The evolution of prostate cancer management within a specialist MDT

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MD

2019

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CONTENTS

Summary 1

Publications and presentations 3

Abbreviations 4

1. Chapter 1. Introduction

1.1. Prostate gland function and anatomy 6

1.1.1. Gross anatomy of the prostate 6

1.1.2. Microscopic anatomy of the prostate 7

1.1.3. Histological and functional anatomy of the prostate 7

1.2. Prostate cancer 8

1.2.1. Adenocarcinoma of the prostate and natural history 8

1.2.2. Other subtypes of prostate cancer 10

1.2.2.1. Small cell prostate cancer 10

1.2.2.2. Ductal adenocarcinoma 11

1.2.2.3. Squamous cell cancer of the prostate 11

1.2.2.4. Sarcoma 11

1.3. Prostate cancer incidence and mortality 11

1.3.1. Incidence 11

1.3.2. Mortality 16

1.4. Risk factors 17

1.4.1. Race and geographical factors 18

1.4.2. Family history and genetics 18

1.4.3. Diet and Obesity 19

1.5. Clinical and pathological staging of prostate cancer 19

1.5.1. Staging of prostate cancer 19

1.6. Grading of prostate cancer 23

1.6.1. Gleason grading 23

1.7. Detection of prostate cancer 25

1.7.1. Digital rectal examination 26

1.7.2. Prostate specific antigen 26
1.7.3. TRUS biopsy 27
1.7.4. Magnetic resonance imaging 28
1.7.5. Isotope bone scan 31
1.7.6. Positron-Emission Tomography – CT 31
1.8. Screening for prostate cancer 32
1.9. Risk stratification for prostate cancer 34
1.9.1. D'Amico classification 35
1.9.2. Epstein criteria 35
1.9.3. NICE 36
1.9.4. EAU 36
1.9.5. NCCN 37
1.10. Treatment options for prostate cancer 38
1.10.1. Localised prostate cancer 38
1.10.1.1. Deferred treatment strategies 40
1.10.1.2. Radical prostatectomy 43
1.10.1.3. Radical radiotherapy 44
1.10.2. Locally advanced non-metastatic prostate cancer 44
1.10.3. Metastatic prostate cancer 45
1.11. The use of MDTs 45
1.12. Summary and thesis aims 46

2. Chapter 2. The Early Prostate Cancer MDT. A 20-year experience of a single centre specialist MDT – results from a prospectively collected database
2.1. Introduction 49
2.1.1. The Early Prostate Cancer (EPC) MDT 49
2.2. Aims 50
2.3. Methods 51
2.3.1. Service evaluation approval 51
2.3.2. Patient population 51
2.3.3. Data collection and amalgamation of different data sets 52
2.3.4. Data quality assurance 56

2.3.5. National Prostate Cancer Audit 56
2.3.6. Data analysis 57
2.4. Results 61
2.4.1. Aim 1 – Data quality 61
2.4.2. Aim 2 – Accuracy of data capture 62
2.4.3. Aim 3 – An overview of EPC data collection 65
2.4.4. Aim 4 – Trends in symptoms at presentation and the relationship on disease stage 80
2.4.4.1. Symptoms and effect on disease presentation 80
2.4.4.2. Symptoms and influence on treatment 83
2.4.5. Aim 5 – Impact of family history on disease stage and treatment undertaken 86
2.4.5.1. Family history and effect on presentation 86
2.4.5.2. Family history and presence of symptoms 89
2.4.5.3. Family history and influence on treatment 89
2.4.6. Aim 6 – Change in treatment patterns 92
2.4.6.1. Treatment of different D'Amico risk groups 92
2.4.6.2. Active surveillance 94
2.4.6.3. Radical prostatectomy 95
2.5. Discussion 96
2.5.1. Data quality and capture rates 96
2.5.2. EPC data 98
2.5.3. Effect of symptoms on disease characteristics and treatment 100
2.5.4. Effect of family history on disease characteristics and treatment 101
2.5.5. Changing patterns of treatment 102
2.5.6. Limitations 103
2.5.7. Summary 104

3. Chapter 3. Refining the use of isotope bone scan in the staging of intermediate risk prostate cancer

3.1. Introduction 105

3.2. Aims 107

3.3. Methods 107

3.3.1. Service evaluation 107

3.3.2. Patient population and analysis 107

3.4. Results 108

3.4.1. Results from EPC cohort between 2002 and 2015 108

3.4.2. Extended results from EPC cohort between 2002 and 2017 – statistical analysis 110

3.5. Discussion 114

3.5.1. Conclusion 118

4. Chapter 4. Has improved MRI technology and protocol improved the accuracy of pre-operative staging and subsequent rate of upstaging at radical prostatectomy

4.1. Introduction 119

4.2. Aims 120

4.3. Methods 120

4.3.1. Service evaluation 120

4.3.2. Patient population 120

4.3.3. Data analysis 121

4.4. Results 122

4.4.1. Prostatectomy data set 122

4.4.1.1. Pre-operative staging data 122

4.4.1.2. Post-operative staging data 126

4.4.1.3. Upstaging and upgrading rates 127

4.4.1.4. Tumour characteristics 129

4.4.1.5. Margin status 130

4.4.1.6. Biochemical recurrence rates 134

4.4.1.7. Pre-operative predictors of BCR 135

4.4.1.8. Post-operative predictors of BCR 138
4.4.2. MRI staging data set 145
4.5. Discussion 155
4.5.1. Aim 1 – Prostatectomy outcomes 155
4.5.2. Aim 2 – MRI staging outcomes 160
4.5.3. Limitations 163
4.5.4. Conclusions 163

5. **Chapter 5. Deferred treatment strategies for men with low risk localised prostate cancer – outcomes from a large contemporary UK series of active monitoring/surveillance, the role of protocol restaging in a stable cohort of active monitoring patients and the use of bi-parametric MRI in restaging men on active surveillance.**
5.1. Introduction 164
5.2. Aims 168
5.3. Methods 169
5.3.1. Service evaluation 169
5.3.2. Patient population 169
5.3.3. Data collection and analysis 171
5.4. Results 172
5.4.1. Aim 1. Outcomes of patients enrolled on an active monitoring or surveillance program 172
5.4.2. Aim 2 – Restaging group 1 – Outcomes of introducing protocol restaging in a cohort of clinically stable active monitoring patients 185
5.4.2.1. Characteristics at diagnosis 185
5.4.2.2. Outcomes of restaging 185
5.4.3. Aim 3 - Compare the outcomes of restaging in the stable active monitoring cohort with clinical change or triggered restaging and protocol restaging as part of active surveillance 194

5.4.3.1. Restaging group 2 – Outcomes of a clinical change/triggered restaging cohort 194
5.4.3.1.1. Characteristics at diagnosis 194
5.4.3.1.2. Outcomes of restaging 194
5.4.3.2. Restaging group 3 – Outcomes of the first protocol restaging in an active surveillance cohort. 199
5.4.3.2.1. Characteristics at diagnosis 199
5.4.3.2.2. Outcomes of restaging 199
5.4.3.3. Overall comparison between restaging groups 1,2 and 3 206
5.5. Discussion 210
5.5.1. Aim 1 - Outcomes of a deferred treatment strategy 210
5.5.2. Aim 2 – Assess the outcomes of introducing protocol restaging in a cohort of clinically stable active monitoring patients 213
5.5.3. Aim 3 and 4 – Outcomes of restaging different populations and the use of MRI in the active surveillance pathway 215
5.5.4. Conclusion 217

6. Chapter 6. Discussion 218
7. References 222

Summary

The use of multidisciplinary team (MDT) meetings have proven benefits in cancer care. In this thesis, prospectively collected data for men with new diagnosis prostate cancer discussed at a single specialist MDT over a 20-year period is analysed to address several clinically relevant questions in the pathway of prostate cancer management.

This study has not shown any significant association between symptomatic men and more aggressive disease but did show that they were less likely to have radical treatment. It also reports that men with a positive family history are more likely to present with low risk disease and are more likely to have radical treatment.

Isotope bone scanning for the staging of metastatic disease remains the most commonly used imaging modality. However, guidelines for use in men with intermediate risk disease are inconsistent. This study represents the largest UK study to date of bone scan positivity rates and supports its use in men with high risk disease and men with intermediate risk disease with ISUP grade group 3.

The role of MRI imaging in prostate cancer spans diagnostics, staging, and disease surveillance. This study has shown that changes in MRI protocol and technology has not decreased the rate of upstaging following radical prostatectomy and established markers of biochemical recurrence remain superior to MRI staging at predicting disease relapse.

The use of MRI in active surveillance regimes remains an area of debate. In this study, a normal bi-parametric restaging MRI in the absence of other clinical markers of progression conveys a very low risk of disease progression and the possibility of avoiding repeat prostate biopsies.

In this study, the effect of introducing protocol restaging in a cohort of clinically stable active monitoring patients is also reported and highlights expected rates of upgrading but significantly higher rates of radical treatment following restaging.

Presentations

1. The results of the introduction of protocol restaging in an established active monitoring cohort of patients with localised prostate cancer.
   Welsh Surgical Society Autumn meeting, London. November 2016.

2. Medium to long term follow-up of a large UK cohort of active monitoring patients.
   BAUS Annual Meeting, Liverpool. June 2016.

3. Should an isotope bone scan be performed in the staging of D'Amico classified intermediate risk prostate cancer?
   BAUS Academic Section, Winter meeting 2015, London.

4. The National Prostate Cancer Audit – were we ready for it?
   BAUS Academic Section, Winter meeting 2015, London.

5. The National Prostate Cancer Audit – were we ready for it?
   Welsh Urological Society, Carmarthen, November 2015.

Publications

KandaSwamy G, Bennett A, Narahari K, Hughes O, Rees J, Kynaston H. Establishing the pathways and indications for performing isotope bone scans in newly diagnosed intermediate-risk localised prostate cancer – results from a large contemporaneous cohort. *BJU Int* 2017; 120: E59–E63.

Abbreviations

ADC – Apparent Diffusion Coefficient

ADT – Androgen Deprivation Therapy

AJCC – American Joint Committee on Cancer

AM – Active monitoring

AR – Androgen Receptor

AS – Active surveillance

ASA – American Society of Anaesthesiologists

ASCO – American Society of Clinical Oncology

BCR – Biochemical Recurrence

CaP – Prostate Cancer

CT – Computed Tomography

DRE – Digital Rectal Examination

DWI – Diffusion Weighted Imaging

EAU – European Association of Urology

EBRT – External Beam Radiotherapy

EPC – Early Prostate Cancer

FHx – Family history

HQIP – Healthcare Quality Improvement Partnership

ISUP – International Society of Uropathologists

LUTS – Lower Urinary Tract Symptoms

MCCL – Maximum Cancer Core Length

MDT – Multi-Disciplinary Team

MRI – Magnetic Resonance Imaging

bpMRI – bi-parametric MRI

mpMRI – multi-parametric MRI

NPCA – National Prostate Cancer Audit

PCa – Prostate Cancer

PCRMG - Prostate Cancer Risk Management Group

PET – Positron Emission Tomography

PIN – Prostate Intra-epithelial Neoplasia

PIRADS – Prostate Imaging – Reporting and Data System

PSA – Prostate Specific Antigen

PSMA – Prostate Specific Membrane Antigen

RALP – Robotic Assisted Laparoscopic Prostatectomy

RP – Radical Prostatectomy

SPECT – Single Photon Emission Computed Tomography

T2W – T2 Weighted

TNM – Tumour Nodes Metastasis

cT-stage – clinical T-stage

pT-stage – pathological T-stage

TPM – Template Prostate Mapping

TRUS – Trans-rectal Ultrasound

UHW – University Hospital of Wales, Cardiff

UICC – International Union Against Cancer

WW – Watchful Waiting

CHAPTER 1 - INTRODUCTION

1.1 Prostate gland function and anatomy

1.1.1 Gross anatomy of the prostate

The prostate is an accessory reproductive organ located within the male pelvis.

Embryologically the prostate develops from the primitive endoderm from which the digestive system also forms. Within the hindgut there is a caudal swelling termed the cloaca that is divided by the uro-rectal septum. From this the respective urinary and digestive outlets develop. The urogenital sinus is formed from the ventral aspect of the uro-rectal septum and from this the cranial end forms the urinary bladder and caudal end the urethra. The prostate is also derived from the uro-genital sinus and develops through dihydrotestosterone stimulation (Berman et al., 2012)

When fully developed, the prostate is intimately related to the base of the bladder superiorly and the urethra runs through the middle of the gland. Anterior to the prostate is the pubic symphysis, posteriorly is the rectum separated by the fascia of Denonvilliers and inferiorly is the urogenital diaphragm. The seminal vesicles lie superiorly and merge with the vas deferens to form the ejaculatory ducts which enter the prostatic urethra at the site of the veru-montanum. The pubo-prostatic ligaments provide support anteriorly, while the external urinary sphincter and the perineal membrane provide support posteriorly.

The true capsule of the prostate is composed of collagen, elastin and smooth muscle (fibromuscular stroma) and forms a distinct layer separating it from the surrounding tissues. It is most well defined posteriorly and posterior-laterally. It is less well defined at the apex, bladder neck and anterior prostate.

1.1.2 Microscopic anatomy of the prostate

Within the adult prostate there are four distinct zones (Berman et al., 2012, McNeal, 1981).

- The *central zone* contains around 25% of the glandular elements and surrounds the ejaculatory ducts
- The *anterior fibromuscular stroma* makes up 30% of the prostate mass, contains smooth muscle and does not have a glandular component.
- The *transitional zone* is the smallest zone and makes 15-30% of the prostate volume. It surrounds the urethra and sphincter and contains around 5% of the glandular elements. It is the site of benign prostatic hyperplasia
- The *peripheral zone* is the largest zone and contains 75% of the glandular component. It is the most common site for prostate cancer.

1.1.3 Histological and functional anatomy of the prostate

The epithelium of the prostate is made up of two major cellular compartments comprising of epithelial cells and stromal cells. There are four different types of epithelial cells; basal cells, intermediate cells, neuroendocrine cells and luminal secretory epithelial cells. It is the luminal secretory cells that make up much of the prostatic epithelium and they are responsible for creating an epithelial barrier that lines acini. They are also responsible for producing prostate secretions which include PSA (prostate specific antigen) and acid phosphatase (PAP)(McNeal, 1988). The stromal cells provide structural stability and are made up smooth muscle cells, fibroblasts and connective tissue.

PSA and PAP have strong proteolytic properties and help to liquefy the semen (Lilja et al., 1987). Specifically, PSA is a 33kD glycoprotein belonging to the kallikrien family of serine proteases under direct androgen control. It is thought to break down semenogelin, a structural protein within seminal fluid that causes it to clot (Lilja et al., 1987). The exact importance to the reproductive cycle of this clotting and subsequent liquefication process within the semen is unknown.

Prostate growth, maintenance and excretory function is under endocrine control with testosterone exhibiting the most influence. The hypothalamic-pituitary-testis axis controls testosterone production. In a healthy male, 95% of testosterone is produced by the Leydig cells within the testes, stimulated by gonadotrophin releasing hormones released from the hypothalamus and subsequent release of LH and FSH from the pituitary gland, which then act upon the testes. The remaining 5% of testosterone comes from androstenedione secreted by the adrenal glands and stimulated by ACTH secreted from the pituitary. Most testosterone is bound to serum proteins such as sex-hormone binding globulin or albumin. Only 1-2% of testosterone is free and unbound. Testosterone is then converted in to its more active form, dihydrotestosterone (DHT), by the cytochrome P450 enzyme 5-alpha reductase (type 1 and 2) in the prostate. It can also be peripherally converted to oestrogen by aromatase. Both processes are irreversible.

DHT and testosterone both bind to the androgen receptor (AR) but DHT has a much higher affinity for it. When bound to the AR it translocates in to the nucleus and result in the upregulation of certain gene expression, such as PSA. AR upregulation is fundamental in prostate cancer development and progression (Berman et al., 2012)

The half-life of testosterone is between 10-20 mins and therefore after surgical castration patients can be functionally castrate within a couple of hours (Berman et al., 2012). This formed the basis of early prostate cancer management and the pharmacological effects of blocking testosterone are central to the treatment of advanced prostate cancer.

1.2 Prostate cancer

1.2.1 Adenocarcinoma of the prostate and natural history

Adenocarcinoma is by far the most common type of invasive prostate cancer. The natural history of prostate cancer is not fully understood but can be divided in to the following stages (PCRMG, 2016).

- Initiation
- Diagnosis by screening
- Diagnosis by clinical symptoms
- Clinically detectable metastatic disease
- Death

The challenge with management lies with detecting aggressive tumours early and treating such cases but avoiding over treatment of indolent disease which may not effect quality or duration of life. The natural course of prostate cancer can often be extremely long from initiation to a point where it has metastasised and is life threatening.

In the initiation from a normal prostate developing to cancer it is thought that prostate intra-epithelial neoplasia (PIN) may play a significant role. PIN is characterised by architecturally benign prostate glands that are lined by cytologically atypical cells. PIN can be sub-classified as low or high grade. However, low grade PIN is not reported histologically as it conveys no increased risk of progression to prostate cancer and the reporting of low-grade PIN lacks reproducibility (Epstein, 2012).

The risk of progression to invasive disease from high grade PIN is not clearly known but around a quarter of cases may progress (Epstein, 2012). Multi-focal PIN confers a higher risk than uni-focal PIN (Merrimen et al., 2009) and in such cases follow up should be more rigorous. Re-biopsy should be considered when greater than 3 cores at biopsy are involved with PIN or atypical cells are found adjacent to PIN (Mottet et al., 2017a).

In those men that do go on to develop invasive adenocarcinoma the course of the disease can be extremely varied. Often screen detected cases of prostate cancer are low grade and reducing the rate of screening reduces such cases (Shah et al., 2018). Low grade or low risk cancers may have no impact on life expectancy and treatment may be unwarranted. In a recent trial, comparing men with low to intermediate risk

screen detected prostate cancer that had no treatment to those that had radical treatment, there was no difference in death rate from prostate cancer after 10 years' follow-up (Hamdy et al., 2016). Other surveillance programmes for men with indolent cancers have also reported 100% 10 year prostate specific survival rates (Dall'Era et al., 2012).

In men with low grade prostate cancer a small proportion will go on to develop higher grade disease that will progress, with the potential to metastasise and cause subsequent mortality. It is not known if the reason behind this progression is de—differentiation of the existing tumour or the development of a new more aggressive separate tumour.

In men with localised disease the more aggressive tumour, or poorly differentiated the tumour, the worse the prognosis. The 20 year death rate from prostate cancer in men with localised Gleason 6, 7 and 8-10 disease was noted to 27%, 45% and 66% (Albertsen et al., 2005).

Men presenting with symptoms often have higher grade disease and indeed men who are diagnosed with metastatic disease at presentation do very poorly. The control arm of the STAMPEDE trial showed men with metastatic disease at presentation have a 3.5 year median survival (James et al., 2015).

1.2.2 Other subtypes of prostate cancer

1.2.2.1 Small cell prostate cancer

Small cell prostate cancer is identical to small cell lung cancer. Approximately half of small cell prostate cancer are mixed with adenocarcinomas. However, this does not affect prognosis which is poor. Gleason grading is not applied to small cell tumours (Epstein, 2012).

1.2.2.2 Ductal adenocarcinoma

Account for less than 1% of prostate cancer. Arise from prostatic ducts and behave in an aggressive manner and can subsequently present at an advanced stage with normal PSA levels (Epstein, 2012).

1.2.2.3 Squamous cell carcinoma of the prostate

Very rare and associated with osteolytic bony metastases and poor prognosis (Epstein, 2012)

1.2.2.4 Sarcoma

Very rare accounting for less 0.1% of prostate tumours. Rhabdomyosarcomas are most common and seen in childhood, whereas, leiomyosarcomas are more common in adulthood (Epstein, 2012).

1.3 Prostate cancer incidence and mortality

1.3.1 Incidence

The lifetime risk of developing of prostate cancer is around 1 in 8 in the UK. Men from an African-Caribbean background are most commonly affected followed by Caucasians and it is least common amongst Asian men.

Globally, prostate cancer is the second most common cancer affecting males. In developed countries, it is the most common cancer and in the developing world it is the 4th most common. In 2012, new cases of prostate cancer in the developed world accounted for nearly two-thirds of the global cases in just 17% of the world's population (Siegel et al., 2013). Incidence rates vary dramatically across the globe with much higher rates in the more developed countries, probably reflecting a greater use of screening tools and disease awareness (Figure 1.1) (Torre et al., 2015). However, it is interesting to note that the much higher incidence rate in certain global areas has not had a marked effect on the mortality rate, probably highlighting an increased detection of insignificant cancers.

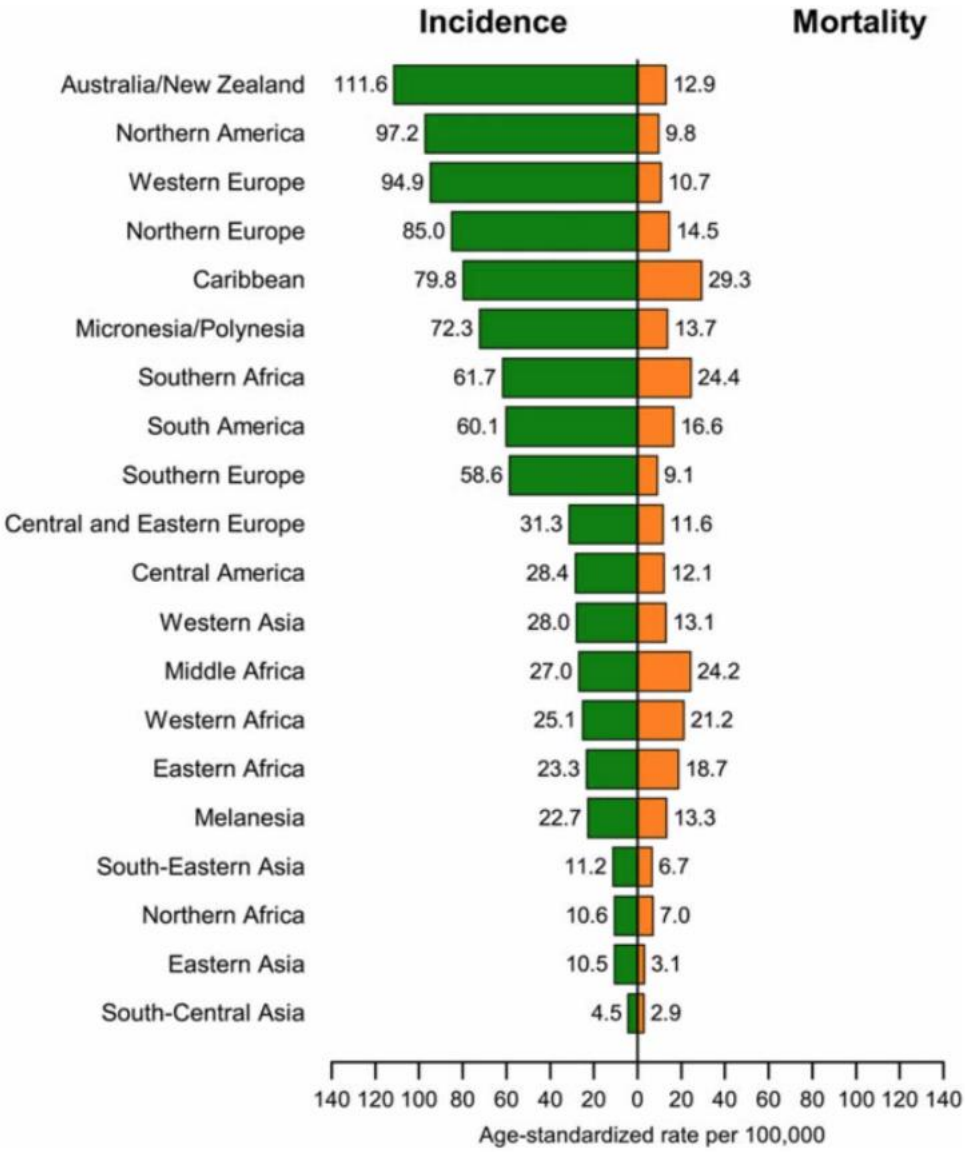


Figure 1.1. Incidence and mortality rates of prostate cancer by world area (Torre et al., 2015).

In North America, incidence rates increased dramatically in the 1990s following the introduction of PSA testing but are now declining (Figure 1.2) (Siegel et al., 2017). This contrasts with other areas of the developed world such as Western Europe that are still seeing a rising incidence due to the slower uptake of PSA testing (Siegel et al., 2013) In 2012 the US Preventive Services Task Force issued evidence against the use of screening for prostate cancer (Klotz, 2015). However, despite the decreasing incidence rates in America new cases of prostate cancer are still expected to account for 19% of all new cancers in 2017 (Siegel et al., 2017).

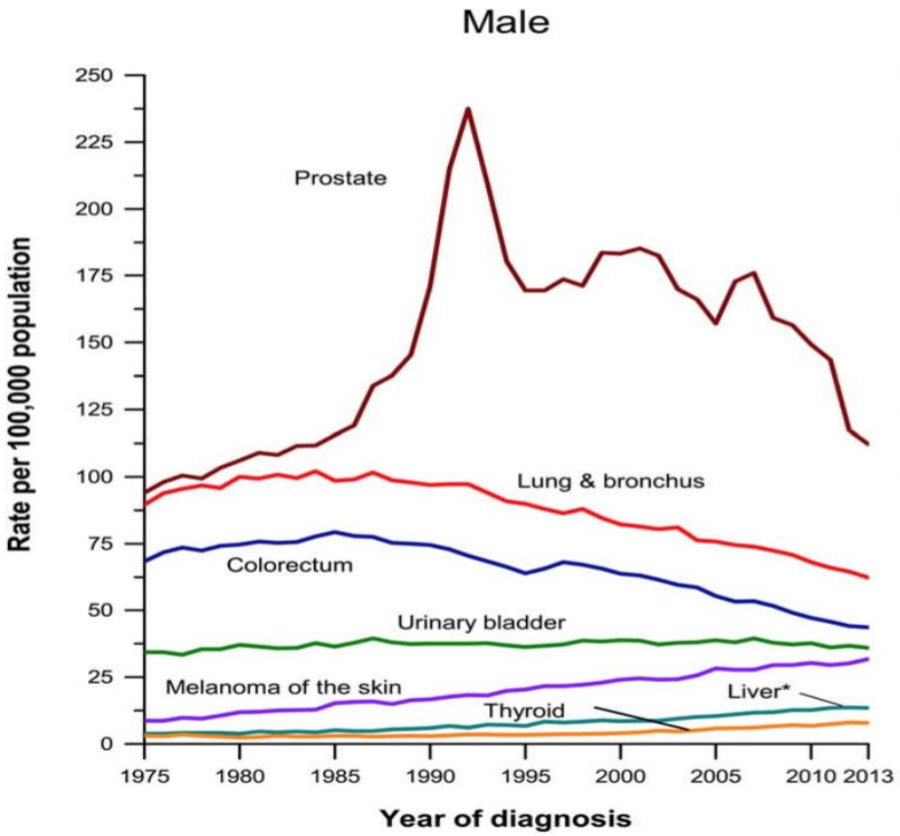


Figure 1.2. Incidence rates for cancers in USA, 1975 to 2013. (Siegel et al., 2017)

Within the UK the incidence of prostate cancer is rising (Figure 1.3). This is multifactorial and can be attributed to increased patient awareness and the widespread use of PSA testing. An ageing population, improved ascertainment rates of cancer registries and the increased use of trans-rectal biopsy have also had an impact on rising incidence rates (PCRMG, 2016). Since the 1970's the incidence has more than doubled with an increase of 155% with further rises predicted over the next 20 years. In the UK in 2014 there were approximately 46,700 new diagnoses of prostate cancer with an incidence rate of 147 cases per 100,000 men (CRUK, 2015) These cases account for 13% of all newly diagnosed cancers making it the second most common type of cancer within the UK and the most common in males (CRUK, 2015).

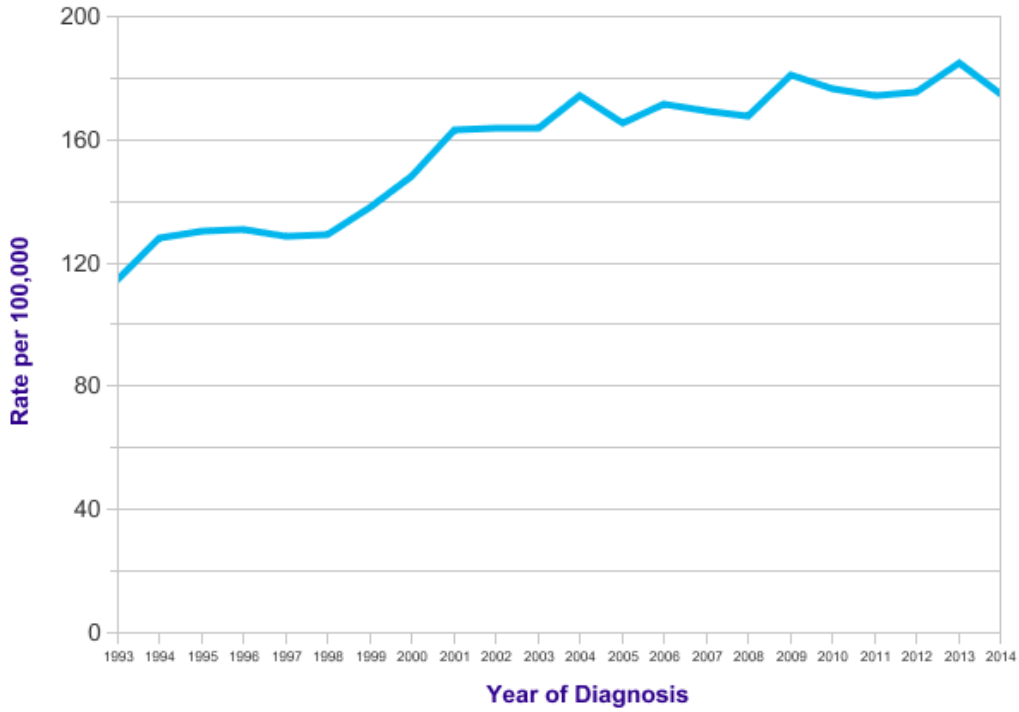


Figure 1.3. Age standardised incidence rates in UK, rate per 100,000, by year of diagnosis (CRUK, 2015).

The incidence of prostate cancer is strongly linked to age (Figure 1.4). Post-mortem studies have identified microscopic lesions in 30% of men in their fourth decade, 50% of men in their sixth decade and 75% of men older than 85 years of age (Grönberg, 2003, Sakr et al., 1993). The majority of new diagnoses are in men over 70 years of age with 54% of cases in this age group between 2012-14 (CRUK, 2015) and 50% for men diagnosed in England between April 2014-15 (NPCA., 2017).

Since the 1990s incidence rates have increased in all age group categories apart from those men above 80 years of age where there has been a fall. The most dramatic rise is seen in younger men with an increase in rates of 507% in men between 25-49 years of age. In men over 80 years there has been a 23% fall in incidence rates. (Figure 1.5) (CRUK, 2015).

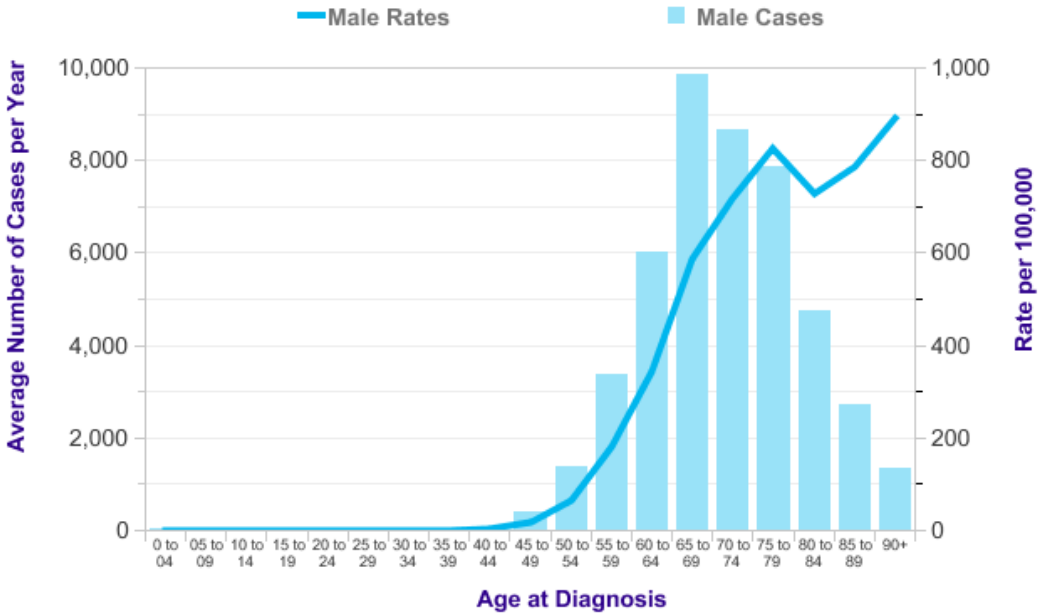


Figure 1.4 Average number of cases per year and incidence rates per 100,000 population (CRUK, 2015)

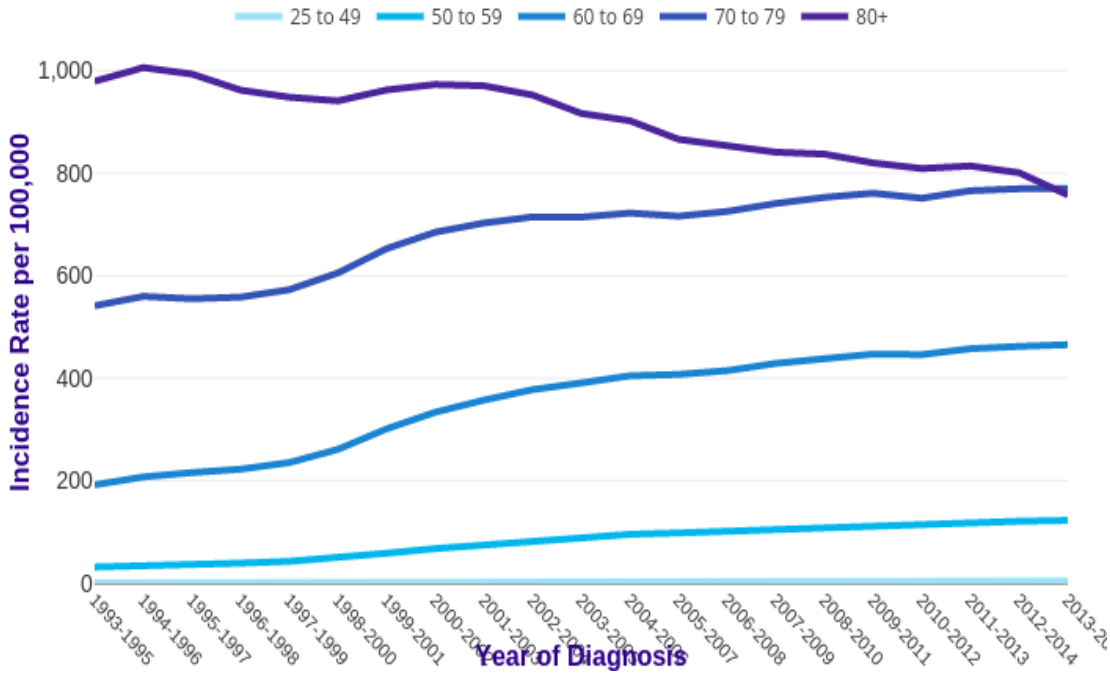


Figure 1.5 European age related incidence rates of prostate cancer, 1993-2015. (CRUK, 2015)

The increased incidence of prostate cancer is associated with a higher percentage of lower stage disease detected. However, there remain many other factors that

influence the disease stage at presentation. Within the UK, geographical variations occur (Figure 1.6), as well as other factors such as age, deprivation and race. Men who are older, more deprived and white British are more likely to present with later stage disease (CRUK, 2015).

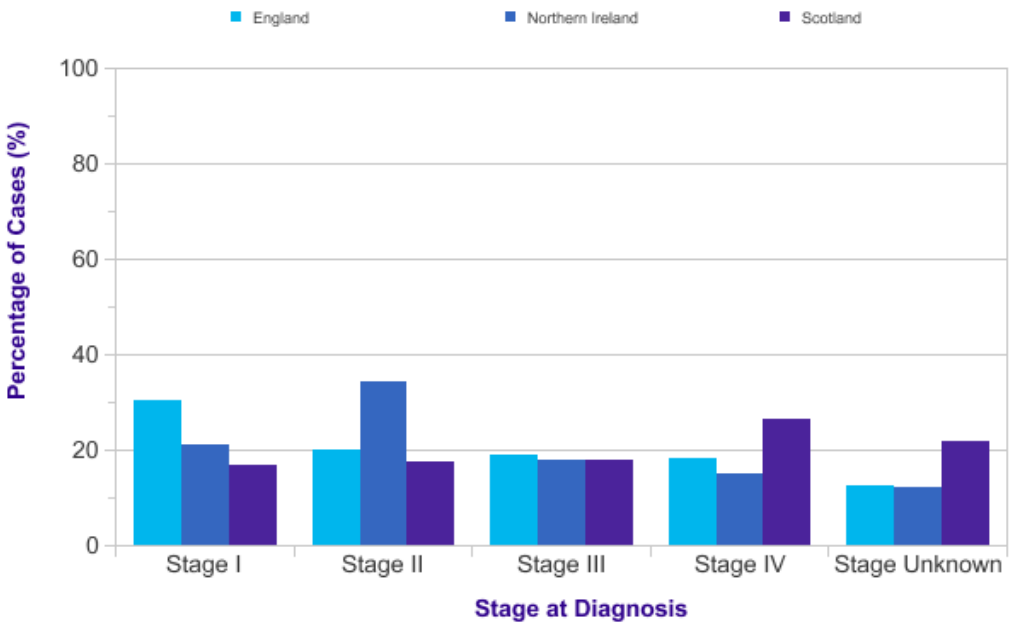


Figure 1.6. Proportion of cases diagnosed at each stage between 2010-2014 in the UK (CRUK, 2015). Stage 1, T1-T2a. Stage 2, T2a-c N0. Stage 3, T3N0. Stage 4, T4N0, or any N1 or M1.

1.3.2 Mortality

Prostate cancer is the fifth leading cause of cancer deaths worldwide. Within the UK in 2016 there were approximately 11,600 deaths from prostate cancer making it the 4th most common cause of deaths from cancer overall and 2nd most common amongst males (13% of all males cancer deaths) (CRUK, 2015). In 2008, globally in the developed world it was the 3rd most common cause of death amongst males and 5th most common in the developing countries (Jemal et al., 2011). Nearly 60% of all death from prostate cancer are in those men aged 80 years or over.

As expected prostate cancer mortality is directly related to age with much higher rates in the elderly (Figure 1.7). Since the 1970's mortality rates in the UK have increased by nearly 20% overall but have decreased in the last 10 years by around

13% (CRUK, 2015) and predicted to fall by a further 16% from now until 2035 (Smittenaar et al., 2016). Age group related mortality rates have remained stable in the younger age groups, with only the 70-79 years age group seeing a decrease of 10% and the over 80s seeing a rise of 44% (CRUK, 2015).

The improvements in mortality rates are thought to be a result of many factors. A higher incidence of indolent cancers through PSA screening, improved diagnostics, as well as advances in treatment pathways and techniques.

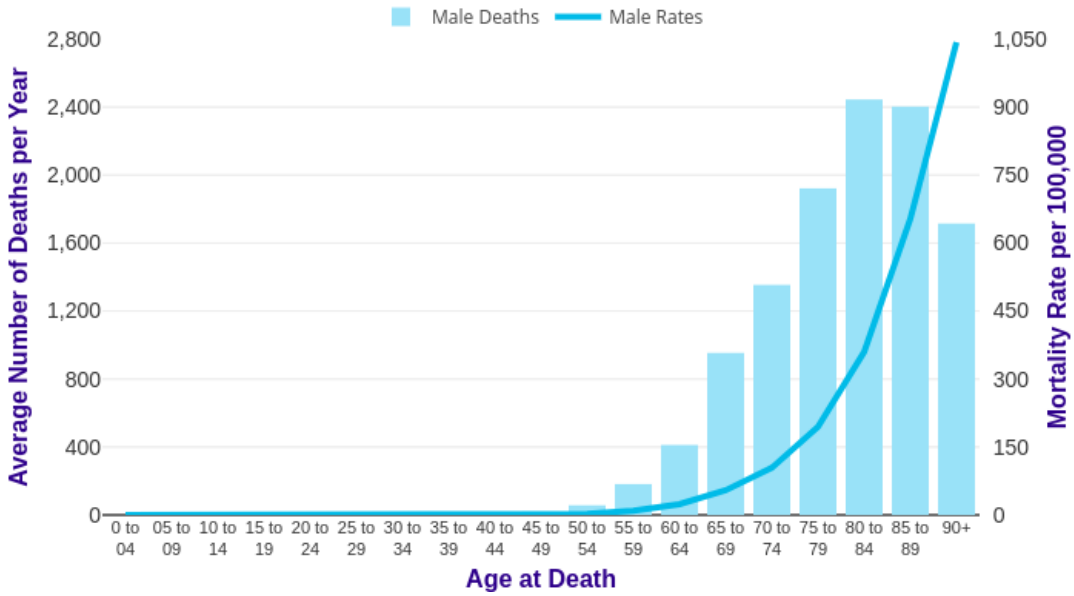


Figure 1.7. Average number of deaths per year and age specific mortality rates per 100,000 population, UK, 2014-26. (CRUK, 2015)

1.4 Risk factors

As already discussed, increasing age represents the biggest risk in developing prostate cancer. However, several other factors play a role including race and geographical location, family history and genetics, obesity, testosterone levels and diet and lifestyle choices.

1.4.1 Race and geographical factors

As emphasised in Figure 1.1 there is a wide variation in global incidence rates across the world with higher rates in Australia and New Zealand and the lowest rates in Eastern and South Central Asia. The highest mortality rates are seen in Southern Africa (26.8 per 100,000 men) compared with very low rates in South Central Asia (3.3 per 100,000) (Bray et al., 2018).

It is not known why there is such a variety in mortality rates between ethnic groups as rates of indolent cancer on autopsy studies have been found to be similar (Breslow et al., 1977). This therefore brings in to question the influence of genetic and environmental factors in developing significant cancer.

1.4.2 Family history and genetics

The first reported evidence of familial clustering in prostate cancer occurred over 50 years ago. Overall, sporadic cancers account for around 85% of new cases and 15% are familial. However, the percentage of familial cases presenting in men younger than 55 years old rises to around 43% and falls to 9% in men over 85 (Abouassaly et al., 2012). Men with a positive family history presenting with prostate cancer often do so earlier but this does not appear to affect disease course (Breslow et al., 1977). Relative risk associated with hereditary prostate cancer is higher when first degree relative are involved and this rises with the number of relatives affected and a lower age at presentation (Kicinski et al., 2011, Bruner et al., 2003).

FAMILY HISTORY	LIFETIME RISK
NO HISTORY	8%
FATHER, DIAGNOSED >60	12%
1 BROTHER AFFECTED >60	15%
FATHER AFFECTED <60	20%
1 BROTHER <60	25%
2 MALE RELATIVES	30%
3 OR MALE AFFECTED RELATIVES	35 to 45%

Table 1.1. Table showing lifetime risk of prostate cancer in men with a positive family history (Bruner et al., 2003).

Germline mutations in genes such as BRCA1 and 2 and HOXB-13 have been shown to increase the risk of developing prostate cancer. BRCA 2 conveys the highest risk with a near 9-fold increase for BRCA 2 (Kote-Jarai et al., 2011) and 4-fold for BRCA 1 (Leongamornlert et al., 2012). BRCA 2 is also though to associated with a more aggressive disease phenotype with a higher rate of locally advanced disease and subsequent risk of metastases (Castro et al., 2013). Family history should therefore be borne in mind when considering PSA testing.

1.4.3. Diet and obesity

Men who are overweight have a lower incidence of low grade cancer but a higher incidence of aggressive cancer (Castro et al., 2013). The higher rate of aggressive cancer in overweight men may be due difficulties in presentation and diagnosis, and also based on hormonal factors that are promoted in obesity. Weak evidence exists suggesting an increase risk in developing prostate cancer with diets high in dairy and alcohol.

1.5 Clinical and pathological staging of prostate cancer

1.5.1 Staging of prostate cancer

Staging is important for several reasons; it helps to characterise the disease, predict outcome and aid treatment decisions as well as helping health care providers and researchers in exchanging information about patients (Buyyounouski et al., 2017).

The first tumour-node-metastasis (TNM) staging system was published in 1958 by the International Union Against Cancer (UICC) having been developed by Frenchman Pierre Denoix as a method of staging cancer uniformly across all sites. Initially it was used to stage breast and laryngeal cancer (Greene and Sobin, 2008) but over the following years more cancer sites were added. In 1982, the UICC collaborated with the American Joint Committee on Cancer (AJCC) to develop the Fourth Edition of TNM and thereby achieve a worldwide agreement on the staging of adult solid tumours (Greene and Sobin, 2008). In 2017, the eighth edition was published and all previous editions since 1982 have been identical to the AJCC classifications.

Currently the eighth edition of the TNM staging remains in use and remains the gold standard for the staging of prostate cancer. This is used in combination with pre-treatment PSA and the Gleason grading of tissue obtained at biopsy to risk stratify patients newly diagnosed and aid treatment decisions.

Tumour stage (T stage)

T stage is used to classify the extent of disease within the prostate. T stage is defined as either clinical tumour stage (cT) or pathological stage (pT).

Clinical stage should only be derived from findings on digital rectal examination (DRE). Findings from radiological investigations may help to plan potential staging investigations, i.e. targeted TRUS biopsy, and to aid subsequent treatment decisions, i.e., presence of T3 disease, but due to the lack of uniformity of staging investigations should not be used to define cT stage.

Pathological stage can only be defined in those patients who undergo radical prostatectomy and have the prostate examined histologically. The boundary of the prostate, or capsule, is a formed by a dense layer of fibromuscular stroma and is most well defined posteriorly and posterior-laterally. It is less well defined at the apex, bladder neck and anterior prostate and subsequently defining extra-prostatic extension at these sites can sometimes be challenging.

Nodal stage (N stage)

N stage is used to determine the extent of nodal disease. Regional nodes are defined as those nodes within the true pelvis and include iliac, obturator, sacral and hypogastric. Involvement of non-regional nodes is defined as metastatic disease and is not defined as part of N stage.

Clinical nodal stage is often identified on staging CT or MRI scans although can be underestimated if nodes to not reach standard size criteria for positivity. Lymphadenectomy is the gold standard for determining pathological nodal status.

Metastasis stage (M stage)

M stage is used to define presence of metastases. This is most often assessed using isotope bone scan as prostate cancer most commonly metastasises to the axial skeleton. CT, MRI and PET scans are also used.

TNM Classification 8th Edition

T categories

Tx	Primary tumour cannot be assessed
T0	**No evidence of primary tumour**
T1	**Clinically unapparent tumour neither palpable nor visible by imaging**
T1a	**Tumour was incidentally found in less than 5% of prostate tissue resected**
T1b	**Tumour was incidentally found in more than 5% of prostate tissue resected**
T1c	**Tumour identified on needle biopsy (e.g. because of elevated PSA)**
T2	**Tumour confined within the prostate**
T2a	**Tumour involves one half or less of one lobe**
T2b	**Tumour involves more than one half of one lobe but not both lobes**
T2c	**Tumour involves both lobes**
T3	**Tumour invades through the prostate capsule**
T3a	**Extra-capsular extension (unilateral or bilateral)**
T3b	**Tumour invades seminal vesicles**
T4	**Bladder invasion, fixed to pelvic side wall, or invasion of adjacent structures**

N categories

Nx	Regional lymph nodes were not assessed

N0	**There is no spread to regional lymph nodes**
N1	**There is spread to regional lymph nodes**

M categories

Mx	Distant metastasis cannot be assessed
M0	**No distant metastasis**
M1	**Distant metastases**
M1a	**Metastasis to non-regional lymph nodes**
M1b	**Metastasis to bone**
M1c	**Metastasis to other distant sites**

Table 1.2. TNM 8th Edition staging classification of prostate cancer.

In 1992, the AJCC and UICC adopted a new TNM system whereby the pT2 stage was sub-classified in to three tiers as seen in the current 7th edition. In 1997, this was revised and the T2a and T2b categories combined to form one category for unilateral disease, T2a, and a second category was created for bilateral tumours, T2b. In 2002, this change was revised again and reverted to the three-tier system used in 1992 (Hong et al., 2008). This classification was kept when the 7th and the most recent 8th TNM editions were published.

The AJCC has recommended the sub-classification of pT2 tumours is to be scrapped in favour of one T2 group incorporating all organ confined tumours. This is following a lack of evidence to suggest prognostic differences between the three sub classifications. This change will eliminate the dilemma that pathologists face in having to create an imaginary midline. It will also eliminate the potential of classifying a small tumour that crosses the midline higher than a large solitary tumour on one side of the prostate (Buyyounouski et al., 2017).

1.6 Grading of prostate cancer

1.6.1 Gleason grading

The histopathological grading system used for prostate cancer was developed in the 1960's and 1970's by Donald F Gleason. It has undergone a number of adaptations since inception with the latest changes made in 2014 by the International Society of Urological Pathology (ISUP)(Epstein et al., 2016a).

Gleason established a system whereby the architectural growth patterns of prostate cells were graded and assigned a score of between 1 and 5. Originally the overall score was the addition of the primary (most common grade present) pattern and secondary (least common grade present) pattern scores. If only one grade is present it is doubled to give an overall score. In 2005, this rule changed whereby if there were 3 grades present the score comprised the most common grade plus the most aggressive grade, regardless of the extent. Overall scores are between 2 – 10. Less well-differentiated cells are given higher scores, therefore, an overall score of 10 conveys the worse prognosis. Following changes to the Gleason scoring system both in 2005 and 2014 by ISUP it is now very different to how it was originally (Epstein et al., 2016a). Scores of between 2 and 5 are no longer used and therefore current scoring for cancer ranges between 6 and 10. Also, Gleason 7 now includes patterns that were once graded 6 and hence current Gleason 6 tumours convey a better prognosis than those diagnosed using original Gleason criteria.

Matoso and Epstein (2016) sought to clarify the all the changes made by ISUP in 2014. Original Gleason scoring criteria had the presence of cribriform glands, regardless of size, as part of pattern 3. In 2005 ISUP modified this and recommended those with large cribriform glands be included in pattern 4. This was further adapted in 2014 by ISUP to incorporate all cribriform glands as part of pattern 4. The decision between this was two-fold; firstly, an increasing body of evidence to suggest that the presence of cribriform patterns is a poor prognostic feature and secondly problems with reproducibility amongst pathologists (Matoso and Epstein, 2016). There were

also clarifications about glomeruloid glands, mucinous carcinoma and intra-ductal carcinoma.

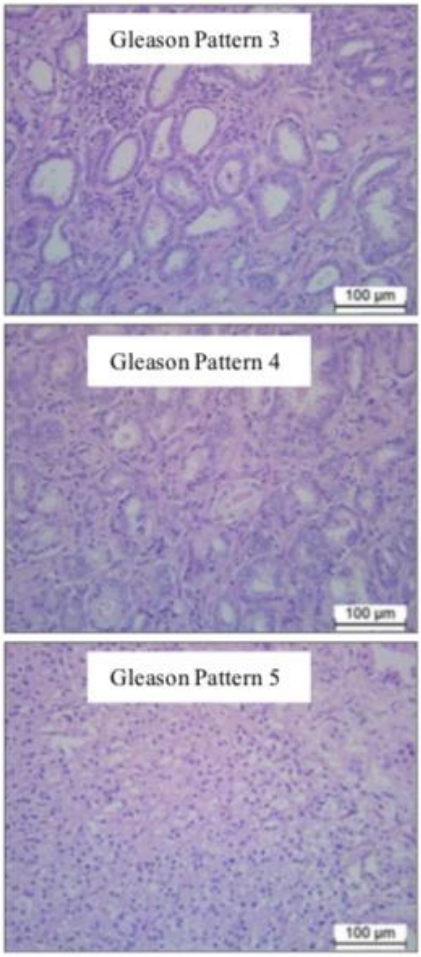


Figure 1.8. Histological representation of different Gleason grade patterns with H&E staining. (Courtesy of Dr D Griffiths, Histopathologist, UHW Cardiff.)

In 2005, ISUP agreed not to report tertiary Gleason scores for prostate biopsy. Tertiary scores would be reserved for radical prostatectomy specimens only to help differentiate more aggressive disease. It was agreed that the third most common pattern of highest grade cancer be considered tertiary only if it was less than 5%. If it was more than 5% it would be considered the secondary pattern. This scoring system helped to differentiate and stratify patients more accurately (Matoso and Epstein, 2016).

The main change at the ISUP in 2014 was to introduce a new grade grouping system (shown in Table 1.3) which better reflected the distinction between the different Gleason groups particularly the 2 types of Gleason 7 and also to separate Gleason 8 from 9 and 10.

ISUP GRADE GROUP	GLEASON SCORE	BCR FREE AFTER RP (%)
1	3+3	96
2	3+4	88
3	4+3	63
4	8	48
5	9-10	26

Table 1.3. Table highlighting ISUP 2014 grade group for prostate cancer and associated biochemical recurrence-free progression after radical prostatectomy (Epstein et al., 2016a, Pierorazio et al., 2013)

Pierorazio et al reported distinct and important differences in biochemical recurrence-free survival between these grade groups and this was later validated in a much larger study (Epstein et al., 2016b). This new grade group system will make it is easier to interpret Gleason grading and emphasises the clinical importance of distinguishing between the different Gleason scores in deciding on how to treat and counsel patients.

1.7 Detection of prostate cancer

Most men with suspected prostate cancer will present with a raised PSA, with or without LUTS, that are often not a result a of the underlying cancer and/or an abnormal feeling prostate on digital rectal examination. Patients are then investigated and staged with a combination of TRUS guided biopsy of the prostate, MRI scan, isotope bone scan and CT imaging.

The challenge for prostate cancer diagnostic remains identifying clinically significant disease and avoiding over diagnosis and subsequent overtreatment of indolent disease.

A point of controversy amongst diagnostics is producing a common definition of clinically significant disease with many existing criteria.

1.7.1 Digital rectal examination (DRE)

Most prostate cancers are located within the peripheral zone of the prostate and hence should theoretically be palpable on digital rectal examination with tumours becoming apparent when greater than 0.2ml in volume (Heidenreich et al., 2014). The obvious pitfall for DRE is with smaller high grade tumours and anteriorly sited tumours and considerable inter-observer variation which may be affected by clinical experience. For this reason, it is essential to incorporate clinical findings with other staging modalities such as MRI and TRUS findings.

1.7.2 Prostate specific antigen (PSA)

Prostate specific antigen is an enzyme produced only by the prostate to liquefy seminal fluid. It is therefore prostate specific but not cancer specific and be elevated in cases of benign prostatic hyperplasia, prostatitis and when there is concurrent urinary tract infection. PSA levels also vary with age and race and must be adjusted accordingly (DeAntoni et al., 1996) (Table 1.4). Interpretation of PSA results does therefore require correlation with the clinical picture. Currently in the UK the PCRMG suggest urgent referral if PSA $\geq$3 for men between 50-69 (PCRMG, 2016).

AGE (YEARS)	WHITE	BLACK	ASIAN
40-49	0-2.3	0-2.7	0-2.0
50-59	0-3.8	0-4.4	0-4.5
60-69	0-5.6	0-6.7	0-5.5
70-79	0-6-9	0-7.7	0-6.5

Table 1.4. Age specific PSA levels (ng/ml), by race (DeAntoni et al., 1996).

Commercial serum PSA assays were introduced in the late 1980s. Prior to widespread PSA testing many patients with prostate cancer presented at a very advanced stage and hence with incurable disease. PSA testing has revolutionised

prostate cancer diagnostics and management and has led to an increase in the number of men presenting with localised disease.

The predictive value of PSA improves with increasing scores. With a normal DRE and an PSA between 4 and 10ng/ml there is a 25% chance of detecting prostate cancer on TRUS biopsy, this rises to 50% if the PSA > 10ng/ml with half of these men having at least T3 disease.

PSA is most accurate in the post treatment period particularly after radical prostatectomy when one would expect PSA levels to be undetectable if all prostate and cancer tissue has been removed. PSA levels are then monitored to identify disease recurrence with a PSA >0.2 widely accepted as the definition of disease recurrence.

In the UK, the prostate cancer risk management group was created to advise primary care physicians on asymptomatic men requesting a PSA test. It is recommended that all men are counselled regarding advantages and disadvantages of PSA testing, what is involved in the investigation of a raised PSA and potential treatment options for prostate cancer. It has been shown that this is not always achieved and that additional patient decision aids may help in the decision-making process (PCRMG, 2016).

1.7.3 TRUS biopsy

Historically patients with elevated PSA levels or abnormal DRE would have been referred for TRUS biopsy.

TRUS biopsy does have potential severe side effects including sepsis and bleeding and these must not be overlooked when counselling men. The biopsy is most commonly performed with local anaesthetic and in a clinic based setting. A more thorough form of prostate biopsy is Template Prostate Mapping (TPM), this involves taking biopsies through the perineum to obtain tissue from the prostate at 5mm intervals. This enables the clinician to create a comprehensive map of the prostate

and offers a more accurate method of diagnosis, with 95% sensitivity for clinically significant cancer (Ahmed et al., 2017). However, TPM involves general anaesthesia and the associated morbidity and logistical problems that come with this and as a result it is less commonly performed.

Prior to the introduction of modern imaging techniques such as multi-parametric MRI TRUS biopsy was performed in a systematic fashion whereby 8-12 random core biopsies were taken. This method has the potential to miss significant cancer and potentially under stage disease. In fact, around a quarter of men with a negative TRUS biopsy or a biopsy that was defined as non-significant cancer were then found to have clinically significant cancer on a subsequent template mapping biopsy (Ahmed et al., 2017).

Given the pitfalls of systematic or blind TRUS biopsy and the difficulties associated with offering a TPM service there was a real need for a better way to diagnose prostate cancer. Advances in MRI diagnostics have now brought about change whereby it is common practice for patients to receive an MRI scan before TRUS biopsy with the aim of targeting abnormal areas.

1.7.4 Magnetic resonance imaging

The usefulness of MRI in the detection of clinically significant prostate cancer has improved significantly in recent years. Historically, the use of MRI in the diagnostic pathway was variable and only in recent years has there been widespread uptake of pre-biopsy MRI in the UK (NPCA., 2018). There has been a shift from using MRI as a tool for staging towards one for cancer detection and targeting at biopsy (Futterer et al., 2015). It also now plays a role in surveillance, guidance for focal treatment, and for assessment of possible disease recurrence (Weinreb et al., 2016b).

The advances in accuracy in MRI have been a result of the introduction of multi-parametric MRI. In the early stages of prostate staging MRI only T1 and T2 images were used. A multi-parametric MRI includes T1 and T2 weighted images, diffusion weighting imaging (DWI) and its derivative apparent-diffusion co-efficient (ADC)

maps, dynamic contrast enhancement (DCE) and sometimes proton spectroscopy. The combined outputs from these sequences define mpMRI and have been instrumental in improving accuracy.

There is still wide variability between different centres as to the type of MRI machine that is used and the sequences that are used to report. The use of contrast may not be available, the age of the MRI machine and the type of magnet, the use of endo-rectal coils and obvious inter-observer variability may all affect ability to produce accurate reports. It is widely accepted that MRI is more accurate for larger and more aggressive tumours.

In an attempt to standardise reporting of MRI, scoring systems have been introduced. The PI-RADS score (Prostate Imaging – Reporting and Data System), now in its second version, was designed by the American Society of Radiology, the European Society of Uroradiology and AdMetech foundation. Aside from introducing a scoring system PI-RADS have recommended minimal standards for mpMRI and guidance on how they should be reported. It has helped decrease variation in acquisition, interpretation and reporting (Weinreb et al., 2016b) making PIRADS useful for everyday practise as well as using it as standard for data collection in clinical trials and research. The PIRADS scoring system uses a five-point scale to indicate the likely presence of clinically significant cancer in each lesion (Table 1.5) Clinically significant cancer is defined as Gleason $\geq$ 7, and/or volume $\geq$0.5cc, and/or extra-prostatic extension (Weinreb et al., 2016b).

PIRADS SCORE	**PROBABILITY OF CLINICALLY SIGNFICANT CANCER**
1	Very low (clinically significant cancer is highly unlikely to be present)
2	Low (clinically significant cancer is unlikely to be present)
3	Intermediate (the presence of clinically significant cancer is equivocal)
4	High (clinically significant cancer is likely to be present)
5	Very high (clinically significant cancer is highly likely to be present)

Table 1.5. PIRADS score of mpMRI indicating likelihood of cancer being present.

The use of PIRADS scoring has helped to increase the detection of cancers likely to cause harm and also decrease the detection of the indolent cancers that one probably does not to treat (Padhani et al., 2018). Other scoring systems such as the LIKERT score use clinical and radiological features to determine the likelihood of cancer rather than PIRADS which is based purely on pre-determined MRI characteristics. As a result of this, PIRADS is used in diagnosis of prostate cancer and scoring cannot be applied to patients with already known prostate cancer, such as those on surveillance.

LIKERT is also preferred in the updated NICE guidance again because of the ability to use other parameters such as DRE findings, PSA scores and PSA density and other clinical features which increase the likelihood of cancer such as family history. LIKERT uses a 5-point scoring system with the same definitions as in PIRADS (Dickinson et al., 2013). Unlike PIRADS it can be used to risk stratify biopsies in the active surveillance cohorts and therefore has a wider scope.

Given improvements in mpMRI, there is now evidence to suggest that MRI be used routinely in the diagnostic pathway before biopsy. The PROMIS trial showed both higher sensitivity (93% vs 48%) and better negative predictive value (89% vs 74%) for MRI compared to TRUS biopsy in detecting clinically significant cancer (defined as Gleason $\geq$4+3 or core length $\geq$6mm). However, TRUS biopsy had better specificity (96% vs 41%) and positive predictive rates (90% vs 51%). In this trial if MRI was used as a triage test and all those patients with a Likert score $\geq$ 3 had targeted biopsies it was predicted that around a quarter of patients could avoid an immediate biopsy and around 5% less clinically insignificant cancers would be detected (Ahmed et al., 2017).

The PRECISION study took this further and compared outcomes of TRUS biopsy alone versus only targeted biopsies following an abnormal mpMRI (classified as PI-RADS $\geq$3) for investigation of men with a raised PSA. Targeted biopsy alone was shown to be non-inferior to TRUS biopsy and in fact led to a higher percentage of clinically

significant cancers being detected and a lower percentage of insignificant disease (Kasivisvanathan et al., 2018).

With this new evidence, NICE guidance has now recommended that mpMRI be performed before TRUS-biopsy in men suitable for radical treatment. If the MRI is abnormal targeted as well as systematic biopsies are still recommended given the lower specificity and NPV of MRI. If the mpMRI is normal (Likert 1 or 2) and other clinical parameters allow one may be able to discuss with patients the opportunity to omit a biopsy but be aware there is still a 28% chance of having significant cancer (NICE., 2019).

In addition to local prostate imaging and staging MRI is also used to stage abdominal lymphadenopathy and there is increasing use of whole body MRI as a means of staging men with more aggressive cancer with a risk of metastatic disease.

1.7.5 Isotope bone scan

Prostate cancer most commonly metastasises to the lymph nodes and to bone, causing an osteoblastic reaction and subsequent sclerotic bony metastases. The detection of metastases is both important for evaluating prognosis and treatment options.

Isotope bone scans are used in the staging of prostate cancer when there is a concern for the presence of metastatic disease. Despite other options being available for the assessment of bony metastases, PET-CT, SPECT and MRI, bone scan remains the investigation of choice. This is largely due its relatively high sensitivity, affordability and availability compared to the other options (Shen et al., 2014).

1.7.6 PET-CT

Positron Emission Tomography (PET) couple with CT, i.e. PET-CT, offers promising results for accurately staging men with advanced disease where accurate nodal and metastatic staging is important in defining disease status. PET is reliant upon the detection of positron emitting radionucleotides which are attached to metabolically

active carriers used in rapidly producing cancer cells, such as flourodeoxyglucose (an analogue of glucose). Within prostate cancer both choline-PET and PSMA (prostate specific membrane antigen)-PET have shown the most encouraging results and their use is increasing. However, what is not clear is how men should be treated who have lesions picked up on PET that would not otherwise have been detected on MRI or CT staging (Heidenreich et al., 2014)

1.8 Screening for prostate cancer

Screening aims to reduce the rate of death from a specific disease with minimal impact on quality of life. Screening for prostate cancer remains a controversial topic as currently many of the required criteria to establish a screening program are not met(Wilson and Junger, 1968). To date the two largest studies assessing outcomes for screening, the ERSCP and the PLCO trials, offer conflicting messages.

The European Randomised Study of Screening for Prostate Cancer (ERSCP), a large multi-centre randomised trial compared the effects of screening on rates of prostate cancer mortality in 182,160 men. At 13 years follow up, there was a relative risk reduction of 21% in a subgroup of men aged 55-69 years of age, and an absolute risk reduction of 1.28 per 1000 men randomised was demonstrated. This equates to 781 men being screened to avoid one death and 27 additional new cases being diagnosed to prevent one death (Schröder et al., 2014).

This reduction in mortality was not seen in the other large screening study, carried out in the United States. The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial randomised 76,693 men to receive annual screening (PSA test for 6 years and DRE) versus the control group. At 15 years' median follow-up, there was no significant difference between rate of death from prostate cancer (Pinsky et al., 2017). There is, however, increasing debate regarding the validity of this study due to the high percentage of patients in the control group that received screening PSA tests. Hence, it is argued this study cannot reliably used when comparing screening to a non-screened group (Shoag et al., 2016).

A Cochrane review of 5 RCT's on screening, published in 2013, did not demonstrate any improvement in prostate cancer specific mortality. They concluded that morbidity from diagnostics tests was not insignificant and over diagnosis and over treatment were common. An increased number of prostate cancer cases was seen, particularly low risk cases. It was highlighted that any improvement in disease specific mortality from screening is likely to take at least 10-15 years to be seen and therefore should not be undertaken in those with a lower expectancy than this (Ilic et al., 2013).

Currently NICE guidelines in the UK make no recommendations on screening. However, the most recent UK National screening committee (NSC) published in 2016, advised against the introduction of screening for prostate cancer. They concluded that PSA remains a poor test for detecting cancer with a better test with higher sensitivity needed, and one that can differentiate between aggressive and non-aggressive cancers, with minimal morbidity (UKNSC, 2016). This mirrors the recommendation made by the United States Preventative Task Force (USPTF) in 2012 to stop routine PSA testing due to concerns over safety. Interestingly one study found that in the 3 years after this recommendation was introduced the biopsy rate decreased but the detection rate, percentage of higher grade tumours and the percentage of positives biopsies all increased (Shah et al., 2018).

One large UK based study assessed whether a one-off PSA test for men between 50 and 69 years of age would reduce the risk of dying from prostate cancer. In the control group (no PSA test) 36 men per 1000 were diagnosed with cancer compared to 43 per 1000 in men that had had a PSA test. The group who had a test were more likely to be diagnosed at a younger age, with a lower grade of disease and less likely to have distant disease and therefore less chance of needing treatment. No difference in death rate from prostate cancer was noticed after 10 years and the trial concluded that a one-off PSA test was of no benefit for screening of prostate cancer (Martin et al., 2018).

The EAU statement regarding PSA testing in 2017 (Mottet et al., 2017a) are detailed below-

- Don't offer men PSA testing without explanation of potential risks and benefits
- Offer an individualised risk-adapted strategy for early detection to a well-informed individual with a good performance status and a life-expectancy of at least 10-15 years
- Offer early PSA testing in well-informed men at elevated risk of CaP
    - Men > 50 years old
    - Men > 45 years old with a family history
    - African-Americans >45 years old
    - Men with PSA level >1ng/ml at 40 years old
    - Men with PSA level >2ng/ml at 60 years old
- Offer risk adopted strategy with 2 yearly PSA testing for those initially at risk
    - Men with PSA level >1ng/ml at 40 years old
    - Men with PSA level >2ng/ml at 60 years old
- Those not at risk offer 8 yearly follow-up.

In conclusion, screening for prostate cancer and the decision for PSA testing should take in to account family history, the presence of symptoms and suitability for treatment. PSA testing should only be done after a well-informed and patient centred discussion.

1.9 Risk stratification for prostate cancer

Risk stratification for newly diagnosed cases of prostate cancer is vital in decision making processes for treatment. They are also used to define clinical trial groups and reports outcomes (Rodrigues et al., 2012). Ideally stratification processes should be simple to use and remember. The prognostic powers of pre-treatment PSA level, Gleason score from diagnostic biopsy and clinical T stage have been used to develop risk stratification tools. National governing bodies have used and adapted pre-existing classification to aid clinicians deciding on treatment course.

1.9.1 D'Amico classification

Published in 1998, D'Amico et al developed a three-tier risk stratification tool to help predict outcomes for patients with clinically localised CaP undergoing radical treatment. Patients were grouped in to low, intermediate and high risk groups based upon pre-treatment PSA level, Gleason score of needle biopsy and clinical T stage as per TNM staging (Table 1.6). Outcome was judged by PSA control post treatment and development of biochemical failure. Treatment groups included radical prostatectomy, external bean radiotherapy and brachytherapy. The study reported no difference in outcome at 5 years for low-risk patients between treatment groups. However, intermediate and high risk patients treated with RP and EBRT did better than those treated with brachytherapy (D'Amico et al., 1998).

Following on from this study there has been a wide scale uptake in the use of the D'Amico risk stratification largely because of its simplicity.

Risk group	**PSA level (ng/ml)**		**Gleason score**		**Clinical T stage**
Low	<10	and	≤6	and	T1a – T2a
Intermediate	10-20	or	7	or	T2b
High	>20	or	8 - 10	or	≥T2c

Table 1.6. D'Amico risk classification of localised prostate cancer (D'Amico et al., 1998).

1.9.2 Epstein criteria

Developed in 1994 by Epstein and colleagues to identify insignificant cancers (Epstein, 1994). They examined pre-treatment clinical and pathological parameters for men with T1c disease undergoing radical prostatectomy and found the following criteria predictors for insignificant disease;

- PSA density 0.1-0.15ng/ml
- Gleason score <7
- 1 positive core
- Longest tumour length <3mm

- Clinically organ confined

Various validation studies have been carried out since Epstein created these parameters and the generally accepted criteria is now defined as;

- PSA density <0.15ng/ml
- Gleason score <7
- <3 positive cores
- <50% volume of core positive for tumour
- ≤T1c

However, the ability of the Epstein criteria to accurately predict insignificant disease has been questioned. Since it was defined over 20 years ago there have been several modifications to Gleason grading criteria, most notably by ISUP in 2005. Oon et al reviewed the accuracy of Epstein criteria in predicting insignificant cancer, Gleason 6 disease and organ confined disease. It remained accurate in predicting organ confined disease with rates between 80 – 96.9% across studies. However, it was less accurate at predicting insignificant disease and Gleason 6 disease and this is thought in part to be down to changes in Gleason grading (Oon et al., 2011).

1.9.3 NICE

NICE guidance 2014 (NICE, 2014) recommend risk stratification as per D'Amico risk stratification and treatment recommendations are based upon this.

1.9.4 EAU

The EAU guidelines 2017 are very like those of D'Amico but also include ISUP grouping in a move to transition away from the use of traditional Gleason scoring. The higher risk group is also divided in to localised and locally advanced disease. It is likely that intermediate risk disease will be further divided in to low and high risk sub-groups based upon ISUP grading and increasing evidence to suggest better outcomes for patients with ISUP group 2 (Table 1.7) (Mottet et al., 2017a).

RISK GROUP	PSA LEVEL (NG/ML)	GLEASON SCORE	ISUP GROUP	CLINCAL STAGE
LOW	<10 and	<7 and	1	T1-2a
INTERMEDIATE	10-20 or,	7 or,	2 and 3	T2b
HIGH - LOCALISED	>20	>7	4 and 5	T2c
HIGH – LOCALLY ADVANCED	any	any	any	T3-4 or cNx

Table 1.7 EAU risk stratification of new diagnosis prostate cancer (Mottet et al., 2017b).

1.9.5 NCCN

The National Comprehensive Cancer Network (NCCN) is an alliance of US cancer centres and produces up to date guidelines for treatment of cancers within the US. Currently their risk stratification for prostate cancer has 7 tiers with 5 tiers for localised cancer with the inclusion of both very low and very high risk disease. Regional (any T stage and N1 disease) and metastatic disease complete the 7 tiers. Treatment strategies are recommended for each stage depending on patient factors such as wellbeing and life expectancy (Table 1.8) (NCCN, 2016).

RISK GROUP	PSA LEVEL (NG/ML)	GLEASON SCORE	CLINICAL STAGE	NUMBER OF CORES POSITIVE	% OF CANCER IN ANY CORE	PSA DENSITY (NG/ML/G)
VERY LOW	<10	≤6	≤T1c	<3	≤50%	<0.15
LOW	<10	≤6	T1-2a	-	-	-
INTERMEDIATE	10-20, or	7, or	T2b-c	-	-	-
HIGH	>20, or	8-10, or	T3a	-	-	-
VERY HIGH	-	Primary Gl pattern 5, or, >4 score 8-10	T3b-4	-	-	-

Table 1.8. NCCN risk stratification of new diagnosis prostate cancer (NCCN, 2016).

In summary, the different risk stratifications are all very similar and all aid to characterise disease for the benefit of decision making and reporting of outcomes. The D'Amico classification remains the most widely used due its simplicity and easy application in clinical practice.

1.10 Treatment options for prostate cancer

The treatment of prostate cancer is varied and depends on the tumour grade and stage. In simplistic terms one can classify disease at presentation in to three main groups, localised prostate cancer, locally advanced non-metastatic prostate cancer and metastatic disease.

1.10.1 Localised prostate cancer

Localised prostate cancer, i.e. T2 or lower, can be treated in several ways and largely depends on the risk classification (as previously discussed) at presentation.

The mainstay of treatment for low risk cases is with deferred treatment strategies with the aim to reduce the morbidity associated with radical treatment. If patient fitness allows, intermediate and high risk cases should be treated with radical (curative) treatments such as radical prostatectomy, external beam radiotherapy or brachytherapy. Other novels techniques such as high intensity focused ultrasound (HIFU) and cryotherapy remain outside the scope of mainstream therapy and are only recommended as part of clinical trials.

Radical treatment options for prostate cancer can result significant in morbidity. As discussed, many newly diagnosed prostate tumours will have a protracted natural history and may pose no threat to overall life expectancy. Despite this, some patients will still choose to have radical treatment and expose themselves to the potential side effects of such treatment. With an increasing incidence of CaP there are real concerns regarding the over-diagnosis and over-treatment of clinically insignificant prostate cancer. The ProtecT study recently demonstrated no difference in overall survival in men with low risk, screening detected prostate cancer, undergoing either

active surveillance, radical prostatectomy or radical radiotherapy. The only benefit seen was in those men that had surgery and radiotherapy had a lower rate of disease progression and metastases but this number was low. They concluded that 27 men would need to have a prostatectomy or 33 receive radiotherapy to prevent 1 man from developing metastases, or 9 men treated with either to prevent one case of disease progression(Hamdy et al., 2016). This study therefore emphasises the indolent course of low risk prostate cancers and the need to try and avoid over treatment of such disease. One could argue that ProtecT results may represent worse outcomes than current practise as current active surveillance protocols include re-biopsy and MRI neither of which were included in ProtecT protocol.

Two other notable studies, PIVOT and SPCG-4, looked at the effect of surgery versus observation in localised prostate cancer have produced interesting results. PIVOT (Prostate cancer Intervention Versus Observation Trial) looked at the difference in all-cause mortality and prostate cancer mortality in patients with localised disease having either surgery or observation. With nearly 20 years' follow-up (13 years' median) there was no difference in all cause or prostate cancer mortality between those that had surgery or observation. Within sub-groups there was slight improvement in all-cause mortality for men with intermediate risk disease but not for low or high risk. Surgery was associated with higher rates of complications such as incontinence and impotence and lower rates of progression. It is worth noting that this study includes men prior to changes in Gleason scoring and therefore men with Gleason 6 disease may now be classified as Gleason 7 with recent changes (Wilt et al., 2017).

SPCG-4 was also carried out in the early days of PSA testing when Gleason scoring was different to today and most patients had palpable disease. They noted a decrease in death from prostate cancer in the surgery group versus observation at 29 years' follow-up. Those that had surgery had a mean increase in life of 2.9 years. This was more marked in patients under 65 years of age and they stated that just under 7 prostatectomies were needed to avoid one death in this subgroup (Bill-Axelson et al., 2018).

1.10.1.1 Deferred treatment strategies

Given the body of evidence suggesting low risk disease follows an indolent course deferred treatment strategies offer an excellent option for men wanting to avoid unnecessary treatment. Encouragingly figures show a shift away from over treatment of low risk disease with only 8% of men in England receiving treatment in 2017 compared with 12% in 2014 (NPCA., 2018).

Deferred treatment strategies for prostate cancer are well established, however, long term follow-up data on these remains limited and patient selection continues to cause debate. The deferred treatment strategy chosen depends on patient fitness and anticipated life expectancy. There are 3 defined strategies- active surveillance, active monitoring and watchful waiting.

Active surveillance

Active surveillance is defined as a deferred treatment strategy with the intention to treat patients with radical intent if evidence of disease progression develops or the patient expresses a wish for treatment.

After initial diagnosis patients are closely monitored with regular PSA blood tests and clinical examination. Restaging prostate biopsies +/- repeat MRI is typically performed arounds 12 months after diagnosis.

To be eligible for active surveillance patients should be in good health and have a life expectancy of at least 10 years.

Active monitoring

A predecessor to active surveillance, this term was coined from the ProtecT study. Again, this strategy involves a plan to treat with radical intent if patient demonstrates disease progression or expresses a wish for treatment.

After diagnosis patients are monitored with PSA blood tests and regular clinical examination. The main difference with this compared to AS is that patients are only offered restaging if clinically triggered i.e. rising PSA or change in clinical staging.
It has now largely been superseded by AS but does remain relevant in a small subset of patients who did not wish to follow the strict regime of AS.

Watchful waiting

Defined as deferred treatment with the intentional to palliate if a patient develops disease progression. This is suitable for elderly or frail patients with a limited life expectancy, typically less than 10 years, who are not suitable for radical treatment. Treatment is usually with hormones when indicated.

Currently NICE guidelines (NICE., 2019) within the UK recommend active surveillance for men with D'Amico low risk disease i.e., Gleason score of 6 or less, PSA <10 and clinical T2a or lower, and suggest considering it in men with intermediate risk disease who wish to defer radical treatment.

The American Society of Clinical Oncology (ASCO) recommend that for most patients with low-risk localised prostate cancer AS is the recommended treatment strategy. This however, comes with a qualifying statement that accepts due to the heterogeneity of the group consideration must be given to young patients (<55yrs), higher volume Gleason 6 disease, patient preference and ethnicity. ASCO also recommend active treatment for most patients with intermediate risk localised disease. However, for patients with low volume intermediate risk disease (Gleason 3+4) AS may be offered. A further qualifying statement from ASCO suggests only men with low volume Gleason pattern 4 or >75 should be considered or AS (Chen et al., 2016).

Including the total number of positive cores, single core positivity rates and parameters such as PSA DT in criteria for enrolment are obviously made with the right intent and should undoubtedly aid decision processes. However, in practice

having straight forward criteria such as suggested by NICE and ASCO is probably beneficial.

The exact follow-up protocols for patients on active surveillance do vary between institutions but it is recommended that patients have regular PSA check between 4-6 monthly and consider repeat MRI at 12-18 months after diagnosis (NICE., 2019). This represents an update from previous NICE guidance which recommended a restaging TRUS biopsy at 12-18 months rather than an MRI (NICE, 2014). In the updated NICE guidance repeat biopsy is suggested if there is a clinical change, PSA rise or MRI change. Evidence suggests repeat biopsy acts as a second gateway to continued surveillance and reduces the risks of under-staging the disease and ensuring there has been no grade progression, although less likely. Re-staging biopsy has been shown to be associated with a better outcome in patients on surveillance ensuring patients are truly low risk (Dall'Era et al., 2012). The use of MRI in surveillance is variable but has been shown to act as a good test for detecting clinically significant disease at enrolment although its use in follow-up is less well known (Schoots et al., 2015).

It is widely accepted that more long term studies (>10-year follow-up) are needed on the outcomes of active surveillance given that it is younger men with a long-life expectancy enrolling on such programmes. Dall'Era et al 2012 performed a systematic review and compared outcomes from 7 large AS series. It showed treatment rates of between 11% at median follow-up of 1.8 years and 33% at 2.7 years. Longest median follow up was 6.8 years with a treatment rate of 30% although this cohort was older at diagnosis. Prostate cancer specific mortality was low across all studies although follow up was limited (Dall'Era et al., 2012). The much larger PRIAS study with 10 year follow up showed that at 5 and 10 year follow up 52% and 73% of men, respectively, had discontinued AS with the main reason being protocol based re-classification. The PRIAS study then went on to look at the pathological features at prostatectomy of men discontinuing AS and found that only Gleason upgrading or clinical T3 disease should be used as a trigger for radical treatment. They did not use MRI scans in this study (Bokhorst et al., 2016).

Deferred treatment strategies provide a key treatment pathway for men with low risk disease although many questions remain unanswered as to the optimum follow-up routine, the timing of re-biopsies and the use of mpMRI in the pathway. With surveillance an attractive strategy for younger men it is essential that the risk of disease progression is minimised with a robust and effective treatment protocol.

1.10.1.2 Radical prostatectomy

Radical prostatectomy can be offered to men, in good health, with intermediate and high risk localised prostate cancer with greater than 10-year life expectancy. The aim being to cure prostate cancer with preservation of continence and minimal impact on potency (Mottet et al., 2017a)

The surgical approach can include open, robotic assisted laparoscopic (RALP) approach or conventional laparoscopy. To date no one study has proved better oncological outcomes with one approach and there remains ongoing debate as to which one is superior. One cannot argue, however, that RALP has over taken conventional open surgery in becoming the standard approach for radical prostatectomy. In England in 2017, RALP accounted for 74% of all prostatectomies with only 12% performed open (NPCA., 2018). It is associated with less morbidity, often a shorter hospital stay and quicker return to normality.

Post operatively PSA levels are monitored and should be undetectable (<0.1ng/ml). The accepted definition for biochemical recurrence (BCR) is 2 or more readings >0.2ng/ml and indicates recurrent disease (Mottet et al., 2017b). Predictors of BCR include Gleason grade, T-stage and PSA at diagnosis. However, not all patients with biochemical recurrence develop clinically apparent disease, with a risk of metastases and disease specific mortality. Risk factors for doing so include a PSA doubling time of <3 months, pT3b disease or higher, Gleason score ≥8 or BCR within 3 years of radical prostatectomy (Antonarakis et al., 2012, Brockman et al., 2015, Freedland et al., 2005).

1.10.1.3 Radical radiotherapy

External beam radiotherapy (EBRT), like surgery is offered to men with intermediate and high risk localised prostate cancer. Men wanting to avoid the potential side effects of surgery may choose EBRT as an alternative option. To date there has been no study which has shown superiority of surgery or EBRT over each other in the setting of localised prostate cancer. The ProtecT study reported excellent survivals rate at 10 years for men having surgery or EBRT (Hamdy et al., 2016). However, it is generally accepted that younger men may gain more benefit from surgery given that if the disease recurs salvage radiotherapy is more straight forward than the other way around of salvage surgery. Radiotherapy also conveys a small risk of secondary cancers the longer one lives after treatment.

EBRT is usually given over a 4-week period with neo-adjuvant and adjuvant hormones given to patients with intermediate and high risk disease respectively. The addition of hormones to EBRT has been shown to improve disease free and overall survival (Bolla et al., 2002). After EBRT the PSA level is expected to fall to a low point (the nadir), recurrence after treatment is defined as a rise of 2ng/ml above the nadir.

1.10.2 Locally advanced non-metastatic prostate cancer

Locally advanced disease defines men who have cancer that has spread outside of the capsule of the prostate (>T2) but has not metastasised elsewhere.

If the patient is fit, the mainstay of treatment for locally advanced non-metastatic prostate cancer is EBRT and long term (3 years) hormone therapy. A number of studies have shown improved disease free survival and overall survival with this regime (Bolla et al., 2002, Warde et al., 2011).

In more recent years there has been a drive to avoid under-treatment of men with locally advanced disease, i.e. offering them radical treatment as opposed to non-curative treatment with hormonal therapy. Increasingly fit men with non-metastatic T3 disease are being offered surgery as the primary treatment accepting the possibility of needing additional EBRT, if the disease recurs or if it is not all removed

(positive margins and detectable post-operative PSA), as part of a multimodality approach. Surgery offers a chance of cure and long term control but at the risk of needing additional treatment. To date, the timing of adjuvant EBRT in this setting is being evaluated by the RADICALS trial (Parker et al., 2007). Two other trials, EORTC 22911 and SWOG 8794, compared immediate adjuvant EBRT versus EBRT at the time of BCR, in the setting of positive surgical margins and/or T3 disease post RP. Both trials showed improved biochemical progression free survival rates, however, only SWOG 8794 showed improved overall survival rates at 10 years (Bolla et al., 2012) (Thompson et al., 2009).

1.10.3 Metastatic prostate cancer

The aim of treatment in men with metastases is to control the disease rather than to cure. This is achieved via the manipulation of testosterone with the aim of reducing it to a castrate level (androgen deprivation therapy). This is done either surgically with bilateral sub-capsular orchidectomy, or via medical castration. Medical castration, can be achieved via several different methods; the hypothalamic-pituitary-testes axis can be turned off with leutinising hormone releasing hormone (LHRH) analogues or antagonists, alternatively the androgen receptor (AR) can be targeted with anti-androgens. Typically, with ADT the disease will be controlled for 12-18 months and then men develop castrate-resistant prostate cancer (CRPC) with AR activity returning. At this time, more novel agents such as enzalutamide and abiraterone are available and offer small but significant survival benefits. Chemotherapy also plays an important role in the management of metastatic disease. Traditionally it was used following the failure of first line hormonal treatment and offered a 2-3 month survival benefit if used at the time of CRPC (Tannock et al., 2004). However, it has now been shown to offer a 10-month survival benefit if used upfront i.e. soon after starting ADT (James et al., 2016).

1.11 Use of MDTs

Multi-disciplinary team meetings bring together all expert clinicians involved in the individual patients care to discuss results of diagnostic investigations and decide on

the correct course of action. They have been mandated in clinical practice in the UK for cancer care for over 15 years and discussion at MDT provides reassurance to both clinicians and patients alike. The benefits of MDT discussion have been shown to improve cancer survival rates in breast cancer and have shown to be financially sustainable (Kesson et al., 2012).

MDTs also provide a record for patient care and are a vital source of data collection for cancer services which can feed into local and national databases to provide up to date and relevant cancer statistics.

In 2014, the National Prostate Cancer Audit was established in England and Wales to ensure the care received by men was as recommended by NICE and ensure that care was uniform. The main outcomes of the audit were to assess –

- Service delivery and organisation of care in England and Wales
- The characteristics of patients newly-diagnosed with prostate cancer
- The diagnostic and staging process and the planning of the initial treatment
- The initial treatments that men received
- The experiences of men receiving care as well their health outcomes 18 months after diagnosis
- Overall and disease-free survival

The use of local MDTs is critical in capturing data required for this and data collection was mandated by the government (NPCA., 2017).

1.12 Summary and thesis aims

This thesis will use a prospectively collected database of newly diagnosed cases of prostate cancer discussed at a single centre specialist MDT (the EPC MDT) over a 20-year period to address several clinically relevant questions. The database provides a unique insight in to the disease characteristics, presentation trends, staging investigations and the treatment of men processed through a large single specialist MDT.

The aims of the thesis will follow the pathway of a patient through from diagnosis to treatment and are as follows:

1. Interrogation of the EPC MDT database, with the specific aims to:
    a. Assess the data quality of the EPC database
    b. Assess patient capture rates post 2014 following the introduction of the National Prostate Cancer Audit (NPCA) in Wales.
    c. Present an overview of the data recorded on the EPC database.
    d. Assess trends in symptoms at presentation and their relationship on disease stage and the primary treatment undertaken in all cases captured by the EPC MDT over a 20-year period.
    e. Assess the impact of family history on disease stage at presentation and the primary treatment undertaken in all cases captured by the EPC MDT over a 20-year period.
    f. Assess changes in primary treatment patterns over the 20-year period of the EPC MDT and compare with national figures.

2. Review the utilisation of bone scan staging, with the specific aims to:
    a. Review bone scan positivity rates in the EPC MDT cohort.
    b. Determine the threshold for requesting a bone scan in newly diagnosed intermediate risk localised prostate cancer patients.

3. Review the outcomes of men undergoing radical prostatectomy as a primary treatment and assess if the changes in MRI technology and protocols have effected upstaging rates. The specific aims are:
    a. Create a radical prostatectomy dataset created from the EPC MDT database
        i. Report on the disease characteristics and staging results of all men undergoing RP as a primary treatment following EPC MDT.

ii. Compare the pre-operative staging and grading parameters with the prostatectomy pathology.
iii. Assess predictive markers of biochemical recurrence.

b. Assess the accuracy of MRI staging.

Compare the staging accuracy of MRI over the time of EPC MDT and effect that different MRI technique and timing has had on:

i. The correlation between a positive MRI (detectable lesion) and different associated prognostic features such as Gleason score, clinical stage, PSA etc.
ii. The effect of upstaging after radical prostatectomy.

4. Review the outcomes of men on a deferred treatment strategy for localised prostate cancer, with the specific aims to:
    a. Assess the outcome of all patients enrolled on an active monitoring or surveillance program.
    b. Assess the outcomes of introducing protocol re-staging in a cohort of clinically stable active monitoring patients – defined as Restaging Group 1.
    c. Compare the outcomes of restaging in Restaging group 1 (protocol re-staging in a stable cohort of AM patients) with patients having both:
        i. Clinical change or triggered re-staging - defined as Restaging Group 2,
        and
        ii. Protocol restaging as part of active surveillance - defined as Restaging Group 3
    d. Assess the use of MRI in restaging and its usefulness in the pathway.

Chapter 2. The Early Prostate Cancer MDT – a 20-year experience of a single centre specialist MDT – results from a prospectively collected database

2.1 Introduction

2.1.1 The Early Prostate Cancer (EPC) MDT

The concept of an MDT meeting was developed to bring together expert opinions from different clinicians within the same field of expertise to agree on the optimum treatment strategy for each individual patient. It is now the standard of care for cancer management within UK practice and has been shown to improve cancers outcomes (Kesson et al., 2012).

A specialist MDT was established at the University Hospital of Wales, Cardiff, in February 1997 with the aim of discussing all new cases of prostate cancer that were suitable for radical treatment. As a result, the MDT was termed the 'Early Prostate Cancer MDT' or 'the EPC MDT' and this term has remained despite evolving in to its current form where the aim is to discuss all new cases of prostate cancer. Other existing prostate cancer cases are also discussed when management decisions are complex and require discussion. From its inception, there has been an aim to prospectively record all new cases discussed on an electronic database. This has led to the creation of an extremely large cohort of patients managed by the many of the same clinicians over a 20-year period and represents a unique insight in to presentation trends, as well as the results of staging investigations and the primary treatment undertaken.

The EPC MDT is comprised of urologists, an expert uro-pathologist, a radiologist, an MDT coordinator from the hospital cancer service department and specialist uro-oncology nursing staff. The composition has remained constant throughout and so have many of the key team members.

Data collection has focused on the presenting disease characteristics and planned primary treatment. There have three amendments to the data collection pro-forma over the period assessed and these reflect changing practice and requirements of the MDT. However, staging protocols have not changed significantly with all patients suitable for radical treatment having an MRI scan at diagnosis and isotope bone scan staging. This level of staging at time of introduction was not routine practice within the UK and probably remains the case. We therefore believe that the database of EPC patients represents a unique insight in the evolution or presentation and management of patients over a 20-year period in a large tertiary referral UK centre where staging protocols have remained largely uniform.

This chapter will interrogate the EPC MDT dataset. Specifically, I will focus on the assessing quality of data to determine its accuracy and its suitability to answer clinically relevant questions addressed later in this thesis. This chapter will provide an overview of the EPC dataset. It will also pay attention to the impact that symptoms and family history have on presenting disease characteristics and how they may influence treatment choices. Also, as discussed previously there is an increasing awareness to avoid overtreatment of low risk disease and under treatment of high risk disease. I will assess how treatment rates in a contemporary UK sMDT have changed over a 20-year period.

It must be acknowledged that some of the aims within this chapter will be subject to bias in data collection as prior to 2014 the EPC MDT was not designed to capture all new cases of prostate cancer within the health board. Therefore, it must be remembered that any conclusions made in this chapter relate to cases discussed at a specialist MDT within an evolving case load and are not inclusive of all new cases of prostate cancer within the health board over a 20-year period.

2.2 Aims

The specific aims of this chapter were:

1. Assess the data quality of the EPC database

2. Assess patient capture rates post 2014 following the introduction of the National Prostate Cancer Audit (NPCA) in Wales.
3. Present an overview of the data recorded on the EPC database
4. Assess trends in symptoms at presentation and their relationship on disease stage and the primary treatment undertaken in all cases captured by the EPC MDT over a 20-year period.
5. Assess the impact of family history on disease stage at presentation and the primary treatment undertaken in all cases captured by the EPC MDT over a 20-year period.
6. Assess changes in primary treatment patterns over the 20-year period of the EPC MDT and compare with national figures.

2.3 Methods

2.3.1 Service evaluation approval

The study was granted approval by the service improvement department within the surgical department in UHW, Cardiff. Patients were also requested to consent at the time of their first appointment, following MDT discussion, for their presenting disease statistics to be stored on the database.

2.3.2 Patient population

As mentioned in the early days of data collection only selected patients with newly diagnosed prostate cancer were discussed at the EPC specialist MDT and it was often only those that were suitable for radical treatment. Other cases of new diagnosis prostate cancer not suitable for radical treatment may have been discussed at a local MDT rather than the specialist EPC MDT.

Over the 20 years of data collection, numbers have increased as patient care is streamlined though a single MDT with the mandate that all new diagnoses be discussed. The most significant change came in 2014 when data collection for the EPC MDT was changed to mirror the data required for the upcoming data collection for the National Prostate Cancer Audit. It was this move that led to a big drive to

discuss all newly diagnosed prostate cancer patients within the local Health Board regardless of stage and patient fitness in a single specialist MDT and one which continues.

The significant majority of patients that are discussed at the EPC MDT will be new diagnosis patients from within the catchment area of the Health Board. However, there are a small subset of patients that are referred by a neighbouring health board, Cwm Taf, that are also discussed at the EPC MDT. These are patients that have been referred for consideration of radical prostatectomy and are subsequently reviewed at the MDT prior to review in an outpatient clinic.

2.3.3 Data collection and amalgamation of different data sets

Data capture for analysis was from February 1st, 1997 to January 31st, 2017.

All data was collected on pre-designed data collection sheets. Data was inputted at two different time points, firstly at the time of discussion in the MDT and secondly after review and discussion with the patient when the treatment plan has been determined in an outpatient clinic. All data was recorded by clinicians.

There have been two changes to the data collection sheets over time, i.e., three different forms have been used. The latest change was in 2014 and was introduced to enable data collection to match the required data items for the National Prostate Cancer Audit (NPCA) which started in Wales in April 2015.

The first data collection sheet used was between 1997 and 2002 (Figure 2.1). It was not coded and relied on freehand descriptive input. The first amendment and subsequent creation of the second datasheet (Figure 2.2) introduced coded descriptions and this was used from 2002 until 2014. The second and most recent amendment to create the third datasheet (Figure 2.3) was done to increase the number of data items recorded to bring it in line with the NPCA dataset. This datasheet has been used since April 2014 and is still currently in use.

At the time of review the data had been recorded on two separate excel databases, one pre-April 2014 and the other post-April 2014. In order to analyse, the data sets were amalgamated to introduce uniformity across data items.

An overview of each data item recorded and amendments made when amalgamating data sets is recorded as follows;

1. *Patient demographics*
    a. Recorded throughout in the same format.
2. *Referral Hospital* –
    a. Recorded throughout in the same format
3. *Referral Doctor*
    a. Recorded throughout.
    b. Coding changed in 2014 with addition of different consultants.
4. *PSA at diagnosis*
    a. Recorded throughout in the same format (ng/ml)
5. *Presentation* – how the patient presented.
    a. Recorded throughout.
    b. One addition in 2014 with the addition of *symptoms due to metastases* to correspond to NPCA dataset
6. *TURP* - if patient presented following TURP this documents the percentage of positive chips involved.
    a. Recorded throughout in the same format (%).
7. *Family History*
    a. Recorded throughout in the same format.
8. *ASA grade*
    a. New addition in 2014 to correlate with NPCA dataset.
9. *Performance score*
    a. New addition in 2014 to correlate with NPCA dataset.
10. *Referral clinical T stage*
    a. Recorded throughout.
    b. Change in 2014 to include stage T2c.

11. Referral Gleason

a. Recorded throughout in the same format.

12. EPC clinical T stage

a. Recorded throughout.

b. Change in 2014 to include stage T2c

13. Random TRUS biopsy

a. Recorded throughout.

b. Change to coding in 2014 to include saturation TRUS biopsy.

14. Perineal biopsy

a. New addition in 2014 to correlate with the NPCA dataset.

15. Additional targeted biopsy

a. Recorded throughout in the same format.

16. EPC Gleason

a. Recorded throughout in the same format.

17. Tertiary Gleason

a. New addition in 2014 to correlate with NPCA dataset.

18. Core features

a. New addition in 2014 to correlate with NPCA dataset.

19. Number of positive cores and total number of cores taken

a. Recorded throughout in the same format.

20. Maximum positive core length

a. Recorded throughout in the same format.

21. Total length of core containing maximum tumour length

a. New addition in 2014 to correlate with the NPCA dataset

22. Bone scan

a. Recorded throughout in the same format.

23. Further bone imaging

a. Recorded throughout in the same format.

24. MRI timing

a. New addition in 2014 to correlate with NPCA dataset.

25. MRI T stage

a. Recorded throughout.

b. Change in 2014 to include stage T2c

26. MRI N stage

a. Recorded throughout in the same format

27. Further biopsy investigation required before final stage

a. New addition in 2014

28. Final stage or Consensus stage

a. Final stage was used until 2014 when this was replaced with consensus stage. The recording of final stage up until 2014 was not as specific as the updated consensus stage. This considers the clinical and MRI stage to provide an agreed TNM stage at the time of MDT.

29. D'Amico risk classification

a. New addition in 2014.

30. Treatment intent

a. New addition in 2014.

31. Patient choice or Planned treatment

a. Recorded up until 2014 and then changed to planned treatment.

32. Treatment undertaken

a. Recorded throughout.

b. Changes in 2014 to add additional treatments and recoding of some treatments.

33. Staging node sampling

a. Recorded up until 2014.

34. Androgen deprivation

a. New addition in 2014.

35. Other therapies

a. New addition in 2014.

36. Trial patient

a. New addition in 2014.

37. Data authority signed

a. New addition in 2014.

2.3.4 Data quality assurance

Prior to analysis a series of measures were taken to ensure accuracy of data. All duplicates were identified and removed. All pathology data on the TRUS biopsy result was reviewed and checked for accuracy against documented reports on the hospital reporting system. Missing items were filled in. The documented treatment undertaken was also verified with actual the actual treatment received and this was used as the marker of data quality.

Patient capture at MDT was also assessed prior to the start of data collection for the NPCA and compared with the local cancer service records and the national data sets.

2.3.5 National Prostate Cancer Audit

The National Prostate Cancer Audit commissioned through HQIP was set up in 2014 in England to capture all new prostate cancer cases. The overriding aims of the audit were to assess (NPCA., 2017);

- Service delivery and organisation of care in England and Wales.
- The characteristics of patients newly diagnosed with prostate cancer.
- The diagnostic and staging process and planning of initial treatment.
- The initial treatments that men received.
- The experiences of men receiving care and their health outcomes 18 months after diagnosis
- Overall and disease-free survival rates

Data collection is mandatory and is the responsibility of individual Health Boards in Wales to comply. Data collection in Wales started a year later than in England in April 2015. Prior to this a year of data collection running from April 1^{st,} 2014 to April 2015 was carried out in UHW, Cardiff, as a pilot to ensure data collection was feasible and robust. As part of the project team for the NPCA and NPCA Clinical Research Fellow for Wales I ensured data capture was accurate and felt the introduction of the NPCA within Wales has had a major impact in ensuring data collection at MDT was improved.

2.3.6 Data analysis

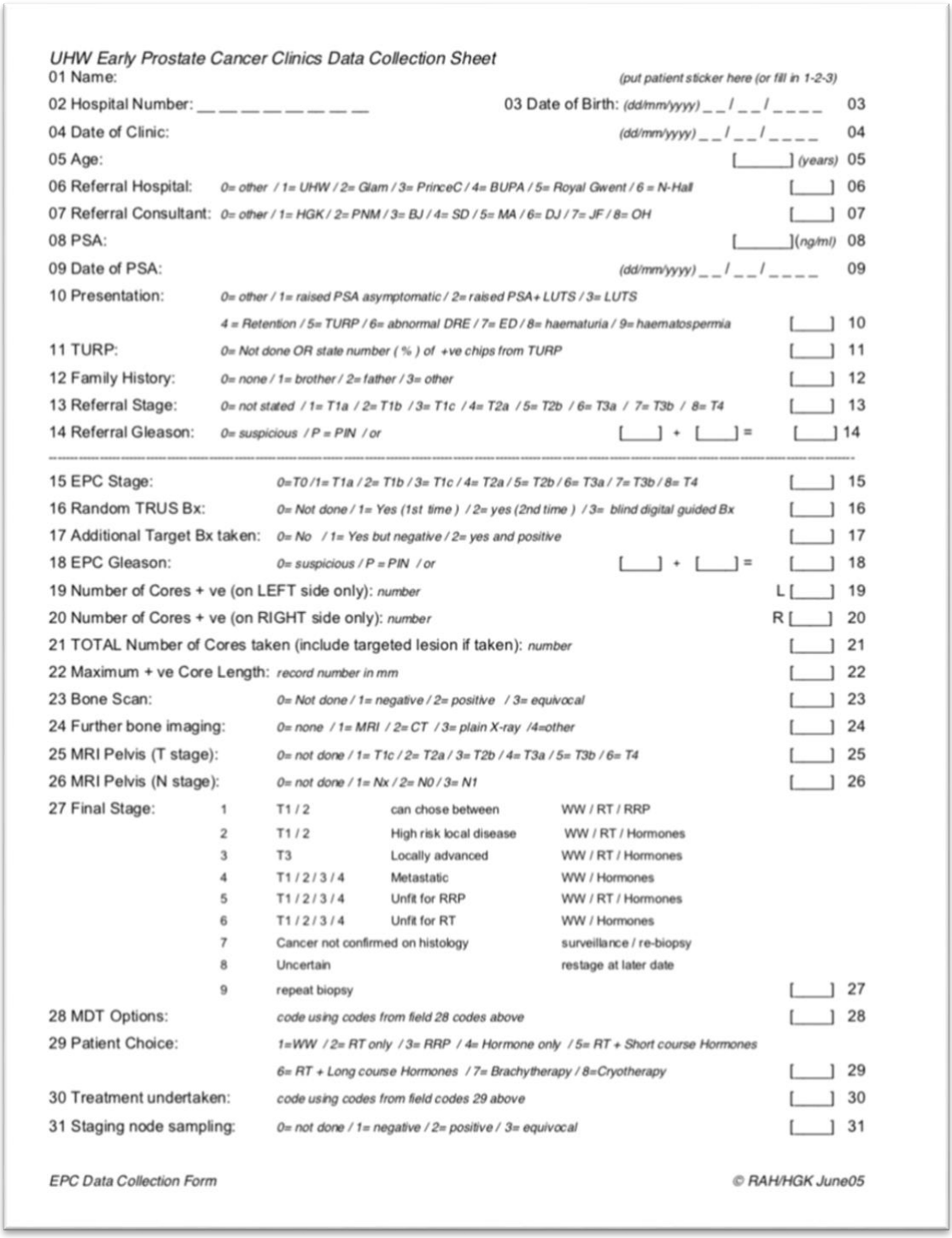
The initial datasets were recorded and amalgamated using Microsoft Excel. The final dataset was then transferred to IBM SPSS version 23 where all statistical analysis was performed.

Chi square test and multi-variate Poisson regression was used to identify factors independently associated with symptomatic presentation and those with family history.

CARDIFF EARLY PROSTATE CANCER CLINIC

	Date of clinic
Name	Hospital Number
Date of Birth	Age at Presentation
Referring Hospital	Referring Consultant
Referral Stage	EPC Stage
PSA	Date of PSA
Presentation	Family History
Co morbidity	
Referral Grade	EPC Grade
TRUS Bx of Lesion	TRUS Random BX
Bone Scan	Further Bone Investigations
Lesion Bx +ve	Number of cores +ve (Left)
Number of Cores +ve (Right)	Number of Cores +ve (Total)
Maximum +ve Core Length	Associated PIN
MRI Pelvis	CT Pelvis
MRI Endorectal	
Pre EPC Recommendation	EPC Options
Patient Choice	Treatment Undertaken
Watchful Wait	Radiotherapy
Neoadjavant Radiotherapy	Hormones
Open Node Sampling	RRP Frozen Nodes
RRP Nerve Sparing	RRP Blood Transfusion
Date of Operation	RRP Side Effects

Figure 2.1. EPC MDT data collection sheet 1. Used from 1997 to 2002.



UHW Early Prostate Cancer Clinics Data Collection Sheet

01 Name: *(put patient sticker here (or fill in 1-2-3)*

02 Hospital Number: __ __ __ __ __ __ __ __ 03 Date of Birth: *(dd/mm/yyyy)* _ _ / _ _ / _ _ _ _ 03

04 Date of Clinic: *(dd/mm/yyyy)* _ _ / _ _ / _ _ _ _ 04

05 Age: [_____] *(years)* 05

06 Referral Hospital: *0= other / 1= UHW / 2= Glam / 3= PrinceC / 4= BUPA / 5= Royal Gwent / 6 = N-Hall* [____] 06

07 Referral Consultant: *0= other / 1= HGK / 2= PNM / 3= BJ / 4= SD / 5= MA / 6= DJ / 7= JF / 8= OH* [____] 07

08 PSA: [_____](*ng/ml*) 08

09 Date of PSA: *(dd/mm/yyyy)* _ _ / _ _ / _ _ _ _ 09

10 Presentation: *0= other / 1= raised PSA asymptomatic / 2= raised PSA+ LUTS / 3= LUTS*
4 = Retention / 5= TURP / 6= abnormal DRE / 7= ED / 8= haematuria / 9= haematospermia [____] 10

11 TURP: *0= Not done OR state number (%) of +ve chips from TURP* [____] 11

12 Family History: *0= none / 1= brother / 2= father / 3= other* [____] 12

13 Referral Stage: *0= not stated / 1= T1a / 2= T1b / 3= T1c / 4= T2a / 5= T2b / 6= T3a / 7= T3b / 8= T4* [____] 13

14 Referral Gleason: *0= suspicious / P = PIN / or* [____] + [____] = [____] 14

---

15 EPC Stage: *0=T0 /1= T1a / 2= T1b / 3= T1c / 4= T2a / 5= T2b / 6= T3a / 7= T3b / 8= T4* [____] 15

16 Random TRUS Bx: *0= Not done / 1= Yes (1st time) / 2= yes (2nd time) / 3= blind digital guided Bx* [____] 16

17 Additional Target Bx taken: *0= No / 1= Yes but negative / 2= yes and positive* [____] 17

18 EPC Gleason: *0= suspicious / P = PIN / or* [____] + [____] = [____] 18

19 Number of Cores + ve (on LEFT side only): *number* L [____] 19

20 Number of Cores + ve (on RIGHT side only): *number* R [____] 20

21 TOTAL Number of Cores taken (include targeted lesion if taken): *number* [____] 21

22 Maximum + ve Core Length: *record number in mm* [____] 22

23 Bone Scan: *0= Not done / 1= negative / 2= positive / 3= equivocal* [____] 23

24 Further bone imaging: *0= none / 1= MRI / 2= CT / 3= plain X-ray /4=other* [____] 24

25 MRI Pelvis (T stage): *0= not done / 1= T1c / 2= T2a / 3= T2b / 4= T3a / 5= T3b / 6= T4* [____] 25

26 MRI Pelvis (N stage): *0= not done / 1= Nx / 2= N0 / 3= N1* [____] 26

27 Final Stage:

1	T1 / 2	can chose between	WW / RT / RRP
2	T1 / 2	High risk local disease	WW / RT / Hormones
3	T3	Locally advanced	WW / RT / Hormones
4	T1 / 2 / 3 / 4	Metastatic	WW / Hormones
5	T1 / 2 / 3 / 4	Unfit for RRP	WW / RT / Hormones
6	T1 / 2 / 3 / 4	Unfit for RT	WW / Hormones
7	Cancer not confirmed on histology		surveillance / re-biopsy
8	Uncertain		restage at later date
9	repeat biopsy		[____] 27

28 MDT Options: *code using codes from field 28 codes above* [____] 28

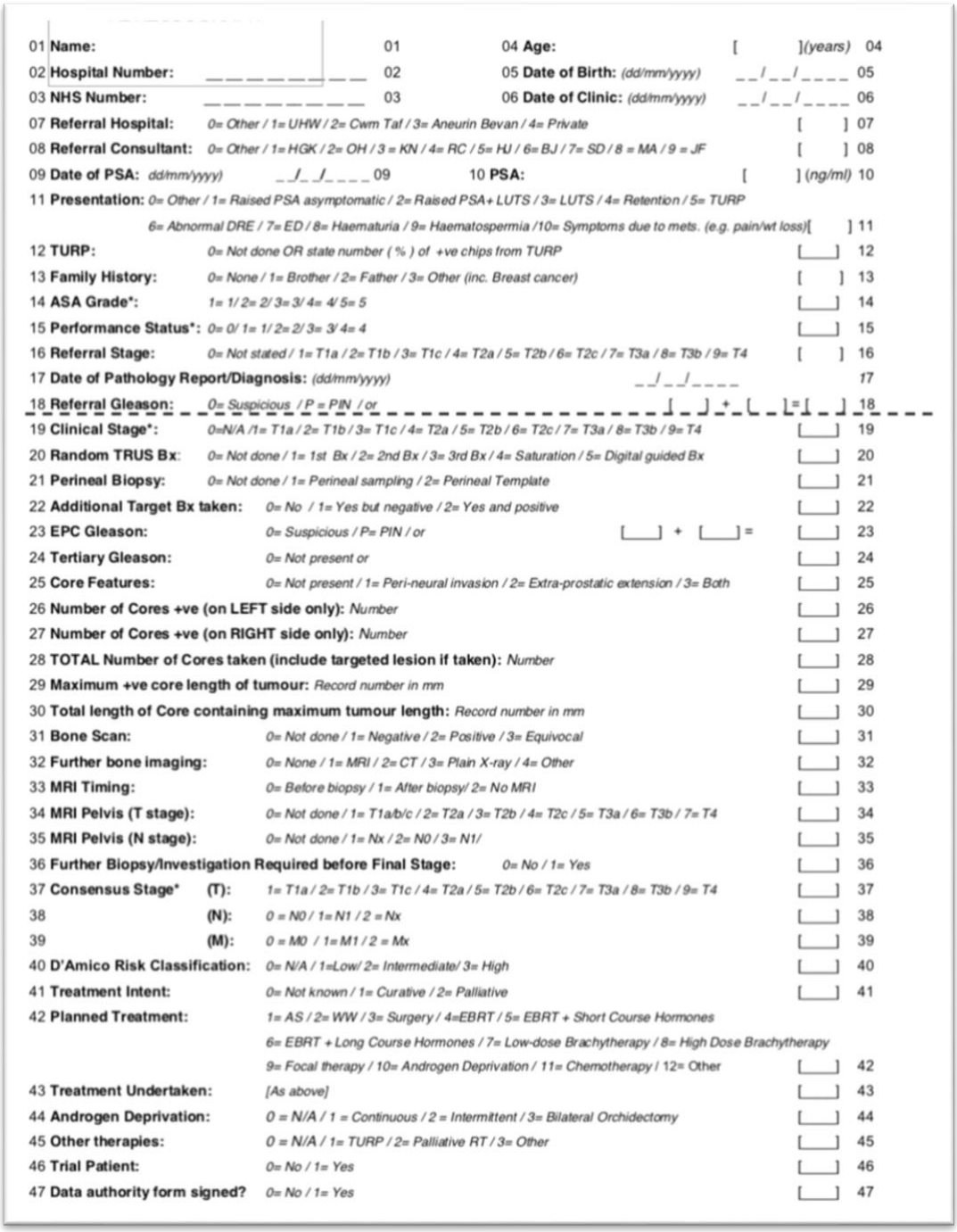
29 Patient Choice: *1=WW / 2= RT only / 3= RRP / 4= Hormone only / 5= RT + Short course Hormones*
6= RT + Long course Hormones / 7= Brachytherapy / 8=Cryotherapy [____] 29

30 Treatment undertaken: *code using codes from field codes 29 above* [____] 30

31 Staging node sampling: *0= not done / 1= negative / 2= positive / 3= equivocal* [____] 31

EPC Data Collection Form *© RAH/HGK June05*

Figure 2.2. EPC MDT data collection sheet 2. Used from 2002 to March 2014.



01 **Name:** 01 04 **Age:** [ ](years) 04

02 **Hospital Number:** __ __ __ __ __ __ __ 02 05 **Date of Birth:** *(dd/mm/yyyy)* __/__/____ 05

03 **NHS Number:** __ __ __ __ __ __ __ __ 03 06 **Date of Clinic:** *(dd/mm/yyyy)* __/__/____ 06

07 **Referral Hospital:** *0= Other / 1= UHW / 2= Cwm Taf / 3= Aneurin Bevan / 4= Private* [ ] 07

08 **Referral Consultant:** *0= Other / 1= HGK / 2= OH / 3 = KN / 4= RC / 5= HJ / 6= BJ / 7= SD / 8 = MA / 9 = JF* [ ] 08

09 **Date of PSA:** *dd/mm/yyyy* __/__/____ 09 10 **PSA:** [ ] *(ng/ml)* 10

11 **Presentation:** *0= Other / 1= Raised PSA asymptomatic / 2= Raised PSA+ LUTS / 3= LUTS / 4= Retention / 5= TURP*
6= Abnormal DRE / 7= ED / 8= Haematuria / 9= Haematospermia /10= Symptoms due to mets. (e.g. pain/wt loss) [ ] 11

12 **TURP:** *0= Not done OR state number (%) of +ve chips from TURP* [___] 12

13 **Family History:** *0= None / 1= Brother / 2= Father / 3= Other (inc. Breast cancer)* [ ] 13

14 **ASA Grade*:** *1= 1/ 2= 2/ 3= 3/ 4= 4/ 5= 5* [___] 14

15 **Performance Status*:** *0= 0/ 1= 1/ 2= 2/ 3= 3/ 4= 4* [___] 15

16 **Referral Stage:** *0= Not stated / 1= T1a / 2= T1b / 3= T1c / 4= T2a / 5= T2b / 6= T2c / 7= T3a / 8= T3b / 9= T4* [ ] 16

17 **Date of Pathology Report/Diagnosis:** *(dd/mm/yyyy)* __/__/____ 17

18 **Referral Gleason:** *0= Suspicious / P = PIN / or* [ ] + [ ] = [ ] 18

19 **Clinical Stage*:** *0=N/A /1= T1a / 2= T1b / 3= T1c / 4= T2a / 5= T2b / 6= T2c / 7= T3a / 8= T3b / 9= T4* [___] 19

20 **Random TRUS Bx:** *0= Not done / 1= 1st Bx / 2= 2nd Bx / 3= 3rd Bx / 4= Saturation / 5= Digital guided Bx* [___] 20

21 **Perineal Biopsy:** *0= Not done / 1= Perineal sampling / 2= Perineal Template* [___] 21

22 **Additional Target Bx taken:** *0= No / 1= Yes but negative / 2= Yes and positive* [___] 22

23 **EPC Gleason:** *0= Suspicious / P= PIN / or* [___] + [___] = [___] 23

24 **Tertiary Gleason:** *0= Not present or* [___] 24

25 **Core Features:** *0= Not present / 1= Peri-neural invasion / 2= Extra-prostatic extension / 3= Both* [___] 25

26 **Number of Cores +ve (on LEFT side only):** *Number* [___] 26

27 **Number of Cores +ve (on RIGHT side only):** *Number* [___] 27

28 **TOTAL Number of Cores taken (include targeted lesion if taken):** *Number* [___] 28

29 **Maximum +ve core length of tumour:** *Record number in mm* [___] 29

30 **Total length of Core containing maximum tumour length:** *Record number in mm* [___] 30

31 **Bone Scan:** *0= Not done / 1= Negative / 2= Positive / 3= Equivocal* [___] 31

32 **Further bone imaging:** *0= None / 1= MRI / 2= CT / 3= Plain X-ray / 4= Other* [___] 32

33 **MRI Timing:** *0= Before biopsy / 1= After biopsy/ 2= No MRI* [___] 33

34 **MRI Pelvis (T stage):** *0= Not done / 1= T1a/b/c / 2= T2a / 3= T2b / 4= T2c / 5= T3a / 6= T3b / 7= T4* [___] 34

35 **MRI Pelvis (N stage):** *0= Not done / 1= Nx / 2= N0 / 3= N1/* [___] 35

36 **Further Biopsy/Investigation Required before Final Stage:** *0= No / 1= Yes* [___] 36

37 **Consensus Stage*** **(T):** *1= T1a / 2= T1b / 3= T1c / 4= T2a / 5= T2b / 6= T2c / 7= T3a / 8= T3b / 9= T4* [___] 37

38 **(N):** *0 = N0 / 1= N1 / 2 = Nx* [___] 38

39 **(M):** *0 = M0 / 1= M1 / 2 = Mx* [___] 39

40 **D'Amico Risk Classification:** *0= N/A / 1=Low/ 2= Intermediate/ 3= High* [___] 40

41 **Treatment Intent:** *0= Not known / 1= Curative / 2= Palliative* [___] 41

42 **Planned Treatment:** *1= AS / 2= WW / 3= Surgery / 4=EBRT / 5= EBRT + Short Course Hormones*
6= EBRT + Long Course Hormones / 7= Low-dose Brachytherapy / 8= High Dose Brachytherapy
9= Focal therapy / 10= Androgen Deprivation / 11= Chemotherapy / 12= Other [___] 42

43 **Treatment Undertaken:** *[As above]* [___] 43

44 **Androgen Deprivation:** *0 = N/A / 1 = Continuous / 2 = Intermittent / 3= Bilateral Orchidectomy* [___] 44

45 **Other therapies:** *0 = N/A / 1= TURP / 2= Palliative RT / 3= Other* [___] 45

46 **Trial Patient:** *0= No / 1= Yes* [___] 46

47 **Data authority form signed?** *0= No / 1= Yes* [___] 47

Figure 2.3. Data collection sheet 3. Used from April 2014 to the present day.

2.4 Results

2.4.1 Aim 1 - Data quality

After the exclusion of duplicates and confirmation of biopsy findings, all cases were assessed. Data quality was defined as the percentage of cases with an accurate recording of the primary treatment undertaken.

3575 new cases of prostate cancer were identified. Incorrect treatment was documented in 178 cases accounting for a 5% error rate. The largest area for error was in the recording of patients who were recorded as on an active surveillance program but were on a watching waiting approach, accounting for just over a quarter (28%) of all mistakes. However, this may reflect a change in terminology rather than incorrect recording (Figure 2.1).

Treatment received	**AS**	**WW**	**RP**	**RT**	**Brachy**	**ADT**	**TOTAL**
Treatment recorded							
AS	N/A	50	24	11	1	3	89
WW	13	N/A	3	16	-	3	35
RP	7	-	N/A	5	-	1	13
EBRT	6	-	4	N/A	-	6	16
Brachy	2	-	1	2	N/A	-	5
ADT	-	-	1	16	-	N/A	17
Focal	-	-	-	-	-	1	1
No record	-	-	1	-	-	1	2
TOTAL	28	50	34	50	1	15	178

Table 2.1. Data quality indicator. Comparison of treatment recorded on the EPC MDT data collection sheet versus the actual treatment undertaken for cases where an error was detected (n=178).

2.4.2 Aim 2 - Accuracy of data capture.

An assessment was made to determine the quality of patient capture at the EPC MDT, i.e., were all new diagnoses being captured and hence, could meaningful comparisons be made.

Three separate databases that should theoretically contain the same patients were compared;

1. Database 1 (DB1) - The EPC MDT database. Generated by clinical referrals
2. Database 2 (DB2) – The hospital cancer services database. Generated by clinical referrals, MDT discussion and pathology reports
3. Database 3 (DB3) – The Welsh national cancer registry data (Canisc). Generated from all the previous data sources.

The period of analysis was between the 1st April 2014 and 1st April 2015 and aimed to mirror the period for the start of the NPCA data collection for England and followed the introduction of the new data collection sheet for the EPC MDT. It was in effect a trial period of data collection for the NPCA data within UHW and was performed to address potential pitfalls in data capture.

The definition for the date of diagnosis did vary between databases and led to discrepancies in number of patients for the defined period (Table 2.2). The date of diagnosis for the EPC database is derived from the date that the TRUS biopsy pathology was reported. However, for hospital cancer services and Canisc the date of diagnosis is taken from the date that the biopsy was taken.

	DB1 - EPC MDT database	**DB2 - Hospital cancer services**	**DB3 - National registry**
No. of patients	320	448	338
Inclusion criteria	Date of pathology report	Date diagnostic biopsy taken	Date diagnostic biopsy taken
No. of patients not on DB1	N/A	52	50
No. of patients need adding to DB1	N/A	31	31

Table 2.2. Table to compare patient capture rates on the EPC MDT database, the hospital cancer service database and the National cancer registry database for men with new diagnosis prostate cancer. Between 1st April 2014 and 1st April 2015.

To account for the discrepancies in patient numbers between each database they were cross-referenced. Where cases were not present on each database the individual case was reviewed. The discrepancies can be accounted for as follows;

1.DB1 – The EPC dataset

The EPC database had 320 patients recorded.

- 37 patients had a biopsy date prior to 1st April 2014 therefore would not have been included on DB2 or DB3
- 19 Patients on DB1 but not on DB2
    - 13 were referrals from peripheral hospital or private
    - 6 were new diagnosis prostate cancer
        - **3 of these were not on DB3**
- 74 patients on DB1 but not on DB3
    - 23 of these are on DB2
    - 51 are not on DB2

2 .DB2 – Hospital cancer service dataset

This database had 448 patients recorded.

- 52 patients were not on the EPC
    - 31 needed adding to EPC database
        - New diagnosis - 22 patients
        - TURP/HoLEP - 5 patients
        - Private patients - 4 RRPs in UHW
    - 9 patients already on EPC MDT database prior to April 2014 (AS re-biopsy or previous RRP)
    - 1 incorrect coding
    - 2 cystectomies with incidental prostate cancer
    - 3 Swansea patients
    - Other 6 patients – logical reason for non-inclusion on EPC database.

3. DB3 – National data registry – Cansic

This database had 338 patients recorded.

- 38 patients on database but not on EPC database between time frame. However, they are all on EPC post 1-4-15.
- 50 patients not on EPC (45 are the same patients as highlighted above by hospital database. 5 additional ones – 4 are private patients with no data and the other was diagnosed in 2009)
    - 31 need adding to EPC database
        - New diagnosis - 22 patients
        - TURP/HoLEP - 5 patients
        - Private patients – 4 RRPs in UHW
    - 7 already on database prior to April 2014 (AS re-biopsy or previous RRP)
    - 1 incorrect coding
    - 2 cystectomies with incidental prostate cancer
    - Other 4 patients – logical reason for non-inclusion on EPC database

In summary:

Data capture for NPCA

There were only three patients that would not have been captured by the hospital cancer services and hence not entered in to the national prostate cancer audit for the pilot year. This equates to an error rate of <1% and represents a robust process for data collection for the NPCA.

Data capture rates for EPC MDT

There were 31 patients detected by both database 2 and 3 that were missing from the EPC database. This equates to a 10% error rate for patient capture on the EPC database.

2.4.3 Aim 3 – An overview of EPC data collection

Number of cases

A total of 3575 cases were discussed. There was a trend of increasing patient numbers over the period with a peak in 2015 of 375 (Figure 2.4). This represents an increasing capture rate of all new diagnoses, particularly post 2014, when NPCA data collection ensured new cases were discussed.

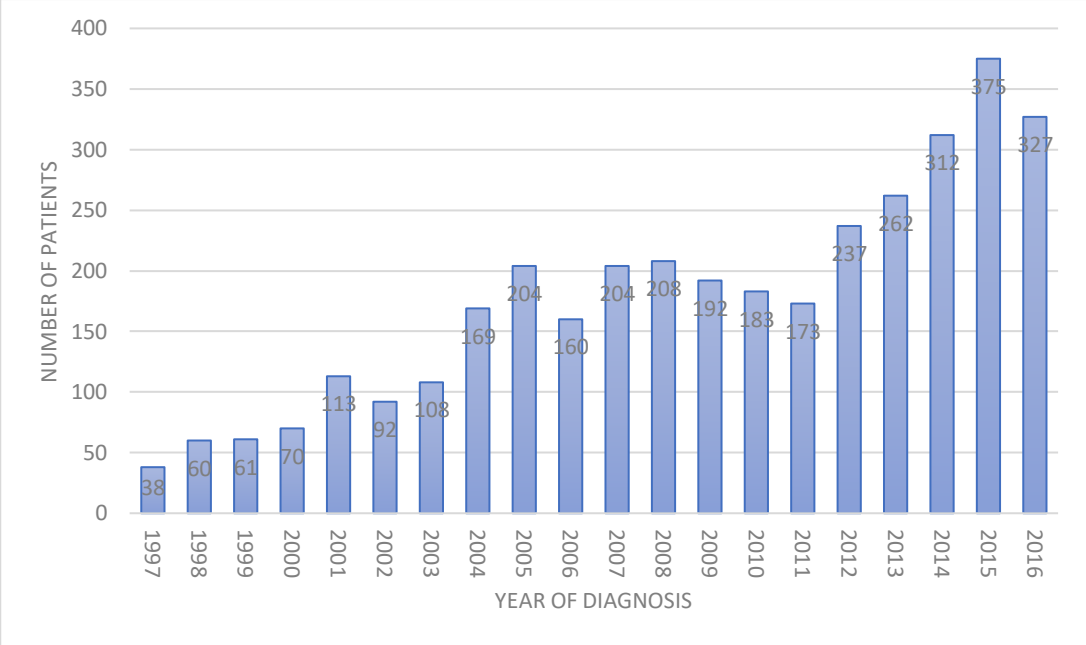


Figure 2.4. Graph showing the number of newly diagnosed patients discussed at EPC MDT per year, 1997-2016 (2017 not included as incomplete year). (N=3575)

Source of referral

76.2% of referrals to the MDT were from within our institution. 13.3% were from Cwm Taf Health Board with the remaining from other sources including private referral. The proportion of external referrals to the MDT has remained very stable over the last 8 years (2009 onwards). Prior to this, 20-40% of cases discussed at the MDT were external referrals. However, when looking at the actual number rather than the proportion one can see that it has not changed dramatically year on year (Figure 2.5).

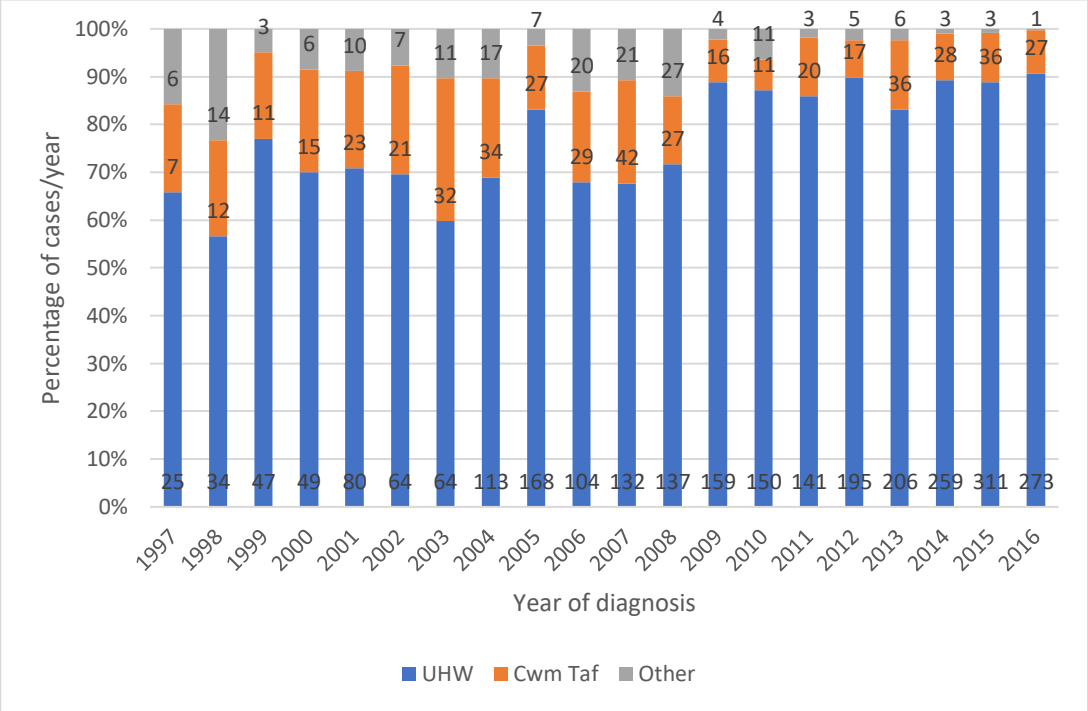


Figure 2.5. Graph to show the source of referral for patients discussed at the EPC MDT by year of presentation. (N=3575)

Age at diagnosis

The mean and median age at diagnosis showed a steady rise from the introduction of the MDT to the present day (Figure 2.6). In 1997, the mean age was 65.2 years old and in 2016 it was 68.5 years. The overall mean was 66.8 with a median of 67 years old (range 39 – 100). The increase in age is most likely to account for the inclusion of all new cases and patients less appropriate for radical treatment. These patients were less likely to have been discussed in the early days of EPC MDT.

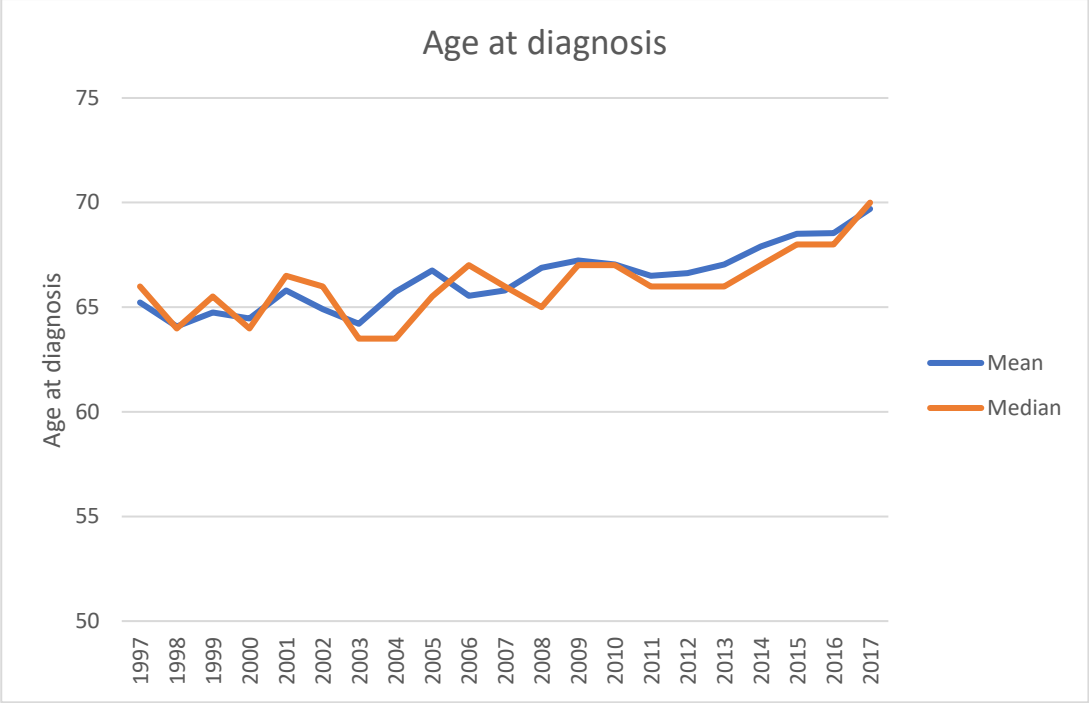


Figure 2.6. Graph to show the mean and median age at diagnosis by year of presentation. (N=3575)

PSA level at diagnosis

The mean PSA at diagnosis varied dramatically year by year but the overall trend was that of an increasing level. During the first three years of the MDT the mean PSA was less than 15ng/ml, however, in 2015 and 2016 the level was greater than 100ng/ml. The median PSA was more consistent over time as one would expect (Figure 2.7). The overall mean PSA was 44.3 and median was 9.2 ng/ml (range 0.2 to 9998ng/ml).

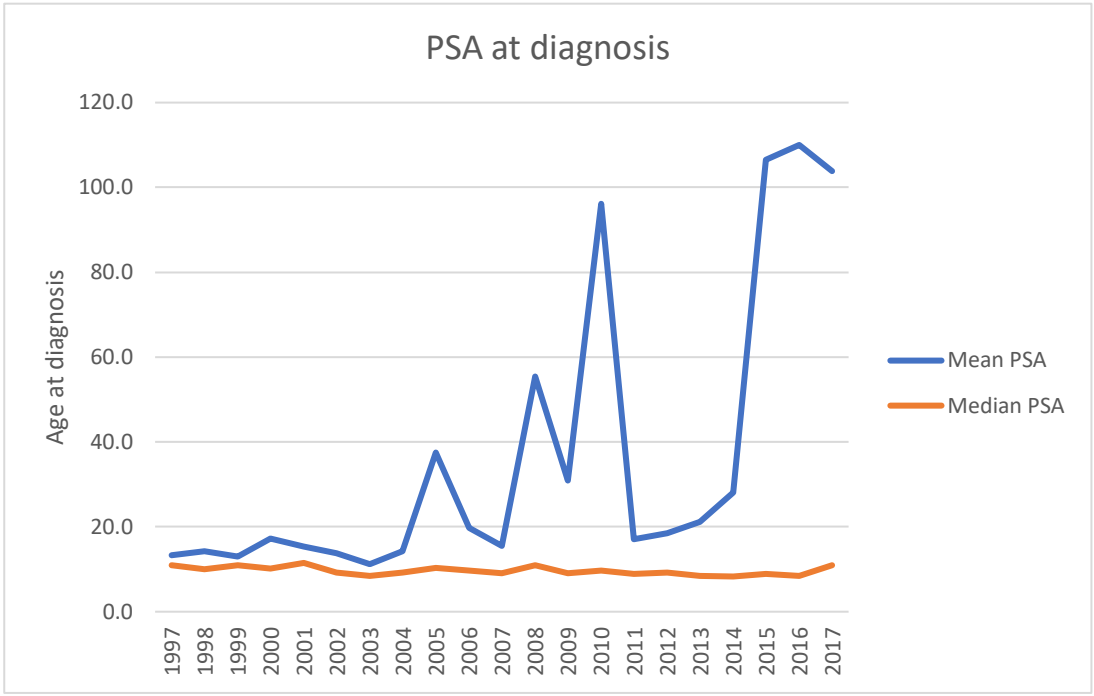


Figure 2.7. Graph to show the mean and median PSA at diagnosis by year of presentation. Large spikes in mean PSA can be accounted for by individuals with very high PSA levels. (N=3575)

Symptoms at diagnosis

There were a similar number of cases presenting with a raised PSA, with and without symptoms, 39.7% and 35.5% respectively. Other symptoms to present with included LUTS alone, urinary retention, haematuria, haematospermia or erectile dysfunction. These combined accounted for 13.4% of presentations. Only 1.4% of patients presented with symptoms of metastases (Table 2.3).

Symptom	Number of cases	Percentage (%)
Asymptomatic raised PSA	1268	35.5
LUTS and raised PSA	1421	39.7
LUTS	206	5.8
Retention	65	1.8
TURP	62	1.7
Haematuria	152	4.3
Haematospermia	38	1.1
Erectile dysfunction	13	0.4
Abnormal DRE	52	1.5
Symptoms of metastases	51	1.4
Other	164	4.6
Not known	83	2.3

Table 2.3. Table to show the range of symptoms that men presented with prior to being diagnosed with prostate cancer. (N=3575)

As a percentage of cases presenting each year, from 1997 to 2002, there was a significant proportion of men presenting with LUTS alone. From 2002 onwards this percentage fell significantly and was replaced by men presenting with a raised PSA and LUTS. From 2003 onwards, there were roughly equal numbers presenting asymptomatic raised PSA and raised PSA with symptoms. The other most notable difference was in men presenting with symptoms of metastases. Almost nobody was discussed at MDT with these symptoms prior to 2014, in 2015 and 2016 these accounted for between 6-7% of cases (Figure 2.8).

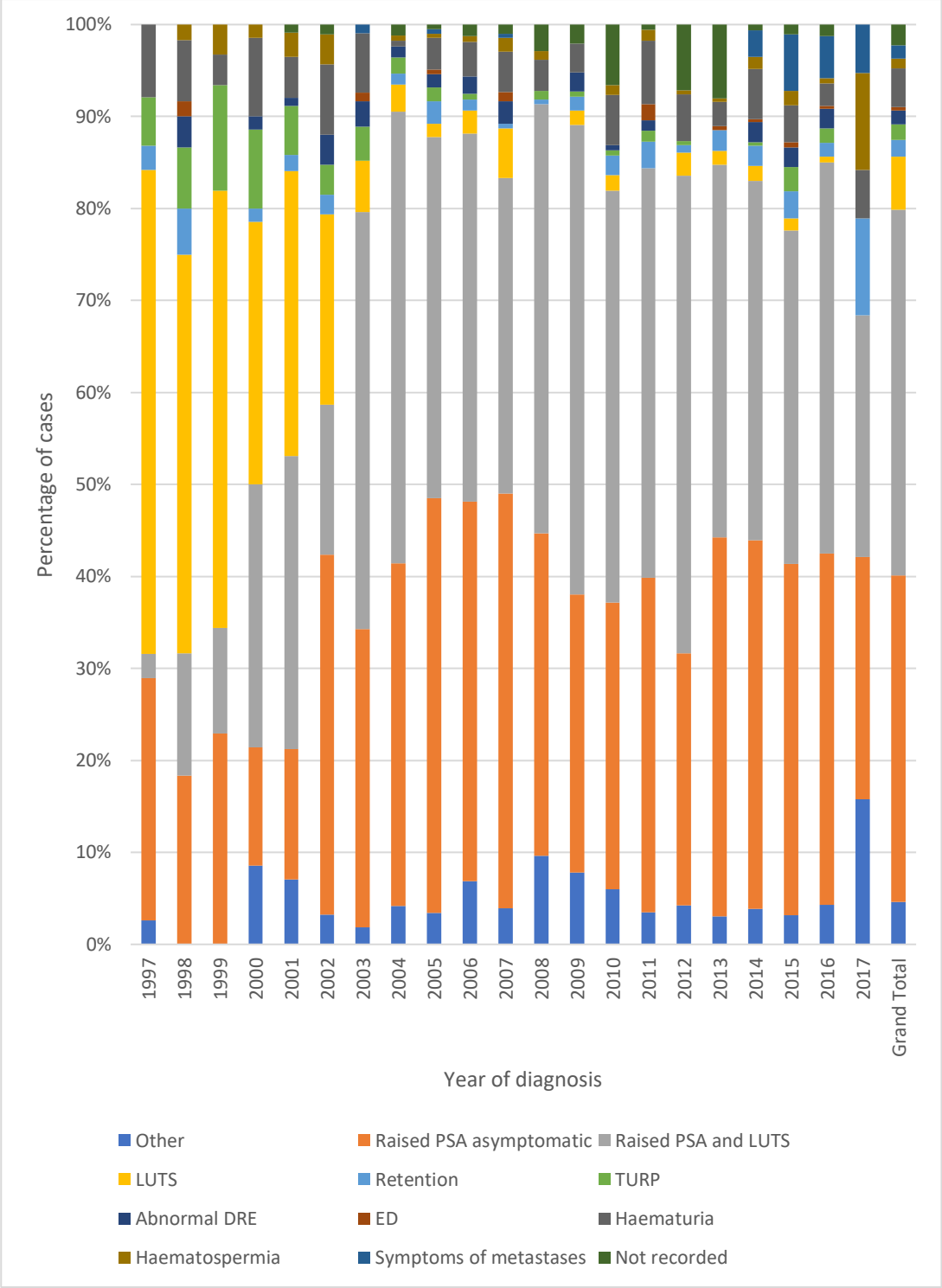


Figure 2.8. Pivot table plot to illustrate the change in presenting symptoms over 20 years of EPC MDT data collection. (N=3575)

Clinical stage at presentation

The clinical T-stage was recorded at the time of referral and again at the time of the outpatient clinic following EPC MDT discussion. The initial referral clinical stage may

have been assessed by one of a variety of clinicians, i.e. general practitioner, nurse specialists, urology registrars or a non-EPC MDT consultant (non uro-oncology sub-specialist). The clinical stage recorded at the EPC MDT is assessed by one of the pelvic oncologists in the department and represents an accurate/expert clinical staging.

Overall, the proportions of documented clinical T-stage appeared to be similar between referral and EPC MDT (Figure 2.9). The only stage that differed dramatically was the number of patients with T2a disease, there appeared to many more patients with T2a at referral stage than were recorded at EPC MDT. However, there were many more patients who did not have their stage recorded at EPC and this may account for this discrepancy.

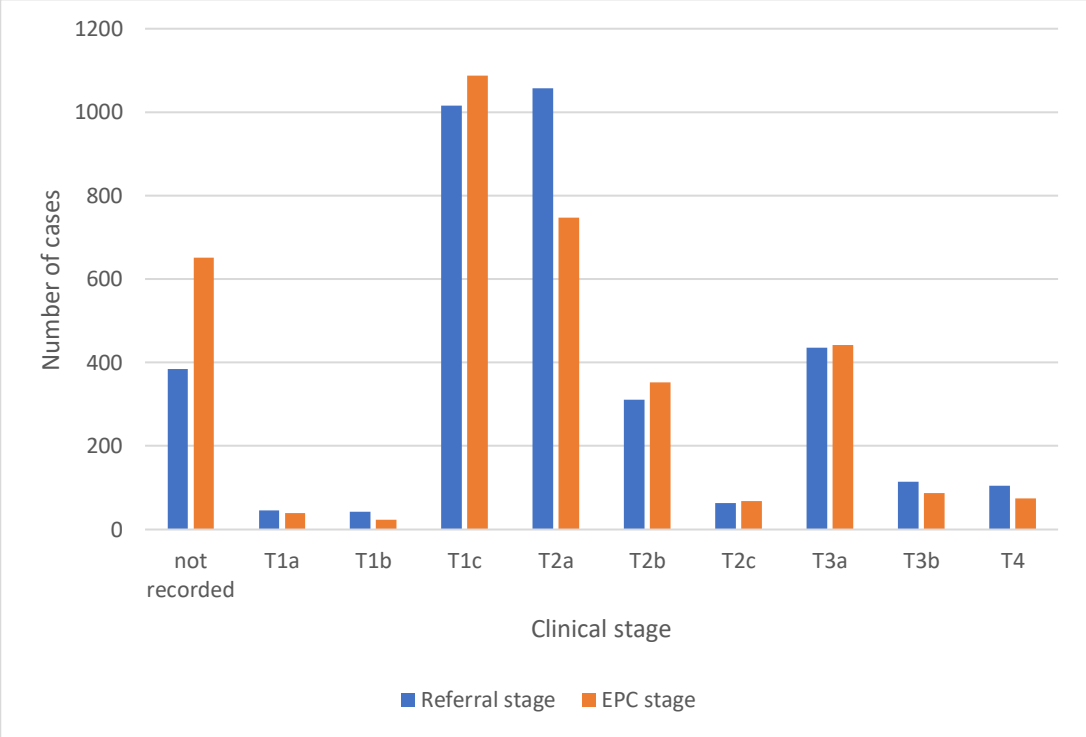


Figure 2.9. Graph showing the overall numbers of clinical T-stage at time of referral to and after assessment at the EPC MDT by a pelvic oncology surgeon. (N=3575)

Comparison of individual referral cT stage and EPC cT stage

Generally, concordance between clinical T-stage at the time of referral and EPC T-stage was poor with rates between 20 to 72.4%. The highest rate of concordance was seen for T1c disease. For T2a disease at referral, there was only 48.8%

concordance with 23.6% upstaged at EPC and 18.2% down-staged, 13.4% were not stated. For higher clinical T-stages, there was again poor concordance and a much higher rate of T stage not being recorded (Table 2.4). This may be a result of clinicians feeling clinical stage was less important to repeat as other diagnostic tests may have already confirmed high risk disease.

	EPC cT-stage										
	N/R	**T1a**	**T1b**	**T1c**	**T2a**	**T2b**	**T2c**	**T3a**	**T3b**	**T4**	**Total**
Referral Stage											
`N/R	23.6% (91)	1.3% (5)	0.3% (1)	29.4% (113)	19% (73)	9.1% (35)	1% (4)	10.9% (42)	3.4% (13)	1.8% (7)	384
T1a	6.7% (3)	40% (18)	2.2% (1)	37.8% (17)	8.9% (4)	2.2% (1)	0	2.2% (1)	0	0	45
T1b	18.6% (8)	0	27.9% (12)	32.6% (14)	11.6% (5)	9.3% (4)	0	0	0	0	43
T1c	7.0% (71)	0.9% (9)	0.2% (2)	72.4% (735)	11.6% (118)	4.4% (45)	1% (10)	2% (20)	0.4% (4)	0.01% (1)	1015
T2a	13.4% (136)	0.6% (6)	0.7% (7)	16.9% (172)	48.8% (497)	11.4% (116)	1.3% (13)	8.7% (89)	1.8% (18)	0.4% (4)	1018
T2b	20.9% (65)	0.3% (1)	0.3% (1)	7.1% (22)	11.3% (35)	43.7% (136)	1% (3)	12.9% (40)	2.6% (8)	0	311
T2c	6.3% (4)	0	0	9.5% (6)	11.1% (7)	3.2% (2)	57.1% (36)	9.5% (6)	1.6% (1)	1.6% (1)	63
T3a	33% (144)	0	0	1.1% (5)	1.6% (7)	3.2% (14)	0.5% (2)	54.4% (237)	4.1% (18)	2.1% (9)	436
T3b	72.2% (83)	0.9% (1)	0	1.7% (2)	0	0	0	5.2% (6)	20% (23)	0	115
T4	44.8% (47)	0	0	1% (1)	1.9% (2)	0	0	1% (1)	1.9% (2)	49.5% (52)	105
Total	652	40	24	1087	748	353	68	442	87	74	3575

Table 2.4. Concordance between clinical T stage at referral stage compared with clinical T-stage at EPC MDT after review by a pelvic oncology surgeon.

Gleason grade at presentation

There was a marked increase in the number of Gleason 6 and 7 disease over the period of the EPC data collection. Over the last ten years of data collection there has been a very similar rise in the number of Gleason 6 and 7 disease. High risk disease

(Gleason >7) numbers were relatively stable over the period, however, numbers have increased over the past 5 years and probably represent an increased capture rate of all new diagnosis cases, including the cases with metastatic disease, that may not have previously discussed at the EPC MDT (Figure 2.10).

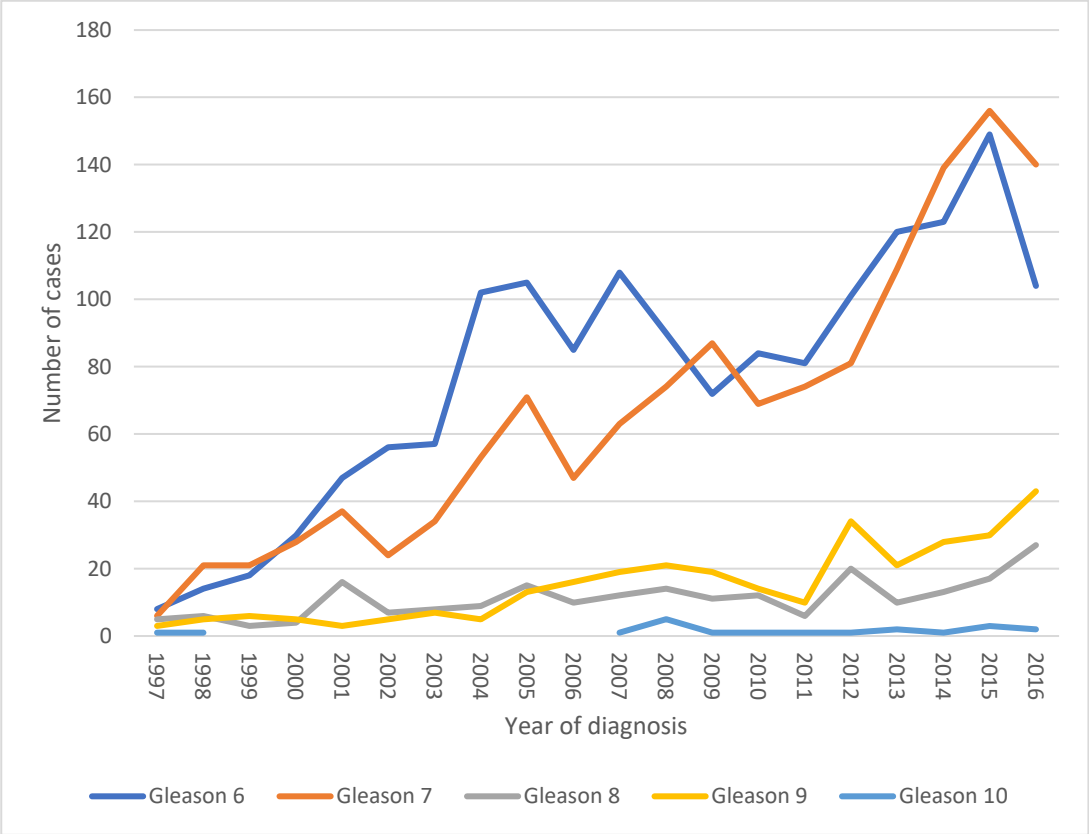


Figure 2.10. Graph showing the overall numbers of Gleason score at diagnosis over the period of EPC data collection, 1997 - 2016. (N=3441)

When reviewing the Gleason score as a percentage of all cases that presented each year there appeared to be a decreasing proportion of Gleason 6 disease compared to higher risk disease. Between 2002 and 2007 the proportion of Gleason 6 disease was between 50-60%, whereas, between 2008 and 2013 the rate was between 40-50% and for the last 3 years the rate was less than 40% (Figure 2.11).

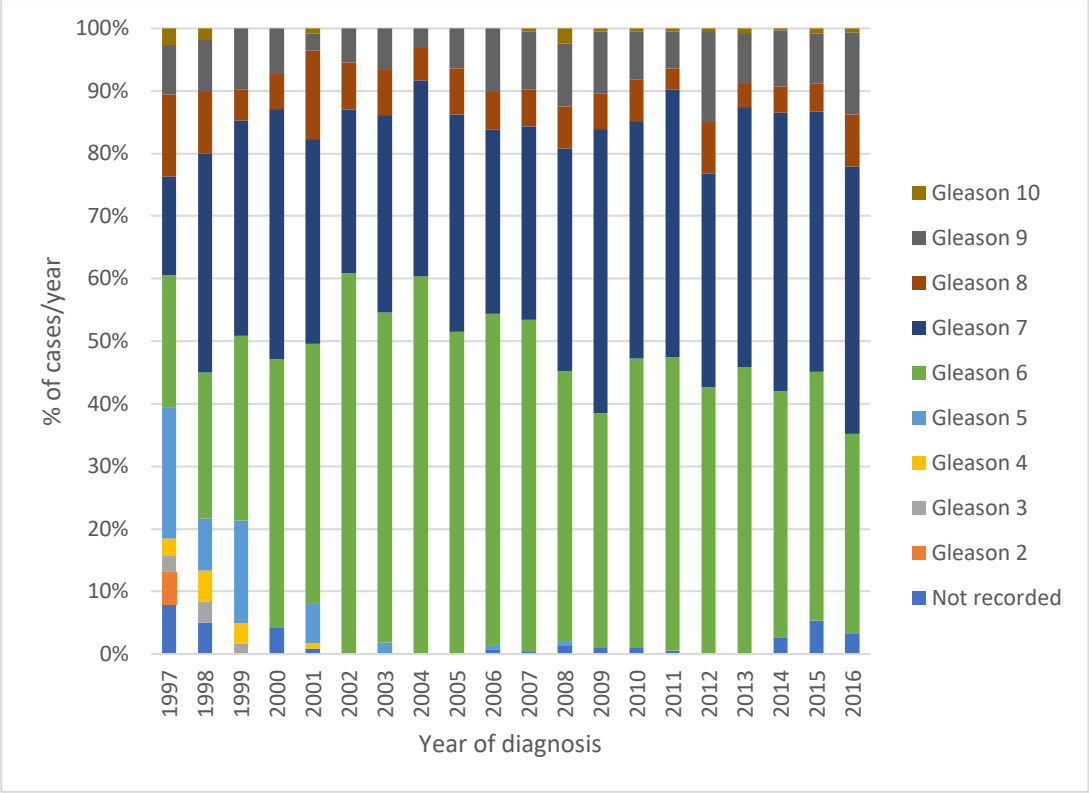


Figure 2.11. Pivot table plot to show the proportions of Gleason disease by year of presentation to EPC MDT, 1997 to 2016. (N=3575)

As for clinical T stage, a comparison was made between the Gleason score recorded at initial diagnosis and the Gleason score after EPC MDT review. Concordance rates were very high across all Gleason scores, >94%, apart from Gleason <6 where rates were 72.1%. As one would expect, all cases that were discordant were upstaged (Table 2.5). This group of Gleason score <6 represent historic practice and it would be interesting to review this cohort and rescore them with contemporary classification to see how it would change.

Overall, given the high rate of concordance with Gleason scores one could argue the benefit of review at MDT as the Gleason scores are already peer reviewed prior to publishing a formal report as set out by ISUP guidelines.

	EPC Gleason						
	<6	**6**	**7**	**8**	**9**	**10**	**Total**
Referral Stage							
<6	72.1% (44)	26.2% (16)	1.6% (1)	0	0	0	61
6	0.2% (3)	96.9% (1511)	2.8% (44)	0.1% (2)	0	0	1560
7	0	1.7% (22)	97.2% (1281)	0.8% (11)	0.3% (4)	0	1318
8	0	0	4.2% (9)	94.4% (204)	1.4% (3)	0	216
9	0	0	6	2.6% (8)	95.5% (299)	0	313
10	0	0	0	0	0	100% (18)	18
Total	47	1549	1341	225	306	18	3486

Table 2.5. Concordance between Gleason score at referral compared with Gleason score recorded after review at EPC MDT. (N=3486)

Number of cores

The current standard for TRUS biopsy of the prostate is a 10-12 needle cores. The database was reviewed and showed a median number of 10 cores taken with a range from 0 to 22 (0 represents a clinical diagnosis of CaP). Median number of positive cores was 3 with a mean of 4.1. Median percentage of positive cores was 40% with a mean of 46.6% (Table 2.6).

	No. of cores taken	**No. of positive cores**	**% of positive cores**
N (missing data)	3411 (164)	3368 (207)	3366 (209)
Mean	9.1	4.1	46.6
Median	10	3	40
Range	0-22	1-14	0-100

Table 2.6. Table showing numbers of cores taken at TRUS biopsy including positivity rates.

Staging investigations

In addition to TRUS biopsy of the prostate, patients also received MRI and isotope bone scans as part of staging.

MRI usage

In total, 80.2% (2813/3506) had an MRI after their TRUS biopsy, 12.1% (424/3506) were before the biopsy and 7.7% (269/3506) did not have an MRI. No information was available for 69 cases (Figure 2.12).

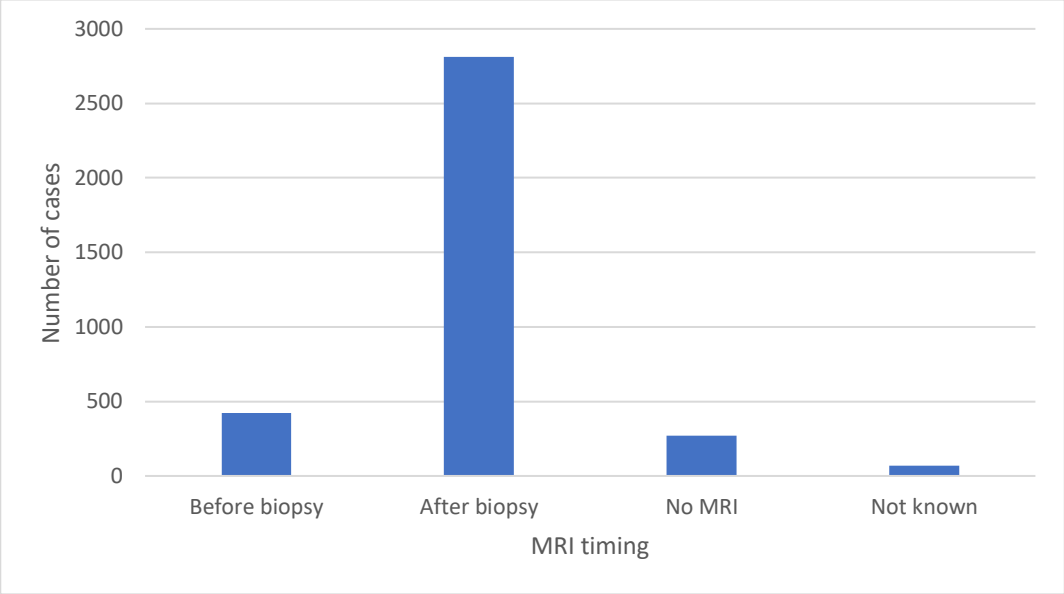


Figure 2.12. Graph showing the timing of MRI compared to TRUS biopsy. (N=3575)

The uptake of pre-biopsy MRI scan increased significantly in the last 3 years of data collection, with 88.6% of all those patients having an MRI scan having it before their biopsy in 2016 (Figure 2.13).

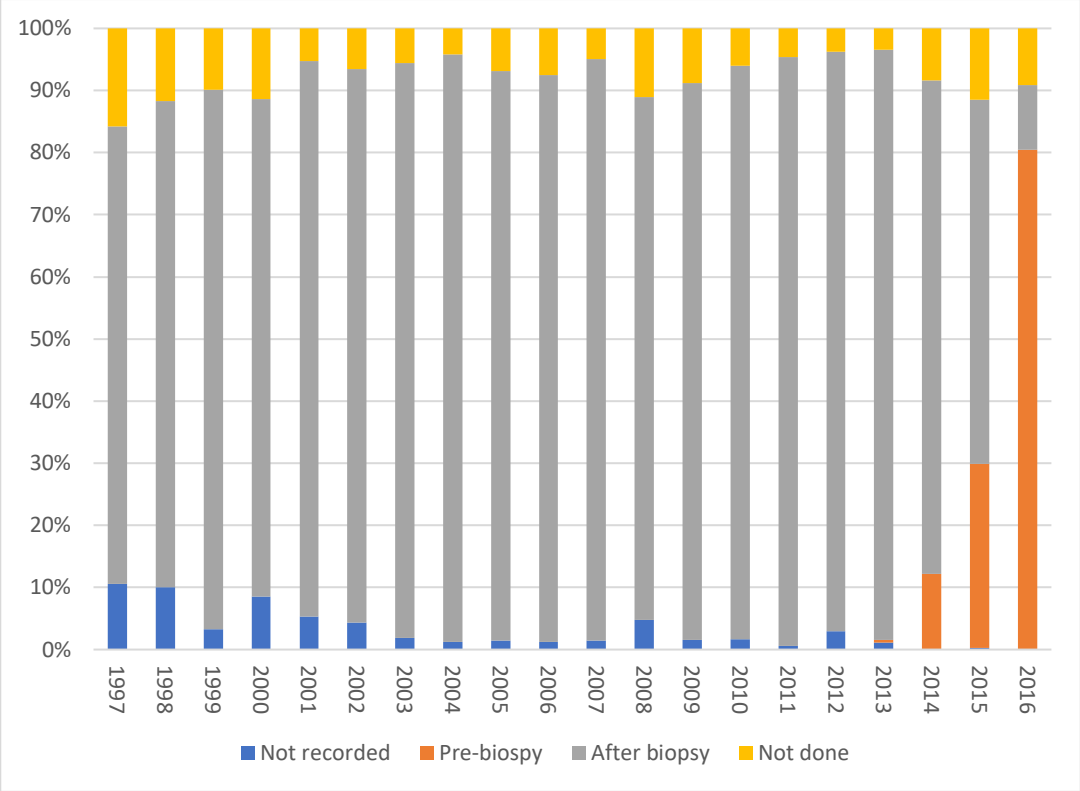


Figure 2.13. Pivot table plot showing the percentage of patients having MRI scans and the timing in relation to their TRUS biopsy of the prostate. (N=3575)

More detailed analysis of the outcomes of MRI will be presented in chapter 4.

Bone scan

In total, 68.7% (2423/3526) had a negative bone scan, 24.0% (845/3526) did not have a scan, 5.4% (192/3526) were positive, 1.9% (66/3526) were equivocal. No record was present for 49 cases.

Over the period of data collection, there was a marked change in the use of isotope bone scans. In more recent years there was a significant increase in the number of patients that did not have a bone scan as part of staging. This led to a marked reduction in the proportion of negative scans (Figure 2.14). There was also an increased rate of positive scans which can probably be accounted to increased number of patients with metastatic disease discussed at EPC MDT.

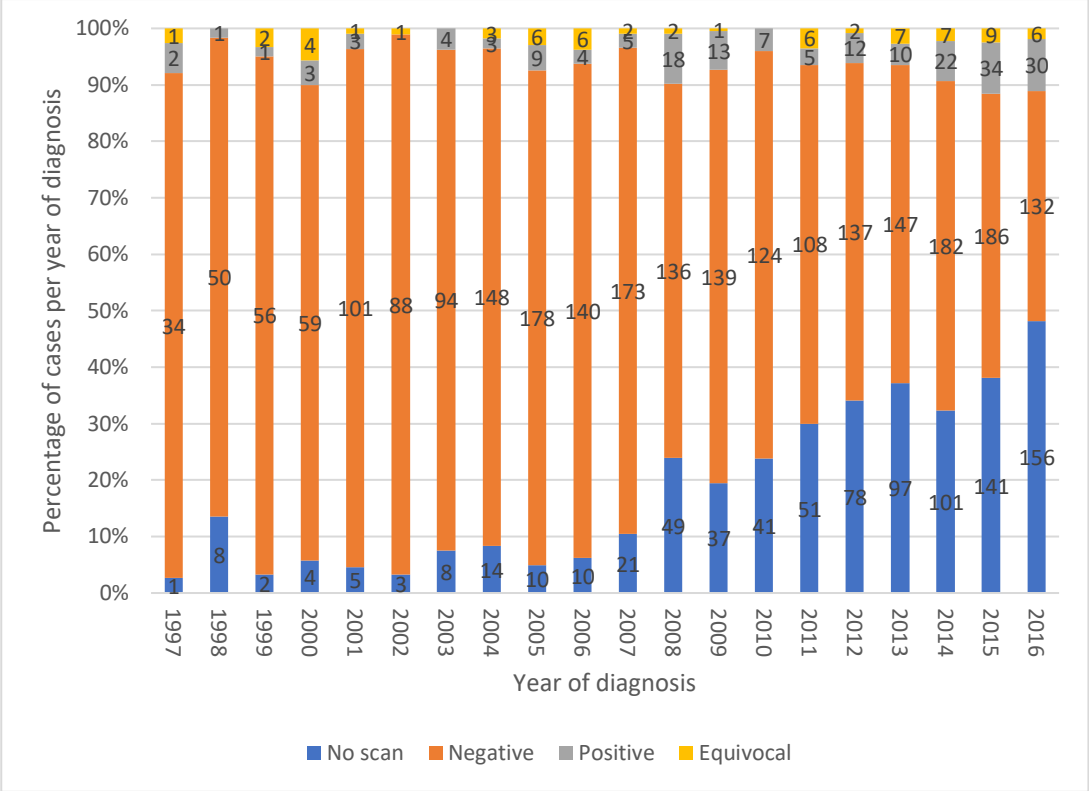


Figure 2.14. Pivot table plot to show the outcomes of staging isotope bone scans over the period of EPC MDT data collection. (N=3575)

More detailed analysis of the outcomes of isotope bone scans will be presented in chapter 3.

D'Amico risk stratification at diagnosis

Overall, 27.7% (990/3575) of cases were D'Amico low-risk, 34.1% (1219/3575) were intermediate risk and 38.0% (1357/3575) were high risk. In the first 6 years of data collection there was a relatively low proportion of low risk cases, however, this slowly increased and from 2003 until 2016 the proportion of different risk groups remained largely similar (Figure 2.15).

For the purposes of data collection at the EPC MDT all cases of node positive cancer and metastatic disease were included in the high-risk category.

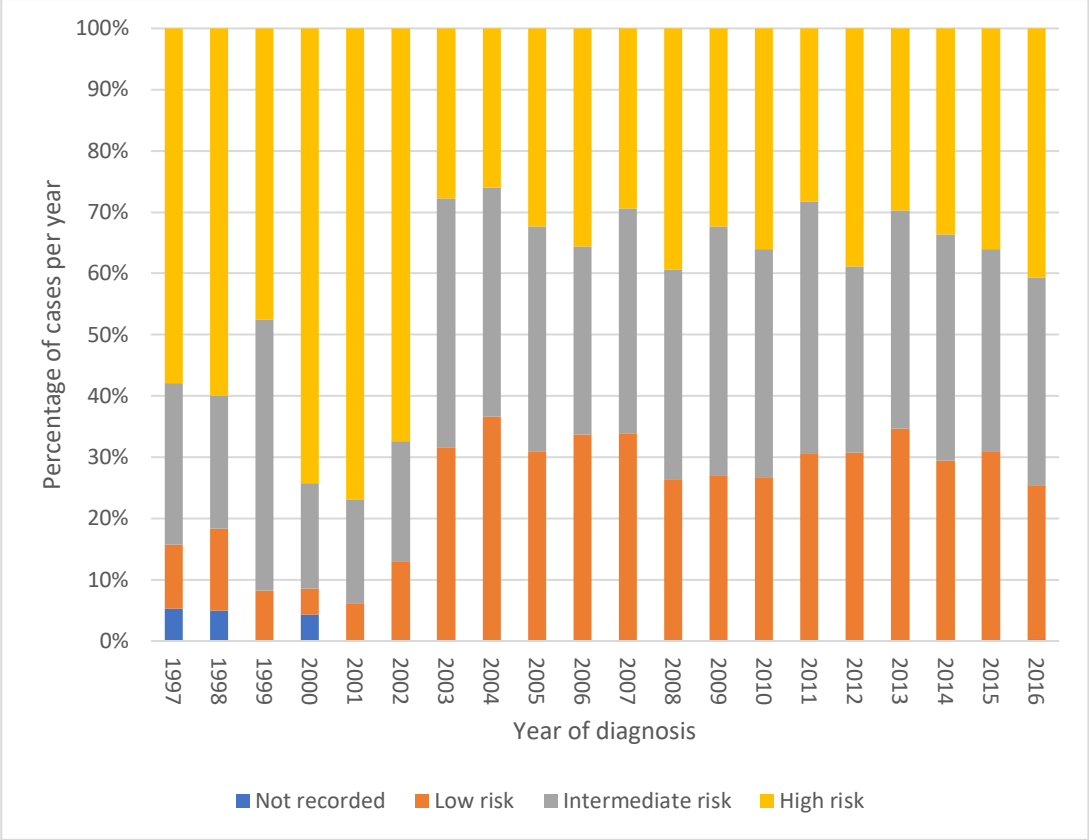


Figure 2.15. Pivot table plot to show the proportion of D'Amico risk classified cases at diagnosis. (N=3575)

Treatment received

Active surveillance was the primary treatment recorded in 23% of cases, 3.8% had watchful waiting, 24.6% went on to radical prostatectomy, 32.1% had radical radiotherapy and 14.3% had androgen deprivation therapy. Treatment was not known in 2.2% of cases (Table 2.7).

Treatment	**Number (%)**
Active surveillance	822(23)
Watchful waiting	135(3.8)
Radical prostatectomy	880 (24.6)
Radiotherapy	1146 (32.1)
ADT	512 (14.3)
Not known	80 (2.2)

Table 2.7. Table highlighting the primary treatment choices for men with discussed at the EPC MDT.

2.4.4 Aim 4 - Trends in symptoms at presentation and the relationship on disease stage

2.5.4.1 Symptoms and influence on disease presentation

Overall, data is available for 3328 patients. 1268 (38.1%) patients were asymptomatic at presentation and 2060 (67.9%) were symptomatic.

Age and symptoms

Asymptomatic men were most numerous in the 60-69-year-old group, the proportion of men who were in the <60 years old group was roughly equal to that in the >70 years old age group. In symptomatic men, there was a marked difference between groups, with a lower proportion of men in the younger than 60 years of age group compared to the older age groups.

There was an increase in the number of men presenting with symptoms as age increased with 69.1% of men symptomatic in the >70-year-old age group versus 55.2% in the < 60-year-old group (Table 2.8).

Year of presentation

When comparing year of presentation, after 2002 the proportion of those presenting with symptoms was roughly equal at around 60%. However, between 1997-2001 a much higher proportion were symptomatic at 81.6%. This may represent an increase in the number of screen detect cases because of increased disease awareness (Table 2.8).

Route of presentation

As one might expect there was a slightly higher proportion of symptomatic patients presenting via the NHS than privately, 62.5% versus 49.7% (Table 2.8).

Disease characteristics

Higher Gleason score, PSA level and clinical T stage were all associated with a higher rate of symptoms at presentation. For patients with a Gleason score between 8-10

or PSA >20 or a clinical T stage T3-4 73% of patient had symptoms compared with between 49.7% - 57.6% with symptoms for patients with D'Amico low risk features (Gleason <7, or PSA <10, or Clinical T stage <T2a) (Table 2.8).

Only age at diagnosis was independently associated with symptomatic presentation with older men having more symptoms. Earlier period of presentation, higher Gleason score, and more aggressive clinical stage did appear to be related associated with higher rates of symptomatic presentation but these were not statistically significant associations (Table 2.8).

	Whole cohort		No symptoms	% of those without symptoms	% of those c charact.	Symptoms	% of those with symptoms	% of those c charact.	Factors associated with symptoms at presentation.		
	N	%	N	%	%	N	%	%	IR	95% CI	p-value
TOTAL	3328	100	1268	**38.1**		2060	**67.9**				
AGE (N=3323)											
<60	643	19.3	288	22.7	44.8	355	17.3	55.2	0.79	0.68-0.92	0.002
60-69	1483	54.7	608	48.0	40.8	875	42.5	59.2	0.86	0.77-0.96	0.010
>70	1197	36.0	370	**29.2**	**30.9**	827	**40.2**	**69.1**	1	-	-
PERIOD (N=3323)											
1997-2001	326	9.8	60	4.7	18.4	266	**12.9**	81.6	1.35	0.93-1.96	0.119
2002-2006	697	21.0	292	20.7	41.9	405	19.7	58.1	1.00	0.86-1.14	0.957
2007-2011	875	26.3	343	27.1	39.2	532	25.9	60.8	1.05	0.93-1.18	0.411
2012-2016	1425	42.9	571	**45.1**	40.1	854	41.5	59.9	1	-	-
NHS/PRIVATE (N=3321)											
NHS	3172	95.5	1191	94.1	37.5	1981	96.4	62.5	1.18	0.93-1.50	0.175
PRIVATE	149	4.5	75	5.9	50.3	74	3.6	49.7	1	-	-
GL SCORE (N=3276)											
<7	1512	46.2	641	**50.8**	42.4	871	43.2	57.6	0.90	0.76-1.07	0.218
7	1249	38.1	485	38.4	38.8	764	37.9	61.2	0.90	0.77-1.04	0.057
8-10	515	15.7	136	10.8	26.4	379	**18.8**	**73.6**	1	-	-
PSA LEVEL (N=3328)											
<10	1784	53.6	761	**60.0**	50.3	1023	49.7	49.7	0.94	0.81-1.09	0.392
10-20	837	25.2	321	25.3	38.4	516	25.0	61.6	0.89	0.76-1.04	0.136
>20	707	21.2	186	14.7	26.3	521	**25.3**	**73.7**	1	-	-
C T-STAGE (N=2725)											
T1A-T2A	1781	65.4	786	**71.5**	44.1	995	61.2	55.9	0.88	0.76-1.03	0.103
T2B-C	394	14.5	166	15.1	42.1	228	14.0	57.9	0.87	0.73-1.04	0.121
T3-4	550	20.2	148	13.5	26.9	402	**24.7**	**73.1**	1	-	-
D'AMICO (N=3322)											
LOW	927	27.9	428	**33.8**	46.2	499	24.3	53.8	-	-	-
INT.	1134	34.1	485	38.3	42.8	649	31.6	57.2	-	-	-
HIGH	1261	37.9	353	27.9	30.0	908	**44.2**	**70.0**	-	-	-

Table 2.8. Table showing the distribution of patients with and without symptoms at presentation and the association with disease characteristic (age, year of presentation, etc.) and patient demographics. Factors associated with symptoms at presentation was assessed with Poisson regression with all co-variates entered simultaneously. D'Amico risk classification was not assessed given co-linearity.

2.4.4.2 Symptoms and influence on treatment

The effect of whether symptoms influenced primary treatment decision was assessed. Patients were divided according to D'Amico risk and age at presentation and the presence of symptoms.

D'Amico risk group

Treatment patterns differed significantly between D'Amico risk groups at referral.

Low risk – the presence of symptoms did not appear to affect the decision to have radical treatment or enter surveillance with roughly equal numbers choosing each treatment (Table 2.9).

Intermediate risk – the presence of symptoms did not appear to affect the decision to enter a deferred treatment strategy. A higher proportion of asymptomatic patients underwent radical prostatectomy. Similar numbers had radical radiotherapy, although slightly more symptomatic patients received this (Table 2.9).

High risk – overall, a higher proportion of patients had radical radiotherapy rather than radical prostatectomy. The presence of symptoms did not appear to affect the treatment decision although a slightly higher proportion of asymptomatic patients had radical prostatectomy than those with symptoms (Table 2.9).

RISK GROUP – SYMPTOMS	**LOW (N =927)**		**INT. (N=1134)**		**HIGH (N=1261)**	
PRIMARY TREATMENT	**NO N=428**	**YES N=499**	**NO N=485**	**YES N=649**	**NO N=353**	**YES N=908**
AS	234 54.7%	282 56.5%	83 17.1%	135 20.8%	11 3.1%	22 2.4%
WW	2 0.5%	9 1.8%	24 4.9%	42 6.5%	11 3.1%	41 4.5%
RP	125 29.2%	130 26.1%	203 **41.9%**	201 **31.0%**	60 **17%**	87 **9.6%**
RT	40 9.3%	64 12.8%	151 31.1%	228 35.1%	177 50.1%	424 46.7%
ADT	17 4%	10 2%	13 **2.7%**	29 **4.5%**	86 **24.4%**	311 **34.3**%
NOT KNOWN	10 2.3%	4 0.8%	11 2.3%	14 2.2%	8 2.3%	23 2.5%
CHI SQUARE P VALUE	0.018		0.007		<0.001	

Table 2.9. Table showing the effect of symptoms on primary treatment received according to D'Amico risk classification.

Age group

Treatment patterns differed significantly between age groups at referral. Overall, as one would expect there were higher numbers choosing watchful waiting and receiving radiotherapy and ADT in the >70-year-old age group. There were also fewer men having radical prostatectomy.

Less than 60 years old – in those choosing either surgery or radiotherapy, those with symptoms had a higher rate of radical radiotherapy and a lower rate of prostatectomy. The proportion having deferred treatment was equal (Table 2.10).

60-69 years old – again those with symptoms had a higher rate of radical radiotherapy and a lower rate of prostatectomy and similar rates of deferred therapy (Table 2.10).

70 years old and above – for older men they were less likely to choose active surveillance if they were symptomatic at presentation. Treatment rates were similar for radical treatment regardless of whether men were symptomatic or not (Table 2.10).

AGE GROUP –	**<60 (N =643)**		**60-69 (N=1483)**		**≥ 70 (N=1197)**	
SYMPTOMS	**NO N=288**	**YES N=355**	**NO N=608**	**YES N=875**	**NO N=370**	**YES N=827**
PRIMARY TREATMENT						
AS	66 22.9%	77 21.7%	156 25.7%	224 25.6%	108 **29%**	141 **17%**
WW	0 0%	1 0.3%	3 0.5%	3 0.3%	34 9.2%	88 10.6%
RP	151 **52.4%**	147 **41.4%**	205 **33.7%**	225 **25.7**%	31 8.4%	44 5.3%
RT	46 **16%**	98 **27.6%**	189 **31.1%**	318 **36.3%**	133 35.9%	300 36.3%
ADT	18 6.3%	27 7.6%	35 **5.8%**	88 **10.1**%	62 **16.8%**	235 **28.4%**
NOT KNOWN	7 2.4%	5 1.4%	20 3.3%	17 1.9%	2 0.5%	19 2.3%
CHI-SQUARE P-VALUE	0.007		0.001		<0.001	

Table 2.10. Table showing the effect of symptoms on primary treatment received according to age at presentation.

2.4.5 Aim 5 - Impact of family history on disease stage and treatment undertaken

2.4.5.1 Family history and effect on presentation

In 16.6% (593/3575) of cases family history was not known. Of the men where it was known, 85.8% did not have documented evidence of a family history of PCa, 5.8% had a history of disease affecting their father and 5.4% their brother, 3.0% had disease affecting another close relative or a history of breast cancer.

The rate of patients presenting with a positive family history fluctuated from around 2% to 22% but did not follow a definite trend over the period of data collection (Figure 2.16).

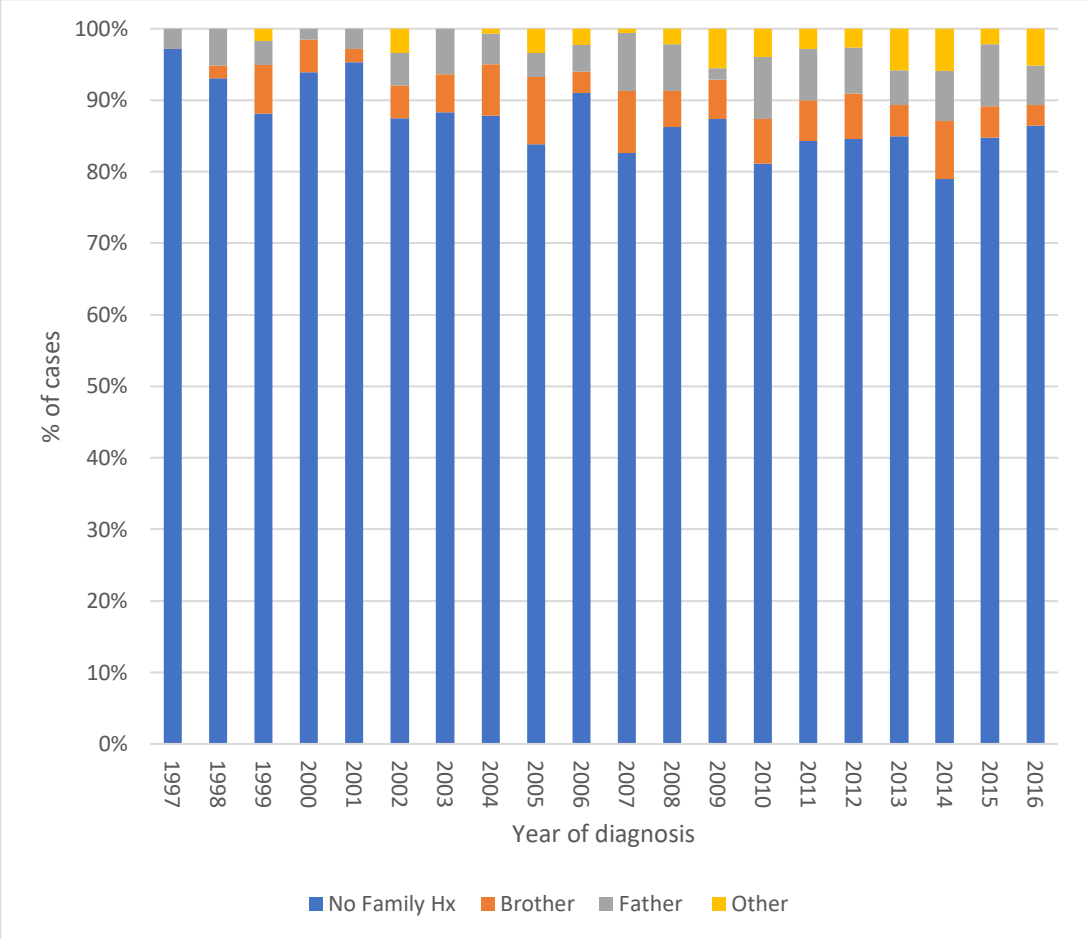


Figure 2.16. Pivot table plot showing the proportion of patients with a positive family history at presentation. (N=3575)

When comparing the proportion of men with a positive family history and disease characteristics at presentation there was a higher rate of family history associated with lower PSA score, 17.4% of patients with a PSA <10 versus 8.3% with a PSA >20. This was also seen for Gleason score, with a positive family history seen in 16.8% of patients with Gleason score <7 versus 7.8% in those with Gleason >8. Higher clinical T stage was also associated with a lower rate of family history compared with lower clinical stage. Overall, 21.1% of patients with D'Amico low risk disease had a positive family history compared with, 14.8% of intermediate risk disease and 9.4% of high risk disease (Table 2.11).

Poisson multivariate analyses highlighted that only Gleason score had a significant correlation with family history. Men with a Gleason score <7 were 1.8 times more likely to have a positive family history than Gleason score 8-10 (p-value 0.011) and men with Gleason 7 disease were 1.64 times more likely than those with a score 8-10 (P-value 0.025). No statistically significant associations were observed for PSA or clinical stage at diagnosis (Table 2.11).

	FHX					FACTORS ASS. WITH FH AT PRESENTATION		
	None	Brother	Father	Other	FHx combined	IR	95% CI	p-value
PSA								
<10 N=1627	1343 (82.5%)	105	126	53	284 (17.4%)	1.27	0.89-1.81	0.192
10-20 N=751	661 (88%)	40	33	17	90 (11.2%)	1.09	0.74-1.60	0.673
>20 N=604	554 (91.7%)	16	13	21	50 (8.3%)	1	-	-
TOTAL N=2982	2558	161	172	91		-	-	-
GLEASON SCORE OF BX								
<7 N=1382	1150 (83.2%)	90	92	50	232 (16.8%)	1.81	1.15-2.86	0.011
7 N=1117	959 (85.9%)	58	66	34	158 (14.1%)	1.64	1.07-2.52	0.025
8-10 N=437	403 (92.2%)	13	14	7	34 (7.8%)	1	-	-
TOTAL N=2936	2512	161	172	91				
CLINICAL STAGE								
T1-2A N=1636	1357 (82.9%)	103	119	57	279 (17.1%)	1.1	0.75-1.62	0.620
T2B-C N=346	290 (83.8%)	23	18	15	56 (16.2%)	1.25	0.82-1.9	0.311
T3-4 N=483	439 (90.1%)	12	19	13	44 (9.9%)	1	-	-
TOTAL N=2465	2086	138	156	85				
D'AMICO RISK								
LOW N=832	665 (79.9%)	63	68	36	147 (21.1%)	-	-	-
INTERMEDIATE N=1024	872 (85.2%)	62	67	23	132 (14.8%)	-	-	-
HIGH N-1120	1015 (90.6%)	36	37	32	105 (9.4%)	-	-	-
TOTAL N=2976	2552	161	172	91				

Table 2.11. Table to highlight the association of family history with presenting disease characteristics, with combined family history and individual previously affected. Factors associated with symptoms at presentation was assessed with Poisson regression with all co-variates entered simultaneously. D'Amico risk classification was not assessed given co-linearity.

2.4.5.2 Family history and presence of symptoms

When comparing men with and without symptoms and the correlation between family history and D'Amico risk classification at diagnosis it can be seen that for asymptomatic men with a family history there is much higher proportion of low-risk disease than for those men with symptoms. For men with symptoms and a family history there is a roughly equal divide of risk groups, whereas, if there is no family history there is double the number of high risk cases compared to low-risk (Table 2.12). For both men with and without symptoms there is a significant difference in the proportion of men with the same D'Amico risk group with more low risk in men with family history and a lower rate of high risk disease.

	Low risk	**Intermediate Risk**	**High risk**	**Total**
Asymptomatic men (Chi square test – P value <0.001)				
No FHx	299 (32.2%)	360 (38.7%)	270 (29.1%)	929
FHx	91 (47.6%)	66 (34.5%)	34 (17.8%)	191
Total	390	426	304	1120
Symptomatic men (Chi-square test – P value <0.001)				
No FHx	338 (22.4%)	474 (31.5%)	694 (46.1%)	1506
FHx	70 (32.6%)	78 (36.3%)	67 (31.2%)	215
Total	408	552	761	1721

Table 2.12. Table showing correlation between family history and disease risk classification in a/symptomatic men at presentation.

2.4.5.3 Family history and influence on treatment

The effect of whether symptoms influenced primary treatment decision was assessed. Patients were divided according to D'Amico risk and age at presentation and the presence of symptoms.

D'Amico risk group

Significant difference in treatment chosen was only seen in the low and high risk groups.

Low-risk - for men with low risk disease and a positive family history less men had active surveillance and more men had a radical prostatectomy, than those without a family history (Table 2.13).

Intermediate risk – slightly less men with a positive family history chose surveillance and slightly more had radical prostatectomy although the difference was not as much as that seen in low risk disease (Table 2.13).

High risk disease – for men with a family history there was a higher rate of radical treatment (both surgery and radiotherapy) and a lower rate of ADT (Table 2.13).

Risk group –	**Low (n =832)**		**Int. (n=1024)**		**High (n=1120)**	
FHx	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Primary treatment	**n=665**	**n=177**	**n=872**	**n=152**	**n=1015**	**n=105**
AS	386 58%	81 **45.8%**	168 19.3%	24 **15.8%**	27 2.7%	3 2.9%
WW	6 0.9%	0 0%	45 5.2%	7 4.6%	40 3.9%	1 1%
RP	174 26.2%	64 **36.2%**	318 36.5%	63 **41.4%**	124 12.2%	23 **21.9%**
RT	76 11.4%	15 8.5%	299 34.3%	49 32.2%	476 46.9%	58 **55.2%**
ADT	22 3.3%	1 0.6%	31 3.6%	4 2.6%	322 31.7%	18 17.1%
Not known	1 0.2%	6 3.4%	11 1.3%	5 3.3%	26 2.6%	2 1.9%
Chi-square p-value	<0.001		0.340		0.004	

Table 2.13. Table showing the effect of family history on primary treatment received according to D'Amico risk classification.

Age Group

Significant difference was only seen in the <60 years and 60-69 year groups. The treatment chosen in men older than 70 was not different in men with and without family history.

Less than 60 years old – for those men with a positive family history there was a higher rate of men having radical prostatectomy and less men receiving radical radiotherapy than those without family history. Similar numbers had active surveillance (Table 2.14).

60-69 years old – treatment for this was very similar between men with and without family history. The only difference noted was a lower number having radiotherapy in those with a family history (Table 2.14).

70 years old and above – a positive family history was associated with a slightly higher rate of radical prostatectomy and a lower rate of ADT (Table 2.14).

AGE GROUP	**<60 (N =605)**		**60-69 (N=1358)**		**≥70 (N=1017)**	
FHX	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**
	N=665	**N=177**	**N=1161**	**N=227**	**N=917**	**N=100**
PRIMARY TREATMENT						
AS	105 15.8%	23 13%	287 24.7%	59 26%	194 21.1%	26 26%
WW	1 0.2%	0	4 0.3%	0	86 9.4%	8 8%
RP	218 **32.8%**	75 **42.4%**	339 29.2%	62 27.3%	58 **6.3%**	12 **12%**
RT	115 **17.3%**	21 **11.9%**	402 **34.6%**	62 **27.3%**	335 36.5%	39 39%
ADT	37 5.6%	3 1.7%	109 9.4%	6 2.6%	229 **25%**	14 **14%**
NOT KNOWN	3 0.5%	4 2.3%	20 1.7%	8 3.5%	15 1.6%	1 1%
CHI-SQUARE P-VALUE	0.004		0.008		0.067	

Table 2.14. Table showing the effect of family history on primary treatment received according to age.

2.4.6 Aim 6 - Change in treatment patterns

2.4.6.1 Treatment of different D'Amico risk groups.

Low risk patients – Between 1997 and 2007 at least half of all low risk patients were receiving radical treatment as a primary treatment. However, there were low numbers of men with low risk disease and meaningful assessment is difficult. From 2011, there was a continual reduction in the proportion of men having radical treatment, and in 2016 84% of men choose active surveillance as a primary treatment. There also appeared to be a reduction in the proportion of men having radical prostatectomy and a more marked reduction in men choosing radical radiotherapy (Figure 2.17). This reduction in the proportion of men having radical treatment is largely due to an increased number of men diagnosed with low disease and captured by the MDT.

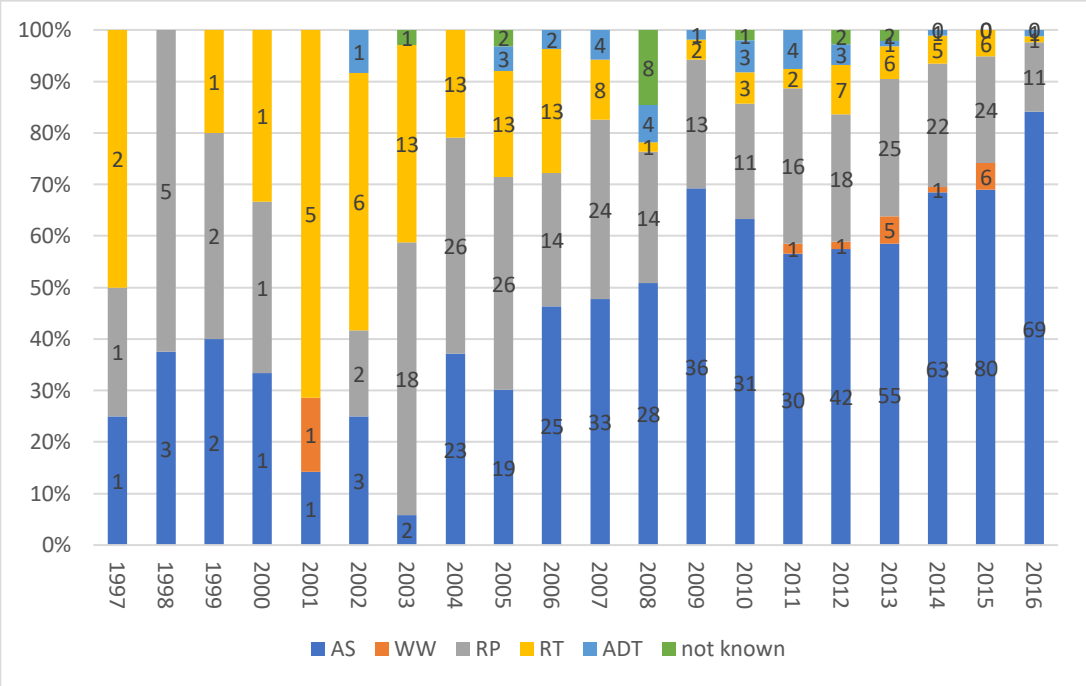


Figure 2.17. Pivot table plot showing the primary treatment low risk patients received, 1997-2016. (N=990)

Intermediate risk – For men with intermediate risk disease there appeared to less marked differences in treatment over the period. The most apparent difference was

a reduction in the use of androgen deprivation therapy and a reduction in the proportion of men having radical radiotherapy (Figure 2.18).

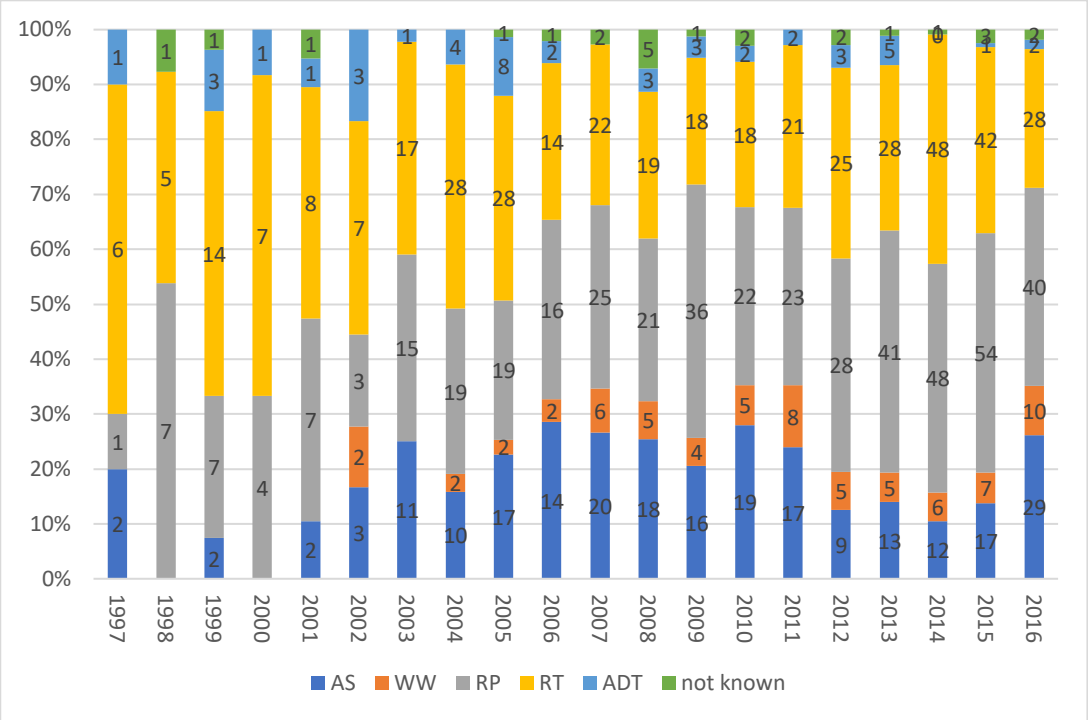


Figure 2.18. Pivot table plot showing the primary treatment received by intermediate risk patients. 1997-2016. (N=1219)

High risk – When looking at primary treatment for all high-risk patients there does not appear to be appear any distinct patterns over the period of EPC (Figure 2.19).

Figure 2.19. Pivot table plot showing the primary treatment received by high risk patients, 1997-2016. (N=1357)

To further, sub-divide the high-risk group (1357 cases) all cases with a positive bone scan, evidence of nodal disease on MRI or a PSA > 200 were excluded. This left 1048 high risk cases that could be considered high risk non-metastatic and therefore eligible for radical treatment. The treatment patterns of this subgroup were reviewed. There did not appear to be a significant change in treatment rates for men with high risk disease. Although from 2014, similar proportions of men were receiving radical treatment, with 76% in 2016. (Figure 2.20).

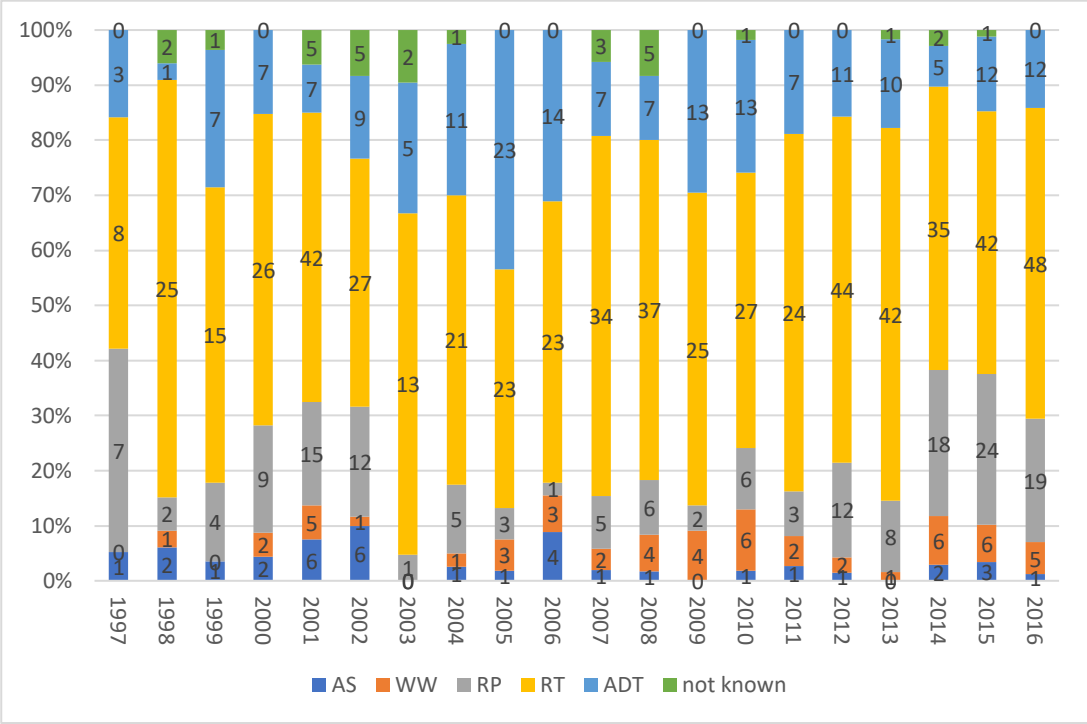


Figure 2.20. Graph showing what primary treatment a subgroup of high risk patients received (all high-risk patients with positive bone scan, PSA>200, or nodal disease on MRI were excluded) (N=1048)

2.4.6.2 Active Surveillance

To further assess changes in treatment patterns the D'Amico risk classification of patients that were entered in to an active surveillance program were reviewed. From 2000, there was a steady reduction in the proportion of intermediate and high risk patients that were enrolled on active surveillance program (Figure 2.21). The would correlate well with the drive to avoid overtreatment of potentially insignificant

prostate cancer. The high proportion of high risk patients that were enrolled in the early years of EPC MDT may have been incorrectly coded as AS rather than watchful waiting. Prior to 2004, the sample sizes per year were also small and therefore difficult to compare with later years.

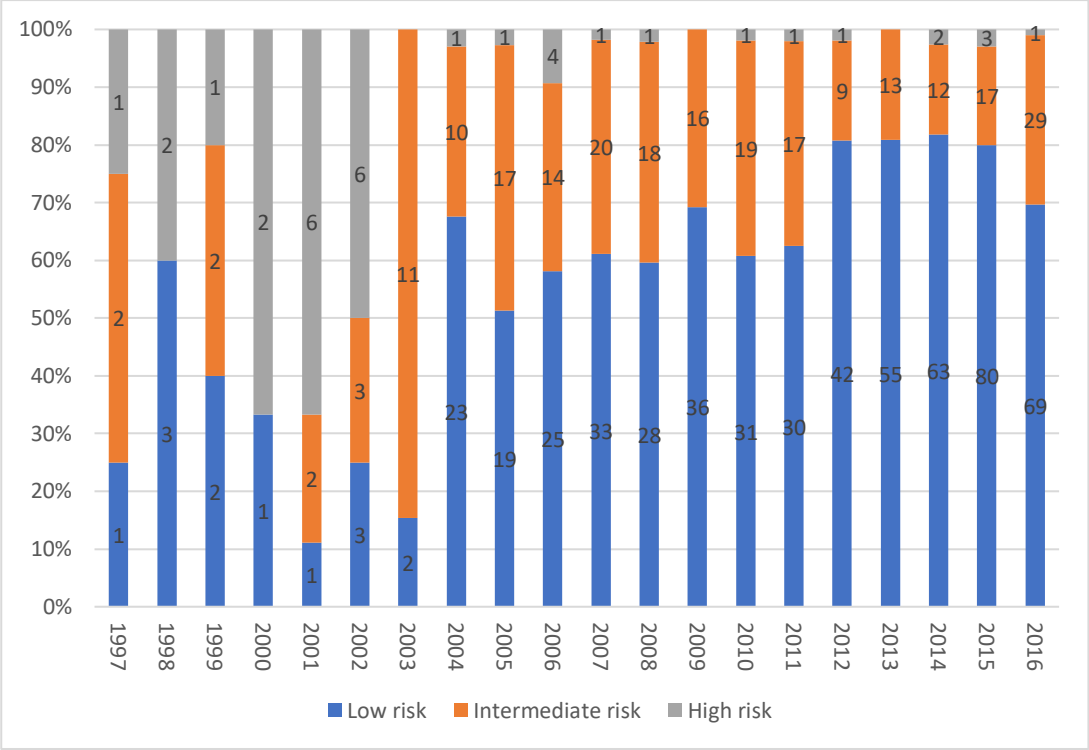


Figure 2.21. D'Amico risk classification of patients entering active surveillance as a primary treatment, 1997-2016. (N=813)

2.4.6.3 Radical prostatectomy

The changes in D'Amico risk classification of patients undergoing radical prostatectomy was also reviewed. As seen with AS there was a steady decline in the proportion of low risk patients having radical treatment. From 2003, the proportion of low risk patients having dropped from over 50% to just over 15% in 2016 (Figure 2.22). Over the same period there was also an increase in the number of high risk patients having surgery which again would correlate with the drive to not under-treat high disease. This change can also be accounted for by a higher number of men with intermediate and high risk disease having surgery, thereby reducing the apparent proportion of men with low risk disease.

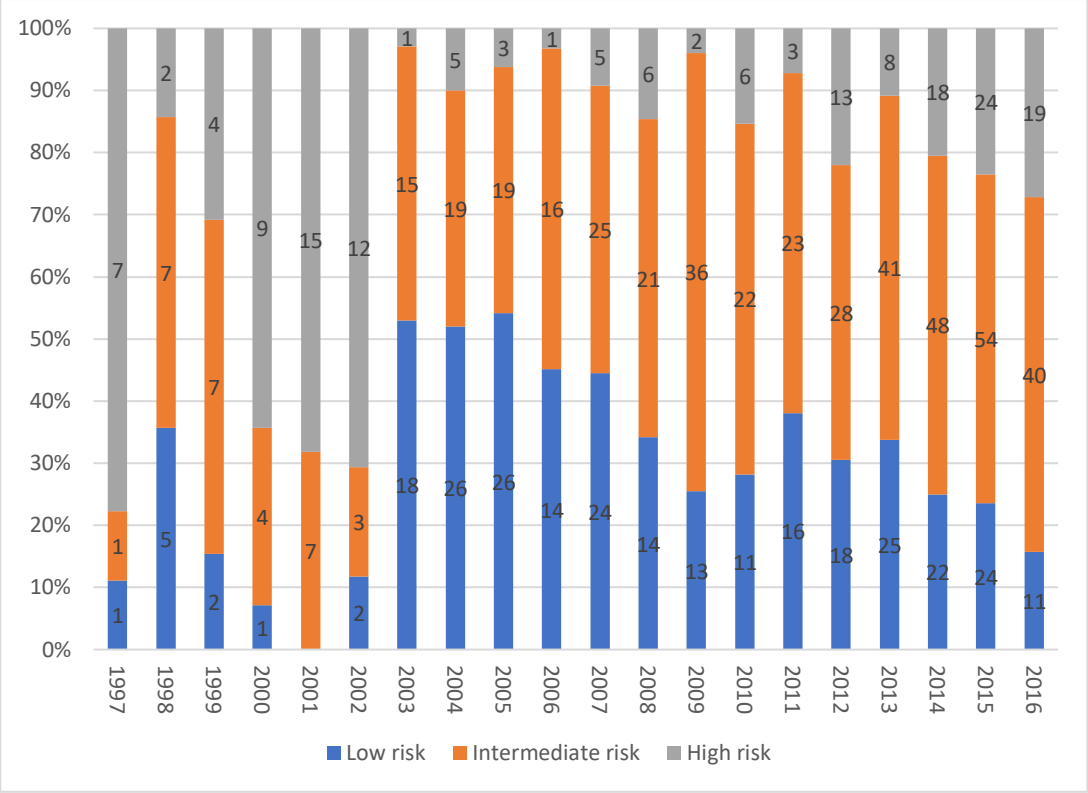


Figure 2.22. D'Amico risk classification of patients having radical prostatectomy a primary treatment, 1997-2016. (N=872).

2.5 Discussion

This chapters reports on the use of a large and prospectively collected dataset for patients with newly diagnosed prostate cancer over a 20-year period. It provides detailed information on how presentation and treatment trends at a specialist MDT have changed over this period and provides valuable insight in to changing managements strategies. It also provides useful information as to how men with symptoms and family history present and how this may influence disease stage and subsequent primary treatment.

2.5.1 Data quality and capture rates

With a 5% error rate the data quality, or accuracy of the data, compares very favourably with large published series of a similar nature (NPCA., 2017), and is much

better than others with reported error rates in clinical databases up to 27% (Goldberg et al., 2008).

The accuracy of data on clinical databases is of vital importance to correct interpretation and to enable one to draw meaningful conclusions. Errors occur from either the non-entry of data items or from inaccurate entry. It is often easier to correct and review missing data retrospectively as it is easily identifiable. However, incorrect data is much harder to account for and correct without laborious intervention. Within this study, the accuracy of the recorded primary treatment received was used as a simple quality indicator. Within this field, only a very small number of cases were missing and many of the errors were due to incorrect data entry and probably related more to a change in the naming and meaning of the treatment rather than a true data error (watchful waiting as opposed to active surveillance in the early days of deferred treatment). Aside from the TRUS biopsy pathology data, where each individual record was checked for accuracy against hospital record, other data items within the EPC MDT database were not checked as vigorously and this is a weakness of the analysis. It must also be remembered that with the most recent data collection form (2014 onwards) there are over 50 data items which must be recorded at MDT by hand and then later inputted on to the electronic database. It is inevitable that errors will occur but within the data field assessed for quality in this study I have demonstrated a low error rate of 5%. Certainly, if data is missing from other data items this poses less of a risk in analysing the data accurately than if incorrect data is entered.

As discussed previously the data present from the EPC specialist MDT database represents a real-time analysis over the last 20 years and only since 2014 was there an attempt to capture all new diagnoses of prostate cancer at the MDT. Prior to this some new cases may have been discussed at the hospitals smaller local MDT, these would often have been clinical diagnoses of CaP or incidental following intervention such as TURP, management would often have been considered straight forward and therefore not referred to a specialist MDT. The introduction of the NPCA to Wales in 2015 mandated changes to data collection at the EPC MDT and an emphasis that all

new cases be discussed from 2014 onwards. The creation of an NPCA data record was through one of three sources, either from discussion at MDT, generation of a positive pathology report or via local hospital cancer services. Through comparison of these data sets it was noted that in 2014 EPC MDT missed 10% of all new diagnoses cases of prostate cancer. This figure is likely to be higher for previous years but it hoped that for the years after 2014 it is lower, given that this was the first year of mandated data collection. One can therefore assume that post 2014 the data is more representative of all new cases of cancer than prior to this and must remember this when interpreting the data.

It is also worth noting that the data collection for the NPCA in Wales was piloted in UHW in 2014, prior to national implantation in 2015. The data capture results for the NPCA pilot were very encouraging with <1% of all new diagnoses not identified by the process that generates a NPCA patient record. Within Wales once a NPCA case note is generated the data collection system for that case note differs significantly to that in England and is worthy of mentioning. Within Wales all data items required by the NPCA are both automatically and manually uploaded on to an electronic database. These case notes are then individually validated and subsequently signed off by a clinician before being automatically uploaded to generate a report for each individual health board. If data items are missing the report will not be able to be validated, hence ensuring high levels of data completeness. This process has resulted in excellent captures rates and data completeness rates of >98% across all health boards for Wales. This same process is not in place in England and completeness levels for the same datasets in England ranges from 31-73% (NPCA., 2017). This has emphasised the importance of how data is captured and processed.

2.5.2 EPC data

The data presented here represents an accurate history of a very contemporary UK MDT practice. The raw data itself is not unique and represents routine patient demographics and disease characteristic at presentation. However, it has many strengths in that many of the clinicians involved with data collection and assessment have remained the same. Staging investigations have remained relatively

homogenous with a high number having both MRI and bone scan at diagnosis and the reporting of TRUS biopsies have remained the same but up to date with current reporting practice.

Over the period of the EPC MDT we have shown that the workload of a specialist MDT has increased dramatically to keep up with modern practice and the increasing number of patients diagnosed. The introduction of the NPCA to England and Wales and the mandate that all patients with new diagnosis cancer should be discussed at MDT has led to not only a higher number of patients discussed each year, but has also resulted in an older population, with a higher mean PSA going through the EPC MDT. These increases can be accounted for by the higher proportion of patients with more advanced disease that may not previously have been discussed at an sMDT or even a MDT at all in the early years of data collection. It is also interesting to note a declining number of patients presenting with Gleason 6 disease with a reduction from around 60% in 2004 to around 30% in 2016. It must be proposed that this drop is in part related to the changes in how Gleason is reported.

When reviewing so many patients at MDT it is important to review the process to see if time is used wisely and if one can make the process more efficient. One could question the use of DRE at the time of referral given such poor correlation between referral stage and that after review at the EPC MDT. One could also question the need for pathology review at MDT given that in most cases there was >95% concordance between the Gleason grade at diagnosis and at review at the sMDT. As TRUS biopsies are peer reviewed at the time of reporting does this process need to be repeated at MDT?

The use of imaging over the time of the MDT has also changed with a significant shift towards pre-biopsy MRI in line with recent evidence highlighting its benefits in targeting abnormal lesions (Ahmed et al., 2017). In 2016, 88.6% of MRI were pre-biopsy and over the period of EPC 92.3% of patients received an MRI as part of staging. In a cohort of this size this represents a unique data set given that prior to updated NICE guidance in 2014 there were no recommendations considering the use

MRI as part of staging in UK practice (NICE, 2014). The high usage of bone scan in this large cohort will also enable valuable questions to be answered as to the most appropriate people to stage with this investigation.

2.5.3 Effect of symptoms on disease characteristics and treatment

There is mixed evidence suggesting men with symptoms have a higher rate of aggressive cancer with some studies suggesting there is a higher rate (Arsov et al., 2015, Miller et al., 2003) and others reporting no association(Martin et al., 2008).

Our findings largely agree with an Australian study of a similar nature with a slightly larger cohort. Fewer men are presenting with symptomatic disease than they did over 15 years ago. This may be due to an increased awareness of the disease and a higher incidence of PSA testing. However, it may be also due to the skew in data presented in this study with patient capture rates different in the early years of the EPC MDT compared to later years. Within this study, it appeared that age at diagnosis was the only the independent factor associated with men presenting with symptoms, with older men more likely to be symptomatic. Whilst men with a higher Gleason grade, clinical stage and PSA had a higher chance of presenting with symptoms this was not found to be statistically significant. This was also highlighted in the Australian study where only age, earlier diagnostic time of presentation and public-sector management were independently associated with symptomatic presentation (Beckmann et al., 2017). The Australian study also found that with multi-variate analysis the risk of having intermediate and high risk disease (NCCN criteria), Gleason 7 disease or PSA 10-20 was lower in men with symptoms. The reasons for this finding were not clear but this study does not support these findings as no statistical significance was highlighted.

This study also supported the findings that men with symptoms are less likely to undergo radical prostatectomy than those men without symptoms. This may be a result of men with symptoms wanting a greater chance of symptom relief rather than radical treatment which may add to symptoms burden.

Unfortunately, unlike the Australian study our study did not have survival outcome. They found that men presenting with symptoms were shown to have a worse disease specific survival at 10 years. This, rather surprisingly, was independent of differences in age, disease characteristics and treatment received. Several reasons were postulated; men with symptoms have more advanced disease, under staging of disease at diagnosis, disparities in treatment of men with and without symptoms and the potential effect of inflammation on disease progression (Beckmann et al., 2017). Whatever the reason it is important to note that men presenting with symptoms may be an independent predictor of worse disease specific survival. Within our study cohort it would be interesting to obtain survival outcome data to determine if the same findings apply.

2.5.4 Effect of family history on disease characteristics and treatment

As discussed in chapter 1, the risk of developing prostate cancer is higher if one has first degree relatives affected by the disease. It is also increased in presence of germline mutations and can be more aggressive with specific BRCA 2 mutations (Castro et al., 2013).

Several studies have reported that cases of hereditary prostate cancer often present earlier, however, clinical characteristics are like those of sporadic cases (Bratt et al., 2002, De Visschere et al., 2016, Roehl et al., 2006). The earlier presentation of men with hereditary prostate cancer, must be due to many different factors, firstly increased awareness of the disease through personal experience and potential earlier PSA testing and secondly national guidance programs have advocated screening men with significant family disease. There is also debate as to the effect of family history on outcomes of radical treatment for localised disease. Several studies have failed to show a difference in both the survival rates and difference in biochemical recurrence (BCR) free rates in men undergoing radical prostatectomy for localized disease for those with and without family history (Heck et al., 2012, Bratt et al., 2002). There is also some evidence to suggest that men with hereditary prostate cancer have a higher rate of BCR after prostatectomy although this is older data (Bratt et al., 2002).

In this study, we have shown that men with a family history of prostate cancer present with a lower Gleason grade. For men with no symptoms, family history has a significant impact on the D'Amico risk group that men have at presentation with a much higher proportion of men having low risk disease if they have a positive family history. A similar pattern can be seen for men with symptoms; there is a much lower proportion of men with high risk disease and have a positive family history.

The presence of a family history also has a significant impact on treatment in men with low and high risk disease and in those men younger than 70 years of age. There appeared to be higher rates of radical prostatectomy in men with low and high risk disease with a positive family history. There was also a lower rate of surveillance in the low risk group with family history. This pattern was also seen in younger men with family history choosing radical prostatectomy.

Despite a lack of outcome data for our cohort we have shown that men with a positive family history are presenting with a lower grade of disease which few studies have shown previously. This is encouraging given the evidence that when these men have radical treatment for localised disease the outcomes are similar to men without familial disease. Obviously, this study has not defined family history more specifically than brother, father or other and therefore it is difficult to draw any further conclusions. Whether patients with germline mutation that present at an early stage do equally well remains to be seen. However, it is important in these men with germline mutations that disease detection is early.

2.5.5 Changing patterns of treatment

The changes seen in treatment patterns very much echo what is happening elsewhere in the treatment of prostate cancer. With continued evidence supporting active surveillance as the primary treatment for low risk cancer there is a real drive to avoid over treatment of such cases. In this study in 2016, 84% of low risk men chose active surveillance as their primary treatment. However, this is lower than the 92% reported in the NPCA for England for the same time period, and lower than 88%

reported for the previous year in England (NPCA., 2017, NPCA., 2018). It will be interesting to note how this figure compares with data from other Health Boards in Wales as this data has yet to be published in previous reports and it is known that the English data is not as complete as the Wales data. We have also seen a significant reduction in the number of intermediate risk patients enrolling on a surveillance program and in the number of low risk men undergoing radical prostatectomy which between 10-15 years ago was between 40-50% of patients having surgery.

For men with high risk disease there is also a move away from treating men with long term hormones towards radical treatment with survival benefit seen even in patients having radiotherapy in patients with small volume metastatic disease (Parker et al., 2018). Within our cohort in 2016, 74% of patients with high risk disease received radical treatment. This compares well with the 73% seen in NPCA data for England for the same year, an improvement from 61% the previous year (NPCA., 2018).

2.5.6 Limitations

The EPC MDT dataset represents the evolution of a contemporary UK specialist MDT. When analysing the data presented one must remember that prior to 2014 not all new cases of prostate cancer were captured. Therefore, there may be bias towards fitter patients with potentially lower risk disease that are more suitable for radical treatment particularly in the earlier years of data collection. Also, the dataset includes external referrals for men to be considered for radical prostatectomy and this will undoubtedly skew some figures towards higher proportions of localised disease. Nonetheless, this dataset represents the workload of a large tertiary sMDT. When reporting on the changes in treatment rates this is specific to disease risk classification and therefore the source of referral is not relevant. Also, one can see that the rate of referral has remained relatively stable over the period.

Unfortunately, the dataset lacks survival data. This would be a significant undertaking to retrospectively obtain but would add significant value to reporting on disease specific outcomes.

2.5.7 Summary

As discussed already the EPC MDT dataset is a large and contemporary record of an sMDT within the UK. We have shown that the data present within the database has low rates of error and in recent years, post 2014, is an accurate reflection of all cases of new diagnosis prostate cancer for Cardiff and the surrounding geographical area. The uniqueness of the dataset should allow meaningful questions to be answered in later chapters.

Within the limitations of early data capture in mind, analysis of the dataset in this chapter has shown how presentation trends have changed over 20 years and how treatment strategies have also changed to reflect new evidence. With an increasing weight of evidence driving the avoidance of over-treatment of low risk disease and the under treatment of high risk disease we have shown that the results from this database reflects this change.

Particularly when looking at men with symptoms and family history at presentation we have shown that age was the only independent factor associated with men presenting with symptoms, however, the presence of symptoms did significantly affect the choice of primary treatment. When looking at men with a family history, it appears that these men present with a lower grade of disease and are more likely to have their primary treatment choice affected by the presence of a positive family history if they have low or high risk disease or are younger than 70 years of age.

Chapter 3. Refining the use of isotope bone scan in the staging of intermediate risk prostate cancer

3.1 Introduction

In England and Wales in 2016, 16% and 13% of men respectively, presented with metastatic disease (NPCA., 2018). The most common sites for metastases are the lymphatics and bones with around 3% of all newly diagnosed cases of prostate cancer having bone metastases at presentation. The detection of metastatic disease is not only important in accurate staging but also in directing specific treatment to limit specific skeletal related events which may cause significant morbidity.

Isotope bone scan (BS) is the most commonly used staging test to determine the presence of bony metastatic disease with sensitivity and specificity rates of around 80% (Shen et al., 2014). MRI, CT and PET/CT are used in certain settings and have the potential to overtake the use of bone scan in staging. However, given the cost and practical benefits that bone scan has over the alternative imaging techniques it remains the most commonly used tool and it is essential that one can accurately define which patients require staging with a bone scan.

In 2016, there were several international guidelines providing inconsistent advice. The AUA's best practice policy do not suggest performing BS routinely in men with a PSA <20ng/ml, unless there is a suspicion of bony metastases and recommend that BS be considered in men with Gleason 8 or higher or cT3 disease or higher, even if PSA is less than 10ng/ml (AUA., 2013). The UK NICE guidelines recommend BS prior to deferring hormonal therapy in asymptomatic men on a watchful waiting program with a high chance of developing bony complications. NICE also recommend against the use of routine bone scanning in men with low risk localised prostate cancer (as defined by D'Amico risk group) but do not offer any recommendations for men with intermediate risk disease or high risk non-metastatic disease (NICE, 2014). ESMO (the European Society for Medical Oncology) guidelines recommend BS for all

intermediate and high risk patients (Parker et al., 2015). The Royal College of Radiologists within the UK recommends performing BS in all high risk patients and in intermediate risk patients when bone symptoms are present (RCR, 2013). The CART (classification and regression tree) risk stratification tool developed initially for patients who are candidates for radical prostatectomy by Briganti el al suggests BS in patients with a Gleason score greater than 7 or a PSA greater than 10 and a clinical T stage T2c or higher (Briganti et al., 2010). Finally, the EAU guidelines recommend BS in men with high-risk disease, and in men with intermediate risk disease and a primary Gleason grade of 4 or greater (Mottet et al., 2017a).

Guideline	Recommendation
AUA (AUA., 2013)	Gleason ≥ 8 or ≥T3. Suggestion of bony involvement.
NICE (NICE, 2014)	In watchful waiting patients at risk of bony metastases. Not for low-risk patients.
NCCN (NCCN, 2016)	Gleason ≥8 or, cT>2 or, cT1 and PSA >20 ng/ml or cT2 with PSA >10 ng/ml or symptomatic.
ESMO (Parker et al., 2015)	All intermediate and high-risk groups.
RCR (RCR, 2013)	In all high-risk patients and those with bony symptoms.
CART (Briganti et al., 2010)	Asymptomatic patients and Gleason ≥8, or, PSA >10ng/ml and ≥cT2c.
EAU (Mottet et al., 2017a)	All high-risk patients and intermediate risk with primary Gleason pattern 4 (ISUP grade ≥3)

Table 3.1. Comparison of different guidelines on the use of isotope bone scanning in the staging of newly diagnosed prostate cancer.

The guidelines are generally consistent regarding low risk and high risk patients. Low risk patients should not have BS unless clearly symptomatic as the BS is unlikely to offer any additional information; it may however be of detriment to both patient safety and mental well-being and convey an additional cost to the service provider. The guidelines concur that BS or equivalent should be performed in high risk patients as the risk of bone metastases is much higher. The guidelines are less consistent and

clear in defining the variables which should trigger the use of BS in the intermediate risk patients. In this chapter, we study the data present in the EPC MDT dataset to determine bone scan positivity rates, paying attention to the intermediate risk group, to more accurately define which patients would benefit from BS staging investigation.

3.2 Aims

The aims of this chapter were:

1. Review bone scan positivity rates in the EPC MDT cohort.
2. Determine the threshold for requesting a bone scan in newly diagnosed intermediate risk localised prostate cancer patients.

3.3 Methods

3.3.1 Service evaluation

This study was approved as part of service evaluation by the surgical directorate, UHW, Cardiff.

3.3.2 Patient population and analysis

As discussed in chapter 2, the EPC MDT database analysed in this thesis contains patients presenting with newly diagnosed prostate cancer between 1997 and 2017 discussed at a single centre specialist MDT. All patient demographics and staging investigations, including TRUS biopsy results, MRI results and bone scan results were recorded prospectively. All intermediate and high risk classified patients had a bone scan as part of staging unless contra-indicated. In some cases, low-risk patients would have had a BS but this was often decided on a case by case basis.

All isotope bone scans performed were technetium (^{99m}Tc)-methylene diphosphonate with planar imaging without single-photon emission. If the BS was equivocal a variety of additional imaging techniques were used as thought best at

the time by the radiologist. These included plain radiograph, CT, SPECT (Single-Photon Emission Computed Tomography) or MRI.

To address aim 1 the database was analysed between 2002 and 2015. Patients prior to 2002 were not analysed due to missing data items and the poor availability of radiology images to review, if required, in equivocal cases. Cases post 2015, were excluded as this study was carried in late 2016 and hence a full year of data was included up to the end of 2015.

In equivocal cases, these may have been discussed and reviewed at the time of EPC MDT and a definitive decision made and recorded as such. If it was equivocal even after EPC MDT review it would have recorded as such and it these cases that were subsequently reviewed by a radiologist to address aim 1 and 2. Further statistical analysis carried out in relation to association of PSA, Gleason score and clinical T-stage was done using the whole EPC cohort 1997-2017 and excluded equivocal cases, including only positive and negative results.

All patients were D'Amico risk classified. Analysis was done in Microsoft Excel and IBM SPSS version 22.

3.4 Results

3.4.1 Results from EPC cohort between 2002 and 2015

Between 2002 and 2015, 2720 new cases of prostate cancer were discussed at the EPC specialist MDT and bone scan positivity rates analysed. There were 858 low-risk cases, 976 intermediate risk cases and 886 high-risk cases. Of the intermediate risk patients, 10.1% (99/976) were primary Gleason pattern 4, i.e. Gleason 4+3, and the remainder were Gleason 3+4.

Overall, 78.9% (2145/2720) patients in this cohort had a bone scan of which 6.2% (133/2145) were positive. Of the positive bone scan results only one patient was previously classified as having intermediate risk disease; he had primary Gleason

pattern 4 and no men with Gleason 3+4 and intermediate risk disease (PSA <20 and clinical T stage <T2c) had a positive bone scan. The remaining 99% of men with a positive bone scan all had high-risk disease (Table 3.2).

D'AMICO RISK GROUP	NO. OF MEN (%TOTAL)	NO. WHO HAD A BONE SCAN (% OF RISK GROUP)	NO. WITH A POSITIVE BS	BS POSITIVITY RATE
LOW RISK	**858 (31.5%)**	**351 (40.9%)**	**0**	**-**
INTERMEDIATE RISK - GL 3+4	**877 (32.2%)**	**816 (93%)**	**0**	**-**
INTERMEDIATE RISK – GL 4+3	**99 (36.4%)**	**99 (100%)**	**1**	**1%**
HIGH RISK	**886 (32.6%)**	**879 (99.2%)**	**132**	**15%**
TOTAL	**2720**	**2145**	**133**	**6.2%**

Table 3.2 Bone scan positivity rates in the EPC MDT cohort of newly diagnosed prostate cancer cases, 2002 to 2015.

There were 61 patients with intermediate risk disease with Gleason 3+4 histology who did not have a bone scan. Further analysis of this cohort, identified that only 3 of the 61 patients were classified as intermediate risk on histology alone. 25 of the 61 were intermediate risk on clinical stage alone and 33 men were classified as intermediate risk based purely on a PSA reading at diagnosis between 10-20ng/ml. Of these 33 men classified intermediate risk on PSA, 24 had a PSA reading between 10-12ng/ml. These would imply that a clinical decision was made on the usefulness of bone scan at the time and not thought necessary given that these patients were very much towards the low risk end of intermediate risk disease. Analysis of these 61 patients has shown no evidence of metastatic disease on most recent follow-up imaging (treatment of disease was not taken in to account and was purely an observation to emphasise no adverse outcomes of not scanning these patients). For the 7 men with high risk disease that did not have a bone scan, all had investigation for metastases with alternatives imaging modalities.

Of the 886 men with high risk disease, 146 were classified as high-risk based on clinical T-stage alone, i.e., all had PSA <20ng/ml and Gleason score <8 but clinical T stage ≥T2c. Of these 146 patients, 5.4% (8/146) had positive bone scans and they all had Gleason 4+3 disease. In many of the guidelines mentioned criteria for recommending BS do specify clinical stage as a specific indicator, however, if these patients had not been clinically staged and as a result not been deemed high risk a significant proportion of patients may have been under staged.

Given that clinical stage may be affected by subjectivity and also omitted in certain clinical scenarios, such as nurse led clinics or MRI led diagnostics clinics, BS positivity rates were analysed according to PSA level and Gleason score alone. 148 patients had both Gleason 4+3 and a PSA <20 ng/ml and 6.1% (9/148) of these had a positive scan. There were no positive bone scans in patients with Gleason 3+4 and PSA<20 ng/ml. Extrapolating these results to men with Gleason 3+4 disease and a PSA <20 ng/ml produces a negative predictive value of 100% and therefore suggesting that only men with a PSA >20 or a Gleason grade with a primary pattern of ≥4 require an isotope bone scan.

3.4.2 Extended results from EPC cohort between 2002 and 2017 - statistical analysis

As previously described the previous study time frame (2002-2015) was chosen to enable analysis of equivocal scans and answer the initial question that was asked prior to locking out the EPC database for final analysis in 2017. With this additional 2-year period I have again reviewed positivity rates to further assess the significance of PSA, Gleason group and clinical stage had on rates of positivity. Binomial logistic regression and chi square tests were performed and for this analysis all equivocal scans that had not been clarified were excluded.

Expanding the date range produced very similar results with only one intermediate risk patient identified as having a positive scan. This was the same patient as previously mentioned in analysis from 2002-2015. As expected D'Amico risk group, PSA level, Clinical T-stage and Gleason grade all had a significant impact on the rates

of bone scan positivity with P values all <0.001 (Table 3.3). Low-risk patients had a positivity rate of 0%, intermediate risk was 0.1% and high risk patients had a rate of 16.9%.

Clinical Parameter	Isotope bone scan results		Total
	Negative	Positive (% of sub-group)	
D'Amico risk group			
Low	330	0 (0%)	330
Intermediate	912	1 (0.1%)	913
High	878	179 (16.9%)	1057
Total	2120	180 (7.8%)	2300
Chi-square test	P <0.001		
PSA level			
<10	982	15 (1.5%)	997
10 to 20	632	17 (2.6%)	649
>20	505	148 (22.7%)	653
Total	2119	180 (7.8%)	2299
Chi-square test	P <0.001		
Clinical T-stage			
T1-T2a	1121	12 (1.1%)	1133
T2b	287	9 (3.0%)	296
T2c	49	3 (5.8%)	52
T3	394	102 (20.6%)	496
T4	23	39 (62.9%)	62
Total	1874	165 (8.1%)	2039
Chi-square test	P <0.001		
ISUP grade group			
Group 1	698	2 (0.3%)	700
Group 2	794	12 (1.5%)	806
Group 3	258	24 (8.5%)	282
Group 4	157	22 (12.3%)	179
Group 5	203	85 (29.5%)	288
Total	2110	145 (6.4%)	2255
Chi-square test	P <0.001		

Table 3.3. Effect of PSA, ISUP grade group, Clinical T-stage and D'Amico risk group on BS outcome.

For the binomial logistic regression analysis PSA level was as recorded as a continuous variable, ISUP grade group was recorded as a categorical data and clinical stage was divided in to T2 or greater than T2 (to create a dichotomous categorical variable). As one would expect, PSA level, ISUP grade group score and Clinical T-stage were all significant independent predictors of bone scan positivity. A higher ISUP grade group is associated with an increased chance of bone scan positivity with ISUP grade group 3 having a 9.8 times higher risk of positivity compared to ISUP group 1 and ISUP grade 5 29.5 times more likely. Men with cT3 or 4 have a 3.2 times higher chance of positivity compared to men with organ confined disease (Table 3.4).

Disease parameter	P-value	Odds ratio	95% CI
PSA level	<0.001	1.014	1.010 - 1.018
ISUP Group 1	<0.001	-	-
ISUP Group 2	0.209	2.691	0.575-12.585
ISUP Group 3	0.003	9.776	2.171-44.020
ISUP Group 4	0.001	12.704	2.771-58.247
ISUP Group 5	<0.001	29.530	6.818-127.894
Clinical stage (T2 or >T2)	<0.001	3.220	1.896 – 5.468

Table 3.4. Outcome of binomial logistic regression to assess if PSA level (continuous), ISUP grade group (categorical) and clinical stage (expressed as categorical variable, T2 or >T2) were independently associated with increased risk of bone scan positivity.

During the initial period of this study, 2002 to 2015, there were 1784 patients with intermediate and high-risk disease who underwent a bone scan (Table 3.1). If only patients with high risk or intermediate risk disease with primary pattern 4 had been imaged 816 patients could have avoided an unnecessary scan. This equates to around 60 scans per year that were not required and would have had both a psychological impact on patients and a financial and time impact on the service provider.

Following this study, it was recommended in our centre that only high risk patients or intermediate risk patients with primary pattern 4 or PSA > 20ng/ml undergo BS staging. When reviewing rates of bone scan use it is clear that before this recommendation came in to force that an increasing number of patients were not undergoing BS and as a result the rate of negative scan was decreasing. In 2006, only 2.6% of patients discussed at the EPC MDT had a positive bone scan, 90.1% had a negative scan and 7.3% did not have a scan. Compare this to 2016, when 9.4% had a positive scan, 41.5% had a negative scan and 49.1% did not have a scan (Figure 3.1). Despite this apparent change in the use of bone scan over this time it is reassuring that local evidence justifies this change. As discussed, it is important to both patients and healthcare providers that staging scans are appropriate.

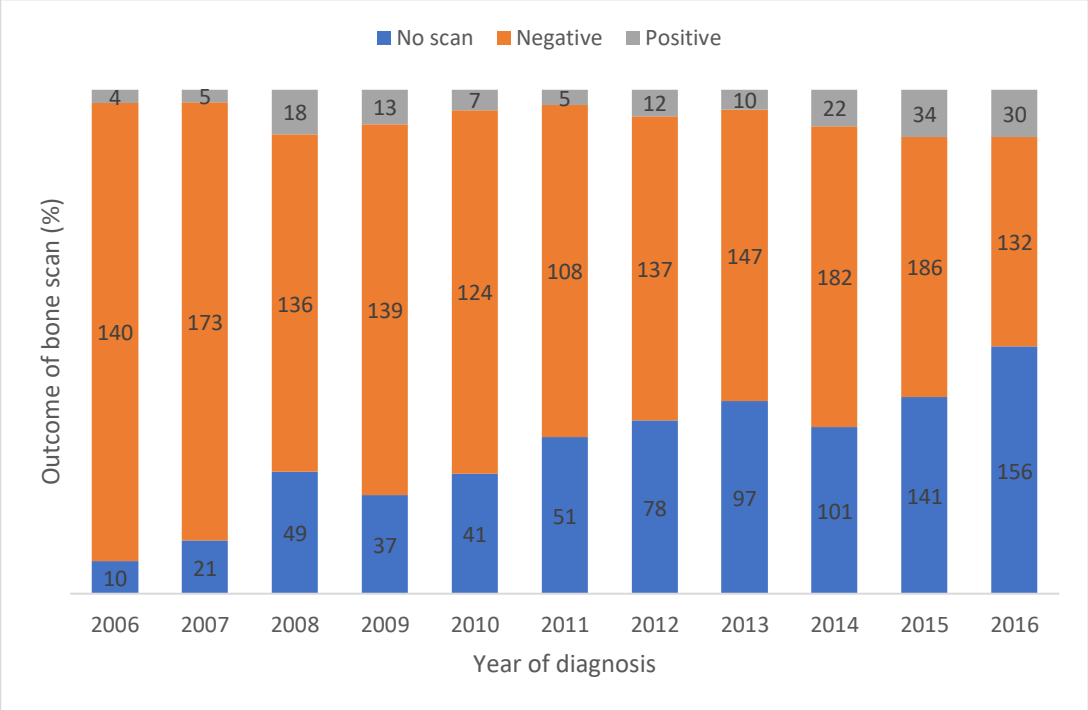


Figure 3.1. Graph to show the outcome of the isotope bone scan of patients discussed at the EPC MDT between 2006 and 2016. N=2546 (Equivocal scans and missing data not recorded).

3.5 Discussion

To date, the results from this study represent the largest single centre review of bone scan positivity rates in the UK. In men with intermediate risk disease only

0.1% were found to have a positive BS and this was only associated with ISUP grade group 3, no men classified as intermediate risk with ISUP grade <3, or men with low risk disease had a positive BS. These results support the guidelines published from the European Association of Urologists and recommend that BS be used in all newly diagnosed high risk men and those men with intermediate risk disease with ISUP grade 3.

The successful uptake of a classification or guideline is dependent upon relevance, accuracy and ease of use. The D'Amico classification remains the most widely used means of classifying newly diagnosed prostate cancer largely due to these factors. Despite many other risk classifications existing D'Amico remains the preferred choice in many national guidelines and research publications. Some of the guidelines recommending the use of staging BS do not include clearly defined risk groups and can therefore be hard to remember and implement. When reviewing the different guidelines on BS usage (Table 3.1) EAU are the most specific regarding the high-risk group and a specific sub-group of intermediate risk patients.

When making recommendations based on clinical stage it must be remembered that this can be very subjective and hence unreliable (Reese et al., 2011). There has been debate regarding the subgroups within clinical T2 disease as across this group all three D'Amico risk categories are represented. There is evidence to suggest that T2c disease should be re-classified as representing intermediate risk disease given that it behaves like this in the context of no other high risk features (Klaassen et al., 2015). There has also been debate as to whether or not clinical stage alone is an independent predictor of BS positivity (Al-Ghazo et al., 2010), however, we have shown along with a number of other UK studies that it is an independent predictor (Ayyathurai et al., 2006, O'Sullivan et al., 2003). In this study, when the clinical stage was excluded, and only patients that were defined by Gleason ≥ 8 or PSA ≥ 20 had had a bone scan, a significant percentage of men with primary pattern 4 disease with a positive BS that would have been missed (around 6%). If clinical stage was factored in, and D'Amico classification used, then this dropped to 1%. This goes against the results from the previous largest study within the UK that

reported a 100% negative predictive value for a positive bone scan when the Gleason score was less than 8 and the PSA was <20 ng/ml (McArthur et al., 2012). Other UK based studies, on a smaller scale, suggested not doing a BS for men with Gleason score <8, clinical stage < T4 and PSA < 20 ng/ml unless primary pattern 4 which is some way towards what our findings suggest but eliminating T3 disease may exclude men with high-risk disease (O'Sullivan et al., 2003, Ayyathurai et al., 2006) Our results suggest the uses of D'Amico classification which obviously includes clinical T-stage as an essential parameter.

Previous studies that have compared the effectiveness of the various guidelines have yielded encouraging results regarding their accuracy. Briganti et al compared EAU, AUA, NCCN and AJCC guidelines with their own CART analysis model. The CART model, or risk stratification tool, divided patients up in to different risk groups and the likelihood of a positive scan. The low risk group included was subdivided into 2 groups; the first with a Gleason score of $\leq$7 and cT1 disease giving a 0.2% chance of BS positivity and the second, with same Gleason score, but including cT2-3 disease with a PSA $\leq$10 giving a 1.3% chance of positive BS. The intermediate risk group was again Gleason $\leq$7, cT2-3 but a PSA > 10 and conferred an 8.3% chance of a positive BS. The high-risk group included Gleason $\geq$8 and conferred a risk of 16.9% positive BS. They concluded it was more accurate than the guidelines assessed with a higher sensitivity. It did, however, include two low risk groups, one of which included patients with clinical T3 disease and was tested in men being considered for radical prostatectomy so therefore must be viewed with caution (Briganti et al., 2010).

Further, external validation of the CART model by De Nunzio, compared CART to EAU guidelines and reported on slightly better accuracy for the CART model but encouragingly excellent negative predictive values of 97% for CART and 98% for EAU. It must also be said that the EAU guidelines compared were from 2011 and did not specify clearly the distinction that intermediate risk patient with primary pattern 4 be scanned (Abdollah et al., 2015). Further studies comparing the CART

model to other national guidelines, this time the AUA and NCCN guidelines, again highlighted similar results and concluded that criteria for performing a BS of PSA >20 and a Gleason score of >7 would lead to fewer negative scans being performed.

Currently BS remains the most common imaging modality. However, whole body MRI does have superior sensitivity over BS (Gutzeit et al., 2009) and is more sensitive and specific than BS combined with plain radiography and CT images (Pasoglou et al., 2014). MRI detects early changes within the haemopoeitic compartment of the bones where normal cells and associated fat cells are replaced by tumour cells (Tombal and Lecouvet, 2012). This change is prior to the osteoblastic reaction that is identified on BS and plain radiographs and hence provides MRI imaging with an advantage over BS. The main issues with remain MRI cost, availability of the technology on a wide enough scale and operator time. BS remains a relatively simple procedure to perform whereas multi-sequence MR can be more complex and take longer to perform. This however, should not be the main driver behind a change to a more sensitive and specific test. Also, as MRI is now offered pre-biopsy, if one is to avoid repeated MRI scans men will need to be triaged appropriately as to the risk of metastatic disease to determine whether they undergo upfront whole body MRI or pelvic MRI.

Choline PET/CT has also been shown to have a higher specificity for bone metastases than BS but it is not clear if it is more sensitive. Perhaps, most promising is PSMA PET/CT which potentially has sensitivity and specificity levels approaching 100% (Mottet et al., 2017a). Unfortunately, little evidence exists to confirm if the effect that these different imaging modalities has on the detection of metastatic disease affects outcomes and how best to treat these men with potentially low volume metastatic disease. Although recent evidence from the Stampede trial may be encouraging to men with low volume metastatic disease (Parker et al., 2018) with survival advantage to men who received radiotherapy to prostate in addition to standard of care hormone therapy.

Despite encouraging new imaging modalities, it is clear is that within current UK practice local MRI staging and bone scan +/- CT imaging remain the most commonly used modalities for the investigation of suspected metastatic disease. At present NICE guidelines do not currently recommend the use of PET CT in routine clinical practice or whole body MRI (NICE., 2019) and with this in mind, this study has provided essential further evidence to support the use of BS in a select population.

This study does have some limitations. The presence of metastases has not been histologically confirmed. There may also be a small margin of error in reporting but this will be hopefully minimised by the fact that all cases have been discussed and reviewed at a specialist MDT. As discussed in chapter 2, we report on the data from a large MDT database with a low data quality error rate and therefore believe that these findings are truly representative. In positive BS cases, all parameters have been reviewed and are correct. It must also be remembered that the data has been collected on a prospective basis over 20 years, at a single centre specialist MDT, with many senior clinicians remaining the same throughout and it is the single largest UK study reporting BS positivity rates to date.

3.5.1 Conclusion

In summary, we have shown that BS can be safely omitted for men with intermediate risk disease with ISUP grade group 2. However, for intermediate risk disease with ISUP grade group 3 and high risk disease BS should be performed. This is in line with and supports the recommendations of the current EAU guidelines.

Chapter 4. Has improved MRI technology and protocol improved the accuracy of pre-operative staging and subsequent rate of upstaging at radical prostatectomy

4.1 Introduction

Pathological grading and staging following radical prostatectomy (RP) provides the most accurate assessment of local disease status and the outcome of such can have a significant impact on the risk of disease recurrence and subsequent long-term survival.

As discussed previously the use of MDTs has been shown to improve cancer outcomes providing consensus expert opinion and hence improving diagnostic accuracy and treatment decisions.

Over the period of 20 years of the EPC MDT there have been changes in the staging and grading of prostate cancer. Advances in MRI technology have brought about changes in how it used in the diagnostic pathway, with transition from not providing MRI in may centres to the present day where it is recommended all patients be imaged with mpMRI; with recent evidence suggesting possible safe omission of prostate biopsies in patients with a low risk of harbouring significant prostate cancer.

In the 20 years of the EPC MDT all appropriate patients have been offered MRI staging and all have been reviewed at MDT providing contemporary expert radiological staging. Initial MRI scans were standard T2 weighted (T2W) and were performed post biopsy, in 2012 this changed to bi-parametric MRI (bpMRI) with T2W and diffusion weighting (DWI), and in 2014 MRI was introduced prior to prostate biopsy.

All diagnostic parameters and post-surgical pathology reports have been MDT reviewed and therefore analysis of this dataset provides important information as to the outcomes of men undergoing surgery for newly diagnosed prostate cancer.

4.2 Aims

The aims of the chapter are -

1. Review the radical prostatectomy dataset

    a. Report on the disease characteristics and staging results of all men undergoing RP as a primary treatment following EPC MDT.
    b. Compare the pre-operative staging and grading parameters with the prostatectomy pathology.
    c. Assess predictive markers of biochemical recurrence.

2. Assess the accuracy of MRI staging

    Compare the staging accuracy of MRI over the time of EPC MDT and effect that different MRI technique and timing has had on:

    a. The correlation between a positive MRI (detectable lesion) and different associated prognostic features such as Gleason score, clinical stage, PSA etc.
    b. The effect of upstaging after radical prostatectomy.

4.3 Methods

4.3.1 Service evaluation

This study was approved as part of service evaluation by the surgical directorate, UHW, Cardiff.

4.3.2 Patient population

A separate database of prostatectomy patients was created using the EPC database to identify all men undergoing surgery as a primary treatment for newly diagnosed CaP. All cases with a planned treatment of radical prostatectomy were included for analysis. All prospectively collected pre-operative staging data from the EPC

database was included for analysis. Prostatectomy pathology data and post-operative PSA record was obtained from clinical reports available on the hospital results reporting system. The need for adjuvant treatment was also based upon information available on the hospital results system and CANSIC (the all Wales Cancer Network database).

All cases recorded between 1997 and February 1st, 2017 were reviewed. 878 patients were recorded as having had a prostatectomy. 91 cases were excluded from analysis for reasons as explained in Table 4.1. Therefore, 787 cases were analysed.

No prostatectomy pathology reports	69
Awaiting surgery	12
Surgery elsewhere	6
No pre-operative staging data	2
Prostatectomy abandoned	2
Total excluded	**91**

Table 4.1 Reasons for excluded cases not included in overall analysis.

UHW, Cardiff was a recruitment centre for the ProtecT study. These patients were excluded from analysis to avoid any potential bias. Only patients discussed at the EPC sMDT and recorded as having radical prostatectomy as the primary treatment were included in this study.

4.3.3 Data analysis

All staging and grading data was as recorded on the EPC database. For radiological staging PIRADS or LIKERT scores were not recorded and the radiological T-stage reported in this study is as was recorded at the time of MDT discussion. For clinical and pathological T-stage, clinical T-stage was subdivided as per TNM classification, however, for pT2 disease it was not subdivided as very few pathological reports included this detail. Margin status was reported as positive and negative as reported length of margin status was again not included in many cases. The dominant tumour was classified as largest tumour irrespective of Gleason grade. In cases when the

dominant tumour was not the area with the highest Gleason grade this was recorded. Biochemical recurrence was defined as per EAU guidelines as two consecutive PSA rises ≥0.2ng/ml and the time to this was defined by the second elevated reading (Mottet et al., 2017b).

Data was collected on using an excel database and transferred to SPSS for statistical analysis.
Chi-square tests were used to analyse differences between groups and binomial logistic regression was performed where appropriate to assess for significant independent variables.

The PROMIS trials definitions of clinically significant and non-significant cancer were used to subdivide groups for comparison. Definition 1 of clinically significant cancer is Gleason ≥4+3 or MCCL ≥6mm. Definition 2 of clinically significant cancer is Gleason ≥3+4 or MCCL ≥4mm (Ahmed et al., 2017).

4.4 Results

4.4.1 Prostatectomy data set

4.4.1.1 Pre-operative staging data

As discussed, 787 cases are presented. There was a general rising trend for the number of prostatectomies performed each year with a peak of 100 cases in 2015. This is important to note when understanding follow-up time and reflects an increasing surgical practice within our centre (Figure 4.1).

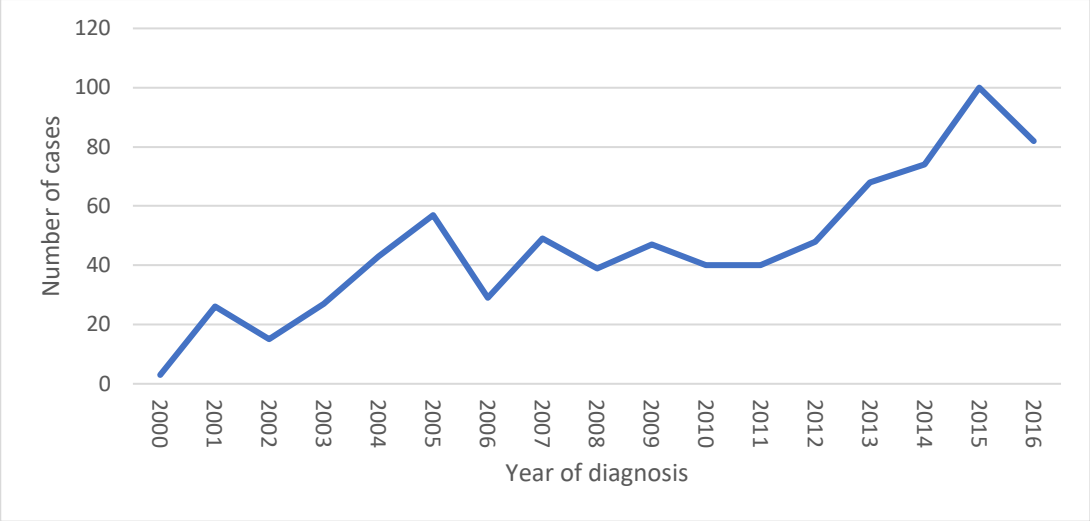


Figure 4.1. Graph to show the number of radical prostatectomies performed each year, 2000 to 2016. (N= 787).

The median age of men having surgery was 62 years (range 39-77), with a median PSA of 7.3. There were very similar numbers of men with clinical T1 and T2 disease with only 2.5% of men having T3 disease. Again, there were similar numbers of men with Gleason 6 and 7 disease with very few men having surgery with Gleason 8,9 or 10 disease. Most men had ISUP grade group 1 or 2 disease with only 11.6% having grade group 3 or higher. Median maximum cancer core length (MCCL) was 6mm (range 1-25mm). In total, 33.9% of men had D'Amico low risk disease, 51.5% were intermediate-risk and 14.6% were high-risk (Table 4.2).

Number of patients	787
Age (years)	
Mean	61.6
Median	62
Range	39 to 77
PSA	
Median	7.3
Range	0.6 to 70
Clinical T stage (%)	
T1	353 (44.9%)
T2	339 (43.1%)
T3	20 (2.5%)
Not known	75 (9.5%)
MRI T stage (%)	
T1	273 (34.7%)
T2	472 (60%)
T3	22 (2.8%)
Not done	20 (2.5%)
ISUP grade group (%)	
1	395 (50.2%)
2	301 (38.2%)
3	51 (6.5%)
4	17 (2.2%)
5	23 (2.9%)
% of positive cores	
Median	37.5%
Range	5-100%
Maximum core length (MCCL)	
Median	6mm
Range	1-25mm
Range	4-100%
D'Amico risk classification (%)	
Low	267 (33.9%)
Intermediate	405 (51.5%)
High	115 (14.6%)

Table 4.2 Presenting patient demographics and disease features of men undergoing radical prostatectomy for newly diagnosed prostate cancer, 2000 to 2016.

Men were also defined according to the PROMIS study criteria for significant cancer using both definition 1 and definition 2. Using these definitions, 53.9% (408/757) men were defined as having significant cancer according to definition 1 and 75.6% (572/757) were defined as having significant disease based on definition 2. There were significant differences between the relationship ISUP grade groups and MCCL. This was seen when MCCL was defined as significant at ≥ 4 or 6mm, with much lower rates of higher Gleason grades when MCCL was less than 4 or 6mm (Table 4.3 and 4.4).

ISUP Grade Group	**Maximum cancer core length**		**Total**
	<6mm	**≥6mm**	
1	263	118	381
2	86	200	286
3	16	35	51
4	4	13	17
5	3	19	22
Total	372	385	757
Chi square	P <0.001		
No. with PROMIS definition 1 **– 408** (with both criteria available)			
No. with PROMIS definition 1 – **409** (with at least one criteria present)			

Table 4.3. Table to identify the number of men with significant prostate cancer, as defined by PROMIS definition 1.

ISUP Grade Group	Maximum cancer core length		Total
	<4mm	**≥4mm**	
1	185	196	381
2	37	249	286
3	9	42	51
4	1	16	17
5	1	21	22
Total	233	524	757
Chi square	P <0.001		
No. with PROMIS definition 2 – **572** (with both criteria available)			
No. with PROMIS definition 2 – **588** (with at least one criteria present)			

Table 4.4. Table to identify the number of men with significant prostate cancer, as defined by PROMIS definition 2.

4.4.1.2 Post-operative staging data

Overall, a quarter of radical prostatectomies were performed robotically with the remainder via an open procedure. Most (83.8%) were classified as either ISUP grade 1 or 2 with a roughly equal proportion between the two groups. Only 12.1% were ISUP group 3 and 4.6% were ISUP group 4 and 5. 59.3% of tumours were pathologically staged as T2 and 40.7% were staged as T3 (Table 4.5).

Type of prostatectomy (%)	
Robotic	202 (25.7%)
Open	585 (74.3%)
Gleason score	
5	5 (0.6%)
6	312 (39.6%)
7	432 (54.9%)
8	14 (1.8%)
9	23 (2.9%)
Total	786 (1 missing)
ISUP grade group	
1	317 (40.3%)
2	337 (42.8%)
3	95 (12.1%)
4	14 (1.8%)
5	23 (2.9%)
Total	786 (1 missing)
Pathological T stage	
T2	466 (59.3%)
T3a	268 (34.1%)
T3b	52 (6.6%)
T4	1 (0.1%)

Table 4.5. Table to highlight the pathological grading (Gleason and ISUP grade group) and staging of men having radical prostatectomy between 1997-2017, n=787.

4.4.1.3 Upstaging and upgrading rates

The rate of upstaging and upgrading between diagnostic investigations and prostatectomy specimen was also reviewed. The rate of concordance between pre-operative grading and prostatectomy grading was between 29.4% and 72%. The best rates were achieved for ISUP grade group 2 where concordance was 72% with a very similar number being upgraded and downgraded. The rate of upgrading for Gleason grade group 1 was around 30.7%. As one might expect there was much lower rates of concordance for ISUP group 4, as this group includes 3+5, 5+3, 4+4 and is more

prone to change when whole specimen is available for analysis. Within this group just over a third were downgraded to ISUP group 2 (Table 4.6).

Diagnosis	**Pathological ISUP grade**					**Total**
ISUP grade group	**1**	**2**	**3**	**4**	**5**	
1	278 (70.3%)	*104 (26.3%)*	*12 (3%)*	*1 (0.4%)*	0	395
2	36 (12%)	216 (72%)	*42 (14%)*	*5 (1.7%)*	*1 (0.3%)*	300
3	3 (5.9%)	11 (21.6%)	30 (58.8%)	*3 (5.9%)*	4 (7.8%)	51
4	0	6 (35.3%)	5 (29.4%)	5 (29.4%)	*1 (5.9%)*	17
5	0	0	6 (26.1%)	0	17 (73.9%)	23
Total	318	337	95	14	23	786

Table 4.6. Table to compare the difference between pre-operative ISUP grade group from TRUS biopsy to ISUP grade group from radical prostatectomy specimen, n=786 (1 patient did not have record of prostatectomy grading).

When comparing the rate of upstaging, from clinical T stage at diagnosis compared to pathological stage, there was an overall rate of 74.9% (533/712). This rate is high and does not factor in MRI staging and a MDT consensus stage (i.e. combined MRI and clinical stage). There were many men with clinical T1 disease and obviously, this accounts for the large number of cases of upstaging. When looking at just cT2 disease or higher there was an upstaging rate of 52.2% (177/339) (Table 4.7).

Clinical	**Pathological T-stage**				**Total**
T-stage	**T2**	**T3a**	**T3b**	**T4**	
N/A	54	19	3	0	75
T1	*244*	*91*	*14*	0	353
T2a	115	*97*	*17*	0	231
T2b	38	*39*	*10*	0	89
T2c	5	*8*	*5*	*1*	19
T3a	3	13	*3*	0	19
T3b	0	1	0	0	1
Total	466	268	52	1	787

Table 4.7. Table to compare the clinical stage at diagnosis with the pathological T stage. Pathological stage was just recorded as T2 and not further sub-divided. N/A = not recorded on the database.

4.4.1.4 Tumour characteristics

Further analysis was performed detailing tumour characteristic and prostate size and relationship with tumour. Just under two-thirds of men had multifocal tumours. The dominant tumour was defined as the tumour with the largest volume (95% of these tumours correlated with the area of highest Gleason grade i.e. the largest tumour was also the highest grade). The median volume of dominant tumour was 1.9cc with median total tumour volume just higher at 2.2cc. Ratio of tumour volume was also calculated and can be seen in Table 4.8.

Tumour multi-focality	
Yes	491 (62.4%)
No	296 (37.6%)
Length of Gleason dominant tumour	
N	772 (15 missing)
Median	22mm (5 to 84.5)
Volume of Gleason dominant tumour	
N	772 (15 missing)
Median	1.9cc (0.1 to 34.0)
Total tumour volume	
N	723 (64 missing)
Median	2.2cc (0.1 to 34.0)
Prostate weight	
N	775 (12 missing)
Median	44g (16 to 165)
Dominant tumour volume to prostate weight ratio	
N	761 (26 missing)
Median	0.043 (0.01 to 0.861)
Total tumour volume to prostate weight ratio	
N	713 (74)
Median	0.05 (0.01 to 0.861)

Table 4.8. Tumour characteristics within the prostatectomy pathological analysis.

4.4.1.5 Margin status

80.1% (630/787) of men had negative surgical margins and 19.6% (154/787) were reported positive. There were 3 (0.4%) equivocal reports. As one would expect, there was a statistically significant difference between the pathological T stage and margin positivity rates. There was a 12.9% positivity rate for men with T2 disease, 28.4% for men with T3a disease and 32.7% for men with T3b disease, or 29% for T3 disease (Table 4.9).

Pathological stage	Margin positivity rates
T2	12.9% (60/466)
T3a	28.4% (76/268)
T3b	32.7% (17/52)
T4	100% (1/1)
Chi-square	P value <0.001

Table 4.9 Margin positivity rates according to pathological T-stage.

When comparing the margin positivity rates between different pre-operative disease parameters we see similar rates for clinical and radiological T-stages with T1 disease conveying a 15% risk and this rising consistently with a higher T stage. Clinical T3 disease conveys a 50% risk and is higher than that seen radiologically. A low risk PSA level conveys a similar risk of margin positivity to that of clinical and radiological T1 disease at 16% and 1 in 3 men with a PSA of greater than 20 had positive surgical margins. The difference in positivity rates between clinical and radiological T stages and PSA groups were significant and as expected saw higher rates with more aggressive disease. Interestingly this statistical significance was not seen for ISUP grade group although higher rates were seen with more aggressive disease (Table 4.10).

cT-stage	**Pos.rate**	**MR T-stage**	**Pos.rate**	**PSA group**	**Pos.rate**	**ISUP group**	**Pos.rate**
N/R	13.3%	**No MRI**	15.8%	**0-9.9**	16.5%	**1**	18%
T1	15%	**T1**	15%	**10-20**	23.8%	**2**	19.9%
T2a	21.2%	**T2a**	16.3%	**>20**	33.3%	**3**	23.5%
T2b	27%	**T2b**	27.7%			**4**	29.4%
T2c	42%	**T2c**	36.6%			**5**	26%
T3a	52.6%	**T3a**	38.9%				
T3b	0%	**T3b**	50%				
Overall	**19.6%**		**19.6%**		**19.6%**		**19.6%**
Chi-square	**<0.001**		**<0.001**		**0.004**		**0.585**

Table 4.10. Pre-operative diagnostic parameters and their associations with margin positive resection at radical prostatectomy.

The margin positive rates between different risk groups was assessed. When defining patients according to the PROMIS study criteria similar rates of positivity were similar for significant cancer whether using definition 1 (Gleason ≥4+3 or MCCL ≥6mm) or 2 (Gleason ≥3+4 or MCCL ≥4mm). If one were to define patients by D'Amico risk similar rates were seen between low and intermediate-risk disease but as one might expect high-risk cases had a much higher rate at nearly 1 in 3 men (Table 4.11).

PROMIS Def. 1	Pos.rate	PROMIS Def. 2	Pos.rate	D'Amico group	Pos.rate
No significant Cancer	17.1%	**No significant Cancer**	14%	**Low**	16.9%
Significant cancer	21.5%	**Significant cancer**	21.1%	**Intermediate**	18.8%
				High	31.3%
Overall	**19.6%**		**19.6%**		**19.6%**
Chi-square	**0.134**		**0.035**		**0.002**

Table 4.11. Pre-operative disease classification as per D'Amico or PROMIS 1 or PROMIS 2 criteria for significant cancer and association with positive margins.

The effect of post-operative pathological markers on margin positive rates was also assessed. Interestingly the rate of positivity for pathological T3a disease was only 28.4% compared with 52.6% for clinical T3a disease. Although I suspect this can be attributed to the lack of patients being assigned clinical T3b disease and if one is to think of T3 as one group comparative positivity figures would be 52.6% versus 61.1% for cT3 and pT3 disease respectively. Again, there was no significant difference seen between different ISUP grade groups although higher rates were seen for groups 4 and 5. Both pT-stage and volume of dominant tumour were shown to have statistically significant different rates of positivity between the different groups. As one would expect higher T-stage and larger tumours were associated with higher rates. No difference was seen between the surgical approach (Table 4.12).

pT-stage	Pos.rate	ISUP group	Pos.rate	Dom. TV (ml)	Pos.rate	Method	Pos.rate
T2	12.9%	**1**	17%	**<0.5**	6.5%	**Robotic**	20.3%
T3a	28.4%	**2**	19.9%	**0.5-0.99**	10.1%	**Open**	19.3%
T3b	32.7%	**3**	22.1%	**1-1.99**	16.7%		
T4	100%	**4**	35.7%	**2-4.99**	19.3%		
		5	30.4%	**>5**	37.7%		
Overall	**19.6%**		**19.6%**		**19.6%**		**19.6%**
Chi-square	**<0.001**		**0.219**		**<0.001**		**0.762**

Table 4.12. Post-operative staging parameters and association with positive margins.

4.4.1.6 Biochemical recurrence rates

The rates of biochemical recurrence were reviewed. As discussed BCR was defined as two separate PSA readings ≥0.2ng/ml. Of the patients with a recorded post-operative PSA level (778 of 787 patients) 5.1% had a detectable PSA (≥0.1ng/ml) at the first check (at least 6 weeks after the operation).

Of the total cohort, 8.9% of patients had immediate adjuvant therapy. Excluding patients who had a detectable PSA and/or immediate adjuvant therapy, there were 680 that were assessed for true BCR. 11.6% (79/680) of patient developed BCR (Table 4.13). Median time to follow-up was 4.4 years (Table 4.14).

First post-op PSA (n=778, 9 missing)	
Less than 0.1	738 (93.8%)
0.1 or greater	40 (5.1%)
Immediate adjuvant treatment (n=771, 16 missing)	
Yes	70 (8.9%)
No	701 (89.1%)
Biochemical Recurrence (n=784, 3 missing)	
No	601 (76.7%)
Yes	79 (10%)
Yes, but post-adjuvant treatment	20 (2.5%)
No, but post-adjuvant treatment	38 (4.8%)
Not known	46 (5.8%)

Table 4.13. First post-operative PSA reading, number of patients receiving immediate adjuvant treatment and biochemical recurrence rates amongst men who underwent radical prostatectomy.

Time to follow-up	
Mean	4.8 years
Median	4.4 years
Range	0.1 to 15.4 years

Table 4.14. Time to follow-up following radical prostatectomy.

4.4.1.7 Pre-operative predictors of BCR

Clinical and radiological T-stage, PSA level at diagnosis and ISUP grade group at biopsy were reviewed to assess association with BCR rates. As one would expect clinical T-stage, PSA level and ISUP grade group were all associated with significant differences between subgroups with more aggressive disease showing higher rates of BCR. BCR rates for different radiological T-stages was not significantly different and the rate of BCR for T3 disease was nearly half that of clinical T3 disease. Rates of BCR for radiological and clinical T2c are very low compared to other T2 disease and which is surprising given that a high percentage (68.4%, Table 4.7) of clinical T2c was upstaged at prostatectomy (Table 4.15).

cT-stage	BCR rate	MR T-stage	BCR rate	PSA group	BCR rate	ISUP group	BCR rate
N/R	6%	**No MRI**	0	**0-9.9**	9.3%	**1**	7.5%
T1	7%	**T1**	9.4%	**10-20**	16.5%	**2**	16.7%
T2a	16.6%	**T2a**	14%	**>20**	15.6%	**3**	11.8%
T2b	14.1%	**T2b**	13.6%			**4**	10%
T2c	7.1%	**T2c**	3.4%			**5**	28.6%
T3a	50%	**T3a**	27.3%				
T3b	0	**T3b**	0				
Overall	**11.6%**		**11.6%**		**11.6%**		**11.6%**
Chi-square	**<0.001**		**0.079**		**0.032**		**0.003**

Table 4.15. Pre-operative diagnostic and staging results and the effect on rate of biochemical recurrence (BCR). Clinical and radiological T-stage, PSA level (represented as 3 different groups) and ISUP grade group. Chi-square tests performed to assess variation between groups.

BCR rate was also assessed on pre-operative risk group. Patients were categorised according to both PROMIS definition 1 and definition 2 and D'Amico risk group. As one would expect there was a significant difference between BCR rates between the significant and insignificant cancer groups for both PROMIS definitions and between the different D'Amico risk groups with higher rates seen for significant cancer and higher risk groups. The BCR rate for significant cancer was near identical for both PROMIS definition at 14% and 13.2%, for definition 1 and 2 respectively. This percentage was like that seen for D'Amico intermediate risk patients but was lower than the 18.2% seen for high risk disease (Table 4.16).

PROMIS Def. 1	**BCR rate**	**PROMIS Def. 2**	**BCR rate**	**D'Amico group**	**BCR rate**
No significant cancer	9.4%	**No significant cancer**	7.2%	**Low**	5.5%
Significant cancer	14%	**Significant cancer**	13.2%	**Intermediate**	14.5%
-		**-**		**High**	18.2%
Overall	**11.6%**		**11.6%**		**11.6%**
Chi-square	**0.065**		**0.031**		**<0.001**

Table 4.16. Pre-operative risk classification according to PROMIS definition 1 and PROMIS definition 2 and D'Amico risk group and associated BCR rate.

Binomial logistic regression was performed to assess for independent pre-operative predictors for BCR. Only clinical T-stage was found to be significant (P-value 0.016) when compared ISUP grade group, PSA level, percentage of positive cores, MCCL and age. For men with cT2a disease their risk of BCR was found to be twice that of men with cT1 disease and for men cT3 disease there was found to be an 8 times higher chance of BCR compared to men with cT1 disease (Table 4.17).

Clinical feature	P-value	Odds Ratio	95% CI
cT stage T1	0.016	-	-
cT stage T2a	0.023	1.958	1.097 – 3.493
cT stage T2b	0.616	1.251	0.521 – 3.000
cT stage T2c	0.448	0.436	0.051 – 3.716
cT stage T3a	0.006	8.236	1.838 – 37.133
ISUP group 1	0.225	-	-
ISUP group 2	0.058	1.795	0.981 – 3.284
ISUP group 3	0.897	1.092	0.289 – 4.124
ISUP group 4	0.517	2.055	0.233 – 18.153
ISUP group 5	0.078	3.703	0.862 – 15.913
PSA 0 – 9.9	0.117	-	-
PSA 10 - 20	0.058	1.746	0.980 – 3.110
PSA >20	0.230	1.938	0.657 – 5.715
% pos. cores	0.032	1.013	1.001 – 1.026
MCCL	0.334	0.960	0.885 – 1.042
Age	0.393	1.019	0.976 – 1.064

Table 4.17. Binomial logistic regression to determine pre-operative predictors of BCR. Clinical T-stage, ISUP grade group, PSA level, percentage of positive cores, maximum cancer core length and age were compared.

4.4.1.8 Post-operative pathological predictors of BCR

Post-prostatectomy pathological markers were also used to compare BCR rates. T-stage, ISUP grade group and margin status were compared. All 3 of these parameters were found to have significantly different BCR rates between their sub-groups. As one would expect higher T-stage, higher ISUP grade and margin positivity were all associated with higher rates of BCR. The size of the dominant tumour volume also affected BCR rates with low rates for very small tumours and much higher rates seen for larger tumours (Table 4.18).

pT-stage	BCR rate	ISUP group	BCR rate	Dom. TV (ml)	BCR rate	Margins	BCR rate
T2	8%	**1**	5.3%	**<0.5**	4.4%	**Positive**	24.5%
T3a	15.9%	**2**	16.4%	**0.5-0.99**	8%	**Negative**	9.1%
T3b	39.1%	**3**	12.5%	**1-1.99**	12.7%		
T4	0	**4**	37.5%	**2-4.99**	11.5%		
		5	26.7%	**>5**	20%		
Overall	**11.6%**		**11.6%**		**11.6%**		**11.6%**
Chi-square	**<0.001**		**<0.001**		**0.011**		**<0.001**

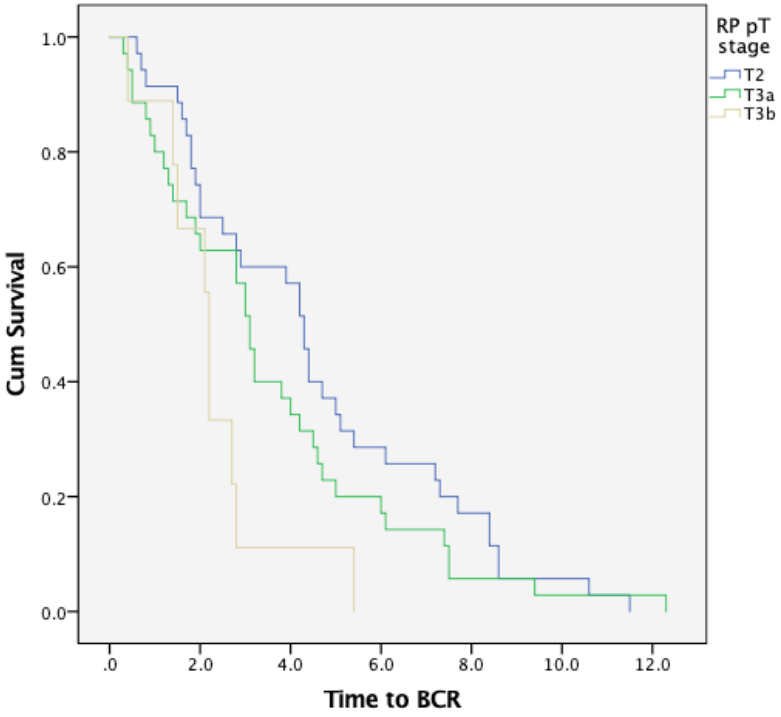
Table 4.18. Post-operative pathological features and association with biochemical recurrence rates.

Binomial logistic regression was also performed to assess for independent post-operative pathological predictors of BCR. Positive surgical margins, ISUP grade group and pathological T-stage were all significant independent predictors of BCR. The volume of the dominant tumour did not significantly affect the BCR rate. Men with a positive surgical margin were 3.5 times more likely to have BCR than those with negative margins. In those men with ISUP grade group 2 (Gleason 3+4) the risk of BCR was 3 times higher than for men with grade group 1 and was 17.5 times higher for men with grade group 4. For men with pT3a disease the risk of BCR was only marginally higher compared to those with T2 disease, however, men with T3b disease has just over 5 times increased risk of BCR (Table 4.19).

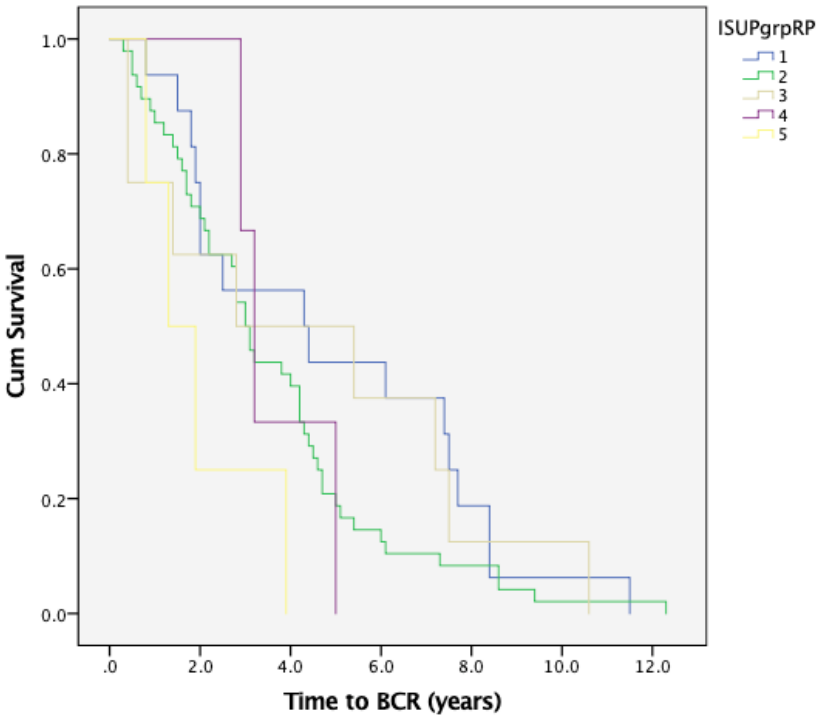
Pathological feature	P-value	Odds Ratio	95% CI
Margin Positive	<0.001	3.509	1.966 – 6.263
ISUP group 1	0.001	-	-
ISUP group 2	0.001	2.983	1.573 – 5.657
ISUP group 3	0.214	1.844	0.703 – 4.837
ISUP group 4	0.002	17.457	2.92 – 104.369
ISUP group 5	0.016	5.295	1.365 – 20.533
T stage – T2	0.015	-	-
T stage – T3a	0.620	1.160	0.645 – 2.085
T stage – T3b	0.001	5.192	1.880 – 14.339
T stage – T4	1.000	0	0
DT vol. <0.5ml	0.697	-	-
DT vol. 0.5-0.99	0.627	1.368	0.387 – 4.842
DT vol. 1 – 1.99	0.423	1.603	0.505 – 5.086
DT vol. 2 – 4.99	0.657	1.303	0.406 – 4.181
DT vol. >5ml	0.255	2.020	0.602 – 6.733

Table 4.19. Binomial logistic regression to determine post-operative pathological predictors of BCR. Margin status, T-stage, ISUP grade group and volume of dominant tumour (DT vol.) were compared.

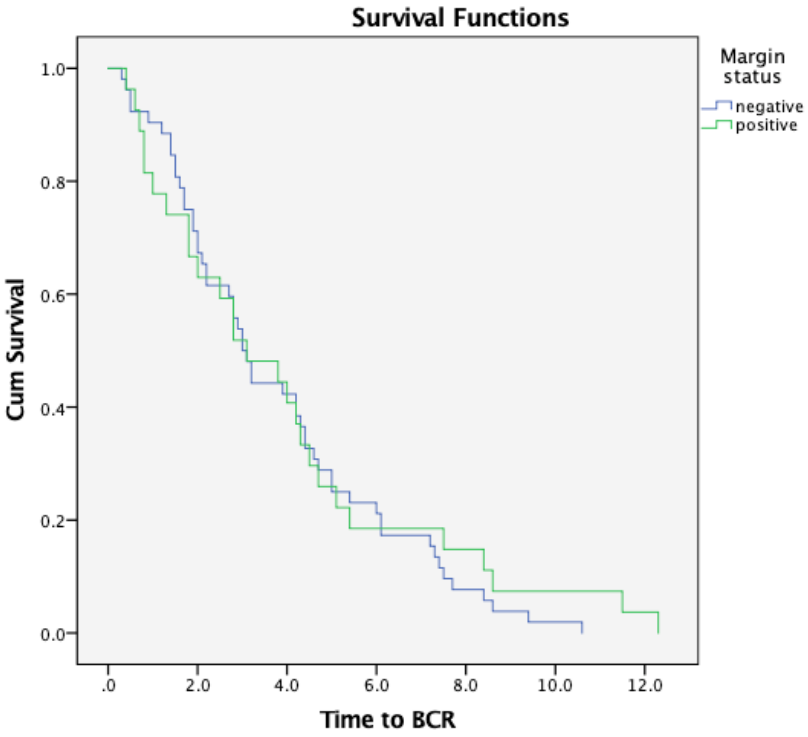
The median time to BCR was 3.1 years with a range of 0.3 years to 12.3 years. When assessing the time to biochemical recurrence only pathological T-stage was a significant factor with higher stage related to an earlier time of recurrence (p-value 0.040) (Graph 4.1). Although ISUP grade group and margin status predicted BCR they did not affect when it occurred. However, this is likely to be due to relatively small sample sizes of men with higher Gleason grades and/or a PSA of >20 rather than a true lack of significance. The dominant tumour size and overall tumour volume, multi-focality, age or PSA at diagnosis did not affect timing of BCR (Graphs 4.2-8).



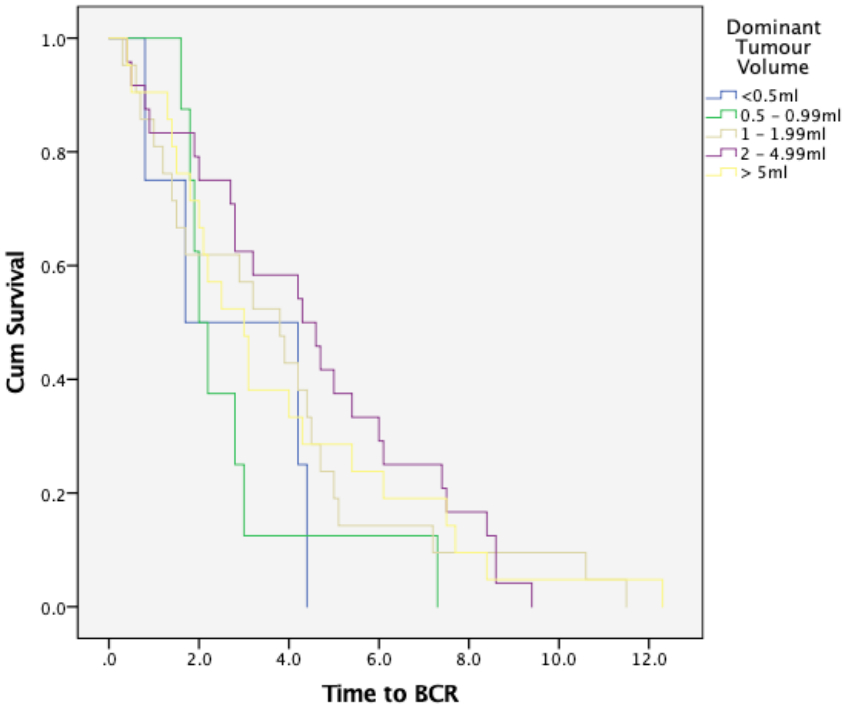
Graph 4.1. Kaplan-Meier curve assessing pathological T-stage and influence on time to BCR. T-stage significantly affected time to recurrence with log rank P-value 0.040.



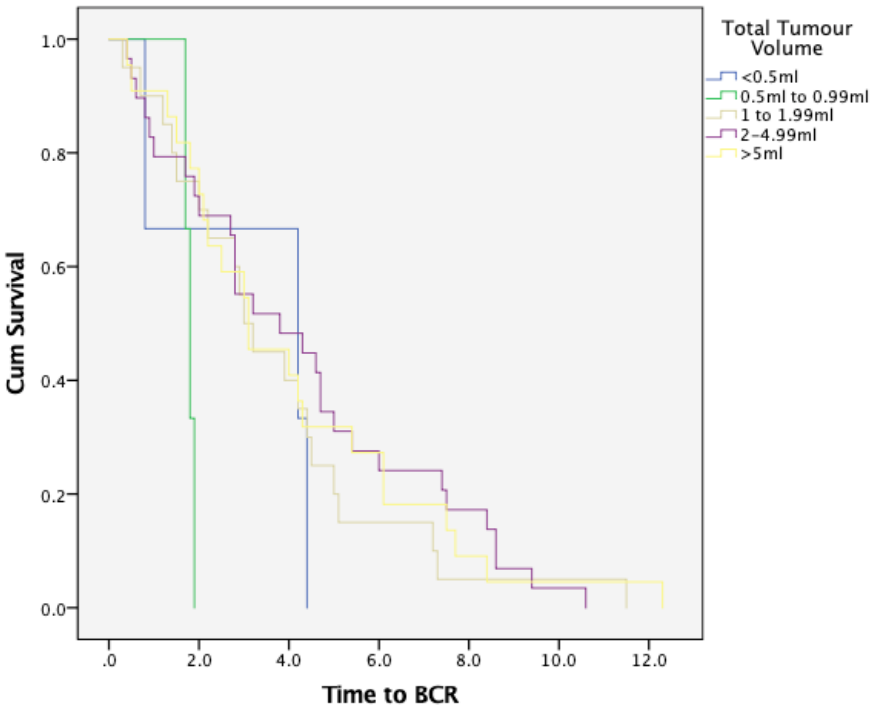
Graph 4.2. Kaplan-Meier curve assessing post-operative pathological ISUP grade group and its effect on time to BCR. No significant difference was found between the different groups and time to BCR. Log rank p-value 0.159.



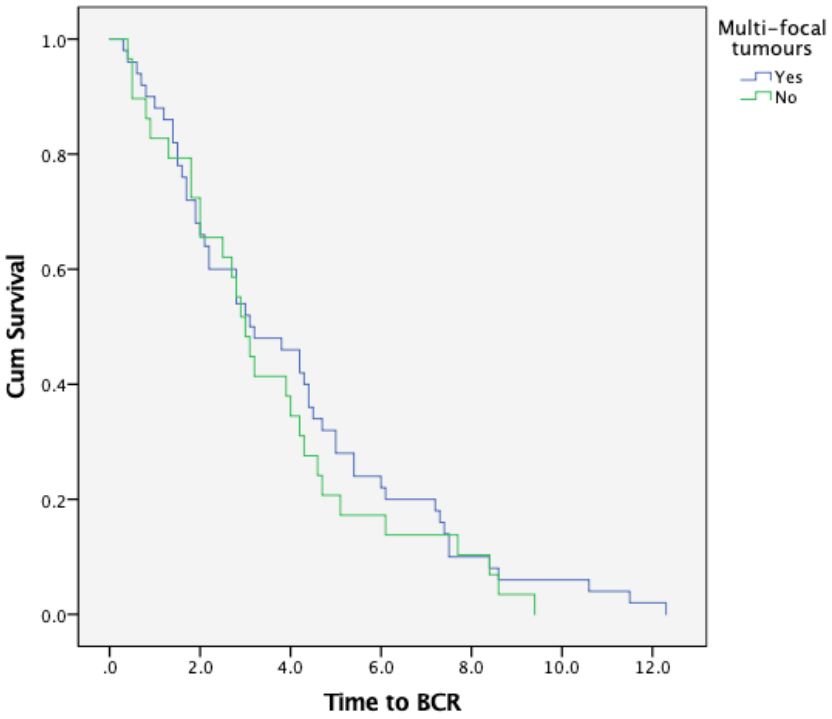
Graph 4.3. Kaplan-Meier curve assessing radical prostatectomy margin status and impact on time to BCR. No significant difference was seen between the groups. Log rank p-value 0.597.



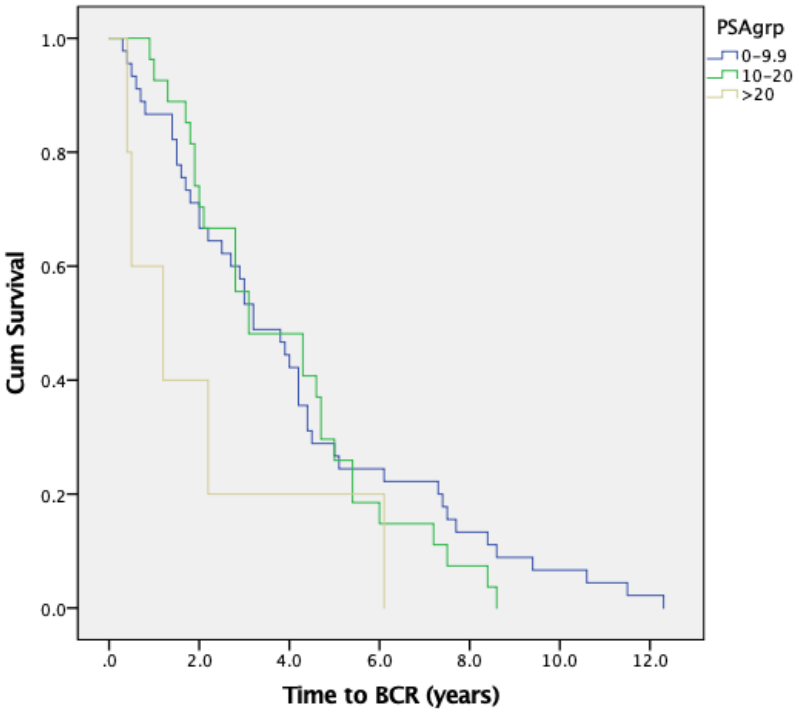
Graph 4.4. Kaplan-Meier curve assessing effect on dominant tumour volume on time to BCR. No significant difference was seen between the different tumour size groups. Log rank p-value 0.391.



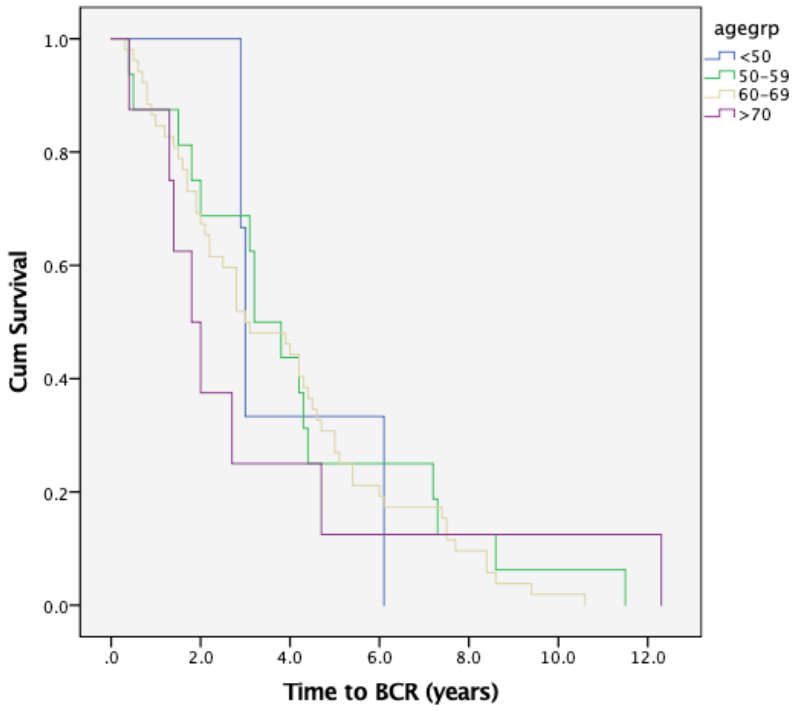
Graph 4.5. Kaplan-Meier curve assessing effect on total tumour volume and time to BCR. No significant difference was seen between the groups. Log rank p-value 0.173.



Graph 4.6. Kaplan-Meier curve assessing effect of tumour multi-focality on time to BCR. No significant difference was seen between solitary or multifocal tumours. Log rank p-value 0.465.



Graph 4.7. Kaplan-Meier curve assessing effect of PSA at diagnosis on time to BCR. No significant difference was seen between the PSA groups. Log rank p-value 0.187.



Graph 4.7. Kaplan-Meier curve assessing effect of age at diagnosis on time to BCR. No significant difference was seen between the age groups. Log rank p-value 0.985.

4.4.2 MRI staging data

As with the prostatectomy dataset 787 patients were assessed, 20 patients who had undergone radical prostatectomy did not have an MRI scan. Therefore, 767 men who had received an MRI scan as part of pre-operative staging were included for analysis. Overall, 459 (59.8%) men had a post-biopsy non-bpMRI, 224 (29.2%) had a post-biopsy bpMRI and 85 (11.1%) men had a pre-biopsy bpMRI (Table 4.20).

Bi-parametric MRI	**MRI timing**		**Total**
	Pre-biopsy	**Post-biopsy**	
No	0	458 (67.1%)	458
Yes	85 (100%)	224 (32.9%)	309
Total	85	682	767

Table 4.20. Type of MRI staging scan performed and timing with respect to TRUS biopsy in all men who then went on to receive radical prostatectomy as primary treatment.

When assessing the overall upstaging rates across all patients 65.6% were noted to have radiological upstaging (comparison of radiological T-stage with pathological T-stage). This is lower than the rate of 74.9% for clinical upstaging. Around 40% of those patients who were upstaged were from radiological T1 disease (a normal scan) to pT2. Around 1 in 3 men were accurately staged and only 0.5% of men were down staged after surgery (Table 4.21 and 4.22).

MRI T-stage	Pathological T-stage				Total
	T2	T3a	T3b	T4	
Not done	15	3	2	0	20
T1	203	63	7	0	273
T2a	148	122	24	0	294
T2b	84	43	10	0	137
T2c	12	23	5	1	41
T3a	3	13	2	0	18
T3b	0	1	3	0	4
Total	464	268	53	1	787

Table 4.21. Comparison of pre-operative radiological (MRI) T-stage compared with pathological T stage at radical prostatectomy.

Change in T-stage from MRI to pT stage	Frequency
Same T stage	260 (33.9%)
Upstaged	503 (65.6%)
- **Upstage from T1 to pT2**	203
- **Significant upstage**	300
Downstage	4 (0.5%)
Total	767

Table 4.22. Overall change from pre-operative radiological T-stage compared to pathological T-stage at radical prostatectomy. Significant upstage was classified as from cT1 to pT3 or higher, or from cT2 to pT3 or 4. There were no cases of upstaging for cT3 disease.

The rate of upstaging was compared across the three different groups who had received either a post biopsy non-bpMRI (defined as group 1), a bpMRI scan post-biopsy (group 2), or a pre-biopsy bpMRI (group 3). Those men in group 1 had a lower overall rate of upstaging (63.5%) compared with Group 2 and 3 which very similar at around 68%. The rate of upstaging from T1 to T2 disease fell from Group 1 where it was 31%, to 21.9% in group 2 and 14.1%. There was a higher rate of disease upstaging from T2 to higher stage for men in group 3 compared to group 2 and group 1 (54.1%, versus 46.9% versus 32.5% respectively). If one were to exclude the patients upstaged from T1 to T2 the overall rates of significant upstaging, from T2 to greater, in groups 1, 2 and 3 would still be significantly different with rates of 47%,

60% and 63% respectively (chi-square p-value <0.001). The rate of no change was roughly equal men between the 3 groups at 30 to 36% (around 1 in 3 men) (Table 4.23).

MRI type and timing	Change from MRI T-stage to Pathological T stage				Total
	Downstage	T1 to T2	Significant upstage	No change	
Group 1	2 (0.4%)	142 (31%)	149 (32.5%)	165 (36%)	458
Group 2	1 (0.4%)	49 (21.9%)	105 (46.9%)	69 (30.8%)	224
Group 3	1 (1.2%)	12 (14.1%)	46 (54.1%)	26 (30.6%)	85
Total	4	203	300	260	767

Table 4.23 Comparison of radiological T-stage and post-prostatectomy pathological T-stage and effect that timing and type of MRI scan had on rate of upstaging. Chi-square P-value <0.001.

Given the significant difference in rates of upstaging in from both T1 to T2 disease and from T2 to higher (significant upstaging) the three different MRI groups were compared according to PROMIS 1 and 2 definitions of significant cancer. Again, there were higher rates of men with significant cancer in Group 1 for men that were upstaged from T1 to T2 disease. There was also a higher rate of men that were upstaged from T2 disease to higher in Group 3 compared to Groups 2 and 1, with the rate of significant upstaging again lowest in group 1 (Table 4.24).

	% of significant PROMIS 1 def.			% of significant PROMIS 2 def.		
	Upstage T1 to T2	Upstage T2 to higher	No change	Upstage T1 to T2	Upstage T2 to higher	No change
Group 1	14.2%	50%	35.3%	21.6%	40.5%	37.3%
Group 2	10.7%	57%	32.2%	16.1%	50.5%	32.8%
Group 3	9.4%	60.9%	28.1%	14.1%	55.1%	29.5%

Table 4.24. Proportion of men with significant cancer at diagnosis according to PROMIS definitions 1 and 2 and the rates of upstaging of disease from pre-operative MRI to pathological T-stage. Grouped according to MRI timing and protocol.

Binomial logistic regression was performed to assess for independent predictors of upstaging in the three different MRI groups. Only men that were upstaged from radiological T2 to ≥pT2 post-prostatectomy were analysed. For both men that had a post-biopsy non bpMRI (group 1) or a pre-biopsy bpMRI scan (group 3) there were no significant predictors of upstaging (Table 4.25 and 4.27). However, for men that a post-biopsy bpMRI scan both clinical T-stage and MCCL were predictors of upstaging. Men with cT2a and cT2b were 3.3 and 4.2 times more likely, respectively, to have radiological upstaging of disease (Table 4.26).

Clinical parameter	P-value	Odds Ratio	95% CI
PSA at diag.	0.082	1.043	0.995-1.094
cT1	0.768	-	-
cT2a	0.411	0.683	0.276-1.693
cT2b	0.404	0.554	0.139-2.216
T3a	0.999	0.000	0.000-
ISUP group 1	0.489	-	-
ISUP group 2	0.948	1.030	0.422-2.514
ISUP group 3	0.673	1.436	0.268-7.699
ISUP group 4	0.161	7.532	0.447-127.015
ISUP group 5	0.223	4.723	0.390-57.256
MCCL	0.371	1.057	0.936-1.193

Table 4.25. Binomial logistic regression to assess predictors of upstaging from radiological T-stage to pathological T-stage in men who received a post-biopsy non-bpMRI scan. Men who were upstaged from T1 to T2 disease were excluded from analysis.

Clinical parameter	P-value	Odds Ratio	95% CI
PSA at diag.	0.606	1.011	0.970-1.054
cT1	<0.001	-	-
cT2a	<0.001	3.307	1.847-5.923
cT2b	0.001	4.255	1.771-10.222
cT2c	0.534	1.540	0.395-6.033
cT3a	0.576	1.522	0.349-6.640
ISUP group 1	0.395	-	-
ISUP group 2	0.800	1.081	0.592-1.972
ISUP group 3	0.235	1.926	0.653-5.678
ISUP group 4	0.496	1.647	0.392-6.931
ISUP group 5	0.106	5.908	0.685-50.988
MCCL	0.011	1.107	1.023-1.197

Table 4.26. Binomial logistic regression to assess predictors of upstaging from radiological T-stage to pathological T-stage in men who received a post-biopsy bpMRI scan. Men upstaged from T1 to T2 disease were excluded from analysis.

Clinical parameter	P-value	Odds Ratio	95% CI
PSA at diag.	0.798	0.989	0.910-1.075
cT1	0.760	-	-
cT2a	0.303	1.888	0.564-6.324
cT2b	0.370	0.445	0.076-2.609
cT2c	0.845	1.189	0.210-6.746
cT3a	0.624	0.442	0.013-13.236
cT3b	1.000	-	0.000 -
ISUP group 1	0.779	-	-
ISUP group 2	0.505	1.492	0.460-4.833
ISUP group 3	0.586	0.553	0.066-4.648
ISUP group 4	1.000	-	0.000-
ISUP group 5	0.729	0.642	0.052-7.878
MCCL	0.059	1.145	0.995-1.318

Table 4.27. Binomial logistic regression to assess predictors of upstaging from radiological T-stage to pathological T-stage in men who received a pre-biopsy bpMRI scan. Men who were upstaged from T1 to T2 disease were excluded from analysis.

The results of radiological staging were also reviewed with respect to prevalence of detectable lesion on MRI, i.e. radiological T≥2, and how this changed over the period of changes in protocol. The proportion of men with detectable lesions increased from Group 1 at 56.9%, to 70.1% of men in group 2 and 75.3% of men in group 3 (Table 4.28).

MRI lesion	**MRI group**			**Total**
	Post-biopsy non-bpMRI	**Post-biopsy bpMRI**	**Pre-biopsy bpMRI**	
No	185 (40.4%)	67 (29.9%)	21 (24.7%)	273
Yes	273 (59.6%)	157 (70.1%)	64 (75.3%)	494
Total	458	224	85	767

Table 4.28. Proportion of MRI scans with detectable lesions according to type and timing of scan.

The presence of a detectable lesion on MRI was then reviewed with respect to diagnostic staging parameters and pathological parameters to determine if there were any independent predictors of a detectable lesion and how this varied between the three MRI groups.

For men who had a post-biopsy non bpMRI (group 1) both diagnostic PSA and clinical T-stage were significant independent factors in detecting a lesion on MRI. Men with clinical T2 disease had a significantly higher chance of having an identifiable lesion than those with cT1 disease, cT2b was nearly 5 times more likely than cT1 disease to have radiological T≥2. ISUP grade group and MCCL did not significantly predict a lesion although men with ISUP grade 3 did have a significantly higher chance than those with grade group 1 (Table 4.29). When reviewing pathological markers T-stage and total tumour volume were significantly associated with an MRI T stage ≥2. Again, neither ISUP grade group or margin positivity was significant (Table 4.30).

Clinical parameter	P-value	Odds Ratio	95% CI
PSA at diag.	0.048	0.952	0.907-1.000
cT1	0.008	-	-
cT2a	0.038	1.812	1.035-3.174
cT2b	0.002	4.807	1.770-13.058
cT3a	0.399	2.878	0.247-33.590
ISUP group 1	0.286	-	-
ISUP group 2	0.313	1.353	0.752-2.437
ISUP group 3	0.042	5.176	1.063-26.196
ISUP group 4	0.999	0.000	0.000-
ISUP group 5	0.553	2.176	0.166-28.463
MCCL	0.066	1.085	0.995-1.183

Table 4.29. Binomial logistic regression to assess diagnostic clinical predictors of an identifiable lesion on MRI (T≥2) for men who had a post-biopsy non-bpMRI (group 1).

Pathological parameter	P-value	Odds Ratio	95% CI
Margin pos.	0.074	1.991	0.934-4.244
pT2	<0.001	-	-
pT3a	<0.001	0.043	0.012-0.156
pT3b	0.999	0.000	0.000-
ISUP group 1	0.284	-	-
ISUP group 2	0.598	0.862	0.497-1.496
ISUP group 3	0.085	2.343	0.890-6.168
ISUP group 4	0.999	-	0.000-
ISUP group 5	0.255	5.351	0.298-96.050
Total TV <0.5ml	<0.001	-	-
TTV 0.5-0.99ml	0.427	0.705	0.297-1.671
TTV 1-1.99ml	0.005	3.098	1.417-6.769
TTV 2-4.99ml	0.001	3.652	1.685-7.912
TTV >5ml	0.367	1.536	0.605-3.898

Table 4.30. Binomial logistic regression to assess post-prostatectomy pathological predictors of an identifiable lesion on MRI (T≥2) for men who had a post-biopsy non-bpMRI (group 1).

For men in group 2 (post-biopsy bi-parametric MRI) MCCL and clinical T-stage was also significantly associated with a detectable lesion on MRI with cT2 disease having at least a 6 times higher chance of an MRI stage ≥T2 than men with cT1 disease. Neither PSA of ISUP grade group were significant (Table 4.31). When reviewing pathological markers, as for group 1, pT-stage was a predictor of an MRI with a detectable lesion. However, total tumour volume was not a significant predictor and neither was ISUP grade group or men with positive margins (Table 4.32). For men who in group 3, who had received a pre-biopsy bi-parametric MRI scan, PSA at diagnosis, cT-stage, ISUP grade group and MCCL at biopsy were not significantly independent predictors of a detectable MRI lesion (Table 4.33). Also, within group 3 no post-prostatectomy pathological markers were significant predictors with a detectable lesion on staging MRI (Table 4.34).

Clinical parameter	P-value	Odds Ratio	95% CI
PSA at diag.	0.882	0.996	0.945-1.049
cT1	<0.001	-	-
cT2a	<0.001	6.532	2.946-14.481
cT2b	0.002	24.847	3.173-194.586
cT2c	0.103	6.067	0.693-53.131
cT3a	0.998	-	0.000-
ISUP group 1	0.683	-	-
ISUP group 2	0.317	1.468	0.692-3.113
ISUP group 3	0.536	1.505	0.413-5.478
ISUP group 4	0.999	-	0.000-
ISUP group 5	0.434	0.470	0.071-3.118
MCCL	0.016	1.130	1.023-1.247

Table 4.31. Binomial logistic regression to assess diagnostic clinical predictors of an identifiable lesion on MRI (T≥2) for men who had a post-biopsy bpMRI (group 2).

Path. parameter	P-value	Odds Ratio	95% CI
Margin pos.	0.222	1.802	0.701-4.636
pT2	<0.001	-	-
pT3a	<0.001	8.365	3.788-18.475
pT3b	0.008	8.971	1.788-45.021
ISUP group 1	0.311	-	-
ISUP group 2	0.495	1.311	0.603-2.851
ISUP group 3	0.089	3.362	0.833-13.574
ISUP group 4	0.382	0.427	0.063-2.874
ISUP group 5	0.651	0.662	0.110-3.963
Total TV <0.5ml	0.491	-	-
TTV 0.5-0.99ml	0.108	3.143	0.778-12.697
TTV 1-1.99ml	0.895	1.086	0.321-3.674
TTV 2-4.99ml	0.600	1.362	0.429-4.318
TTV >5ml	0.590	1.469	0.362-5.955

Table 4.32. Binomial logistic regression to assess post-prostatectomy pathological predictors of an identifiable lesion on MRI (T≥2) for men who had a post-biopsy bpMRI (group 2).

Clinical parameter	P-value	Odds Ratio	95% CI
PSA at diag.	0.475	1.060	0.904-1.242
cT1	0.809	-	-
cT2a	0.131	3.154	0.710-14.003
cT2b	0.999	-	0.000-
cT2c	0.999	-	0.000-
cT3a	0.999	-	0.000-
cT3b	1.000	2.277	0.000-
ISUP group 1	0.958	-	-
ISUP group 2	0.421	0.565	0.140-2.271
ISUP group 3	0.999	-	0.000-
ISUP group 4	1.000	0.261	0.000-
ISUP group 5	0.999	-	0.000-
MCCL	0.092	1.175	0.974-1.416

Table 4.33. Binomial logistic regression to assess diagnostic clinical predictors of an identifiable lesion on MRI (T≥2) for men who had a pre-biopsy bpMRI (group 1).

Path. parameter	P-value	Odds Ratio	95% CI
Margin pos.	0.653	1.375	0.343-5.520
pT2	0.953	-	-
pT3a	0.761	1.214	0.348-4.238
pT3b	0.878	1.266	0.062-25.773
ISUP group 1	0.932	-	-
ISUP group 2	0.362	1.847	0.494-6.913
ISUP group 3	0.600	1.884	0.176-20.163
ISUP group 4	0.999	-	0.000-
ISUP group 5	0.999	-	0.000-
Total TV <0.5ml	0.300	-	-
TTV 0.5-0.99ml	0.434	3.228	0.172-60.607
TTV 1-1.99ml	0.502	2.456	0.178-33.985
TTV 2-4.99ml	0.098	12.478	0.626-248.738
TTV >5ml	0.204	6.742	0.356-127.878

Table 4.34. Binomial logistic regression to assess post-prostatectomy pathological predictors of an identifiable lesion on MRI (T≥2) for men who had a pre-biopsy bpMRI (group 1).

4.5 Discussion

This chapter reports on the outcomes of a large series of men who have undergone radical prostatectomy as a primary treatment for newly diagnosed prostate cancer over a 20-year period. Surgical outcomes and the accuracy of staging is reported on patients all discussed at the same single specialist MDT.

4.5.1 Aim 1 - Prostatectomy outcomes

Overall cohort characteristics

As discussed in chapter 2, there are an increasing number of men undergoing radical prostatectomy as a primary treatment for prostate cancer within our institution. Within this surgical cohort analysed just over half had D'Amico classified

intermediate risk disease, however, there were a significant number of men with low risk disease at 33.9% and only 14.6% were classified as high risk. As again discussed in chapter 2, in more recent years we have seen a move away from the treatment of low risk disease with surgery and an increase in its use in men with high risk disease. Within the UK in 2015-2016 only 8% of men with low-risk disease underwent radical prostatectomy (NPCA., 2018) while for men in this study in 2016 16% had surgery for low risk disease, compared with just under 50% in 2006 (Figure 2.22). In the earlier years of the EPC MDT there was a lower proportion of men presenting with low risk disease probably a result of lower rates of PSA testing (Figure 2.15). In 2003, the proportion of men presenting with low risk dramatically increased (Figure 2.15) and this is mirrored in the increase percentage of men having surgery with low risk. It then slowly falls, year on year, to the present time. Prior to this relatively few men presented with low-risk disease and it was certainly common place within UK practice to offer these men radical treatment. The eagerness to offer low risk men surveillance was significantly lower than the present day. It must also be remembered that Gleason grading changed in 2005 and this may have effected some men that would historically have been graded as Gleason 6 (low risk) but with new criteria were Gleason 7 (intermediate risk).

Therefore, the high number of men with low-risk disease within this cohort probably reflects the changing surgical management of prostate cancer within the UK over 20 years, and we have shown a marked reduction in the number of low risk men in this cohort having surgery in the more recent years.

It is also interesting to note that within this cohort only a quarter of cases were performed robotically. Current practice within the England and Wales would suggest that that at the time of analysis 88% and 75% of cases respectively, were performed robotically (NPCA., 2018). This itself should not have an effect when interpreting the results as to date no oncological benefit has been proven between the two different techniques (Mottet et al., 2017a).

Comparison of Biopsy Gleason grade with prostatectomy Gleason grade

Accurate Gleason grading at the time of diagnostic biopsy is vital in ensuring patients choose the most appropriate treatment pathway. Errors in sampling, pathology reporting and borderlines grades are known as potential reasons for changes in grading. Within this study, the rate of upgrading from ISUP group 1 disease at biopsy was just under 30% with most these upgraded to ISUP group 2 (26.3%). These figures compare well a large series of nearly 8000 men reviewed by Epstein et al, although in this series there was a slightly lower rate of upgrading in men with Gleason 6 disease on biopsy (25.1% versus 29.7% in this study)(Epstein et al., 2012). Encouragingly there was a high rate of concordance at 72% for ISUP group 2 with a roughly equal split of patients downgraded and upgraded, with very few upgrades more than ISUP group 3. This compared favourably to around 50% with Epstein at al. (Epstein et al., 2012) The low rate of men downgraded is important as men downgraded from Gleason 7 on biopsy to 6 at prostatectomy have a higher rate of BCR compared to Gleason 6 disease on both (Ham et al., 2017).

Poor concordance was seen for ISUP group 4 with around a third the same and roughly the same proportion downgraded to both ISUP group 2 and 3 equally. Concordance with higher grade groups range between around 30%-60% (Moussa et al., 2009, Imamoto et al., 2010) and it is widely appreciated that concordance is lower for higher grade disease. Possible explanations for this include under sampling and needle biopsy sampling tertiary disease that is not subsequently reported (Epstein et al., 2012).

Factors associated with upgrading include higher PSA, larger tumour volume and presence of perineural invasion, T-stage, age, PSA density and smaller prostates (Epstein et al., 2012, Alchin et al., 2016, Moussa et al., 2009). It is, of course, important to be able to predict who has a higher risk of upgrading as ISUP grade group is an important prognostic feature but to date being able to predict upgrading is somewhat down to clinical acumen.

Comparison of staging

Excluding those men that had clinical T1 disease the overall rate of upstaging after surgery was 52.2%, this is a lower rate than that of radiological upstaging, but still reflects a large rate of change. There has been debate as to usefulness of clinical T-stage given the advances in imaging technology, however, this study has shown that clinical T-stage remains an important significant predictor of both margin positivity and biochemical recurrence, unlike radiological T-stage and therefore should remain a vital part of the diagnostic pathway.

Predictors of margin positivity

With an overall margin positivity rate of 19.6%, with 12.9% for pT2 disease and 29% for pT3 disease this compares favourably with an overall margin positive rate of 31% for patients in England and Wales undergoing radical prostatectomy in 2015-16 (NPCA., 2018). This itself may reflect the higher proportion of low risk patients in the study cohort.

As expected there was significantly different rates of margin positivity for clinical T-stage, PSA level at diagnosis and ISUP grade group with more aggressive disease associated with higher rates. When assessed with logistic regression only clinical T-stage was a significant independent predictor of margin positivity. This study did not assess the impact of nerve sparing on margin rates and it must be remembered that this may have had an effect.

Interestingly, the PROMIS study definition of significant cancer, be that definition 1 or 2, carried the same rate of margin positivity as D'Amico intermediate risk disease and there was no significant difference in rates of positivity between significant and non-significant cancer when using definition 1. However, there were significant differences between the subgroups for both PROMIS definition 2 and D'Amico classification.

As highlighted positive surgical margin status has, in this study, and other series been predictive of BCR (Karakiewicz et al., 2005, Stephenson et al., 2014). However, there

is evidence to suggest that positive surgical margins alone are not an independent predictor of metastases, or indeed prostate cancer specific mortality (Stephenson et al., 2014, Mithal et al., 2016). Adjuvant treatment based on positive surgical margins alone is not recommended and results from RADICALS trial aims to address this important question (Parker et al., 2007).

Surgical experience is also an important factor on the rate of positive surgical margins. For this study cohort, rates are not presented on an individual surgeon basis. Data on site and length of margin positivity are also not presented and this may have had an effect when assessing the significance of margin positivity on BCR rates.

Predictors of BCR

Excluding those patients that had immediate adjuvant treatment the biochemical recurrence rate was 11.6% with a median follow-up of 4.4 years. Biochemical recurrence post-prostatectomy is seen in around a quarter to a half of all men (Mottet et al., 2017b). Whilst a rising PSA post-surgery almost always represents disease progression it is not always associated with metastatic disease. A shorter interval to BCR, a higher ISUP grade group, higher T-stage and increasing age are all associated with worse outcomes in the setting of BCR (Mottet et al., 2017b).

This study noted that there were significant differences in rates of BCR between subgroups for clinical T-stage, PSA and ISUP grade group at diagnosis. It was interesting to note that this was not the case for radiological T-stage. It must also be noted that clinical T3 conveys a much higher risk of BCR than that of radiological T-stage, with the rate nearly double for clinical disease, 50% vs 27%.

It was again noted that the BCR rates for significant cancer, whether defined by PROMIS definitions 1 or 2, had almost the same rates as that of D'Amico intermediate risk disease. Again, there was not a statistically significant difference between the rates of BCR between non-significant and significant cancer as per PROMIS definition 1 but there was for definition 2 and when using D'Amico

classification. When reviewing the results of logistic regression, it again highlights the importance of clinical T-stage as this was the only significant independent predictor of BCR from pre-operative staging parameters. Increasing ISUP grade did have a strong association with BCR but did not reach statistical significance.

As one would expect when reviewing post-op parameters significant difference were seen within sub-groups for pathological T-stage, ISUP grade group, size of tumours and margin positivity. However, only positive margins, higher T-stage and ISUP grade group were significant independent predictors of BCR. Tumour volume was not associated with BCR. When reviewing the time to BCR only pT-stage was a significant factor in time to BCR with higher stages associated with a shorter time to recurrence. A lower proportion of men with high risk disease may have affected results for ISUP grade group and PSA level at diagnosis.

4.5.2 Aim 2 MRI staging outcomes

MRI imaging of the prostate has improved dramatically in recent years to the extent where recent evidence and updated NICE guidance (NICE., 2019) suggests possible omission of diagnostic TRUS biopsy in cases where the MRI is reported as normal (Ahmed et al., 2017, Kasivisvanathan et al., 2018). Studies assessing the accuracy of MRI at diagnosis often use template mapping biopsies as the reference point. However, to truly analyse the accuracy of a diagnostic test it widely accepted that comparison with the pathological specimen obtained post-surgery represents the most accurate tool for comparison. This study reports on the accuracy on MRI staging over a 20-year period of a specialist MDT and how the rate of upstaging has changed.

As previously discussed mpMRI includes T2 weighted imaging, diffusion weighted imaging (DWI) and dynamic contrast enhanced (DCE) phases, whereas bpMRI omits DCE and in doing reduces time to scan and avoids potential risks of giving contrast. DCE can help to differentiate equivocal PIRADS 3 lesions in the peripheral zone (Bayne et al., 2016) however its role has been debated since introduced (Weinreb et

al., 2016a). Numerous studies have compared the accuracy of bpMRI to mpMRI and found the two to be comparable (Alabousi et al., 2019, Van Nieuwenhove et al., 2019).

A large meta-analysis assessing accuracy of MRI for local staging demonstrated sensitivity rates of 58% and specificity rates of 88% for detecting T3 disease with similar sensitivity rates for detecting extra-capsular extension but higher rates for detecting seminal vesical invasion at 91% (de Rooij et al., 2016). The use of DWI and higher field strengths (3-Tesla vs 1.5T magnets) improved sensitivity (de Rooij et al., 2016).

Within this study cohort patients received either T2W MRI alone or bpMRI and the timing of scans changed from post-biopsy to pre-biopsy following updated NICE guidance in 2014. Overall, there was a general increase in the rate of upstaging from men who received a post-biopsy non-bpMRI compared to those that that had a post-biopsy bpMRI and indeed the highest rate of upstaging was seen with men who had a pre-biopsy bpMRI.

As shown men with a post-biopsy non-bpMRI had a lower rate of detectable lesions and this can be assumed to be the reason why there was a higher rate of upstaging of men from radiological T1 disease to T2 disease. However, even when these numbers are excluded from analysis there is still a significant difference in the rate of upstaging with more men being upstaged with pre-biopsy bpMRI compared with post-biopsy non-bpMRI. This rate of upstaging was still apparent even when risk adjusted to significant and non-significant cancer according to PROMIS 1 and 2 definitions.

It was highlighted in this study that the rate of detectable lesions on non-bpMRI was lower than with more modern pre-biopsy bpMRI. With post-biopsy, non-bpMRI both higher clinical and pathological T-stage, PSA at diagnosis, larger tumour volume were all significantly associated with detectable lesion on MRI. For men with a post-biopsy bpMRI again both clinical and pathological T-stage were significantly associated with

a lesion on MRI and maximum cancer core length. For the most recent regime of pre-biopsy bpMRI there were no significant associations for either diagnostic or pathological disease parameters. One may postulate that the reason that for this is that the more modern MRI regime and technology is able to identify lesions of a lower grade and aggressiveness making the association with palpable disease, of a larger volume and potentially more aggressive (higher PSA) less significant. This is of course important in disease detection at the time of biopsy but as this study results have shown relying on the accuracy of MRI staging must still be viewed with caution. This study has again highlighted that the sensitivity of MRI for accurately staging prostate cancer has not changed significantly over time. It has however, shown that very few patients are downgraded following surgery and this has not changed over time. This study would support evidence that T2 weighted imaging is most beneficial for the staging of disease and diffusion weighted images are more useful as a diagnostic tool.

When using MRI T-staging as part of the decision-making process it is essential that other clinical parameters be considered as well and it can be suggested that clinical T-staging remains a more significant predictor of disease outcome following surgery.

Within the PROMIS trial, patients were risk stratified according to different definitions of significant cancer. The subsequent risk of detecting 'significant cancer' on TRUS biopsy was dependent upon mpMRI PIRADs score. In this study, the rates of BCR were very similar for significant cancer when using either PROMIS definition 1 or 2 and these mirrored results for D'Amico classified intermediate risk disease. However, patients with non-significant cancer as defined by definition 1 had nearly double the rate of BCR compared with the D'Amico low risk group and the rate of BCR was not significantly different to those that had significant cancer. This information must be considered when counselling patients regarding treatment or indeed whether to have a biopsy. It also highlights that D'Amico classification remains more sensitive at predicting BCR than PROMIS definitions of significant cancer.

4.5.3 Limitations

Unfortunately, no long-term outcome data is available with a skew in the data with larger numbers having surgery more recently. When interpreting the MRI results the reduced numbers in group 3 (men who had a pre-biopsy bpMRI) may also have had an impact in reducing the significance levels particularly for associations with detectable lesions. It would be interesting to repeat this analysis when the cohort has matured.

4.5.4 Conclusions

This study has highlighted encouraging surgical outcomes for a large cohort of men treated through a single specialist MDT.

Despite changes in protocol and technology MRI remains an investigation with a low sensitivity for accurately staging prostate cancer. The use of other clinical parameters remains essential in identifying those patients that have a higher chance of disease recurrence and indeed requirement for additional treatment post-surgery. It also highlights the importance of risk stratification of disease of significant disease and how this can impact on disease recurrence figures.

Chapter 5. Deferred treatment strategies for men with low-risk localised prostate cancer - outcomes from a large contemporary UK series of active monitoring/surveillance, the role of protocol restaging in a stable cohort of active monitoring patients and the use of bi-parametric MRI in restaging men on active surveillance.

5.1 Introduction

With the introduction of widespread PSA testing the incidence of prostate cancer has increased (CRUK, 2015). The rise in screen detected prostate cancer cases has led to a higher number of cases that are potentially 'clinically insignificant', i.e. may not impact on a patient's quality of life or life expectancy. As a result, there is an increasing awareness to avoid over-treatment and prevent subsequent morbidity. Encouragingly, figures from contemporary UK data demonstrate a decreasing number of low risk patients receiving radical treatment (NPCA., 2018).

Deferred treatment or surveillance for low risk localised prostate cancer has long been a recognised treatment strategy and it is now the standard of care, however, terminology for such regimes is evolving as are the entry criteria. Watchful waiting, active monitoring and active surveillance are all surveillance strategies with the intention to avoid treatment when appropriate. However, there are significant differences between these three groups and it is vital to appreciate this.

Watchful waiting (WW)

In contemporary practice, watchful waiting is a treatment strategy for men with prostate cancer who wish to avoid treatment and the side effects of such for as long as possible. It is reserved for men who are generally not fit enough for radical treatment or whose life expectancy is less than 10 years. Treatment is commenced when men become symptomatic or develop metastases and is based on disease control rather than cure. As such surveillance whilst on a watchful waiting program is less intensive and invasive and usually involves a PSA blood test at regular intervals.

Active monitoring (AM)

This term was introduced by the ProtecT study that was designed to investigate the outcomes of immediate radical treatment (surgery or radiotherapy) versus deferred treatment for low to intermediate risk localised prostate cancer in screen detected patients aged 50 to 69 years old (Hamdy et al., 2016).

After enrolment on an AM programme patients only undergo restaging (further prostate biopsy or imaging) if clinical progression was suspected either by a rise in PSA level or a clinical change such as a change in the clinical stage on DRE. Treatment was offered if disease progression was noted, but equally could also be triggered at patients request or if a clinical change was noted without undergoing restaging. The AM protocol used for patients in this study was adapted from the ProtecT study protocol (Hamdy et al., 2016) and can be seen in Figure 5.1.

AM monitoring differs to WW in that if disease progression is noted men are offered treatment with the intent to cure rather than to palliate. AM differs to AS because it does not include protocol based restaging as part of surveillance, i.e., when men are stable repeat imaging or biopsies are not offered to assess for silent disease progression. They are however, monitored with regular PSA tests and DRE.

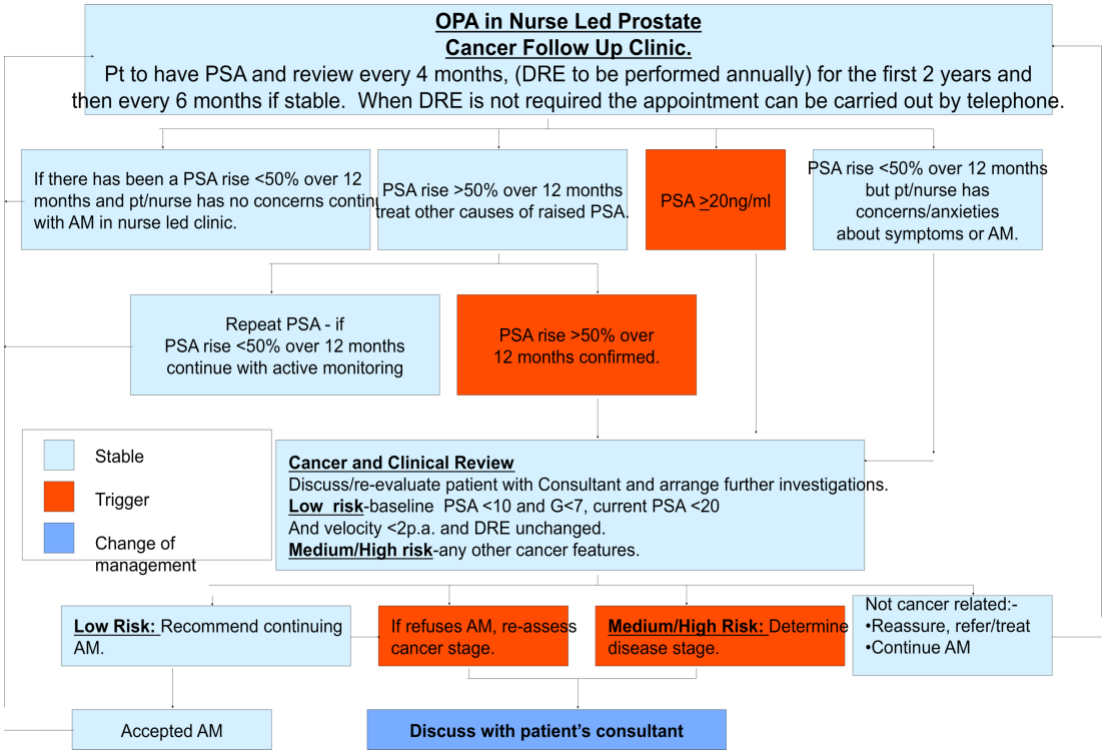


Figure 5.1. Follow-up protocol used for patients on an active monitoring programme (adapted from ProtecT study).

Active surveillance (AS)

This term is now widely accepted and is the preferred terminology for fit patients choosing a deferred treatment strategy. As for AM, men on an AS program are offered radical (curative) treatment if disease progression is noted and hence they are men with a good performance status and a life expectancy of at least 10 years.

Prior to 2014, there were no formal statements in the UK NICE guidance regarding who should be offered active surveillance. Updated NICE guidance in 2014 recommended that all patients with low risk organ confined prostate cancer, suitable for radical treatment, be offered active surveillance (NICE, 2014). For those diagnosed with intermediate risk cancer not willing to undergo immediate treatment AS should also be considered. High risk patients should not be offered AS. In patients enrolling on an active surveillance program the following protocol was suggested and was the first attempt to introduce a nationwide uniform follow-up programme (Table 5.1).

Timing	**Tests** [1]
At enrolment in active surveillance	Multi-parametric MRI if not previously performed
Year 1 of active surveillance	Every 3–4 months: measure PSA[2] Throughout active surveillance: monitor PSA kinetics[3] Every 6–12 months: DRE[4] At 12 months: prostate re-biopsy
Years 2–4 of active surveillance	Every 3–6 months: measure PSA[2] Throughout active surveillance: monitor PSA kinetics[3] Every 6–12 months: DRE[4]
Year 5 and every year thereafter until active surveillance ends	Every 6 months: measure PSA[2] Throughout active surveillance: monitor PSA kinetics[3] Every 12 months: DRE[4]
[1] If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multi-parametric MRI and/or re-biopsy. [2] May be carried out in primary care if there are agreed shared-care protocols and recall systems. [3] May include PSA doubling time and velocity. [4] Should be performed by a healthcare professional with expertise and confidence in performing DRE.	

Table 5.1. Follow-up protocol for patients on an active surveillance programme as recommend by NICE CG175 (NICE, 2014).

The aim of protocol restaging, particularly the first restage after diagnosis, is to ensure the disease has not been under-staged at diagnosis and to assess for disease progression. It is a method of ensuring continued optimum patient selection for deferred therapy and reduces the risk of the disease progressing and missing the opportunity for radical treatment. Protocol led restaging is the major difference between AM and AS.

In 2014, the updated NICE guidance recommended the use of MRI as part of restaging only if there were changes in clinical parameters and its use as re-staging tool in stable disease, as a checkpoint, rather than a repeat biopsy was not discussed. The use of MRI in this setting is still not clear but potentially very promising as any measure that can avoid a repeat biopsy, without compromising patient safety, would be welcome.

5.2 <u>Aims</u>

The aim of this study was four-fold.

1. Firstly, to assess the outcome of all patients enrolled on an active monitoring or surveillance program.

2. Secondly, to assess the outcomes of introducing protocol re-staging in a cohort of clinically stable active monitoring patients – defined as Restaging Group 1.

3. Thirdly, to compare the outcomes of restaging in Restaging Group 1 with patients having both –

    a. Clinical change or triggered re-staging - defined as Restaging Group 2,

    and

b. Protocol restaging as part of active surveillance - defined as Restaging Group 3

4. Fourthly, assess the use of MRI in restaging and its usefulness in the pathway.

5.3 Methods

5.3.1 Service evaluation

This study was approved as part of service evaluation by the surgical directorate, UHW, Cardiff.

5.3.2 Patient population

As discussed in chapter 2, all patients with a new diagnosis of prostate cancer from 1997 onwards were discussed at the EPC MDT. Data collection sheets were uploaded to an Excel database on a prospective basis. All patients that were recorded as commencing on an active monitoring or active surveillance programme following the EPC MDT were identified to create a new database of active monitoring/surveillance patients.

Prior to 2014, patients in the EPC MDT cohort were followed up based upon an active monitoring protocol adapted from the ProtecT study as described (Figure 6.1) and would not have been offered protocol restaging unless there were pre-defined triggers.

Following the introduction of updated NICE guidance in 2014 (NICE, 2014) all new patients entering a deferred treatment strategy, and suitable for radical treatment if required, were defined as on active surveillance (AS) and were offered protocol restaging in line with guidance i.e. at 12 months after diagnosis. Additional to the recommendation by NICE, all patients on AS after 2014 in UHW were offered a re-staging MRI pre-biopsy at 12 months' post diagnosis. This MRI scan was not multi-

parametric, but included T2W sequences and diffusion weight imaging (DWI), i.e., bi-parametric (bpMRI). Contrast enhanced imaging was not included.

Prior to 2014 the entry criteria for AM was based on ProtecT inclusion criteria and included low to intermediate D'Amico risk stratified patients. Entry, may also have been at the discretion of the clinician or MDT and criteria was not as clearly defined as some published institutional surveillance strategies. Post 2014, entry criteria to AS was based on NICE guidance and was offered to all newly diagnosed cases of low risk cancer as recommended and to intermediate risk patients who chose to defer radical treatment.

It must be noted that UHW was a recruitment centre for the Protect study, but none of these patients are included in this study.

Therefore, the four study groups highlighted in the aims are as follows;

1. The overall cohort of all patients on an AM or an AS program over the period of the EPC MDT.

2. **Restaging Group 1** - Men that were on active monitoring up to 2014 and had not previously been restaged with either a biopsy or an MRI. Therefore, these men were theoretically stable and 'restaging naïve'. Protocol based restaging was performed to bring them in line with the active surveillance program recommended by NICE guidance.

3. **Restaging Group 2** - Men that were on AM or AS but had undergone triggered staging based upon a clinical change (rise in PSA, DRE change) indicating possible disease progression.

4. **Restaging Group 3** - Men that were on an active surveillance program and had undergone their first protocol restaging as recommended by NICE guidance (CG175) 12-18 months after diagnosis.

5.3.3 Data collection and analysis

Results were collected in Microsoft Excel and transferred to SPSS for analysis. For reporting of overall results follow up time was defined as date of diagnosis to date of last clinical encounter. If the patient was lost to follow-up, follow-up was again recorded up to time of last clinical encounter. Radical treatment was defined as treatment with intent to cure.

For comparison of the restaging outcomes clinical progression was defined as upstaging of the clinical T stage documented at diagnosis versus at restaging. MRI progression was defined by the reviewing the official radiologist report and defining that a scan showed progression if the radiologist had stated as such, if there was a new lesion present or if the radiological T staging was higher. Grade progression was defined as a Gleason grade on restaging higher than that at diagnosis. Volume progression was defined as having a higher number of positive cores at restage than at diagnosis.

Kaplan-Meier Survival curves and Chi-Square tests were performed using SPSS and all table and graphs were created with either Microsoft Excel or Microsoft Word.

5.4 Results

5.4.1 Aim 1 - Outcomes of patients enrolled on an active monitoring or surveillance program

Number of cases

Between 1st February 1997 and 1st February 2017 811 were enrolled on an active surveillance or active monitoring program. 101 cases were excluded from analysis as the date of diagnosis was after January 1st, 2016, hence, excluding patients with less than 12 months' follow-up. Therefore, 710 cases are presented. A general increasing trend in the number of patients entering active surveillance year on year (Figure 5.2).

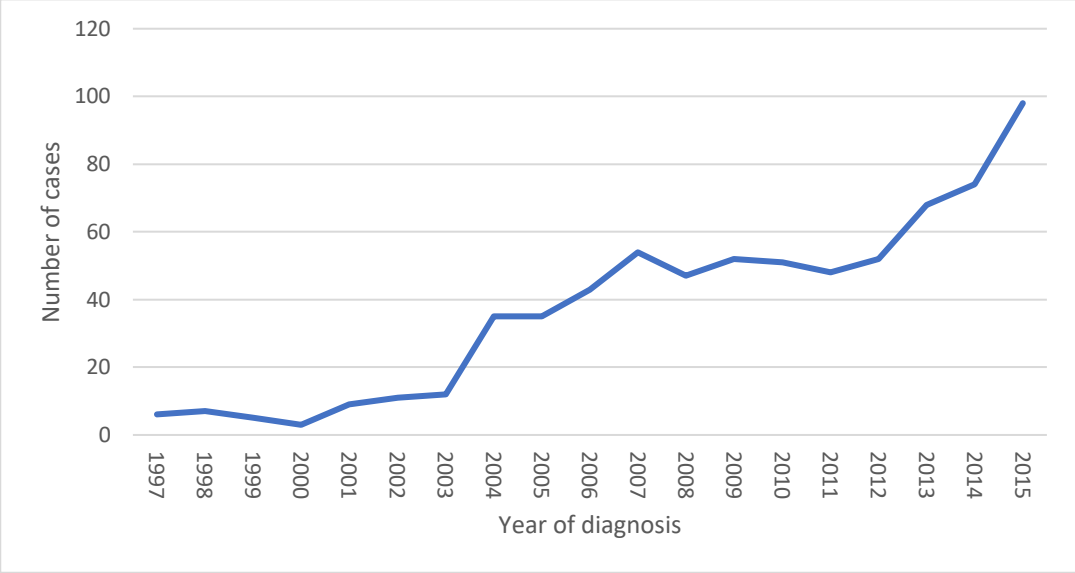


Figure 5.2. Graph showing the number of cases enrolled on an AM or AS program by year of diagnosis, 1997-2015 (n=710).

Source of referral

85% of cases were from the University Hospital of Wales. 10% of cases were from Cwm Taf Health board and 5% were from other sites.

Mode of presentation

There was an equal number of patients presenting who were asymptomatic with a raised PSA and presenting with a raised PSA and symptomatic LUTS. Other modes of

presentation were generally lower. There was not a significant difference in symptoms at presentation between patients choosing a deferred treatment strategy and the whole EPC population (Figure 5.3)

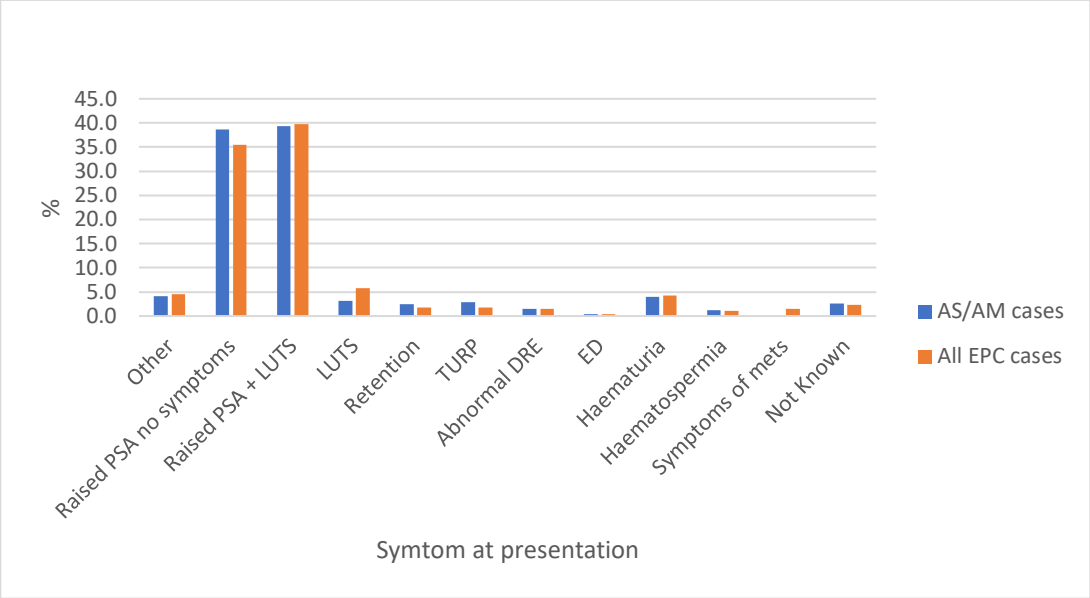


Figure 5.3. Graph showing how men presented at diagnosis, including a comparison of the AS/AM cohort with the whole EPC MDT population (n=710 and n =3575 respectively), 1997-2017.

Age at diagnosis

Mean and median age at diagnosis was 66 years old. Range 42 - 85 years of age.

PSA at diagnosis

Mean PSA was 7.6ng/ml. Median was 7 ng/ml. Range was 0.4 – 38.

Gleason score at diagnosis

85.9% of cases were Gleason 6 at diagnosis and 11.1% were Gleason 7. 1.6% of cases were Gleason 5 or lower (Table 5.2).

Gleason score	**Number of cases**	**Percentage of cases**
≤ 5	12	1.6%
6	610	85.9%
7	79	11.1%
Not recorded	9	1.3%

Table 5.2. Gleason grade of diagnosis of all patients enrolled on an AS or AM treatment strategy, 1997-2015 (n=710).

Clinical stage at diagnosis

Clinical stage was recorded at the time of EPC MDT. 3.6 % of cases were T1a or T1b. 50.3% of cases were clinical stage T1c. 22.8% were T2a. 6.1% were T2b. 0.8% of cases were T2c or higher. 16.5% of cases were not recorded, in these cases the clinical stage at time of referral will have been used to determine D'Amico classification (Figure 5.4)

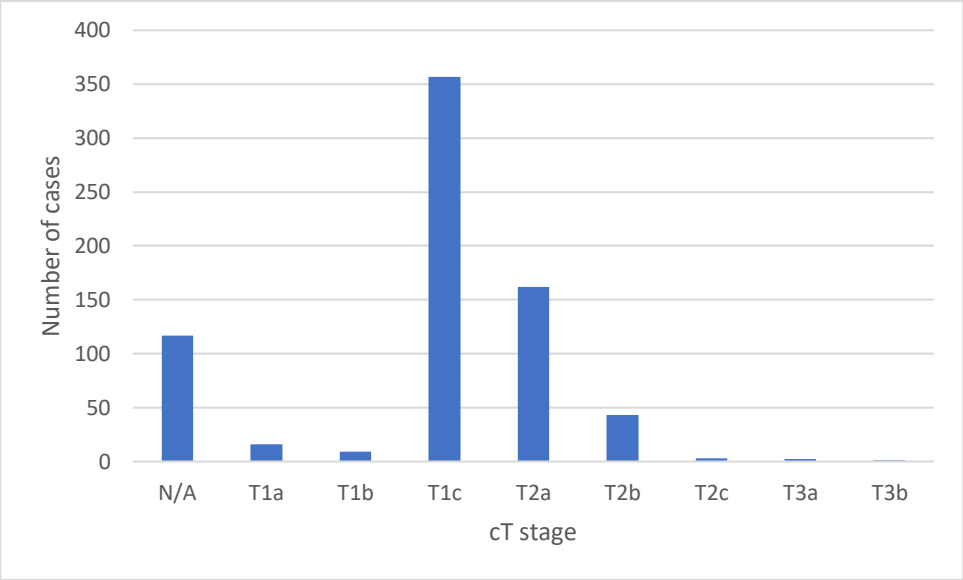


Figure 5.4. Graph showing the clinical T stage at presentation and entry in to AS or AM (n=710).

MRI timing and MRI T stage at diagnosis

3.8% (27/710) patients did not have an MRI as part of staging. 6.5% (46/710) had a pre-biopsy MRI and the remaining 89.7% (637/710) patients had a staging MRI following TRUS biopsy.

All staging MRI scans were reviewed at the EPC MDT and staging documented. 53.5% were staged at T1. 25.2% were T2a and 15.8% were T2b. 1.7% of cases were staged at T2c or higher (Figure 5.5).

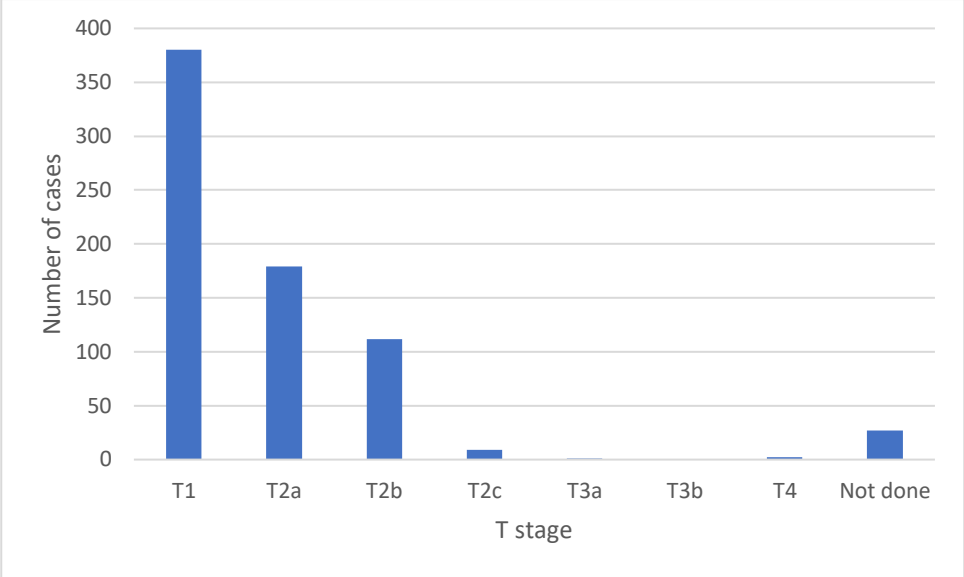


Figure 5.5. Graph showing the MRI stage at presentation and entry in to AM/AS, 1997-2015 (n=710)

Maximum cancer core length (MCCL) and percentage of core of maximum tumour length

MCCL was 3.6mm with a range from 1 to 16mm. Mean percentage of core with maximum tumour length was 22.2% with a range from 1 to 100% (Table 5.3).

	MCCL	**% of core with max. tumour length**
Number	644 (46 not known)	578 (132 not known)
Mean	3.6mm	22.2%
Median	3.0mm	17%
Range	1-16mm	1-100%

Table 5.3. Table showing the TRUS biopsy core characteristics at diagnosis and entry in to AS/AM program, 1997-2015 (n=710).

D'Amico risk classification at diagnosis

72.4% of patients were classified a low risk at diagnosis, 25.6% were intermediate risk and 2.0% were high risk.

Follow-up time

Follow-up time was calculated from date of diagnosis to last documented follow-up. Information was not available for 10 patients; therefore, data was for 700 patients. Mean time was 4.7 years and a median of 3.7 years. Range was 0-18.9 years.

Still on an AS/AM program

At the time of undertaking this study 39.4% (280/710) of patients were still on an AS/AM program. 52.8% (375/710) were known to have stopped. 5.6% (40/710) were known to have been followed up elsewhere and information regarding outcome was not known. There was no information available for 2.1% (15/710) of patients (Figure 5.6). Therefore, accurate follow-up data on outcome is available for 655 patients.

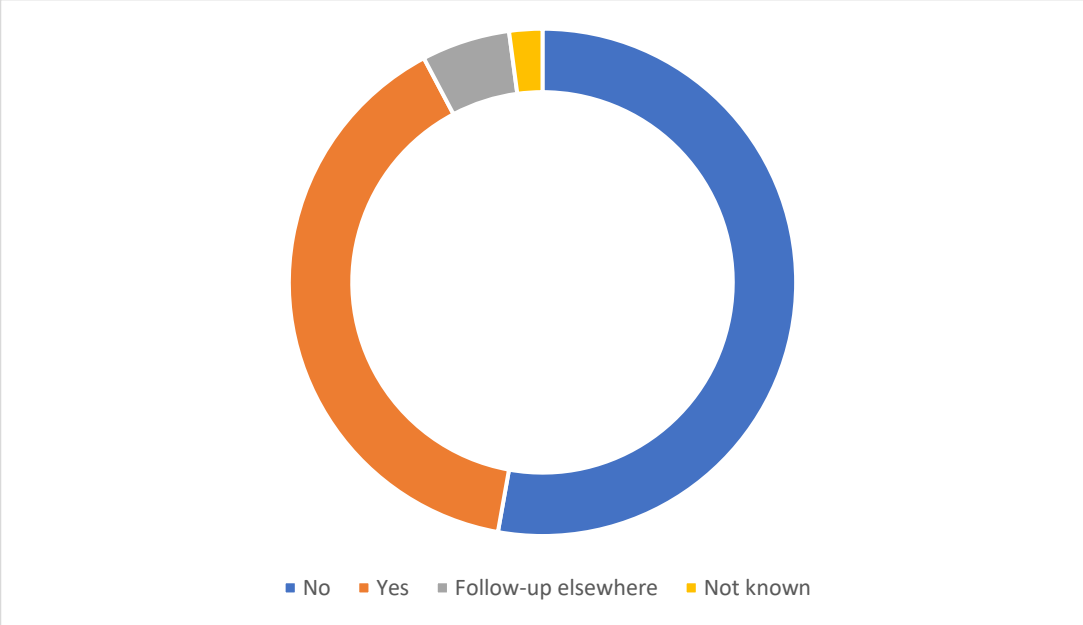


Figure 5.6. Chart to show proportion of patients still on AS or AM at the time of review, 1997-2015 (n=710).

Treatment received

Of the 655 patients with known follow-up 42.7% (280/655) were still on an active surveillance/monitoring program and 57.3% (375/655) had stopped. Of the patients that stopped 60.8% (34.8% of the total cohort) went on to have radical treatment (21.6% had surgery and 39.2% radiotherapy), 20.5% moved to watchful waiting, 4.5%

started hormonal therapy, 13.3% died and information was not known for 0.8% (Figure 5.7).

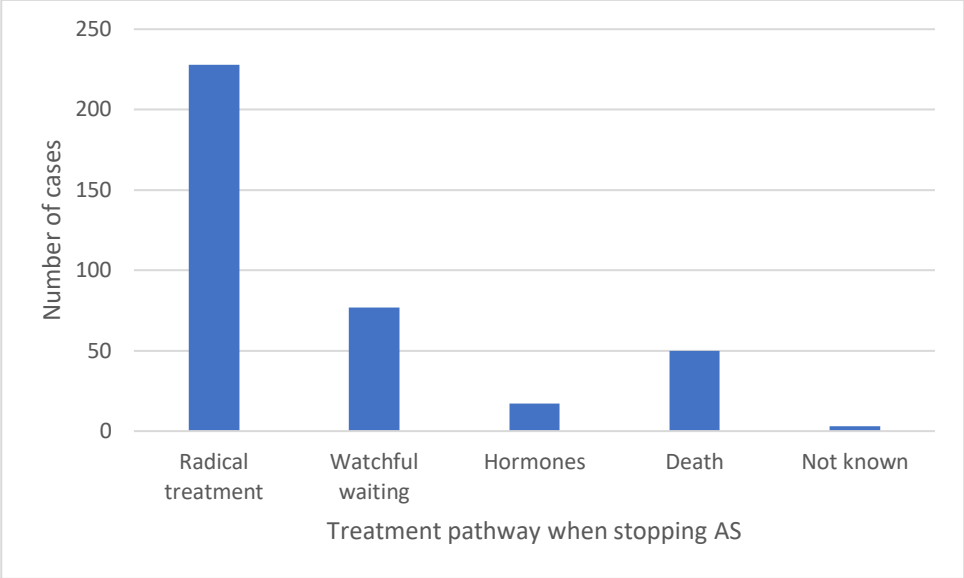


Figure 5.7. Graph showing the treatment pathway of patients stopping active monitoring/ surveillance, 1997-2015 (n=655).

In total, 37.6% (246/655) had received treatment (radical treatment or hormones) and 62.4% (409/655) had not.

Time to treatment

Mean time to treatment was 3.3 years (median was 2.4 years) with a range of 0.2 to 15.2 years. Patients with at least 5 years follow up had a 28.3% (77/272) treatment rate and those with at least 10 years' follow-up had a 39.4% treatment rate (28/71). The rate of treatment by year of follow-up was roughly 5% per year up to five years follow up (Figure 5.8 and Table 5.4). This rose to just over 10% at 10 years' follow-up and 25% at >15 years (i.e. 25% of the total number of patients with that had reached more than 15 years' follow-up had received treatment).

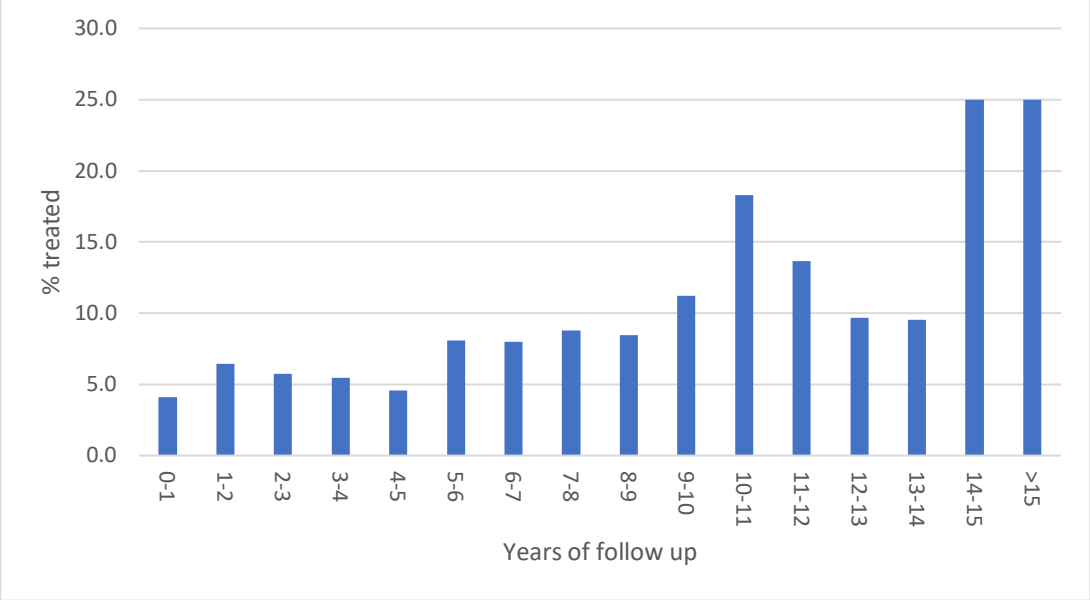


Figure 5.8. Graph showing the percentage of patients that had received treatment based on their year of follow-up, i.e., 4.6 % of patients had treatment in their 4-5th year of follow-up and 18.3% of patients had treatment in their 10-11th year of follow-up.

No. to reach F/U time	F/U Time (yrs)	No. treated	% treated by year of F/U
710	0-1	29	4.1
620	1-2	40	6.5
489	2-3	28	5.7
403	3-4	22	5.5
327	4-5	15	4.6
272	5-6	22	8.1
225	6-7	18	8.0
171	7-8	15	8.8
130	8-9	11	8.5
98	9-10	11	11.2
71	10-11	13	18.3
44	11-12	6	13.6
31	12-13	3	9.7
21	13-14	2	9.5
16	14-15	4	25.0
8	>15	2	25.0

Table 5.4. Table showing the number and percentage of patients that had received treatment based on the number of years follow up.

Of all the patients that had received treatment, just over 70% had received it by 5 years and only 11% patients remained untreated at 10 years follow up (Figure 5.9).

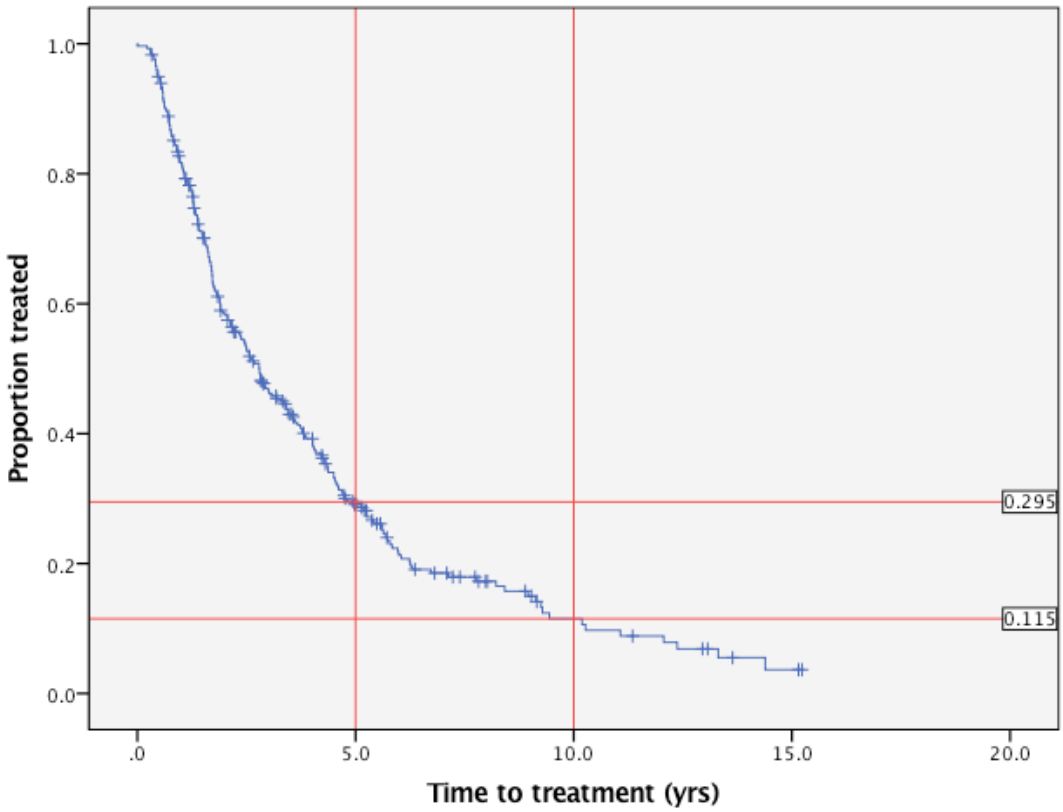


Figure 5.9. Kaplan-Meier plot showing time to treatment in the AS/AM cohort.

Reason for change in treatment course

The reason for change in treatment was due to rising PSA in 40.5% of cases, 19.3% of cases was due to patient choice and a request to stop surveillance, 7.8% was due to a change in other clinical parameters separate from PSA and 20.9% was due to patient co-morbidities (i.e. transferred to watchful waiting as not fit for radical treatment). The reason was not clear in 11.5% of cases (Figure 5.10).

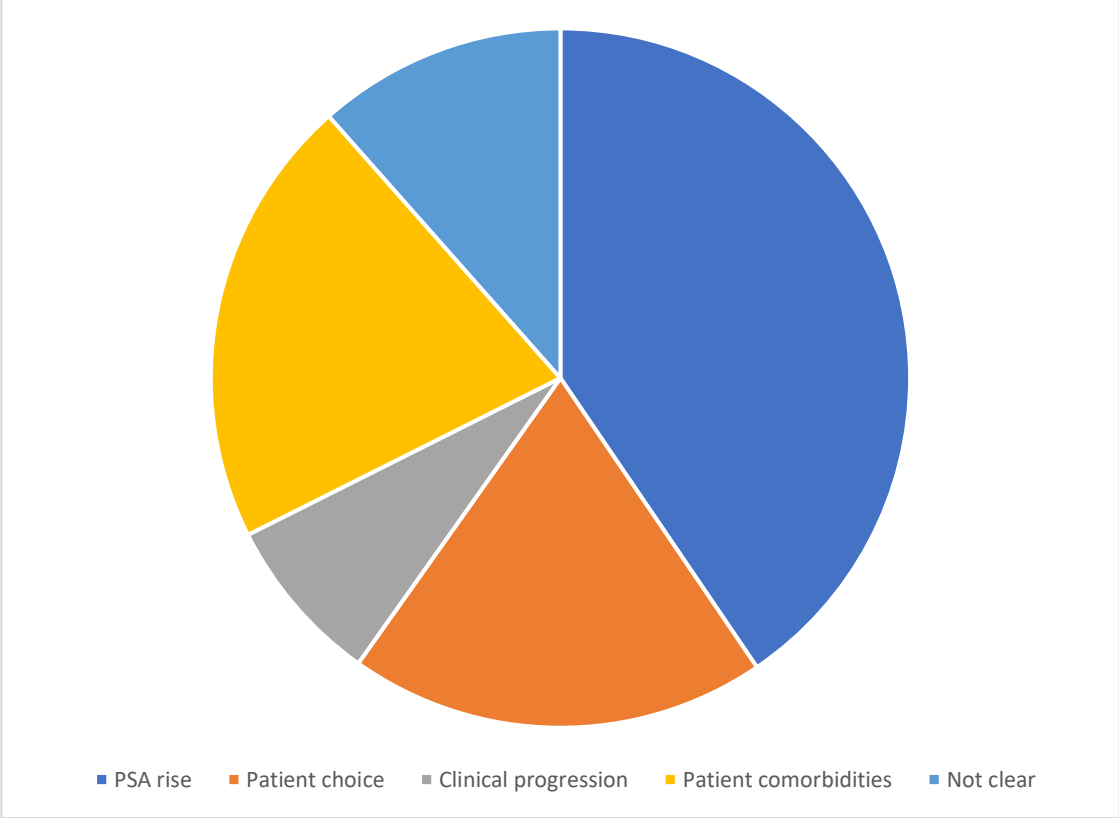


Figure 5.10. Pie chart showing reason for change in treatment of patients stopping AM/AS.

Effect of initial diagnostic parameter on outcome of AS

Chi-square tests were run to see if there were differences in the rate of treatment between different D'Amico risk groups, clinical T-stage sub-groups, Gleason grades, and maximum cancer core length (defined as MCCL - <6mm or ≥6mm). There were significant differences observed between all of these groups, apart from Gleason grade, with more advanced disease associated with higher rates of treatment (Table 5.5)

For time to treatment only higher Gleason grade was a significant factor with a shorter time to treatment (Figure 5.11). Time to treatment was shorter for higher D'Amico risk groups, clinical T-stage and patients with a core length ≥6mm but this was not significant (Figure 5.12-4). The significance of D'Amico risk group may not have been demonstrated due to the low sample size for high risk patients.

Clinical Parameter	Treatment	
	YES	**NO**
Gleason grade		
3+3	201 (34.7%)	378
3+4	26 (37.7%)	43
Chi-square p-value	0.625	
Clinical T stage		
T1	116 (32.1%)	245
T2a	63 (43.4%)	82
T2b	20 (45.5%)	24
Chi-square P-value	0.023	
MCCL		
<6m	166 (34.7%)	313
≥6mm	69 (50.4%)	68
Chi-square P-value	0.001	
D'Amico risk		
Low	165 (35.1%)	315
Intermediate	77 (47.5%)	85
High	4 (30.8%)	9
Chi-square P-value	0.010	

Table 5.5. Table to assess the effect of Gleason grade, clinical T-stage, MCCL and D'Amico risk group on rate of treatment for men enrolled on an AM/AS program.

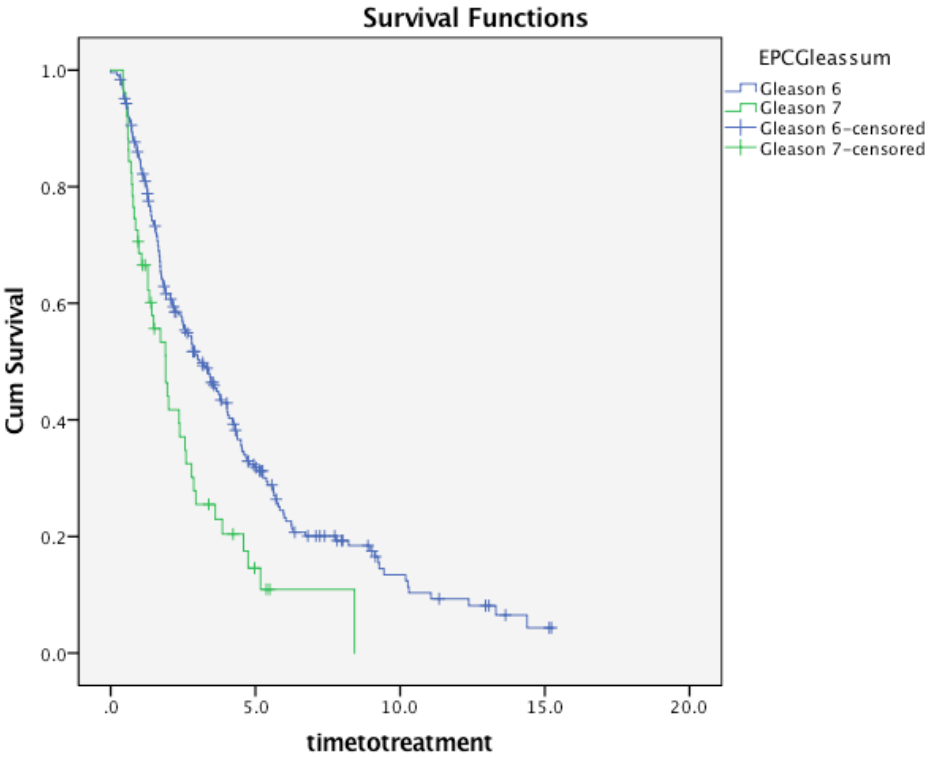


Figure 5.11. Kaplan-Meier plot to assess effect of Gleason score on time to treatment. P-value 0.001.

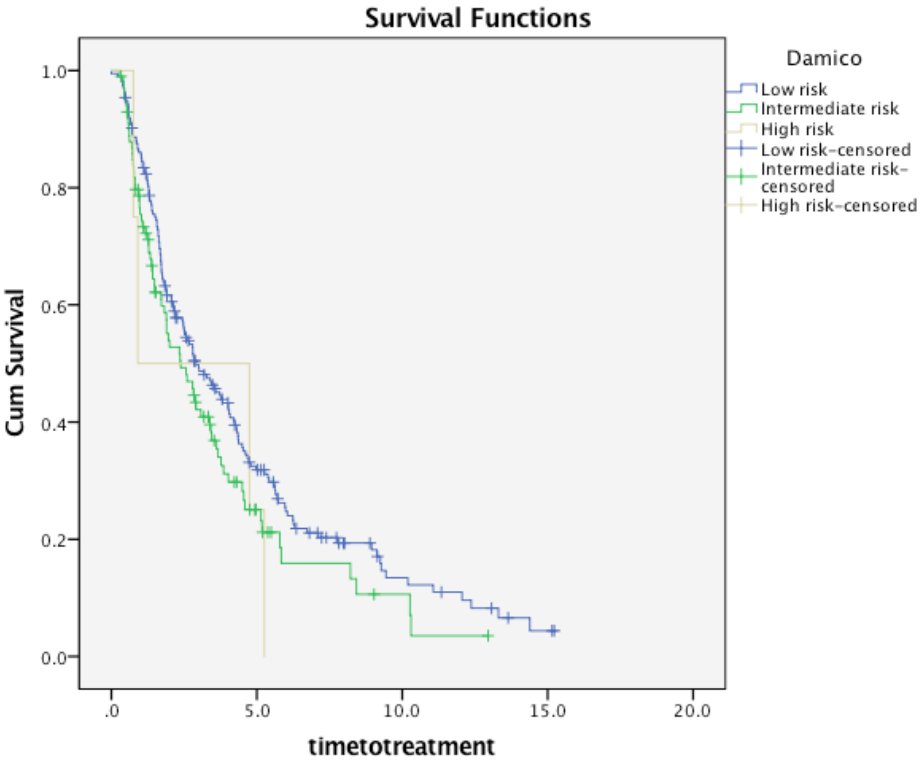


Figure 5.12 Kaplan-Meier plot to assess effect of D'Amico risk group on time to treatment. P-value 0.15.

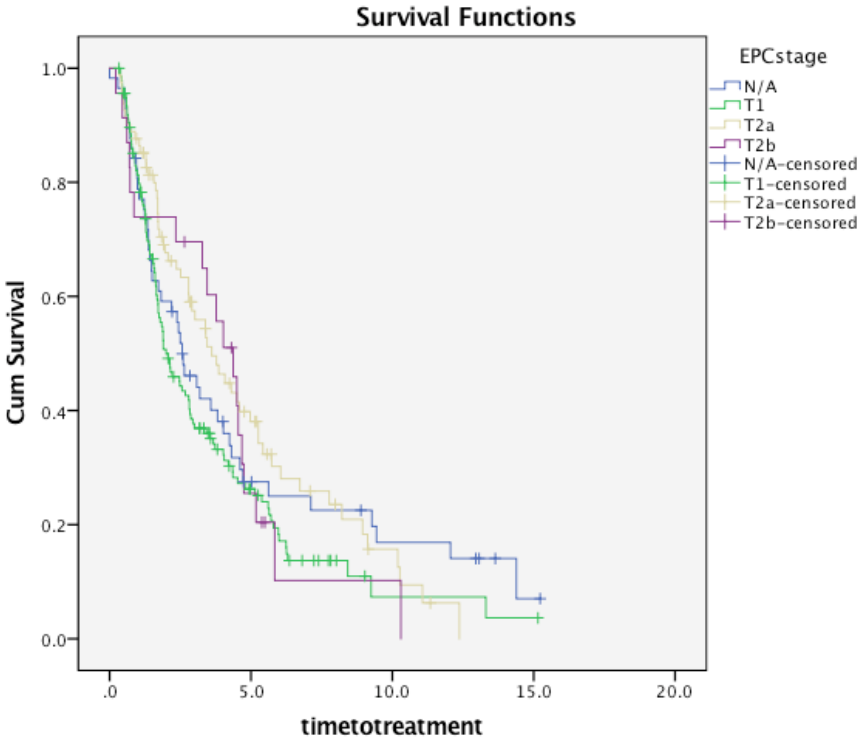


Figure 5.13 Kaplan-Meier plot to assess effect of clinical T-stage on time to treatment. P value 0.187.

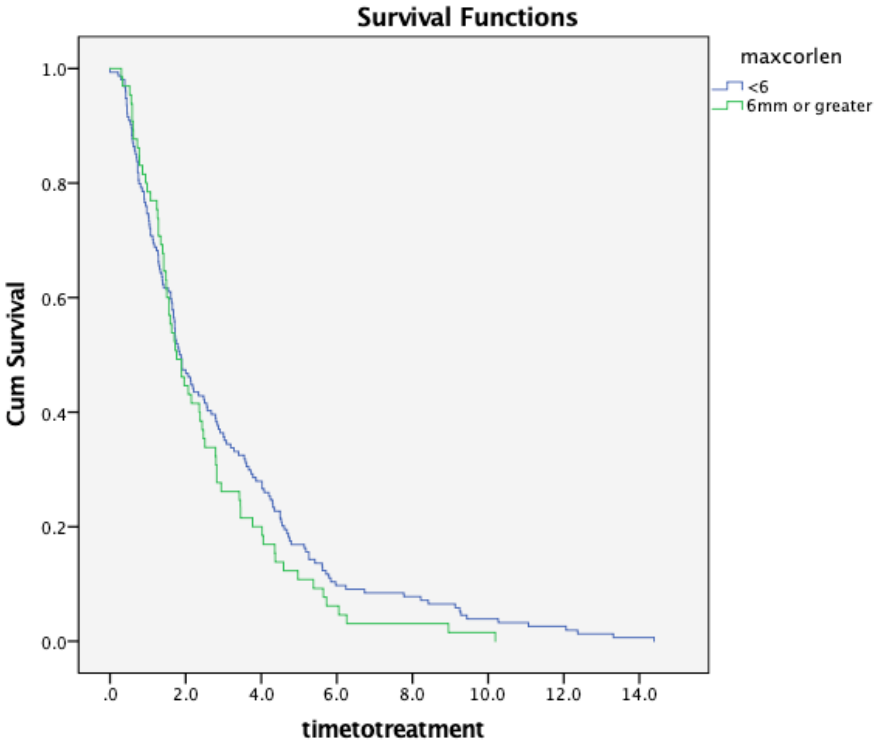


Figure 5.14 Kaplan-Meier plot to assess effect of maximum cancer core length on time to treatment. P value 0.217.

Restaging

Restaging classified as either an MRI, biopsy or both was performed in 57.2% of patients. A third of patients were not restaged. Of the patients that were restaged the majority were protocol driven (i.e. no change in clinical parameters), the remainder were either a result of a rise in PSA or other clinical change (Table 5.6). Very few patients were restaged by request although it is difficult to accurately assess this retrospectively.

Reason	Number	Percentage
Not done	236	33.3%
Protocol	262	36.8%
PSA rise	135	19%
Other clinical change	6	0.8%
Patient request	4	0.6%
Not known	67	9.4%

Table 5.6. Table showing the number and percentage of men undergoing restaging investigations whilst on AM/AS (n=710).

5.4.2 Aim 2 – Restaging Group 1 - Outcomes of introducing protocol re-staging in a cohort of clinically stable active monitoring patients.

Number of cases

Between 2014 and 2016, 144 cases were identified as having been enrolled on an active monitoring programme and had had restaging based on updated NICE guidance (CG175). All patients were suitable for radical treatment and had not previously undergone restaging in the form of either an MRI or a TRUS biopsy or both.

5.4.2.1 Characteristics at diagnosis

Median was 64.8 years of age (range 42.1 to 78.2 years). Median PSA was 5.7ng/ml. (range 0.5 to 18.2 ng/ml. 1 patient had Gleason 5 disease and 1 had Gleason 3+4=7 at diagnosis. The remaining 98.6% had Gleason 6 disease. Clinical and radiological T-stage, number of positive cores and MCCL can be seen in Table 5.21.

93.8% of cases had a post-biopsy MRI at diagnosis. Only 2.8% had a pre-biopsy bpMRI and 1.4% patients did not have an MRI. The timing was not known for 2.1% of patients.

88.2% of cases were low risk and 11.8% were intermediate risk at diagnosis.

5.4.2.2 Outcomes of restaging

Time to restage

Mean time to restage was 3.7 years and median time was 2.6 years. The range was 1.0 to 12.6 years.

MRI timing at restaging

All restaging MRI scans were bi-parametric with T2W and DWI sequences. 93.1% of patients had pre-biopsy MRI at restaging. 4.2% were performed following TRUS biopsy, 2.1% did not have an MRI and 0.7% (1 patient) did not have a biopsy.

Change in PSA

Mean PSA at restage was 6.9ng/ml and median was 6.5. The mean change in PSA was 0.7 with a range from an 11.4 decrease to an increase of 12.5.

Gleason grade at restage

14.9% (21/141) of patients demonstrated grade progression at restage. There were no cases that were a higher grade than Gleason 3+4. 25.6% of patients had a negative biopsy and 60.3% demonstrated no change in grade (Table 5.7).

GLEASON GRADE	AT DIAGNOSIS	AT RESTAGE
NEGATIVE	0	36
5	1	0
3+3	142	85
3+4	1	22
NO BIOPSY	0	1

Table 5.7. Table to show the Gleason grading at diagnosis and re-staging in men who underwent protocol restaging in a stable AM cohort (n=144).

Of the patients with grade progression, 5/21 (23.8%) demonstrated radiological progression, 12/21 (57.1%) demonstrated clinical stage progression and 13/21 (62%) had an increased number of positive cores (Table 5.8).

	GRADE PROGRESSION	NO GRADE PROGRESSION
RADIOLOGICAL PROGRESSION (4 NO MRI TO COMPARE)		
YES	5 (23.8%)	14 (11.8%)
NO	16 (76.2%)	105 (88.2%)
VOLUME PROGRESSION		
YES	13 (62%)	34 (27.6%)
NO	8 (38%)	89 (72.4%)
cT STAGE PROGRESSION		
YES	12 (57.1%)	12 (9.8%)
NO	9 (42.9%)	111 (90.2%)

Table 5.8. Table to highlight the association between those with grade progression and appearance on MRI, clinical staging and presence of volume progression in men who underwent protocol restaging in a stable AM cohort.

MRI stage at restage

2.8% of cases did not have an MRI for comparison. 59.7% had stable appearances on restaging. 24.3% had improved appearances and were staged lower than at diagnosis. Only 13.2% of cases had documented progression on MRI at restaging.

When comparing MRI T stage at diagnosis to restage marginally fewer numbers of T1c, T2a and T2c were seen at diagnosis. The biggest change was seen in the staging of T2b cancers with very few being seen at restage compared to diagnosis. This may be attributed to resolution of post-biopsy haemorrhage (Figure 5.15). Improved MRI diagnostics may also contribute given the introduction of bpMRI whilst these patients were on surveillance.

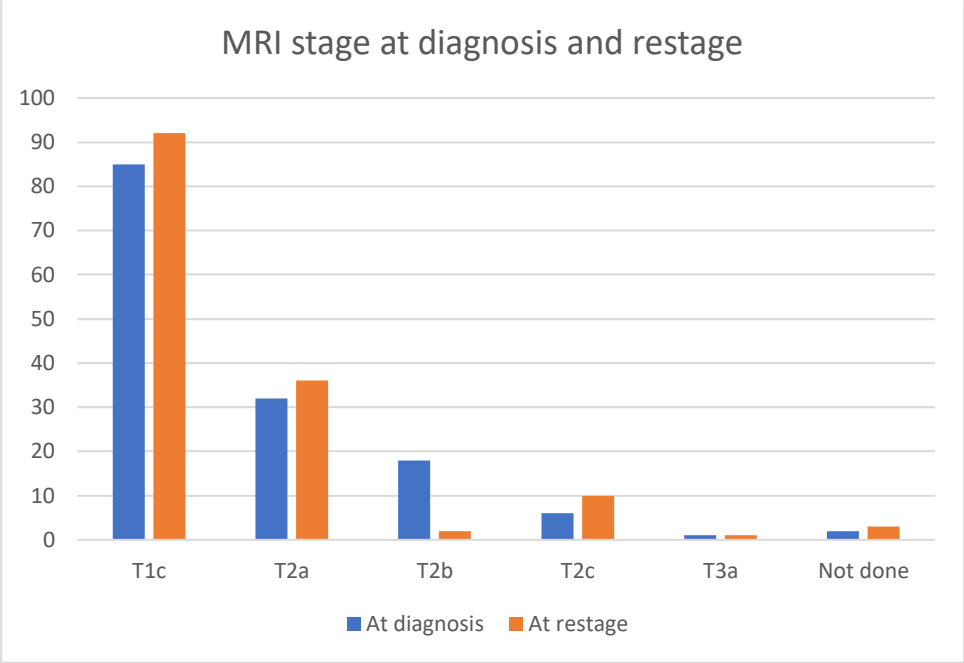


Figure 5.15. Graph to compare MRI stage at diagnosis and at re-stage in men who underwent protocol restaging in a stable AM cohort.

When comparing all restaging MRI scans, 34.8% (49/141) of men had a scan with a visible lesion i.e. ≥T2a. Of the 49 patients with a visible lesion, 23 (46.9%) had additional targeted biopsies at TRUS biopsy, i.e. biopsies taken in addition to the standard systematic biopsy. Of the remaining 26 patients with visible lesions, 2 had MRIs that were taken post biopsy and one patient did not have a biopsy. These 3 men were excluded from analysis, therefore, the remaining 23 patients all had standard systematic TRUS biopsies. If the visible lesion was in the field of a standard or systematic template this could still be classified as a targeted biopsy but not an 'additional targeted biopsy'. Therefore, it assumed that all patients with a visible lesion in theory will have had a cognitive fusion targeted biopsy.

When analysing the 46 patients with a visible lesion on pre-biopsy MRI, 38 (82.6%) had a positive biopsy that correlated with the lesion seen on MRI. The remaining 8 patients with visible lesions on MRI had biopsy results that did not correlate with the scan (Table 5.9).

Of the 23 patients that had an additional targeted biopsy, 15 were positive and 8 were negative. The cases that did not correlate with MRI included 4 negative biopsies and 4 with low volume Gleason 6 (Table 5.9).

PATIENTS WITH VISIBLE MRI LESIONS (N=46)	**CORRELATION WITH BIOPSY**	**NO CORRELATION WITH BIOPSY**
NO. OF CASES	38	8
MEDIAN MAX CORE LENGTH	7mm Range 2-20mm	3mm (only 4 patients) Range 1-6mm
OUTCOME OF BIOPSY		
NEGATIVE	0	4
GLEASON 6	24	4 (3 had 1 positive core, 1 had 3 positive cores)
GLEASON 3+4	14	0

Table 5.9. Table to highlight the outcome of TRUS biopsy in men whose biopsy outcome did and did not correlate with the lesion seen on pre-biopsy MRI. In men who underwent protocol restaging as part of a stable AM cohort.

Of the 140 patients with MRI scans (and biopsy) at restaging 48 (34.3%) had visible lesions and 92 (65.7%) did not. In these men, there were nearly identical percentages of Gleason 6 disease identified on subsequent biopsy for both groups. However, for those patients with a detectable lesion nearly a third (31.2%) had Gleason 3+4 disease compared to just 7.6% in the group that had normal MRIs (Table 5.10). The presence of a higher Gleason grade on biopsy was significantly associated with a visible lesion on scan when compared to a normal MRI, P-value of <0.001 (Table 5.10).

	VISIBLE LESION ON MRI	NORMAL MRI	P-VALUE
NUMBER OF CASES (N=140)	48	92	
MEDIAN MAX CORE LENGTH	6mm Range 1-20mm	2mm Range 1-11mm	<0.001 Kruskal-Wallace
OUTCOME OF BIOPSY			0.00014 (chi square)
NEGATIVE	4 (8.3%)	31 (33.7%)	
GLEASON 6	29 (60.4%)	54 (58.7%)	
GLEASON 3+4	15 (31.2%)	7 (7.6%)	
NO BIOPSY	1 (2.1%)	0	

Table 5.10. Outcome of TRUS biopsy following a normal or abnormal MRI scan. Effect of having a lesion on the scan was significantly associated with higher grade disease on biopsy, P-value 0.00014. Maximum positive core length was significant predictor of lesion on MRI. In men who underwent protocol restaging as part of a stable AM cohort.

Further sub-analysis of the 7 patients that had Gleason 3+4 disease at restaging and a normal MRI shows that 2 patients had a significant PSA rise and should probably have been offered triggered restaging. Aside from this, one could also argue that given the PSA rise they would have been recommended to have a re-biopsy regardless of the MRI result. For the remaining 5 patients, all the other clinical parameters were stable and therefore if one had relied on MRI alone to decide on ongoing surveillance the grade progression would be missed (Table 5.11). Based on the PROMIS definition 1 (Gl ≥4+3 or maximum core length >6mm) two of these patients would be classified as having significant cancer not identified on MRI. Therefore, 2/92 (2.2%) men with a normal MRI had significant cancer based upon these criteria.

	PSA AT RESTAGE (NG/ML)	PSA CHANGE FROM DIAGNOSIS	CLINICAL STAGE AT RESTAGE	MRI STAGE AT RESTAGE	MAX CORE LENGTH (MM)	POSITIVE CORES (NO. INCREASED)	TIME TO RESTAGE (YRS)
PT 1	8.9	2.7	T1c	T1c	5	1	4.1
PT 2	5.9	-1.5	T1c	T1c	1	1	1.4
PT 3	4.4	-0.3	T1c	T1c	7	4 (1)	1.2
PT 4	6.5	2.6	T1c	T1c	2	3 (2)	4.5
PT 5	6.5	0.4	T1c	T1c	3	4 (3)	1.1
PT 6	14.3	6.7	T1c	T1c	1	3 (2)	1.1
PT 7	14.5	7.4	T1c	T1c	8	3 (1)	2.0

Table 5.11. Table identifying the clinical and pathological parameters of the 7 patients that had Gleason 3+4 disease at restaging with a normal MRI scan. In men who underwent protocol restaging as part of a stable AM cohort

Clinical stage at restage

16.7% (24/144) of patients had clinical stage progression at the time of restage. 50% of these had grade progression on biopsy and 50% also had progression on MRI. 75% of these had an increase in the number of positive cores at restaging.

Volume of disease at restage

One patient did not have a re-biopsy. Of those that did have re-biopsy 32.9% (47/143) had an increase in at least one positive core. Those cases with an increased number of positive cores, 40.4% had just one more positive core, 25.5% had two and 23.4% had an increase of three. The highest number of increased positive cores was 5.

Change in D'Amico risk classification

25% of restaging TRUS biopsies were negative therefore this group could not be classified as per D'Amico. For purposes of comparison this group were deemed low risk.

At diagnosis 88.2% of cases were low risk versus 74% at restaging (including group with negative biopsy). 11.8% were intermediate risk at diagnosis versus 23.6% at restaging. 1.4% of cases were classified high risk after restaging

.

Outcome following restaging

76.4% of patients that were restaged continued with active surveillance. 22.2% went on to receive treatment with 12.5% having a prostatectomy and 9.7% having external beam radiotherapy. 1.4% were changed to a watchful waiting regime.

When comparing treated and non-treated groups the time to restage and age at diagnosis were very similar. There was a slightly higher PSA change in the group that received treatment. As one would expect there were a higher number of patients with Gleason 3+4 at restage that went on to have treatment. Patients that were treated also had higher levels of volume, grade, stage and MRI progression and all were statistically significant reasons for treatment with P-values all <0.001. However, 25% of those that had treatment were still classified as low-risk, 72% were intermediate risk compared to 11% in the non-treated group (Table 5.12).

	TREATED (N=32)	NON-TREATED (N=112)	CHI-SQUARE TEST
TIME TO RESTAGE (YRS)	Mean 3.3 Median 2.6	Mean 3.8 Median 2.6	-
MEDIAN AGE AT DIAGNOSIS	64.6	64.9	-
MEDIAN PSA AT RESTAGE	7.5	6.4	-
MEDIAN PSA CHANGE	2	0.2	-
GL SCORE RESTAGE			P-value <0.001
3+3	12	73	
3+4	20	2	
NEGATIVE	0	36	
NO BIOPSY	0	1	
MEDIAN NO. POS CORES	4 (Range 1 to 10)	2 (Range 0 to 7)	-
% MAX CORE LENGTH	38.8	15	-
VOLUME PROGRESSION	78% (25/32)	19.8% (22/111) 1 case did not have biopsy	P-value <0.001
GRADE PROGRESSION	59.4% (19/32)	1.8% (2/111) 1 case did not have biopsy	P-value <0.001
STAGE PROGRESSION	56.3% (18/32)	5.4% (6/112)	P-value <0.001
MRI PROGRESSION	34.4% (11/32)	8.3% (9/109) 3 cases did not have MRI	P-value <0.001
D'AMICO RISK GROUP			P-value <0.001
LOW	25% (8/32)	88% (99/112)	
INTERMEDIATE	72% (23/32)	11% (12/112)	
HIGH	3% (1/32)	1% (1/112)	

Table 5.12. Table to compare results of re-staging investigations between those men that went on to receive treatment after re-staging versus those that continued with surveillance. In men that who underwent protocol restaging as part of a stable AM cohort.

5.4.3. Aim 3 - Compare the outcomes of restaging in the stable active-monitoring cohort with clinical change or triggered re-staging and protocol restaging as part of active surveillance (at 12 months)

5.4.3.1 Restaging Group 2 - outcomes of a clinical change/triggered restaging cohort

Number of cases

132 patients were identified with a date of diagnosis between 8th August 2000 and 8th March 2013. All patients were enrolled on an active monitoring program and had restaging following clinical change/trigger.

5.4.3.1.1 Characteristics at diagnosis

Median age was 66 years. (range 45 to 83 years). Median PSA was 7.2ng/ml (range 0.5 to 21.2ng/ml). 89.4% were Gleason 3+3=6 at diagnosis and 10.6% were Gleason 7. All but one of the Gleason 7 cases were 3+4. Clinical and radiological stage, number of positive cores and MCCL can be seen in Table 5.21.

68.9% were low risk at diagnosis. 30.3% were intermediate risk and 0.8% were high risk.

5.4.3.1.2. Outcomes of Restaging

Time to restage

Mean time to restage was 3.9 years and median was 3.4 years. Range was 0.5 to 12.5 years.

Reason for re-stage

91.7% (121/132) had re-staging due to a rise in PSA level, 4.5%(6/132) had clinical change and 3.8% (5/132) did so at patients request.

Re-MRI

90.9% (120/132) of patients who were restaged because of a clinical trigger had a repeat MRI. All the patients that did not have restaging MRI did however have a re-biopsy (Figure 5.22).

Of the patients that did have a repeat MRI, 90% had one scan and 10% had 2 (i.e. were restaged on more than occasion). 30.8% of those that had both an MRI and biopsy as part of restaging had the MRI prior to the biopsy.

Re-biopsy

65.2% (86/132) of patients who were restaged because of a clinical trigger had a repeat TRUS biopsy (Table 5.13). Of the patients that had a re-biopsy 89.3% had only 1 re-biopsy, 9.5% had 2 biopsies and 1.2% had 3 biopsies.

	RE-MRI		
	NO	**YES**	**TOTAL**
RE-BIOPSY			
NO	0	46	46
YES	12	74	86
TOTAL	12	120	132

Table 5.13. Table to show number of men who received a TRUS biopsy and a MRI scan as part of clinically triggered re-staging.

When reviewing those patients who had a change in treatment following restaging 44.7% had a biopsy prior to this

Change in PSA

Mean change in PSA at the time of restaging was a rise of 4.9 ng/ml and median change was 4.3 ng/ml. Range in change was a decrease of 8.4 to a rise of 31.5ng/ml (Figure 5.22)

MRI at restage

90.9% (120/132) of patients had an MRI as part of restaging. Of those that had an MRI 90% had one MRI and 10% had 2 MRI scans, i.e. had restaging on more than one occasion.

When comparing MRI at diagnosis with the restaging scan 57.6% had evidence of progression, 25% did not and 9.1% could not be assessed for progression as did not have an MRI and 8.3% could not be assessed.

Grade progression

Of the 65.2% (86/132) patients that a re-biopsy 33.7% (29/86) demonstrated grade progression and 65.1% (56/86) did not. 27 patients progressed Gleason 3+3=6 to Gleason 3+4, 2 from Gleason 3+3 to 4+3, and 1 progressed from Gleason 3+4 to 4+3. 15.3% had a negative biopsy (1 patient histology not available) (Table 5.14).

GLEASON GRADE

	AT RESTAGE			
AT DIAGNOSIS	**NEGATIVE**	**3+3**	**3+4**	**4+3**
3+3	13	40	27	2
3+4	0	0	3	1

Figure 5.14. Table showing change in Gleason score at diagnosis compared to restage in men who had triggered restaging (n=86).

Clinical stage progression

18.9% of cases had documented clinical stage progression. 37.1% did not progress and 43.9% could not be assessed due to lack of documentation.

Volume of disease at restage

46 patients did not have a biopsy, 1 result was unavailable. Of the cases that had a re-biopsy 56.5% (48/85) had an increase in at least one positive core. Those with an increase number of positive cores at restaging, 20.1% had an increase of one positive core, 25% had an increase in 2 positive cores and 31.3% and increase in 3 positive cores.

Change in D'Amico risk classification

26.6% of patients could not accurately be assigned D'Amico classification following restaging due to lack of clinical stage data or lack of histological diagnosis. Despite this there did appear to a significant shift to patients with more advanced risk groups (Figure 5.16).

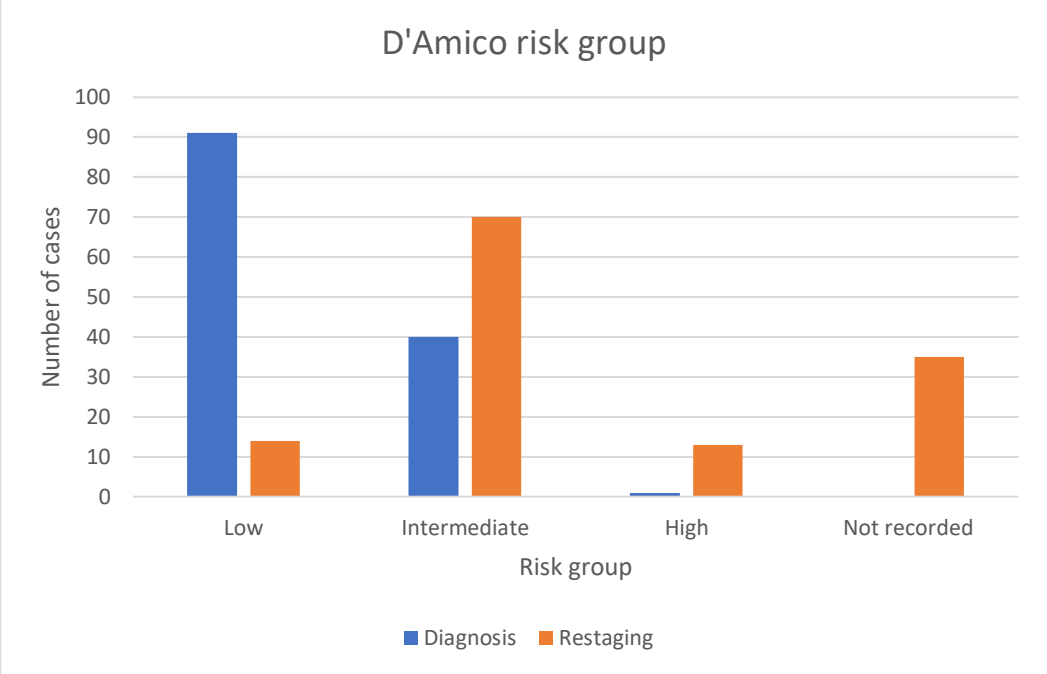


Figure 5.16. D'Amico risk stratification at diagnosis and following triggered re-staging.

Outcome following restaging

21.2% of patients continued active surveillance following restaging. 69% of patients went on to receive treatment with the remaining 9.8% patients moving to a watchful waiting program. 17.4% of patients went on to have radical prostatectomy and 47.7% had radical radiotherapy. 2.3% and 1.5% had hormones and brachytherapy respectively.

When comparing those patients that had treatment with those that did not after triggered re-staging there are many obvious differences. Those that continued with active surveillance had a longer time to restage, a slightly lower PSA, significantly

lower rates of grade and radiological progression and a much lower percentage of D'Amico intermediate risk disease (Table 5.15).

	TREATED (N=91)	**CONTINUE AS (N=28)**
TIME TO RESTAGE (YRS)	Mean 3.5 Median 3.2	Mean 4.3 Median 4.0
MEDIAN AGE AT DIAGNOSIS	66	66
MEDIAN PSA AT RESTAGE	12	10.1
MEDIAN PSA CHANGE	4.7	3.5
GLEASON SCORE RESTAGE		
3+3	26	11
3+4	23	1
4+3	3	-
NEGATIVE	3	9
NO BIOPSY	36	7
GRADE PROGRESSION	43.6% (24/55) 36 cases did not have biopsy	4.8% (1/21) 7 cases did not have biopsy
STAGE PROGRESSION	42 cases not recorded so not compared	11 cases not recorded so not compared
MRI PROGRESSION	36.4% (28/77) 14 cases not comparable	4.8% (1/21) 7 cases not comparable
D'AMICO RISK GROUP		
LOW	5.5% (5/91)	28.6% (8/28)
INTERMEDIATE	59.3% (54/91)	32.1% (9/28)
HIGH	11% (10/91)	3.6% (1/28)
NOT CLASSIFIED	24.2% (22/91)	35.7% (10/28)

Figure 5.15. Table to demonstrate differences in patients undergoing treatment compared those that continue with active surveillance after a triggered re-stage.

5.4.3.2 Restaging group 3 - Outcomes of the first protocol restaging in an AS cohort

Number of cases

114 cases were identified with a date of diagnosis between 14th March 2014 and 4th December 2015. All patients were enrolled on an active surveillance program and had undergone restaging.

5.4.3.2.1 Characteristics at diagnosis

Median age at diagnosis was 65.0 years of age (range 51-80 years). Median PSA was 5.9ng/ml (range 0.2 to 37.6 ng/ml). 96.5% (110/114) were Gleason 6 at diagnosis and the remaining 4 patients all had Gleason 3+4=7 disease. Clinical and radiological stage, number of positive cores and MCCL can be seen in Table 5.21.

24.6% of MRIs were performed pre-biopsy. 74.6% were post-biopsy and only one patient did not have a staging MRI

86.8% cases were classified as low-risk. 10.5% were intermediate risk and 2.6% were high risk.

5.4.3.2.2 Outcomes of restaging

Time to restage

Mean time to restage was 1.3 years and median time was 1.2 years. Range was 0.9 years to 2.3 years.

MRI timing at restage

All restaging MRI scans were bi-parametric. Of the 114 patients identified 1.8% did not have a repeat MRI and 21.1% did not have a repeat biopsy. 76.3% had a pre-biopsy MRI and 0.9% (1/114) had an MRI post re-biopsy.

Change in PSA

Mean and median PSA at restage was 5.9. The mean change in PSA at restage was -0.7 and median was 0. Range in change of PSA was a decrease of 35 to a rise of 8.

Gleason grade at restage

24 (21.1%) patients did not have a repeat biopsy. Of those that had a biopsy 16.7% (15/90) demonstrated grade progression. One patient was upgraded from Gleason 6 to Gleason 4+4, 13 patients progressed from Gleason 6 to Gleason 3+4 and one had Gleason 3+3 but new tertiary pattern 4. 22.2% had a negative restaging biopsy (Table 5.16)

Gleason grade

	At restage				
At diagnosis	**Negative**	**3+3**	**3+4**	**4+4**	**No biopsy**
3+3	20	53	13	0	24
3+4	0	1	2	1	0

Table 5.16. Table to show outcomes of TRUS biopsy and at first protocol re-stage in an AS cohort.

MRI at restage

Only one patient did not have a restaging MRI. Of the remaining 113 patients only 1 (0.9%) demonstrated progression on MRI. 22.1% (25/113) of those that had a restaging MRI had a lesion (i.e. T2a or above). Of the 25 patients with a lesion, 5 patients did not go on to have a restaging biopsy.

When comparing the MRI with the biopsy results of the 20 patients that had had both investigations it was found that 65% (13/20) of the MRIs correlated with biopsy results. 14 patients had additional targeted lesions above the standard template if this was thought not to include the lesion seen on MRI. 10/14 of these additional targets were positive for tumour. There was a higher percentage of higher grade disease in those cases where MRI and biopsy correlated. The 8 patients that had Gleason 3+4 disease and correlation of MRI and biopsy all had grade progression at restaging (Table 5.17).

PATIENTS WITH VISIBLE MRI LESIONS N=20	CORRELATION WITH BIOPSY	NO CORRELATION WITH BIOPSY
NO. OF CASES	13	7
MEDIAN MAX CORE LENGTH	7mm Range 3-18	3mm Range 2-11
OUTCOME OF BIOPSY		
NEGATIVE	0	3
GLEASON 6	5	3
GLEASON 3+4	8	1

Table 5.17. Table to highlight the outcome of TRUS biopsy in men whose biopsy outcome did and did not correlate with the lesion seen on pre-biopsy MRI.

	VISIBLE LESION ON MRI	NORMAL MRI	P-VALUE
NUMBER OF CASES	25	88	
MEDIAN MAX CORE LENGTH	5mm Range 2-18	4mm Range 1-12	0.300 Kruskal-Wallis
OUTCOME OF BIOPSY			0.005 (Chi-square)
NEGATIVE	3 (15%)	17 (27.5%)	
GLEASON 6	8 (40%)	45 (65.2%)	
GLEASON 3+4	9 (45%)	6 (8.7%)	
GLEASON 4+4	-	1 (1.5%)	
NO BIOPSY	5	19	

Table 5.18. Outcome of TRUS biopsy following a normal or abnormal MRI scan. Effect of having an abnormal scan did significantly alter the outcome of biopsy, P-value 0.005. Length of max positive core length was not significant.

Comparison of those men with a normal MRI and those with a visible lesion shows those with a visible lesion to have a higher percentage of patients with higher grade disease, with 45% having Gleason 3+4 disease compared with 8.7% with a normal MRI. This was statistically significant with a p-value 0.005. The length of maximum

positive core length was not a significant predictor of abnormality on MRI (Table 5.18).

As in the protocol restaging of an AM cohort I have further sub-analysed the patients with higher grade disease but a normal MRI (i.e. Gleason 3+4 and 4+4 in this cohort).

	GL SCORE DIAG	GL SCORE RESTAGE	PSA AT RESTAGE (NG/ML)	PSA CHANGE	CLINICAL STAGE	MRI STAGE	POSITIVE CORES (NO. INCREASED)	MAX TUM. LEGNTH	TIME TO RESTAGE (YRS)
PT 1	3+3	4+4	7.1	-0.8	T2a	T1c	2 (1)	5mm	1.22
PT 2	3+3	3+4	7.0	0.6	T1c	T1c	3	9mm	1.34
PT 3	3+3	3+4	6.8	-0.1	T1c	T1c	1	5mm	1.11
PT 4	3+3	3+4	5.4	0.3	T1c	T1c	2 (1)	3mm	1.03
PT 5	3+3	3+4	6.7	-0.8	T1c	T1c	3 (2)	4mm	1.22
PT 6	3+3	3+4	8.8	2.3	T2a	T1c	4 (1)	12mm	1.1.42
PT 7	3+3	3+4	10.1	3.9	T1c	T1c	2 (1)	4mm	2.0

Table 5.19. Table identifying the clinical and pathological parameters of the 7 patients that had Gleason 3+4 disease at restaging with a normal MRI scan.

All the patients with a normal MRI but higher grade disease on biopsy did demonstrate grade progression at restaging. When assessing other clinical parameters one patient demonstrated clinical stage progression (Patient 1) and one patient had a significant PSA rise of 3.9 (Patient 7) (Table 5.19). Again, based on PROMIS definition 1, 3 out of 88 (3.4%) patients would be defined as having significant cancer and a normal MRI.

Clinical stage progression

Only 2.6% had clinical stage progression documented and 94.7% of patients did not. 2.6% did not have stage documented so could not be assessed. Of the patients that had stage progression only one also demonstrated grade progression. None had progression on MRI

Volume of disease at restage

30% (27/90) of the patients who had a re-biopsy had an increase in at least one positive core; 59.3% had an increase of just one positive core, 22.2% had an increase of 2 cores and 7.4% an increase of 4 cores.

Change in D'Amico risk classification

There was a decrease in low-risk patients from 86.6% to 78.9% following restaging and an increase in the number of intermediate risk patients from 10.5% to 18.4%.

Regarding the high-risk patients at diagnosis, two were clinical T2c but both T1c on MRI and low volume Gleason 6, the third had a PSA in the 30's which dropped to 11 on restage and was likely related to a UTI at presentation. At restage, one case remained high risk as was still thought to be cT2c and the other two cases both dropped risk groups (Figure 5.17).

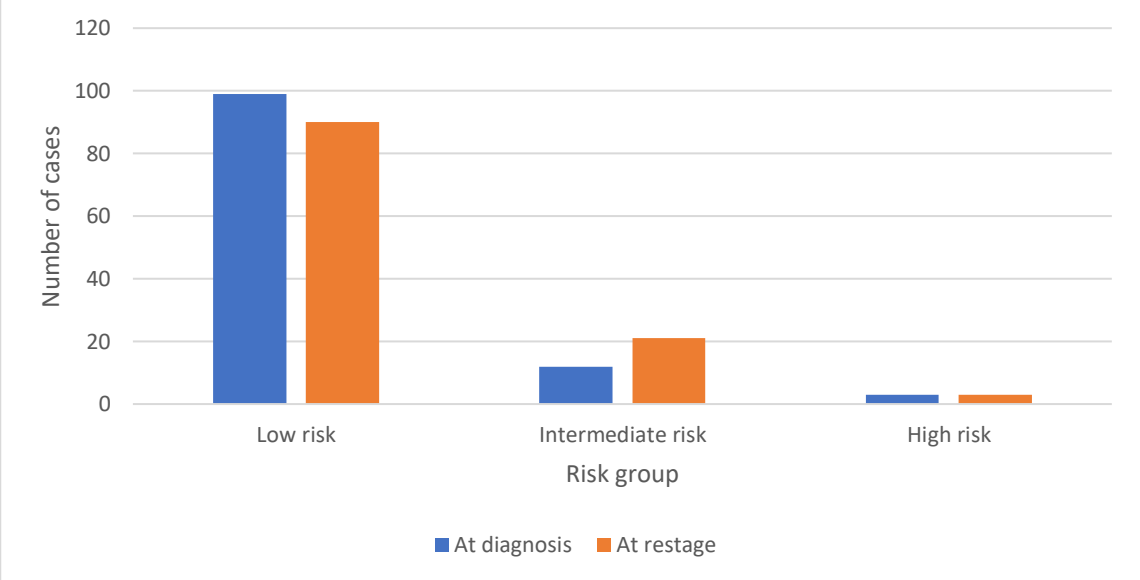


Figure 5.17. Graph to show the D'Amico risk classification before and after protocol re-staging.

Outcome following restaging

84.2% of patients continued active surveillance following re-staging. 13.1% received treatment with equal numbers having surgery and external beam radiotherapy and

one patient (0.9%) having brachytherapy. 1.8% changed to a watchful waiting approach and one patient was still yet to decide on treatment course at the time of review.

When comparing outcomes of men following their first protocol re-staging higher Gleason grade at restage, evidence of grade progression and higher D'Amico risk groups were all associated with significantly higher treatment rates. Neither MRI progression or clinical stage at restage were significant in those patients receiving treatment (Table 5.20).

	TREATED (N=15)	CONTINUE AS (N=97)	P-VALUE (CHI-SQUARE)
TIME TO RESTAGE (YRS)	Mean 1.3 Median 1.2	Mean 1.3 Median 1.3	
MEDIAN AGE AT DIAGNOSIS	67	65	
MEDIAN PSA AT RESTAGE	6.7	5.4	
MEDIAN PSA CHANGE	0.5	-0.1	
GLEASON SCORE RESTAGE			<0.001
3+3	3	51	
3+4	9	6	
4+4	1	-	
NEGATIVE	0	20	
NO BIOPSY	2	20	
GRADE PROGRESSION	69.2% (9/13) 2 cases did not have biopsy	7.8% (6/77) 20 cases did not have biopsy	<0.001
STAGE PROGRESSION	7.1% (1/14) 1 cases did not have recorded	2.1% (2/95) 2 cases did not have recorded	0.738
MRI PROGRESSION	0/15	1% (1/96) 1 case did not have MRI	0.986
D'AMICO RISK GROUP			<0.001
LOW	20% (3/15)	88.7% (86/97)	
INTERMEDIATE	66.7% (10/15)	10.3% (10/97)	
HIGH	13.3% (2/15)	1% (1/97)	

Table 5.20 Table to compare results of re-staging investigations between those men that went on to receive treatment after first protocol re-staging versus those that continued with surveillance.

5.4.3.3 Overall comparison between groups 1, 2 and 3

The three restaging groups represent distinctly different populations. Restaging group 1, are men who have been under AM without prior protocol or triggered. Restaging group 2, represent men who have had a clinically triggered restaging investigation, and restaging group 3 represent men who are on surveillance having their first protocol led restage.

When comparing characteristics at diagnosis between the three groups that were restaged the ages were very similar and PSA levels were slightly higher in the triggered restage group. There were lower rates of clinical and radiological T1 disease in the triggered restage group although a significant number were not recorded for clinical stage in this. The numbers of positive cores and max cancer core length were not significantly different between the groups. There was also a higher proportion of D'Amico intermediate risk in the triggered restage group compared to the other two groups which were very similar (Table 5.21).

S	GROUP 1. PROTOCOL RESTAGE STABLE AM COHORT	GROUP 2. TRIGGERED RESTAGE	GROUP 3. PROTOCOL RESTAGE AS
NUMBER OF CASES	144	132	114
AGE AT DIAG. (YRS)			
MEAN	64.0	65.6	65.0
MEDIAN	64.8	66	65.0
RANGE	42.1 to 78.2	45 to 83	51 to 80
PSA AT DIAGNOSIS (NG/ML)			
MEAN	6.2	7.8	6.6
MEDIAN	5.7	7.2	5.9
RANGE	0.5 to 18.2	0.5 to 21.2	0.2 to 37.6
GLEASON SCORE (N)			
3+3	143	118	110
3+4	1	13	4
4+3	-	1	-
CLINICAL STAGE (%)			
T1	81.8	50	80.8
T2A	16.1	20.5	15.8
T2B	2.1	9.8	-
T2C	-	0.8	2.6
T3A	-	-	-
N/R	-	18.9	0.9
MRI STAGE (%)			
T1	59	49.2	77.2
T2A	22.2	28.0	14.9
T2B	12.5	18.2	0.9
T2C	4.2	-	5.3
T3A	0.7	-	0.9
NOT DONE	1.4	4.6	0.9
MRI TIMING (%)			
PRE-BIOPSY	2.8	-	24.6
POST-BIOPSY	93.8	95.4	74.6
NO MRI	1.4	4.6	0.9
NOT KNOWN	2.1	-	-
NUMBER OF POSITIVE CORES (%)			
1	50	40.2	38.6
2	27.1	20.5	21.9
3	10.4	18.9	23.7
>4	11.3	18.9	12.4
NOT KNOWN	-	1.5	3.5
MAX. CANCER CORE LENGTH (MM)			
MEAN	2.9	3.5	3.4
MEDIAN	2	3	3
RANGE	1 to 15	1 to 14	1 to 15
D'AMICO RISK GROUP (%)			
LOW	88.2	68.9	86.8
INTERMEDIATE	11.8	30.3	10.5
HIGH	-	0.8	2.6

Table 5.21. Table showing patient demographics and disease status at diagnosis of three different AM/AS re-staging groups.

When comparing the results of restaging in the three different groups as expected the median time to restage was longer in the triggered restaging group (group 2). The timing of MRI in those patients that had both an MRI and a biopsy was also more likely to be before the biopsy in those patients undergoing protocol restaging. The median PSA change was very similar in the protocol-led groups (group 1 and 3) with very little change from diagnosis, as one would expect the PSA rise in the triggered group (group 2) was significant.

In those patients that had a restaging biopsy the rates of upgrading were again similar between the protocol groups (group 1 and 3) but was more than double in the triggered restaging cohort (group 2) with just over a third of patients upgraded.

The rates of progression on MRI scan was also significantly different between the groups with <1% of patients having progression in the protocol restaging AS group (group 3), rates were higher in the stable AM protocol restaging group (group 1) but still only 13.6%, while over two-thirds of men demonstrated progression in the triggered restaging cohort (group 2). No meaningful comparisons could be made between the groups with clinical stage progression due to high rates of missing data in the triggered restage cohort. When comparing volume progression this was again very similar in the two protocol restaging groups and nearly twice as high in the triggered restage group (Table 5.22).

The outcome on course of treatment after restaging was significantly different between the 3 groups. Only 1 in 5 men continued surveillance after triggered restaging (group 2) and of those that went on receive treatment only a quarter chose radical prostatectomy and over two-thirds having radical radiotherapy. For patients having protocol restaging treatment rates were slightly higher in the AM group than the AS (23% vs 13%), however, treatment chosen was roughly equal between radiotherapy and surgery (Table 5.22).

	GROUP 1. PROTOCOL RESTAGE STABLE AM COHORT	GROUP 2. TRIGGERED RESTAGE	GROUP 3. PROTOCOL RESTAGE AS	P-VALUE CHI SQ.
TIME TO RESTAGE (YEARS)				-
MEAN	3.7	3.9	1.3	
MEDIAN	2.6	3.4	1.2	
RANGE	1.0 to 12.6	0.5 to 12.5	0.9 to 2.3	
MRI TIMING (%)				-
PRE-BIOPSY	95.7	30.8	98.9	
POST BIOPSY	4.3	69.2	1.1	
PSA CHANGE (NG/ML)				-
MEAN	0.7	4.9	-0.7	
MEDIAN	0.6	4.3	0	
RANGE	-11.4 to 12.5	-8.4 to 31.5	-35 to 8	
GRADE PROG (%)				0.0014
YES	14.9	34.1	16.7	
NEGATIVE BIOPSY	25.6	15.3	22.2	
MRI PROG. (%)				<0.001
YES	13.6	69.7	0.9	
NO	86.4	30.3	99.1	
CLINICAL STAGE PROGRESSION (%)				n/a
YES	16.7	N/A	2.6	
NO	83.3	N/A	94.7	
N/R	-		2.6	
VOL. PROG. (%)				0.0003
YES	32.9 (47/143)	56.5 (48/85)	30 (27/90)	
NO	67.1 (96/143)	43.5 (37/85)	70 (63/90)	
IF YES, NO. INCREASE,				
1	40.4%	20.1%	59.3%	
2	25.5%	25%	22.2%	
3	23.4%	31.3%	-	
>4	10.7%	23.6%	18.5%	
D'AMICO AT RESTAGE (%)				-
LOW	74	10.6	78.9	
INTERMEDIATE	23.6	53.0	18.4	
HIGH	1.4	9.8	2.6	
N/A	-	26.6	-	
OUTCOME OF RESTAGE (%)				<0.001
CONTINUE AS	76.4	21.2	84.2	
WW	1.4	9.8	1.8	
TREATMENT	23.2	69	13.1	
NOT KNOWN	-	-	0.9	
TREATMENT RECEIVED (%)				0.054
SURGERY	53.9	25.3	46.7	
EBRT	46.1	69.2	46.7	
BRACHYTHERAPY	-	2.2	6.7	
HORMONES	-	3.3	-	

Table 5.22. Table showing the outcomes of restaging when comparing three different restaging cohorts.

5.5 Discussion

This chapter reports the outcomes for men with localised prostate cancer on a deferred treatment strategy be that active surveillance or its predecessor active monitoring. It reports on the outcomes of introducing re-staging protocols in to an established clinically stable population on active monitoring and the effect that this can have on treatment rates. It also reports on the outcomes of restaging in 3 different surveillance populations; clinically triggered restaging, protocol restaging in an established stable active monitoring group and the first standard protocol restaging in an active surveillance group. Finally, it reports on the potential use of bi-parametric MRI in active surveillance and the possibility of avoiding prostate restaging biopsy in men with a normal scan.

5.5.1 Aim 1 – Outcomes of a deferred treatment strategy

The results from this cohort of patients represent a group that were surveyed using both active monitoring and active surveillance protocols. Initial inclusion criteria in the early stages of recruitment were based on criteria similar to the ProtecT study (Hamdy et al., 2016), and then subsequently based on new NICE guidance. However, it must be remembered that there was not a strict entry criteria like other published single institution surveillance protocols. Over the period of the study the surveillance strategies changed with the introduction of protocol restaging, the timing of MRI and the upgrading of MRI technology. Therefore, when reviewing the outcomes of deferred treatment in this cohort it must be remembered that it represents a heterogeneous group and one that accurately reflects practice at the time. In view of all these factors one would expect outcomes potentially to be worse than those with strict entry criteria.

Entry criteria

In this study, the median age at diagnosis of 66 years was similar to large published cohorts of a similar and larger size (Hamdy et al., 2016, Dall'Era et al., 2012, Bokhorst et al., 2016). The majority were D'Amico low risk (72.4%) and Gleason 6 (87%) at diagnosis. All, except the Royal Marsden group, of the surveillance cohorts reviewed

by Dall'Era et al recruited only Gleason 6 disease and criteria were such that only low volume D'Amico low risk would have been eligible for enrolment (Dall'Era et al., 2012). ProtecT was less strict and had a lower percentage of Gleason 6 disease at 77%, however, PRIAS reported 99%(Hamdy et al., 2016, Bokhorst et al., 2016). The Klotz et al cohort had a similar number of Gleason 6 and 7 cases to this cohort (Klotz et al., 2010). It must also be remembered nearly 97% of this study cohort had an MRI scan at diagnosis, few other studies are able to match this. The reported series from Dall'Era's review have similar median follow up times to our cohort but as one would expect the prospective studies such as ProtecT and PRIAS report figures from a longer period. Overall, this study represents a large series of a contemporary UK practice with good medium to long term follow-up with a more heterogeneous patient population than many published series of AS cohorts.

Time to treatment

Of the 7 different active surveillance series, in Europe and North America, reviewed by Dall'Era et al median follow-up times ranged from 1.8 to 3.9 years. The percentage of patients treated varied from 11 to 33 % with median time to treatment varying between 1.3 to 3.5 years (related to median follow-up time). The percentage of patients treated at 2 years was around 20% although this statistic was missing from a number of studies (Tosoian et al., 2011, Klotz et al., 2010, Cooperberg et al., 2011, van den Bergh et al., 2009, van As et al., 2008, Adamy et al., 2011, Soloway et al., 2010) The more recent ProtecT trial published around 20% radical treatment rates at 2 years follow up and 54.8% had had treatment at 10 years' follow-up (Dall'Era et al., 2012). PRIAS reports 48% still on AS at 5 years and 27% at 10 years with 34% and 41% discontinued for clinical reasons (clinical progression) (Bokhorst et al., 2016). In another large series of AS patients with good median follow-up Klotz et al reported that 72% remained on AS after 5 years and 62% after 10 years (Klotz et al., 2010).

This study reports a median follow-up time of 3.7 years with an overall radical treatment rate of 34.8% and 42.7% of patients continuing AS at the time of review. The rate of treatment for patients that reached 5 years and 10 years was 28.3% and 39.4% respectively. These figures compare very favourably with the ProtecT and

PRIAS studies. It is difficult to determine the exact reason for lower treatment rates seen in our cohort. With only 10% of our study population reaching 10 years' follow-up and only a third reaching 5 years it may be that when the cohort matures higher treatment rates are seen. Higher treatment rates for the Protect study may equally be a result of higher numbers of men with higher Gleason disease at presentation. Also, the PRIAS study included multiple protocol restaging biopsies which detected disease progression in around 1 in 8 men. This will have affected treatment rates. Lower treatment rates in this study cohort is unlikely to have been a result having protocol restaging as only a third of patients received it. These patients would have been part of the more recent patients and would not have reached 5 and 10 year follow up. The widespread use of MRI at diagnosis may have reduced the number of patients potentially under staged at hence reduced the number of un-detected significant cancers that could progress. It is well known that MRI can detect more aggressive tumours and is useful at the entry point of AS (Radtke et al., 2015, Ahmed et al., 2017). It must also be remembered that many of these patients would not have had mpMRI, let alone bpMRI and therefore if the lower rates of treatment are a result of high use of MRI then the effects that modern mpMRI may have on ensuring optimum patient selection will hopefully be much more encouraging.

In men that went on to receive treatment it was only Gleason grade at diagnosis that was a significant predictor of time to treatment and this must be remembered when counselling patients regarding the likely outcome for surveillance. The large multicentre PRIAS study also demonstrated that Gleason grade, and clinical T3 disease, were the only significant predictors for adverse pathology for men exiting AS and proceeding to prostatectomy (Bokhorst et al., 2016). This is important information to know particularly when counselling younger men on surveillance programmes.

5.5.2 Aim 2 – Assess the outcomes of introducing protocol re-staging in a cohort of clinically stable active monitoring patients

Grade progression

Most surveillance strategies now have repeat or confirmatory biopsies with the aim to avoid under-staging the disease and to detect any potential tumour growth or grade progression/de-differentiation (Dall'Era et al., 2012). However, the timing of such biopsies is still a subject of debate and the earlier that it is done the lower the likelihood of detecting tumour progression but the higher chance of avoiding under-staging. Several studies, with the timing of first protocol re-biopsy between 3 months and 2 years, reported rates of grade progression between 8.9 and 28% and negative biopsies rates of between 21-37% of cases (Berglund et al., 2008, Bul et al., 2012, Venkitaraman et al., 2007).

The PRIAS study, a larger and more up to date study, followed over 5000 men on an active surveillance regime over a period of 10 years. A re-biopsy was performed and 1, 4, 7 and 10 years after diagnosis and grade progression rates were noted to be between 13-16% at each subsequent re-biopsy (Bokhorst et al., 2016).

The 14.9% grade progression rate noted in this study correlates well with other reported rates, however, it must be remembered that the population in our study is different to the reported studies and had been under surveillance for a median time of just under 3 years already.

MRI progression

The PRIAS study did not initially use MRI re-staging as standard and recommended its use when there were 2 or more positive cores present. This recommendation however was amended and its use was suggested as the best method for predicting grade progression (Bokhorst et al., 2016). The use of MRI in AS has previously been shown to have a negative predictor value of near 100% for detecting Gleason grade progression (Barrett and Haider, 2017, Schoots et al., 2015). Therefore, if a lesion is detected it should be targeted at subsequent biopsy. It is suggested that MRI and targeting may be able to replace systematic biopsies but more information is

required on the number of men who have a negative MRI and the outcomes of subsequent systematic biopsies (Bokhorst et al., 2016).

In this study, we demonstrated that those patients with a lesion visible on pre-biopsy MRI and went on to have targeted biopsies had a high correlation with higher grade tumours (Gleason 3+4). Those biopsies that were positive and did not correlate with the lesion on MRI were all Gleason 6 and appropriate to continue with surveillance. For those patients with a normal MRI, 7.6% were found to harbour biopsies indicating grade progression, albeit 28.6% (2/7) of these patients did demonstrate a significant PSA rise and would have been offered biopsies because of that alone. On this basis, one could argue that if MRI alone were used as a re-staging tool, a normal MRI would miss around 5% of grade progression, and if a lesion were present only targeted biopsies are required and the morbidity of systematic biopsies could be avoided.

Clinical progression

One could argue the benefit of repeat DRE in the context of AS if patients are also receiving MRI scans. With previously reported progression rates of around 10% (Bokhorst et al., 2016) this study was slightly higher at around 17%. With around 50% of patients with clinical progression demonstrating grade and MRI progression this further highlights the relevance of DRE and whether patients should be spared this on a less frequent basis.

Overall usefulness of the study

The main difference of this study compared to previous studies is that the population being re-staged was different to a standard surveillance group. They had not previously been re-staged and not had been through a second checkpoint to ensure suitability for a surveillance population. Despite this we have demonstrated a similar rate of grade progression at re-biopsy. The study has also highlighted the value of bi-metric MRI in restaging and a potential move away from the standard use of systematic biopsies and the potential for only targeted biopsies.

Despite only 14.9% patients demonstrating Gleason grade progression, just over 1 in 5 went on to receive radical treatment after restaging. The reason for this must be assumed to be multifactorial; Patient choice and progression in other parameters other than Gleason grade influencing decision, given that Gleason grade progression is the only statistically significant predictor of adverse features at RP. Patients should be aware of the difficult decisions that may arise after restaging and have this discussed at the outset of starting surveillance.

5.5.3 Aim 3 and 4– outcomes of restaging different populations and the use of MRI in the AS pathway

As one might expect the rates of grade, radiological and volume progression are very similar between the group of patients that had their first protocol restaging following diagnosis (group 3) and those patients that were stable on an active monitoring program (group 1). However, it is interesting to note that nearly a quarter of men in the stable AM group went on to receive radical treatment after restaging compared to around 1 in 8 men in the AS cohort despite only being on surveillance for around one and a half years longer (median). This decision again must be attributed to other factors and it is well known that the longer patients are on surveillance there is a natural tendency for patients to opt for treatment due to anxiety (Latini et al., 2007).

The rates of progression in all parameters noted in the clinically triggered restaging cohort (group 2) clearly justify the need for triggered restaging. There was a higher proportion of men with intermediate risk disease at diagnosis in the triggered re-stage group which would suggest that these men potentially require more intense follow-up than low-risk men. There was a significantly higher proportion of patients with progression noted on MRI compared with the other groups and around double the percentage of patients with grade progression. Unfortunately, only a third of patients in the triggered cohort had MRI pre-biopsy therefore no meaningful assessment can be made comparing the MRI with biopsy results as in the other 2 cohorts. If patients underwent triggered restaging only 1 in 5 continued surveillance following with a much higher proportion of men who had treatment receiving

radiotherapy compared with surgery, whereas it is similar for the men having treatment in the other cohorts. Considering the age at diagnosis between the 3 cohorts was very similar the reason for the difference is not clear and requires further investigation.

When reviewing the use of bpMRI in the protocol restaging of AS only 10.2% of patients with a normal MRI (no lesion seen) had Gleason >6 on re-biopsy and of these only 3 had significant cancer based on PROMIS definition 1. If one combines this cohort of normal bpMRIs with the normal bpMRIs in the stable AM cohort only 3% (5/170) would harbour significant cancer. Of this 3%, 40% (2/5 men) had changes in other clinical parameters that may have led to re-staging biopsies despite a normal MRI. Therefore, one could argue that in this cohort of patients, those with a normal MRI scan and no other change in clinical parameters have a 1.8% (3/170) chance of significant cancer if biopsied. Therefore, one could considering omitting a biopsy. Further reassurance can be seen in those patients where the biopsy result does not correlate with the lesion on MRI, only one patient had Gleason 3+4 disease, the remainder were all Gleason 6 or negative. It must also be remembered that within this study the MRIs used in these cohorts were bi-metric and not mpMRI. The other striking figure in the protocol restaging group (group 3) is that 99% of MRIs were unchanged at 1 year suggesting that it is too soon to re-stage with MRI. In a similar study by Gallagher et al using mpMRI they concluded that men who had a normal MRI at restaging had a 1.6% chance of detecting Gleason 3+4 cancer on subsequent systematic biopsy (Gallagher et al., 2019).

One recent study, by Thurtle et al (2018), has suggested that including annual mpMRI scans has led to a significant reduction in the number of men progressing to radical treatment, with only 7.6% having treatment after 3 years' surveillance. In 104 men on surveillance, 20 were detected to have grade progression, with half detected on MRI, but only half of these corresponding to the targeted biopsy. This emphasised the need for both targeted and systematic biopsies and raised the question as to whether the biopsy had indeed missed the MRI lesion (Thurtle et al., 2018). This study data, as well as that from a recent meta-analysis supports the conclusion that

changes in MRI should not alone be used to recommend a change in treatment strategy (van den Bergh et al., 2014).

Given that nearly a third of patients with grade progression in the Thurtle et al (2018) study had a normal MRI they suggested the continued use of systematic biopsy and this was also suggested by another study using template biopsy as a baseline, suggesting that MRI has a relatively low sensitivity in this setting (Ma et al., 2017, Thurtle et al., 2018). However, this study would suggest that if the MRI scan is normal, i.e. no lesions present, then a biopsy can be safely avoided, as the risk of having significant cancer is very low, <2%, particularly if there were no other clinical parameters that had changed. This would be supported by Gallagher et al (2019) who showed that PSA velocity was significantly associated with disease progression in men with a normal MRI (Gallagher et al., 2019).

5.5.4 Conclusion

Active surveillance is an important treatment option for men with low-risk organ confined prostate cancer with the aim of avoiding over-treatment of potentially insignificant disease.

Restaging represents an essential part of AS and this study has shown that its results can have a significant impact on the treatment pathway that a patient takes.

MRI will improve the restaging process and this study has shown that bpMRI offers a safe alternative to mpMRI. There is little potential value in performing a re-staging MRI at 12 months after diagnosis as it is unlikely to have changed and affect treatment. If, when a restaging bpMRI is performed and it is normal, in the presence of stable clinical parameters then repeat biopsy may be avoided, in discussion with the patient. Indeed, the use of MRI in the restaging pathway has been identified by NICE as an area for further research (NICE., 2019).

Chapter 6. Discussion

It is well known that the use of MDT meetings improves cancer outcomes and as such is mandatory within UK practice for all new cases of cancer. This study has highlighted that prospectively collected data from patients discussed at a specialist MDT can be of high quality and as a result be used to address a wide range of clinical questions, further adding to the value of MDT discussion. MDT meetings are undoubtedly labour intensive but we have shown that with the correct personnel and data capture process data quality can be high.

This study has been able to demonstrate changes in disease presentation and treatment over a long period in a cohort whose staging investigations has remained essentially the same throughout. It has shown that, in line with UK practice, the rates of radical treatment for low risk disease appear to be falling and the rate of men receiving radical treatment for high risk disease increasing. Encouragingly, the proportion of men with low risk disease choosing surveillance is also high.

There is debate as to whether the presence of symptoms at presentation is associated with more aggressive disease. This study did not show that, the only significant association of symptoms was with age, with older men presenting with more symptoms. This is most likely associated with age related LUTS rather than any association with aggressive cancer. This study did show that men with symptoms were less likely to have radical treatment than those without symptoms. It would be worth exploring this further given results from an Australian study which suggested that men presenting with symptoms have a poorer disease specific survival at 10 years (Beckmann et al., 2017).

Encouragingly this study has shown that men with a family history are presenting with higher rates of low risk disease than men without. They are also more likely to have radical treatment. This would seem logical given the potential anxiety associated with a positive family history. It is also reassuring to note that no strong

evidence exists to suggest that men with a positive family history treated early do worse than men without it. This information is vital when counselling men with a positive family history prior to deciding on diagnostic investigation.

As discussed, men have been staged in a very uniform manner through the period of the EPC database with over 90% receiving a staging MRI and over 93% of intermediate and high risk men receiving isotope bone scans. This widespread and uniform staging process has enabled the thesis aims to answered with accuracy.

The use of isotope bone scan remains the most common imaging modality for the investigation of bone metastases. Prior to this study the available guidelines on the use of bone scan were inconsistent in men with intermediate risk disease with the EAU offering the most concise recommendation (Mottet et al., 2017a). This study has provided strong evidence that BS can be safely omitted in men with intermediate risk disease with ISUP grade group 2. However, for intermediate risk disease with ISUP grade group 3 and high risk disease BS should be performed. This is in line with current EAU guidelines.

The use of MRI in the diagnostic pathway of prostate cancer is a fast-changing field with two recent landmark papers, PROMIS and PRECISION, changing the way MRI is now used pre-TRUS biopsy (Ahmed et al., 2017, Kasivisvanathan et al., 2018). Recently published updated NICE guidance now recommends pre-TRUS biopsy mpMRI with a possibility of avoiding TRUS biopsy in certain low risk cases (NICE., 2019). However, it is less clear the impact that updated MRI technology has had on the correct staging of prostate cancer. This study has shown that the ability of MRI has not changed significantly over time in accurately predicting disease stage and indeed radiological T-stage was not shown to be a significant predictor of disease recurrence regardless of the MRI technology used. This study has emphasised the importance of established predictors of biochemical recurrence, specifically T-stage, ISUP grade group and margin status.

This study also highlighted the use of PROMIS definitions of significant cancer and how these must be used with caution in the context of predicting disease outcome. Rates of BCR were very similar for significant cancer when using either PROMIS definition 1 or 2, mirroring results for D'Amico classified intermediate risk disease. Patients with non-significant cancer as defined by definition 1 had nearly double the rate of BCR compared with the D'Amico low risk and the rate of BCR was not significantly different to those that had significant cancer. This information must be considered when counselling patients regarding treatment or indeed whether to have a biopsy or not. It also highlights that D'Amico classification remains more sensitive at predicting BCR than PROMIS definitions of significant cancer.

The outcomes in this study for men on an active monitoring or surveillance regime for localised prostate cancer demonstrate encouraging results when compared to other large established series. It is also reassuring to note that the rate of grade progression when introducing protocol restaging in to a cohort of stable active monitoring patients was equivalent to that of the first protocol restage in an active surveillance cohort. However, despite this the treatment rate following restaging was significantly higher in the stable AM cohort suggesting that men who have been surveyed longer may be more inclined to consider treatment despite any evidence of disease progression. This must be considered when counselling men about protocol restaging whilst on AS.

The use of MRI in surveillance strategies remains a topic of debate. Updated NICE guidance suggests repeat MRI at 12-18 months following entry in to AS (NICE., 2019). This study would suggest that protocol restaging with an MRI at 1 year offers no benefit and should perhaps be deferred to at least 2 years. This study also reports a very low risk, <3%, of significant cancer if the MRI scan is reported as normal and there is no other evidence of disease progression, such as a rising PSA, and hence a re-staging biopsy can be avoided. It must be remembered that this study reports on the use of bpMRI rather than mpMRI with equivalent results. This therefore, represents a potentially safer, cheaper and quicker alternative that is not inferior. Further work is required to define the optimum active surveillance

protocol and has been started within the department because of this study. We are extending the current study to the present day to review the outcomes of all bpMRI performed at the time of first restaging. This updated cohort will have a significantly higher proportion of patients with a pre-biopsy bpMRI at diagnosis than in the current study and hence eliminate any uncertainty that post-biopsy artefact may cause. It is hoped that this future study will further clarify the use of bpMRI in the AS pathway.

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