Title:

AN EXAMINATION OF THE OUTCOMES OF THERAPEUTIC GI ENDOSCOPY USING NATIONAL DATA SETS

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ABSTRACT

Background

Prospective research in therapeutic endoscopy is challenging. Database studies are widely reported, but with recognised limitations. Reported in this thesis are targeted analyses of databases with the aim improving patient outcomes and providing examples of database studies in gastro-intestinal therapeutic endoscopy.

Methods

Hospital Episode Statistics (HES, secondary care) and The Health Improvement Network (THIN, primary care) were used to investigate therapeutic endoscopy outcomes and the populations that undergo such procedures.

Analyses included; ERCP for malignant biliary obstruction, colonic stents as a bridge to curative resection, 10-year outcomes of endoscopic pneumatic dilatations and myotomy for achalasia, morbidity and mortality following PEG placements in learning disability subjects, and long term outcomes of achalasia subjects from population based data.

Results

HES demonstrated excellent coding of procedures and mortality. Complications of procedures and provision of chemotherapy were variable. Key strengths of HES data were large subject cohorts and a mechanism to examine provider volume effects.

THIN data was limited for peri-procedure outcome data. However, long term population health data items describe important outcomes observed in primary care and are therefore unavailable in HES.

Conclusions

Careful application of database studies can yield useful clinical observations to target research and support service design.

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Table of Contents

1. Introduction 11

1.1.1 The History of Endoscopy 12

1.1.2 Quality Improvement in Endoscopy 13

1.2.1 Informatics and database analyses 14

1.2.2 NHS information technology 14

1.2.3 Examples of large or national scale databases in other countries 15

1.2.4 Comparison of database studies to other study designs 17

1.2.5 The current evolution of database analysis in endoscopy 18

1.2.6 A previous MD thesis including HES analyses of endoscopy 19

1.3 Background: Endoscopic retrograde cholangio-pancreatography (ERCP) for relief of malignant biliary obstruction 21

1.3.1 ERCP 22

1.3.2 Complications of ERCP 22

1.3.3 Malignant biliary obstruction 24

1.3.4 Pancreatic cancer 24

1.3.5 Other primary cancers causing malignant biliary obstruction 24

1.3.6 Associations of malignant biliary obstruction 25

1.3.7 Therapeutic strategies for relief of biliary obstruction 26

1.3.8 Current Outcomes for relief of biliary obstruction by PTBD 26

1.3.9 Comparison of PTBD and ERCP 27

1.3.10 ERCP Volume effect 28

1.3.11 Volume effect in ERCP for malignant biliary obstruction 30

1.4 Background: Outcomes of colorectal stents when used as a bridge to curative resection in obstruction secondary to colorectal cancer 31

1.4.1 Colorectal Cancer 32

1.4.2 Elective Colorectal Cancer Treatment. 32

1.4.3 Emergency Colorectal Cancer Treatment 33

1.4.4 Self-expanding Metal Stents 33

1.4.5 Colonic Self-expanding Metal Stents Evidence 34

1.5 Background: Outcomes of pneumatic dilatation and Heller's myotomy for achalasia in England between 2005 and 2016 37

1.5.1 Achalasia aetiology and diagnosis 38

1.5.2 Achalasia Treatment Modalities 38
1.5.2 Evidence for Achalasia Treatment Modalities 39
1.6. Background: Incidence, morbidity and mortality of subjects with achalasia in England: findings from a study of nationwide hospital and primary care data 42
1.6.1 Incidence of achalasia 43
1.6.2 Association between Oesophageal Cancer and Achalasia 44
1.6.3 Co-morbidity associated with achalasia 45
1.6.4 Achalasia in two databases 45
1.7 Background: Outcomes following percutaneous endoscopic gastrostomy insertion in patients with learning disability 46
1.7.1 The role of PEG feeding 47
1.7.2 PEG placement procedure 47
1.7.3 PEG placement in Dementia 48
1.7.4 Learning Disability cohort 48
1.7.5 Learning dissability research 49
2. Aims of this thesis 51
3. Materials and methods 52
3.1.1 Hospital Episode Statistics 53
3.1.2 Hospital Episode Statistics Data 53
3.1.3 Example HES data capture 54
3.2.1 The Health Improvement Network 56
3.2.2 Example THIN data capture 57
3.3.1 Comparison of THIN and HES 57
3.3.2 Coding structure 58
3.4.1 Study design 59
3.4.2 Study Process 60
3.4.3 Charlson co-morbidity score 61
3.4.4 Age quintiles 62
3.4.5 Deprivation 63
3.4.6 English residency 63
3.4.7 External Data validation methodology 64
3.4.8 Internal data validation methodology 64
3.4.9 Ethical approval 65
4. The outcomes of ERCP for the palliation of malignant biliary obstruction in England between 2006 and 2017 66

4.1. Chapter specific materials and methods 67
4.1.1 Subject cohort 67
4.1.2 Data Extraction 67
4.1.3. Data validation 67
4.1.4. Analysis 67
4.2. Chapter specific results 69
4.2.1. Validation 69
4.2.2 Demographics 69
Figure 4.1: Study flow chart 70
Table 4.1: Study subject demographics 71
4.2.3 Complications 72
4.2.4 Repeat biliary drainage procedures 72
Table 4.2: Short term complications of ERCP 73
Table 4.3: Proportion of subjects undergoing repeat biliary drainage procedures within 30 days of index ERCP 74
4.2.5 Chemotherapy 75
Table 4.4: Rates of chemotherapy following ERCP by age, co-morbidity, cancer type and year of procedure 76
4.2.6 Mortality 77
4.2.7 Standardised mortality rates 77
Table 4.5: Multivariable logistic regression of factors associated with 30 day mortality following ERCP for malignant biliary obstruction including provider volume analysis 78
Table 4.6: Multivariable logistic regression analysis of factors associated with 30 day mortality following ERCP for malignant biliary obstruction including provider volume of ERCP for unresectable cancer 79
Figure 4.2: Funnel plot of standardised 30 day mortality rate following ERCP for palliative malignant biliary obstruction 80
4.3 Chapter specific discussion 81
5. Outcomes of colorectal stents when used as a bridge to curative resection in obstruction secondary to colorectal cancer 84
5.1 Chapter specific materials and methods 85
5.1.1 Inclusion and Exclusion Criteria 85
5.1.2 Data Validation 85
5.1.3 Data Analysis 85
5.1.4 Statistical Analysis 86
5.2 Chapter specific results 88

5.2.1 Data Validation 88
5.2.2 Subject Demographics (Un-matched) 88
Figure 5.1 Study flow chart 89
Table 5.1 Study subject demographics in the whole study population and after propensity matching 90
5.2.3 Propensity Matched Analysis 91
5.2.4 Procedure outcomes following propensity matching 91
Table 5.2 Surgical outcomes following colon cancer resection in the whole study population and after propensity matching 92
5.2.5 Mortality and complications after resection following propensity matching 93
Table 5.3 Complications within 30 days of colon cancer resection in the whole study population and after propensity matching 94
Figure 5.2 Propensity matched Kaplan Meier curves with 95% confidence intervals for 1 year survival post resection for colon cancer 95
5.3 Chapter specific discussion 96
6. Outcomes of pneumatic dilatation and Heller's myotomy for achalasia in England between 2005 and 2016 99
6.1. Chapter Specific materials and methods 100
6.1.1Subject Cohort 100
6.1.2 Data extraction 100
6.1.3 Data Validation 101
6.1.4 Statistical analysis 101
6.2 Chapter specific results 102
6.2.1 Validation 102
6.2.2 Demographics 102
Table 6.1 Demographic characteristics of study subjects based upon their initial treatment modality 103
6.2.3 Achalasia treatment failure 104
Figure 6.1: Cumulative incidence plot demonstrating durability of Pneumatic dilatation and Surgical myotomy for achalasia 105
6.2.4 Multivariable analysis of factors associated with treatment failure 106
Table 6.2 Cumulative incidence regression analysis of factors associated with failure of treatment in the surgical myotomy and pneumatic dilatation groups 107
6.2.5 Mortality 108
Table 6.3 Logistic regression analysis of factors associated with 30 day mortality following pneumatic dilatation therapy 109

6.2.6 Complications of therapy 110
Table 6.4 The complications of achalasia treatment within 30 days 111
6.4 Chapter specific discussion 112
7. Incidence, morbidity and mortality of subjects with achalasia in England: findings from a study of nationwide hospital and primary care data 115
7.1 Chapter specific materials and methods 116
7.1.1 Data Sources 116
7.1.2 Validation 116
7.1.3 Incidence and Prevalence Data 116
7.1.4 Retrospective Cohort Study of morbidity and mortality outcomes in the THIN database 117
7.1.5 Statistical Analysis 117
7.2 Chapter specific results 119
7.2.1 Validation 119
7.2.2 Subject demographics 119
Table 7.1: The demographics of the Hospital Episode Statistics and The Health Improvement Network achalasia subjects 120
7.2.3 Incidence and prevalence of achalasia 121
Table 7.2 The incidence and prevalence of achalasia reported in Hospital Episode Statistics and The Health Improvement Network by year 122
7.2.4 Demographics and co-morbidity in the matched achalasia and control groups 123
Table 7.3 The Health Improvement Network achalasia and matched control groups characteristics 124
7.2.5 Morbidity outcomes in the matched achalasia and control groups 125
Table 7.4 Comparison of disease outcomes between achalasia cases and matched controls in The Health Improvement Network 126
Figure 7.1: The cumulative incidence plot of time from achalasia diagnosis to oesophageal cancer 127
Figure 7.2: The cumulative incidence plot of time from achalasia diagnosis to lower respiratory tract infection 127
7.2.6 Mortality in achalasia subjects 128
Table 7.5 Mortality in achalasia subjects and controls in The Health Improvement Network .. 129
Figure 7.3: Cumulative incidence plot of time from achalasia diagnosis to death 129
7.3 Chapter Specific discussion 130
8. Outcomes following percutaneous endoscopic gastrostomy insertion in patients with learning disability 133
8.1 Chapter specific materials and methods 134

8.1.1 Study population 134
8.1.2 Co-variates and outcome measures 134
8.1.3 Statistical analysis 134
8.2 Chapter specific results 136
8.2.1 Subject Demographics 136
8.2.2 Exposed and unexposed cohorts 136
Table 8.1: Study subject demographics 137
8.2.3 Lower respiratory tract infection 138
8.2.4 Rate of respiratory tract infections before and after PEG placement 138
8.2.5 Mortality 138
Table 8.2: Incidence of lower respiratory tract infections and mortality following PEG placement 139
Table 8.3: Poisson regression model for lower respiratory tract infection within 1 year of PEG placement 139
Table 8.4 Poisson regression model for mortality following PEG placement 140
Figure 8.1: Cumulative incidence regression for lower respiratory tract infections following PEG placement 141
Figure 8.2: Cumulative incidence regression for mortality following PEG placement 141
8.3 Chapter specific discussion 142
9. Thesis Summary 144
9.1. Summary of chapter results 145
9.1.1 Summary - The outcomes of ERCP for the palliation of malignant biliary obstruction in England between 2006 and 2017 145
9.1.2 Summary - Outcomes of colorectal stents when used as a bridge to curative resection in obstruction secondary to colorectal cancer 145
9.1.3 Summary - Outcomes of pneumatic dilatation and Heller's myotomy for achalasia in England between 2005 and 2016 146
9.1.4 Summary - Incidence, morbidity and mortality of subjects with achalasia in England: findings from a study of nationwide hospital and primary care data 146
9.1.5 Summary – Outcomes following percutaneous endoscopic gastrostomy in patients with Learning Disability 146
9.2 Key attributes and limitations of database analyses in the setting of interventional GI endoscopy 147
9.2.1 Recruitment completeness 147
9.2.2 Volume effect data 148
9.2.3 Data Validation 149

9.2.4 Follow-up 151
9.2.5 Surrogates of absent data items 152
9.2.6 Mortality data 153
9.2.7 Propensity score matching 153
9.2.8 Cumulative incidence regression 154
9.2.9 Procedural Complications in HES 155
9.3 The health improvement network and hospital episode statistics comparison 156
9.3.1 Primary care events 156
9.3.2 Epidemiology for service provision 156
9.3.3 Procedural coding 157
9.3.4 Peri-procedural outcomes 158
10. Impact of this thesis 159
10.1.1 NCEPOD 160
10.1.2 RICOCHET – ReceIpt of Curative resection Or palliative Care in HPB Tumours 160
10.1.3 Potential future implications – National Endoscopy Database 160
10.1.4 Potential future implications – Service design 161
10.1.5 Potential future implications – Clinical studies 162
10.2 Conclusions 163
11. Publications arising from this thesis 164
11.0.1 Manuscripts 165
11.0.2 Published Abstracts 165
12. References 167

1. Introduction

Endoscopy has developed to become an important component to modern healthcare with both diagnostic and therapeutic applications. Programmes of quality improvement have led the practice of diagnostic endoscopy to evolve rapidly over a several year period with continuous delivery of incremental improvements in outcomes. Therapeutic endoscopic interventions are minimally invasive, varied and clinically important treatments for patients. Due to the relative infrequency of such procedures, large scale, up to date outcome data is currently limited.

In the present thesis we aim to investigate outcomes, both short and long term, and compare endoscopic to non-endoscopic alternative treatments for a varied set of endoscopic therapies. Population based analysis has also been performed to identify outcomes of subjects with conditions treated endoscopically to predict future service needs. Furthermore the specific utility of database analyses, their strengths, and limitations for investigating therapeutic endoscopy will be discussed.

1.1.1 The History of Endoscopy

The first recognisable modern endoscope was developed by Georg Wolf of "Brückner & Wolf", in the early twentieth century. This was a revolutionary concept as the first flexible gastroscope. This permitted significantly better visualisation of hollow organs than preceding rigid endoscopes. At this stage in the development of the endoscope both light, view and an equivalent of the modern day "working channel" represented significant challenges. Despite these difficulties, over the following century technological advances have allowed stepwise improvements to develop what is now recognised as the modern endoscope. This is routinely equipped with a high fluorescence light source, air insufflation capacity and provides a high resolution white light image. Dependent upon size, modern endoscopes are also equipped with a working channel of varying diameter which allows targeted tissue sampling and washing of the mucosa. Fundamentally it also accommodates the placement of guide wires and the use of other accessories under direct vision or x-ray guidance. It is this capacity, combined with the above features, that allows interventions varying from the removal of impacted gall stones to the insertion of feeding tubes between the stomach and skin. These therapies can be performed within the colon and terminal ileum via a colonoscope or within the stomach, oesophagus or first two parts of the duodenum via a gastroscope. For specific indications a duodenoscope (A flexible gastroscope adapted to provide a side facing view instead of forward and a "bridge" to manipulate accessories into that field of view) may be passed to the second part of the duodenum. This permits cannulation of, and therapeutic procedures to be undertaken within, the pancreatic and bile ducts under x-ray guidance.

Procedures that we would recognise as therapeutic endoscopy first emerged with in the 1970's with the injection of hypertonic saline and adrenaline into the base of bleeding peptic ulcers. As ulcers

had limited treatment options aside from major oesophago-gastric resections these interventions had a dramatic impact(1). Other interventions followed that we now recognise as therapeutic endoscopy and form the contents of this thesis including oesophageal dilatation, gastrostomy and self expanding stent placement. Endoscopic Retrograde Cholangiopancreatography (ERCP) was first described in 1968(2). At the time this represented the only non-surgical approach for imaging of the biliary tree as ultrasound was not yet widely available and magnetic resonance imaging was yet to be invented. This was a significantly safer procedure when compared to open surgery under general anaesthetic, however ERCP was recognised to be not without risks.

1.1.2 Quality Improvement in Endoscopy

Over the last 20 years there has been significant improvement in the overall quality of diagnostic endoscopy in the United Kingdom. There are several components to this including; increased structure and experience for endoscopy trainees, the implementation of performance standards for all Endoscopists to achieve and the "Global rating scale". This quality improvement programme has been led by the Joint Advisory Group on GI endoscopy (JAG), which is housed within the Royal College of Physicians. Although when compared to the historical advances described above, these improvements have been individually relatively small, the combination of many incremental improvements has led to a significant improvement in quality.

An example of this is educational reform, specifically the development of the Joint Endoscopy Training system (JETs). This provides trainees with a portfolio into which their procedural experience can be logged alongside indications, degree of assistance from the trainer, adverse events and achievement of quality markers. This also provides summary statistics, for example of a trainee's intubation rate of the second part of the duodenum, which represents a technically successful upper GI endoscopy. Trainees are also required to complete Directly Observed Procedure Skills (DOPS) formative assessments. Their progress can then be mapped until they reach the volume of procedures and meet the key performance indicators for them to be considered competent to perform a diagnostic procedure independently. Trainees perform summative DOPS assessments which if satisfactory will allow them to progress to full JAG certification. The portfolio undergoes regular updates to improve the quality of training records so that they more accurately reflect a trainees skills and learning needs. A welcome example of an incremental addition to this was the recent update of forms to better reflect training in endoscopy. By recognising that the spectrum of competency for the majority of endoscopy trainees is relatively narrow, the new form focuses on this. More potential responses that represent this narrow degree of competency are permitted. Therefore forms can provide a more detailed reflection of the trainee's development. This therefore improves the quality of feedback given and allows trainers to personalise the instruction given to a

trainee. This is particularly valuable in the current training environment of the NHS, where trainee Endoscopists may have several trainers rather than a single trainer with whom they perform all of their procedures. Furthermore it allows better tracking of a trainee's progress, such that a more accurate picture of their development can be used to predict when they should be assessed for accreditation in a procedure.

It is inconceivable that improvements such as this are not important in endoscopy. In the recent past, creation of new techniques and novel approaches provided an opportunity to improve quality and patient outcomes. Modern endoscopy is now associated with such strongly positive outcomes that such leaps forwards are unlikely to be forthcoming. Therefore improvements must be achieved by continuous small increments including; enhanced protocols, careful patient selection and accurate evaluation of interventions. Thus these small incremental gains lead to a significant overall improvement in quality, and fundamentally better outcomes for our patients. The use of large data-sets to detect small differences is a potentially important methodology for achieving these incremental gains.

1.2.1 Informatics and database analyses

Informatics is a commonly used term with various interpretations. A broad consensus definition would be the collation, manipulation and analysis of large datasets. Furthermore the principle supports the integration of data from multiple, diverse sources. Within health examples of such sources could include the Office for National Statistics (ONS), National Cancer Intelligence Unit registry or care.data. The concept of connecting records on such databases, termed "data linkage" requires that data sources link patient records together from by a unique patient identification code. Therefore considering the examples above, this would allow a database analysis that includes data items held separately by the National Cancer Intelligence registry and the ONS for a group of individual patients. This therefore facilitates innumerable combinations of detailed analyses including a broad range of data items. Furthermore linkage methodologies are a topic of active research, providing a steady stream of new possibilities for data analysis(3). Healthcare informatics is therefore a powerful, constantly growing tool for evaluating outcomes in healthcare.

1.2.2 NHS information technology

From a national perspective, information technology (IT) systems within the NHS in England are heterogeneous. It is anecdotally recognised that whilst some hospital trusts possess modern, efficient systems, other trusts are less well equipped. A very large number of trusts use different, incompatible systems, leading to an inability to cross reference between them. Not only does this impact on healthcare provision when several different trusts hold records and results relevant to a

single patient, it also creates challenges incorporating individual trusts data as part of any multi-trust analysis. Attempts to rectify this are publically considered to have been unsuccessful and vastly expensive(4, 5). The direct result of this is that data linkage between a large number of smaller datasets is currently impractical. General practice across the UK also has numerous IT systems in use. Although there are fewer than are found in hospital medicine, this still creates a significant barrier to linking systems to generate a national dataset for analysis.

The NHS is the largest single healthcare provider in the world. Hence although combination of data across individual healthcare trusts is impractical, as a single entity there are fewer barriers. Healthcare systems in other countries attempting to construct national databases need to overcome concerns regarding inter-company governance, corporate interest and competition. Therefore although systems in use in other countries may have more developed and inter-compatible IT infrastructure, there is benefit to performing informatics research within the NHS.

Hospital Episode Statistics (HES) is a hospital care database (described in depth in chapter 3) used for secondary research from NHS administrative data. By using central data that all trusts upload, problems with software heterogeneity between trusts can be overcome. The Health Improvement Network (THIN) accepts the limitations of heterogeneous software in general practice, including practices which use a single system. Therefore data is presented for 6% of the population for research purposes (THIN is described in detail in chapter 3). HES and THIN are the data sources utilised in the present thesis

1.2.3 Examples of large or national scale databases in other countries

Several opportunities exist internationally for database studies. The USA National Inpatient Sample (NIS) is an example of a large secondary care database, a component of the Healthcare Cost and Utilisation project (HCUP)(6). Other HCUP databases include the National Emergency Department Sample (NEDS) database (2006) and the National Readmissions Database (NRD), (2010). The NIS is particularly relevant to inpatient endoscopic procedures, although for USA based researchers, each has advantages depending on the field of study.

The NIS is similar to HES in that it includes hospitalised patients. At present 46 states are currently included and all payer types are represented including Medicaid, Medicare, private insurance and uninsured subjects. Therefore although only 20% of admission discharge details are sampled, this is representative of the 97% of the population of the USA included in those 46 states.

The coding system is also similar to HES, as it utilises the International Classification of Diseases, version 10 (ICD-10) diagnostic coding structure (CM) and the ICD-10 procedural coding system (PCS).

The NIS included 20% sample is based upon discharge summaries, in a similar manner to the diagnostic coding data from discharge summaries in HES. Data is collected from a range of different secondary care settings, although long term rehabilitation and long term acute care hospitals are excluded. Unfortunately there are no state or hospital identification methods since the most recent update in 2012, therefore the NIS cannot now be used to seek a volume effect. This also represents a challenge when validating data quality as it is impossible to compare database results to local audit results provided by sources independent of the original database. Data validation is discussed in detail in the methods section. Although longitudinal analyses are facilitated by data that spans back to 1988, there have been several reorganisations. This is recognised by HCUP as a significant source of anomalies in long term trend analyses.

Unfortunately due to the different structure of healthcare provision in the USA, a significant proportion of endoscopy is undertaken in the community. This is therefore not captured in the NIS. Hence manuscripts relating using NIS often refer to either upper gastrointestinal bleeding outcomes(7) or ERCP(8).

Sweden is well recognised for high quality database analyses. This is due to a large network of smaller state run registries that have been prioritised by government. These are interconnected and linked to healthcare data. This achieves complete national population coverage and cannot be "opted out of"(9).

An example is the "GallRiks", a nationwide registry of gall stone surgery which includes ERCP. This was used to provide detailed description of ERCP practice including findings, cannulation rates and complications. Furthermore data validation for this study highlighted data accuracy of 97%(10). The degree of specific detail provided is clearly exceptional and beyond that which more general databases can provide, due to the amount of data entry that this would entail. The validation results also show extremely high data accuracy. However these databases, although numerous, are limited to the specific study questions that they are designed to answer.

More generalised data is available in the Swedish inpatient register (IPR). This became established in 1970, including approximately 80% of the population. Now similar to HES, the IPR covers all inpatient activity and uses ICD-10 coding. Procedural work is also coded within the database. However, although outpatient consultations are mandated, primary care data are not reported(11). Furthermore hospital based outpatient care is only reported in approximately 80% of cases. Although this still represents significant coverage, studies that use repeat procedures as surrogate of failure will report artificially reduced proportions of failure.

The Skaraborg Primary Care Database (SPCD) was set up in Skaraborg district of Sweden in 2000, to meet the need for primary care data of suitable quality to undertake research. Similarly to the IPR, this uses Swedish variant of ICD-10. However a recent valuation study demonstrated the completeness of diagnostic coding is variable between diagnoses and as low as 69% in congestive heart failure but up to 89% in diabetes mellitus(12). Although there is currently a project ongoing to establish a national database, this is not yet available for research purposes.

1.2.4 Comparison of database studies to other study designs

When compared to other types of medical evidence, database studies are a relatively new methodology. Such studies have only become possible since the development of digital healthcare systems and their apparatus for focused interrogation. It is unsurprising, therefore, that this relatively new study format, allowing large numbers of subjects to be analysed at little associated cost, are sometimes viewed with suspicion.

The current hierarchy of medical evidence is well established. Prospective randomised studies represent the gold standard quality of evidence including the ability to demonstrate cause and effect, although well conducted meta-analyses of such studies are considered to provide even stronger evidence. Cohort studies are considered less authoritative and have previously been criticised for over reporting the success of an intervention. However several studies have suggested this may not be the case. Analysis of randomised, prospective controlled trials and meta analyses were compared to well performed cohort studies with respect to their outcome measures. The outcomes of well performed observational studies were found to be within the 95% confidence intervals of those prospective studies(13, 14). This suggests, therefore, that although not a replacement for prospective data, observation study methodology can lead to accurate results.

A more recent study aimed to compare outcomes between a randomised control trial and a database analysis performed using an American insurance claims database, with national coverage(15). The aim of the study was to establish the validity of database studies for use in regulatory approvals for new indications of already available medications. In this database analysis subjects were included following newly prescribed Ramipril or Telmisartan. The primary outcome measure was a composite of new stroke, myocardial infarction and hospitalisation with congestive cardiac failure. The study aimed to replicate the protocol used in the “Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial” (ONTARGET)(16). When outcomes are compared it is clear that the database study findings match those of ONTARGET closely. The risk of the primary composite outcome on telmisartan compared to Ramipril was reported as RR 0.99 (0.85 to 1.14), compared to RR 1.01 (0.94 to 1.09) in ONTARGET. The authors are cautious in their

recommendations, “In certain clinical scenarios, database studies may support supplemental effectiveness applications for already approved medications”. The results may only be relevant to medication use; however it demonstrates the potential of database studies, if the area that they are to be applied to is appropriate to their use and if they are performed to a high standard.

1.2.5 The current evolution of database analysis in endoscopy

The study of large databases is not a new concept, nor is it unique to the UK. The data has been available for many years as a tool to allow; healthcare funding, monitoring healthcare usage and to provide system level statistics to government and regulatory agencies. However in the last 5 years there has been increased interest in using such databases to examine healthcare outcomes at the patient level and to attempt to answer epidemiological questions.

Early examples of database analyses are generally limited to those initially intended uses. Ackerman et al used the American Medicare database(17), which now forms a part of the Healthcare Cost and Utilisation project (HCUP) to provide several current databases. The author described the volume of endoscopic procedures undertaken in a community setting in the US, compared to those performed in a hospital setting.

Within 10 years more detailed analyses of system level statistics were being produced. Harewood et al, in 2004, used the Clinical Outcomes Research Initiative database to describe terminal ileal intubation rates at colonoscopy(18). This database was established by the American Society of Gastrointestinal Endoscopy (ASGE) in 1995 to provide system utilisation statistics for endoscopy. This analysis was developed further to determine which settings, and which particular groups of subjects were more likely to undergo terminal ileal intubation.

Current database examinations now reveal the detailed analyses that are being undertaken. A prominent example includes the training of new Endoscopists, focusing on the learning curve for upper gastrointestinal endoscopy (OGD). The data source used comes from the JETs portfolio provided by JAG to all trainees (described in chapter 1.1.2). Data is to be entered contemporaneously and once a trainee has logged sufficient numbers of procedures, and achieves pre-specified key performance indicator (KPI) thresholds, they will be certified as competent. An analysis of this database by Ward et al to predict the rate at which trainees reach technical competence, as defined by intubation of the second part of the duodenum (D2) in more than 95% of cases is published in a high impact journal (19). This uses two statistical methodologies (moving average and LC-cusum) to determine the number of OGDs a trainee needs to perform before they achieve the required KPI. The paper concludes that the required number of OGD procedures required before becoming competent (currently set at 200) should remain the same.

However as analyses become more complex, the problems of using data for a task that it was not intended for become more evident. A letter to the editor responding to this manuscript highlights two concerns; firstly that key components of competence are not available within the data. Secondly those factors beyond the trainees control may distort their D2 intubation rate, such as an obstructing cancer. This demonstrates that as a general principle, as analyses of databases become more sophisticated in an attempt to answer more complex questions, great care must be taken to ensure analyses warrant the conclusions they are assigned. This is one of the major challenges for database analyses.

1.2.6 A previous MD thesis including HES analyses of endoscopy

A recent MD thesis by Bowering manipulates limited HES data in conjunction with patient and institutional level data for inpatient gastroenterology care(20). Analyses are aimed to establish the robustness of HES data for analysing clinical outcomes in situations relevant to gastroenterology by incorporating survey results and local clinical audit.

The first chapter describes a retrospective audit of sedation practice using a local endoscopy database. Data was collected prior to a change in unit procedure followed by re-audit at the unit. Although mean sedation doses by each endoscopist are reduced, the expected reduction in mortality due to this was not found. It is noted that mortality within 30 days of endoscopy is a rare event. Therefore despite improving the process related outcome of sedation dose, no change in patient outcome was found. One of the possible reasons for this was an insufficient number of cases to identify a difference between groups in rare events.

The author laments that the study was resource intensive to complete, therefore regular cycle repeats would be impractical. This highlights the value of a national dataset such as HES, if it were to include sedation data, as this would allow the complete baseline and outcome data to be sought over the same database. This would be more practical, and the data more accessible for analysis that could contribute to evidence based sedation practice.

A later chapter discusses outcomes following PEG placement in HES data. All subjects undergoing a PEG are included, in comparison to only subjects with learning disability in the analysis presented later in this thesis. Over 2 years of HES data, 10,952 PEGs were placed for non-cancer indications. The major findings were that several indications including dementia and NMD were associated with increased mortality, as were advanced age and emergency admission type. No volume effect could be elicited; however variable case mix and patient selection may have obscured an effect.

The methodology of this chapter is developed further in some of the analyses presented in this thesis. The provider volume effect for therapeutic endoscopy seems likely to be important, but at present the effect, and the size of that effect is uncertain. However further database analyses are also within the scope of the present thesis including comparisons between treatment modalities, long term outcomes outside of hospital care and epidemiological questions impacting demand for future services. These database analyses require access to primary care data, which is provided in THIN alongside secondary care data in HES.

One of the goals of the thesis by Bowering is to engage clinicians both in leadership roles for HES analyses, but also through general engagement to ensure the methodologies are clinically meaningful. The present thesis advances that goal.

1.3 Background: Endoscopic retrograde cholangio-pancreatography (ERCP) for relief of malignant biliary obstruction

1.3.1 ERCP

ERCP is an endoscopic procedure in which a side viewing duodenoscope is passed orally to the second part of the duodenum. The Ampulla of Vater is located and cannulated. This allows the injection of radio-opaque dye into the bile ducts, demonstrating the anatomy of the biliary tree including any stones, cancers or other pathology. This is a technically challenging procedure done by a small proportion of endoscopists. ERCP has long been recognised as a high risk form of endoscopy, encompassing both an unwell patient group who undergo the procedure, and endoscopic interventions with significant risk of complications including; pancreatitis, cholangitis, perforation of the lumen and procedure related bleeding.

Due to the advent of magnetic resonance imaging of the biliary tract (MRCP), ERCP is now not performed for solely diagnostic reasons. Therefore there has been a significant shift in the types of procedure undertaken and the population it is performed on. Despite this there is a heterogeneous spectrum of pathology including; benign gall stone disease, pancreatitis and cancer in both elective and emergency patients.

1.3.2 Complications of ERCP

ERCP is recognised to be associated with significant complications even when performed by experienced biliary Endoscopists. Post ERCP pancreatitis is the most common complication, rates of which have been reported from 3.5%, up to as high as 20% in subjects with Sphincter of Oddi dysfunction who are at the highest risk. Post ERCP pancreatitis can range from mild to severe. This has been classified by cotton et al incorporating raised serum amylase, abdominal pain more than 24 hours following procedure and duration of hospital admission(21). This allows this patient group to be distinguished those with from post ERCP hyper-amylaseamia, which is seen in up to 75% of subjects(22). Various risk factors have been identified including age, gender, normal serum bilirubin, previous post-ERCP pancreatitis, pancreatic contrast injection, pancreatic sphincterotomy, difficult cannulation, sphincteroplasty and pre-cut sphincterotomy (22, 23). Multiple strategies have also been recommended for reducing pancreatitis risk. Relating to those recognised factors, avoidance of sphincteroplasty, pancreatic injection and pancreatic sphincterotomy are recommended. Several strategies reduce the risk of post ERCP pancreatitis; wire guided cannulation is now the standard practice in the UK, rectal diclofenac use is now anecdotally widely used in the UK, and pancreatic ductal stents are being used for instances following significant volume pancreatic injection or for those at the greatest risk. Careful patient selection, including avoidance of those with the greatest risk of pancreatitis; younger females, those with sphincter of Oddi dysfunction and patients with a normal serum bilirubin can also reduce rates of pancreatitis. In such patients when ERCP is essential careful consent with full disclosure of risks can be taken. Unfortunately these factors represent a

challenge to database studies, as few are sufficiently detailed to allow them to be included in analyses.

Cholangitis is both an indication and complication of ERCP. In ERCPs the primary therapeutic aim is usually to relieve blockage, either by removing stones or placement of a stent, and ensure adequate flow of bile through the CBD to the duodenum. Risk factors for cholangitis include failed or incomplete drainage of the CBD, malignant strictures which make drainage more challenging and Primary Sclerosing cholangitis in which there are often multiple strictures(24). Although it is a rare complication (<1%), cholangitis is associated with significant mortality (7.85% (95% CI 4.39–11.4%))(25).

Haemorrhage at ERCP is most commonly related to sphincterotomy, but is usually mild and self limiting. The complication is often immediately visible to the endoscopist, however due to the electrocautery effect of the sphincterotome there may be temporary haemostasis leading to delayed presentation by up to 2 weeks. A systematic review of prospective studies demonstrated a bleeding rate of 1.34% (95% CI 1.16–1.52). Of those patients having post ERCP haemorrhage, mortality was 3.54% (95% CI 1.08–6.00%)(25).

Perforation at ERCP is the source of significant anxiety amongst Endoscopists. An inherent flaw of the side viewing endoscope is that forward vision is limited, therefore previously unrecognised pathology such as a pharyngeal pouch or an oesophageal stricture represents a significant hazard. Fortunately such complications are uncommon, a large single centre American study had a rate of 0.45% (30/6620), of which 11/30 were peri-ampullary(26). Unfortunately when perforation does occur, significant mortality is associated with it (9.90%)(25).

ERCP related mortality is difficult to attribute. Patients undergoing ERCP are often at significant risk of mortality caused by their underlying disease, particularly cholangitis or cancer. Studies have therefore sought to define attributable mortality and raw 30 day mortality. In England the current mortality following ERCP for all indications is approximately 5% at 30 days(27), however this is likely to be variable based upon patient selection and procedure indication. The same study described 0.06% ERCP attributable mortality, arguing that such a figure represents deaths caused directly by ERCP. This argument is challenging as a causal link between death and ERCP may not always be clear when individual cases are examined. Causes for mortality are also often multifactorial and

subjective. The present thesis chapter investigating outcomes of ERCP therefore reports all cause mortality.

1.3.3 Malignant biliary obstruction

Patients with cancer within the region of their biliary tree may progress to develop obstruction of their bile ducts. This is due either to extrinsic compression of the bile duct or infiltration and subsequent obstruction of the duct. The patient will then develop clinically visible jaundice which can be quantified biochemically by measuring the serum bilirubin concentration. This jaundice is often painless, a feature which is classically used to distinguished malignant biliary obstruction from biliary stone disease.

Pancreatic cancer is the culprit aetiology in the majority of cases; however cholangiocarcinoma, other biliary tree or liver malignancies and potentially metastasis from distant cancers also contribute cases. Curative treatment requires diagnosis at an early stage followed by resection of the cancer. Unless malignant jaundice is secondary to a primary, resectable hepatobiliary cancer, it heralds a poor prognosis. In this chapter outcomes for unresectable patients are investigated.

1.3.4 Pancreatic cancer

In 2014 pancreatic cancer was the 11th most common form of cancer and the 5th commonest source of cancer related mortality in England and Wales. The incidence is observed to be rising nationally. The outcome from pancreatic cancer is recognised to be poor, the survival rate is 3% at 5 years and 1% at 10 years(28). Unfortunately pancreatic cancer presents late and the progress of the cancer is recognised to be rapid due to the aggressive nature of this type of tumour. Symptoms are often non-specific including weight loss, abdominal discomfort and lethargy. Jaundice is the symptom which most commonly precipitates urgent investigation; however this often develops at a late stage. Only surgical resection of pancreatic cancer provides the opportunity for a cure. This cannot be undertaken in those patients who have already advanced beyond an early stage cancer. The combination of these factors is considered to be the reason for the poor outcomes for pancreatic cancer.

1.3.5 Other primary cancers causing malignant biliary obstruction

Cholangiocarcinoma is the second most common cause of malignant biliary obstruction. This uncommon cancer arises from the bile duct itself and can be categorised based upon location; either intrahepatic or extrahepatic. Cholangiocarcinoma is rare, the incidence rate is 3.58 per 100,000 in the English population(29). Unfortunately the 5 year survival is poor at approximately 5% for both men and women. However those with only local disease at diagnosis have a better prognosis; 15%

intrahepatic, and 30% extrahepatic cancer subjects survive 5 years or more(30). ICD10 has separate code domains for intrahepatic cholangiocarcinoma (C22.1) and extrahepatic cholangiocarcinoma, which is included in “Malignant Neoplasm of other and unspecified parts of biliary tract” (C24), with sub-domains discerning the geographical location in the extrahepatic duct.

Gall bladder and small intestinal tumours are also primary cancer aetiologies that may cause biliary obstruction. However these are extremely rare at 1.28 and 0.80 per 100,000 population in England respectively(29).

1.3.6 Associations of malignant biliary obstruction

Cholangitis is the most concerning adverse event seen in malignant biliary obstruction, however this is less common than in biliary stone disease as, anecdotally, the tumour obstructing the bile duct prevents access by bacteria to the obstructed duct proximal to it. Infection within the obstructed biliary tree carries a high mortality and is therefore an urgent indication for relief of obstruction even if curative resection is planned (31). Furthermore, prevention of this event with early relief of obstruction is considered beneficial by some experts, even for incurable disease (32). However, a recent study of patients undergoing curative surgery for malignant lesions causing biliary obstruction demonstrated that outcomes appear to be worse in those undergoing decompression prior to surgery due to complications of the decompression(33).

Patients with jaundice can suffer from pruritus. Anecdotally this can vary in severity with some patients experiencing persistent, troublesome itching. By comparison other patients, particularly older patients, despite significant jaundice, can have very few symptoms. Although drugs such as cholestyramine can be of limited benefit, this symptom is difficult to manage. Only resolution of jaundice reliably provides significant or complete relief of this symptom(34).

Unfortunately jaundice contraindicates chemotherapy. Chemotherapy regimens have been extensively investigated in high quality randomised control trials. Although the size of benefit is often variable, these have demonstrated that chemotherapy improves outcomes. In patients with incurable disease it can be used for palliation, both prolonging and increasing quality of life(35, 36).

The receipt of chemotherapy is therefore the most common indication for relief of malignant biliary obstruction. Although pruritus can be distressing for patients, it is often tolerable. Cholangitis and other indications for decompression are rare in this patient group.

1.3.7 Therapeutic strategies for relief of biliary obstruction

Options for decompression of the biliary tree include either ERCP or percutaneous transhepatic biliary drainage (PTBD). ERCP achieves this by insertion of a stent across the point in the biliary tree that is obstructed. This then restores the flow of bile through the biliary tract. This is more challenging if the obstruction is more proximal (i.e. in close proximity to the liver) compared to more distal lesions which are more easily accessible. PTBD is done under ultrasound guidance to locate the dilated duct proximal to the point of obstruction. Once identified, this is cannulated and a stent is placed across the obstruction. If this is not possible then a catheter draining to the skin may be left in situ to allow drainage of bile. If the duct is opacified (i.e. radiolucent contrast is injected into the duct) but the obstruction cannot be relieved, an urgent alternative method of decompression is required.

Although not considered in this thesis, patients who are amenable to curative treatment do not always require biliary drainiage. Although drainage is essential to permit neoadjuvant chemotherapy, patients planned for “fast track” surgery do not need pre-operative relief of their biliary tree obstruction(33).

1.3.8 Current Outcomes for relief of biliary obstruction by PTBD

A recent analysis of HES data examining palliative patients undergoing PTBD for relief of obstructive jaundice has shown poor outcomes(37). All patients in England were included (n=16,822) between 2001 and 2014 who underwent PTBD without a subsequent curative resection. Mortality at 7 days (5.2%), 30 days (23.1%) and in hospital mortality (15.3%) was high, which is in keeping with anecdotal experience. Re-admission within 30 days was 20.8%. The commonest primary cancer aetiology was pancreatic, representing 58% of cases, followed by cancer of the liver or intrahepatic bile ducts (30.1%) which contained more than 90% cholangiocarcinomas. The high incidence of intrahepatic cancers is a result of the study selection criteria, as ERCP is often technically less successful in cancers arising from here. 61.3% of the included patients had undergone ERCP prior to PTBD.

Multivariable regression analysis with 30 day mortality demonstrated several associations: Advancing age quintile (older than 80 years of age, OR 2.68 (2.37-3.03), $p<0.001$), increasing Charlson co-morbidity score (>20, 2.29 (1.99 – 2.65), $p<0.001$), pre-existing renal dysfunction (2.37 (2.12 – 2.65), $p<0.001$), increasing deprivation quintile (1 (the most deprived), 1.28 (1.13 – 1.44), $p<0.001$), Malignancy of extrahepatic and unspecified bile ducts (1.28 (1.08 – 1.52), $p=0.004$), and malignancy of the liver and intrahepatic bile ducts (1.14 (1.04 – 1.24), $p=0.004$). A negative

association was observed between high annual PTBD provider volume (84 – 180) and 30 day mortality (OR 0.68 (0.58 - 0.79) p<0.001). This suggests significant variation in mortality between providers.

More than twenty-percent of patients developed a complication of PTBD within 3 months, of which almost half were sepsis related. Others included GI bleeding, acute kidney injury and stent blockage. Median survival following decompression was 94 days. Rates of complications and requirement for repeat procedure are not given by provider volume.

Patients under the age of 61 were most likely to receive chemotherapy (38.7%) compared to older age quintiles; 62 – 68 (30.4%), 69 – 74 (23.7%), 75 – 80 (13.5%) and >80 (2.5%). Those with pancreatic cancer were more likely to receive chemotherapy compared to patients with other primary malignancies. When considering the indications for relief of malignant jaundice, given the low proportion receiving chemotherapy, careful consideration of the procedure indication should be given renewed attention.

1.3.9 Comparison of PTBD and ERCP

ERCP has previously been considered to be a safer procedure for achieving relief of biliary obstruction than PTBD in subjects with malignant obstruction. Meta-analyses have compared outcomes between ERCP and PTBD with conflicting results. Zhao et al included 8 studies (5 retrospective, 3 randomised control trials) with a total of 692 subjects. They found that subjects were more likely to develop cholangitis following attempted drainage by ERCP compared to PTBD. However no difference was found for success of biliary decompression(38). Of the studies included 5 included cancers affecting the proximal biliary tree (hilar cholangiocarcinoma, Klatskin tumour, unresectable hepatocellular carcinoma). Three studies included gall bladder cancer, cholangiocarcinoma and pancreatic cancer with conflicting results. An included study from 1987 reports 75 prospectively randomised subjects, of similar baseline characteristics including age, biochemical parameters and ASA grade. Mortality was lower in subjects undergoing endoscopic decompression compared to percutaneous transhepatic approach (n = 6, (12%), 12 (33%), p=0.016). Success rate, defined as a 20% fall in serum bilirubin, was also higher in endoscopic group (30/37, 80%) compared to percutaneous transhepatic approach (20/33, 61%, p=0.017)(39).

By contrast Pinol et al described a contrasting finding in 2002. 54 subjects were prospectively randomised to either percutaneous or endoscopic relief of biliary obstruction. Technical success was reported in 71% (20/28) and 42% (11/26, p=0.03) of percutaneous and endoscopic procedures respectively using the same outcome measure(40).

Comparisons between the two modalities, even in the context of a meta-analysis are challenging due to the limited amount of high quality prospective randomised data. Comparisons are further complicated as each procedure has its own advantages, with PTBD favouring more proximal cancers and ERCP being more efficacious in those more distal within the bile duct. This is reflected in the retrospective literature included within the meta-analysis described above. Four of the five included studies describe cholangiocarcinoma, which can cause obstruction at any location within the duct. Therefore either procedure may be appropriate, facilitating comparison(38). However the location of obstruction was also found to be a determinant of prognosis by Speer et al(39). Therefore establishing if any effect is related to the location of the lesion or the procedure undertaken is challenging. Given the small size of both studies, it is not possible to use the data to delineate a meaningful answer to this question.

Instead of attempting comparison between these different procedures to establish which is best, they should be examined individually. This chapter does not aim to compare PTBD and ERCP for biliary decompression, although success rates for ERCP in individual cancers are presented. Instead outcome measures including failure rates (as measured by the need for repeated attempt at ERCP or PTBD), 30 day mortality, and receipt of chemotherapy are adopted to investigate the efficacy of ERCP in this patient group.

1.3.10 ERCP Volume effect

A volume effect has long been suspected amongst ERCP Endoscopists, with several studies attempting to answer this important question with variable results. Other specialities with complex procedural work, including colorectal surgery have established that such an effect existed in their discipline. Large database analyses have demonstrated that long term outcomes following resection are improved at higher volume units, as a surrogate of the quality of resection performed and of the peri-procedural care(41). Further UK analyses have demonstrated that by splitting providers into tertiles further demonstrates improved long and short term outcomes both by operator and by hospital trust provider volume(42).

Investigation of procedure volume is often focused on outcome by units. It is widely accepted that, although processes vary, expertise, protocols and governance arrangements are shared between Endoscopists within a unit. Therefore being part of higher volume unit influences the performance of the individuals within that unit. Current practices of Multi disciplinary team working, mentoring, and group development of protocols likely produces this effect.

However the evidence for the volume effect phenomenon in ERCP is conflicting. Current British Society of Gastroenterology guidelines recommed a unit performs more than 200 procedures

annually, with a minimum of 150(43). Several studies have attempted to delineate this effect, with variable results. Cote et al investigated an american population including 16,968 ERCPs done over a 10 year period by 130 operators. They demonstrated that those performing more than 25 procedures per year had better outcomes (failure rate 9.5% compared to 5.7%, $p<0.001$)(44). However a threshold of 25 ERCPs per year has limited relevence to most health care settings. Kalaitzakis and Toth examined Swedish outcomes by unit between 2005 – 2008, including 12,695 ERCPs for benign disease. They also considered volume effect using a cut off at 87 index procedures per unit per year. Outcome variables included failed procedures based on a requirement for re-intervention, 30 day readmission rates, length of hospital stay and mortality at 30 and 90 days. Not only did they demonstrate a relationship between high volume and successful procedures, but also a weak mortality benefit(45).

Bodger et al did not find a relationship when examining 20,246 index ERCPs over a 2 year period. Although a significant number of predictors for a poor outcome were found, volume status was not among them(27). This finding was unexpected by the ERCP endoscopist community, as displayed in a response to the article. Several references were sited that have previously suggested such an effect exists although they do not robustly demonstrate it (46, 47). There was subsequent clarification that although a volume effect was not seen, the question of a mortality effect in ERCP in the UK remains unanswered. Varadarajulu presented the most compelling available data including 199,625 ERCPs covering american inpatients between 1998 – 2001. Although the group reported technical success was greater in higher volume centres, there was no mortality difference. Importantly they also demonstrated that many units performed few ERCPs with only 5% of units performing 200 procedures per annum(48).

It is therefore possible that a relationship between volume and outcome exists, although the nature of this relationship is not defined. The only UK paper and the largest dataset did not ellicit an association with mortality. Much of the data presented is from 10 years ago. Given the changes in organisation of ERCP delivery, and the change to therapeutic ERCPs only, which are associated with a worse adverse event profile, it is now widely recommended that unit procedure volume is significantly higher than the procedure counts described in much of the above literature. Equipment and training in ERCP have also developed dramatically over this time period.

Following evidence of variation in outcomes in colorectal surgery there has now been a significant remodelling of services to ensure that units are providing sufficient volume of specifically identified procedures, in the hope of improving patient outcomes. Simmilarly now is the time to revisit these

analyses and provide definitive answers regarding the volume effect and the impact that ongoing changes in patient demographic has on ERCP outcomes. This is fundamental to guiding any change in organisation and service delivery of ERCP in the UK.

1.3.11 Volume effect in ERCP for malignant biliary obstruction

As discussed in detail above, a volume effect has been sought previously in ERCP using the HES dataset over a 2 year time period. All ERCPs were included, not only those for the relief of malignant biliary obstruction. The primary outcome measure was 30 day mortality, in which no provider volume effect was found(27). The difference between the data presented in this chapter and the paper by Bodger et al is important, as ERCP for malignant biliary obstruction carries a significantly higher mortality than benign disease. By diluting the overall cohort mortality compared to malignant disease alone, variation in 30 day mortality may be lost.

1.4 Background: Outcomes of colorectal stents when used as a bridge to curative resection in obstruction secondary to colorectal cancer

1.4.1 Colorectal Cancer

Colorectal cancer is the 3rd most common cancer in the UK, accounting for 12% of all cancers diagnosed. Rates of bowel cancer have increased by 14% in Great Britain when compared to the period between 1970 and 1979, and have increased by 5% over the last 10 years alone(49).

Approximately 20% of colorectal cancer presents at a late stage, including metastatic disease (49). This is despite a concerted public health campaign entitled “be clear on cancer”, which has run several times over the past 5 years. The message implores those who have seen a change in bowel habit or blood within their stool for 3 weeks or more to attend their GP urgently(50), but has had little benefit.

The Bowel Cancer Screening Programme is now running in the UK, with promising results. This requires subjects to return a completed stool sampling kit, which is sent to them following their 60th birthday. Those that test positive will be invited for a screening colonoscopy. Early pre-cancerous polyps can then be removed. However results also demonstrate that participation within the programme leads to cancer diagnoses in those who have not yet noticed symptoms. These are generally identified at a significantly earlier stage compared to those referred for colonoscopy based on symptoms alone (51).

At present, despite the above initiatives approximately 25% of subjects are diagnosed with colorectal cancer on attending hospital with obstruction of their bowel(52, 53).

1.4.2 Elective Colorectal Cancer Treatment.

Surgical resection is essential for any potentially curative of treatment of colorectal cancer. The elective mortality for a bowel resection operation is currently 0.7% (54). Although chemotherapy and radiotherapy have been shown to improve outcomes dramatically, the essential universal aspect to curative treatment for colorectal cancer is resection of the tumour. Prior to treatment a patient will be reviewed in a multidisciplinary team comprising surgeons, gastroenterologists, oncologists and other relevant specialists. This team will review the scans that have been undertaken so far to determine the stage of cancer and the histology. A plan can then be made including further scans if needed, chemotherapy, radiotherapy and surgery as best suited to the individual. This may include chemotherapy or radiotherapy either before or after surgery. The plan may be palliation and symptom management. In many cases, further MDT discussions will be required, lengthening the time from presentation to resection.

1.4.3 Emergency Colorectal Cancer Treatment

Twenty-five percent of subjects with bowel cancer present with an obstructing tumour. Due to blockage of the bowel by the tumour the bowel proximal to this becomes distended. This causes abdominal discomfort and vomiting leading to electrolyte disturbances and dehydration. The bowel will perforate if the obstruction is not relieved. Current mainstream treatment options include conservative management or surgery to either remove the tumour or bring out a proximal loop of bowel to the abdominal wall (stoma). Emergency major surgery for bowel cancer was 11.5% in the latest UK national audit data(55).

There are several reasons for the higher mortality compared to subjects undergoing an elective resection; subjects presenting as an emergency are acutely unwell. Although they will be hydrated and their biochemistry corrected as far as possible they are less fit for the operation than an elective patient. Secondly, although imaging will be undertaken, it is less likely they will be able to have complete staging or the benefit of MDT discussion prior to the resection. They are also more likely to have more advanced cancer, as they have reached a stage where the bowel is blocked by tumour. This will also contribute to worse nutrition compared to elective subjects.

An alternative to surgery is placement of a self-expanding metal stent (MS). A surgical procedure can then be undertaken at a later stage, once the patient is recovered, their nutrition is better and they have had the benefit of a full MDT, staging scans and chemotherapy or radiotherapy if considered beneficial.

1.4.4 Self-expanding Metal Stents

A stent is a tube that can be deployed within a hollow organ, such as bowel, with the intention of keeping it open. The goal of this procedure is to allow the passage of material that should be passing through the blocked bowel to continue to do so. Within the GI tract blockages can be caused by multiple types of pathology, including both benign and malignant.

Stents are most commonly placed in the upper GI tract for oesophageal cancer, in the setting of a cancer that cannot be cured, but is blocking the passage of food and fluid into the stomach. It would be unethical to expose the subject to a high risk surgical procedure with a prolonged recovery period for only temporary relief of a symptom, when they are unlikely to survive beyond the short term. Hence by placing a stent to re-open the blockage they can be allowed to eat and drink again. In this instance such a procedure provides significant improvement in quality of life, although the prognosis of oesophageal cancer is unchanged. The same principle is applied for colonic stents. Due to locally advanced cancer the bowel becomes obstructed. This leads to dilatation of the bowel, symptoms of vomiting and the inability to tolerate food or fluids. Therefore as a direct result of the obstruction

subjects then become very unwell. Colonic stents are similarly used, most commonly in subjects who have a cancer that cannot be cured. The same argument applies, that a surgical procedure with associated risk and recovery time is not in the subject's best interests when the blockage can be relieved with a stent.

The placement of a Stent within the colon is usually done at colonoscopy with real time X-ray guidance, however if the tumour is low down a radiologist may place the stent under X-ray guidance alone. Subjects are awake and aware of events around them so that they can change position if required by the endoscopist. The endoscope is passed to the site of the obstruction, at which point a guide wire will be passed through the blockage. A collapsed stent will then be passed through the endoscope and over the wire, using the X-ray guidance to confirm that the position is correct. Once placed the stent can be opened to relieve the obstruction. Regular bowel function following a stent can take up to 48 hours to return following the procedure.

1.4.5 Colonic Self-expanding Metal Stents Evidence

In some subjects stents are now being employed with a different intention, still to relieve the obstruction, but in subjects when the underlying malignancy remains potentially curable. However this remains significantly less common than their use in palliation. A Canadian cohort study of 225 stent insertions demonstrated that over a nine year period, 71% were placed for palliation rather than in subjects with a curative goal. There was a clear trend of increasing popularity of colonic stents being placed, with numbers quadrupling over the study period from 2000 – 2009. Unfortunately trends in stent placement with curative intent are not described(56).

Due to the nature of malignant colonic obstruction, large randomised controlled trials have found limited success in recruitment. CReST is one such study, the recruitment target for which was 400 subjects. Unfortunately only 246 could be included from 39 units between 2009 and 2014. Stent insertion was standardised between units to a combined endoscopic, fluoroscopy guided technique. Subjects were required to present acutely with left sided obstruction. Stents would be inserted as a bridge to resection, which was then undertaken within a 4 week period following placement. Stent insertion provided relief of obstruction in 82% of subjects and was demonstrated to give a statistically significant reduction in stoma formation. However no difference in 30 day or 1 year mortality was found. The authors also examined Quality of Life by questionnaire, finding no difference between groups at either 3 or 12 months.

A smaller Italian multicenter randomised control trial "ESCO" was published in December 2016. From March 2008 to November 2015 they were able to recruit 144 randomised subjects to either a colonic stent as a bridge to surgery or emergency surgery. Inclusion criteria restricted subjects to

cancers between the splenic flexure and 15cm proximal to the anal margin. Unfortunately due to diagnostic errors 29 subjects were excluded from this cohort, therefore only 56 patents received a colonic stent. Although they were able to demonstrate a lower rate of stoma formation in the stent group, no other statistically significant difference between the treatment arms could be elicited at 60 days follow-up(57).

Several meta-analyses have been performed looking at colonic stents. The most recent of which included only randomised control trials looking at colonic stents as a bridge to surgery compared to emergency surgery from January 2001 to September 2013. Five studies could be included generating 273 subjects. The authors were careful to exclude any study looking at right sided obstruction and any study using stents in subjects who were not intended for curative treatment. Their results correlate to the randomised studies described above in that the colostomy rate was lower in the stented group. Their data also suggests that those with a stent rather than emergency surgery had lower rates of complications, fewer surgical site infections and improved rate of primary anastamosis. No data could be presented regarding long term survival as this was not a primary outcome for the included studies, however in the small numbers seen, recurrence was numerically higher in the stent group compared to emergency surgery(58).

Oncological recurrence rates in the stent group compared to emergency surgery is an important question. It has been theorized that the placement of a stent within the tumour leads to fracturing with the potential for increased rates of both local spread and distant metastasis. Single centre retrospective analyses of 3 year and 5 year recurrence free survival do not support this theory. Unfortunately no large, prospective data set with sufficient power is available to definitively answer this question(59, 60). Although an important consideration for the utility of colonic stents as a bridge to potentially curative resection, this question has not been explored within this thesis.

A survey of surgeons from the Colorectal Surgical Society of Australia and New Zealand was undertaken to examine attitudes to colonic stenting given the difficulties in recruitment to high quality randomised trials. All surgeon members of the association were contacted by post, with 65% responding. Questions enquired about their willingness to enter subjects into trials of stents for curable disease, potential barriers to their usage and scenario based questions. Only 29% of surgeons would enter subjects into such a trial. The commonest reasons for not using stents in practice were varied including 90% believing that stents are not cost effective, 80% stating subjects did not prefer stents, 68% were concerned regarding perforation rate and 49% felt stents had no role in the curative setting (61).

The studies discussed above represent the current literature regarding the use of colonic stents for potentially curable colorectal cancer presenting as obstruction. It is clear that stoma rates are reduced in those using stents as a bridge to therapy. No difference in survival is observed in these studies. However there are clearly barriers to recruitment for clinical trials that relate to both the clinicians and the subjects. As subjects with bowel obstruction will be admitted under the care of the surgical on call team, the involvement of surgeons in studies is essential. Challenges in recruiting subjects are likely to explain why prospective trials have not reached recruitment targets, and therefore may lack the power to detect mortality differences. Therefore further data is required to clarify if stenting prior to surgery is a beneficial treatment option. Utilising HES data, this chapter aims to overcome the challenges faced in recruiting subjects to randomised controlled trials. This will allow a large, albeit retrospective cohort for analysis.

1.5 Background: Outcomes of pneumatic dilatation and Heller's myotomy for achalasia in England between 2005 and 2016

1.5.1 Achalasia aetiology and diagnosis

The mechanism behind the development of idiopathic achalasia is poorly understood. There appear to be loss of nitrergic neurons within the myenteric plexus at the lower oesophageal sphincter(62). Infiltration with lymphocytes has also been documented. The aetiology for this change is unclear although autoimmune, degenerative and viral infections have all been hypothesized. The effect of this is a failure of relaxation at the lower oesophageal sphincter(63). Any swallowed material therefore is unable to pass through easily, leading to stasis within the oesophagus and eventual oesophageal dilatation. The associated symptoms therefore include a sensation of food becoming lodged within the oesophagus and weight loss. Subjects often also report chest pain as a major symptom. These symptoms will not usually be variable between solids and liquids and there may be vomiting or regurgitation of minimally digested food.

Given the nature of symptoms, the initial investigation undergone by a majority of subjects is most commonly an endoscopy, however this often appears normal with no discrete abnormality. However A barium swallow will demonstrate the functional hold-up of contrast. Should the barium examination be performed first, an endoscopy should still be undertaken to exclude malignancy as a cause of pseudo achalasia. There are many published case reports describing the presentation of oesophageal or gastric cancers mimicking that of achalasia, described as pseudo achalasia. Extrinsic compression from other local malignancies such as lung cancer have also been reported to cause a similar phenomenon(64). This is challenging when examining the relationship between oesophageal cancer and achalasia. The gold standard for diagnosis is high resolution oesophageal manometry, which will show the classical distribution of a lower oesophageal sphincter that is not relaxing and loss of peristalsis above it.

1.5.2 Achalasia Treatment Modalities

Treatment of achalasia is segregated into three broad categories. These include medical treatments, endoscopic interventions or surgical procedures. Each has associated risk profiles and is generally suited to subjects with different degrees of co-morbidity.

Medical treatment

Several pharmacological strategies have been trialled with the aim of enhancing relaxation of the lower oesophageal sphincter prior to oral intake. Medication classes include calcium channel blockers and nitrates. Due to diminishing response and significant side effects this strategy is often considered less effective than endoscopic or surgical modalities and is not generally used(65).

Endoscopic Intervention

Several types of endoscopic treatment exist for achalasia, the most common of which is a dilatation of the lower oesophageal sphincter by a pressure controlled balloon. During this procedure an endoscope is passed down the oesophagus to the gastro-oesophageal junction. At this position a wire is passed from the oesophagus into the stomach and the endoscope removed, leaving the wire in place. The deflated balloon is then passed down the wire and positioned over the defective sphincter. The balloon is then inflated to dilate the opening, either in a single session or by two dilatations with increasing balloon size. Variations on this technique include the use of a more rigid balloon or a rigid endoscope, however these are uncommon.

An alternative endoscopic treatment is to inject botulinum toxin into the lower oesophageal sphincter. This intends to reduce the incomplete relaxation and improve of symptoms. Practically this treatment requires an endoscope to be passed to the gastro-oesophageal junction at which point the toxin is injected circumferentially around the lower oesophageal sphincter.

A new endoscopic treatment, Per Oral Endoscopic Myotomy (POEM), has been performed in recent years at some specialist centres. This technique allows dissection of the muscular sphincter at the lower oesophageal sphincter at endoscopy. This is considered to carry significant risk or perforation and is done by only a few Endoscopists in England.

Surgical Treatment

The surgical procedure most commonly performed for achalasia is laparoscopic Hellers myotomy. This is undertaken under general anaesthetic by either thoracic or abdominal approach. The layer of muscle surrounding the lower oesophageal sphincter is dissected leading to free passage of food and fluid into the stomach. Subjects often undergo a fundoplication operation at the same time as their myotomy, as this reduces the amount of acid now able to reflux into the oesophagus.

1.5.2 Evidence for Achalasia Treatment Modalities

Due to the low incidence of Achalasia, randomised control trials are challenging to recruit to in large numbers. Furthermore as the condition is chronic, subjects will live with achalasia for many years. Therefore not only is there a challenge to complete adequately power trials, but they must also be of significant duration to test the durability of any given treatment.

A recent high quality trial has compared pneumatic dilatation with laparoscopic Hellers myotomy in a prospective, randomised design. Boeckxstaens et al report outcomes in 201 achalasia subjects over 43 months (95% CI 40-47 months) comparing these modalities. The primary outcome was Eckdart score of less than 3, which was considered a therapeutic success. This score is based upon severity of symptoms including regurgitation, retrosternal chest pain, weight loss and dysphagia. Secondary

study outcomes included the requirement for further treatment, quality of life and lower oesophageal sphincter pressure. Analysis by intention to treat demonstrated success rates of greater than 90% in both groups at one year follow-up and suggested that there was no statistical difference between the modalities at the end of 2 years follow-up(66).

Perforation in the dilatation group was 4% and mucosal tears were noted in 23% of the laparoscopic Hellers myotomy. Of subjects undergoing pneumatic dilatation 4 were considered treatment failures due to an insufficient drop in their Eckdart score. A further dilatation was required in 23 subjects during the study period. Fifteen subjects undergoing laparoscopic Hellers myotomy were considered to fail by Eckdart score and were referred for subsequent dilatation.

Moonen et al reported 5 year outcomes for this study population. The primary outcome remained an Eckardt score less than 3. Repeat dilatation was now permitted twice in the dilatation group (i.e. up to 3 dilatations in total) before the subject was considered to have failed treatment. At 5 years 128 subjects remained under active follow-up with the trial. At 5 years there was no difference between treatment modalities. Two analyses are described based upon the intention to treat and pragmatically based upon treatment received. Although the per protocol analysis benefits from the intention to treat analysis, the full analysis includes adverse events and patient refusals to follow the protocol as treatment failure rather than censoring them. For this reason the full analysis provides a more realistic evaluation of the treatment modalities(67).

The manuscripts above describe a high quality, prospective study with a good follow-up length. Unfortunately with this trial design subjects lost to follow-up are problematic, with almost 40% lost by the end of the study. Furthermore although 5 years is a considerable length of time, achalasia is a long term disease and as such greater lengths of follow-up data are still required.

Similar outcomes are reported between very different treatments. Numerically fewer subjects undergoing the dilatation compared to laparoscopic Hellers myotomy required further treatment rapidly after their initial intervention. The balloon dilatation treatment is less resource intensive; it has a better adverse event profile and has a shorter recovery time. Even when taking account that up to 3 dilatations were considered acceptable over a 5 year period this seems less burdensome than the laparoscopic Hellers myotomy. However as only 57 subjects who initially underwent dilatation were included by the study end point at 5 years, further data is required.

Although large trials are not forthcoming, several meta-analyses have included endoscopic botulinum toxin injection in comparison to other strategies. These suggest that the effect of Botox injection is less effective than dilatation, although some studies report comparable outcomes at 6

months when compared to Hellers myotomy(68). However it is also clear that the benefit is less durable with a higher incidence of repeated interventions in the botulinum toxin group (OR 2.6 95% CI, 1.05-6.5; P = 0.04) when compared to a single dilatation and by a greater margin when compared to laparoscopic Hellers myotomy(69, 70).

The aim of this study is to use secondary care data from the Hospital Episode Statistics (HES) database to provide a large patient cohort in this uncommon condition. The HES data will facilitate analysis of long term outcome data and complication rates and 30 day mortality for pneumatic dilatation and myotomy. Botox injection is accounted for in the analysis, however the lack of long term efficacy is already established. Therefore only outcomes of pneumatic dilatation and myotomy are compared.

1.6. Background: Incidence, morbidity and mortality of subjects with achalasia in England: findings from a study of nationwide hospital and primary care data

1.6.1 Incidence of achalasia

The incidence of achalasia in western populations is currently estimated to be 1 in 100,000 subjects. However the evidence base for this is currently limited and variation in incidence and prevalence is observed in studies of different populations. The largest published study (1987) includes 6306 in Great Britain and Ireland combined, of whom 4,920 subjects were identified in England. The incidence of achalasia calculated from this cohort was 0.9 per 100,000 in England, which remains the largest cohort of English achalasia subjects published to date (71).

A review article collating studies of incidence and prevalence tabulates epidemiological studies of achalasia internationally (72). Although the incidence was not universally reported, estimates vary between 0.03 per 100,000 in a black Zimbabwean population(73) and 1.63 per 100,000 in Canada(74). However these studies included cohorts of 25 and 463 subjects with achalasia respectively. Therefore the results must be considered carefully given that the number of included achalasia subjects was small, and therefore estimates may not be precise. They may also represent a picture of varying incidence based upon the population studied.

Achalasia can also be secondary, however this is uncommon in western populations. In South and Central America the Trypanosoma cruzi parasite is common, potentially leading to Chagas disease and secondary achalasia. Incidence and prevalence figures may therefore not be comparable to western populations. However this is unlikely to impact on epidemiological studies that are based in the UK, as is the case in the present thesis chapter.

Achalasia has been found to hold a strong association to HLA-DQ β1, which appears to confer susceptibility(75, 76). This has been further localised to geographical regions within Europe including a north to south gradient of increasing incidence greatest in southern Europe. This finding supports the notion that there is variation in incidence and prevalence between different populations(77).

A further recent study based in Chicago compared incidence rates of achalasia in neighbourhoods served by hospitals performing high resolution manometry (HRM) compared to those that do not (78). This resulted in significant differences in incidence rates of 1.07 per 100,000 compared to 2.92 per 100,000 in subjects without access to HRM and those with HRM respectively. However the number of subjects was modest, as seen in the studies described above, only 379 cases were identified over a 10 year period. This suggests that a significant number of achalasia cases may be missed with conventional diagnostic methods. However as those subjects presumably continue with their lives, are able to achieve sufficient nutritional intake and do not re-present recurrently (in which case they would likely be diagnosed) this may represent subclinical achalasia which does not mandate treatment.

As described in a previous chapter, the treatments for achalasia are often endoscopic. However, the incidence of achalasia subjects that will require treatment is currently unclear. A key goal for this chapter is to delineate the current epidemiology of achalasia in England.

1.6.2 Association between Oesophageal Cancer and Achalasia

The baseline incidence of oesophageal cancer in the United Kingdom is 18 per 100,000. There are many recognised associations, including cigarette smoking, alcohol consumption, age, male gender, gastro-oesophageal reflux disease and deprivation amongst others. Several studies have now suggested a link between oesophageal cancer and achalasia. This should not be confused with the diagnostic phenomenon of pseudo-achalasia in which subjects with appearances in keeping with achalasia are then found to have oesophageal cancer (79, 80).

The association with squamous cell carcinoma is well documented. Brucher et al demonstrated that of 124 incident achalasia cases four developed cancer within a median follow-up of 5.6 years from diagnosis. Similarly, a proactive approach established a diagnosis in 1.5% of all other squamous cancers presenting to their unit within the same time period(81). This is not a finding in isolation, a more recent study of 448 incident achalasia subjects were followed of whom 3.3% developed cancer at a median follow-up of 11 years despite treatment with graded dilatation. A relative risk of developing cancer in those with achalasia was calculated at 28 (CI 17-46). Although this is a substantial increase from baseline, as the authors point out, the absolute risk is still very low(82). Further studies have reproduced this albeit with less impressive case numbers(83).

There has been significant interest in modifying the risk of oesophageal cancer with surgical treatment. A manuscript published in the British Journal of Surgery described 228 subjects contacted a median 18.3 years following their myotomy for achalasia. Four subjects had since developed oesophageal cancer, with a single survivor. This gives an incidence of oesophageal cancer in this cohort of 141.7 per 100,000. This is thirty-five times greater than the population average suggesting that myotomy does not resolve the cancer risk. Furthermore these cancers were squamous carcinoma, as associated with achalasia. Adenocarcinoma would raise the suspicion that perhaps these cancers were related to reflux following myotomy. The relationship between myotomy and squamous cell carcinoma in achalasia therefore requires greater investigation(84), however this is outside of the remit of this thesis.

The aetiology of the apparent association of squamous cell carcinoma and achalasia is unclear. It is often considered likely that incomplete oesophageal emptying leads to stasis of oral intake in the oesophagus, followed by inflammation and dysplasia. However this could also be expected in to

increase the risk of adenocarcinoma. If an alternative mechanism also influences the associated increased risk, there may also be an increased incidence of other cancers in subjects with achalasia. Therefore in this chapter not only will the link between achalasia and oesophageal cancer be sought, but also a link between any other types of cancer.

1.6.3 Co-morbidity associated with achalasia

Achalasia most commonly presents in the middle of the 6th decade of life. At this time there are numerous other prevalent health conditions commonly diagnosed, including ischaemic heart disease, respiratory tract infections and peripheral vascular disease. Numerous cancers have increasing incidence over this period in life including colon, lung and pancreatic. With the exception of a single, large hospital case series, which was negative, there has been no investigation of the mortality associated with achalasia(85). However such a relationship would be important for two reasons. Firstly subjects at increased risk may benefit from screening or primary preventative measures. Secondly, the treatment provided to specific demographic subgroups might need to be reconsidered if achalasia subjects were found to have associations to conditions that altered their suitability to any specific therapy.

1.6.4 Achalasia in two databases

As described above, the epidemiology and public health outcomes regarding achalasia require revisiting. The resulting data will guide treatment decisions for achalasia and support the provision of holistic care. However in the UK achalasia is diagnosed in secondary care and most of the outcomes sought in this chapter will be better documented in primary care. Therefore any diagnosis data is more likely to be robust in secondary care data. However primary care data will support better analysis of comorbidities and allow construction of a matched cohort to compare such outcomes. Therefore this analysis therefore makes use of data from both healthcare settings.

This is an uncommon opportunity to put together The Health Improvement Network (THIN) primary care data and Hospital Episode Statistics (HES) secondary care data (both of which are described in detail in the general methodology chapter). By combining the two data sets in this chapter, results will be both robust and provide important outcomes that span secondary and primary care.

By providing robust incidence and prevalence data, combined with other key health outcomes, this chapter describes subjects with achalasia. This is important when considering GI endoscopy service provision for achalasia patients, whose treatment is heavily dependent on endoscopic intervention.

1.7 Background: Outcomes following percutaneous endoscopic gastrostomy insertion in patients with learning disability

1.7.1 The role of PEG feeding

A Percutaneous endoscopic gastrostomy (PEG) is a feeding tube, placed during an upper GI endoscopy. The tube provides a route to pass feed directly into the stomach without any need for eating or swallowing. The primary role of a PEG is to support subjects to meet their nutritional needs through the GI tract, even when swallowing or passing food through the oesophagus is not possible. This enteral route has significantly fewer complications compared with non-enteral feeding, which requires nutrition to go directly into the circulation though an indwelling venous catherter. Most commonly PEGs are placed in subjects who have lost the ability to swallow for neurological reasons, most commonly a stroke. A further common indication is impending obstruction of the upper GI tract eg prior to surgery, radiotherapy or chemotherapy in subjects with head and neck cancers.

1.7.2 PEG placement procedure

Prior to the PEG placement procedure, subjects sign a consent form following careful explanation of the procedure itself including the risks and intended benefits. To sign a consent form, a subject must have capacity including the ability to understand, retain and weight up information given to them regarding the procedure, and to be able to make and communicate their decision. In those with profound LD informed consent may not be possible. Therefore, for example, procedures such as a PEG placement are often done in the best interests of LD subjects, in which case a consent form will be signed by 2 doctors. In some instances the subject may not understand what is being done to them, leading to a traumatic and challenging procedure.

The PEG placement is performed by passing an endoscope into the stomach, which is inflated with air. Using clinical examination and transillumination a point on the abdomen is located that is directly opposed to the gastric antrum. Local anaesthetic is then injected into the skin and a needle passed through the skin into the stomach to confirm adequete opposition. A small incision is made with a scalpel allowing a trochar to be passed through the skin into the stomach. A thread is then passed through the trochar into the stomach, grasped by the endoscopist and pulled out through the mouth. The thread is attached to the gastrostomy tube with internal bumper and pulled through the mouth into the stomach and out of the hole left by the trochar so that the bumper is flush to the gastric mucosa. It is then secured with gentle pressure at the skin leaving a tube into the stomach. Subjects tolerate the procedure with concious sedation provided by the endoscopist including midazolam and fentanyl.

1.7.3 PEG placement in Dementia

Previously subjects with dementia regularly underwent PEG insertion. Due to progressive cognitive decline subjects often lose their appetite and therefore do not meet their nutritional needs, or become unable to swallow safely. Both of these developments often represent a late stage in the disease process. Both of these problems would therefore be corrected by placement of a PEG so that subsequent fluid and nutritional needs could be met without the need to eat or swallow. However this has been shown to not imporve overall outcome in such subjects(86, 87). This finding was counter intiuitive as good nutrition should theoretically improve outcomes in this cohort.

Despite the evidence being found to be robust and reproducible, PEGs were still being placed at the time of the 2004 National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) report "Scoping our practice". The report suggested that an MDT approach should be taken to patient selection for PEG placement. This has now been widely adopted and, anecdotally, PEGs are now not placed in subjects with dementia.

It is now important to be clear that other indications for PEG placement are carefully scruitinised. It is therefore not reasonable to consider that a PEG is beneficial in such cases as this is intuitively a positive intervention.

1.7.4 Learning Disability cohort

Learning disability (LD) is a broad term that represents a heterogenous population cohort. Such subjects range from those that function well within society but struggle with some aspects of social interaction to those with profound disabilities with respect to mobility, commnication and cognition. A robust definition of such a population is challenging and subjective even amongst an expert group. A report examining access to healthcare complied by the Health and Social Care Information Centre (HSCIC) has addressed this previously(88). By utilising a panel of experts, Read codes for LD were identified by consensus amongst 3 or more of the 4 person panel. This set of codes has now been used in several examinations of this patient cohort(89, 90).

Subjects with LD are often excluded from clinical trails as there are significant differences between those with LD and subjects without LD. They are more likely to suffer from long term illness such as epislepsy and mental health conditions. There can also be a physical element to their disability including reduced mobility and sensory impairment. Unfortunately they are also a group that can struggle to interact with healthcare services, either because they are physically unable to access

them or because service planning has not adequetely taken account of their needs. This can lead to significant hardship, reduced quality of life and potentialy reduced length of life in LD subjects (91).

1.7.5 Learning dissability research

Several studies have investigated the impact of interventions to improve access to healthcare(89, 90), however these are limited other examples of investigations tailored to this population compared to non-LD cohorts. When considering PEG insertion a search of the National Institute for Health pubmed.gov index for ""percutaneous endoscopic gastrostomy" AND "Learning disability"" yields 0 results, compared to 152 for ""percutaneous endoscopic gastrostomy" AND "stroke"" and 2847 for "percutaneous endoscopic gastrostomy" alone. It must be recognised when considering these figures that PEG insertion in stroke subjects is of significant academic interest for stroke physicians. However simmilar results can be achieved for seeking other interventions when comparing LD to non-LD cohorts.

Systematic exclusion from academic inquiry has therefore led to LD subjects being described as a "cinderella population" in a report by the National Patient Safety Association (NPSA) in 2004(91). Findings were based on a literature review, one to one interviews were undertaken with carers and people with learning disabilities, and workshops. Focus groups were also run with frontline staff members in general and specialist areas of health and social care to provide a broad representation of the issues affected by this group. Four priorities were established, of which one was dysphagia. This is more common in LD subjects than in the general population and can lead to both recurrent aspiration of food and nutritional problems as LD suffers or their carers become nervous about eating, leading to reduced oral intake. Aspiration leads to recurrent episodes of pneumonia, often including hospitalisation. Outside of their normal environment while acutely unwell can contribute to further deterioration in nutritional status. Recurrent aspiration and episodes of pneumonia also contribute to the high incidence of chronic lung disease(92) and disproportionately high mortality from respiratory conditions seen in subjects with LD (93). A Confidential Inquiry into premature deaths of people with learning disabilities (CIPOLD) supports this finding and recommends that people with learning disabilities should be considered at high risk of death from respiratory conditions.

Epilepsy in association with LD is also reported to be associated with increased mortality. A recent meta-analysis of peer reviewed studies demonstrated that the increase in mortality risk for the general population associated with epilepsy (Standardised Mortality Ratio 1.5 (95% CI 0.3 - 4.3)) was

minimal. However when compared to those with LD that risk is significantly higher (13.2 (7.6 – 21.5))(94). The present chapter therefore accounts for additional risk from epilepsy, as well as other possible factors including age, co-morbidity and deprivation quintile.

PEG insertion is, anecdotally, generally undertaken in this group for multifactorial indications. In some cases either failure to meet nutritional requirements or recurrent aspiration pnuemonia are indications, however often both are present. However data is lacking to tell us if aspiration risk is reduced or increased in those undergoing PEG insertion. Although ameliorating the risk of aspiration from dysphagia, aspiration of stomach contents during PEG feeding is a recognised problem.

It is therefore important to examine the incidence of respiratory tract infections in this cohort following PEG insertion. THIN is ideal for this question as such subjects may often attend hospital for only a small proportion of infections, although support from general practice including home visiting is more accessible. Due to the challenges of hospital admission in LD subjects(91), this may even be actively avoided unless severely unwell.

2. Aims of this thesis

The aim of this thesis is to explore the role of national scale database analyses for investigating outcomes related to therapeutic endoscopy. From a clinical perspective this will include important outcome measures including mortality, success rates and complications. From a service perspective questions regarding the impact of provider volume on procedure outcome, incidence rates in rare diseases commonly treated endoscopically, and broader public health outcomes for subjects.

Each chapter will also seek to use different data analysis methodologies and statistical techniques to explore their use in database analyses for endoscopy. It is intended that this demonstration of concept will increase the number and quality of database studies for endoscopy.

Chapter aims:

1. What are the outcomes of ERCP for the relief of biliary tree obstruction secondary to cancer in subjects who have incurable disease?

2. What are the outcomes of colonic stents when compared to emergency surgery in subjects presenting with acute large bowel obstruction secondary to colorectal cancer?

3. What are the outcomes of surgical and endoscopic therapy for achalasia in long term follow-up?

4. What are the current demographics of achalasia, and what are the long term outcomes for this patient cohort?

5. Following Percutaneous Endoscopic Gastrostomy (PEG) placement in subjects with LD, what are the outcomes with respect to aspiration pneumonia and mortality?

3. Materials and methods

3.1.1 Hospital Episode Statistics

Hospital Episode Statistics (HES) is a national administrative data warehouse covering all inpatient admissions, critical care, outpatient appointments and Accident & Emergency activity in England. At present the warehouse represents more than 125 million episodes per year. The primary function of HES is to provide the basis for administrative functions and secondary research in secondary and tertiary care. The data source is also used to administrate the Payment by Results (PBR) tariff, which came into existence in 2006. However HES data is available from 1989 for inpatients and for outpatients from 2003, although the inclusion of diagnostic data for outpatients is not mandatory. Prior to HES that equivalent data was collected sub-nationally by the regional Strategic Health Authorities. (95)

3.1.2 Hospital Episode Statistics Data

HES data can be categorised into several domains. These include Demographics, allowing entry of variables such as age, gender, and ethnicity. Geographical location data is available for the place of treatment and area in which they reside. This geographical data is subsequently used to generate Index of Multiple Deprivations (2010) scores for each patient, as discussed in more detail below.

Procedural data is coded using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, version 4. (OPCS4). This includes all procedures including, endoscopy, surgery and other interventions. Codes are sufficiently detailed to discriminate between types of endoscopic intervention or subgroups of surgical procedure, such as a type of right hemi-colectomy. Furthermore coding adjuncts are available for the use of additional detail including laparoscopic technique or image guidance. Administrative data is also included within HES detailing method of admission and length of stay which therefore add further detail to the information available regarding the circumstances of a procedure.

Clinical details are coded by the International Classification of Diseases, 10th edition (ICD10). This exhaustive list of diagnoses also permits coding of procedural complications, as well as previous operations and some lifestyle factors such as smoking and obesity(96). Each admission includes a diagnosis in “the primary position”, which is the main cause for that admission. A further set of 19 ICD10 codes can then be included which represent other significant pre-existing diagnoses or any additional diagnoses attained during the admission including the complications of a procedure.

Unfortunately although the HES warehouse contains a large volume of data, the information beyond clinical diagnosis, procedures undertaken and complications is limited. There is no access to blood test results or imaging outcomes, except for any specified diagnoses. A significant problem that has been well recognised is the lack of histological data or staging data for cancer, this represents a key

challenge to overcome in this analyses presented in this thesis. Although this data exists in national cancer registry databases, it is not linked to HES. Patient symptoms are also not available for inclusion in any analysis, in contrast to primary care data in THIN.

The HES data is linked to the ONS allowing accurate mortality data. The ONS is the official UK national statistics institute and is the largest provider of official population, societal and economic statistics. It is responsible to the parliamentary statistics authority, allowing it to be independent of political agenda. All statistics provided are publically available via their internet site and further, detailed information can be requested.

For the purposes of this thesis the ONS provides data covering cause of death, age, and other specific data to be linked with HES. This allows standardised ICD10 classifications for the cause of death for subjects. Importantly it is also a robust information source covering hospital and community settings so that mortality statistics provided by HES are not limited to in-hospital deaths.

3.1.3 Example HES data capture

A 63 year old Afro-Caribbean patient attends the accident and emergency department with abdominal pain and vomiting. The staff perform routine observations, blood tests an abdominal X-ray and he is referred to the surgical team.

Prior to his admission, details are already available within HES including his demographic data; ethnicity, age, index of multiple deprivation and GP practice as collected at his last contact with secondary care. He has a unique identifier that will link any prior outpatient attendances along with the diagnosis list (up to a maximum of 19, including a primary diagnosis for that episode) and any procedures performed based upon the OPCS4 coding system.

At this stage his accident and emergency department admission is recorded alongside diagnostic data in HES. His method of admission will be documented as emergency rather than elective. Information regarding observations, bloods and imaging will only be available from local IT systems. Documentation of symptoms or planned treatment is not available.

After review by the surgical team the patient undergoes CT suggestive of gastric outlet obstruction secondary to gastric cancer. He undergoes endoscopy which confirms gastric outlet obstruction, biopsies are taken to confirm this is a cancer and he is placed on intravenous fluids. Due to a combination of vomiting and contrast given for his CT scan he develops oliguria and acute kidney injury. His biopsies are discussed at the MDT and gastric adenocarcinoma in confirmed.

The HES data can now demonstrate several diagnoses; gastric outlet obstruction (K31.0), gastric cancer (C16) and acute kidney injury (N17). However his gastric cancer diagnosis will lack information regarding the stage or how advanced the cancer is. We can establish that he presented with gastric cancer as an emergency and that he does not have known metastasis (this is coded separately under C79), however staging systems such as TNM or information regarding multi-disciplinary meeting discussion and their decisions are not available. Similarly the presence of his acute kidney injury is available but severity other then any requirement for dialysis is not. OPCS4 codes for upper GI endoscopy and biopsy (G45.1) will also be included in HES. However exact findings or procedural details such as sedation or the grade of Endoscopists are not available. Alternative data sets such as Somerset or the National Cancer Data Repository (NCDR) will contain these data items. Unfortunately they are not linked to HES and therefore research utilising their data cannot be easily undertaken.

Following MDT discussion it is agreed that due to local invasion this cancer is incurable. The patient now undergoes a palliative operation to bypass his obstruction. He is planned to receive palliative chemotherapy. Unfortunately he deteriorates following surgery and is admitted to intensive care.

His operation is coded in HES and given the type of operation it is assumed to be palliative. This assumption is based on the coding of the procedure, as details of tumour stage (beyond the presence of metastases) and functional status are not available. Unfortunately the information regarding surgical intention is not explicitly provided. The intention to provide chemotherapy is also not coded for in HES, this will only be available if he receives it. His intensive care admission is coded, but as previously more granular data is not provided by HES. Databases such as the Intensive Care Network and Research Centre (ICNARC) will document more detailed information but this is not linked for analysis. Complications of his surgery such as peritonitis and sepsis can also be coded for in HES as a further diagnosis, although this is not mandatory.

The patient recovers and is discharged, however he is now unfit for chemotherapy. He dies several weeks after discharge at home, supported by the palliative care team.

Upon discharge his summary will be coded by the primary care team. A proportion of general practices are included in the THIN data set, as described below. HES will not include data beyond his discharge unless he comes into contact with secondary care again. Mortality data is coded for in the ONS, irrespective if he died in hospital or in the community providing diagnosis at discharge.

3.2.1 The Health Improvement Network

The Health Improvement Network (THIN) is the second source of data for analysis in this thesis. THIN is a database of linked general practice records for users of the Vision software. Six percent of the population of the United Kingdom are included within the database, equating to approximately 5 million subjects(97). This patient group is representative of the demographics in the United Kingdom. Records are identified by an allocated code number only. All patient identifying information is removed prior to uploading to the network from individual practices. Individual practices are not identifiable to researchers, although subjects can be matched with others from the same GP practice to improve likeness of matched pairs and reduce unseen bias in specific study designs.

Data recording quality is monitored in THIN participating GP practices and support is available to practices that require support to ensure their data is of sufficiently high quality. Funding is also provided as an incentive to GP practices for participating in THIN. Practices are required to achieve the acceptable mortality recording standard as a bench mark of data quality. This compares the number of deaths reported to those expected considering the demographic structure of the population served. Therefore, once achieved, this provides evidence that practice records are up to date and contemporaneous(98).

Practices are also required to use the Vision software for 1 year prior to being eligible to provide data for analysis within studies. Therefore practices have sufficient time to ensure records are updated and all items of past medical history and patient demographics are transferred to the new software for upload to THIN. The date at which patient data can be included is set at the latest of: 1 year after software installation, 1 year after the practice achieves the acceptable mortality recording standard, or 1 year after the patient registration with the included practice. This ensures maximal data accuracy and avoidance of under reporting of outcomes.

Data items in THIN are described using “Read codes”, a hierarchical system(99), instead of the diagnostic ICD-10 and procedural OPCS4 codes as utilised by HES. Standardised electronic recording methods are effectively mandated by the NHS due to the role of the Quality Outcomes Framework that determines individual funding levels for each general practice. Read codes can describe not only medical diagnoses, but also symptoms, examination findings and procedures. They are also employed to describe ethnicity and other social data such as weight, alcohol consumption and smoking status. Furthermore descriptions of interventions in these areas such as smoking cessation advice are coded. Additional health data coding also facilitates descriptions of varied health parameters, in particular this includes medication prescriptions. This is often of significant practical

value when designing a study to answer research questions that are based upon or significantly influenced by medication usage.

3.2.2 Example THIN data capture

A 42 year old white patient registers with a new GP practice that uses Vision software. The practice is already part of THIN, having used the software for 5 years and has achieved an acceptable mortality recording standard in previous years. The patient will become eligible for inclusion in THIN 1 year after his date of registration with the practice.

At a later date the patient attends a new registration appointment, at which they provide details of their past medical history of ischaemic heart disease and current medication. This is described with Read codes within the practice system, as are all available demographic details.

The patient attends again with symptoms of chest pain several weeks later. The chest pain symptom can then be Read coded. He is admitted to hospital by his general practitioner as an emergency, were his symptoms are treated as angina, medications are changed and he is discharged. Once the discharge summary is received by his practice, this episode will be Read coded as an emergency admission and a Read code for ischaemic heart disease will be added. His medications will be updated using the drug Read codes for the exact preparation, dose and form as prescribed.

Several weeks later he attends hospital for a planned day case percutaneous coronary intervention with stent insertion. Upon receipt of the discharge letter, his practice will apply a Read code to specify the type of procedure performed.

One year following his initial registration with the practice the Read codes above are eligible for inclusion in THIN. These are therefore uploaded without associated patient identifiable data to protect anonymity.

Due to practice policy he may be asked to attend a routine appointment on an annual basis to discuss his ischaemic heart disease and review medications. At this appointment he has a Read code for ischaemic heart disease, despite not having a further episode. Although there will be variation between practice coding, he may therefore have Read codes for up to 3 recurring episodes of ischaemic heart disease.

3.3.1 Comparison of THIN and HES

The strengths of THIN when compared to HES are a product of the different population described. THIN includes subjects in primary care with additional data provided by secondary care. HES only covers subjects at the time of contact with secondary or tertiary care. As such HES is likely to have

significant limitations when considering epidemiological questions as it can only look at contacts with hospitals. If all subjects with a given diagnosis will unavoidably require hospital care then by utilising national statistics provided by the ONS, it may be assumed that the entire national population is included, but this is uncertain. THIN, however, will include a code for all patient episodes regardless of care setting for 5% of the population. This removes that assumption that HES is dependent upon. Unfortunately a further assumption, that the 5% are reflective of national population is instead mandated.

Another important benefit is the increased granularity of data found in THIN. Data including blood results, medication prescriptions and social variables such as smoking and alcohol consumption are all available. In contrast to HES, in which these are not included and represent a potential confounding variable for various research questions. Furthermore medication use is often a key component to research, as such its presence in THIN is of potential importance.

When considered together the HES and THIN data sources are different and have potential for answering different questions. Admitted patient care research is better served by HES, however other questions involving epidemiology, medication use, social confounding factors or when looking at non-hospital events are better investigated within THIN. Areas of overlapping questions are likely to be challenging.

3.3.2 Coding structure

THIN uses a system of Read codes, this is a hierarchical system of general codes with more specific detailed codes contained within. Read codes can relate to a wide subject matter ranging from "telephone contact" to "achalasia of cardia". The purpose of these codes is for primary care use to identify actions, diagnoses (formal or suspected) and non-medical information that may be searched by primary care providers. ICD10 is similar in that it is hierarchical, however the scope is much narrower, covering only medical diagnoses. Office of Population Censuses and Surveys (OPCS) version 4 is a highly specific coding structure used for procedures. Although almost all medical procedures carried out have a suitable code, some require additional code suffixes to denote, for example a laparoscopic procedure or fluoroscopic guidance. Therefore such codes can very clearly delineate what procedure has been undertaken and specific detail of how it has been done.

An important weakness of THIN is the coding structure. As codes are inserted based upon text entered directly by General Practitioners during routine practice there is a risk of input error. Codes will also be entered by administrative staff that, although often very skilled, may not be sufficiently knowledgeable about a specific disease area to ensure the Read codes they enter are accurate. Although THIN makes significant efforts to ensure data integrity and quality by supporting practices,

this is a potential concern. Furthermore due to recurrent coding in THIN as in the example above, recurring events may be coded more times than they have occurred. Although similar issues are considered with HES, this is based on the same data framework that supports the funding structure for hospital care, including often expensive procedures and admissions. Therefore, although this is by non-medically trained administrators, more resources are likely provided to ensure it is accurate. HES also has the benefit of being available for validation by comparing the data that should be submitted by a trust to that which has actually been submitted. This is discussed further below, but represents an excellent opportunity to ensure results are robust if an appropriate methodology can be established.

From 2020 SNOMED codes will replace Read codes in primary care datasets. The change will happen gradually as the new system is phased in to use. At the time of writing there is some uncertainty how these codes will be applied in practices, but it seems most likely that GPs will enter them in similar fashion to read codes, therefore many of the research concerns stated above remain. It is unclear how longitudinal research will be affected by this change, however as the data in the present thesis represents the period before their introduction, they have not been discussed further.

3.4.1 Study design

Five studies are included in this thesis, with each focusing on a question that is important to therapeutic endoscopic practice. In each instance the question was considered to be answerable by analysis of an appropriate database. The chapter analyses are stated below, including how each uses the database analysis model.

1. What are the outcomes of ERCP for the relief of biliary tree obstruction secondary to cancer in subjects who have incurable disease? Analysis of complications and 30 day mortality using HES data, to identify malignant biliary obstruction and to investigate a possible volume effect observed in this high risk patient cohort.

2. What are the outcomes of bridging colonic stents when compared to emergency surgery in subjects presenting with large bowel obstruction secondary to colorectal cancer? A comparison of subjects identified in HES, allocated to either bridging stent or surgery only based upon local clinician preference compared using propensity matching.

3. What are the outcomes of surgical and endoscopic therapy for achalasia in large cohort with long term follow-up? A study using HES to identify, follow-up, and analyse treatment outcomes by replicating the treatment algorithm of a high quality, prospective study.

4. What are the current demographics of achalasia, what long term co-morbidities are associated with these subjects, and how does analysis compare between primary care and secondary care data? A novel study using 2 national databases to attempt to accurately describe the epidemiology and long term outcomes of this increasingly endoscopically treated condition.

5. Following Percutaneous Endoscopic Gastrostomy (PEG) insertion in adult subjects with learning disability, what are the outcomes with respect to aspiration and mortality? A study using THIN primary care data to investigate outcomes observed in primary care following a procedure performed in secondary care.

In all cases the use of large scale, national data provides an advantage when compared to prospective trials, despite these being rightly considered to be the gold standard of medical evidence. An example of this can be seen clearly in the colonic stents chapter, a treatment strategy which has represented a recruitment challenge for prospective randomised control trials. Therefore by including all colonic stents done nationally over a period of years allows an analysis that other studies have thus far been unable to achieve.

Furthermore the database examined was selected based upon the question or component of question. For example HES was expected to provide better detail when seeking procedural outcomes. THIN has better population level data, facilitating matching between patient groups including factors such co-morbid conditions, deprivation or GP practice.

3.4.2 Study Process

All studies were designed prospectively prior to initial data extraction, based upon the clinical questions. The number of variables available for analysis in any proposed study, and therefore the potential permutations for any analysis are vast. Therefore by providing a prospective design including an analysis plan, any suggestions of data mining can be refuted.

Knowledge of both the background literature and current clinical practice was important to ensure that an analysis was both academically relevant and compatible with current practice. When using databases for secondary research, it is essentially to understand the setting in which the data was collected, otherwise analyses are unlikely to be an accurate representation of their intended

question. With this information the relevant codes can then be reviewed so that an accurate and question specific set can be provided for extraction. This includes the diagnostic codes detailing the inclusion and exclusion criteria, complication codes, and any other outcomes of interest. The order in which these codes should be placed to extract the correct set of subjects was also be decided. The data analysis including descriptions of patient demographics, univariate and multivariate regression analysis was also decided at this time.

The coding system is dependent upon the database to be analysed. For HES based projects this would be done using ICD10 codes. Similarly OPCS4 codes would be specified for any procedure in HES prior to data extraction. Read codes, stored as comma delineated files, would be used when extracting data from THIN, in which the files could be uploaded into the extraction software directly.

Data validation would also be considered in the planning and design of a study. This was often challenging and due to the nature of each analysis was subject to significant variation. This process is described in greater detail below.

Abstracts describing the results were then presented at regional, national and international gastroenterology conferences for feedback on methodology and results. Comments received were then incorporated into a final revised analysis. Completed chapters have been submitted to peer reviewed journals for publication.

3.4.3 Charlson co-morbidity score

The Charlson co-morbidity score was first described in 1987(100). In this report it is applied to provide a score for co-morbidity that facilitates comparison between subjects. A score is generated by assigning a numerical value of 1, 2, 3 or 6 to medical diagnoses. These are assigned based upon the mortality related to a given diagnosis. An example would include a previous myocardial infarction which would score 1 point. The sum of all scores in a given patient is the overall score for that individual. The system has been updated from the original system as the mortality from conditions has been updated since. An example of this includes the Acquired Immuno-Deficiency Syndrome for which the score has been reduced as the mortality has reduced following treatment advances.

This scoring system lends itself to database analysis as diagnostic codes can be used to generate the score for each patient. It is particularly useful because looking at the impact of individual co-morbidities would introduce a large number of binary co-variates into any analysis. Instead by grouping Charlson scores (e.g. 0, 1, 2-4,>4) this can be converted to ordinal data for analysis of subjects with similar burdens of co-morbidity.

The use of Charlson scores has been validated in urology subjects in HES by Nuttall et al. All subjects (n= 20,138) due to undergo radical urological cancer surgery over 4 years were extracted from HES. Scores were calculated using ICD-9CM and ICD-10 coding to generate the Charlson score which was then used to construct a risk model for procedure related mortality. Mortality data was robustly provided by ONS linked records, as in the present thesis. This demonstrated a robust association of rising co-morbidity, as measured by increasing Charlson score calculated from HES data, to rising mortality.(101)

3.4.4 Age quintiles

All outcome variables considered in the studies in this thesis represent categorical data (e.g. 30 day mortality, perforation rate at endoscopy). Therefore logistic regression models are an important statistical tool. Such models allow interpretation of factors predicting an outcome such as mortality or treatment failure. Furthermore such models provide an estimate of the magnitude of an association. Age is split into quintiles for use in these models because the impact of age is unlikely to be linear. For example an additional 10 years of age in a 25 year old patient undergoing an endoscopic procedure does not confer the same change in mortality risk as an additional 10 years of age in a 70 year old patient. Therefore age is split into quintiles instead of being placed in models as a continuous variable. This allows differentiation between the magnitudes of increased risk of mortality likely associated with increasing age, as modified by the baseline age.

Unfortunately this results in a reduction in statistical power and in small cohort a statistically significant result may therefore be overlooked. However given the likely size of the majority of chapters in this thesis statistical power is sufficient to accommodate this without risk of type 2 errors. Furthermore the benefit in accuracy and applicability of the results is significant.

3.4.5 Deprivation

The index of Multiple Deprivations (IMD) groups subjects into quintiles (1 being the most deprived) based upon seven measures of deprivation. These include; Income deprivation, Employment deprivation, Education skills and training deprivation, Health deprivation and disability, Crime, Barriers to Housing and Services and Living Environment Deprivation. These are weighted and form an index by which to classify overall deprivation. This data is produced by the ONS in conjunction with the Department for Communities and Local Government. The index is recognised as a robust measure of deprivation for use in national statistics and research.

The Townsend index is used in THIN to provide a deprivation score (1 being the least deprived, the opposite of IMD). This score is less complex than IMD, assessing material deprivation in 4 domains; households without use of a car, overcrowded households, households not owner-occupied and unemployment(102).

The scores have been compared using the west midlands population for their composite parts to demonstrate areas of overlap. Townsend was compared specifically to each domain of IMD (2004 version), with excellent correlation for; income deprivation, employment deprivation, education skills and training deprivation and health deprivation of disability. However the correlation was weaker between services and living environment deprivation, and crime. There was no relationship between barriers to housing deprivation. When the entire composite score was compared a strong correlation was observed(103).

3.4.6 English residency

All HES analyses in this thesis exclude subjects who are of no fixed abode or resident outside of England, as HES only covers hospitals in England. The intention here is that this should limit, as far as possible, subjects who do not have all of their secondary care records within HES. For example any patient resident in Wales travelling in to England for a colonic stent may then have a resection in Wales. This group of subjects will therefore add a systematic source of bias to our data as those geographically outside England are much more likely to have unrecorded care, and therefore incomplete outcome data.

3.4.7 External Data validation methodology

All analyses in this thesis use data validation to ensure the accuracy and completeness of the data included. Some studies described below employ additional, different methodologies, dependent on the specific analysis. In each instance the exact methods used will be described further, in detail, within the chapter methodology. There is no recognised standard methodology used for data validation, interestingly some published studies utilise a validation method, others do not. The requirement for such a process is also variable based upon the data base being searched.

The broad methodology for this includes seeking out subjects who would have undergone the procedure in question through multiple sources that are separate to those that contribute data to THIN or HES. Subjects may then be screened out if further characteristics are required, for example to have had a treatment for achalasia. Through doing this we can then confidently state how many subjects should be included in a chapter. As HES data is anonymous subjects are not identifiable. Therefore the number of subjects included from the data base is compared to the number found by trust level search to provide an estimate of concordance. Following this process, given a sufficiently high concordance we will be confident that our data represents the subjects it portends to. We can therefore be more certain that our results regarding outcomes are robust.

3.4.8 Internal data validation methodology

THIN data sets cannot currently be validated against external GP data. Although a process for this has previously been available for small proportions of data sets, at high cost, this has currently been withdrawn. Internal validation is therefore required to ensure all of the strict data quality thresholds are achieved. Data sets generated when extracting data from THIN include columns for acceptable mortality recording date (AMR), installation of the electronic medical recording software (Vision), index event (event triggering study entry) date, date of death and transfer out dates. A standardised process is undertaken in all THIN studies to ensure that the AMR is at least 1 year prior to the study index date, that transfer out and date of death, if present, are after the index date. In ensuring that all records comply with these criteria, we can be confident that the data extraction process has run as planned. This provides reassurance that the data provided for analysis meets the data quality thresholds mandated by the THIN database.

HES does not require a similar internal validation. The patient unique identification number that facilitates longitudinal analysis of episodes is generated using key demographic data items. Therefore if these are missing the patient will not be within the extractable data.

3.4.9 Ethical approval

As data is pseudonymised, HES data has been shared by NHS Digital under a data sharing agreement for the purpose of service evaluation and consequently ethics approval is not required.

THIN data access was provided by IQVIA to the University of Birmingham under a generic multicentre research ethics committee approval in 2003. Individual study approval was granted for each use of THIN data as detailed in the chapter specific methods sections.

4. The outcomes of ERCP for the palliation of malignant biliary obstruction in England between 2006 and 2017

4.1. Chapter specific materials and methods

4.1.1 Subject cohort

All subjects with an OPCS4 code for ERCP (Appendix 4.1) from April 2006 to March 2017 and an ICD10 code for a primary hepatobiliary, pancreatic or small bowel malignancy (Appendix 4.2) in the preceding 2 years or the following 6 months were included to allow for delays in coding of a cancer diagnosis, and to ensure diagnoses were chronologically appropriate. Subjects under 18 years of age or with missing or invalid age or sex data were excluded, as these variables along with NHS number are used to generate the unique patient identifiers in HES. Subjects not resident within England or of unknown region of residence were also excluded as their follow-up may occur outside of England and thus not be captured in HES. Any subjects undergoing a potentially curative operation following ERCP (Appendix 4.3) were excluded to ensure only palliative subjects were included.

Cancer aetiology was considered to be the most frequently recurring cancer diagnosis code in HES in the preceding 2 years or 6 months following ERCP. Any subject in whom this did not match their initial diagnosis code were excluded, as subjects were included based on their initial diagnosis meeting the criteria for inclusion.

4.1.2 Data Extraction

The demographic data extraction included gender, age quintile, ethnicity, IMD quintile and primary malignancy. Charlson co-morbidity score was constructed using ICD10 codes as a surrogate of overall co-morbidity, a technique that has been validated in HES analyses previously (100, 101, 104). Cancer was excluded from the Charlson score, as it was universal in this subject cohort. Coded complications were extracted (Appendix 4.4) as were PTBD (Appendix 4.5) or repeat ERCP within 30 days, mortality at 7 days, in hospital and 30 days, and emergency readmissions within 30 days. Post-ERCP receipt of palliative chemotherapy (Appendix 4.6) was also collected.

4.1.3. Data validation

Subjects undergoing ERCP for palliation of malignant biliary obstruction were sought at Sandwell and West Birmingham NHS Trust by searching the endoscopy reporting system on which all procedures are documented. Once identified, electronic records for potential cases were reviewed to confirm the cancer diagnosis and that study inclusion criteria were met. The number of subjects was then compared to the number of subjects meeting the study criteria found in the HES database.

4.1.4. Analysis

Rates of procedural failure as defined by the surrogate measure of undergoing PTBD or further ERCP within 30 days were given for the whole cohort, by each provider volume tertile, and based upon cancer aetiology. This allowed comparison of procedural success between intrahepatic or hilar

lesions and more distal biliary obstruction. Chi^2 tests were performed to determine statistical significance between further intervention and provider volume.

Multivariable logistic regression models utilising 30 day mortality as the dependent variable included: gender, age quintile, deprivation quintile, ethnicity, Charlson co-morbidity score, primary cancer aetiology, year of ERCP and unit ERCP volume per annum by tertile for both total and unresectable cancer only. Variables were selected based upon clinical relevance.

A standardised mortality funnel plot was constructed using the regression model for all ERCPs to generate expected numbers of deaths per unit. Control limits were set at 2 and 3 standard deviations using a random effects adjustment for over-dispersion(105).

Data were analysed using Stata® version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP), p-values < 0.05 were considered statistically significant. Funnel plots were constructed using Spotfire® version 6.5.

4.2. Chapter specific results

4.2.1. Validation

Between April 2013 and March 2015, 465 subjects had an ERCP recorded at Sandwell and West Birmingham NHS trust compared to 462 (99.4%) found within HES. 38 subjects underwent their first malignant ERCP but did not progress to curative surgery. When sought in HES by the same criteria 41 (92.7%) subjects were found. This suggests a high degree of accuracy in the HES data.

4.2.2 Demographics

515,532 subjects underwent their first ERCP between April 2006 and March 2017. Of those 49,487 subjects had a cancer diagnosis within 2 years before or 6 months after index ERCP. 8,930 were excluded having undergone a potentially curative operation following ERCP. 39,702 subjects were included in the final analysis following all exclusions, as described in Figure 4.1.

The median age of included subjects was 75 (IQR 66-88) years. Males constituted 49.4% and the majority ethnicity was “White”, including 84.5% of subjects. The majority of subjects did not have any Charlson co-morbidities recorded (59.0%). The commonest primary cancer was pancreatic, seen in 63.9% of subjects. Full demographic details are reported in table 4.1.

Figure 4.1: Study flow chart

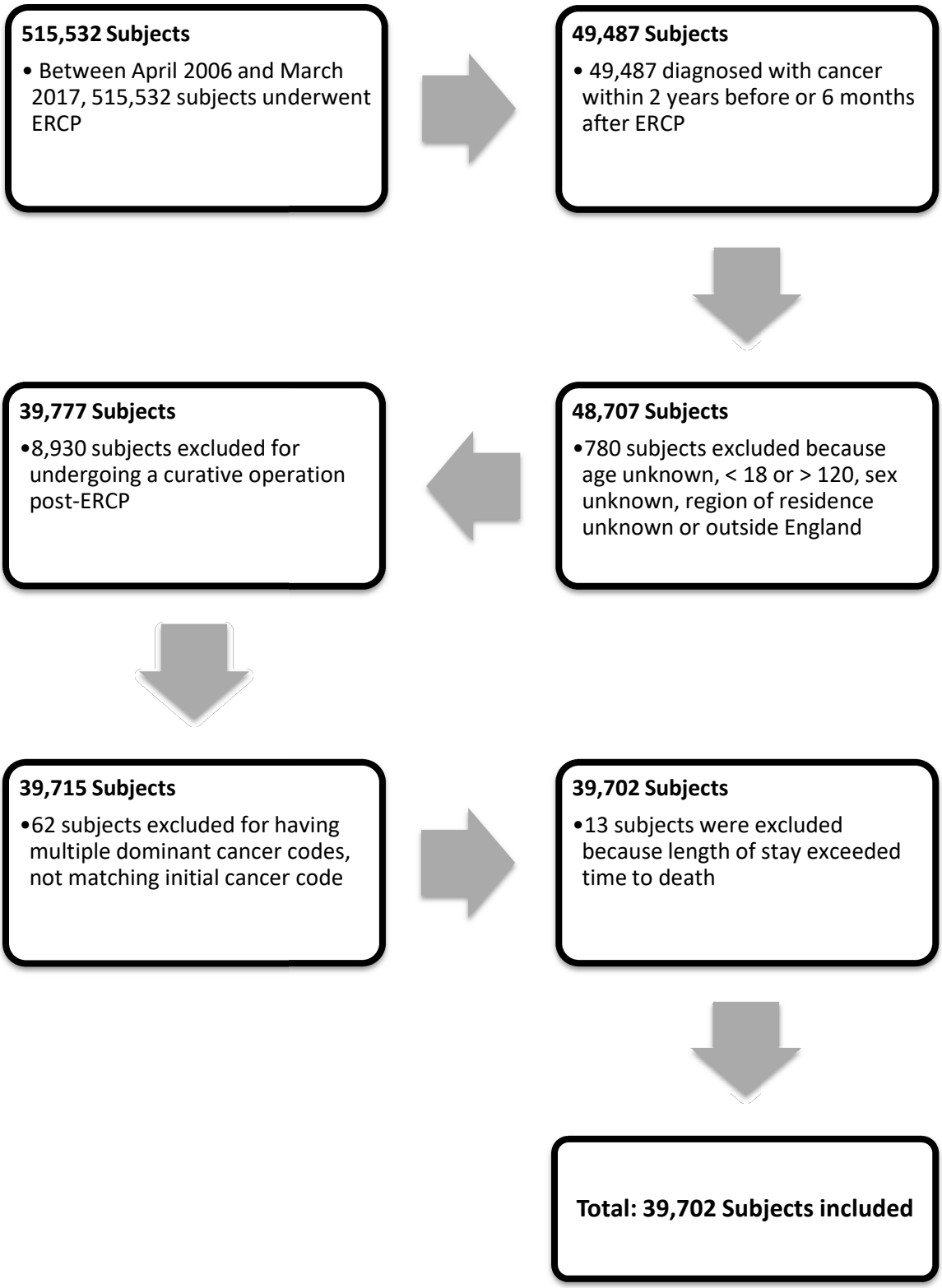


Table 4.1: Study subject demographics

Gender	**Male**	19603 (49.4)
	Female	20099 (50.6)
Age quintile	**< 64**	8041 (20.3)
	64 to 71	8189 (20.6)
	72 to 77	7709 (19.4)
	78 to 83	8059 (20.3)
	> 83	7704 (19.4)
Deprivation quintile	**1**	7035 (17.7)
	2	7664 (19.3)
	3	8333 (21.0)
	4	8592 (21.6)
	5	8049 (20.3)
	Unknown	29 (0.1)
Ethnic Group	**White**	33536 (84.5)
	Asian or Asian British	843 (2.1)
	Black or Black British	667 (1.7)
	Mixed	116 (0.3)
	Any other ethnic group	494 (1.2)
	Unknown	4046 (8.5)
Charlson co-morbidity score	**0**	23443 (59.0)
	1 to 5	8548 (21.5)
	6 to 10	3421 (8.6)
	11 to 15	2267 (5.7)
	16 to 20	1033 (2.6)
	> 20	990 (2.5)
Type of Cancer	**Small Intestine**	754 (1.9)
	Liver and Intrahepatic Bile Ducts	7964 (20.1)
	Gallbladder	1510 (3.8)
	Extrahepatic and unspecified biliary tract	4115 (10.4)
	Pancreas	25359 (63.9)
	Previous PTBD	1620 (4.1)

4.2.3 Complications

Following ERCP the 30 day emergency re-admission rate was 24.9%. Renal failure within 30 days developed in 3.3%, cholangitis in 3.7% and pancreatitis in 0.6%. Full details of complications are described in table 4.2.

4.2.4 Repeat biliary drainage procedures

Within 30 days of initial ERCP, 9.3% of subjects underwent a repeat ERCP and 5.6% had PTBD. In those undergoing ERCP in an upper tertile volume provider (all ERCPs >318), repeat ERCP at 30 days was 8.0% compared to 13.4% in the lower tertile volume providers (all ERCPs < 204, $p<0.001$). Similarly PTBD within 30 days was 4.5% and 8.7% in the upper and lower tertile ERCP volume providers respectively ($p<0.001$) (table 4.3).

Within 30 days of initial ERCP, repeat ERCP was most commonly undertaken in cancers of the intrahepatic biliary tree and liver (11.3%), followed by cancers of the extrahepatic biliary tree (10.7%). PTBD in the same time period was most common in small intestine malignancy (9.4%).

Table 4.2: Short term complications of ERCP

Emergency Re-Admission	4228 (10.6)	9876 (24.9)
Repeat ERCP	1098 (2.8)	3700 (9.3)
PTBD following ERCP	834 (2.1)	2238 (5.6)
Any Complication below	786 (2.0)	2601 (6.6)
Cholangitis	422 (1.1)	1479 (3.7)
Renal Failure following ERCP	449 (1.1)	1315 (3.3)
Gastrointestinal Bleeding	132 (0.3)	442 (1.1)
Pancreatitis	163 (0.4)	257 (0.6)
Perforation	33 (0.1)	113 (0.3)
Sedation	122 (0.3)	575 (1.4)
Other Complication	12 (0.0)	50 (0.1)

Table 4.3: Proportion of subjects undergoing repeat biliary drainage procedures within 30 days of index ERCP

<204 ERCPs per annum, per provider	853 (13.4)	557 (8.7)
204-318 ERCPs per annum, per provider	1181 (9.4)	751 (6.0)
>318 ERCPs per annum, per provider	1666 (8.0)	930 (4.5)
Malignancy of Liver and Intrahepatic Bile Ducts	903 (11.3)	622 (7.8)
Gallbladder malignancy	141 (9.3)	73 (4.8)
Malignancy of extrahepatic and unspecified biliary tract	442 (10.7)	177 (4.3)
Pancreas malignancy	2174 (8.6)	1295 (5.1)
Small Intestine malignancy	40 (5.3)	71 (9.4)

4.2.5 Chemotherapy

Subjects with gall bladder cancer were the most likely to receive chemotherapy following ERCP (28.5%) followed by pancreatic cancer (28.2%). The rate of chemotherapy reduced with increasing age quintile; 2.1% of subjects over 83 years compared to 46.8% of those younger than 64 years. Subjects with higher Charlson co-morbidity scores were less likely to receive chemotherapy; Subjects with score 0, 29.4%; subjects with score >20, 4.5%. Full results are presented in table 4.4.

Table 4.4: Rates of chemotherapy following ERCP by age, co-morbidity, cancer type and year of procedure

Age quintile	<64	3766 (46.8)
	64-71	3131 (38.2)
	72-77	2031 (26.3)
	78-83	950 (11.8)
	>83	159 (2.1)
Charlson co-morbidity score	0	6893 (29.4)
	1-5	2141 (25.0)
	6-10	627 (18.3)
	11-15	232 (10.2)
	16-20	99 (9.6)
	>20	45 (4.5)
Small Intestine malignancy		158 (21.0)
Malignancy of Liver and Intrahepatic Bile Ducts		1530 (19.2)
Gallbladder malignancy		430 (28.5)
Malignancy of extrahepatic and unspecified biliary tract		767 (18.6)
Pancreas malignancy		7152 (28.2)
2006/2007		732 (20.8)
2007/2008		721 (20.6)
2008/2009		846 (22.8)
2009/2010		827 (23.6)
2010/2011		888 (24.5)
2011/2012		894 (25.1)
2012/2013		972 (27.1)
2013/2014		1029 (28.2)
2014/2015		1014 (27.1)
2015/2016		1054 (29.0)
2016/2017		1060 (28.9)

4.2.6 Mortality

Mortality at 7 days, in hospital and 30 days was 4.1%, 9.7% and 19.1% respectively. The median survival from the initial ERCP was 4 months (IQR 1-10).

The mortality rates for tertiles of total ERCP volume per provider were; <204 ERCPs 19.9%, 204-318 ERCPs 19.9%, and >318 ERCPs 18.3%. Mortality by tertile of unresectable cancer ERCP volume per provider were <23 ERCPs 20.5%, 23-40 ERCPs 19.5% and >40 ERCPs 18.4%.

Multivariable regression analysis demonstrated factors associated with increased 30 day mortality include; male gender (OR 1.20 (95% CI 1.14-1.26),p<0.001), increasing age quintile; >83 (2.70 (2.48-2.94),p<0.001), increasing deprivation; quintile 1 (1.21(1.11-1.32),p<0.001), increasing Charlson co-morbidity score; >20 (3.36(2.94-3.84),p<0.001), earlier year of ERCP; 2006/2007 (1.37 (1.22-1.55),p<0.001), cancer of liver and intrahepatic bile ducts (1.10 (1.03-1.17),p=0.005) and small intestine cancer (1.45(1.22-1.72),p<0.001). Factors associated with reduced 30 day mortality included; extrahepatic biliary tract malignancy (0.67(0.61-0.73), p<0.001), upper tertile providers for total ERCP volume >318 (0.91(0.84-0.98),p=0.010). Complete results are displayed in table 4.5.

A further multivariable regression analysis was undertaken including volume of ERCP in unresectable cancer only. An increased volume of ERCPs in unresectable cancers (>40) was also associated with decreased mortality (0.91(0.85-0.98), p=0.014). Full results of this model are shown in table 4.6.

4.2.7 Standardised mortality rates

98.7 % of individual unit 30 day mortality rates were within 3 standard deviations of the mean within the study period (figure 4.2).

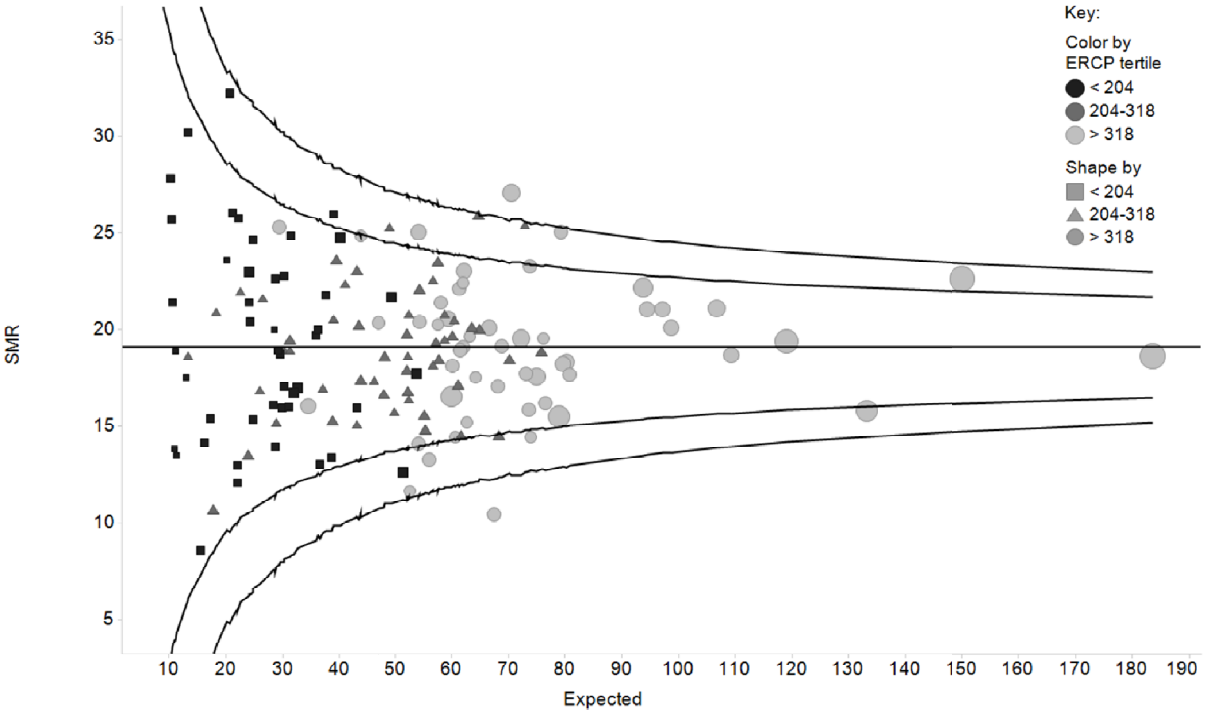
Table 4.5: Multivariable logistic regression of factors associated with 30 day mortality following ERCP for malignant biliary obstruction including provider volume analysis

Gender	Female	Reference category			
	Male	1.20	1.14	1.26	<0.001
Age	<64	Reference category			
	64-71	1.30	1.19	1.43	<0.001
	72-77	1.52	1.39	1.67	<0.001
	78-83	1.73	1.59	1.89	<0.001
	>83	2.70	2.48	2.94	<0.001
Deprivation Quintile **1 is the most deprived*	1	1.21	1.11	1.32	<0.001
	2	1.11	1.02	1.20	0.018
	3	1.11	1.02	1.20	0.013
	4	1.09	1.00	1.18	0.040
	5	Reference category			
	Unknown	0.36	0.08	1.52	0.164
Ethnic Group	White	Reference category			
	Asian or Asian British	0.87	0.72	1.06	0.139
	Black or Black British	0.93	0.76	1.15	0.528
	Mixed	1.01	0.62	1.65	0.977
	Other Ethnic Group	0.83	0.64	1.07	0.147
	Unknown	1.26	1.16	1.37	<0.001
Comorbidities	0	Reference category			
	1-5	1.16	1.08	1.23	<0.001
	6-10	1.38	1.26	1.50	<0.001
	11-15	1.81	1.63	2.00	<0.001
	16-20	2.20	1.92	2.52	<0.001
	>20	3.36	2.94	3.84	<0.001
Type of Cancer	Pancreatic	Reference category			
	Small Intestine	1.45	1.22	1.72	<0.001
	Liver and Intrahepatic Bile Ducts	1.10	1.03	1.17	0.005
	Gallbladder	1.11	0.97	1.28	0.112
	Extrahepatic and unspecified biliary tract	0.67	0.61	0.73	<0.001
Year of ERCP	2006/2007	1.37	1.22	1.55	<0.001
	2007/2008	1.33	1.18	1.50	<0.001
	2008/2009	1.27	1.13	1.44	<0.001
	2009/2010	1.24	1.10	1.40	0.001
	2010/2011	1.23	1.09	1.39	0.001
	2011/2012	1.19	1.06	1.35	0.004
	2012/2013	1.18	1.04	1.33	0.008
	2013/2014	1.07	0.94	1.20	0.315
	2014/2015	1.16	1.03	1.31	0.016
	2015/2016	1.03	0.91	1.17	0.613
	2016/2017	Reference category			
Mean annual ERCP volume tertile	<204	Reference category			
	204-318	0.99	0.92	1.07	0.845
	>318	0.91	0.84	0.98	0.010

Table 4.6: Multivariable logistic regression analysis of factors associated with 30 day mortality following ERCP for malignant biliary obstruction including provider volume of ERCP for unresectable cancer

Gender	Female	Reference category			
	Male	1.20	1.14	1.27	<0.001
Age	<64	Reference category			
	64-71	1.30	1.19	1.43	<0.001
	72-77	1.52	1.39	1.67	<0.001
	78-83	1.73	1.59	1.89	<0.001
	>83	2.70	2.48	2.94	<0.001
Deprivation Quintile **1 is the most deprived*	1	1.20	1.10	1.30	<0.001
	2	1.10	1.01	1.19	0.029
	3	1.10	1.02	1.19	0.019
	4	1.08	1.00	1.17	0.054
	5	Reference category			
	Unknown	0.35	0.08	1.50	0.158
Ethnic Group	White	Reference category			
	Asian or Asian British	0.87	0.72	1.06	0.162
	Black or Black British	0.94	0.76	1.16	0.575
	Mixed	1.01	0.62	1.65	0.969
	Other Ethnic Group	0.83	0.64	1.07	0.150
	Unknown	1.27	1.17	1.37	<0.001
Comorbidities	0	Reference category			
	1-5	1.16	1.08	1.23	<0.001
	6-10	1.38	1.26	1.51	<0.001
	11-15	1.81	1.63	2.00	<0.001
	16-20	2.20	1.92	2.53	<0.001
	>20	3.36	2.94	3.84	<0.001
Type of Cancer	Pancreatic	Reference category			
	Small Intestine	1.45	1.22	1.72	<0.001
	Liver and Intrahepatic Bile Ducts	1.09	1.03	1.17	0.006
	Gallbladder	1.11	0.97	1.27	0.130
	Extrahepatic and unspecified biliary tract	0.67	0.61	0.74	<0.001
Year of ERCP	2006/2007	1.38	1.22	1.55	<0.001
	2007/2008	1.33	1.17	1.50	<0.001
	2008/2009	1.28	1.13	1.44	<0.001
	2009/2010	1.24	1.10	1.40	0.001
	2010/2011	1.23	1.09	1.39	0.001
	2011/2012	1.20	1.09	1.39	0.004
	2012/2013	1.18	1.04	1.33	0.008
	2013/2014	1.07	0.94	1.21	0.304
	2014/2015	1.16	1.03	1.31	0.016
	2015/2016	1.03	0.91	1.17	0.605
	2016/2017	Reference category			
Mean annual ERCP volume for unresectable cancer	<23	Reference category			
	23-40	0.95	0.88	1.03	0.216
	>40	0.91	0.85	0.98	0.014

Figure 4.2: Funnel plot of standardised 30 day mortality rate following ERCP for palliative malignant biliary obstruction



Lines represent 2SD and 3SD

4.3 Chapter specific discussion

In the present study, considerable short term mortality following an ERCP for malignant biliary obstruction was observed. Mortality increased with advancing age and greater co-morbidity. Low volume providers had lower 30 day survival, when considering all ERCPs, but also restricting analysis to those for unresectable cancer only. Low volume providers also required more ERCPs to be repeated or PTBD to be undertaken within 30 days of initial ERCP.

30 day mortality in the present study is high. A significant component of this will be the natural history of a subject with advanced cancer. The regression models also demonstrate that there is variation in mortality between providers based on procedure volume. This suggests that a significant component to the observed mortality is related to the procedure, not merely the underlying cancer. Subject selection will also play an important role; subjects who are likely to die within 30 days should not be subjected to a palliative procedure as it is of no benefit to them. A recent meta-analysis of ERCP for any indication did not demonstrate variation in mortality based upon provider volume (106). However all indications were included, compared to the present study that only includes subjects with palliative malignant biliary obstruction. ERCP in malignant biliary obstruction is often more technically challenging, therefore the impact of higher annual ERCP volume is potentially more important.

Repeat ERCP or PTBD within 30 days of first ERCP was used as a surrogate for failed or inadequate biliary decompression. Lower rates of repeat procedures were observed in higher volume providers. This further supports the suggestion of a volume effect, whereby those providers doing more ERCPs for cancer have better outcomes. A recent meta-analysis of ERCP outcomes by annual provider volume included 3 studies reporting procedure success rates of ERCP for any indication defined as success at cannulation or intended therapies. A similar effect was observed, high volume providers had better success rates (OR 2.0) (106). However the definition of volume varied between studies, the largest effect (OR 5.65) defined high volume as >87 ERCPs per annum(45). The remaining 2 studies considered high volume to be >200 ERCPs per annum, of which one reported improved success rates of ERCP in higher volume providers (OR 1.9), in keeping with the present study(107), however the other study did not(108).

A negative association with mortality for higher volume providers has also been reported in subjects undergoing PTBD (37). Both studies use HES data linked to the ONS to provide accurate mortality statistics following a procedure. 30 day mortality was 23.1% after PTBD compared to 19.1% after

ERCP. In keeping with the present study; increasing age, co-morbidity, male gender and greater deprivation were found to be associated with 30 day mortality.

Ascertainment bias is an important consideration for database studies. Data validation by comparison to local audit data, from sources independent of HES, supports the accuracy of the database coding. The number of index ERCPs identified in local audit matched the number found in HES. The number of subjects meeting the inclusion criteria identified in local audit compared to HES was also very similar, providing reassurance that the inclusion and exclusion criteria for the study were accurately coded, therefore supporting the validity of the results presented.

Although OPCS codes were available for metal stent insertion, there is no code specific for plastic stent insertion. Stent type has been shown to be important, as fewer complications are seen with fully covered metal stents, even over short time periods(109). Unfortunately cannot analyse the impact of metal stents on ERCP outcomes in the management of malignant biliary obstruction. Mortality was noted to fall over the study period, which is likely to be a result of better peri-procedural medical care, but also may potentially be related to increasing use of metal stents.

Subjects will present for ERCP only when biliary obstruction has occurred. This cohort will therefore include variably advanced cancers. Considering this, the natural development and observation of improved survival of the distal cholangiocarcinoma group is likely due to biliary obstruction at an earlier stage of cancer progression. It is a significant limitation of HES that cancer staging data is not available for analysis.

The coding structure of HES requires a primary diagnosis for each episode with up to 19 further diagnoses listed. Therefore if a complication occurs following discharge from hospital it would be more likely to be listed as the primary diagnosis in a new episode. However should the complication occur during the same episode as the ERCP procedure, the complication may not be recorded during coding and therefore the number of complications may under represent the actual number of such events. Complications may be further obscured by the palliative nature of this patient cohort. For example patients with post-ERCP pancreatitis presenting with abdominal pain may receive symptomatic control instead of investigations which may identify pancreatitis. As such pancaretitis may be under diagnosed. This may lead to an artificially lower rate of pancreatitis when compared to a non-palliative cohort.

Despite these concerns, the complication rates observed in the present study cohort from HES is similar to those described elsewhere in the literature. Post procedure bleeding was 1.1% in HES compared to 1.3% in a systematic review. Similarly perforation was seen in 0.3% of cases in the

present study compared to 0.45% in a large single centre American study. However there is substantial variation for cholangitis, 3.7% in the present study compared to descriptions of less than 1% in other studies. However this is potentially reflection of different case mix. The present study report only malignant obstruction, therefore cases are likely to have multiple strictures and incomplete drainage rates may be higher. Unfortunately HES does not hold sufficiently detailing information to support or refute this theory.

Chemotherapy has previously been considered to be under coded in HES. A recent validation study of chemotherapy in lung cancer split subjects into 4 groups, those with evidence of chemotherapy in; HES, the national lung cancer audit (NCLA), both HES and NCLA, and evidence in neither. Outcomes were similar with codes in NCLA, HES and both, compared to subjects with evidence in neither data set that had worse outcomes. This suggests that chemotherapy coded in HES has a strong positive predictive value. Unfortunately chemotherapy still appeared to be under coded in HES and therefore correlation with audit data for case finding was recommended(110). A comparison of chemotherapy for head and neck cancers from the national cancer data registry (NCDR) to HES between 2004 and 2006 demonstrated good concordance. Overall 89.3% (2096/2346) of subjects receiving chemotherapy in the NCDR were also coded on HES. The quality of chemotherapy coding appeared to improve in that study in HES up to 2006(111). In the present study the observed 8.9% increase in chemotherapy provision over the study period is likely attributable to both improving coding and increasingly common use in clinical practice.

In conclusion this, the largest study of outcomes for ERCP in unresectable malignant biliary obstruction, demonstrates high 30 day mortality. Mortality was associated with increasing age, deprivation and co-morbidity. Mortality fell over the study period and was higher in low volume ERCP providers. Future research should focus on the reasons for variable mortality and identifying those subjects most likely to benefit from ERCP.

5. Outcomes of colorectal stents when used as a bridge to curative resection in obstruction secondary to colorectal cancer

5.1 Chapter specific materials and methods

5.1.1 Inclusion and Exclusion Criteria

Subjects were included if they had an ICD10 diagnosis code between January 2006 and December 2015 for an emergency admission with bowel obstruction (Appendix 5.1). A diagnosis code for colon cancer within 12 months prior or up to 3 months after the episode of obstruction was also required (Appendix 5.2). A co-existing OPCS4 code for colorectal resection (Appendix 5.3) at the same time or within the subsequent 12 months to the colon cancer diagnosis was also mandatory.

Subjects were included in the MS group if an OPCS4 code for colorectal MS (appendix 5.4) was present within 4 weeks of being admitted with obstruction. If no MS code was present they were included in the surgery only group.

Subjects were excluded if there was a code for metastatic disease (except lymph node metastasis) prior to surgery to ensure only those treated with curative intent were included (Appendix 5.5). Subjects were also excluded if they were under 18 years of age at the time of presenting with obstruction, if they were resident outside of England or of no fixed abode, as follow-up may occur outside of England and not be captured. Subjects with missing age or sex and those with a death date recorded prior to initial presentation were excluded, as this information is used to generate the unique HES patient ID. Subjects undergoing MS followed by resection more than 12 months later were also excluded.

5.1.2 Data Validation

All subjects undergoing a MS insertion for colon cancer were identified over a 3 year period (January 2012-December 2014) at Sandwell and West Birmingham NHS trust from multiple sources including endoscopy reporting software, the radiology reporting system and individual operator logs. This was then compared to the number of MS for colon cancer in HES for the same time period for the same provider to assess the accuracy of HES data extraction for MS in colorectal cancer.

The rate of stent failure in the MS group, defined as requirement for surgical resection during the same admission as stent insertion, was compared to published studies(112).

5.1.3 Data Analysis

Time to surgery was calculated from the date of emergency admission with obstruction to subsequent resectional surgery. When multiple colorectal surgeries were found, the surgery closest to the admission with obstruction was included with further procedures considered as re-operations.

Demographic data extraction included gender, age, ethnicity and deprivation quintile based on the Indices of Multiple Deprivation (2010) (1 being the most deprived, 5 the least deprived). The type of resection including stoma formation and if the surgical resection was during the same admission as the presentation with obstruction, were also extracted from HES. A Charlson co-morbidity score was also calculated at the time of obstruction, however, cancer was excluded from this score. This scoring system has previously been validated in HES (101, 113). Length of stay data was collected to allow a comparison of bed days between different treatment strategies.

Following resection Codes for complications (Appendix 5.6) were sought in HES within 30 days of discharge and the 30 day emergency re-admission rate. The proportion of open versus laparoscopic surgery and stoma formation was also calculated. Cases were also linked to ONS mortality data to provide 7 and 30 day mortality.

5.1.4 Statistical Analysis

Statistical analysis was performed using STATA version 14 (114). Univariable analyses were performed utilising Chi-squared and Fishers exact test where appropriate for categorical variables (for large and small groups respectively), and Mann Whitney tests for non-parametric continuous data items. P values of <0.05 were considered statistically significant. Values of 5 or fewer are suppressed and expressed as <6 in line with national guidelines on the publication of HES data.

Preliminary comparison of unmatched MS and surgery only groups revealed significant demographic differences and therefore propensity score matching was performed. The user written program "PSMATCH2" in STATA was used to pair each MS subject to a surgery only subject (57). Subjects with similar propensity scores were selected using 1:1 nearest-neighbour matching with calliper width of 0.001 and no replacement. Each pair was used once and unpaired cases were excluded from further analysis. Subjects with a transverse or non-extended right hemicolectomy were excluded from propensity score matching as right colon tumours were unlikely to be managed with a MS. All patients undergoing tranverse hemicolectomy were excluded as distal lesions found at the splenic flexure, which could potentially be managed with a MS, could not be identified. Although some lesions that could be managed with a stent are therefore excluded, this ensures that no ineligible subjects are included in the cohort presented. The matching model included gender, age at obstruction, resection type and Charlson co-morbidity score. Once matched, the remaining included subject outcomes, including mortality and complications, were compared using univariable analysis. Kaplan Meier graph of matched cohorts were constructed for 1 year survival and compared using log-rank test.

5.2 Chapter specific results

5.2.1 Data Validation

Between 2012 and the end of 2014 at Sandwell and West Birmingham Hospitals NHS Trust, 27 MS were inserted for obstruction secondary to cancer. Over the same time period 25 were coded within HES as undergoing MS for obstruction secondary to colorectal cancer, giving a 92.6% concordance.

The CREST study (Randomised phase III study of stenting as a bridge to surgery in obstructing colorectal cancer—Results of the UK ColoRectal Endoscopic Stenting Trial), currently published in abstract form only, provides further opportunity for validation(112). Stenting success was reported in the trial as 82% compared to 86.5% in the current study. Similarly the largest meta-analysis reported technically successful stent placement in 88.5% in 1,061 subjects(115).

5.2.2 Subject Demographics (Un-matched)

There were 4,571 subjects who met the inclusion criteria, of whom 401 underwent MS insertion, from an initial group of 32,039 (793 MS) who presented with bowel obstruction between 2006 and 2015 secondary to colorectal cancer, reasons or exclusions are shown in Figure 5.1.

The study subject demographics are described in Table 5.1. In the whole study population, the surgery only group were numerically older (73 (IQR 64-81 versus 71 (63-79) years) and less likely to have no co-morbidities recorded (64.6% versus 69.8%, p=0.005). There appeared to be no statistically significant differences in sex, deprivation or ethnicity.

The most common initial surgical resection type in the MS group was rectal operations (174, 43.4%) or left hemicolectomy (119, 29.7%). Subjects undergoing surgery only were most likely to have a right hemicolectomy (1,808, 43.4%) followed by rectal surgery (913, 21.9%), (p<0.001).

Figure 5.1 Study flow chart

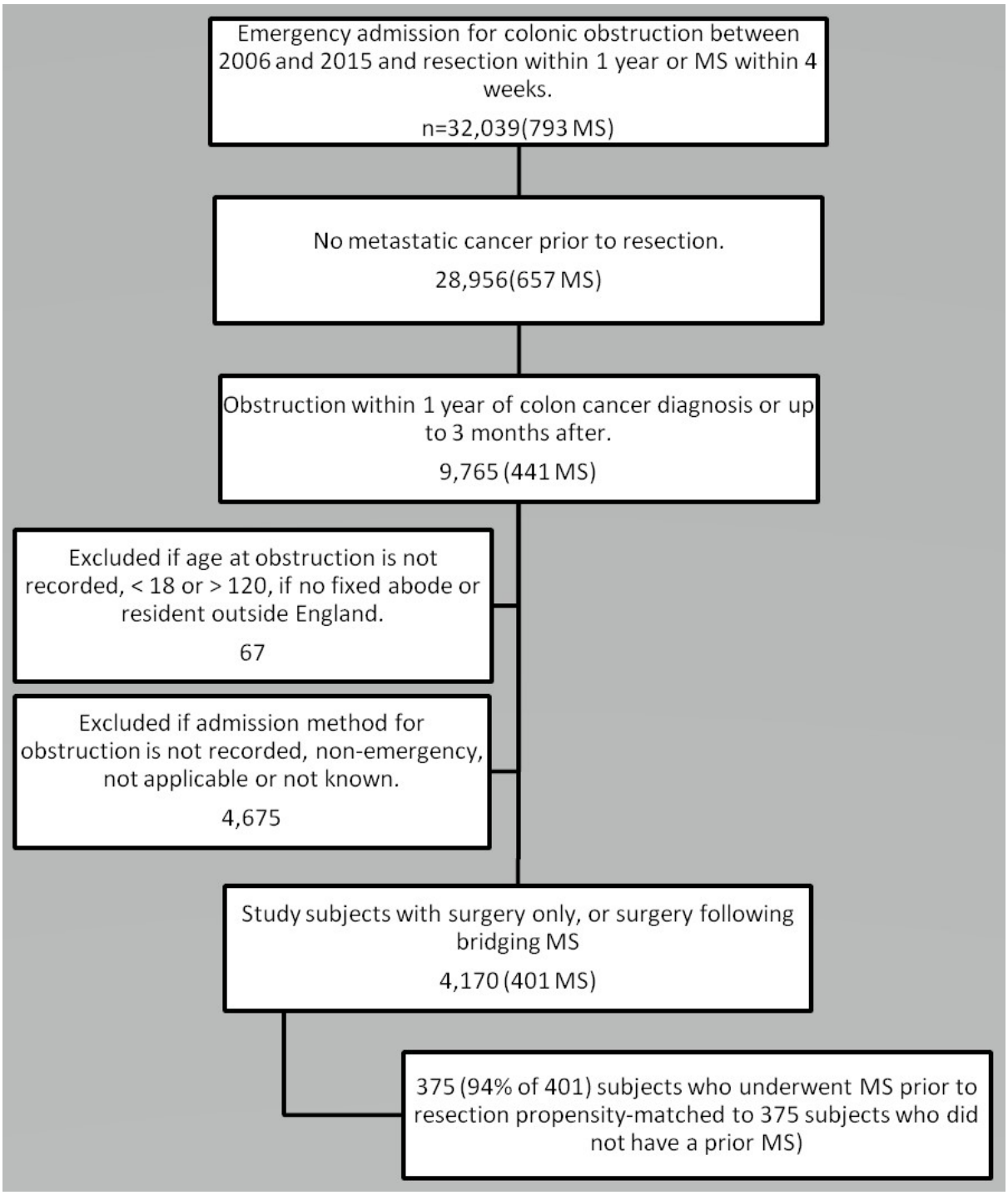


Table 5.1 Study subject demographics in the whole study population and after propensity matching

Age in years						
≤29	32 (0.8)	-		-	-	
30-39	74 (1.8)	10 (2.5)		7 (1.9)	9 (2.4)	
40-49	188 (4.5)	21 (5.2)		20 (5.3)	20 (5.3)	
50-59	450 (10.8)	48 (12.0)	0.051	45 (12)	46 (12.3)	0.997
60-69	886 (21.3)	95 (23.7)		90 (24)	90 (24)	
70-79	1,345 (32.3)	139 (34.7)		128 (34.1)	128 (34.1)	
≥80	1,195 (28.7)	88 (22.0)		85 (22.7)	82 (21.9)	
Sex						
Male	2,165 (51.9)	226 (56.36)	0.089	211 (56.3)	212 (56.5)	0.941
Female	2,005 (48.1)	175 (43.64)		164 (43.7)	163 (43.5)	
Deprivation						
Quintile 1	>720 (>17.3)	70 (17.5)		66 (17.6)	63 (16.8)	
Quintile 2	798 (19.1)	81 (20.2)		77 (20.5)	76 (20.3)	
Quintile 3	884 (21.2)	82 (20.5)	0.963	76 (20.3)	74 (19.7)	0.994
Quintile 4	876 (21.0)	87 (21.7)		80 (21.3)	84 (22.4)	
Quintile 5	888 (21.3)	81 (20.2)		76 (20.3)	78 (20.8)	
Unknown	*	0 (0)		0 (0)	0 (0)	
Ethnicity						
White	3,637 (87.2)	352 (87.8)		311 (82.9)	328 (87.5)	
Asian	64 (1.5)	*		*	*	
Black	76 (1.8)	7 (1.75)	0.761	10 (2.7)	7 (1.9)	0.486
Mixed	16 (0.4)	*		*	*	
Other	59 (1.4)	*		8 (2.1)	*	
Unknown	318 (7.6)	31 (7.7)		39 (10.4)	30 (8)	
Charlson co-morbidity Score						
0	2,695 (64.6)	280 (69.8)	0.005	272 (72.5)	272 (72.5)	0.96
1 – 4	690 (16.6)	72 (18.0)		63 (16.8)	65 (17.3)	
5+	785 (18.8)	49 (12.2)		40 (10.7)	38 (10.1)	
Surgical resection Type						
Right Hemicolectomy	1,808(43.4)	>5 (>1.2)		**	**	
Rectal Operation	913 (21. 9)	174 (43.4)		172 (45.8)	172 (45.9)	
Extended right hemicolectomy	749 (18.0)	34 (8.5)	<0.001	32 (8.5)	34 (9.1)	0.987
Left Hemicolectomy	339 (8.1)	119 (29.7)		109 (29.1)	110 (29.3)	
Sigmoid colectomy	316 (7.6)	61 (15.2)		62 (16.5)	59 (15.7)	
Transverse Colectomy	45 (1.1)	*		**	**	

**Indicates that the figure is <6. If a single figure is censured another will be marked as ">" reflecting a value up to 5 points higher than that stated, to ensure the censured figure cannot be calculated.*

*** Right Hemicolectomy and Transverse colectomy were excluded from the propensity matched data.*

5.2.3 Propensity Matched Analysis

Following propensity matching 375 MS were paired to 375 surgery only subjects for analysis. Univariable comparison of Charlson scores (p=0.960), age (p=0.997), gender (p=0.941) and resection type (p=1.0) no longer revealed a statistical difference between the groups.

5.2.4 Procedure outcomes following propensity matching

The MS procedure appeared to have a similarly high degree of technical success in the matched cohort with 330 (88.0%) subjects not requiring a resection during the initial admission with obstruction (Table 5.2). In the surgery only group 104 (27.7%) subjects did not require surgical resection at the time of presentation with obstruction. This is likely to represent successful conservative management. Median time to resection in the MS group following presentation with obstruction was 32 days and 3 days in the surgery only group. Subjects were more likely to have a laparoscopic resection following MS (41.1%) compared to the surgery only group (6.7%, p<0.001). MS subjects were also less likely to be left with a stoma (13.1%) than surgery only group subjects (42.4%, p<0.001).

Table 5.2 Surgical outcomes following colon cancer resection in the whole study population and after propensity matching

Obstruction episode length of stay (Days)		14 (8 - 23)	6 (4 - 10)	N/A	13 (8 - 23)	6 (4 - 10)	N/A
Time to MS insertion (days)			2 (1 - 3)	N/A		2 (1 - 3)	N/A
Time to resection (days)		2 (1 - 9)	32 (20-48)	<0.001	3 (1 - 14)	32(20 - 46)	<0.001
Length of stay for resection (days)		12 (7 - 20)	7 (5 - 13)	<0.001	12 (8 - 22)	7 (5 - 13)	<0.001
Stoma required		997 (23.91)	52 (13.0)	<0.001	159 (42.4)	49 (13.1)	<0.001
Resection method	Conversion Lap to open	108 (2.6)	33 (8.2)	< 0.001	9 (2.4)	32 (8.5)	< 0.001
	Lap	300 (7.2)	166 (41.4)		25 (6.7)	154 (41.1)	
	open	3,762 (90.2)	202 (50.4)		341 (90.9)	189 (50.4)	
Resection during admission for obstruction		3,330 (79.9)	49 (12.2)	<0.001	270 (72.3)	45 (12)	<0.001
Death within 30 days of resection		392 (9.4)	7 (1.8)	<0.001	33 (8.8)	7 (1.9)	<0.001
Death within 1 year of resection		984 (23.6)	40 (10.0)	<0.001	71 (18.9)	37 (9.9)	<0.001
Re-admission within 30 days of resection		538 (12.9)	30 (7.5)	0.002	44 (11.7)	28 (7.5)	0.047

5.2.5 Mortality and complications after resection following propensity matching

Univariable analyses following propensity matching demonstrated that subjects in the MS group had lower 30 day mortality compared to the surgery only group (7(1.9%) versus 33(8.8%), p<0.001) and lower 1 year mortality (37(9.9%) versus 71(18.9%)(Table 5.2). The difference in mortality at one year is shown in Figure 5.2.

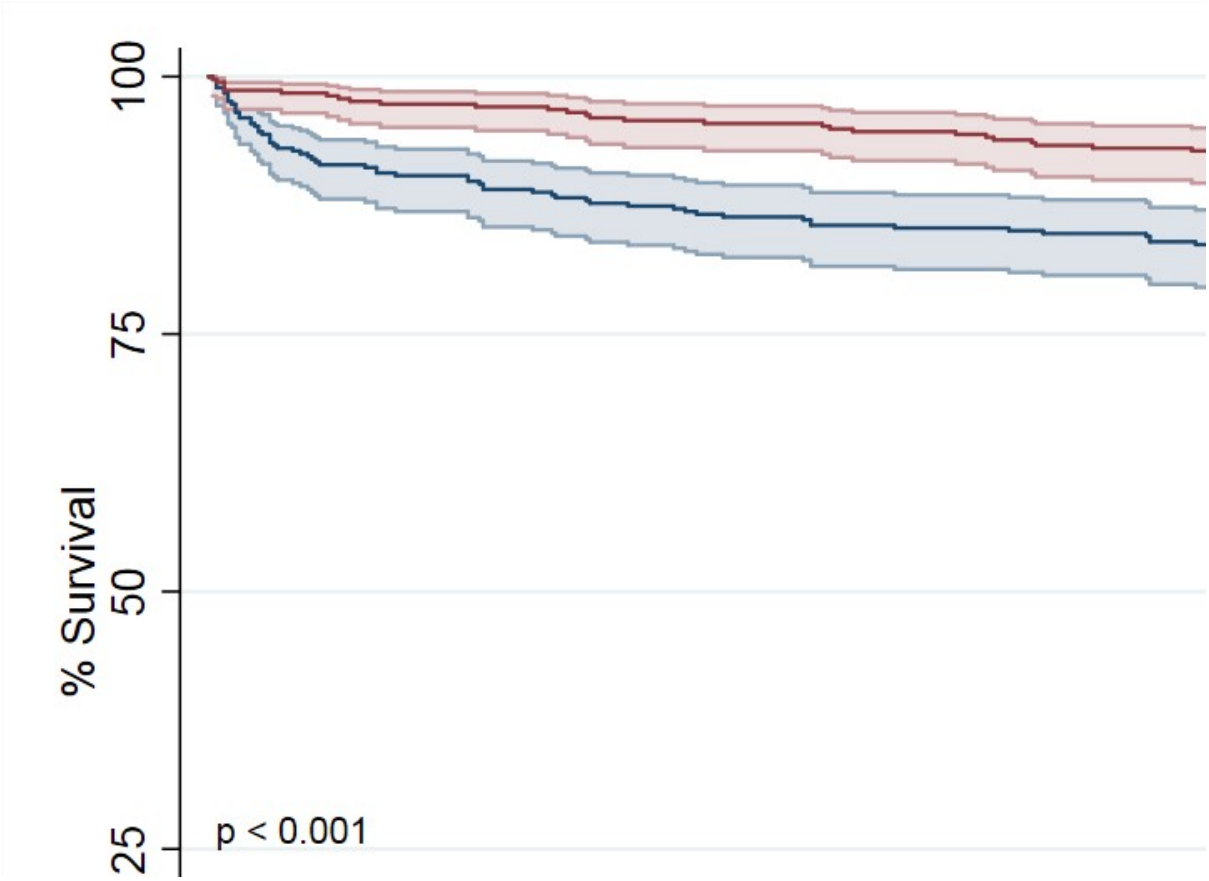
At 30 days, readmission rates were higher following surgery only compared to MS (7.5% versus 11.7%, p=0.047). Respiratory complications were also significantly lower in the MS group (p<0.001) (Table 5.3).

Table 5.3 Complications within 30 days of colon cancer resection in the whole study population and after propensity matching

Acute Kidney Injury	166 (4.0)	7 (1.8)	0.025	13 (3.47)	7 (1.87)	0.174
Anastamotic complication	65 (1.6)	7 (1.8)	0.774	8 (2.13)	7 (1.87)	0.794
Cardiovascular	356 (8.5)	25 (6.2)	0.111	29 (7.73)	23 (6.13)	0.388
Colostomy	37 (0.9)	0 (0)	0.072	*	0 (0)	0.062
Respiratory	317 (7.6)	*	<0.001	28 (7.47)	*	<0.001
Sepsis	280 (6.7)	15 (3.74)	0.021	22 (5.87)	14 (3.73)	0.172
Thrombosis	93 (2.2)	*	0.044	8 (2.13)	*	0.223
Wound complication	107 (2.6)	*	0.017	8 (2.13)	*	0.223

**Indicates that the figure is <6.*

Figure 5.2 Propensity matched Kaplan Meier curves with 95% confidence intervals for 1 year survival post resection for colon cancer



** The shaded area represents the 95% confidence interval.*

5.3 Chapter specific discussion

Following propensity score matching of MS and surgery only subjects to control for differences in co-morbidity score and age between the groups, subjects receiving a bridging MS had significantly lower 30 day mortality (1.9%) when compared to their surgery only counterparts (8.8%). Consequently 1 year mortality was also lower for MS subjects (9.9%) compared to the surgery group (18.9%). MS subjects also had lower rates of stoma formation, open surgery, emergency readmission and respiratory complications.

The most recent meta-analysis of colorectal MS as a bridge to surgery, including 136 bridging stents, reported that 30 day mortality after MS was 5.9% compared to 7.3% in the surgery only group (58). A larger meta-analysis from 2004 of non-randomised studies included 407 bridging stents and reported 0.58% 30 day mortality, albeit without a comparator surgical group without a MS(115). In ESCO, a multicentre Italian randomised control study, 60 day mortality was reported as 7.1% and 5% for MS and Surgery only groups respectively(57). A preliminary report of the CReST trial describes 5.3% and 4.4% 30 day mortality for MS and surgery only groups respectively(112). The present study differs from previous studies in that our sample population is larger, including 401 MS compared to 136 in the latest meta-analysis, 56 in ESCO and 246 total randomised subjects (actual stent number not yet reported) in CReST. It is also important to note that until recently MS have only been placed in large units, by subspecialist clinicians. Therefore many of the patients included in the earlier years of the analysis may benefit from this effect when compared to more recent studies. Furthermore there are significant methodological differences, CReST and ESCO both report shorter times to surgery within 4weeks and a median of 5 days respectively. By comparison median time to surgery was 32(IQR 20-46) days in the present study. This is a significant difference, as one of the main arguments for using bridging MS is to facilitate a period of medical stabilisation prior to surgery. Shortening the time between resection and MS insertion will potentially reduce the benefit of MS in comparison with proceeding straight to surgery for obstruction.

Hospital Episode Statistics data provides a powerful tool to examine subject outcomes, but has a number of limitations in this setting, in particular, a lack of data regarding tumour stage, illness severity markers, treatment intention, and other data important to outcomes. However trials of MS in left sided obstruction require a potentially unwell or unstable patient group and surveys have demonstrated clinician reluctance to use MS in the scenario of potentially curable colorectal cancer (61). It is therefore not surprising that multicentre randomised studies of bridging MS have struggled to recruit subjects. An analysis using HES data is therefore a pragmatic method of analysing a large

dataset to address questions concerning outcomes of bridging MS. Having used the HES coding to exclude any subject with metastatic disease and by only including those undergoing a resection intended to be curative, study subjects should only represent a narrow spectrum of tumour stages. Future studies would benefit from linkage to the national cancer registry, data including staging data, although this is not currently available under the terms of access to HES.

A systematic source of selection bias which could not be entirely corrected for derives from those subjects who are at higher operative risk. If surgery is performed initially then they will be included in the present study. Should a MS be placed with bridging intent in such subjects, once the higher operative risk is fully assessed, the treatment plan may change to not include resection. Therefore in this analysis the MS group will exclude some very high risk subjects who do not proceed to resection compared to the surgery only group.

Selective-survival bias will similarly impact on the results in that any subject who undergoes an intended bridging MS insertion but does not survive to resection will not be included in the MS group. Selection bias will be reduced by utilising propensity matched analysis. This method gives a propensity score to each subject based upon age at obstruction, gender, type of surgery and Charlson co-morbidity score. Subjects can then be matched carefully based on these parameters. In non-randomised studies with large numerical and constitutional discrepancies between participant numbers per cohort, this technique allows close matching of the study groups. Furthermore those without a suitable match are excluded. This will therefore reduce the potential for selection bias described above.

As a non-randomised study subject selection for bridging MS was by the treating physician. Therefore there will be a potential bias towards those subjects in whom a MS is expected to give a good outcome. Propensity matching allows us to ameliorate this bias based upon measureable variables, but as noted above some important variables, such as physiological status and tumour stage, are not available within HES.

Data validation represents a key challenge. Stent placement is a relatively uncommon event on an individual provider basis. It is even less common when used as a bridge to surgery. Therefore local validation focused on all stents inserted for colorectal cancer. The use of national data sources to support validation is not feasible, as there are no comparable data sets including only subjects presenting with obstruction. Clinical trial data demonstrates comparable technical success of stent insertion to the present study. However the pragmatic nature of the current study, including all subjects undergoing bridging stenting, provides a different subject cohort to that seen in clinical

trials. Local provider and clinical trial data demonstrated good correlation with study data in the present study, supporting the validity of the data reported.

The coding of failed colorectal MS insertion is challenging, as there is no nationally recognised nomenclature for how to code this. It was also not possible to discern between radiologic and endoscopic stent placement. Therefore a procedural success rate for colorectal MS insertion cannot be accurately calculated. However the close correlation between the number of subjects assumed to have failed MS insertion, as they required immediate resection, to the reported CREST, 2004 meta-analysis and 2014 meta-analysis MS insertion procedural success rates suggests this is a reasonable proxy for technical stent insertion failure.

In this, the largest study to date of colorectal MS as a bridge to surgery, compared with emergency surgery, a significant reduction in early and late mortality for those undergoing MS was observed. Subjects undergoing MS insertion also had lower stoma rates, a higher incidence of laparoscopic surgery and a lower incidence of respiratory complications. Our study supports the hypothesis that bridging colorectal MS for subjects presenting with bowel obstruction are of benefit to patients, by avoiding the need for high risk emergency surgery. Prospective randomised studies should focus on the opportunities provided by MS to optimize subjects prior to eventual curative resection.

6. Outcomes of pneumatic dilatation and Heller's myotomy for achalasia in England between 2005 and 2016

6.1. Chapter Specific materials and methods

6.1.1Subject Cohort

Subjects were initially identified by the presence of a primary diagnosis code for achalasia, defined by ICD10 codes (see appendix 6.1), between January 2006 and December 2015. Subjects were also required to have a suitable procedure code for treatment of achalasia (see appendix 6.2). Subjects were then grouped by initial treatment into HM and PD groups. PD procedures in England are performed by secondary care providers and are all coded in HES, even though they are usually performed as a day case or outpatient procedure. Subjects were excluded if they had a prior diagnosis of achalasia in the preceding five years since the introduction of ICD10 coding in 2001. The following subjects were excluded: those without a treatment code, any subject not resident within England, as we would potentially lose any follow-up data if they went to a hospital within their own country; those under 18 years of age or with missing age or sex, as these variables are used along with the NHS number to validate subject identity; and subjects with Chagas' disease. All subjects within HES have a unique identification number, allowing complete follow-up of subjects throughout the study period

6.1.2 Data extraction

Demographic data were extracted from HES based upon initial treatment, including age, gender, ethnicity, Index of Multiple Deprivation (2010) quintiles (1 being the most deprived, 5 being the least), and Charlson co-morbidity scores(100). The use of Charlson scores has previously been validated for HES in several settings, including accurately representing the co-morbidity burden in subjects undergoing urological surgery(101), and a good correlation to co-morbidities as documented in primary care(113).

Repeated treatment or a change in treatment modality (including botulinum toxin injection) for achalasia was collected as a surrogate for failure of the previous treatment. Any treatment beyond a single HM or more than three PDs was considered to represent treatment failure as these were the criteria utilised in the largest multicentre randomised controlled trial of achalasia(66). A series of PD including any procedures within a 30 day period were considered permissible as a single dilatation treatment, as per trial criteria(66).

Complications within 30 days after treatment were recorded as mortality, emergency re-admission, perforation, bleeding, complications of sedation, and complications of surgery for the relevant groups, by way of ICD10 codes (Appendix 3). The proportion of perforations not diagnosed on the day of procedure, as demonstrated by an emergency re-admission at least one day after PD, is also reported. Provider volume was described by index procedure. Only a single procedure was

permitted per subject when calculating provider volume to reduce potential confounding due to multiple ineffective procedures potentially leading to more procedures being undertaken by a provider and obscuring an association between provider volume and outcome.

6.1.3 Data Validation

Subjects with achalasia were sought over the duration of the study period at Sandwell and West Birmingham NHS trust including data on initial treatment modality. Endoscopy reporting software, gastrointestinal physiology laboratory records and coding records of surgical procedures were interrogated for potential cases. Reports and electronic medical records were then reviewed to confirm a diagnosis of achalasia, that the date of diagnosis corresponded to the study period, and that treatment was provided and its modality. Data obtained were then compared with that recorded in HES for Sandwell and West Birmingham Hospitals NHS trust for the same period.

6.1.4 Statistical analysis

Comparisons between treatment groups were made using chi-squared tests for categorical and Kruskal-Wallis for continuous variables. Multivariable cumulative incidence regression models were used to measure treatment failure for PD and HM groups after adjusting for age, sex, deprivation, ethnicity, Charlson comorbidity score and provider volume. Subjects that died during their index admission with an achalasia diagnosis were excluded from these models. A multivariable logistic regression model was also constructed for PD, to measure associations with 30 day mortality after adjusting for demographic variables as previously described. Incidence rates for further treatments are reported per 1000 person-years, censoring on the date of treatment failure, death or end of follow-up (31st December 2016). Time to treatment failure was compared between PD and HM by cumulative incidence regression, allowing for death as a competing risk(116). Proportionality was checked for cause-specific hazards and satisfied using Schoenfeld residuals. All analysis was conducted using Stata SE 14 (Stata Statistical Software: College Station, TX: Stata Corp LP)(114). P values <0.05 were considered significant.

6.2 Chapter specific results

6.2.1 Validation

At Sandwell and West Birmingham NHS Trust during the study period 50 eligible subjects were found, compared to 48 in HES (96% agreement). Individual treatment modalities also correlated strongly; 36 PDs were identified in HES compared to 39 locally (92.3%) and 12 HMs in HES compared to 11 locally (91.6%).

6.2.2 Demographics

From all hospital episodes (source population) 11,415 subjects were identified with a new achalasia ICD10 code within the study period. 6,938 subjects were included in the final analysis and the list of reasons for exclusion is shown in Appendix 6.2. 2,190(31.6%) underwent HM and 4,748(68.4%) PD, the full demographic details of each group is described in Table 6.1. The HM group were younger, with a median age of 44(IQR 32-57) years compared to 65(48-78) for PD ($p<0.001$). More males underwent HM (55.7%) than PD (50.5%) ($p<0.001$). Subjects undergoing HM had lower Charlson scores than PD subjects.

At the time of HM 95.0% of subjects also underwent a surgical treatment to prevent gastro-oesophageal reflux.

Table 6.1 Demographic characteristics of study subjects based upon their initial treatment modality

Sex	Male	1219 (55.7)	2400 (50.5)	<0.001
	Female	971 (44.3)	2348 (49.5)	
Deprivation quintile	1	427 (19.5)	829* (>17.5)	0.251
	2	427 (19.5)	940 (19.8)	
	3	444 (20.3)	983 (20.7)	
	4	447 (20.4)	1019 (21.5)	
	5	439 (20.4)	968 (20.4)	
	Unknown	6 (0.3%)	<6* (<0.1)	
Ethnic group	White	1801 (82.2)	4172 (87.9)	<0.001
	Asian or Asian British	33 (1.5)	25 (0.5)	
	Black or Black British	140 (6.4)	213 (4.5)	
	Mixed	74 (3.4)	125 (2.6)	
	Any other ethnic group	39 (1.8)	73 (1.5)	
	Unknown	103 (4.7)	140 (2.9)	
Age quintile	18-38	798 (36.4)	676 (14.2)	<0.001
	39-52	662 (30.2)	788 (16.6)	
	53-65	457 (20.9)	934 (19.7)	
	66-77	231 (10.5)	1114 (23.5)	
	78+	42 (1.9)	1236 (26.0)	
Charlson co-morbidity score	0	1886 (86.1)	3673 (77.4)	<0.001
	1-4	238 (10.9)	475 (10.0)	
	>4	66 (3.0)	600 (12.6)	
Total		2190	4748	

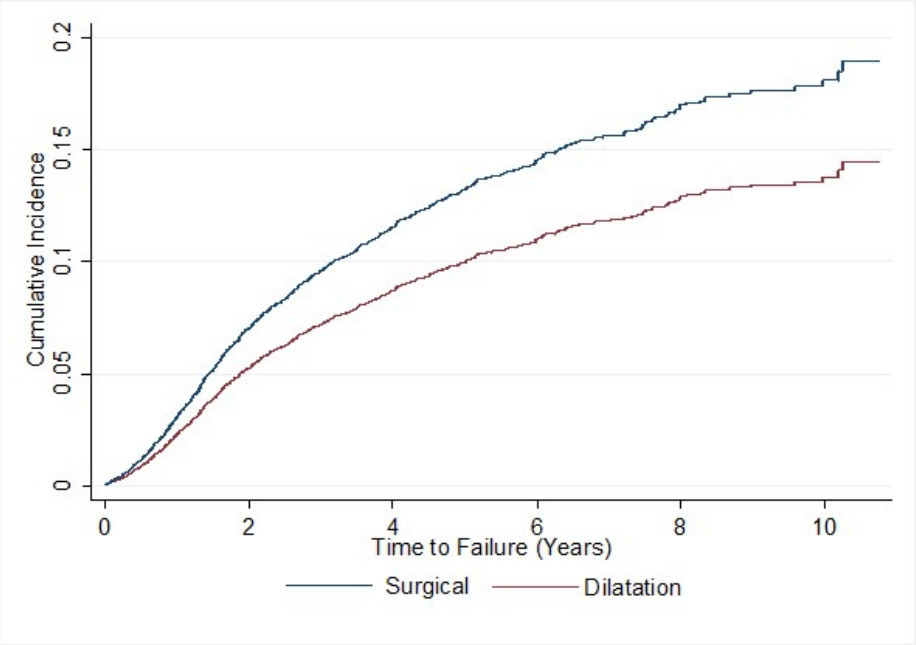
**Value censored from publication due to HES data sharing guidelines to protect subject anonymity*

6.2.3 Achalasia treatment failure

19,608 and 9,600 person years were included for PD and HM subjects respectively over the study period. The median follow-up per subject was 4.0 (range 0-10.7) years. Within 5 years of initial treatment the incidence rates of subjects requiring further treatment were 26.5 (95% CI 24.0 – 29.2) and 32.5 (95% CI 28.7 – 36.9) per 1000 person-years after PD and HM respectively. Over the study period the rate of subjects requiring further therapy was 24.0 (95% CI 21.9 – 26.2) per 1000 person-years post-PD and 28.3 (95% CI 25.2 – 31.9) post-HM.

At 10 years follow-up, the cumulative incidence of treatment failure, treating death as a competing risk, was 13.8% in PD and 18.1% for subjects undergoing HM ($p<0.001$) (Figure 6.1). During the study period, the rate of subjects undergoing HM after failing initial treatment with PD is 65.1 per 1000 person-years (95% CI 60.4 – 70.1) compared to 22.9 per 1000 person-years (20.2 – 25.9) for subjects undergoing PD following HM.

Figure 6.1: Cumulative incidence plot demonstrating durability of Pneumatic dilatation and Surgical myotomy for achalasia



P<0.001

6.2.4 Multivariable analysis of factors associated with treatment failure

Between 2006 and 2015, per provider, the median number of HM per annum was 5 (IQR 2-22) and 5 (IQR 3-9) PD procedures. In total 174 providers were included.

In multivariable cumulative incidence regression models, male gender (SHR 0.77 (0.61 – 0.99),p=0.038) was negatively associated with treatment failure in the HM group. PD appeared to be less effective with increasing age (66-77 years(1.63 (1.18- 2.26),p=0.003), >77 years(1.50 (1.08 – 2.10) p =0.021) and more effective in Charlson score >4 (0.66 (0.48-0.91), p=0.011). There was no association between the volume of procedures performed and failure of treatment in either the PD or HM groups. There was no association between treatment failure and deprivation. (Table 6.2).

Table 6.2 Cumulative incidence regression analysis of factors associated with failure of treatment in the surgical myotomy and pneumatic dilatation groups

		SHR (95% CI)	p-value	SHR (95% CI)	p-value
Gender	Female	1 (baseline)		1 (baseline)	
	Male	0.77 (0.61-0.99)	0.038	0.93 (0.77-1.11)	0.412
Age quintile	18-38	1 (baseline)		1 (baseline)	
	39-52	0.76 (0.56-1.03)	0.076	0.94 (0.65 - 1.36)	0.741
	53-65	0.78 (0.56-1.10)	0.161	1.38 (0.99 - 1.93)	0.098
	66-77	1.10 (0.74-1.62)	0.634	1.63 (1.18 - 2.26)	0.003
	> 77	1.32 (0.62-2.79)	0.474	1.50 (1.08 - 2.10)	0.017
Deprivation	1	1.01 (0.69-1.48)	0.952	0.90 (0.66 - 1.22)	0.490
	2	0.97 (0.67-1.41)	0.879	1.00 (0.75 - 1.33)	0.982
	3	0.95 (0.65-1.38)	0.789	1.04 (0.79-1.38)	0.767
	4	0.78 (0.53-1.15)	0.204	1.03 (0.79-1.35)	0.825
	5	1 (baseline)		1 (baseline)	
Ethnic group	White	1 (baseline)		1 (baseline)	
	Not White	1.08 (0.95-1.91)	0.689	0.92 (0.64 - 1.34)	0.675
	Unknown	0.40 (0.19-0.84)	0.016	0.57 (0.31 - 1.04)	0.065
Charlson co-morbidity category	0	1 (baseline)		1 (baseline)	
	1 to 4	1.35 (0.95-1.91)	0.096	1.06 (0.80-1.41)	0.694
	> 4	1.09 (0.55-2.16)	0.805	0.66 (0.48-0.91)	0.011
Provider volume tertile**	Low	0.94 (0.71 - 1.25)	0.812	0.91 (0.71 - 1.17)	0.480
	Medium	0.99 (0.72 - 1.35)	0.936	0.98 (0.79 - 1.21)	0.821
	High	1 (baseline)		1 (baseline)	

**SHR – subdistribution hazard ratio*

***Provider volume tertiles are: <4, 4-14 and >14 for lower, medium and upper tertiles of Heller's myotomy respectively and <3, 3-4, and >4 for lower, medium and upper tertiles of pneumatic dilatation.*

6.2.5 Mortality

The 30 day mortality over the study period was 0.0% for subjects undergoing HM and 1.9% following PD, of whom 1.3% died within the admission associated with PD. Mortality in subjects undergoing PD by age group was: 0.3%, 1.3% and 5.3% in subjects aged 18-65 years, 66-77 years and >77 years respectively. Less than 8% of subjects who suffered an endoscopic perforation died within 30 days (data censored). Multivariable regression analysis demonstrated that the following were associated with 30 day mortality after pneumatic dilatation; age 66-77, age >77, previous myotomy for achalasia, 1-3 previous pneumatic dilatations, >4 previous pneumatic dilatations and Charlson co-morbidity score >4. (Table 6.3)

Table 6.3 Logistic regression analysis of factors associated with 30 day mortality following pneumatic dilatation therapy

		Odds Ratio	p-value
Age group	**18-38**	Reference category	
	39-52	0.95 (0.33 - 2.73)	0.919
	53-65	1.85 (0.75 - 4.53)	0.181
	66-77	4.55 (2.00 - 10.38)	<0.001
	> 77	9.78 (4.33 - 22.06)	<0.001
Deprivation	**1**	1.36 (0.85 - 2.18)	0.196
	2	1.35 (0.87 - 2.12)	0.184
	3	1.19 (0.76 - 1.86)	0.451
	4	0.69 (0.42 - 1.13)	0.144
	5	Reference category	
Ethnicity	**White**	Reference category	
	Not White	0.82 (0.42 - 1.60)	0.555
	Unknown	0.44 (0.22 - 0.88)	0.020
Gender	**Female**	Reference category	
	Male	1.01 (0.75-1.35)	0.953
Previous myotomy	**Yes**	2.00 (1.05-3.79)	0.035
	No	Reference category	
Charlson co-morbidity category	**0**	Reference category	
	1 to 4	0.77 (0.41-1.41)	0.393
	> 4	2.87 (2.08-3.95)	<0.001
Number of prior dilatations	**0**	Reference category	
	1 to 3	1.58 (1.15-2.16)	0.005
	4+	1.97 (1.21 - 3.19)	0.006

6.2.6 Complications of therapy

The coded complications of achalasia treatment are described in Table 6.4. The 30 day emergency readmission rate over the study period was 2.6% and 3.8% for subjects undergoing HM and PD respectively.

The coded perforation rate following dilatation was 1.6% and sedation complications were noted in 3.4%. Following PD, 55.8% of perforations were diagnosed and admitted to hospital on the same day. Multivariable regression analysis did not reveal any associated factors for perforation (data not shown). Mortality following PD perforation was low (<8%) (Data censored due to low numbers).

Table 6.4 The complications of achalasia treatment within 30 days

30 day readmission		57 (2.6)	181(3.8)
30 day mortality		0 (0)	89 (1.9)
Endoscopic	**Bleeding**	-	29 (0.6)
	Perforation	-	77 (1.6)
	Sedation	-	163 (3.4)
Surgical	**Bleeding**	22 (1.0)	-
	Perforation	151 (6.9)	-
	Venous Thrombosis	6 (0.3)	-
	Anaesthetic complications	30 (1.4)	-

6.4 Chapter specific discussion

This is the largest ever study of the outcomes of achalasia therapy. Long term outcomes appear to be better following up to three PDs when compared to HM. There was no mortality associated with surgery suggesting excellent subject selection, which is consistent in other studies that include older subjects undergoing myotomy (117). Pneumatic dilatation was associated with 1.9% 30 day mortality, which appears largely related to the co-morbidity seen in this group. Increasing age, co-morbidity and previous HM or PD were associated with increasing mortality in PD subjects. Perforation following PD was rare, generally recognised early and associated with relatively low mortality.

The durability of HM and PD demonstrated in this study at 5 years was similar to that reported in a large European randomised control trial comparing PD (82% versus 88% in the present study) to laparoscopic HM (84% versus 87% in the present study)(67). Moonen et al used an Eckardt score <4 as their primary end point, which is likely to result in a slightly higher failure rate than the current study, as those with limited residual symptoms not requiring further intervention may still be considered a failure in that study, but not in the present study. Unfortunately this could not be addressed in the validation study, as Eckardt scores are not routinely recorded in the medical records examined. However, the similarity between the 5 year results reinforces the methodology of the current study and the validity of the longer term outcomes described.

Durability is not reported in the present study for botulinum toxin injection treatment. Prospective, randomised data have compared injection to HM, demonstrating that although short term benefit was seen, after 2 years only 34% of injection subjects were symptom free compared to 87.5% in the HM group(68). Systematic reviews support this finding, concluding that injection therapy is less durable than either PD or HM(69, 70).

The present study has been able to report 10 year outcomes for PD and HM with sustained results for PD but some loss of benefit for HM. Although long term outcomes for subjects with achalasia undergoing HM are reported elsewhere over periods beyond 5 years, the numbers described are often small. In a study of 54 subjects at a single site over a 10 year period following a single PD 36% remained symptom free at structured interview(118). A further prospective 15 year review of 39 subjects demonstrated 58% symptom free survival based upon symptom score following a single PD(119). Variations of treatment failure definition make comparisons with the present study of limited value.

Unfortunately the data on which this analysis is based does not reveal a reason why PD was found to be more durable than HM. Therefore consideration of the mechanism for this benefit is speculation. It is important to note that the difference in outcome between the treatment modalities is relatively small. However it is biologically plausible that repeated disruptions of the lower oesophageal sphincter leads to a more long lasting result. Furthermore the use of a high pressure balloon dilates a functional passage through the sphincter in comparison to performing a myotomy.

An association was observed between older subjects (>66 years of age) and treatment failure following PD and subjects with higher Charlson co-morbidity score (>4) and apparent treatment success. As these subjects become more frail over the 10 year follow-up period, they may undergo botulinum toxin injection rather than repeat PD, or in those with significant co-morbidity, no further endoscopic treatment at all. This is the likely explanation for these minor associations with failure rate observed in the PD cohort.

The complication rates described in the present study are lower than those seen by Boeckxstaens et al(66). The perforation rate in the present study was 1.6% compared to 4% for pneumatic dilatations and 6.9% compared to 12% for HM(66). It is important to recognise that the impact for a patient of perforation during HM is much less than following PD. Perforations during HM can be recognised intra-operatively and treated at the time with no significant consequences. Multivariable regression did not identify any factors associated with perforation, which in combination with the low observed perforation rate is reassuring. However, under-reporting of complications is possible in HES data due to the coding structure. Subjects acquire a primary diagnosis per episode, and although significant complications can be added as a further diagnosis, this can be less complete. The coding is more accurate if a subject were discharged and returned in a new episode, which would have the complication as a primary diagnosis.

Significant variation in provider procedure volume for HM and PD was observed in the present study. Unfortunately due to censorship of small numbers in HES data, the lower volume tertile bounds cannot be published. However, although the lower bounds are not specified, no association between provider volume tertile and treatment outcome was seen on multivariable analysis.

Ascertainment bias is a concern in large database studies. However the results of the local validation provide reassurance that both achalasia as a diagnosis and its treatment modalities (with the exception of injection therapy) are accurately coded in HES. Comparison to high quality randomised data with similar outcomes reported, provides further reassurance the results of the present study are valid(67). Selection bias is also important to consider when comparing treatment modalities, as

subjects are not assigned randomly, resulting in different cohort demographics in those undergoing each treatment modality. Furthermore diagnosis in the present study is based upon ICD10 codes. Due to the limitations of HES coding, consistent oesophageal manometry findings could not be included in the case selection criteria. Furthermore, distinct subtypes of achalasia cannot be distinguished from ICD10 codes, and therefore cannot be included in the logistic regression models. Achalasia subtype influences the response to treatment (120) and may have influenced the choice of treatment modality in some of the subjects studied.

Two key strengths of this study are the size of the cohort and 10 year duration of follow-up. As achalasia is a chronic condition, which subjects will live with for decades, it is important to be able to provide data mapping the likely long term outcomes of each treatment modality, so that subjects can make an informed treatment choice. As there was only a small difference in outcomes seen between up to three PD episodes compared to a single HM, subjects can choose with a reassurance of a good outcome between one or more endoscopic procedures and a single, more invasive operation.

This study does not include POEM, as the procedure is not yet commonly undertaken in the UK and there is no OPCS4 code currently for POEM. Although a small number of POEM procedures may potentially have been coded as HM, their low numbers to date would have no significant impact on such a large HM cohort. However, the present study suggests that HM represents a safe, efficacious, single therapy in selected subjects, including those with higher Charlson co-morbidity scores and advanced age. PD has similar outcomes for those unsuitable for surgery, with low mortality and few perforations. High quality, long term randomised trial data is now needed to establish which patients with achalasia would benefit from POEM instead of current established achalasia therapy options.

In conclusion, the present study demonstrates a small increase in durability of PD compared to HM for achalasia, in a large national database, over 10 years. There was no mortality associated with HM, suggesting excellent case selection. 30 day mortality following PD was 1.9% and was associated with advancing age, increasing co-morbidity and previous HM or PD. Perforation was an uncommon event, was usually recognised rapidly and associated with relatively low mortality.

7. Incidence, morbidity and mortality of subjects with achalasia in England: findings from a study of nationwide hospital and primary care data

7.1 Chapter specific materials and methods

7.1.1 Data Sources

Both HES and THIN are used in this chapter to provide data spanning primary and secondary care. HES is used to provide the incidence of achalasia in secondary care. THIN is used to provide incidence and prevalence of achalasia. THIN is also used to assess morbidity and mortality in a matched cohort study.

7.1.2 Validation

HES data were validated by interrogation of local endoscopy reporting software, an oesophageal manometry database and surgical operation logs during the study period at Sandwell and West Birmingham Hospitals NHS Trust. All subjects with achalasia listed as a reported finding, prior diagnosis or indication were collated and electronic records were then hand searched to ensure suitability for inclusion in the study. This figure was then compared to the equivalent data generated from HES. The validity of the presented THIN data is supported by the stringent minimum data quality standards described above. The integrity of extracted THIN data is supported by the internal data validation described above.

7.1.3 Incidence and Prevalence Data

HES were searched for any subject with a diagnostic code in the primary position for achalasia (appendix 7.1) from 1st of January 2006 to 31st Dec 2015. The code may be associated with any hospital attendance including outpatient consultation, endoscopy or other diagnostic test, or for treatment and complications of achalasia. Subjects were considered to have an existing diagnosis if a diagnostic code for achalasia was present in HES at any time prior to this period. Sex, Index of Multiple Deprivations (IMD) and Ethnicity were extracted for this group. Incidence was calculated using annual mid-year England population figures provided by the Office for National Statistics and reported per 100,000 population with 95% Confidence Intervals. HES data only includes subjects in England, rather than the whole UK, and the incidence was calculated on the basis of the source population (approximately 50 million persons).

THIN was searched using the Read code for achalasia for both new and previously diagnosed cases of achalasia (appendix 7.1) in the period from 1st January 1996 to the 1st September 2015 as communicated from secondary care. Incidence is reported annually per 100,000 person years with 95% confidence intervals and prevalence as on 1st of January each year per 100,000 populations with 95% confidence intervals.

7.1.4 Retrospective Cohort Study of morbidity and mortality outcomes in the THIN database

For outcome analysis only the THIN database was utilised because it is possible to generate controls from the source population to compare outcomes. The index date of the achalasia subjects in THIN were defined as the date they were eligible to take part in the study if they already had a diagnosis of achalasia, or the date they were diagnosed with achalasia if they were incident cases. Achalasia subjects in THIN were matched for age at index date (within 2 years), sex, deprivation (Townsend deprivation score) and smoking status to two control subjects without a diagnosis of achalasia. The controls were selected from the same general practice as the matched case. Group demographics and incidence rates for pre-specified outcomes of interest were calculated for achalasia and control groups during the study period from 1st January 1996 to the 1st September 2015. New outcome codes were sought in matched groups from the index date until the first of the following outcomes occurred (exit date); subject died, subject left practice, last data collection from practice, study end date or subject diagnosed with the outcome of interest. Subjects were excluded if there was a diagnosis of the outcome of interest prior to achalasia diagnosis. Subjects were also excluded from the study if they had a diagnosis of oesophageal cancer within one year of achalasia diagnosis, or if they had a diagnosis of Chagas' disease.

Prospectively determined new outcomes included: any cardiovascular disease (including ischaemic heart disease, stroke or TIA, and heart failure), oesophageal cancer, any cancer (excluding oesophageal), peripheral vascular disease, aspiration pneumonia, lower respiratory tract infection (LRTI), dementia and all-cause mortality (Appendix 7.2).

7.1.5 Statistical Analysis

The matched groups baseline characteristics in THIN are described in proportions for categorical variables (sex, Townsend deprivation score, smoking status, hypertension, diabetes mellitus, and use of lipid lowering medications) and with mean (standard deviation) for normally distributed continuous variables (age and BMI) and Mann-Whitney U test for skewed continuous variables (person years).

An estimated incidence rate ratio (IRR) was calculated for each outcome within the achalasia and control groups. Then adjusted IRRs were calculated using the Poisson regression for individual patient covariates (age, sex, Townsend deprivation score, smoking status, hypertension, diabetes mellitus and the use of lipid lowering medications) as appropriate. "Any cardiovascular disease", stroke or TIA, heart failure and peripheral vascular disease were further adjusted for diabetes, lipid

lowering drug use and hypertension. The median and interquartlie range (IQR) of time from achalasia diagnosis to oesophageal cancer, LRTI and death is also reported. In control subjects, start time was considered to be the time of study entry. Cumulative incidence plots were constructed for time to oesophageal cancer, LRTI and all cause mortality. BMI was treated as a categorical variable to address missing values. Mortality was adjusted for Charlson Score in addition to the factors listed above. The Charlson score is based on a list of co-morbidities, each with an assigned score. The sum of a patient's individual co-morbidity scores is the final score(100). Incidence rate ratios were calculated with 95% confidence and a statistical significance threshold of $p<0.05$.

All analysis was conducted using Stata v14.0 software(114).

The THIN data analysis received scientific committee approval of this particular study in March 2017 (SRC17THIN133) from 'IMSHealth' (data provider). Pseudonymised HES data has been shared by NHS Digital under a data sharing agreement.

7.2 Chapter specific results

7.2.1 Validation

At Sandwell and West Birmingham Hospital NHS Trust there were 56 subjects with a new diagnosis of achalasia within the study period. This correlates strongly (96%) with the 54 coded for within the HES database for Sandwell and West Birmingham Hospitals NHS Trust during the study period.

7.2.2 Subject demographics

The HES subjects included 10,509 incident cases of achalasia in England over a 10 year period. The median age was 59 (IQR 43-75) years and the cohort was split evenly with respect to sex (49.7% male, 50.3% female). The THIN subjects included 711 incident achalasia diagnoses in the UK. The median age was 62 (IQR 45-75) years and the cohort was split evenly with respect to sex (47.1% male, 52.9% female). Full cohort demographics are shown in table 7.1.

Table 7.1: The demographics of the Hospital Episode Statistics and The Health Improvement Network achalasia subjects

Sex	Male	5226 (49.7%)	335 (47.1)
	Female	5283 (50.3%)	376 (52.9)
Age (median, IQR)		59 (43-75)	62 (45-75)
Deprivation Quintile*	Most deprived quintile	1848 (17.6%)	80 (11.3)
	2nd most deprived quintile	2094 (19.9%)	124 (17.4)
	Middle quintile	2176 (20.7%)	161 (22.6)
	2nd least deprived quintile	2199 (20.9%)	148 (20.8)
	Least deprived quintile	2173 (20.7%)	176 (24.8)
	Unknown	19 (0.0%)	22 (3.1)
Ethnic Group**	White	9117 (86.8%)	301 (42.3)
	Asian or Asian British	79 (0.8%)	17 (2.4)
	Black or Black British	480 (4.6%)	9 (1.3)
	Mixed	282 (2.7%)	-
	Any other ethnic group	176 (1.7%)	-
	Unknown	375 (3.6%)	384 (54.0)

*HES uses Index of multiple deprivations (2010), quintile 1 is the most deprived. THIN uses Townsend index, quintile 5 is the most deprived. Therefore this is displayed from most to least deprived quintiles.

** THIN was found to include multiple ethnicities per subject depending on the scale applied. Therefore when there was ambiguity subjects were listed as unknown.

7.2.3 Incidence and prevalence of achalasia

The overall incidence per 100,000 population over the study period in HES was 1.99 (95% CI 1.87-2.11) and 1.53 (1.42-1.64) per 100,000 person years in THIN. The mean prevalence measured in THIN was 27.1 (25.4-28.9) per 100,000 population. The incidence seen in HES increased over the study period from 1.73(1.62-1.85) in 2006 to 2.24(2.11-2.36) per 100,000 population in 2015. A similar increase was not observed in achalasia subjects in THIN. The annual incidence and prevalence from each database is presented in table 7.2.

Table 7.2 The incidence and prevalence of achalasia reported in Hospital Episode Statistics and The Health Improvement Network by year

2006	1.73	1.62-1.85	1.41	1.01-1.74	21.14	19.79-22.56
2007	1.80	1.69-1.92	1.66	1.08-1.81	21.72	20.37-23.14
2008	1.80	1.68-1.91	1.55	1.30-2.08	22.49	21.12-23.91
2009	1.85	1.74-1.97	1.70	1.21-1.96	23.16	21.79-24.6
2010	2.02	1.90-2.14	1.66	1.34-2.12	23.66	22.27-25.12
2011	1.78	1.67-1.90	1.42	1.31-2.09	24.62	23.19-26.12
2012	2.03	1.91-2.16	1.55	1.20-1.96	25.23	23.77-26.76
2013	2.18	2.06-2.31	1.62	1.26-2.05	26.06	24.56-27.62
2014	2.42	2.29-2.56	1.48	1.11-1.91	26.34	24.78-27.97
2015	2.24	2.11-2.36	1.34	0.96-1.80	27.10	25.44-28.85

*per 100,000 person years

7.2.4 Demographics and co-morbidity in the matched achalasia and control groups

There were 2,369 achalasia cases matched to 3,865 controls within THIN. There was a mean of 6.1 (SD 5.4) and 6.4 (5.4) person years follow-up for achalasia subjects and controls respectively. Achalasia subjects were slightly older as they were matched to within 2 years (56.7 vs. 55.5 years, p=0.03), however there was no difference in sex, BMI or deprivation index quintile. The incidence of hypertension (506(21%) vs. 928(24%), p=0.016), diabetes (126(5.3%) vs. 278(7.2%), p=0.004) and lipid lowering medication use (342(14.4%) vs. 635(16.4%), p=0.04) was lower in the achalasia cohort compared to the matched controls (table 7.3).

Table 7.3 The Health Improvement Network achalasia and matched control groups characteristics

Number of subjects	2,369	3,865	-
Person years of follow-up (SD)	6.1 (5.4)	6.4 (5.4)	0.02
Age (SD)	56.6 (19.8)	55.5 (19.3)	0.03
Male Sex	1166 (49.2%)	1902 (49.2%)	0.995
Body mass index (SD)	25.62 (5.3)	25.37 (4.1)	0.07
Current smoking	379 (16%)	573 (14.8%)	0.211
Hypertension	506 (21%)	928 (24%)	0.016
Lipid regulating medications	342 (14.4%)	635 (16.4%)	0.04
Diabetes mellitus	126 (5.3%)	278 (7.2%)	0.004
Charlson Co-morbidity score: 0	1468 (62.0%)	2550 (66.0%)	0.001
1	496 (20.9%)	797 (20.6%)	
2	220 (9.3%)	285 (7.4%)	
3	110 (4.6%)	129 (3.3%)	
>3	75 (3.2%)	104 (2.7%)	
Townsend index*: 1	1026 (27%)	592 (25%)	0.377
2	890 (23%)	525 (22%)	
3	776 (20%)	482 (21%)	
4	612 (16%)	390 (17%)	
5	400 (10%)	267 (11%)	
Not available	108 (3%)	81 (3%)	

*1 is the least deprived group in the Townsend deprivation index

7.2.5 Morbidity outcomes in the matched achalasia and control groups

Following adjustment for potential confounding factors, oesophageal cancer was more common (16 cancers) in the achalasia group compared to the control group (6 cancers); adjusted IRR 5.22 (95% CI 1.88-14.45), p=0.001. Also more common in the achalasia group were aspiration pneumonia 13.4(1.7-107.8), p=0.015 and lower respiratory tract infection (LRTI) 1.3(1.1-1.7), p=0.02 (table 7.4). The incidence of ischaemic heart disease, peripheral vascular disease, heart failure, dementia and cancer (excluding oesophageal cancer) did not differ between the groups. The median time from achalasia diagnosis to oesophageal cancer and LRTI was 15.5 (IQR 5.8-26.2) and 7.5 (1.5–13.6) years respectively. Cumulative incidence plots of the time from achalasia diagnosis to oesophageal cancer and LRTI are displayed in figures 7.1 and 7.2 respectively.

Table 7.4 Comparison of disease outcomes between achalasia cases and matched controls in The Health Improvement Network

	All cardio-vascular Disease		Ischaemic Heart Disease		Stroke/TIA		Heart Failure		Peripheral Vascular Disease		Oesophageal Cancer		Any Cancer		Aspiration Pneumonia		LRTI		Dementia	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
No. Subjects	2,033	3,369	2,147	3,520	2,262	3,706	2,289	3,776	2,303	3,801	2,366	3,863	2,226	3,699	2,359	3,864	2,263	3,744	2,338	3,824
No. of Outcomes	278	451	128	242	113	182	97	120	63	73	16	6	150	224	9	1	135	170	86	127
Person-years	15,379	26,027	15,985	26,818	16,218	27,503	16,306	27,841	16,379	27,925	16,632	28,229	16,071	27,420	16,617	28,235	16,207	27,630	16,468	27981
Incidence Rate (per 1000 person-years)	18.1	17.3	8.0	9.0	7.0	6.6	5.9	4.3	3.8	2.6	1.0	0. 2	9.3	8.2	0. 5	0.04	8.3	6.2	5.2	4.5
Incidence Rate Ratio (95% CI)	1.01 (0.83-1.21)		0.97 (0.74 - 1.26)		1.02 (0.79-1.31)		1.27 (0.94-1.72)		1.21 (0.82-1.78)		5.09 (1.85-14.01)		1.12 (0.89-1.40)		13.62 (1.70-108.87)		1.34 (1.05-1.70)		1.11 (0.82-1.49)	
***p*-value**	0.958		0.802		0.892		0.118		0.331		0.002		0.3333		0.014		0.018		0.507	
Adjusted Incidence Rate Ratio (95% CI)	1.04 (0.86-1.26)		1.00 (0.76-1.31)		0.99 (0.77-1.28)		1.32 (0.97-1.80)		1.31 (0.88-1.94)		5.22 (1.88-14.45)		1.10 (0.88-1.38)		13.38 (1.66-107.79)		1.33 (1.05-1.70)		1.10 (0.82-1.50)	
***p*-value**	0.714		0.993		0.953		0.077		0.186		0.001		0.413		0.015		0.02		0.521	

Figure 7.1: The cumulative incidence plot of time from achalasia diagnosis to oesophageal cancer

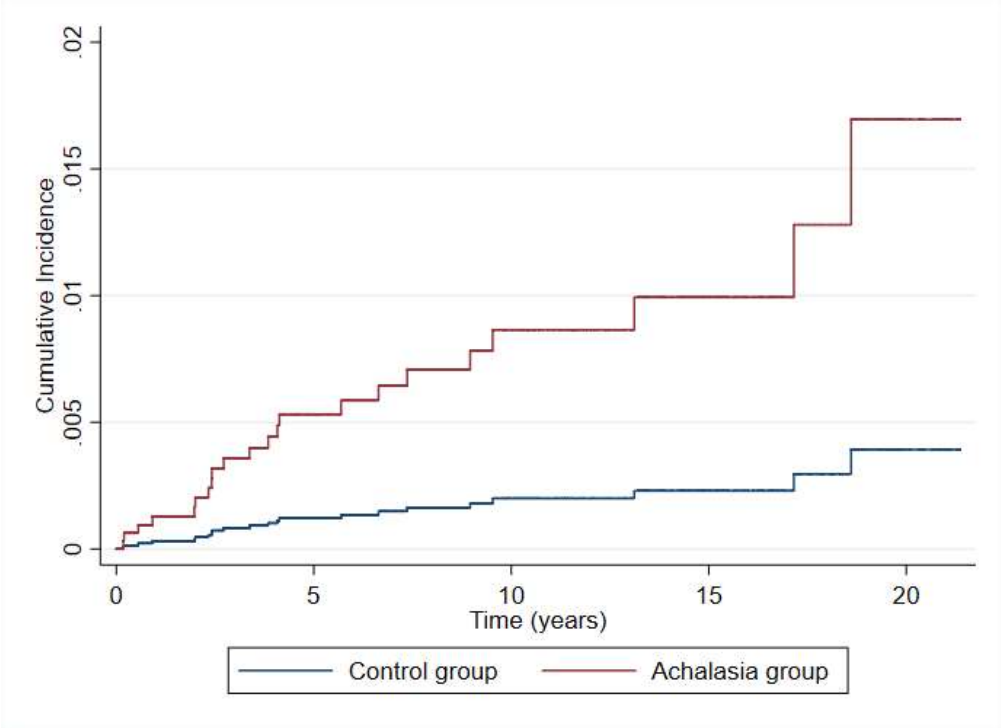
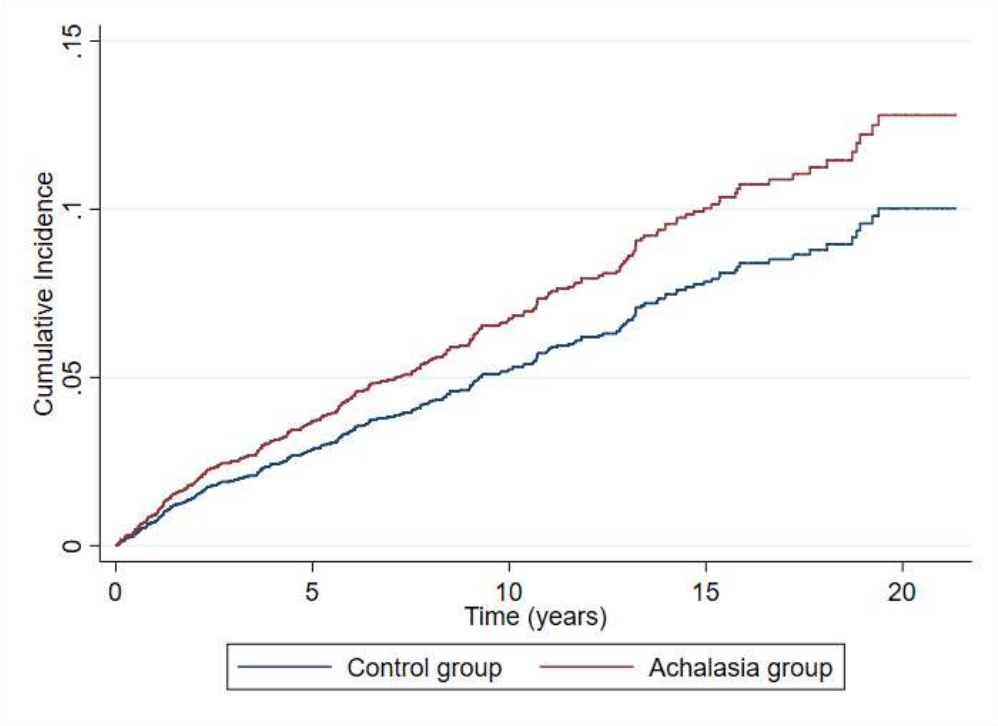


Figure 7.2: The cumulative incidence plot of time from achalasia diagnosis to lower respiratory tract infection



7.2.6 Mortality in achalasia subjects

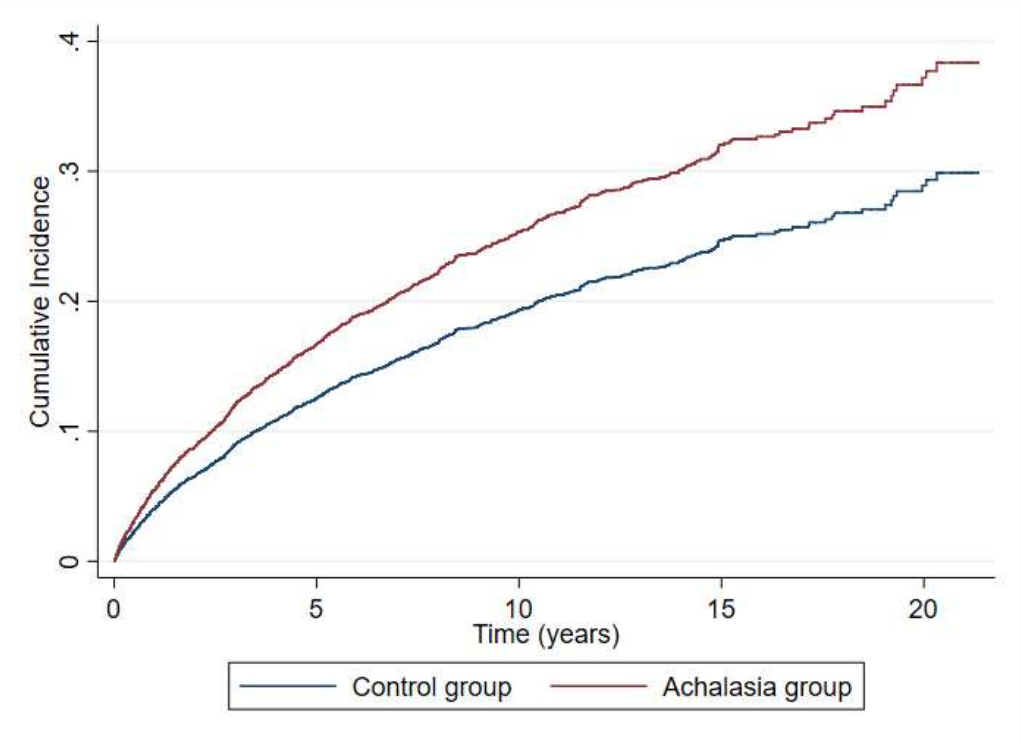
There were 441 deaths in 14,321 person years in the achalasia group compared to 553 deaths in 24,594 person years in the control group. The incidence rate ratio was 1.37 (1.21-1.55). Mortality remained significantly higher in the achalasia group despite adjusting for Charlson score, BMI, age, sex, smoking status, diabetes, lipid lowering drug use and hypertension; adjusted IRR 1.33(95% CI 1.2-1.5, $p<0.001$)(table 7.5). The median time to death was 6.8 (IQR 0.6-12.9) years. The cumulative incidence plot of time from achalasia diagnosis to death is displayed in figure 7.3.

Table 7.5 Mortality in achalasia subjects and controls in The Health Improvement Network

Number of Subjects	2,369	3,865
Numbers of deaths	441	553
Person-years	14321	24594
Incidence Rate (per 100 person-years)	3.08	2.25
Incidence Rate Ratio (95% Confidence intervals)	1.37 (1.21-1.55)	
***p*-value**	<0.001	
Incidence Rate Ratio (95% Confidence intervals) adjusted*	1.33 (1.17-1.51)	
***p*-value**	<0.001	

* Adjusted for Charlson Score, Body mass index, age, sex, smoker, diabetes, lipid lowering drugs and hypertension

Figure 7.3: Cumulative incidence plot of time from achalasia diagnosis to death



7.3 Chapter Specific discussion

The incidence of achalasia in England was between 1.42 and 2.11 per 100,000 between 2006 and 2016 and its prevalence 27.1 per 100,000. Both the incidence and prevalence are higher than previously thought in the UK population. A previously unrecognised increased mortality in achalasia subjects has been demonstrated, as has an association between achalasia and aspiration pneumonia and lower respiratory tract infections. Furthermore this study confirms a significant association between oesophageal cancer and achalasia with a fivefold higher incidence in achalasia.

There are limited recent data on the incidence and prevalence of achalasia. Although significantly higher than the incidence reported in the largest English study (0.9 per 100,000)(71), the results reported here are in keeping with the incidence reported in a more recent Canadian study, which reported an incidence of 1.63(95% CI 1.2-2.1) per 100,000(74). However the prevalence reported in the current study is significantly higher than that reported in Canada (10.8(9.7-11.9)). A potential reason for this discrepancy is due to case finding, as any achalasia subject was included in the present study, whereas the Canadian study only included subjects attending for treatment by pneumatic dilatation or surgical myotomy. Therefore any subject in the Canadian study that did not present for treatment would not be included. Although the authors have validated their data showing excellent sensitivity and specificity, the validation population were those attending for treatment. This important source of bias was not addressed in the prevalence analysis.

High resolution manometry diagnoses achalasia more accurately and provides information on subtypes that is relevant to response to therapy (120). The widespread use of high resolution manometry might be expected to marginally increase the incidence of achalasia and such a rise in incidence over time was seen in the HES database but not the THIN database.

An association with oesophageal cancer has been previously reported in achalasia. The mechanism is not understood, but, it has been postulated that poor oesophageal emptying leads to stasis and inflammation and subsequently dysplasia and eventually to neoplasia(121). Estimates of the magnitude of the increased risk vary. In a Swedish cohort study a 16-fold increase (SIR 16.6(8.8-28.3))(79) has been reported. However a more recent Swedish study described a 10-fold increase (SIR 10.5(7.0-15.9)) in risk of oesophageal cancer (80). The higher background UK oesophageal cancer incidence compared to Sweden is likely to have reduced the relative increase in risk in achalasia subjects in the present study. The median time from achalasia diagnosis to oesophageal cancer was 15.5 (IQR 5.8-26.2) years. This estimate is imprecise due to the small number of observed

events, as oesophageal cancer remains a rare event even in this population. It is therefore not possible to discern a discrete period of increased risk following achalasia diagnosis, however cancers within 5 years of diagnosis appear uncommon. Unfortunately, a limitation of the present study is the inability to distinguish between oesophageal squamous cell carcinoma and oesophageal adenocarcinoma, as neither database is linked to a cancer registry.

Several case reports describe recurrent respiratory tract infections in the presence of recently or undiagnosed achalasia (122-124). There are no population based studies that have previously demonstrated an association between achalasia and aspiration pneumonia or lower respiratory tract infection (LRTI). The peak incidence of LRTI was 7.5 years following diagnosis, however, the cumulative incidence plot (figure 7.2) suggests this event occurs regularly in the years following diagnosis. 75% of these episodes occurred at least 18 months after diagnosis but a small proportion of LRTIs may be related to initial achalasia treatment (surgery or pneumatic dilatation). However it seems likely that generally this association represents the same process as may contribute to oesophageal cancer, i.e. incomplete emptying of the oesophagus with consequent risk of aspiration of oesophageal contents.

More subjects died in the achalasia group compared to the matched controls when adjusted for a number of risk factors. The median time to death was 6.8 (IQR 0.6-12.9) years, potentially coinciding with both any peri-procedural mortality from treatment (125) and excess LRTI in this group. However, these factors alone may be insufficient to explain the increased mortality. The increased incidence of oesophageal cancer is also likely to contribute, but this cause of increased mortality is later in the natural history and uncommon. Unfortunately the cause of death as stated on the death certificates was not available in this study. Although mortality in achalasia has been investigated previously in a tertiary centre case series, in that study, no increase in mortality was reported(85).

This analysis is dependent upon accurate coding of achalasia and associated diagnoses. The data provided by HES has been validated, demonstrating high levels of agreement in an individual provider. Data completeness can also supported by comparison of the median age to other studies including Samo (median age 56)(78) and Enestvedt (mean age 62)(126) compared to 59 in HES and 62 in THIN. Unfortunately oesophageal manometry data were not available within HES or THIN to support the coded diagnosis of achalasia. THIN data is centrally quality controlled, therefore providing reassurance that coding is accurate. However as the diagnosis is established in secondary care, the primary care Read codes are dependent on accurate communication. Therefore

ascertainment bias may lead to under-estimation of the incidence and prevalence of achalasia in THIN data. This potentially explains the variation in incidence between the two datasets, although this is small with the peak discrepancy between 95% CI 0.38 per 100,000. However, the similarity seen between data from THIN and HES is reassuring. A diagnosis of achalasia will be made in a hospital setting and recorded on HES, and then coded in THIN once the diagnosis is communicated to primary care. The similarity in incidence figures between the datasets supports the accuracy of coding and subsequent case ascertainment.

Several risk factors for oesophageal cancer were not available for this analysis. The prevalence of acid reflux, alcohol and dietary information were not available, therefore they could not be included in the matching or corrected for in the analysis. However groups were matched by age, sex, smoking status and deprivation. In addition mortality was also corrected for Charlson score. The use of two national databases to address the same question increases confidence in the accuracy of the incidence of achalasia reported here. THIN and HES are independent of each other, utilising different coding systems and different sources of clinical data. Therefore it is reassuring that the variation in reported incidence is small. This is also the largest epidemiological description of achalasia ever reported, including over 11,000 cases with no study since Mayberry et al in 1987 having reported more than 1000 cases (71).

This is the first study to report from population based data on increased mortality and key morbidities associated with achalasia. Our findings are crucial to the prevention of LRTI in achalasia through, for example, encouraging smoking cessation, and to the consideration of screening and risk factor modification (smoking and alcohol intake) for oesophageal cancer in subjects with achalasia. Clinical guidelines should consider highlighting identified complications of achalasia and urge vigilance among the clinicians to detect and manage them early. Future studies should aim to replicate our findings in other nations.

8. Outcomes following percutaneous endoscopic gastrostomy insertion in patients with learning disability

8.1 Chapter specific materials and methods

The present study is a retrospective, population based cohort study of subjects with LD undergoing PEG placement. Subjects were segregated by those with coded lower respiratory tract infection (LRTI) including specific aspiration pneumonia codes within 1 year prior to PEG placement (exposed) and those without (unexposed). Subjects in the exposed group were considered to be those at high risk for aspiration.

8.1.1 Study population

Subjects with LD were identified by Read codes developed by NHS Digital for a previous study (Appendix 8.1). A panel of four experts reviewed each potential Read code. A code was included If there was agreement by 3 or more experts(88).

PEG placement was identified by one of two methods; Read code for PEG placement (appendix 8.2), or first prescription of non-oral, enteric, tube feed from the British National Formulary (appendix 8.3). Although these may also be used with a nasogastric tube, it is highly unlikely that this would be performed outside of a hospital setting.

Subjects aged 16-46 with an LD code from any time point and incident PEG placement between May 1995 and May 2017 were included. The age range of subjects included was chosen to include as many subjects as possible, however it is recognised that as subjects become older with LD they have increasing mortality and likely risk of respiratory tract infections that are unrelated to PEG insertion.

8.1.2 Co-variates and outcome measures

Further variables sought included age, gender, smoking status, body mass index (BMI), Townsend deprivation index, epilepsy and Charlson co-morbidity score.

Episodes of LRTI were identified by Read code following the PEG placement. Mortality was also sought in the THIN database. The full list of Read codes for covariates can be found in appendices 7.2, 8.4 and 8.5.

8.1.3 Statistical analysis

Demographic characteristics were described for the exposed, unexposed and total cohorts. Age is converted to quintiles because any relationship was considered unlikely to be linear. Baseline variables were compared between exposed and unexposed cohorts.

The incidence rate (IR) of LRTI and mortality within 1 year of PEG placement are reported for exposed and unexposed cohorts. The rate of LRTI in the year prior to PEG placement was reported.

IRs were calculated for LRTI and mortality at any time point following PEG placement, in the exposed and unexposed cohorts. Incidence rate ratios (IRR) and 95% confidence intervals (95% CI) are reported. Median time to event and interquartile range (IQR) are reported for LRTI and mortality. Cumulative incidence charts were plotted for mortality and LRTI by exposure group and compared with competing risk regression to allow for competing risks.

A multivariable Poisson regression model was constructed for factors associated with LRTI up to 1 year after PEG placement. Covariates included age, gender, deprivation, Charlson score category (0 or 1+) epilepsy and exposure group.

All statistical analysis was undertaken in Stata version 15(114). The threshold for statistical significance was set at $p<0.05$.

This study was granted study specific ethics approval (SRC 18THIN008).

8.2 Chapter specific results

8.2.1 Subject Demographics

There were 38,521 subjects with an LD code in THIN, of whom 214 met the inclusion criteria for PEG placement between ages 16-46. The median age of the cohort was 27.6 (IQR 19.6-38.6) years and 53.7% were male. Charlson co-morbidity scores were 0, 1, 2 and 3 or more in 155 (72.4%), 39 (18.2%), 9 (4.2%), and 11 (5.1%) respectively. 69.6% had a coded diagnosis of epilepsy. Body mass index (BMI) was available in only 82 (38.3%) subjects, median 20kg/m^2 (IQR 16.5-24.2kg/m^2).

8.2.2 Exposed and unexposed cohorts

The exposed cohort (subjects with one or more LRTIs in the year prior to PEG placement) included 58 subjects, 55.2% of whom were male, median age 30.8 (IQR 19.4 – 39.1) years, and there were 97.6 person years follow-up. The unexposed cohort included 156 subjects, 53.2% of whom were male, median age 27.0 (IQR 19.9 – 36.7) years. The unexposed cohort had 645.8 person years follow-up. Full cohort demographics for the whole study population and split by exposure are shown in Table 8.1.

Table 8.1: Study subject demographics

Gender	**Male**	83(53.2)	32 (55.2)	115 (53.7)	p= 0.8
	Female	73(46.8)	26 (44.8)	99 (46.3)	
Median age in years (IQR)		27.0 (19.9-36.7)	30.8 (19.4-39.1)	27.6 (19.6-8.6)	p=0.6
Townsend	**1**	31 (19.9)	9 (15.5)	40 (18.7)	p=0.3
	2	30 (19.2)	16 (27.6)	46 (21.5)	
	3	38 (24.4)	14 (24.1)	52 (24.3)	
	4	21 (13.5)	12 (20.7)	33 (15.4)	
	5	25 (16.0)	4 (6.9)	29 (13.6)	
	Missing	11 (7.1)	3 (5.2)	14 (6.5)	
Epilepsy	**Yes**	103 (66.0)	46 (79.3)	149 (69.6)	p=0.06
	No	53 (34.0)	12 (20.7)	65 (30.4)	
Charlson co-morbidity score	**0**	115 (73.7)	40 (69.0)	155 (72.4)	p=0.53
	1	27 (17.3)	12 (20.7)	39 (18.2)	
	2	5 (3.2)	4 (6.9)	9 (4.2)	
	3+	9 (5.8)	2 (3.5)	11 (5.1)	

Values are n(%) unless otherwise specified

8.2.3 Lower respiratory tract infection

40 subjects developed LRTI within 1 year of PEG placement, which was more common in the exposed group compared to the unexposed group; IR 606 per 1000 person years and 149 per 1000 person years respectively. IRR 4.07 (95% CI: 2.09 - 8.06), (p<0.001).

Over the study period IR for LRTI in the exposed group was 369 per 1000 person years. In the unexposed group this was 91 per 1000 person years, IRR 4.04 (95% CI 2.59-6.21, p<0.001). (Table 8.2 and figure 8.1). The time from PEG placement to LRTI in the whole study population was 1.33 (IQR 0.4-3.72) years. In the exposed group this was 0.64 (0.27-1.84) years and in the unexposed group 2.37 (0.71-4.90) years.

In a multivariable Poisson regression model female gender (IRR 0.48(95% CI: 0.23-0.97), p=0.042), age 33-40 years (3.36 (1.11-10.16), p=0.031), age >40 years (5.22 (1.73-15.75), p=0.003) and LRTI in the year prior to PEG placement (exposed group) (4.05 (2.09-7.87), p<0.001) were significantly associated with developing LRTI in the year following PEG placement (Table 8.3).

8.2.4 Rate of respiratory tract infections before and after PEG placement

The proportion with LRTI in the year prior to PEG placement was 27.1%. 18.7% developed LRTI in the year after PEG placement, albeit with less than 1 year of follow-up in some subjects. The LRTI incidence ratio for the complete cohort in the year prior to PEG placement was 317 per 1000 person years compared to 254 per 1000 person years in the year after PEG placement.

8.2.5 Mortality

Over the study period 58 subjects died and median age at death was 38.2 (27.8-42.0) years. Exposed group IR was 80 per 1000 person years and 45 per 1000 person years in the unexposed group (adjusted IRR 1.76 (95% CI 1.00-3.11),p=0.047)(Table 8.2 and Figure 8.2).

In a multivariable Poisson regression model, age 33-40 years (2.59 (1.03-6.52), p=0.043) and age >40 years (2.62 (1.01-6.77), p=0.047) were significantly associated with mortality during study follow-up following PEG placement. Previous respiratory tract infection in the year prior to PEG placement (exposed group) (1.80 (1.00-3.23), p=0.05), was of borderline significance in this model (Table 8.4).

Table 8.2: Incidence of lower respiratory tract infections and mortality following PEG placement

	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Events	22	18	36	59	20	38
Person years	36	121	98	645	251	842
Incidence Rate (per 1000)	606	149	369	91	80	45
Incidence Rate Ratio	4.07 (2.09-8.06)		4.04 (2.59-6.21)		1.76 (1.00-3.11)	
P value	<0.001		P=0.001		P=0.047	

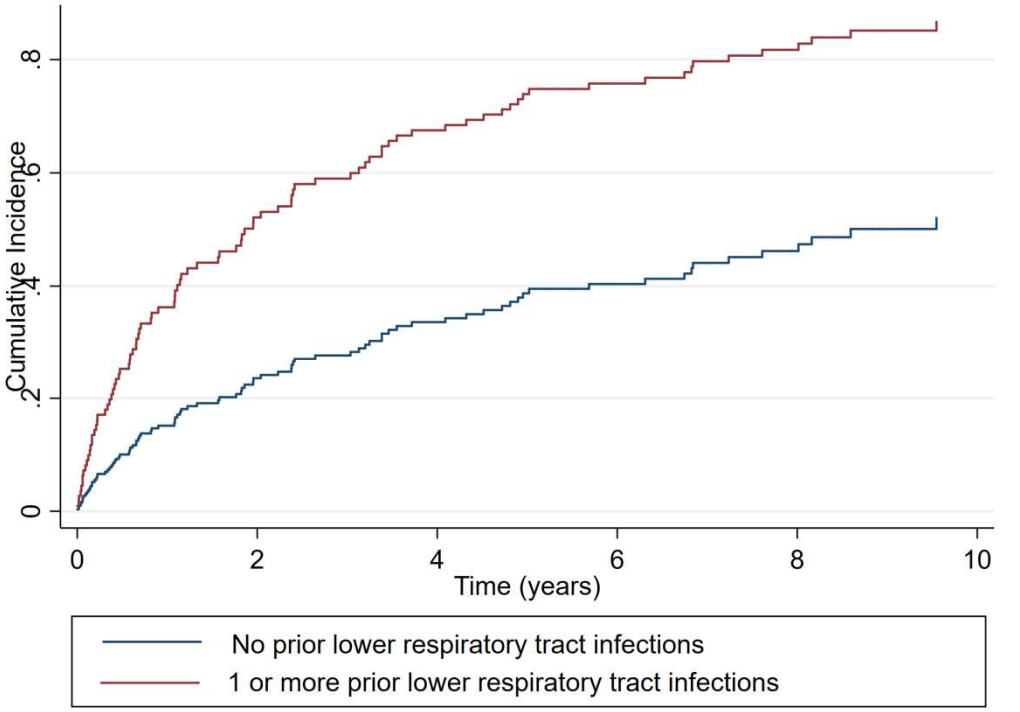
Table 8.3: Poisson regression model for lower respiratory tract infection within 1 year of PEG placement

Age quintile	**<19**	Reference category		
	19-24	1.38	0.43-4.43	0.586
	24-33	1.28	0.36-4.63	0.699
	33-40	3.36	1.11-10.16	0.031
	>40	5.22	1.72-15.75	0.003
Gender (female)		0.48	0.23-0.97	0.042
Epilepsy		1.73	0.78-3.81	0.177
Charlson score 1 or above		1.73	0.86-3.47	0.125
Townsend deprivation score *(5 is the most deprived)*	**1**	Reference category		
	2	0.68	0.25-1.83	0.441
	3	1.11	0.43-2.86	0.822
	4	0.67	0.21-2.19	0.513
	5	0.68	0.17-2.70	0.580
	Missing	0.54	0.10-2.80	0.462
LRTI in the year prior to PEG placement *(Exposed group)*		4.05	2.08-7.87	<0.001

Table 8.4 Poisson regression model for mortality following PEG placement

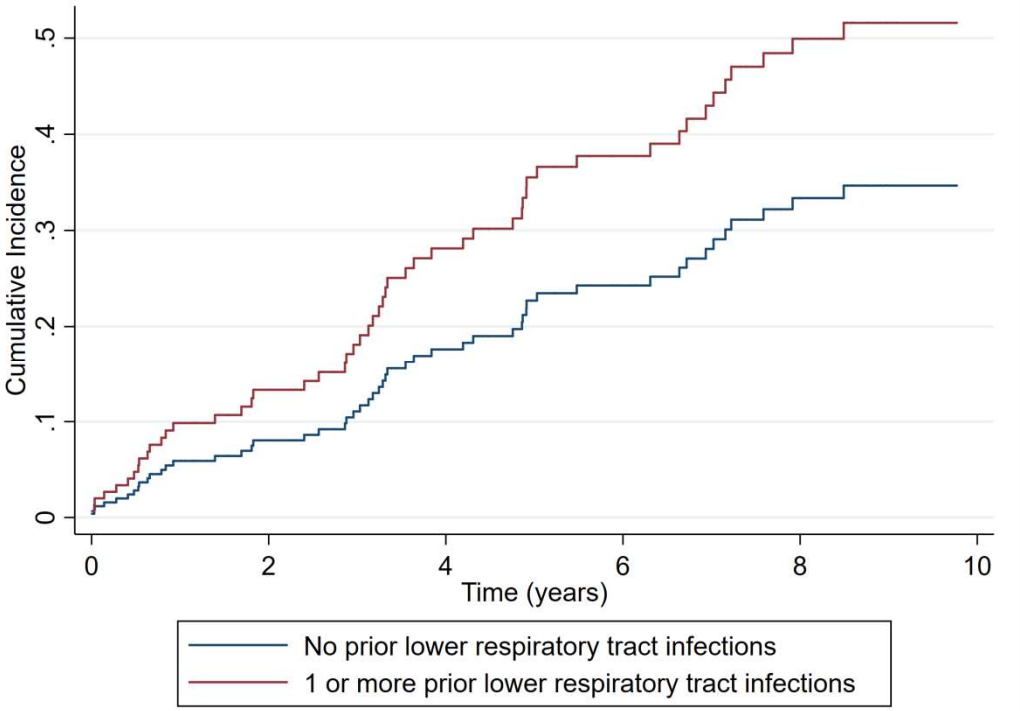
Age quintile	**<19**	Reference category		
	19-24	1.84	0.71-4.82	0.210
	24-33	1.65	0.62-4.39	0.315
	33-40	2.59	1.03-6.52	0.043
	>40	2.62	1.01-6.77	0.047
Gender (female)		1.08	0.62-1.87	0.792
Epilepsy		0.80	0.44-1.44	0.452
Charleson score 1 or above		1.21	0.68-2.18	0.508
Townsend deprivation score *(5 is the most deprived)*	**1**	Reference category		
	2	0.57	0.25-1.30	0.183
	3	0.63	0.29-1.38	0.250
	4	0.79	0.33-1.88	0.594
	5	0.42	0.15-1.17	0.098
	Missing	0.32	0.7-1.49	0.146
LRTI in the year prior to PEG placement *(Exposed group)*		1.80	1.00-3.23	0.050

Figure 8.1: Cumulative incidence regression for lower respiratory tract infections following PEG placement



P<0.001

Figure 8.2: Cumulative incidence regression for mortality following PEG placement



P=0.044

8.3 Chapter specific discussion

This is the first study to assess the outcomes of PEG insertion in a cohort of LD subjects. No reduction in LRTI following PEG placement was observed. Furthermore subjects having one or more LRTIs prior to their PEG were more likely to have LRTIs after PEG placement, both in the first year after their PEG and in long term follow-up. Subjects with one or more LRTIs prior to PEG placement also had a small increase in mortality over the study period. Female gender provided a small protective effect for LRTI within 1 year. Increasing age was associated with both increased mortality and LRTI within 1 year of PEG placement.

There are no other studies looking at outcomes following PEG placement specific to subjects with LD. A prospective PEG audit including 350 PEG placements over 571 person years of data found a 1 year mortality of 35%, significantly higher than reported in the above study(127). However the median age was 62 years compared to 28 years in the present study and all indications were included. 31 of 350 PEGs were placed in subjects with LD in whom 5 (16.1%) died over median 20 months follow-up. In the present study 11 (5.1%) died within 12 months and over the study period 55 (25.7%) subjects died, albeit with a median time to death of 3.5 years. Although the proportions observed are different, only small numbers of deaths are observed and therefore comparison may be misleading. There is also likely to be variation in practice between providers, with a national overview provided by the present study compared to a single provider in the study by Clarke et al.

Short term mortality could not be addressed in this study as there were too few outcomes despite the sample size. There was also a wide variation in time to LRTI with large interquartile ranges. Therefore, although there appears to be shorter time to LRTI following PEG placement in subjects in the exposed group compared to the unexposed group, this result requires further evaluation before any implications for clinical practice can be considered.

LRTI are used as a surrogate of aspiration pneumonia in the present study. Although there are codes specifically for aspiration pneumonia, the study included all LRTI codes to provide good sensitivity. In subjects who have a PEG in situ or proceed to have a PEG placed up to one year later, it was assumed that aspiration at least contributed to their LRTI.

A key strength of this analysis compared to others examining the impact of PEG placement is the use of primary care data. The THIN database is an important tool to examine the LD population. The database is recognised to have a high accuracy and is therefore used for analysis for a wide range of conditions and outcomes. Specific benefits for the present study include a relatively large number of LD subjects with robust diagnostic and demographic data. Respiratory infections in this cohort are

commonly managed in primary care and as such, only a small minority of cases present to secondary care. Therefore, presentation to primary care is a more sensitive measure of such infections.

LD subjects are often challenging to identify from medical records. The Read codes used in the current cohort were developed by an expert group, in which codes were only included in the final set if 3 out of 4 panel members agreed that the code was representing a group of subjects with LD. This set of Read codes has been utilised a number of studies previously(89). This provides reassurance that the cohort in the present study accurately represents LD subjects. Although over 200 were included, and most clinically significant associations are likely to have been identified, a larger cohort would have allowed detection of more subtle factors, including an accurate estimate of their effects.

Identification of subjects undergoing PEG placement in the THIN database was also difficult. As a procedure performed in secondary care, the PEG placement was not always coded in primary care data. Therefore first feed prescription was used as a surrogate marker to identify when a PEG had been placed. Despite these methods, it is likely that not all PEG placements are captured within the data, however we can be confident that those included represent a cohort of LD subjects undergoing PEG placement.

Unfortunately data on BMI was missing in a very high proportion of subjects. As such this could not be included in the analysis. It is hypothesised that subjects requiring a PEG are less mobile and therefore, in the absence of appropriate equipment, they do not routinely have their weight checked and recorded in primary care.

This is a novel population-based study demonstrates that PEG placement does not appear to confer a reduction in LRTIs in the LD cohort. A small increase in mortality was also noted in subjects with a recent history of respiratory tract infections prior to PEG placement. Physicians making decisions regarding PEG placement in LD subjects should incorporate this into their assessment of risk and benefit and ensure subjects, carers and family members are aware of likely outcomes following PEG placement. Further research is required in subjects with LD to establish sub-groups that are most likely to benefit from PEG placement.

9. Thesis Summary

9.1. Summary of chapter results

Each chapter of this thesis has yielded clinically important observations that advance the current literature for interventional GI endoscopy. This has been demonstrated with high impact presentations and publications. Such clinical outcomes are an important output of this thesis. However the unifying theme conveyed is the application of database studies to interventional GI endoscopy, both in primary and secondary care data. Below the results of each chapter are summarised and the specific impact of database study designs and statistical techniques employed are considered further.

9.1.1 Summary - The outcomes of ERCP for the palliation of malignant biliary obstruction in England between 2006 and 2017

The high mortality seen following ERCP for malignant biliary obstruction is concerning, but not unexpected. Although the mortality was less than mortality following PTBD, these groups have subtle differences and, as such, should not be directly compared. The variation in risk between demographic groups is important to clinicians when making treatment choices in partnership with patients. Variation in the provision of chemotherapy is also significant. Although there is some concern that chemotherapy coding may be an under representation, this finding mandates further investigation. The most important finding is that there is significant variation based on provider volume. Hospitals providing only a low number of these procedures should now be considering the reasons for this variation and if there are opportunities to improve outcomes for their subjects. The BSG sets standards for the numbers of procedures a provider should undertake as a minimum. This is currently provided only as a whole number of ERCPs, however a minimum recommended annual number of “cancer” ERCPs should now be considered.

9.1.2 Summary - Outcomes of colorectal stents when used as a bridge to curative resection in obstruction secondary to colorectal cancer

The finding that colonic stents, when used as a bridge to curative surgery are associated with reduced mortality at 1 year following resection, in subjects presenting with bowel obstruction secondary to cancer, is novel. However the finding and explanation offered for the variation to other published figures is biologically plausible. Furthermore this is a finding that has been anticipated by others but not found. Comparison to current literature highlights that, although this finding has not been observed, other, prospective randomised clinical trials have faced significant methodological and recruitment difficulties. As theorised in the chapter discussion section, a longer period for subjects to recover and gain benefit from MDT decision making, more detailed staging and potentially chemotherapy seems a highly likely contributing factor for this finding. Future prospective studies of colonic stents used as a bridge to curative resection should incorporate this finding into the trial design.

9.1.3 Summary - Outcomes of pneumatic dilatation and Heller's myotomy for achalasia in England between 2005 and 2016

Achalasia treatment data, including prolonged follow-up, is important for subjects with this chronic condition. There are no other studies analysing outcomes that are a similar size and of 10 years duration currently published. Several smaller, often single centre studies report outcomes over 10 year periods or greater, but cohort sizes are too small to provide robust results. Demonstrating that after 10 years there is a small benefit of up to 3 dilatations when compared to Heller's myotomy is important for subjects. It is also important to be able to describe real world complication rates and mortality, especially stratified by age and other demographic factors. However, more important than demonstrating a small benefit of one treatment regime, is to be able to use this data to allow subjects to make an informed choice between treatments. This is only robust due to the large sample size captured in HES and subsequent reassuring data validation. The lack of a statistically significant volume effect is also interesting and unexpected when considering future service provision. This particular attribute is discussed further below.

9.1.4 Summary - Incidence, morbidity and mortality of subjects with achalasia in England: findings from a study of nationwide hospital and primary care data

Accurate, current epidemiological data for rare conditions is important when considering service design and delivery. This chapter is directly concerned with the requirement for treatment of achalasia, which is often endoscopic. It appears that the prevalence of achalasia is higher in the UK population than currently thought based on previous studies. This has ramifications for workforce planning both with respect to the currently available treatments and those that are being developed that require a higher degree of training.

Therapy decisions in achalasia are dictated by the underlying patient, therefore understanding of the associations to respiratory tract infection and mortality that were seen early in the disease course following diagnosis are important. Although previously demonstrated, an association to oesophageal cancer, and furthermore the likely time to diagnosis will also help to inform the debate regarding screening in this population subgroup.

9.1.5 Summary – Outcomes following percutaneous endoscopic gastrostomy in patients with Learning Disability

Subjects with LD are a difficult group of subjects to study with conventional, prospective trials. Therefore this analysis of THIN data has many design benefits. The study demonstrates that PEG placement is not associated with reduced incidence of lower respiratory tract infections in subjects with LD. This is an important and novel finding, particularly as PEGs are often placed with the

understanding that future respiratory tract infections will be less likely. Furthermore those who had such infections prior to their PEG are at the greatest risk of having further episodes and have a small increase in mortality compared to those who do not. Such findings are enormously important for LD subjects, their families and carers when deciding if PEG placement is in the best interests of a subject with LD.

9.2 Key attributes and limitations of database analyses in the setting of interventional GI endoscopy

Discussed below are several components of the database studies included within this thesis. These have been selected because they are an important aspect of one or more studies. The discussions aim to highlight how chapter studies benefit from each, how the chapter study designs have specifically used these components, and therefore developed their applicability for use in this study design.

9.2.1 Recruitment completeness

Large database analyses have significant benefits when considering recruitment. They are highly effective for outcomes of uncommon conditions as these are often challenging to recruit in significant numbers to randomised controlled trials. Recruitment also offers an advantage over randomised prospective studies when the timing of interventions in such studies renders recruitment challenging. A prominent example of this is the colonic stenting chapter of this thesis. For prospective, randomised studies subjects would need to be recruited when clinically obstructed, having been just informed of a new, imminently life threatening cancer diagnosis. This is clearly a difficult time for the subject in question and they are likely to struggle with the life changing impact of this news. It is therefore understandable that recruiting subjects to prospective studies in this situation has proven difficult. Several prospective studies have only managed to include small numbers, including CREST and ESCO as described in the chapter discussion(57, 112). A meta-analysis of colonic stent studies only identified approximately 400 subjects undergoing a bridging stent(115). The study presented within this thesis included 401 stents and is therefore an important contribution to published literature, even in the presence of prospective randomised data, which represents the gold standard of scientific evidence.

The chapter analysis of PEGs in subjects with LD also derived recruitment benefits provided by the database study design. The opportunity to investigate a large cohort of subjects who are often excluded from clinical trials, often due to concerns regarding informed consent to participate, is

valuable. This group is also poorly catered for in prospective randomised studies as they are less engaged with medical services. Rates of non-attendance are also often higher in this group and due to the younger age groups seen in this study compared to more common indications for PEG placement, they are not as well known to hospital services. Furthermore as LD subjects who are undergoing PEG insertion are both uncommon and without any individual high volume providers, it would therefore require a multicentre, resource intensive study design to locate them in sufficient numbers. Using the THIN database allowed inclusion of a large group that could not otherwise be available for analysis in a single cohort.

Large scale database recruitment has also demonstrated its value in achalasia, a rare disease. Achalasia has an incidence (as defined in this thesis) of approximately 1.5 – 2.0 per 100,000 person years. Therefore the coverage provided by HES, including a population of over 50 million people, over a 10 year period allows a very large population to be analysed for a variety of different outputs. This cohort is the largest in published literature. Such a large cohort is not possible without significant cost, which is unlikely to be provided for either epidemiological studies or for rare diseases that are of limited interest to funding bodies, pharmaceutical companies or medical device industries.

9.2.2 Volume effect data

Demonstration of a provider volume effect can represent a significant challenge as demonstrated by Bodger et al and subsequently published letter of criticism from Dawwas et al (27, 128). This thesis includes 2 chapters which have considered a volume effect with differing results. Looking at a volume effect for ERCPs performed in subjects with incurable cancer demonstrated a significant effect. However when seeking a volume effect in treatment for achalasia, none was found. Both used the same methodology of splitting providers into tertiles to generate a variable “high volume”, “middle volume” and “lower volume” tertile which could then be used in a regression model, including other factors, to look for a relationship to an outcome of mortality. In ERCP this was 30 day mortality, in Achalasia the outcome of interest was treatment durability.

To be able to establish a volume effect, all cases need to be included. Therefore prospective randomised studies of an intervention are unable to provide an estimate as subjects may not consent, or for other reasons may not be invited to participate in a study. It is not possible to ascertain if those consenting to undergo the intervention within a study setting are representative of all such interventions performed by that provider. It is also often not possible to ascertain the total number of interventions that have been performed by a provider, therefore it is not possible to accurately categorise into a high, lower or middle volume provider. Retrospective audit is similarly

unable to provide data for all cases, as inclusion will always be biased towards those that are easily identified. Prospective audit could potentially provide the data required to perform a volume effect analysis, however the required scale would likely be prohibitive.

Unfortunately as THIN represents 6% of the UK population, it is not suited to providing volume effect data, with many issues in common with prospective audit in this regard.

As such the ability to look at volume effect is an important role for database studies within HES. This is an important question when considering service redesign, a recent example of which has been undertaken within several surgical specialities. As therapeutic endoscopy is a group of procedures that are often associated with significant risk of complications, a similar change to the design of services, including centralisation of higher risk procedures could improve the overall safety profile. This thesis demonstrates how HES database analyses are an ideal tool to provide the evidence base for such a change.

Although unavailable for studies included within this thesis, it is possible to ascertain the consultant provider specified for a particular patient procedure. This has several limitations when considering if a given consultant actually undertook a procedure. However with careful and detailed analysis it is theoretically plausible to distinguish further, to look at provider volume by individual rather than at trust level.

9.2.3 Data Validation

Databases containing data collected for purposes other than for research including administration or routine clinical use warrant careful consideration. The integrity and accuracy of the data contained within them must be scrutinised before any result can be accepted as valid. Therefore data validation is a key step in any robust database study. Database studies are not the only study type that requires such validation. Multi-site, prospective trainee collaborative projects are also considered to need validation of data accuracy.

Analysis of data that was collected for another purpose may also be subject to other sources of bias, depending on the extraction strategy. Therefore by validating the outcome of a study can also demonstrate that the methods used for extraction are an accurate representation of local data.

There is currently no standardised methodology for validating research data, however in the studies included in this thesis, three broad strategies have been applied:

1. Comparison to other published data. This methodology was found to be highly dependent upon the available literature for a given study. For example in the treatment of achalasia

chapter, good quality randomised data was available at 5 years follow-up. This, by design, used several definitions in common with the study reported in this thesis Therefore allowing comparison between the results of each study. By ensuring that results were accurate at 5 years, we have extrapolated that those at 10 years are robust as the criteria and data extraction are the same.

Unfortunately this situation was not replicated in all studies. In the PEG chapter there was no comparable literature available and therefore the method could not be applied.

2. Comparison to local audit. In HES, as all data comes from secondary care it is possible to perform local audit to generate data for comparison. By seeking out the same group of subjects, using the same criteria, the accuracy of the coding within HES could be established confidently.

   This methodology has two problems; firstly that the audit must be retrospective, as all HES data is retrospective. Therefore a robust methodology for case finding is important. With achalasia subjects this was simple, as they could be sought by oesophageal manometry laboratory lists, endoscopy lists or surgical lists. By using each of these it could be confidently established that all subjects were included. This approach also avoided using the hospital informatics service, as this is used to upload data for HES. Therefore any errors would simply be duplicated and the results would be misleadingly reassuring. The Cancer ERCP study was more challenging as HES is able to draw data from all trusts, however generally we only have access to our own trust data. Therefore applying complex inclusion criteria which mandate information regarding operations at other trusts required extended access to data from other trusts and appropriate pairing.

   The second consideration is that a provider that undergoes local audit for comparison to HES may not reflect coding on a national scale. If our local unit that HES was compared to has higher coding standards than are adopted elsewhere it may be falsely reassuring. Unfortunately the only method for addressing this would be to take a representative group of hospital care providers and complete a validation at each. Not only is this technically unfeasible, but there is also no method for delineating which cohort of providers have coding standards representative of the national cohort.

3. Internal data validation. THIN cannot be validated against local data in this way because it is a national sample. Previously it has been possible to seek records from GPs of specific subjects to ensure that the data provided by the database is accurate, however this process is currently unavailable. In previous validations, this has demonstrated that the data contained within THIN is both accurate and complete.

The methodology applied in the achalasia and PEG studies in this thesis is of internal validation. By seeking data on start, event and exit dates any anomalies that suggest there may be an inaccuracy within the data can be identified. None were found in either study. Although this is a different type of validation, it is still important in demonstrating data accuracy. No similar method was applied to HES, however the unique subject identifier used to link episodes within HES is constructed from several demographic details and therefore data is vetted to this standard prior to becoming accessible for research.

Validation of results has provided strong evidence that the data provided by HES and THIN is accurate and therefore that the results presented in this thesis are robust. All chapters when compared to locally gathered data have demonstrated a close correlation to that provided by HES. Furthermore with a single exception, the studies reported have shown a good correlation to published literature when components have been compatible for comparison.

The only example of a significant disparity comes from the colonic stents study, which demonstrates a novel finding. However even in this study the similarities between reduced stoma rates, increased rates of laparoscopic surgery and complication rates suggest the data itself is accurate.

9.2.4 Follow-up

When considering uncommon conditions and procedures, HES provides significant recruitment benefits, as discussed in detail above. However chronic disease requires not only recruitment but continued follow-up. HES provides this by universal national coverage, therefore as long as a subject remains in the country and treatment is provided in a secondary care setting, long term longitudinal data is available. This facilitates long term analyses such as that undertaken in the treatment of achalasia chapter which requires both long term follow-up and a pre-specified outcome measure that encompasses numerous episodes of care.

Often both initial and repeat procedures may be undertaken in an emergency setting or for acutely unwell subjects. These may not be amenable to follow-up by prospective strategies or easily identified in retrospective methodologies. To have complete follow-up for all subjects is therefore an important strength, as utilised in the repeat procedure analysis of the ERCP study in this thesis.

Furthermore those subjects who move to different care providers and would be lost to follow-up in other study designs can remain under observation in HES. This permits long follow-up of subjects, particularly in chronic conditions for which long term data on the durability of treatment is important for subjects, but also difficult, expensive and time consuming for prospective trials.

Unfortunately THIN does not support the movement of subjects between geographical providers as facilitated in HES. Whilst remaining with a GP practice within the THIN group all activity will be incorporated into a linked, longitudinal record. If moving to a practice outside of the THIN group (more than 90% of UK practices are not included in this group) subjects will be lost. Fortunately THIN provides a "transfer out" date variable, so that analysis can correct for this loss to follow-up.

9.2.5 Surrogates of absent data items

At the beginning of this research degree, it became clear that both THIN and HES had limitations in the data items available to answer questions regarding interventional GI endoscopy. From HES, the lack of performance status, tumour staging and histology were significant challenges. Surrogates have therefore been used in several different settings.

Performance status has been substituted with Charlson co-morbidity score in all HES studies. As described in the methodology chapter this is a well validated tool. In studies including ERCP and achalasia, it appears to have provided a suitable alternative, with corresponding 30 day mortality as would be expected in all studies.

Tumour staging represented a more significant challenge; both the colonic stents and ERCP chapters have included assumptions about the patient groups included. In the colonic stents chapter, subjects who went on to have a potentially curative resection were assumed to have a curable stage of disease at the time of resection. Furthermore it was assumed that the range of tumour stages were similar in each group following propensity matching. The ERCP study assumes that because subjects did not have a curative resection for their HPB tumour that it was unresectable or that the subject was unfit for resection. This assumption was made on the basis that no curative resection was undertaken, however it is likely that some subjects will have declined surgery. There will also be variation in the extent of tumour, for instance the degree of vascular resection that is offered by different providers. This will inevitably introduce a degree of variation between subjects, however this could not be avoided.

Histology did not have a suitable surrogate, although this was not essential to any of the chapters. However at peer review a comment was made regarding the epidemiology focused Achalasia chapter that it would be useful to know if the cancers associated were squamous cell carcinoma or adenocarcinoma. The basis of this comment is that squamous tumours are often associated with achalasia however there is little evidence to suggest a link to adenocarcinoma. Therefore if adenocarcinomas were present in large numbers this may suggest a flaw in the data. Either subjects with pseudo-achalasia were included, or that our cohort was subject to an unrecognised source of bias.

The available variables in a dataset are a fundamental concern when conducting any secondary research. As the data set was not designed for the research question being proposed, there will always be ideal variables that are not available. This is a flaw generic to all database studies, and limits the research questions that can be answered by database analyses. However the examples above represent examples of pragmatic strategies to address them which have been acceptable to peer reviewers.

9.2.6 Mortality data

The ONS linked data to provide robust mortality was described in the introduction of this thesis. However in light of the chapter results, the utility of this highly robust and clinically significant outcome is extremely important. Mortality is reported as an outcome in all chapters, however the HES only chapters rely particularly heavily on this, due in part to a cancer focus. Even studying treatments for achalasia, generally considered a condition with low treatment associated mortality, further confirmed in the chapter above, has yielded interesting results in relation to mortality. This is a result of robust mortality data in combination with a high volume of subjects. The value of such outcomes in database studies cannot be understated.

9.2.7 Propensity score matching

Lack of randomisation is also an important drawback of observational data such as is described in this thesis. Subjects are allocated to treatments based upon clinician and patient choice. Propensity matching is a technique employed in the colonic stents manuscript to assign subjects into matched pairs to give 2 groups with similar demographics. This is an increasingly popular alternative to conventional covariate adjusted analyses for confounding in observational studies.

The large number of surgery only subjects compared to those with bridging colonic stents (a tenfold increase) provides an ideal setting to utilise propensity matching. This study utilised nearest neighbour propensity score matching methodology rather than stratification, utilising the score as a covariate, or inverse probability weighting. The calliper distance can therefore be set very tightly to ensure that subjects included in the matched analysis in the surgery only group are closely matched on all appropriate, available measures. Matching criteria were set clinically including those factors that impact on colorectal cancer survival rather than using factors in the cohort that predicted stent insertion. This is a recognised approach to ensure a clinically relevant match is selected.

Different propensity score matching methodologies have been compared between four previously published data sets (129). Propensity score matching performed well in all analyses, providing improved covariate balance. Included in the analysis was a THIN study of statin use for cardiovascular mortality. The published study (not using propensity matching) results demonstrated

a reduction in all cause mortality (n=17,296 HR 0.79) (130), compared to (HR 0.85) (129) when the analysis was repeated with a propensity score matching (nearest neighbour matching technique). A large, randomised prospective study has reported results that are more similar to the propensity matched result (HR 0.87)(131). This analysis demonstrates how propensity matching can improve the accuracy of reported results in specific settings.

Propensity matching does have limitations, subjects in whom a "nearest neighbour" was not available within the desired calliper width, subjects will be excluded with resulting loss of power and precision. Even when co-morbidity, age and other demographic variables available within the given database will be taken account of, there will likely be variables that are not included and therefore unavailable to include in a matching model. Therefore even statistical methodology that corrects for discrepancies in cohort demographics is imperfect. When interpreting results these need to be taken into account, therefore explicit recognition is fundamentally important.

Concerns have also been raised that by matching on available variables "dormant" sources of bias that are undetected by the available data points can have an increased effect.

9.2.8 Cumulative incidence regression

Cumulative incidence plots were used because they better correct for loss to follow-up when compared to Kaplan Meier analysis. Long term outcome data described in HES and THIN has the benefit of providing large cohorts by ensuring that all subjects are included every year over a several year period. However when considering the follow-up of these subjects, those included in the later years will have less follow-up. If only small numbers achieve the criteria for leaving the study then almost all will eventually be censored. A Kaplan Meier plot will only give an outcome as either event or censored, therefore any competing risk, such as mortality, will be analysed as if the case was censored. This is important in several situations in this thesis such as respiratory tract infections following PEG placement or development of oesophageal cancer following an achalasia diagnosis. Analysis with Kaplan Meier would overestimate the probability of the event of interest, in the above examples; oesophageal cancer or respiratory tract infection. However in the treatment of achalasia chapter, by overestimating the likelihood of further treatments being required, which constituted treatment failure, Kaplan Meier analysis would have under estimated the effect of both treatments.

This is of even greater importance when the risk of death is different in each group. This is a particular problem in database studies, as there is generally no randomisation between treatment groups. Therefore in this example the dilatation cohort, as there is greater co-morbidity and older

median age, could reasonably be expected to have higher mortality that is unrelated to achalasia or the treatment provided. Hence Kaplan Meier would overestimate the likelihood of treatment failure by a greater margin than would be expected for this methodology to overestimate treatment failure in the cohort undergoing myotomy. Hence it is of particular benefit for this type of database analysis to ensure competing risks are adequately corrected for using cumulative incidence regression.

9.2.9 Procedural Complications in HES

Procedural complications are a weakness of several chapters within this thesis. Several approaches have been taken in HES, as highlighted by comparing the complication tables of the colonic stents and ERCP chapters. Colonic stents categorises by system, compared to ERCP which set categories by commonly recognised complications. The ERCP output is more easily validated as there are well established rates. Furthermore this seems more meaningful to the reader, for example pancreatitis rate compared to cardiovascular or respiratory complications.

There has often been concern that complications are under coded in HES. However this has not been a significant problem in the studies reported above. In the ERCP study, although there is no specific data regarding complications for this group, a rate of approximately 6% is in keeping with current literature. However the perforation rate found in the treatment of achalasia chapter, 1.6% was notably lower than 3-5% as is generally reported in other studies (66, 119). This thesis therefore supports the concern that complications may be under coded in HES. Chapter specific discussions provide transparency on how this may impact the results of each specific study. Any future work in which complications of a procedure is an important aspect of the analysis should take care to ensure that rates of complications are either able to be validated in comparable published literature or, where possible, compared to with local audit data to be able to assure the reader of its accuracy.

However other, less conventional, methods of examining complication rates were more successful. Failed stenting was measured in the colonic stents chapter as needing a repeated procedure on the same admission. This provided a figure almost identical to carefully collected, prospective data. This strategy was therefore felt reasonable to apply to the ERCP chapter when looking at the need for repeated procedures within 30 days as a measure of success. This demonstrated an important volume effect, which would not be measurable by other study designs.

9.3 The health improvement network and hospital episode statistics comparison

As a thesis investigating the role of national databases for GI therapeutic endoscopy, it is important that this thesis does not look at secondary care in isolation but also examines primary care datasets. THIN is a prominent example of primary care data, containing over 6 million active primary care subjects that are representative of national demographics. This has provided valuable insight in achalasia and PEG chapters of this thesis. However secondary care data, as described in the introduction, provides more detailed procedure centred information regarding endoscopy. Therefore in tandem, primary and secondary care data sets can provide a broader set of outcome measures. These databases provide very different types of data, however directly compared strengths and limitations are described below.

9.3.1 Primary care events

HES includes secondary and tertiary care events in discrete episodes per patient, which are subsequently linked for longitudinal analysis. However this leaves a significant number of question types that cannot be answered, as key components are occurring in general practice (primary care). The PEG chapter was an important example of this. Not only will respiratory tract infections predominantly present to primary care, but LD subjects may also have hospital avoidance strategies. Therefore such events will be a substantial underestimate of actual events if examined in HES only. THIN has also been validated for hospital admissions and diagnoses. A study sought to compare hospital records to a random set of those with admission for pneumonia in THIN, finding that the positive predictive value was 86% (132). Therefore although it appears that some secondary care data is available in THIN, primary care data is not available in HES, although there has been no study to demonstrate this in the style of the above reference.

9.3.2 Epidemiology for service provision

THIN allows better examination of population epidemiology questions, some of which are important to therapeutic endoscopy, particularly with respect to the number of procedures that will be required in the future. The chapter examining the demographics and mortality in achalasia subjects is a representative example. This will provide perspective to the results of therapy outcomes in the group of subjects that are included in the HES analysis chapter.

Primary care datasets such as THIN extract data for all registered subjects at all included practices. When seeking to extract incident and prevalent cases, a number of person years over the extraction period can be calculated, because the database has a source population denominator. This is not possible in secondary care data, HES lists episodes per subject but the source population in those

with a hospital episode, therefore ONS figures needed to be used. This represents a reasonable strategy in Achalasia subjects as all those with a diagnosis will be diagnosed and therefore coded in secondary care. Unfortunately if this strategy were applied to conditions such as LD, which may be diagnosed in a hospital setting but equally is often diagnosed after birth in the community, many of the cases would be missed leading to an inaccurate estimate with using a population denominator from the available ONS figures.

The ability to provide a control group from the same source population (primary care) is also an attribute of primary care datasets that is not achieved in secondary care. Including GP practice as an additional matching variable can also permit matching by unseen variables that may be common across a geographical area covered by a GP practice. This allows a control group of subjects that can be matched on demographic details to allow for comparison.

An alternative primary care dataset that is available is the Clinical Practice Research Database (CPRD) (previously known as the GP Research Database). Similarly to THIN, this works from the Vision software used in primary care. There is significant overlap of the patient cohort included in the 2 databases; therefore this also represents a high quality source of data for epidemiological research questions.

9.3.3 Procedural coding

HES was found to have excellent procedural coding. The OPCS4 classification permitted clear identification of procedures undertaken. Although treatment intentions could not be seen, in a given set of circumstances, these could be assumed. The requirement of this assumption is a limitation of database analyses as described with other examples in section 9.2.5. Local audit demonstrated that this data was both accurate and complete in all studies using HES data in this thesis.

Procedural coding was found to be incompletely coded in THIN, and therefore it was found to be a difficult tool for investigating interventional GI endoscopy. However THIN facilitated a very different set of analyses to be undertaken and increases the breadth of questions that can be answered. Read codes often focus on diagnoses rather than procedures undertaken in secondary care, as these can sometimes lack relevance to those working primary care. The PEG chapter is a good example, as not all subjects with a PEG placed were coded as such under the Read code system. When interrogated for new recipients of PEG feed, an important prescribing task undertaken in primary care, a significant number were found. This therefore made seeking procedure outcomes in primary care data challenging unless there is ongoing prescription or other means to identify appropriate subjects by.

9.3.4 Peri-procedural outcomes

Considering that procedural coding was found to be limited, and alternatives required for case finding, it is expected that analysis of peri-procedural outcomes was limited to HES. The Read code structure was unsuitable for performing this analysis in THIN. THIN is more suited, as demonstrated by the PEG and achalasia epidemiology chapters, to longer term population based outcome measures.

HES has several important limitations when considering peri-procedural outcomes. As described above, the coding of complications can be incomplete, although in several chapters of this thesis we have been able to establish strategies to either correct for this or at least recognise any underestimation. Mortality is well coded in both HES and in THIN. Readmissions are robustly coded in HES as this represents a new episode of care, however although admission to hospital has been validated within THIN, re-admission has not been considered. Fortunately this was not a requirement for any of the THIN studies reported in this thesis. Length of stay is also an important peri-procedural outcome which is available in HES, as used in the colonic stents study. Unfortunately the specific reasons for length of stay are not available, as this might highlight that a person was awaiting social care rather than having a turbulent post procedure recovery. For these reasons the studies reported in HES generally use a product of additional procedures or mortality as the main outcome measure. Although other outcomes are reported, these are considered to be less important due to being less robust.

An item, available in HES, that was not used in this thesis was intensive care data. This has been included in HES more recently, and would represent an opportunity to investigate procedural outcomes. However as with length of stay the reason behind intensive care unit admission and the type of admission (emergency vs. planned) would not be available. Furthermore, due to the subject matter of interventional GI endoscopy, few subjects require intensive care input.

10. Impact of this thesis

10.1.1 NCEPOD

Following the presentation of the ERCP results chapter, an NCEPOD topic proposal was submitted entitled “Management and outcome of acute biliary obstruction”. This was submitted on behalf of the BSG and several partner organisations including Joint Advisory Group (JAG) on GI endoscopy, the Pancreatic Society of Great Britain and Ireland (PSGBI), and AMMF – The Cholangiocarcinoma Charity. The aim of this application was to understand the reasons for the high 30 day mortality, as seen in the data presented from the ERCP study in this thesis. There was particular attention to diagnostic pathways, timelines and interventions performed.

10.1.2 RICOCHET – ReceIpt of Curative resection Or palliative Care in HPB Tumours

Ricochet was developed following the results of the ERCP study included within this thesis and a previous project undertaken by the same research group to examine outcomes of percutaneous transhepatic biliary drainage. Both studies demonstrated high mortality and variation in outcomes.

Ricochet was designed as a national multicentre audit, using trainee led collaborative research networks. The objectives are to seek the causes for variation in mortality in malignant HPB tumours, including malignant biliary obstruction and pathways to curative surgical resection. At the time of writing Ricochet includes over 110 sites across the UK and has attracted expressions of interest globally.

Both of these ongoing projects have used the data presented in the ERCP chapter above as the basis for further investigation. This highlights the granularity that is often lacking in HES data, which has been discussed in detail above under the heading “9.2.5 surrogates of missing data items”. Although meaningful alternatives, that provide valuable information, they have limitations. For service quality improvement this granularity of the data is important. In the ERCP example this pertains to choosing investigations and their timing, MDT involvement and blood results amongst others. This is particularly true at the level of an individual patient, in whom pathway design is key, when the level of detail seen in HES needs extrapolation.

Despite this, data provided from database studies provides the foundation for this further work, without which such concerns may never be investigated. This therefore highlights the importance of database studies and their potential impact.

10.1.3 Potential future implications – National Endoscopy Database

Several initiatives that are currently in development represent future opportunities for database studies. The most important of these with respect to endoscopy is the National Endoscopy Database (NED). Once fully rolled out it is envisioned to provide links to all endoscopy units in the UK. Results

data will be uploaded centrally allowing detailed analysis of all endoscopy results not only for research purposes but also setting quality control benchmarks and measuring achievement of these benchmarks amongst the endoscopy community. Furthermore this will have the potential to easily discriminate between individuals compared to the provider comparisons performed here. Although the individual consultant responsible can be found in HES, and potentially used for analysis, this does not explicitly inform an analysis of who has performed the procedure or even if the named consultant was present in the procedure room. NED will answer questions related to this and is therefore an important advance.

However the NED will likely have some disadvantages; there is no current plan for linking the database to histology results, patient factors including co-morbidity, or to surrounding clinical care including complications. Therefore, although useful data analysis will be available as a result, applications to interventional GI endoscopy will be limited by an inability to provide clinical outcomes beyond technical procedural success. Although this is disappointing, it would likely be possible to link NED to HES. Although currently prohibited, it is possible to identify individual patients described in HES. Similarly NED is likely to use a unique identifier to link procedures between a single patient. If the NHS numbers from NED and HES could be identified then cases could theoretically be linked. This would require detailed ethical consideration, however the resultant data would have significant research potential.

10.1.4 Potential future implications – Service design

The impact of eliciting a volume effect is important for the design of clinical services. As discussed in the chapter specific introduction to the ERCP malignant study, other procedural specialities have already undertaken this in the interests of improving outcomes for subjects.

There appears to be a volume effect for ERCPs performed in the setting of HPB cancers that did not undergo curative operations. Therefore it should be considered if subjects undergoing ERCP should only have their procedure performed in a high volume provider. The evidence offered by this thesis contributes to what is already a contentious debate regarding the presence of a volume effect. Having demonstrated the effect in this cohort, it is important to consider if a similar effect is present in ERCP for benign indications. Assuming that only ERCPs for cancer are associated with a volume effect, it would seem reasonable to design a service with fewer sites performing ERCP in this subgroup of subjects. Once a geographical template is constructed, it would be possible to establish the likely volume of subjects seen at each proposed cancer ERCP provider. Therefore the potential benefit that may be achieved by redesigning the system could be calculated by comparing outcome statistics between the current service and a proposed system of high volume providers only.

In contrast, no benefit was seen in treatment of achalasia. Neither performing more pneumatic dilatations nor high volumes of laparoscopic myotomy was shown to change outcomes. This interesting finding was unexpected, but equally impactful to subjects who can, without risking the success of their procedure, continue to undergo their treatments, endoscopic or surgical, at a provider that suits them.

10.1.5 Potential future implications – Clinical studies

Further research possibilities have arisen as a result of the chapters above. As this body of work has developed, alternative tools have also become available. Specific future directions and their potential delivered by database studies of HES, THIN and others are suggested below.

Per Oral Endoscopic Myotomy (POEM), a new treatment modality for achalasia, is slowly becoming more widely performed. However, although examined in smaller series with good results, this would lend itself to an analysis that is similar to the investigation performed in the achalasia treatment chapter. This would require the development of a new OPCS4 code that is specific to POEM. Once available that would allow long term, all provider analysis of POEM treatment compared to PD or myotomy. This could use propensity matched analyses as seen in the colonic stents chapter above, as there would be small numbers of POEMs compared to much larger numbers of conventional treatments. This would help to ensure good quality matches and comparable treatment cohorts for analysis.

Following an analysis of PEG procedures in THIN including respiratory tract infections and mortality as an outcome, a larger study is required. A registry study would be the most beneficial methodology to achieve this, including similar outcome measures from the time of PEG placement. However this is likely to be high cost and therefore less likely to be forthcoming in practice. An analysis in HES would provide a larger cohort, however LD subject identification may be challenging. The Read codes used in THIN allowed this to be done, hence a similar set would need to be synthesised in ICD-10. A HES analysis would be less sensitive for respiratory tract infections, however it would provide longer outcome data and allow for more accurate analysis of mortality.

ERCP procedural outcomes in unresectable cancer have been clearly delineated by the chapter above. However a limitation of that study, as made clear in the chapter discussion section, is the completeness of chemotherapy data in HES. Therefore although chemotherapy results are an interesting and important component, there is potential to develop this further. HES can be linked to the Public Health England Anti-Cancer Therapies database (SCAT), a detailed and more complete database including chemotherapy agents. This would provide a detailed and robust measure of subjects receiving chemotherapy following ERCP or PTBD. Those undergoing the procedure with the

intention of alleviating symptoms or for treatment of cholangitis, but prospectively unsuitable for chemotherapy, would be impossible to separate. Therefore the study would under-estimate the proportion of subjects receiving chemotherapy, in those undergoing biliary decompression with the intention of receiving chemotherapy. However the outcome would be an important tool when making decisions regarding ERCP or PTBD, despite this limitation.

10.2 Conclusions

Database studies are an important research tool for GI interventional endoscopy, as the results of studies within this thesis have demonstrated, with impactful results. A variety of benefits make secondary care databases such as HES ideally suited to performing research into procedural outcomes. Furthermore the use of primary care databases such as THIN can support the rationale for the provision of such endoscopic services and provide long term, primary care outcome data. Careful attention to data validation, which is possible through a variety of robust methods described above, is important to ensure data accuracy. Various study design attributes and carefully selected statistical techniques can assist investigators in overcoming the disadvantages of specific databases. Good quality database analyses have the potential to identify future hypotheses for research.

11. Publications arising from this thesis

11.0.1 Manuscripts

Harvey PR, Baldwin S, Mytton J, Dosanjh A, Evison F, Patel P, Trudgill NJ. Higher volume providers are associated with improved outcomes following ERCP for the palliation of malignant biliary obstruction. EClinM. 2019. Currently in production

Harvey PR, Rees J, Baldwin S, Waheed H, Tanner JR, Evison F, Patel P, Trudgill NJ. Outcomes of colorectal stents when used as a bridge to curative resection in obstruction secondary to colorectal cancer. Int J Colorectal Dis. 2019 Jul;34(7):1295-1302. doi: 10.1007/s00384-019-03302-5. Epub 2019 Jun 7

Harvey PR, Coupland B, Mytton J, Evison F, Patel P, Trudgill NJ. Outcomes of pneumatic dilatation and Heller's myotomy for achalasia in England between 2005 and 2016. Gut. 2019 Jul;68(7):1146-1151. doi: 10.1136/gutjnl-2018-316544. Epub 2019 Jan 3.

Harvey PR, Patel P, Trudgill NJ. Mortality rate after pneumatic dilatation for achalasia: authors' reply. Gut. 2019 Sep 18. pii: gutjnl-2019-319762. doi: 10.1136/gutjnl-2019-319762. [Epub ahead of print]

Harvey PR, Thomas T, Chandan JS, *et al*. Incidence, morbidity and mortality of patients with achalasia in England: findings from a study of nationwide hospital and primary care data. Gut. 2018 Jun 20. pii: gutjnl-2018-316089. doi:10.1136/gutjnl-2018-316089. [Epub ahead of print] PubMed PMID: 29925629.

Harvey PR, Thomas T, Chandan JS, Bhala N, Nirantharakumar K, Trudgill NJ. Outcomes following feeding gastrostomy (FG) insertion in patients with learning disability: a retrospective cohort study using the health improvement network (THIN) database. BMJ Open. 2019 Jun 19;9 (6):e026714. doi: 10.1136/bmjopen-2018-026714

11.0.2 Published Abstracts

Oral presentations

Harvey P, Baldwin S, Mytton J*, et al.* OC-002 The outcomes of ercp for the palliation of malignant jaundice in england between 2001 and 2014. *Gut* 2017;**66:**A1-A2.

Harvey P, Coupland B, Mytton J*, et al.* The results of endoscopic and surgical treatment for achalasia in england between 2005 and 2016. United European Gastroenterology Journal 2017; 5 (Supplement 1)

Poster presentations

Harvey P, Baldwin S, Mytton J*, et al.* The outcomes of ercp for the palliation of malignant jaundice in england between 2001 and 2015. United European Gastroenterology Journal 2017; 5 (Supplement 1)

Harvey P, Coupland B, Mytton J*, et al.* PWE-122 The results of endoscopic and surgical treatment for achalasia in england between 2005 and 2016. *Gut* 2017;**66:**A188-A189.

Harvey P, Thomas T, Chandan J, *et al*. The incidence and prevalence of achalasia in England in two national databases. United European Gastroenterology Journal 2017; 5 (Supplement 1)

Harvey P, Coupland B, Mytton J*, et al.* PWE-121 The incidence of achalasia in england and its association to deprivation and ethnicity. *Gut* 2017;**66:**A188.

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