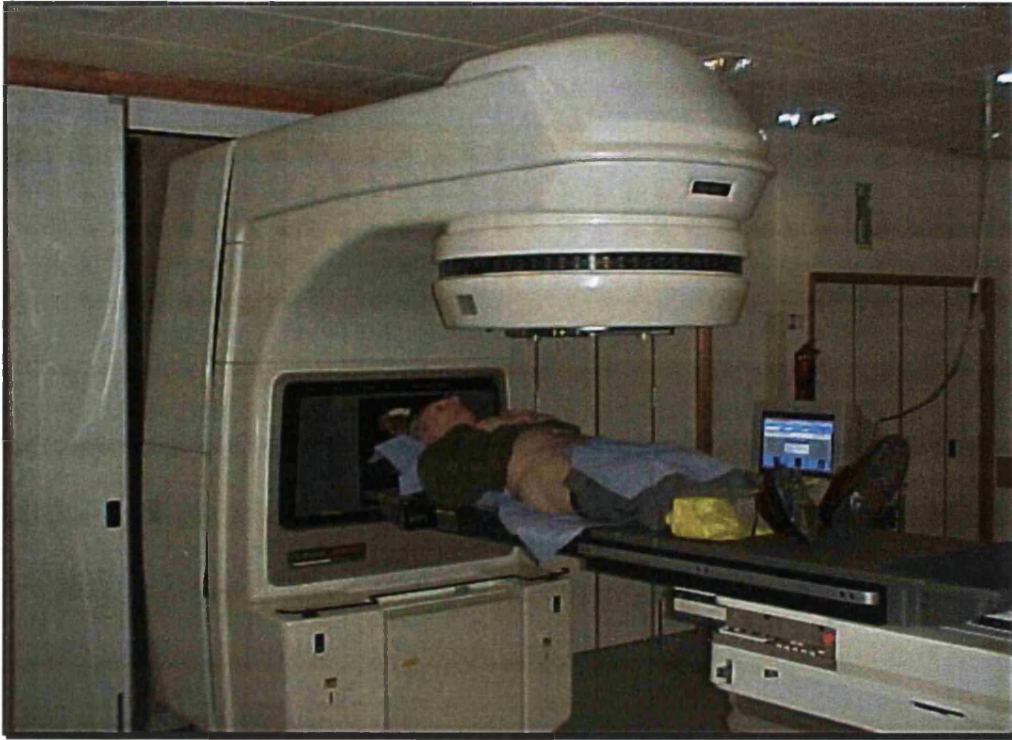
Fig. 1.2 Patient receiving pelvic radiotherapy

Three-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) are newer techniques which are being adopted, although these are currently only being used at a few centres in the UK. Three-dimensional conformal radiation therapy and IMRT allow dose distributions that conform closely to the three-dimensional shape of the target volume while minimizing dose to adjacent structures [Verhey, 1999]. However, a benefit of 3DCRT and IMRT is to allow dose escalation to the target volume but this may result in surrounding areas receiving similar doses to traditional field set-ups.

Radioactive prostatic implants are an attractive alternative to external beam RT. Pasteau implanted the first radium needles in 1910. In the 1970's open retro-pubic implantation of iodine seeds was carried out. Due to operative morbidity and poor seed positioning and dose distribution the procedure was largely abandoned. The

introduction of Trans Rectal Ultrasound (TRUS) and template guidance allowed trans-perineal insertion of needles and much more accurate positioning of the seeds [Holm et al., 1983]. The current options are iodine or palladium seeds that have the advantage of rapid dose fall off according to the inverse square law effect and short range of emission, in theory providing high doses to the target volume without affecting the surrounding structures. The procedure has the advantage that it can be performed as a single outpatient procedure and is reported to cause less morbidity than external beam RT. Seed implantation does however require live radioactive sources and is only carried out in specialist centres. Control of disease as defined by PSA level, has been reported in 98% of patients at 2 years and 76% at 5 years. Irritative urinary symptoms are common but the risk of urinary incontinence is less than 0-1% unless the patient had recently undergone TURP, when this rises to 50%. Recent TURP is therefore now considered a contraindication for this treatment modality [Holm, 1997].

High-dose rate brachytherapy is another method of dose escalation. A brachytherapy boost (e.g. 16.5 Gy in 3x 5.5Gy fractions) is received in addition to a shorter course of fractionated external beam RT (e.g. 46Gy in 23fractions over 4½ weeks). Hollow rods are positioned in the prostate via a trans-perineal route under trans-rectal ultrasound guidance. The brachytherapy source can then be introduced via the hollow rods into the prostate. Remote after-loading systems allow post-implant manipulation of source position and treatment duration to optimise the dose distribution within the target volume. The isotope used is iridium-192 which has higher emission energies than iodine or palladium resulting in higher rectal and bladder doses than seed implants with complication rates similar to external beam RT. This makes it more

suitable for bulkier tumours. High dose rate monotherapy involving giving the whole RT dose via high emission energy brachytherapy is being investigated at a few centres although results are not yet available [Duchesne GM, 2001].

1.4.3 Bladder Cancer

Bladder cancer is the fourth commonest malignancy in men and the ninth commonest in women. Between 1971 and 1997 the total number of cases of bladder cancers in England and Wales has increased by 66.7% from 7245 to 12080 [Arya M, Hayne D, et al., 2001]. The 5-year survival in the UK has been improving although this may largely be related to improved diagnosis and treatment of early lesions. Bladder cancer typically presents with painless haematuria, irritative urinary symptoms, abdominal pain or with metastatic disease. The standard investigations for any patient with haematuria, microscopic or overt, are cystoscopy, urine cytology and either intravenous urography or a plain abdominal x-ray with a renal ultrasound. Transitional cell carcinoma accounts for more than 90% of all cases of bladder cancer, 80% of which are superficial with a low rate of progression to invasive disease. The full TNM staging of transitional cell carcinoma of the bladder is described below.

TNM Staging For Bladder Cancer

Primary tumour (T)

TX: Primary tumour cannot be assessed
T0:   No evidence of primary tumour
Ta: Non-invasive papillary carcinoma
Tis: Carcinoma in situ: "flat tumour"
T1:   Tumour invades subepithelial connective tissue
T2:   Tumour invades muscle T2a: Tumour invades superficial muscle (inner half)
T2b: Tumour invades deep muscle (outer half)
T3:   Tumour invades perivesical tissue
T3a: microscopically

T3b: macroscopically (extravesical mass)
T4: Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, or abdominal wall.
T4a: Tumour invades the prostate, uterus, vagina
T4b: Tumour invades the pelvic wall, abdominal wall

Regional lymph nodes (N)

Regional lymph nodes are those within the true pelvis; all others are distant lymph nodes.

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2: Metastasis in a single lymph node, >2 cm but <5 cm; or multiple lymph nodes
N3: Metastasis in a lymph node more than 5 cm in greatest dimension

Distant metastasis (M)

MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

Superficial bladder cancer (Ta, T1 and Tis) is managed differently from muscle invasive bladder cancer (T2-T4). Superficial bladder cancer is initially treated with transurethral resection. In patients with low-grade Ta tumours, cystoscopy at regular intervals and repeat resection or cystodiathermy as necessary is usually adequate. For multiple or frequent recurrences and those with high grade or T1 tumours at presentation, intravesical immunotherapy (e.g. BCG) or chemotherapy (e.g. mitomicin or epirubicin) is generally employed. The 5-year survival for superficial disease is around 80%. Muscle invasive bladder cancer (T2-T4) requires radical cystectomy with urinary diversion or radiotherapy. Radical cystectomy involves bilateral pelvic lymphadenectomy and wide excision of the bladder and prostate including the urachal remnant, the overlying peritoneum, and the vascular pedicles. In selected cases, nerve-sparing cystoprostatectomy with a more limited dissection of the

posterior vesical pedicles is indicated and does not compromise cancer control. In women radical cystectomy may also involve anterior pelvic exenteration including uterus, fallopian tubes, ovaries, anterior vaginal wall, complete excision of the urethra and urinary diversion. In a long term follow up study of 1054 patients, the 10-year recurrence-free survival in patients with muscle invasive lymph node-negative tumours was 78% in T2 and 76% in T3a, 61% for T3b and 45% in T4 tumours [Stein et al., 2001]. Unfortunately, a significant proportion of patients (24% in the above series) have lymph node involvement at the time of surgery.

Multi-modality bladder preservation therapies involving transurethral resection followed by planned combination chemotherapy and radiotherapy are employed in selected patients. The outcomes of such bladder preservation therapies may be similar to those reported in a like population treated with radical cystectomy. The major benefit in conservatively treated patients is a functioning bladder in 50% of cases.[Petrovich et al., 2001].

1.4.4 Radiotherapy For Bladder Cancer

External beam RT for bladder cancer is administered using a similar regime to prostate cancer, although the patients are planned with the bladder empty. Higher stage tumours unsurprisingly have a worse prognosis. Higher-grade tumours have a better initial response to RT but the chance of distant metastases is greater resulting in poorer survival. Shelly et al reviewed the randomised controlled trials assessing surgery versus radiotherapy for muscle invasive bladder cancer. Three randomised trials comparing pre-operative radiotherapy followed by radical cystectomy (surgery) versus radical radiotherapy with salvage cystectomy (radical radiotherapy) were

eligible for assessment. These trials represented a total of 439 patients, 221 randomised to surgery and 218 to radical radiotherapy. The mean overall survival (intention-to-treat analysis) at 3 and 5 years were 45% and 36% for surgery, and 28% and 20% for radiotherapy, respectively. The results were also significantly in favour of surgery at 3 years and at 5 years when analysed on a treatment received basis suggesting an overall survival benefit with surgery. However, only three trials were included for analysis and many patients did not receive the treatment they were randomised to. It must also be noted that many improvements in both radiotherapy and surgery have taken place since the initiation of these trials. [Shelly et al., 2001]

1.5 FUNCTIONAL DISTURBANCE AFTER PELVIC RADIOTHERAPY

1.5.1 Clinical Features Of Rectal Complications

More than 75% of patients [Counter et al., 1999;Sedgwick et al., 1994] undergoing pelvic RT will experience some rectal symptoms during the treatment period [Perez et al., 1999] and these can be so severe as to interrupt treatment [Sandeman, 1980]. This is acute phase radiation proctitis; late phase radiation proctitis describes proctitis presenting or persisting 3 months after completion of RT. Late phase radiation proctitis is also described as chronic radiation proctitis. Radiation-induced proctitis causes significant rectal bleeding in 6-8% of patients [Silva et al., 1999] as a result of mucosal friability and neovascular telangiectasias [Taylor et al., 1993]. Proctitis can present with a number of other distressing symptoms including rectal pain, diarrhoea, tenesmus, faecal frequency and urgency.

Proctitis can be graded on reported symptoms, endoscopic appearance and histology. Talley et al (1997) described a scoring system that provided an objective measurement of proctitis. (**Table 1.1**)

Wachter et al (2000) described a more detailed endoscopic scoring system for post-radiation changes seen in the rectum. Neither of these systems has been widely adopted. The Radiation Therapy Oncology Group(RTOG) scoring system for acute intestinal toxicity of all types, is based on symptoms only. (**Table 1.2**)

Table 1.1 Scoring System For Symptoms, Endoscopic and Histological Results

		SCORE	0	1	2
Symptoms	Urgency		Nil	Mild (5-20 mins)	Moderate/severe (<5 mins)
	PR bleeding/week		0	≤4	>4
	PR blood quantity		None	Streaks	Obvious
	Diarrhoea (days/week)		0	1	>1
	No. of stools		≤1	2-3	>3
	Pain (rectal)		Nil	Pain present	
Endoscopy (rectum)	Erythema		Nil	Mild	Moderate
	Granularity/oedema		Nil	Mild	Moderate
	Telangectasia		Nil	Few or some	Sparse or florid
	Ulcers		Nil	Few or numerous	-
Histology	Overall grade		Normal	Abnormal	-

PR= per rectum

Table 1.2 RTOG Acute Intestinal Toxicity Score

ORGAN TISSUE	0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
LOWER G.I. INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholytic drugs (e.g., Lomotil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics	Diarrhoea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads/abdominal distension (flat plate radiograph demonstrates distended bowel loops)	Acute or sub-acute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion	Death directly related to RT

The long-term sequlae following pelvic RT can be disabling. It has been shown that pelvic irradiation causes widespread persistent disturbance of gastrointestinal function affecting not only anorectal function, but also gut transit and intestinal absorption of

fat, bile acids and vitamins [Yeoh et al., 1993a]. Other permanent effects may take months or even years to become apparent[Anseline et al., 1981], the peak incidence for late complications occurring between two and five years after RT [Perez et al., 1994]. For example, patients with radiation induced rectal stricture often present with obstruction a number of years after RT. Obstructive symptoms, therefore, should not be assumed to be secondary to incurable malignancy as these patients may be amenable to surgery [Schofield et al., 1983]. In a series reported by Lucarotti et al (1991), a patient presented with late rectal complication 30 years after receiving pelvic RT. Irradiated tissue has vastly reduced regenerative properties and relatively trivial traumatic or infective insults can result in severe tissue breakdown, leading to problems when operating in an irradiated field [Gilinsky et al., 1983].

The precise incidence of late radiation-induced injury depends on the delivery technique, combination with chemotherapy and patient factors including co-existing diseases such as diabetes[Greven et al., 1991];[Herold et al., 1999]. In a series of 738 patients treated with external beam RT for prostate cancer, there was a cumulative 10-year incidence of 8% of moderate intestinal injury such as proctitis, enteritis and anorectal stricture and a 3% incidence of severe intestinal injury such as severe proctitis, small bowel obstruction and fistula formation [Perez et al., 1994]. Another large retrospective study reported long-term toxicity in 199 men treated with radical RT for localized prostate cancer. In the rectum, toxicity of grade 2 or above according to the RTOG score was seen in 10 (5%) patients [Maartense et al., 2000]. In a further study by [Gerard et al., 1999] of 231 patients treated with curative intent external beam RT for carcinoma of the prostate, nine (4%) patients developed severe acute proctitis, two (1%) patients showed late severe grade 3 toxicity and both required a

colostomy and thirty-three (14.3%) patients had rectal bleeding, although only 7 (3%) required local treatment. Anorectal function after RT, according to the Memorial Sloan Kettering Cancer Centre scoring system was excellent in 90% of patients with a median follow up of 5 years. In a prospective long-term follow up (mean follow up time of 46 months) study after RT for prostate cancer Borghede et al (1997) reported mild gastrointestinal complications in 42% of patients. Only 16 (9%) patients had moderate or severe complications. Interestingly, the risk of complications strongly correlated with the presence of intestinal symptoms prior to treatment. Boersma et al (1998) investigated late gastrointestinal (GI) complications after conformal radiotherapy for localized prostate cancer in 130 patients. Intestinal complications were classified using the RTOG/European Organisation for Research and Treatment of Cancer (EORTC) and the Subjective Objective Management Analysis / Late Effects Normal Tissue Taskforce (SOMA/LENT) scoring systems. The incidence at 2 years for GI complications of Grade 2 or greater was 14% and 20% for the (RTOG/EORTC) and (SOMA/LENT) scores respectively. Dose volume histogram (DVH) parameters did not identify risk groups for late complications. No significant correlation was found between any of the DVH parameters and the actuarial incidence of complications. However, a trend was observed that a total radiation dose above 74 Gy resulted in a higher incidence of severe rectal bleeding.

An increased incidence of rectal cancer is reported in the long term following pelvic RT[Kleinerman et al., 1995]. MacMahon and Rowe, (1971) showed that early and late radiation proctitis, rectal stenosis and induration of the rectovaginal septum constituted risk factors for development of secondary cancer. Jao et al (1987) reported a series of 76 cases of radiation induced colorectal cancer, of which 85% had

histological evidence of a radiation reaction around the cancer but only 17% had presented with symptoms of proctitis. Denman et al., (1978) suggested high radiation dose and severe radiation damage are not essential for radiation-associated colorectal cancer. This was supported by animal studies that involved irradiating the descending colon of rats with a range of doses from 25-65Gy. The dose producing the maximum number of tumours was 45Gy. Due to these risks Cohen and Winawer (2000) recommended surveillance for rectal cancer, beginning five years after pelvic RT even in the absence of clinical symptoms of proctitis.

1.5.2 Clinical Features Of Anal Complications

Anal discomfort can occur in the acute phase after RT and may be compounded by radiation-associated diarrhoea. The dose received by the anal canal depends on its proximity to the target volume. Injury to the anal sphincter complex after pelvic RT has been reported although evidence is indirect and is mainly based on observed functional disturbances[Varma et al., 1986].

1.5.3 Anorectal Injury And Incontinence

Anal continence is dependant on stool consistency, bowel activity, sphincter function [Engel et al., 1995] rectal compliance and rectal capacity [Cherry and Rothenberger, 1988]. Pelvic RT can affect all these factors [Yeoh et al., 1993a] thus impairing continence. The reported incidence of faecal incontinence following pelvic RT ranges from 0-27% [Iwamoto et al., 1997]. The wide variation may be explained by differences in target site, patient mix, delivery techniques, dose received and the vigilance in symptomatic assessment. Furthermore, much of the RT morbidity data are not comprehensive. Of note the RTOG and the EORTC do not include a number of anorectal symptoms in their Late Intestinal Toxicity Scoring, specifically

anal/rectal pain, faecal urgency and faecal incontinence (**Table 1.3**). Patients are

reluctant to report these symptoms and their omission from the scoring systems may

be a major cause of under-reporting.

Table 1.3 RTOG Late Intestinal Toxicity Score Grade 1-5

ORGAN TISSUE	0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
SMALL/LARGE INTESTINE	None	Mild diarrhoea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhoea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula	Death directly related to RT

Hanlon et al drew further attention to the failings of the RTOG Late Intestinal

Toxicity Score and stressed the importance of the inclusion of late chronic rectal

bleeding requiring multiple fulgurations [Hanlon et al., 1997]. This group reported

late rectal toxicity in 352 patients treated with external beam RT for non-metastatic

prostate cancer using three different morbidity scales. The median dose was 74 Gy

(range 63-81) and the median follow-up for these patients was 36 months (range 2-

76). The morbidity scales compared were: the RTOG, the Late Effects Normal Tissue

Task Force (LENT), and Hanlon et al's own modification of the LENT (FC-LENT)

which included late chronic rectal bleeding. The 5-year rate of Grade 3/4

complications by each scale was 0.7%, 2%, and 6% respectively. This clearly demonstrated how widely different morbidity scales can vary and the importance of a meaningful uniformly agreed criteria.

The reported rate of incontinence following external beam RT for anal carcinoma varies widely from 0 to 57% [Papillon et al., 1987];[Doggett, Green, et al. 1988]; [Cummings, 1990];[Miller et al., 1991];[Tanum et al., 1991];[Martenson and Gunderson, 1993];[Touboul et al., 1994];[Touboul et al., 1995]with an average incidence of about 25%. These patients receive 45-60 Gray directly to the anus, a greater anal dose than that received in any of the pelvic RT regimes for urological malignancy. Were direct sphincter injury the main aetiology of incontinence following pelvic RT, one would expect a higher incidence of incontinence in patients receiving RT for anal carcinoma, than that which is reported.

1.5.4 Anorectal Physiology Studies

The results of anorectal physiological studies after pelvic RT have been inconsistent (**Table 1. 4**). The reported studies comprise retrospective and prospective data on different groups of patients undergoing different radio-therapeutic regimens [Varma et al., 1986];[Birnbaum et al., 1992];[Birnbaum., et al. 1994];[Iwamoto et al. 1997];[Kim et al., 1998];[Yeoh et al., 1993, 1998, 2000].

Table 1.4   Effects of radiation on anorectal physiology

Author	DXT Dose	Target Organ	Maximum anal canal resting pressure	Squeeze increment	Rectal threshold volume	Maximum tolerated rectal volume
Varma et al 1985, 1986	50Gy	Prostate	▼	▶	●	▼
Birnbaum et al 1994	45Gy	Rectum	▶	▶	●	●
Birnbaum et al 1996	45Gy	Rectum	▶	▶	●	●
Yeoh et al 1996	44-50Gy	Cervix	▼	▼	▼	▼
Iwamoto et al 1997	8.5-9.5Gy	Cervix	▲	▶	●	▼
Kim et al 1998	44-54Gy	Cervix	▶	▼	●	▼
Yeoh et al 1998	55-64Gy	Prostate	▼	▼	▼	●
Yeoh et al 2000	55-64Gy	Prostate	▶	▼	▶	●

KEY:

▲	Increased after RT
▼	Decreased after RT
▶	No change after RT
●	Not reported in study

Varma et al (1985,1986) studied a group of 10 patients with chronic radiation proctitis and incontinence. This group had significantly lower resting anal canal pressures and a markedly reduced maximum tolerable rectal volumes when compared to asymptomatic matched controls. Kim et al (1998) studied 24 patients with late radiation proctitis following treatment for carcinoma of the cervix. Again in comparison to aged matched female controls the rectal threshold, urge and maximum tolerable volumes were reduced, perhaps explained by reduced rectal compliance related to radiation induced inflammation and fibrosis. The maximal squeeze pressure was significantly reduced but the resting pressure was unchanged.

Birnbaum et al investigated the acute (1992) and chronic (1994) effects of preoperative RT for rectal cancer. No significant change in anal canal resting or squeeze pressures was demonstrable four weeks after treatment in the 20 patients initially investigated. In 10 of these patients who were followed up for 14 to 42 (mean 35.5) months, the sphincter pressures remained unaltered. However due to variations in the site of the tumours within the rectum, patients would have received very different doses to the anal canal, indeed the authors described the anal canal as being in the target volume in only three of the patients. Iwamoto et al (1997) published a study investigating manometric changes during and six months after RT for cervical cancer. A significant reduction in maximum tolerated rectal volume and in rectal compliance was demonstrated. While there was no effect on anal squeeze pressures the resting pressure was increased. However, these patients were mainly treated with intracavitary RT and according to the authors, the dose to the anal canal was negligible. They hypothesised that the increase in anal canal resting pressure may have been due to "oedema of the anal canal" or as a "response to diarrhoea stool". If

the dose to the anal canal dose was negligible, anal canal oedema seems an unlikely explanation. A response to diarrhoea stool might be a better explanation of the finding of an increased anal canal resting pressure. However, anal canal resting pressure should be a measure the involuntary tone of the internal anal sphincter. An increase in the measured value suggests that some external sphincter component was being measured and a true resting pressure was not recorded.

Yeoh et al (1996) examined the prevalence of anorectal dysfunction in a randomly selected group of 15 women who had received pelvic RT five to ten years previously. When compared with controls there was a reduction in anal resting and squeeze pressures, rectal compliance and maximum tolerable rectal volume. Fourteen of the 15 patients had at least one physiological parameter of anorectal function outside the control range. Yeoh and his colleagues then undertook a prospective evaluation of the effects of pelvic RT in 34 patients with prostatic carcinoma. Anorectal symptoms and anorectal physiology were assessed before, four to six weeks (1998) and one year (2000) after RT. After six weeks 19 (56%) had faecal frequency, 16 (47%) faecal urgency and 8 (23%) patients had faecal incontinence. The basal and squeeze sleeve recorded pressures were significantly reduced (54 v 49 mm Hg and 111 v 102 mm Hg) before and after RT respectively. The rectal compliance was also reduced (1.2 v 1.4 mm Hg/ml). Those patients, who experienced urgency, were found to have a lower threshold volume to rectal distension after RT.

One year after RT the anorectal disturbance persisted with 19 (56%), 17 (50%) and 9(26%) patients having increased frequency of defecation, faecal urgency, and

incontinence, respectively. The threshold volume to rectal distension remained lower, though decreases in anal sphincteric pressures were not sustained.

1.6 STRUCTURAL CHANGES IN THE ANORECTUM AFTER PELVIC RADIOTHERAPY

1.6.1 Histopathological Features In The Rectum

Due to its fixed position in the pelvis the rectum is the most common site of bowel injury following pelvic RT [Montana and Fowler, 1989];[Crook et al., 1996];[Beard et al., 1997]; [Koper et al., 1999];[Perez et al., 1999]. Early inflammation is described as acute phase radiation proctitis. Late phase radiation proctitis refers to radiation-induced injury to the rectal mucosa, occurring three months after treatment. The clinical incidence varies from 5-20% in published series[Babb, 1996] and is dependant on the dose of radiation and the rectal volume in the irradiated field[Roeske et al., 1997]. Factors such as diabetes and combination with chemotherapy have been shown to increase the incidence of proctitis[Greven et al., 1991;Herold et al., 1999].

The microscopic features of acute phase proctitis include meganucleosis, fibroblastic proliferation, inflammation of the lamina propria, eosinophillic infiltrate, lack of mitotic activity, and loss of crypts[Varma et al., 1986]. There is mucosal hyperaemia, which may be accompanied by excessive production of mucus. With increased doses a pellicle of dead cells forms on the mucosal surface and this may separate before the epithelial and submucosal layers have regenerated leaving an ulcerated area. When complete epithelial loss occurs it is replaced with fibrous tissue resulting in a scar.

The microscopic appearances in late phase radiation proctitis include severe vascular changes with narrowing of arterioles by subintimal fibrosis, telangectasia of capillaries and post-capillary venules, endothelial degeneration and platelet thrombi

formation. These vascular changes are associated with severe fibrosis of the lamina propria and crypt distortion[Haboubi et al., 1988]. After chronic radiation exposure, fibrosis of supporting tissues results in contraction and stricture formation and the decreased regenerative properties of damaged tissue can result in fistula formation.

Other features of chronic radiation injury include histological changes in the smooth muscle and neuronal plexuses in the gut wall. Varma et al[Varma et al., 1986] described hypertrophy of the muscularis mucosae and the muscularis propria. Neuronal hypertrophy was seen in the muscular (Auerbach's) plexus but not in the submucosal (Meissner's) plexus. Decreased numbers of ganglion cells with vacuolation and degranulation also provide evidence of significant insult to the myenteric nerves.

1.6.2 Histopathological Features In The Anal Canal

Despite an extensive search of the literature, histological reports of post-radiation changes in the anal canal are lacking. Short and long term effects on sphincter morphology are unknown. The reasons for this include the inability to biopsy the anus without general anaesthesia combined with the risk of anal injury in doing so, as well as the inherent difficulties in obtaining tissue specimens from the anal canal of patients who have previously received pelvic RT.

1.6.3 Imaging The Radiation Injured Anorectum Rectum

Sigmoidoscopy

The classical appearances of radiation proctitis, which may be directly visualised via a rigid or flexible sigmoidoscope, are pallor or erythema, prominent telangectasia,

mucosal friability and ulceration[Babb, 1996](**Fig. 1.3**). Sigmoidoscopy has the advantage of allowing tissue diagnosis, although fibrosis, luminal narrowing and rigidity of the rectal wall may impede advancement of the instriment, preventing examination of the entire abnormal area[den Hartog et al., 1989]. Wachter et al described rectal mucosal damage after conformal radiotherapy of prostate cancer and introduced a six-scaled rectoscopy score based on the standardization of the endoscopic terminology published by the ESGE (European Society for Gastrointestinal Endoscopy) [Wachter et al., 2000].
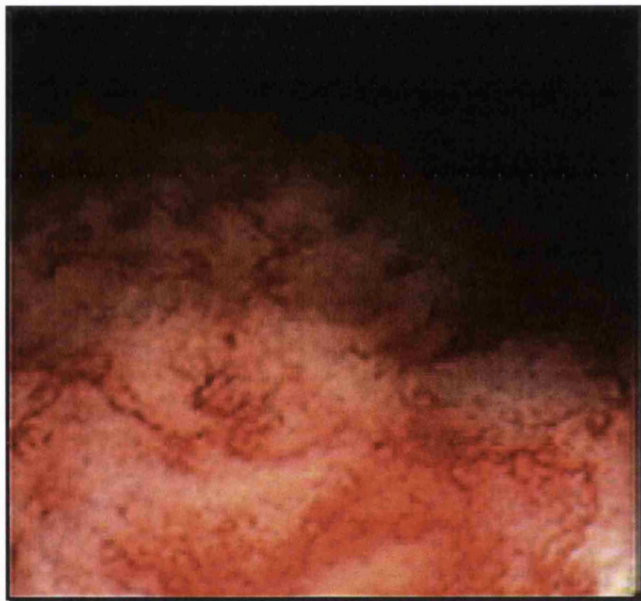
Fig. 1.3 The sigmoidoscopic appearance of radiation proctitis

Barium enema

The main radiological features of radiation injury are decreased distensability of the bowel wall, intestinal fixation, stenoses and fistula formation. If stenosis is present a lack of pre-stenotic dilatation is characteristic. Barium enema is less sensitive than

endoscopy in outlining mucosal abnormalities and ulceration, but is reliable in showing the extent of disease and structural deformity [den Hartog et al., 1989].

Ultrasound

Trans-rectal Ultrasound (TRUS)

TRUS involves passage of a dedicated ultrasound probe allowing longitudinal and transverse images of pelvic structures through the rectum. This has been employed in the assessment of chronic rectal complications after pelvic RT for carcinoma of the cervix. In 67 patients the most consistent finding was thickening of the perirectal connective tissue associated with obscuring of the echogenic submucosal layer in the anterior rectal wall[Shiojima et al., 1998]. TRUS has been used to detect recurrent prostate and bowel cancer but there are no reports on its reliability in differenting malignant from radiation changes.

Endoanal Ultrasonography

A dedicated ultrasound probe is inserted into the anal canal providing a 360-degree view of the anal canal. Endoanal ultrasonography has been employed to assess the anal sphincters after pelvic RT although the results have been inconclusive [Solomon et al., 1995];[Yeoh et al., 1996, 2000]. Again these studies represented a mix of retrospective and prospective data on different groups of patients undergoing different radiotherapeutic regimens. A study of 35 patients treated for carcinoma of the prostate four to six weeks previously did not demonstrate any morphological changes in the internal anal sphincter or external anal sphincter at this early stage [Yeoh et al., 1998] or one year after RT [Yeoh et al., 2000]. A study including five patients who had RT to the rectum three to six months previously showed a significant increase in anal wall

thickness when compared to controls[Solomon et al., 1995]. Anal wall thickness was measured from the anal mucosa to the extreme portion of external anal sphincter. In a retrospective study of patients who had been irradiated for cervical and endometrial carcinoma five to ten years previously four of the 15 patients had a thinner internal anal sphincter, but the external anal sphincter was unchanged [Yeoh et al., 1996]. There have been no prospective data on the long-term changes in sphincter morphology.

Computerised Tomography (CT)

The commonly described features of radiation injury on CT scanning are increased density and thickening of the perirectal fat, thickening of the perirectal fascia and rectal wall and fibrosis between the sacrum and rectum[Doubleday and Bernardino, 1980]. However, the sensitivity of CT scanning in differentiating radiation changes from recurrent or secondary malignancy is debated[Doubleday and Bernardino, 1980]'[Watanabe et al., 1995].

Positron Emission Tomography (PET)

PET has been investigated as a tool for distinguishing tissue changes associated with RT from tumour recurrence. Due to the enhanced glycolytic activity of proliferating cells following radiation injury it has not been possible to distinguish between proliferation, repair, inflammation, and residual viable tumour cells[Engenhart et al., 1992]. PET may prove more useful in detecting recurrence six months after RT, by which time much of the inflammatory reaction may have resolved[Haberkorn et al., 1991].

Magnetic resonance imaging (MRI)

MRI shows increased signal intensity with the inflammatory changes associated with pelvic RT and a characteristic pattern of varying oedema has been described by Blomlie et al (1996). The increased signal intensity reported in this study was assessed visually. Irradiated soft tissues also show enhancement with intravenous gadolinium contrast [Fletcher et al., 1990]. Dynamic gadolinium enhanced MRI has been used to outline changes in the vascularity of pelvic tumours (cervical cancer) [Gong et al., 1999] and the subsequent response to RT but there are no reports of its utilisation in the quantitative assessment of post-RT changes in the anorectum. Sugimura et al (1990) employed un-enhanced MRI techniques to determine post-irradiation changes in the pelvis and reported a grading system for the bladder and the anorectum. They showed dose-related changes in a number of pelvic organs once a threshold prescribed radiation dose of 45Gy had been exceeded. However this study was retrospective, included a wide variation of target organs, a large proportion of the patients received adjunct chemotherapy and a number of the patients also received brachytherapy.

MRI may be reliable in differentiating radiation changes from recurrent tumour in cases of carcinoma of the vagina and cervix[Chang et al., 1988;Ebner et al., 1988], but appears less reliable in rectal cancer[de Lange et al., 1992]. Dynamic contrast enhanced MRI has been investigated in differentiating benign and malignant recurrent pelvic masses after RT and/or surgery for pelvic cancer, but it did not reliably separate lesions in patients who had radiotherapy [Hawnaur et al., 1998].

1.7 THERAPUTIC OPTIONS AFTER RADIATION INJURY TO THE ANORECTUM

1.7.1 Haemorrhagic Proctitis

i) Chemoprevention

The prophylactic use of certain agents in an attempt to reduce rectal complications has been reported. Eicosanoids and free radical release have been implicated in the pathogenesis of radiation damage. *Mesalazine* (5-ASA) is a potent inhibitor of their synthesis in the mucosa and has therefore been tested as a chemopreventative agent. However a multi-centered double-blind placebo controlled trial involving 153 patients failed to show any benefit over placebo in the prevention of acute radiation enteritis[Resbeut et al., 1997]. Another study suggests that 5-ASA containing compounds may actually increase proctitis during radiation therapy[Martenson, Jr. et al., 1996].

Sucralfate is an aluminium hydroxide complex of sulphated sucrose and is believed to reduce microvascular injury and promote angiogenesis through its action on mucosal basic fibroblast growth factor[Korman et al., 1994]. Oral sucralfate has been used prophylactically to reduce the incidence of proctitis and has been shown to be beneficial in some double-blind placebo controlled trials[Henriksson et al., 1992;Henriksson et al., 1991]. A further double-blind controlled trial involving 86 patients using sucralfate enemas failed to show any significant benefit over placebo in the short term[O'Brien et al., 1997]. A recent randomised study of 123 patients showed no benefit from oral sucralfate and some symptoms including nausea and faecal incontinence were significantly worse in the sucralfate treated group[Martenson et al., 2000].

WR-2721 is an organic thyophosphate with radioprotective properties. It has been tried both intravenously[Mitsuhashi et al., 1993] and in an enema form[Montana et al., 1992] to reduce radiation injury. Again, no significant benefit was shown with either route of administration.

Misoprostol is a prostaglandin E_1 analogue with anti-inflammatory properties. Suppositories used one hour before each fraction of RT have been shown to be effective in reducing both acute and chronic proctitic symptoms in a prospective randomised study[Khan et al., 2000]. However with only 16 patients reported, larger studies are necessary before this strategy can be widely embraced.

ii) Pharmacotherapy

Amino salicylic acid derivatives either orally or rectally have not been shown to be of benefit in the treatment of radiation proctitis and may actually increase the severity of proctitis when given prophylactically [Martenson, Jr. et al., 1996];[Baum et al., 1989];[Triantafillidis et al., 1990].

Steroids have been used to treat radiation proctitis both alone and in combination with other agents. Experiments in dogs investigating the value of oral prednisolone in treating the irradiated rectum showed no benefit[Stryker et al., 1976]. Kochhar (1991) performed a small prospective randomised double blind study comparing oral sulfasalazine and prednisolone enemas (n=15) with oral placebo and sucralfate enemas (n=17). Both groups were comparable in duration of symptoms and

endoscopic scores of proctitis. Improvement was seen in both groups but patients were significantly better by clinical criteria on the sucralfate regime.

Topical sucralfate suspension has been reported to be beneficial in the acute phase and in treating chronic proctitis [Kochhar et al., 1991];[Sasai et al., 1998];[Stockdale and Biswas, 1997]. A study of 26 patients treated with 20mls of 10% sucralfate enemas twice daily, showed a good response in 20 patients at four weeks and in 24 patients at 16 weeks. At a mean of 45.5 months, seven patients had further bleeding, who again responded to further sucralfate therapy. Two patients required surgery to stop bleeding and 10 had other complications including rectal stricture (3) intestinal stricture (1), vaginal stenosis (1) and haematuria (6) [Kochhar et al., 1999].

Short chain fatty acids are the main energy source of colonocytes and their use may be impaired in chronic radiation proctitis. It has been hypothesized that a plentiful supply of this substrate might prevent mucosal hypoplasia and progression to chronic inflammatory changes. Pinto et al (1999) described their use in a placebo-controlled double-blind randomised controlled trial in 19 patients. They were found to accelerate the healing process with a significant early reduction in bleeding episodes and endoscopic scores. However at six months no significant difference was demonstrable when compared to placebo. Another randomised double-blind placebo controlled crossover study involving 15 patients performed by Talley et al (1997) found no benefit.

A *4% formalin solution* instilled into the rectum has been shown to be safe and effective in stopping bleeding in more than 75% of cases including those resistant to

other therapies[Counter et al., 1999];[Saclarides et al., 1996]. Counter et al (1999) reported a study of 16 patients with chronic haemorrhagic proctitis requiring transfusion and resistant to other treatments. Formalin was instilled into the rectum, aspirated and the rectum irrigated with saline every 30 seconds between each 50ml aliquot. Bleeding stopped in all patients although more than one treatment was sometimes required and two patients developed significant anal fissures. One of these patients also had significant tenesmus and reduced rectal capacity. Rectal instillation has been carried out with or without anaesthesia. Formalin soaked onto gauze or a cotton tipped applicator has also been applied in the outpatient setting[Roche et al., 1996].

Hyperbaric oxygen

Hyperbaric oxygen therapy has been reported to be effective in more than 50% of cases in a number of small studies[Woo et al., 1997];[Warren et al., 1997]. The largest of these was a study by Warren et al (1997) who treated 14 patients in 100% oxygen at two atmospheres. Symptoms resolved completely in eight patients with significant improvement in another patient. Hyperbaric oxygen therapy is thought to act by promoting neoangiogenesis and revascularisation [Plafki et al., 1998]. However experience is limited as there are only a few centres with the facilities for this treatment.

iii) Endoscopic Treatment

This can be most successful in treating haemorrhage secondary to bleeding telangectasia as opposed to diffuse haemorrhagic proctitis.

Endoscopic bipolar electro coagulation and *heater probe* treatment were shown to be effective (75% and 67% respectively) in treating chronic bleeding from radiation telangectasia in a randomised prospective study of 21 patients [Jensen et al., 1997]. Patients responded within four treatment sessions and all patients reported an improvement in their quality of health as well as in their ability to travel and exercise.

Argon beam coagulation has been used with some success. Fantin et al (1999) reported complete symptom relief in 7 patients with bleeding and tenesmus from late-phase radiation proctitis. Silva et al (1999) reported significant improvement in rectal bleeding in all but two of 28 patients with persistent proctosigmoiditis resistant to medical treatment. Taylor et al (1993) reported good control of bleeding treated with argon laser after only two outpatient sessions although 10 of the 14 patients in the study required maintenance treatment.

Nd:Yag laser treatment has also been shown to be effective in mild to moderate bleeding by Barbatzas et al (1996) who treated nine patients and reduced the bleeding to spotting only in six. Alexander and Dwyer (1988) treated eight patients with persistent radiation induced proctosigmoiditis significantly reducing transfusion requirements. Multiple treatments were required and there were three major complications due to prolonged ileus. No other major complications were reported in any of the other endoscopic treatment studies described above.

iv) Surgery

Surgery is reserved for the minority of cases with intractable proctitis resistant to the above therapies[Lucarotti et al., 1991];[Yegappan et al., 1998]. Resection and colo-anal-pull-through, may be possible [Nowacki et al., 1986];[Gazet, 1985];[Cooke and de Moor, 1981] in those patients who have retained good sphincter function. Allen-Mersh et al (1987) reported a successful result in eight of 11 patients using the Park's technique. This technique involves resection of the diseased segment, the mucosa is then stripped off the rectal remnant and healthy colon brought down through the "rectal sleeve" to be anastomosed to the mid-anal canal at the dentate line. Von Flue et al (1996) developed an ileocaecal reservoir to improve functional outcome. The ileocaecal segment was isolated on its lymphovascular pedicle, rotated counter clockwise, and anastomosed at the dentate line, thus providing a neorectal segment with intact intrinsic and extrinsic nerve and lymphovascular supply. Only two patients were treated but a good functional result was achieved. Maximum tolerated volumes, compliance, and anal manometry were comparable to those in patients undergoing a low anterior resection for rectal cancer.

A colostomy is the preferred option in unfit patients or where recurrent malignancy is established or expected [Anseline et al., 1981].

1.7.2 Rectal Stricture

(i) Endoscopic treatment

Although there are isolated reports of endoscopic balloon dilatation and stenting for radiation induced rectal stricture, there are no large series to define the criteria for

patient selection, the functional outcome or the long term results following this form of treatment.

(ii) Surgery

As with other radiation-induced complications, restorative surgery should only be considered if the patient is otherwise healthy and cured of cancer and if the surgery can be performed safely and with a satisfactory functional result that is dependant on an intact sphincter mechanism. In these patients resection of the diseased segment with a pull-through coloanal technique avoiding anastomosis to an ischaemic irradiated rectum and a temporary proximal defunctioning stoma is a feasible option [Miholic et al., 1988]. Otherwise, diversion alone is the preferred alternative.

1.7.3 Faecal Incontinence

Although there are numerous therapeutic options for the treatment of faecal incontinence many of these are contraindicated in patients with radiation damage to the anal canal. The presence of proctitis may increase the severity of symptoms. Conservative therapies include the use of anti-diarrhoeal agents such as loperamide [Yeoh et al., 1993c] or codeine, but long-term use of medications may be an unsatisfactory solution for some patients. The use of pads may lead to further excoriation to radiation damaged perineal skin and many patients find anal plugs uncomfortable[Mortensen and Humphreys, 1991]. Topical agents to enhance internal anal sphincter muscle function such as phenylephrine cream may have a role in faecal incontinence [Carapeti et al., 1999] but these have yet to be tested in radiation-induced incontinence. Injectable bulking agents such as cross-linked collagen have had limited success when placed around a weakened internal anal sphincter

muscle[Kumar et al., 1998] but the risk of local complications in these patients does not justify this approach.

A major drawback for any surgical intervention in an irradiated field is the increased risk of tissue breakdown and infection. An artificial anal sphincter has been implanted in one patient with radiation injury and this resulted in intense perineal pain, which necessitated removal of the device[Lehur et al., 1998]. Radiation damage is now regarded as a contra-indication to the use of this device and the use of the dynamic graciloplasty[Sielezneff et al., 1999] is probably equally hazardous. Sacral nerve stimulation has proved beneficial in some patients with passive faecal incontinence. It is believed to work, at least in part through an alteration of local reflexes affecting rectal capacity and compliance[Matzel et al., 1995];[Vaizey et al., 1999] though these effects may be compromised in patients with proctitis. The simplest surgical option for intractable faecal incontinence secondary to radiation injury is a colostomy.

CHAPTER 2:

AIMS OF STUDY

AND

STUDY PLAN

2.1 INTRODUCTION

Radiotherapy is an essential treatment modality for urological malignancy, but its benefit is associated with anorectal injury that constitutes a major clinical problem. Symptomatic treatment has not been satisfactory and is of limited value. Surgery is the only resort for complications that may ensue and even with careful patient selection outcomes are frequently unfavourable. Chemoprevention has been largely unsuccessful although misoprostol deserves further evaluation. The use of newer techniques such as CT planning, three-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) may improve outcome. However, these techniques are often concerned with dose escalation to the tumour being treated in order to increase the chance of cure as opposed to reducing the dose to the surrounding structures. The lack of effective therapies to treat anorectal radiation injury makes protection of the anorectum from radiation damage so important. This is better approached with some understanding of the exposure of the anorectum to irradiation during treatment and measurement of functional and structural changes in relation to treatment dose.

Current knowledge of the effects of radiation therapy on the anorectum is based on a limited number of studies, mostly retrospective and often on small numbers of patients with variable periods of follow-up. The reported studies have involved different target organs, varied doses and delivery techniques. Although total treatment doses are usually reported there is frequently a lack of accurate dosimetric information. As there has been no direct measurement of the dose received by the anorectum, the evidence is somewhat indirect and circumstantial. With accurate

dosimetric data causative association between radiation injury and functional disturbance could be clearer.

Radiotherapy delivery varies between centres and there is rapidly evolving technical development in a field that is constantly changing. One example of new technology was seen within the duration of this study (a change from the use of the TARGET™ to the HELAX™ treatment planning system). Differences in delivery technique compounded by numerous and varied criteria in classifying the reported post-irradiation sequlae, has lead to further confusion in the literature.

Since anal canal dysfunction after radiotherapy was reported by Varma et al (1986) the precise underlying disturbance in the anal canal after radiotherapy has not been broadly examined. Faecal incontinence after pelvic radiotherapy is a particularly unpleasant disability and is of particular concern, especially in elderly patients with degenerate anal sphincters who are more likely to receive this form of treatment. Anal canal irradiation may be an important causative factor in anal canal dysfunction because of the close proximity of the anal canal to the prostate gland. Differing doses received by the anal canal, therefore, would seem a reasonable explanation for some of the discrepancies in the reported incidence of faecal incontinence in the literature. Currently, there is no data available as to the degree of anal canal irradiation during pelvic radiotherapy for urological malignancy.

Several studies have examined the changes in anorectal function after RT by anorectal physiology (ARP). Of the reported work, the only prospective studies were those performed by Yeoh and his colleagues (1998) (2000) who have identified a high

incidence of anorectal symptoms after radiotherapy for prostate cancer and demonstrated evidence of physiological disturbance. Yeoh and his colleagues further observed that anorectal symptoms commonly persisted for a year after completion of treatment, and were associated with 'heightened rectal sensitivity'. 'Rectal sensitivity' was measured by inflating a rubber balloon in the rectum and recording the insufflated volume at which the patient first perceived a stimulus and first sensed the urge to defecate. 'Heightened rectal sensitivity' was a conclusion drawn from an observation of lower volumes of insufflation resulting at first perception (threshold volume) and desire to defecate (urge volume). A reduction in rectal capacity and compliance as a consequence of post-irradiation inflammation and oedema with tissue rigidity could be an alternative explanation for lower threshold and urge volumes that Yeoh reported. While rectal sensation is frequently measured in this manner rectal electrical sensitivity is a more accurate, quantifiable and reproducible measurement that avoids the variables of balloon dynamics, rectal diameter and compliance [Kamm et al., 1990]. An electrode is inserted into the rectum and a 10 Hz current applied at increasing amplitudes until the patient detects a dull ache. The amplitude of this current is the rectal electrical sensitivity. This technique for the assessment of rectal sensation has not been reported in the context of radiation injury and may be more relevant.

There are few studies that have investigated the structural changes in the anorectum following pelvic radiotherapy. Endoanal ultrasound studies have been equivocal. In one study there was no change in the morphology of the anal sphincters [Yeoh et al., 1998, 2000]. An earlier study from the same group (1996) reported thinness of the internal sphincter in four of 15 patients when endoanal ultrasonography was

performed five to ten years after radiotherapy. In another study of only 5 patients anal wall thickness was increased [Solomon et al., 1995]. MRI has been utilised mainly to differentiate radiation changes from recurrence following treatment of pelvic tumours. Dynamic gadolinium enhanced MRI has been employed in measuring the response of pelvic tumours by comparing the vascularity in the tumour before and after treatment. The imaging properties of dynamic MRI could provide quantitative assessment of post RT changes in the anorectum.

While several studies have investigated anorectal dysfunction after radiotherapy for pelvic malignancy many were retrospective on a mix of patients undergoing different radiotherapeutic regimes. Only a few prospective studies were related to the effects of RT for urological malignancy [Borghede et al.,1997];[Yeoh et al., 1998, 2000] [Boersma et al ., 1998];[Wachter et al., 2000]. Borghede's study analysed anorectal symptoms following RT according to the RTOG Toxicity scale (Table 1.3). This score may be flawed as it does not include a number of anorectal symptoms, specifically anal/rectal pain and faecal urgency. Detailed dosimetric data was not included in this report. Boersma et al (1998) utilised Dose-Volume Histogram (DVH) parameters to attempt to identify risk groups for developing late gastrointestinal (GI) complications after conformal radiotherapy prostate cancer. The impact of the total radiation dose, and the maximum radiation dose to the rectum and bladder was analysed. No significant correlation was found between any of the DVH parameters and the actuarial incidence of complications though a trend towards a higher incidence of rectal bleeding was observed with a total radiation dose more than 74 Gy. Wachter et al (2000) described rectal mucosal damage in an endoscopic study after conformal radiotherapy for prostate cancer. In general, the endoscopic findings

increased from the upper (proximal) rectum to the anorectal transition, as well as from the posterior to the anterior rectal wall. This corresponded to the area of highest dose according to the DVHs. Symptomatic patients had worse endoscopic scores though significant mucosal damage was also detected in asymptomatic patients. Yeoh's studies (1998) (2000) have already been discussed in some detail.

A prospective study addressing the weaknesses of previous work is the main theme of this thesis.

2.2 AIMS OF THE STUDY

This work attempts to clarify some of the controversial issues raised with the aim of determining prospectively the incidence and extent of radiation injury to the rectum and anus and the functional and structural changes that follow RT for urological malignancy. This is conducted by:

1. Measurement of the dose of radiation received by the anal canal and rectum in order to correlate any functional and structural changes, to the dose received.

2. Determining the acute effects of pelvic RT on anorectal function using a combination of questionnaire and anorectal physiology.

3. Determining the acute effects of pelvic RT on the structure of the anorectum using endoanal ultrasonography and dynamic contrast enhanced MRI.

Serial rectal biopsy in order to follow the histological changes in the rectum after RT is desirable. Due to potential risk of healing of the biopsy site prior to RT and risk of impaired healing after RT, only a biopsy at six months gained Ethical approval. However this was abandoned because the majority of patients recruited to the study were reluctant.

2.3 PATIENTS AND STUDY PROTOCOL

2.3.1 Patient Selection

Ethical approval for the study was obtained from the Joint University College London/University College London Hospitals Committees on the Ethics of Human Research. Patients were recruited from the Oncology Clinics at the Middlesex Hospital and at Ashford Hospital. Potential patients for the study were given an information sheet **(Appendix 1)** at their clinic appointment. Prior to the commencement of treatment the project was discussed in detail and consent was obtained **(Appendix 2)**. Occasionally patients were willing to participate in most but not all parts of the study.

Patients included in the study were male patients of up to 85 years of age with urological malignancy due to undergo pelvic RT as the main treatment for their disease. The exclusion criteria included patients:

- who have had previous pelvic RT.

- with anorectal malignancies.

- with rectal prolapse.

- with perianal sepsis.

- already taking medications likely to influence anorectal function.

The selection criteria were designed to avoid any confounding variables that may influence the results. Restricting the study to males within a reasonably tight age range (55-82 years median age 70) eliminated the effects of pelvic floor abnormalities found predominantly in women. Patients who had previously received RT to the

pelvis were excluded to avoid the compounding unknown effect of this previous treatment. Patients with anorectal malignancies were unsuitable candidates as the lesion would have affected anorectal function and those with rectal prolapse and perianal sepsis often have associated anal sphincter dysfunction. While several of the patients were receiving zoladex™ (goserelin acetate, Astra Zeneca™) injections before and during the study as part of the management of their disease, intestinal side effects from zoladex™ injections are very uncommon, and this was unlikely to interfere with the results of the study. The fact that almost all the patients received the same total prescribed radiation dose ensured consistency within the study group.

2.3.2 Study Protocol

Patients were interviewed and completed detailed incontinence and proctitis questionnaires prior to commencement of their RT. A full anorectal physiological assessment, endoanal ultrasonography and a pelvic MRI including a dynamic gadolinium enhanced sequence were then performed. After RT, a number of the patients underwent in-vivo measurements using a specially modified diode containing rectal probe to determine anorectal doses. Six weeks and six months after completion of the RT course patients were again interviewed and the investigations repeated.

Table 2.1 Study Protocol

	Day 0	1st Week Of RT	6 Weeks After RT	6 Months After RT
1. Fully informed consent	X			
2. Measure dose of radiation		X		
3. Incontinence score questionnaire	X		X	X
4. Proctitis score	X		X	X
5. Anorectal physiological testing	X		X	X
6. Endoanal ultrasound	X		X	X
7. Gadolinium enhanced pelvic MRI	X		X	X

2.3.3 Patient Demographics/Completion

The study included 30 men with prostate (n=27) and bladder cancer (n=3). The median age of the group was 70 years (range 55-82 years). Three other patients, a man with advanced prostate cancer and two women with gynaecological malignancy were involved in the initial dosimetry study but did not take part in the main study. Only 1 patient dropped out of the main study prior to completing the six-week post-RT investigations. At the patients' discretion some investigations were not performed. **Appendix 3** shows patient demographics and **Appendix 4** details the completion of investigations for individual patients. These tables will be referred to throughout this thesis.

The study size provided adequate statistical power for a non-randomised single sample study such as this one. For example, to detect a 10% change in anal canal pressure after RT, 27 patients provide greater than 98% power and 10 patients provides greater than 85% power. Data collected was tested for normality of distribution using the Shapiro-Wilk test. The significance of differences between results after RT was examined by the paired t-test when data were normally distributed and by the Wilcoxon signed-rank test when the data were not normally distributed. Changes in measured parameters after RT were correlated with radiation dose using Pearson's correlation.

CHAPTER 3:

ESTIMATION OF

ANORECTAL DOSE

3.1 INTRODUCTION

In order to carry out a meaningful study on the effects of radiotherapy on the anorectum it is necessary to obtain dosimetric data. The relationship of rectal radiation dose during RT for prostate cancer with rectal complications [Boersma et al., 1998] and endoscopic changes [Wachter et al.,2000]has been reported. These studies relied on dosimetric information from a dose volume histogram (DVH) that has been derived from a planning CT scan. This is an indirect assessment of rectal dose. There have been no studies that correlate rectal dose and its relation to subsequent functional disturbance with anorectal physiology.

No studies whatsoever have attempted to measure anal canal irradiation.

In order to estimate the degree of anorectal irradiation during pelvic RT a device was developed to measure *in-vivo* dose to allow comparison with the predicted dose data obtained from the radiotherapy treatment plans.

3.2 DEVELOPMENT OF DOSIMETRY TECHNIQUE

3.2.1 The anorectal probe in a simulated model

A Scanditronix[TM] rectal probe containing 5 radiation-detecting diodes, used for the measurement of rectal doses in patients undergoing brachytherapy for cervical cancer, was supplied by the Medical Physics Department (**Fig. 3.1**). This device is not designed for the measurement of mega-voltage x-rays and has not previously been used for this purpose. It was therefore necessary to modify the probe and evaluate its application for the purpose of the study. A restricting collar was incorporated to limit the level of insertion of the probe into the anorectum, and ensure that the positions of the diodes were constant and were sited across the anal canal and lower rectum. The collar was constructed from a 30mm diameter Perspex cylinder with a 7mm hole bored through the centre to allow it to fit over the body of the rectal probe.
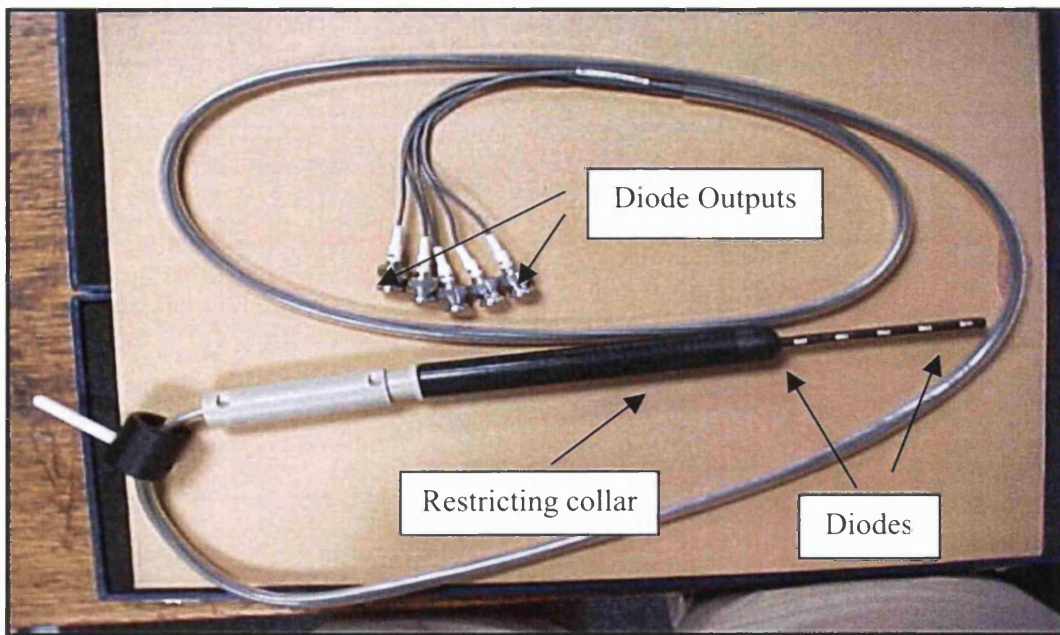
Fig. 3.1 Scanditronix rectal probe with restricting collar

The basic set up for the dosimetry measurements is as shown in **Fig. 3.2** below. Diodes are used to detect photons and thus measure radiation doses. Silicon diodes contain a sandwich of a second metal, which acts as an electron donor or recipient. The disparity in electron number provides a potential difference across the diode. P type diodes are positive (less electrons) and N type are negative (more electrons). As the x-rays collide with the diodes they result in ionisation and liberated electrons flow as a current to the electrometer and are registered as a count. This count is directly proportional to the number of photons hitting the diodes and hence the radiation dose. The five diodes contained within the probe each have their own output and are attached via a five channel co-axial cable to a five-channel electrometer.
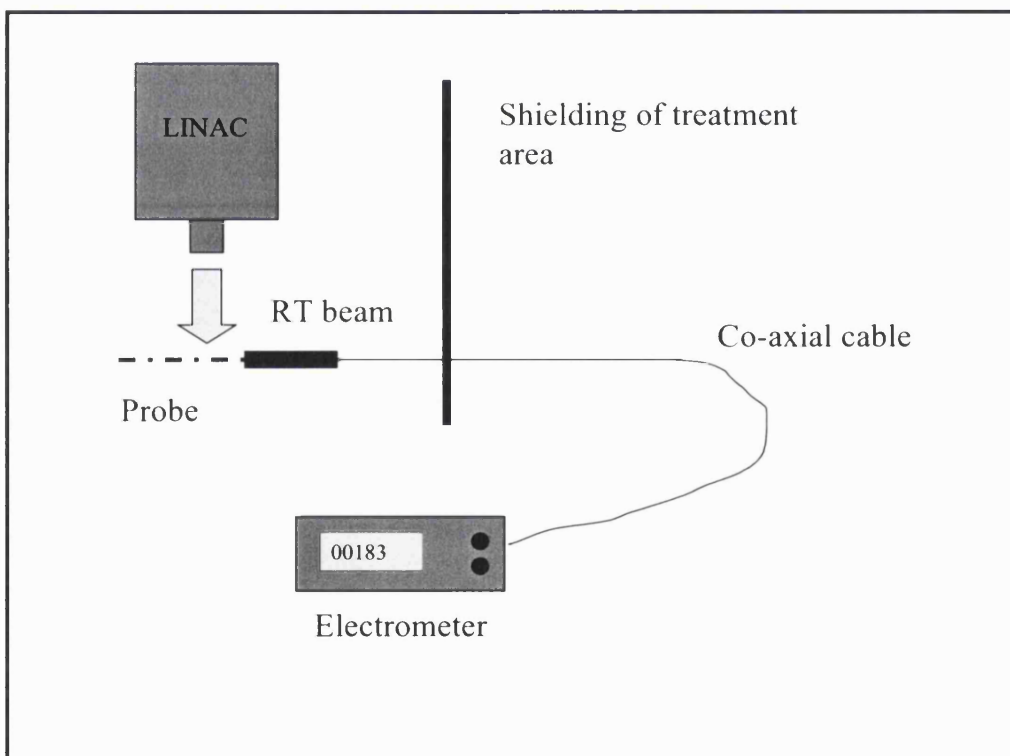
Fig. 3.2 Set-up for dosimetry experiments

3.2.2 Calibrating the diodes in the probe

Before measurements were undertaken in patients, a simulated model was used with the probe surrounded by gel bags of a similar radio-density to body tissue. The diodes were calibrated and a correction factor calculated in order to convert the count on the electrometer to a dose in Gray. Using the 'LINAC 21' (Linear accelerator 2100CD ($Varian^{TM}$) an ionisation chamber was irradiated with a uniform field large enough to irradiate all the diodes. Having obtained an accurate dose from the treatment machine the diodes were then irradiated and the electrometer count for each diode was noted. A correction factor (actual dose / diode measured dose) was then calculated for each of the diodes individually. The N-type diodes contained in the probe are both dose-rate and energy dependent in their response and were therefore calibrated in the same field that is used in treatment. N-type diodes are not designed for exposure to mega-voltage x-rays and can change their characteristics and become less sensitive after repeated exposure. Periodic recalibration of the diodes was therefore necessary and this was performed three times throughout the duration of the dosimetry experiments. The individual correction factors for each diode on each calibration are shown in **Table 3.1**. As shown the standard deviation in any particular diode was no greater than 5% throughout the course of the study.

Table 3.1 Correction Factors For Individual Diodes (No units)

DIODE NO	CALIB 1	CALIB 2	CALIB 3	STD.DEV
1	1.298	1.211	1.224	0.047
2	1.238	1.201	1.224	0.019
3	1.264	1.238	1.242	0.014
4	1.318	1.313	1.271	0.026
5	1.227	1.228	1.197	0.018

To further verify the diode doses when measurements were being taken in patients,

Thermo-Luminescent Dose-meters (TLDs) were attached over the sites of the diodes with adhesive tape in the first few cases. TLDs give a dose accuracy within 5-10% and are generally less reliable than diodes. They were included initially as the diodes had not been used in this particular field strength previously. Precise agreement between diodes and TLDs was not expected. **Appendix 5a** shows the agreement between diode-measured doses and the TLDs.

3.2.3 A problem with dosimetry

During the first attempted measurements in a patient there seemed to be leakage from the diodes (or reversal of current) i.e. the counter measuring dose was counting negatively between bursts of radiation. This had not occurred in the simulated model.

The mega-voltage x-rays are produced by accelerating electrons along a wave-guide using radiofrequency (RF) electromagnetic waves and are then stopping them abruptly with a heavy metal target. The RF device is called a magnetron, and is essentially a very powerful electromagnet. The RF electromagnetic field produced by this magnetron appeared to be a likely cause for this reversal of current. It was unclear why this only seemed to occur with the probe in the anorectum but not in the simulated model. This phenomenon was further investigated.

The above phenomenon was reproducible in the 'LINAC 8' machine when the probe tip was immersed in a water bath to simulate the patient as but not in the gel bag model. A water bath was utilised in case the composition of the patient (i.e. mainly water) was affecting the measurements. The negative count therefore seemed to be related to an interaction between the radio-frequency electromagnetic field and the

water/patient. The magnetron from the 'LINAC 8' produces its magnetic field out of phase (not in time with) delivery of the photon beam and the magnetron itself was an older model. The water bath experiment was therefore repeated in the 'LINAC 21' as this is a more modern machine with a magnetron, which is in phase with the photon beam it produces. The erroneous count presumed to be due to the reversal of current was abolished. Therefore either the newer magnetron did not produce this 'reversal of current' or the effect was masked as there was no time gap between switching on the magnetron and the delivery of the photon beam (i.e. no time to notice the electrometer counting backwards).

The 'LINAC 8' was reinvestigated with the water bath experiment using an oscilloscope to test the waveform from the diodes. Initially the phenomenon was not seen at all. The only change in set-up on this occasion was the use of a different co-axial cable from the probe to the electrometer. When the cable used previously was reconnected, leakage of current again occurred. It was clear that inadequate shielding of this one co-axial cable was responsible for the reversal of the count on the electrometer. The faulty cable was therefore discarded and no further problems were encountered.

3.3 COMPARISON OF TARGET™ PREDICTED AND DIODE MEASURED DOSES IN PELVIC RADIOTHERAPY

3.3.1 Introduction

During RT the expected doses at any target organ are calculated by computerised systems based on an initial planning CT scan. These systems account for changes in the energy of the radiation beam as it collides with the tissues including calculation of photon interactions and scatter. Over the initial period of the study patients were planned for RT using a GE *TARGET*™ treatment planning system, which was subsequently replaced with the more sophisticated *HELAX*^{TM} treatment planning system. The purpose of the study was to compare anorectal doses measured with the probe and those predicted by the *TARGET*™ treatment planning system. Comparisons of measured doses with predicted doses from the *HELAX*^{TM} treatment planning system are described in 3.4.

3.3.1 Patients and methods

Nine patients were recruited with prostate (5), bladder (2), cervical (1) and endometrial (1) cancer. All patients were CT planned using a GE *TARGET*™ treatment planning system with the rectal probe placed in the anorectum during the planning CT scan.

After performing a digital rectal examination the probe was inserted with the patient lying in the left lateral position. The patient was then returned to the supine position on the CT table and aligned in the normal way for planning. Knee rests were avoided as these interfered with the probe position. Once alignment was complete the probe was

secured to the table with adhesive tape after ensuring that the restricting collar was abutting the anal verge. This ensured that the probe position was standardised with the diodes at 2cm intervals from the anal verge (**Fig. 3.3**). Diode 1 is situated in the rectum (most proximal). Diodes 3-5 cross the anal canal,
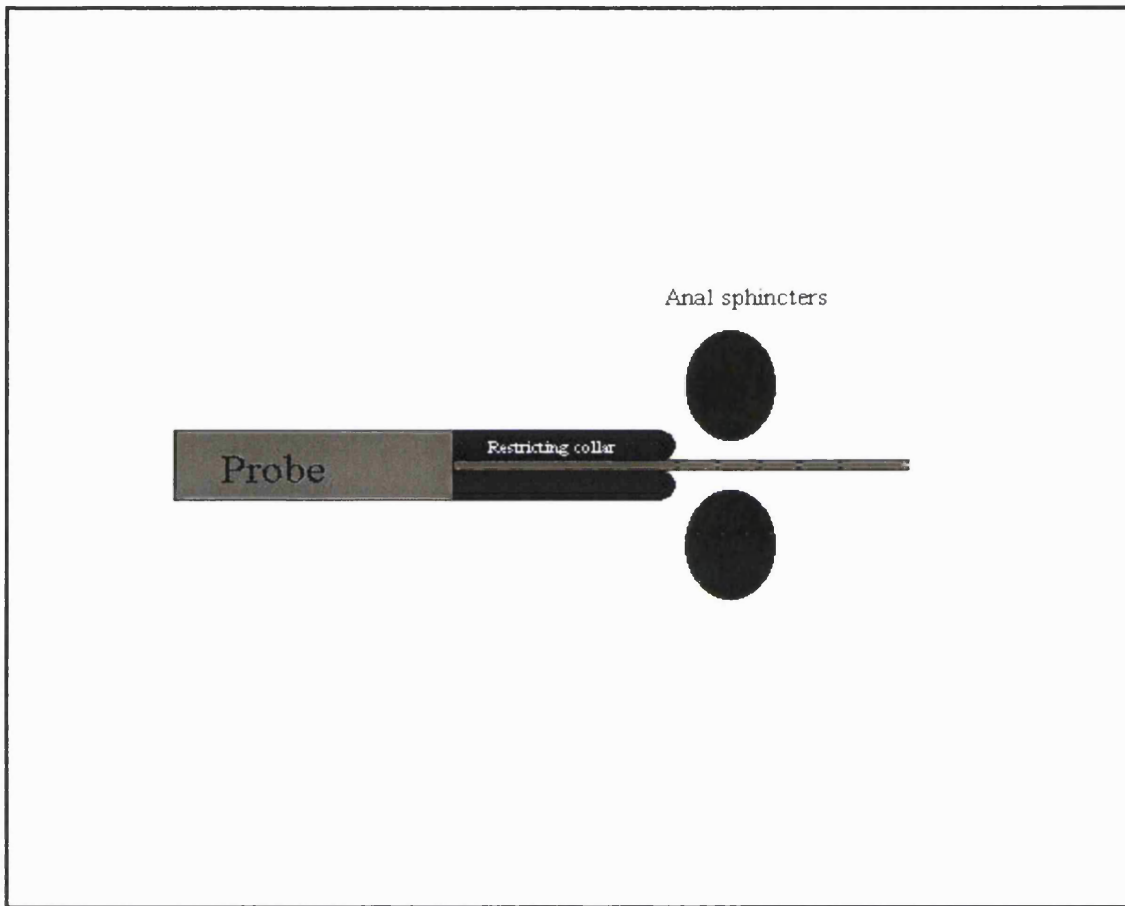
Fig. 3.3 Schematic representation of anorectal probe

The planning CT scans were taken with 5mm cuts to a level 5mm below the last diode in the probe. All patients had the position of their tattoos confirmed on a mock –up of their treatment known as a simulated check. In the first five patients the probe was also placed at the simulated check. Its position in relation to bony landmarks in the anterior-posterior (AP) and lateral films taken at the simulated check could then be compared with the AP

and lateral scannograms from the planning CT scan (**Fig.3.4**). One patient required re-planning allowing direct comparison of probe position on the two planning CTs.
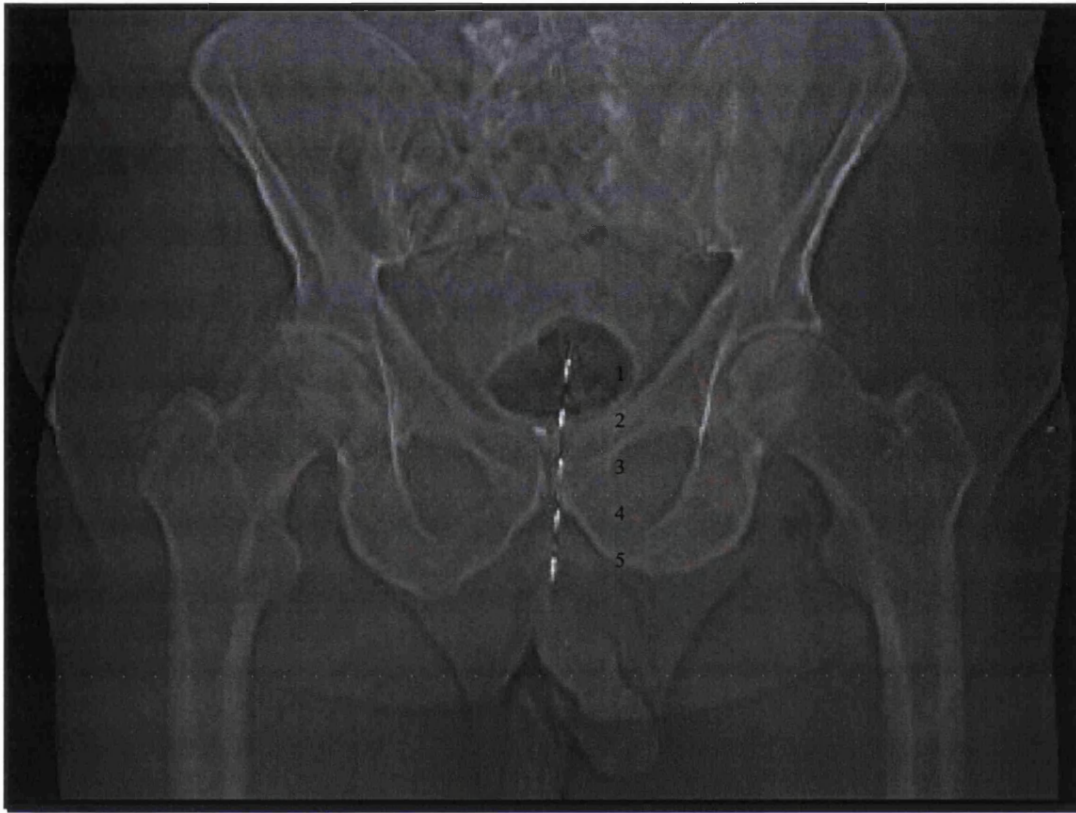
Fig. 3.4 diodes position in the anorectum on CT scannogram.

Before measurement commenced the probe diodes were individually calibrated for 10 MV photons using the linear accelerator on which the patients were due to be treated as described in 3.2.2. The diodes were recalibrated on two further occasions throughout the study. During measured fractions of radiotherapy the probe was inserted and secured in exactly in the same way as for the planning CT scan. The probe was connected to a 5- channel electrometer via a co-axial cable and readings recorded for each diode on 2 consecutive fractions in the first four patients and on 5 consecutive fractions in the remaining 5 patients. Readings on greater than 5 consecutive fractions was not feasible due to patients acceptability and time

constraints on the treatment machines. *TARGET*™ doses were calculated using the CT slice closest to the centre of the each diode. It was noted if the diode was in (IV), at the edge of (EV) or outside of (OV) the target volume according to the treatment plan. Conversion of diode readings into Gray and determination of *TARGET*™ measured doses were performed at the end of the study. Average diode measured dose from 2 or 5 consecutive fractions was calculated and compared to the *TARGET*™ predicted dose.

3.3.2 Results

The dosimetry comparisons after measurement on 2 and 5 consecutive fractions are shown in **Tables 3.2 and 3.3**. The full data set is shown in **Appendices 5b** and **5c**. The average measured doses from diodes situated in the target volume after 2 consecutive fractions were within 8% of predicted doses. The average measured doses from diodes situated in the target volume after 5 consecutive fractions were within 3% of predicted doses.

For diodes at the edges of the target volume wide variability existed between measured and predicted doses by as much as 297%.

Outside the target volume considerable doses (up to 30cGy per fraction) were measured in the anal canal, which were not predicted by *TARGET*™.

Shown in **Figure 3.5** are four examples of dosimetry comparisons between predicted doses and average measured doses on 5 consecutive fractions.

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Table 3.2 *TARGET*™ **Predicted/Diode Measured Dosimetry Comparison**

– Readings On 2 Fractions

Patient	Cancer Site	Diode Number	Average Measured Dose (cGy)	TARGET™ Predicted Dose (cGy)	Percent Difference TARGET™/ Measured (%)
4	PROSTATE	1	**185**	**198**	**+7**
		2	**189**	**204**	**+8**
		3	*145	*202	+39
		4	*129	*184	+42
		5	43	28	- 65
C	UTERUS	1	**191**	**184**	**-4**
		2	**173**	**182**	**+5**
		3	*95	*115	+21
		4	*18	*31	+74
		5	11	1	-91
3	PROSTATE	1	**190**	**198**	**+4**
		2	**185**	**196**	**+6**
		3	*153	*194	+27
		4	80	170	+112
		5	33	80	+141
B	CERVIX	1	**171**	**173**	**+1**
		2	**149**	**153**	**+2**
		3	*20	*29	+41
		4	12	0	E
		5	8	0	E

KEY:
Bold font   = diode in target volume (IV)
*   = diode at edge of target volume (EV)
                      = diode outside target volume (OV)
E   = infinity

Table 3.3 *TARGET*™ **Predicted/Diode Measured Dosimetry Comparison**

–Readings On 5 Fractions

Patient	Cancer Site	Diode Number	Average Measured Dose (cGy)	TARGET™ Predicted Dose (cGy)	Percent Difference TARGET™ / Measured (%)
A	PROSTATE	1	**195**	**200**	**+3**
		2	**195**	**200**	**+3**
		3	**196**	**200**	**+2**
		4	**195**	**198**	**+2**
		5	**195**	**198**	**+2**
5	BLADDER	1	*159	*120	-25
		2	*87	*74	-15
		3	31	0	E
		4	11	0	E
		5	7	0	E
8	PROSTATE	1	**201**	**200**	**-1**
		2	**195**	**198**	**+1**
		3	*92	*140	52
		4	*25	*100	+297
		5	9	0	E
7	PROSTATE	1	**200**	**198**	**-1**
		2	**192**	**188**	**-2**
		3	*146	*114	-22
		4	*32	*10	-68
		5	9	0	E
9	BLADDER	1	**238**	**243**	**+2**
		2	*221	34.85	-19
		3	*76	54.61	+68
		4	28	80.07	-53
		5	11	23.04	E

KEY:
Bold font = diode in target volume
* = diode at edge of target volume
E = infinity

Patient A (Prostate cancer with anal canal involvement)
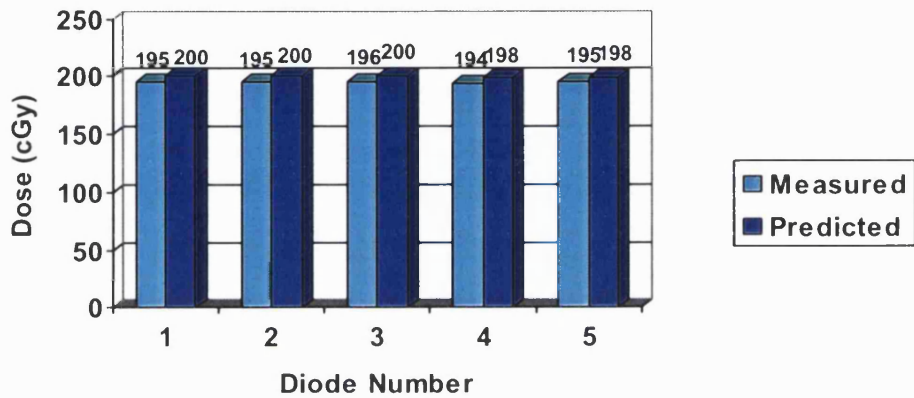
In this patient diode measured doses were very reproducible over 5 readings (SD<1% of mean. Range 0.2-0.9%). Reproducibility of probe position may have been increased due to the involvement of the anal canal with tumour preventing probe movement. The close agreement between measured and predicted doses can be explained by all diodes being in the target volume.

Patient 7 (Prostate Cancer)
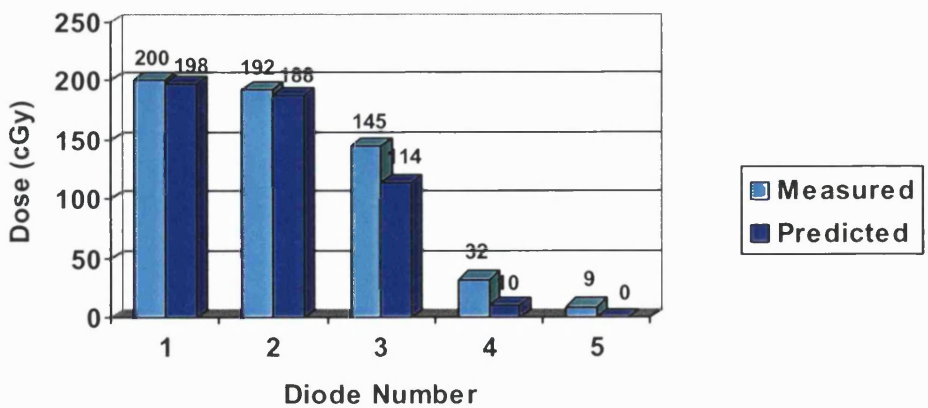
Diodes 3 and 4 were situated at the edge of the target volume. Note the increased measured doses in comparison with predicted in diodes 4 and 5. Scatter not predicted by *TARGET*™ may explain this discrepancy.

Patient 8 (Prostate Cancer)
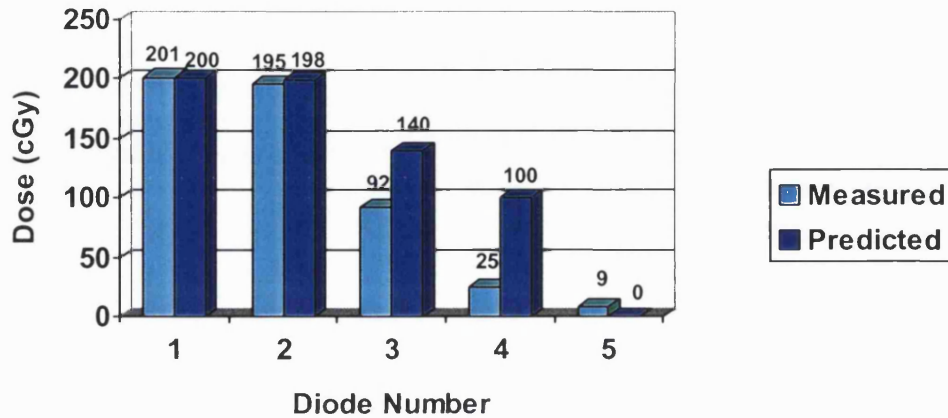
Diodes 3 and 4 were situated at the edge of the target volume.

Patient 5 (Bladder Cancer)
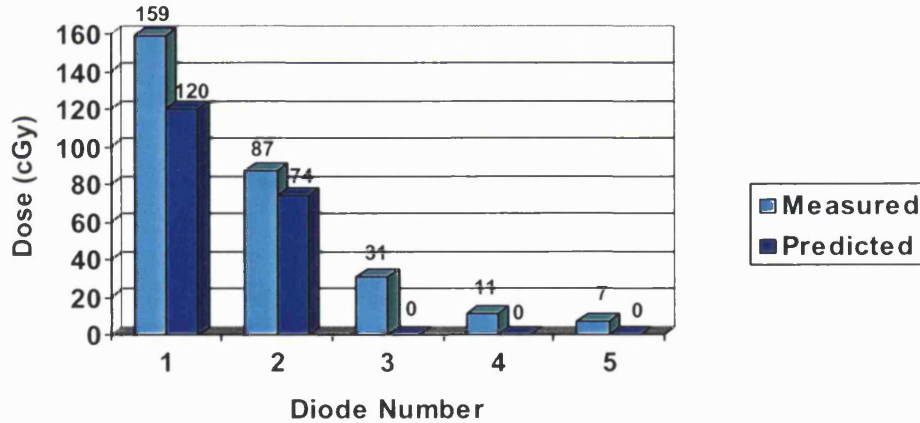
In this patient none of the diodes were in the target volume. Note the measured doses in diodes 3-5 which were not predicted by *TARGET*™.

Fig. 3.5 A comparison between diode measured and target predicted doses in four

patients

3.3.3 Conclusions

TARGET™ planned doses were accurate within the confines of the target volume as they agreed with the measured doses for diodes in the target volume.

There was marked variability at the edges of the target volume with measured doses varying by 297% of predicted doses. Although probe positioning appeared constant in relation to bony landmarks at the simulated checks, minor displacement of the probe between planning CT and treatment could easily account for these large differences. Variability in the patient's position, bladder filling or rectal distension could also be responsible. This is because at the edges of the target volume (penumbra) dose can vary by as much as 50% across a 1cm distance in the anterior-posterior plane. It cannot be determined from this data if the predicted or the measured doses are the more accurate reflection of the true dose.

The probe position is most constant within the anal canal itself as the restricting collar prevents it from moving further into the patient (thus nearer to the target volume). As *TARGET*™ does not account for scattered dose beyond the field edges the measured doses in the anal canal are likely to be accurate. *TARGET*™, therefore underestimates the anal dose. This is exemplified in Patient 5, the average measured dose in diode 3 was 31cGy whereas the *TARGET*™ predicted dose was zero. *TARGET*™ predicted doses, therefore, did not provide an accurate reflection of anorectal irradiation for the purpose of this study.

3.4 COMPARISON OF HELAX™ PREDICTED AND DIODE MEASURED DOSES IN RADIOTHERAPY FOR PROSTATE CANCER

3.4.1 Introduction

The TARGET™ treatment planning system at our centre was replaced by the more sophisticated HELAX™ treatment planning system during the period of the study. Further experiments were therefore undertaken to compare anorectal doses measured with the probe and those predicted by HELAX™.

3.4.2 Patients and Methods

Eleven men undergoing RT for localized prostate cancer were recruited. One patient (patient number 17) was subsequently withdrawn because he became distressed by the measurements. All were CT planned using AQSim™ planning software and the HELAX™ treatment planning system. The rectal probe containing 5 n-type photon-detecting diodes was used and the diodes were again individually calibrated for 10 MV photons. The probe was placed in the anorectum during the planning CT scan as described in the previous section 3.3.1. Patients underwent dosimetric measurements on five occasions on consecutive fractions wherever possible and were completed by the end of seven fractions of treatment. All patients were treated on the same LINAC with a prescribed dose of 64Gray in 32 fractions.

The HELAX™ predicted doses were calculated using the CT slice closest to the centre of each diode. The position of the diode was determined as *in* (*IV*), at the *edge* of (*EV*) or *outside* of (*OV*) the target volume from their positions in relation to the field in the treatment plan. The edge of the target volume was arbitrarily defined as the area where

the dose varied between 90% and 10% of the prescribed dose as there is no consensus on

a precise definition. The average diode-measured dose from five consecutive fractions

was compared to the HELAX™ predicted dose. A Wilcoxon sign-rank test was used to

determine the statistical significant of differences between measured and predicted doses

in each diode group (*IV, EV, OV*). The percentage difference between the predicted dose

and the average measured dose was calculated for all diodes and compared between

diode groups (*IV, EV, OV*).

3.4.3 Results

The full data set showing the individual diode measurements on each fraction is

shown in **Appendix 5(d)**. Histograms showing dosimetry comparisons for individual

patients are shown in **Appendix 5(e)**.

HELAX predicted and measured dose data, divided up by diode groups (*IV, EV, OV*)

is shown in **Table 3.4**. This table also includes the percentage difference between the

predicted and measured doses for the individual diodes. Diodes in the target volume

had a predicted dose of >180 cGy, diodes at the edges of the target volume had a

predicted dose of 20 to 180 cGy and diodes outside the target volume had a predicted

dose of < 20 cGy.

Table 3.4 HELAX™ Predicted and Average Measured Dose (cGy) With Percentage Difference

IV (n=21)		EV (n=16)		OV (n=13)		IV	EV	OV
Helax	Measured	Helax	Measured	Helax	Measured	% diff Helax vs Measured		
190	200	178	104	12	9	0.05	0.71	0.33
188	189	35	16	18	27	0.01	1.19	0.33
198	195	126	115	9	9	0.02	0.10	0.00
185	188	167	70	16	10	0.01	1.39	0.60
202	196	146	126	6	17	0.03	0.16	0.65
200	191	174	102	10	10	0.05	0.71	0.00
197	155	42	46	10	20	0.28	0.09	0.50
186	187	180	113	6	7	0.00	0.59	0.14
188	185	96	65	14	26	0.01	0.47	0.46
186	168	101	168	10	68	0.11	0.40	0.85
192	194	166	120	6	30	0.01	0.38	0.80
188	184	86	74	14	31	0.02	0.16	0.55
193	196	83	145	8.6	9	0.02	0.43	0.04
186	192	22	157			0.03	0.86	
193	157	22	94			0.23	0.77	
192	160	22	38			0.20	0.42	
188	190					0.01		
200	194					0.03		
194	186					0.04		
191	202					0.06		
187	192					0.03		
					Mean:	0.06	0.55	0.40

n = number of diodes in each group (IV, EV, OV)

The average difference between measured dose (from 5 consecutive readings) and HELAX™ predicted dose was 6 % for diodes in the target volume (*IV*), 55 % for diodes at the edge of the target volume (*EV*) and 40% for diodes outside the target volume (*OV*) on the planning CT.

There was no statistically significant difference between measured and predicted doses for diodes in the target volume (IV) or at the edge of the target volume (EV) i.e. any differences were random. For diodes outside the target volume, the measured doses were significantly greater than the HELAX™ predicted doses (p=0.022 Wilcoxon signed-rank test).

3.4.4 Conclusions

This study represents the first attempt to compare predicted anorectal doses from a HELAX™ treatment planning system and measured anorectal doses. The agreement between measured and predicted doses for diodes within the confines of the target volume (*IV*), infers that HELAX™ predicted doses are correct within the target volume.

A large average difference of 55% was seen between HELAX^{TM} predicted and diode-measured doses for diodes at the edge of the target volume. These differences were random (diodes did not consistently read higher or lower). At the edges of the target volume dose changes rapidly across very small distances, sometimes by as much as 50% across a 1cm distance in the anterior/posterior plane. The wide variation between readings on individual fractions shows how un-reproducible in-vivo measurements in this area can be. This could be explained by probe movement, set-up error or by variable degrees of distension of the bladder or rectum. It is therefore difficult to draw out specific conclusions from this part of the data in terms of the accuracy or otherwise of predicted doses for diodes at the edges of the target volume.

The measured doses for diodes outside the target volume varied from HELAX^{TM} predicted doses on average, by 40%. Furthermore, measured doses were higher than those predicted by HELAX™ to a statistically significant degree. HELAX™ may therefore be under-estimating the anal canal dose. However, it must be pointed out that the doses measured here are small and a large percentage difference between measured and predicted doses may represent only a few centi-Gray of little clinical importance.

3.5 DETERMINATION OF ANORECTAL DOSE IN INDIVIDUAL PATIENTS

3.5.1 Introduction

In order to correlate the functional and structural changes following radiotherapy to dose, a data set comprising individual patient doses to the rectum and anal canal was required. Several major problems existed. Firstly, the treatment planning system used changed after the study commenced. Secondly, it was not practically possible to physically measure anorectal doses in all patients due to time constraints on the treatment machines. Thirdly, the measured doses were only point doses at 5 sites from the anal canal to lower rectum and therefore did not estimate the rectal dose.

Rectal dose can be derived from a dose volume histogram (DVH) as discussed in section 1.3.5. There is some debate that application of a DVH to a hollow organ such as the rectum is inappropriate as the rectum is a shell, the contents of which are of no clinical importance[Ting et al., 1997]. The complexities of trying to create dose wall histograms (DWHs) i.e. to exclude the rectal contents, may have severe practical problems in the clinical setting and there is evidence they show a worse correlation to clinical outcome than a DVH[Dale et al., 1999].

In this study the DVH generated by the individual treatment plan (where available) has been used to estimate the rectal dose. This included only the volume of the rectum in the treatment field as opposed to the whole rectum. HELAX can produce a DVH and furthermore calculates a mean rectal dose. This is done by dividing the irradiated area into '3 dimensional pixels' called voxels. Each voxel is allocated a mean dose

and the total dose for the organ is calculated by summing the voxels. The anal dose is estimated from a point dose in the mid anal canal.

3.5.2 Methods

All patients in this study were CT planned with the probe (**Fig. 3.1**) in the anorectum.

The rectal dose

In patients planned on HELAX™, the rectal DVH was obtained and the mean rectal dose determined. In patients not planned on HELAX™ no rectal dose was available.

The anal dose

In patients planned on HELAX™, the HELAX™ predicted dose for the diode closest to the centre of the anal canal was determined.

In patients planned on TARGET™ and who underwent in-vivo dosimetry, the planning CT scan films were used to determine the diode to use for the anal canal dose. In each case the scans were reviewed and the diode that appeared to be lying closest to the middle of the anal canal was noted. This was diode 4 in all but one case. The average measured dose for the appropriate diode was taken as the anal canal dose. The measured dose was used because TARGET™ predicted doses in this area are unreliable as was demonstrated in the earlier study 3.3. No anal canal dosimetry was available for the few patients who were planned on TARGET™ but did not undergo in-vivo dosimetry.

3.5.3 Results

A wide variation was seen in both the anal and rectal doses received by patients. The summarised results are shown in **Table 3.5 below.** The complete patient dose data set is tabulated in **Appendix 5.f.**

Table 3.5 Summary of anal and rectal doses

	n	Mean (Gy)	Median (Gy)	Range (Gy)	Standard deviation
Anal canal dose	25	17.1	10.0	2.7-53.6	15.8
Rectal dose	19	47.3	47.0	20.7-61.7	8.8

n = number of patients with dose data available

3.5.4 Conclusion

The patient dose data set (**Appendix 5.f**) has specific rectal and anal canal doses for the majority of the patients in the study. There are inevitably inaccuracies for the following reasons; Firstly, the predicted data is based on a single planning scan and internal organ movement and set up errors are bound to occur resulting in variations in dose delivered to the rectum. Secondly point doses have been applied to the whole of the anal canal and are a combination of measured and predicted data. Thirdly the anal canal commonly lies at the field edges, were dose is changing rapidly over short distances making accurate estimation of anal canal dose extremely difficult. It has not been possible to physically measure every patient's doses and as discussed earlier there are also problems with measured doses. Therefore this seems to be the most coherent way to present dose data and to apply it to the rest of the thesis. Previous

studies have made no attempt to differentiate anal canal and rectal dose in this way

and usually only a total prescribed dose with the fractionation regime is reported.

3.6 DISCUSSION OF DOSIMETRY EXPERIMENTS

3.6.1 Probe Movement

Of the various factors that may have contributed to the differences between measured and predicted doses, probably the most important was probe movement. Any change in the position of the diodes in relation to the field will affect the measured dose and it is unlikely that the probe position was entirely consistent on each occasion. While the restricting collar on the probe prevents its migration beyond the anal sphincters (further into the patient), it does not prevent it slipping out and taping the probe to the treatment table may not have provided sufficient security. This is corroborated by the findings in Patient A in the initial study in whom the tumour mass prevented probe movement and the field incorporated all the 5 diodes in the target volume. These results showed how accurate measurements with the probe can be. A better probe design securing a constant position should improve the results although measurements and the edges of the target volume will always be difficult.

3.6.2 Other Methodological Problems

In-vivo measurements were taken on 2 or 5 occasions to obtain an average reading. Measurements were limited to five occasions for reasons of acceptability to patients as well as time constraints on busy treatment machines. Allowing for the inconsistency of probe position these measurements should be sufficiently representative. Although it would have been desirable to obtain an average predicted anorectal dose, it would have been logistically and ethically difficult to justify performing 5 planning CT scans on each patient. Thus predicted doses were obtained from diode positions on a single occasion during CT planning as opposed to the average of five measurements. Diode doses are point doses in a three-dimensional

field and movement in the superior/inferior, anterior/posterior or indeed any plane can occur. Diodes in the target volume on the planning scans agreed well with the corresponding measured doses and as stated, this strongly suggests that predicted doses are accurate.

The average dose from five consecutive measurements is likely to give a more accurate assessment of anorectal irradiation over an entire treatment period than the predicted dose. This is a reflection of the methodology of the study rather than the ability of either the TARGET™ or HELAX™ treatment planning system to predict doses. It does, however, serve as a reminder that any single treatment plan only represents an anatomical snapshot on that particular day at that particular time. However sophisticated the imaging or the planning software, set-up error and internal organ movement will still occur.

3.6.3 Comparison Of HELAX™ Predicted And TARGET™ Predicted Doses

HELAX™ is a newer and more sophisticated dose prediction tool than TARGET™. HELAX™ predicted doses for diodes in the target volume unexpectedly did not agree so closely with measured values as TARGET™ predicted doses in the earlier study. Measurements with diodes in the target volume were all within 7% of TARGET™ predicted values whereas these varied by as much as 28% with HELAX™ predicted doses. This may be due to a number of reasons. Variation in predicted and measured dose will be dependant on the position of a diode in relation to the field between planning and measured fractions. The previous study using TARGET™ involved a less homogeneous group of patients with a wider variation in field shapes. The inclusion of Patient A in the initial study provided not only a field which included all

the 5 diodes in the target volume but also an anatomically abnormal anal canal which probably helped prevent probe movement. This one patient was an ideal 'in-vivo' model for testing the probes ability to measure doses in the field and the reproducibility of the results in this patient speaks for itself. The results in this one patient will have influenced the overall results due to the size of the study group. These data therefore, do not show that HELAX™ has a poorer ability to predict dose in the target volume than TARGET™.

Measured doses at the edges of the target volume differed greatly from predicted doses for both treatment-planning systems. This is due to the very rapid decay in dose over very short distances making a small movement in the patient or probe between planning and treatment result in a big discrepancy in dose.

For diodes outside of the target volume, TARGET™ does under-predict dose. This is because the software does not allow for the contribution of scatter radiation to dose. Outside of the boundaries of the field TARGET™ therefore predicts the dose as zero. This is clearly not the case as the results have shown with OV diodes measuring up to 30cGy. HELAX™ does calculate for scatter in three dimensions outside of the field as well as within the target volume. The HELAX™ predicted values are therefore far superior to TARGET™ predicted values outside of the field. This is of particular significance when it comes to assessing anal canal dose, as the anal canal may be situated outside of the field edge. Unfortunately the anal canal commonly lies at the field edges, were dose is changing most rapidly over short distances. This is a significant problem in terms of estimating anal canal dose with any accuracy.

CHAPTER 4:

FUNCTIONAL

CHANGES

AFTER RADIOTHERAPY

4.1 INTRODUCTION

The degree of functional anorectal disturbance following pelvic RT is probably understated in the literature. Patients are embarrassed and may not volunteer to describe their symptoms unless specific enquiry is made. The Late Intestinal Toxicity Scoring of the RTOG and the EORTC does not include a number of anorectal symptoms (anal/rectal pain, faecal urgency and faecal incontinence) and therefore does not reflect the true size of the problem. Physiological studies of anorectal function have been inconsistent if not largely contradictory. Only one group [Yeoh et al., 2000;Yeoh et al., 1998] studying 34 patients who had received RT for prostate cancer has provided some detailed prospective assessment of functional anorectal disturbance although the reported incidence of symptoms was higher than others. Yeoh et al's (1998, 2000) study found increased frequency of defecation and faecal urgency in around half the patients and faecal incontinence in 26% of patients four to six weeks after RT, whose symptoms persisted a year later. Diminished anal sphincter pressures at rest and in response to voluntary squeeze were noted 4-6 weeks after RT suggesting anal sphincter weakness but were normal at a year suggesting recovery. The volumes of rectal distension with first perception of stimulus and desire to defecate were lower than pre RT values. They concluded that heightened rectal sensitivity in these patients contributed to their symptoms. Although rectal sensation is frequently measured in this manner rectal electrical sensitivity may be a more realistic measure that avoids the variables of rectal compliance and diameter [Kamm., 1990]. Previous studies have measured rectal compliance that is the change in volume of the rectum per unit change in pressure. A compliant rectum expands easily to allow for distension with stool or flatus without significant increase in intra-luminal

pressure that might compromise continence. Compliance is calculated from the gradient of a graph plotting volume versus pressure. Since the rectum is not a 'closed system' rectal compliance cannot be measured accurately, although an appropriately compliant balloon and a micro-transducer for pressure monitoring during insufflation should provide the nearest measure of rectal compliance. However, for the purpose of this study rectal electrical sensitivity and rectal volumes (rectal threshold, urge threshold and maximum tolerated volume) rather than compliance were deemed more relevant measures of the functional elements of the rectum. Therefore in this study rectal compliance was not measured.

Anorectal symptom questionnaires and anorectal physiological studies were employed to determine the functional changes seen after RT and these changes correlated with the anal and rectal doses received by the patients.

4.2 ASSESSMENT OF ANORECTAL SYMPTOMS AFTER RT

4.2.1 Patients and methods

Thirty men with carcinoma of the prostate (27) and bladder (3) were formally interviewed for anorectal symptoms before RT and the proctitis (**Table 4.1**) and incontinence (**Table 4.2**) scores were completed. Twenty-nine were available for re-assessment six weeks and 10 patients six months after completion of RT. (**Appendices 3 & 4**)

The maximum proctitis score possible was 11 but because relatively common anorectal symptoms are included a patient may have a proctitis score above zero without apparent clinical proctitis. Similarly the incontinence score describes a range of symptoms from totally continent (scores 0) to totally incontinent (scores 24). An incontinence score of above 4 will be considered clinically apparent faecal incontinence.

The frequency of the individual symptoms is shown for comparison. The results from the scores were compared using a paired Wilcoxon signed rank test.

Table 4.1 Proctitis Score (from Talley et al)

	Score	0	1	2
Symptom	Urgency	Nil	Mild (5-20 min)	
	PR bleeding/ week	0	≤4	>4
	PR blood quantity	None	Streaks	Obvious
	Diarrhoea* (days/week)	0	1	>1
	No. of stools per day	≤1	2-3	>3
	Pain (anal**/rectal)	Nil	Pain present	

*Diarrhoea was taken to mean very loose or liquid stool.

**Inclusion of 'anal' pain is a modification of the proctitis score as originally described, because patients could not be specific about the exact site of pain experienced in the 'back passage'.

Table 4.2 'Vaizey modification' of Wexner Incontinence Score

	Never	Rarely	Sometimes	Weekly	Daily
Incontinence for solid stool	0	1	2	3	4
Incontinence for liquid stool	0	1	2	3	4
Incontinence for gas	0	1	2	3	4
Alteration in lifestyle	0	1	2	3	4

	No	Yes
Need to wear a pad or plug	0	2
Taking constipating medicines	0	2
Lack of ability to defer defecation for 15 minutes	0	4

KEY:

Never	= no episodes in the last four weeks
Rarely	=1 episode in the past 4 weeks
Sometimes	>1 episode in the past 4 weeks but < 1 a week
Weekly	=1 or more episodes a week but < 1 a day
Daily	=1 or more episodes a day
Minimum score (0)	= perfect continence
Maximum score (24)	= totally incontinent

4.2.2 Results

The median incontinence and proctitis scores for all the are shown in **Table 4.3** below. The prevalence of individual symptoms of proctitis and incontinence are shown in **Tables 4.4 and 4.5**.

Appendix 6 shows the proctitis and incontinence scores for individual patients

Table 4.3 Incontinence and Proctitis Score Results

	INCONTINENCE SCORE			PROCTITIS SCORE		
	PRE N=29	6 WKS N=29	MTH N=10	PRE N=29	WKS N=29	6 MTH N=29
MINIMUM	0	0	0	0	0	0
MAXIMUM	5	11	8	4	7	5
MEDIAN	0	4	2.5	0	2	2

KEY:

Arbitrary units according to score

Table 4.4 Prevalence of Individual Proctitis Symptoms

PROCTITIS SYMPTOMS	PRE RT N=29	6 WKS N=29	6 MTH N=10
Urgency	4 (14%)	16 (53%)	5 (50%)
Rectal bleeding	2 (7%)	5 (17%)	1 (10%)
Diarrhoea	3 (10%)	6 (21%)	4 (40%)
Frequency	8 (28%)	15 (52%)	8 (80%)
Rectal / Anal pain	0 (0%)	7 (24%)	0 (0%)

Table 4.5 Prevalence of Individual Incontinence Symptoms

INCONTINENCE SYMPTOMS	PRE RT N=29	6WKS N=29	6 MTH N=10
Incontinent to solid stool	0 (0%)	3 (10%)	0 (0%)
Incontinent to liquid stool	1 (3%)	8 (28%)	1 (10%)
Incontinent to gas	5 (17%)	9 (31%)	1 (10%)
Alteration in lifestyle	1 (3%)	7 (24%)	4 (40%)
Needs to wear pads	0 (0%)	0 (0%)	0 (0%)
Taking constipating medicines	0 (0%)	1 (3%)	1 (10%)
Lacks ability to defer defecation	1 (3%)	13 (45%)	4 (40%)

The median proctitis score increased from 0 (range 0-4) to 2 (range 0-7) p< 0.001 at six weeks and to 2 (Range 0-5) p= 0.068 at six months after RT. There was no statistical significance in the changes in the proctitis score from six weeks to six months (**Figure 4.1**). Twenty-two out of 29 (76%) six weeks and six out of 10 (60%) six months after RT had a proctitis score of two or greater. Faecal urgency was seen in 4 patients (14%) before RT, 16 of 29 patients (55%)six weeks and 5 of 10 patients (50%) six months after RT. Faecal frequency (2-3 or greater stools per day i.e. scoring 1 or 2 in the proctitis score for frequency) in 8 patients (28%) increased to 15 patients (52%) at six weeks and 8 of 10 patients (80%) six months post RT. None had anorectal pain before or six months after RT but 7 patients (24%) had anorectal pain six weeks after RT.

The median incontinence score increased from 0 (Range 0-5) to 4 (Range 0-11) p<0.001 at six weeks and was 2.5 (Range 0-8) p= 0.107 at six months after RT. There

was no statistical significance in the changes in the incontinence score from six weeks to six months (**Figure 4.1**). Ten out of 29 patients (34%) six weeks and three out of 10 (30%) six months after RT had an incontinence score greater than four (clinical faecal incontinence). Only 8 out of 29 (28%) patients six weeks and four out of ten (40%) six months after RT had an incontinence score of zero.

No patient before RT, 3 (10%) at six weeks and none six months after RT were incontinent to solid stools. Incontinence to liquid stool was noted in one (3%) patient before, 8 (26%) patients at six weeks and 1 (10%) patient at six months; incontinence to flatus was observed in 5 (17%) patients before, 9(31%)patients at six weeks and one (10%) patient at six months after RT. One (3%) patient before RT, 13 (45%) patients at six weeks and 4(40%) patients at six months had urge incontinence. Altered lifestyle due to incontinence was reported by one (3%) patient before, 7 (24%) patients at six weeks and 4 (40%)patients at six months after RT. No patient reported the use of pads.
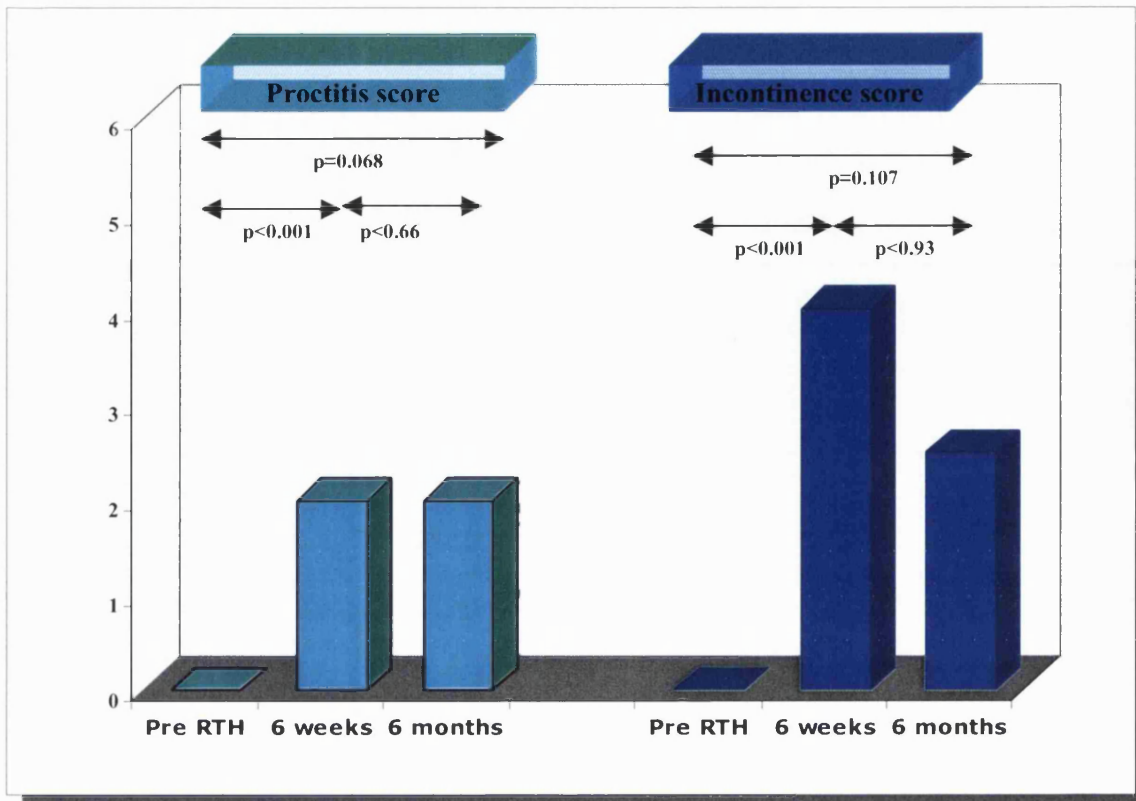
Figure 4.1 Changes In Proctitis And Incontinence Scores After RT

4.2.3 Conclusions

A significant degree of functional anorectal disturbance is seen in the majority of the patients six weeks after RT for urological cancer. Faecal urgency, frequency and incontinence were the predominant symptoms. Based on this a clinical diagnosis of proctitis could be reasonably made in well over half the patients six weeks after RT. Although changes in the proctitis and incontinence scores failed to reach statistical significance six months after RT, there was considerable evidence of persistent functional disturbance at six months. Only four out of ten patients had normal continence scores six months after RT and only four out of ten patients had proctitis scores of less than two. Furthermore, two patients who were fully continent before RT had significant faecal incontinence (incontinence scores of 6 and 8) six months after RT.

4.3 ANORECTAL PHYSIOLOGY STUDIES

4.3.1 Patients and methods

Twenty-nine men with carcinoma of the prostate (26) and bladder (3), had their studies completed before and six weeks after RT. One patient who received heater probe treatment to his haemorrhoids a week prior to his initial tests was excluded from anal and rectal sensitivity as well as the rectal volume measurements. At six months after completion of RT 10 patients underwent repeated anorectal physiology.

ANORECTAL PHYSIOLOGY MEASUREMENTS:

Anorectal physiology (ARP) was performed at the GI Clinical Measurement Unit (**Fig. 4.2**). The parameters measured were anal canal manometry (resting pressure, squeeze increment and cough increment), rectal volumes (threshold, urge and maximum tolerable), anal electrical sensitivity, rectal electrical sensitivity, recto-anal inhibitory reflex and pudendal nerve terminal motor latencies (PNTML). The study was conducted with the patients in the left lateral position.
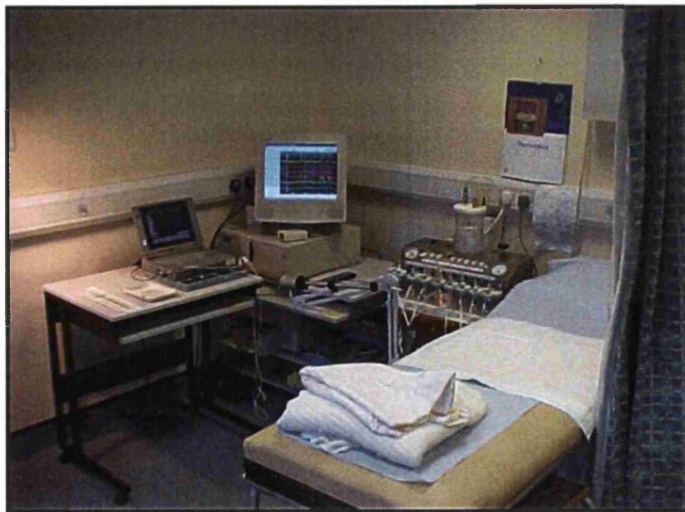
Figure 4.2 GI Clinical Measurement Unit

MANOMETRY

Manometry readings were taken using an 8 radial channel water perfused catheter (Lewis Medical, London UK) with a pump (MUI scientific Mississauga, Canada) providing a perfusion rate of 0.6ml per minute at 15 psi. MMS UPS 20/20 software (Lewis Medical, London UK) was used to interpret the manometric traces and calculate individual results.

Anal Canal Resting Pressure

Anal canal resting pressure provides information about the internal anal sphincter and its contribution to anal canal tone at rest. The catheter was placed in the high-pressure zone of the anal canal. This was achieved by slowly advancing the catheter into the anal canal until it was lying in the rectum demonstrated by a decrease in the measured pressure. The catheter was then withdrawn until the highest pressure was recorded. The catheter was held at this position until a steady trace was achieved (for a minimum of 60 seconds). This pressure was recorded as the anal canal resting pressure and expressed in cmH2O (Normal range 60-130 cmH2O).

Squeeze Increment

The squeeze increment or voluntary squeeze increment provides an assessment of the voluntary function of the external anal sphincter. The catheter was placed in the high-pressure zone of the anal canal (as previously), and the patient asked to squeeze the catheter whilst recording the anal canal pressure. The squeeze was performed at least twice and the squeeze increment calculated as the maximum squeeze pressure less the resting pressure, expressed in cmH2O (normal range 50-180 cmH2O). If the squeeze

increment was less than twice the resting pressure the process was re-explained and repeated.

Cough Increment

The cough increment or involuntary squeeze increment provides an assessment of the involuntary function of the external anal sphincter. With the catheter placed in the high-pressure zone of the anal canal the patient was asked to cough forcibly whilst recording the anal canal pressure. This process was repeated if the cough increment was less than twice the resting pressure or if the cough produced was unconvincing. Cough increment was calculated as the maximum value less the anal canal resting pressure expressed in cmH2O (normal range 50-100 cmH2O).

Endurance Increment

The endurance increment provides an assessment of the ability of the external anal sphincter to maintain a squeeze. With the catheter placed in the high-pressure zone of the anal canal (as previously) the patient was asked to maintain a squeeze for a 5 second count whilst recording the anal canal pressure. Endurance increment was calculated as the mean squeeze over the five-second period minus the resting pressure expressed in cmH2O (normal range 40-160 cmH2O). Mean squeeze was calculated directly from the trace using the computer software.

RECTAL VOLUMES

In each case a standard balloon (party balloon) was attached to a 20 cm length of 4mm diameter thin walled PVC tubing. A three-way tap and 50ml syringe was attached to the distal end. The lubricated balloon and tubing was inserted into the

rectum. The position of the balloon in the rectum was established by advancing the tubing 6 to 8cm from the anal verge feeling for loss of resistance as the balloon passed through the sphincters. Air was sucked into the 50ml syringe via the three-way tap and then pumped into the balloon and was repeated until the volume required was reached. The balloon was completely deflated after each separate test. The measurements were *Rectal Threshold Volume-* the volume of air that first caused the patient to experience a new sensation, once insufflation had commenced, expressed in ml (normal range 20-70ml); *Urge Threshold Volume-* the volume of insufflated air that first caused the subject to feel the desire to defecate, expressed in ml (normal range 35-120ml); and *Maximum tolerable volume-* the volume of insufflated air at which point, the subject could no longer hold on, felt pain or distress, expressed in ml (normal range 100-260ml).

ANAL AND RECTAL ELECTRICAL SENSITIVITY, RECTO-ANAL INHIBITORY REFLEX & PNTML

Anal electrical sensitivity

This is a measurement of anal sensation that reflects on the afferent nerve supply of the anal canal. It was measured using a urethral ring electrode (21L10 DANTEC^{TM}, Denmark) mounted on a 3.3mm (10Ch) suction catheter. The tip of the electrode was lubricated with jelly and placed in the anal canal. Alternating current was applied at a frequency of 5Hz starting from zero mA with increasing amplitude until the patient felt a ticking or tingling sensation. This was repeated three times and the middle (median) value recorded in mA (normal range 2-9.4mA).

Rectal electrical sensitivity

This is a measurement of rectal sensation that reflects on the afferent nerve supply from the rectum and was measured using a similar technique as anal electrical sensitivity. The position of the catheter in the rectum was ascertained by advancing the electrode 6 to 8cm from the anal verge while feeling for resistance as the electrode passed the sphincters. When the electrode was in the rectum a current was applied at a frequency of 10 Hz increasing the amplitude until the patient could detect a dull ache rather than a ticking or tingling sensation, measured in mA (normal range 7-36mA). A value of < 7mA was regarded as suspicious of the electrode lying in the anal canal.

Recto-anal inhibitory reflex

This is a local anorectal reflex, which results in relaxation of the anal sphincters when the rectum is distended. The rectal balloon apparatus was placed in the rectum and the manometry catheter placed in the high-pressure zone of the anal canal. The rectal balloon was rapidly inflated to 50mls and rapidly deflated again. Relaxation of the anal sphincter (positive recto-anal inhibitory reflex) was measured via the water-perfused catheter. A reduction in anal canal pressure of greater than $15cmH_2O$ was treated as positive reflex.

Pudendal Nerve Terminal Motor Latency (PNTML)

Left and right PNTML were measured using an St Mark's Pudendal Electrode (MEDITRONIC^{TM} 8100 series). The current frequency was set at 0.1 Hz and the amplitude of the current set at approximately 50% of the rectal electrical threshold value. The St Mark's electrode was attached to the EMG and nerve conduction velocity testing equipment, lubricated and mounted on a gloved finger. The finger was

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then inserted into the rectum and the left ischial spine palpated to stimulate the nerve as it leaves the pelvis through the greater sciatic notch. Once contraction of the EAS was detected digitally the amplitude of the current was increased to the level of the rectal electrical threshold and the latency trace visualized on the screen. The process was then repeated on the right.

Statistical Methods

All data were tested for normality of distribution using the Shapiro-Wilk test. The significance of differences between groups was examined by the paired t t-test when the data were normally distributed and by the Wilcoxon signed-rank test when the data were not normally distributed.

4.3.2 Results

The full data are shown in **Appendices 7-9**. Data were normally distributed and were expressed as means and ranges except the cough increment, which is expressed as median and range.

Note: to provide consistency in the analysis using paired data the mean pre-RT values of the 10 patients followed up to six months are used for analysis quoted in the text. These data will differ from the mean of the whole group shown in the results tables.

Patients found that the PNTML test particularly uncomfortable. Due to initial difficulty eliciting the sphincter response in over a third of cases it was abandoned and thus meaningful analysis of the data was not possible.

Manometry Results

The full manometry data are shown in **Appendix 7** and summarised in **Table 4.6 &**

Figure 4.3.

Table 4.6 Manometry results

PHYSIOLOGICAL INDICES	PRE RT n=29	6 WKS n=29	6 MTHS n=10
Resting Pressure (cmH20) (Range)	83.3 (35-137)	78.2 (26-152)	73.7 (57-84)
Significance (p value)		0.267	0.029
Squeeze Increment (cmH20) (Range)	152 (51-325)	162 (63-321)	156.3 (56-296)
Significance (p value)		0.288	0.007
***Cough Increment** (cmH20) (Range)	96 (29-243)	105 (59-201)	111 (67-151)
Significance (p value)		0.227	0.018
Endurance Increment (cmH20) (Range)	107 (20-300)	105.5 (0-263)	99 (30-200)
Significance (p value)		0.902	0.1

Mean values shown except * (median)

The mean anal canal resting pressure did not change to a statistically significant level six weeks after RT (83.3 pre-RT to 78.2 six weeks post RT). In the ten patients followed up six months after RT, the mean anal canal resting pressure decreased significantly from 87.9mmHg to 74mmHg six months after RT (p=0.029). (**Fig. 4.3.**)

The mean squeeze increment, cough increment and endurance increments did not change to a statistically significant level six weeks after RT. In the ten patients studied six months after RT the mean squeeze increment increased from 112mmHg to 156mmHg (p= 0.007) and the mean cough increment increased from 84 to 113 mmHg six months after RT (p= 0.018) to statistical significance but not the mean endurance increment although it increased from 80mmHg to 99mmHg six months after RT (p= 0.1). There was no statistical significance in any of the changes in anal canal pressures between 6 weeks and six months.

Rectal Volumes

There was a decrease in the rectal threshold and urge threshold volumes at six weeks and six months but this failed to reach statistical significance. The mean maximum tolerable volume decreased from 240 ml to 193 ml six weeks after RT (p= 0.002), **Fig. 4.3** but the decrease in the ten patients investigated six months after RT from 204ml to 175 ml, was not statistically significant (p=0.237). There was no statistical significance in any of the changes in rectal volumes between 6 weeks and six months. The complete rectal volume data are shown in **Appendix 8**. **Table 4.7** and **Fig. 4.3** below summarise the results.

Table 4.7 Rectal Volume Results

PHYSIOLOGICAL INDICES	PRE RT n=28	6 WKS n=28	6 MTHS n=10
Mean Rectal Threshold Volume (ml) (Range)	66 (30-140)	58 (40-100)	53 (24-100)
Significance (p value)		0.204	0.462
Mean Urge Threshold Volume (ml) (Range)	133 (70-240)	120 (80-190)	104 (79-160)
Significance (p value)		0.113	0.358
Mean Maximum Tolerable Volume (ml) (Range)	240 (115-400)	193 (112-288)	176 (109-260)
Significance (p value)		0.002	0.237
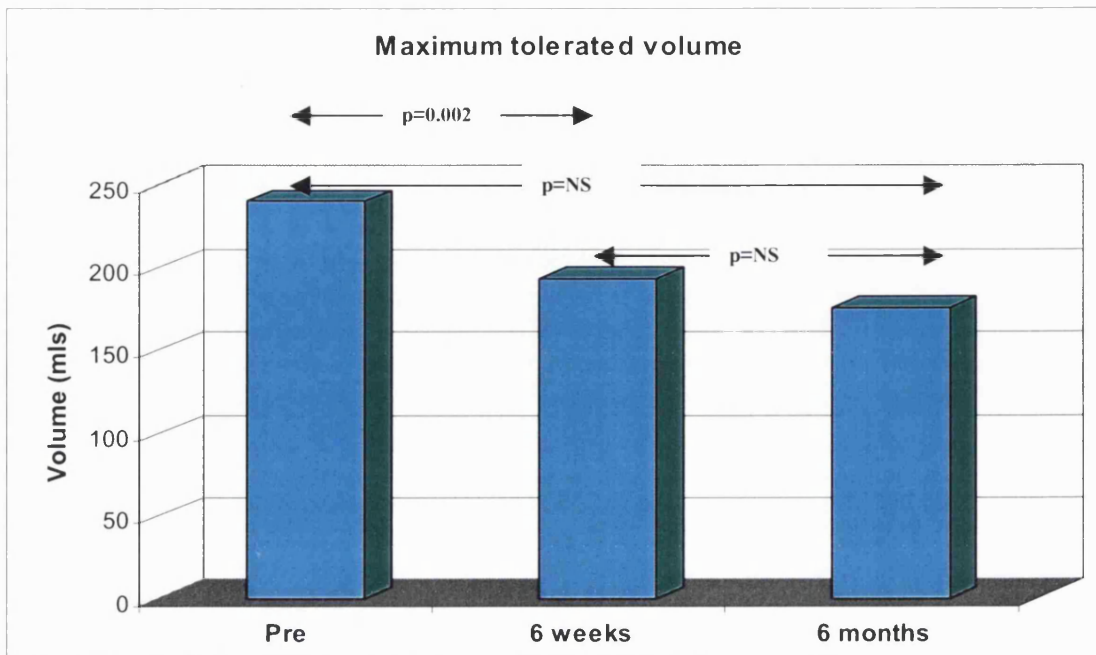
Fig. 4.3 Change In Mean Maximum Tolerable Volume After RT

Anal and rectal electrical sensitivity, recto-anal inhibitory reflex and PNTML

Anal and rectal electrical sensitivity results are shown in **Table 4.8**. The full data are

shown in **Appendix 9.** There was no statistical significance in the changes between 6

weeks and six months.

Table 4.8 Anal & Rectal Electrical Sensitivity Results

	PRE RT n=28	6 WKS n=28	6 MTHS n=10
Mean Anal Electrical Sensitivity (mA)	7.56	8.43	7.68
(Range)	(2.2-12.6)	(3.6-16.2)	(6.6-10.2)
Significance (p value)		0.119	0.401
Mean Rectal Electrical Sensitivity (mA)	20.8	28.25	35.95
(Range)	(5.4-44)	(9-50.5)	(21.5-52)
Significance (p value)		0.006	0.001

The anal electrical sensitivity did not change after RT to a statistically significant degree.

The mean rectal threshold of electrical sensation increased from 20.8mA before RT to 28.3mA six weeks after RT (p= 0.006) and in the 10 patients followed to six months the mean rectal electrical sensitivity increased from 19.8mA before RT to 36mA six months after RT (p=0.01). (**Fig. 4.4**)
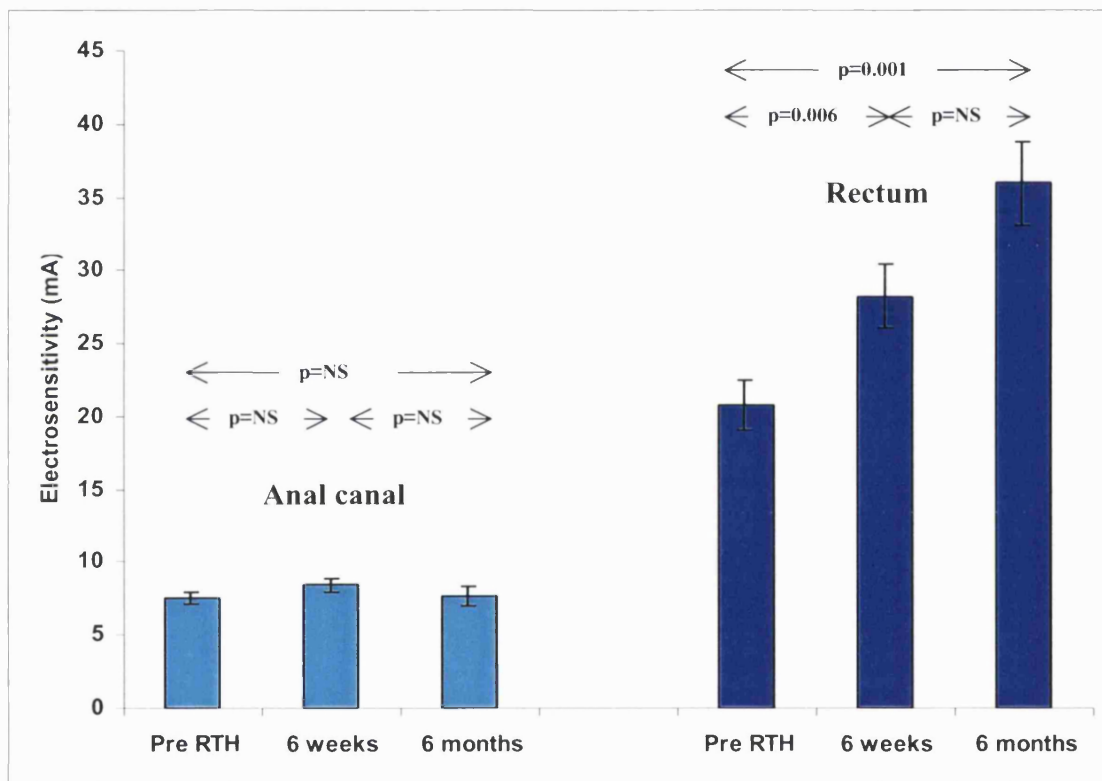
Fig. 4.4 Changes in anal and rectal electrical sensitivity after RT

The Recto-Anal Inhibitory Reflex was present in all patients before and after RT.

4.3.3 Conclusions

Proctitis presents with a number of symptoms including faecal frequency (52%), urgency (53%), rectal pain (24%), diarrhoea (21%) and bleeding (17%) six weeks after RT. Much of the anorectal disturbance (faecal frequency (80%), urgency (50%), diarrhoea (40%)) persists at six months. Proctitis as reflected by the increase in proctitis scores that was statistically significant at six weeks is probably the underlying factor. These symptoms can be explained by the reduced rectal sensation demonstrated at six weeks and six months after RT. When rectal sensation is reduced a poorer perception of the state of fullness of the rectum may be a causative factor for the urgency. A reduced rectal capacity at six weeks possibly due to loss of rectal wall elasticity by post-irradiation inflammation and oedema will evidently compound faecal urgency and frequency although changes in stool consistency and other gastrointestinal effects of RT may also have an effect.

Faecal incontinence occurred in a third of patients as measured by the increased incontinence scores. Yeoh and his colleagues (1998) reported a 26% incontinence rate although they applied different criteria to define incontinence. There was no manometric change in internal or external sphincter function six weeks after RT. This is in contrast to other's findings [Yeoh et al., 1998] of a slightly decreased resting pressure. The anal electrical sensitivity did not change significantly after RT and therefore sensory neurological radiation injury to the anal canal does not seem to occur and therefore is unlikely to be a causative of the anorectal symptoms experienced. However diminished rectal sensation and rectal capacity are probably responsible for incontinence at six weeks.

The was a decrease in resting anal canal pressure six months after RT that suggests

IAS dysfunction and must be related to radiation injury.

The possible enhancement in the EAS function, demonstrated by increase in squeeze

increment and cough increment, six months after RT is interesting. It is recognised

that the EAS, which is skeletal muscle, responds to training. This is the rationale

behind biofeedback, which has been shown to be effective specifically in the

treatment of urge incontinence[Norton and Kamm, 1999]. Following RT these

patients suffer with stool frequency and with urgency. The improvement in the EAS

function demonstrated at six months is possibly a physiological compensatory

response.

4.4 RELATIONSHIP OF ANORECTAL FUNCTION AND DOSES RECEIVED

4.4.1 Methods

Symptom Score Variables

Changes in the symptom scores calculated as the score difference before and after RT were correlated with anal and/or rectal doses as appropriate using the patient dose data set (**Appendix 5.f**).

The changes in the symptom scores at six months after RT were not plotted as these failed to reach statistical significance. The changes in incontinence scores were correlated with both anal and rectal doses as both rectal and anal radiation injury could plausibly contribute to faecal incontinence. The change in proctitis score was only correlated with rectal dose.

Anorectal physiological measurements

Those anorectal physiological measurements that showed a statistically significant change following RT were correlated with anal or rectal dose. The differences in the anal canal resting pressure six months after RT were plotted against the measured anal canal doses (**Appendix 5.f**) as anal canal irradiation was likely to disturb anal canal function. The differences in rectal electrical sensitivity and maximum tolerable volume six weeks after RT were plotted against the rectal dose as rectal irradiation injury was likely to affect rectal sensitivity and capacity. There was no rectal dose data available for the patients followed to six months as they had been planned with the older TARGET™ treatment planning system.

Pearson's correlation was used to measure the significance of any relationship between rectal and anal canal dose and changes in the symptom scores or anorectal physiological parameters.

4.4.2 Results

Symptom score measurements

There was no correlation between the increase in the incontinence score before and six weeks after RT and the rectal dose (Pearson's 0.184; p=0.479), **Fig. 4.5**.
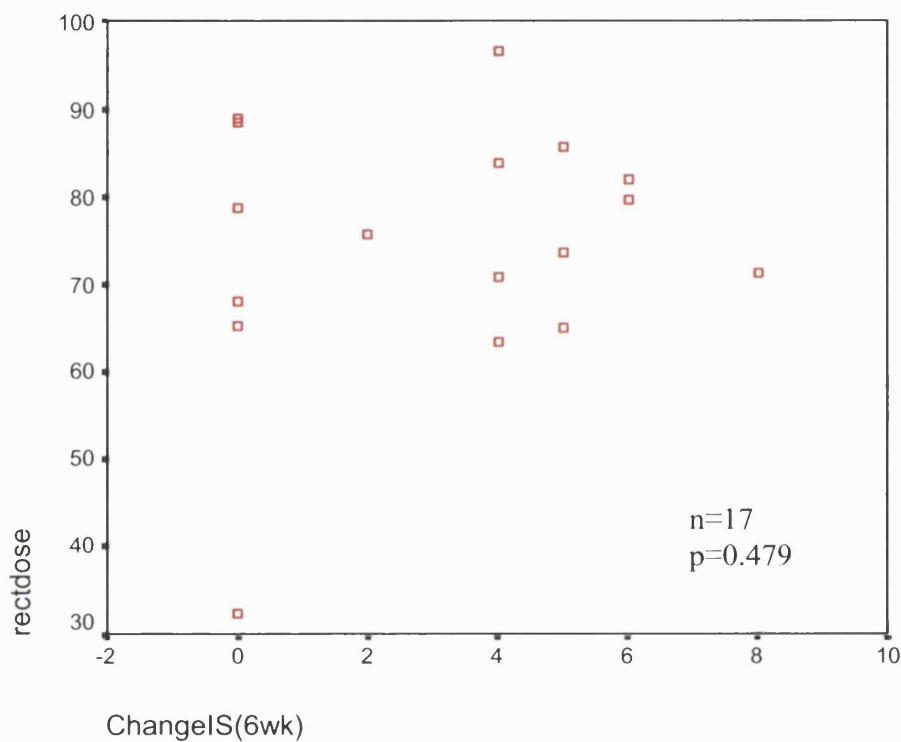
Fig. 4.5 Scatter plot of change in Incontinence Score 6 weeks after RT and rectal dose

KEY:

ChangeIS(6wk)	= Change in Incontinence Score 6 weeks after RT (arbitrary units)
Rectdose	= Rectal dose (%)

There was no correlation between the increase in the proctitis score six weeks after RT and the rectal dose (Pearson's -0.125; p=0.622), **Fig. 4.6**.
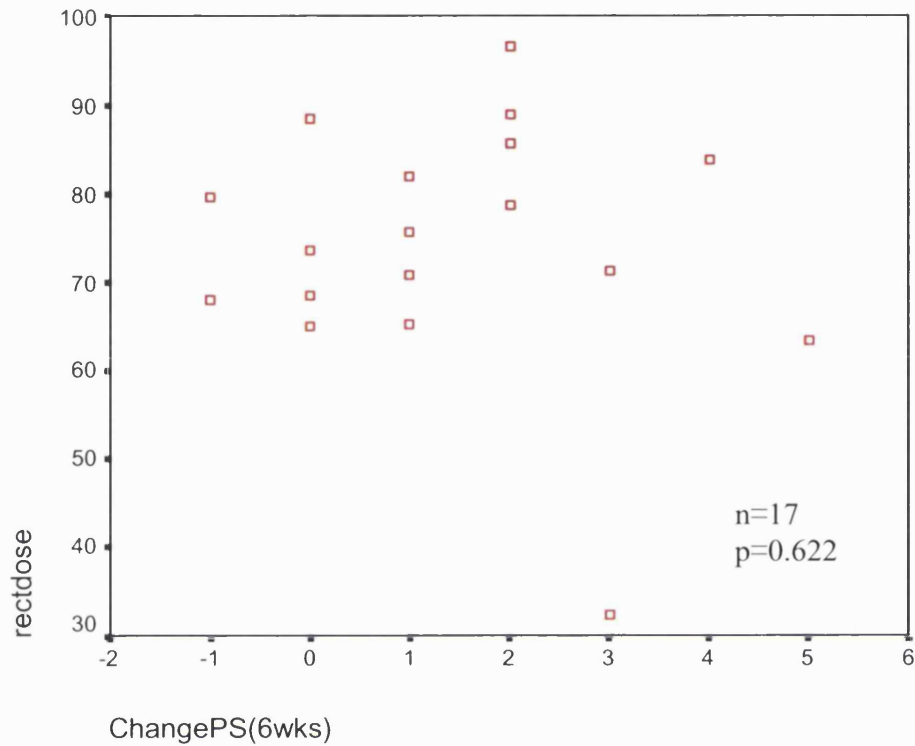
Fig. 4.6 Scatter plot of change in Proctitis Score 6 weeks

after RT and rectal dose

KEY:

ChangePS(6wks) = Change in Proctitis Score 6 weeks after RT (arbitrary units)

rectdose = Rectal dose (%)

There was no correlation between the increase in incontinence score six weeks after RT and the anal dose (Pearson's -0.079; p=0.720), **Fig. 4.7**.
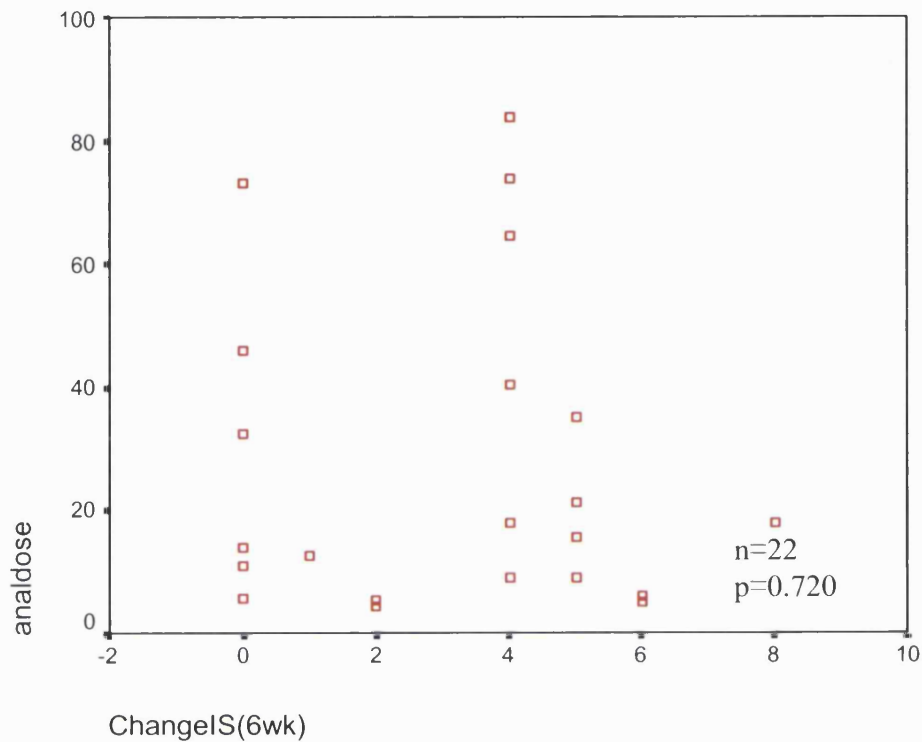
Fig. 4.7 Scatter plot of change in Incontinence Score 6 weeks after RT and anal dose

KEY:

ChangeIS(6wk) = Change in Incontinence Score 6 weeks after RT (arbitrary units)

Analdose   = Anal canal dose (%)

ARP measurements

There was no significant correlation between the reduction in anal canal resting pressure and the anal canal dose (Pearson's -0.292; p=0.526), **Fig.4.8**. The data were available for only 7 patients.
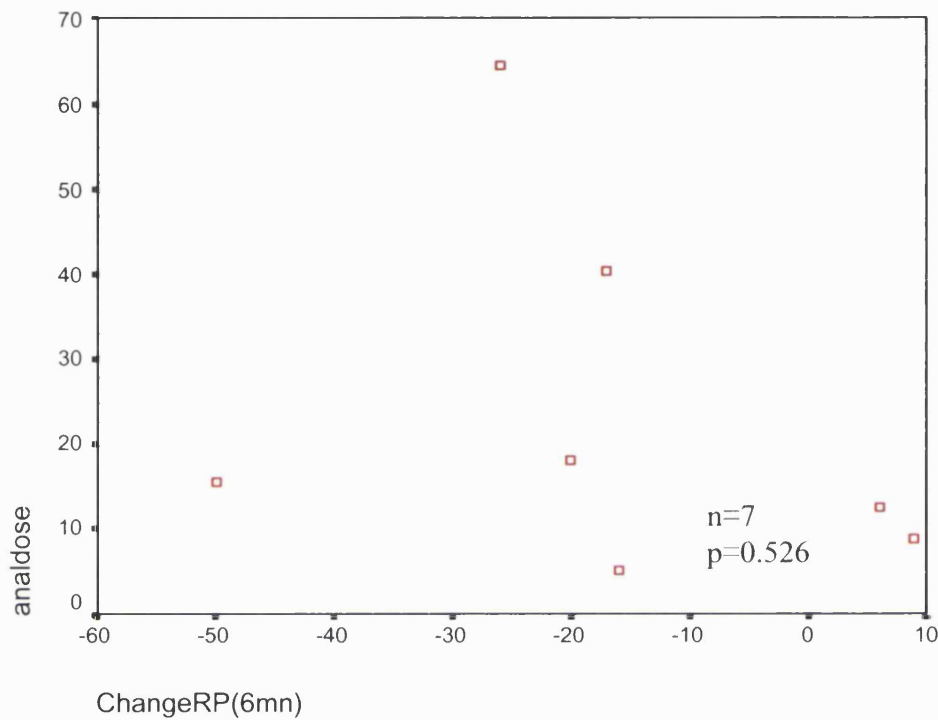
Fig. 4.8 Scatter plot of change in anal canal resting pressure 6 months after RT and anal dose

KEY:

ChangeRP(6mn)   = Change in anal canal resting pressure 6 months after RT (cmH2O)

Analdose   = Anal canal dose (%)

There was no significant correlation between rectal dose and the increase in rectal electrical sensitivity (reduction in rectal sensitivity) six weeks after RT (Pearson's -0.167; p=0.521), **Fig.4.9**.
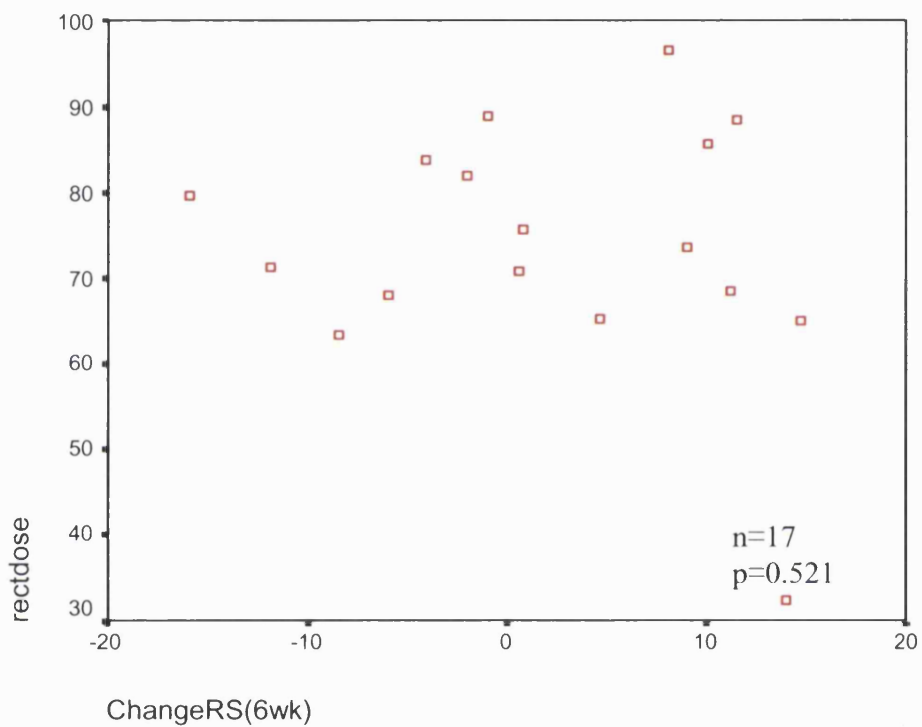
Fig. 4.9 Scatter plot of change in rectal electrical sensitivity before and 6 weeks after RT vs. rectal dose

KEY:

ChangeRS(6mk)   = Change in rectal electrical sensitivity 6 weeks after RT (mA)

Rectdose   = Rectal dose (%)

There was no correlation between the decrease in maximum tolerable volume seen six weeks after RT the rectal dose (Pearson's 0.23; p=0.359), **Fig.4.10.**
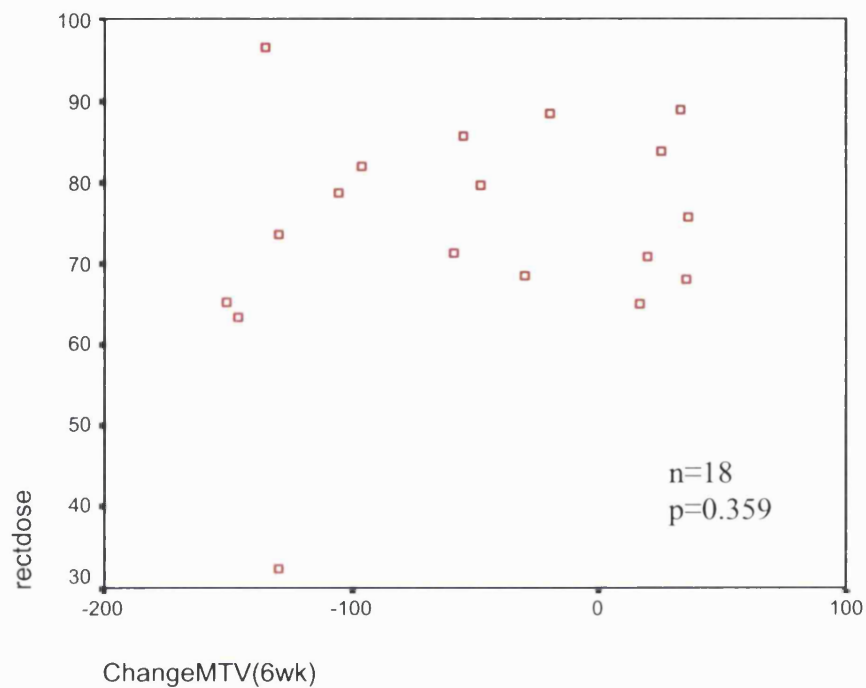
Fig. 4.10 Scatter plot of change in maximum tolerable volume before and 6 weeks after RT vs. rectal dose

KEY:

ChangeMTV(6mk)	= Change in maximum tolerable volume 6 weeks after RT (ml)
rectdose	= Rectal dose (%)

4.4.3 Conclusions

There was no correlation between the anal and rectal dosimetry data and the functional disturbance detected by patient interview or ARP. This is surprising, as it might seem a reasonable hypothesis that the greater the radiation dose, the greater the degree of anorectal dysfunction. A possible reason for failure to demonstrate any correlation would be biological variability between patients in response to radiation injury. Another explanation would be inaccuracy of the dosimetry data. Inaccuracy of the anal canal dosimetry data is probable. This is because , as discussed in Chapter 3 the anal canal commonly lies at the field edges, were dose is changing most rapidly over short distances thus making accurate estimation of dose extremely difficult. The accuracy of the rectal dose is dependant on HELAX^{TM}, the accuracy of the treatment planning as well as other factors such as internal organ movement and set up error.

CHAPTER 5:

STRUCTURAL CHANGES AFTER

RADIOTHERAPY

5.1 INTRODUCTION

Acute rectal radiation injury is well established and is visible endoscopically. Wachter et al, (2000) described rectal mucosal damage on rectoscopy after radiotherapy for prostate cancer and attempted to correlate rectoscopy findings and clinical symptoms to dose. The site of maximum mucosal inflammation on rectoscopy increased from the proximal rectum to the anorectal transition, as well as from the posterior to the anterior rectal wall. This corresponded to the area of maximal dose as determined from the DVHs. Unsurprisingly, there was a degree of correlation between florid features on endoscopy and severe symptoms, although a significant proportion of asymptomatic patients also had florid endoscopic features. The involvement of the anal canal in the aetiology of functional disturbance after pelvic RT remains unclear. Both anatomical and physiological disturbance might result in anal canal dysfunction but this has not been fully explored. The subsequent work aims to define the structural changes in the anal canal that may be attributed to radiation injury using a combination of endoanal ultrasound and MRI.

5.2 ENDOANAL ULTRASOUND OF THE ANAL CANAL BEFORE AND AFTER RADIOTHERAPY

5.2.1 Introduction

Endoanal ultrasound is a useful technique for investigating the anal canal and sphincters. It is a quick and safe procedure that has been widely adopted in the investigation of faecal incontinence, anal pain, anal malignancy, and obstetric trauma. Normal anal canal anatomy on endoanal ultrasound gives an acoustic pattern with four layers (**Fig. 5.1**) corresponding anatomically to the sub-epithelial layer (moderately reflective), internal sphincter (clearly defined ring of low reflectivity) longitudinal muscle (moderately reflective) and the external sphincter (variable reflectivity and pattern)[Bartram et al,. 1997].

Sub-epithelial layer

Internal Anal Sphincter

Longitudinal muscle

External Anal Sphincter
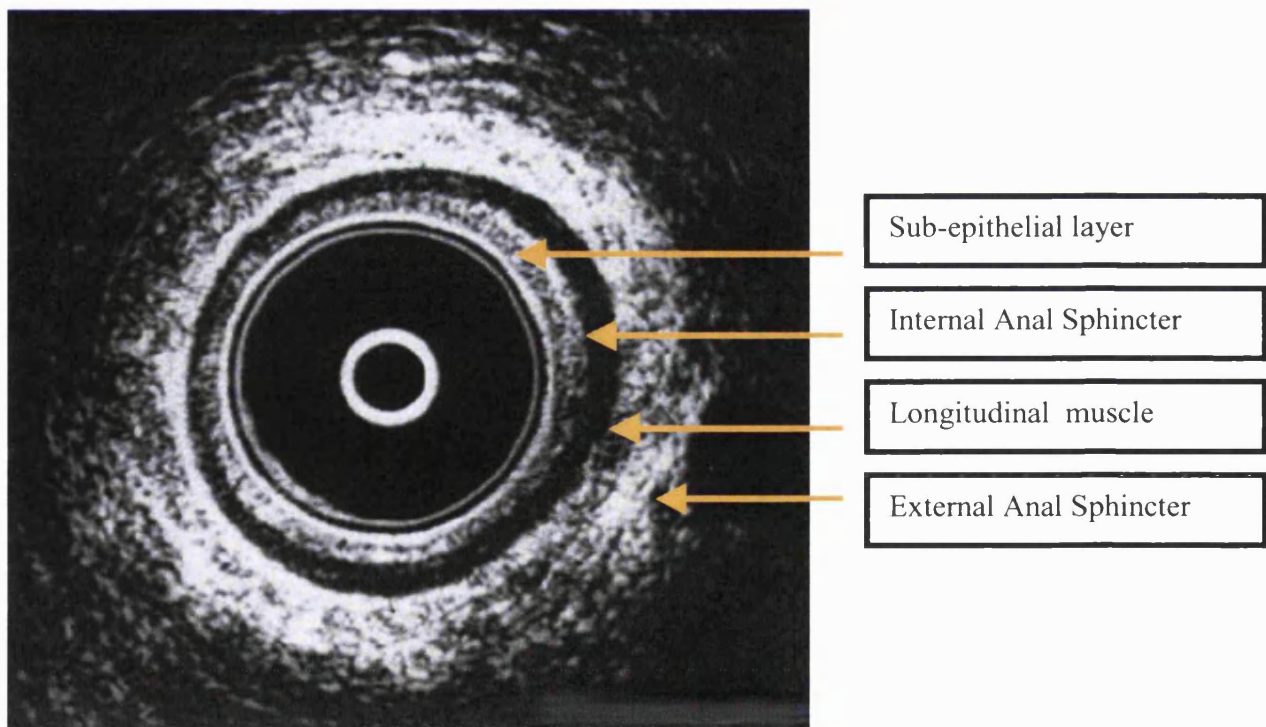
Fig. 5.1 Endoanal ultrasound image

Endoanal ultrasonography has been employed to assess the anal sphincters after pelvic RT in only a few studies. In a study of 35 patients treated for carcinoma of the prostate no changes in the Internal Anal Sphincter (IAS) or External Anal Sphincter (EAS) were demonstrable at four to six weeks [Yeoh et al., 1998]or one year after RT[Yeoh et al., 2000]. A retrospective study including five patients, who had RT to the rectum three to six months previously, showed a significant increase in anal wall thickness when compared to controls[Solomon et al., 1995]. In another retrospective study of patients who had been irradiated for cervical and endometrial carcinoma five to ten years previously, four of the 15 patients had a thinner IAS, but the EAS was unchanged[Yeoh et al., 1996]. There are no prospective data on the long-term changes in sphincter morphology after RT.

5.2.2 Methods

Endoanal ultrasonography was carried out in 26 men with carcinoma of the prostate (23) and bladder (3) before and 6 weeks after RT. In 10 patients ultrasound examination was carried out 6 months after RT (**Appendices 3 & 4**). The same consultant radiologist, who was experienced in the technique, performed all scans. A B&K Medical (Sandtofen 9, Gentofte, Denmark) Ultrasound 3535 scanner, 1850 axial type endosonic probe and the 6004 type 10MHz transducer (**Fig.5.2**) were used in every study. Scans were performed with the patient prone if possible; otherwise a left lateral position was adopted. The probe was orientated in the anal canal with the prostate anteriorly and views of the high, mid and low anal canal obtained. Measurements of the thickness of the sub-endothelial layer, internal anal sphincter (IAS), longitudinal muscle (LM) and external anal sphincter (EAS) were taken at the 3 o'clock and 9 o'clock positions in the mid-anal canal and expressed in mm.

Measurements taken were added onto the hard copy of the ultrasound image at the end of the investigation. The author collated and entered the individual measurements into a database so the radiologist was unaware of the results until the end of the study. The mean thickness of each layer was calculated from the measured thickness at 3 and 9 o'clock. The results (difference between the mean thickness of each layer before and after RT) were tested for normality of distribution using a Shapiro-Wilk test. The statistical significance of differences between measurements was tested using paired t-tests where the data was normally distributed and a Wilcoxon sign-rank test where the data was not normally distributed.
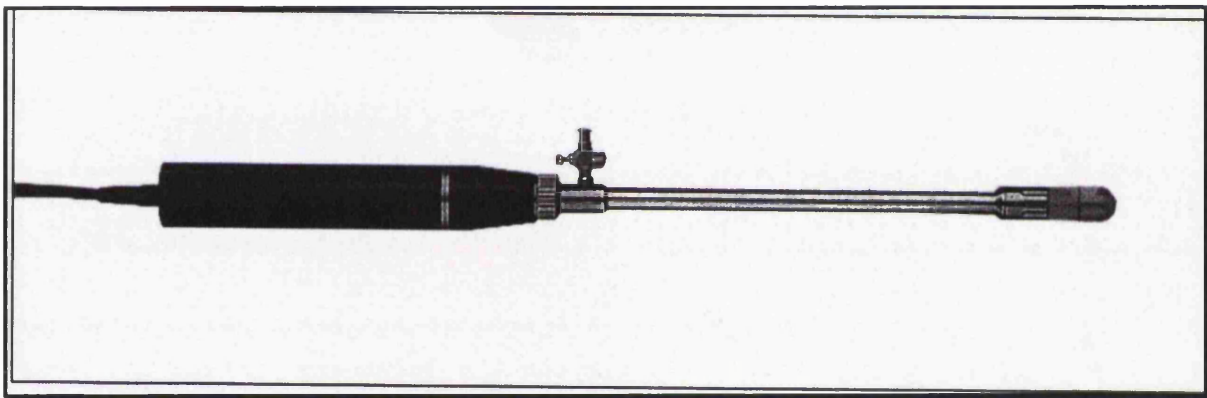
Fig. 5.2 Endoanal ultrasound probe

5.2.3 Results

The data were normally distributed and a paired t-test was employed except for the data relating to the longitudinal muscle thickness, which were analysed by a Wilcoxon sign-rank test. The results are shown in **Appendix 10** and summarised in **Table 5.1**.

Table 5.1 Change in endosonographic thickness of anal canal layers after RT (mm)

	SUBEPITHILEUM			IAS			LONGITUDINAL M			EAS		
	Pre	6wk	6mth	Pre	6wk	6mth	Pre	6wk	6mth	Pre	6wk	6mth
N	27	27	10	27	27	10	27	27	10	27	27	10
Maximum	3.5	3.05	2.9	4.1	2.9	2.9	4	4.8	3.75	8.2	9.3	9.5
Minimum	1.2	1.15	1.4	1.3	1.4	1.5	1.4	1.8	1.9	2.1	2.1	5.3
Mean	2.03	1.85	2.04	2.33	2.36	2.15	2.63	2.66	2.60	6.01	6.33	7.08
Median	1.88	1.70	2.03	2.33	2.28	2.23	2.68	2.50	2.58	6.68	6.68	6.63
P value		.032	.304		.836	.420		.796*	.508*		.451	.062

KEY:

*P values were calculated by a Wilcoxon test. In analysis of six-month post-RT measurements, the mean value is compared with corresponding pre-RT values for those patients i.e. not the mean of the whole group shown in the table.

The mean thickness of the sub-epithelial layer decreased to a statistically significant degree six weeks after RT from 2.03 to 1.85mm (p = 0.032) but not at six months (2.03 vs. 2.04mm). There was no significant change in the thickness of the internal anal sphincter, longitudinal muscle or external anal sphincter six weeks or six months after RT.

5.2.4 Conclusions

There was no demonstrable change in the thickness of the EAS, IAS or LM at six weeks or six months after RT.

The change in thickness of the sub-endothelial layer was 0.2 mm and this change may be of little or no clinical significance. However, before the finding is dismissed, the

following points should be addressed. Firstly, the data were collected prospectively with an average thickness calculated from the 3 and 9 o'clock position measurements in a large number of patients. Secondly, a difference of 0.2 mm represents 10% of the overall thickness of the sub-endothelial layer. Thirdly, the sub-epithelial layer is perhaps the easiest to measure accurately as the inner margin is the defined signal at the edge of the probe and the outer margin is the easily identifiable signal void marking the internal anal sphincter.

The sub-endothelial layer represents the anoderm and haemorrhoidal cushions. The observed decrease in thickness of this highly vascular and rapidly dividing tissue layer following RT may represent an acute response to radiation injury. Whether this has any clinical significance is unknown.

5.3 CONTRAST ENHANCED DYNAMIC MRI OF THE ANAL CANAL BEFORE AND AFTER RADIOTHERAPY

5.3.1 Introduction

MRI relies on the presence of hydrogen nuclei in the tissue being examined. A powerful magnet aligns the hydrogen nuclei and a radio-frequency pulse is applied deflecting the net magnetization of the hydrogen nuclei in the tissue. The excited nuclei spin around the axis of the magnetic field and produce an electric signal detected in a receiver coil. The decay of the signal as the nuclei return to equilibrium is monitored. The return to equilibrium is called magnetic relaxation and is a unique property of each tissue, described by T1 and T2 relaxation times. These are important determinants of image contrast and signal intensity in MRI.

MRI shows increased signal intensity with the inflammatory changes associated with pelvic RT. A characteristic pattern of varying oedema post-radiation has been described [Blomlie et al., 1996]. Irradiated soft tissues also show enhancement with intravenous gadolinium contrast[Fletcher et al., 1990]. Dynamic gadolinium enhanced MRI has been used to show changes in the vascularity of pelvic tumours (cervical cancer) [Gong et al., 1999] and the subsequent response to RT but there are no reports of the utilisation of dynamic MRI in the quantitative assessment of post-RT changes in the anorectum.

The MR scanner available for this work was a $Siemens^{TM}$ $Magnetom^{TM}$ open magnet scanner, **Fig. 5.3**. This utilises a relatively low field strength magnet (0.2 Tesla) and therefore provides reduced signal to noise ratio and hence poorer resolution than

conventional higher field strength scanners (1.5 Tesla). However, the open scanner has the advantages of easy access and is less likely to make patients feel claustrophobic.

MR scanning cannot produce an absolute density value for a specific tissue density such as a Hounsfield number that can be applied in CT scanning. However, dynamic gadolinium enhanced MR scanning can be used to quantify the degree of enhancement of a specific anatomical site. Enhancement is dependant on the rate of delivery of the contrast, blood flow and vascular permeability. Following injury and inflammation there is increased blood flow and vascular permeability resulting in increased uptake of contrast. Irradiation of the anal canal resulting in inflammation might be detectable by increased enhancement on dynamic gadolinium enhanced T1 weighted MRI.

Any detectable enhancement in the rectum following dynamic gadolinium enhanced MRI would also be of relevance and interest. However this was considered unreliable because the resolution of the MRI images obtainable with the MRI scanner available for this work and the thickness and variable position of the rectal wall impact on the accuracy of the findings.

Fig. 5.3 Open magnet MRI scanner

5.3.2 Methods

Dynamic gadolinium enhanced MRI of the pelvis was performed in men with carcinoma of the prostate (25) and bladder (3) before, 6 weeks and in 10 patients 6 months after RT. With the patient lying supine on the table, a 45cm diameter body coil was positioned around the pelvis, with the inferior border of the coil at the upper level of the symphysis pubis. A *Vasculon*™ 20 Gauge IV cannula (Becton Dickinson) was sited in the ante-cubital fossa and attached to a 3-way tap. After an initial scout scan axial, coronal and saggital images were taken and these were centred over the anal canal.

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The dynamic sequences were aligned over the anal canal from the previous axial and coronal images. The dynamic sequence involved 20 acquisitions, each consisting of three saggital slices, centred on the anal canal. Each acquisition of three slices took 11 seconds to complete. Immediately after the end of the second acquisition 10mls of DOTAREM ^{TM} (gadoteric acid 279.3mg/ml Guerbet Laboratories Ltd) was injected as rapidly as possible via the ante-cubital fossa cannula. After completion of each scan images were saved and stored on an optical disk. On completion of all the scans the anal canal slices that were most anatomically central were collated into individual series and sent to a computer via the DICOM (Digital Imaging and COmmunications in Medicine) server. DICOM is the universal data language for imaging technology.

Two elliptical regions of interest (ROI) each of 194.4mm^2, were identified in the anal canal in each series. One ROI was situated in the lower anal canal and one in the upper anal canal. See **Fig 5.4** below.
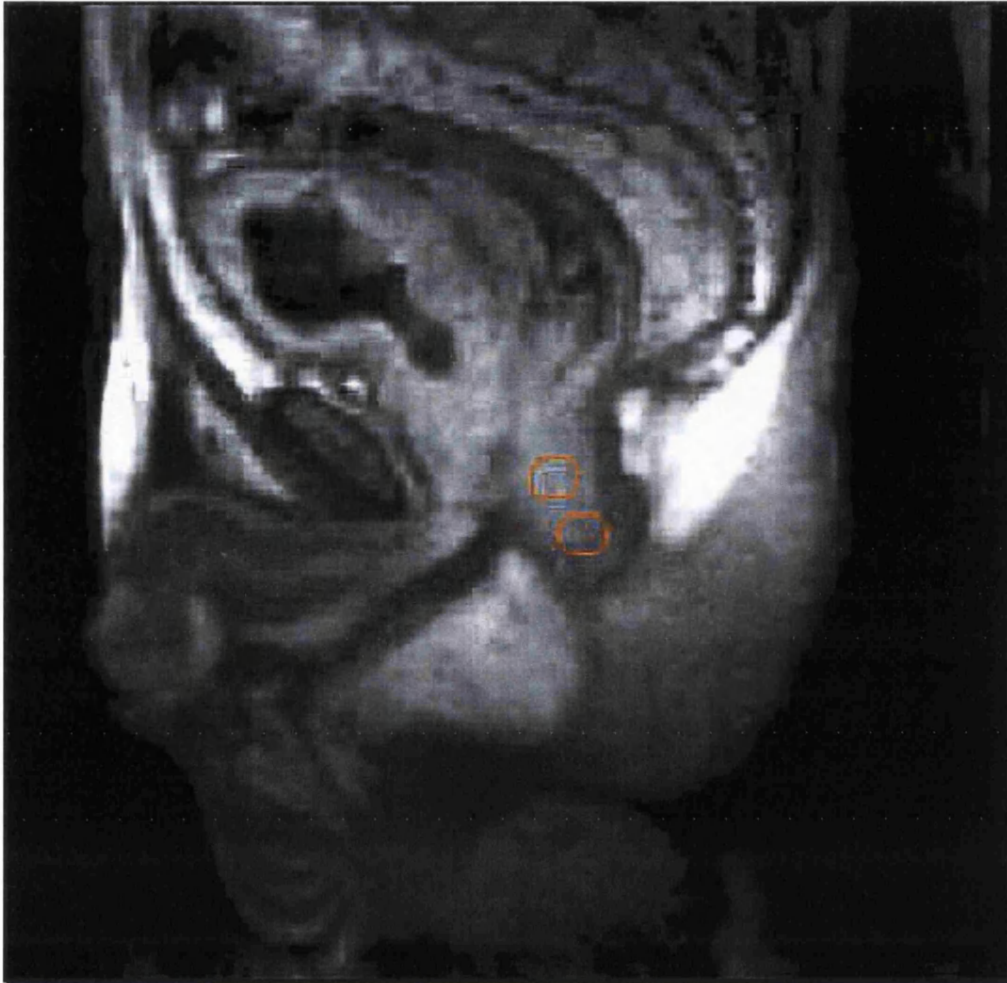
Fig. 5.4 Saggital MRI showing upper and lower anal ROI (orange ellipses)

Numeric signal data throughout each scan were created from each ROI and the data collated on spread sheets. The data were plotted and the degree of enhancement (calculated as final enhancement-enhancement at time zero) and the rate of enhancement over the first 55 seconds (calculated as the gradient of the enhancement curve using Microsoft Excel^{TM}) were determined for each ROI on each scan. The results (differences between before and after RT) were tested for normality using a Shapiro-Wilk test. The statistical significance of differences between measurements was tested using either paired t-tests if the data were parametric and normally distributed or a Wilcoxon signed-rank test if the data were non-parametric.

The data were further utilised to identify evidence of a dose related response. As discussed in Chapter 3 there was a large variance in the estimated anal canal dose between patients (from 4.2 to 83.7% of the total treatment dose – see Patient Dose Data Set -**Table 3.6**). Anal canal dose (**Appendix 5.f**) was therefore plotted against the subsequent change in the rate and degree of anal canal enhancement after radiotherapy to identify any correlation between dose and enhancement.

The set-up for each scan in this study was strictly consistent. Positioning of the patient and coil, orientation of acquisitions, injection of gadolinium and outlining of the regions of interest were all personally performed/supervised by the author. An automated injection of the gadolinium was not available. This would have allowed precise timing of the delivery of the contrast, although the variability in delivery time would be negligible. This with other minor set-up variations should contribute only random and not cumulative error to the results.

5.3.3 Results

An example of the enhancement curves produced for the lower anal canal in one patient is shown in the graph below (**Fig. 5.5**).
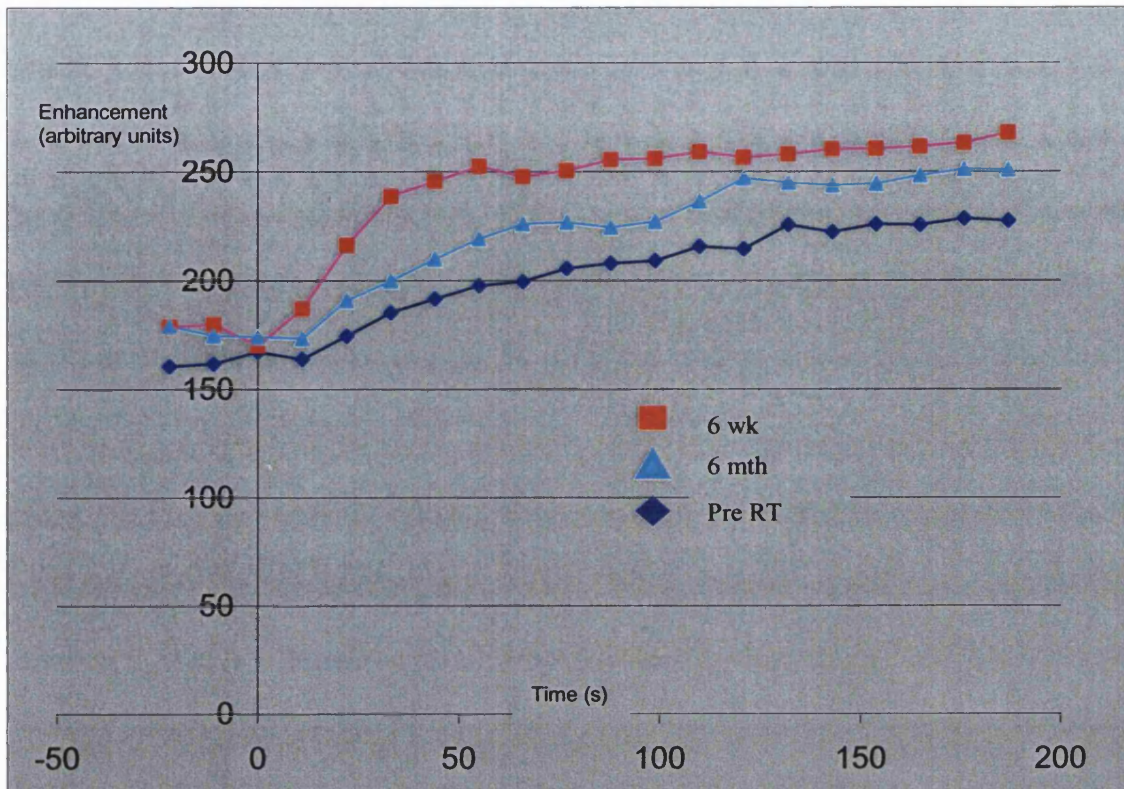
Fig. 5.5 Anal enhancement curves after radiotherapy in one patient

KEY:

Pre RT   = enhancement curve pre radiotherapy

6 wk   = enhancement curve six weeks after radiotherapy

6 mth   = enhancement curve six months after radiotherapy

The complete data set showing enhancement values for individual patients is shown in **Appendix 11**.

The change in mean anal canal enhancement in the lower and upper anal canal for the whole group is shown in **Table 5.2** and **Fig. 5.6**.

Table 5.2 Degree of anal canal enhancement (%En) before and after RT

	LOWER ANAL CANAL			UPPER ANAL CANAL		
	Pre %En	6wk %En	6mth%En	Pre %En	6wk %En	6mth%En
n	28	28	10	28	28	10
MIN	17	25	33	17	31	32
MAX	54	63	57	60	80	85
MEAN	**33.96**	**42.50**	**44.20**	**38.25**	**52.28**	**57.40**
MEDIAN	32.5	41	41	38	50	62.5
p Value		<0.001	<0.001		<0.001	<0.005
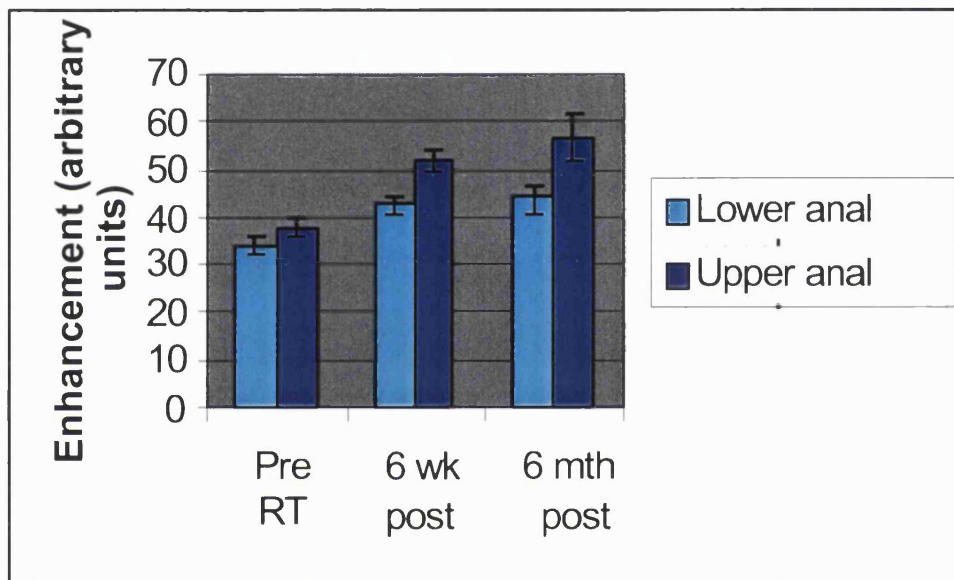
Fig. 5.6 Mean anal canal enhancement in the lower and upper anal canal after RT

Error bars show standard error of the mean

The mean enhancement in the lower anal canal was 33.96% pre-RT increasing to 42.5% at six weeks (p<0.001) and 44.2 % at six months (p<0.001). The mean enhancement in the upper anal canal was 38.25% pre-RT increasing to 52.28% at six weeks (p<0.001) and 57.4% at six months (p = 0.005). There was no statistical difference between 6 weeks and six months.

The mean change in the rate of enhancement (gradient of the enhancement curve) in the lower and upper anal canal for the whole group is shown in **Table 5.3**. and **Fig 5.7**.

Table 5.3 Rate of anal canal enhancement [i.e. Gradient (Grd)] over the 1st 55 seconds before and after RT

	LOWER ANAL CANAL			UPPER ANAL CANAL		
	Pre Grd	6wk Grd	6mth Grd	Pre Grad	6wk Grd	6mth Grd
n	28	28	10	28	28	10
MIN	0.13	0.24	0.23	0.09	0.3	0.39
MAX	1.26	1.59	1.11	1.78	2.73	2.39
MEAN	**0.61**	**0.83**	**0.86**	**0.78**	**1.19**	**1.24**
MEDIAN	0.64	0.83	0.89	0.78	1.02	1.12
p Value		0.005	0.009		<0.001	0.028
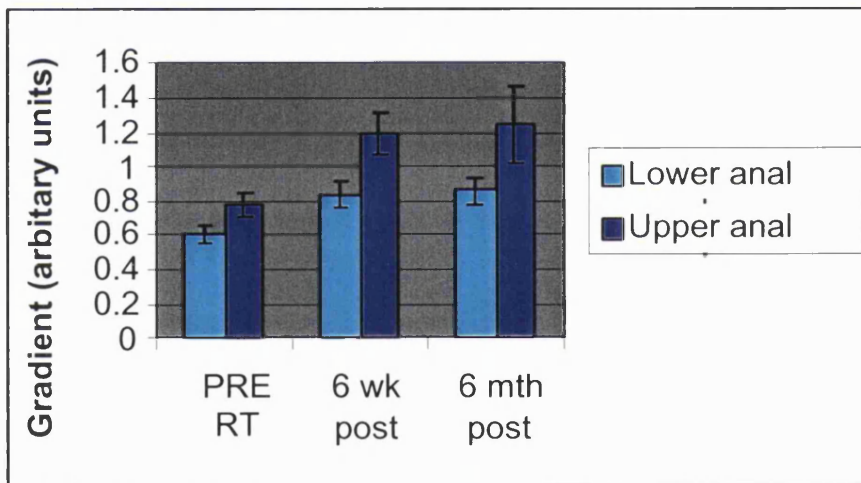
Fig. 5.7 Mean gradient of enhancement curves (1st 55 seconds) after RT

Error bars show standard error of the mean

The mean gradient of the enhancement curves in the lower anal canal over the first 55 seconds was 0.61 pre-RT increasing to 0.83 at six weeks (p=0.005) and 0.86 at six months (p = 0.009). The mean gradient of the enhancement curves in the upper anal

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canal was 0.78 pre-RT increasing to 1.19 and 1.24 six weeks and six months post-RT (p < 0.001). There was no statistical difference between 6 weeks and six months.

The upper anal canal showed significantly greater rate and degree of enhancement than the lower anal canal before any RT had been given; mean gradient of enhancement 0.61 vs 0.78 p= 0.006 and mean percentage enhancement 34 vs 38 p= 0.006. However, the upper anal canal showed significantly increased rate and degree of enhancement at six weeks after RT when compared to the lower anal canal. This was calculated using a paired t-test to compare the change in the rate and degree of enhancement in the lower and upper anal canal before and six weeks after RT. The change in the mean gradient of enhancement before and six weeks after RT was 0.41 in the upper anal canal vs 0.22 in the lower anal canal (p<0.001) and change in the mean percentage enhancement was 14% in the upper anal canal vs 8.5 % in the lower anal canal (p=0.003) **Table 5.4**.

Table 5.4 Comparison of upper and lower anal canal enhancement

	LOWER ANAL CANAL	UPPER ANAL CANAL	P VALUE
Mean anal canal enhancement Pre RT (%) (Range)	33.96 (17-54)	38.25 (17-60)	0.006
Mean gradient of enhancement curves Pre RT (arbitrary units) (Range)	0.61 (0.13-1.26)	0.78 (0.09-1.78)	0.006
Change in mean anal enhancement (%) Pre vs. 6 wks after RT	8.5	14	0.003
Change in mean gradient of enhancement (arbitrary units) Pre vs. 6 wks after RT	0.22	0.41	<0.001

Correlation of enhancement and dose

There was no correlation between anal canal dose and either the rate (Pearson's 0.026; p=0.906) or degree (Pearson's -0.201; p=0.347) of anal canal enhancement six weeks after RT. (**Figures 5.8 and 5.9**)
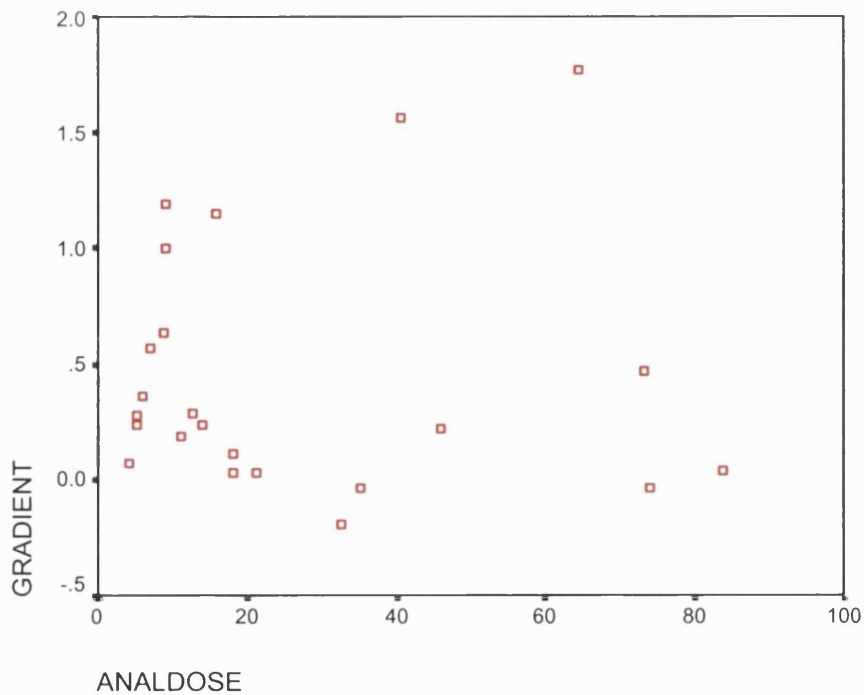
Fig. 5.8 Scatter plot for change in rate of anal canal enhancement pre and

6wk post RT and anal dose

 KEY:
GRADIENT = Change in gradient of anal canal enhancement curves 6 weeks after RT (arbitrary units)
ANALDOSE = Anal canal dose (%)
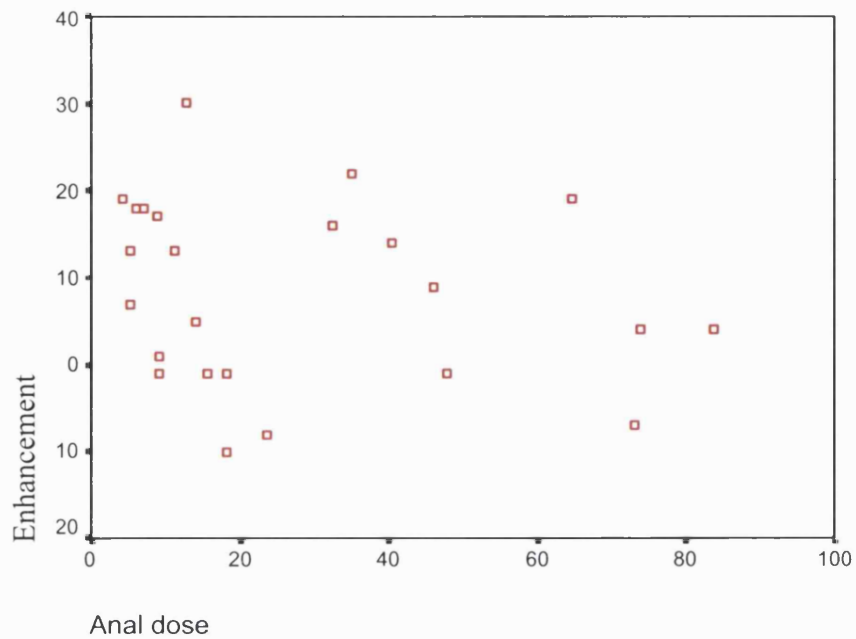
Fig. 5.9 Scatter plot for change in degree of anal canal enhancement pre

and 6wk post RT and anal dose

KEY:
Enhancement = Change in anal canal enhancement 6 weeks after RT (arbitrary units)
Anal dose = Anal canal dose (%)

Similarly there was no correlation between dose and rate or degree of enhancement

six months after RT. Further scatter plots not shown.

5.3.4 Conclusions

The upper anal canal enhanced more than the lower anal canal probably reflecting a greater blood supply.

The enhancement of the anal canal increased by 30-50% after RT. The rate of enhancement increased by 40- 60 % after RT. This is almost certainly due to increased blood flow and/or increased capillary permeability related to an inflammatory response to RT. This represents the first quantitative radiological evidence of acute anal canal injury after pelvic RT and suggests that the inflammatory process persists for at least 6 months. This may have implications in the aetiology of anorectal dysfunction.

In order to further investigate structural changes in the anal canal conventional MRI used in a similar fashion would be valuable. Possibly endo-luminal MRI would provide the exquisite anatomical detail necessary to detect subtle changes[Stoker and Rociu, 1999].

It might seem a reasonable hypothesis that the higher the anal canal dose, the greater the degree of inflammation detected by increased anal canal enhancement. However, there was no correlation between the measured rate or degree of anal canal enhancement and the measured anal doses. This is possibly because of biological variability between patients in response to radiation injury and differences in set up during the MRI scan. However inaccuracy of the dosimetry data seems to be a much more likely explanation because as discussed earlier the anal canal commonly lies at

the field edges where the dose is changing most rapidly over short distances thus making accurate estimation of dose extremely difficult.

There is one piece of evidence that an increased inflammatory response occurs with increased dose. The prostate is situated immediately anterior to the upper anal canal and lower rectum. Therefore the upper anal canal receives a greater radiation dose than the lower anal canal due to its close proximity to the target volume. The increased rate and degree of enhancement in the upper anal canal when compared to the lower anal canal is therefore evidence for a causative positive relationship between dose and inflammatory response.

CHAPTER 6:

DISCUSSION

6.1 FUNCTIONAL CHANGES AFTER RT

Faecal urgency (53%), frequency (52%) and incontinence (31%) were the predominant symptoms six weeks after RT and are related to reduced rectal sensation and rectal capacity demonstrated on anorectal physiology. A reduced rectal capacity will evidently contribute to faecal frequency although changes in stool consistency and other functional effects of the RT on the gastrointestinal tract may also play a role. A smaller rectal reservoir would also contribute to urgency. The finding of a reduced rectal capacity is supported by similar findings by other workers [Varma et al., 1986] [Iwamoto, Nakahara, et al. 1997] [Kim et al., 1998] [Yeoh et al., 1996]. This is the first study to investigate rectal mucosal electrosensitivity after RT. The identified reduction in rectal sensation may be of some importance in understanding the aetiology of anorectal disturbance post RT. A poorer perception of the rectal contents seems likely to be a causative factor for the symptoms of urgency and incontinence that are experienced by patients.

Manometric parameters in the anal sphincters and anal electrical sensitivity did not change six weeks after RT, indicating anal canal injury at this stage is unlikely to be causative of the anorectal symptoms experienced. Birnbaum [Birnbaum et al., 1994] reported no changes in resting or voluntary squeeze pressures in 20 patients studied at 4 weeks after treatment for rectal cancer, but Yeoh and his colleagues demonstrated a significant diminution of these pressures in 35 patients with prostate cancer studied six weeks[Yeoh et al., 1998] but not at one year[Yeoh et al.,2000] after RT. There have not been other studies at six months and the possibility of sphincter recovery at one year cannot be ruled out.

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There is persistent functional anorectal disturbance six months after RT. Faecal urgency (50%), frequency (80%), diarrhoea (40%) and incontinence (33%) are the main symptoms. Rectal electrical sensitivity remained reduced six months after RT showing persistence of rectal radiation injury. This may be responsible for the anorectal disturbance seen in this group of patients. A decrease in resting anal canal pressure at six months represents evidence of radiation injury to the smooth muscle of the IAS or to its nerve supply. Anal electrical sensitivity however, was not significantly altered and the anorectal reflex was unaffected by RT. Another possibility is that an abnormality of rectal sensation affects the IAS via some local mechanism. Certainly the recto-anal inhibitory reflex results in relaxation of the internal anal sphincter when the rectum is rapidly distended. This is usually a very transient response although supramaximal stimulation of the rectum causes the IAS to remain relaxed[Farouk R and Bartolo D.C.C, 1993]. With proctitis the threshold sensation level may be diminished and submaximal stimulation is likely to cause IAS relaxation. The observed increase in squeeze and cough increments may represent improvement in external anal sphincter function, which presumably is a biological response by the EAS to persistent faecal urgency and frequency resulting in training of the EAS.

There was no correlation between the anal and rectal dosimetry data and the functional disturbance detected by patient interview or ARP. However, the relevance of these observations is questionable because of the methodological limitations in obtaining accurate anal and rectal dosimetry.

6.2 Structural Changes After RT

Endoanal ultrasonography revealed a small decrease in the mean thickness of the sub-endothelial layer six weeks after RT. This layer on endoanal US represents the haemorrhoidal cushions; masses of mucous membrane lining the anal canal containing the internal rectal venous plexus. The reduction in this layer may represent radiation injury to the haemorrhoidal cushions, although as there were no manometric changes detectable in the anal canal six weeks after RT the clinical relevance of this is questionable. There was no demonstrable change in the thickness of the EAS, IAS or LM at six weeks or six months after RT. The studies by Yeoh et al (1998,2000) failed to demonstrate any change in anal sphincter morphology at six weeks or one year after RT for prostate cancer although an earlier study looking at women five to ten years after RT for gynaecological malignancy revealed a thinner IAS in four of 15 patients. Clearly structural changes in the anal sphincters may take much longer than 6 months to become evident.

The upper anal canal receives blood from both the middle and inferior rectal arteries, whereas below the dentate line the blood supply is mostly from the inferior rectal artery. The upper anal canal and venous plexus drains to the superior rectal and inferior mesenteric veins to the portal system, whereas the lower anal canal drains via the inferior and middle rectal veins to the internal iliac. The anal canal is thus a site of portal-systemic anastomosis. Topographical studies suggest the anal canal receives a relatively poorer blood supply in the lower anal canal and in the posterior quadrants, which has implications in the aetiology of chronic anal fissure [Lund JN et al., 1999]. Increased blood supply in the upper anal canal is probably reflected by the increased

enhancement that was demonstrated in this study. MRI revealed a significant increase in the degree of enhancement of the anal canal by 30-50% and in the rate of enhancement by 40- 60 % both six weeks and six months after RT. This is almost certainly due to increased blood flow and/or increased capillary permeability related to an inflammatory response to the RT.

Although there was no correlation between the measured rate or degree of anal canal enhancement and the measured anal doses, the increased rate and degree of enhancement in the upper anal canal after RT other than its richer blood supply is likely due to its closer proximity to the RT target volume and hence a greater dose and subsequent inflammatory response.

6.3 AETIOLOGY OF ANORECTAL DISTURBANCE AFTER RT

The above evidence suggests that rectal injury is a causative factor in the disturbance in anorectal function after RT for urological malignancy. Faecal urgency, frequency and incontinence are the predominant symptoms and are related to decreased rectal sensation and decreased rectal capacity. Sphincter dysfunction at six months may compound symptoms. The mechanism behind this process will of course relate to the injurious effects of the photon beam upon the rectum but the precise nature of the injury and how this affects functional disturbance remains to be elucidated.

6.3.1 Neurological Injury

In order to consider the role of a neurological insult, anorectal innervation must be considered. The sensory supply to the rectum consists of only one intra-epithelial receptor, with abundant beaded non-myelinated fibres in the mucosa. However, just above the anal valves a much richer supply of nerve endings are encountered explaining the increased sensory differentiation in the anal canal and the concept of anal sampling. Motor supply to the anorectum is both intrinsic via the myenteric (Auerbach's) and submucosal (Meissner's) plexuses (part of the enteric nervous system) and extrinsic. Extrinsic supply consists of preganglionic parasympathetic and postganglionic sympathetic nerves supplying the anorectum..

Rectal distension stimulates sensory afferents, which travel via the pelvic splanchnic nerves to S2 and S3. Nocioceptive pathways travel in both parasympathetic and sympathetic systems via the inferior and superior hypogastric plexus to L1 and L2. An important subdivision of the inferior hypogastric plexus is the peri-prostatic plexus,

which is adjacent to the rectum and prostate and supplies parasympathetic and sympathetic input to the prostate, seminal vesicles, corpora, vas deferens, urethra, ejaculatory ducts and bulbourethral glands.

Radiation injury could disturb rectal sensation (reduced rectal electrical sensitivity) by direct effect on the rectal mucosa (such as oedema), damage to rectal intra-epithelial receptors, injury to nerve fibres or to a combination of all. Rectal oedema or other mucosal events such as excessive mucus production could increase the distance between the urethral ring electrode and the intraepithelial receptors resulting in reduced rectal electrical sensitivity (increased amplitude of current being necessary to be sensed by the patient). However, persistence of significant oedema six months after RT seems unlikely and in five patients who underwent endoscopic examination of the rectum six months after RT, no mucosal abnormality was evident.

Radiotherapy for prostate cancer is known to result in sexual dysfunction related to damage to the peri-prostatic plexus, which commonly lies within the target volume. The anal canal also receives autonomic innervation from this plexus and reductions in resting pressure in the IAS seen six months after RT could be related to neurogenic damage at this site.

This study has not demonstrated evidence to suggest neurological injury to the motor supply of the anorectum as the recto-anal inhibitory reflex was present in all patients. However injury to intra-epithelial receptors or their afferent nerve fibres may be responsible and this would explain the reduction in rectal electrical sensitivity. Varma et al (1986) described neuronal hypertrophy of the muscular (Auerbach's) plexus

associated with a diminution, vacuolation and degranulation of ganglion cells, consistent with injury to the myenteric nerves. Similar histological changes such as these might occur. However, the degree of functional disturbance seen and the persistence of the recto-anal inhibitory reflex in all of the patients studied, shows that much of the rectal afferent supply as well as the motor supply continue to function normally.

6.3.2 Reduced Rectal Capacity After Radiation Injury

The rectum has the ability to act as a dynamic reservoir for faeces and its role is not only dependent on perception of filling, but also on functional capacity. Previous studies have reported reductions in rectal capacity and/or rectal compliance after pelvic RT [Varma et al., 1986];[Yeoh et al., 1996];[Iwamoto, Nakahara, et al. 1997]; [Kim et al., 1998] . Rectal compliance is calculated from the gradient of a graph plotting volume versus pressure. A compliant rectum expands easily without intra-luminal pressure increasing greatly to allow for distension with stool or flatus, without compromising continence. As discussed the rectum is not a 'closed system' and therefore rectal compliance cannot be measured accurately. In this study rectal electrical sensitivity and rectal volumes (rectal threshold, urge threshold and maximum tolerated volume) rather than compliance were deemed more relevant measures of the functional elements of the rectum.

Mean rectal volumes were reduced after RT, although only the maximal tolerable volume six weeks post RT was reduced to a statistically significant degree. Certainly a reduction in rectal capacity would tend to result in faecal frequency and urgency. The demonstrated reduction in rectal capacity might result from smooth muscle

hypertrophy such as that described in chronic radiation injury. Fibrosis is another possibility although six weeks post RT would seem early for such changes to have occurred. A further explanation is that there is no real change in compliance or capacity of the rectum at this early stage, but that distension of the rectum is more painful and therefore the maximum tolerable volume is reduced. As rectal electrical sensitivity is clearly reduced, this explanation seems less likely.

6.3.3 Failure Of Correlation Between Dose And Post RT Changes

It is indisputable that there is increasing biological injury with increasing dose. However, the relationship is complex and depends upon multiple factors including target site, irradiated volume, tissue oxygenation, delivery technique, fractionation regime and in particular the inherent radio-sensitivity of the irradiated tissue. Radio-sensitivity of the same tissue type, varies significantly between individuals. Proteins involved in the regulation of the DNA damage response, cell cycle progression, and apoptosis are thought to be largely responsible for determining this sensitivity or resistance to ionising radiation. Despite recent advances in knowledge of these cellular functions, most of the clinically observed heterogeneity of normal tissue responses to radiotherapy is unaccounted for[Rosen et al., 1999].

Most previous studies have reported dose only in terms of the total prescribed dose and the fractionation regime. This is the first study that attempted to measure rectal and anal canal doses and relate them to functional and structural changes. The vast majority of patients received the same prescribed dose of radiation, but despite this, large variations were seen in the 'measured' rectal and anal canal doses. No correlation was demonstrable between any of the functional and structural parameters

that were investigated and the measured doses. This may be because the number of patients investigated was not sufficiently large to show this difference over the background of random variation between patients for the reasons discussed above. There is one strong piece of evidence of a dose related response. Due to the anatomical position of the prostate the upper anal canal will receive a greater radiation dose than the lower anal canal. This gradient of dose was demonstrated by the in-vivo dosimetry measurements, which, though highly variable showed a greater dose in the lower rectum and upper anal canal than in the lower anal canal. The increased degree and rate of enhancement seen on MRI in the upper anal canal after RT, suggests a greater inflammatory response related to this increased dose.

It is possible that late radiation effects will correlate better with the doses reported in this study. Another future study is required to address late radiation effects and with better MRI resolution the morphological changes may also be better quantified. Both radiological and histological evidence of structural post RT change in the anal canal are lacking and this area demands further attention. With better understanding of rectal protection in terms of dose delivery and possibly mucosal protective agents the damage may be minimized.

6.4 CONCLUSION

Rectal radiation injury resulting in reduced rectal sensation and capacity is the major cause of acute anorectal symptoms following pelvic radiotherapy. There is some radiological evidence of acute anal canal injury but this does not appear to have great significance in terms of functional disturbance at this stage. The measured radiation doses could not be correlated with any of the functional or structural changes that were demonstrated. There is a physiological response to the faecal frequency and urgency after RT that can result in enhanced external sphincter function and improvement in squeeze pressures. Rectal protection is paramount, particularly in view of the poor response to any of the currently available treatments for radiation induced anorectal injury. Future work should concentrate on reducing rectal dose if side-effects from this important therapy are to be minimized.

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Appendix 1
Patient Information Sheet

Confidential

The Relationship Of The Dose Effect And Anorectal Function In Pelvic Radiotherapy

What is this study about?

You are asked to take part in this study. During the course of your treatment you will be receiving radiotherapy. Radiotherapy is a process where x-rays are used to treat cancer cells. During your treatment healthy tissues may also be damaged due to effects of the x-rays. Sometimes the back passage (anus and rectum) can be affected although we try to minimize this. The purpose of our study is to assess the function of your anus and rectum before and after radiotherapy and to measure the exact amount of radiotherapy, which the anus and rectum receive. This will help to understand why some people have upsetting symptoms after radiotherapy and may allow improvements in methods and techniques in the future. Travel expenses incurred taking part in this study can be reclaimed.
Your contribution would be greatly appreciated.

You do not have to take part in this study if you do not want to. If you decide to take part you may withdraw at any time without having to give a reason. Your decision whether or not to take part will not affect your care and management in any way. You will not directly benefit from taking part in this study.

What exactly is involved if I agree to take part?

Firstly, taking part will not alter the treatment you receive. You will however be asked to undergo some extra tests to find out if the radiotherapy has affected your anus and rectum. An ultrasound examination and an MRI scan of your anus will be performed as well as some other tests called anorectal physiology. The anorectal physiology tests involve passing a soft plastic catheter 3-4cm into your back passage and taking measurements from your anus and rectum. This set of tests is carried out before the radiotherapy starts (it takes about 20 minutes). It may be uncomfortable but should not be painful. At 3-4 weeks and again at 6 months after finishing your treatment sessions the tests are repeated. At the third session you will also have a sigmoidoscopy, which examines the rectum with a plastic pipe. At the same time I may ask to take a tiny piece of tissue (a biopsy), which will be examined under a microscope. This won't hurt but can occasionally cause some bleeding. During two of the radiotherapy sessions another tube may be placed in the back passage to measure the amount of x-rays reaching the anus and rectum. In total this will mean 3-4 extra visits to the hospital.

Please note: All proposals for research using human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the Joint UCL/UCLH Committees on the Ethics of Human Research.
Prof. PB Boulos is the supervising consultant responsible for this study.

Thank you for your time

Dickon Hayne.
Principle Investigator   **Supervisor**
Mr Dickon Hayne FRCS   **Prof PB Boulos**

Appendix 2

CONSENT FORM

CONFIDENTIAL

The Relationship Of The Dose Effect And Anorectal Function In Pelvic Radiotherapy

Participating Medical Practitioner

I confirm that I have explained the nature of the study to the patient, and I am acting

within the guidelines stated by the Joint UCL/UCLH Committees on the Ethics of

Human Research.

Signature………………………………….. **Date**………………

Name of Doctor…………………………………

Patients

Signing this consent form shows that you are willing to participate in the above study. Before signing please check that you :
➢ **Have read the information sheet about the study**
➢ Have had an opportunity to ask questions and discuss this study
➢ Have received satisfactory answers to all your questions
➢ Have received enough information about this study
➢ Understand that you are free to withdraw from this study…
> ➢ At any time
> ➢ Without giving a reason for withdrawing
> ➢ Without affecting your future medical care

Do you agree to take part in this study?
I confirm that I am the patient and that I wish to participate in the trial "Investigation of Radiation Doses to the Anus and Subsequent Effects On Ano-Rectal Function"
I have understood the nature of the study and am satisfied with the explanations provided.
I understand that no other procedure other than that explained in the information sheet may be carried out without my express consent.

Signature………………………………………… *Date*……………………………

Appendix 3: Patient Demographics

PAT Nº	INITALS	AGE	SITE	STAGE	GRADE	PLANNING	OTHER RELEVANT INFORMATION
							(64Gy in 32 fractions unless otherwise stated)
1	SS	70	Prostate	T1c	3+3	target	3/12 zoladex. AF. HT. CRF
2	AW	66	Prostate	T1c	3+3	target	6/12 zoladex MI. HT, AAA
3	SG	55	Prostate	T2a	3+3	target	3/12 zoladex
4	DH	66	Prostate	T1b	3+3	target	
5	JBu	70	Bladder	PT1b	Grade 3	target	MRC study asoc. With in-situ
6	WA	73	Bladder	T1 G3	Grade 3	target	
7	WM	58	Prostate	T1a	3+3	Helax	
8	AS	74	Prostate	T3a	4+3	target	Prev laser ablation + zoladex
9	SS	82	Bladder	PT2	Grade 3	target	TURBT 1997(G2Pt1b) '99 rec+prostatic involvement
10	BLK	71	Prostate	T1c	4+3	target	
11	KV	71	Prostate	T1c	3+2	Helax	
12	EP	80	Prostate	T3a	4+5	Helax	3/12 zoladex
13	JPh	71	Prostate	T1c	3+3	Helax	3/12 zoladex
14	JPa	62	Prostate	Recurrent	3+4	target	Prostatectomy ' 97 (60 Gy 30 fracts)
15	DM	76	Prostate	T1a	3+3	Helax	3/12 zoladex Diabetes (NIDDM)
16	TA	78	Prostate	T1c	3+3	Helax	
17	AM	62	Prostate	T2	4+4	Helax	3/12 zoladex
18	HL	70	Prostate	T1		Helax	
19	AA	77	Prostate	T2	3+3	Helax	3/12 zoladex
20	JBa	63	Prostate	T1c	3+3	Helax	
21	PB	61	Prostate	T1c	4+4	Helax	
22	CR	59	Prostate	Recurrent		Helax	Prostatectomy (60 Gy)
23	RO	67	Prostate	T2b/T3a	4+3	Helax	
24	JH	76	Prostate			Helax	
25	AD	57	Prostate	T1c	3+3	Helax	
26	SM	64	Prostate			Helax	
27	GL	71	Prostate	T2a	3+3	Helax	
28	AT	64	Prostate	T1c		Helax	
29	MH	73	Prostate	T1c	Intermediate	Helax	
30	JMc	71	Prostate	T2b/T3a	3+2	Helax	
A	LO'C	75	Prostate	T4	3+3	Target	
B	CG	41	Cervix			Target	
C	SB	59	Endometrium			Target	

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Appendix 4: Patient Completion

PAT N°	INITALS	MALIGNANCY	ARP			MRI			ENDOANAL US			DOSIMETRY	NON-COMPLETION REASON
			Pre	6 wk	6 mth	Pre	6 wk	6 mth	Pre	6 wk	6 mth		
1	SS	Prostate	Y	Y	N	Y	Y	N	Y	Y	N	N	Lost to follow-up (no phone)
2	AW	Prostate	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	
3	SG	Prostate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
4	DH	Prostate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
5	JBu	Bladder	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
6	WA	Bladder	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
7	WM	Prostate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
8	AS	Prostate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
9	SS	Bladder	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
10	BLK	Prostate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
11	KV	Prostate	Y	Y		Y	Y		Y	Y		Y	
12	EP	Prostate	Y	Y		Y	Y		Y	Y		N	
13	JPh	Prostate	Y	Y		Y	Y		Y	Y		Y	
14	JPa	Prostate	Y	Y		Y	Y		Y	Y		N	
15	DM	Prostate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
16	TA	Prostate	Y	Y		Y	Y		Y	Y		Y	
17	AM	Prostate	Y	Y		Y	Y		Y	Y		N	Dropped out of dosimetry
18	HL	Prostate	Y	N	N	Y	N	N	N	N	N	Y	Dropped out of study
19	AA	Prostate	Y	Y		Y	Y		Y	Y		Y	
20	JBa	Prostate	Y	Y		Y	Y		Y	Y		Y	
21	PB	Prostate	Y	Y		Y	Y		Y	Y		Y	
22	CR	Prostate	Y	Y		Y	Y		Y	Y		N	
23	RO	Prostate	Y	Y		Y	Y		Y	Y		Y	
24	JH	Prostate	Y	Y		Y	Y		Y	Y		N	
25	AD	Prostate	Y	Y		Y	Y		Y	Y		N	
26	SM	Prostate	Y	Y		Y	Y		Y	N		N	Only dynamic MRI 6/52
27	GL	Prostate	Y	Y		Y	Y		Y	N		N	
28	AT	Prostate	Y	Y		Y	Y		Y	Y		N	No phone
29	MH	Prostate	Y	Y		Y	Y		Y	Y		N	
30	JMc	Prostate	Y	Y		Y	Y		Y	Y		N	

Appendix 5a
Comparison Between TLD measured and diode measured doses in 3 patients

Patient Number	Diode Number	Diode Dose (cGy)	TLD Dose (cGy)	Tld/Diode	St Dev
4	1	179	185	1.03	4.24
	2	200	189	0.95	7.78
	3	200	145	0.73	38.89
	4	131	130	0.99	0.71
	5	43	43	1.00	0.00
C	1	197	179	0.91	12.73
	2	181	168	0.93	9.19
	3	102	98	0.96	2.83
	4	19	18	0.95	0.71
	5	12	11	0.92	0.71
3	1	212	190	0.90	15.56
	2	204	185	0.91	13.44
	3	185	153	0.83	22.63
	4	124	80	0.65	31.11
	5	26	34	1.31	5.66

KEY:
Appendix 3 shows patient demographics

Appendix 5b

TARGET™ Predicted/Diode Measured Dosimetry Comparison –Readings On 5 Fractions

Patient	Site	Diode	Dose Measured (cGy)						Std Dev (%)	*TARGET*™ Dose (cGy)	*TARGET*™ /Measured
			Frac 1	Frac 2	Frac 3	Frac 3	Frac 5	Average			
A	PROSTATE	1	193.39	195.84	194.62	194.62	195.84	**194.86**	0.53	**200**	1.03
		2	194.62	194.62	195.84	195.84	194.62	**195.11**	0.34	**200**	1.03
		3	194.99	196.24	194.99	196.24	196.24	**195.74**	0.35	**200**	1.02
		4	195.73	194.46	194.46	195.73	194.46	**194.97**	0.36	**198**	1.02
		5	195.11	195.11	197.51	195.11	192.72	**195.11**	0.87	**198**	1.02
5	BLADDER	*1	201.96	121.18	80.78	198.29	193.39	*159.12	34.60	*120	0.75
		*2	123.62	69.77	68.54	99.14	74.66	*87.15	27.4	*74	0.85
		3	75.76	19.87	19.87	19.87	19.87	31.05	80.50	0	E
		4	15.25	8.90	10.17	10.17	10.17	10.93	22.67	0	E
		5	9.58	7.18	4.79	7.18	5.99	6.94	25.57	0	E
8	PROSTATE	1	201.96	199.51	203.18	200.74	201.96	**201.47**	0.69	**200**	0.99
		2	194.62	195.84	195.84	192.17	197.06	**195.11**	0.95	**198**	1.01
		*3	84.46	90.67	131.65	18.63	135.38	*92.16	51.17	*140	1.52
		*4	13.98	68.63	19.07	8.90	15.25	*25.17	97.6	*100	3.97
		5	8.38	10.77	9.58	5.99	9.58	8.86	20.49	0	0.00
7	PROSTATE	1	199.51	198.29	200.74	198.29	203.18	**200.00**	1.02	**198**	0.99
		2	190.94	189.72	193.39	189.72	197.06	**192.17**	1.62	**188**	0.98
		*3	166.43	89.42	186.30	96.88	188.78	*145.56	33.45	*114	0.78
		*4	62.28	19.07	43.21	13.98	19.07	*31.52	65.41	*10	0.32
		5	9.58	8.38	10.77	8.38	9.58	9.34	10.72	0	0.00
9	BLADDER	1	187.27	250.92	247.25	257.04	247.25	**237.95**	12.02	**243**	1.02
		*2	113.83	238.68	225.22	199.51	328.03	*221.05	34.85	*180	0.81
		*3	24.84	126.68	29.81	80.73	67.07	*76.07	54.61	*128	1.68
		4	12.71	64.82	13.98	17.79	15.25	27.96	80.07	13	0.47
		5	8.38	14.36	9.58	10.77	8.38	10.77	23.04	0	0.00

KEY:

Bold font = diode in target volume
* = diode at edge of target volume
Frac = Measured fraction

Appendix 5c

TARGET™ Predicted/Diode Measured Dosimetry Comparison -Readings On 2 Fractions

Patient	Site	Diode	Dose Measured (cGy)				Std Dev (%)	*TARGET*™ Dose	*TARGET*™ /Measured
			Frac 1	Frac 2		Average			
4	PROSTATE	1	194.97	174.38		**184.68**	7.88	**198**	1.07
		2	186.16	190.96		**188.56**	1.80	**204**	1.08
		*3	95.33	194.37		*144.85	48.35	*202	1.39
		*4	66.96	191.70		*129.33	68.20	*184	1.42
		5	9.82	76.14		42.98	109.10	28	0.65
C	UTERUS	1	186.91	196.00		**191.46**	3.36	**184**	0.96
		2	168.37	177.03		**172.70**	3.55	**182**	1.05
		*3	26.54	163.06		*94.80	101.82	*115	1.21
		*4	14.50	21.09		*17.79	26.19	*31	1.74
		5	8.59	13.50		11.04	31.43	1	0.09
3	PROSTATE	1	191.34	187.71		**189.52**	1.36	**198**	1.04
		2	186.16	183.75		**184.95**	0.92	**196**	1.06
		*3	123.80	181.99		*152.89	26.91	*194	1.27
		4	70.90	89.28		80.09	16.23	170	2.12
		5	14.74	51.58		33.16	78.57	80	2.41
B	CERVIX	1	168.91	172.58		**170.75**	1.52	**173**	1.01
		2	134.64	164.02		**149.33**	13.91	**153**	1.02
		*3	16.15	24.84		*20.49	30.00	*29	1.41
		4	11.44	12.71		12.07	7.44	0	0.00
		5	8.38	8.38		8.38	0.00	0	0.00

KEY:

Bold font   = diode in target volume
*   = diode at edge of target volume
Frac   =Measured fraction

Appendix 5d

HELAX™ Predicted/Diode Measured Dosimetry Comparison

| Patient N°	Diode N°	Dose Measured (cGy)						Std Dev (%)	Measured Dose (Average x diode correction factor) (cGy)	HELAX™ Dose (cGy)
		Frac 1	Frac 2	Frac 3	Frac 3	Frac 5	Average			
15	1	162	162	162	160	161	161	0.55	200	190
	2	158	156	153	152	153	154	1.63	189	188
	3	148	66	72	64	69	83.8	43	104	178
	4	18	10	15	10	11	12.8	27.8	16	35
	5	9	7	9	6	7	7.6	17.7	9	12
11	1	158	157	158	158	156	157	.57	195	198
	2	154	158	149	156	151	154	2.37	188	185
	3	24	153	73	154	60	92.8	62.8	115	126
	4	8	13	10	66	10	21.4	117	27	18
	5	5	7	7	10	7	7.2	24.8	9	9
13	1	156	157	162	160	156	158	1.7	196	202
	2	151	156	160	159	152	156	2.59	191	200
	3	71	129	155	154	114	125	27.8	155	197
	4	56	58	19	85	61	55.8	42.4	70.4	107
	5	9	8	6	8	11	8.4	21.6	10	16
16	1	145	149	155	152	152	151	2.51	187	186
	2	149	151	157	149	150	151	2.21	185	188
	3	135	152	158	81	151	135	23.3	168	186
	4	76	126	146	10	140	99.6	57.4	126	146
	5	12	18	14	5	21	14	43.7	17	6
20	1	156	158	154	158	156	156	1.07	194	192
	2	148	151	148	155	150	150	82.6	184	188
	3	66	73	79	125	70	82.6	29.3	102	174
	4	10	13	54	54	53	36.8	62.8	46	42
	5	7	7	11	8	10	8.6	21.1	10	10

Appendix 5d CONTINUED

Patient N°	Diode	Dose Measured (cGy)						Std Dev (%)	Measured Dose (Average x diode correction factor) (cGy)	HELAX™ Dose (cGy)
		Frac 1	Frac 2	Frac 3	Frac 3	Frac 5	Average			
23	1	158	160	158	159	157	158	**0.72**	196	193
	2	159	154	159	154	157	157	**1.6**	192	186
	3	158	136	156	30	151	126	**43.2**	157	22
	4	27	10	23	9	12	16.2	**50.8**	20	10
	5	8	8	8	5	0	5.8	**25.9**	7	6
21	1	157	156	142	148	154	154	**2.62**	190	188
	2	146	148	62	148	107	137	**3.7**	168	101
	3	75	69	51	96	64	76	**15.5**	94	22
	4	55	50	7	59	51	53.8	**6.9**	68	10
	5	9	31	5	51	7	24.5	**71**	30	6
19	1	161	157	157	154	156	157	**1.62**	194	200
	2	164	152	156	139	150	152	**5.99**	186	194
	3	161	81	77	68	97	96.8	**38.6**	120	166
	4	149	60	13	11	62	59	**94.9**	75	86
	5	116	12	6	7	15	31.2	**152**	38	22
7	1	163	162	164	162	166	163	**1.02**	202	191
	2	156	155	158	155	161	157	**1.62**	192	187
	3	134	72	150	78	152	117	**33.5**	145	83
	4	49	15	34	11	15	24.8	**65.4**	145	83
	5	8	7	9	7	8	7.8	**10.7**	9	9
18	1	156	159	153	13	153	127	**50.2**	157	193
	2	67	157	146	149	133	130	**28**	160	192
	3	62	109	79	139	68	91.4	**35.2**	113	180
	4	14	60	62	65	57	51.6	**41.1**	65	96
	5	7	11	12	62	14	21.2	**108**	26	14

APPENDIX 5e: Histograms Showing HELAX Predicted Vs Measured Dose in 10 patients

Please note the edge of the target volume was strictly defined as the area where the dose varied between 90% and 10% of the prescribed dose. Diodes in the target volume therefore have a predicted dose of >180 cGy, diodes at the edges of the target volume have a predicted dose of 20 to 180 cGy and diodes outside the target volume have a predicted dose of < 20 cGy.
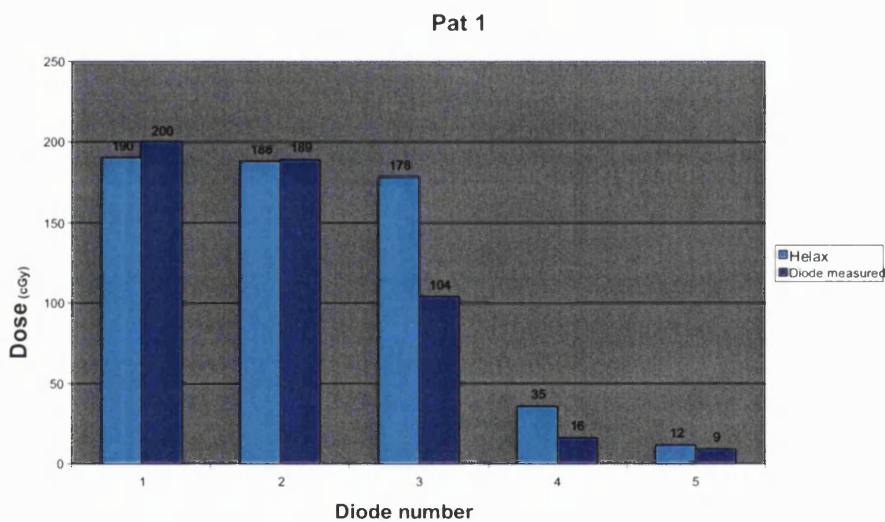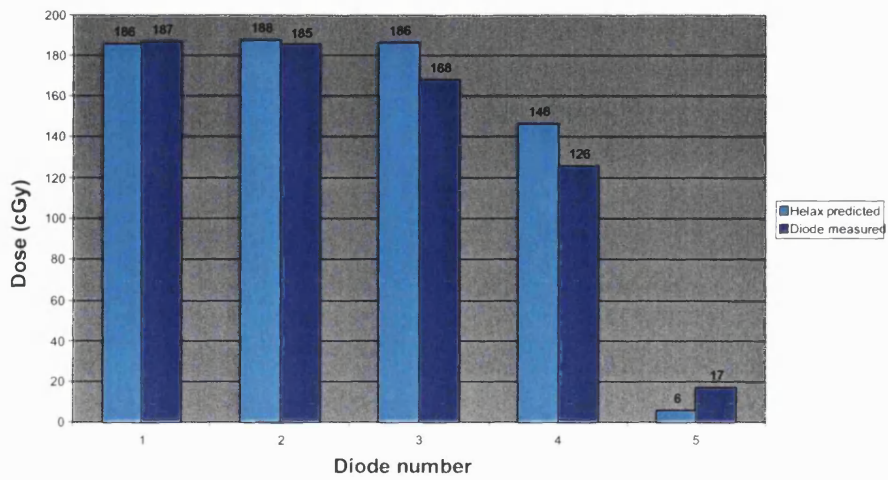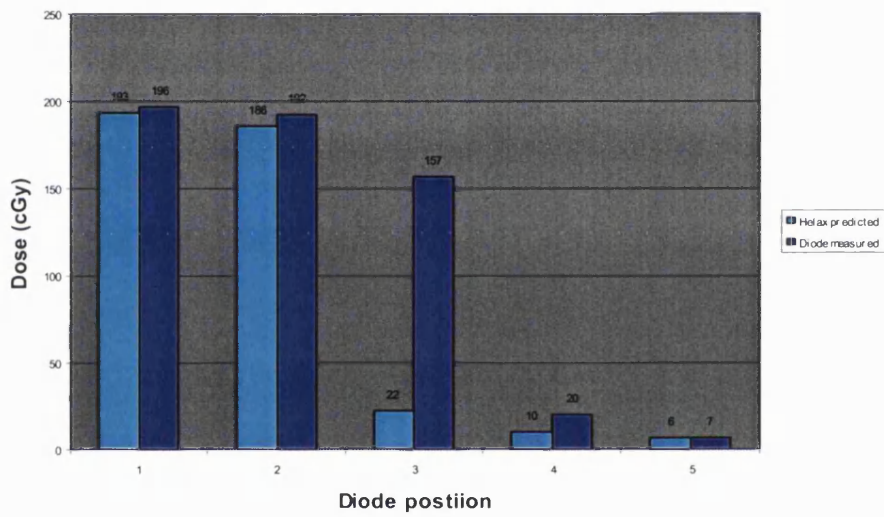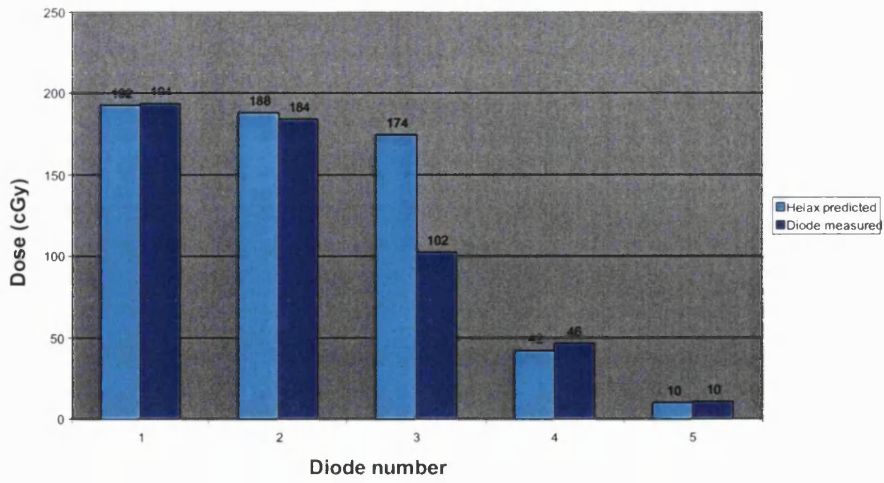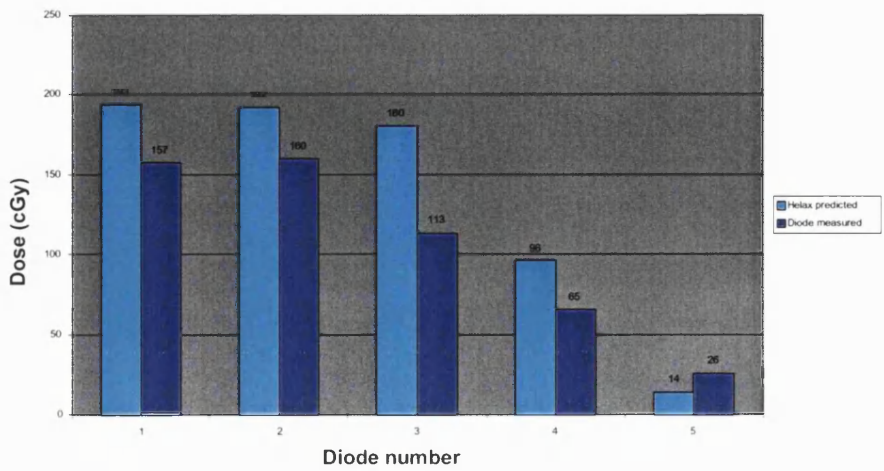

Pat 1

Pat 2
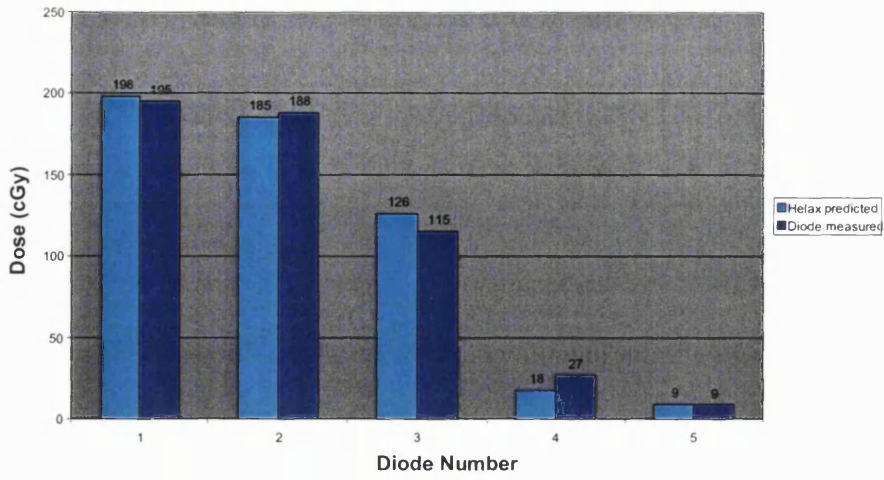
Pat 3
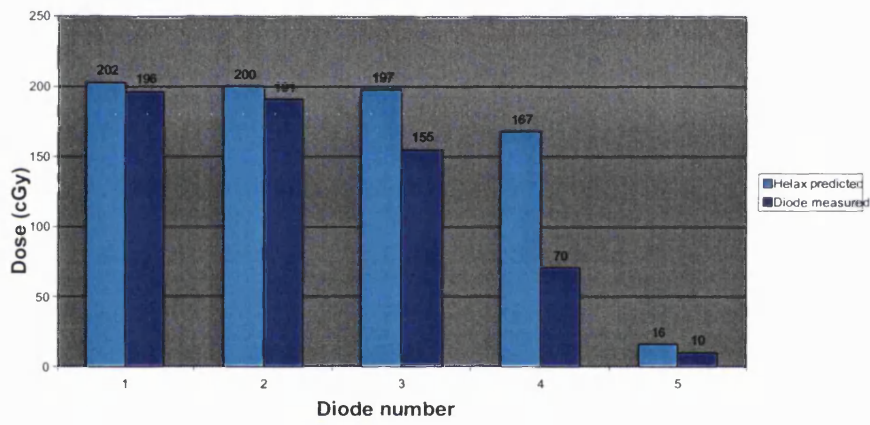
Pat 4
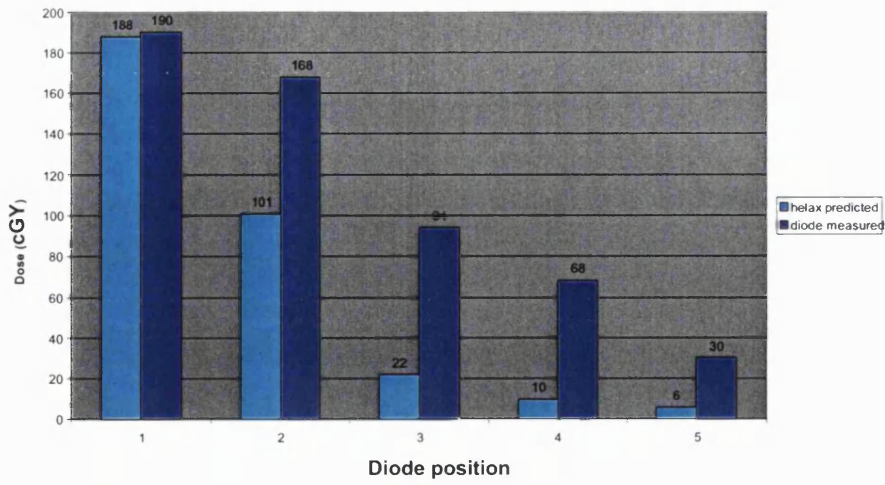
Pat 5

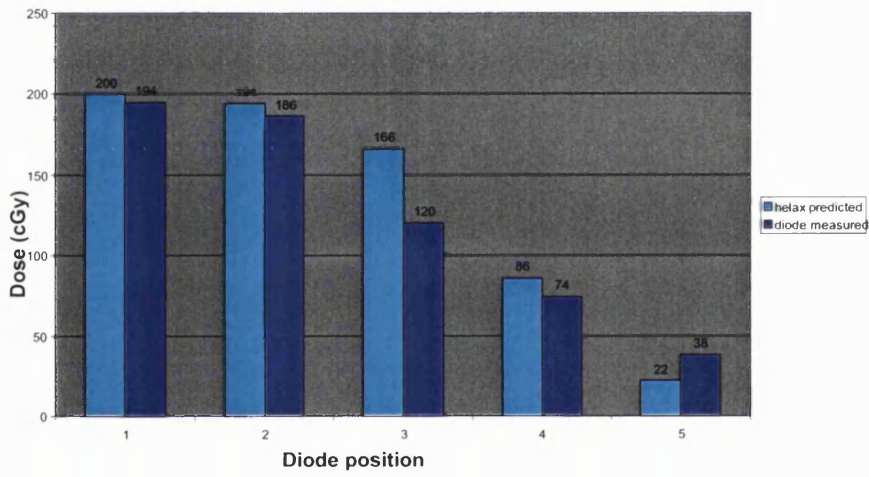
Pat 7

Pat 8

Pat 9

Pat 10

188
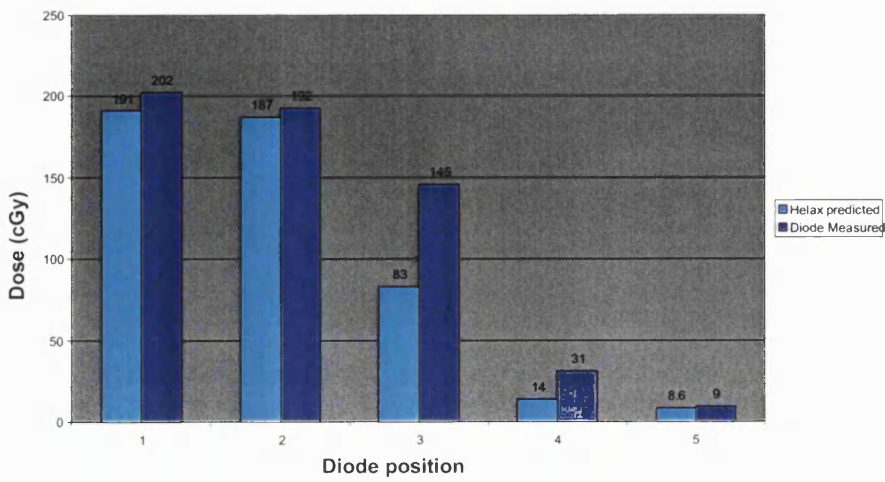
APPENDIX 5.f: Patient dose data set

Patient	Anal Dose (%)	Rectal Dose (%)
1	NA	NA
2	NA	NA
3	40.4	NA
4	64.5	NA
5	5.20	NA
6	NA	NA
7	15.6	NA
8	12.6	NA
9	8.8	NA
10	NA	NA
11	9.0	85.6
12	32.4	32.4
13	83.7	63.3
14	NA	NA
15	18.0	83.7
16	73.1	88.4
17	14.0	78.6
18	47.8	67.7
19	5.6	65.2
20	21.2	73.5
21	11.0	68
22	5.9	81.9
23	5.1	79.6
24	7.0	68.4
25	4.2	75.7
26	74.0	96.5
27	18.0	71.2
28	35.0	65
29	46.0	88.9
30	9.0	70.8
Min	**4.2**	**32.4**
Max	**83.7**	**96.5**
Median	**15.6**	**73.5**
Mean	**26.7**	**73.9**

KEY:

Dose (%) refers to percentage of total prescribed dose (64Gy in all cases)

NA   = No data available

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Appendix 6: Incontinence and Proctitis Score Results

Patient Number	Incontinence Score			Proctitis Score		
	Pre	6 wks	6 mth	Pre	6 wks	6 mth
1	0	0		1	0	
2	0	7	4	1	7	4
3	0	4	0	0	2	3
4	0	4	1	3	2	1
5	0	2	0	1	0	1
6	5	4	4	3	2	2
7	0	5	6	0	4	4
8	3	4	7	0	3	2
9	0	4	0	0	2	
10	3	9	0	0	3	0
11	0	5		0	2	1
12	0	0		0	3	
13	0	4		0	5	
14	0	2		0	2	
15	0	4	8	0	4	5
16	0	0		0	0	
17	0	0		0	2	
18	0	*	*	0	*	*
19	0	0		2	3	
20	0	5		0	0	
21	0	0		1	0	
22	1	7		4	5	
23	0	6		4	3	
24	0	0		0	0	
25	4	6		1	2	
26	0	4		1	3	
27	3	11		0	3	
28	4	9		4	4	
29	0	0		0	2	
30	0	4		0	1	
Minimum	0	0	0	0	0	0
Maximum	5	11	8	4	7	5
Median	0	4	2.5	0	2	2

KEY:

Arbitrary units according to score

* = dropped out of study

Appendix 7: Manometry Results

Pat No	RP pre	RP 6wk	RP 6 mth	SI pre	SI 6wk	SI 6 mth	CI pre	CI 6wk	CI 6 mth	EI pre	EI 6wk	EI 6 mth
1	74	78		193	222		154	120		45	0	
2	82	64	84	115	110	157	106	76	107	70	100	100
3	98	77	81	180	228	296	108	179	134	184	200	200
4	94	102	68	92	156	190	118	128	102	50	85	140
5	82	152	66	152	186	219	52	73	120	137	147	180
6	92	107	78	107	103	114	111	101	151	52	2	40
7	133	94	83	81	85	132	29	75	67	20	60	50
8	71	88	77	52	76	56	53	77	139	37	25	30
9	48	26	57	155	132	151	96	87	115	140	120	120
10	94	74	78	75	95	99	98	64	97	32	0	30
11	83	40		51	63		84	69		35	43	
12	81	59		113	157		71	112		104	60	
13	72	83		176	166		93	132		150	50	
14	71	79		183	321		143	201		160	260	
15	85	70	65	115	164	149	70	119	96	80	130	100
16	35	38		82	85		111	130		55	70	
17	137	93		229	280		148	140		200	263	
18												
19	42	38		215	187		85	84		100	140	
20	42	30		121	95		45	136		43	47	
21	51	78		200	224		68	60		140	190	
22	115	96		223	170		119	75		200	117	
23	108	104		144	190		126	182		100	156	
24	92	109		119	162		92	105		104	79	
25	96	93		186	185		155	150		120	160	
26	127	101		273	172		91	98		200	101	
27	57	41		143	83		61	59		80	75	
28	112	104		153	131		243	80		100	80	
29	66	97		163	220		51	162		57	100	
30	76	52		325	250		155	199		300	200	
Minimum	35	26	57	51	63	56	29	59	67	20	0	30
Maximum	137	152	84	325	321	296	243	201	151	300	263	200
Mean	83.3	78.2	73.7	152	162	156.3	101	112.9	112.8	107	105.5	99
Median	82	79	77.5	152	164	150	96	105	111	100	100	100
p Value		.267	.029		.288	.007		.227	.018		.902	.10

KEY:

All values in centimetres of water (cmH2O)

RP   = Resting Pressure

SI, CI, EI   = Squeeze Increment, Cough Increment, Enduance Increment

Pre, 6wk, 6mnth   = Before, 6 weeks and 6 months after RT

Appendix 8: Rectal Volume Data

PAT N°	Rec T pre	Rec T 6wk	Rec T 6 mth	Urge T pre	Urge T 6wk	Urge T 6 mth	Max V pre	Max V 6wk	Max V 6 mth
1	130	65		180	140		250	183	
2	30	50	41	80	80	91	150	130	211
3	50	75	24	100	165	106	185	255	194
4	50	50	45	100	139	95	400	172	220
5	50	44	48	100	94	88	160	194	132
6	45	42	40	75	82	79	115	117	109
7	100	50	100	240	190	160	380	285	260
8	100	50	90	150	90	135	200	140	180
9	40	45	44	90	90	94	160	125	144
10	70	50	50	120	115	100	170	195	167
11	33	50		107	100		205	150	
12	98	50		148	118		298	168	
13	50	89		100	139		385	239	
14	44	50		138	91		362	269	
15	30	40	50	70	80	91	120	145	141
16	45	50		185	158		270	250	
17									
18									
19	79	43		174	93		344	193	
20	100	43		200	120		300	170	
21	85	100		115	150		165	200	
22	50	50		130	96		235	139	
23	50	92		130	142		280	232	
24	50	80		135	175		270	240	
25	46	46		96	136		181	217	
26	73	50		212	80		247	112	
27	140	95		195	139		245	186	
28	50	50		123	140		173	190	
29	100	85		150	133		200	233	
30	50	50		90	91		268	288	
Min	30	40	24	70	80	79	115	112	109
Max	140	100	100	240	190	160	400	288	260
Mean	**65.6**	**58.4**	**53.2**	**133**	**120.2**	**103.9**	**239.9**	**193.46**	**175.8**
Median	50	50	46.5	127	119	94.5	240	191.5	173.5
p value		.204	.462		.113	.358		**.002**	.237

KEY: Values are in mls

Rec T   = Rectal Threshold Volume

Urge T   = Urge Threshold Volume

Max V   = Maximum Tolerable Volume

Min/ Max   = Minimum value / Maximum value

Appendix 9: Anal and Rectal Electrical Sensitivity Data

PAT NO	AS pre	AS 6 wk	AS 6 mth	RS pre	RS 6 wk	RS 6 mth
1	9.2	6.2		12.2	35.5	
2	5.4	5.8	6.6	7.6	40.5	45.5
3	7	6.8	6.8	35	42	22
4	7	6.4	8.6	17.2	17.4	33.5
5	8.2	10.6	8.2	16.8	21.5	40
6	11	10.2	7.2	10.2	45	21.5
7	5.6	6.2	6.6	23.5	26.5	31.5
8	4.6	4.6	6.6	9.2	19	52
9	8.2	7.8	8.2	20	30.5	34.5
10	6.2	6.2	10.2	8.8	50.5	51.5
11	10.6	11.2		28.5	38.5	
12	11.2	9.2		23.5	37.5	
13	7.8	16.2		25.5	17	
14	5.4	3.6		44	50	
15	8	7.4	7.8	23.5	19.4	27.5
16	8	10.6		20	31.5	
17						
18						
19	12	9		17.4	22	
20	12.6	13		30.5	39.5	
21	7.4	15.6		30.5	24.5	
22	2.2	5.8		17.6	15.6	
23	9.4	7.6		29	13	
24	4.6	8.2		5.4	16.6	
25	5	7.2		16.8	17.6	
26	7.2	8.6		32	40	
27	10.4	7.2		27.5	15.6	
28	5.6	10.8		18.8	33.5	
29	6.2	7.2		23	22	
30	5.6	7		8.4	9	
MIN	2.2	3.6	6.6	5.4	9	21.5
MAX	12.6	16.2	10.2	44	50.5	52
MEAN	7.56	8.43571	7.68	20.8	28.2571	35.95
MEDIAN	7.3	7.5	7.5	20	25.5	34
p value		.119	.401		.006	.001

Appendix 10: Endoanal Ultrasound Results

10a) Summary

Patient Number	Average Subepithelium			Average IAS			Average Longitudinal M			Average EAS		
	PRE	6wk	6mth	PRE	6wk	6mth	PRE	6wk	6mth	PRE	6wk	6mth
1	3.1	2.75		2.6	2.5		3.5	2.6		5.4	4.2	
2	1.7	1.7	1.9	1.6	2.1	**2.3**	2.3	2.3	2.6	3.1	3.1	6.6
3	1.5	1.5	2.1	2.3	2.3	2.6	2.7	2.7	2.5	2.1	2.1	8.9
4	1.8	2.1	1.5	1.8	3	2.2	3.5	2.2	1.9		6.9	9.5
5	2.7	2.2	2.7	2.9	2.2	2.5	4	4.8	3.4	5.7	7	6.1
6	3.5	2.4	2.9	1.7	2	2	3.3	2.8	3.75	4.4	4.9	7.8
7	1.6	1.7	1.4	2.8	1.9	2.4	1.5	3.2	2.6	6.7	7.6	5.3
8	2.3	1.4	1.5	2.5	1.4	1.5	2.6	3.6	2.55	3.6	8.5	8
9	3	3.05	2	3	2	2.9	3.1	2.3	2.65	8	7.5	5.9
10	2.3	1.65	2.5	2.3	2.1	1.7	3	2.3	2.05	5.5	5.7	6.7
11												
12	2.1	1.55		3.2	3		2	3.2		7.9	6.1	
13	1.9	1.8		2.8	2.5		1.6	2.3		8	7.6	
14	1.6	1.7		4.1	2.9		3.6	2.5		6.9	5.6	
15	1.9	1.85	2.1	2.2	2.6	1.6	1.9	3	1.95	6.8	7.2	6.2
16	2	1.7		1.8	1.5		2.9	2.3		6.3	6.7	
17	1.2	1.8		2.6	2.6		1.4	1.9		7.9	6.5	
18												
19	2.9	2.45		2.3	2.3		3.8	3.3		6.3	7.6	
20	2.3	1.6		1.3	2.5		3.3	2.5		6.7	6.9	
21	1.5	1.9		2.4	2.3		1.6	2.3		5.1	5.1	
22	1.8	1.8		1.4	1.9		2.8	2.8		7	9.3	
23	1.4	1.4		2.4	4		1.5	2.7		8.2	6.7	
24	1.5	1.7		3.2	3.7		3.4	2.2		7.3	8.8	
25	2.1	2.35		2	2.2		2.6	2.4		7.4	9.1	
26												
27												
28	1.7	1.15		2.5	2.3		2.7	1.8		6.9	5.6	
29	1.8	1.3		1.9	1.6		2	2.2		8.3	5.4	
30	2.1	1.5		1.6	2.6		2.6	3.4		5.4	3.3	
MEAN	2.03	1.85	2.04	2.33	2.36	2.15	2.63	2.66	2.60	6.01	6.33	7.08
MEDIAN	1.88	1.70	2.03	2.33	2.28	2.23	2.68	2.50	2.58	6.68	6.68	6.63
P value		.032	.304		.836	.420		.796*	.508*		.451	.062

KEY:

PRE, 6/52, 6/12   = Before, six weeks and six months after RT

P values with an asterisk were calculated with a Wilcoxon test. In analysis of six-month post-RT measurements, the mean value is compared with corresponding pre-RT values for those patients i.e. not the mean of the whole group shown in the table.

10b) Endoanal Ultrasonographic Measurements Taken At 3 O'clock Mid Anal Canal

Pat No	Subepithelium (mm)			IAS (mm)		
	pre	6wk	6mth	pre	6wk	6mth
1	2.1	1.8		2	1.7	
2	2	2	1.7	1.3	1.3	1.8
3	1.5	1.5	1.7	2.3	2.3	2.1
4	2.1	2.4	1.2	1.4	2.6	1.9
5	3	2.5	2.8	2.6	2	2.4
6	3.7	3	3.3	1.9	1.8	2.2
7	1.4	1.7	1.4	2.5	1.9	2.3
8	2.3	1	1.4	2.3	1	1.1
9	3.1	3.1	1.6	3.3	2.2	3
10	1.9	1.8	2.7	1.9	1.9	1.5
11		3			1.7	
12	2.3	1.4		3.7	3.1	
13	2.3	2.1		2.7	1.9	
14	1.4	1.8		4.2	3.7	
15	2.2	1.8	2.6	2.5	2.7	1.3
16	1.8	1.7		1.8	1.3	
17	1	1.8		2.6	2.8	
18						
19	3	2.2		2.3	2.3	
20	2.7	1.7		1	2.1	
21	1.3	2.3		2.3	2.3	
22	1.9	1.8		1.4	1.8	
23	1.4	1.4		2.9	4.2	
24	1.7	1.9		3.5	4.1	
25	2.8	2.4		2.3	2	
26	1.7			1.7		
27	1.8			1.7		
28	1.7	1		2.8	2.3	
29	1.7	1.5		2.1	1.8	
30	2.5	1		1.7	2.9	

10b) Endoanal Ultrasonographic Measurements Taken At 3 O'clock Mid Anal Canal

Pat No	Longitudinal muscle (mm)			EAS (mm)		
	pre	6wk	6mth	pre	6wk	6mth
1	3.2	2.7		4.7	4	
2	2.3	2.3	2.3	2.5	2.5	5.5
3	2.6	2.6	1.9	2.1	2.1	8.6
4	3.1	2.2	1.7		5.5	10
5	4	5.1	3	6.3	7	6.2
6	3.6	3	3.6	3.9	4.8	7.9
7	1.5	2.8	2.5	6	8	5.1
8	2.7	3.2	2.6	3	5.9	10
9	3.4	2.1	2.2	8.8	7.7	6.4
10	3	1.9	1.9	5	5.3	6.7
11		3			7.7	
12	2.1	3.1		6.9	7.1	
13	1.8	2.1		6.7	7.6	
14	2.5	2.8		7.7	8	
15	1.8	3.2	1.8	6.4	7.2	6.2
16	2.2	1.9		6.3	6.2	
17	1.4	1.9		7.4	6.5	
18						
19	3.7	2.4		5.4	8	
20	3.6	2.9		7.8	6.5	
21	1.7	2.2		5.5	5.8	
22	3.1	2.6		6.6	10	
23	1.5	3.7		8.2	6.8	
24	3.6	2.6		7.5	10	
25	2.6	2.5		7.5	10	
26	2.1			5.4		
27	3.1			5.9		
28	2.9	1.8		7.1	5.5	
29	1.9	2.4		8	5.6	
30	2.8	3.4		5.5	3	

10c) Endoanal Ultrasonographic Measurements Taken At 9 O'clock Mid Anal Canal

Pat No	Subepithelium (mm)			IAS (mm)		
	pre	6wk	6mth	pre	6wk	6mth
1	4	3.7		3.2	3.3	
2	1.4	1.4	2	1.9	2.9	2.7
3	1.5	1.5	2.5	2.3	2.3	3
4	1.5	1.8	1.8	2.2	3.4	2.5
5	2.3	1.9	2.6	3.1	2.4	2.5
6	3.3	1.8	2.5	1.5	2.2	1.8
7	1.8	1.7	1.3	3.1	1.9	2.4
8	2.2	1.8	1.5	2.6	1.8	1.9
9	2.9	3	2.4	2.6	1.7	2.8
10	2.6	1.5	2.3	2.6	2.2	1.8
11		2.8			2.1	
12	1.8	1.7		2.6	2.8	
13	1.4	1.5		2.9	3.1	
14	1.7	1.6		4	2.1	
15	1.6	1.9	1.5	1.8	2.4	1.9
16	2.2	1.7		1.7	1.7	
17	1.4	1.8		2.6	2.4	
18						
19	2.8	2.7		2.2	2.2	
20	1.8	1.5		1.6	2.8	
21	1.7	1.5		2.4	2.3	
22	1.7	1.8		1.4	1.9	
23	1.4	1.4		1.9	3.7	
24	1.2	1.5		2.8	3.3	
25	1.4	2.3		1.7	2.3	
26	1.7			1.9		
27	2.3			1.7		
28	1.7	1.3		2.2	2.2	
29	1.8	1.1		1.7	1.3	
30	1.7	2		1.5	2.3	

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10c) Endoanal Ultrasonographic Measurements Taken At 9 O'clock Mid Anal Canal

Pat No	Longitudinal muscle (mm)			EAS (mm)		
	pre	6wk	6mth	pre	6wk	6mth
1	3.7	2.5		6	4.4	
2	2.3	2.3	2.9	3.6	3.6	7.7
3	2.8	2.8	3.1	2.1	2.1	9.1
4	3.8	2.1	2.1		8.2	8.9
5	3.9	4.5	3.8	5.1	7	6
6	3	2.5	3.9	4.9	4.9	7.6
7	1.5	3.6	2.7	7.4	7.1	5.5
8	2.5	3.9	2.5	4.1	11	5.9
9	2.7	2.4	3.1	7.2	7.2	5.4
10	3	2.6	2.2	6	6	6.6
11		1.9			8	
12	1.8	3.2		8.9	5.1	
13	1.4	2.4		9.3	7.6	
14	4.6	2.2		6	3.2	
15	1.9	2.7	2.1	7.2	7.2	6.2
16	3.5	2.7		6.2	7.2	
17	1.3	1.8		8.3	6.4	
18						
19	3.9	4.2		7.2	7.2	
20	2.9	2.1		5.5	7.3	
21	1.4	2.4		4.6	4.4	
22	2.4	2.9		7.4	8.6	
23	1.5	1.7		8.2	6.5	
24	3.1	1.8		7	7.6	
25	2.5	2.3		7.2	8.1	
26	1.8			5.8		
27	1.8			4.6		
28	2.4	1.8		6.7	5.7	
29	2.1	1.9		8.5	5.1	
30	2.3	3.4		5.2	3.6	

Appendix 11: MRI Results

11a) Lower Anal Canal : Percentage Enhancement (Arbitrary Units) & Gradient of Enhancement Curve (Arbitrary Units) Before and After Radiotherapy

PAT NO	PRE %EN	6wk %EN	6mth%EN	PRE GRAD	6wk GRAD	6mth GRAD
*1	29	35		0.35	0.24	
2	30	44	40	0.22	0.35	1.04
3	17	36	35	0.13	1	0.75
4	53	60	57	0.89	1.35	1.11
5	25	38	33	0.14	0.33	0.23
6	37	36	40	0.97	0.85	0.96
7	20	50	35	0.45	1.5	0.88
8	31	48	51	0.69	1.35	1.11
9	39	52	42	0.64	1.59	0.89
10	49	50	56	0.87	0.94	0.85
11	32	48		0.45	1.1	
12	39	43		0.72	0.77	
13	29	36		0.4	0.54	
**14	41	31		0.79	0.68	
*15	32	25	53	0.69	0.44	0.8
16	33	38		0.63	0.87	
17	32	31		0.38	0.69	
18						
19						
20	30	43		0.43	0.48	
21	21	39		0.17	0.25	
22	26	39		0.67	0.8	
23	34	52		0.87	0.95	
24	28	47		0.46	0.98	
25	33	37		0.47	0.59	
*26	47	46		1.18	0.96	
27	35	57		0.86	1.04	
*28	54	63		1.26	1.33	
29	38	37		0.56	0.66	
*30	37	29		0.64	0.51	
MIN	17	25	33	0.13	0.24	0.23
MAX	54	63	57	1.26	1.59	1.11
MEAN	33.96	42.50	44.20	0.61	0.83	0.86
MEDIAN	32.50	41.00	41.00	0.64	0.83	0.89

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11b) Upper Anal Canal : Percentage Enhancement (Arbitrary Units) & Gradient of Enhancement Curve (Arbitrary Units) Before and After Radiotherapy

PAT NO	PRE %EN	6wk %EN	6mth%EN	PRE GRAD	6wkGRAD	6mthGRAD
1	33	50		0.32	0.38	
2	29	79	85	0.32	0.96	2.23
3	23	51	36	0.09	1.65	0.8
4	60	79	66	0.96	2.73	2.39
5	38	46	45	0.28	0.52	0.44
6	21	31	32	0.25	0.52	0.39
7	34	58	55	0.75	1.9	1.4
8	39	46	66	1.06	1.35	1.49
9	57	80	63	1.78	2.41	1.14
10	46	58	64	0.87	1.18	1.1
11	46	69		0.87	2.06	
12	49	50		1.19	1	
13	38	39		0.59	0.63	
14	37	33		0.83	0.87	
15	34	39	62	0.74	0.77	0.99
16	38.1	54.7		1	1.47	
17	42	50		0.8	1.04	
18						
19						
20	31	48		0.61	0.64	
21	17	43		0.11	0.3	
22	23	42		0.51	0.87	
23	42	58		1.02	1.3	
24	34	48		0.73	1.3	
25	33	39		0.7	0.77	
26	45	58		1.35	1.31	
27	39	55		0.87	0.98	
*28	59	58		1.39	1.35	
29	32	40		0.66	0.88	
*30	52	62		1.3	2.3	
MIN	17	31	32	0.09	0.3	0.39
MAX	60	80	85	1.78	2.73	2.39
MEAN	38.25	52.28	57.40	0.78	1.19	1.24
MEDIAN	38.00	50.00	62.50	0.78	1.02	1.12

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