AN INVESTIGATION OF WHETHER MEANINGFUL SURGICAL OUTCOMES FOR UROLOGICAL MALIGNANCIES CAN BE OBTAINED USING HEALTH INFORMATICS

By

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Abstract

Background

Urological malignancies represent more than 1 in 10 cancer diagnoses in the United Kingdom annually. This incidence is rising and examination of treatment outcomes is increasingly important. The aim of this thesis is to consider whether health informatics can provide a viable solution to analysing high volumes of routinely collected data, in order to examine outcomes for urological cancers.

Methods

Retrospective cohort studies were utilised to examine outcomes for multiple urological malignancies. National level studies were performed utilising the Hospital Episode Statistics (HES) dataset of routine administrative data. Studies performed using local data at University Hospitals Birmingham NHS Foundation Trust allowed multiple data sets to be linked. Cancers examined included prostate, bladder and testis.

Results

This collection of studies provides insight into the advantages and challenges of health informatics at this time. Routine administrative data provides an accurate record of patient events in the English National Health Service (NHS); however, the lack of clinical detail can hamper interpretation of results. Linkage to clinical data systems can provide clinical information suitable for risk stratification. There are however, concerns regarding data accuracy and missingness. Informatics data works well to support clinical research, however the ability of informatics alone to perform complete studies depends on the research question and completeness of datasets.

Conclusions

Development within the field of health informatics represents a potential future direction for research into urological malignancies. Improved data sharing and linkage will allow for robust and powerful studies without need for dedicated data collection. Data privacy must be maintained throughout.

Dedication

I dedicate this thesis to my family. Mum, Dad, Kiranjeet, Ravi, Torra, Kiran, Raj and Rajveer Thank you for your support. Love you all.

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Contribution Statement

This thesis is an aggregation of works that completed by myself, with support in conception and direction by my supervisory team: Mr Prashant Patel and Professor Nicholas James. Whilst not part of my formal supervisory team, Dr Nigel Trudgill provided support and advice on HES related projects.

All data extraction, methodology and presentation of results was my own work. However, where advice on data analysis and statistical techniques was required, it was sought from my team members within the *Informatics Department* and *University Hospitals Birmingham NHS Foundation Trust*: Mr Simon Baldwin, Miss Jemma Mytton, Miss Felicity Evison and Dr David McNulty.

Consultant urologists Mr Mohammed Belal and Mr Prasanna Sooriakumaran were consulted for specialist advice on continence surgery and prostate cancer treatment, respectively, in order to complete the studies in chapter 3.

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List of abbreviations

IT	Information Technology
UK	United Kingdom
PSA	Prostate Specific Antigen
MRI	Magnetic Resonance Imaging
TURBT	Trans-urethral Resection of Bladder Tumour
MIBC	Muscle Invasive Bladder Cancer
NMIBC	Non-Muscle Invasive Bladder Cancer
RPLND	Retroperitoneal Lymph Node Dissection
NHS	National Health Service
NICE	National Institute of Clinical Excellence
BAUS	British Association of Urological Surgeons
IOG	Improving Outcomes Guidance
GIFRT	Getting It Right First Time
NCRI	National Cancer Research Institute
HES	Hospital Episode Statistics
ICD-10	International Classification of Diseases, Version 10
OPCS-4	Office of Population Censuses and Surveys, Version 4
EHR	Electronic Health Record
GDPR	General Data Protection Regulation
EU	European Union
AI	Artificial Intelligence
SUS	Secondary Uses Service
APC	Admitted Patient Care
OPA	Outpatient
ONS	Office of National Statistics
PAS	Patient Administrative service
IMD	Index of Multiple Deprivations
UHB	University Hospitals Birmingham
HID	Hospital Interaction Data
PICS	Prescribing Information and Communication System
PID	Patient Identification Number
WHO	World Health Organisation
SQL	Structured Query Language
CARMS	Clinical Audit Registration and Management System
DSA	Data Sharing Agreement
HIRRG	Health Informatics Request Review Group
BMI	Body Mass Index
TURP	Transurethral Resection of Prostate
RFS	Recurrence Free Survival
CCI	Charlson Co-morbidity Index
EBRT	External Beam Radiotherapy
LINAC	Linear Accelerator
NSGCT	Non-Seminomatous Germ Cell Tumour
EPVM	Extra-Pulmonary Visceral Metastasis

List of presentations throughout this MD

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CHAPTER 1: INTRODUCTION

Throughout my medical career I have experienced the transformation of patient record keeping from handwritten notes, requests and reporting to completely digitised systems. The arrival of digitally stored data enhanced the ability of both clinical and non-clinical researchers to access patient records in order perform retrospective audit, quality improvement and research. However, even with modern information technology (IT), manual case note review requires significant time and resource, inevitably limiting sample size or data points collected. Health informatics techniques allow for high-volume data processing, in order to perform analysis with larger cohorts and increased variables.

The sub-speciality of Urological Cancer Surgery is rapidly advancing with novel treatments, adoption of robotic procedures and innovative randomised control trials. This provides a suitable area to focus informatics research to examine novel and established treatments. My experience as Urology trainee will help me to interpret the results and direct these works.

This thesis seeks to explore and present results from the utilisation of informatics techniques to inform outcomes for patients with urological malignancies.

1.1 Urological cancers in the United Kingdom

Urological cancers pose a significant challenge for modern medicine, with 14% of cancer cases detected per year in the United Kingdom (UK) originating from the urological system[1]. There is a significant requirement for research to examine and advance outcomes for these patients. Malignancy can occur anywhere within the urinary tract and external genitalia, including but not limited to: prostate, bladder and testes, which will be considered within this collection of works.

1.1.1 Prostate Cancer

Prostate cancer is the most common cancer diagnosed in male patients in the UK, with over 52,000 cases per year[1]. Age, race and positive family history are established risk factors for the development of prostate cancer. Initial referral for investigations is typically triggered via the prostate specific antigen (PSA) blood test or through physical examination of the prostate[2]. Patients will subsequently undergo magnetic resonance imaging (MRI) of the prostate and biopsy if suitable for further treatment[3,4].

Treatment for prostate cancer typically depends on the stage and grading of the disease, utilising TNM stage and Gleason grading. Patients with metastatic disease at diagnosis are not offered radical treatment, as it will not be curative. Radical treatment will involve radiotherapy or radical prostatectomy, which is removal of the entire prostate, and the latter will be examined by projects within this thesis.

In addition to peri-operative complications, there are long term functional impacts on patients' impotence and urinary continence following radical prostatectomy. The majority of

patients will experience erectile dysfunction post-operatively and incontinence rates are estimated at nearly half of patients[5,6]; these complications may require surgical management. Research based around these quality-of-life procedures, for complications of prostatectomy, can be considered to improve outcomes for prostate cancer patients and hence fall under the umbrella of urological cancer research.

1.1.2 Bladder Cancer

The annual incidence of bladder cancer in Britain is over 10,000 cases, with 3 in 4 cases in males[1]. Patients will typically present with blood in their urine and undergo a cystoscopy in order to examine their bladder. This is when an endoscopic camera is passed into the bladder via the urethra and the lining of the bladder is visually inspected for tumours. Those with bladder tumours will undergo a Transurethral Resection of Bladder Tumour (TURBT), this is a procedure where a cystoscope is passed into the bladder the tumour is cut away from the lining of the bladder and subsequently sent to the pathology lab to stage the tumour.

Bladder cancer is staged as per TNM, where the T stage gives an idea to the depth of tumour invasion. Localised/Locally advanced bladder cancers are more broadly categorised as to whether they have invaded the muscle of the bladder or not: Muscle invasive (MIBC) and Non-muscle invasive (NMIBC).

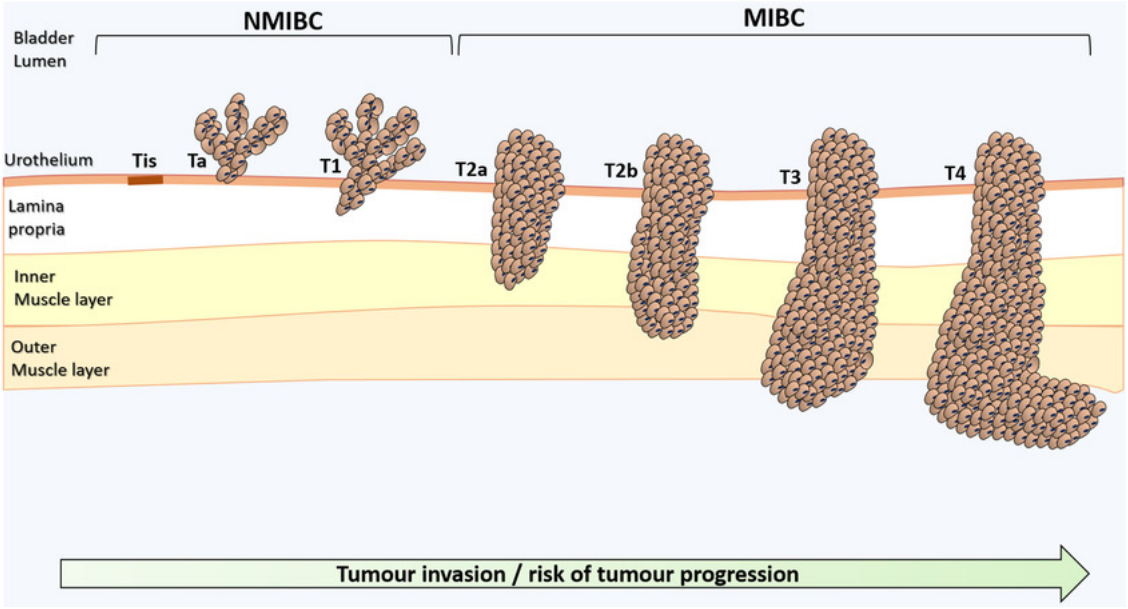

Figure 1. Schematic representation of bladder cancer T stage (Adapted from Azevedo et al, 2017)[7]

MIBC cannot be completely removed with TURBT and these patients will need to undergo radical treatment, again in the form of radiotherapy or radical surgery. Radical cystectomy is the removal of the entire bladder and the reconstruction of the lower urinary tract, either with a stoma or neo-bladder. There is much debate regarding which treatment is superior for MIBC and both will be examined in this thesis.

1.1.3 Testicular cancer

Although testicular cancer contributes less than 1% to annual overall cancer cases, it is a disease almost always affecting young, fit patients[1]. Therefore, the importance in optimising surgical outcomes, both oncological and functional, in a patient cohort that have lengthy life expectancy cannot be understated.

Treatment for testicular cancer is with radical orchidectomy (removal of the affected testis and spermatic cord), and systemic chemotherapy for those with high risk and metastatic disease. Disseminated disease does not prevent attempts at curative treatment and survival is high even for this cohort[8]; albeit short term survival will decrease for a proportion of advanced cases[9]. This highlights the need for research into advanced disease to further improve mortality.

As well as systemic therapies retroperitoneal lymph-node dissection (RPLND) is utilised for advanced cases. Whilst it can be used as a primary surgery as part of multimodality treatment, in the UK it is almost exclusive used for patients with post-chemotherapy residual masses. Therefore, it is rarely performed and usually by low volume surgeons[10]; despite it being high risk, complex surgery. A project in this thesis will seek to examine whether health informatics data can yield meaningful results for this uncommon group of patients where outcomes are critically important.

1.1.4 Current Challenges for the management of urological malignancy in the United Kingdom

In the early 2000s the "two week wait" rule was introduced in the *National Health Service* (NHS). It is the principle that patients with a suspected malignancy, with set criteria put forward, are referred to be seen by a specialist within 2 weeks. This has increased the incidence of identified urological malignancies. Although this program may not improve stage at diagnosis, it has been recognised that earlier diagnosis does improve mortality[11]. An increasing population with urological malignancies highlights the importance of uro-oncological research and investigation of outcomes.

The need for novel diagnostics and therapies, in particular minimally invasive treatments that pose a lower risk to patients has been at the forefront of urological research.
There are a number of therapeutic technologies recommended by the *National Institute of Clinical Excellence* (NICE) to be performed only the context of clinical research[12]; health informatics at a national level can serve to consider adherence to such guidance and help provide large cohort studies in these areas of interest.

Surgical outcome research and audit is a critical part of improving results for patients with urological cancers. Within the UK urological community there is a culture of quality improvement and research. The *British Association of Urological Surgeons* (BAUS) maintains and publishes national level data for most urological cancer surgery outcomes[10,13–15]. These create transparency in outcomes down to an individual surgeon level. Regular research and audit at this scale will influence local and national level policy making, for the benefit of patients and the health service. Administrative datasets can produce and support projects like these through linkage of datasets and informatics techniques, in order to generate robust outcome data for examination.

In 2002, the *Improving Outcomes Guidance* (IOG) for Urological cancers was published[16]. It focussed on a number of key aspects as to how cancer care is delivered throughout the entire pathway. Crucial parts of this guidance involve the recommendation of 'improved IT interface'[17], the development of regional multidisciplinary cancer networks, improved patient education and recommendations for the direction of research. Informatics processes can enhance the implementation of this guidance; multidisciplinary teams can improve care co-ordination and thus patient management. Tracking of patient outcomes will feedback the

efficacy of IOG recommendations and linkage of informatics analysis to patient records can provide methods of dissemination of patient information to target populations[18].

Getting It Right First Time (GIRFT) is a national initiative, stemming from its initial conception for orthopaedics in 2012 and expanding to encompass other specialities. Similar to the IOG guidance it aims to improve outcomes for patients within the NHS. A mainstay of this initiative is data-driven benchmarking. This led to the development of the *Model Health System*; an online tool for all NHS staff to review outcomes at local and national levels. Needless to say, informatics processes are critical for the running of this project. Health informatics data has also been vital in examining the potential impacts of guidance[19].

Whilst the focus of this work is on surgical outcomes, the concept of active surveillance is an important tool in cancer management and must be discussed in this background. Active surveillance is the process of postponing curative treatment for patients with low-risk disease and minimal symptoms, in the form of surgery or systemic treatments, until such a time comes it is absolutely necessary. This is to enhance quality of life by giving patients extended time from diagnosis to avoid the adverse effects of treatment[20,21]; it also provides a practical method for avoiding overtreatment for patients in whom the disease would not progress[22].

Active surveillance protocols differ, however are generally all similar with regards to intensity; requiring regular PSA blood tests, MRI scans and examinations[4,23]. This requires significant clinician input and resource; hence many centres find adherence with active surveillance difficult[24,25]. Informatics data can serve to reduce this burden through automation of parts of the surveillance pathway and flag patients with concerning results sooner. This will also serve to enhance the financial savings active surveillance already offers[26].

The process of automating PSA follow-up can extend to those patients on surveillance of disease relapse following radical treatment for prostate cancer or those managed with non-curative treatment, such as hormonal manipulation.

1.1.5 The unmet need and thesis rationale

It is clear from this background that there is a distinct unmet need within the field of urological oncology that health informatics can serve to fulfil. There is an increasing incidence of urological malignancy within the United Kingdom, with earlier presentation and diagnosis. Hence there is an increasing population with disease amenable to radical treatment; this will typically occur with the NHS. This generates large volumes of data at local and national levels, that can be utilised for research to improve outcomes within that same population. This includes strategy-based research, such as examining adherence to guidance and resource allocation, in addition to obtaining a better understanding of disease progression and decision making in treatment approach. Health informatics can serve to process and analyse this large volume of data in order to improve outcomes for patients.

This large volume of patients will require intense follow-up to ensure established recovery from urological cancer and the adverse effects of treatment. There are significant data points pertaining to cancer follow up captured at patients every interaction with the NHS, irrespective of who or why a diagnostic test was requested. For example, blood tests performed for a different pathology may still be relevant to the follow-up for a urological cancer. Health informatics can be utilised in order to compile such data to provide a more comprehensive overview.

1.2 Background to Health informatics

The late 20th century saw the advent of IT particularly in the western and developing world. Healthcare was a sector of industry that accepted this advancement in data and communication technology. This coupled with greater accountability and an increasingly patient centred approach to health care has driven an increase in storage of high-quality data worldwide[27]. The English NHS in particular benefited greatly from the technological progress of IT services and data collection; the formation of NHS Digital from a number of public bodies in 2005 highlights the importance of digital health care data to the NHS.

In 2006 the National Cancer Research Institute (NCRI) published their informatics initiative; to enhance data sharing and catalyse cancer science[28]. This, however, did highlight the technological challenge that would ensue with such an endeavour, albeit the proposed gains would outweigh the efforts. In the developed world the view is shared that investment in health informatics infrastructure will serve to enhance global cancer treatment[29].

Health informatics is the discipline of utilising this population-based data in order to positively influence public health and provide clinical benefit to patients[30]. There is no standard way in which data is collected; it is dependent upon on intended use, method of collection and feasibility within the designated infrastructure. This has resulted in a multitude of data repositories globally, some of which are purpose-built registries for research, others are repositories of data that can be used for research despite a differing primary intended use.

Cancer policy in the western world and applied health informatics are typically linked concepts, with almost 90% of countries with a national cancer framework having dedicated registries[31]. Clinical registries are purpose-built databases that exist to collate patient data

defined by specified criteria. These, however, are not exclusive to modern medical practice; examples of registries, which fit with the current day definition of a registry, are documented as far back as the mid-19th Century[32]. Hansen Armauer is credited with being the catalyst for eradication of leprosy in Berlin through his published research in 1874; a key component of this was a registry based epidemiological study that led to the isolation of leprosy sufferers, thus preventing further spread[33]. This has, for the most part, been digitised as a practice and mining of registry data allows for large case control studies[34]; these studies have great statistical power and capture a true to life population.

In the UK in particular, health informatics is at the forefront of government and NHS research strategy. The National Institute of Health Research (NIHR) launched an informatics collaborative, in order to promote equitable access to NHS data to promote translational research across all disciplines[35]. Furthermore, the UK government have signposted that private technology firms may form part of national initiatives to drive the development of artificial intelligence within health informatics[36].

Within the NHS itself a graduate management training scheme has been developed, specifically for health informatics[37]. This aims to establish a dedicated stream of knowledge and experience to grow informatics infrastructure. Learning health systems is another proposed NHS initiative pertaining to digital health. By using informatics, a continuous cycle of quality improvement projects and adaptive national policy can drive enhanced patient outcomes.

Health informatics is a rapidly advancing discipline and within the UK there are a number of polices designed to explore it's potential.

1.2.1 Routine Administrative data and Hospital Episode Statistics

Routine administrative data is collected by many hospitals in England and stored in a data warehouse. This was previously maintained by *NHS Digital*, now by *NHS England*, called *Hospital Episode Statistics* (HES). However, questions rose about the validity and quality of data stored[38]. This changed in 2005 when a new NHS billing policy was introduced: payment by results. Payment by results is an initiative that attributes a fixed cost to a health care event, determined by the average cost across the NHS for that year[39]. Initially it was used only for a selection of elective procedures but by 2008 it became mandatory for all publicly funded hospital care episodes. This has greatly improved data quality and coding standards within the NHS[40], although this was not the primary aim of the policy. Derivative uses for these administrative data are increasingly being discovered, clinical quality improvement and research being two of them. There are a number of strengths that pertain to the use of English routine administrative data for research purposes. As mentioned above, we can be confident of the accuracy of the data stored. There is also a great deal of variety and contextual information contained in the data.

Due to the mandatory HES uploads, administrative data are stored in a standardised format across all NHS England sites. Beyond demographics and residential data there are also diagnostic and procedural data, also stored in standardised formats such as International Classification of Diseases version 10 (ICD-10) and Office of Population and Statistics Classification of Interventions and Procedures version 4 (OPCS-4) codes. The advantage of such consistent data is the confidence that all patient records are subject to the same review for coding. Furthermore, through review of code combinations, for inclusion and exclusion criteria, relevant controls and checks can be made whilst building patient cohorts.

It is important, however, to bear in mind that coding practices are dynamic and change over time. Further to this, changes in organisational structure must be accounted for when reviewing events retrospectively. The NHS has undergone several organisational changes within the last decade[41]; these will impact the interpretation of data as the present-day context may differ to historical circumstance.

As mentioned above, routine data differs from registry studies as they are not purpose built for clinical research, therefore they may lack relevant details important for interpretation of health outcomes[42]. In particular, for this project, lack of cancer staging information may prove a challenge. There are however a number of linkable datasets that can provide this supplementary information[43].

A reality of using routine data sources, in addition to restrictions on access, is cost[44]. Relevant infrastructure must be in place in order to cope with large datasets and maintain sufficient IT security. Furthermore, routine data are often owned by companies; for example, HES is owned by NHS Digital, which can lead to high tariffs levied against data access. Henceforth, routine data, whilst being a rich and varied data source, is not feasible for some sections of the research community.

1.2.2 Electronic Health Record (EHR)

Increasingly throughout the world, electronic health records and prescribing systems are employed in order to aid clinical communication between specialities. They are a central communication tool that collates all clinically relevant information, directly benefiting patients and clinical teams. Improved documentation is a recognised advantage of EHR systems and leads to improved patient care[45]; due to an improved ability to communicate

relevant issues and linkage to relevant information and diagnostics. Furthermore, they result in improved resource and time efficiency[46]: clinicians can quickly access all relevant details surrounding a patient's care.

I have a particular advantage within this body of work, where projects involve the EHR and clinical systems. Having utilised them in a clinical capacity in order to deliver patient care, I have an understanding of how data is inputted, stored and displayed. Knowledge of which systems would be required in order to assess and treat a patient, for research purposes I am able to identify the most complete and appropriate data source in order to answer the research question.

A further source of rich data that is not primarily designed for research purposes, EHRs tend to be automatically populated, hence encompass all data, providing a level of granularity to the data that is rare for a non-purpose-built repository. This, of course, depends upon the EHR system in question to what specific data would be contained.

Unlike routine administrative data, EHRs are not mandatory within the NHS and their presence is sporadic[47]. Data storage is not standardised and challenges would exist when trying to gather information from multiple sites[48]. Coding systems used within EHRs are system based and do not always follow internationally validated coding systems; instead, they are based around the needs of the system. This can lead to inaccuracies in data captured. There are also free text sections, such as clinician generated reports; it is proposed that machine learning and algorithmic searches will be able to extract data from these resources in future[49].

Noise and missingness are another concern that will be evaluated whilst using EHRs in this project; a particular area of concern is discerning between outliers and errors. Techniques can be employed to reduce said risk[50]; however, such approaches can lead to restricted datasets. Furthermore, transcription errors or technical difficulties during clinical use can result in erroneous entries into any EHR database.

1.2.3 Data Privacy

Data privacy is a key consideration whilst performing any type of medical research; informatics data in particular must employ stringent data protection management strategies. Digital healthcare data is vulnerable to the opportunity for data breaches, especially considering the scale and sensitive nature of data collated. General Data Protection Regulation (GDPR) was introduced throughout the European Union (EU) in May 2018; with increasing digitisation of data, GDPR is a framework to ensure that privacy standards will not slip[51]. The introduction of this new regulation has created some concerns that the ability of "big data" to continue to operate fully will be impaired[52]. The need for data protection must be balanced with the requirement of certain data items to operate for data analytic processes. Pseudo-anonymisation and anonymisation exist as techniques for ensuring data privacy whilst minimising disruption to data analytics[53]. Pseudo-anonymisation provides a more suitable technique for healthcare data, as the use of a pseudonym permits follow-up of patients whilst concealing their identity[54]. This however must still be considered sensitive data; re-identification of patients is possible with advanced data analytic technologies.

The '*Goldacre review'*, highlighted that NHS data should be leveraged for improvement of outcomes but can only be done so if there is public trust in robust data security[55]. As a result, there was the development of government secure data environments (SDE). These are

specialised platforms that allow authorised users, typically governments, to access, store and analyse sensitive data securely[56,57]. In the UK, SDEs are used for health and social care data, predominantly NHS data. Through controlled access, data security and compliance with legal framework, research and analysis can confidently be performed using this data.

1.2.4 Potential wider applications of health informatics

Screening

The UK government have produced a *Strategy for Improvement of Cancer Care*[58]. Part of this strategy involves the use of cancer registry data to aid in predictive models and screening opportunities. Screening in selected cancers has been shown to facilitate early diagnosis and improve patient management[59]. Informatics data, in particular national datasets, provide large repositories of data on clinically relevant patients and those without cancer, that can be utilised as a control group; large datasets in cancer prediction modelling provide high power and greater certainty of inferred outcomes[60].

Population Health Management and Disease Prevention

Public health informatics is crucial in disease surveillance and prevention. The ability to access national-level datasets reduces reaction time to public health events. In the past public health relied on clinician reporting and manual recognition of trends, real time data analysis allows for timely outbreak identification; measures to prevent spread and trace contacts can be employed. Furthermore, at risk populations can be identified and provided with appropriate lifestyle modifications, targeted at individual and local population levels.

Predictive Modelling

Precision healthcare is a realisable goal from informatics analysis. Predictive modelling techniques have the potential to achieve this ambition. The level of care a patient is expected to require during a hospital admission can be predicted from modelling[61]; this will allow a healthcare provider to allocate resource efficiently, reducing surplus but also crucially ensuring sufficient reserve is available.

Predictive modelling has the ability to directly benefit patient care at an individual level. Predictive analysis can alert speciality teams to patients who may require specialist consultation[62], ensuring patients benefit from the whole multi-disciplinary team. Furthermore, prognostication can reduce the information imbalance between clinician and patient[63]. Allowing for discussions that pertain directly to the patient and their unique host factors, as opposed to more broad aggregated outcomes from clinical research.

Big data analyses in particular can help drive healthcare policy and conserve finite resources in a healthcare system. The assimilation of the available data into an analytical framework can help identify inefficiencies and wastage in the NHS as a whole.

Machine learning

Within the field of health informatics machine learning has played a pivotal role in the direction of urological cancer research. Machine learning, a branch of artificial intelligence (AI), is the principle of an IT system to learn through experience and exposure[64]. Predictive modelling is an area of informatics that can seek to gain from machine learning and AI in

general. Through identification of patterns, large complex datasets can be analysed. Deep learning in particular has been investigated for its strength in predictive and prognostic output[65–67].

These techniques are had been utilised outside of informatics and administrative data for image analysis, for radiographic and endoscopic images[68,69]. The intention is to aid clinical decision making and prevent missed diagnoses or delays. The discussion of these techniques falls outside the objectives of this thesis, however they will in future have a continued and expanding role in health informatics and 'big data' as a whole.

1.3 Current applications of health informatics for cancer outcomes

1.3.1 Health informatics utilisation in UK Cancer outcomes

Health informatics has been utilised by medical and surgical specialties to examine outcomes for cancer patients, they do however almost always pertain to HES data, in order to perform retrospective studies[70–75]. National infrastructure in place however, does present an opportunity to utilise such data for prospective data capture and supporting clinical research. HES data has been used to support randomised control trials in the UK, however only in the case of urological malignancies, notable examples of which will be discussed later in this chapter, and non-cancer studies[76,77].

1.3.2 COVID-19 and cancer informatics

In March 2020 the COVID pandemic presented a huge challenge globally, not only to public health but specifically to delivery of cancer care[78,79]. Health informatics were crucial in ensuring adverse impact to patient's cancer care was minimised. In order to reduce footfall,

telemedicine and remote monitoring capabilities were widely expanded and utilised[80]. Whilst it is accepted that detection of cancer and diagnostics were inevitably impacted[81], digital healthcare allowed for continuation of adapted care.

Cancer patients are a vulnerable group, typically immunosuppressed and at high risk of thrombo-embolic events. Machine learning algorithms were developed throughout covid to benefit these patients. Through prediction of COVID severity and adverse sequelae of infection, patients can have their treatment planned according to risk and ensure those most vulnerable receive appropriate care and advice[82–84].

Collaboration and data sharing among cancer researchers was accelerated by the pandemic. The need for research into the effect of COVID on cancer patients and what treatment was safe to continue, lead to the development of large cohort data-sets and joint analyses[85,86]. This enhanced research collaboration leading to faster and more informed decision making, to benefit patients.

1.3.3 Current applications for urological cancers

Clinical trials

Informatics data have been used to inform clinical trials over many years. Given the increasing utility and quality of routine administrative data, there have been a few notable examples of clinical trials using it to inform patient follow-up, for urological cancers.

The *STAMPEDE* trial is a randomised control trial examining treatments for newly diagnosed advanced prostate cancer. What is unique about this trial is the successful use of routine

administrative data to identify disease progression in trial participants[87]. This highlights an efficient method of follow-up that may become standard practice in future, avoiding costly and time intensive formal follow up.

The *BLADDERPATH* trial is also a randomised control trial that planned to employ informatics techniques[88]. It was planned that follow-up and significant events would be flagged utilising national level routine administrative data and then verified locally at trial sites[89], reducing the burden on staff to identify and record outcomes and resulting in a more complete data-set. This did not occur due to practicalities of HES data acquisition[89].

Retrospective studies

There are a number of successful examples of routine administrative data utilised in retrospective cohort studies to investigate urological cancer outcomes[90–92]. In 2017 an informatics research group in Birmingham produced a paper examining the impact of IOG guidelines for radical cystectomy performed for bladder cancer[18]. This strategy involved the recommendation of minimum numbers of surgeries required, at a clinician and site level, in order to ensure high quality outcomes. The paper is not just an example of how informatics techniques can be used to examine adherence to policy, as it also considered how the provision of surgery has changed over time, since the guideline was published.

The concept of mining electronic health records and linkage of multiple datasets within the field of urological malignancies is a novel concept; the practicalities of which will be examined in this thesis.

1.3 Thesis Format, Aims and Objectives

This body of work is written in accordance with the University of Birmingham guidelines for submission of an alternative thesis (detailed in regulation 7.4.1 (g)). All results chapters are divided into and structured as published or publish-ready manuscripts. Published manuscripts are inserted directly into the manuscript. There is, therefore, repetition of methods throughout the projects, the methods chapter (chapter 2) will give an overview of shared methodology, with the specific details for each project contained within each results chapter. A final discussion chapter will summarise the works in this thesis and provide the platform for discourse on the role of informatics research for urological malignancies.

1.3.1 Aims

Numerous studies have utilised informatics techniques in order to produce clinical research, however the discussion of very few pertain to the methodology and practicalities of doing so.

This thesis aims to investigate treatment outcomes for urological malignancies in order to illustrate how informatics data can be used effectively for research. This is at both a national level and local trust provider level. The thesis will achieve this through 1) Utilising administrative datasets to answer research questions 2) Demonstrating how local datasets and the electronic health record can be mined and linked to generate usable datasets 3) Examining rare procedures to efficiently generate large case series, that would otherwise require significant resource to develop. The clinical outcomes will be discussed within each project; however, the aim of this thesis is to consider the strengths and limitations of the informatics-based methodology.

1.3.2 Objectives

1. Utilise Hospital Episode Statistics data to perform national level retrospective and cross-sectional research to examine outcomes for patients with prostate cancer, using pseudonymised routine administrative data

2. Perform retrospective studies through linkage of multiple administrative databases to the electronic health record, with the goal of generating rich datasets with clinically relevant variables

3. Identify rare procedures in routine administrative data and in order to perform high powered studies with granularity of comparators

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CHAPTER 2: METHODS

This chapter seeks to give an overview of common methods utilised within this thesis. All data are presented in the format of projects suitable for submission to peer-reviewed journals, in keeping with the submission of an alternate thesis. Hence detailed descriptions of project methodology are contained within each subchapter. Given this, there may be repetition of methodology throughout this thesis.

2.1 Data sources

2.1.1. Hospital Episode Statistics

HES overview

HES is a nationally captured database of all patient interactions with secondary care, funded by the English NHS. It primarily functions as an administrative dataset for the purpose of billing and payment by results; the details of which are covered within the introduction of this thesis. The data are passed to the secondary uses service (SUS), in order to facilitate a variety of reporting and analyses supporting the delivery of healthcare in the NHS, such as health care planning, commissioning of services and research[1].

Data format

Information is captured longitudinally in the form of *spells* and *episodes*. A *spell* captures all information from admission to discharge at a single NHS trust and this may be comprised of one or more *episodes*. An *episode* is the time, within the admission, spent under the care of a single named consultant[2]. Therefore, should a patient be transferred between hospital specialities in the same trust, there will be multiple episodes. Data is initially captured at a local NHS trust, then uploaded to NHS England. At the time of completion of research for this thesis, HES was managed by NHS Digital.

There are a number of datasets contained within HES, included but not limited to: Admitted patient care (APC), outpatients (OPA), accident and emergency, diagnostic imaging, critical care, maternity services, children and young persons and mental health services. For the

purpose of this thesis only the APC and OPA datasets were required. Patients are assigned a pseudonymised identification number within HES, known as the HESID[3]. This allows them to be followed up throughout the entirety of the datasets. It also permits linkage to certain datasets, such as the Office of National Statistics (ONS) for date of death[3].

Data are formatted into separate tables for *episodes* and *spells*, where they each will form a row in their respective tables. The data captured in a subject record, visualised as a row in the table, for a hospital spell will be an aggregation of the data within all episodes of that admission.

There are a number of demographic data fields that are auto-populated from the patient administrative system (PAS), in addition to admission dates and residence information (in the form of a truncated post-code)[4,5]. From this basic information, other fields deemed necessary can be calculated: e.g., age at surgery, length of stay, Index of Multiple Deprivations (IMD) quintile. Diagnostic and procedural information are coded by expert clinical coders that review patient notes and record them in the form of ICD-10 and OPCS-4 codes respectively. Within the APC there is a field for primary diagnosis and a subsequent 20 fields for secondary diagnoses and comorbidities. There are up to 24 fields for procedures with their associated date. This allows for understanding of host factors, complications and whether re-intervention was required.

Despite pseudonymisation patient data may still be identified and care must be taken to protect sensitive data. In addition, low numbers must be censored to prevent patient identification. Any patient level number that aggregates as less than or equal to 5 must be reported as < 6 and another category rounded to the nearest 5.

2.1.2 Local databases

All research involving local data was performed at *University Hospitals Birmingham NHS Foundation Trust (UHB)*. UHB is one of the largest trusts in England with an annual patient turnover of 2.2 million people. It is a completely paperless trust with all interactions captured electronically, hence its status as a *"digital exemplar"*[6]. For this reason, it was possible to conduct all research utilising health informatics. The *Hospital Interaction Data* (HID), is the precursor data prior to HES upload, hence mirrors it exactly.

The *Prescribing Information and Communication System* (PICS) was developed at UHB as an electronic health record and contains nearly all clinical information required. A unique PICS identifier is assigned to each patient that can easily be linked to their distinct patient identification numbers (PID); all other databases use PID. Data obtained via PICS has formed the basis for a number of published studies[7–12].

2.2 Selection of projects

The concept of this thesis is to examine the ability of health informatics to examine outcomes for urological malignancy. Therefore, the selection of clinical research questions was decided in conjunction with the supervisory team for this thesis. Questions pertinent to current issues, advancements and guideline research recommendations were selected, whilst ensuring they were in keeping with the research objectives of this thesis.

2.3 Coding

In order to classify, record and analyse data into datasets it must be coded. This can be as string or numeric variables. HES utilises clinical coding, as described earlier, through a specific profession of clinical coding. These are individuals employed and trained to review medical notes and complete the coding of diagnoses and procedures. Within the local datasets, clinical systems follow their own coding or record fields auto populated from inputted data and generated reports, e.g., blood tests, vital sign observations etc.

It is important to consider the fact that clinical coding systems are dynamic overtime, adapting to reflect new technologies and changes in common practice. Furthermore, new coding systems are introduced to replace older ones. These are taken into account when performing informatics research and considering the feasibility of projects.

2.3.1 International Classification of Disease Codes, Version 10

At the time of writing this thesis and performing the research, the 10th iteration of ICD codes was utilised. Initially compiled in 1893 by the World Health Organisation (WHO), this version (ICD-10) was mandated for use in the United Kingdom in 1995 and utilised until 2022. They follow a hierarchical code structure of alphanumeric levels. For example: C67.1 indicates a bladder cancer at the dome of the bladder.

C	**67**	**.**	**1**
Indicates malignant neoplasm	Indicates malignancy within the bladder		Indicates site of tumour within the bladder

Table 1. Table displaying breakdown of ICD-10 coding

Codes of interest were identified by myself, as a urologist in training, and subsequently reviewed by a consultant urologist. This two-person approach, with urology experience, prevented the inclusion of inappropriate diagnoses. Coding for comorbidities and aggregation to a Charlson Comorbidity Index is established[13,14].

2.3.2 Office of Population Censuses and Surveys Classification of Interventions and Procedures, Version 4

The Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4 (OPCS-4) codes are utilised to classify procedures in secondary care. Each code is a standardised yet detailed alphanumeric system to describe a procedure. Multiple codes may be required to fully describe all the steps and details in a procedure e.g., laparoscopic approach – Y50.2. The initial letter indicates the body system, then the subsequent 2-digit code describes the procedure and the final number gives further detail. For example, M61 codes for the excision of the prostate, a prostatectomy.

M	**62**	**.**	**1**
Indicates urinary system	Indicates excision of prostate		Indicates total excision of prostate and capsule

Table 2. Table displaying breakdown of OPCS-4 coding

Selecting procedural codes followed the same process as for diagnosis. Care was taken to ensure X, Y and Z codes were reviewed for relevance. These indicate *miscellaneous operations* and *subsidiary classifications of methods of operation*.

2.3.3 Local coding

Coding within databases at UHB was unique to the clinical system that they correspond to. These coding systems were detailed within reference tables that could be directly linked into the data extraction to identify the desired data, for example when considering volume of blood transfused the code for *packed red cells* allowed for identification of administered units of blood. My working knowledge of the PICS system "front end" and associated databases as a clinician allowed for efficient identification of data fields and review of coding tables.

2.4 Data extraction

Following the development of research questions. All data extractions were designed and performed by myself in Microsoft SQL Server, utilising Structured Query Language (SQL) coding. A period of initial training and assessment on a test database was completed prior to commencing this thesis. Data were extracted from their primary source into a data collection tool within SQL server, designed by myself.

Aggregated tables were generated within SQL server itself, Microsoft Excel or STATA. All statistical analysis was performed in STATA version 15, with advice sought from statisticians where required.

Data validation techniques were unique to each project and are detailed within each chapter.

2.5 Ethics and approvals

In order to perform this work and handle the data, I was employed as an *Informatics Officer* within the *Research Informatics Team* at *University Hospitals Birmingham NHS Foundation Trust*. This allowed me to access all necessary data, obtain appropriate training and support in SQL and statistical programming.

All projects were registered with the Clinical Audit Registration and Management System (CARMS). Any project utilising HES data required further approval, in terms of scope, datasets permitted and timeframe of data access, by stakeholders at UHB; in line with data sharing agreements (DSA) with NHS digital. All requests to utilise HES data for research were considered and approved if appropriate by Health Informatics Request Review Group (HIRRG), before work could commence. No patient consent was required for the completion of any of these projects.

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CHAPTER 3: UTILISING ROUTINE ADMINISTRATIVE DATA AT A TO EXAMINE SURGICAL OUTCOMES AT A NATIONAL LEVEL

In this chapter I will present the findings from two studies. These were both completed using only Hospital Episode Statistics data to produce retrospective cohort studies.

The first study in this chapter was published in *European Urology Focus,* it examines the provision of High Intensity Focused Ultrasound therapy for treatment of prostate cancer and associated outcomes; in particular urethral stricture and fistula rates which are lifechanging adverse effects of prostate cancer treatment.

The second study within this chapter was published in the *British Journal of Urology International* and was publicised as article of the month. It examines the outcomes associated with the two main types of continence surgery offered for "post-prostatectomy incontinence" and factors associated with device failure requiring removal or exchange, including provider volume. I have seen first-hand the impact that urinary leakage following radical surgery for prostate cancer can impair quality of life, for an already vulnerable group of patients. Hence the value in large cohort studies for this type of surgery.

Manuscript One: High-intensity Focused Ultrasound for the Treatment of Prostate Cancer: A National Cohort Study Focusing on the Development of Stricture and Fistulae

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High-intensity Focused Ultrasound for the Treatment of Prostate Cancer: A National Cohort Study Focusing on the Development of Stricture and Fistulae

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Abstract

Background: High-intensity focused ultrasound (HIFU) is a novel therapy for prostate cancer. Owing to a lack of long-term data, HIFU is recommended for use only in the context of research.
Objective: To examine the trend for HIFU use nationally and rates of strictures and fistulae.
Design, setting, and participants: Patients undergoing HIFU for prostate cancer between April 2007 and March 2018 were studied in an English national database (Hospital Episode Statistics). Data on complications were included for patients with a minimum of 1-yr follow-up. Analysis of complications was controlled for other interventions.
Outcome measures and statistical analysis: Descriptive analyses of HIFU rates and the incidence of strictures and fistulae were carried out. Cox and logistic regression models were built for urethral stricture incidence.
Results and limitations: A total of 2320 HIFU treatments among 1990 patients were identified. The median age was 67 yr (interquartile range 61–72). Some 1742 patients met the criteria for follow-up analysis. The highest-volume centre performed 1513 HIFU procedures, followed by 194 at the second highest. The number of HIFU procedures increased annually, rising from 196 to 283 per year. There were 208 patients (11.9%) who went on to have radiotherapy and 102 (5.9%) radical prostatectomy after HIFU. Following HIFU, stricture developed in 133/1290 patients (10.3%) and urinary fistula in 16/1240 (1.3%) before any further intervention. More recent years for HIFU were associated with a lower likelihood of stricture formation (2016/2017 vs 2007/2008: hazard ratio 0.30, 95% confidence interval 0.11–0.79; $p = 0.015$). Limitations include the lack of staging information and unknown rates of HIFU outside of publicly funded health care.
Conclusions: HIFU is performed at a large number of low-volume centres and complication rates do not differ from those for established therapies.
Patient summary: This report highlights the trend for provision of high-intensity focused ultrasound treatment for prostate cancer in England. The results suggest that the rate of urethral structural complications may not be lower than that for established prostate cancer treatments.

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1. Introduction

High-intensity focused ultrasound (HIFU) directs focused ultrasound waves at cancer tissue, which heats the tissue and leads to coagulative necrosis [1]. These areas are no larger than a grain of rice and are built up to cover a larger area [2]. It is believed that focal ablative therapies such as HIFU are associated with more favourable outcomes for patients with prostate cancer, including continence and erectile function, in comparison to more radical treatment modalities [3].

Long-term outcome data for HIFU efficacy and adverse events are currently lacking; HIFU should be offered with caution and all data pertaining to the treatment must be collected. Current National Institute for Health and Care Excellence (NICE) guidance states that HIFU should be limited to use in clinical trials, or when subject to special arrangements for clinical governance, consent, and audit or research [4,5].

Since 2007, few clinical trials measuring the effectiveness of HIFU for the treatment of prostate cancer have been registered with the National Institute of Health Research [6]. At present, there is no single publicly identifiable regulatory body for monitoring the provision of HIFU and outcomes for patients.

We used Hospital Episode Statistics (HES) data to determine the number of patients undergoing HIFU as primary and salvage therapy for prostate cancer in England and to calculate long-term urethral stricture and fistula rates.

2. Patients and methods

2.1. HES database

HES is an administrative database containing data relating to patient interaction in secondary care funded by the National Health Service (NHS) in England [7]. Data are stored in longitudinal episodes that can be linked for follow-up and evaluation of outcomes. Diagnostic (International Classification of Diseases v10 [ICD-10] codes), procedural (Office of Population Census and Surveys Classification of Interventions and Procedures v4 [OPCS-4] codes), and administrative information can be extracted. The Office of National Statistics (ONS) provides linked mortality data. HES data reporting guidelines state that all data items for five or fewer patients must be suppressed from publication. HES and HES-ONS Linked Mortality Dataset 2018 were reused with the permission of NHS Digital.

2.2. Cohort

All patients with an OPCS-4 code for HIFU administered to the prostate (Supplementary material) between April 1, 2007 and March 31, 2018 make up the descriptive cohort (Box A in Fig. 1). All patients were required to have a diagnosis of prostate cancer (Supplementary material). The follow-up cohort consists of the same patients but excluding any patient without a minimum of 1-yr follow-up between the index HIFU and the end of the study period (Box B in Fig. 1). Patients residing outside England were excluded owing to lack of follow-up, and patients with missing age and sex variables were also excluded. Further exclusions are outlined in Fig. 1.

2.3. Data

Age, sex, region of residence, Index of Multiple Deprivations 2010 (IMD) quintile (where 1 is the most deprived and 5 is the least deprived), and ethnicity were extracted. A Charlson comorbidity score was calculated from the episode ICD-10 coded diagnoses, a technique previously validated in other HES analyses [8,9]. As all patients were cancer patients, the score was modified to exclude cancer from the comorbidity score. Patients were categorised into comorbidity score groups.

Long-term outcomes examined in the follow-up cohort included new stricture (urethral stricture, urethral stenosis, bladder neck stenosis, prostatic strictures) and fistula (rectourethral and rectovesical fistulae; Supplementary material). Due process was maintained to allocate post-HIFU complications for each patient in relation to timing of therapies (radical prostatectomy [RP], radiotherapy [RT], and transurethral resection of prostate [TURP]); stricture and fistula were attributed to HIFU in patients who had no other interventions to the prostate or those for whom the diagnosis was identified in HES before prostate therapies following HIFU: a pure HIFU cohort.

Data on the incidence of prostate cancer in England were obtained from the ONS annual cancer registration statistics [10].

2.4. Analysis

A multivariable Cox regression model using the analysis cohort (Box B in Fig. 1) was constructed for time to stricture as a consequence of HIFU using a pure HIFU cohort. Gender, age quintile, deprivation quintile, ethnicity, Charlson comorbidity score, year of HIFU, and whether the annual HIFU volume at the centre over the study period was greater than the median of two were included variables.

The same variables were included in a logistic regression for stricture formation (Supplementary Table 1); the output was used to construct a funnel plot (Fig. 2) with control lines set at two and three standard deviations from the mean using Spotfire v6.5.

Annual caseload was calculated for each centre individually as the mean number of cases over the total number of years when HIFU was performed. If no HIFU for prostate cancer was performed in a financial year, it was not considered in the denominator.

Data were analysed using Stata v15 (StataCorp, College Station, TX, USA). Statistical significance was set at $p < 0.05$.

2.5. Stricture validation

The development of stricture following TURP for benign indications was used to validate the coding of strictures in HES. TURP is an established procedure with long-term data published so the rate of strictures identified in HES can be compared to available data.

Patients undergoing index TURP in HES between April 1, 2007 and March 31, 2016 were identified. Patients with prostatic intervention (RT, RP, HIFU) before TURP or after HIFU but before stricture coding were excluded; all patients with a diagnosis of prostate cancer at any time were also excluded.

3. Results

3.1. Study subjects

Following exclusions, 2320 HIFU treatments administered by the NHS to 1990 patients from April 2007 to March 2018 were used for analysis. Of these patients, 1742 had at least 1 yr of follow-up after their first HIFU treatment and were included in the follow-up cohort (Box B in Fig. 1).

The median age at the time of HIFU was 67 yr (interquartile range [IQR] 61–72). There were more patients in the less deprived IMD quintiles (least deprived 11.9%, most deprived 29.7%). The majority of HIFU episodes were among

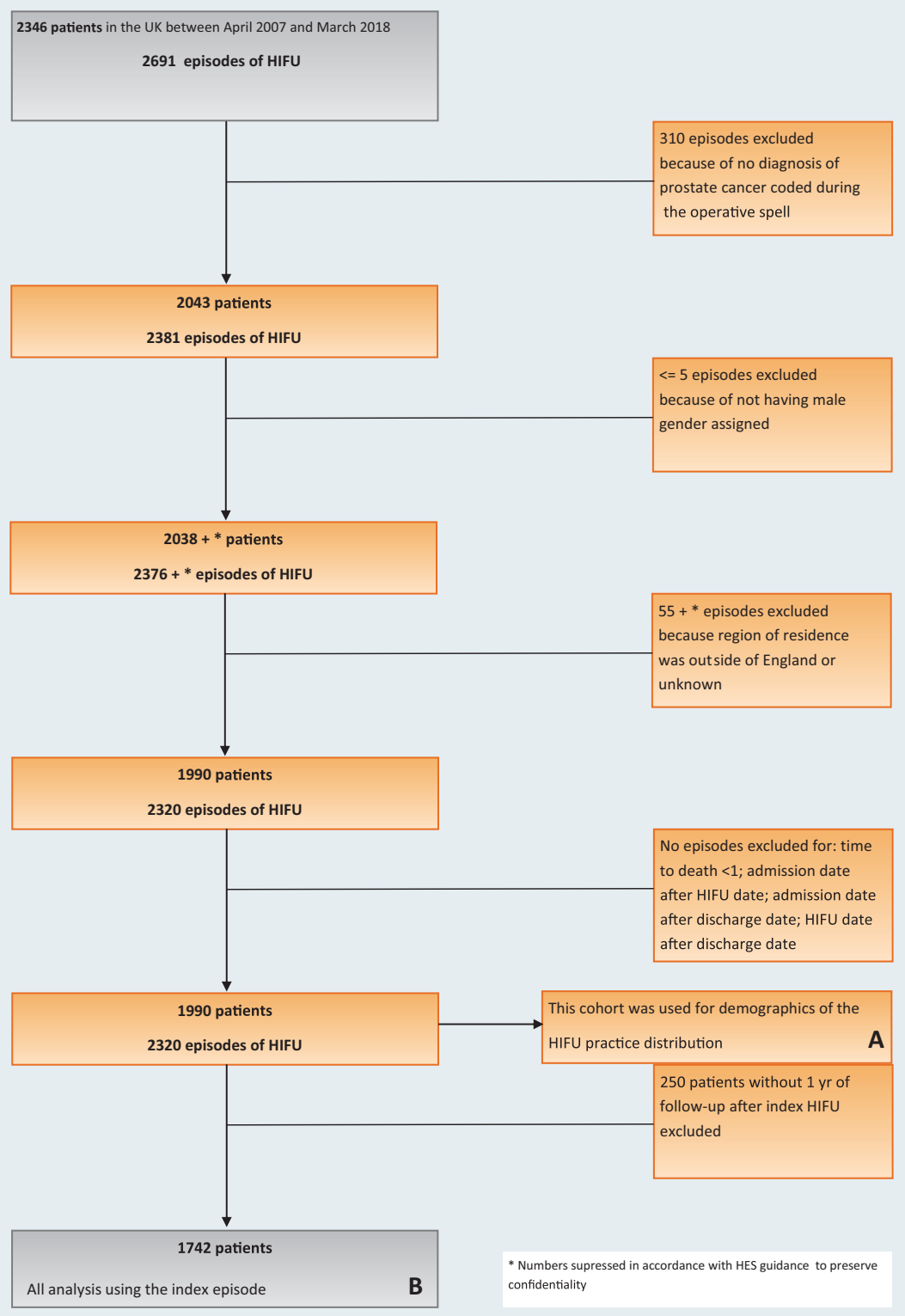

Fig. 1 – Flow diagram of study exclusions. HIFU = high-intensity focused ultrasound.

white patients (84.7%) followed by black or black British (5.2%). Most patients had no comorbidities recorded (82.9%; Table 1). The median follow-up was 5.1 yr (IQR 2.9–8.2).

3.2. *HIFU procedures and salvage*

The overall number of HIFU procedures performed per annum increased from 196 (8.4%) in 2007/2008 to 283

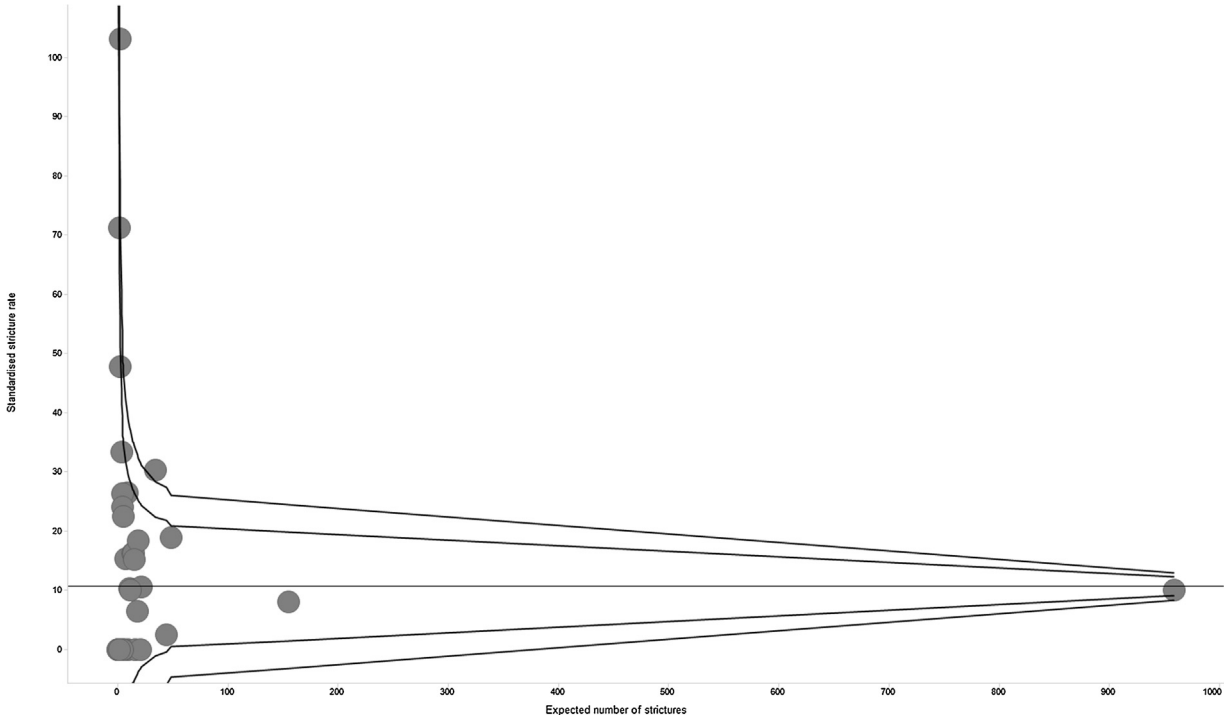

Fig. 2 – Funnel plot of the standardised urethral stricture rate versus the expected number of strictures (surrogate for centre volume). The control lines are set at two and three standard deviations from the mean stricture rate.

(12.2%) in 2017/2018; the mean number per annum was 210. There were 5.01 and 6.19 HIFU treatments per 1000 incident cases of prostate cancer in 2008 and 2017, respectively. The number of procedures since 2011 showed an increasing linear trend (Supplementary Table 3, Supplementary Fig. 1).

There were 50 centres identified in the study, including some private centres that have provided NHS-funded care. The centre with the highest volume performed 1513 (65.2%) HIFU procedures, followed by 194 (8.4%) at the centre with the second highest volume. Forty centres (80%) performed <20 HIFU procedures, of which 28 (56%) undertook fewer than six (Table 4).

The rates of primary and salvage therapies in the follow-up cohort are shown in Table 2. There were 208 patients (11.9%) that went on to have RT following HIFU and 102 (5.9%) underwent RP. Eight patients (0.5%) had both RT and RP, so 302 patients (17.3%) went on to have a second curative treatment that was not repeat HIFU. At least 5 yr of follow-up data were available for 1027 patients, of whom 189 (18.4%) went on to have salvage RT or RP within 5 yr of their index HIFU.

3.3. TURP stricture validation

There were 122 770 patients identified, of whom 10 043 (8.2%) had a post-TURP stricture at any time (median follow-up 7 yr, IQR 5–9). The number of patients with strictures was 4548 (3.7%) at 1 yr and 6361 (5.2%) 2 yr postoperatively. Data at 5-yr follow-up were available for 103 906 patients, of whom 7147 (7.6%) had a stricture by 5 yr.

3.4. HIFU stricture and fistula

In the HIFU follow-up cohort, 174 patients (10.0%) developed a stricture and 27 (1.5%) developed a fistula following index HIFU; the ratios were unchanged when controlling for other therapies (Table 3). The median time to development of stricture (controlled for other procedures) was 2.1 yr (IQR 0.6–4.0). The likelihood of developing a urethral stricture decreased with more recent index HIFU (2016/2017 vs 2007/2008: hazard ratio [HR] 0.30 95% confidence interval [CI] 0.11–0.79; $p = 0.015$; Table 5). Older age (in years) was associated with a higher likelihood of urethral stricture (HR 1.03, 95% CI 1.00–1.05; $p = 0.024$).

In univariable Cox analysis, the likelihood of stricture formation was significantly higher for centres with a mean annual caseload of two or fewer HIFU procedures (HR 2.05, 95% CI 1.08–3.91; $p = 0.029$) when compared to centres performing more than two procedures per year (Supplementary Table 1).

4. Discussion

It appears that HIFU for prostate cancer in England is not confined to registered clinical trials. Approximately 850 patients can be accounted for by currently published clinical trials and registry studies in the relevant time frame [11–15], representing less than half of the publicly funded procedures identified in this study. There are a large number

Table 1 – Demographics for the descriptive and follow-up cohorts.

Variable	Descriptive cohort	Follow-up cohort
Patients (*n*)	2320	1742
Median age, yr (interquartile range)	67 (61–72)	67 (61–72)
Deprivation quintile, *n* (%)		
1	276 (11.9)	202 (11.6)
2	390 (16.8)	285 (16.4)
3	465 (20.0)	350 (20.1)
4	494 (21.3)	392 (22.5)
5	689 (29.7)	513 (29.4)
Unknown	6 (0.3)	0 (0.0)
Ethnicity, *n* (%)		
White	2005 (84.7)	1521 (85.6)
Asian or Asian British	48 (2.1)	34 (2.0)
Black or Black British	121 (5.2)	90 (5.2)
Other	60 (2.6)	40 (2.2)
Unknown	86 (3.7)	57 (3.3)
Charlson score, *n* (%)		
0	1923 (82.9)	1458 (83.7)
1–5	302 (13.0)	216 (12.4)
>5	95 (4.1)	68 (3.9)
Year of high-intensity focused ultrasound, *n* (%)		
2007/2008	196 (8.4)	188 (10.8)
2008/2009	177 (7.6)	143 (8.2)
2009/2010	151 (6.5)	134 (7.7)
2010/2011	169 (7.3)	145 (8.3)
2011/2012	161 (6.9)	133 (7.6)
2012/2013	165 (7.1)	139 (8.0)
2013/2014	231 (10.0)	197 (11.3)
2014/2015	225 (9.7)	199 (11.4)
2015/2016	277 (11.9)	225 (12.9)
2016/2017	285 (12.3)	239 (13.7)
2017/2018	283 (12.2)	0 (0.0)
Region of residence, *n* (%)		
North East	24 (1.0)	16 (0.9)
North West	60 (2.6)	46 (2.6)
Yorkshire and Humber	69 (3.0)	54 (3.1)
East Midlands	103 (4.4)	86 (4.9)
West Midlands	120 (5.2)	93 (5.3)
East of England	373 (16.1)	282 (16.2)
London	749 (32.3)	540 (31.0)
South East	658 (28.4)	501 (28.8)
South West	164 (7.1)	124 (7.1)

Table 2 – Primary and salvage HIFU for the follow-up cohort.

Procedure	Patients, *n* (%)	Median TTP (mo)
Transurethral resection of prostate		
Before HIFU	40 (2.3)	
Concomita nt	54 (3.1)	
After HIFU	122 (7.0)	12
Prostatectomy		
Before HIFU	23 (1.3)	
After HIFU	102 (5.9)[a]	27
Radiotherapy		
Before HIFU	37 (2.1)	
After HIFU	208 (11.9)[a]	24
HIFU procedures		
One	1453 (83.4)	
Two	253 (14.5)	21
Three or more	36 (2.1)	24

HIFU = high-intensity focused ultrasound; TTP = time to procedure.
[a] Eight patients underwent both salvage radiotherapy and prostatectomy.

Table 3 – Frequency of strictures and fistulae following HIFU.

	Stricture		Fistula	
	Patients, *n* (%)	Denominator	Patients, *n* (%)	Denominator
All	174 (10.0)	1742	27 (1.5)	1742
Pure HIFU[a]	133 (10.3)	1287	16 (1.3)	1240
Other procedures	41 (9.0)	455	11 (2.2)	502

HIFU = high-intensity focused ultrasound.
[a] Pure HIFU cohort defined as patients with a stricture/fistula diagnosis date preceding the second therapy date and following the HIFU date.

Table 4 – Number of providers by HIFU procedure frequency over the study period.

HIFU procedures	Providers, *n* (%)
≤5	28 (56)
6–10	6 (12)
11–20	6 (12)
21–50	5 (10)
50–100	2 (4)
100–1000	2 (4)
>1000	1 (2)

HIFU = high-intensity focused ultrasound.

Table 5 – Cox proportional-hazards regression for the development of stricture following HIFU in the HIFU-only cohort.

Variable	HR (95% CI)	*p* value
Age (per year)	1.03 (1.00–1.05)	0.024
Deprivation quintile (vs 1)		
2	1.21 (0.60–2.43)	0.588
3	1.20 (0.61–2.34)	0.597
4	1.05 (0.54–2.02)	0.892
5	1.21 (0.64–2.26)	0.560
Ethnicity (vs White)		
Asian or Asian British	0.31 (0.04–2.22)	0.243
Black or Black British	0.48 (0.18–1.33)	0.161
Other	0.34 (0.05–2.48)	0.289
Unknown	0.32 (0.04–2.29)	0.254
Charlson score (vs 0)		
1–5	0.80 (0.44–1.45)	0.461
>5	0.85 (0.31–2.33)	0.749
Year of HIFU (vs 2007/2008)		
2008/2009	0.93 (0.53–1.62)	0.791
2009/2010	0.59 (0.31–1.15)	0.122
2010/2011	0.97 (0.54–1.73)	0.909
2011/2012	0.75 (0.39–1.44)	0.387
2012/2013	0.57 (0.28–1.20)	0.140
2013/2014	0.27 (0.12–0.62)	0.002
2014/2015	0.32 (0.14–0.74)	0.008
2015/2016	0.37 (0.17–0.84)	0.018
2016/2017	0.30 (0.11–0.79)	0.015
Annual HIFU caseload (vs >2 per year)		
≤2 per year	1.65 (0.84–3.28)	0.148

CI = confidence interval; HIFU = high-intensity focused ultrasound; HR = hazard ratio.

of low-volume centres throughout England with no published reports or known case series from the corresponding regions.

The European Association of Urology guidelines for patient selection for HIFU advise that patients "should be counselled with caution as no data on functional and oncological outcomes are available". The guidelines also state that focal therapies "cannot be recommended as a therapeutic alternative outside of clinical trials" as a grade A recommendation, echoed by NICE [4,5]. The NICE guideline further recommends that data for all patients undergoing HIFU are recorded in the European Registry for Cryosurgical Ablation of the Prostate.

It has been proposed that case volume influences complication rates for other urological cancer interventions; there are well-documented volume effects for RP and cystectomy [16,17]. A high proportion of centres perform a low volume of HIFU procedures and there is a suggestion in the univariable analysis that a volume effect is also present for stricture development following HIFU for prostate cancer, supporting the suggestion that mentorship is vital to improve outcomes [18].

The likelihood of stricture development is lower for more recent HIFU treatments; while this observation could be enhanced by the shorter time for stricture detection, the median time to stricture is 2.1 yr, so changes in practice such as focal and hemi-gland HIFU are likely to have had a beneficial impact on stricture rates.

Complication rates after TURP have been reported as 2.2–9.9% for stricture and 0.3–9.2% for bladder neck contracture [19]. The data in the validation exercise revealed a post-TURP stricture rate of 3.7–8.2%; it can therefore be inferred that stricture coding in HES is accurate.

It is well documented that strictures, contractures, and fistulae are common among men treated with all modalities for prostate cancer [20]. Our study identified stricture and fistula rates similar to those for other prostate cancer therapies, suggesting that HIFU is not necessarily associated with fewer complications. Prostate specimens at prostatectomy following HIFU revealed increased fibrosis and scarring and contracture [21]; hence, it is likely that HIFU causes damage to areas other than the targeted lesion.

The salvage procedure rate (RT or RP) for patients following HIFU is 18.4% at 5 yr, while 3.5% of patients are treated with salvage HIFU. It has been reported that the rectourethral fistula rate for patients receiving HIFU following combined brachytherapy and external beam RT is as high as 60%, although this was a cohort of five patients [22]; in such cases it is important to ensure patients are counselled appropriately.

We observed an association between older age and a higher likelihood of urethral stricture development; it is known that older men are more susceptible to strictures [23]. The demographics of this cohort indicate a young patient population with little comorbidity, suggesting it is less likely that HIFU is being offered to patients who are unfit for radical surgery. The rationale for this potential approach is on the grounds that HIFU has fewer complications as a prostate cancer therapy.

Our study has limitations. HES only captures NHS-funded treatments and procedures in the private sector cannot be examined. There were a number of private health care providers within the data, but these are NHS-funded initiatives. Furthermore, HES does not contain laboratory data, so we were unable to capture biochemical recurrence or staging and grading information. The indication for HIFU is not captured in HES, so there is uncertainty regarding which patients underwent a period of active surveillance before HIFU. RT may be undercoded in HES, so there is potential for underdetection of radiotherapy events. HIFU is purported to preserve sexual function better than surgery or RT, but documentation of this is outcome sporadic so it could not be assessed in this study. The severity of stricture and fistula complications observed cannot be discerned from the diagnostic coding, so these complications cannot be graded. OPCS coding does not differentiate between whole-gland and focal ablation so we could not definitively identify which treatment patients had undergone. However, anecdotal reports indicate that there has been a change in practice away from whole-gland treatments; more recent treatments are likely to comprise partial ablation and this may contribute to the improvement in stricture rates over time.

We estimate that approximately 50% of the HIFU procedures for prostate cancer in England are being performed outside the context of audit and research, with HIFU rates and locations displaying a trend for delivery by mostly low-volume providers. This study demonstrates that the prevalence of strictures and fistulae following HIFU cannot be underestimated, even though rates have fallen in recent years, presumably because of focal HIFU.

Author contributions: Prashant Patel had full access to all analyses in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Patel, Dosanjh.
Acquisition of data: Dosanjh.
Analysis and interpretation of data: Dosanjh, Baldwin.
Drafting of the manuscript: Dosanjh.
Critical revision of the manuscript for important intellectual content: Patel, Harvey, Trudgill, Mintz, James, Gallier, Evison, Baldwin, Sooriakumaran.
Statistical analysis: Dosanjh.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euf.2019.11.014.

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Manuscript Two: A national study of artificial urinary sphincter and male sling implantation after radical prostatectomy in England.

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Functional Urology

A national study of artificial urinary sphincter and male sling implantation after radical prostatectomy in England

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Objectives

To consider the provision of post-radical prostatectomy (RP) continence surgery in England.

Materials and Methods

Patients with an Office of Population Census and Surveys Classification of Interventions and Procedures, version 4 code for an artificial urinary sphincter (AUS) or male sling between 1 January 2010 and 31 March 2018 were searched for within the Hospital Episode Statistics (HES) dataset. Those without previous RP were excluded. Multivariable logistic regressions for repeat AUS and sling procedures were built in STATA. Further descriptive analysis of provision of procedures was performed.

Results

A total of 1414 patients had received index AUS, 10.3% of whom had undergone prior radiotherapy; their median follow-up was 3.55 years. The sling cohort contained 816 patients; 6.7% of these had received prior radiotherapy and the median follow-up was 3.23 years. Whilst the number of AUS devices implanted had increased each year, male slings peaked in 2014/2015. AUS redo/removal was performed in 11.2% of patients. Patients in low-volume centres were more likely to require redo/removal (odds ratio [OR] 2.23 95% confidence interval [CI] 1.02–4.86; $P = 0.045$). A total of 12.0% patients with a sling progressed to AUS implantation and 1.3% had a second sling. Patients with previous radiotherapy were more likely to require a second operation (OR 2.03 95% CI 1.01–4.06; $P = 0.046$). Emergency re-admissions within 30 days of index operation were 3.9% and 3.6% fewer in high-volume centres, for AUS and slings respectively. The median time to initial continence surgery from RP was 2.8 years. Increased time from RP conferred no reduced risk of redo surgery for either procedure.

Conclusion

There is a volume effect for outcomes of AUS procedures, suggesting that they should only be performed in high-volume centres. Given the known impact of incontinence on quality of life, patients should be referred sooner for post-prostatectomy continence surgery.

Keywords

artificial urinary sphincter, sling, prostate cancer, prostatectomy, incontinence

Introduction

It has been reported that 42% of men have impaired urinary function 5 years after radical prostatectomy (RP) [1]; 70% of men report some persisting urine leakage within this time frame [2]. Urinary function after RP is a considerable postoperative concern for men with prostate cancer [3]. Incontinence can range from minimal disruption to quality of life to being extremely disabling.

The current 'gold standard' in the UK for the management of severe urinary incontinence is the implantation of an artificial urinary sphincter (AUS). This device requires placement of an inflatable cuff around the bulbar urethra or bladder neck, pressurized by an abdominal balloon reservoir and a control button in the scrotum. It acts to support the urinary sphincter; when inflated, it does not permit the passage of urine down the urethra and the patient can deflate the cuff in order to urinate. Other methods used prior to AUS insertion or as an alternative include pelvic floor muscle training, injectable bulking agents and, more recently, male transurethral slings.

Most male slings in the UK are transobturator slings [2]. These are not bone-anchored like their predecessors. The male sling is threaded under the bulbar urethra and creates light compression to reduce urine leakage. It is thought, however, that this type of sling owes its success to the

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proximal repositioning of the urethra rather than via direct compression [4].

Whilst an AUS can be used as a salvage therapy following sling placement with reasonable efficacy [5], this is not the case when the sequence of procedures is reversed [6]. This is thought to be attributable to decreased laxity of the urethra after AUS explantation. Radiotherapy has a similar effect on the urethra and may make the AUS a more suitable device for patients who have received pelvic radiotherapy.

This retrospective, population-based study examined the rates of AUS procedures and male slings for the management of incontinence in men after RP. It also aimed to establish complication rates, re-admission rates and whether radiotherapy impacts the rates of procedure and treatment success.

Methods

Hospital Episode Statistics

Hospital Episode Statistics (HES) is a dataset of all publicly funded interactions between patients and hospitals in England. The primary function of HES is administrative, to determine financial reimbursement to healthcare providers. Data are organized into longitudinal episodes, the time whilst under the care of an individual consultant. Diagnoses and procedural information are stored as International Classification of Diseases version 10 (ICD-10) codes and Office of Population Census and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) codes, respectively. All data items in this study that aggregate to < 6 at patient level have been suppressed in accordance with HES guidance, to prevent possible identification of patients. Approval to use HES data was granted by the Health Informatics Request Review Group at University Hospitals Birmingham NHS Foundation trust: UHB registration number CARMS-14338.

Validation

A reference dataset at University Hospitals Birmingham was compiled using the theatre's appointment system and operation notes. The routine hospital interaction data, stored by hospitals as a precursor to HES, were extracted and the OPCS code recorded against each patient was compared with the reference dataset. The sensitivity of OPCS codes within the hospital interaction data to detect AUS and male slings was calculated.

Cohort

All patients that had undergone an AUS implantation (M642) or a male sling (M647) placement between 1 January 2010 and 31 March 2018 were identified in the HES database. All patients have a minimum of 6-month follow-up in HES. Those without a diagnosis of prostate cancer and prostatectomy (M61/M341) preceding first incontinence surgery were removed; further exclusions are detailed in Fig. 1. Patients were not excluded from the AUS cohort if a prior male sling had been attempted, as there is no statistically significant evidence that a prior sling alters the efficacy of an AUS [5]; therefore, there was some overlap of cohorts.

Data and Analysis

Age, sex, region of residence, Index of Multiple Deprivations 2010 quintile, and ethnicity were extracted for the index admission. The Charlson comorbidity index, modified to exclude cancer, was calculated from the episode ICD-10 coded diagnoses (Appendix S1), a technique previously validated in past HES studies [7,8].

Previous radiotherapy was identified in the HES (Appendix S2). Time to treatment, complications and re-admissions were extracted. Provider volume was determined by the number of procedures performed over the study period and split by tertile, for AUSs and for slings.

Volume of procedures was determined by the total number of procedures performed over the study period, for AUS and sling procedures separately.

Multivariable logistic regression models were generated with redo/removal of AUS or redo of sling/implantation of AUS following a sling procedure as the dependent variables. Demographic and clinically relevant variables were included in both models.

The rate of AUS device revisions per year is included in Table S1.

All data were extracted with Microsoft SQL Server and analysed using STATA 15. Statistical significance was set at $P < 0.05$. A funnel plot was created with Spotfire using the standardized redo/removal rate for AUS providers, with confidence limits set at 2 and 3 standard deviations (SD) from the mean.

Results

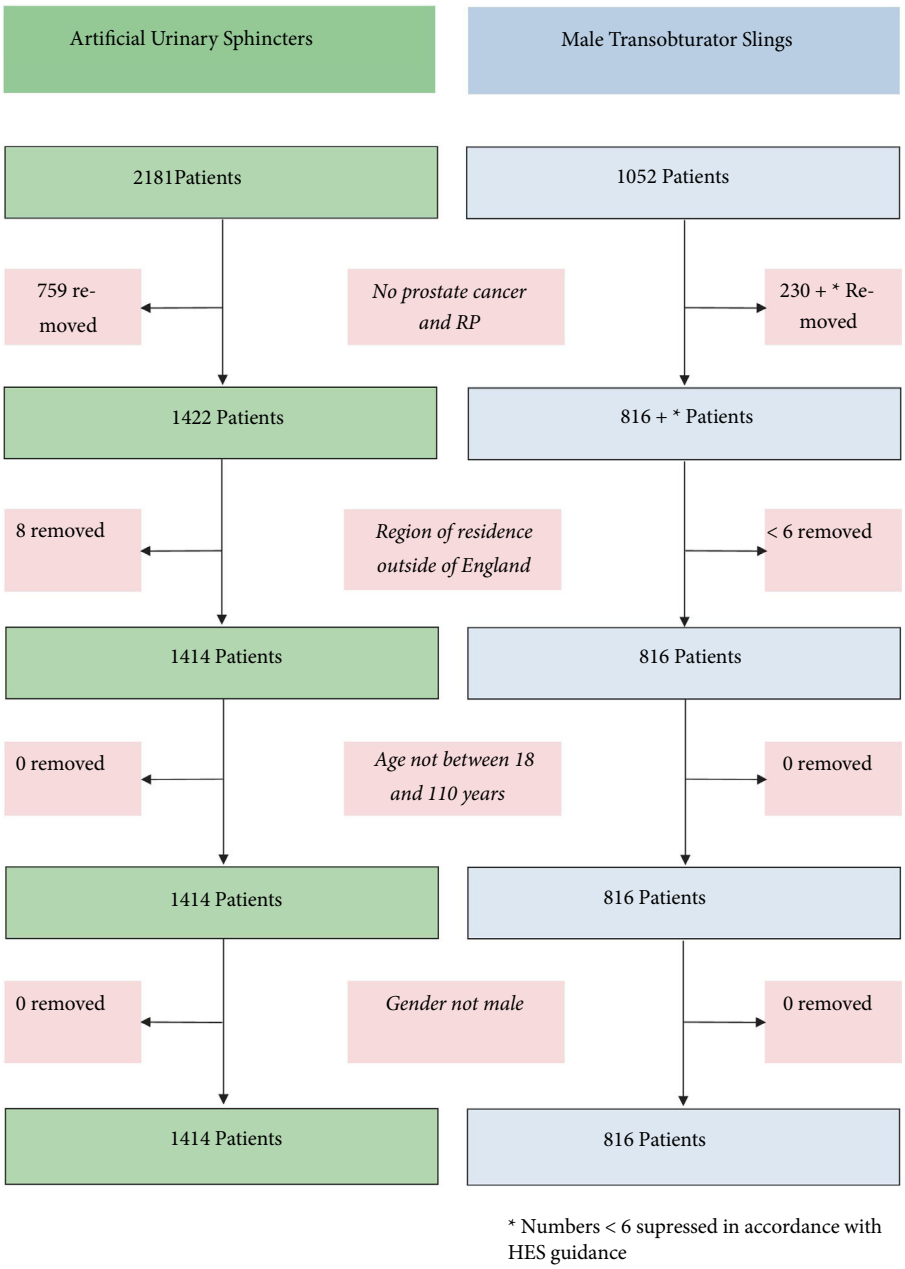
Validation

The validation exercise identified 36/39 AUS and 34/41 sling procedures, giving 92.3% and 82.9% accuracy of coding, respectively, against the local dataset.

Artificial Urinary Sphincter

A total of 1414 patients had received an index AUS within the study period, with a median (range) follow-up of 3.55

Fig. 1 Flow diagram of exclusions for artificial urinary sphincter and sling cohorts. HES, Hospital Episode Statistics; RP, radical prostatectomy.



(0.5–8.75) years. In the 2010/2011 financial year, 8.4% of patients received their first AUS; this increased annually, with 16.3% performed in 2017/2018 (Fig. 2). A total of 10.3% had also undergone previous radiotherapy. The median (interquartile range [IQR]) age was 68 (64–72) years and the majority of patients (75.5%) had no recorded comorbidities (Table 1). The number of patients receiving an AUS increased for each deprivation quintile from the most deprived to the least, with 12.5% in quintile 1 and 23.8% in quintile 5 (Table 1).

A total of 7.7% of patients had received a second AUS and 0.8% had undergone the procedure three or more times (Table 1). The median (IQR) time to second AUS was 1.77 (0.9–3.2) years. A total of 12.5% of patients had undergone an AUS redo or removal; 0.6% of these were within 6 weeks of the index AUS procedure. Previous sling operation did not confer an increased likelihood of redo/removal ($P = 0.631$). A total of 3.1% had experienced at least one episode of urinary retention, 0.6% had a prosthetic/wound infection, 0.8% had a UTI, and 0.8% had mechanical dysfunction within 6 weeks of

AUS placement. Unplanned re-admissions and suprapubic catheter insertion are detailed in Table 1. Of patients in the lowest-volume tertile, 5.0% had an emergency re-admission within 30 days, compared to 3.9% in the highest.

A total of 49 centres performed index post-RP AUS insertion; 17/49 (34.7%) of centres performed fewer than six post-RP AUS insertions in the study period, 9/49 of centres (18.4%) had performed > 50 post-prostatectomy operations in the study period.

Regression of redo or removal of AUS showed an association with low-volume providers (Table 2); patients who had an AUS in centres that had performed ≤11 total male AUS procedures over the whole study period were more likely to require a redo or removal procedure compared to those who had performed >47 total male AUS procedures (odds ratio [OR] 2.22, 95% CI 1.02–4.86; $P = 0.045$). Increasing time from RP to AUS, previous sling operation and previous radiotherapy did not confer higher risk of redo or removal of AUS. The funnel plot of the standardized redo/removal rate is shown in Fig. 3; there were two centres in the high-volume tertile near the 2-SD confidence limit; these centres had 19.3% of patients with prior radiotherapy compared to 9.4% for the other providers combined.

Slings

A total of 816 patients had received a male sling as their first continence surgery; the median (range) follow-up was 3.23 (0.5–8.75) years. The numbers of slings performed in a single year peaked in 2014/2015, when 19.0% of slings in the study period were inserted; thereafter there was a decline in the number of sling operations, with 11.5% in 2017/2018 (Fig. 2).

The median (IQR) patient age was 68 (63–71) years and the majority of patients (79.4%) had no recorded comorbidities (Table 1). The pattern of sling provision with regard to deprivation showed the same trend as in the AUS group; 9.3% of patients receiving a sling were in the most deprived quintile compared to 30.5% in the least. A total of 6.7% of patients had received prior radiotherapy in the sling group.

A total of 1.3% of patients had a second sling and 12.4% had an AUS following a sling procedure (Table 1). The median (IQR) time to second sling or AUS implantation from first operation was 2.4 (1.57 −3.39) years. A total of 6.6% of patients experienced urinary retention within 6 weeks of sling implantation, 0.7% had a surgical site infection; UTI or mechanical sling dysfunction occurred in fewer than six patients. In the lowest-volume tertile, 7.9% of patients were

Fig. 2 Line graph displaying the number of artificial urinary sphincter (AUS) and sling procedures performed each financial year over the study period.

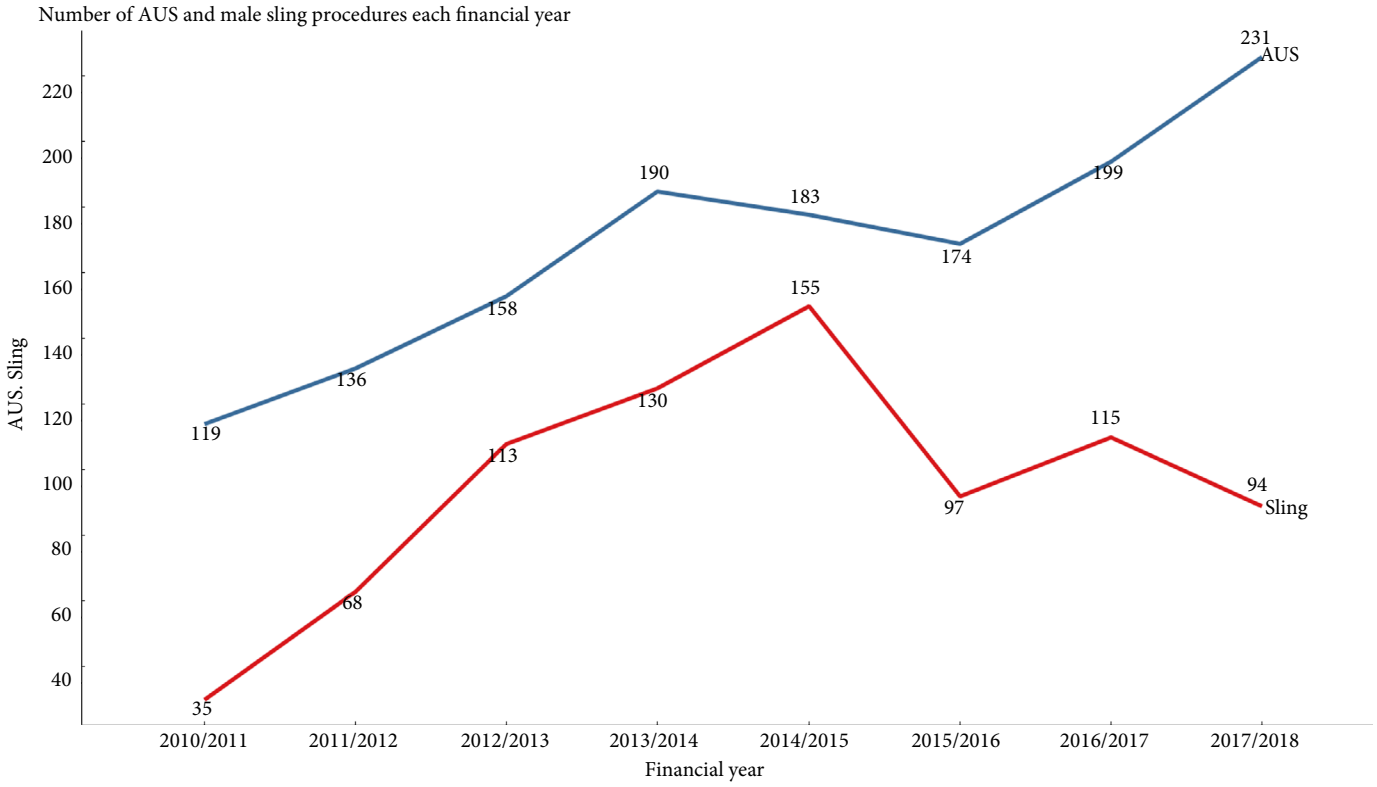


Table 1 Table of demographics for artificial urinary sphincter (AUS) and sling cohorts.

	AUS, *n* (%)	Sling, *n* (%)
N	1414	816
Age, years		
Median	68	68
IQR	64–72	63–71
Range	21–84	43–87
Deprivation		
1	179 (12.7)	76 (9.3)
2	245+* (15+*)	130+* (15+*)
3	316 (22.3)	179 (21.9)
4	332 (23.5)	177 (21.7)
5	337 (23.8)	249 (30.5)
Unknown	<6	<6
Ethnicity		
White	1147 (81.1)	659 (80.8)
Asian or Asian British	18 (1.3)	15 (1.8)
Black or Black British	44 (3.1)	19 (2.3)
Mixed	6 (0.4)	<6
Any other ethnicity	12 (0.8)	5+*
Unknown	187 (12.7)	113 (13.7)
Charlson score		
<1	1067 (75.5)	648 (79.4)
1–5	287 (20.3)	133 (16.3)
>5	60 (4.2)	35 (4.3)
Subsequent surgery		
Removal AUS	56 (4.0)	
Subsequent AUS	109 (7.7)	11 (1.3)
Three or more AUS procedures	11 (0.8)	N/A
Subsequent sling	N/A	91 (12.4)
Unplanned re-admissions		
30-day	58 (4.1)	34 (4.2)
1-year	153 (10.8)	68 (8.3)
30-day urology	37 (2.6)	25 (3.1)
1-year urology	64 (4.5)	31 (3.8)
Suprapubic catheter		
30-day	<6	<6
1-year	12 (0.8)	<6

**Numbers suppressed in accordance with Hospital Episode Statistics guidance.*

admitted to hospital as an emergency within 30 days compared with 3.6% of patients in the high-volume tertile.

A total of 48 centres were identified as performing male sling operations after RP; 16/48 (33.3%) performed fewer than six post-prostatectomy sling procedures in the study period and 2/48 (4.2%) performed >50. Low-volume centres and high-volume centres were identified as those who had performed seven or fewer and >25 sling procedures over the study period, respectively. There was no association of centre volume with the likelihood of sling revision. Previous radiotherapy was associated with a twofold increased risk of sling revision (OR 2.03, 95% CI 1.01–4.06; $P = 0.046$). Deprivation quintiles 2, 3 and 5 were associated with poorer outcomes; they did, however, have broad CIs (Table 2).

Time to Treatment

There were 2139 distinct patients in the overall study. The median (IQR) time from RP to initial continence treatment with either a sling or AUS was 2.8 (1.90–4.55) years. Provider volume status was determined from the first surgery, either sling or AUS, and the median time to surgery was 2.5 years, 2.9 years and 2.8 years for low-volume, medium-volume and high-volume centres, respectively.

Discussion

The present study captured almost all post-prostatectomy continence surgery within the English NHS. Selection of continence surgery appears to be unrelated to demographics; patients with prior radiation and severe incontinence are less likely to be offered the male sling than an AUS [9–11]. Radiotherapy was also found to be associated with poorer outcomes for patients receiving a sling in this study. The yearly procedure rate increased every year for AUS procedures, and sling procedures followed the same trend up until the 2014/2015 financial year, at which point the number of sling procedures fell. There has been growing concern regarding erosion from a mesh material used in women for pelvic prolapse and urinary incontinence. In light of these findings, the National Institute for Health and Care Excellence (NICE) proposed mesh as a 'last resort' in women [12]; it has since been re-instated as part of the recommended surgical management of female urinary incontinence [13]. The first reported urethral erosion from a male transobturator sling was in 2008 [14], although this patient did receive radiotherapy prior to prostatectomy. Patients are currently counselled about urethral erosion as a potential adverse effect [15]. Current NICE guidance recommends the male sling 'only as part of a randomized controlled trial' [16]; it is unlikely, however, that this reduced patient uptake, as increasing numbers of slings were implanted since 2010. The MASTER trial, a randomized controlled trial directly comparing male sling with AUS procedures, began recruitment in 2014 [2]. This may be the most influential cause of the reduced number of male sling procedures, as fewer would be performed outside of a trial setting.

After RP, stress urinary incontinence is at its most severe in the early postoperative recovery period. In most men this will recover to some degree without any measures in place; however, conservative treatment should begin even before the operation. Pelvic floor strengthening has been shown to improve continence in men 16 weeks postoperatively, with benefits becoming more limited after this and plateauing at 1 year [17]. Concurrent use of urethral bulking agents can maximize recovery to continence in men [18]; however, should these fail, surgical management is required. The wait from RP to continence surgery was 3 years, a finding similar to that of a Canadian population-based study [19]. Given that most improvement in functional urinary outcomes occurs in the early postoperative period and the present study has not demonstrated benefit of delayed surgical intervention, patients

Table 2 Logistic regression model for redo/removal of artificial urinary sphincter.

	AUS redo/removal	Odds ratio	*P* > |z|	95% CI	
Age	Continuous				
	Increasing year	0.99	0.451	0.96	1.02
Deprivation quintile1 = most deprived5 = least deprived	Baseline = 1				
	2	0.74	0.312	0.42	1.32
	3	0.78	0.371	0.45	1.34
	4	0.77	0.334	0.45	1.31
	5	0.78	0.374	0.45	1.35
	Unknown	1.00			
Ethnic group	Baseline = white				
	Asian	1.31	0.677	0.37	4.67
	Black	0.90	0.828	0.37	2.24
	Mixed	1.00			
	Other	1.00			
	Unknown	0.53	0.032	0.30	0.95
Charlson score	Baseline <1				
	1–5	1.03	0.885	0.69	1.54
	>5	1.21	0.615	0.58	2.54
Total volume AUS implanted study period	Baseline >47				
	<12	2.23	0.045	1.02	4.86
	12–47	1.20	0.396	0.79	1.84
Previous radiotherapy	Baseline = no radiotherapy				
	Radiotherapy	1.16	0.561	0.70	1.94
Previous male sling	Baseline = no sling				
	Sling	1.46	0.207	0.81	2.63
Time from RP to AUS	Continuous				
	Increasing days	1.00	0.980	1.00	1.00

AUS, artificial urinary sphincter; RP, radical prostatectomy.

Fig. 3 Funnel plot displaying the standardized redo/removal rate for centres implanting artificial urinary sphincter, coloured by provider volume tertile. The inner control lines are set at 2 SD from the mean and outer at 3.

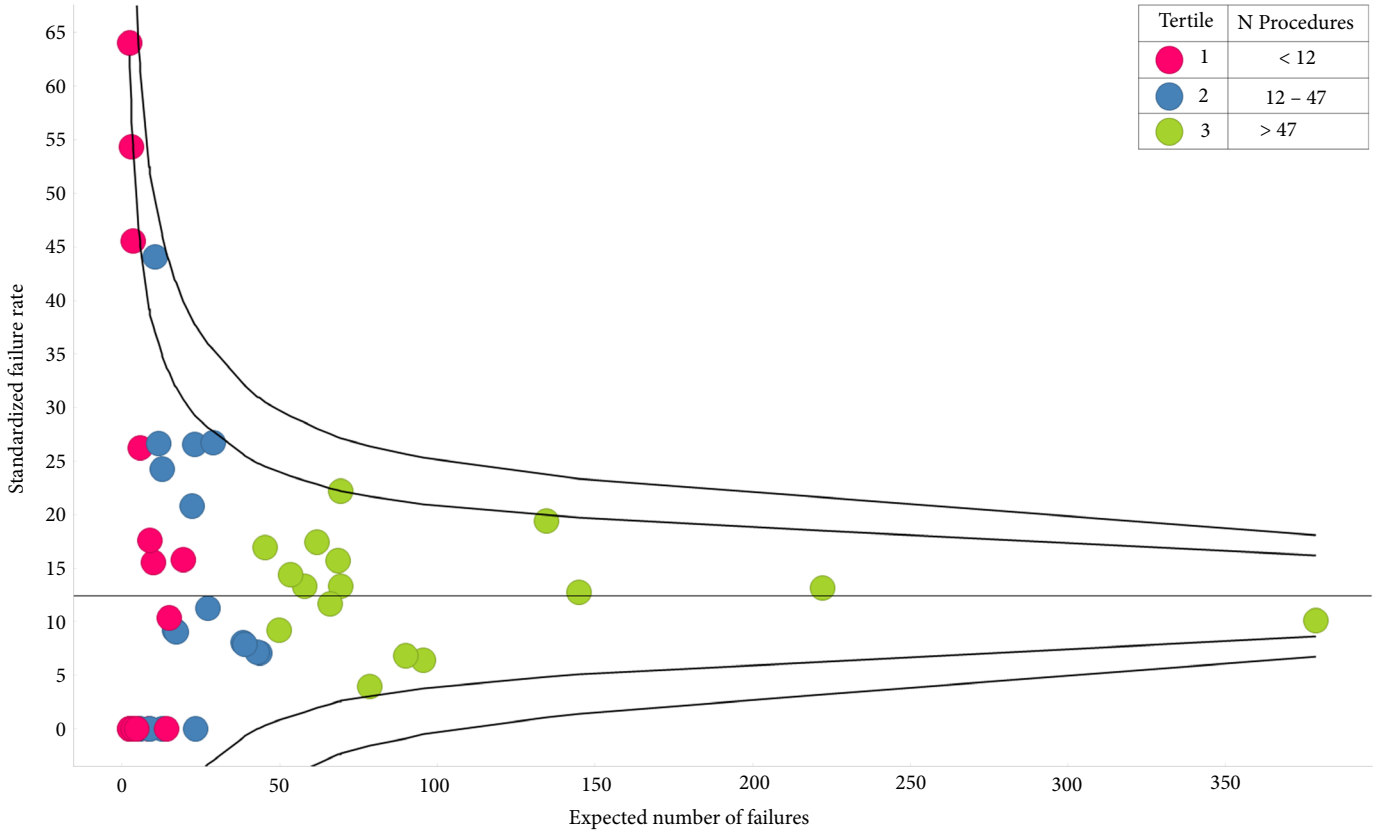


Table 3 Logistic regression model for redo of sling or progression to artificial urinary sphincter.

	Sling redo/AUS	OR	$P > \|z\|$	95% CI	
Age	Continuous variable				
	Increasing year	1.00	0.962	0.97	1.03
Deprivation quintile1 = most deprived5 = least deprived	Baseline = 1				
	2	4.55	0.019	1.29	16.12
	3	5.20	0.009	1.52	17.75
	4	2.78	0.116	0.78	9.94
	5	4.21	0.021	1.24	14.28
	Unknown	1.00			
Ethnic group	Baseline = white				
	Asian	0.44	0.429	0.06	3.43
	Black	0.73	0.685	0.16	3.34
	Mixed	1.00			
	Other	3.67	0.149	0.63	21.47
	Unknown	1.17	0.605	0.65	2.08
Charlson score	Baseline <1				
	1–5	0.87	0.631	0.48	1.56
	>5	1.57	0.355	0.61	4.05
Total volume slings implanted study period	Baseline >25				
	<8	1.87	0.146	0.81	4.32
	8–25	0.96	0.884	0.56	1.65
Previous radiotherapy	Baseline = no radiotherapy				
	Radiotherapy	2.03	0.046	1.01	4.06
Time from RP to sling	Continuous				
	Increasing days	1.00	0.035	1.00	1.00

AUS, artificial urinary sphincter; RP, radical prostatectomy.

should be referred to a continence team within 6–12 months of prostate surgery [20].

The primary complication evaluated in this study for AUS was removal or redo procedures, and fewer than one in 10 men with an AUS will require removal of their AUS or a redo procedure. Surgeon procedure volume has been shown to influence post-surgical outcomes for other urological procedures [21] and AUS implantation appears to be the same; patients in low-volume centres were more likely to require removal of their sphincter and there were 4.3% more re-admissions in the lowest-volume providers compared to the highest. Although there were two centres above the inner confidence limit, these centres had a higher proportion of post-radiotherapy patients; radiotherapy is known to increase complications [9,10]. This may indicate that the centres in question undertake a higher proportion of complex operations. Most patients receiving a sling who progress to further surgery opt for an AUS rather than another sling. Although there was no volume effect demonstrated in the regression model for slings, there were 3.7% fewer unplanned 30-day re-admissions in the high-volume providers compared to the low.

Quality of life is impaired in incontinent patients; more than half of men will report 'severe emotional distress' due to incontinence after RP [22]; AUS implantation has a significant positive impact on the lives of these patients [23], although this is diminished in patients undergoing multiple revisions [24]. Centralizing continence surgery will help create a clear referral pathway and reduce impaired quality of life and financial implications for patients.

The NHS national tariffs for an AUS and a male sling are £8422 and £4429, respectively [25], in addition to the cost of unplanned re-admissions and non-surgical complications. For any intervention required as a complication of these implants, the NHS will pay trusts, £1645–£2835, depending on the level of intervention required. There is a clear incentive to reduce repeat operations and emergency re-admissions.

A limitation of performing this study using HES is the unknown severity of incontinence pre- and postoperatively, which precludes direct comparison of slings and sphincters. This clinical question, however, will be answered by the MASTER trial. Although this study captures most publicly funded slings and AUSs, we estimate that approximately 17% and 8%, respectively, of procedures will not have been identified; as per the validation exercise. As there is no OPCS-4 code for removal of a male sling, we were unable to include this in our revision rates and could only look at further operations; however, this is a rare event [4]. Furthermore, this study could not differentiate between brand, type or material of sling; outcomes for male slings may vary providing the type of sling implanted. A study comparing ARGUS™ and AdVance™ slings identified a variation in revision rates, for urinary incontinence, of 19% [26]; it should be noted, however, that one sling type is

adjustable. Adjustments of these slings may contribute to the revision rates. There may be some other relevant confounding factors that cannot be identified in HES, such as body mass index and cancer staging at time of RP. The responsible consultant for the relevant episode is recorded in HES, however, this is not always the lead surgeon; it is therefore difficult to examine individual surgeon outcomes on a national scale, using HES data.

In conclusion, whilst the AUS is considered the gold standard for treatment of male stress incontinence in England, it is evident that several factors must be considered when selecting whether an AUS or sling is most appropriate. Prior radiotherapy is prognostically negative for a male sling, but not for AUS procedures; nevertheless, it may indicate a more complex operation.

High-volume centres are expected to be experienced in the implantation of AUSs and in managing these patients; observed outcomes are generally better and more consistent. While it is possible to have reasonable outcomes in low-volume centres, a high variability is seen in revision rates.

Given the known impact of incontinence on quality of life, patients would benefit from earlier referral for post-prostatectomy continence surgery.

Conflict of Interest

None declared.

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Abbreviations: AUS, artificial urinary sphincter; HES, Hospital Episode Statistics; ICD-10, International Classification of Diseases, version 10; IQR, interquartile range; NICE, National Institute for Health and Care Excellence; OPCS4, Office of Population Census and Surveys Classification of Interventions and Procedures version 4; OR, odds ratio; RP, radical prostatectomy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Table displaying the number of revisions (redo/removal) per year of AUS (*suppressed in accordance with HES guidance).

Appendix S1. List of ICD-10 codes used in this study.

Appendix S2. List of OPCS-4 codes used in this study.

CHAPTER 4: LINKAGE OF ROUTINE ADMINISTRATIVE DATA TO CLINICAL SYSTEMS

This chapter explores how routine administrative data can be linked to clinical systems in order to provide in-depth data on patients. The linkage to electronic health records and other administrative databases, provides important clinical context to patient cohorts, such as biochemical and cancer staging data.

The first manuscript explores a single site retrospective cohort of patients undergoing radical prostatectomy for prostate cancer and associated outcomes, that would not be measurable with routine administrative data alone. It aims to serve as a proof of concept, that databases can be linked in order to provide robust data.

The second manuscript within this chapter is a single site retrospective study of patients undergoing treatment for muscle invasive bladder cancer with curative intent. The data was initially presented at the *European Association of Urology Annual Congress, Barcelona 2019*, where it was awarded the best poster prize in section *Advancing the outcome of advanced and metastatic bladder cancer*. Special acknowledgment is given to Miss Jemma Mytton for her assistance in propensity score matching the cohorts in this study, Professor Nicholas James for providing the LINAC data and Dr Harriet Mintz for collaborating on data validation.

Chapter 4 manuscript one: Can informatics data provide robust surgical outcome data radical prostatectomy for prostate cancer?

Structured abstract

Introduction

Radical prostatectomy is used to treat localised and locally advanced prostate cancer, in patients fit for surgery. Consideration of risk profiles is imperative in order to prognosticate surgical outcomes and likelihood of biochemical relapse. This study aims to evaluate whether health informatics are a viable alternative to case note review.

Materials and methods

This is single site retrospective study of all patients coded for radical prostatectomy between 1/1/2011 and 31/12/2018. Relevant demographic, pre-operative risk, peri-operative outcomes and post-operative outcomes were obtained through linkage of multiple clinical system databases to routine administrative data.

Results:

1267 prostatectomies were identified within routine administrative data in the study period, of which 1265 were successfully linked to the electronic health record. Median age was 64 years old and 83.1% patients had no recorded comorbidity. The body mass index was available for 76.2% patients, of which 17.9% were not overweight or obese. There were 18.8% patients without a pre-operative PSA available, of those with a pre-operative PSA median result was 7.7 ng/l. T2 was the most common pathological T stage, in 31.6% patients. The median operative time was 3.4 hours and 2.1% patients required a blood transfusion. There was a follow-up PSA available for 83.0% patients, the rate of biochemical recurrence

at 5 years was 31.5% and 5-year overall survival was 94.2%. Biochemical recurrence free survival at 5 years was 82.6%

Conclusions:

Utilisation of health informatics has allowed a detailed examination of radical prostatectomy outcomes at this institution. However, there are missing data fields crucial to contextualising results, therefore it cannot yet fully eliminate the need for case-note review.

Background

Radical prostatectomy is used to treat patients with localised and locally advanced prostate cancer. It is estimated that more than 2000 radical prostatectomies are performed per year in Britain with surgical approaches of open, laparoscopic and robotic[1]. Whilst traditionally an open retropubic approach has been utilised, within western healthcare there has been a paradigm shift to minimally invasive approaches; predominantly robotic assisted laparoscopic surgery[2,3].

Biochemical recurrence is a rise in the Prostate Specific Antigen (PSA) levels following radical treatment for prostate cancer, it is widely accepted as a marker of failure of curative treatment and a marker of disease progression or metastasis. PSA levels are expected to be undetectable following radical prostatectomy however 20-40% of men will experience biochemical recurrence, a third of which will go on to have distant metastasis[4,5]. Prompt recognition of biochemical recurrence may help identify patients in whom early initiation of salvage treatment could prevent clinical progression or mortality[6].

Routine administrative data, electronic health records and clinical recording systems are used day to day in health care settings; although data may overlap within clinical systems with regards to what they store, what is recorded will depend on their primary function. Through linkage of these distinct datasets, it is possible that robust research data can be obtained.

This study aims to utilise informatics data and link databases in order to examine risk profiles, intraoperative data and surgical outcomes for patients with prostate cancer

undergoing radical prostatectomy in a single site series, as a proposed alternative to case note review.

Methods

Data sources

Hospital interaction data (HID) at University Hospitals Birmingham NHS Foundation Trust (UHB)

HID is the precursor of information uploaded by a provider to Hospital Episode Statistics. Identifiable patient data is stored longitudinally into episodes and spells. A spell is an admission to hospital, from start to finish, an episode is the length of time spent under the care of a single consultant; a single spell may constitute several episodes. Diagnostic (International classification of diseases version 10 (ICD-10) codes), procedural (Office of Population Census and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) codes) and administrative information can be extracted. As this data has not been uploaded to HES it is identifiable and can be linked to other systems.

Prescribing Information Clinical System (PICS)

This is the EHR that is used at UHB. It is a central communication system that contains all data pertaining to admissions, including but not limited to: drug prescribing and administration, patient observations, imaging tests, laboratory results, procedure reports and ward location. Data are automatically generated from this software. Patients are identified with a unique patient identifier, that is separately linked to their hospital registration number and demographic details.

Galaxy theatres management system

The *Galaxy theatre* administration database contains all operative administration data. All times of relevant surgical events are recorded against a patients' hospital number and operation details. The first time recorded is the time of arrival to the anaesthetic room and the final time is the time of departure from recovery. It is populated in real time by theatre staff.

The Somerset cancer registry

The *Somerset cancer registry* contains all pertinent information to cancer patients passing through the NHS. Data is inputted at multidisciplinary team meetings and details cancer site and stage. Other details are recorded as string text.

NHS spine

The NHS spine contains all records of births and deaths. Selected hospital registration numbers can be uploaded to the spine in order to extract patient death data. This can only be performed for patients at the trust where the request originates from.

Data and analysis

Cohort

All patients coded for radical prostatectomy between 1/1/2011 and 31/12/2018 were identified in the HID. Patient were excluded if there was no coded diagnosis of prostate cancer at the time of procedure.

Data Linkage

All systems were linked on the unique patient identifier, also known as the hospital number or unit number. The exception to this was PICS; each patient had a patient identification

number unique to PICS, called the PICS ID. There was a reference table with the hospital number and the PICS ID for each patient that was used for data linkage. In the case of multiple PICS ID for a single patient, the record pertaining to the relevant admission were used.

Demographics

Demographic data for age, sex, ethnicity and Index of Multiple Deprivations 2010 (IMD) quintile (where 1 is the most deprived and 5 is the least deprived) were extracted from the HID. A modified Charlson comorbidity score, to exclude cancer, was calculated from coded diagnoses; this technique has been previously validated in HES based studies[7,8].

Pre-operative risk

Variables pertaining to pre-operative risk were identified as body mass index (BMI), pre-operative PSA and pathological T staging. BMI and PSA were obtained from the PICS EHR. Pathological T-stage was obtained as the first recorded staging within Somerset Cancer Registry database following prostatectomy.

Previous transurethral resection of the prostate (TURP) and radiotherapy to the prostate are known to complicate radical prostatectomy operation, as such these were identified in the HID and included as variables of pre-operative risk[9].

Surgical data

Surgical approach was categorised as open, laparoscopic or robotic assisted within the HID. Operative time was taken from the Galaxy theatres database as “knife to skin” until “Wound Closure”, to the nearest minute.

Surgical outcomes

Surgical outcome variables were identified as mortality, biochemical recurrence and complications (within 30-days). Complications were identified in the HID and mortality data was obtained from the NHS spine.

Biochemical recurrence was defined as >= 0.2 ng/ml greater than 6 weeks post-operatively. Survival analysis was performed in Stata® version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

Ethics

This study was registered with the clinical audit registration and management system (CARMS) at UHB

Results

Cohort

There were 1267 radical prostatectomies performed at the single institution in the 7-year study period (table 1). The median age at operation was 64 (IQR 59 – 69) and 22.9% of patients had a co-morbidity. The majority of patients were white, 66.9%. 25.4% patients were in deprivation quintile 1. A unique EHR identifier was found and linked for 1265 patients.

Demographic Variable		**n (%)**
		1267
Age	<60	338 (26.7)
	60-64	301 (23.8)
	65-69	370 (29.2)
	70-74	216 (17.0)
	75-79	42 (3.3)
Deprivation quintile	1	316 (24.9)
	2	214 (16.9)
	3	271 (21.4)
	4	230 (18.2)
	5	233 (18.4)
	Unknown	3 (0.2)
Ethnicity	White	847 (66.9)
	Asian or Asian British	44 (3.5)
	Black or Black British	99 (7.8)
	Mixed	11 (0.9)
	Any Other Ethnicity	10 (0.8)
	Unknown	256 (20.2)
Charlson co-morbidity index	<1	977 (77.1)
	1-5	243 (19.2)
	>5	47 (3.7)

Table 1. Demographics of patients undergoing Radical Prostatectomy

Risk profile

BMI information was available electronically for 966 (76.2%) patients. Of these 49.8% were overweight followed by 32.3% who were obese; 17.4% patients were within the normal range and 0.5% were underweight.

TURP was performed in 0.6% patients prior to radical prostatectomy. Radiotherapy was administered in 0.2% of patients prior to prostatectomy.

Pre-operative PSA was identified for 1029 (81.2%) patients. Of the available results, median pre-operative PSA was 7.7 (IQR 5.2-11.2); the majority of patients (42.6%) had a PSA between 6 and 10 followed by 28.5% patients between 11 and 20. There were 0.5% patients with a PSA > 50 and 23.8% with a PSA between 0 and 5 (table 2).

PSA	n (%)
0-5	245 (19.3)
6-10	438 (34.6)
11-20	293 (23.1)
21-50	48 (3.8)
> 50	5 (0.4)
Unknown	238 (18.8)

Table 2. Table displaying pre-operative PSA

T2 was the most common stage of prostate cancer, 31.6% patients had T2 prostate cancer. Similar rates of T1 and T3 were observed, 23.4% and 22.7% patients respectively. There were 0.1% patients with T4 disease and 22.1% patients had unknown T staging (table 3).

T-Stage	n (%)
T1	297 (23.4)
T2	401 (31.6)
T3	288 (22.7)
T4	1 (0.1)
Unknown	280 (22.1)

Table 3. Table displaying pathological T-stage

Surgical data

A laparoscopic approach was undertaken in 29.0% patients, 5.7% patients were robotically assisted and the remainder, 65.3%, were open prostatectomies.

The duration of the operation was available for 967 (76.3%) cases. Median operative time was 3.4 hours (IQR 3.0 – 4.2); the longest procedure was 8.6 hours and the shortest was 1.0 hour.

Complications

Blood transfusion following procedure was required in 2.1% patients. The median volume of blood transfused post-operatively was 700ml (IQR 560 -1120). The most frequent 30-day complication was abdominal organ injury, which occurred in 1.8% patients, followed by haemorrhage in 0.6%. Ileus occurred in 0.4% patients and 0.2% had wound infection. Urinary retention occurred in 0.3% patients.

Biochemical recurrence and survival

A PSA level reported greater than 6 weeks post-operatively was identified in 1052 (83.0%) patients. Of these, biochemical recurrence was identified in 17.2% of patients: 9.8 % occurred by 1 year post-operatively and 171/543 (31.5%) patients had biochemical recurrence by 5 years.

Overall survival at 8 years was 94.2% crude and 99.8% age adjusted. 5-year survival, crude and unadjusted, was 96.6% and 99.9% respectively.

Recurrence free survival (RFS) for the cohort was examined. At 8 years median survival was not reached, crude recurrence free survival was 75.4 (88.5% age adjusted). RFS at 5 years was 82.6% and 92.1%, crude and age adjusted respectively (figure 1.).

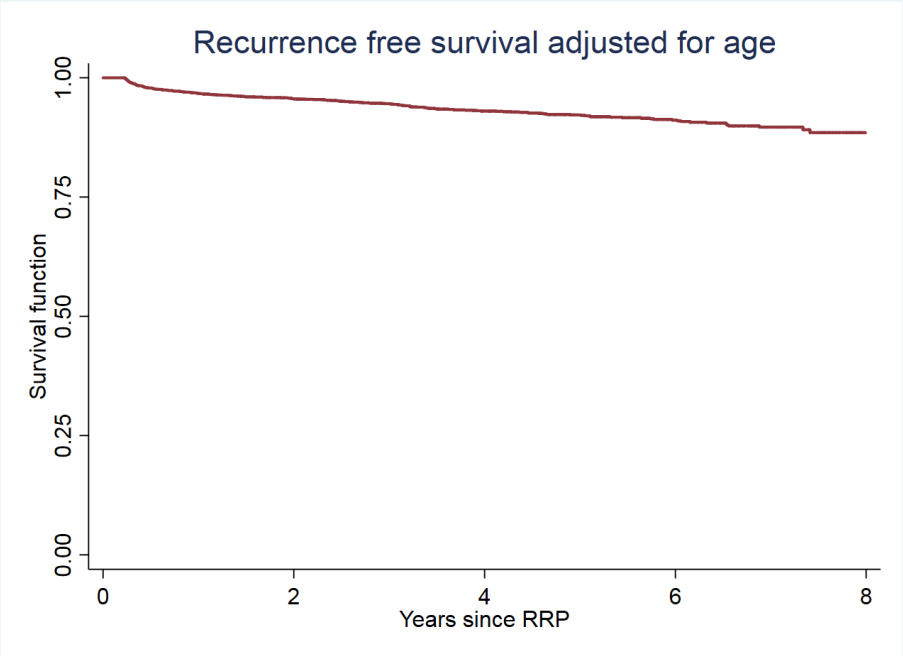

Figure 1. Kaplan-Meir curve for age adjusted biochemical recurrence free survival

Discussion

This study has been able to create a large cohort study of patients undergoing radical prostatectomy using only informatics-based techniques. The initial challenge with this study was identifying the optimal database to identify a primary cohort to link data to. Consideration of the datasets primary functions was therefore a key factor in devising the search strategy. The electronic health record is primarily used as a communication system for efficient working between clinical staff. The database is automatically populated, consequently, although the data is rich and granular there is a great deal of noise and "missingness"[10]. The routine data are designed to be an accurate record of events, manually inputted by trained clinical coding staff, in order for hospitals to claim financial reimbursement; accuracy of the surgical coding at this institution is high[11]. Therefore, routine administrative data serves as a robust starting point for cohort identification.

Subsequently, data linkage was successful, only 2 surgical patients were missing from the electronic health record data. Prostatectomies with missing durations were performed prior to implementation of the theatre administrative database. These small amounts of missing data have highlighted the completeness of administrative data and the ability to link databases to it.

Electronically recorded laboratory results can be used to identify trends as well as clinically significant events in a large cohort. Manual review of clinical notes for over 1000 patients would be resource intensive and laborious for those charged with this task. Through use of the laboratory results in the EHR, this study has been able to observe the biochemical recurrence. This study has been able to retrospectively identify those patients who

experienced biochemical recurrence and those who went on to have further treatment. Timing of recurrence is clinically relevant for counselling of patients to the natural history of prostate cancer following treatment. Therefore, as well as electronic blood results increasing efficiency of data collection/analysis, they provide a basis for alerts speeding up recognition of significant events.

Risk stratification adds a level of detail to surgical outcomes that contextualises results; it is an important consideration in interpretation of results. In addition to pre-operative PSA, obesity is considered a complicating factor for prostatectomy due to a technically more challenging operation[12]. Height and weight are traditionally stored on a bedside observational chart; in this instance the electronic health record has allowed access to data that would not typically be available in retrospective studies. Cancer staging is another key measure of risk or likelihood of cancer success. Multidisciplinary team working within the NHS improves outcomes by ensuring evidence-based approaches to all cancer cases[13,14]; this generates a further data source for linkage. For the three quarters of men with cancer staging information, more meaningful outcomes can be discerned; the remaining patients may benefit from multiple imputation techniques to create sensible assumptions regarding the data[15]. Risk stratification data can be obtained for most patients and clinically relevant variables for most cancers can be obtained through database linkage.

Prescriptions and drug administration in the hospital are recorded, with the exclusion of chemotherapy and radiotherapy, within PICS. The transfusion data are an example of how this can be used to generate meaningful outcomes. As well as volume of blood transfused and when it was administered, the time of prescription can also be analysed. It was possible in the algorithm used in this instance, to filter on only those prescriptions that were administered.

The EHR in this institution requires visual, verbal and computerised identification of patients, giving confidence that the correct prescription data is being identified; although inevitably it cannot rule out human error, such as prescriptions written for the wrong patient. Drug errors are rare occurrences within an electronic prescribing system[16].

The duration of a procedure is correlated with increased risk of surgical site infection and can allude to surgeon experience or complexity of the case[17,18]. The theatre administration system can be used to interrogate all aspects of a patient's operative experience. Times include but are not limited to: time called from ward, time into anaesthetic room, time to knife to skin, time into recovery and time sent back to ward. This allows for very granular examination of all temporal aspects of theatre cases; henceforth close review of efficiencies within the theatres system. There were a number of patients from the administrative cohort where the operation was not identified in the theatre database. This is a further example of "missingness" in electronic databases which are automatically populated.

Additional measures, such as sarcopenia, nutritional status, hand grip strength, and frailty, are now recognized as important predictors of surgical outcomes and postoperative length of stay[19–22]. These factors collectively indicate a patient's physiological reserve. Whilst nutritional status can roughly be identified from BMI and blood results, a comprehensive evaluation often requires detailed imaging or clinical assessments, and are considered on a case-by-case basis[23].

Other limitations identified are as follows: There may be some under coding of radiotherapy events, payment by results was implemented later in outpatient interactions than inpatient[24,25]; therefore, earlier events of radiotherapy may not be captured. Hence, it may lead to

underestimation of patients who proceed to salvage radiotherapy. There was also some missing data in the supporting datasets; likely due to patients referred from other centres, where they would have had their pre-operative investigations and follow-up. Data storage format can create difficulties in comparison of variables; in particular the format of lab results[18]. Implicit conversion of string values to numeric cannot always occur; for example, PSA may be stored as "<0.01" or "NA". Hormone treatment forms the basis of treatment for nearly all biochemically recurrent prostate cancer and plays a role in adjuvant and neo-adjuvant therapy[26–28]. This is typically administered in the community and would not be recognised by the hospital data systems.

Summary

This study has been able to utilise data from a number of different data sources in order to create a clear picture of radical prostatectomy outcomes. Careful selection of data source order was required in order to ensure the primary outcomes were successfully evaluated. Through linkage of datasets risk stratification gave context to the results. Administrative data provides the most accurate record of events due to its intended purpose; EHR data supplements the relevant data fields well, however there is too much "noise" and "missingness" to identify an initial cohort. Informatics research can support clinical research but at this institution cannot replace case-note review completely.

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Chapter 4 manuscript two: Assessing selection bias in outcomes for muscle-invasive bladder cancer: A tertiary centre experience

Introduction

Cystectomy has long been considered the gold standard management of muscle invasive bladder cancer. This view was formulated on historic retrospective series, yet patients selected for surgery are typically those patients that are younger and with fewer comorbidities than the general bladder cancer population. This study aims to assess selection bias between cystectomy and radiotherapy for primary treatment of locally advanced bladder cancer.

Materials and methods

This is a single institution study, from January 2011 - June 2018, of patients receiving radical treatment for muscle invasive bladder cancer. Radiotherapy patients were identified from the LINAC machine prescription history and cystectomy patients were identified within the routine administrative data using OPCS-4 codes. Patient notes were reviewed to find pre-op cancer stage for all cystectomy patients. Propensity matching and survival analysis (Cox proportional hazards) were performed in STATA 15.

Results

128 primary cystectomies were performed for MIBC with a median age of 67 (IQR 59-74) and the Charlson comorbidity index (CCI) was >5 in 22.6%. Radical radiotherapy was delivered to 336 patients. Median age was 76 (IQR 69-82) and the CCI was > 5 for 24.1% of patients. Crude 5-year survival for cystectomy and radiotherapy were was 52.8% and 32.0% (83.7% and 55.8% age adjusted), respectively. There were 85 equally matched pairs following propensity score matching: 5-year survival was 49.1% for matched cystectomy patients (55.7% with neo-adjuvant chemotherapy and 47.3% without). Matched radiotherapy

patients had a 5-year survival of 42.2% (53.5% with synchronous chemotherapy and 37.8% without).

Conclusion

Patients undergoing radical cystectomy are younger and fitter than those undergoing radiotherapy. This indicates there is a selection bias; survival advantage following surgery cannot be based upon cohort studies.

Introduction

Cystectomy has long been viewed as the gold standard treatment for non-metastatic muscle invasive bladder cancer (MIBC)[1]. This opinion has been formed on the basis of limited data, predominantly from retrospective cohort studies that are likely subject to selection bias[2–6]. Patients undergoing radical cystectomy are typically younger, fitter and less comorbid than their counterparts who undergo primary radical radiotherapy[7].

Selection of treatment modality for radical bladder cancer therapy must take into account host factors, disease factors, provision of services and most importantly patient choice. Therefore, it is difficult to construct an ethical randomised control trial, when informed consent and suitability for treatment are a key part of the treatment selection process. Furthermore, systematic reviews are limited by heterogenicity of studies and a high degree of publication bias[7].

Propensity score matching is a technique employed in order to balance and create homogenous cohorts within studies[8]. It can be utilised to reduce selection bias in situations where randomisation is not feasible or unethical[9], such as this.

The aim of this study is to consider case bias between patients undergoing primary radical cystectomy or radical external beam radiotherapy (EBRT) for MIBC within a single tertiary cancer unit and outcomes for these populations

Methods

Data sources

Hospital interaction data (HID) contains all administrative data pertaining to a hospital stay in a longitudinal format, for the purposes of billing. Demographics data, procedural and diagnostic information is captured, using *International classification of diseases version 10 (ICD-10) codes* and *Office of Population Census and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) codes*.

The linear acceleration (LINAC) is used to deliver EBRT and contains an accurate prescription and delivery record. This was used to identify a gold standard cohort of patients. Both cystectomy and radiotherapy coding in the HID for these cohorts was validated in another study and showed a high accuracy of data[10].

Radical cystectomy cohort

All patients undergoing cystectomy between 1/1/2011 and 30/6/2018 were identified in the HID. Patient notes were manually reviewed for indication and staging and those with non-muscle invasive bladder cancer (NMIBC), partial cystectomies and those without bladder cancer (i.e., cancers originating from the prostate only or benign conditions) were excluded. The cohort was compared with the LINAC prescription data and those with prior radiotherapy for bladder cancer were excluded

Radical radiotherapy cohort

All patients prescribed radiotherapy for bladder cancer between 1/1/2011 and 30/6/2018 were extracted from the LINAC machine.

Patients with palliative prescriptions were excluded from analysis as were those undergoing salvage EBRT (identified from cystectomy cohort). The Charlson comorbidity index (CCI) was calculated from the closest inpatient episode to the data of EBRT commencement.

Data variables

Age, sex, ethnicity and comorbidities were extracted from the HID. The CCI was calculated, with a modification to exclude cancer, as previously validated in other studies[11,12]. Whether a patient underwent neo-adjuvant chemotherapy for surgery or adjuvant chemotherapy for radiotherapy were identified from the HID. Date of death was obtained from the NHS spine.

Statistical analysis

All statistical analysis was performed in Stata® version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

Propensity score matching was performed using age, sex and comorbidities. Three cohorts have been analysed: 1. Total unadjusted cohort, 2. Propensity score matched, 3. Patients where an appropriate match was not found, referred to as the unmatched cohort. Kaplan-Meir curves were constructed.

Please note the outcomes for the unadjusted cohorts should not be compared and have not been in this study

Ethics

This study was registered with the clinical audit registration and management system (CARMS) at University Hospitals Birmingham NHS Foundation Trust

Results

Total cystectomy cohort

There were 222 primary cystectomies performed at the single centre, 166 of these were for malignant disease. Of those performed for cancer 128 (77.1%) were for patients with T2 or above disease (MIBC); these were included in analysis

Median age at the time of surgery was 67 (IQR 59-74). Ages were calculated within comorbidity groups, median ages were 66, 67.5 and 69 for those with a CCI of 0, 1-5 and >5 respectively. There were 47 (36.7%) patients with at least one comorbidity, that was recognised as part of the CCI, recorded (Table 1).

With regards to ethnicity, patients with a recorded ethnicity of white constituted 117 (91.4%) of the cohort, 6 (4.7%) patients were recorded as Asian or Asian British and 1 (0.8%) patient was recorded as Black or Black British; 4 (3.2%) patients were other or unknown ethnicity (Table 1).

Total radiotherapy cohort

Within the LINAC machine there were 569 patient prescriptions for radiotherapy with a diagnosis of bladder cancer. Of these 336 (59.5%) were radical treatments directed at the primary tumour site; these were the patients examined.

Median age was 75.5 (IQR 69-82) at time of index treatment. There were 179 (53.3%) patients with no comorbidity recorded, that contributed towards the CCI. Of these, median ages were 74, 76 and 77 for those with a CCI of 0, 1-5 and >5 respectively (Table 1).

Propensity matched cohort

Following propensity matching on age, sex and comorbidity, there were 83 matched pairs identified. These had a median age of 69 (IQR 64-75) and the majority of patients were male – 63 (75.9%). The CCI was 0 in 56 (67.5%) of patients (Table 1).

Cystectomy patients without a match

There were 45 cystectomy patients that had no corresponding individual, with identical age, sex and CCI. The median age was 45 (IQR 55-65) and 25 (55.6%) had no recorded comorbidities. There were 34 (75.6%) male patients and 38 (84.4%) had their ethnicity recorded as white (Table 1).

Radiotherapy patients without a match

The cohort of unmatched radiotherapy patients consisted of 253 patients with a median age of 79 (IQR 72-83). Within this cohort 123 (48.6%) had no recorded comorbidities. Males made up 184 (72.7%) of the cohort and 186 (73.5%) of patients were white (Table 1).

The ages of the unmatched cystectomy and unmatched radiotherapy are compared in figure 1.

Demographic		Overall Cohort (464)		Propensity matching			
				Matched		Un-matched	
N (%)		EBRT	Cystectomy	EBRT	Cystectomy	EBRT	Cystectomy
		336	128	83	83	253	45
Age (yrs)	Median age	75.5	67	69	69	79	59
	IQR	69 - 82	59-74	64 - 75	64 - 75	72-83	55-67
Gender	Male	247 (73.5)	97 (75.8)	63 (75.9)	63 (75.9)	184 (72.7)	34 (75.6)
	Female	89 (26.5)	31 (24.2)	20 (24.1)	20 (24.1)	69 (27.3)	11 (24.4)
Ethnicity	White	256 (76.2)	117 (91.4)	70 (84.3)	79 (95.2)	186 (73.5)	38 (84.4)
	Non-white	80 (23.8)	11 (8.6)	13 (15.7)	4 (4.8)	67 (26.5)	7 (15.6)
Charlson score	<1 (no co-morbidities) [Median age]	179 (53.3) [74]	81 (63.3) [66]	56 (67.5)	56 (67.5)	123 (48.6) [79]	25 (55.6) [55]
	1-5 [Median age]	76 (22.6) [76]	18 (14.1) [67.5]	10 (12.0)	11 (13.3)	66 (28.0) [79]	7 (15.6) [55]
	> 5 [Median age]	81 (24.1) [77]	29 (22.6) [69]	17 (20.5)	16 (19.2)	64 (25.3) [80]	13 (28.8) [69]

Table 1. Demographics table displaying the characteristics of all cohorts

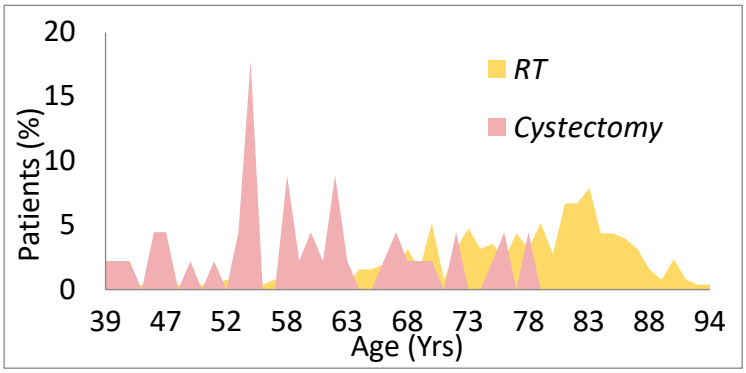

Figure 1. Graph plotting age in years against frequency within the unmatched cohorts, separated by cystectomy and EBRT

Survival

Crude 5-year survival within the total cohort of cystectomy patients was 52.8% (Table 2), however when age adjusted was 83.7% (Figure 2). Patients who received neo-adjuvant chemotherapy had a 5-year survival of 99.1% as compared to 61.8% who did not, when adjusted for age (Figure 2).

Crude 5-year survival for all radiotherapy patients was 32.0% (Table 2). When adjusted for age, overall 5-year survival was 55.8%: 74.3% for those who received chemotherapy and 45.3% for those who did not (Figure 2).

	EBRT	Cystectomy	HR	*p* =
Overall	32.0%	52.8%	N/A	N/A
Matched	42.2%	49.1%	1.04	0.872
Un-matched	28.1%	56.9%	1.70	0.038

Table 2. Crude 5-year survival displayed for all cohorts

Within the matched cohorts there was no statistically significant difference in crude 5-year survival of 42.2% and 49.1% for EBRT and radical cystectomy respectively (Table 2). However, within the unmatched cohorts there was with the survival being 28.1% and 56.9% for EBRT and cystectomy respectively (Table 2).

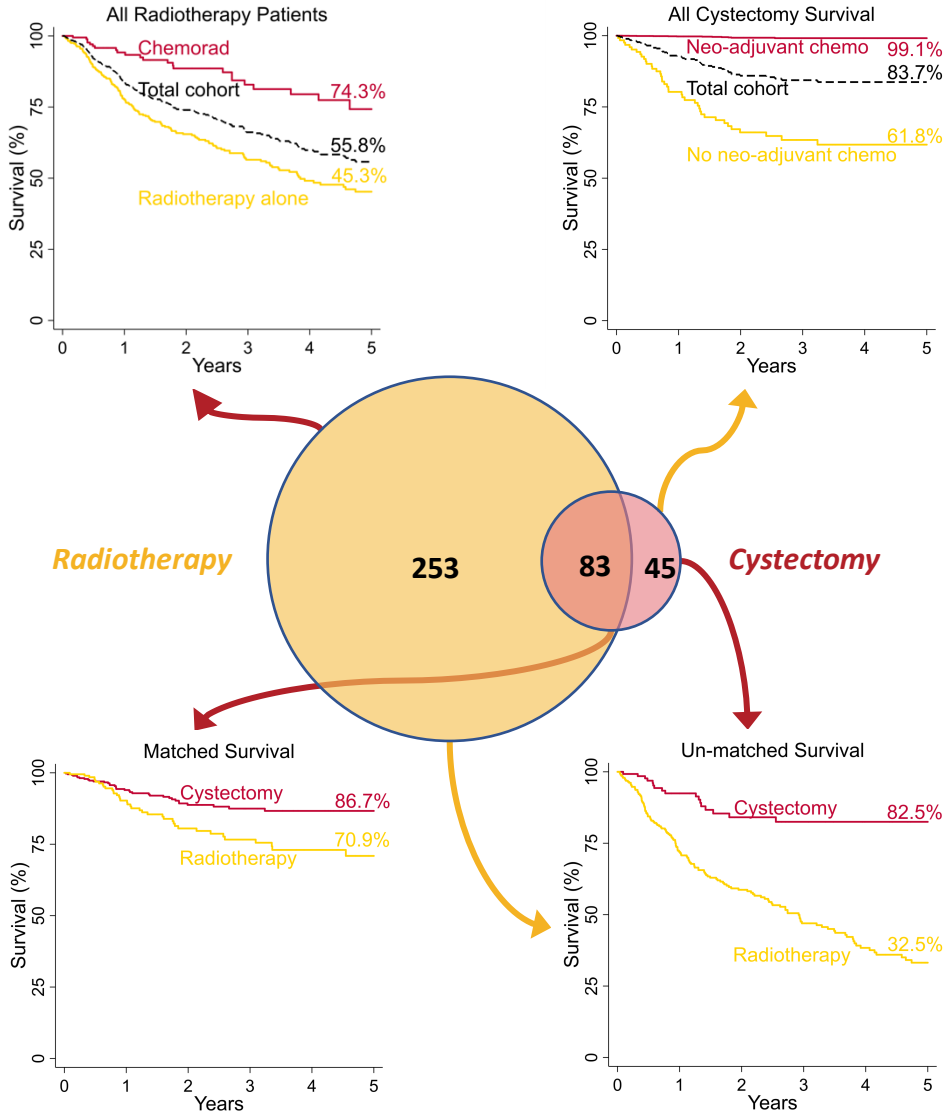

Figure 2. Venn diagram displaying size of cohorts and age adjusted Kaplan-Meir Curves

Discussion

This study has shown that patients undergoing radiotherapy are typically older and less fit than those who are treated with radical cystectomy, in the context of muscle invasive bladder cancer. The patients identified in the matched cohort are those who are likely to be fit for EBRT or surgery, where treatment selection was not influenced by age or comorbidities. Whereas the patients that were not matched, in the EBRT cohort, have been shown to be older and less fit than their unmatched cystectomy counterparts.

There was no significant survival difference in the matched cohort between those receiving EBRT and radical cystectomy. This is similar to the findings of other studies that have used propensity score weightings to create homogenous cohorts to answer this question[13]. Further adding weight to the hypothesis that radical radiotherapy itself is not inferior to radical cystectomy as a treatment modality, in terms of oncological outcomes.

Other considerations to treatment selection will include renal function, bladder and bowel function and pre-treatment sexual function. Patients undergoing treatment with radical RT, may experience a worsening in any pre-existing bladder and bowel symptoms[14]. However, those looking to preserve maximum sexual function may opt against surgery, in particular male patients where the prostate is also resected.[15,16] Surgery also carries a risk of worsening renal function due to the loss of anti-reflux mechanism within the ureters[17]. These could not be accounted for in the present study.

There are over 10,000 diagnoses of bladder cancer per year[18], of which it is estimated 1 in 4 is muscle invasive[19]. Cystectomy however, is very much a treatment reserved for the minority

of patients[20], as further shown by this study, that are fit for major pelvic surgery. Despite this the majority of research for locally advanced bladder cancer is based around surgical outcomes. This highlights the unmet need for research to advance radical radiotherapy outcomes, which would benefit the majority of patients.

There are a number on strengths within this study. The HID data has been shown to be very accurate in previous studies. Furthermore, by taking data directly from the LINAC machine we can be sure of a complete and accurate radiotherapy cohort.

Given that all patients are from the same institution, they will have been subject to the same multidisciplinary team process. Therefore, this uniformity within the decision making and treatment options recommended to patients, is likely to reduce confounding.

Propensity score matching has allowed comparison of patient cohorts that would not typically be able to be compared. By reducing confounding variables, more meaningful conclusions can be drawn. Caution however must be taken in trying to interpret these, as not all confounding variables are eliminated.

There were a number of limitations to this study, as follows: The data can only be considered level 3 evidence at best, as it cannot replicate the conditions of a randomised control trial. Full pathological T-staging is not available for radiotherapy patients; hence pre-treatment staging cannot directly be compared. This was a study using informatics techniques, however given missingness in the staging data for cystectomy specimens, manual case note review was required.

Summary

Due to significant differences in patient populations, radical radiotherapy cannot be declared as having inferior oncological outcomes to radical cystectomy. These differences in patient characteristics highlight the careful consideration of patient fitness by surgeons, prior to undertaking major surgery for bladder cancer. More research is required in the area of radical radiotherapy to better understand mortality and outcomes.

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CHAPTER 5: COMPLEX CODED PROCEDURES WITHIN ROUTINE ADMINISTRATIVE DATA

In this chapter I present a manuscript regarding retroperitoneal lymph node dissection for testicular cancer. This is a rare procedure performed in few centres and there is no defined surgical coding for it. Due to this, existing case series are small and underpowered. This chapter displays how these patients can be identified in administrative data, in order to build larger cohort studies.

This project was presented at the *European Association of Urology Annual Congress, Barcelona 2019*, where it was awarded "Best Poster" in the section *Testis cancer: Complex problems - here are the solutions!*

Special acknowledgement is given to Miss Felicity Evison, who developed the original algorithm used in this study.

Chapter 5: A national study of post-chemotherapy retroperitoneal lymph node dissection (RPLND) for non-seminomatous germ cell tumours (NSGCT) of the testis, considering the site of metastasis and survival outcomes

Introduction

In England RPLND is a rarely performed, complex procedure indicated for resection of 1cm or greater residual masses following chemotherapy for NSGCT. Extra-pulmonary visceral metastases (EPVM) are associated with poorer survival following testis cancer treatment. This study aims to examine outcomes in England for patients undergoing RPLND.

Materials and methods

An algorithm has been developed in order to identify patients undergoing RPLND within Hospital Episode Statistics (HES). All patients identified between April 2001 and March 2018 were included within the study. Demographics, mortality and metastasis data were extracted. Survival analysis was performed in STATA 15.

Results

A total of 2049 patients were identified, of which 18.8% patients were over 50 years old. There were 87.6% of patients with no recorded co-morbidity and re-do RPLND was performed in 5.8% patients. EPVM were present in 10.8% patients and 8.0% had pulmonary metastasis only. In patients where orchidectomy preceded chemotherapy, the median time between them was 6 weeks.

Having residence in a less socioeconomically deprived area was associated with improved survival [IMD quintile 5, HR 0.67, 95% CI 0.45-0.96, $p = 0.031$]. Increasing age [HR 1.06, 95% CI 1.05-1.07, $p < 0.001$] and Charlson comorbidity score > 5 [HR 1.60, 95% CI 1.01-

2.52, $p = 0.043$] were associated with poorer survival. Furthermore, as compared to patients with nodal metastases only, poorer survival was observed in EPVM [HR 3.21, 95% CI 2.36 – 4.38, $p < 0.001$] and pulmonary metastasis [HR 1.97, 95% CI 1.30 – 2.98, $p = 0.001$].

Conclusion

Extra-nodal metastasis is associated with poorer survival following RPLND, as are increasing age and comorbidities. Re-do RPLND is not associated with poorer survival and should be considered where indicated. Patients in less deprived areas have lower mortality and this may indicate health inequality in England for patients undergoing RPLND.

Introduction

Testicular cancer is a relatively rare malignancy contributing to less than 1% to all cancer cases in the UK[1]. It does however present a key concern within urological oncology due to its peak incidence in young and middle-aged males[1]. Amongst its histological variants, non-seminomatous germ cell tumours (NSGCTs) of the testis are particularly significant given their aggressive nature and potential for metastases, primarily to the retroperitoneal lymph nodes.

Platinum based chemotherapy revolutionised the treatment of nodal disease due to testicular cancer. Hence retroperitoneal lymph node dissection (RPLND), in England, is used almost exclusively for post-chemotherapy residual mases >= 1cm for NSGCT. It is a technically demanding surgery offered in only a few tertiary centres within England, typically at a low volume[2]. Whilst there is no universal consensus on recommended surgeon volume, there is evidence to suggest, as with all complex surgery, there is a volume-outcome effect[3].

Visceral metastasis site is of considerable importance for patients undergoing RPLND. Pulmonary metastases have been considered favourable over other visceral metastases, as they indicate a likely favourable response to chemotherapy. The International Germ Cell Cancer Collaborative Group (IGCCCG) produced prognostication prediction models for NSGCT, predicting those patients with non-pulmonary visceral metastasis (NPVM) have inferior survival to those with pulmonary metastasis only[4,5].

The aim of this study is to consider the changing trends in provision of RPLND in England and factors associated with poor mortality post-operatively.

Methods

Hospital Episode Statistics

Hospital episode statistics (HES) is a data repository of all patient interactions with NHS secondary care in England. Data are organised into chronological episodes and spells. A spell is the entire admission, made up of a single or multiple episodes, which is the time spent under the care of a particular named consultant. Demographic data is stored according to HES coding, procedural and diagnostic data are stored as Office of Population Census and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) codes and international classification of diseases version 10 (ICD-10) codes respectively. All data items of < 6 patients are censored in accordance with HES guidance, to protect patient confidentiality.

Algorithm

An algorithm was devised to identify patients undergoing RPLND for testis cancer. It was previously validated against a gold standard case series maintained with University Hospitals Birmingham NHS foundation trust: Sensitivity for this case series was 90.3%, specificity was 100% [Unpublished].

Cohort

The algorithm was applied to all HES episodes from 1st April 2001 to 31st March 2018. Data cleaning to exclude patients with missing demographic data and those without follow-up in England was performed as part of the extraction. The algorithm itself ensured all patients had a diagnosis of testis cancer.

Demographics

Age, sex, gender, coded ethnicity and index of multiple deprivations (IMD) quintile were extracted for demographic data. Comorbidities were extracted to calculate the Charlson comorbidity index (CCI), modified in order to exclude cancer; this technique has been validated in multiple other HES studies[6,7].

Variables and outcomes

Incidence of RPLND and total testis cancer by year was calculated. Time between relevant treatments, such as orchidectomy, chemotherapy and RPLND, was calculated in weeks.

Site of metastasis was identified using ICD-10 coding, these were categorised as per organ system. Patients were separated into three sub-cohorts: those with no visceral metastasis, patients with pulmonary metastasis only (in addition to retroperitoneal lymph nodes) and those with extra-pulmonary visceral metastasis (EPVM). Patients with both pulmonary metastasis and other visceral metastasis were classified as EPVM.

Mortality Outcomes

Crude 30- and 90-day all-cause mortality were extracted. A cox survival regression analysis to include clinically relevant variables was performed in STATA 15, in order to generate hazard ratios. A Kaplan-Meir survival curve was generated to compare long term survival of cohorts depending on site of metastasis.

Ethics

Approval to use HES data was granted by the Health Informatics Request Review Group at University Hospitals Birmingham NHS Foundation trust.

Results

National trends

There was a 184% increase in the number of RPLND procedures identified over the study period, with 85 identified in 2002 and 156 identified in 2017 (Figure 1). The incidence of first testis cancer diagnoses also increased by 10% over the study period, with 1,813 diagnoses in 2002 and 2,001 diagnoses in 2017 (Figure 1).

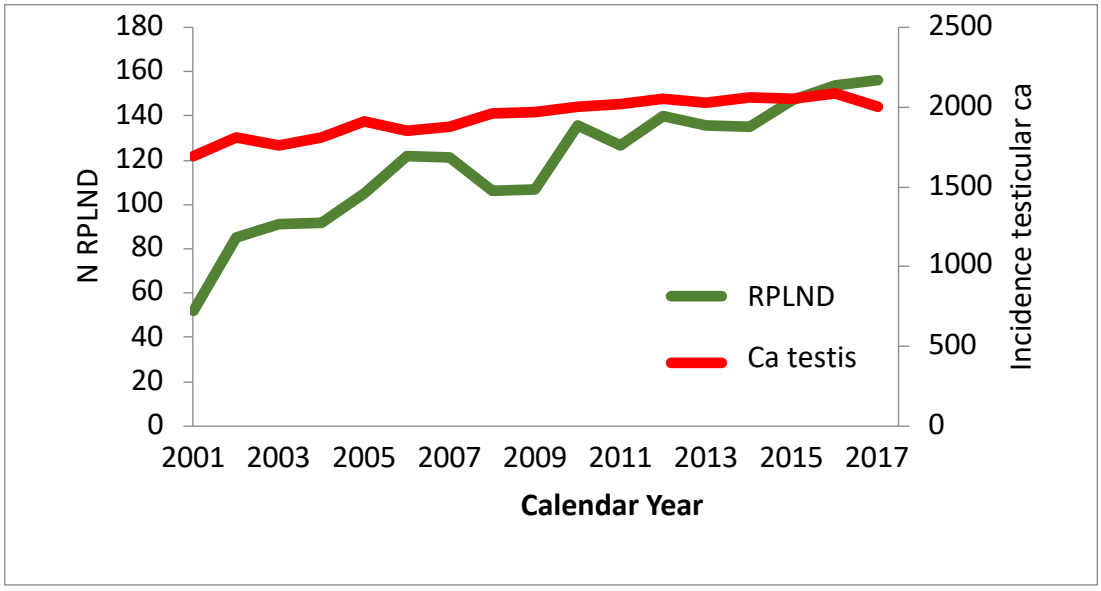

Figure 1. Graph showing the number of RPLND and incidence of testis cancer by calendar year

The median time from orchidectomy to initiation of chemotherapy was 6 weeks. Following initial chemotherapy, median time to RPLND was 17 weeks. For those patients that had further RPLND procedures had a median time of 64 weeks from first RPLND to second procedure.

Cohort

There were 2,049 patients identified by the algorithm as undergoing RPLND following testis cancer diagnosis. The majority of patients, 1663 (81.2%), were under 50 years old and only 255 (12.4%) patients had a recorded comorbidity. Patients with ethnicity recorded as white made up 1,845 (89.1%) of the cohort, followed by Asian/Asian British with 81 (4.0%) patients. There was no trend in provision of procedures split by socio-economic deprivation status (Table 1).

The most common comorbidity was pulmonary disease, followed by diabetes mellitus (Table 2).

Few patients underwent multiple procedures: 106 (5.2%) had a second RPLND procedure and 12 (0.6%) had three or more procedures (Table 1).

Learning difficulties were recorded in 39 (1.9%) of patients (Table 1).

Demographic		N (%)
N = 2049		
Age	**<=20**	141 (6.9)
	21-30	699 (34.1)
	31-40	484 (23.6)
	41-50	339 (16.5)
	> 50	386 (18.8)
Deprivation quintile	**1**	396 (19.3)
	2	406 (19.8)
	3	426 (20.8)
	4	427 (20.8)
	5	390 + * (19.0 + *)
	Unknown	< 6
Ethnicity	**White**	1845 (89.1)
	Asian or Asian British	81 (4.0)
	Black or Black British	10 (0.5)
	Mixed	19 (0.9)
	Any Other Ethnicity	38 (1.9)
	Unknown	56 (2.5)
Charlson co-morbidity score	**<1**	1794 (87.6)
	1-5	194 (9.5)
	> 5	61 (3.0)
Number of RPLND	**One**	1931 (94.2)
	Two	106 (5.2)
	Three or more	12 (0.6)
Metastasis	**Nodal only**	1664 (81.2)
	EPVM	222 (10.8)
	Pulmonary only	163 (8.0)
Learning difficulties	39 (1.9)	

*Table 1. Demographics table of whole cohort - * numbers <6 suppressed in accordance with HES guidance*

Co-morbidity	N (%)
Acute MI	21 (1.0)
Stroke/TIA	< 6
Heart failure	< 6
Connective tissue disorder	6 (0.3)
Diabetes	49 (2.4)
Liver disease	< 6
Vascular disease	21 (1.0)
Pulmonary disease	144 (7.0)
Renal disease	29 (1.4)

Table 2. Table of comorbidities – Numbers < 6 supressed in accordance with HES guidance

Site of metastasis

The majority of patients, 1,664 (81.2%) had nodal metastasis only; there were 222 (10.8%) with EPVM and 163 (8.0%) had pulmonary and nodal metastasis only (Table 1). Of those patients with EPVM the most common sites were multiple metastases, followed by peritoneal metastases; which were 93 (41.9%) and 51 (23.0%) respectively (Table 3).

Organ system	N (%)
N = 222	
Gastrointestinal	< 6
Hepatic	18 (8.1)
Urinary	11 (5.0)
Neurological	< 6
Bone	9 (4.1)
Peritoneal	51 (23.0)
Other	36 (16.2)
Multiple sites	93 (41.9)

Table 3. Table showing sites of EPVM – Numbers <6 suppressed in accordance with HES guidance

Mortality

Crude 30-day and 90-day death occurred in 13 (0.6%) and 39 (1.9%) of patients respectively. On further review of those patients who died within 90 days of RPLND, the demographics represented a high-risk subsection with 64.1% patients > 50 years old and 20.5% had a CCI > 5.

Factors associated with increased risk of mortality following RPLND were: Increasing age by year [HR 1.06, p < 0.001, 95% CI 1.05 – 10.07], Unknown ethnicity [HR 1.84, p = 0.034, 95% CI 1.04 – 3.23], CCI > 5 [HR 1.60, p = 0.43, 95% CI 1.04 – 3.23] and having visceral metastasis: EPVM [HR 3.21, p < 0.001, 95% CI 2.46 – 4.38], Pulmonary only [HR 1.97, p = 0.001, 95% CI 1.30 – 2.98] (Table 4).

When baseline category for metastasis was set as EPVM the results for pulmonary metastasis were HR 0.61, p = 0.041

Living in a less socioeconomically deprived area (IMD quintile 5) was associated with improved survival [HR 0.67, p = 0.031, 95% CI 0.45 -0.96] (Table 4).

All cause, age adjusted survival at 18 years was 98.3%, 96.0% and 94.3% for nodal metastasis only, pulmonary metastasis and EPVM respectively (Figure 2). Median survival was not reached for any sub-cohort.

Demographic		Cox regression for survival		
		HR	***p***	**95% CI**
Age	**<=20**	***Continuous variable, year***		
	21-30	**1.06**	**0.000***	**1.05-1.07**
	31-40			
	41-50			
	> 50			
Deprivation quintile	**1**	***Baseline***		
	2	1.08	0.682	0.75-1.54
	3	0.82	0.281	0.57-1.17
	4	0.74	0.107	0.51-1.06
	5	**0.67**	**0.031***	**0.45-0.96**
	Unknown	1.88	0.537	0.25-13.9
Ethnicity	**White**	***Baseline***		
	Asian or Asian British	1.31	0.401	0.69-2.48
	Black or Black British	0.95	0.946	0.23-3.85
	Mixed	0.36	0.315	0.04-2.63
	Any Other Ethnicity	0.79	0.692	0.25-2.48
	Unknown	**1.84**	**0.034***	**1.04-3.23**
Charlson co-morbidity score	**<1**	***Baseline***		
	1-5	1.06	0.751	0.74-1.50
	> 5	**1.60**	**0.043***	**1.01-2.52**
Number of RPLND	**One**	***Baseline***		
	Two	1.01	0.963	0.61-1.66
	Three or more			
Metastasis	**Nodal only**	***Baseline***		
	EPVM	**3.21**	**0.000***	**2.36–4.38**
	Pulmonary only	**1.97**	**0.001***	**1.30-2.98**

Table 4. Table displaying the results of Cox survival analysis

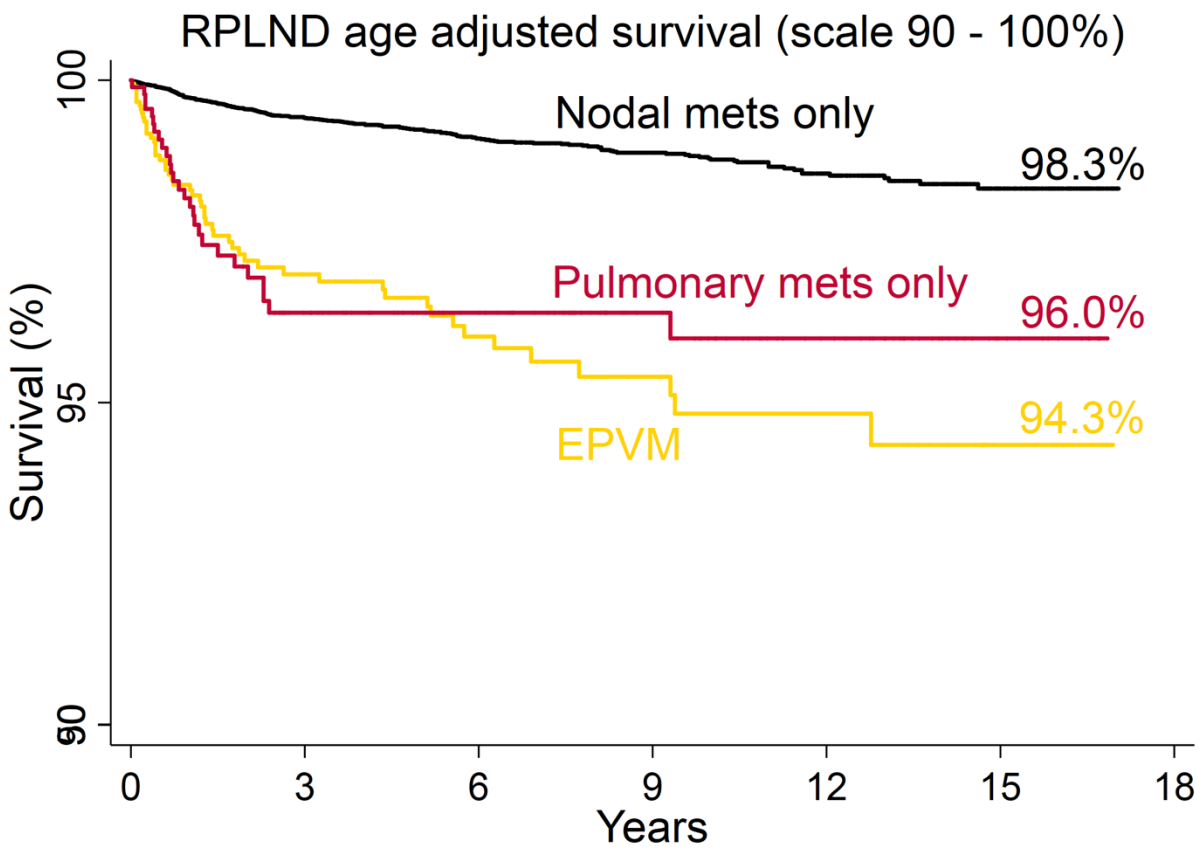

Figure 2. Age adjusted Kaplan-Meir survival curve by site of metastasis. The y axis shows only the 90% - 100% portion of the scale

Discussion

This study has identified an almost two-decade national cohort of patients undergoing RPLND for testis cancer, creating a large cohort with varying degrees of follow up. The aim of this study was to consider the site of metastasis on RPLND survival. It has long been established that EPVM are a poor prognostic factor for advanced NSGCT regardless of treatment modality[4,5,8]. Within this study patients with visceral metastases undergoing RPLND have worse survival outcomes, with EPVM being a poorer prognostic factor than those with pulmonary metastasis. It is important to note however that age-adjusted survival for all cohorts was still high, despite these differences. Therefore, patients must be counselled appropriately and considered for curative treatment even in advanced metastatic disease.

A key negative finding of this study was that re-operation was not associated with poorer survival. The relapse rate following RPLND for NSCGT is estimated at 3-9%[9–11], in keeping with the findings of this study. Patents that have disease recurrence are estimated to have a higher risk of re-recurrence following RPLND[12]; however, they are still recommended to under-go further RPLND resections, with or without salvage adjuvant chemotherapy[13]. As this increased risk of recurrence does not translate into poorer survival, an aggressive and multi-modal approach to relapse, following MDT, is appropriate.

As expected, patients that are old and more co-morbid have an increased likelihood of mortality. Less than 10% of men with testis cancer are aged < 55 at the time of diagnosis[14] and data is extremely limited for patients of this age undergoing RPLND. Studies are typically cross-sectional cohort studies where there are little to no patients over 45 years

old[15,16]. Therefore, this finding, whilst important is not unexpected and has limited application in clinical practice. Patients must be considered on a case-by-case basis.

Within the UK, and the world, the association with socio-economic deprivation and impaired surgical outcomes has been established across a variety of surgical specialties[17–19]. This study has identified that patients with lower levels of socioeconomic deprivation have improved all-cause mortality. Patients living in deprived areas have high levels of mortality from testis cancer itself, with unemployment identified as a key component[20]. Whilst there is a lower incidence of testis cancer overall within this group, as compared to their less socioeconomically deprived counterparts, they do present with later stage disease[20]. Possible reasons for this could be improved education on self-examination and better access to services. It is likely that patients with less deprivation are presenting with less advanced disease, leading to improved RPLND survival outcomes.

The main strengths of this study pertain to having a large cohort with good granularity of data. This study identified the site of metastasis, comorbidity profiles and detailed demographic data. Therefore, a national cohort could be analysed effectively. Current national data sets rely on voluntary self-reporting, therefore there may be an element of missing data. Furthermore, RPLND procedures may be performed by other speciality surgeons with expertise in complex abdominal surgery, who also may not contribute to such a dataset. Through utilisation of HES all NHS interactions with secondary care can be identified.

The limitations of this study are as follows: HES is primarily an administrative dataset therefore important biochemical and staging information is not available. Mortality is all-

cause, so testis cancer specific death cannot be examined. The algorithm was validated at a single centre, as there is no single code, coding practices may differ at other centres. Volume effect could not be accurately examined as most centres are low volume, given the rarity of the procedure.

Summary

EPVM are associated with poorer survival following RPLND, however these patients still experience very good long-term mortality; EPVM should not preclude them from treatment. Aggressive multi-modality treatment should be offered to such patient, at centres with experience of managing advanced testicular cancers.

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CHAPTER 6: DISCUSSION

A detailed discussion of the individual project outcomes is found within each subchapter. This chapter will summarise the overall findings and discuss how the entire body of work fits within existing informatics research, within the United Kingdom and globally. It will also consider the implications of this work and future directions of informatics-based research.

5.1 Hospital Episode Statistics

5.1.1 Summary of studies using Hospital Episode Statistics

Data Validation

Within this thesis, chapters 3 and 5 contained a total of three studies, performed using only data captured by HES; all of which followed a similar broad methodology. The initial step for all projects involved a data-validation exercise, in order to ensure quality of coding, so that the projects were viable. The projects entitled "*A national study of artificial urinary sphincter and male sling implantation after radical prostatectomy in England*" and "*A national study of post-chemotherapy retroperitoneal lymph node dissection (RPLND) for non-seminomatous germ cell tumours (NSGCT) of the testis, considering the site of metastasis and survival outcomes*" were validated on the local dataset. This was achieved by searching for procedures and diagnoses within a specified time period, within HES, and comparing that to manually collected local datasets. This however proved a challenge for the first project within this thesis "*High-intensity Focused Ultrasound for the Treatment of Prostate Cancer: A National Cohort Study Focusing on the Development of Stricture and Fistulae*", as these procedures are not performed at the local provider and are only undertaken in a limited number of centres within the NHS. Whilst it was not possible to validate the procedure itself, it was important to validate the outcomes. Provision of service was an important outcome; however, the focus of the paper was to consider long term complications, in the form of strictures and fistulae. Transurethral resection of the prostate (TURP) was first described in 1926 and many data series have since been published on the rate of post-TURP strictures with an established rate[1–3]. Post-TURP strictures were identified within HES and compared to these published data, thus validating the quality of stricture coding. A number of groups have validated HES data

for research pertaining to, but not limited to: urological surgery, gastroenterology and mental health[4–11]. These are a diverse range of clinical and research specialties, highlighting a high quality of coding throughout HES.

Search Strategy and Data Cleaning

Identification of cohorts, search strategy and data cleaning were imperative to the success of these projects. There was a simple search strategy for coded procedures, such as artificial urinary sphincters, male sling procedures and HIFU for prostate cancer; however, data pre-processing was still a key step. Whilst this reduces the size of the patient cohort it ensures a high level of accuracy in identified patients. For both projects within the first chapter of this thesis, a "show your working" approach was taken to the processing of the initial data. This involved a stepwise process of whitling down, decreasing the cohort with each cleaning rule implemented. The algorithm utilised in the project for chapter 3 required specific criteria within the search, thus cleaning the data during the identification process and presenting a cohort ready for analysis. This was because there was no specific code for RPLND, therefore the algorithm required combinations of testicular cancer diagnostic coding as well lymph node sampling/dissection procedural codes. Further data-cleaning criteria were integrated into this algorithm, such as region of residence, sex and age. Depending on the projects needs either approach is viable. Both require a defined inclusion criteria, however a stepwise approach has the advantage of identifying errors within the data extraction process earlier, through review of data output at each stage.

Managing Repeat Procedures

A particular outcome of interest in oncological surgical research are re-intervention rates[12], this was the case for all HES based studies in this thesis; with it actually being the primary outcome for "*A national study of artificial urinary sphincter and male sling implantation after radical prostatectomy in England*". In order to extract and process data for patients with multiple procedures careful design and planning of data collection tools was imperative, to maintain accuracy and ensure the data was extracted in a useable format. Through my own learned experience throughout performing this body of work all HES based projects involved the generation of a "procedures table" and a "patient table". All relevant information pertaining to admission, such as demographics, procedures and diagnoses, was extracted directly into the "procedures table" at the time of patient identification. This provided a master dataset of all procedures that could be used to perform the initial descriptive analysis for provision and trends in procedures. It also ensured that the further analysis data tool could be aggregated as 1 patient per row, ultimately included as the "patient table". The master dataset was not suitable for data processing, however it did provide a back-up and point of reference should refinements be made to the methodology, increasing efficiency and reducing frequency of access to HES servers. Therefore, a recommendation of this thesis for all HES based studies considering at post-procedure outcomes, would be to generate a master table of all procedures then base an analysis data collection tool for a processed output of this.

Socio-economic Deprivation

In order to contextualise and interpret surgical outcomes, appropriate risk adjustment must be made. This consists of demographic data and clinically relevant variables. HES contains a rich granularity of demographics data with great accuracy. A recent study identified that certain risk criteria, such as comorbidity, was more accurate in HES than surgeon self-reported data[13].

The commonest risk adjustment used by HES based studies are age and gender[14]. Social deprivation has consistently been shown across the United Kingdom and internationally to be associated with poorer outcomes following surgery[15–19]. When conducting HES studies, it is prudent to consider whether inclusion of deprivation is for risk adjustment, or an outcome measure in its own right. Within the HES studies in this thesis, an association with socioeconomic deprivation was seen with increased mortality following RPLND. A similar trend was not seen for development of complications following HIFU or re-operation following AUS. Interestingly an inverse relationship was seen with re-operation or progression to AUS, following a male sling continence procedure. There are a number of explanations to why a clear association was not seen in these studies. HIFU is an experimental treatment offered in limited centres, hence the population undergoing treatment are unlikely to be representative of patients undergoing prostate cancer treatment overall. Furthermore, likelihood of urethral stricture development pertains mostly to peri-operative care[20]; deprivation is less likely to impact this. Therefore, socio-economic status was important for standardising risk adjustment but was not relevant as an outcome measure. For patients undergoing post-prostatectomy continence surgery, the other project in chapter 1, reasons for less deprived patients having a higher re-intervention rate following a sling

procedure should be considered. In this case, re-intervention is a surrogate marker for procedural failure. Whilst the procedure may have failed regardless of socio-economic status, those with lower deprivation may be more likely to have planned revision surgery[21]. Again, highlighting the importance of inclusion of deprivation for risk adjustment but the need for caution when interpreting the clinical implications if considering it as an outcome.

Resource Management and Adherence to Guidelines

Since the conception of HES, it has been used to examine trends in the provision of surgery at a national level, in particular for urological procedures[22,23]. Access to details of hospital trust and truncated patient postcode allows for geo-spatial mapping in addition to temporal description. This function was used for multiple uses within Chapter 1; both projects examined hospital trusts by volume and mapped them onto funnel plots in order to consider the volume effect. When these projects were initially performed hospital postcodes were converted into latitude and longitude, then subsequently plotted onto a scaled map of England. A decision was undertaken to not include these in the final project, as to maintain data privacy. It does however highlight how resource planning and service evaluation can be considered at both local and national levels over time. This is of particular importance and can help to assess the known disparities in commissioning of treatment in different areas of the English NHS, thus driving healthcare policy and equitable access to healthcare[24,25].

The *National Institute of Clinical Excellence* (NICE) is a public body with the remit to provide guidelines and develop quality standards within the NHS[26]. The *Getting It Right First Time* (GIRFT) initiative is a national program aiming to tackle variations in how medical care is delivered within the NHS[27]. It is important that in a broad sense care is standardised,

although there should always be clinician input and judgement utilised for each individual case; this maintains consistent best practice throughout the healthcare system and facilitates continuous improvement. A number of studies have utilised HES in order to review adherence to national guidance[28,29]. Within the project "*High-intensity Focused Ultrasound for the Treatment of Prostate Cancer: A National Cohort Study Focusing on the Development of Stricture and Fistulae*", in chapter one, adherence to NICE guidance was specifically addressed in the discussion. HIFU should only be utilised in the context of research, however the number of NHS providers and patients did not correlate to published research and case series, highlighting it was likely being performed against national guidance; this however could not be confirmed from HES data alone. Data from HES will highlight regions where there is deviation from the standard of care, however thorough analysis of centres is required in order to understand the reasons for this; ensuring the significance of clinical judgement is not undermined.

A brief cost analysis was performed in "*A national study of artificial urinary sphincter and male sling implantation after radical prostatectomy in England*", using the NHS national tariff to estimate cost of procedures. This was included only as a discussion point within this project, however other HES based studies have considered cost within their outcome analysis[30,31]. The accuracy and utility of economic evaluation has been examined and found to be a valid technique, in particular a study examining accuracy of HES for costing PSA testing for prostate cancer[32].

Follow-up

All of the studies involved in chapters 1 and 3 involved procedures that typically require tertiary or even quaternary referral to a specialist centre, where follow up events are likely to be captured at other hospitals. Traditional cohort studies will typically miss these events. The pseudonymisation of data within HES allows patients' entire history of interaction with the English NHS, ensuring completeness of outcome data. NHS digital provide data-linkage for locally collected cohorts, allowing for comprehensive follow up[33]. A number of retrospective and prospective studies have utilised this to enhance the quality of their results and efficiency[34–36].

When summarising the results of the HES based studies, it is important to recognise the practicalities of utilising the data itself. This body of work was performed at a centre where HES data was available in its entirety, providing its use was restricted to be in line with the terms of use and data was only shared in an aggregated form. The reason this was possible was due to the large secure data servers and team of persons managing the data itself. Furthermore, as described in the methods chapter, specialist software was required in order to perform data extraction and processing. This is not necessarily a limitation of HES based studies, however is important when considering HES based research that the appropriate infrastructure and data sharing agreements are in place.

5.1.2 Strengths of studies using Hospital Episode Statistics

In addition to the strengths of HES data that have been touched upon within the summary of projects, there are some key considerations pertaining to the advantages of using HES for research. This can either be studies complete entirely using only HES data and those where

HES data has supported other clinic research. All studies in chapters 1 and 3 of this thesis were completed wholly using HES data and the benefits experienced are summarised:

HES studies generally provide highly powered studies, in particular for rare or centralised procedures. As mentioned earlier, all HES based studies within this thesis pertain to procedures that are either uncommonly performed (RPLND) or those that occur in only specialist centres (HIFU or male continence surgery). The most extensive single database of patients undergoing HIFU for prostate cancer consists of 598 patients[37]. Through utilisation of HES data, chapter one has compiled a case series of 1,742 patients undergoing 2200 procedures; this represents a more than threefold increase in cohort size. Similarly, the largest British case series or study for RPLND consists of around 170 patients[38,39]; compared to 2,049 in chapter 3. This represents a substantial increase in the volume of patient data that is available, highlighting the ability to perform robust evaluation of post-procedure outcomes and complications when utilising HES data.

The ability to capture an almost complete population is huge advantage of HES based data. The populations within Chapters 1 and 3 are likely to encompass nearly everyone in England undergoing male continence procedures or RPLND. Given the restrictions on the use of HIFU in NHS settings by NICE, this is less likely for this cohort but given the wide geography, number of centres and large cohort; it is, however, expected to be a representative sample of patients. This highlights the findings being generalisable to an English population and the ability of clinicians to extrapolate findings to provide higher quality prognostic counselling to their patients. Ultimately validation of the findings against local patient populations by providers would give a measure of how generalisable findings from HES based studies are.

HES data have been stored in a longitudinal manner since 1990[40], therefore patient outcomes can be examined over extended periods of time. This is particularly important where follow-up events are rare. Mortality following RPLND is a rare event, given a typically young and fit cohort. Chapter 3 encompassed an almost two-decade period of follow up for patients with RPLND. This allowed for a cohort study rather than a case-control study, that would typically be used for rare event studies. Cohort studies provide a higher level of evidence than other observational studies: they have the advantage of improved exposure measurement, reduced selection bias, the ability to consider temporal relationship and can evaluate multiple outcomes[41,42].

The reproducibility of HES studies highlights their reliability. When initially working with HES data there were multiple drafts of the initial extractions. This was part of the learned experience alluded to earlier within this chapter, until an optimal method of generating procedures and patient tables was established. Following this the same cohort could be extracted using difference techniques to provide the same data. Further to this, given the ability to re-extract identical data, regardless of technique used, existing studies can be expanded to create longer term follow up or examine variables previously not considered with a high degree of accuracy.

5.1.3 Limitations of studies using Hospital Episode Statistics

A particular concern, as mentioned within the introduction of this thesis, when performing clinical research utilising routine administrative data is the lack of clinical detail. In particular cancer staging data, disease factors and operative detail. This is a limitation common to all HES based projects, with other authors commenting on the lack of context when interpreting

surgical outcomes[13]. This was of particular importance when considering discussion of outcomes of HIFU for prostate cancer. The cancer stage and characteristics, for example histological variants, allow for risk stratification, in order to interpret results with understanding of the disease process and prognosis. Furthermore, biochemical PSA recurrence is considered a marker for treatment failure, however for some patients it may be their only sign of disease progression[43,44]. In the absence of local (prostate bed or lymph node) recurrence or metastasis, these events are likely only to be captured in local trust laboratory databases, rather than routine administrative data. Hence, a decision was made to not consider oncological outcomes for this study and focus on complications. In contrast to this for RPLND, mortality as an oncological outcome could be examined. The indication for RPLND, in England, is solely for post-chemotherapy residual masses > 1cm secondary to non-seminomatous germ cell tumours of the testis. Therefore, a reasonable assumption could be made about disease profile. Nonetheless, the lack of biochemical data, for tumour markers, did limit the ability to perform a complete risk stratification[45]. This can have practical implications of the ability of clinicians to offer prognostication to patients based on HES data alone. Linkage of data to other data sources, using patient identifiable local data, is described later in the chapter and proposed as a future solution to this limitation.

Overall data completeness is a concern when performing any database research. In particular with HES data prior to 2008, outpatient data was estimated at 50% completeness then a sudden increase in accuracy[46]. This is likely due to the expansion of the payment by results scheme to outpatient interactions that year. Data accuracy for inpatient procedural coding was found to be high within this thesis and other studies, typically above 90%, although 100% accuracy was not achieved in any so far[4]. In particular, around 17% of male sling procedures not identified in the routine administrative data, highlighting the need for validation studies.

Ideally these would be multisite validations to account for coding variability amongst NHS trusts. It is also important to consider coding variability and change in practice over time. Despite this, datasets are considered accurate, whilst accepting a degree of tolerance must be expected for incomplete and inaccurate data.

Overfitting is a key concern, with regards to data completeness, when utilising algorithmic extractions is and can lead to falsely re-assuring data validation. Overfitting is a concept within machine learning and informatics to describe a predictive algorithm performing too well on training data, preventing it become generalisable. The algorithm provided to me for chapter 3 had a high sensitivity and specificity for detection of RPLND. However, the validation study occurred at the same institution as the development of the algorithm. Hence the inability to quantify the generalisability and the risk of overfitting to a single institution was a limitation.

Pseudonymisation allows for follow up of patients in a longitudinal manner. However certain events are not captured or restricted. Such as those procedures performed in the private sector or patients followed up in Scotland, Wales or Northern Ireland. HIFU for prostate cancer is performed in private centres as well as NHS, therefore studies linking clinical registries to administrative data have been unable to analyse results for these patients[47]. The paediatric dataset, as would be expected, has extra-restrictions placed on its use. It would however have been useful in particular for RPLND outcomes, paediatric diagnoses such as crypto-orchidism and previous scrotal surgery contribute to the risk of developing testis cancer[48].

At the end of each financial year the "*HES annual refresh*" allows NHS trusts to verify and finalise their data upload to *NHS Digital*[40]. This may result in changes to data contained for

the most recent financial year. Thus, limiting the ability to use the most contemporary data for the purpose of research and follow-up.

5.2 Electronic health record and locally stored data

5.2.1 Summary of studies using the electronic health record and locally stored data

Chapter 4 utilised the *PICS* electronic health record that has been developed at *University Hospital Birmingham NHS Foundation Trust* (UHB). The output of which has been utilised to perform clinical research and quality improvement[49–53]. However, linking the EHR to routine data and other administrative databases was a novel concept and one which was achieved in both projects within chapter 4. A total of 6 data sources were successfully linked over both projects. There was some overlap in the data contained within each system's data repositories; the accuracy of the inputted data will depend upon the function of the clinical systems. In order to consider the optimal data source for any given variable, knowledge of how the systems are used and information is inputted is vital. Having experienced all systems in clinical practice, I was able to bring this insight to the projects.

Identifying Cohorts

Surgical and radiotherapy coding at this institution is known to be highly accurate, hence routine administrative data was used to identify cystectomy and prostatectomy events[4]. It was however decided to identify patients undergoing radiotherapy directly from the LINAC prescription, the extract was filtered to only those patients that received radical radiotherapy, to the bladder for bladder cancer. This created a complete and accurate dataset for this patient cohort. *PICS* has been shown to have a large degree of missing data[52], likely due to

diagnostic information being generated automatically at the time of clerking rather than formally coded by trained clinical coders. Although EHRs contain a huge volume of data to build information onto an already identified cohort, they are a less suitable starting point.

Risk Stratification and Cancer Staging

One of the key limitations with performing cancer research in HES was the inability to risk stratify. Therefore, an aim of the studies within chapter 4, where patient data was identifiable and could be linked, was to isolate biochemical and histopathological data in order to provide clinical background to patients. Within chapter 4, the patients undergoing radical prostatectomy were almost completely linked to the *PICS* EHR. Following this a pre-operative PSA level was found in 80% of patients. All patients undergoing radical prostatectomy will have had a PSA blood test pre-operatively, those without a value identified will likely have details within their referral letter from primary care or an external referrer. Likewise post-operative follow-up PSA was again identified in a similar proportion of patients, those without are likely to have their follow up at the original referring centre. The lack of PSA in the HES based HIFU study was a key limitation and was one of the main factors preventing assessment of oncological efficacy.

Cancer staging information is critical to the understanding of post-treatment outcomes. In particular for surgery the T-stage; it is a descriptor of how advanced the primary tumour is. Removal of the prostate or bladder in patients with advanced T stages can be considered more complex procedures with greater difficulty in removing all cancerous tissue and more likely to incur damage to surrounding structures; it can be a predictor of treatment failure or risk of complications. Within the radical prostatectomy project, T-staging was found entirely from

database research and for around 1 in 5 patients a pathological T-stage was not identified within the *Somerset Cancer Registry*. This is data inputted into the registry by clinicians or cancer pathway staff, hence missingness is expected. A manual review of case notes and pathology reports could have been performed on the missing patients, as it was in the project "*Assessing selection bias in outcomes for muscle-invasive bladder cancer: A tertiary centre experience*". All patients undergoing radical radiotherapy would have non-metastatic muscle invasive bladder cancer, therefore review of staging was not required. However, it was important for the clinical conclusions to ensure patients undergoing radical cystectomy were only those undergoing surgery for muscle invasive bladder cancer, to ensure both cohorts had comparable inclusion criteria. Whilst manual case note review is laborious, depending on the volume and importance of missing data, it may be necessary to ensure robust studies. A number of clinical trials automate follow-up data, then verify it manually. This reduces the burden of data-collection whilst ensuring accuracy[35,36]. In future, data may be extracted from free-text reports, in order to complete missing data[54].

Peri-operative Data

Detailed data regarding intra-operative specifics can be identified from a combination of theatre management systems and routine data. Operating theatre staff typically input set checkpoints within each patients' theatres admission, such as knife to skin; this is in order to monitor performance, maintain quality of surgery[55] and enhance communication within the operating theatre complex. Within chapter 4, surgical approach and duration of surgery were identified. Missing data within this project was for those surgeries which occurred prior to the implementation of the digital theatre management software. This peri-operative data, in particular analysis of surgical times, helps with resource and workforce planning. Informatics

techniques have been utilised, with high levels of predictive accuracy, in order to forecast estimated surgical time by speciality, day and time of year[56]. They have also been used to analyse potential reasons for redundant or lost time within theatre lists, allowing for these to be addressed and overall efficiency improved[57,58]. With waiting times for elective procedures within the NHS increasing exponentially[59], maintaining theatre efficiency and planning theatre lists appropriately is crucial for sustaining surgical health care.

When performing informatics-based studies, peri-operative haemorrhage is typically identified within the routine administrative data[60]. The severity of bleeding that has been coded may vary between cases. Capturing patients that undergo blood transfusion would likely restrict identification to only those that have had a significant bleed. Within chapter 4 patients undergoing transfusion were identified and also the volume of blood administered. Cell salvage is typically avoided in cancer surgery; therefore, all blood product replacement was captured from the drug administration data. Using this data, prediction models can estimate the need for blood transfusion[61–63]. Anticipation of blood transfusion will lead to better patient safety, less wastage and pre-operative optimisation of patients. This is an example of how database linkage, in this case the EHR prescription and administration records, onto the cohort extracted from routine administrative data, can be used to improve outcomes for patients undergoing surgery for urological malignancies.

Outcome measures

Mortality was the primary outcome of choice for both studies utilising locally stored data. There was sufficient clinical information available to risk stratify patients, hence mortality outcomes could be interpreted in clinical context. Patients undergoing radical prostatectomy

had a risk profile stratified, whereas a narrow inclusion criterion was set for the bladder cancer project to ensure all patients had a similar risk profile. This allows for reliable and clinically relevant results regarding mortality.

Biochemical recurrence often serves as the initial indicator for failure of prostate cancer treatment. Patients with a post-operative PSA level at or above 0.2 ng/ml at any time were flagged, along with the date of the result. This approach enabled accurate identification of biochemical recurrence, allowing for analysis of recurrence-free survival. Manual case review of 1,267 patients, with all their follow up blood results, would be incredibly time consuming and subject to human error[64]. While biochemical recurrence is a crucial factor in monitoring prostate cancer patients, it should not be viewed in isolation as definitive evidence of recurrence or disease progression[65]. It could be argued that further treatment or the presence of solid metastasis, identified in routine administrative data, may still be a relevant indication of treatment failure.

Chapter 4 has highlighted the breadth of data that can be found, albeit manual checks may be still be required. Current informatics practices serve to support clinical audit and research, in future they may eliminate completely the need for spot checking, validation and case note review. This will however require improved education for clinicians when completing assessments, to ensure data that is automatically collected is complete, accurate and can be used for research.

5.2.2 Strengths of studies using the electronic health record and locally stored data

Whilst summarising the studies within chapter 4, that utilised linkage of the EHR and other local datasets to the routine administrative data, a number of strengths within their methodology were identified. This section aims to summarise those strengths.

The key strength of working with local/EHR data is the ability to get granular clinical detail. The high accuracy of routine administrative data for identifying cohorts based on procedure and diagnosis has already been discussed, as has its limitation in clinical detail. Through linkage of local datasets this detail can be identified. It has been shown in this thesis that there were high levels of successful linkage despite a large number of clinical systems. Through obtaining relevant clinical data, confounders can be adjusted for and causal relationships examined.

An advantage of linking local clinical systems pertains to the function and purpose of said systems. Although all of the systems required to perform these studies had different functions, they were all aids to clinical communication; such as the EHR, LINAC prescription and theatres database. This ensured that the information contained within was clinically relevant. As an active clinician, I was able to determine the best clinical system for each research question and link accordingly. As there is a worldwide shift to paperless healthcare, it will be possible to analyse all aspects of a patient's operative journey through use of informatics research.

Another strength of working with local data is the fact that information is patient identifiable. Aberrant clinical findings can be investigated and data validation can be performed. As mentioned, manual verification of bladder tumour staging was required for precision, this

allowed for accurate comparison. Furthermore, data can be "spot checked" against the patient notes in order to ensure accuracy.

Data stored has associated dates and times and can be extracted in a longitudinal format, reducing recall bias and allowing for tracking of changes over time. This in particular allowed for examination of biochemical recurrence free survival, for an in depth look at post-prostatectomy outcomes. For patients undergoing bladder cancer treatment it allowed a distinction between adjuvant and neo-adjuvant chemotherapy, as well as examination of survival. This temporal variable further enhances the ability to review causative relationships.

HES data typically "lags" and has a 3 monthly delay with an annual refresh[66]. EHR and other local clinical system output data is generated in real time. This allowed for maximal follow up time, following radical prostatectomy or cystectomy in the included studies. In practical terms, it also allows for benchmarking and timely intervention.

5.2.3 Limitations of studies using the electronic health record and locally stored data

As there is a transition to 'hub and spoke' hospital models and centralised services, increasing numbers of patients will have healthcare delivered at multiple trusts. Whilst linkage of local datasets can enhance data captured, it relies on test results being stored locally. This was highlighted by the 'missing' PSA results in chapter 4. Pre-operative PSA is utilised for risk stratification prior to radical prostatectomy, it is unlikely that a patient will undergo surgery without this[67–69]. Patients cannot be followed up between sites without data sharing agreements.

Data storage is subject to the software developer, rather than in a standardised format. This variability in data storage can make linkage of datasets complex and data pre-processing is required before linkage. This may lead to inaccuracies and less efficiency. Furthermore, data may be stored in free text reports, such as radiology and pathology reports. Natural language processing is a technique being developed in order to extract data from these reports[70].

Some data within the EHR is clinician inputted, such as admission assessments and diagnostic coding[71]. The inputting of both standardised and non-standardised information during daily practice is not infallible to inaccuracies. The priority of clinical staff is to deliver safe and efficient patient care for the presenting complaint, hence there may be missing information within the EHR, for data that may not pertain directly to the presenting complaint.

In addition to data quality, there are ethical considerations of utilising EHR data and linking datasets; safeguarding of personal and identifiable data must be considered. Patients may not be aware of the diversity of computer systems within the NHS and the use of their personal data for research and audit. This raises the question of patient autonomy and consent, also whether a robust opt-out system should be considered.

Data governance, within healthcare, is predominately the responsibility of the healthcare provider. As there are advances in regional networks and data sharing for research, there will be a concern over the involvement of private entities, such as pharmaceutical and insurance companies, and access to data. Industry funding ultimately plays an important role in the necessary resource to carry out medical research[72]; agreements for such funding must ensure

patient data is protected from use by private companies. Furthermore, future researchers should be transparent about access to data and influence of third parties on research outcomes

In order to mitigate these concerns, design must follow strict approval process and be restricted to appropriate use. Private companies should not store or have access to patient records. Data privacy issues must be considered prior to investigation and the importance of local and national regulatory bodies should not be underestimated.

5.3 Key findings

Informatics based practices have been shown, in a variety of projects and methodologies within this thesis, to successfully perform and support research into urological malignancies. Using national routine data allows for powerful studies that are generalisable to a national population, whereas local data systems offer smaller studies with rich data allowing for clinical interpretation and risk stratification.

Common strengths, in addition to the ability to process and analyse large volumes of data, to both HES based studies and those using local datasets include reliable outcomes and longitudinal data analysis. Temporal relationships can be examined and inferences about causation, as well as correlation can be made.

There are inevitably some concerns regarding data quality and completeness when using informatics-based processes. Pre-study data validation and regular checks throughout the research process will help to reduce this. Furthermore, given the high power of these studies, there can be a tolerance for this small volume of data inaccuracy.

This thesis has displayed that a significant amount of detailed data can be obtained utilising informatics techniques, in order to perform robust research. As research utilising informatics techniques continues to expand in scope and complexity, concern will always be present regarding data privacy and handling of potentially sensitive data. Pseudonymisation is used in HES in order to protect data privacy whilst enabling longitudinal follow-up; it is still important to be cautious with this data, as patients still could potentially be identified.

5.4 Vision for the future

As a result of this thesis there is a vision for the future direction of informatics research within urology. Machine learning and precision healthcare appear to be a viable tool in order to improve public health pertaining to urological cancers, in particular for prostate cancer. Informatics processes and automated follow-up can enhance PSA monitoring in target populations, such as those with risk factors, those on surveillance regimes and to detect disease relapse following radical treatment. Furthermore, predictive analysis could be applied to routine national datasets in order to highlight "high risk" populations, for enhanced screening.

This thesis sought to examine the ability of routine administrative data at a national level and then examine the feasibility of dataset linkage. It has shown that both have significant advantages for clinical research and audit of practice. A focus should be on improvement of data sharing, linkage of datasets and integration of clinical data at a national level. This will however need to consider data privacy and the ethical implications of doing so. Furthermore, there is substantial variability throughout the English NHS of IT systems used and electronic data-capture. Standardisation of the EHR across the NHS will improve the quality of data capture and ensure all patients have access to high quality clinical notes.

Improvements in data linkage and processing will help advance the setting of direction for national guidance and resource allocation. This thesis has highlighted health inequalities between deprived and wealthy areas. Up to date informatics analysis within routine administrative data already poses a credible option for examining allocation of resources. Should data sharing and linkage be achieved, as described previously, further data fields can be considered and national guidance can be set, in order to allow equitable access to healthcare within the English NHS.

As healthcare becomes increasingly digitised the volume of clinician inputted data will increase. It is important that clinicians are educated as to the importance and uses of this data, in order to ensure high data completeness and accuracy. As a clinician myself, it was only when utilising the EHR for research did I understand how data were captured and how they are used for research.

A challenge highlighted throughout this thesis is non-standardised information. In particular radiology, histopathology and cystoscopy reports that are produced in free text, are crucial for the diagnosis and surveillance of urological malignancies. Natural language processing has shown promising results in the ability to categorise such reports[70]. Investment in this technology will allow more efficient large scale data extraction and add granularity to datasets.

5.5 Conclusion

This thesis aimed to explore the utility of informatics research practices in order to examine outcomes for urological malignancies. With objectives of 1) Using Hospital Episode

Statistics Data to examine outcomes at a national level for prostate cancer patients, 2) Perform retrospective studies through linkage of multiple administrative databases to the electronic health record, 3) Identify rare procedures in routine administrative data.

This thesis has produced 5 projects, that as a body of work achieve these objectives, the key findings of which are summarised above. The recommendations as a result of this are as follows, providing data privacy and patient confidentiality standards are maintained:

1. Hospital Episode Statistics is a valuable resource for epidemiological and outcome studies. Predictive modelling and machine learning may be applied to national datasets in order to enhance screening and deliver precision healthcare.

2. As more data is auto-generated from clinician inputted coding during admissions, education of clinical staff regarding the importance of accurate data will enhance the robustness and accuracy of datasets.

3. Locally stored data is a rich resource for quality improvement and clinical research. Natural language processing may enhance the ability to extract relevant data and should be a focus of research

4. NHS providers should consider automating aspects of patient cancer follow-up, in order to identify the need for further treatment early and improve outcomes.

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Appendices

Appendices for Chapter 3, Manuscript 1

Appendix 1 – ICD-10 Codes

Diagnosis	ICD10 Code	Description
Prostate cancer	C61X	Malignant Neoplasm of prostate
	D07.5	Carcinoma in-Situ: Prostate
	D40.0	Neoplasm of unknown or uncertain behaviour: Prostate
Stricture	N32.0	Bladder-neck obstruction (Bladder neck stenosis acquired)
	N35X	Urethral Stricture
	N99.1	Post-procedural urethral stricture
Fistula	N32.1	Vesicointestinal Fistula/Vesicorectal Fistula
	N32.2	Vesical fistula, NEC
	N36.0	Urethral fistula
	N50.8	Urethroscrotal Fistula
Charlson Score Codes		
Diagnosis	**ICD10 Code***	**Weight**
Acute MI	I21X I22X I23X I25.2 I25.8	5
Cerebral Vascular Accident	G45.[012389] G46X I6X	11
Congestive Heart Disease	I50X	13
Connective Tissue Disorder	M05X M06.[039] M3[24]X M33.2 M35.3	4
Dementia	F0[0123]X F05.1	14
Diabetes	E1[0134].[15689]	3
Diabetes Complication	E1[0134].[2347]	-1
HIV	B2[01234]X	2
Liver Disease	K70.[23] K71.7 K7[34]X	8
Paraplegia	G04.1 G81X G82.[012]	1
Peptic Ulcer	K2[5678]X	9
Peripheral Vascular Disease	I71X I73.9 I79.0 R02X Z95.[89]	6
Pulmonary Disease	J4[01234567]X J6[01234567]X	4
Renal Disease	I1[23]X N0[13]X N05.[23456] N07.[234] N1[89]X N25X	10
Severe Liver Disease	K72.[19] K76.[67]	18

Appendix 2 – OPCS-4 Codes

Operation	Code	Description
HIFU	M71.1	High intensity focused ultrasound of prostate
TUR	M65.1	Endoscopic resection of prostate using electrotome
	M65.2	Endoscopic resection of prostate using punch
	M65.3	Endoscopic resection of prostate NEC
	M65.4	Endoscopic resection of prostate using lase
	M65.5	Endoscopic resection of prostate using vapotrode
Prostatectomy	M34.1	Cystoprostatectomy
	M61.1	Total excision of prostate and capsule of prostate
	M61.2	Retropubic prostatectomy
	M61.3	Transvesical prostatectomy
	M61.4	Perineal prostatectomy
	M61.8	Other specified open excision of prostate
	M61.9	Unspecified open excision of prostate
Radiotherapy	M70.6	Radioactive seed implantation into prostate
	M71.2	Implantation of radioactive substance into prostate
	X63.1	Preparation for intensity modulated radiation therapy (OPCS 4.3)
	X63.4	Preparation for simple radiotherapy with imaging and dosimetry (OPCS 4.3)
	X63.5	Preparation for simple radiotherapy with imaging and simple calculation (OPCS 4.3)
	X63.8	Preparation for complex conformal radiotherapy OR Other specified preparation for external beam radiotherapy (OPCS 4.3)
	X63.9	Unspecified preparation for external beam radiotherapy (OPCS 4.3)
	X64.2	Preparation for intracavitary brachytherapy
	X64.3	Preparation for interstitial brachytherapy
	X64.8	Preparation for RT or brachytherapy (OPCS4.3/4.4) x10 choices/ Preparation for intraluminal brachytherapy
	X65.2	Delivery of a fraction of intracavitary radiotherapy
	X65.3	Delivery of a fraction of interstitial radiotherapy
	X65.4	Delivery of a fraction of external beam radiotherapy NEC
	X65.8	Other specified radiotherapy delivery
	X65.9	Unspecified radiotherapy delivery
	X67.1	Preparation for intensity modulated radiation therapy
	X67.3	Preparation for hemi body irradiation
	X67.4	Preparation for simple radiotherapy with imaging and dosimetry
	X67.5	Preparation for simple radiotherapy with imaging and simple calculation
	X67.6	Preparation for superficial radiotherapy with simple calculation
	X67.7	Preparation for complex conformal radiotherapy
	X67.8	Other specified preparation for external beam radiotherapy
	X67.9	Unspecified preparation for external beam radiotherapy
	X68.1	Preparation for intraluminal brachytherapy

	X68.2	Preparation for intracavitary brachytherapy
	X68.3	Preparation for interstitial brachytherapy
	X68.8	Other specified preparation for brachytherapy
	X68.9	Unspecified preparation for brachytherapy
	Y35.4	Introduction of radioactive substance into organ for brachytherapy NOC
	Y36.3	Radioactive seed implantation NOC
	Y36.8	Other specified introduction of non-removable material into organ NOC
	Y90.2	Radiotherapy NEC (overlaps with other RT codes but OPCS4.2)
	Y91.1	Megavoltage treatment for complex radiotherapy
	Y91.2	Megavoltage treatment for simple radiotherapy
	Y91.3	Superficial or orthovoltage treatment for radiotherapy
	Y91.4	Megavoltage treatment for adaptive radiotherapy
	Y91.5	Megavoltage treatment for hypofractionated stereotactic radiotherapy
	Y91.8	Other specified external beam radiotherapy
	Y91.9	Unspecified external beam radiotherapy
	Y92.8	Other specified support for preparation for radiotherapy
	Y92.9	Unspecified support for preparation for radiotherapy

Supplementary tables and figures

	Hazard Ratio	[95% Conf. Interval]		P>z
Annual HIFU caseload (Baseline = > 2 per year)	2.05	1.08	3.91	0.029

Supplementary table 1. Univariable cox proportional hazards regression for development of stricture following HIFU in the HIFU only cohort, utilising annual case load

		Odds Ratio	[95% Conf. Interval]		*p* >|z|
Age (Continuous)	**Increasing year**	1.03	1.01	1.06	0.019
Deprivation Quintile (Baseline = 1)	**2**	1.21	0.56	2.60	0.628
	3	1.15	0.55	2.41	0.703
	4	1.03	0.50	2.11	0.946
	5	1.21	0.61	2.43	0.587
Ethnicity (Baseline = White)	**Asian or Asian British**	0.27	0.04	2.11	0.214
	Black or Black British	0.45	0.15	1.32	0.146
	Other	0.32	0.04	2.46	0.272
	Unknown	0.30	0.04	2.28	0.244
Charlson Score (Baseline = 0)	**1-5**	0.76	0.40	1.46	0.409
	> 5	0.78	0.26	2.36	0.666
Year of Hifu (Baseline = 2007/2008)	**2008/2009**	0.85	0.45	1.63	0.628
	2009/2010	0.49	0.23	1.01	0.053
	2010/2011	0.80	0.41	1.55	0.508
	2011/2012	0.52	0.25	1.05	0.069
	2012/2013	0.33	0.15	0.73	0.006
	2013/2014	0.14	0.06	0.33	0.000
	2014/2015	0.14	0.06	0.34	0.000
	2015/2016	0.13	0.06	0.31	0.000
	2016/2017	0.08	0.03	0.20	0.000
Annual HIFU caseload (Baseline = > 2 per year)	**<= 2**	1.89	0.83	4.31	0.132

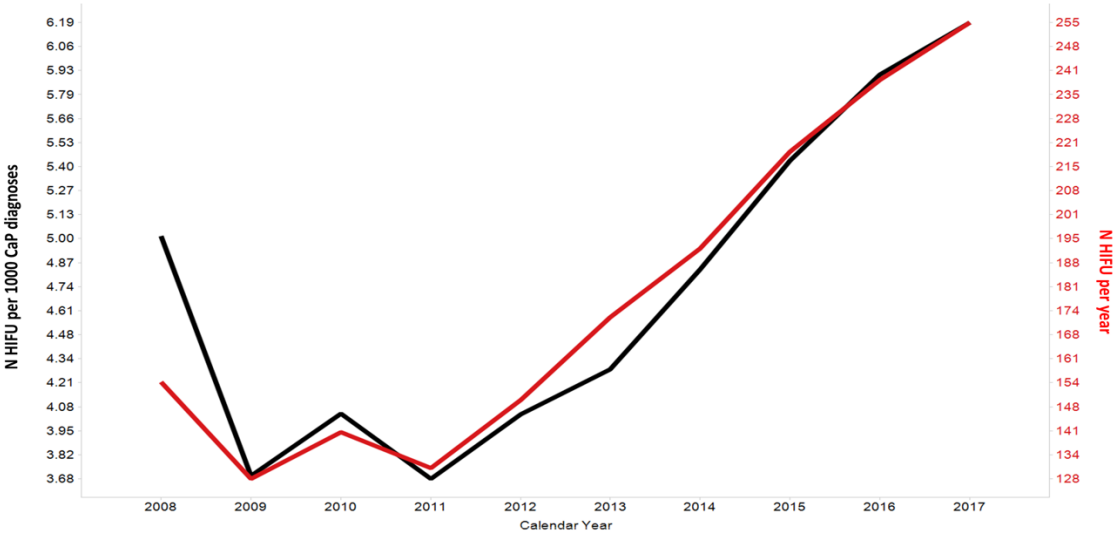
Supplementary table 2. Logistic regression for development of urethral stricture using the pure HIFU cohort

Calendar year	HIFU	Incidence CaP	HIFU per 1000 CaP
2008	155	30,893	5.01
2009	128	34,593	3.70
2010	141	34,892	4.04
2011	131	35,567	3.68
2012	150	37,136	4.03
2013	173	40,372	4.28
2014	192	39,741	4.83
2015	219	40,331	5.43
2016	239	40,489	5.90
2017	255	41,201	6.18
2008	155	30,893	5.01

Supplementary table 3. Table displaying the trend of HIFU, incidence of prostate cancer in HES and rates of HIFU per 1000 incident cases of prostate cancer

Procedure financial year	n	Stricture (%)
2007/2008	188	40 (21.3)
2008/2009	143	30 (21.0)
2009/2010	134	19 (14.2)
2010/2011	145	31 (21.4)
2011/2012	133	16 (12.0)
2012/2013	139	10 (7.2)
2013/2014	197	9 (4.6)
2014/2015	199	9 (4.5)
2015/2016	225	10 (4.4)
2016/2017	239	6 (2.5)

Supplementary table 4. Table displaying the rates of strictures over time



Supplementary figure 1. Line graph showing the trend of HIFU procedures for prostate cancer and the trend of HIFU procedures per 1000 incident cases of prostate cancer against financial year

Appendices for Chapter 3, Manuscript 2

Appendix 1 – ICD-10 Codes

Diagnosis	ICD10 Code	Description
Prostate cancer	C61X	Malignant Neoplasm of prostate
	D07.5	Carcinoma in-Situ: Prostate
	D40.0	Neoplasm of unknown or uncertain behaviour: Prostate
Charlson Score Codes		
Diagnosis	**ICD10 Code**	**Weight**
Acute MI	I21X I22X I23X I25.2 I25.8	5
Cerebral Vascular Accident	G45.[012389] G46X I6X	11
Congestive Heart Disease	I50X	13
Connective Tissue Disorder	M05X M06.[039] M3[24]X M33.2 M35.3	4
Dementia	F0[0123]X F05.1	14
Diabetes	E1[0134].[15689]	3
Diabetes Complication	E1[0134].[2347]	-1
HIV	B2[01234]X	2
Liver Disease	K70.[23] K71.7 K7[34]X	8
Paraplegia	G04.1 G81X G82.[012]	1
Peptic Ulcer	K2[5678]X	9
Peripheral Vascular Disease	I71X I73.9 I79.0 R02X Z95.[89]	6
Pulmonary Disease	J4[01234567]X J6[01234567]X	4
Renal Disease	I1[23]X N0[13]X N05.[23456] N07.[234] N1[89]X N25X	10
Severe Liver Disease	K72.[19] K76.[67]	18
6 week complication codes		
Urinary retention	R33X	Retention of urine
Prosthetic/wound infection	T81.3	Disruption of operation wound, not elsewhere classified
	T81.4	Infection following a procedure, not elsewhere classified
	T83.5	Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary system
	T83.6	Infection and inflammatory reaction due to prosthetic device, implant and graft in genital tract
Mechanical failure	T83.1	Mechanical complication of other urinary devices and implants (sphincter implant)
	T83.4	Mechanical complication of other prosthetic devices, implants and grafts in genital tract

	T83.8	Other complications of genitourinary prosthetic devices, implants and grafts
Urinary tract infection	N39.0	Urinary tract infection, site not specified

Appendix 2 – OPCS-4 Codes

Operation	Code	Description
AUS	M64.2	Implantation of artificial urinary sphincter into outlet of male bladder
Sling	M64.7	Introduction of transobturator sling (male)
SPC	M38.2	Cystostomy and insertion of a suprapubic tube into bladder
TURP	M65.1	Endoscopic resection of prostate using electrotome
	M65.2	Endoscopic resection of prostate using punch
	M65.3	Endoscopic resection of prostate NEC
	M65.4	Endoscopic resection of prostate using lase
	M65.5	Endoscopic resection of prostate using vapotrode
Prostatectomy	M34.1	Cystoprostatectomy
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	M61.2	Retropubic prostatectomy
	M61.3	Transvesical prostatectomy
	M61.4	Perineal prostatectomy
	M61.8	Other specified open excision of prostate
	M61.9	Unspecified open excision of prostate
Radiotherapy	M70.6	Radioactive seed implantation into prostate
	M71.2	Implantation of radioactive substance into prostate
	X63.1	Preparation for intensity modulated radiation therapy (OPCS 4.3)
	X63.4	Preparation for simple radiotherapy with imaging and dosimetry (OPCS 4.3)
	X63.5	Preparation for simple radiotherapy with imaging and simple calculation (OPCS 4.3)
	X63.8	Preparation for complex conformal radiotherapy OR Other specified preparation for external beam radiotherapy (OPCS 4.3)
	X63.9	Unspecified preparation for external beam radiotherapy (OPCS 4.3)
	X64.2	Preparation for intracavitary brachytherapy
	X64.3	Preparation for interstitial brachytherapy
	X64.8	Preparation for RT or brachytherapy (OPCS4.3/4.4) x10 choices/ Preparation for intraluminal brachytherapy
	X65.2	Delivery of a fraction of intracavitary radiotherapy
	X65.3	Delivery of a fraction of interstitial radiotherapy
	X65.4	Delivery of a fraction of external beam radiotherapy NEC
	X65.8	Other specified radiotherapy delivery
	X65.9	Unspecified radiotherapy delivery
	X67.1	Preparation for intensity modulated radiation therapy
	X67.3	Preparation for hemi body irradiation
	X67.4	Preparation for simple radiotherapy with imaging and dosimetry
	X67.5	Preparation for simple radiotherapy with imaging and simple calculation
	X67.6	Preparation for superficial radiotherapy with simple calculation
	X67.7	Preparation for complex conformal radiotherapy
	X67.8	Other specified preparation for external beam radiotherapy

	X67.9	Unspecified preparation for external beam radiotherapy
	X68.1	Preparation for intraluminal brachytherapy
	X68.2	Preparation for intracavitary brachytherapy
	X68.3	Preparation for interstitial brachytherapy
	X68.8	Other specified preparation for brachytherapy
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	Y91.2	Megavoltage treatment for simple radiotherapy
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	Y91.5	Megavoltage treatment for hypofractionated stereotactic radiotherapy
	Y91.8	Other specified external beam radiotherapy
	Y91.9	Unspecified external beam radiotherapy
	Y92.8	Other specified support for preparation for radiotherapy
	Y92.9	Unspecified support for preparation for radiotherapy

Supplementary table

	n AUS	n Revisions	Revision rate
2010/2011	119	22	18.5
2011/2012	136	22	16.2
2012/2013	158	32	20.3
2013/2014	190	31	16.3
2014/2015	183	25	13.7
2015/2016	174	21	12.1
2016/2017	199	13	6.5
2017/2018	231	<6	*

Supplementary table 1. Table displaying the number of revisions (redo/removal) per year of AUS (*suppressed in accordance with HES guidance)