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Cancer survival in New South Wales (NSW) and the impact of distance from and access to cancer surgical services: A data linkage study

Elizabeth Ann Tracey

Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy
Sydney Medical School Sydney School of Public Health, The University of Sydney
August 2014

Contents

Tables and figures

Abbreviations

AACR	Australian Association of Cancer Registries
ABS	Australian Bureau of Statistics
ACIM	Australian Cancer Incidence and Mortality
AHS	Area Health Service
AIC	Akaike Information Criterion
AIHW	Australian Institute of Health and Welfare
AMI	Acute Myocardial Infarction
APDC	Admitted Patient Data Collection
ARIA	Accessibility and Remoteness index of Australia
ASA	American Society of Anaesthesiologist
ASGC	Australian Standard Geographical Classification
CART	Classification and Regression Tree
CAT	Computer Assisted Topography
CCR	Central Cancer Registry
CHRL	Centre for Health Record Linkage
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
CS	Cause specific survival
CT	Computerised Tomography
DCI	Death Certificate Index
ECOG	Eastern Cooperative Oncology Group
FEBRL	Freely Extensible Biomedical Record Linkage
GI	Gastro Intestinal
GIS	Geographic information software
GNAF	Geocoded National Address File
GOS	Gynaecological oncology service
GP	General Practitioners
HIV	Human immunodeficiency virus
HR	Hazard Ratio
IACR	International Association of Cancer Registries
IARC	International Association for Research in Cancer
ICBP	International Cancer Benchmarking Partnership
ICD	International Classification of Disease
ICSS	International Classification of Standardised Survival
IPTAAS	Isolated Patients Travel and Accommodation and Assistance Scheme
IRSD	Index of Relative Socioeconomic Disadvantage
LGA	Local Government Areas
LHD	Local Health Districts
MDT	Multidisciplinary team
MFP	Multivariable fractional polynomial

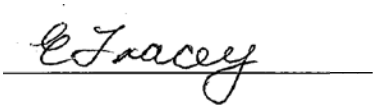
MRI	Medical Resonance Imaging
NAACR	North American Association of Cancer Registries
NASH	Nearest accessible specialist hospital
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NLI	National Locality Index
NSAHS	Northern Sydney Area Health Service
NSCLC	Non small cell lung cancer
NSW	New South Wales
NY	Northern and Yorkshire
NYCRIS	NY Cancer Registry Information Service
ONS	Office of National Statistics
PATS	Patient Assisted Travel Schemes
PCI	Percutaneous coronary intervention
PET	Positron Emission Tomography
PO	Post office
PP	Pohar Perme
RFDS	Royal Flying Doctor Service
RPA	Royal Prince Alfred
SAS	Statistical Analysis System
SE	Standard errors
SEER	Surveillance Epidemiology and End Results
SEIFA	Socioeconomic Index For Areas
STRS	Survival Time Relative Survival
SWSAHS	South Western Sydney Area Health Service
TNM	Tumour Nodes and Metastases
UCL	University College London
WA	Western Australia

Disclosure

This thesis is submitted to the University of Sydney in fulfilment of the requirements for the Degree of Doctor of Philosophy.

The work presented in this thesis as a series of published and unpublished manuscripts are an original contribution. All information obtained from other sources is acknowledged in the text. I carried out the research and compilation of this thesis under the supervision of Professor Bruce Armstrong and Professor Jane Young both from the Sydney School of Public Health, The University of Sydney. My specific contributions to jointly authored papers are outlined at the end of this section.

I hereby declare I have not submitted this material, in either full or in part, for a degree at this or any other institution.

Signature:  Date:_07 January 2015

Acknowledgement

I would like to express my sincere thanks and gratitude to my supervisor Professor Bruce Armstrong for his thoughts, advice, high standards, and expectations of excellence. Particularly, for his forensic considered review of all aspects of my work. I would also like to thank Professor Jane Young for her insightful comments and suggestions particularly in the abstract, introduction and discussion sections. Most importantly, for her kindness and for making me feel welcome and part of the Cancer Epidemiology Services Research Team.

I am extremely grateful to Associate Professor Hunter Watt, Professor Neville Hacker and Professor Brian McCaughan for their clinical interpretation of the data and for their helpful comments. I would also like to thank the Cancer Institute NSW for the time that I worked there and for their approval that I undertake this PhD. I would particularly like to thank the NSW Central Cancer Registry staff for their diligence and attention to detail in collecting and processing the data and the Centre for Health Record Linkage for linking the cancer registry and hospital data.

I would also like to thank Professor Michel Coleman and his team for sponsoring me as a visiting researcher for six months at the London School of Hygiene and Tropical Medicine where I undertook an advanced survival course and worked on my thesis.

Lastly, I would like to thank Alan for his love, kindness, understanding and practical support provided to me during this thesis. I also appreciate his proofreading of my abstract, introduction and discussion and for providing me with a laypersons perspective. I would also like to thank James and Belinda for the great times we had together in London and Katherine, and Evan who have always been supportive and encouraging when I reached milestones like getting papers published.

Short abstract

Cancer survival is poorer in rural NSW but specialist cancer surgical services are predominately located in the Sydney region. The aim of this thesis is to examine whether increasing distance from cancer surgical services affects access to those services and ultimately cancer survival after adjusting for patient, cancer and treatment factors. The first objective was to explore and discuss the literature as well as methodological issues associated with measuring distance and cancer survival. The second objective was to determine the influence of actual distance to surgical services on cancer survival for patients with bladder cancer and distance to the closest specialist service for patients with ovarian and lung cancer. Factors known to mediate survival were also investigated, including whether advanced or unknown stage cancer or the patient not receiving surgery were associated with increasing distance to a specialist hospital and whether these influenced the hospital of treatment. The method used was population based data linkage for patients diagnosed between 2000 and 2008 (data obtained from the NSW Central Cancer Registry database and linked to hospitalisations in the Admitted Patients Data Collection) and followed to the end of 2008. Distance was measured in kilometres from a person's home to their hospital of surgery (bladder cancer) or the closest specialist hospital (ovarian and lung cancer) by using geographical coordinates based on address information and the "Great Circle Distance Calculator". Associations were modelled using logistic and multinomial logistic regression and the hazard of death was modelled using Cox regression and the survival time parametric method (`stpm2`).

Results The hazard of death decreased with distance to hospital of surgery for people with bladder cancer who had a cystectomy but not for people who had another type of surgical resection. People with ovarian and lung cancer who lived further from specialist surgical hospitals were much more likely to attend general hospitals for their care than people who lived near a specialist hospital. People admitted to general hospitals were more likely to have advanced or unknown stage cancer at diagnosis and to have limited or no surgery. Treatment in a specialist hospital and surgery were the best predictors of survival in women with

ovarian cancer. The same was true for people with lung cancer. With increasing distance, people with lung cancer who attended specialist hospitals had less advanced cancer suggesting greater selection for operability.

Understanding the factors that impede referral to and attendance at specialist surgical hospitals for NSW residents particularly those who live remotely is essential if everyone is to have the best chance of cancer survival regardless of where they live.

Long abstract

In 2012, 30 per cent of the Australian population and cancer patients lived in rural and remote areas. The challenge for people diagnosed with cancer particularly those who live in rural and remote locations is that medical specialists and specialist surgical hospitals are predominantly located in cities. Centralisation of services is important to ensure a concentration of clinical expertise and surgical volume both known to be associated with cancer survival. Distance from treatment is an access measure that takes into account the distance from a person's home to appropriate affordable treatment and ultimately whether that person receives treatment. Previous studies of distance to treatment on cancer survival had limitations. Many were not population-based with limited or no stage information and did not take account of the hospital of treatment or include surgery. Adjustment for a number of patient, tumour and treatment factors known to influence cancer survival was also not possible because the information was not available.

Most studies of distance and cancer survival assumed that people who were diagnosed with cancer died from it because cause of death information was not available to them or was of poor quality. Linkage of cancer registry data to hospital data and the ability to measure distance, stage at diagnosis and cause of death for people in NSW provides a comprehensive population-based dataset to enable the investigation of the impact of distance to specialist care. The aim of this thesis is to examine whether increasing distance from cancer surgical services affects access to those services and ultimately cancer survival after adjusting for patient, cancer and treatment factors. This issue was examined for three cancer types, namely bladder, lung and ovarian cancers

Chapter 1

Chapter 1 reviews the current literature on distance from the patients home to treatment for any health condition and then specifically for cancer treatment. This chapter examines literature on why distance to treatment is important, particularly, in the current policy framework of specialisation and centralisation of services. An individual's health problem and the availability of services determine whether a person needs to travel to access that service.

There are a number of ways of measuring distance to health services. Previous health related studies using straight-line distance to treatment and outcome are discussed. When a patient's health problem is an emergency, for example in the case of acute myocardial infarction (AMI), longer time to care significantly influences a patient's survival because urgent immediate care and, therefore, proximity to services is important.

Increasing distance from treatment may affect whether a person with cancer refuses or has the suboptimal alternative because it involves less travel. For example, radiotherapy requires daily visits for a number of weeks. The recommended treatment for women with early stage breast cancer is a lumpectomy and radiotherapy, with mastectomy recommended for women whose cancer has spread beyond the breast. However, a number of registry studies report that women with early stage breast cancer are more likely to have a mastectomy with increasing distance to radiotherapy so that they do not have to attend radiotherapy.

Distance to treatment can also depend on the type of cancer and the range of treatments available. Surgical services are often located in cities because of the policy framework that supports the centralisation and specialisation of surgical services.

Surgery (both the likelihood and the type)depends on the stage of cancer at the time of diagnosis and is often the definitive treatment for cancers where the primary tumour has not spread beyond the organ of origin. In this thesis three cancer sites: bladder, ovarian and lung cancer are examined in detail. Stage at diagnosis, whether patients undergo surgery and whether treatment occurs in specialist hospital is examined to determine what impact these factors have on cancer survival. Therefore, these issues are emphasised in this review.

Literature associated with patient, tumour and treatment factors that could confound the relationship between distance and survival is examined. International and Australian best practice clinical guidelines for bladder, ovarian and lung cancers are also reviewed.

Finally, specific aims of this thesis are outlined. The first two questions of interest are methodological and underpin subsequent analyses. Firstly, how valid is the measure of distance in NSW? Secondly, does it matter whether we use cause specific or relative survival

methods? What effect do different methods of allocating cause of death have on our survival estimates?

The remaining aims relate to the three cancers of interest with the questions influenced by what is already known about their cancer survival. Bladder cancer survival in NSW is poorer in women than it is in men. However, unknown is whether distance from the patient's home to where they have surgery (cystectomy or resection) explains this survival difference.

Survival from ovarian cancer in NSW is influenced by stage at diagnosis and histological subtype, but also unknown is whether distance to specialist care influences access to that care, a woman's likelihood of having surgery or ultimately survival.

Surgery is the recommended treatment for people who are diagnosed with non small cell lung cancer and survival is higher when the tumour is localised to the lung. Therefore, does distance from the nearest accessible specialist hospital increase the likelihood of presenting with a tumour of advanced or unknown stage? Or the likelihood of having no surgery? Moreover, how do both of these factors affect survival from lung cancer after adjustment for patient, cancer and treatment factors?

Chapter 2

The objective of this chapter is to present the methods used to geocode the longitude and latitude coordinates of a person's residential address at the time they were diagnosed with cancer as it appears on the NSW Central Cancer Registry. The quality checks undertaken to consider the validity of allocating geographic areas and distance using these geocodes is discussed. Historically, the patient address at diagnosis in the NSW Cancer Registry allocates a defined geographic region based on the Australian Standard Geographical Classification (ASGC) using an Australian Bureau of Statistics (ABS) National Locality Index (NLI) coder. A comparison of the number of people with cancer determined using the LGA for the census period 2001 is undertaken. Little difference between the numbers of cancer patients derived from the historical method compared to the new geocode derived LGA occurred. This shows that the new method produced similar results. In addition, mean distance from each LGA to Royal Prince Alfred Hospital (RPA), by period of diagnosis and

by Area Health Service of Residence (AHS) provided further evidence that distance in kilometres was calculated correctly.

Chapter 3

This chapter investigates relative, net and cause specific cancer survival methods for breast, prostate, colorectal and lung cancer at each month from diagnosis up to 12 months and then each year up to 8 years to determine the impact that different methods have on cancer survival. This was necessary to ensure that differences in survival results were true and not due to methodological artefact

Survival estimates using different methods were compared in the New South Wales Central Cancer Registry (CCR) and a UK registry, the Northern and Yorkshire cancer registry (NYCR), which has a similar population size to NSW. Many studies of straight-line distance to cancer treatment were conducted in northern England using this registry. It is important to know whether different methods of measuring survival and allocating the cause of death affect the reporting of cancer survival.

The cause of cancer death for cases in the NYCR is allocated using similar rules to the CCR. Differences in five year age adjusted survival estimates between NSW and Northern and Yorkshire (NY) were calculated. Survival estimates in NSW were found to be similar at each period from diagnosis regardless of survival method used and for each cancer site investigated. A four-percentage point difference in survival estimates for bowel cancer at five years was explained by the differences in the cause of death allocation. Differences in registry practices and implications associated with the cause of cancer death allocation are discussed. Cause specific is an acceptable alternative to the relative method for reporting cancer survival. The method is also easier to implement because life tables are not required making the adjustment of patient, tumour and treatment factors easier to model. Cancer survival in NSW was 5-11% higher than in NY at five years (depending on cancer site). Higher survival in NSW is real and not artefact due to differences in survival methods or differences in the allocation of the cause of death between registries.

Chapter 4

This chapter addresses whether increasing distance from the patient's home to where they have surgery (cystectomy or resection) is associated with poorer survival and whether this factor explained the previously observed poorer survival in women relative to men. This study included an analysis of linked data population cancer registry and hospital data for 6,880 people diagnosed with bladder cancer between 2000 and 2008. Distance was measured in kilometres from the person's home to their hospital of surgery or their first hospital if they had no surgery.

The estimated five year, cause specific survival from bladder cancer was 56 per cent for women diagnosed in NSW in 2000-08 and 68 per cent in men (P<0.0001). This poorer survival in women was observed regardless of whether they had a cystectomy or resection (including endoscopic destruction) or had no specific therapy.

Adjustment for a wide range of other variables associated with survival had little impact on women's higher risk of death from bladder cancer following cystectomy.

The higher risk of death in women relative to men undergoing a cystectomy reduced after adjusting for the following factors summary stage, age at diagnosis, distance from treatment facility and, the presence of haematuria, country of birth and time to cystectomy.

Patients who had a cystectomy had a greater hazard of death if they lived within 25 kilometres of a treatment facility than if they lived further from the hospital: 26 to 75 km (Hazard Ratio (HR) 0.61 95% Confidence Interval (CI) 0.43-0.88), 76 to 125 km (HR 0.50 95%CI 0.29-0.88) or 125 km or further away. Specialty of hospital was not investigated because there are no Australian guidelines that recommend treatment in them. The reduction in death is consistent with patients experiencing better survival because they travelled further to a hospital in Sydney. Examination of interactions between sex and other covariates found a possibly meaningful interaction of sex with a history of cystitis in influencing death after cystectomy (HR was 1.55, 95%CI 1.15-2.10) in women with a history of cystitis. No such interaction was evident in women who underwent resection. Poorer survival in women diagnosed with bladder cancer remains unexplained.

Chapter 5

In contrast, this chapter considers an area of cancer surgical care where patients should be treated in specialist centres by gynaecological oncologists but can also be treated in general hospitals by gynaecologists or general surgeons. The questions of interest include

1. Does distance from, and access to the closest Gynaecology Oncology Service affect ovarian cancer survival?

2. What are the characteristics of women treated in public hospitals? and

3. What factors influence the likelihood of surgery? These questions are important because guidelines recommend that all women should be referred to a gynaecological oncologist if they are to have the best survival outcomes.

Access to a gynaecological oncology service (GOS) was measured in kilometres from a woman's geocoded address to the geocoded address of the closest public GOS hospital. Flexible parametric survival, Cox proportional hazards and logistic regression models were fitted to examine whether better access to a GOS was associated with a better outcome.

There were 3,749 women diagnosed with ovarian cancer between 2000 and 2008. The aspects of care that most strongly reduced a woman's hazard of dying from epithelial ovarian cancer were treatment in a GOS hospital (HR 0.68 95%CI 0.56-0.83), or private general hospital and having appropriate surgery (HR 0.35 95%CI 0.28-0.43). Women were more likely to attend a GOS hospital the nearer they lived to one and more likely to have appropriate surgery if they were treated in GOS hospitals.

Thus, distance was an important factor in determining whether women would receive the best care for their ovarian cancer. With increasing distance to a specialist centre, women who attended specialist hospitals had less advanced cancer suggesting greater selection for operability. Understanding what factors impede referral of women with ovarian cancer to gynaecological oncology services, particularly when women live remotely from such services, is important.

Chapter 6

- what the research questions are,
- why they are important,
- how the research questions were answered, what was found and

what the implications are. Having some consistent structure to these sections would add greatly to the clarity, and this may require a substantial rewriting of the Long Abstract.

The next three chapters focus on exploring issues of distance to the closest specialist hospital in 11,147 people diagnosed with non small cell lung cancer in NSW between 2000 and 2008 and admitted to hospital within 12 months of diagnosis. This chapter focuses on the question "Are patients who live further from the nearest accessible specialist hospital (NASH) more likely to have advanced or unknown stage non small cell lung cancer (NSCLC) at diagnosis"? This is important because appropriate staging is necessary before surgery can be considered and because treatment options are limited when patients present with advanced disease.

Distance from the patient's home to the NASH was measured in kilometres. Two groups of potential predictor variables were considered for inclusion in multivariate models based on temporality: (1) those variables that were plausibly associated with and antecedent to stage at diagnosis; and (2) variables not antecedent to stage but likely to be associated with accuracy and completeness of clinical determination of stage and its reporting to the CCR.

People diagnosed with NSCLC and treated in general hospitals had 40% to 60% higher odds of advanced stage cancer than people treated in specialist hospitals that lived 0-39 km from the NASH. The opposite was true for people who attended a specialist hospital. In people with unknown stage at diagnosis, distance from the NASH, hospital of treatment and the odds of unknown stage showed a similar pattern to that observed for advanced stage. With increasing distance to a specialist centre, people who attended specialist hospitals had less advanced or unknown stage cancer suggesting greater selection for operability.

Chapter 7

This chapter asks the question

Does increasing distance from the NASH determine whether 3,240 people diagnosed with localised NSCLC are admitted to a specialist or general hospital within 12 months of their date of diagnosis and do they miss out on potentially curative surgery? This is important because guidelines recommend curative surgery for all patients with localised NSCLC and curative surgery improves survival.

Cancer registry, hospital and death records were linked. Distance from, the patient's home to the NASH was measured in kilometres. People diagnosed with localised NSCLC were 30 times more likely to be admitted to a general hospital when they lived 100+ kilometres from the NASH. People treated in specialist hospitals (public or private), were more likely to have surgery with increasing distance when treated in a specialist hospital, confirming that with increasing distance from the NASH people were selected depending on their suitability for surgery.

Chapter 8

While the previous chapter addressed the likelihood of having NSCLC removed surgically, Chapter 8 addresses the question

Is survival for people with NSCLC poorer with increasing distance to the NASH and do factors predictive of survival vary by stage at diagnosis? This is an important question because survival is influenced by stage at diagnosis as is the likelihood of undergoing curative surgery. Therefore, stratifying by stage and examining surgery while adjusting for other factors is important to better understand the factors influencing distance.

This analysis included 3,240 people with localised NSCLC, 2,435 regional stage and 3,540 people with distant stage hospitalised within 12 months of their date of diagnosis. Distance from the person’s home to the NASH was measured in kilometres. Cox proportional hazards models examined predictors of death for people diagnosed with NSCLC. People who had a surgical resection for their cancer, which admission to a specialist hospital made more likely,

were much less likely to die. People were less likely to have a resection the further they lived from the NASH. However, people who lived distant from the NASH and who were admitted to a specialist hospital were more likely to have a resection and were less likely to die. These patterns varied little with lung cancer stage.

Greater distance to the NASH can affect a person's outcome by reducing the likelihood of them being treated in a specialist hospital. Research is needed into health service barriers to referral of people with NSCLC to enable them to obtain specialist care, increasing their likelihood of surgery and, therefore, reducing their likelihood of death.

Chapter 9

Chapter 9 provides an overall discussion of common findings in relation to cancer survival in NSW and the impact of distance from and access to cancer surgical services for people with bladder, ovarian and lung cancer. Attendance at a specialist hospital and having surgery contributed to better survival. People who lived further from a specialist hospital were more likely to have advanced or unknown stage, be treated in a general hospital and not receive potentially curative surgery.

The aims of each of the studies are revisited and placed in context with findings in the literature and previous registry based patterns of care studies in NSW. Particular emphasis is given to the literature on clinician referral prior to diagnosis, factors that influence who sees a specialist and travel barriers to surgery for people living further from specialist care. This chapter also discusses limitations and implications for current practice. It also suggests recommendations that may assist people who are diagnosed with cancer in NSW to obtain better specialist surgical care and outcomes regardless of where they live.

Publications arising out of this thesis

1. Tracey E, Watt H, Currow D, Young J, Armstrong B. Investigation of poorer bladder cancer survival in women in NSW, Australia: a data linkage study. *BJUInternational.* Mar 2014;113(3):437-448.

2. Tracey E, Hacker N, Young J, Armstrong B. Effects of access to and treatment in specialist facilities on survival from epithelial ovarian cancer in Australian women: A data linkage study. *International Journal of Gynaecological Cancer*. Sept 2014;24 (7):1232-1240.

3. Tracey E, McCaughan B, Badgery-Parker T, Young J, Armstrong B. Survival of Australian lung cancer patients and the impact of distance from and attendance at a thoracic specialist centre: a data linkage study. *Thorax.* July 29, 2014. 0:1–9. doi:10.1136/thoraxjnl-2014-205554.

4. Tracey E, McCaughan B, Badgery-Parker T, Young J, Armstrong B. Do patients with localised non small cell lung cancer miss out on potentially curative surgery with increasing distance to specialist care? *Australian New Zealand Journal of Surgery*. Accepted for publication 8th August 2014

5. Tracey E, McCaughan B, Badgery-Parker T, Young J, Armstrong B. Distance from the NASH and the likelihood of advanced or unknown stage at diagnosis in Australian non small cell lung cancer patients: A data linkage study. *Submitted to the British Journal of Cancer*.

6. Tracey E, Woods L, Dickman P, Young J, Armstrong B. Effects of method of survival analysis and allocation of cause of death on estimates of cancer survival in an Australian and a UK cancer registry population. Manuscript in preparation.

Awards

A 5,000 dollar Travelling fellowship was awarded from the Sydney Medical School to undertake an advanced course in cancer survival methods and spend six months at the London School of Hygiene and Tropical Medicine as a visiting researcher.

I was invited and funded as a visiting researcher for two days to the International Association of Cancer Registries office in Lyon France to meet with Professor David Forman and other International Association for Research in Cancer (IARC) staff.

A University of Sydney Postgraduate Scholarship was awarded in January 2014.

I was a participant in the three-minute thesis (3M Challenge) competition August 2013.

Abstracts presented

1. Tracey E, Watt H, Young J, Currow D, Armstrong B Determinants of bladder cancer survival in NSW: Why is bladder cancer survival in NSW poorer in women than men? Clinical Oncological Society of Australia November 2011 (Poster).
2. Tracey E, Hacker N, Young J, Armstrong B. Do patients with epithelial ovarian cancer in Australia have better outcomes if they are treated in a specialist centre: a data linkage study. Research Presentation Day "New Minds, Fresh Discoveries – July 2013.The University of Sydney. (Oral presentation).
3. Tracey E, McCaughan B, Badgery-Parker T,Young J, Armstrong B. Do non small cell lung cancer patients that live further from specialist centres present with advanced disease at diagnosis? 2013 Newcastle Translational Cancer Research Conference 23rd, October 2013. (Oral presentation).
4. Tracey E, Presentation to the Royal Prince Alfred Hospital lung cancer priority setting focus group. “Overview of lung cancer survival in NSW 2000-2008 and distance from a specialist hospital” Wednesday 11 September 2013. Royal Prince Alfred Hospital.
5. Investigation of poorer bladder cancer survival in women in NSW Australia: A data linkage study. 12th National Conference of Emerging Researchers in Ageing “Enabling Active Ageing” 25-26 November 2013, Sydney (Oral presentation).

Contribution statement paper one

Contribution statement

Dear co-authors,

Re: Investigation of poorer bladder cancer survival in women in NSW, Australia: a data linkage study. *BJU Int* 2014; 113(3): 437-48.

I would like to use the above paper as a chapter in my PhD thesis and request your permission to do so. It is a requirement of the Academic Board of the University of Sydney, that a signed written statement is obtained from all co-authors attesting to my contribution to this paper as evidence to satisfactorily identify the sections of the work for which I was responsible.

Author contributions

Elizabeth Tracey conceived and designed the analysis, reviewed the literature, analysed and interpreted the data and drafted and revised the manuscript. **Bruce Armstrong** suggested analyses, interpreted the data, critically revised the paper, and provided feedback on reviewer comments. **Jane Young** critically revised the paper and provided feedback on reviewer comments. **Hunter Watt** critically revised the paper and provided clinical advice in relation to bladder cancer surgery. **David Currow** critically revised the paper. All authors read and approved the final manuscript.

If you agree with the contributions outlined above and give permission for this paper to be part of my PhD thesis, please sign your name below. Thank you for your contributions.

Kind Regards Elizabeth Tracey

Bruce K Armstrong

Jane M Young

Hunter Watt

David Currow

Contribution statement paper two

Contribution statement

Dear co-authors,

Re Effects of access to and treatment in specialist facilities on survival from epithelial ovarian cancer in Australian women: A data linkage study. IJGC Accepted for publication on the 10th June 2014

I would like to use the above paper as a chapter in my PhD thesis and request your permission to do so. It is a requirement of the Academic Board of the University of Sydney, that a signed written statement is obtained from all co-authors attesting to my contribution to this paper as evidence to satisfactorily identify the sections of the work for which I was responsible.

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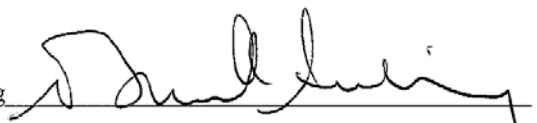
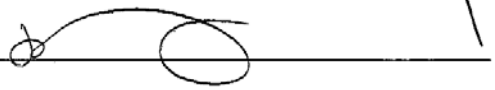
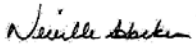
Kind Regards Elizabeth Tracey

Bruce K Armstrong 

Jane M Young 

Neville Hacker 

Contribution statement paper three

Contribution statement

Dear co-authors,

Patients with localised non-small cell lung cancer miss out on curative surgery with distance from specialist care reviewer comments have been forwarded directly to the editorial board of the ANZ Journal of Surgery for their consideration

I would like to use the above paper as a chapter in my PhD thesis and request your permission to do so. It is a requirement of the Academic Board of the University of Sydney, that a signed written statement is obtained from all co-authors attesting to my contribution to this paper as evidence to satisfactorily identify the sections of the work for which I was responsible.

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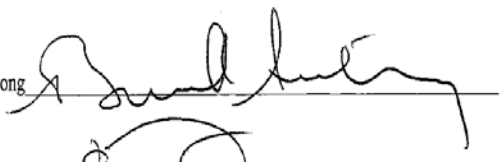
Bruce K Armstrong 

Jane M Young

Brian McCaughan 

Tim Badgery Parker 

Contribution statement paper four

Contribution statement

Dear co-authors,

Re Survival of Australian lung cancer patients and the impact of distance from and attendance at a thoracic specialist centre: A data linkage study. Accepted for publication in Thorax on July 3rd 2014

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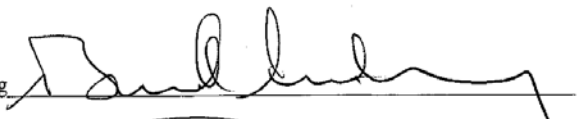
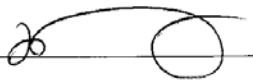
Author contributions

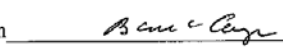
Elizabeth Tracey conceived and designed the analysis, reviewed the literature, analysed and interpreted the data and drafted and revised the manuscript. **Bruce Armstrong** suggested analyses, interpreted the data, critically revised the paper, and provided feedback on reviewer comments. **Jane Young critically** revised the paper and provided feedback on reviewer comments. **Brian McCaughan** critically revised the paper and provided clinical advice in relation to lung cancer surgery. **Tim Badgery-Parker** critically revised the paper and provided biostatistical advice. All authors read and approved the final manuscript.

If you agree with the contributions outlined above and give permission for this paper to be part of my PhD thesis, please sign your name below. Thank you for your contributions.

Kind Regards Elizabeth Tracey

Bruce K Armstrong 

Jane M Young 

Brian McCaughan 

Tim Badgery Parker 

Contribution statement paper five

Contribution statement

Dear co-authors,

Re Distance from the NASH and stage at diagnosis of Australian NSCLC patients: a data linkage study. Submitted to the British Journal of Cancer.

I would like to use the above paper as a chapter in my PhD thesis and request your permission to do so. It is a requirement of the Academic Board of the University of Sydney, that a signed written statement is obtained from all co-authors attesting to my contribution to this paper as evidence to satisfactorily identify the sections of the work for which I was responsible.

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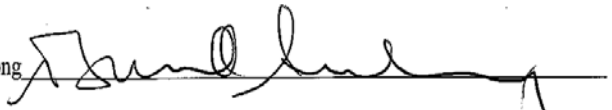
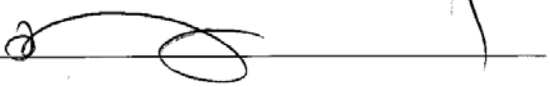
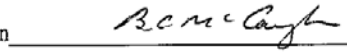
Bruce K Armstrong 

Jane M Young 

Brian McCaughan 

Tim Badgery Parker 

Contribution statement paper six

Contribution statement

Dear co-authors,

Effects of method of survival analysis and allocation of cause of death on estimates of cancer survival in an Australian and a UK cancer registry population

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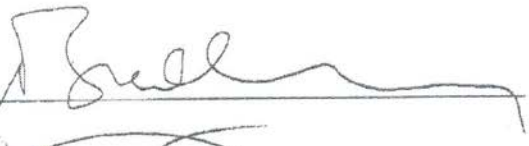
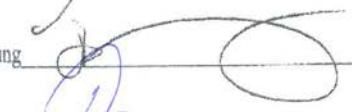
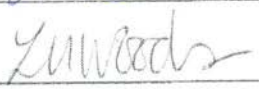
Bruce K Armstrong 

Jane M Young 

Paul Dickman 

Laura Woods 

1. Introduction

1.1. Introduction

The relationship between distances to appropriate treatment and cancer survival is complex and multifactorial. Distance from treatment is an access measure that takes account of the distance from a patient's home to appropriate affordable treatment and ultimately whether a person receives treatment. Improvements in cancer survival are widely accepted as the definitive outcome for people diagnosed with cancer and the goal of cancer treatment.

The aim of this thesis is to examine whether people with cancer in New South Wales (NSW) have poorer survival when they live further from specialist surgical care. Three cancer types, namely bladder, lung and ovarian cancer are examined in detail.

Previous studies have shown that the impact of distance to surgical care varies by cancer type.. Bladder cancer patients are often referred to urologists while lung cancer patients are referred to a thoracic physician or surgeon for specialist assessment. Gynaecologists or gynaecological oncologists treat ovarian cancer patients.

Specialist services are influenced by the availability of clinical practice guidelines. There are Australian clinical practice guidelines exist for people diagnosed with lung and ovarian cancer, but none for bladder cancer. Therefore, designated specialist centres were determined for lung and ovary but not for bladder cancer

. The number and location of specialist services are also influenced by health service policies. Australian, US, and UK policies that specifically focus on access to specialist care for cancer are examined in chapter 1.

Specific emphasis is given to stage at diagnosis and the receipt of surgery as factors that may mediate the relationship between distance and specialist care. Patient, tumour and treatment factors likely to mediate the effect of distance on cancer survival are also considered.

1.2. Cancer in rural Australia

Distance from a patient’s home to specialist care and hospital of treatment is important in Australia and NSW because Australia is a large continent with a dispersed population

mainly located in cities and coastal regions. In 2013, 30 per cent of the Australian population and cancer patients lived in rural and remote areas.[1, 2]

This thesis focuses on people living in NSW. NSW is 800,642 square kilometres[3] in size and is the most populated state in Australia with 7.41 million people or 32% of the Australian population[1]. Overall, NSW has a population density is 9.3 persons per 1000 square kilometre, but in reality, most people live in the metropolitan Sydney region or Greater Sydney (4.67 million or 63% of the population).[1]

Cancer is unique compared to other diseases because improvements in cancer survival can be measured using mandatory data collections that cover the entire population. Cancer registries have registered new cases of cancer, cancer deaths and survival for over 40 years in many countries including Australia.[4-6] In 2012 an estimated 120,700 Australians were diagnosed with cancer[7] with approximately a third or 37,525 new cases diagnosed in NSW.[8]

Compared to people living in major cities, higher death rates for specific cancers, particularly lung cancer, is reported in people living in remote and very remote areas of Australia and NSW. Furthermore, while death rates from cancer have been declining since the 1990s in Australia, they are declining at a much slower rate in rural areas than they are for urban areas. [2, 7, 9 , 10]

Poorer cancer survival in rural and remote areas of Australia and NSW is reported for many cancer sites. [2, 7, 11, 12]Poorer cancer survival in people who live further away from treatment may be explained by a number of factors including lack of timely detection due to lower numbers of general practitioners (GPs) per head of population,[13, 14] the limited availability of diagnostic equipment, diagnosis at an advanced stage, [12, 15, 16] limited treatment [17] or suboptimal treatment.[18, 19] Even after taking account of age, stage, socioeconomic status and type of cancer, people living in rural areas of NSW have been found to be less likely to be diagnosed with localised cancer.[20]

Treatment for cancer can only commence once diagnosis has occurred, with the type of treatment strongly influenced by the stage at diagnosis. In Australia, patients present either to their GP or to the emergency department of their local hospital with symptoms or their

cancers are diagnosed incidentally as part of another investigation. Referral patterns from GPs to specialist doctors influence treatment options. Treatments for people with bladder, lung and ovarian cancer include surgery, chemotherapy, radiotherapy or a combination of therapies and may include palliative care if curative treatment is not an option.

People concerned about symptoms need to access a GP and other cancer health professionals to obtain a diagnosis, referral and follow up treatment. Rural Health Services in Australia and NSW are smaller and dependent on services provided by GPs.[13, 14] The ratio of primary and secondary health care professionals in rural populations (GPs, registered nurses and allied health staff) is significantly lower than in urban populations. [21] A similar pattern is observed for oncology services in rural and regional Australia where a survey of 160 rural hospitals (98% response rate) reported significant deficiencies in services including that only 21% had a medical oncology service, 7% had radiation oncology service, 6% had surgical oncology and 24% a palliative care specialist.[21]

Rural lung cancer patients have more symptoms and take longer to consult their GPs leading to a later diagnosis and fewer treatment options.[22] Surveyed residents in rural areas believed that they waited longer for a GP appointment (23% in Rural and Remote;16% in Urban Areas).[23] In addition, people in rural and remote areas in Queensland were over four times more likely to report difficulty accessing health services than those living in major cities (odds ratio (OR) 4.3 95% CI 2.72-6.80).[24]

Surgery (to remove cancerous tissue from the body) is the oldest cancer therapy available. The goal of surgery varies. It can be used to diagnose cancer, determine where it is located and whether it has spread to other organs in the body.[25] For patients whose cancer is localised to the organ of origin, surgery, is often the definitive treatment. [23, 26] Lower post-operative mortality[27-29] and better long term survival has been found when patients are treated by specialists[30, 31] in specialist hospitals[32, 33] or hospitals with high volume surgical procedures for cancer.[34 35, 36]

The challenge for Australian and NSW residents and cancer patients from remote and rural locations is that specialist hospitals are located mainly in the cities. To access specialist doctors, people need a referral to one or more specialists and therefore care coordination.[37]

They will also need to travel to the city. Many may need to obtain accommodation and take time off from work and family commitments. Any one of these factors could be a barrier to timely diagnosis, surgery and other treatment options and ultimately explain why survival is poorer in rural and remote regions.

Treatment in specialist hospitals has many other advantages. Apart from best practice surgery, patients treated in specialist centres have access to multidisciplinary team review which has recently been shown in an Australian study to be an independent predictor of survival:[38, 39] Furthermore, surgery in a private hospital[40] or having private health insurance has also been shown to improve survival outcomes. [41-48] Even patients with lung cancer who are older or those with comorbidities, have a survival advantage if they have surgery in a high volume specialist centre.[36, 49] For patients for whom surgery is not an option, attendance at a specialist centre will also increase the likelihood of clinical trial participation.[50-52]

Few population-based studies have examined the impact on cancer survival of access to and receipt of best practice cancer surgery. There have been a number of patterns of care studies in Australia and in NSW for cancers of the lung, [53-56] ovary, [57] breast[41] and colorectum.[58] Many of these studies have documented surgical management but have not examined cancer survival. More recently, linkage of cancer registry data to hospital data has enabled the examination of surgical treatment in cancer patients. Many early data linkage studies were conducted in Western Australia (WA) [42, 46, 59-61] and more recently in Queensland.[17, 62] These studies have examined rural and urban differences in access to surgery and survival but they have either not taken into account stage at diagnosis (WA) or hospital of treatment (Queensland).

The studies reported in this thesis are possible due to reasons unique to NSW. Firstly, the NSW CCR routinely records summary stage (extent of disease) at diagnosis along with other patient and tumour information. Hospital and surgical treatment information, available from the NSW Admitted Patient Data Collection (APDC) is linked to the CCR. Geocoding of the CCR has also enabled distance to be measured to surgical services. Furthermore, recently, a number of comparative studies have compared linked NSW data for lung, colorectal cancer[63] and prostate cancer[64] with patterns of care data and have concluded that linked routinely

collected data in NSW provides accurate information on potentially curative surgical treatment.

This chapter, initially, examines the literature on the impact of distance from a person's home to a health service for people with any condition. Next, appraised are studies of distance to cancer services and specialist surgical services. Priority is given to studies that focus on cancer registry linked data for bladder, ovarian and lung cancer. Discussed also are relevant papers for other cancer sites particularly those that consider straight-line distance from surgical treatment and cancer survival.

1.3. Access to health services in rural Australia

There are a number of ways of measuring distance to and access to services. Currently, the majority of Australian studies that have examined the impact of distance to treatment and access to services in Australia have used the Accessibility/Remoteness index for Australia (ARIA).[65, 17, 66-69 2, 11, 70]This index is based on five categories: highly accessible, accessible, moderately accessible, remote and very remote based on groupings of the ASGC.[71, 65, 72]

National and state cancer registry reports[2, 11] of five year relative survival by ARIA grouping report poorer survival for cancers of the bowel, breast (female), liver, lung, ovary, pancreas, stomach and tongue in rural areas.[11] Poorer survival in rural areas could be due to many factors including presentation at a late stage or limited treatment options. Population-based ecological studies of cancer survival provide some understanding of the effects of cancer stage and treatment.

One of the earliest studies of cancer survival in NSW that also took account of cancer stage [12] reported that rural residents in NSW had 35% poorer survival compared to those living in urban areas. This study examined cancer survival by ARIA grouping for 20 cancer sites in NSW and found higher risks of death for people with cancers of cervix, prostate and for all cancers combined, with significant variations in other cancer sites. After adjusting for stage at diagnosis, the risk of death for cancer sites combined reduced to 25%. Not all people had lower survival in remote areas. People with lung cancer were more likely to die when they lived in moderately accessible areas even after adjusting for stage. This suggests that variation in treatment or other factors may influence survival.

A number of Queensland studies[17, 69] have examined whether survival was lower in rural and remote regions due to treatment differences by comparing incidence, mortality and surgical procedures by ARIA grouping. Baade et al. [17] examined whether access to surgery varied for men with prostate cancer depending on urban or rural residence at the time of diagnosis. The authors reported that while incidence rates were similar for men in urban and rural areas (indicating similar risk profiles), rates of surgery (radical prostatectomy 182.2/100000 Rural v 239.2/100000 Urban; P<0.01) were lower in rural areas. Furthermore, death rates were higher in rural areas (56.9/100000 Rural v 45.8/100000 Urban P<0.01) and survival poorer (5-year relative survival, 87.7% Rural v 91.4% Urban; P<0.01) in rural areas.[17]

Access to and use of health services in Australia using ARIA groupings have been more thoroughly investigated in women than men, mainly because of the contribution of the Australian Longitudinal study of Women's Health.[73-76] This study included three cohorts of women interviewed regularly over a 17-year period. Overall, women were found to have less access to bulk billing GPs and fewer visits to specialists in rural areas than in major cities. Women, living in rural and remote areas, also, had higher death rates from their lung cancer, had more chronic obstructive pulmonary disease, higher smoking prevalence rates (particularly in older women) and higher obesity rates than women in urban areas. [2]

One limitation of ARIA as a measure of distance to services is its potential correlation with the socioeconomic index for areas (SIEFA) measure. This is a measure of socioeconomic disadvantage that has geographic groupings in common with ARIA.[2] To distinguish the effects of ARIA and Socioeconomic index for areas (SEIFA) for people with lung cancer, a Queensland study[77] used a method called Classification and Regression Tree (CART) analysis. High incidence rates occurred in males when they lived in disadvantaged or remote and very remote areas of the middle SEIFA grouping. While for females, rates were higher in middle or low SEIFA regions in major cities.

A further limitation of ARIA is that it is a measure of distance to and access to general goods and services rather than health or cancer-specific services in particular. A number of Queensland studies have also noted this limitation.[78, 79] Therefore; straight-line distance has

an advantage in that it measures distance to and access to specific hospitals and cancer services.

1.4. Distance to treatment and how to measure it

There are a number of ways of measuring distance and access to a variety of health services. Straight-line distance (in kilometres or miles), measures distance from the patient's home or the centroid of a patient's postcode of residence at diagnosis to a specific treatment facility.[79,78] The treatment facility may be an outpatient facility[80-83] or a GP surgery; the closest hospital to the patient's home; the closest specialist hospital that provides surgery;[84-86] the closest medical oncology facility that provides chemotherapy;[85] or the closest radiotherapy facility.[87, 88]Apart from straight-line distance, distance travelled by car, or time taken to travel, have also been used as measures of distance.[16, 87-89]

There are numerous software applications available to calculate straight-line distance provided two geocoded coordinates are available. Calculation of straight-line distance can occur using any geographic information software (GIS).[90, 91 92]A number of cancer registry based studies of distance have used an algorithm referred to as the "Great Circle Distance Calculator"[93] which measures the shortest distance between any two points. The method, based on spherical geometry, takes account that the earth is a sphere. The distances calculated are as the crow flies. The North American Association of Central Cancer Registries (NAACCR) first developed this algorithm in Statistical Analysis System (SAS) software [94] and a number of US cancer registry studies have applied this algorithm[95-98] to their studies or used GIS software to calculate travel distances.[99, 100]

In this thesis, calculation of straight-line distance occurs using the geocoded longitude (X) and latitude (Y) coordinate from a patient's cancer registry geocoded address at diagnosis to the geocoded longitude (X) and latitude (Y) coordinate in an appropriate specialist public hospital by applying the SAS program developed by NAACCR. Specialist hospitals are identified using Canrefer, [101] a NSW web based directory of cancer services managed by the Cancer Institute NSW, Australia's first statewide cancer control agency. Because all Australians are entitled to treatment free-of-charge in public hospitals, [102] straight-line distance is a measure of access to best care that includes both distance to and affordability of

care. Compared, are the current and new geocoded methods of allocating boundaries in the CCR. In addition, the advantages and limitations of the straight-line distance is provided in Chapter 3.

1.5. Measurement of cancer survival

Trends in survival over time and differences between geographical regions are used by cancer control agencies, researchers and the health system to determine priorities and evaluate cancer control efforts. Relative survival is the common method used by cancer registries to report survival. Cancer survival is the proportion of patients diagnosed with cancer who are alive at the end of a defined period, usually five years. Population-based cancer registries routinely report five year relative survival rates.[103, 104, 105] Relative survival "rate" is a misleading term because it is a ratio namely the ratio of deaths experienced in a cancer cohort over a defined period after adjusting for the background mortality (all deaths experienced in the population, by age and sex).[103, 106-108] Background mortality, in the form of life tables for specific years is obtained from the ABS.

Following up a cohort of cancer patients to determine whether they are alive or dead is essential for complete and accurate reporting of cancer survival. Cancer registries undertake population-based survival analysis by following a cohort of patients diagnosed within a defined time up to a particular date, for example 30th December 2008. Survival time is the difference between the date of diagnosis of a patient and the date of death recorded on the death certificate.[5, 109] Follow-up of patients to determine the date of death is either active or passive. Active follow-up, involves contacting doctors, hospitals and coroner's offices to determine, whether a patient is dead or alive at a point in time.[105, 110] Whereas, passive follow-up requires matching the cancer registry database, to state and national death registers.[105] US SEER registries, use active follow up while Australian registries use passive follow up supplemented by writing to doctors for discrepant cases. In NSW when a match occurs (based on patient demographic factors (e.g., name, address and date of birth) the date of death, and sometimes the cause of death is added to a person's record on the cancer registry database. If a match is uncertain, cancer registry staff resolve this discrepancy by writing to doctors and hospitals seeking further information.

Studies that compare five year relative survival rates, for example between hospitals with varying caseloads, or between geographical areas such as, Europe,[111-121] Australia[11] and the United States -[122, 123] can be used to evaluate progress in cancer control efforts. This is particularly informative when survival information can be analysed with other information for the same country, for example risk factor profiles, screening participation rates, the proportion of patients presenting with localised stage and the distribution of cancer services. Recently, the International Cancer Benchmarking Partnership (ICBP) compared cancer survival in 2.4 million patients in 12 jurisdictions. Cancer survival was higher in Sweden, Australia and Canada for lung, ovarian, bowel and breast cancer and lower in the UK and Denmark.[124-128] These survival comparisons while providing valuable insight are limited to comparisons of age, sex, tumour histology and stage. For each additional variable of interest (for example socioeconomic status or ethnicity) specific life tables need to be developed which can be both impractical and resource intensive to produce. For example, to undertake the International Benchmarking Partnership study of cancer survival, 250 different life tables were developed.[124]

Cause specific survival may be an acceptable alternative to relative survival for population-based registries provided follow up of patients is comprehensive and recording of cause of death complete.[129-131]Similar results using both methods within the same population should provide a level of reassurance that one method can be a substitute for the other. Recently, an Australian study found similar cause specific and relative survival estimates for all cancer and many cancer sites for indigenous and non indigenous Australians at one and five years post diagnosis. [132] Furthermore, the Geneva Cancer Registry found less than one per cent difference in survival estimates for breast cancer using cause specific and relative survival methods after 20 years of follow up. [133] In addition, cause specific survival is more familiar to clinicians because Kaplan Meier survival curves and Cox proportional hazards modelling are methods commonly used to evaluate outcomes in clinical trials. Furthermore, cause specific survival analysis allows for easy adjustment of patient, tumour and treatment factors because life tables for every variable of interest are not required.

Fortunately, all cancer registries in Australia[11] and Scandinavia[134], and most in the US, [130] record the cause of cancer death on their databases. For example, people diagnosed with

lung cancer who die from it, have their death recorded as a lung cancer death or if they die from an unrelated cause, for example, AMI, have a non cancer death recorded. In this thesis, the cause specific survival method is compared to other more routinely used methods of survival (net and relative) to determine whether cause specific survival is an acceptable method for use in chapters 4-8. These methods of survival are compared in two registries (NSW and Northern and Yorkshire (NY) for four cancer sites (breast, prostate, colorectal and lung). Allocation of cause of death to NY cancer cases occurs by applying similar rules as those used in NSW. Finally, differences in survival between the two registries, are investigated and discussed in Chapter 3.

1.5.1. Cancer registration standards

Cancer registration processes vary by country, particularly completeness of data and the source that initiates the registration of a case of cancer. International differences in survival rates may be due to different cancer registration practices that may influence completeness of cancer registration and result in differences in the reporting of cancer survival.

Internationally, cancer registries code and report cancer incidence and survival to a common standard. Registries contribute to the international publication Cancer Incidence in Five Continents,[135] which requires them to follow the International Association of Cancer Registries (IACR) standards.[4] Registries routinely measure and report indicators which can be used to benchmark the quality of their data against other registries. The highest quality registries have high proportions of registered cases that are histologically verified, low proportions of registered cases that are notified by a death certificate and mortality incidence ratios that approximate measured cancer survival estimates. . Beral and Peto[136] suggested that the higher survival in Sweden compared to the UK might be due to differences in registration practices. Their concern was the lack of mandatory notification in the UK may affect the completeness of the registry incidence data and commencing a registration from a death certificate may lead to biased estimates of survival because good prognosis cancers may be missing. Others have refuted these suggestions based on simulation studies. [137, 138]

Regardless of who is correct, it is clear that comparison of survival needs to take account of different cancer registration practices. In NSW, and in other Australian registries, cancer

notification, is legislated under the Public Health Act.[139] Pathology notifications have been mandatory since 1986 and inpatient hospital notifications have been received since 1992.[140] Initiation of a registration of cancer occurs after receiving a notification from any one of the following sources: hospitals, pathology laboratories, cancer care centres, radiotherapy centres and death registers. The greater the number of notification sources the more likely that a registry has accurate and complete data. In the UK, notification of cancer is not mandatory; registries receive death certificates and obtain further information by checking with family doctors and hospital files using this information to register a case..

1.5.2. Allocation of the cause of death in Australian cancer registries

The cause of cancer death recorded by cancer registry coders in Australian cancer registries is not always concordant with the cause of death determined by the ABS.[11]The ABS records the cause of death based on information recorded on the death certificate only.[141] Australian registries including the NSW CCR use all notification sources and not just death certificates to determine the cause of death.[142, 143] Furthermore, Australian registries follow up with doctors and hospitals to resolve and determine the cause of death when a discrepancy arises.

Linking cancer registry data with hospital data, as has been done in the studies in this thesis, provides a previously unavailable opportunity to examine survival due to distance to a specialist surgical hospital while taking account of patient, tumour and surgical treatment factors in cancer registry patients.

Relative survival is currently the established method used by cancer registries, epidemiologists and health service providers. Cause specific survival ~~needs to~~ might be an acceptable alternative~~.~~ provided similar results are obtained. Further discussion of this topic occurs in Chapter 3.

1.6. Studies of distance to treatment in non cancer patients

This section explores the issue of distance to health services and treatment outcomes in several non cancer contexts. This section explores the issue of distance to health services and treatment outcomes in several non cancer contexts, to determine whether access to service due to distance is influenced by the type of disease or the type of service.

1.6.1. Distance and the likelihood of receiving treatment for mental health patients

Patients with mental illness often present with an acute mental health crisis. The ability to deal with a crisis depends on what services are available. One of the earliest studies to consider distance and the impact on health services was conducted in 1964. This study [144] looked at veterans who attended a mental health outpatient clinic. Distance was measured in miles from the patient's address to the Denver Mental Hygiene clinic. This study found that the closer a veteran's residence was to the clinic, the greater the probability that the veteran would receive treatment. A subsequent study looked at the travel distance for outpatient treatment of depression in Pittsburgh and also found that patients received less treatment with increasing distance from services.[80]

A number of single institution studies have examined the impact of increasing distance from treatment on access to that treatment, with different results depending on the health condition and type of service. Evaluation of people with eating disorders occurred to see whether distance affected treatment adherence or attendance. No significant impact on outpatient attendance or treatment adherence occurred.[83] However, patients who travelled greater distances attended fewer appointments than those who lived closer, had longer appointments and had their treatment planned ahead of time. The authors suggest that the improved compliance with treatment was most likely a result of these factors. In contrast, patients admitted for inpatient substance abuse treatment were 2.6 times more likely to attend when they lived within 10 kilometres of an outpatient's health service. [82]Longer time in drug treatment was a predictor of better client outcomes.[81] Of the 1,735 clients attending the clinic, those who travelled more than one mile from their treatment centre were 50% less likely to complete their treatment.

1.6.2. Distance and increased hospitalisation in diabetic children and young adolescents

The effect of distance from the patient's home to hospital of care was investigated in diabetic children and young adolescents living in Germany. [145] Increased length of stay occurred for patients with increasing distance from hospital after adjustment for age, duration of diabetes, metabolic control and hypoglycaemia. This study involved a third of all

German children who needed diabetic care with the authors concluding that "patient near" care was required to reduce hospitalisation for these children.

1.6.3. Distance and compliance to treatment for human immunodeficiency virus (HIV)

There has only been one study, to my knowledge, to investigate distance and patient compliance with treatment for people with the HIV. Distance measured as driving distance from the patient's home to the US Department of Defence hospitals did not influence treatment utilisation in these patients.[146] However, staff could only use defence force health services and treatment centres, available only in major cities. As patients did not have a choice of provider, people had no choice but to travel for treatment of their disease.

1.6.4. Distance to specialist care for a common acute disease – AMI

Two US studies have observed the impact of driving time and straight-line distance to treatment for people having an AMI. [147, 148] This study, using data from the US Census and the American Hospital Association annual survey, focused on access to specialist care. Driving distance measured from the population centres of each census area to the closest treatment centre for each survey participant had no impact on specialist care. However, most of the adult population (80%) lived within one hour of the facility where appropriate treatment was available. Therefore, access was not considered a barrier to health care.[147]

The second study, a US study of 218,247 Medicare beneficiaries older than 65 years, examined straight-line distance from the patient's home to the nearest specialist hospital (defined as providing cardiac catheterisation to 75 or more AMI patients annually) and survival to four years after an AMI. People living further away had a 6% higher mortality than those that lived close to a specialist centre as well as less access to treatment. Admission to a high volume hospital within the first 24 hours resulted in the best survival outcomes.[148]

Varying results in outcome in the non cancer setting depends on the type of presenting problem and the availability or otherwise of a service.[146] Distance from outpatient care, the type of service and compliance with treatment were important for patients with mental health, drug abuse, depression and eating disorders. While for patients with myocardial

infarction, the first study showed that most people lived within proximity of service, whereas the second showed poorer survival, due to less intensive treatment and reduced access to expert care.

1.7. Specialisation and centralisation of cancer services

Cancer patients do not generally have the same requirement for emergency medical attention as patients who have an AMI, or an acute mental health episode. The typical journey of a cancer patient varies depending on the type of presentation and the health system. In Australia, the typical process for a person who is concerned about symptoms is to consult their family GP for diagnostic work-up and referral. Other people are asymptomatic at diagnosis, with their cancer identified through screening or as an incidental finding during medical investigations for an unrelated health problem.

The usual pathway for both symptomatic and asymptomatic patients is for the GP to undertake some diagnostic tests and then refer to a specialist for further investigation and management. Some patients present and have their cancer diagnosed via an emergency department attendance and subsequent hospital admission. Clinical management for people with cancer usually involves one or more treatment modalities including surgery, chemotherapy and radiotherapy. Given the specialist nature of these therapies, and varying availability across the state, consideration of the centralisation and specialisation of cancer services has been the focus of health policy, both in Australia and internationally, and has stimulated research into the impact of distance to cancer treatment. This next section addresses these issues.

1.7.1. Specialisation and centralisation of services in the UK and US

To date, most studies of distance from a person's home to a cancer treatment centre focused on whether increased specialisation or centralisation of services led less treatment in people who live more remotely. In the UK, the policy framework for the commissioning of cancer services more commonly referred to as the Calman-Hine framework[149, 150]recommended the centralisation of cancer services. A number of studies of straight-line distance were undertaken to determine whether cancer patients had less treatment (surgery, radiotherapy or chemotherapy) when they lived further away from specialist cancer care.[84-86, 89, 151-158]

However, only a small number of studies have examined the impact of distance to cancer treatment on cancer survival. [85, 159]

Other studies have evaluated the effectiveness of the Calman-Hine framework to improve clinical service delivery, finding for breast[151, 152] and colorectal patients[151, 153]that there was an increase in adherence to standards and surgical specialisation after implementation with a trend towards an improvement in five year survival. [152] A comparison of surgeon workloads in breast and colorectal cancer (CRC) surgery in the NY Area for the period 1990-93, 1994-97 and 1998-2000 also found that there had been a major shift towards surgical specialisation.[151] The Calman-Hine framework replaced by the UK Cancer Plan in 2000[160] emphased improving patients experience of care, reducing inequalities improving quality of care and ultimately survival. Since then, a number of studies have measured differences between National Health Service (NHS) trusts including the proportion undergoing surgery,[161] differences in cancer survival,[162-165] differences due to specialisation[151] and most recently, variation in 30 mortality rates.[166] In all cases considerable variation exists between NHS trusts.

Most US studies have focused on the centralisation of cancer surgery and consolidation of services into high volume hospitals. These studies show that with increasing surgical volume, the proportion undergoing surgery had better short and long term survival. [29, 34, 167-173, 174] One study specifically examined the impact of centralisation over a 10 year period and found that as travel distance increased so did hospital volume. Patients who had surgical procedures for pancreatic, oesophageal, colon and rectal cancers moved from surgery in low volume hospitals to high volume hospitals with an increase in travel burden occurring for patients who lived more remotely. Importantly though, in-hospital mortality declined in those receiving cancer procedures in high volume centres (with the exception of rectal cancer), a desirable outcome regardless of the travel burden.[172]

1.7.2. Specialisation and centralisation of services in Australia

In Australia, the National Strategic Framework for Rural and Remote Health a collaboration between the Commonwealth and State Government endorsed by the Standing Council on Health in 2011,[175] has as its first goal “to improve access to appropriate and comprehensive

health care." Issues identified as priorities for people living in rural areas include improving access, developing appropriate models of care, having a sustainable workforce and the development of collaborative partnerships.[175, 176]

The goal of cancer care is to provide equitable access to improve cancer care.- Rural patients need to have increased access to diagnostic testing, coordinated care, multidisciplinary team review, patient accommodation and appropriate cancer oncology and radiotherapy services locally. [177] In the 2009/2010 Australian Federal budget, $1.3 billion was dedicated to building two integrated cancer centres (Lifehouse at Royal Prince Alfred (RPA) and Parkville in Melbourne) with $560 million [178] [177] dedicated to enhance or build 10 regional cancer centres. The new or enhanced services ranged from radiotherapy bunkers, linear accelerators, Computer Axial Tomography (CAT), MRI and Positron Emission Tomography (PET) scanners. Additional patient accommodation was also funded for three NSW regional cancer centres.[179] These centres will mostly provide diagnostic services as well as chemotherapy and radiotherapy.

However, most specialist surgical care in NSW and in other Australian states will be located in major cities. Furthermore, plans recommend consolidation of specialist surgical services.[180, 181] Therefore, travelling to cancer-specific specialist surgical care for people who live more remotely will continue to be required even when all regional centres are built and operational.

To assist patients and GPs in rural and remote locations, a number of programs and projects have been introduced. For example, Cancer Network (CanNET)' was a large demonstration program funded by Cancer Australia to develop strategies to link regional and metropolitan cancer services. Seven cancer service networks were set up in 2009. The purpose of these networks was to build pilot projects that managed the diagnosis and treatment of rural patients through clinical networks. Each state set up a web based directory of cancer services and overall 1,196 health care providers underwent education about issues facing rural patients. [182] In addition, a comprehensive literature review was undertaken on the effectiveness of "managed clinical networks".[176]

In NSW, the web based service directory 'Canrefer 'was developed by the Cancer Institute NSW as part of the CanNet initiative.[101] This directory of NSW public specialist hospitals referred to in chapters 5 -8 of this thesis identified specialist surgical services where cardiothoracic surgeons and gynaecological oncologists operate.

1.8. The impact of distance to treatment in cancer patients

Outlined below are all known UK, US and Australian registry studies that have measured straight-line distance to cancer services. These studies highlight issues associated with accessing cancer treatment services for people who live more remotely.

1.8.1. Increasing distance from radiotherapy services and the likelihood of best practice surgery for breast cancer

Historically, the majority of cancer registry studies that have examined distance to treatment have measured distance to radiotherapy centres. A large number of US Surveillance Epidemiology and End Results (SEER) cancer registry studies demonstrate that with increasing straight-line distance from radiotherapy centres, women diagnosed with breast cancer were more likely to have a mastectomy instead of the recommended breast conserving surgery and post-operative radiotherapy.[96, 98, 183-187]

Additional barriers that reduce the likelihood of breast conserving surgery and follow up radiotherapy are the weather and reliance on public transport. Travelling in winter was found to be an additional barrier for US patients who lived >20 miles from a radiation treatment facility (P = 0.002).[100] In contrast, in northern England the likelihood of breast conserving surgery in women with breast cancer (n=6,014)[158] was not significantly different with increasing distance or length of a car journey, after adjusting for age, deprivation and hospital type. However, women with breast cancer who lived in areas without a regular bus service were less likely to undergo radiotherapy after breast conserving surgery. [158]

1.8.2. Distance to cancer treatment and the likelihood of treatment

The majority of studies on distance to cancer treatment services occurred in the UK. Distance measured from the patient's home to a hospital of treatment, or cancer centre or GP surgery and the likelihood of receiving treatment (surgery, chemotherapy, radiotherapy) was examined.[84-86, 156-158, 188] Jones[86] also estimated travel time and travel distance from the

patient's postcode to the nearest hospital offering cancer treatment for people diagnosed with breast, colon, rectum, lung, ovary and prostate cancer. This study reported that regardless of cancer site, all patients were significantly less likely to receive radiotherapy with increasing distance to a radiotherapy centre. Lung cancer patients were also less likely to have surgery with increasing distance. Rectal and lung cancer patients were also less likely to receive chemotherapy. Ovarian cancer patients who lived in the most remote quartile were more likely to undergo surgery if they were younger than 70 years whereas, men living in the same quartile, were less likely to undergo surgery when they were aged 70 years or older. It is possible that some degree of patient selection, due to clinical judgement or patient preference was occurring because of distance to cancer treatment.

A later study found that among people living in northern England with non small cell lung cancer (NSCLC), those who lived further from a specialist centre were less likely to undergo surgery after adjustment for age, sex socioeconomic status and another treatment (chemotherapy and radiotherapy). Access to surgery further reduced with increasing deprivation.[157] In addition, patients whose closest NHS facility was a district hospital (their general public hospital) were significantly less likely to undergo thoracic surgery than those whose closest hospital was a cancer centre, regardless of whether a medical oncology facility was available, after adjustment for age and sex. Patients in the most distant quartile and those most socially deprived were least likely to receive treatment. Those living in the most deprived areas were least likely to have a histological diagnosis, active treatment and thoracic surgery for NSCLC.

In contrast, a US study of people diagnosed with NSCLC who lived further from specialist cancer centres were more likely to have surgery, but much less likely to receive radiotherapy or chemotherapy.[189] Surgery, the authors suggest was provided as an alternative to radiotherapy for patients who lived further from a cancer centre because radiotherapy was less accessible and would have required frequent visits. [189] A more recent US study of NSCLC patients reported similar results to those reported in the UK, with 61% of patients attending a National Cancer Institute (NCI) centre for surgery when they lived less than 30 minutes away. The likelihood of attendance decreased with increasing distance.[190] Other

factors predictive of attendance at an NCI hospital included treatment by a specialist six months prior to diagnosis and urban residence.

1.8.3. Distance to cancer treatment and survival

The relationship between distance from treatment and cancer survival is complex with the impact of distance on survival, mediated by factors like stage and varying by type of cancer. Early Scottish [191-193] and UK studies[84-86, 194]found that for the majority of cancer sites examined, the hazard of death increased with increasing straight-line distance to a cancer centre. Campbell, [192] in Scotland, used straight-line distance to treatment and found the hazard of death for women with ovarian cancer was greater with increasing distance to a cancer centre. In contrast, Jones, [85] in a study in northern UK, examined a number of accessibility measures, including distance and travel time to a cancer centre, but observed no association of distance with late stage or poorer survival for women diagnosed with ovarian cancer[86]. He did find, though, that being treated first at a cancer centre rather than a general hospital resulted in better survival.

In a further Scottish study of people diagnosed with lung cancer, a higher hazard of death was reported for those who lived 6–23 kilometres from a cancer centre compared with those who lived within 5 km of their home after adjusting for age, sex and settlement size.[191]

In contrast, rural USA non small lung cancer patients living further away from a specialist cancer centre were significantly more likely to undergo surgery but much less likely to receive radiotherapy or chemotherapy. Patients were more likely to be treated with surgery if they had private medical insurance (1.52; 1.03 to 2.26). Among patients who did not have surgery, those with private insurance were more likely to receive another form of anticancer therapy-either radiation or chemotherapy (1.57; 1.18 to 2.09). Residing farther from a cancer treatment centre was associated with a greater chance of having surgery. **[195]**

Most of the early studies, did not measure cancer stage, and could only adjust for a handful of factors usually those routinely captured in the cancer registry. In addition, most studies

used all cause survival rather than cause specific survival because they did not record the cause of death and therefore assumed that patients died of their cancer.

1.8.4. Distance to cancer treatment in an Australian setting

Four WA studies used linked cancer registry and hospital data and evaluated the impact of distance from and access to cancer surgery for breast, lung, colorectal and prostate cancers. After adjustment for ARIA and type of hospital, the proportion undergoing surgery was found to vary by cancer type.[42, 46, 59, 196]Men diagnosed with prostate cancer were more likely to undergo a radical prostatectomy when admitted to a rural hospital or a public hospital.[42] Colorectal patients,[46] breast cancer patients[47] and lung cancer patients[22, 59] had less surgery when admitted to rural or public hospitals and had more surgery when admitted to private hospitals.

The Queensland Cancer Registry (also geocoded) has examined straight-line distance to radiotherapy for people with lung, breast and CRC. Waiting times for lung cancer patients were found not to vary due to distance to radiotherapy after adjustment for sex, age, therapy intent, cancer histology and stage, and performance status based on Eastern Cooperative Oncology Group (ECOG) score.[197] More recently, straight-line distance to the closest radiotherapy facility and travel time were examined for people diagnosed with breast and CRC. Poorer survival occurred with rectal cancer but not colon cancer as a result of increasing distance. A six per cent increase in mortality occurred for every 100 km increase in distance to the closest radiotherapy centre. [16, 88 78]

One of the earliest studies to consider distance from treatment, the hospital that the treatment was received in and whether surgery was undertaken was a Queensland Registry study of breast cancer by Thompson et al.[19] This study found the likelihood of women having a mastectomy was higher in rural areas, in those treated in public hospitals, and for women who had the comorbidities of anaemia or heart failure. In contrast, appropriate treatment (breast conserving therapy) was more likely for women when they were treated in private hospitals or hospitals with high surgical caseloads.

A subsequent Queensland study examined actual road travel distances and travel time to the closest radiotherapy facility and cancer survival (five year cause specific) for 6,848 rectal cancer patients. [87] Travel distances and times were calculated using geocoded coordinates from the patients address to the nearest radiotherapy facility. Relative to patients living within 50 kilometres and adjusting for age, sex and stage at diagnosis, patients living 100-200, 200 -399 and 400 + kilometres from a radiotherapy facility were more 16%, 30% and 25% more likely to die from any cause.[87] There were a number of limitations to this last study. Whether patients actually received radiotherapy was unknown, 25% of the sample had unknown stage and while cause specific survival was used, the accuracy of the cause of death had not been evaluated.

1.8.5. Patient assisted travel schemes in Australia

Distance can be considered an impediment to accessing health care for many Australians. Health transport may be required at different points within the health system. [198] In 2011, Australia had the highest passenger car usages per 1000 population (558 per 1000), compared to any other developed country (UK 453, Canada 420 and US 403 per 1000 population) [199] reflecting strong reliance on the car for transport.

Each state in Australia has Patient Assisted Travel Schemes (PATS).[200] These schemes provide travel assistance to people living in rural and remote locations to assist them to access health care. The current patient transport schemes require that patients need to fund the upfront costs of travel and accommodation, with reimbursement at a later date. There are inconsistencies across jurisdictions in how much is provided. Out of pocket expenses and lack of support for care givers have been documented as barriers to accessing health care in rural and remote residents.[201] One suggestion to improve access is for regional health authorities to issue vouchers for patients.[201]

Historically, in Australia, the Royal Flying Doctor Service (RFDS) [202] has provided 24 hour emergency service to patients to attend GPs and other specialist services. However, the RFDS is a not for profit organisation that receives some funding from the Australian Government, but mostly relies on fund raising and donations. Australia wide, 63 planes

operate from 21 bases that on average provide a total of 290,000 patient transportations in a year.[202]

In NSW, patients who have a car and travel over 100 kilometres are partly subsidised and can apply for Isolated Patient Transport and Accommodation Scheme (IPTAAS) funding to cover transport and accommodation costs. This policy, developed by the NSW Ministry of Health, does not include the cost of meals and incidental expenses (road tolls, parking, booking fees) which are not reimbursable. Patients who are pensioners and health care cardholders are not required to contribute. The specific purpose of IPTAAS is to assist patients to travel to specialist medical appointments.[203]In this thesis, the potential impact of IPTAAS funding is evaluated for people diagnosed with NSCLC who live 100km or more from the nearest accessible specialist hospital (NASH). The likelihood of advanced or unknown stage, no surgery and predictors of cancer survival are discussed in chapters 7, 8 and 9.

As the work in this thesis focuses on three types of cancer, namely bladder, lung and ovarian cancer, a rationale for selecting these cancer sites is provided in the next section.

1.9. Why bladder, ovarian and lung cancer?

Bladder, ovarian and lung cancer were selected for analysis in this thesis as each has surgical resection as - a component of treatment but each represents a different surgical context in terms of service delivery. Bladder cancer surgery is performed by urologists throughout NSW and is not a sub-specialty procedure. Furthermore, there are no national clinical practice guidelines, such as those endorsed by the National Health and Medical Research Council (NHMRC), to promote evidence-based best practice or to guide referral pathways. In contrast, ovarian cancer surgery can be performed by general gynaecologists or specialist gynaecological oncologists and there are NHMRC clinical practice guidelines [204] which describe recommended surgical care, including management by a specialist gynaecological oncologist. [205, 206] Lung cancer resection is peformed in only a few centres, but like ovarian cancer, national guidelines recommend treatment by sub-specialist thoracic surgeons. [202, 203]

Currently, little is known about the surgical management of bladder cancer patients in Australia. An earlier NSW study shows that survival is poorer in women, and older age at

diagnosis is a characteristic of these patients with 40 per cent of women who are diagnosed with bladder cancer aged 80 years or older. [207] Distance to specialist care may account for this survival difference.

An Australian patterns of care study has investigated pathways to diagnosis in women who are diagnosed with ovarian cancer. [57, 208] However, to our knowledge, surgery, hospital of treatment and the impact of distance to a specialist hospital have not been investigated.

For lung cancer, if detected at a localised stage, surgical intervention is potentially curative. While there have been a number of NSW patterns of care studies, [53-56, 209] type of surgery, hospital of treatment and distance to the nearest accessible hospital have not been examined.

There are a small number of UK and US studies that have considered distance to specialist care and cancer survival for bladder,[210] ovary and lung. [85, 86] However, these studies have lacked important covariates, like stage at diagnosis, comorbidity and have used all cause survival because they did not have cause of death information.

1.10. Best practice clinical guidelines

1.10.1. Best practice surgery for bladder cancer

Bladder cancer represents 2 per cent of all new cancer cases diagnosed in Australia and NSW.[7, 211] Unlike most other cancers survival from bladder cancer is consistently higher in men.[115, 212, 213] Women diagnosed with bladder cancer in NSW have a 13% higher likelihood of death than men, after adjusting for age, stage, histology, socioeconomic status and period of diagnosis.[207]

Clinical practice guidelines developed by the National Comprehensive Cancer Network (NCCN) [214] in the US and the National Institute of Clinical Excellence (NICE) in the UK [215]recommend that people diagnosed with bladder cancer be referred to a urologist at centres that undertake more than 50 cases per annum.[215] In addition, there is consistent evidence that survival is poorer in bladder cancer patients when cystectomy occurs more than 90 days after diagnosis. [216-218]

The only Australian guidelines are consensus guidelines developed by the Australian & New Zealand Faculty of Radiation Oncology Genito-Urinary Group who recommend radiotherapy and adjuvant chemotherapy as the standard treatment option for muscle invasive bladder cancer.[219] Little is known about clinical management particularly surgical management of bladder cancer in Australia. One paper provided an overview of the current recommended treatment[220] but there are no studies that have examined surgical management of bladder cancer. The Royal Australian College of GPs recommend that patients presenting with haematuria, the most common symptom at presentation, be referred to a urologist and that patients with bladder cancer that is invading muscle are best treated with cystectomy. [220] According to the Urological Society of Australia and New Zealand, the majority of urologists are located in large rural and Sydney hospitals. [220]

1.10.2. Best practice surgery for ovarian cancer

Ovarian cancer is a poor prognosis cancer that is characterised by vague symptoms and late stage at presentation. In 2008, ovarian cancer was the tenth most common cancer in females in NSW and the sixth most common cause of female cancer deaths.[211] Internationally, NSW has good ovarian cancer survival compared to other countries.[126, 221]

Survival from ovarian cancer in NSW women has previously been found to be most influenced by extent of cancer at diagnosis and the cell type of the cancer.[222] Clinical practice guidelines recommend referral of women suspected of or who have symptoms of epithelial ovarian cancer to a gynaecological oncologist and treatment in a gynaecological oncology service (GOS) hospital. [204, 223-227] NCCN guidelines[227] do not specifically nominate such a service but recommend surgical cytoreduction to 1cm or less. Cytoreductive surgery (resection of macroscopic metastatic disease) is the accepted standard of care for women with advanced ovarian cancer. [228, 229]

1.10.3. Best practice surgery for lung cancer

In 2008, lung cancer was the fourth most common cancer and the most common cancer causing death responsible for 20% of all Australian and NSW cancer deaths.[7, 211] Lung cancer is comprised of two main cell types, small cell lung cancer (SCLC) and NSCLC.[230]

Patients with small cell lung cancer and those with distant metastases have the poorest survival.[124, 125]

Internationally, NSW has good lung cancer survival with patients in the UK and Denmark having lower survival than elsewhere, partly because of a more adverse stage distribution in these countries.[125, 221] For NSCLC, the proportion with metastatic disease at diagnosis ranged from 46.8% in Sweden, 47.5% in Australia to 61.2% in Denmark.[125] However, patients presenting with localised NSCLC are considered potentially curable if treated surgically.[206, 231] Therefore, rapid diagnosis and appropriate staging are essential if patients are to obtain the best outcomes.

Surgical resection of lung cancer with curative intent was introduced in 1933.[232] A review in 1994 reported that no randomised control trials had assessed the effectiveness of surgery in the treatment of localised non small cell lung cancer because of ethical concerns.[233] In 2010, a Cochrane review of surgery for local NSCLC, examined the results of 13 clinical trials of surgery and 2,290 patients and concluded that there was no compelling evidence that lung cancer surgery improved survival compared with other types of therapy such as radiotherapy and chemotherapy although, one trial found that overall survival was superior in patients with stage I to III NSCLC who underwent resection and complete mediastinal lymph node removal. Another trial found that the recurrence rate was higher when patients had a segmental resection as opposed to a lobectomy. None of the other trials demonstrated a significant improvement in survival compared with non surgical therapy.[234]

Nevertheless, US[231], UK[235, 236] and Australian guidelines[206] all recommend surgery for localised NSCLC. In 2005, the Australian NHMRC guidelines recommended surgical resection for patients with early stage NSCLC, with lobectomy the preferred procedure.[206] In 2007, the American College of Chest Physicians produced evidence-based clinical practice guidelines [237] recommending that surgical resection should be the treatment of choice for stage I and stage II NSCLC, with adjuvant chemotherapy required for stage II patients. Radiotherapy is recommended for patients with inoperable NSCLC or for patients who refuse surgery. [237] According to NICE guidelines in the UK, [169, 175] patients not considered suitable for a lobectomy because of comorbid disease or inadequate lung function are recommended to have limited resection or radical radiotherapy. Before patients undergo

surgery, lymph node sampling, Endobronchial Ultrasound (EBUS) and biopsy to determine stage is recommended.[226, 235]

US guidelines recommend evaluation by a thoracic surgical oncologist for patients with stage I and II lung cancer regardless of whether non surgical options are used. [237] More recently, two studies[167, 238] compared outcomes of lobectomy between cardiothoracic and general surgeons, finding better adherence to guidelines, lower post-operative morbidity and better long term survival among patients treated by cardiothoracic surgeons.

While none of the lung cancer guidelines specify the type of hospital patients should be treated in, appropriate staging of lung cancer depends on the availability of equipment including imaging CT and PET scans, needle biopsies, and surgical staging (mediastinoscopy and video assisted thoracoscopic surgery (VATS)) [239] and skilled staff to perform these procedures.

1.11. Mediating factor–stage at diagnosis

1.11.1. Advanced stage at diagnosis

Determining cancer stage at diagnosis is important to ensure that patients get stage appropriate treatment. Surgery would be required for early stage solid tumours whereas at late stage, chemotherapy or radiotherapy may be the most appropriate treatment option. In addition, if diagnosed at late stage, referral to palliative care and appropriate pain management is recommended.[206, 231, 235]

Stage at presentation and receipt of treatment are two factors known to influence survival. Scottish patients were found to have a high chance of disseminated disease at diagnosis with increasing distance from a cancer centre.[193] Patients were less likely to have histologically verified tumours, receive chemotherapy or undergo surgery with increasing time to a thoracic surgical hospital.[33, 85, 86, 157] UK patients living in the most deprived quintile were more likely to be diagnosed with stage four CRCs, less likely to receive chemotherapy and colon patients were less likely to receive surgery. [156] Distance to treatment was not significant for either rectal or colon cancer. The most likely reason for this is that the variance attributed to distance was captured through other factors like late stage, lower

likelihood of chemotherapy and no surgery.[156] One of the limitations of this study is that only 65% of the sample had stage information.

In a recent US study, travel burden using driving time or driving distance was found not to be significantly associated with later stage at diagnosis for lung cancer and CRC but was for breast cancer. However, a major limitation of this study was that 11% of information was missing, which on investigation was found to be mainly lung cancer patients.[99] Scoggins et al. [99] also compared driving time and driving distance and found that both predicted late stage at diagnosis for breast cancer patients and longer time to treatment for CRC patients. For lung cancer patients, male gender, older age and severe comorbidity were associated with an increased likelihood of advanced stage. Higher education, considered a proxy for high socioeconomic status was associated with a greater likelihood of diagnosis at a localised stage and less than 28 days between referral and admission.[240, 241]

1.11.2. Unstaged or unknown stage at diagnosis

Lack of staging information can indicate suboptimal investigation or poor cancer registration practices. Most studies that have investigated factors predictive of unknown stage have done so to investigate cancer registration practices. [235] [236] Gurney et al.[242] suggested a number of reasons why a registry did not stage a cancer. These were; a cancer type may be difficult to stage or investigations may have been limited or that some services or providers did not provide data on staging to the registry. Males compared with females experienced significantly lower levels of unstaged cancers of the liver, pancreas, oesophagus, and stomach, but significantly higher levels of unstaged lung, bronchial and thyroid cancer. [243] Other factors predictive of unknown stage include older age [244] those with any comorbidity[242, 243] and non married patients. [242, 243]

There is only one study to have investigated distance to treatment and the likelihood of unknown stage at diagnosis. [245] Silverstein et al., found that lung cancer patients were more likely to be unstaged if they were older, not living with a spouse and lived in rural areas with fewer primary care physicians. Consequently, including unknown stage, rather than excluding it from our analysis, as many studies do, [99,240,241] and examining factors associated

with its likelihood will provide valuable information. These issues are discussed further in Chapters 5 and 7.

1.12. Mediating factor - likelihood of appropriate surgery

The likelihood of appropriate surgery for cancers where presenting symptoms are often vague and at a late stage (as is the case for lung and ovarian cancer) increased if treatment occurs in specialist centres. A number of studies have demonstrated a relationship between specialist centres and the likelihood of cancer surgery.[27, 174, 246]

1.12.1. Bladder cancer and surgery

Studies that have examined the relationship between bladder cancer surgery and hospital type have provided mixed results and there is currently debate about whether radical cystectomy procedures should be centralised.[247] A metanalysis of post-operative mortality after cystectomy found that it was inversely associated with high volume providers. [247] A SEER study examined 4,465 bladder cancer patients who underwent cystectomy[28]and found that patients treated in low volume hospitals were 48% more likely to die in the post-operative period. High volume hospitals had higher rates of preoperative testing and higher use of continent diversion than low volume hospitals.

1.12.2. Lung cancer and surgery

The effect of volume on mortality depends on the procedure with mortality varying by as much as 10 per cent in patients undergoing a lobectomy. The mortality risk was much higher for patients who were older. Canada, like NSW, has a single payment system where equal access for all is the underlying principle. Evaluation of the proportion of patients undergoing lung cancer surgery occurred after services at 43 hospitals moved to 13 specialist centres. This study found that the number of lung cancer resections increased and patients had lower 30-day mortality after a pneumonectomy and lobectomy.[29] Receiving treatment in an institution with an approved residency program was found to be positively associated with receiving recommended guideline based treatment[248] after adjusting for age, stage, comorbidity and ethnicity. People with lung cancer were found to have better post-operative mortality[167] and 6% higher five year survival when treated in a high volume hospital.[249]

1.12.3. Ovarian cancer and surgery

Improved survival has been demonstrated in women with ovarian cancer who have cytoreductive surgery with a positive 6.3% increase in survival for every 10% increase in the proportion of patients undergoing cytoreductive surgery.[250] Furthermore, a US study of 31,897 women with stage III and IV ovarian cancer [251] found that women had a lower likelihood of death if they were treated in high volume centres HR 0.76 ($p<0.001$) compared to low volume centres. Patient characteristics associated with the likelihood of receiving surgery in high volume hospitals was evaluated using a Californian patient discharge database of 719,608 patients. Referral to the high volume hospital was less likely to occur for non whites, Medicaid and underinsured ovarian cancer patients. A similar pattern occurred for the other nine conditions examined by Liu.[35, 252]

In a large US registry (SEER) study, women treated at a facility "with an approved residency training program" had better survival after adjustment for age, stage, comorbidity and ethnicity. The authors suggested that appropriate surgical staging was the most likely explanation.[248] Similarly, ovarian cancer patients operated on at a teaching hospital in Norway were found to have significantly lower risks of death compared to those treated at other hospitals after adjustment for surgery and other independent predictors of survival.[253]

Furthermore, patients referred to thoracic surgical centres were 51% (OR 1.51 95%CI 1.16-1.97) more likely to have surgery than those referred to non surgical centres after adjusting for age, sex, performance status, comorbidity and stage.[33]

A study of 45,929 ovarian cancer patients with stage III and IV advanced epithelial cancer concluded that a surgical volume of greater than 21 cases per year was associated with a higher likelihood of patients receiving standard treatment and significantly predictive of improved overall survival.[254] A more recent review of ovarian cancer surgery concluded that increasing age, performance status, surgical complexity and nutritional status all affected surgical risk.[255]

1.13. Patient, tumour and treatment factors that impact on cancer survival

Important patient, tumour and treatment factors need to be considered as potential confounders in the analyses of associations between distance from specialist services and cancer survival. Presented below are individual patient, tumour and treatment factors known independently to influence cancer survival that need to be analysed in statistical modelling. The most common method used to model the hazard of death is Cox proportional hazards. Studies that use this method associated with bladder, ovarian and lung cancer are discussed.

1.14. Patient factors and cancer survival

1.14.1. Sex

Cancer survival is generally poorer in men than it is for women for most cancer sites largely because men tend to present at a later stage than women.[11, 143, 207, 211, 221, 256] Bladder cancer survival is consistently poorer in women and the reason for this survival difference is largely unexplained. [207, 257 213 258] A small number of studies have suggested potential reasons including, anatomical differences (women have a thinner detractor muscle potentially increasing invasion of the urethra);[259] longer delay in women; more advanced disease at diagnosis[260-263] and a higher proportion of muscle invasive transitional cell carcinoma than men.[264]

In a recent analysis of a UK lung cancer audit of 34,513 NSCLC patients, males were found to have a greater hazard of death after adjusting for age, socioeconomic status, stage, comorbidity, performance status, chemotherapy, surgery, radiotherapy, clinical trial participation and hospital of treatment.[33, 265]

In contrast, while Australian based lung cancer patterns of care have not examined survival by sex[53-56] females were however, found to be less likely to have treatment than males after adjustment for other factors. Therefore, sex is an important factor to consider as a potential confounder in analyses of the impact of distance on patient outcomes.

1.14.2. Age

NSW, [143] Australian[11] and international studies[124, 256, 266] of five year cancer survival overall and for individual cancer sites show that a patient's cancer survival reduces with increasing age at diagnosis. Five year survival from all cancer in NSW for the latest available period was 86% for patients aged less than 40 and decreased to 43% for patients aged 80 years and older.[143] However, population registry studies of survival take into account a limited number of factors. For example, sex, age, period of diagnosis and sometimes stage, but they cannot take into account other factors.[11]

Age alone can be a direct factor that influences survival or it can interact or mediate another factor, indirectly influencing cancer survival. Older patients may have one or more comorbid illnesses[267] or be less extensively investigated. Both factors influence treatment options.

In a recent SEER study of 28,977 stage III and IV NSCLC patients, younger age at diagnosis predicted a greater likelihood of referral to specialists, which predicted a higher likelihood of adherence to guideline based therapies.[268] Janda et al[269] predicted treatment outcomes and other risk factors for early death of elderly women with advanced ovarian cancer. They found that a woman's age, stage at presentation, presence of comorbidities, and oncology treatment facility was independently associated with overall survival at 12 months from diagnosis. Patients who received both surgery and chemotherapy showed significantly improved survival as compared to patients who received only surgery or chemotherapy. For patients 80 years and over who had surgery first, perioperative mortality was significantly greater in the high-risk group compared to patients within the moderate and low-risk group.

1.14.3. Ethnicity

Most studies of ethnicity or race have been undertaken in the US using SEER data.[123, 212, 270]In a SEER study [271] of 17,739 patients (stage one and stage two lung cancers) who were recommended for surgical therapy (mean age, 75 years; 89% white, 6% black), black patients less frequently underwent resection compared with white patients (69% vs 83%, respectively; P <.001). After adjustment, black race was associated with lower odds of receiving surgical therapy (odds ratio = 0.43; 99% CI, 0.36-0.52).

The US Department of Veterans affairs extended data from clinical trials and collected additional socioeconomic and genetic data for patients with lung and colon cancer.[272] They found that black patients had significantly lower tumour resection rates, increased mediastinal involvement and advanced stage at diagnosis compared to whites. However, once stage was taken into account there was no significant difference in survival.[273, 274]

Unadjusted 5-year survival rates were lower for black patients compared with white patients (36% vs 42%, respectively; P <.0001).Mulligan et al[275] found that there were no differences in survival between black and white patients when access to medical care is universal. Male sex, incomplete resection, and advanced stage were significant predictors of poor lung cancer survival. Predictors of good survival were bronchoalveolar carcinoma histology and smoking cessation of seven years or more. The international CONCORD study of cancer survival [256] found survival was substantially lower in black patients with breast, colorectal and prostate cancer in 16 US states and six metropolitan areas. Depending on the cancer site, when all ethnicities were combined, relative survival ranged from 2% lower for breast cancer and 5% lower for prostate cancer.

1.14.4. Socioeconomic status

Differences in cancer survival by socioeconomic status (SES) have been reported in many countries, with poorer survival found in people living in deprived areas.[11, 276-289] The Index of Relative Disadvantage is used in most population-based Australian studies as the measure of SES. It is a composite variable derived from census indices of education and occupation.[290]

Five year survival in NSW declines with each SES grouping for cancer overall (all types except non-melanoma skin cancer), prostate, breast, cervical, lung mesothelioma, myeloma, non-Hodgkin's lymphoma and cancer of unknown primary.[11]

In NSW, the most comprehensive study of survival and SES status was undertaken by Yu.[68] Five year relative survival of 13 cancer types diagnosed between 1992 and 2000 were compared by SES, before and after adjusting for stage at diagnosis. Patients in the lowest SES areas had a 10 to 20% higher risk of death than those in the highest SES areas. Significantly, worse survival occurred in lower SES areas for cancers of the stomach, liver, lung and breast. [68]

Greenwald et al[291] found that SES grouping and whether or not surgery was received most explained differences in the hazard of death. Patients in the top 10 per cent income group were 45% more likely to receive surgical treatment and 102% more likely to attain 5-year survival than those in the lowest 10 per cent group.

In a recent review and metanalyses of SES inequalities and lung cancer treatment, 46 papers were reviewed and 23 met the criteria for inclusion. [292] Patients in lower SES groups had less surgery and chemotherapy but not radiotherapy. The reduced likelihood of surgery due to SES remained are adjusting for stage. Furthermore, the reduced likelihood of surgery due to low SES occurred in both universal and non universal health systems. SES is a proxy for many relationships. For example, patients living in lower SES tend to have higher rates of smoking, more advanced stage at diagnosis and less treatment.

1.14.5. Comorbidity

Coexisting conditions or comorbidities are important mediators in the distance survival relationship. [210]Cancer and comorbidities are more prevalent in the elderly patients.[293] Comorbidity may also preclude a patient from undergoing surgery, or if they do undergo surgery, impact on outcome[210, 294, 295] A systematic review of indices of comorbidity identified 13 different methods.[296] Compared to other indices, the Charlson index was found to be the most extensively studied index for predicting mortality.

Most studies of linked cancer registry and hospital data in NSW use the Charlson index as the measure of comorbidity. Examination of the quality of NSW comorbidity data for lung and CRC patients occurred by comparing linked administrative data and survey data for same patients. The comorbidity diabetes had the highest level of agreement between the two data sets of the 17 comorbid conditions while chronic obstructive pulmonary disease (COPD) was found to have the lowest level of agreement.[63, 64]

A later study also compared the quality of comorbidity information in two separate sources for NSW prostate cancer patients and found that diabetes also had the highest level of agreement while COPD and heart disease the lowest. Agreement between the two data sets increased, however, by 14-16% for each of the 17 conditions recorded in the Charlson index

when all hospitalisations for the study period were included.[64] In this thesis comorbidity is measured using the Charlson index and is discussed further in Chapters 4 to 8.

1.15. Tumour related factors and cancer survival

1.15.1. Histological subtype of cancer

Cancer is a heterogeneous disease made of many cell types. Cancer can be classified in two ways; by the tissue in which the cancer originates (histological type) and by the primary site.[297] Cancer survival varies by histological type[140]. This section focuses on the histological types of cancer for people diagnosed with primary bladder, ovary and lung cancer. Cancer registries determine the cell type of cancer or morphology code from pathology reports notified to the registry. [297] Morphology codes are grouped into histological types using the International Classification of Diseases for Oncology.[135, 298] Regular updates are specified in Cancer Incidence in Five Continents.[135] Therefore, comparison of histological types of cancer captured in registries should be consistent and able to be compared.

Bladder cancer has two main histological groups. [212] The most common type of bladder cancer arising in the lining is transitional or urothelial carcinoma and constitutes more than 90% of bladder cancer cases. Papillary transitional cell urothelial carcinoma (70%) has the appearance of finger like fronds and does not invade the muscle wall of the bladder. Papillary transitional has a five year survival rate of 91.5% and non papillary has once of 61.2%.[212] The most common symptom for papillary and non papillary transitional cell carcinoma is microscopic haematuria. [299]

Estimates of relative survival vary widely for bladder cancer. US estimates are always higher than Australian estimates because US registries include in situ cases when reporting invasive bladder cancer. Five year relative survival estimates for papillary transitional carcinoma were 65 per cent in Victorian males and females and 66 per cent in NSW females. Whereas, survival from transitional cell carcinoma was 43 per cent in Victorian males and females and 43 per cent for NSW females. NSW males had higher five year survival estimates of 49.3 per cent.[140]

Lung cancer is comprised of two main histological groups small cell and NSCLC. [230] Within the NSCLC group, the most common histological type is squamous cell lung carcinoma. [230] The second most common type of NSCLC is adenocarcinoma (found on the periphery of the lung) which has been increasing in recent years surpassing squamous carcinoma as the most common histologic subtype in a number of countries. Adenocarcinoma is more often asymptomatic relative to other forms of NSCLC. The third most common cell type is large cell carcinoma which accounts for approximately 9% of all lung cancers. Large cell is a poorly differentiated cancer that has the lowest survival. In order, five year survival for SEER NSCLC ranged from 20% for adenocarcinoma, 17% for squamous and 12% for large cell. [230] Similar survival differences as those reported by SEER registries were observed by histological subtype in Australian lung cancer patients.[300]

Ovarian cancer is comprised of a number of different histological types with serous adenocarcinoma (arises directly from the ovarian surface epithelium) regarded as the most common and relatively homogeneous group [301] with five year survival estimates of 40% in NSW[140] and Australia.[302] Survival for other ovarian tumours reflect the cell type. Mucinous, endometriod and clear cell carcinomas have higher five year survival estimates than serous tumours. Survival estimates in NSW and Australia was 58%, 77% and 65% respectively. [140] [302] Unspecified carcinoma of the ovary has the poorest survival at 14%. [140] [302]

1.16. Treatment factors and cancer survival

1.16.1. Emergency department presentation

Lower SES, older age at diagnosis, and female sex have been identified as predictors of emergency department admissions for lung cancer.[188, 303, 304] Type of hospital admission (emergency versus elective) was examined in UK breast, lung and CRC patients admitted to hospital between 1999 and 2006. Fifty-two per cent of all lung cancer patients were admitted as emergency patients. Patients admitted to hospital through the emergency department are less likely to have surgery for their lung cancer, regardless of their age at diagnosis (adjusted odd's ratio for lung cancer surgery of 0.52 (0.46 to 0.59) in patients aged 80-89 compared to those aged 50-59. Breast and colorectal patients admitted via the emergency department were also less likely to undergo resection.[304]

About half of all Northern and Yorkshre lung cancer patients admitted through the emergency department had only a chest x-ray and no definitive diagnosis of lung cancer. These patients were also less likely to be histologically confirmed, receive specialist care or have private health insurance.[188] In a more recent study of breast, lung and prostate cancers in the east of England for the period 2006-2008, advanced stage and older age were found to most predict an emergency presentation, followed by comorbidity and female sex. After adjusting for age, stage and comorbidity, an emergency department presentation remained predictive of short-term mortality (defined as death within a month of diagnosis).[305]

Two WA linkage studies have investigated emergency department presentations. In the first study, 20% of all lung cancer patients had their cancer detected at an emergency department admission.[60] The second study found that the proportion of women diagnosed with ovarian cancer at an emergency department presentation decreased from 26.5% in 1982–1987 to 15.4% in 1994–1998. At the same time the proportion of women with ovarian cancer undergoing surgery increased and a 15% increase in relative survival occurred.[61]

1.16.2. Delay in diagnosis of cancer

Understanding reasons for a delay in diagnosis may alter the progression of the disease and improve patient survival. Reasons for delays in diagnosis depend on patient and provider factors and is stongly influenced by presenting symptoms. Macleod [306] in a systematic review noted that misdiagnosis was a common reason for delay regardless of cancer site because symptoms were attributed incorrectly to non cancer causes. For other cancer sites, the most common reasons for a delay in diagnosis included: inadequate patient examination; use of inappropriate tests or failure to follow up inconclusive test results. Most studies of cancer patients that have measured delay from symptom awareness to diagnosis are limited. Many were retrospective and, therefore, subject to recall bias, qualitative and therefore based on views of a small number of patients[307, 308] or were systematic reviews of existing literature.[306, 309] Consequently, few studies have examined survival due to a delay from first symptoms to diagnosis.

In Swedish study of 343 bladder cancer patients, the median delay from symptom awareness to the first consultation was 15 days. The delay was longer when the presenting symptom

was urgency rather than haematuria. The average time from the GP to the urologist was 62 days but longer in patients who were older, and those who had more referrals particularly women. [310]

There is no evidence that reducing the time from symptom onset to presentation at a GP improves survival outcomes for women diagnosed with ovarian cancer.[311] In a representative sample of Australian women diagnosed with ovarian cancer between 2002 and 2005, 90% of whom presented to a general practitioner with symptoms, 55% had presented at one month 70% at two months and 92% within 6 months of diagnosis. Cancer survival was similar regardless of time from symptom onset to diagnosis. Consequently, it is unlikely that reducing the time from symptom onset to diagnosis will alter the progression of ovarian cancer.

Delays in lung cancer were examined in a retrospective audit of electronic medical records in 587 patients in two tertiary centres. Two clinicians independantly reviewed the records and found that the most common preventable delay was the failure to recognise abnormal imaging results and failure to complete key diagnostic procedures (first needle biopsy) in a timely manner.[312]

1.16.3. Delay from diagnosis to surgery

Cancer site and histological subtype determine whether a delay from diagnosis to surgery influences cancer survival. Colorectal and breast cancer patients who had surgery 12 or more weeks after their diagnosis had hazard ratios of 2.65 and 1.91 respectively. No increase in the hazard of death was found in lung and thyroid patients.[313] After adjusting for cancer site, people who had higher incomes had shorter delays to surgery and lower mortality, while those who travelled further had longer delays and higher mortality. Most people who travelled outside of their hospital referral area did so to access specialist care. Therefore, while travelling to a high volume specialist centre may improve outcome it may also lead to a delay in surgery. [313]

Timely referral to surgery is particularly important for bladder cancer patients. With the exception of one study[314] that showed no impact on survival, the majority of people with bladder cancer who had a cystectomy later than 12 weeks from diagnosis had worse survival

and poorer clinical outcomes (increase in muscle invasion – more advanced stage and grade).[28, 216, 217, 310, 313, 315-317]

However, for women with ovarian cancer a full diagnosis is often not made until the patient undergoes surgery. Therefore, reducing the time from diagnosis to surgery was found to have no impact on survival.[308, 311]

Similarly, for people with NSCLC, reducing the time from diagnosis to surgery was not associated with better cancer survival regardless of stage at diagnosis, [318, 319] and did not result in an increase in tumour progression for patients who waited longer for radiotherapy.[197]

1.16.4. Patient insurance status

Numerous US [44, 48, 320-323 35] and Australian[46, 57, 285, 324] studies document the impact of having private health insurance status on overall survival for prostate, breast, lung and colorectal cancers.[322] Lung[132, 138] and breast cancer patients [325] were more likely to undergo surgery if they had private medical insurance. Conversely, lung cancer patients had a reduced likelihood of undergoing a lobectomy[44] or any resection[326] for NSCLC without health insurance. Uninsured lung, oesophagus and breast cancer patients and those with Medicaid only were less likely to receive care in high volume hospitals. They also had lower rates of surgery.[35] In addition, patients with private insurance, who did not have surgery, were more likely to receive another form of anticancer therapy, either radiation or chemotherapy (1.57; 1.18 to 2.09). [325]

Australian CRC patients treated in private hospitals[327 46, 328, 329] were found to have significantly better survival outcomes, after adjustment for age, sex and stage. European prostate cancer patients with localised stage who had private health insurance were found to have more staging procedures, more surgery less recurrence and a lower hazard of dying than patients without insurance.[48]

1.17. Thesis aims

The overall aim of this thesis is to understand whether distance from, and access to, surgical care (bladder), and specialist surgical care (ovary and lung cancer) influences the likelihood of presenting with advanced or unknown stage, receiving no surgical treatment and whether these lead to poorer survival, after adjusting for patient, tumour and treatment factors.

More specifically, the aims for each chapter in this thesis are:

1. To examine two methodological issues related to the measurement of distance and cancer survival. Specifically to
    a. compare current and new methods of allocating small geographical areas and verify that geocoded coordinates applied to the NSW CCR can be used to measure straight-line distance by (Chapter 2) and
    b. determine whether relative, net and cause specific survival methods have similar results in NSW and Northern and Yorkshire. Compare the difference in survival between NSW and another registry (the Northern and Yorkshire cancer registry). Different survival methods will be compared for selected cancer sites (Chapter 3).
2. To investigate why bladder cancer survival is consistently poorer in women who undergo a cystectomy or have a segmental resection after adjustment for patient, tumour and treatment factors. and

a. To investigate whether distance to surgical hospitals is an independent predictor of bladder cancer survival. This study evaluates the impact of distance to actual care rather than specialist care because of the absence of guidelines providing advice on the surgical management of bladder cancer (Chapter 4).

3. To investigate whether distance to specialist care is associated with ovarian cancer survival after taking account of patient, tumour and treatment factors. In addition, to investigate factors associated with treatment in public general hospitals (as opposed to specialist hospitals or private general hospitals) and factors predictive of surgery for ovarian cancer (Chapter 5).
4. To investigate whether increasing distance to a specialist centre was associated with advanced stage or unknown stage NSCLC and whether this influences hospital of attendance after adjustment for patient, tumour and treatment factors (Chapter 6).

5. To investigate whether increasing distance to the nearest accessible specialist hospital (NASH) a public hospital with a thoracic surgical service is associated with failure to receive surgical treatment for localised primary NSCLC after adjusting for for patient, tumour and treatment factors (Chapter 7).
6. To investigate whether increasing distance to the NASH is associated with poorer survival for patients with localised, regional and distant stage primary NSCLC after adjusting for potentially confounding variables (Chapter 8).

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2. Evaluating geocoding of the CCR and measuring distance in people diagnosed with cancer in NSW

2.1. Abstract

Background The New South Wales (NSW) Central Cancer Registry (CCR) records the residential address of all people with cancer at the time of diagnosis. On the basis of this address, a National Locality Index (NLI) encoder is applied that determines Local Government Areas and subsequently, the Area Health Services (AHS) at the time of diagnosis. The aims of this study are to evaluate the impact of geocoding the CCR data, by comparing historical and geocoded methods of allocating Local Government Areas (LGAs) and to evaluate whether straight-line distance can be calculated from geocodes. **Methods**. Numbers of cases of cancer diagnosed between 1999 and 2004 and grouped to 2001 LGAs based on geocode coordinates were compared with the number of cases allocated using the current NLI method. Straight-line distance was calculated from each persons case address at diagnosis to Royal Prince Alfred (RPA) hospital using the Great Circle Distance Calculator. The mean distance in kilometres for all cases diagnosed between 1972 and 2004 within an LGA was obtained and the minimum and maximum distance values calculated. **Results.** For 86% of LGAs there was a plus or minus 0.02% difference in the proportion of total cases within each NLI and geocode allocated LGA. Mean distance in kilometres for cases within an LGA to RPA were consistent with known distances. The proportion of cases that lived further than 100 km was consistent and increased by year of diagnosis. As expected all rural AHSs were located 100km or more from RPA. **Conclusion.** The number of incidence cases within an LGA is similar regardless of the method of allocation. Therefore incidence, mortality and survival estimates for each LGA will be consistent. The mean distance in kilometres from the LGA to RPA using the Great Circle Distance Calculator was consistent with the known location of LGAs providing confidence that distance in kilometres to other specialist hospitals in Sydney Australia can be obtained using this method and applied to subsequent studies in this thesis.

2.2. Introduction

Cancer Registries report geographic differences in patterns of cancer incidence, mortality and survival to evaluate progress in cancer control programs. The NSW Central Cancer Registry (CCR) publishes incidence and mortality rates by Local Health Districts (LHD) and small geographical regions or Local Government Areas (LGAs) annually and reports survival every three to five years.

The CCR is a historical database of all cases of cancer diagnosed in NSW from 1972 to 2009. The residential address of all persons with cancer at the time of diagnosis is recorded. Applied to this address is a National Locality Index encoder (NLI) [1] developed by the Australian Bureau of Statistics (ABS). The NLI coder consists of a localities index and street index. A locality is where people live, most localities are associated with one LGA but sometimes these are split into two LGAs on the basis of street information.[2] Since 1984, LGAs are updated annually to reflect changes proclaimed by State and Territory government authorities.[2] With every change in boundaries, the ABS would publish annual updates to the NLI coder and produce concordance maps. An LGA at the time of diagnosis is allocated to a person's case address (the full address of a person at diagnosis for each case of cancer). Subsequently groups of LGAs are associated with an LHD at the time of diagnosis.

Geocoding is the process of linking address data to a location on the Earth's surface.[3 4] Geographical coordinates expressed as longitude and latitude are assigned to a person's address at diagnosis. Changes in geographical regions occur in NSW due to census and population changes. Therefore, the entire cancer registry database needs updating to reflect boundary changes.

In 2007, the ABS announced that it would no longer provide new versions of the NLI coder because from 2011 onwards population boundaries would be geocoded based on the census. Therefore, geocoding the NSW CCR was both a necessity and an opportunity to develop new measures like distance.

A major advantage of geocoding each person's address is that the geocoded coordinates can be linked to a defined shape or polygon of geocoded coordinates (that outline the boundaries of a population area) using a spatial join using geocoding software like ESRI ArcGIS 9.3

software. [5] As new population boundary files are developed, cancer cases (numerator) can easily be linked to populations (denominator) and rates calculated. Furthermore, geocode coordinates allow the measurement of distance from a patient's home to where they are treated.

Addresses on the cancer registry were geocoded by the Northern Rivers University Department of Rural Health as part of a consultancy. Two geocoding methods were applied to the case addresses of people diagnosed with cancer and living in NSW between 1972 and 2004 using two different geocoding methods. These were FEBRL (Freely Extensible Biomedical Record Linkage)[6] and Map Marker[7]. Both methods can clean and georeference individual records. The FEBRL[6] software was developed by the Ministry of Health and used the extensive Geocoded National Address File (GNAF) to allocate geocodes. The GNAF data file[8] has 13 million geocoded physical addresses derived from a variety of national and state based datasets. Map Marker is a geocoding product from MapInfo that allocates a geocode using a set of weights that scores each portion of the address against an Address Dictionary. Both methods provide a longitude and latitude coordinate for every case associated with a 2001 census boundary code and a final geocode was assigned based on the most precise estimate.[9]

Of the 809,551 cases geocoded 82.7%, were geocoded using the complete address 7.8% were geocoded to a street only 8.5% to a locality and for 0.87% there was not enough information to geocode. There were also 6,419 records that did not geocode. Therefore, the reasons why these records did not geocode needed to be investigated and rectified. It was also necessary to check the quality of geocoding in the CCR to ensure that there had not been any incorrect assignment of longitude and latitude coordinates.[10] In addition, the distance measure required validation.

This study investigates three aims. The first aim compares the number of cases within each LGA using the current and new-geocoded methods. The second aim evaluates whether the Great Circle Distance Calculator can calculate plausible distance in kilometres from each person's geocode coordinates at diagnosis to one treatment facility (RPA hospital). The last aim evaluates the proportion of the population who lived greater than 100 kilometres from RPA by year of diagnosis and within rural AHS of residence.

2.3. Methods

2.3.1. Methods aim one - comparison of 2001 boundaries

All NSW cases of cancer with a date of diagnosis between 1999 and 2004 were included in this comparison. The number of cases within an LGA was determined by the National Locality coder.[1] To determine the numbers of cases within each 2001 LGA, some 1999 LGAs were grouped. For example, the Blacktown LGA in 1999 was one area but by 2001, it had split into three LGAs (north, south-east and south-west Blacktown). Geocode coordinates within 2001 LGA boundaries were linked back to the NSW CCR database by unencrypting the ID provided to Northern Rivers. The numbers of cases of cancer within each LGA using the NLI and geocoded methods were compared and the difference in numbers of incidence cases obtained by subtracting one number from the other. The contribution of each LGA as a proportion of the total cases was calculated for each method. For example, if an LGA contributed 1.75% of cases for both methods then the difference in the proportion of total cases would be 0.

2.3.2. Methods aim two - distance to RPA

All NSW cases of cancer with a date of diagnosis between 1972 and 2004 were included in this comparison. Distance between each case on the cancer registry database and RPA was calculated using the Great Distance Circle Calculator a Statistical Analysis Systems (SAS)[11] algorithm obtained from the North American Association of Cancer Registries (NAACR) [11] using SAS 9.2. [12] The longitude and latitude coordinates for RPA were obtained from the NSW Ministry of Health. The Great Circle Distance is the shortest distance between two points on the surface of the earth. The shape of the earth is a flattened spheroid the distance calculated in the SAS program ignores the differences in the effect of elevation. Distance is calculated in miles as the crow flies if the crow flies at sea level and then converted into kilometres.[11, 13] The law of cosines for spherical geometry is used.

The SAS program includes the following formula

SAS Code:

Distance in miles= 1.150779 * 60 * (180/CONSTANT ('PI')) *

Arcos (sin (latr1) * sin (latr2) + cos (latr1) *cos (latr2) * cos (longr2-longr1));

latr1= Latitude of a person's address

latr2= latitude of RPA

longr1=longitude of a person's address

longr2=longitude of RPA

Arcos (arc of a cosine) is in radians which are converted to degrees (60) and then nautical miles, then statute miles (1.150779).

For example

- the latitude of RPA hospital = -33.889637
- the longitude of RPA hospital =151.182475
- distance in miles between a patient home and RPA is obtained by applying the algorithm and is converted to kilometres by multiplying by a conversion factor of 1.60943.

Distance in kilometres from each person's residential address at the time of diagnosis (for each case of cancer) to RPA hospital. The mean distance within an LGA was calculated for all cases of cancer as well as the shortest (minimum) and longest distance (maximum) distance from the LGA to RPA. Mean distance for each LGA was mapped using ArcGIS 9.3 with different colours representing five categories. The lowest and highest categories were open ended and categories in between grouped into 150 km groupings (2-100, 101-255,256-396, 397-558 and 559-931).

2.3.3. Methods aim three-distance to RPA by AHS

The number and the proportion of cases that live 100 km or more from RPA tabulated by year of diagnosis and by 2005 AHS Regions of residence.

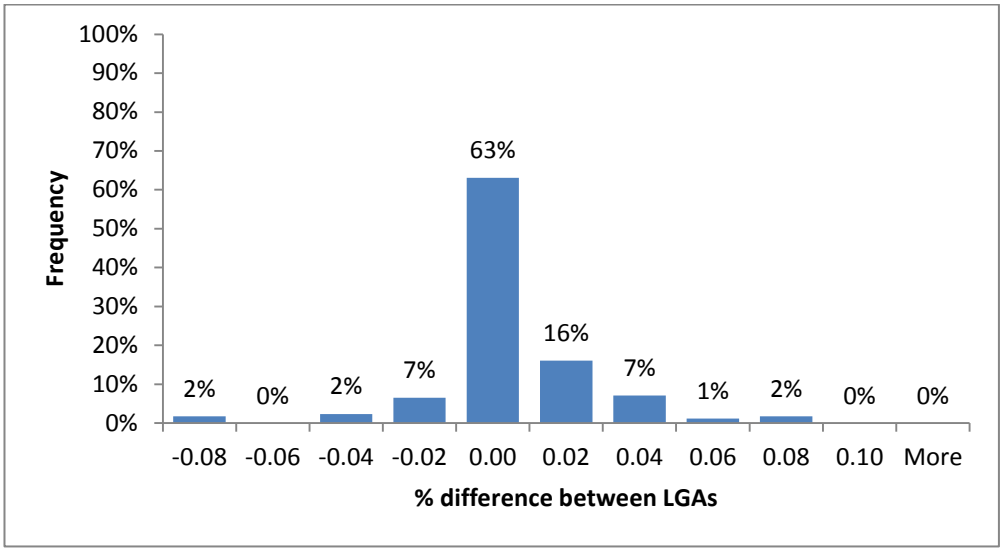
2.4. Results

There were 1,144 indeterminate address records in people diagnosed between 1999 and 2004 (approx. 1%) that failed to geocode. Case addresses were not assigned geocodes for the following reasons: the address included the name of a caravan park only, or a nursing home, hostel or post office (PO) box. To correct these records, cancer registry staff added the closest street address by checking other notifications for the same case and by looking up address details of historical and current nursing homes. The address of the post office was used for case addresses where only a PO Box was available. All address records on the CCR database were eventually geocoded for the period 1972 to 2004.

2.4.1. Results aim one - comparison of 2001 boundaries

The difference between the two methods is the difference in the number of cases between the historical LGA method and the new geocoded method. There was zero or no difference between 63% of all LGAs, 23% had a difference of 0.02% and 9% had a difference of 0.04%. For 86% of LGAs there was plus or minus 0.02% difference in the numbers of cases within each NLI and geocode allocated LGA.The largest difference was Hurstville LGA with a difference of 178 cases or 0.1%. Case addresses that did not map were those designated as indeterminate by Febryl and MapMarker and rectified as described above (Chapter 2Appendix 1 Table 1, Figure 1).

Chapter 2 Figure 1 Frequency histogram of the percentage difference in the number of cases within 2001 LGAs allocated using the geocoded method and the NLI coder in NSW between 1999 and 2004.



2.4.2. Results aim two - distance to RPA

The mean distance for cases within a LGA was calculated and mapped. The most distant LGA was Broken Hill where residents lived a mean distance of 931 km (929 km minimum or 934 km maximum) from RPA. The closest LGA was Leichardt with a mean distance of two kilometres (minimum 0 km maximum 5km). All LGAs were internally consistent with the known distances (Appendix 1 Table 1 Figure 2).

The proportion of people diagnosed with cancer that lived greater than 100 km from RPA by year of diagnosis was similar and consistent, with a gradual increase in the proportion of people who lived 100kms or more from RPA for each year of diagnosis (Chapter 2 Table 1).

2.4.3. Results aim three - distance to RPA by AHS

Finally, most people diagnosed with cancer who lived in a rural AHS lived 100km from RPA, which is consistent and expected (Chapter 2 Table 2).

Chapter 2 Table 1 NSW CCR incidence cases by year of diagnosis and the proportion of cases less than 100km or more than 100km from each person's home to RPA hospital.

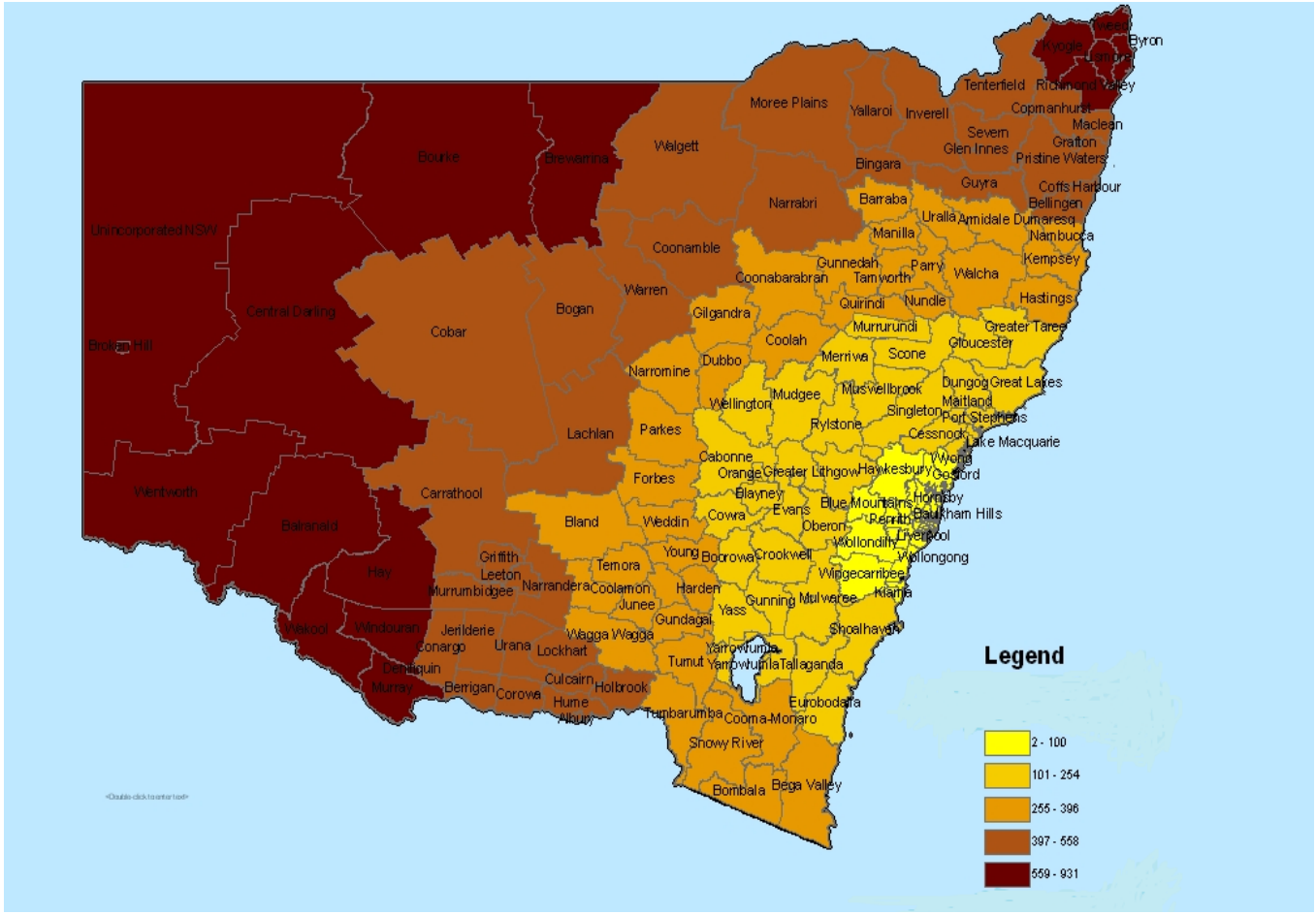
year of diagnosis	100k or less	101 k or more	Total cases	% 100 k or less	% 100K or more
1972	8,265	3,134	11,399	73%	27%
1973	8,292	3,204	11,496	72%	28%
1974	8,829	3,465	12,294	72%	28%
1975	9,101	3,547	12,648	72%	28%
1976	9,573	3,897	13,470	71%	29%
1977	9,670	4,007	13,677	71%	29%
1978	9,820	4,030	13,850	71%	29%
1979	10,265	4,278	14,543	71%	29%
1980	10,774	4,436	15,210	71%	29%
1981	11,138	4,658	15,796	71%	29%
1982	11,335	5,047	16,382	69%	31%
1983	11,921	5,175	17,096	70%	30%
1984	12,180	5,608	17,788	68%	32%
1985	12,550	5,764	18,314	69%	31%
1986	12,908	6,254	19,162	67%	33%
1987	13,482	6,422	19,904	68%	32%
1988	13,582	6,781	20,363	67%	33%
1989	13,836	7,104	20,940	66%	34%
1990	14,237	7,386	21,623	66%	34%
1991	15,198	7,663	22,861	66%	34%
1992	15,622	8,306	23,928	65%	35%
1993	16,523	8,909	25,432	65%	35%
1994	17,325	9,374	26,699	65%	35%
1995	17,422	9,654	27,076	64%	36%
1996	17,136	9,380	26,516	65%	35%
1997	17,784	9,749	27,533	65%	35%
1998	18,114	9,722	27,836	65%	35%
1999	18,188	10,132	28,320	64%	36%
2000	18,653	10,644	29,297	64%	36%
2001	19,221	11,168	30,389	63%	37%
2002	19,963	11,863	31,826	63%	37%
2003	20,570	12,019	32,589	63%	37%
2004	20,561	12,194	32,755	63%	37%
Total	464,038	234,974	699,012		

** distance is as the crow flies and is not road distance
* excludes indeterminate codes - 2005 extraction

Chapter 2 Table 2 NSW CCR incidence cases 1972-2004 by AHS with the proportion of cases less than or more than 100 km from each person's home to RPA hospital.

AHS of Residence	100 k or less	101 k or more	total cases	%100k or less	%100k or more
South-Western Sydney	117,792	1,602	119,394	99%	1%
South-Eastern Sydney-Illawarra AHS	127,481	10,737	138,218	92%	8%
Western Sydney	80,479	2,286	82,765	97%	3%
Northern Sydney Central Coast AHS	133,201	168	133,369	100%	0%
Hunter-New England	4,796	88,821	93,617	5%	95%
North Coast	68	51,014	51,082	0%	100%
Greater Southern	115	47,206	47,321	0%	100%
Greater Western	43	33,113	33,156	0%	100%
Total	463,985	234,965	698,950	66%	34%

Chapter 2 Figure 2 The mean distance in kilometres for NSW CCR cases within each LGA to RPA Hospital for cases diagnosed between 1972 and 2004



2.5. Discussion

The first aim compared whether the number of cases within each LGA was similar using the current and new-geocoded methods. In 86% of LGAs, there was a difference of plus or minus 0.02% in the numbers of cases within each NLI and geocode allocated LGA, providing confidence that both methods resulted in similar numbers of incidence cases for an LGA. The second aim evaluated whether the Great Circle Distance Calculator could be used to calculate plausible distance in kilometres from each LGA to RPA. Mean distances in kilometres from each LGA to RPA hospital were consistent with the known distance for each LGA providing further certainty that geocode coordinates applied to the Great Circle Distance Calculator was the correctly measured distance in kilometres in NSW. The last aim evaluated whether the proportion of the population who live greater than 100 kilometres from RPA was consistent by year of diagnosis and AHS of residence. The proportional breakdown by year of diagnosis was consistent, and all rural AHS located 100km or more from RPA provided further reassurance.

It was important that LGAs allocated using new methods are consistent with and similar to LGAs allocated using historical methods. Otherwise, increases in the numbers of cases within an LGA may be a methodological artefact due to the new method rather than a real occurrence. Furthermore, census variables like SES[14] and the Accessibility and Remoteness Index of Australia (ARIA)[15] and other census characteristics[16] need to be routinely linked to LGA boundaries. For example, NSW has the third highest incidence rate of melanoma in the world of all registries that contribute to Cancer Incidence in Five Continents. [17] Exposure to ultraviolet (UV) radiation is a known risk factor for melanoma. Incidence rates of melanoma increase the closer a person lives near the equator which is consistent with increasing UV radiation.[18] There is an increasing trend in the rates of melanoma in NSW in coastal LGAs as they move closer to the Queensland.[18] Therefore, sun protection initiatives need implementation and monitoring in these LGAs. A decline in incidence rates and mortality rates and an improvement in survival are indicative of success. Another example is the 50% reduction in the incidence of cervical cancer that has occurred since the 1990s. This reduction in incidence occurred after the introduction of the Cervical Screening program, indicating that it had been successful. The little or no difference in the allocation of cases within each 2001 LGA regardless of method provides confidence that rates should be

consistent over time and that differences observed for incidence, mortality and survival are real and not the result of a methodological artefact.

The mean distance in kilometres from each LGA to RPA hospital calculated in this study used the Great Circle Distance Calculator which provided consistent plausible distance measures providing confidence that the method could be used to calculate distance to other hospitals satisfactorily. Furthermore, the algorithm and SAS code had already been developed and validated by the North American Association of Cancer Registries.[11] Moreover, the method has been applied to a large number of cancer registry studies. [19, 20 21, 22 23, 24 25-27] However, other methods of calculating distance could have been used if these had been available. Therefore, it is important to consider whether different methods of allocating straight-line distance produce different results. Recently, Geoscience Australia[28] compared the Great Circle method, with the approximate ellipse and Vincentys' formula method. All three methods produced similar estimates of straight-line distance with less than one kilometre difference between methods at 1000 kilometres, [28] the maximum distance from a person's residence to RPA that is recorded on the CCR database. This provided reassurance that the method used would give similar distance results.

One limitation is that we were not able to measure travel distances and compared this to straight-line distance because this information was not available. However, a comparison of straight-line and travel distances in the UK indicated that there was a high degree of correlation between the two measures ($r = 0.856$).[29] Furthermore, a study of travel time and six different methods of accessibility to the closest medical provider found that road distance and straight-line distance (from the geocoded street of a person to the geocoded street of the provider) predicted 96% and 94% of the variability in travel time respectively. Other measures, for example, rural or urban residence or providers per head of population explained only 30% and 83% of the variability in travel time respectively.[30]

Apart from the ability to measure distance to treatment there are many advantages of geocoding the NSW CCR database. Population and other demographic data link to registry data by spatial joining in ArcGIS software. The ABS has produced small areas of population referred to as mesh blocks based on geocoded boundaries. Mesh Blocks are the smallest geographic region of population for which census data is available. In 2011, there were

approximately 347,000 Mesh Blocks covering the whole of Australia.[31] For the first time cancer and population, data will be geocoded.

Ideally, all agencies that use geocodes should investigate the impact of boundary changes on historical data by comparing the results of existing methods with boundaries created using the geocodes. These comparisons provide confidence that distance to hospital is a reliable measure that can be calculated for subsequent studies in this thesis. While this study compared cases to the end of 2004, geocoding now routinely undertaken in the NSW CCR, with the 2004 to 2008 data geocoded using the same methodologies as described.

Discussed in Chapter 4 is the impact of distance to hospital of surgery on bladder cancer survival for people who undergo a cystectomy or resection. Discussed also is the impact of distance and treatment in a specialist hospital on cancer survival for women with ovarian cancer in Chapter 5. Similarly, the impact of distance to the nearest accessible specialist hospital (NASH) on the likelihood of advanced or unknown stage, no surgery and cancer survival is examined for people with lung cancer in Chapters 6, 7 and 8.

2.6. Acknowledgment

The Northern Rivers University Department of Rural Health - University of Sydney, and North Coast Area Heath Service undertook a $30,000 consultancy, commissioned by Elizabeth Tracey when Manager of the NSW CCR at the Cancer Institute NSW. Dr Geoff Morgan conducted the geocoding of the CCR database on case addresses for people diagnosed between 1972 and 2004. The initial Research into geocoding methods by the Northern Rivers University Department of Rural Health – University of Sydney was funded by the Australian Research Council (Grant LP0348628), NSW Health, The Commonwealth Department of Health and Ageing, and the North Coast AHS.

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Chapter 2 Appendix 1 Table 1 NSW CCR incidence cases grouped to 2001 LGA groups using Geocoded coordinates and the conventional NLI encoder.

2001 LGA Geocoded boundaries	number	Per cent	2001 NLI coded boundaries	Frequency	Per cent	%difference	cases different
Albury (C)	1081	0.71	Albury	1095	0.71	0	14
Armidale Dumaresq (A)	443	0.29	Armidale	519	0.34	-0.05	76
Armidale Dumaresq (A)	64	0.04	Dumaresq	10	0.01	0.03	-54
Ashfield (A)	922	0.6	Ashfield	912	0.59	0.01	-10
Auburn (A)	957	0.63	Auburn	966	0.63	0	9
Ballina (A)	1116	0.73	Ballina	1141	0.74	-0.01	25
Balranald (A)	65	0.04	Balranald	67	0.04	0	2
Bankstown (C)	3830	2.51	Bankstown	3885	2.53	-0.02	55
Barraba (A)	82	0.05	Barraba	82	0.05	0	0
Bathurst (C)	667	0.44	Bathurst	684	0.45	-0.01	17
Baulkham Hills (A)	2834	1.86	Baulkham Hills	2748	1.79	0.07	-86
Bega Valley (A)	910	0.6	Bega Valley	913	0.59	0.01	3
Bellingen (A)	381	0.25	Bellingen	392	0.26	-0.01	11
Berrigan (A)	238	0.16	Berrigan	235	0.15	0.01	-3
Bingara (A)	68	0.04	Bingara	55	0.04	0	-13
Blacktown (C) - North	1063	0.7	Blacktown	4184	2.72	0.01	-26
Blacktown (C) - South-	1838	1.21					
Blacktown (C) - South-	1257	0.82					
Bland (A)	185	0.12	Bland	190	0.12	0	5
Blayney (A) - Pt A	112	0.07	Blayney	172	0.11	-0.01	60
Blayney (A) - Pt B	45	0.03					
Blue Mountains (C)	1766	1.16	Blue Mountains	1762	1.15	0.01	-4
Bogan (A)	101	0.07	Bogan	101	0.07	0	0
Bombala (A)	86	0.06	Bombala	99	0.06	0	13
Boorowa (A)	79	0.05	Boorowa	78	0.05	0	-1
Botany Bay (C)	889	0.58	Botany	895	0.58	0	6
Bourke (A)	58	0.04	Bourke	59	0.04	0	1
Brewarrina (A)	45	0.03	Brewarrina	48	0.03	0	3
Broken Hill (C)	601	0.39	Broken Hill	628	0.41	-0.02	27
Burwood (A)	645	0.42	Burwood	654	0.43	-0.01	9
Byron (A)	646	0.42	Byron	647	0.42	0	1
Cabonne (A) - Pt A	35	0.02	Cabonne	349	0.23	-0.01	-1
Cabonne (A) - Pt B	19	0.01					
Cabonne (A) - Pt C	294	0.19					
Camden (A)	732	0.48	Camden	784	0.51	-0.03	52
Campbelltown (C)	2190	1.44	Campbelltown	2188	1.42	0.02	-2
Canterbury (C)	2822	1.85	Canterbury	2736	1.78	0.07	-86
Carrathool (A)	85	0.06	Carrathool	76	0.05	0.01	-9
Central Darling (A)	57	0.04	Central Darling	59	0.04	0	2
Cessnock (C)	1162	0.76	Cessnock	1183	0.77	-0.01	21
Cobar (A)	109	0.07	Cobar	107	0.07	0	-2
Coffs Harbour (C) - Pt A	1279	0.84	Coffs Harbour	1673	1.09	-0.01	-32
Coffs Harbour (C) - Pt B	362	0.24					
Conargo (A)	24	0.02	Conargo	7	0	0.02	-17
Concord (A)	648	0.43	Concord	641	0.42	0.01	-7
Coolah (A)	105	0.07	Coolah	110	0.07	0	5
Coolamon (A)	99	0.06	Coolamon	108	0.07	-0.01	9
Cooma-Monaro (A)	229	0.15	Cooma-Monaro	237	0.15	0	8
Coonabarabran (A)	181	0.12	Coonabarabran	185	0.12	0	4
Coonamble (A)	120	0.08	Coonamble	122	0.08	0	2
Cootamundra (A)	262	0.17	Cootamundra	262	0.17	0	0
Copmanhurst (A)	104	0.07	Copmanhurst	76	0.05	0.02	-28
Corowa (A)	292	0.19	Corowa	300	0.2	-0.01	8
Cowra (A)	346	0.23	Cowra	349	0.23	0	3

Chapter 2 Appendix 1 Table 1 NSW CCR incidence cases grouped to 2001 LGA groups using Geocoded coordinates and the conventional NLI encoder.

2001 LGA Geocoded	number	Per cent	2001 NLI coded	Frequency	Per cent	%difference	cases different
Crookwell (A)	140	0.09	Crookwell	142	0.09	0	2
Culcairn (A)	115	0.08	Culcairn	117	0.08	0	2
Deniliquin (A)	250	0.16	Deniliquin	315	0.21	-0.05	65
Drummoyne (A)	898	0.59	Drummoyne	916	0.6	-0.01	18
Dubbo (C) - Pt A	788	0.52		851	0.55	0.01	-4
Dubbo (C) - Pt B	59	0.04	Dubbo				
Dungog (A)	203	0.13	Dungog	212	0.14	-0.01	9
Eurobodalla (A)	1176	0.77	Eurobodalla	1177	0.77	0	1
Evans (A) - Pt A	22	0.01	Evans	96	0.06	0	4
Evans (A) - Pt B	78	0.05					
Fairfield (C)	3136	2.06	Fairfield	3170	2.06	0	34
Forbes (A)	299	0.2	Forbes	300	0.2	0	1
Gilgandra (A)	123	0.08	Gilgandra	121	0.08	0	-2
Glen Innes (A)	170	0.11	Glen Innes	214	0.14	-0.03	44
Gloucester (A)	134	0.09	Gloucester	132	0.09	0	-2
Gosford (C)	4637	3.04	Gosford	4720	3.07	-0.03	83
Goulburn (C)	532	0.35	Goulburn	589	0.38	-0.03	57
Grafton (C)	525	0.34	Grafton	577	0.38	-0.04	52
Great Lakes (A)	1256	0.82	Great Lakes	1256	0.82	0	0
Greater Lithgow (C)	523	0.34	Greater Lithgow	536	0.35	-0.01	13
Greater Taree (C)	1284	0.84	Greater Taree	1289	0.84	0	5
Griffith (C)	480	0.31	Griffith	481	0.31	0	1
Gundagai (A)	137	0.09	Gundagai	135	0.09	0	-2
Gunnedah (A)	340	0.22	Gunnedah	357	0.23	-0.01	17
Gunning (A)	48	0.03	Gunning	45	0.03	0	-3
Guyra (A)	102	0.07	Guyra	112	0.07	0	10
Harden (A)	117	0.08	Harden	106	0.07	0.01	-11
Hastings (A) - Pt A	1350	0.89					-29
Hastings (A) - Pt B	943	0.62	Hastings	2322	1.51	0	
Hawkesbury (C)	1056	0.69	Hawkesbury	1058	0.69	0	2
Hay (A)	102	0.07	Hay	106	0.07	0	4
Holbrook (A)	72	0.05	Holbrook	71	0.05	0	-1
Holroyd (C)	1828	1.2	Holroyd	1875	1.22	-0.02	47
Hornsby (A)	3177	2.08	Hornsby	3244	2.11	-0.03	67
Hume (A)	164	0.11	Hume	165	0.11	0	1
Hunter's Hill (A)	414	0.27	Hunter's Hill	403	0.26	0.01	-11
Hurstville (C)	1901	1.25	Hurstville	2079	1.35	-0.1	178
Inverell (A) - Pt A	131	0.09					
Inverell (A) - Pt B	277	0.18	Inverell	422	0.27		-14
Jerilderie (A)	40	0.03	Jerilderie	43	0.03	0	3
Junee (A)	133	0.09	Junee	132	0.09	0	-1
Kempsey (A)	819	0.54	Kempsey	812	0.53	0.01	-7
Kiama (A)	551	0.36	Kiama	546	0.36	0	-5
Kogarah (A)	1362	0.89	Kogarah	1286	0.84	0.05	-76
Ku-ring-gai (A)	2842	1.86	Ku-ring-gai	2872	1.87	-0.01	30
Kyogle (A)	234	0.15	Kyogle	260	0.17	-0.02	26
Lachlan (A)	188	0.12	Lachlan	193	0.13	-0.01	5
Lake Macquarie (C)	4836	3.17	Lake Macquarie	4844	3.15	0.02	8
Lane Cove (A)	809	0.53	Lane Cove	821	0.53	0	12
Leeton (A)	274	0.18	Leeton	271	0.18	0	-3
Leichhardt (A)	1325	0.87	Leichhardt	1333	0.87	0	8
Lismore (C) - Pt A	759	0.5					
Lismore (C) - Pt B	246	0.16	Lismore	979	0.64		26
Liverpool (C)	2309	1.51	Liverpool	2288	1.49	0.02	-21

Chapter 2 Appendix 1 Table 1 NSW CCR incidence cases grouped to 2001 LGA groups using Geocoded coordinates and the conventional NLI encoder.

2001 LGA Geocoded	number	Per cent	2001 NLI coded	Frequency	Per cent	%difference	cases different
Lockhart (A)	69	0.05	Lockhart	88	0.06	-0.01	19
Lord Howe Island	10	0.01	Lord Howe Island	10	0.01	0	0
Maclean (A)	681	0.45	Maclean	690	0.45	0	9
Maitland (C)	1214	0.8	Maitland	1218	0.79	0.01	4
Manilla (A)	91	0.06	Manilla	89	0.06	0	-2
Manly (A)	1056	0.69	Manly	1057	0.69	0	1
Marrickville (A)	1437	0.94	Marrickville	1436	0.94	0	-1
Merriwa (A)	63	0.04	Merriwa	72	0.05	-0.01	9
Moree Plains (A)	283	0.19	Moree Plains	287	0.19	0	4
Mosman (A)	700	0.46	Mosman	699	0.46	0	-1
Mudgee (A)	443	0.29	Mudgee	432	0.28	0.01	-11
Mulwaree (A)	153	0.1	Mulwaree	111	0.07	0.03	-42
Murray (A)	232	0.15	Murray	176	0.11	0.04	-56
Murrumbidgee (A)	50	0.03	Murrumbidgee	53	0.03	0	3
Murrurundi (A)	58	0.04	Murrurundi	62	0.04	0	4
Muswellbrook (A)	280	0.18	Muswellbrook	283	0.18	0	3
Nambucca (A)	571	0.37	Nambucca	585	0.38	-0.01	14
Narrabri (A)	302	0.2	Narrabri	332	0.22	-0.02	30
Narrandera (A)	214	0.14	Narrandera	224	0.15	-0.01	10
Narromine (A)	152	0.1	Narromine	153	0.1	0	1
Newcastle (C) - Inner	108	0.07	Newcastle	3818	2.49		
Newcastle (C) -	3659	2.4	5902	2	0		
North Sydney (A)	1351	0.89	North Sydney	1355	0.88	0.01	4
Nundle (A)	25	0.02	Nundle	30	0.02	0	5
Oberon (A)	113	0.07	Oberon	100	0.07	0	-13
Orange (C)	884	0.58	Orange	907	0.59	-0.01	23
Parkes (A)	371	0.24	Parkes	375	0.24	0	4
Parramatta (C)	2987	1.96	Parramatta	2935	1.91	0.05	52
Parry (A) - Pt A	118	0.08				0.08	49
Parry (A) - Pt B	174	0.11	Parry	243	0.16	-0.05	69
Penrith (C)	2778	1.82	Penrith	2775	1.81	0.01	-3
Pittwater (A)	1599	1.05					
Port Stephens (A)	1565	1.03	Port Stephens	1586	1.03	0	21
Pristine Waters (A) -	109	0.07	Nymboida	80	0.05	0.02	-29
Pristine Waters (A) -	169	0.11	Ulmarra	147	0.1	0.01	-22
Queanbeyan (C)	486	0.32	Queanbeyan	534	0.35	-0.03	48
Quirindi (A)	138	0.09	Quirindi	138	0.09	0	0
Randwick (C)	2968	1.95	Randwick	2969	1.93	0.02	1
Remainder of ACT	10	0.01					-10
Richmond Valley (A) -	319	0.21	Casino	338	0.22	0.18	-29
Richmond Valley (A)	273	0.18	Richmond River	283	0.18		
Rockdale (C)	2340	1.54	Rockdale	2319	1.51	0.03	-21
Ryde (C)	2305	1.51	Ryde	2317	1.51	0	12
Rylstone (A)	124	0.08	Rylstone	122	0.08	0	-2
Scone (A)	210	0.14	Scone	219	0.14	0	9
Severn (A)	93	0.06	Severn	65	0.04	0.02	-28
Shellharbour (C)	1246	0.82	Shellharbour	1247	0.81	0.01	1
Shoalhaven (C) - Pt A	790	0.52	Shoalhaven	2935	1.91		-18
Shoalhaven (C) - Pt B	2127	1.4					
Singleton (A)	418	0.27	Singleton	404	0.26	0.01	-14
Snowy River (A)	117	0.08	Snowy River	129	0.08	0	12
South Sydney (C)	1905	1.25	South Sydney	1911	1.24	0.01	6
Strathfield (A)	673	0.44	Strathfield	687	0.45		14

Chapter 2 Appendix 1 Table 1 NSW CCR incidence cases grouped to 2001 LGA groups using Geocoded coordinates and the conventional NLI encoder.

2001 LGA Geocoded	number	Per cent	2001 NLI coded	Frequency	Per cent	%difference	cases different
Sutherland Shire (A) -	2801	1.84	Sutherland	4990	3.25		-3
Sutherland Shire (A) -	2186	1.43					
Sydney (C) - Inner	191	0.13	Sydney	408	0.27		2
Sydney (C) - Remainder	219	0.14					
Tallaganda (A)	86	0.06	Tallaganda	88	0.06	0	2
Tamworth (C)	925	0.61	Tamworth	978	0.64	-0.03	53
Temora (A)	171	0.11	Temora	173	0.11	0	2
Tenterfield (A)	161	0.11	Tenterfield	163	0.11	0	2
Tumbarumba (A)	98	0.06	Tumbarumba	150	0.1	-0.04	52
Tumut (A)	288	0.19	Tumut	293	0.19	0	5
Tweed (A) - Pt A	1862	1.22	Tweed	2626	1.71		-42
Tweed (A) - Pt B	722	0.47					
Unincorp. Far West	35	0.02	Unincorp Far West	7	0	0.02	-28
Uralla (A)	135	0.09	Uralla	121	0.08	0.01	-14
Urana (A)	41	0.03	Urana	51	0.03	0	10
Wagga Wagga (C) - Pt A	1091	0.72	Wagga Wagga	1203	0.78		-50
Wagga Wagga (C) - Pt B	62	0.04					
Wakool (A)	101	0.07	Wakool	98	0.06	0.01	-3
Walcha (A)	120	0.08	Walcha	119	0.08	0	-1
Walgett (A)	158	0.1	Walgett	166	0.11	-0.01	8
Warren (A)	80	0.05	Warren	88	0.06	-0.01	8
Warringah (A)	3449	2.26	Warringah	5084	3.31	-1.05	36
Waverley (A)	1625	1.07	Waverley	1634	1.06	0.01	9
Weddin (A)	126	0.08	Weddin	126	0.08	0	0
Wellington (A)	234	0.15	Wellington	246	0.16	-0.01	12
Wentworth (A)	158	0.1	Wentworth	161	0.1	0	3
Willoughby (C)	1400	0.92	Willoughby	1397	0.91	0.01	-3
Windouran (A)	5	0	Windouran	4	0	0	-1
Wingecarribee (A)	1103	0.72	Wingecarribee	1124	0.73	-0.01	21
Wollondilly (A)	702	0.46	Wollondilly	680	0.44	0.02	-22
Wollongong (C)	4648	3.05	Wollongong	4651	3.03	0.02	3
Woollahra (A)	1612	1.06	Woollahra	1633	1.06	0	21
Wyong (A)	4078	2.68	Wyong	4129	2.69	-0.01	51
Yallaroi (A)	69	0.05	Yallaroi	72	0.05	0	3
Yarrowlumla (A) - Pt A	185	0.12	Yarrowlumla	148	0.1	0.02	-37
Yass (A)	217	0.14	Yass	221	0.14	0	4
Young (A)	322	0.21	Young	339	0.22	-0.01	17
	152421		not allocated in 2001 boundaries because they were indeterminate	153562			
	diff	**1,141**					

Chapter 2 Appendix 1 Table 2 The mean distance within each LGA to RPA and the minimum and maximum distance values within each LGA for people diagnosed with cancer between 1972-2004 (ranked from most distant to RPA and the least distant)

LGA	1972-2004 'Mean Distance	1972-2004 'Min. Distance	1972-2004 'Max Distance
Broken Hill	931	929	934
Unincorporated NSW	898	783	1004
Wentworth	839	795	916
Central Darling	767	610	849
Balranald	718	639	779
Wakool	675	637	730
Tweed	664	628	675
Bourke	653	575	810
Byron	630	610	641
Murray	621	605	649
Kyogle	607	564	636
Brewarrina	603	557	667
Ballina	603	586	618
Windouran	603	592	655
Lismore	600	573	626
Deniliquin	597	592	602
Hay	588	571	646
Richmond Valley	582	542	600
Cobar	558	445	714
Conargo	556	543	591
Tenterfield	555	507	632
Berrigan	545	518	569
Walgett	543	449	613
Maclean	532	512	546
Jerilderie	522	487	547
Moree Plains	520	463	595
Carrathool	509	447	574
Copmanhurst	507	496	555
Corowa	502	472	529
Yallaroi	498	474	566
Grafton	495	488	498
Murrumbidgee	492	476	505
Pristine Waters	481	410	514
Severn	476	436	510
Urana	475	440	501
Griffith	474	451	503
Inverell	466	441	556
Glen Innes	464	460	467
Bogan	460	430	531
Hume	459	422	478
Albury	456	449	461
Bingara	448	412	460
Leeton	446	436	471
Coffs Harbour	441	423	467
Narrandera	433	400	461
Culcairn	430	404	461
Lockhart	420	401	440
Guyra	417	399	440
Bellingen	416	403	435
Coonamble	415	356	473
Narrabri	414	369	492
Holbrook	405	365	419
Lachlan	404	350	453

Chapter 2 Appendix 1 Table 2 The mean distance within each LGA to RPA and the minimum and maximum distance values within each LGA for people diagnosed with cancer between 1972-2004 (ranked from most distant to RPA and the least

LGA	1972-2004 'Mean Distance	1972-2004 'Min. Distance	1972-2004 'Max Distance
Warren	404	364	452
Barraba	396	383	422
Nambucca	394	365	405
Coolamon	387	366	404
Bombala	384	357	412
Armidale Dumaresq	378	354	409
Wagga Wagga	376	344	420
Bland	375	327	461
Uralla	371	334	418
Tumbarumba	360	338	399
Kempsey	357	330	384
Snowy River	354	315	396
Manilla	352	334	362
Coonabarabran	347	307	407
Junee	345	320	367
Temora	343	314	379
Bega Valley	342	276	396
Gilgandra	340	317	372
Narromine	337	309	374
Gunnedah	331	287	357
Walcha	320	265	329
Cooma-Monaro	319	256	357
Tumut	318	291	345
Gundagai	311	282	343
Tamworth	311	303	330
Parry	309	283	346
Hastings	309	278	328
Cootamundra	302	286	314
Dubbo	300	279	327
Parkes	300	267	364
Forbes	299	267	356
Weddin	283	252	337
Coolah	274	244	302
Nundle	272	258	294
Quirindi	271	254	296
Harden	269	247	285
Young	268	242	315
Wellington	254	215	281
Greater Taree	252	216	281
Eurobodalla	246	205	298
Murrurundi	243	225	265
Queanbeyan	242	239	249
Cabonne	238	180	275
Yass	236	220	269
Yarrowlumla	232	211	274
Cowra	230	184	258
Boorowa	227	202	240
Gloucester	221	204	249
Merriwa	216	192	243
Tallaganda	213	169	259
Great Lakes	212	155	252

Chapter 2 Appendix 1 Table 2 The mean distance within each LGA to RPA and the minimum and maximum distance values within each LGA for people diagnosed with cancer between 1972-2004 (ranked from most distant to RPA and the least

LGA	1972-2004 'Mean Distance	1972-2004 'Min. Distance	1972-2004 'Max Distance
Mudgee	211	178	252
Scone	206	190	235
Orange	204	189	225
Gunning	204	182	223
Blayney	187	170	209
Muswellbrook	181	152	194
Crookwell	171	140	200
Dungog	167	147	194
Goulburn	165	159	170
Rylstone	162	124	192
Evans	158	125	190
Bathurst	157	149	164
Mulwaree	153	112	207
Port Stephens	148	126	159
Singleton	145	107	185
Shoalhaven	140	102	210
Maitland	133	128	145
Oberon	128	105	149
Cessnock	120	85	138
Newcastle	119	114	129
Greater Lithgow	109	91	150
Lake Macquarie	106	80	117
Wingecarribee	99	72	132
Kiama	94	87	105
Shellharbour	81	78	90
Wyong	72	60	92
Blue Mountains	69	46	96
Wollongong	65	36	85
Wollondilly	62	44	74
Hawkesbury	51	39	96
Gosford	50	38	79
Camden	46	34	52
Penrith	44	34	54
Campbelltown	36	27	51
Blacktown	32	24	43
Pittwater	28	22	35
Liverpool	27	19	50
Baulkham Hills	24	17	59
Fairfield	24	18	34
Hornsby	22	14	59
Holroyd	21	17	25
Sutherland Shire	19	13	33
Parramatta	18	13	25
Warringah	17	12	30
Ku-ring-gai	16	11	23
Bankstown	16	10	20
Auburn	14	11	16
Manly	13	11	19
Hurstville	13	9	17
Kogarah	12	9	15
Ryde	12	7	15
Willoughby	10	7	12

Chapter 2 Appendix 1 Table 2 The mean distance within each LGA to RPA and the minimum and maximum distance values within each LGA for people diagnosed with cancer between 1972-2004 (ranked from most distant to RPA and the least

LGA	1972-2004 'Mean Distance	1972-2004 'Min. Distance	1972-2004 'Max Distance
Strathfield	9	8	11
Rockdale	9	5	14
Canterbury	9	5	14
Mosman	9	7	11
Concord	9	6	11
Waverley	8	6	10
Lane Cove	8	5	10
Randwick	8	4	13
Burwood	7	6	9
Hunter's Hill	7	5	9
North Sydney	7	5	9
Woollahra	7	4	11
Botany Bay	6	4	9
Drummoyne	5	4	7
Ashfield	5	3	6
Sydney	3	2	5
South Sydney	3	0	5
Marrickville	3	0	5
Leichhardt	2	0	5

3. Effects of method of survival analysis and allocation of cause of death on estimates of cancer survival in an Australian and UK registry population

This chapter is a manuscript that has not yet been finalised

Tracey E, Woods L, Dickman P, Young J, Armstrong B. Effects of method of survival analysis and allocation of cause of death on estimates of cancer survival in an Australian and a UK cancer registry population. Manuscript not yet finalised.

3.1. Abstract

Background Understanding the impact of differences in the measurement of cancer survival is important to ensure reported differences in state, national and international studies are due to survival experienced between regions and not due to differences in methodology. This study has three aims. The first aim is to compare three survival analysis methods in two registries for high (breast and prostate cancer) medium (bowel) and poor (lung) prognosis cancers diagnosed between 2000-2008 in New South Wales (NSW), Australia, and the Northern and Yorkshire Cancer Registry and Information service (NYCRIS). The second aim is to apply the NSW cause of death allocation rules to NYCRIS data and evaluate measurement of cause specific survival. The third aim is to measure the difference in age adjusted survival by cancer type between NSW and Northern and Yorkshire (NY) at each time from diagnosis. **Methods** Survival estimates were calculated for NSW and NY using the cause specific survival (CS) method, the Ederer II method of relative survival (RS) and the recently recommended Pohar Perme (PP) method of survival. Age adjusted estimates for each method were obtained after applying the International Classification of Standardised Survival (ICSS) weights to age-specific survival estimates resulting in adjusted survival estimates. **Results** In NSW, unadjusted survival estimates varied little method for all sites and times from diagnosis analysed. This was also true for most cancer sites in NY except for bowel cancer where cause specific survival estimates were higher than relative or net estimates. The difference in age adjusted survival estimates in NSW and NY were between 5 and 11% higher in NSW than in NY depending on the cancer site regardless of the method and at each time from diagnosis. **Conclusions** The cause specific method of survival produced similar estimates to relative and net survival estimates in NSW. Therefore, cause specific survival in an acceptable alternative to relative and net survival methods. Differences in survival reported in NSW and NY appear real and not due to differences in survival methodology or the cause of death allocation.

3.2. Introduction

Benchmarking of cancer survival between regions or countries, as in the International Cancer Benchmarking Partnership (ICBP)[1, 2] requires accurate estimates of survival. Artefactual differences in survival from particular cancers may arise because of differences in completeness of ascertainment of incident cancers,[3, 4] methods of estimating cause specific survival,[5, 6] methods for ascertaining the fact of death and cause of death,[7] and age structures of the populations.[8]

The New South Wales Central Cancer Registry (NSWCCR) and the Northern and Yorkshire Cancer Registry and Information Service (NYCRIS) as part of UK registries are participants in the ICBP. To date there have been a number of publications that have compared survival by country for the major cancers of breast, [9] colorectal [10], lung [11] and ovary. [12] These papers show a similar pattern of better survival in Sweden, NSW and Canada and poorer survival in the UK and Denmark.

However, Beral and Peto,[13] suggest poorer survival in the UK might be due to lack of statutory cancer registration in England and Wales, resulting in under registration and high proportions of cases registered from death certificates only.[14] Under registration, is strongly refuted by Woods et al. who consider that 40% of long-term survival in patients would need to have been missed to explain the survival differential between the UK (poor survival) and Sweden (highest survival). [15,16,17]

Relative survival is the preferred method for estimating cancer survival in populations, because of the uncertain accuracy of cause of death ascertained from death certificates.[18, 19] Relative survival requires date of death only with period, country, age and sex specific life tables used to adjust for effects on survival of causes of death other than the cancer of interest. [20]

Recently, a new estimator (Pohar Perme or net survival) is suggested as an alternative to the relative survival method. This method implemented in the new Concord-2 (Global surveillance of cancer survival) study calculates the average predicted survival for each individual.[21, 22] Unlike relative survival, that calculates the ratio of the observed survival divided by the expected survival, this new method uses the background mortality to estimate

death from other causes to produce an unbiased estimate of true net survival. Danieli [23] suggests the net method be used when comparing the cancer impact between countries and within time periods because it takes into account the association between increasing age at diagnosis and the excess hazard of dying from cancer.[24]

Cause specific survival may be an acceptable alternative to relative survival provided the cause of death is recorded accurately. SEER registries currently examine cancer survival in racial and ethnic population subgroups routinely using this method. [6,25] Furthermore, the cause specific survival method is familiar to clinicians because it allows modelling of treatment and other prognostic factors known to influence survival without the requirement of life tables.

When making international comparisons [2, 17, 26]age standardisation is required to adjust for differences in the age structures between populations and is routinely used when reporting cancer survival in the UK.

In this paper, there are three questions of interest:

1. Is cause specific survival a practical alternative to the more traditional relative or net survival methods?
2. What is the effect on cancer-specific survival estimates for NY of using two methods of allocating the cause of death?
3. What are the differences in cancer survival estimates between NSW and NY for each cancer type at each time after diagnosis?

3.3. Methods

3.3.1. Data sources:

The New South Wales (NSW) Central Cancer Registry (CCR) is a population based registry of all new cases of cancer and deaths from cancer in the population of NSW.[27] In 2011, just under one-third (32%) of Australia's population resided in NSW with 7.2 million people. [28] Notification of invasive cancer and in situ breast cancer and melanoma is mandatory under

the NSW Public Health Act for all public and private hospitals, cancer centres, radiotherapy units and public and private pathology laboratories. [27]

The Northern and Yorkshire Cancer Registry Information Service (NYCRIS) is a population based cancer registry covering 13.3% of the UK population with a mean population of 6,555,870 [29] which is a similar size to NSW. NYCRIS receives weekly death certificate information for all patients who have a mention of cancer on the death certificate or those previously flagged by the registry with a diagnosis of cancer. The information updates existing records or initiates new registry records by searching for hospital or GP records. [30] The data source for NYCRIS was a merged data set, obtained from the National Cancer Intelligence Network UK, National Cancer Data Repository (NCDR)[31] of cancer registry and Office of National Statistics (ONS) provided death certificate data.

Both CCR and NYCRIS registries contribute to Cancer Incidence in Five Continents indicating that both registries meet an agreed quality standard. [32] In addition, five year observed relative and age-standardised survival were compared for an earlier time (1992–2000) for lung, breast and colorectal cancers which, will offer some insight into previously reported differences in survival between NSW and NY.[33]

Incident cases for cancers of the breast (C50) and prostate (C61); colon rectum and anus (C18, C19, C20, C21) and cancers of lung and bronchus (C33, C44) were followed up to the end of 2008 in the CCR and NYCRIS. These cancers were chosen to cover the range from high survival (breast and prostate), medium survival (colon, rectum and anus) and the poor survival (lung and bronchus). [34]

3.3.2. Methods aim one - is cause specific survival a practical alternative to the more traditional relative or net survival methods?

Analysis was undertaken using STRS (Survival Time Relative Survival), a programme developed by Paul Dickman [35] using STATA 12.1. [36] Unadjusted survival estimates calculated for NSW and NY using the cause specific survival (CS) method, the Ederer II method of relative survival (RS) and the recently recommended Pohar Perme (PP) method of survival. [37-39]

Ederer II, replaced the original Ederer I method [39] in the US Surveillance Epidemiology End Results (SEER) cancer statistics review in 2011.[5] Age, sex and year specific life tables used in the International Cancer Benchmarking Project [1] were used for relative and net survival estimation in both NSW and NYCRIS.

3.3.3. Methods aim two - What is the effect on cancer specific survival estimates for Northern and Yorkshire of using two methods of allocating the cause of death?

The NSW CCR derives the cause of death using the following process. The CCR receives person-identified text based death certificates fortnightly from the NSW Registry of Births, Deaths and Marriages and an annual file of ICD-10 coded cause of death information (up to 20 codes per death certificate) from the Australian Bureau of Statistics. The final cause of death allocation uses a hierarchy of rules. If a person has the same three-digit cause of death code as they have for a registered cancer then they are deemed to have died of that cancer. If the registered cancer has a specific code (e.g. C50.4) and the cause of death is a less specific (C50.9), then the most specific code is taken to be the cause of death. If there are no C codes that correspond to the registered cancer, a non-cancer death is recorded. If the cause of death is different from the C code of the registered cancer, records are examined, by a medical coder and the cause of death is manually determined with reference to pathology reports, other registered cancers and responses to letters sent to doctors, and in accordance with written procedures.

UK registries do not allocate the cause of cancer death. Instead four cause of death codes from each of Parts 1 (sections a, b and c) and 2 of the death certificate are linked to each person on the NYCRIS database who has died. [40] Therefore, in this study the cause of cancer death was allocated for NYCRIS by applying rules used in the NSWCCR.

For each person who had died two causes of death (method 1 and method 2) were assigned. The first cause of death method reviewed all ICD-10 codes in Part 1 (sections a, b and c) of the death certificate and provided the cause of death C code was the same as their registered case, the person was considered to have died from their cancer. The second method repeated the procedure but looked for a valid C code in Part 2 of the death certificate. Part 1 of the death certificate lists the disease or condition directly leading to death with a, b and c due to

(or as a consequence of each other. Whereas Part 2 of the death certificate refers to other significant conditions contributing to the death, but not related to the disease or condition causing it. For both methods if there was no mention of the cancer that the person was registered with then the person was recorded as dying from another cause of death.

For each case, the vital status in both registries was determined using the following criteria: died from their cancer, died from another cause, alive or censored at the 30th of December 2008. Cases with no date of death were considered alive. People categorised as having "died from another cause" were checked to determine that the relevant site-specific cancer code had not been overlooked.

3.3.4. Methods aim three - differences in age adjusted survival estimates for cancer specific, relative and net survival methods

Age standardised survival rates for each cancer site and each analysis type were obtained by applying the International Classification of Survival (ICSS) weights to age-specific survival estimates for each method of survival. The difference, between the NSW and NYCRIS age standardised point estimates of survival, for each period, from diagnosis was subtracted. The confidence limits for the difference in point estimates were calculated by squaring and then summing the standard errors (SE) of the age adjusted survival estimates for NSW and NYCRIS and then taking the square root of the sum.

3.4. Results

3.4.1. Results aim one - is cause specific survival a practical alternative to the more traditional relative or net survival methods?

Differences between five year unadjusted cause specific, relative and net survival percentages in NSW ranged from 0.0 to 1.4 percentage points depending on cancer type (Chapter 3 Table 1). Breast cancer survival at five years was 88.0%, 88.4% and 88.4% for cause specific, relative and net respectively and showed the least difference. Lung cancer survival in NSW males at five years was slightly higher at 15.1% for cause specific; 13.7% and 14.2% respectively for relative and net.

In NY cause specific survival was mostly higher than relative and net survival (ranged 1.0 to 4.3 for relative and 1.1 to 2.9 for the net survival method), and net survival was usually the

same as relative survival (0.0-1.5). However, differences varied by cancer site - ranging from 0.0 for prostate cancer (relative and net) to 4.3% higher for cause specific bowel cancer (Chapter 3 Table 1).

The smallest differences in survival estimates between analysis methods were for breast cancer (0.0 to 0.4 in NSW and 0.5 to 1.5 in NY) and the greatest for bowel cancer in NY (1.1-4.3) (Chapter 1 -Table 1).

3.4.2. Results aim two - What is the effect on cancer specific survival estimates for Northern and Yorkshire of using two methods of allocating the cause of death?

Five year cause specific survival estimates for breast cancer were similar to the relative and net when the cause of death was allocated using method one (breast: method one 83.1% relative 82.1% and net 81.6 %). Similarly, observed for prostate cancer (method one 79.5% relative 80.6%. and net 80.9%).

Five year cause specific bowel and lung cancer estimates were similar to relative and net only after the additional cancer specific deaths from method two were included (bowel cause specific (method 2) 50.9% relative 51.4% and net 52.9 %) and lung (cause specific (method) two 6.9% relative 6.9% and net 7.3%) (Chapter 3, Figure 2).

3.4.3. Results aim three - differences in cancer survival estimates between New South Wales and Northern and Yorkshire for each cancer type at each time after diagnosis?

Survival estimates in NSW were 5-11% higher than NY depending on the cancer site even after taking account of the cause of death allocation.

For breast cancer patients, there was little difference in age adjusted cancer survival between NSW and NY for the first year post diagnosis. At five years, age adjusted breast cancer survival in NSW was 4.8% (95%CI 4.2-5.4) higher than NY females for cause specific and 6.7% (95%CI 5.0-8.4) and 6.6% (95%CI 4.5-8.7) for relative and net survival (Table 2).

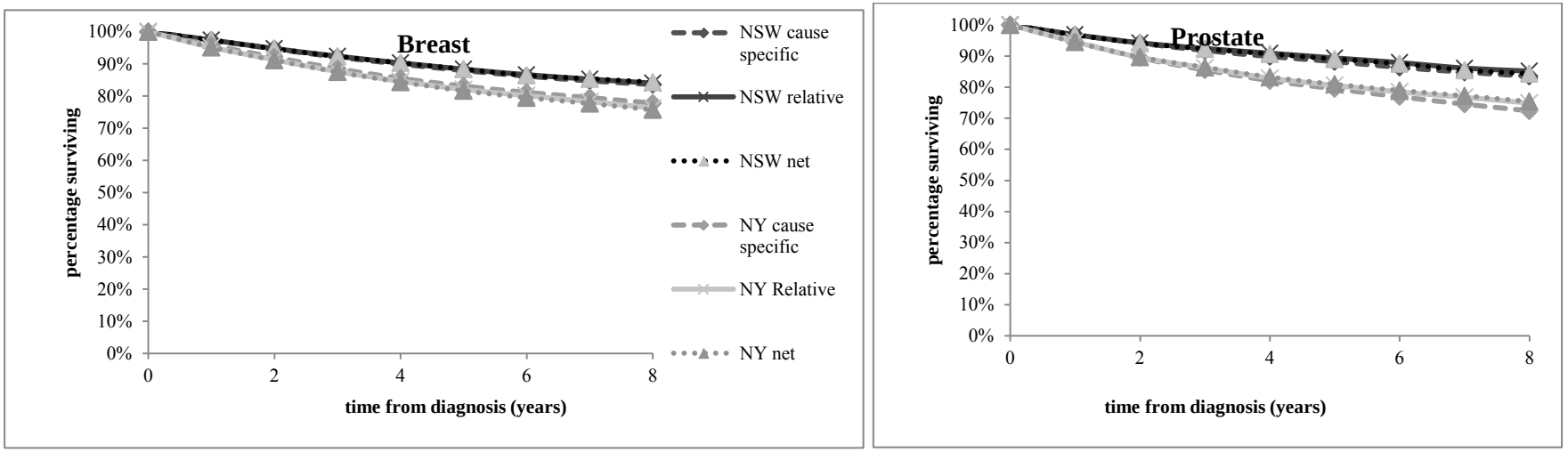
The difference in five year prostate cancer estimates of survival were similar regardless of the method used with 8.0% (95%CI 5.6-10.5) higher survival in NSW males than NY males for cause specific; 8.3% (95%CI 5.0-11.5) and 7.7% (95%CI 2.4-12.0) for relative and net survival. At five years, age adjusted cause specific bowel cancer survival estimates were

8.3% (95% CI 5.7-10.9) higher in NSW males and 7.8% (95%CI 5.0-10.6) higher in NSW females than NY males and females. However, relative and net survival estimates and confidence intervals were the same with NSW survival on average 11.0% higher than NY males and females.

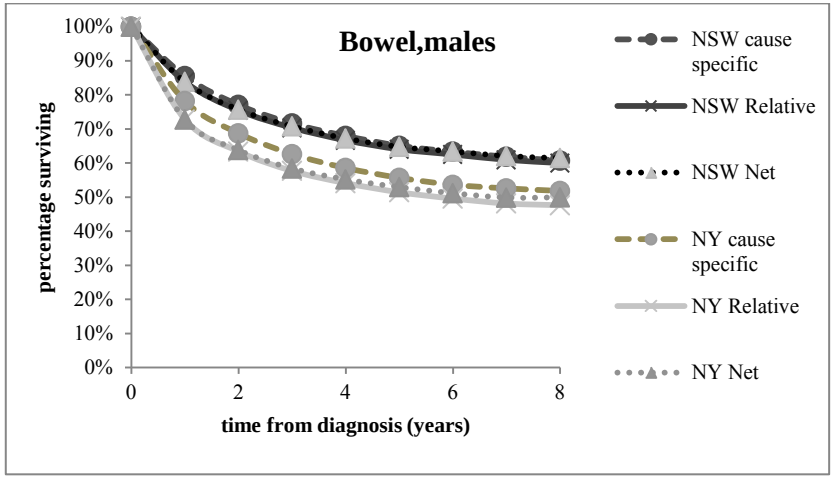
Differences in lung cancer survival were greatest at six months post diagnosis with 11.0% and 14.0% higher estimates of survival in NSW males and females compared to NY males and females. However, by five years there was a 7% higher estimate in NSW males regardless of the method and between 7.9% and 8.5% higher survival in NSW females.

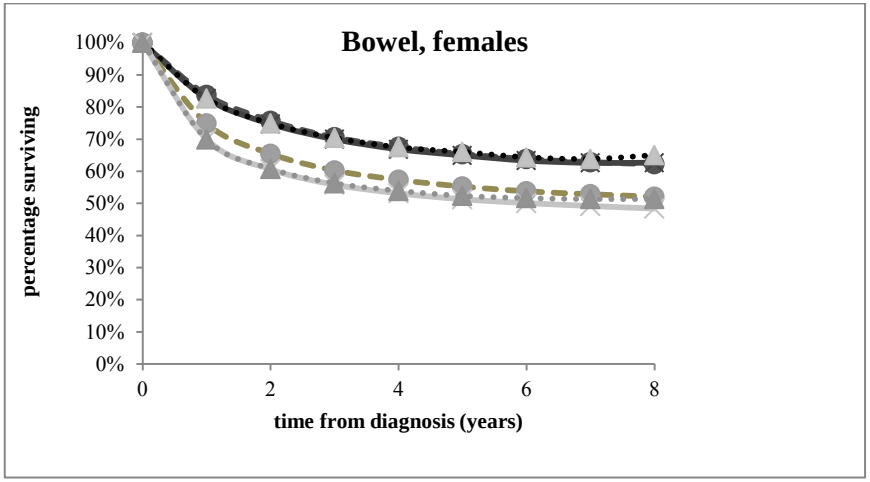
Confidence limits at each period since diagnosis were narrower for cause specific and widest for the net survival method. The confidence intervals are much wider for net survival because the standard errors are large and they also increase over time. Regardless of the survival method used, confidence limits became wider over time (Figure 3 Table 2).

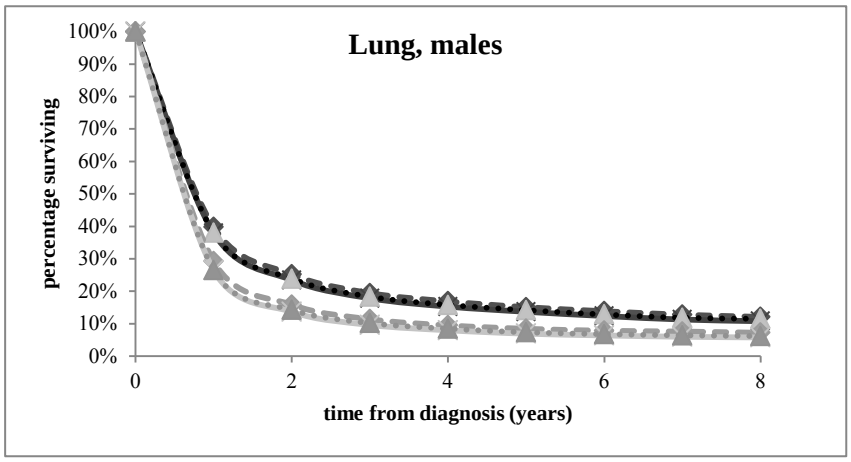
Chapter 3 Figure 1a Comparisons of cause specific, relative and net survival in New South Wales and the Northern and Yorkshire Region of England 2000-2008 for breast and prostate cancers

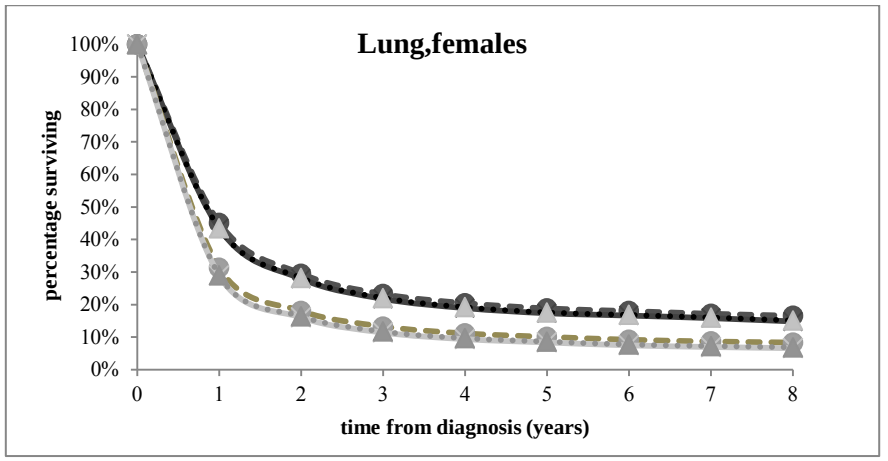


Chapter 3 Figure 1b Comparisons of cause specific, relative and net survival in New South Wales and the Northern and Yorkshire Region of England 2000-2008 for bowel and lung cancers (continued)

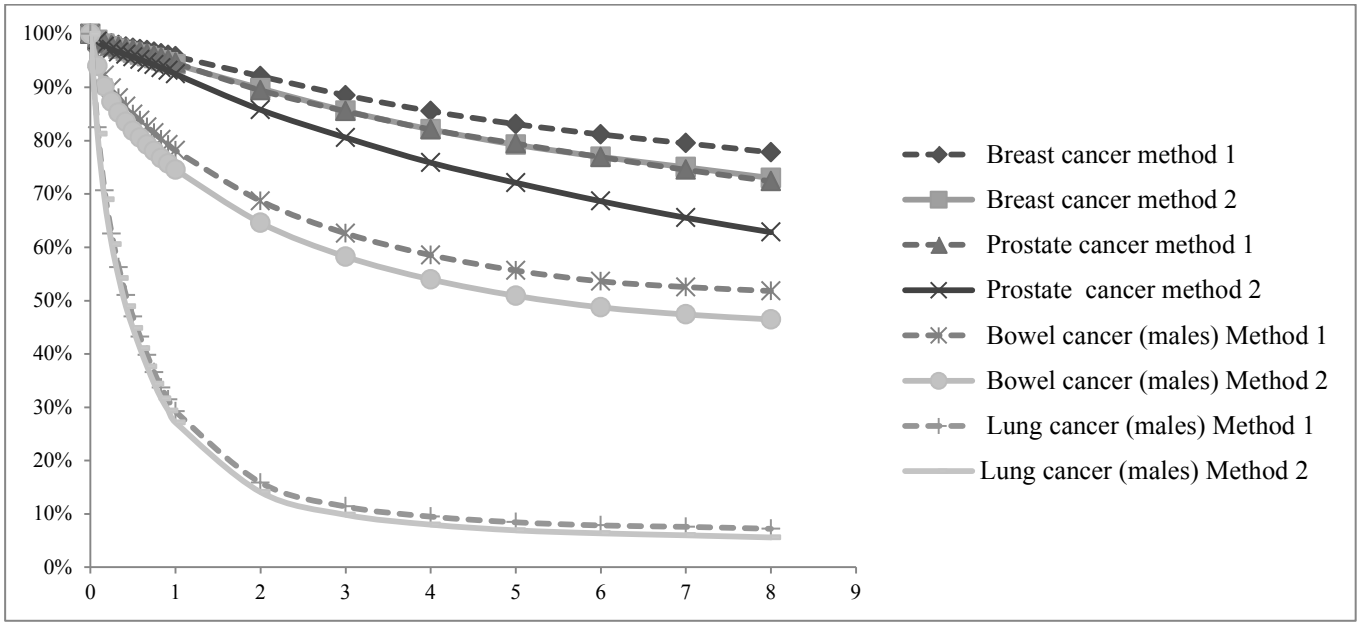








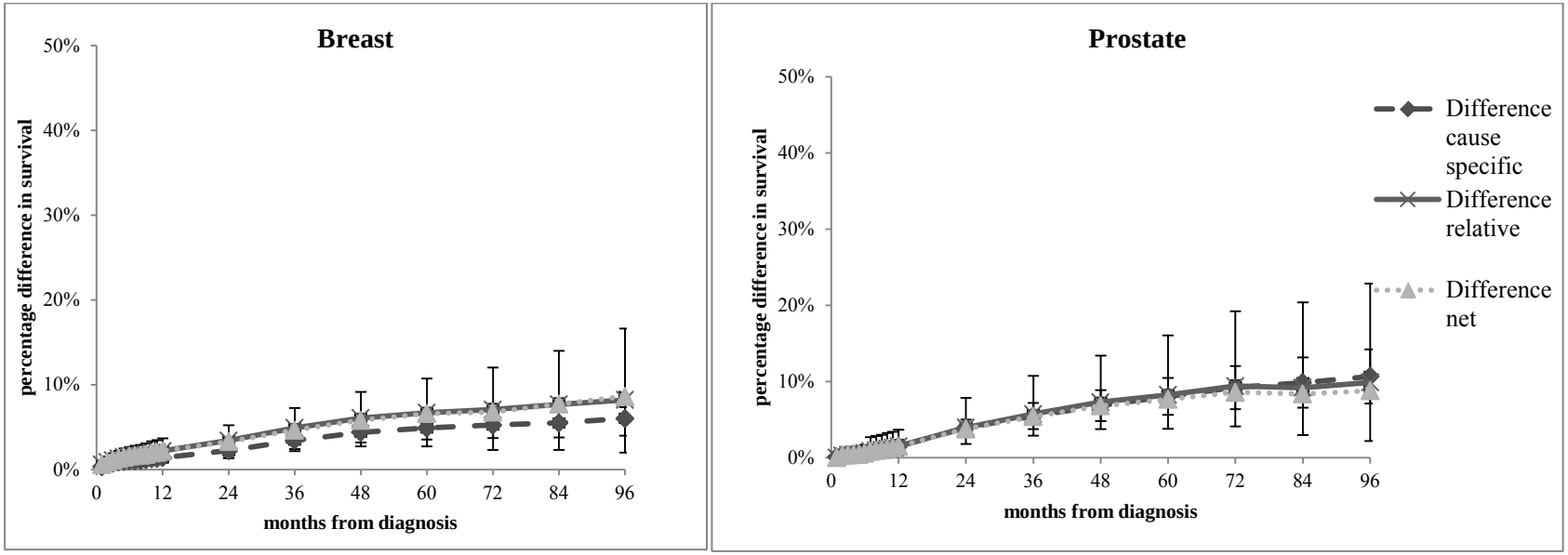
Chapter 3 Figure 2 Comparisons of age adjusted survival for breast, prostate, bowel and lung cancers for cause specific, relative and net survival in New South Wales and Northern and Yorkshire regions 2000-2008



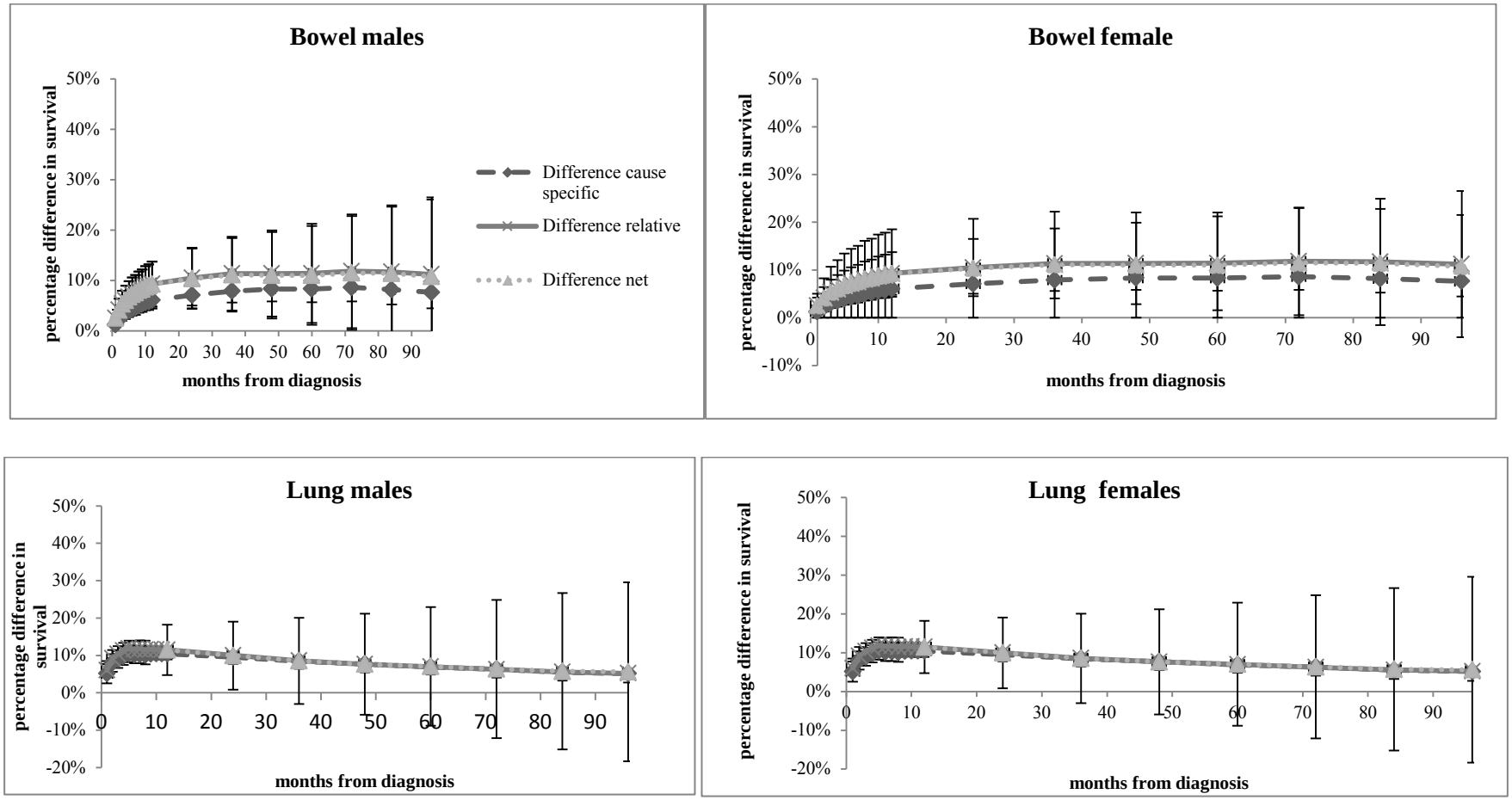
Method 1 –The relevant cause of death code is found in Part 1(sections a, b and c) of the death certificate

Method 2 – The relevant cause of death code is found in Parts 1 (sections a, b and c) and 2 of the death certificate

Chapter 3 Figure 3 Comparisons of New South Wales and Northern and Yorkshire regions of the difference in age adjusted for cause specific, relative and net survival of breast, prostate, 2000-2008



Chapter 3 Figure 3 Comparisons of New South Wales and Northern and Yorkshire regions of the difference in age adjusted for cause specific, relative and net survival of breast, prostate, bowel and lung cancers, 2000-2008



Chapter 3 Table 1 Unadjusted five year cause specific, relative and net survival estimates for New South Wales and Northern and Yorkshire regions by 2000-2008

	New South Wales						Northern and Yorkshire					
	Cause specific	95%CI	Relative	95%CI	Net	95%CI	Cause specific	95%CI	Relative	95%CI	Net	95%CI
Breast	88.0	(87.5-88.4)	88.4	(87.8-88.9)	88.4	(87.8-88.9)	83.1	(82.7-83.5)	82.1	(81.5-82.6)	81.6	(81.0-82.3)
Prostate	88.0	(88.0-89.0)	89.0	(89.0-90.0)	89.0	(88.0-90.0)	79.0	(79.0-80.0)	81.0	(80.0-81.0)	81.0	(80.0-82.0)
Bowel males	65.1	(64.3-65.8)	64.0	(63.1-65.0)	64.7	(63.8-65.7)	55.7	(54.8-56.5)	51.4	(50.4-52.4)	52.9	(51.9-53.9)
Bowel females	65.4	(64.5-66.2)	65.0	(64.0-66.0)	66.0	(64.9-67.0)	55.3	(54.3-56.1)	51.3	(50.3-52.4)	52.4	(51.2-53.5)
Lung males	15.1	(14.4-15.8)	13.7	(13.0-14.4)	14.2	(13.5-14.8)	8.4	(8.0-8.9)	6.9	(6.5-7.3)	7.3	(7.0-7.7)
Lung females	18.8	(17.9-19.8)	17.4	(16.4-18.3)	17.6	(16.7-18.5)	10.1	(9.6-10.6)	8.4	(7.9-8.9)	8.6	(8.2-9.1)

*LCI lower confidence interval, UCI Upper confidence interval

Chapter 3 Table 2 The percentage difference in five year age adjusted cause specific, relative and net survival estimates and associated 95% confidence limits between NSW and Northern and Yorkshire regions by cancer site

	Cause specific survival		Relative survival		Net survival	
		95%CI		95%CI		95%CI
Breast	4.8	(4.2-5.4)	6.7	(5.0-8.4)	6.6	(4.5-8.7)
Prostate	8.1	(5.6-10.5)	8.3	(5.0-11.5)	7.7	(3.4-12)
Bowel males	8.3	(5.7-10.9)	11.4	(1.6-21.2)	11	(1.2-20.8)
Bowel females	7.8	(5.0-10.6)	11	(1.0-21.1)	11.1	(1-21.1)
Lung males	6.9	(4.7-9.1)	7	(4.8-9.1)	7.0	(-8.8-22.9)
Lung females	7.9	(5.0-10.7)	8.5	(5.8-11.2)	8.5	(-7.3-24.4)

3.5. Discussion

In NSW, five year unadjusted survival estimates were similar at each period from diagnosis regardless of the method used and for each cancer site. Similarly, in NY cause specific survival estimates were similar for most cancer sites with the exception of colorectal cancer, which was 4% higher than relative and net survival estimates at five years. The effect of cause of death on five year cancer specific survival estimates in NY depended on cancer site. For the higher survival cancers, breast and prostate method one provided similar estimates to relative and net survival. Whereas, for the poorer survival cancers of bowel and lung, method two provided similar cause, relative and net survival estimates. Differences in age adjusted five year survival estimates in NSW were 5% to 11% higher depending on the cancer type. The differences by cancer site were similar regardless of the method except for the five year cause specific estimates for breast cancer and bowel cancer which were 2% and 3% lower than net or relative survival methods.

Survival estimates in NSW were similar regardless of the method used or the cancer site. This finding is consistent to the findings of a recent Australian study that also compared relative and cause specific survival for the same cancer sites and reported that one and five year relative survival estimates produced similar results.[41]

Cause specific survival is only a viable alternative if there is good cause of death coding. The most plausible reason for the similar survival estimates in NSW compared to the slightly higher cause specific estimates in NY (compared to relative and net) are the procedures undertaken to allocate the cause of death. NSW uses multiple sources of notification to determine a case of cancer. The cause of death is determined by death certificate and supplemented by pathology and another notification sources. Other Australian registries have similar practices to those described in NSW.

Recently, the Geneva Cancer Registry compared cause specific and relative survival estimates for breast cancer and reported almost perfect survival estimates with a difference at 20-year survival of less than 1%.[42] The Geneva Cancer Registry like the CCR determines the cause of death of each registered cancer patient by examining all available clinical

information relating to the patient's disease. Furthermore, they also examine all treatment information.

In NY, there are a number of differences in registry practices compared to NSW. For example, while hospital notifications, pathology reports and GP records are used to register a case there is a heavy reliance on death information to first initiate a case and then trace back to the GP and other hospital records. Furthermore, a person can die from cancer without having a corresponding case of that cancer. These two issues will influence the allocation of the cause of death and therefore cause specific survival estimates; which may explain why cause specific survival estimates for NY were slightly higher for colorectal and lung cancer compared to relative and net survival estimates.

In NSW and NY relative and net methods showed similar results at each period from diagnosis for a cancer site. Survival estimates using relative and net methods are considered the same provided there is no one particular demographic variable that is strongly influencing the hazard of death. [38] Age at diagnosis is an important demographic variable known to influence the excess hazard of death. The net survival method better adjusts for this effect. [24]

In addition, there are some issues associated with the net method that may cause difficulties for cancer registries. We found that while point estimates were similar using the relative and net survival method, confidence limits were wider using the net survival method for each cancer site. Dickman [43]and Roche[22] both report that the survival estimates using the net survival method have large variances explaining the wide confidence limits. In comparison, the Ederer II method of relative survival has smaller confidence limits and it has also been implemented in the SEER STAT application. [5] Therefore, in the absence of cause of death information, the Ederer II method would appear to be the most appropriate and easily accessible method of survival for registries.

3.5.1. What is the effect on cancer-specific survival estimates for Northern and Yorkshire of using two methods of allocating the cause of death?

The cancer specific survival estimates for NY using method 1 that is allocating the cause of death based on Parts 1 (sections a, b and c) of the death certificate resulted in similar survival estimates as relative and net survival for cancers of the breast, prostate and lung. Whereas, the inclusion of Parts 1 and 2 of the death certificate resulted in similar estimates of survival for colorectal cancer. Others [6, 44] have similarly reported good agreement between the relative survival and cause specific survival estimates, for most cancer sites, with colorectal cancer showing the most variability due to the differences in the misallocation of rectal or colon cancer as the cause of death. Had examination of pathology and other sources of notification occurred, as is the practice in NSW and Geneva, the death recorded as bowel cancer in part 2 of the death certificate may have been considered when determining the cause of death.

Percy[45] compared the underlying cause of death from the death certificate and hospital diagnoses in SEER registry data and found a high level of agreement of 98.7% for breast and 98.1% for prostate but lower agreement of 95.6% for large bowel and 94.3% for lung. Furthermore, clinician assigned cause of death and death certificate cause of death coding were compared for cancer of the prostate. [46] A high concordance or K statistic of 0.91 was reported.

Not surprisingly, most studies report that the level of agreement is higher in people who have one primary cancer. Lund et al[47] in a study of 229,181 patients found that agreement between the coded cause of death and the initial diagnosis was 85% in patients with one primary and 64% in patients with one or more primary cancers. Similarly, Boer found that in people diagnosed with colorectal cancer who died of cancer within 5 years, 94.5% died from colorectal cancer, 3.0% died from metastases and 2.5% from other cancer death. For people diagnosed with colorectal cancer who have more than one cancer and die within 5 years, only 64.1% have a cause of death of colorectal cancer recorded.[44] In the NSW and NY registries, the majority of cases were primary only (88% NSW and 91% for NY). Therefore, misallocation of cause of death because a person has more than one primary cancer is unlikely to be a major issue.

3.5.2. Differences in age adjusted survival estimates between NSW and Northern and Yorkshire

The 5-11% difference in five year age adjusted survival estimates (depending on cancer site) between NSW and NY for the period 2000-2008 reported in this study, is similar to that reported in the earlier study undertaken by Yu et al.[33] For example, five year age adjusted relative survival estimates for breast cancer were 6.3% higher in NSW than in NY for women diagnosed in 1992-2000 which is similar to the 6.7% (relative) and 6.6% (net) found in this study. Also, five year colorectal cancer survival estimates in 1992-2000 were 9.8% higher in NSW than NY compared to 11.4% (relative) and 11.0% (net) found in this study. Therefore, for breast and colorectal cancer the better survival in NSW and NY appear consistent regardless of method and diagnostic period.

Both registries in our study code cases of cancer using the International Classification for diseases for Oncology Revision 3,[34] follow the International Association of Cancer Registries (IACR) definitions for multiple primaries [48] and the IACR definitions for recording the date of diagnosis. Nevertheless, there are some differences; cancer registration in NSW is mandated under the Public Health Act whereas in NY, it is not. Furthermore, because death information is used to initiate a notification it has been suggested [13] that good prognosis cancers may be missing because they have not been notified independently from other sources. To investigate, a comparison is made of reported data quality indicators for NSW and NY for the same period. [32]

Accordingly, for most cancer, registry gold standard indicators that can be compared in NSW and NY they were comparatively similar. Both registries had high proportions of cases that were histologically verified (over 85% for breast, prostate and bowel cancers and slightly lower for lung cancer in males NSW 84.9%, NY 57.3% and females NSW 82.9% NY 52.8%). [32]. Both registries had a low death certificate only proportion, indicating that the majority of registered cases had notifications from other sources besides a death certificate. Furthermore, one minus the difference in mortality incidence ratios previously found to be a good proxy for cancer survival were also similar. [49] [32]

In summary, survival estimates were similar regardless of method used in NSW and for most cancer sites in NY (with the exception of bowel cancer). Therefore, cause specific survival is a satisfactory alternative to relative and net survival in NSW and NY for most cancer sites except bowel cancer. Secondly, the difference in the cause of death allocation was greatest for bowel cancer in NY, which reduced when cancer deaths mentioned in section 2 were included. Thirdly, age adjusted survival estimates, were between 5 and 11% higher in NSW, than in NY (depending on cancer site), and after taking account two methods of cause of death allocation. Furthermore, reported data quality indicators were high in both registries. Therefore, the differences in survival rates between NSW and NY are unlikely to be an artefact due to method of survival or allocation of the cause of death. They may be due to other factors like earlier stage at presentation or different treatment in NSW compared to Northern and Yorkshire as has been suggested in recent International Benchmarking studies of cancer survival [9, 11, 50] or perhaps treatment differences that are yet to be investigated.

3.5.3. Conclusion

The cause specific method of survival produced similar estimates to relative and net survival estimates in NSW. Therefore, cause specific survival in an acceptable alternative to relative and net survival methods. Differences in survival reported in NSW and NY appear real and not due to differences in survival methodology or the cause of death allocation.

3.6. References

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4. Investigation of poorer bladder cancer survival in women in NSW Australia: A data linkage study

This is a published manuscript

Tracey E, Watt H, Currow D, Young J, Armstrong B. Investigation of poorer bladder cancer survival in women in NSW, Australia: a data linkage study. *BJUI International.* Mar 2014;113(3):437-448.

4.1. Abstract

Objective: To investigate the associations of a range of personal and clinical variables with bladder cancer survival in men and women in NSW to see if we could explain why bladder cancer survival is consistently poorer in women than in men.

Patients and Methods: All 6,880 cases of bladder cancers diagnosed in NSW between 2000 and 2008 were linked to hospital separation data and to deaths. Separate Cox proportional hazards regression models of hazard of bladder cancer death were constructed in those who did or did not undergo cystectomy.

Results: Sixteen per cent of bladder cancer patients underwent cystectomy (16 per cent of men and 15 per cent of women). Women who underwent cystectomy were 26 per cent more likely to die than men (Hazard Ratio (HR) 1.26 95% confidence interval, CI 1.00-1.59) after adjustment for age, stage, time from diagnosis to cystectomy, distance from treatment facility and country of birth. None of these covariates had a material effect on the difference in hazard between women and men. However, when stratified by a history of cystitis, the adjusted hazard was 55 per cent higher in women (HR 1.55, 95%CI 1.15-2.10) than men with a history of cystitis while, in the absence of this history, there was no difference in the hazard between men and women (HR 0.99, 95%CI 0.57-1.70). This apparent modification of the effect of sex on bladder cancer outcome was not seen in patients treated only by resection: the adjusted HRs in women relative to men were 1.10 (95% CI 0.92-1.31) in those with a history of cystitis and 1.21 (95% CI 0.98-1.50) in those without. History of haematuria did not modify appreciably the association of sex with bladder cancer outcome.

Conclusions:.Women's poorer survival from bladder cancer than men's remains unexplained. The possibility, however, that some factor associated with a history of cystitis may contribute to or explain the poorer outcome in women merits further investigation. (326 words)

Keywords: Bladder cancer, survival, cancer registry, cystitis, surgery, distance

4.2. Introduction

Unlike most other cancers where cancer survival is better in women than men, bladder cancer survival is consistently higher in men.[1], [2], [3], [4],[5]We previously examined predictors of case fatality for bladder cancers diagnosed in 1980–2003 to understand why unadjusted bladder cancer survival fell over time and why survival was poorer in women than in men. After adjusting for age, extent of disease, socioeconomic status (SES), period of diagnosis and histological type, the hazard of death from bladder cancer was 13 per cent (95% CI 5–21%) higher in women than men. Fatality was most influenced by age at diagnosis, extent of disease, and histological type [6].

The aim of the present study is to extend our earlier study [6] and further investigate reasons for the poorer survival in females; the study links cancer registry records to hospital separation records for bladder cancer cases diagnosed in 2000 to 2008. The latter contain a range of additional variables that could be relevant to the difference in bladder cancer survival between women and men, including risk factors, symptoms, procedures, comorbid conditions and distance from the treatment facility. This analysis uses these additional data in a search for an explanation for the poorer survival in women.

4.3. Patients and methods

4.3.1. Data Sources:

The NSW Central Cancer Registry (the Registry) was the primary data source for the present study. Death information was retrieved by electronic linkage of the Registry with NSW death records up to 2008 and the National Death Index at the Australian Institute of Health and Welfare for cases diagnosed up to 2006. Registry operational details have been described previously [1]. In addition to the registered cause of death provided by the ABS, pathology details regarding the cancer and follow up with doctors are used by the Registry and are thought to classify cause of death more accurately than is possible when relying solely on death certificate information. Bladder cancers (International Classification of Diseases and Related Health Conditions 10th revision code C67[7], which encompasses all malignant, that is stage T1 or worse, bladder cancers), notified to the Registry between 2000 and 2008 were investigated in the present study. The NSW Central Cancer Registry does not

register in situ bladder cancer[8]. Notifications of invasive bladder cancer are followed up to ensure that they have been verified histologically and where possible a cancer registry coder physically sights and codes from the original pathology report.

The NSW Ministry of Health administers the NSW APDC, the source of hospital separation records. Separation records are prepared after patients leave (separate from) hospital and provide a complete census of all patients receiving inpatient (including day-only) services from NSW public and private hospitals. Hospital separation records have been included in this analysis for the fiscal years 1999–2000 to 2008–09. Hospital medical record coders record and code, in the separation record, all procedures and diagnoses, symptoms and risk factors recorded in the medical discharge summary for a patient's stay in hospital in accordance with the International Classification of Diseases – Australian Modification.[9], [7]

There were 6,880 people (5,026 men, 1,854 women) diagnosed with bladder cancer in NSW between 2000 and 2008. The majority (92.1 per cent) were histologically verified (75.8 per cent by CCR coders sighting the pathology report and 15.4 per cent sighted only by hospital coders), 6.4 per cent were verified clinically and 0.9 per cent were verified by cytology only. There were 105 cases, or 1.5 per cent, identified only by death certificate or autopsy, which were excluded from the survival analysis but included in the descriptive and comparative analyses.

The 150 registered bladder cancer cases that did not link to a hospital separation record may have been treated in hospitals in adjoining Australian States or Territories missed links or had only outpatient treatment. They were excluded from the analysis. The combined automated and manual linkage process had an estimated false positive rate of 0.4 per cent.[10]

4.3.2. Variables available for analysis

The following variables were obtained from cancer registry records: age at diagnosis; month and year of diagnosis; summary stage (extent of disease) at diagnosis, classified as localised, regional, distant or unknown [11]; histological subtype of cancer, summarised as transitional cell, papillary transitional cell and other (International Classification of Disease of Oncology (ICD-O) version 3 morphology codes - M81203, M81303 all other M codes were grouped as

other) [12]; country of birth, as notified to the cancer registry and reported by the patient at admission to hospital; place of residence, classified as metropolitan, outer metropolitan and rural; socioeconomic status, allocated in five categories using the Australian Bureau Statistics' Index of Relative Socioeconomic Disadvantage [13]; survival time in months from diagnosis to death or end of 2008; and status at the end of 2008 – alive, died of bladder cancer or died of another cause.

These additional variables were obtained from hospital separation records: history of haematuria, absent or present (any of International Classification of Diseases Codes – tenth revision (ICD-10) disease codes Z54.2, Z51.1, Z51.2 in any record for each bladder cancer patient); history of cystitis, absent or present (any of ICD10 codes N30.0-N30.9 in any record); smoking history, current or past (any of ICD-10 codes Z86.43, Z72.0, Z71.6, F17 in any record); procedures undergone for the management of bladder cancer (see below); date of procedure to which the patient's management was classified (see below); type of hospital of admission for this procedure, public or private; distance of residence from the treatment facility (see below); and Charlson comorbidity index (see below).

4.3.3. Bladder cancer procedures

Patients' management was classified to the bladder cancer procedure they underwent that was most likely to be curative. Thus, cystectomy was classified ahead of resection or endoscopic destruction of bladder tissue and total cystectomy ahead of a prior partial cystectomy. Patients who did not undergo cystectomy were classified to resection if they underwent any resection of bladder tissue or endoscopic destruction of bladder tissue (hereafter any reference to resection is a reference to resection or endoscopic destruction). All other patients were considered to have had no specific treatment for bladder cancer. Chemotherapy and radiotherapy are not reliably recorded in separation records and so were not considered for the analysis. The hospital admission for the most curative procedure was used to determine the time from diagnosis to treatment, and the distance the patient travelled to obtain that treatment.

4.3.4. Treatment delay

Time from diagnosis to treatment was calculated as the time in months from the date of diagnosis to the date of the procedure from which the patient's management was classified. There were 362 bladder cancer patients who apparently had a bladder cancer procedure before their date of diagnosis and did not have a subsequent surgical procedure; they were excluded from the analysis.

4.3.5. Comorbidities

Comorbidities were classified using the Charlson index[14]. The index for each patient was obtained by scanning 20 diagnosis fields and 11 procedure fields in the hospital separation record of their treatment or, with no treatment, the first bladder cancer admission at or after their diagnosis. The Charlson score was grouped into no, low (1-2), medium (3-4) or high comorbidities (5-18). Secondary cancer, most often a code reflecting the stage of the bladder cancer, was excluded from the comorbid conditions.

4.3.6. Distance from treatment facility

Distance from the treatment facility was determined by calculating the distance in kilometres from the patient's geocoded address to the treatment facility's geocoded address using the "Great Circle Distance Calculator"[15].

4.3.7. Statistical analysis

An analysis was done first to see which variables were independently associated with sex. All variables except survival time and status at the end of 2008 were included in a logistic regression analysis in which sex was the dependent variable and variables removed by stepwise backward elimination was undertaken with the likelihood ratio test used to compare two models. At each step, the remaining variable with the highest type III test p value was the next eliminated [16].

Survival analyses were limited to patients who were managed by cystectomy or, in its absence, resection; 78 per cent of women and 77 per cent of men were managed in one or other of these ways, the remainder had apparently received no surgical treatment (Table 1). Kaplan Meier survival curves were plotted to visualise the associations of survival with sex

and type of bladder cancer procedure. As there were intersecting survival curves for treatment with cystectomy and treatment with resection (Figure 2), separate multivariate Cox proportional hazards models of case fatality were constructed in patients managed by cystectomy and patients managed by resection. Again, variables were removed stepwise by backward elimination as described above. A stepwise, forward regression analysis was also undertaken as a check.

Several sensitivity analyses were done. First, patients who died within one month of their procedure (cystectomy, resection), regardless of whether death was from bladder cancer or another cause, were excluded from the Cox regression models to examine the sensitivity of results to early deaths. Second, only cases whose histopathological diagnosis of invasive bladder cancer was verified by cancer registry staff were analysed to assess possible effects of coding bias, a well-known issue with bladder cancer[17]. Third, because of uncertainty of completeness of ascertainment (due to differences in coding practices in hospitals) possible effects of presence or absence of an ileal conduit and presence or absence of lymph node removal was examined only in sensitivity analyses.

4.4. Results:

Among the 6,880 bladder cancer patients diagnosed between 2000 and 2008 and followed to the end of 2008, a higher proportion of women (37%) than men (28%) had died from their bladder cancer (Table 1). There were no material differences between men and women in the proportions receiving a cystectomy, a resection, or no potentially curative bladder cancer surgery.

4.4.1. Variables associated with patient's sex

The odds that a person diagnosed with bladder cancer was a woman were greater if aged 80 years and older, born in Australia, diagnosed with other than transitional cell or papillary transitional cell carcinoma and with distant metastases at diagnosis. Women were more likely to receive treatment within one or two months of diagnosis, less likely to present with medium or high comorbid conditions and with haematuria, more likely to present with

cystitis, less likely to be current or ex-smokers, less likely to live in rural areas at diagnosis and less likely to receive treatment in private hospitals (Table 2).

Chapter 4 Table 1 Characteristics of people diagnosed with bladder cancer and their cancers, management and outcome, NSW, 2000 to 2008

Descriptive characteristics		Men n=4656	Women n=1,712	Total n=6,368
Age group	15-49	3%	3%	3%
	50-59	10%	7%	9%
	60-69	22%	17%	21%
	70-79	37%	34%	36%
	80+	28%	39%	31%
Country of birth	Australian born	63%	72%	65%
	Born in English speaking	13%	11%	12%
	Born in non- English speaking	24%	17%	22%
	Unknown country of birth	0%	0%	0%
Socioeconomic status	Highest SES	18%	19%	18%
	Second highest SES	19%	17%	18%
	Middle SES	19%	17%	18%
	Second lowest SES	21%	23%	22%
	Lowest SES	24%	24%	24%
Summary stage (extent of disease)	Localised	51%	51%	51%
	Regional	19%	18%	18%
	Distant	6%	9%	7%
	Unknown	24%	23%	24%
****Histological type	Transitional cell	43%	45%	43%
	Papillary transitional cell	50%	44%	48%
	Other	7%	12%	9%
Period of diagnosis	2000-2004	47%	48%	47%
	2005-2008	53%	52%	53%
*History of haematuria	No haematuria	70%	76%	72%
	Haematuria	30%	24%	28%
**History of cystitis	No cystitis	50%	39%	47%
	Cystitis	50%	61%	53%
***Smoking history	Non smoker	31%	23%	29%
	Current smoker	41%	23%	36%
	Ex smoker	28%	54%	35%
Potentially curable surgical	#Cystectomy	18%	16%	17%
	##Resection	66%	67%	67%
	### No specific treatment	16%	17%	16%
Charlson index	No comorbidity	23%	32%	26%
	Low comorbidity	34%	35%	34%
	Medium comorbidity	24%	20%	23%
	High comorbidity	19%	12%	17%
Time from diagnosis to treatment	One month	68%	71%	69%
	Two months	6%	7%	7%

Descriptive characteristics		Men n=4656	Women n=1,712	Total n=6,368
	Three months	4%	5%	4%
	Four or more months	22%	17%	20%
Region of residence at diagnosis	Metropolitan	38%	39%	39%
	Outer metropolitan	36%	37%	36%
	Rural	26%	24%	25%
Distance from treatment facility	Less than 25 km	77%	80%	78%
	26- to 75km	13%	12%	13%
	76 to 125km	5%	4%	5%
	126 plus kilometres	5%	4%	5%
Type of hospital	Public hospital	57%	61%	58%
	Private hospital	43%	39%	42%
Status at the end of	Alive	52%	47%	51%
	Died of bladder cancer	28%	37%	30%
2008	Died of another cause	20%	17%	19%
	Total	73%	27%	100%

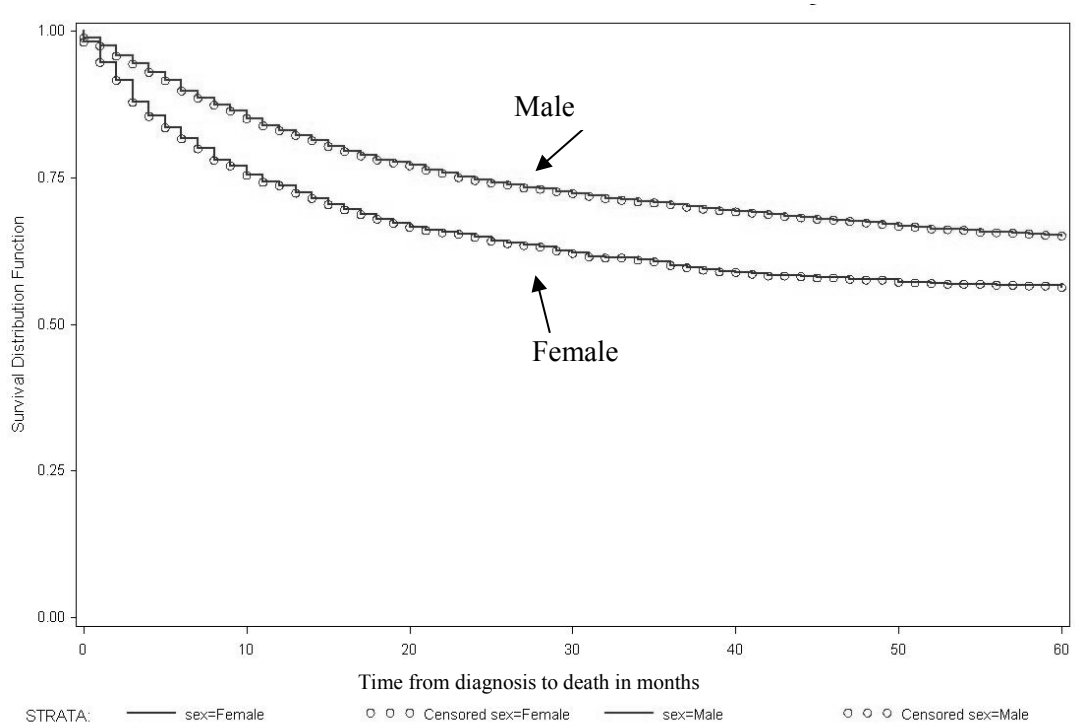
* Haematuria codes (Z54.2, Z51.1,Z51.2),
**Cystitis codes (N30.0-N30.9)
***Smoking codes (Z86.43, Z72.0, Z71.6,F17)
****Morphology codes (M81203, M81303 and all other grouped together)
Cystectomy codes (37014-00, 37000-00, 37000-01)
##Resection of bladder tissue or endoscopic destruction codes (36839-04,36845-04, 36845-05,36840-02,36854-02,36839-00,36839-02,36845-01,36840-00, 36845-00,36845-02,36845-03,36845-06,36845-07,36840-01
Includes cystoscopy, biopsy or other diagnostic procedure codes (36812-00, 36812-01, 36842-00, 36860-00, 36821-02, 36818-00, 36818-01, 3685700, 36806-02, 36854-00, 36854-01, 36851-00) and no procedure codes

Chapter 4 Table 2 Comparison of women and men with bladder cancer, NSW, 2000 to 2008 (multivariate logistic regression analysis – odds ratios and 95% confidence limits)

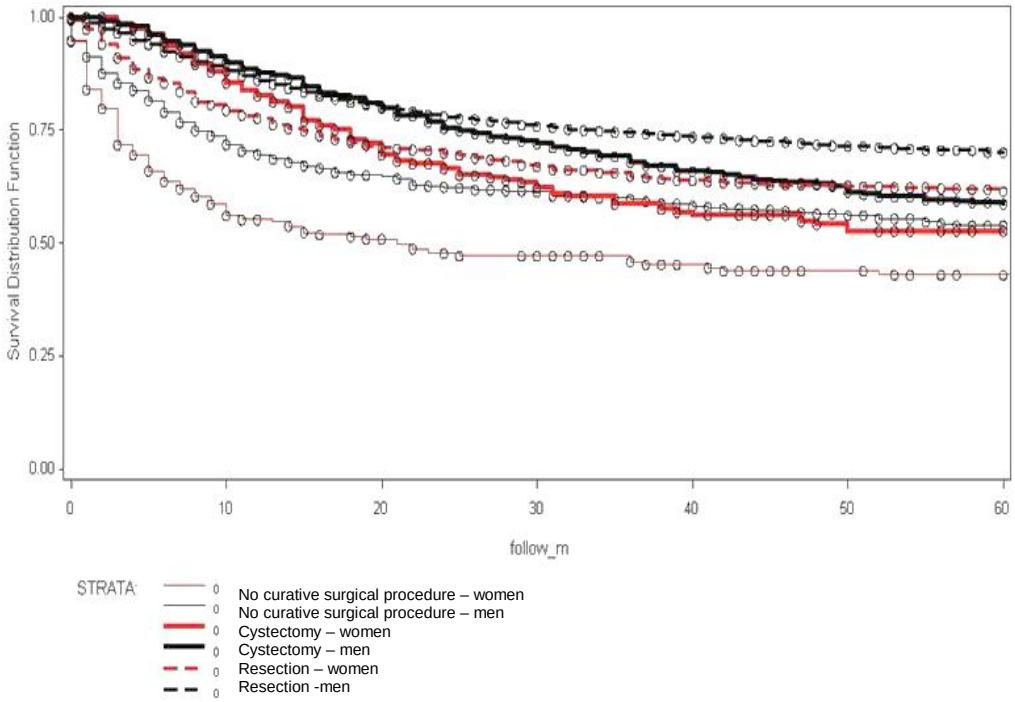
Descriptive	Characteristics	OR#	LCI#	UCI#	P value
Age group	15-49	1.00			
	50-59	0.89	0.61	1.31	
	60-69	0.99	0.69	1.41	
	70-79	1.32	0.93	1.86	
	80+	1.86	1.31	2.64	<.0001
Country of birth	Australian born	1.00			
	Born in English speaking countries	0.59	0.51	0.70	
	Born in non- English speaking countries	0.73	0.61	0.88	
	Unknown country of birth	0.64	0.20	2.01	<.0001
Summary stage (extent of disease)	Localised	1.00			
	Regional	0.90	0.76	1.06	
	Distant	1.29	1.02	1.63	
	Unknown	0.94	0.81	1.10	0.0434
****Histological subtype	Transitional cell	1.00			
	Papillary transitional cell	0.90	0.79	1.02	
	Other	1.38	1.12	1.69	0.0003
*History of haematuria	No haematuria	1.00			
	Haematuria*	0.67	0.58	0.77	<.0001
**History of cystitis	No cystitis	1.00			
	Cystitis**	1.90	1.68	2.15	<.0001
***Smoking	Non smoker	1.00			
	Current smoker	0.46	0.40	0.53	
	Ex smoker	0.33	0.29	0.38	<.0001
Charlton index	Low comorbidity	0.69	0.59	0.80	
	Medium comorbidity	0.53	0.45	0.63	
	High comorbidity	0.43	0.35	0.53	<.0001
Time to cystectomy	Four months or greater	1.00			
	One month	1.20	1.03	1.41	
	Two months	1.38	1.06	1.81	
	Three months	1.16	0.85	1.58	0.0557
Region of residence	Metropolitan	1.00			
	Outer metropolitan	0.95	0.83	1.09	
	Rural	0.80	0.68	0.94	0.019
Type of hospital	Public hospital	1.00			
	Private hospital	0.68	0.60	0.77	<.0001

Odds Ratio, Lower 95% Confidence interval, Upper 95% Confidence Interval (CI)
* Haematuria codes (Z54.2, Z51.1,Z51.2),
**Cystitis codes (N30.0-N30.9)
*** Smoking codes (Z86.43, Z72.0, Z71.6,F17)
****Morphology codes (M81203, M81303 and all other grouped together)

Chapter 4 Figure 1 Kaplan Meier cause specific bladder cancer survival curves by sex, NSW, 2000 to 2008



Chapter 4 Figure 2 Kaplan Meier cause specific bladder cancer survival curves by treatment, NSW, 2000 to 2008



4.4.2. Overall survival

Bladder cancer cause specific five year survival was 68 per cent for men and 56 per cent for women ($p<0.0001$) (Figure 1) and for those having any procedure 68 per cent for men and 59 per cent for women compared to 44 per cent in men and 35 per cent in women without a procedure (data not shown). Survival in women was poorer than in men in each treatment category. Survival after cystectomy was initially better than survival after resection but fell to less than that for resection after about 20 months (Figure 2). Because of this departure from proportionality of hazards, further analyses were stratified into those who had a cystectomy and those who had resection. Those who had no surgical procedure were excluded from further analysis.

4.4.3. Survival in patients who had a cystectomy

There were 1,081 patients (275 women and 806 men), who underwent cystectomy. The median time from diagnosis to cystectomy was two months for both men and women, with 75 per cent of patients receiving their cystectomy within three months for men and four months for women. Women had a 31 per cent higher hazard of death in the univariate model, falling to a 26 per cent higher hazard of death from bladder cancer (HR =1.26 95% CI 1.00-1.59) after multivariate adjustment(Table 3). In addition, bladder cancer patients who underwent cystectomy were more likely to die if aged 80 years or older, had distant spread of disease or were within one or two months from diagnosis at the time of cystectomy. Patients with bladder cancer who lived between 26 and 125 kilometres from a their treatment facility were the least to die from it. Period of diagnosis, socioeconomic status, type of hospital, smoking status, histological type and comorbidity were not significantly associated with fatality following cystectomy in the multivariate model. Summary stage and age at diagnosis were the strongest predictors of fatality in the multivariate model

The model was rerun excluding 37 people with bladder cancer who died from any cause within one month of their cystectomy. With this exclusion, the HR increased to 1.33 (95% CI 1.03-1.71) in women. When only bladder cancer cases coded by NSW registry staff were included in the analysis, the HR fell slightly to 1.25 (95% CI 99-1.60). Neither addition of

receiving an ileal conduit nor addition of having a lymph node dissection had an effect on the multivariate model.

Interactions between sex and all other covariates included in Table 3 were fitted individually in the multivariate model. Only the interaction between sex and history of cystitis was statistically significant (P=0.0096). Women who had a history of cystitis had a 55 per cent higher hazard of death following cystectomy than men with this history (HR1.55 95% CI 1.15-2.10) while controlling for all other covariates in the multivariate model. There was no difference in the hazard of death between men and women who did not have a previous history of cystitis (HR 0.99 95%CI 0.57-1.70) (Table 5).

4.4.4. Patients who received resection or endoscopic resection of bladder tissue

In the 4,235, or 62 per cent of, bladder cancer patients who underwent bladder cancer resection, women had a 47 per cent higher hazard of death from bladder cancer (HR=1.47 95% CI 1.30-1.66) than men in the univariate model. This fell to 18 per cent (HR=1.18 95% CI 1.03-1.34) in the multivariate model (Table 4). Other variables that were independently associated with death following bladder cancer resection included in order of association: summary stage, age, histology, history of haematuria, smoking, comorbidity, time from diagnosis to resection, socioeconomic status, country of birth, region of residence and hospital (Table 4). There was no significant interaction between sex and any other variable in the multivariate model. The p value for the interaction of sex with cystitis was 0.7366. On stratification of the multivariate model by history of cystitis, the HR for death after resection was 1.07 (95%CI 0.90-1.29) in those with a history of cystitis and 1.21 (95%CI 0.96-1.52) in those with no history of cystitis.

The model was rerun excluding bladder cancer patients who died within one month of their resection; the HR for death following resection in women fell a little to 1.16 (95% CI 1.01-1.34). When only bladder cancer cases verified by Cancer Registry staff were included in the analysis, the HR for resection in women was unchanged at 1.18 (95% CI 1.02-1.37) (Table 5).

Chapter 4 Table 3 Associations of outcome in people with bladder cancer treated by cystectomy with personal characteristics and aspects of their cancer and their management, NSW, 2000 to 2008 (Multivariate proportional hazards regression - hazard ratios and 95% confidence intervals)

Descriptive	Characteristics	Cases	Deaths	HR	LCI	UCI	P value
		n= 1,087	n =368				
Sex	Males	816	262	1.00			
Age group	Females	271	106	1.26	1.00	1.59	=0.0523
	15-49	65	27	1.00			
	50-59	147	33	0.62	0.37	1.05	
	60-69	323	105	1.05	0.68	1.62	
	70-79	443	155	1.08	0.71	1.64	
Summary stage	80+	109	48	1.85	1.14	2.99	<.0001
	Localised	470	112	1.00			
	Regional	454	182	2.44	1.90	3.12	
	Distant	49	39	7.62	5.16	11.25	
	Unknown	114	35	1.38	0.94	2.04	<.0001
Time from diagnosis to cystectomy	Four of more month	333	103	1.00			
	One month	406	158	1.38	1.06	1.82	
	Two months	234	74	1.04	0.69	1.55	
	Three months	114	33	1.01	0.73	1.40	=0.0444
Distance from treatment facility	Less than 25 km	799	276	1.00			
	26-75 km	139	43	0.70	0.50	0.97	
	76-125 km	58	16	0.58	0.35	0.96	
	126- plus	91	33	1.16	0.80	1.69	=0.0198
Country of birth	Australian born	681	231	1.00			
	Born in English speaking countries	136	57	1.29	0.96	1.74	
	Born in non- English speaking countries	267	79	0.60	0.08	4.33	
	Unknown country of birth	3	1	0.79	0.61	1.02	=0.0423
*Haematuria	No haematuria	865	282	1.00			
	Haematuria	222	86	1.32	1.03	1.70	=0.0297

HR – Hazard Ratios and 95% Confidence Limits (CI)
* Haematuria diagnosis codes (Z54.2, Z51.1,Z51.2),
# Cystectomy procedure codes (37014-00, 37000-00, 37000-01)

Chapter 4 Table 4 Associations of outcome in people with bladder cancer treated by resection with personal characteristics and aspects of their cancer and their management, NSW, 2000 to 2008 (Multivariate proportional hazards regression - hazard ratios and 95% confidence intervals)

Descriptive	Characteristics	Cases n=	Deaths n=	HR	LCI	UCI	P value
Sex	Males	3,090	745	1.00			
	Females	1,145	379	1.18	1.03	1.34	=0.0175
Agegroup	15-49	103	14	1.00			
	50-59	341	52	1.07	0.59	1.94	
	60-69	815	147	1.47	0.85	2.57	
	70-79	1,511	393	2.15	1.25	3.70	
	80+	1,465	518	3.57	2.07	6.15	<.0001
Country of birth	Australian born	2,787	784	1.00			
	Born in English speaking countries	519	135	0.74	0.63	0.86	
	Born in non- English speaking countries	916	204	0.83	0.69	1.00	
	Unknown country of birth	13	1	0.24	0.03	1.69	=0.0005
Socioeconomic status	Highest SES	779	194	1.00			
	Second highest SES	786	195	1.08	0.86	1.34	
	Middle SES	736	197	1.29	1.03	1.62	
	Second lowest SES	918	267	1.45	1.14	1.83	
	Lowest SES	1,016	271	1.26	1.00	1.59	=0.0126
Summary stage	Localised	2,346	463	1.00			
	Regional	590	269	2.91	2.50	3.40	
	Distant	217	177	8.01	6.65	9.65	
	Unknown	1,082	215	1.11	0.94	1.30	<.0001
Histology	Transitional cell	1,669	587	1.00			
	Papillary transitional cell	2,326	433	0.54	0.48	0.62	
	Other	240	104	1.23	0.99	1.53	<.0001
*Haematuria	No haematuria	2,977	686	1.00			
	Haematuria	1,258	438	1.34	1.18	1.52	<.0001
***Smoking	Non smoker	1,204	297	1.00			
	Current smoker	1,557	368	0.96	0.82	1.12	
	Ex smoker	1,474	459	0.84	0.73	0.97	=0.0511
	No comorbidity	1,201	249	1.00			
Comorbidity	Low comorbidity	1,364	394	1.14	0.97	1.35	
	Medium comorbidity	961	302	1.15	0.96	1.37	
	High comorbidity	709	179	0.92	0.76	1.13	=0.0451
Time from diagnosis to resection	Four of more months	663	142	1.00			
	One month	3,294	909	1.50	1.25	1.79	
	Two months	149	43	1.38	0.97	1.94	

Descriptive	Characteristics	Cases n=	Deaths n=	HR	LCI	UCI	P value
	Three months	129	30	0.93	0.63	1.39	<.0001
Region of residence at diagnosis	Urban	1,622	434	1.00			
	Outer metro	1,576	439	0.87	0.73	1.03	
	Rural	1,037	251	0.67	0.55	0.81	=0.0002
Hospital	Public	2,220	688	1.00			
	Private	2,015	436	0.73	0.64	0.83	<.0001

HR – Hazard Ratios and 95% Confidence Limits (CI)
Resection of bladder tissue or endoscopic destruction procedure codes (36839-04,36845-04, 36845-05,36840-02,36854-02,36839-00,36839-02,36845-01,36840-00, 36845-00,36845-02,36845-03,36845-06,36845-07,36840-01)
* Haematuria codes (Z54.2, Z51.1,Z51.2),
*** Smoking codes (Z86.43, Z72.0, Z71.6,F17)

Chapter 4 Table 5 Results of sensitivity analyses in multivariate proportional hazards regression analyses of outcome in bladder cancer patients who underwent cystectomy and resection, NSW, 2000-2008

Regression models	HR	LCI	UC1	P value
Patients treated by cystectomy				
Univariate model (n =1,087)	1.31	1.05	1.64	0.0189
Multivariate model in Table 3 (n =1,087)	1.26	1.00	1.59	0.0523
Multivariate model in Table 3 excluding deaths at one month (n=1,051)	1.33	1.05	1.69	0.0178
Multivariate model in Table 3 including records coded by cancer registry staff (n=1,015)	1.27	1.00	1.61	0.0483
Patients treated by resection				
Univariate model (n = 4,241)	1.47	1.30	1.66	<0.0001
Multivariate model in Table 4 (n = 4,241)	1.18	1.03	1.34	0.0175
Multivariate model in Table 4 excluding deaths at one month (n=4,107)	1.16	1.01	1.34	0.0332
Multivariate model in Table 3 including records coded by cancer registry staff (n= 3,333)	1.18	1.03	1.36	0.0198

Cystectomy procedure codes (37014-00, 37000-00, 37000-01)

Resection of bladder tissue or endoscopic destruction procedure codes (36839-04,36845-04, 36845-05,36840-02,36854-02,36839-00,36839-02,36845-01,36840-00, 36845-00,36845-02,36845-03,36845-06,36845-07,36840-01)

4.5. Discussion

Estimated five year, cause specific survival from bladder cancer was 56 per cent for women diagnosed in NSW in 2000-08 and 68 per cent in men (P<0.0001), and this poorer survival in women was observed regardless of whether they were treated by cystectomy or resection (including endoscopic destruction) of bladder tissue, or had no specific therapy. Adjustment for a wide range of other variables associated with survival had little impact on women's higher risk of death from bladder cancer following cystectomy (unadjusted HR for female sex 1.31, 95% CI 1.05-1.64; fully adjusted HR 1.26, 95% CI 1.00-1.59). Adjustment weakened the association of female sex with risk of death following resection but did not eliminate it (unadjusted HR for female sex 1.47, 95% CI 1.30-1.66; fully adjusted HR 1.18, 95% CI 1.03-1.34). The variable(s) principally contributing to the weakening of the association of female sex with risk of death in cystectomy patients were in order of strength: summary stage, age at diagnosis, distance from treatment facility, the presence of haematuria, country of birth and time to cystectomy. For bladder cancer patients who underwent resection the variables principally contributing to the weakening of the association of female sex were in order of strength: summary stage, age at diagnosis, histology, time to resection, hospital type, the presence of haematuria, country of birth, region of residence at diagnosis, socioeconomic status, comorbidity and smoking. Examination of interactions between sex and other covariates found a possibly meaningful interaction of sex with a history of cystitis in influencing death after cystectomy: HR was 1.55, 95%CI 1.15-2.10, in women with a history of cystitis and 0.99, 95% CI 0.57-1.70 in those without; p for interaction 0.0096. No such interaction was evident in women who underwent resection.

Advantages of this study include that it is population-based and that linkage of cancer registry to hospitalisation records was near complete; only 150 cases did not link. There are several limitations: we did not have information on the grade of bladder cancer and we had only summary stage. However, the proportional breakdown and survival by histological subtype and summary stage in NSW was very similar to those in SEER [2] and our findings with respect to sex difference in survival are similar to those of population-based studies of AJCC or tumour, nodes and metastases (TNM) staged bladder cancer [18]. We also had no

information about whether radiotherapy or adjuvant chemotherapy was received and could not address methods of bladder replacement at all adequately. As our study used only inpatient data, the length of time or frequency of cystitis is unknown in patients that only receive chemotherapy or radiotherapy and it will be important to examine this issue in future work.

Haematuria, cystitis and smoking, as risk factors for or symptoms associated with a poorer outcome, have not been previously examined in bladder cancer using coded inpatient data. We could not find estimates of the proportion of bladder cancer patients who would normally present with haematuria or cystitis, nor were we able to characterise them well with respect to the time of onset. However, we could compare our estimates of smoking in bladder cancer patients with results of surveys of primary care patients and the NSW population [19]and the Australian Health Survey [20]and found that our results were similar. Although, some under-reporting of current smokers may occur due to social pressure where other household members were present at the interview, the extent of this issue is unknown[21].

Furthermore, in review of data quality in systematic databases smoking derived from hospital data was found to have positive predictive value of 93-96 and a specificity of 99[22]. Therefore, coding of smoking would appear to be relatively complete. In addition, we have no reason to believe that there would be systematic coding or reporting differences in haematuria and cystitis between men and women.

The survival difference between men and women remained after adjustment, which suggests that other factors not considered in this study account for this difference. For example, we could not evaluate possible effects of anatomical differences between men and women. It has variously been suggested that the thicker detrusor muscle in men [18], the less robust bladder neck in women[23] and effects of growth of glandular prostatic tissue on angiolymphatic drainage in men [24] may contribute to sex differences in the spread of bladder cancer. Differences in the suspicion of bladder cancer between men and women with haematuria might also lead to stage differences that are not fully controlled by stage

adjustment [18]. Our adjustment for haematuria in the Cox proportional models addresses this possibility, at least to some extent.

Differences in histological type have also been considered responsible for survival differences between men and women; with men reported to have a 32 per cent greater chance of diagnosis with superficial disease than females [25]. 'Other' histological types were more prevalent in women than men in our data and there was a greater hazard of death from bladder cancer in patients with 'other' types who underwent resection, but adjustment for histological type did not fully explain the higher hazard of death in women. Moreover, histological type was not an independent predictor of survival in patients who had a cystectomy.

Our findings that a history of cystitis was significantly associated with poorer survival from bladder cancer and that this association was present only in women were unexpected. A history of cystitis was substantially more prevalent in women, and this is true in the general population .[26, 27]Mungan [25] suggests that more prevalent cystitis in women may explain a delay in care seeking behaviour and higher stage bladder cancer at diagnosis. In addition, there is recent evidence of greater delay at the primary care level for women than for men; symptomatic treatment for voiding disorders or pain was much more likely to be given without further evaluation and, therefore with probable delay in referral, in women than in men in the year before the diagnosis of bladder cancer [28] While we could find no other evidence directly relevant to an association between cystitis and bladder cancer survival, cystitis may increase bladder cancer risk. Kantor [29] found a significantly elevated level of bladder cancer in those who reported three or more infections (RR =2.0). The higher hazard of death we observed in women with a history of cystitis who underwent cystectomy may suggest that progression of bladder cancer is faster in women than in men with a history of, or current, bladder infection.

Mechanisms have been sought to explain the observed association of bladder cancer risk with urinary infection, such as urinary concentration due to urinary retention [30] and lower levels of glycosaminoglycan, which protect the urothelium, in women with interstitial cystitis[31]. Several studies [32, 33] show loss of impermeability of bladder urothelium in patients with interstitial

cystitis and abnormal expression of molecular markers, one of which is E-cadherin. It has been suggested that change in E-cadherin expression is an adaptation to the increased permeability of the urothelium[32]. In addition, a number of authors have reported an association between loss of E-cadherin and high grade and advanced stage breast, prostate [34], pancreas[35] and head and neck[36] cancers. One study has suggested that cystitis mimics Barrett's metaplasia both etiologically and histologically[32], but it was based on only 13 samples. Apart from these studies we could find none that suggest possible mechanisms for poorer survival in women with a history of cystitis".

It has been suggested that delaying radical cystectomy in organ-confined disease is associated with poorer survival and that patients with low grade or low stage tumours have the largest increases in mortality when diagnosis is delayed[37]. We did not have data on the interval between onset of symptoms and bladder cancer treatment and could not address this issue directly, although it should, in principle, be dealt with by adjustment for stage. US studies have found that bladder cancer patients who wait longer than three months between diagnosis and radical cystectomy have a greater risk of disease progression [38, 39] and death[37]. Most of our patients who had a cystectomy, 75 per cent, underwent it within three months of their diagnosis, which compares well with 73 per cent in a US population-based study[40].

However, we did not find worse survival in patients who underwent cystectomy, or resection, three months or more after diagnosis. In contrast, we found that patients who underwent cystectomy within one month of diagnosis had a 34 per cent higher hazard of death than those who underwent it four or more months after. It is possible that patients in NSW who underwent cystectomy within a month of diagnosis had more advanced disease and were sicker at presentation than those who were treated later. NSW patients that underwent cystectomy and died within the first month had a higher proportion of either regional or distant metastases (66.0%) compared to patients that died later (47.3%) or were alive at the end of the period (34.1%). Men and women did not have different distributions of distance from the treatment facility. Patients who underwent cystectomy had a higher adjusted hazard of death if they lived within 25 kilometres of a treatment facility than if they lived 26 to 75 (HR 0.61 95%CI 0.43-0.88), 76 to 125 kilometres (HR 0.50 95%CI 0.29-0.88) or 125 kilometres away. Distance from treatment facility was not an independent predictor of the hazard of death for patients who underwent resection. However, greater distance from

the treatment facility was found to reduce the likelihood of receiving potentially curative surgery and radiotherapy. [41-44] [45]

When we investigated comorbidity using the Charlson index, we found no significant difference in the number of comorbid conditions between men and women and that comorbidity was not independently associated with survival after cystectomy. It was with survival after resection. The Charlson index has been found to be a reliable indicator of comorbidity. [46] Other studies have also found no association between sex and comorbidity. [47-49]

Socioeconomic status was not independently associated sex or with survival after cystectomy but was with survival after resection, with poorer survival in the lower socioeconomic groups. Other studies have found worse survival from bladder cancer in poorer, less educated people and in minority ethnic groups. [50] [51] [52]

4.6. Conclusion

There is poorer survival from bladder cancer in women regardless of treatment and after adjustment for a range of other prognostic variables, and this was true in this study whatever the treatment received. Among the variables studied, only a history of cystitis recorded at the time of hospital admission appeared affect survival in women treated by cystectomy. There was an apparent 55% greater hazard of death from bladder cancer in women who had a history of cystitis and had a cystectomy than in men with this history. There was no such difference in those who did not have a history of cystitis. The poorer survival from bladder cancer in women remains largely unexplained. That a history of cystitis in women diagnosed with bladder cancer and treated by cystectomy may contribute to this poorer outcome merits further investigation.

4.7. Acknowledgement

We would like to thank the NSW Central Cancer Registry data for their work in processing the data and the Centre for Health Record Linkage (CHeReL) for linking the NSW Central Cancer Registry data to the NSW Admitted Patient Data Collection.

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5. Effects of access to and treatment in specialist facilities on survival from epithelial ovarian cancer in Australian women: A data linkage study

Tracey E, Hacker N, Young J, Armstrong B. Effects of access to and treatment in specialist facilities on survival from epithelial ovarian cancer in Australian women: A data linkage study. *International Journal of Gynaecological Cancer*. Sept 2014;24 (7):1232-1240.

5.1. Abstract

Objective: To determine whether distance of residence from a gynaecological oncology service (GOS) was associated with a better survival from ovarian cancer. **Methods** We linked cancer registry records to hospital records for 3,749 women with ovarian cancer diagnosed between 2000 and 2008 in New South Wales, Australia. Access to a GOS was measured in kilometres from a woman's geocoded address to the geocoded address of the closest public GOS hospital. Flexible parametric survival, Cox proportional hazards and logistic regression models were fitted to examine whether better access to a GOS was associated with a better survival, and whether extensive surgery was received for ovarian cancer after adjustment for patient, tumour and treatment factors. **Results:** The hazard of death from ovarian cancer was lower in women who were treated in a in GOS hospitals (HR 0.77 95%CI 0.64-0.95), and lower in those who had extensive surgery (HR 0.47 95%CI 0.38-0.58). The further women with ovarian cancer lived from a public GOS hospital, the more likely they were to be treated in a public general hospital. Women were 19 times more likely (OR 19.40 (95% CI 13.92-27.04) to be treated only in a general hospital when they lived 187km or more from a public GOS hospital than women who lived within 5km of one. **Conclusion** Distance of residence from GOS hospitals in Australia is an important determinant of access to GOS hospitals. Treatment in a public or private GOS hospital and having surgery were the strongest predictors of survival from epithelial ovarian cancer. Research is required into the barriers to referral of patients with ovarian cancer for care in GOS hospitals; low population density limits options for supply of GOS in rural areas.

5.2. Key words

Key words –Ovarian cancer, access, distance, gynaecological oncology, resection, Cox proportional hazards, cause specific mortality or survival, logistic regression, hospital referral

5.3. Introduction

Ovarian cancer is characterised by vague symptoms and late stage at diagnosis. It has a poor prognosis. While stage at diagnosis is the strongest determinant of survival from ovarian cancer there is regional variation in survival among women presenting with advanced cancer that suggests factors other than stage might be important in determining survival.[1]

Australian clinical practice guidelines for ovarian cancer recommend that women who are diagnosed with epithelial ovarian cancer should be treated in a hospital with a gynaecological oncology service (GOS).[2] US guidelines[3] do not specifically nominate such a service but recommend surgical cytoreduction to 1cm or less. Cytoreductive surgery (resection of macroscopic metastatic disease) is the accepted standard of care for women with advanced ovarian cancer. [4]Women treated by gynaecological oncologists in high volume specialist centres, [4] where cytoreductive surgery is usual for advanced cancers, have lower post-operative mortality[5] and better survival.[4, 6] Thus access to gynaecological oncology care could be an important factor, if not the major factor, underlying regional variations in ovarian cancer outcome.

Most registry based studies of ovarian cancer survival are limited in their ability to examine the effects of patient, tumour and treatment related factors on cancer outcome. The NSW Central Cancer Registry routinely records stage at diagnosis and tumour morphology; and we know from an earlier NSW registry based study that a woman's age, stage at diagnosis and histology are the factors that most influence survival from ovarian cancer.[7] In this paper, we extend this analysis by linking cancer registry data to hospital data and by geocoding patients' residences and treating hospitals to measure distance from a patient's home to their closest public hospital with a GOS as an indicator of access to best care for ovarian cancer Australians are entitled to free care in public hospitals and financial assistance with travel and accommodation if they live 100km or more from necessary treatment). We investigate whether access to a GOS hospital is associated with ovarian cancer survival after taking

account of patient, tumour and treatment characteristics. We also examine factors associated with treatment in public general hospitals (as opposed to GOS hospitals or private general hospitals) and factors associated with having surgery for their ovarian cancer.

5.4. Methods

5.4.1. Study population:

Women diagnosed with invasive ovarian cancer (including cancer of fallopian tubes and associated adnexae; ICD-10 C56; C57.0-C57.9) notified to the NSW Central Cancer Registry between 2000 and 2008 were investigated. NSW is the third largest and most populated state in Australia with population of 7,290,000 and an area of 800,642 square kilometres. Women's Registry records were linked to NSW APDC records (records of all hospital separations in NSW) and they were followed up for death or survival to the end of 31st of December 2008. Patient characteristics available included age, place of birth, socioeconomic status, smoking history, comorbidity, region of residence at diagnosis, payment status at admission to hospital, order of ovarian cancer and patients' cancers characterised by stage at diagnosis and histopathological type. (See also Appendix 1, Table 1). Histopathological types were combined into three groups based on similarity of survival.[7)]

5.4.2. Treating hospital:

There were 207 treating hospitals: nine were public GOS hospitals (all were teaching hospitals affiliated with university medical schools), seven private GOS hospitals, 103 public general hospitals and 88 private general hospitals. GOS hospitals were those identified as such in the NSW Directory of Gynaecological Services.[8] For each patient, the treating hospital was the hospital at which they had their most extensive surgery or the first hospital to which they were admitted after diagnosis if they had limited or no surgery.

5.4.3. Access to gynaecological oncology:

For each patient, we calculated the straight-line distance from the patient's home to the closest public GOS hospital using the "Great Circle Distance Calculator".[9] The straight-line distance has been found to be highly correlated with travel time or travel distance in the UK

(R=0.86).[10] We grouped distance in kilometres from a patient's home to the nearest public GOS hospital into five categories, each containing 20% of patients. For survival, we also modelled distance in kilometres as a continuous variable.

5.4.4. Treatment:

Patients were grouped into two treatment categories based on all surgical procedures coded at each hospitalisation (up to 50 allowed) for all public and private inpatient admissions in the linked dataset. Patients were classified as having had extensive surgery if they had surgery that involved the removal of one or both ovaries with or without associated hysterectomy and salpingectomy, debulking or surgical staging. Patients were classified as having had limited or no surgery if they had any other procedure related to ovarian cancer (e.g. biopsy) or no surgery at all. A preliminary analysis showed no difference in hazard of death over five years between subgroups of limited surgery and no surgery (data available on request). Information on whether residual disease remained after surgery was not available. The complete list of the ICD-10-AM Version 6 MBS-Extended procedure codes included in these two surgical treatment groups is given in Appendix 1. Other treatment characteristics analysed included method of diagnosis, period of diagnosis, time from diagnosis to treatment and financial status (Appendix 1, Table 1).

5.4.5. Statistical analysis

We estimated cause specific survival from ovarian cancer and its predictors using Kaplan Meier curves, log rank tests, and unadjusted five year hazard [1-(5 year survival)]. We used the multivariable fractional polynomial (MFP) command in Stata 12.1 and found minimum distance from a public GOS hospital to be linear and age to be a first order polynomial with a cubic distribution. We fitted Royston-Parmar regression models using the log odds command in `stpm2` implemented in Stata 12.1.[11)] We chose the Royston-Parmar model in preference to the more commonly used Cox model so that we could deal more easily with non proportional hazards and plot covariate adjusted survival curves.[11] Proportionality of hazards was examined and, if not proportional, we took account of the time varying effect using the tvc command.

Minimum distance from a public GOS (the variable of primary interest) and age, stage and comorbidity (known to be associated with survival) were retained in the model regardless of their statistical significance. All other univariable predictors in Appendix Table 1 were included in the backward elimination model if they were associated with survival; that is if they had a p value less than 0.2. We removed the least significant variable from the backward elimination model after conducting nested likelihood ratio tests, a p value for retention in the model was <0.05. All hazard ratios and their confidence limits were calculated using the predict command at one year and five years after diagnosis. We tested model fit by comparing Kaplan Meier unadjusted survival curves with the mean covariate adjusted survival curves for each covariate (Appendix 1).[11]

We repeated our data analysis using the Cox proportional hazards modelling procedure in Stata 12.1 to check the `stpm2` model and because multiple imputation using chained equations is easily implemented using Cox modelling. We used the LINCOM command to calculate confidence intervals for variables with time varying effects. We repeated our model with unknown stage included. We also imputed unknown stage using mi estimate to run the final Cox model with imputed stage.

We used logistic regression to examine determinants of a woman's odds of being treated in a public general hospital rather than any other type of hospital, and of having extensive surgery or not. Minimum distance from a public GOS, age, stage and comorbidity were included a priori, other patient, disease and treatment factors were included in the backward elimination model if they had a p value of less than 0.2 in the chi squared analysis (Appendix 1 table 1). A p value of less than 0.05 in the nested likelihood ratio test was used to decide whether a variable was retained in the final model.

5.5. Results:

Of 3,749 women diagnosed with ovarian cancer who were eligible for the study, 3,411 were included in the logistic regression analysis. Women were excluded from analysis if they had no hospital admission (114), appeared to have been first treated before diagnosis (32) or had non-epithelial tumours (150) or if their cancer had been registered only from a death

certificate mentioning ovarian cancer (42). Women were excluded from survival models if their stage at diagnosis was unknown (342) leaving 3,069 for analysis.

Altogether, 37% of analysed women were treated in public GOS hospitals, 32% in public general hospitals, 17% in private GOS hospitals and 14% in private general hospitals. There was an average of 14 patients (range 3 to 27) per hospital per year treated in the GOS hospitals. There was a strong association between distance and type of hospital (Table 1). Of women who lived within five kilometres of a public GOS hospital, 58% attended one for their treatment; a further 22% attended a private GOS hospital. By contrast, only 16% of women who lived 187 or more kilometres from a public GOS hospital attended one; and 4% attended a private GOS hospital. There was also a strong association between hospital type and type of surgical treatment. The proportions of patients who had extensive surgery were 86% in private GOS hospitals, 73% in public GOS hospitals, 62% in private general hospitals and 42% in public general hospitals.

5.5.1. Determinants of survival

Results of the Royston Parmer regression model are shown in Table 2. We compared the hazards and the cumulative odds models and found that the cumulative odds scale better fitted our data than the hazards model (a lower Akaike Information Criterion and Bayesian Information Criterion). Hazard ratios for minimum distance and age at diagnosis were calculated. Because of the age and stage interaction, p=0.0001 the hazard ratios for age are presented at localised stage and at a mean age of 63. Age at diagnosis, histological type, and surgery for ovarian cancer had time varying effects.

There was an increasing trend in the unadjusted hazard of death with increase in distance from a public GOS hospital (HR 1.002 at 5 km distant, 1.004 at 9km, 1.013 at 27 and 1.102 at 187+km, p=0.007 for heterogeneity – results not shown) but after adjustment for covariates this trend was no longer significant (p=0.16; Table 2) because of a strong association of distance with type of treating hospital. The unadjusted hazard of death from ovarian cancer was least in those treated in private GOS hospitals (Figure 1a): relative to treatment in a public general hospital (HR of 1), the adjusted HR was 0.57 for treatment in a

private GOS hospital, 0.67 for treatment in a private general hospital and 0.77 for treatment in a public GOS hospital (Table 2, p<0.0001 Figure 1b).

As expected, age, stage and histopathological type were very strong predictors of a poor ovarian cancer outcome (Table 2). The relative hazard of death in women with more advanced (regional and distant stage) cancers was less at five years after diagnosis than one year. Relative to serous cancers (HR 1), the hazard at one year was greater in both mucinous, endometrioid and clear cell cancers, HR 1.54, and in adenocarcinomas and other and unspecified histopathological types of cancer, HR 2.65. At five years, however, the opposite was the case: the HR for mucinous, endometrioid and clear cell cancers was 0.20 and for adenocarcinoma and other types 0.64 (although consistent with a value of 1.0). These different patterns at one and five years reflect that survival from serous carcinomas continued to decline over time while for patients with mucinous, endometroid and clear cell carcinomas after three years remains higher and consistently poorer for patients with adenocarcinoma from two years onwards.

Method of diagnosis, as recorded by the CCR, was also associated with outcome (Table 2); with the highest hazard of death in those with a clinical diagnosis only and the lowest in women with histopathologically verified cancer. These associations probably reflect stage and treatment effects on outcome.

The unadjusted survival curve for extensive surgery showed at large survival difference between patients who has limited or no surgery and those who had extensive surgery (Figure 2a).A one year after diagnosis, the adjusted hazard of death in women who had extensive surgery for their primary cancer (79.4% done within a month of diagnosis) was less than half that for those who did not (HR 0.47 95%CI 0.38-0.58) (Table 2). However, the adjusted survival curves converged over time and at 5-years the HR was 0.72 (95%CI 0.52-0.99) (Table 2 Figure 2 b). Results using Cox proportional hazards were not materially different to those using the Royston Parmer method. In addition, results for all variables in the model that included imputed values for unknown stage were not materially different from those in Table 2 (data not shown). Graphs of model fit can be found in Appendix 1 and sensitivity analyses are available on request.

5.5.2. Determinants of treating hospital

Women living 187+km from a public GOS hospital had 19 times the odds of being treated in a public general hospital than women living less than 5km from a public GOS hospital (Table 3). Other variables significantly associated with attending a public general hospital were older age, diagnosis in 2005-08, having public financial status at admission, unknown stage, having an adenocarcinoma, or other specified or unspecified histopathological type and increasing time from diagnosis to treatment.

5.5.3. Determinants of extent of surgery

Women were less likely to have extensive surgery for ovarian cancer if they were older, had adenocarcinoma, other specified or unspecified histopathological type, had advanced or unknown stage of cancer, attended a public or private general hospital for treatment, had their surgery two or more months after diagnosis or had public financial status at admission (Table 4). There was no consistent association between distance to a public GOS hospital and having extensive surgery. However, when we removed hospital type from the model, the odds of having extensive surgery fell with increasing distance from a public GOS hospital, and was particularly low in women living 187 km or more from a GOS hospital (OR 0.45 95%CI 0.34-0.59; $p<0.001$) relative to women living within 5 km of one (data not shown).

5.6. Discussion

The aspects of care that most strongly reduced a woman's hazard of dying from epithelial ovarian cancer were treatment in a GOS hospital or a private general hospital and having extensive surgery for the ovarian cancer. Women were more likely to attend a GOS hospital the nearer they lived to one and were more likely to have extensive surgery if they were treated in GOS hospitals. Thus, distance was an important factor in determining whether women would receive best care for their ovarian cancer because it influenced the hospital that she attended and, in consequence, the likelihood of surgery.

The association of ovarian cancer survival with distance from a woman's home to her closest hospital or family doctor has been examined in UK registry studies.[12, 13] Distance appeared not to be important; only being first treated in a cancer centre showed a significant

reduction in the hazard of death after adjustment for age and deprivation. This study, is consistent with our findings, regarding, the importance of type of hospital, but did not identify the importance of distance in determining the type of hospital attended. A recent population-based study in British Columbia, [14] that like Australia has a publically funded health system, also provides indirect evidence for an influence of distance on outcome of ovarian cancer. Examining ovarian cancer survival differences by Health Region, the study found that once disease characteristics (stage and grade) and treatment (optimal debulking and chemotherapy) were taken into account, survival differences previously attributed to Health regions were no longer significant. Only two of the five regions had GOS hospitals and therefore patients resident in the three other regions would have had to travel to access gynaecological oncology services.

While the type of hospital in which a woman was treated was a strong determinant of whether she had extensive surgery, our results suggest that women treated in public or private GOS hospitals had a lower risk of death from ovarian cancer independently of whether they had extensive surgery. Similarly other large registry based studies of ovarian cancer survival have shown that women treated in teaching hospitals or, specifically, GOS hospitals, had a lower risk of death than women treated in non teaching (general) hospitals,[6, 12] even after adjusting for extensive surgery and chemotherapy.[15]

Patient volumes may be one reason for these survival difference; hospitals managing fewer than ten patients with ovarian cancer per year have been found not to provide optimal cytoreduction.[16] The average numbers of cases for all GOS hospitals was 14 per annum. Mercado et al. [6] also found that patients had lower hazard of death when treated in higher volume hospitals over and above the lower hazard that resulted from surgery. Similarly, a Finnish study [17] found that higher hospital volumes and surgery with less residual tumour were independently associated with better survival for woman with ovarian cancer. A systematic review has found, in addition, that treatment in a specialist hospital and surgery by a gynaecological oncologist both reduced the hazard of death.[4]

Lack of adequate staging may also be an important contributor to poorer survival of women treated in general hospitals. We found a higher proportion of unknown stage at diagnosis in

patients treated in general hospitals. Others have found that lack of adequate staging was more prevalent in the absence of specialist gynaecological services and women with unstaged disease were more likely not to receive care from a gynaecological oncologist and not to receive recommended treatment than women who were adequately staged. [17]

We found an even lower hazard of death for women treated in private GOS hospitals than we did for those treated in public GOS hospitals. It is possible that gynaecological oncologists in NSW, who often operate in co-located public and private hospitals, will select patients who have better performance or nutritional status for treatment in private hospitals.[18] It is also likely that gynaecological oncologists themselves, rather than their residents, operate on patients treated in private hospitals.

We found most women (86%) were treated within six months of diagnosis; about 10% were treated seven months or more after diagnosis. The Australian ovarian cancer patterns of care study [18] reported a similarly high proportion of women (90%) treated within six months of diagnosis. Lower income and more remote residence were characteristics of the 10% of women who were treated six months or later after diagnosis. [19]

It is a limitation of our study that we could not determine for individual women whether gynaecological oncologists treated them when they were referred to GOS hospitals. However, it is likely that most were; an Australian patterns of care study found that 60% of women with ovarian cancer were treated by a gynaecological oncologist, [18] which compares well with the 57% of women we found who were treated at either a public or private GOS hospital. Lack of information on residual disease in patients who had extensive surgery and whether or not chemotherapy was given are also limitations.

Major strengths of this study are that it is population-based and has high quality linkage of cancer registry records to all public and private hospital records. Our measure of distance was a measure of access to recommended care and therefore applied to all patients and not just to those who received a particular kind of care. We were also able to estimate cause specific survival and to include comorbidity as a covariate in analysis, which are noted gaps in earlier studies. [12, 13]

A recent Australian study found that 93% of ovarian cancer patients presented first to their family doctors; only 4% presented to a hospital emergency department. [19] This observation suggests that access to a GOS hospital in Australia would be strongly influenced by family doctors' referral patterns. Referral also depended on symptoms, for example, women who presented with bleeding were more likely to be referred to a gynaecologist. Overall, 85% of women were found to visit three or fewer doctors before their cancer was diagnosed**.** [(19)] An Australian survey of family doctors' referral practices [20] reported that most patients suspected of having ovarian cancer were referred initially to a general gynaecologist (70% of the 83% referred) rather than a gynaecological oncologist. Metropolitan GPs reported greater access to public gynaecological oncology services and multidisciplinary teams (80% and 63%) than rural GPs (58% and 40% respectively). Therefore, it would appear that GP referral preferences are important determinants of whether or not women are referred to a gynaecological oncologist or to a GOS hospital when ovarian cancer is suspected or diagnosed. The frequency with which Australian general gynaecologists on refer women with ovarian cancer to a gynaecological oncologist has not been documented.

A woman's own choice is another important factor in determining whether or not when suspected of, or diagnosed with, ovarian cancer, she will see a gynaecological oncologist or attend a GOS hospital; for the 631 of women in our study who lived 187+km from the nearest public GOS hospital, travelling, time away from home and the cost of both would have been important considerations.

Distance of residence from gynaecological oncology services appears to be an important determinant of hospital of treatment, which influences the likelihood of surgery and whether women diagnosed with ovarian cancer in Australia achieve the best outcomes. Research is needed into factors that impede referral of women with ovarian cancer to gynaecological oncology services, particularly when women live remotely from such services. Low population densities limit provision of additional GOS services in rural areas.

5.7. Acknowledgement

We would like to thank Professor Patrick Royston from the MRC Clinical Trials Unit at University College London (UCL) for his patience, invaluable advice and assistance in

relation to the following: use of fractional polynomials, suggesting the use of the proportional odds `stpm2` model, and his advice about directly adjusted survival curves. In addition, for providing the method and Stata syntax to determine model fit by comparing Kaplan Meier unadjusted survival curves with the average adjusted survival curves predicted for each covariate grouping. We would also like to thank Mr Tim Badgery-Parker who provided general biostatistical advice and specific advice on multiple imputation. Lastly, we would like to thank the staff of the NSW Central Cancer Registry who collected and registered the data and the Centre for Health Record linkage who undertook data linkage of this dataset.

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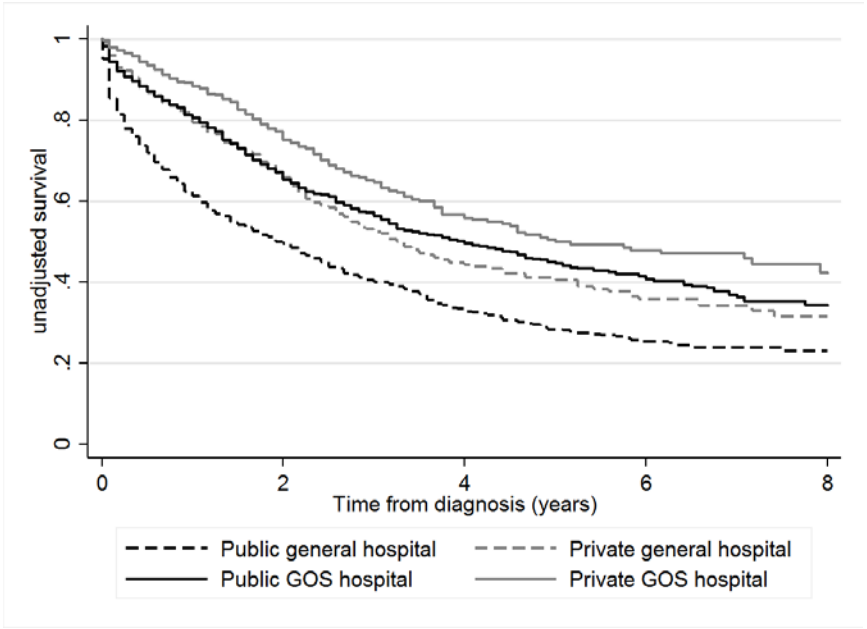
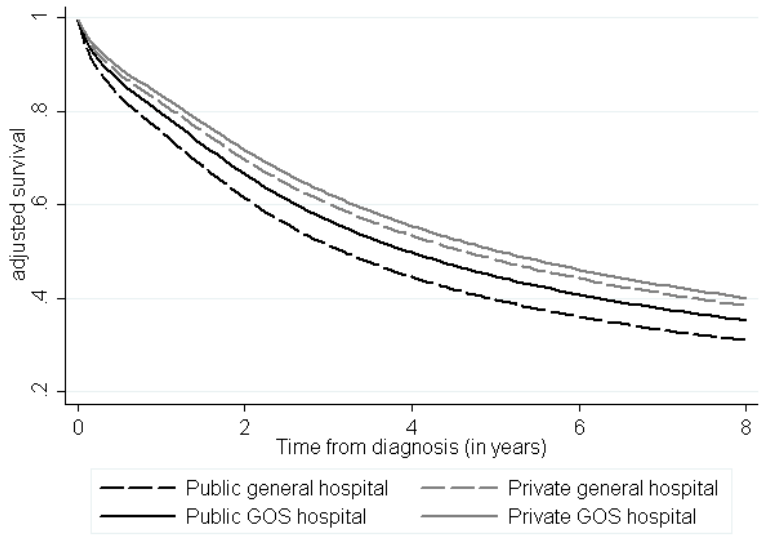
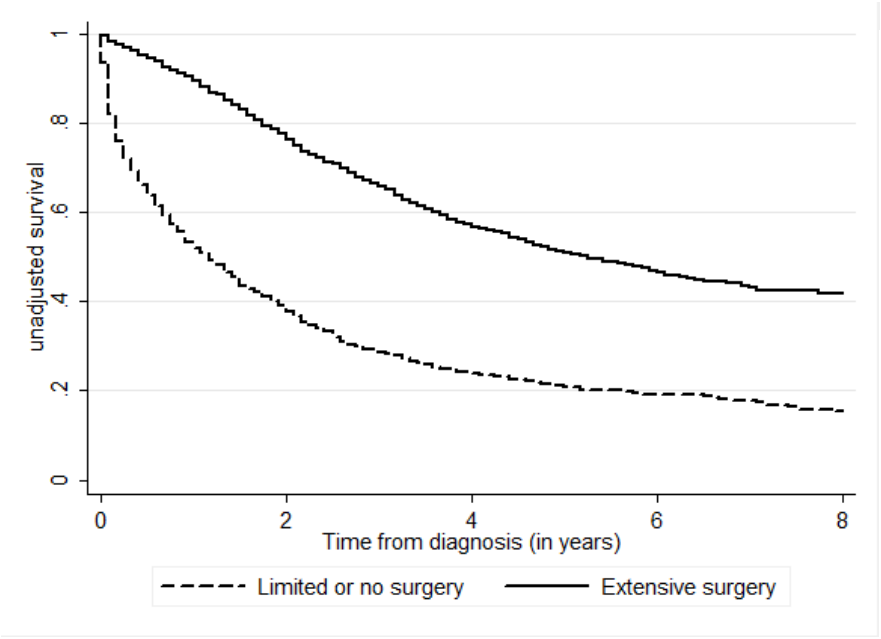
Chapter 5 Figures 1a and 1b Unadjusted and adjusted survival for women diagnosed with ovarian cancer by type of hospital of treatment,NSW, 2000 to 2008 (n=3,069)

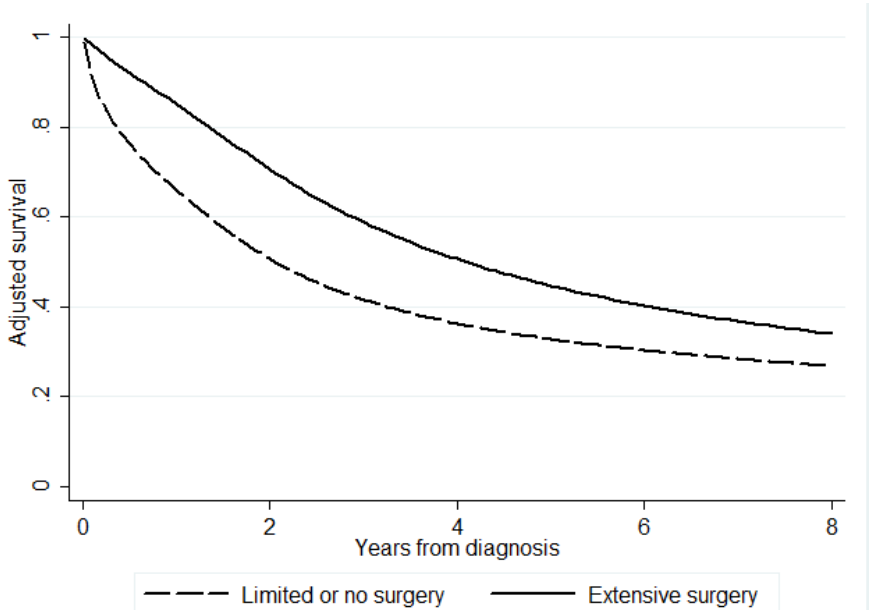




Based on model in Chapter 5 Table 2

Chapter 5 Figures 2a and 2b Unadjusted and adjusted survival for women diagnosed with ovarian cancer and whether or not extensive surgery was received,NSW, 2000 to 2008 (n=3,069)





†Based on model in Chapter 5 Table 2

Chapter 5 Table 1 Type of hospital attended for treatment for ovarian cancer by minimum distance to a public GOS hospital

	Minimum distance from public GOS hospital (km)					
Type of hospital attended	0-5.0	5.1-9.0	9.1-27.0	27.1-187.0	187.1+	*Number*
Public general	9.7%	25.6%	22.4%	42.1%	61.0%	*1,075*
Private general	10.3%	10.3%	12.8%	19.0%	19.0%	*484*
Public GOS	57.6%	43.2%	36.8%	30.0%	16.2%	*1,273*
Private GOS	22.4%	21.0%	28.0%	9.0%	3.8%	*579*
Number	*740*	*672*	*657*	*711*	*631*	*3,411*

Chapter 5 Table 2 Hazard of dying at one year and five year from ovarian cancer and minimum distance to a public specialist hospital and other covariates (n=3069)

Characteristics	One year HR(95%CI)[1]		Five years HR(95%CI)[1]		p value[2]
Minimum distance to a public GOS hospital (km)					
1.0 km	1		1		
5.0 km	1.00	(0.99-1.00)	1.00	(0.99-1.00)	
9.0 km	0.99	(0.99-1.00)	0.99	(0.99-1.00)	
27.0.km	0.99	(0.97-1.00)	0.99	(0.97-1.00)	
187 km	0.93	(0.83-1.03)	0.93	(0.83-1.03)	p=0.1633
Age (years)[3]					
Age 49	1		1		
Age 59	1.56	(1.54-1.59)	1.36	(1.28-1.45)	
Age 69	2.89	(2.76-3.03)	1.95	(1.65-2.31)	
Age 79	6.11	(5.42-6.89)	2.73	(2.01-3.71)	p=0.0001
Comorbidity					
None	1		1		
Any	1.25	(1.06-1.48)	1.25	(1.06-1.48)	P=0.009
Summary stage[4]					
Localised	1		1		
Regional	7.50	(4.09-13.74)	2.84	(1.79-4.49)	
Distant	18.56	(10.40-33.12)	4.09	(2.44-6.87)	p<0.0001
Histological type[5]					
Serous	1		1		
Mucinous, endometriod and clear cell	1.54	(1.56-2.05)	0.20	(0.09-0.41)	
Adenocarcinoma and other specified and unspecified histopathological types	2.65	(2.08-3.37)	0.64	(0.37-1.12)	p<0.0001
Method of diagnosis					
Cytology	1		1		
Clinical	1.59	(1.04-2.46)	1.59	(1.04-2.46)	
Histologically verified	0.57	(0.41-0.81)	0.57	(0.41-0.81)	p<0.0001
Type of treating hospital					
Public general	1		1		
Private general	0.67	(0.53-0.85)	0.67	(0.53-0.85)	
Public GOS	0.77	(0.64-0.95)	0.77	(0.64-0.95)	
Private GOS	0.57	(0.44-0.73)	0.57	(0.44-0.73)	p<0.0001
Surgery for ovarian cancer[6]					
Limited, Biopsy only or no surgery	1		1		
Extensive surgery	0.47	(0.38-0.58)	0.72	(0.52-99)	p<0.0001

[1]Hazard Ratios (HR) and 95% Confidence Intervals (95%CI)
[2]The p values for the time varying covariates reflect both nested main and time varying effects. Age at diagnosis, histology and surgery were time varying covariates.
[3] Effects of age are estimated at localised stage.
[4] Effects of stage are estimated at age 63 (the mean age).
[5]Morphology codes were grouped empirically based on similar IARC groupings and similar survival curves. The full list of codes is provided in Appendix 1
[6] Appropriate surgery: ICD-10-AM Version 6 MBS-Extended procedure codes are provided in Appendix 1

Chapter 5 Table 3 Predictors of attending a public general hospital for treatment of ovarian cancer rather than a public or private GOS hospital or a private general hospital (n=3,411)

Characteristics	OR*	(95%CI)*	p value
Patient			
Minimum distance to a public GOS hospital (Km)			
0-4.9	1		
5.0-8.9	3.96	(2.84-5.52)	
9.0-26.9	3.40	(2.42-4.76)	
27.0-187.1	8.30	(6.09-11.44)	
187.5+	19.40	(13.92-27.04)	p<0.0001
Age at diagnosis			
15-49	1		
50-59	1.17	(0.85-1.60)	
60-69	1.43	(1.04-1.95)	
70-79	1.83	(1.34-2.50)	
80+	2.96	(2.11-4.15)	p<0.0001
Comorbidity			
None	1		
Any	0.89	(0.73-1.10)	p=0.5034
Stage			
Localised	1		
Regional	1.01	(0.73-1.41)	
Distant	1.22	(0.93-1.60)	
Unknown	1.69	(1.18-2.43)	p=0.0094
Histology[5]			
Serous	1		
Mucinous, endometriod and clear cell	1.19	(0.92-1.55)	
Adenocarcinoma and other specified and unspecified histological types	2.26	(1.83-2.81)	p<0.0001
Year of diagnosis			
2000-2004	1		
2005-2008	1.41	(1.17-1.69)	p=0.0002
Time to treatment	1		
At diagnosis plus or minus one month	0.52	(0.31-0.87)	
Two to six month	1.06	(0.61-1.81)	
Seven months or greater	2.42	(1.82-3.22)	
No procedure undertaken	4.77	(2.94-7.73)	p<0.0001
Financial status			
Public patient	1		
Private patient	0.16	(0.14-0.20)	p<0.0001

Odds Ratios (OR) and 95% Confidence Intervals (95%CI)

[5]Morphology codes were grouped empirically based on similar IARC groupings and similar survival curves. The full list of codes is provided in Appendix 1

Chapter 5 Table 4 Predictors of having extensive surgery for ovarian cancer (N=3,259)

Characteristics	OR	95%CI	p value
Minimum distance to a public GOS hospital (km)			
0-4.9	1		
5.0-8.9	1.12	(0.83-1.50)	
9.0-26.9	0.83	(0.62-1.11)	
27.0-187.1	1.30	(0.97-1.74)	
187.5+	0.81	(0.60-1.10)	p=0.0010
Age at diagnosis (years)			
15-49	1		
50-59	0.83	(0.60-1.14)	
60-69	0.54	(0.39-0.74)	
70-79	0.38	(0.28-0.52)	
80+	0.21	(0.15-0.29)	p<0.0001
Comorbidity			
No	1		
Yes	0.93	(1.05-1.15)	p= 0.5045
Stage			
Localised	1		
Regional	0.62	(0.43-0.89)	
Distant	0.30	(0.22-0.41)	
Unknown	0.34	(0.22-0.51)	p<0.0001
Histological subtype[5]			
Serous	1		
Mucinous, endometriod and clear cell Adenocarcinoma and other specified	0.91	(0.70-1.18)	
and unspecified histological types	0.31	(0.25-0.39)	p<0.0001
Period of diagnosis			
2000-2004			
2005-2008	1.26	1.05-1.52	p< 0.0169
Method of diagnosis			
Cytology	1		
Clinical	2.88	(1.27-6.55)	
Histological	12.01	(5.89-24.50)	p<0.0001
Type of treating hospital			
Public general	1		
Private general	1.65	(1.25-2.17)	
Public GOS	2.37	(1.88-3.01)	
Private GOS	5.85	(4.21-8.12)	p<0.0001
Time from diagnosis to surgery (months)			
At diagnosis plus or minus one month	1		
Two-three months	0.40	(0.24-0.65)	
Four-six month	0.15	(0.09-0.27)	
Seven months or greater	0.29	(0.22-0.38)	p<0.0001

[1]Odds Ratios (OR) and 95% Confidence Intervals (95%CI)
[2] 152 women had no procedure
[5]Morphology codes were grouped empirically based on similar IARC groupings and similar survival curves. The full list of codes is provided in Appendix 1
[6] Appropriate surgery: ICD-10-AM Version 6 MBS-Extended procedure codes are provided in Appendix 1

5.9. Appendix 1 Online only text – methods

5.9.1. Patient characteristics

The following variables were obtained from cancer registry records: *Age at diagnosis* was treated as a continuous variable for the survival analysis and grouped into five categories for the logistic regression, 15-49 years, 50-59 years, 60-69 years, 70-79 years and 80 years and older. *Country of birth*, as notified to the cancer registry and supplemented where unknown with the information on the hospital admission data, was grouped into Australian born, born in an English speaking country and born in a non- English speaking country and unknown. *Socioeconomic status* was allocated in five categories using the Australian Bureau Statistics Index of Relative Socioeconomic Disadvantage (IRSD) based on the 2001 and 2006 Local Government Area Census Boundaries, depending on the appropriate diagnostic period. [1] *Smoking history*, no recorded history, current or past smoker (any of ICD-10 codes Z86.43, Z72.0, Z71.6, F17 in any record). *Comorbidities* were conditions counted using the Charlson index [2] and classified as no comorbidity or any comorbidity because of the small number of comorbid conditions. Secondary cancer, most often a code reflecting the stage of the ovarian cancer was excluded from the comorbid conditions. : *Place of residence at diagnosis* was, classified as metropolitan, outer metropolitan and rural based on groupings of Local Health Districts (2010 boundaries). *Order of ovarian cancer* was based on whether the ovarian cancer was the women's first cancer or second of subsequent cancer.

5.9.2. Cancer characteristics

Histological type of cancer, was summarised using the International Classification of Disease of Oncology (ICD-O) version 3 morphology codes[3] which were grouped based on Cancer Incidence in Five Continents Vol IX[4]. Histological subtypes were further combined into three groups on the basis of similarity of survival as determined in a previous publication[(5)]: Serous (84413, 84603-84633, 90143); mucinous, endometriod and clear cell carcinoma; (mucinous carcinoma (84703-84903, 90153), endometriod carcinoma (83803-83833, 85603, 85703), clear cell (83103-83133, 91103) and adenocarcinoma and other specified and unspecified histopathological types (adenocarcinoma (81403-81473, 81703-81903, 82113-82313, 82603, 83843, 84403, 85763), other specified types (80413, 80503, 80703, 80713, 81203, 82003, 82403, 82463, 83203), unspecified types (80103-80223,

80003-80053)). *Summary stage (extent of disease)* at diagnosis was classified as localised, regional, distant or unknown. [6]

5.9.3. Treatment characteristics

Year of diagnosis was grouped into time periods 2000-2004 and 2005-2008*; Method of diagnosis* whether a woman's ovarian cancer was diagnosed clinically, cytologically or histologically verified as determined by the NSW Central Cancer Registry; *Surgery undergone for the management of ovarian cancer* (see below); *Time from diagnosis to surgery* to which the patient's management was classified (see below) and A payment status of private or a public patient at the treatment admission for a procedure was also included.

5.9.4. Surgery undergone for the management of ovarian cancer

The surgical categories were obtained by examining all procedures coded in a separation (up to 50 allowed), for all public and private inpatient hospitalisations in the linked dataset. Extensive surgery: ICD-10-AM Version 6 MBS-Extended procedure codes: one of the following codes (35653-03, 35717-04, 35667-00, 35664-00, 35713-11, 35670-00, 35713-07, 35653-02, 35638-11, 35661-00, 35638-12, 35653-01, 35717-01, 35638-02, 35753-01, 35713-06, 35753-00, 35638-03, 35653-00, 35717-05, 35638-01, 35673-01, 35638-06, 35638-13, 35673-00, 35756-02) alone or in conjunction with Staging (30094-06, 35713-14, 35723-01, 96189-00, 35723-00, 35637-10, 35551-01, 35723-02) or Debulking (35720-00, 30566-00, 30392-00, 35658-00, 90450-00, 90450-01, 90450-02).Limited surgery or no surgery one of the following codes: ICD-10-AM Version 6 MBS-Extended procedure codes (30094-06, 35713-14, 35723-01, 96189-00, 35723-00, 35637-10, 35551-01, 35723-02, 35720-00, 30566-00, 30392-00, 35658-00, 90450-00, 90450-01, 90450-02, 30075-37) or no ovarian cancer procedure code. [7]Chemotherapy and radiotherapy are not reliably recorded in separation records and so were not considered for the analysis.

5.9.5. Time from diagnosis to surgery

The NSW Central Cancer Registry determined date of diagnosis using International Association of Cancer Registries (IACR) rules. In NSW, cancer is a notifiable disease under the NSW Public Health Act. Notifications are received from pathology laboratories,

hospitals' outpatient cancer clinics and radiation therapy centres. Coding staff review all notifications and the diagnosis date recorded is the date the specimen was taken if there is histological or cytological confirmation. In the absence of histological verification then the hospital of first admission is given as the date of diagnosis. When a woman is diagnosed at death through an autopsy or postmortem, the date of diagnosis is reported as the date of death. There were only 42 patients that met this criteria and we excluded them from the survival analysis. There were 152 women with a hospital admission but no procedure or procedure date for who time from diagnosis to surgery could be calculated.

5.9.6. Quality of the NSW Central Cancer Registry data and the admitted patient data collection

When compared with other cancer registries internationally, the NSW Central Cancer Registry has higher than average histological verification proportions; lower than average death certificate only registration percentages and good mortality incidence ratios, that is 1-ratio compares well to survival figures. [8]Hospital data in NSW is subject to data quality checking when it is submitted to the Ministry of Health and when it is reported nationally to the Department of Health and Ageing. Procedures and diagnoses are incorporated in patient administration systems within hospitals to ensure consistent coding and are reviewed regularly by the National Centre for Classification in Health.[7]

Chapter 5 Appendix 1 Table 1 Patient, cancer and treatment characteristics and deaths within 8 years of diagnosis in 3,411 women diagnosed with ovarian cancer in NSW 2000 to 2008

Characteristics	Number of women	%	Number of deaths	%
	3,411	100	1,652	100
Patient				
Minimum distance to a public specialist hospital (Km)				
0-4.9	740	21.7	344	20.8
5.0-8.9	672	19.7	333	20.2
9.0-26.9	657	19.3	295	17.9
27.0-187.1	711	20.8	348	21.1
187.5+	631	18.5	332	20.1
Age				
15-49	561	16.4	155	9.4
50-59	745	21.8	280	16.9
60-69	742	21.8	337	20.4
70-79	795	23.3	473	28.6
80+	568	16.7	407	24.6
Place of birth				
Australia	2,221	65.1	1,125	68.1
English speaking countries	212	6.2	115	7.0
Non English speaking countries	891	26.1	401	24.3
Unknown	87	2.6	11	0.7
Socioeconomic status				
Lowest	488	14.3	272	16.5
Second lowest	502	14.7	274	16.6
Middle	748	21.9	357	21.6
Second highest	748	21.9	339	20.5
Highest	925	27.1	410	24.8
Smoking history[1]				
Non smoker	2,301	67.5	1,163	70.4
Current smoker	550	16.1	266	16.1
Previous smoker	297	8.7	116	7.0
Unknown	263	7.7	107	6.5
Comorbidity (Charlson index)				
None	2,547	74.7	1,168	70.7
Any	864	25.3	484	29.3
Region of residence at diagnosis				
Metropolitan	1,481	43.4	697	42.2
Outer metropolitan	844	24.7	412	24.9
Rural	1,086	31.8	543	32.9
Order of ovarian cancer				
First case of cancer	3,224	94.5	1,589	96.2
Second or subsequent case	187	5.5	63	3.8
Cancer				
Summary stage at diagnosis				
Localised	643	18.9	80	4.8
Regional	528	15.5	211	12.8
Distant	1,898	55.7	1,199	72.6
Unknown	342	10.0	162	9.8
Histological type[2]				
Serous	1591	46.6	761	46.1
Mucinous, endometriod and clear cell	755	22.1	183	11.1
Adenocarcinoma, specified and carcinoma NOS and unspecified histopathological types	1065	31.2	708	42.9
Treatment				
Period of diagnosis				
2000-2004	1,422	41.7	903	54.7
2005-2008	1,989	58.3	749	45.3

Method of diagnosis				
Clinical only	277	8.1	183	11.1
Cytology	168	4.9	129	7.8
Histologically verified	2966	86.9	1,340	81.2
Surgery for ovarian cancer[4]				
Limited, biopsy only or no surgery	1,312	38.5	902	54.6
Extensive surgery	2,099	61.5	750	45.4
Time from diagnosis to treatment				
Plus or minus one month	2,708	79.4	1,154	69.9
Two to six months	190	5.6	129	7.8
Seven months or greater	361	10.6	248	15.0
No procedure date	152	4.5	121	7.3
Type of hospital attended				
Public general	1,075	31.5	635	38.4
Private general	484	14.2	243	14.7
Public GOC	1,273	37.3	568	34.4
Private GOC	579	17.0	206	12.5
Payment status				
Public financial status	1,787	52.4	924	55.9
Private financial status	1,624	47.6	728	44.1

[1]Smoking codes (Z86.43, Z72.0, Z71.6,F17)

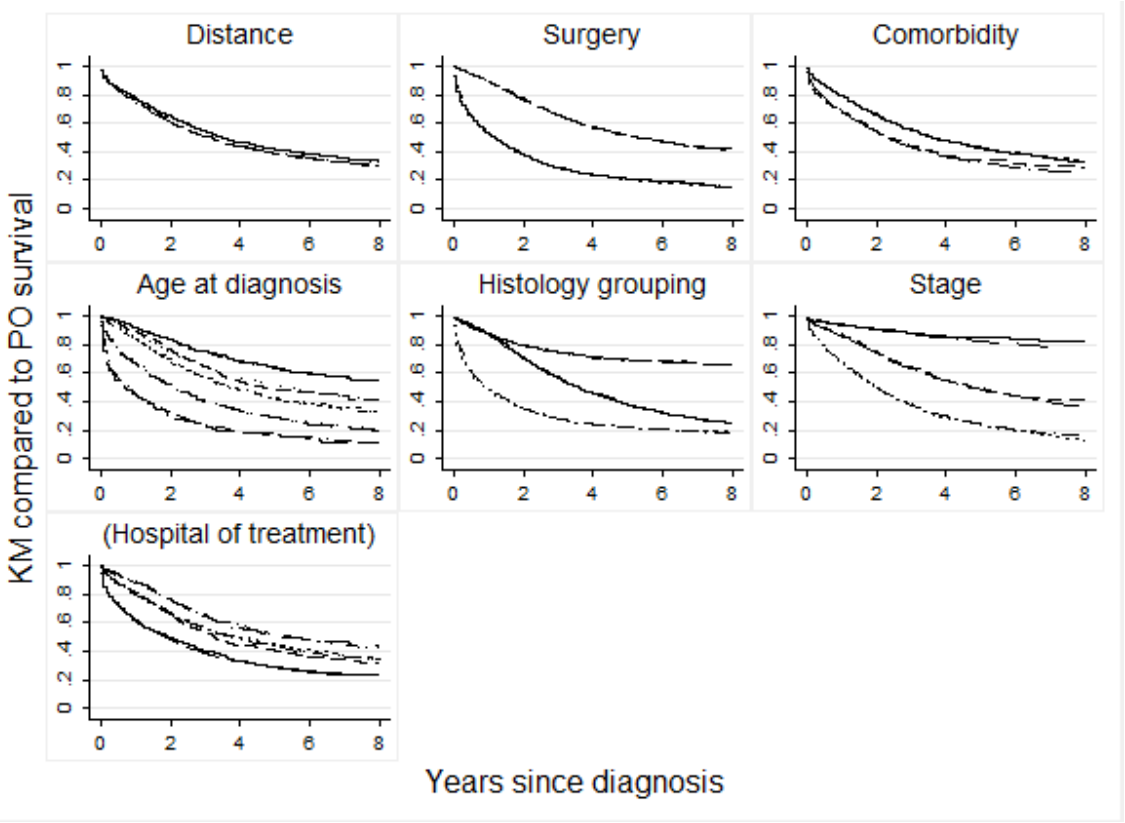
[5]Morphology codes were grouped empirically based on similar IARC groupings and similar survival curves. The full list of codes is provided in Appendix 1

[6] Extensive surgery: ICD-10-AM Version 6 MBS-Extended procedure codes are provided in Appendix 1 methods

5.9.7. Determining model fit

To determine model fit we plotted the unadjusted Kaplan Meier survival curves and the adjusted survival curves predicted from our model. With the exception time to surgery, which was removed from the model because of poor fit, we found very little difference between the survival curves within each of the covariates indicating good model fit.

Chapter 5 Appendix 1 Figure 1 Comparison of Kaplan Meier unadjusted curves with the adjusted survival curves predicted using the proportional odds model in `stpm2` undertaken to assess model fit



The following variables included a time dependent variable – age at diagnosis, major surgery and histological subtype. Age was modelled as a continuous variable with a cubic polynomial shape; in addition, there was an interaction between age and stage.

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Uziel Beller, MD
EIC
The IJGC

Uziel Beller, MD
Professor and Chairman
Dept. of Gynecology
Shaare Zedek Medical Center
The Hebrew University of Jerusalem
P.O.Box 3235
Jerusalem 91031
Tel. 972-2-6555164 Fax: 972-2-6666053
E-mail: uzib@szmc.org.il

6. Distance from accessible specialist care and other determinants of advanced or unknown stage at diagnosis of people with non small cell lung cancer: A data linkage study

This paper is submitted but not yet published

Tracey E, McCaughan B, Badgery-Parker T, Young J, Armstrong B. Distance from the NASH and the likelihood of advanced or unknown stage at diagnosis in Australian non small cell lung cancer patients: A data linkage study. Submitted to the British Journal of Cancer.

Keywords: Lung cancer, cancer registry, advanced stage, access to treatment, distance to treatment facility, logistic regression

6.1. Abstract

Background: Access to specialist services may influence the stage at which cancer is diagnosed and whether or not the cancer is ever adequately staged. We investigated whether increasing distance to the nearest accessible specialist hospital (NASH) is associated with a higher likelihood of advanced or unknown stage cancer at diagnosis in Australian non-small cell lung cancer (NSCLC) patients. **Methods:** We analysed linked cancer registry and hospital records for 11,147 NSCLC patients diagnosed between 2000 and 2008 admitted to hospital within 12 months of diagnosis. Distances from patients' homes to the NASH were measured in kilometres using geographical coordinates. Multinomial logistic regression analysis examined relationships of distance from the NASH, type of hospital of treatment (specialist or general) and other characteristics of NSCLC patients with advanced and unknown cancer stage. **Results:** Odds of advanced stage NSCLC was significantly higher in people who lived 100+ km from the NASH, OR 1.29 (95%CI 1.15-1.45), than in those living 0-39 km from it. Furthermore, odds of unknown stage NSCLC was significantly higher in people who lived 40-99km OR 1.29 (1.07-1.55) and those who lived 100 km+ OR 1.58 (1.27-1.84) from the NASH. The likelihood of both advanced and unknown stage NSCLC was significantly higher in patients treated in general hospitals than in specialist hospitals. Furthermore, in patients treated in specialist hospitals the odds of unknown stage was significantly lower OR 0.63 (95%CI 0.47–0.85). Whereas, patients treated in general hospitals had double the likelihood of unknown stage OR 2.13 (1.78-2.54) when they lived more than 100km+ from the NASH. These associations were independent of key confounding variables, including age, sex, comorbidity and histopathological subtype. **Conclusions:** People living remotely from accessible specialist services may be at greater risk of being diagnosed with advanced NSCLC. A higher prevalence of unknown NSCLC stage in patients who lived more than 40 km from the NASH and those attending general hospitals suggests they are inadequately investigated this limiting their treatment options.

6.2. Introduction

Determining cancer stage at diagnosis is important in ensuring that patients are given stage appropriate care [1]. Most lung cancer patients present with late stage disease [2]; and the proportion of patients for whom stage is unknown, at least to cancer registries, tends to be higher for lung cancer than for many other common cancers [3, 4].

UK studies have shown that the greater the distance non-small-cell lung cancer (NSCLC) patients lived from a cancer centre the more likely they were to have disseminated disease at diagnosis [5-7] and to have no histological verification of their cancer or to be first diagnosed at death or autopsy [8]. The likelihood of histological verification also diminished with increasing deprivation.[9, 10]

However, not all relevant studies show a relationship between advanced lung cancer and distance to treatment. A number of United States registry based studies found that the odds of presenting with advanced stage lung cancer were higher in urban areas and very remote areas, but lower in suburbs and outer metropolitan areas [11, 12].These differences in stage at diagnosis appeared to be due to higher proportions of young patients and black patients in urban locations. Advanced stage lung cancers were found to be more common in younger patients. After adjusting for age and ethnicity, patients living outside of cities were less likely to present at an advanced stage. The urban-rural differences were accentuated after adjusting for socioeconomic status and access to primary care, suggesting that unmeasured factors like awareness of symptoms or diagnostic differences were responsible[11].

We know of only one study that has examined the likelihood of unstaged lung cancer with access to care. Patients were more likely to be unstaged if they were older, poorer, black, had "other histological types of cancer" and resided in rural areas with fewer physicians.[13]

We investigated whether increasing distance to a specialist centre was associated with advanced or unknown stage at diagnosis. This study considers factors antecedent to and plausibly associated with actual stage at diagnosis and subsequent factors that are likely to be associated with accuracy and completeness of stage determination and its reporting to the Central Cancer Registry (CCR).

6.3. Methods

We included patients registered by the New South Wales (NSW) CCR as diagnosed with NSCLC; ICD-O topography codes C33-C34 excluding morphology codes for lung small cell cancer, M80413-M80453, M82463) between 2000 and 2008. CCR records for these patients were linked to matching records in the NSW Admitted Patient Data Collection. This collection records diagnosis and surgical treatment for all separations from NSW public and private hospitals. The combined automated and manual record linkage process had an estimated false positive rate of 0.4 per cent.[14]

6.3.1. Stage

CCR coders record stage at diagnosis on the basis mainly of hospital notifications (which report degree of spread at diagnosis coded as 1, localised to tissue of origin, 2, regional spread to adjacent organs and/or regional lymph nodes, 3 distant metastases or 4 – unknown). Hospital notifications supplemented by pathology reports (which are obligatorily provided), outpatient cancer centres notifications of patients treated with chemotherapy or radiotherapy and doctors' responses to CCR queries. Studies have shown that the "degree of spread" categories used provide broadly similar information to other methods of staging.[4, 15, 16]

6.3.2. Distance

Distance to the NASH ("nearest accessible specialist hospital", a public hospital with a thoracic surgical service) was obtained for each patient by calculating the distance in kilometres from the patient's geocoded address to the geocoded address of the NASH using the "Great Circle Distance Calculator"[17]. This measure of distance is similar to other measures of distance over Earth's surface [18]; and UK studies using travel time and straight-line distance [19] have found them to be highly correlated (R=0.856).We considered distance to the NASH to be a measure of access to best care because it encompasses both distance to and affordability of specialist care; all Australians are entitled to treatment free-of-charge in public hospitals [20]. Distance to a patient's actual hospital of treatment may be a biased measure of access because more mobile patients may be referred to hospitals at longer distances; in addition it can only apply to those who received treatment. [21]

Patients were grouped into three categories of distance: 0–39 km, 40–99 km and ≥100 km. We plotted the frequency distribution of patients by distance from the NASH in five kilometre groupings and found that the progressively diminishing proportion of patients plateaued at 40 kilometres and remained constant thereafter. One hundred or more kilometres was selected as the lower bound of the most distant category because patients living this distance from required care can obtain financial support for travel and accommodation through the Isolated Patient Travel Accommodation and Assistance Scheme (IPTAAS) [22].

Patients' area of residence was also classified broadly as metropolitan, outer metropolitan and rural based on the 2010 boundaries of NSW Local Health Districts.

6.3.3. Hospitals

Eleven public thoracic surgery hospitals were identified using Canrefer, a web directory of public and private cancer services [23]; all were in Sydney, the State capital, except for one in Newcastle, the State's second largest city. We classified hospitals in which patients were treated as specialist hospitals (public teaching hospitals or private hospitals with a thoracic surgical service) or general hospitals (public or private hospitals without such a service).

Because there was an obvious correlation between distance as defined above and the type of hospital in which a patient was actually treated, we created a six-category variable from hospital type (specialist and general) and distance from the NASH (0–39 km, 40–99 km, ≥100 km) for use when both variables were included in models.

6.3.4. Patient characteristics

The following patient characteristics were obtained from cancer registry records: sex, age at diagnosis (grouped into four categories, 15-59 years, 60-69 years, 70-79 years and 80 years and older); country of birth (grouped as Australian born, born in an English speaking country, born in a non-English speaking country and unknown); socioeconomic status (allocated in five categories using the Australian Bureau Statistics' Index of Relative Socioeconomic Disadvantage [24] from the 2001 or 2006 Census depending on the period of diagnosis); and year of diagnosis (grouped as 2000–2004 and 2005–2008).

Additional patient characteristics obtained from Admitted Patients Data Collection records were: smoking status (non-smoker, past smoker, current smoker based on ICD-10 codes Z86.43, Z72.0, Z71.6, F17 in any separation record); any or no comorbidity (any or no condition in the Charlson index [25], except secondary cancer, coded as a primary or other diagnosis in any record); and any or no history of chronic obstructive pulmonary disease (based on relevant four-digit ICD-10 codes in the range J41.0-J44.9 in any separation record).

6.3.5. Tumour characteristics

In addition to stage at diagnosis (see above) classified by extent of disease as localised, regional, distant or unknown, histological subtype of cancer, was coded by the CCR from pathology reports using ICD-O version 3 morphology codes [26]. NSCLC subtypes were combined into four categories, squamous cell carcinoma, adenocarcinoma, large cell, and other and unspecified cancers and carcinomas, in accordance with Cancer Incidence in Five Continents Vol IX. [27]

6.3.6. Treatment characteristics

Treatment characteristics were categorised as period of diagnosis (grouped as 2000-2004 and 2005-2008) andmethod of diagnosis (clinical, cytology or histopathology), which is recorded by the CCR because a number of studies have reported it to be a reliable indicator of lack of investigation.[8] Type of hospital admission (admitted via the emergency department, planned admission or other usually outpatients). Time from diagnosis to surgery or admission to hospital in the absence of surgery in months was used to subset cases treated within 12 months of diagnosis.

6.3.7. Statistical analyses

Stata 12.1 was used for the statistical analysis. Multinomial logistic regression was conducted with stage as the outcome variable in three categories: localised (as the reference category), advanced (regional and distant spread) and unknown. Potential predictor variables considered for inclusion in multivariate models fell into two groups depending on their temporal relationship [28] to stage at diagnosis: (1) variables that were antecedent to and

plausibly associated with actual stage at diagnosis (patient and tumour characteristics, distance from the NASH); and (2) variables subsequent (not antecedent) to actual stage but likely to be associated with accuracy and completeness of determination of stage and its reporting to the CCR (type of hospital admission, type of hospital of treatment and time from diagnosis to admission).

Sex, age, comorbidity and history of chronic obstructive pulmonary (all antecedent variables) were retained in the final model regardless of their statistical significance because of their clinical importance. All other univariable predictors were included in a backward elimination model if they had p value of less than 0.2 and retained in the final model if, as a result of nested likelihood ratio tests, they had a p value of less than 0.05. [29] Area Health Service of Residence had a variance inflation factor of more than three with distance from the NASH and was excluded from the model.

To examine the sensitivity of associations of advanced stage with distance and hospital type to presence of unknown stage cancers, we undertook logistic regression analyses with unknown stage replaced by stage imputed using multiple imputation methods [30]. Multiple imputation with chained equations was used because it has been found to be effective in a registry setting. [31]

6.4. Results

There were 23,871 people with NSCLC, of whom 11,147 were included in this analysis. These patients were admitted to hospital at or within 12 months after their date of diagnosis (Table 1). Patients were excluded from the analysis if they were registered only from death certificates (737), or not hospitalised at any time (874), or any time after their diagnosis of lung cancer (10,684), or not until 12 months or more after diagnosis (429). We excluded these patients because we required contemporary variables from Admitted Patients Data Collection records for measurement of key antecedent variables (Chronic Obstructive Pulmonary Disease (COPD) and other comorbidity) and all subsequent variables, importantly type of hospital of admission.

People who lived ≥100 km from the NASH were less likely than people who lived 0–39 km from the NASH to have localised stage (25.8% vs. 30.5%) and more likely to have unknown stage cancer (21.1% vs. 15.5%). After adjustment for other variables antecedent to stage at diagnosis, odds of advanced stage and, more strongly, unknown stage cancer increased with increasing distance from the NASH ($p<0.0001$ in each case; Chapter 6 Table 2b).

Considering other antecedent variables, advanced stage cancer was also more likely in males, younger people, people of higher socioeconomic status, people diagnosed in 2000-04 (rather than in 2005-2008), people without COPD, people with cancers other than squamous cell cancers and cancers not verified histopathologically (Chapter 6 Model 1, Table 2b). The pattern of associations with unknown stage cancer was similar except that it was not significantly associated with sex, age, or socioeconomic status.

Addition of variables subsequent to stage at diagnosis but possibly associated with clinical determination of stage and its reporting to the CCR (Chapter 6 Table 2b Model 2) had little impact on the associations of antecedent variables with advanced and unknown stage.

Considering the main effects of the subsequent variables, patients treated in general hospitals had consistently higher odds of advanced stage and, particularly, unknown stage cancer than people treated in specialist hospitals (Chapter 6 Table 2b Model 2). For patients who lived 100km+ from the NASH, the odds of unknown stage was significantly lower in patients treated in a specialist hospitals OR 0.63 (95%CI 0.47–0.85) and significantly higher in patients treated in general hospitals OR 2.13 (1.78-2.54) than for patients who lived 0-39km from the NASH. There was little evidence of a similar pattern for advanced stage cancer. Odds of both advanced and unknown stage were highest in patients admitted as emergencies and lowest for those with planned admissions. The odds of unknown stage was particularly high for patients admitted to hospital more than 6 months after diagnosis compared to those admitted within a month of diagnosis (Chapter 6 Table 2b, Model 2). This pattern was not evident in patients with advanced stage. The ORs for advanced stage changed little from those shown in Chapter 6 Table 2b Model 2 on repeating the analysis using imputed stage in place of unknown stage. Country of birth and smoking status were not significantly associated with advanced or unknown stage cancer in the fully adjusted model.

Chapter 6 Table 1 Personal, cancer and treatment characteristics of NSW NSCLC patients diagnosed between 2000-2008 (n=11,147) hospitalised within 12 months

Characteristics	Total	Localised		Advanced		Unknown		
		3,240		5,975		1,932		
Distance from the NASH		n	%	n	%	n	%	
Specialist hospital 0-39.9	5,282	1,757	54.2	2,783	46.6	742	38.4	
Specialist hospital 40-99.9	611	263	8.1	293	4.9	55	2.8	
Specialist hospital 100 plus	858	371	11.5	424	7.1	63	3.3	
General hospital 0-39.9	1,482	306	9.4	868	14.5	308	15.9	
General hospital 40-99.9	828	153	4.7	468	7.8	207	10.7	
General hospital 100 plus	2,086	390	12.0	1,139	19.1	557	28.8	p<0.0001
LHD of residence								
Urban	4,297	1,365	42.1	2,337	39.1	595	30.8	
Outer metropolitan	3,162	904	27.9	1,731	29.0	527	27.3	
Rural	3,688	971	30.0	1,907	31.9	810	41.9	p<0.0001
Sex								
Males	6,983	2,005	61.9	3,748	62.7	1,230	63.7	
Females	4,164	1,235	38.1	2,227	37.3	702	36.3	p<0.0001
Age at diagnosis								
0-59	2,662	662	20.4	1,659	27.8	341	17.7	
60-69	3,414	970	29.9	1,948	32.6	496	25.7	
70-79	3,653	1,176	36.3	1,782	29.8	695	36.0	
80+	1,418	432	13.3	586	9.8	400	20.7	p<0.0001
Socioeconomic status								
Lowest SES'	2,376	670	20.7	1,262	21.1	444	23.0	
Second lowest SES'	2,114	623	19.2	1,071	17.9	420	21.7	
Middle SES'	2,357	694	21.4	1,223	20.5	440	22.8	
Second highest SES'	2,314	672	20.7	1,289	21.6	353	18.3	
Highest SES'	1,986	581	17.9	1,130	18.9	275	14.2	p<0.0001
Period of diagnosis								
2000-2004	5,824	1,588	49.0	3,058	51.2	1,178	61.0	
2005-2008	5,323	1,652	51.0	2,917	48.8	754	39.0	p<0.0001
Chronic obstructive pulmonary disease								
No COPD	8,167	2,147	66.3	4,665	78.1	1,355	70.1	
COPD	2,980	1,093	33.7	1,310	21.9	577	29.9	p<0.0001
Comorbidity								
No comorbidity	7,381	2,035	62.8	4,131	69.1	1,215	62.9	
Comorbidity	3,766	1,205	37.2	1,844	30.9	717	37.1	p<0.0001
Histology								
Squamous	2,478	962	29.7	1,104	18.5	412	21.3	
Adenocarcinoma	4,120	1,214	37.5	2,444	40.9	462	23.9	
Large cell	3,204	692	21.4	1,810	30.3	702	36.3	
Other	1,345	372	11.5	617	10.3	356	18.4	p<0.0001
Method of diagnosis								
Cytology	1,204	164	5.1	648	10.8	392	20.3	
Clinical	1,082	144	4.4	490	8.2	448	23.2	
Histologically verified	8,861	2,932	90.5	4,837	81.0	1,092	56.5	p<0.0001
Emergency status								
Emergency	4,510	730	22.5	2,781	46.5	999	51.7	

Planned	6,247	2,440	75.3	2,961	49.6	846	43.8	
Other	390	70	2.2	233	3.9	87	4.5	p<0.0001
Time from diagnosis								
At diagnosis	8,554	2,600	80.2	4,730	79.2	1,224	63.4	
2-3 months	1,286	409	12.6	717	12.0	160	8.3	
3-6 months	782	154	4.8	347	5.8	281	14.5	
7-12 months	525	77	2.4	181	3.0	267	13.8	p<0.0001

[1]Smoking codes: ICD10-AM codes Z86.43, Z72.0, Z71.6, F17.
[2]Chronic obstructive pulmonary disease codes: ICD10-AM codes J41.0, J41.1, J41.8, J42.0, J42, J43, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.8, J44.9
[3]Cancer codes: ICD0-3 morphology codes: Squamous 80503-80783, Large cell 80353, 83103,80103-80123,80143-80313, Adenocarcinoma 82303-82313, 82503-82603, 81403, 82113, 83233, 85763, 82463 Other 80003-80053, 88003, 88013, 88023, 88053, 88103, 88113, 88303, 88903, 89203, 90403, 90413, 91203, 91333, 91503, 95403, 88403-89213, 89903-89913, 91203-91333, 95403-95813, 88303, 91503.

Chapter 6 Table 2a Stage at diagnosis by distance from the closest public specialist hospital for NSCLC patients admitted to hospital within 12 months of diagnosis NSW, 2000 to 2008

Stage	Number	0-39	40-99	100+
Localised	3,240	30.5	28.9	25.8
Regional	3,540	32.3	30.3	31.3
Distant	2,435	21.7	22.6	21.8
Unknown	1,932	15.5	18.2	21.1
Total	11,147	6,764	1,439	2,944

Chapter 6 Table 2b Odds ratios and 95% confidence limits for advanced and unknown stage (referent to localised stage) in NSCLC patients diagnosed in NSW between 2000-2008) – Patients admitted to hospital within 12 months of diagnosis

	Model I Antecedent variables						Model 2 Antecedent and subsequent stage at diagnosis					
	Advanced stage			Unknown stage			Advanced stage			Unknown stage		
	OR	95% CI	pvalue	OR	95% CI	pvalue	OR	95% CI	pvalue	OR	95% CI	pvalue
Distance from the NASH (km)												
0-39 km	1			1								
40-99 km	1.10	(0.96-1.27)		1.29	(1.07-1.55)							
100+km	1.29	(1.15-1.45)	p<0.000	1.58	(1.37-1.84)	p<0.0001						
Distance from the NASH and hospital of treatment												
Specialist hospital 0-39.9							1			1		
Specialist hospital 40-99.9							0.96	(0.80-1.16)		0.77	(0.56-1.06)	
Specialist hospital 100 plus							1.08	(0.92-1.28)		0.63	(0.47-0.85)	
General hospital 0-39.9							1.33	(1.14-1.55)		1.26	(1.03-1.54)	
General hospital 40-99.9							1.48	(1.21-1.82)		1.97	(1.53-2.52)	
General hospital 100 plus							1.49	(1.29-1.73)	p<0.0001	2.13	(1.78-2.54)	p<0.0001
Sex												
Males	1			1			1			1		
Females	0.86	(0.78-0.94)	p=0.01	0.93	(0.82-1.05)	p=0.23	0.88	(0.80-0.96)	p=0.01	0.94	(0.82-1.07)	p=0.34
Age at diagnosis												
15-60	1			1			1			1		
60-69	0.85	(0.75-0.96)		0.93	(0.78-1.11)		0.87	(0.76-0.98)		0.99	(0.83-1.19)	
70 -79	0.64	(0.57-0.72)		0.96	(0.81-1.15)		0.64	(0.56-0.72)		1.02	(0.86-1.22)	
80+	0.49	(0.42-0.58)	p<0.000	1.08	(0.88-1.33)	p= 46	0.43	(0.36-0.51)	p<0.0001	1.06	(0.86-1.32)	p=0.92
Socioeconomic status												
Low SES	1			1			1			1		
Second lowest SES	0.93	(0.81-1.07)		1.12	(0.93-1.34)		0.94	(0.82-1.09)		1.12	(0.93-1.36)	
Middle SES	0.98	(0.85-1.12)		1.07	(0.89-1.28)		1.02	(0.88-1.17)		1.10	(1.00-1.33)	
Second highest SES	1.13	(0.98-1.30)		0.99	(0.82-1.20)		1.23	(1.07-1.43)		1.04	(0.85-1.26)	
Highest SES	1.17	(1.01-1.37)	p=0.01	0.99	(0.80-1.23)	p=0.650	1.29	(1.10-1.50)	p<0.0001	1.07	(0.86-1.33)	p=0.77
Chronic obstructive pulmonary												
No	1			1			1			1		
Yes	0.61	(0.55-0.68)	p<0.000	0.83	(0.72-0.95)	p=0.0082	0.64	(0.57-0.71)	p<0.0001	0.90	(0.78-1.04)	p=0.17
Comorbidity												
None	1			1			1			1		
Any	0.96	(0.87-1.06)	p=0.45	0.93	(0.81-1.06)	p=0.26	0.89	(0.80-0.99)	p=0.02	0.88	(0.77-1.02)	p=0.09

Period of diagnosis												
2000-2004	1			1			1			1		
2005-2008	0.91	(0.83-1.00)	p<0.004	0.68	(0.60-0.77)	p<0.0001	0.96	(0.88-1.06)	p=0.43	0.80	(0.71-0.91)	p<0.0007
Histology												
Squamous	1			1			1			1		
Adenocarcinoma	1.57	(1.40-1.76)		0.86	(0.73-1.01)		1.61	(1.43-1.81)		0.88	(0.74-1.05)	
Large cell	1.95	(1.71-2.22)		1.56	(1.32-1.85)		1.66	(1.46-1.90)		1.39	(1.17-1.66)	
Other	1.15	(0.97-1.35)	p<0.000	1.41	(1.15-1.74)	p<0.0001	1.07	(0.90-1.26)	p<0.0001	1.34	(1.08-1.66)	p<0.0001
Method of diagnosis												
							1			1		
Cytology	1											
Clinical	0.94	(0.72-1.22)		0.97	(0.74-1.28)		0.84	(0.65-1.10)		0.97	(0.73-1.28)	
Histologically verified	0.42	(0.35-0.50)	p<0.000	0.16	(0.13-0.20)	p<0.0001	0.59	(0.49-0.72)	p<0.0001	0.22	(0.18-0.28)	p<0.0001
Type of hospital admission												
Emergency							1			1		
Planned							0.36	(0.32-0.40)		0.57	(0.50-0.66)	
Other							0.82	(0.62-1.10)	p<0.0001	0.75	(0.53-1.08)	p<0.0001
Time from diagnosis												
to surgery or admission												
At diagnosis							1			1		
2-3 months							1.11	(0.96-1.27)		0.98	(0.80-1.21)	
3-6 months							1.08	(0.88-1.32)		3.70	(2.96-4.62)	
7-12 months							0.91	(0.69-1.20)	p=0.39	5.49	(4.16-7.24)	p<0.0001

[1]ORs are relative to specialist hospital 0-39.9 km
Smoking codes: ICD10-AM codes Z86.43, Z72.0, Z71.6, F17.
[2]Chronic obstructive pulmonary disease codes: ICD10-AM codes J41.0, J41.1, J41.8, J42.0,
J42, J43, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.8, J44.9
[3]Cancer codes: ICD0-3 morphology codes: Squamous 80503-80783, Large cell 80353, 83103,80103-80123,80143-80313, Adenocarcinoma 82303-82313, 82503-82603, 81403, 82113, 83233, 85763, 82463
Other 80003-80053, 88003, 88013, 88023, 88053, 88103, 88113, 88303, 88903, 89203, 90403, 90413, 91203, 91333, 91503, 95403, 88403-89213, 89903-89913, 91203-91333, 95403-95813, 88303, 91503
88103, 88113, 88303, 88903, 89203, 90403, 90413, 91203, 91333, 91503, 95403, 88403-89213, 89903-89913, 91203-91333, 95403-95813, 88303, 91503

6.5. Discussion

Odds of advanced stage and unknown stage NSCLC at diagnosis were higher for people who lived 100km or more from the NASH. Odds of advanced stage and of unknown stage cancer were also higher in people who attended general hospitals than people who attended specialist hospitals for their care; and odds of attending a general hospital increased with distance from the NASH. Somewhat paradoxically, perhaps, odds of unknown stage cancer in people admitted to specialist hospitals were less the further they lived from the NASH. These associations were independent of key confounding variables, including age, sex, comorbidity and histopathological subtype.

Our finding that distance from the NASH influenced stage at diagnosis, is consistent with the small number of population based studies that have examined the effect of distance to specialist care. Early Scottish registry based studies reported that patients with lung cancer were diagnosed with more advanced disease or had higher death rates or poorer survival with increasing distance to a cancer centre. [5, 7, 32] Two US registry based studies[13, 33] have considered straight-line distance and the likelihood of advanced stage lung cancer with mixed results. Consistent with our findings, Silverstein et al (Silverstein *et al*, 2002) reported that distance from hospital and the histological subtype of a person's lung cancer most explained the likelihood of advanced stage at diagnosis after adjusting for age, sex, marital status, education and place of residence. [13] Scoggins et al measured distance to primary care rather than distance to hospital and found no association of it with advanced stage. [33]

A few studies have investigated why people who live remotely are more likely to have cancer of unknown stage. Older age [13 3], rural residence and fewer primary care physicians [13] and lack of investigation [10] appear to be the most common answers. Linkage studies in Western Australia have shown that rural lung cancer patients take longer to consult their GPs [34] and to present with more symptoms, which were associated with later diagnosis and fewer treatment options. [34]

Considering factors associated with the accuracy and recording of stage, type of presentation, hospital of treatment and time to treatment are most likely associated with later or unknown stage at diagnosis. To be diagnosed, people with symptoms of NSCLC must

attend their GP or a hospital emergency department. In Australia, GPs are not subject to direct government control and can locate surgeries wherever they please [35]. People who live remotely in NSW have reduced access to primary care due to lower GP ratios per head of population than in urban areas [36]. Furthermore the GP to population ratios in rural areas are declining over time [37]. These barriers to primary care probably increase the likelihood that people will first present to the emergency department at their local general hospital. We found as have others that people eventually diagnosed with NSCLC who attended non-specialist hospitals were more likely to be emergency admissions than planned admissions [38] [39] [40] without a diagnosis or without a chest x-ray or histological confirmation [10] and were less likely than other patients to receive specialist care (62% vs 94%)[41].

Advanced stage patients may be admitted to general hospitals because they are unlikely to benefit from surgery. However, unknown stage patients will have limited options for investigation when referred to general hospitals. Lung cancer patients treated in regional public hospitals in the Australian State of Queensland were less likely to have had their cancer histologically or cytologically confirmed (7%) than patients treated in specialist hospitals (27%). This difference remained after adjusting for age, sex, and comorbidities. [42] Similarly, UK patients were less likely to be histologically verified when they lived further from the closest hospital or thoracic unit; and patients in the most deprived areas the least likely to have histological verification of their cancer. [10] [8]

Other barriers identified in NSW that may have contributed to a lack of staging at an emergency department include the limited availability of radiology and pathology services, the reliance on the private sector, the lack of ultrasound services and interventional radiologists and the lack of access to cytology and frozen sections, which are all necessary to diagnose lung cancer.[43]

Patients referred to specialist hospitals were less likely to have unknown stage cancer when they lived 100+ km from the NASH. This finding suggests that patients living in remote areas who are admitted to a specialist hospital are more highly selected for referral than patients who live closer to the NASH. It would also possible that some level of investigation has been done prior to referral, perhaps on advice from a consultant at the specialist hospital. Stabilising symptoms, encouraging smoking cessation and evaluating functional status are

suggested for NSCLC patients prior to their surgery. These factors may assume even more significance when travel is required to access staging and surgery.[44] Studies of patients who attend specialist centres for their treatment show that they are more likely to be appropriately staged by a thoracic surgeon and have surgery,[45], be reviewed by a multidisciplinary team [40], have better survival because of the higher surgical volumes even for patients who were older and had comorbidities [46]. For people where surgical treatment is not an option, a greater likelihood of clinical trial participation occurs when they attend a specialist hospital. [47]

Other factors examined and found to be independently associated with advanced stage NSCLC patients were consistent with the existing literature. Males had higher odds of advanced stage compared to females, and higher odds with younger age at diagnosis [48, 49 50] Older patients have been found to have their cancer detected earlier and incidentally as part of other investigations [13]. The lower likelihood of advanced stage with a diagnosis of COPD is consistent with increased monitoring. Patients with COPD are counselled to stop smoking and have their lung function monitored. [51]Not expected, and contrary to most UK studies [48 13] that have used deprivation as their measure of socioeconomic status, were the increased odds of advanced stage in people of higher socioeconomic status. A plausible explanation for this finding is that patients of higher SES were more likely to be investigated and staged, although there was not a compensating reduction in odds of unknown stage cancer. The reduced odds of unknown stage cancer in patients diagnosed between 2005 to 2008 compared to the earlier period corresponds to the period after the introduction of the Australian National Health and Medical Research Council's clinical practice guidelines for lung cancer, [52] which are likely to have increased the proportion of patients adequately staged.

There was a strong association of unknown stage with increasing delay in hospitalisation. Delays in the diagnosis of lung cancer have occurred because of failure to recognise abnormal images or complete diagnostic procedures in a timely manner [53] or because of the limited access to radiology and pathology diagnostic services as previously discussed. [43] Unstaged patients may also have been hospitalised at a terminal stage of their disease.

6.5.1. Limitations and strengths

This analysis was limited to linked cancer registry and hospital data. Therefore, we had no information on presenting symptoms, whether patients had multidisciplinary team review or why they were treated in a general rather than a specialist hospital with increasing distance to the NASH. NSW and Victorian lung cancer patterns of care studies have reported high proportions of lung cancer patients see at least one specialist [54-57] [40] indicating that most patients should have had some opportunity to have their cancer staged. Review by a multidisciplinary team (MDT) has also been found to be an independent predictor of survival.[40] Furthermore, seeing three or more specialists have been associated with the receipt of guideline based care[58].

While TNM staging was preferred, it was not available. However, there may be an even greater difference in the proportion of advanced stage with increasing distance from NASH because patients seen at general hospitals would probably have not had a PET scan to stage their disease compared to those treated at specialist hospitals who do. Therefore a significant proportion of apparent "localised disease" is upstaged on PET scans to "advanced disease." However, a major strength of this study is that unknown stage was included in our analysis. The majority of registry based studies exclude unknown stage because they assume missing stage is due to poor follow up practices within a registry. However, in Australian registries, notifications are from multiple sources legislated by the Public Health Act. In addition, registries contact doctors to obtain missing or discrepant information as part of the cancer registration process. Therefore, unknown stage in this study is most likely due to a lack of investigation or minimal investigation of the patient. A further strength of this study is that it is population based with good linkage to all public and private hospitalisations.

6.5.2. Conclusion

People living remotely from accessible specialist services have an increased risk of being diagnosed with advanced and particularly unknown stage NSCLC and are more likely to be treated in general hospitals than in specialist hospitals. People who attended general hospitals when they live 100km from specialist care had double the likelihood of unknown stage, suggesting they are inadequately investigated thus limiting their treatment options .

Furthermore, NSCLC who attended a specialist hospital when they lived 100km or more from one had less advanced or unknown stage cancer at diagnosis suggesting selective referral of patients may have been occurring because of the requirement to travel. All patients require proper staging in order to determine appropriate treatment, regardless of distance to specialist care.

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7. Patients with localised non small cell lung cancer miss out on curative surgery with distance from specialist care

Chapter 7 has been accepted for publication.

Tracey E, McCaughan B, Badgery-Parker T, Young J, Armstrong B. Do patients with localised non small cell lung cancer miss out on potentially curative surgery with increasing distance to specialist care? Australian New Zealand Journal of Surgery. Accepted for publication 8th August 2014

7.1. Abstract

Aim: To determine whether increasing distance to the nearest accessible specialist hospital (NASH) a public hospital with a thoracic surgical service) increases a patient's likelihood of missing out on curative surgery for localised non small cell lung cancer "(NSCLC)". Method: Population-based study of cancer registry records for 27,033 people with lung cancer diagnosed in New South Wales, Australia, between 2000 and 2008 linked to hospital admission records. This analysis includes 3,240 patients with localised (NSCLC) admitted to hospital within 12 months of diagnosis. Results: Patients who lived 100+km from the NASH were more likely to have no surgery (50.6%) than those living 0-39 km away (37.6%) and more likely to attend general hospitals for their care (52.2% at 100+km, 14.8% at 0-39 km). Relative to patients living 0-39 km from the NASH and attending a specialist hospital for their care, the odds ratio of not having surgery was high if patients attended a general hospital (adjusted OR 5.99, 95%CI 3.87-9.26, for those 0-39 km distant) and even higher as distance from the NASH increased (24.68, 95%CI 12.37-49.13 for 40-49 km and 30.10, 95%CI 18.2-49.40, for 100+km). For patients treated in specialist hospitals (public or private), the trend with distance was opposite: relative to 0-39 km, the OR was 0.29 (95%CI 0.15-0.50) at 40-99 km and 0.14 (95%CI 0.08-0.26) at 100+km. Conclusions Patients with localised NSCLC are most likely to have no potentially curative surgery if they live distant from a specialist hospital and attend a general hospital for their care.

7.2. Introduction

In 2008, lung cancer was the fourth most common cancer and the most common cancer causing death in Australia.[1] Although, patients with small cell lung cancer or distant metastases have a poor prognosis,[2, 3] those presenting with localised non small cell lung cancer (NSCLC) are potentially curable if treated surgically.[4] NHMRC guidelines recommend surgical resection for patients with early stage NSCLC, with lobectomy the preferred procedure.[4] Potentially curative surgery has been found to be one of the best determinants of cancer survival with a recent UK lung cancer audit of 34,513 NSCLC patients reporting a HR of 0.41 (95%CI 0.39-0.44) in patients who underwent surgery relative to those who did not after adjusting for age, sex, performance status, stage and Charlson index of comorbidity.[5] NSCLC patients have better survival if they are treated in high volume surgical centres, even if they are older, of low socioeconomic status, or have comorbidities.[6] In addition, those treated by thoracic surgeons have lower post-operative mortality and morbidity and better adherence to established practice standards than patients treated by general surgeons.[7, 8]

Most studies of the effects of distance to specialist care on treatment of NSCLC have been done in the UK. The majority of them have shown that patients' access to surgical treatment is influenced by distance, clinician specialty and hospital of treatment. [5, 9-11] Most studies could not take account of effects of lung cancer stage on their conclusions. NSW Cancer Registry based studies have shown that the probability of no surgical treatment varies by patients' Local Health District of residence and is higher for patients living in outer metropolitan areas.[12-14] In this study, we investigate whether increasing distance to the nearest accessible specialist hospital (NASH) a public hospital with a thoracic surgical service is associated with failure to receive surgical treatment for localised primary lung cancer after adjusting for potentially confounding variables.

7.3. Methods

The NSW CCR was the primary data source. [15] We included in this analysis all NSW patients with NSCLC (ICD topography codes C33-C34 excluding morphology codes M80413-M80453, M82463) diagnosed between 2000 and 2008 whose CCR record linked to one or more records in the NSW APDC, which details diagnosis and surgical treatment for

all separations from NSW public and private hospitals.[16 17] The combined automated and manual record linkage process had an estimated false positive rate of 0.4 per cent.[18]

Summary stage at diagnosis was classified as localised, regional, distant or unknown, based on the extent of disease notified to, or determined by, the CCR [19]. We included only patients with localised stage at diagnosis who were admitted to hospital at or up to 12 months after diagnosis. We applied this restriction so the admission records would provide contemporary information on chronic obstructive pulmonary disease, smoking, other comorbidities, type of hospital and other treatment related variables.

7.3.1. Distance

Distance to the NASH was obtained for each patient by calculating the distance in kilometres from the patient's geocoded address to the closest public hospital with a specialist cardiothoracic or thoracic surgical service using the "Great Circle Distance Calculator".[20] We considered this to be a measure of access to best care because it encompasses both distance and affordable care; all Australians are entitled to treatment free-of-charge in public hospitals. Distance to a patient's actual hospital of treatment as an alternative measure of accessibility may be biased because more mobile patients may be referred to more distant hospitals; also, it can only apply to those who received treatment.[11] UK studies using travel time and straight-line distances [21]have found them to be highly correlated (R=0.856).

Patients were grouped into three categories of distance: 0-39 km, 40-99 km and 100+km. We plotted the frequency distribution of distance from the NASH in five kilometre groupings and found that it reached a plateau at 40 kilometres. We selected 100 km as the lower bound of the most distant category because patients living this distance or further from required care can obtain financial support through the Isolated Patient Travel, Accommodation and Assistance Scheme (IPTAAS).[22] Patients' place of residence was also classified broadly as metropolitan, outer metropolitan and rural based on the 2010 boundaries of NSW Local Health Districts.

7.3.2. Hospitals

Eleven public specialist hospitals (public hospitals with a cardiothoracic or thoracic surgical service) were identified in Canrefer, [23] a Cancer Institute NSW web directory of cancer

services. We classified other hospitals as private specialist (private hospitals with a cardiothoracic or thoracic surgical service, also identified in Canrefer) or general hospitals (public or private hospitals without such a service).

The "patients' financial status at admission" was also included in the analysis, because of its relevance to which hospitals a person might have access to. The APDC variable was grouped into three categories (public financial status treated in a public hospital, private financial status treated in a private hospital and private financial status treated in a public hospital).

Our outcome of interest was whether patients had potentially curative surgery or not within 12 months of diagnosis. Whether or not patients had their primary cancer treated surgically by lobectomy, segmental resection or pneumonectomy (any major surgery) or not (no surgery) was determined from procedure codes in APDC records covering the period from a month before diagnosis to 12 months after diagnosis. Other characteristics of patients, cancer and treatment are available in Appendix 1.

7.3.3. Statistical analysis

Stata 12.1 was used for the statistical analysis. Logistic regression analysis was conducted with surgery (no or any) as the dependent variable. Univariable predictor variables were considered for inclusion in a full multivariable model if, on their own, they were significantly associated with no surgery ($p<0.2$) (Appendix 1 Table 2).They included distance to the NASH and hospital type, the primary variable of interest in the analysis, which we modelled as a six category composite variable because of a strong statistical interaction between distance and hospital type in determining absence of major surgery (p for interaction $p<0.0001$). The six categories were all combinations of hospital type in two categories (specialist and general) and distance in three categories (0-39km, 40-99km, 100+km).

Sex, age, comorbidity and history of chronic obstructive pulmonary were retained in the final model, regardless of their statistical significance, because of their clinical importance. For all remaining variables, we conducted a series of nested maximum likelihood ratio tests with a p value for retention in the model of less than 0.05. [24] We checked by adding back previously discarded variables in the backward elimination model to determine if they improved model

fit. We used the Fitstat procedure and compared the AIC and the pseudo R square for each of the nested models.

7.4. Results

There were 5,456 patients with localised NSCLC diagnosed in 2001 to 2008. From these, we excluded 119 with no hospital admission, those whose only linking admissions occurred two or more months before (2,013) or more than 12 months after (84) their diagnosis. This left 3,240 patients who were eligible for these analyses.

Of the 3,240 patients with localised NSCLC, 40.8% (1,320) did not have major surgery. A greater proportion of patients who lived 100km or more from the NASH did not have surgery (50.6%) than patients living 0-39km (37.6%) away. This disparity was more pronounced for lobectomy than it was for segmental resection or pneumonectomy (data available on request).

The adjusted odds ratio (OR) for not having surgery in patients admitted to a general hospital (relative to a value of 1 in patients admitted to a thoracic surgery hospital and living 0-39km from the NASH) increased with increasing distance from the NASH: OR 5.99 (95%CI 3.87-9.26) for those 0-39 km distant, 24.68 (95%CI 12.37-49.13) for 40-49km and 30.01 (95%CI 18.2-49.40) for 100+km (Figure 1 and Table 1). These ORs were adjusted for all other variables independently associated with no surgical treatment in the final model (Table 1). In contrast, for patients treated in specialist hospitals the adjusted ORs fell with increasing distance from the NASH: relative to the OR of 1 for patients 0-39km distant, the ORs were 0.29 (95%CI 0.16-0.50) at 40-99 km and 0.14 (95%CI 0.08-0.25) at 100+km (Figure 1 and Table 1).

Other variables in the final model significantly associated with a higher odds of not having surgery (Table 1) were, absence of any recorded comorbidity, being a non smoker, if the lung cancer was the first cancer diagnosed in the person having a squamous or large cell cancer, diagnosis in the years 2000 to 2004 (the earlier half of the period studied), having

cancer that was not verified histopathologically, having an emergency presentation to hospital, and being a private financial status patient treated in a public hospital. Sex, age, and COPD although included in the final model, were not significantly associated with lack of surgery. Local Health District was excluded from the final model because it was highly correlated with distance from a specialist centre (variance inflation factor of 3). Remoteness (p=0.29) was not included in the backward elimination model and socioeconomic status (p=0.51) and country of birth (p=0.35) were not retained. Overall, the model had a pseudo R square of 81.9. [25]

Distance of residence from the NASH and hospital of treatment made the largest contribution to model fit with a pseudo R square of 47.0, followed by emergency presentation that increased the pseudo R square to 67.1; effects of other variables explained the difference of 14.9 between this value and the overall pseudo R square.

Given the large number of patients (2,013) who were excluded from the analysis because they did not have a hospital admission after diagnosis, we did a supplementary logistic regression analysis in which these patients were compared, with respect to as many variables as possible included in the model in Table 1with patients who had a hospital admission at or up to 12 months after diagnosis but no surgery. The excluded patients were older and more likely to be smokers and to have COPD. They are also more likely to live 100+km from the NASH (OR 1.26, 95%CI 1.06-1.50) (Appendix 1 Table 3).

7.5. Discussion

Our results show that patients with localised NSCLC who attend general hospitals for care are much more likely not to have surgery for their cancer than those who attend a specialist hospital. In patients who attended a general hospital, the likelihood of not having major surgery increased with their distance from the NASH. Somewhat unexpectedly, the opposite was true for patients who attended a thoracic surgery hospital; that is, patients living 100+km from the NASH had the lowest risk of not having major surgery (i.e. were most likely to

have surgery). The type of hospital of treatment and whether the admission was an emergency presentation were the strongest predictors of risk of not having major surgery.

Most studies addressing distance to surgical treatment in patients diagnosed with lung cancer were undertaken in the UK or US and did not taken account of stage at diagnosis. UK lung cancer patients were less likely to have surgery when they lived further from a specialist hospital or cancer centre than when they lived closer to one, after adjusting for age, sex, selected tumour pathology characteristics and socioeconomic deprivation. [11] [9] However, a US study that used a similar measure of distance to ours did not find distance to specialist care to be associated with the likelihood of patients having lung cancer surgery after adjusting for age, sex, race, stage, and year of diagnosis. [26] This study, was limited to patients with Medicaid insurance, and did not take account of type of hospital of treatment, which we found to be highly correlated with distance, or other factors potentially important factors, like comorbidity. A UK study, which adjusted for stage at diagnosis but did not measure distance, found, as we did, that NSCLC patients who were referred to non specialist hospitals were less likely to have surgery than those referred to specialist hospitals, after adjusting for age, sex, performance status, comorbidity and stage.[5]

UK[27] and some Australian registry based studies[12-14] but not all[28] have also shown that surgery rates vary by health regions. A UK registry based study showed that lung cancer surgery rates varied widely among 26 health authorities.[29] Australian lung cancer patterns of care studies have shown mixed results for geographical variation in surgery rates. In NSW, [13] the proportion of patients having surgery varied between 17% and 26% when three area health services were compared. In Victoria, there was no significant difference between urban residents and rural and regional residents in the proportion having surgery.[28] A NSW registry based study of NSCLC patients, which reported on surgery by physician provided TNM stage, found that patients who lived in outer metropolitan health service areas were 51% more likely get no treatment than patients who lived in urban area health services.[14]

Our observed fall in risk of not having surgery with increasing distance from the NASH in patients who attended a specialist hospital was somewhat unexpected. While we know of no directly relevant evidence, we believe the most plausible explanation is that more remote

patients referred to specialist hospitals are likely to have had a thorough assessment of their suitability for surgery including PET before admission to hospital than patients referred over shorter distances Whereas patients seen in general hospitals particularly with greater distance from NASH are unlikely to have a PET scan to stage their disease, indeed some "localised disease" may have been based on chest xray only leading to under staging. This difference in type of staging (upstaging for patients in specialist hospitals and downstaging for patients in general hospitals) will artificially increase the staging disparity between hospitals with increasing distance to the NASH.

We found a number of factors other than hospital attended and distance that were independently associated with not having major surgery. Patients were more likely to have no major surgery before 2004 than after it; this difference is probably explained by the release in 2004 of the Australian NHMRC guidelines for the treatment and management of lung cancer, [4] that recommend surgery for localised lung cancer. Our patients were also less likely to have major surgery if their first admission for lung cancer was an emergency. Emergency admissions appear to put patients on a suboptimal care pathway; others have reported that lung cancer patients who attended emergency departments without a diagnosis or without a chest x-ray were less likely than other patients to receive specialist care (62% vs 94%),[30] or to have their lung cancer confirmed pathologically.[31] Patients with large cell carcinomas were also less likely to have surgery than patients with other types of non small cell cancer, perhaps because care decisions are influenced by the often higher grade and known poorer prognosis of these cancers.[32, 33] Private financial status patients admitted to public hospitals were less likely to have major surgery than public patients in public hospitals and private patients in private hospitals. Speculatively, this observation may reflect a preference for thoracic surgeons to receive sicker patients at public hospitals where, with the exception of smaller rural hospitals, medical staff are on-call and on-site 24 hours a day. A reduced odds of no surgery for lung cancer patients treated in private hospitals has also been found in a WA linkage study.[34]

Unlike previous studies on distance, [10, 11, 34] –the likelihood of no surgery in our study did not vary with age or by socioeconomic status after adjustment for other covariates. The effect of socioeconomic status in our study disappeared when type of admission was included in the model (730 or 23% of patients had emergency admissions) because most patients having emergency admissions did not have surgery. We also found that patients whose NSCLC was a second cancer as opposed to their first cancer were less likely to have no surgery, probably because of their existing links with expert care. Surprisingly, we found that patients with comorbidity were less likely to have no surgery, which is not consistent with other studies.[35] While we have no certain explanation for this finding; it is plausible that patients being prepared for surgery have their comorbidities recorded more fully because of their preoperative assessment. Unexplained confounding might also have produced it.

7.5.1. Limitations and strengths

This study was limited to surgical treatment. We had no information on whether patients received chemotherapy or radiotherapy as these are provided in outpatient cancer care centres. However, other studies have shown that, like surgery, there is lower use of radiotherapy,[11 27, 36] chemotherapy[9 27] and combined treatment[27] with increasing distance to specialist treatment and that their use varies depending on the specialty of the hospital[9 11] or whether a centre with radiotherapy was the first attended.[27, 36] We also used a cancer registry based definition of localised stage (localised to the tissue or organ of origin); TNM definitions[32] would have been preferable but were not available.

The major strengths of our study are its coverage of a whole population; our ability to link cancer registry and hospital separation records both public and private; a routinely recorded measure of cancer stage, albeit imperfect; use of geocoded data to provide more precise measures of distance between patients' residences and treating hospital; and use of a distance measure that related to directly to patients' access to care at the time referral decisions were being made.

7.5.2. Conclusions

The likelihood that patients with localised NSCLC would be treated in a general hospital for their cancer increased with distance from the NASH. Patients treated in general hospitals were much less likely to have potentially curative surgery for their cancer than those treated in specialist hospitals because they were not offered, or they declined, referral to expert care. It is urgent that we understand the reasons these patients are not referred and take steps to address them.

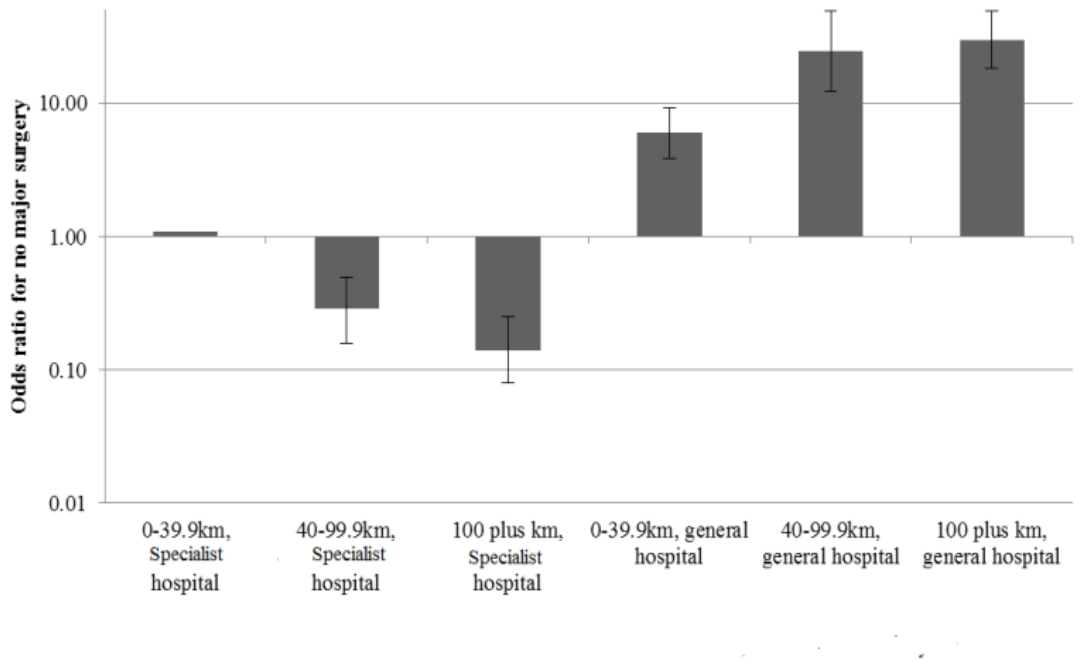
Chapter 7 Table 1 localised non small cell lung cancer patients and the odds of no major surgery in patients admitted to hospital within 12 months of diagnosis

Characteristics	Major surgery N	%	No surgery N	%	OR	(95% CI)	p value
Total	1,918	100	1,322	100			
Distance of residence from the NASH and type of hospital where treated							
0-39.9km, thoracic surgery hospital	1,225	63.9	532	40.2	1		
40-99.9km, thoracic surgery hospital	241	12.6	22	1.7	0.29	(0.16-0.50)	
100 plus km, thoracic surgery hospital	351	18.3	20	1.5	0.14	(0.08-0.25)	
0-39.9km, general hospital	63	3.3	243	18.4	5.99	(3.87-9.26)	
40-99.9km, general hospital	13	0.7	140	10.6	24.65	(12.37-49.13)	
100 plus km, general hospital	25	1.3	365	27.6	30.01	(18.22-49.40)	p<0.0001
Sex							
Males	1,144	61.9	861	65.1	1		
Females	774	38.1	461	34.9	0.87	(0.67-1.13)	p=0.2905
Age at diagnosis							
15-59 years	422	20.4	240	18.2	1		
60-69 years	633	29.9	337	25.5	1.07	(0.76-1.52)	
70 -79 years	697	36.3	479	36.2	1.05	(0.75-1.48)	
80 plus years	166	13.3	266	20.1	1.34	(0.85-2.12)	p=0.6484
Comorbidity							
No comorbidity	1,184	61.7	851	64.4	1		
Comorbidity	734	38.3	471	35.6	0.38	(0.29-0.50)	p<0.0001
Chronic obstructive pulmonary disease‡							
no COPD	1,184	62.8	851	64.4	1		
COPD	734	37.2	471	35.6	0.84	(0.63-1.13)	p=0.2483
Smoking status†							
Non smoker	316	16.5	404	30.6	1		
Previous smoker	888	46.3	483	36.5	0.41	(0.28-59)	
Current smoker	714	37.2	435	32.9	0.39	(0.27-0.56)	p<0.0001
Period of diagnosis							
2000-2004	733	38.2	855	64.7	1		
2005-2008	1,185	61.8	467	35.3	0.39	(0.31-0.51)	p<0.0001
Method of diagnosis							
Cytology	17	0.9	147	11.1	1		
Clinical	7	0.4	137	10.4	0.86	(0.24-3.12)	
Histologically verified	1,894	98.7	1,038	78.5	0.07	(0.03-0.14)	p<0.0001
Cancer							
Order of lung cancer							
First cancer	1,771	94.8	1,301	98.4	1		
Second or subsequent cancer	147	5.2	21	1.6	0.39	(0.20-0.78)	P=0.0079
Histology§							
Squamous	553	28.8	409	30.9	1		
Adenocarcinoma	909	47.4	305	23.1	0.44	(0.32-0.60)	
Large Cell	219	11.4	473	35.8	2.29	(1.64-3.21)	

Other	237	12.4	135	10.2	0.35	(0.22-0.56)	p<0.0001
Type of admission							
Emergency	45	44	685	51.8	1		
Planned admission	1,857	52.9	583	44.1	0.04	(0.02-0.06)	
Referred from outpatients	16	1.6	54	4.1	0.26	(0.11-0.66)	p<0.0001
Financial status							
Public financial status treated in public hospitals	971	50.6	950	71.9	1		
Private financial status treated in public hospitals	132	6.9	258	19.5	2.48	(1.74-3.52)	
Private financial status treated in private hospitals	815	42.5	114	8.6	0.21	(0.15-0.29)	p<0.0001

Odds Ratios (OR) and 95% Confidence Intervals (95% CI)
†Smoking codes: ICD10-AM codes Z86.43, Z72.0, Z71.6, F17.
‡Chronic obstructive pulmonary disease codes: ICD10-AM codes J41.0, J41.1, J41.8, J42.0, J42, J43, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.8, J44.9
§Cancer codes: ICD0-3 morphology codes: Squamous 80503-80783, Large cell 80353, 83103,80103-80123,80143-80313, Adenocarcinoma 82303-82313, 82503-82603, 81403, 82113, 83233, 85763, 82463 Other 80003-80053, 88003, 88013, 88023, 88053, 88103, 88113, 88303, 88903, 89203, 90403, 90413, 91203, 91333, 91503, 95403, 88403-89213, 89903-89913, 91203-91333, 95403-95813, 88303, 91503.

Chapter 7 Figure 1 Odds ratios for having no major surgery for primary non small cell cancer by distance from a public thoracic surgery hospital and type of hospital where treated



Adjusted for age, sex, chronic obstructive pulmonary disease and whether a person's lung cancer was their first or second cancer and each other variable in Chapter 7 Table 1

7.6. Appendix 1

7.6.1. Patient characteristics

The following variables were obtained from CCR records: Sex, age at diagnosis (grouped into four categories, 15-59, 60-69, 70-79 and 80 years and older); country of birth (grouped as Australian born, born in an English speaking country, born in a non English speaking country and unknown); socioeconomic status (allocated in five categories using the Australian Bureau Statistics' Index of Relative Socioeconomic Disadvantage based on the 2001 and 2006 Census, depending on the period of diagnosis[37]).

Additional variables obtained from APDC records were: smoking status (non smoker, past smoker, current smoker based on ICD-10 codes Z86.43, Z72.0, Z71.6, F17 in any separation record); any comorbidity (any condition, except secondary cancer, in the Charlson index[38] and coded as a primary or other diagnosis in any record); and any or no history of chronic obstructive pulmonary disease (based on relevant four-digit ICD-10 codes in the range J41.0-J44.9 in any separation record).

7.6.2. Cancer characteristics - histological subtype

Histological subtype of cancer was coded by the CCR from pathology reports using the ICD-O version 3 morphology codes, [16] which were grouped in accord with Cancer Incidence in Five Continents Vol IX.[39]Order of lung cancer –whether the lung cancer was the first or subsequent cancer diagnosed.

7.6.3. Treatment

Period of diagnosis (grouped as 2000-2004 and 2005-2008). Method of diagnosis (clinical, cytology or histopathology), which is recorded by the CCR, was also included because a number of studies have reported it to be a reliable indicator of lack of investigation.[40] Type of hospital admission admitted via the emergency department, planned admission or other (usually outpatients). Time from diagnosis to surgery or admission to hospital in the absence of surgery in months was used to subset cases treated within 12 months of diagnosis.

Chapter 7 Appendix 1 Table 1 Characteristics of patients with localised non small cell lung cancer diagnosed between 2000 and 2008 in NSW and admitted to hospital within the first 12 months after diagnosis

Total	**3,240**	**100**
Patient		
Distance from the NASH and hospital of treatment		
Specialist hospital 0-39.9	1,757	54.2
Specialist hospital 40-99.9	263	8.1
Specialist hospital 100 plus	371	11.5
General hospital 0-39.9	306	9.4
General hospital 40-99.9	153	4.7
General hospital 100 plus	390	12.0
Index of remoteness		
Accessible	3,156	97.4
Not accessible	84	2.6
LHD of residence		
Urban	1,365	42.1
Outer metropolitan	904	27.9
Rural	971	30.0
Sex		
Males	2,005	61.9
Females	1,235	38.1
Age at diagnosis		
15-59 years	662	20.4
60-69 years	970	29.9
70 -79 years	1,176	36.3
80 plus years	432	13.3
Country of birth		
Australian born	2,094	64.6
Born in an English Speaking country	232	7.2
Born in a Non English speaking country	772	23.8
Unknown country of birth	142	4.4
Socioeconomic status		
Lowest SES'	670	20.7
Second lowest SES'	623	19.2
Middle SES'	694	21.4
Second highest SES'	672	20.7
Highest SES'	581	17.9
Comorbidity		
No comorbidity	2,035	62.8
Comorbidity	1,205	37.2
****Smoking status**		
Non smoker	720	22.2
Previous smoker	1,371	42.3
Current smoker	1,149	35.5
*****Chronic obstructive pulmonary disease**		
no COPD	2,035	62.8
COPD	1,205	37.2
Cancer		
Histology		
Squamous	962	29.7
Adenocarcinoma	1,214	37.5
Large cell	692	21.4
Other	372	11.5
Order of lung cancer		
First cancer	3,072	94.8
Second or subsequent cancer	168	5.2
Treatment		
Period of diagnosis		

2000-2004	1,588	49.0
2005-2008	1,652	51.0
Method of diagnosis		
Cytology	164	5.1
Clinical	144	4.4
Histology hospital	770	23.8
Histology by cancer registry staff	2,162	66.7
Type of admission		
Emergency	730	22.5
Planned admission	2,440	75.3
Other	70	2.2
Time from diagnosis to treatment		
At diagnosis	2,600	80.2
2-3 months	409	12.6
3-6 months	154	4.8
7 to 12 months	77	2.4
Financial status		
Public financial status treated in public hospitals	1,921	59.3
Private financial status treated in public hospitals	390	12.0
Private financial status treated in private hospitals	929	28.7

†Smoking codes: ICD10-AM codes Z86.43, Z72.0, Z71.6, F17.
‡Chronic obstructive pulmonary disease codes: ICD10-AM codes J41.0, J41.1, J41.8, J42.0, J42, J43, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.8, J44.9
§Cancer codes: ICD0-3 morphology codes: Squamous 80503-80783, Large cell 80353, 83103,80103-80123,80143-80313, Adenocarcinoma 82303-82313, 82503-82603, 81403, 82113, 83233, 85763, 82463 Other 80003-80053, 88003, 88013, 88023, 88053, 88103, 88113, 88303, 88903, 89203, 90403, 90413, 91203, 91333, 91503, 95403, 88403-89213, 89903-89913, 91203-91333, 95403-95813, 88303, 91503.

Chapter 7 Appendix 1 Table 2 Patient, cancer and treatment characteristics, chi squared p values and univariable odds ratios and 95%Confidence intervals for no surgery in non small cell lung cancer patients diagnosed between 2000 and 2008 in NSW and admitted to hospital within the first 12 months after diagnosis

Characteristics	**Any Surgery n %**		**No Surgery n %**		p value	Univariable OR and 95% confidence Intervals		p value
Total	1,918	100	1,32	100.		OR	95% CI	
Patient								
Distance from the NASH and								
0-39.9km, specialist hospital	1,225	63.9	532	40.2		1		
40-99.9km, specialist hospital	241	12.6	22	1.7		0.21	(0.13-0.33)	
100 plus km, specialist hospital	351	18.3	20	1.5		0.13	(0.08-0.21)	
0-39.9km, general hospital	63	3.3	243	18.4		8.88	(6.61-	
40-99.9km, general hospital	13	0.7	140	10.6		24.80	(13.92-	
100 plus km, general hospital	25	1.3	365	27.6	p<0.0001	33.62	(22.14-	p<0.0001
Index of remoteness								
Accessible	1,873	97.7	1,28	97.0		1		
Not accessible	45	2.3	39	3.0	p=0.288	1.27	(0.82-1.95)	p=0.288
LHD of residence								
Urban	857	44.7	508	38.4		1		
Outer metropolitan	577	30.1	327	24.7		0.96	(0.80-1.14)	
Rural	484	25.2	487	36.8	p<0.0001	1.70	(1.44-2.01)	p<0.0001
Sex								
Males	1,144	59.6	861	65.1		1		
Females	774	40.4	461	34.9	p=0.002	0.79	(0.68-0.92)	p=0.0016
Age at diagnosis								
15-59 years	422	22.0	240	18.2		1		
60-69 years	633	33.0	337	25.5		0.94	(0.76-1.15)	
70 -79 years	697	36.3	479	36.2		1.21	(0.99-1.47)	
80 plus years	166	8.7	266	20.1	p<0.0001	2.82	(2.19-3.62)	p<0.0001
Country of birth								
Australian born	1,215	63.3	879	66.5		1		
Born in an English Speaking country	122	6.4	110	8.3		1.25	(0.95-1.64)	
Born in a Non English speaking country	474	24.7	298	22.5		0.87	(0.73-1.03)	
Unknown country of birth	107	5.6	35	2.6	p<0.0001	0.45	(0.31-0.67)	p<0.0001
Socioeconomic status								
Lowest SES'	359	18.7	311	23.5		1		
Second lowest SES'	333	17.4	290	21.9		1.01	(0.81-1.25)	
Middle SES'	383	20.0	311	23.5		0.94	(0.76-1.16)	
Second highest SES'	450	23.5	222	16.8		0.57	(0.46-0.71)	
Highest SES'	393	20.5	188	14.2	p<0.0001	0.55	(0.44-0.70)	p<0.0001
Comorbidity								
No comorbidity	1,184	61.7	851	64.4		1		
Comorbidity	734	38.3	471	35.6	p=0.126	0.89	(0.77-1.03)	p=0.126
Smoking status†								
Non smoker	316	16.5	404	30.6		1		
Previous smoker	888	45.3	483	36.5		0.43	(0.35-0.51)	
Current smoker	714	37.2	435	32.9	p<0.0001	0.48	(0.39-0.58)	p<0.0001
Chronic obstructive pulmonary								
no COPD	1,184	61.7	851	64.4		1		
COPD	734	38.3	471	35.6	p=0.882	0.99	(0.85-1.15)	p=0.882
Cancer								
Histological subtype§								
Squamous	553	28.8	409	30.9		1		
Adenocarcinoma	909	47.4	305	23.1		0.45	(0.38-0.54)	
Large Cell	219	11.4	473	35.8		2.92	(2.38-3.58)	
Other	237	12.4	135	10.2	p<0.0001	0.77	(0.60-0.99)	p<0.0001
Order of lung cancer								
First cancer	1,771	92.3	1,30	98.4		1		
Second or subsequent cancer	147	7.7	21	1.6	p<0.0001	0.19	(0.12-0.31)	p<0.0001
Treatment								
Period of diagnosis								
2000-2004	733	48.2	855	64.7		1		
2005-2008	1,185	61.8	467	35.3	p<0.0001	0.34	(0.29-0.39)	p<0.0001
Method of diagnosis								
Cytology	17	0.0	147	11.1		1		
Clinical	7	0.4	137	10.4		2.26	(0.91-5.63)	
Histologically verified	1,894	98.7	1,03	78.5	p<0.0001	0.06	(0.03-0.10)	p<0.0001
Type of admission								
Emergency	45	2.3	685	51.8		1		
Planned admission	1,857	96.8	583	44.1		0.02	(0.02-0.03)	
Other	16	0.8	54	4.1	p<0.0001	0.22	(0.12-0.42)	p<0.0001
Financial status								
Public financial status treated in public	971	50.6	950	71.9		1		
Private financial status treated in public	132	6.9	258	19.5		2.00	(1.59-2.51)	
Private financial status treated in private	815	42.5	114	8.6	p<0.0001	0.14	(0.12-0.18)	p<0.0001

†Smoking codes: ICD10-AM codes Z86.43, Z72.0, Z71.6, F17.

‡Chronic obstructive pulmonary disease codes: ICD10-AM codes J41.0, J41.1, J41.8, J42.0, J42, J43, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.8, J44.9
§Cancer codes: ICD0-3 morphology codes: Squamous 80503-80783, Large cell 80353, 83103,80103-80123,80143-80313, Adenocarcinoma 82303-82313, 82503-82603, 81403, 82113, 83233, 85763, 82463 Other 80003-80053, 88003, 88013, 88023, 88053, 88103, 88113, 88303, 88903, 89203, 90403, 90413, 91203, 91333, 91503, 95403, 88403-89213, 89903-89913, 91203-91333, 95403-95813, 88303, 91503.

Chapter 7 Appendix 1 Table 3 Multivariable logistic regression model of NSW localised non small cell lung cancer patients who did not undergo surgery and were not admitted to hospital after diagnosis relative to those who were admitted within 12 months of their diagnosis.

	Did not have		Admitted		Not admitted				
Characteristics	N	%	N %		%	%	OR	(95%CI)	P value
Patient	3,335	1.0	1,322	100.0	2,013	1.0			
Distance from the NASH									
0-39.9km	1,862	55.8	755	57.1	1,087	54.0	1		
40-99.9km	416	12.5	162	12.3	254	12.6	1.09	(0.85-1.38)	
100 plus km	1,057	31.7	385	29.1	672	33.4	1.26	(1.06-1.50)	p=0.0318
Sex									
Males	2,166	64.9	861	65.1	1305	64.8	1		
Females	1,169	35.1	461	34.9	708	35.2	1.13	(0.96-1.33)	p=0.1635
Age at diagnosis									
15-59 years	430	12.9	240	18.2	190	9.4	1		
60-69 years	738	22.1	337	25.5	401	19.9	1.34	(1.05-1.78)	
70 -79 years	1,282	38.4	479	36.2	803	39.9	1.99	(1.63-2.67)	
80 plus years	885	26.5	266	20.1	619	30.8	3.01	(2.35-4.03)	p<0.0001
Charlson comorbidity index									
No	2,005	60.1	851	64.4	1154	57.3	1		
Any	1,330	39.9	471	35.6	859	42.7	1.16	(0.97-1.37)	p<0.0893
Smoking status†									
Non smoker	757	22.7	404	30.6	353	17.5	1		
Previous smoker	1,325	39.7	483	36.5	842	41.8	1.62	(1.32-1.99)	
Current smoker	1,253	37.6	435	32.9	818	40.6	2.02	(1.63-2.51)	p<0.0001
Chronic obstructive pulmonary disease ‡									
no COPD	1,930	57.9	878	66.4	1052	52.3	1		
COPD	1,405	42.1	444	33.6	961	47.7	1.63	(1.37-1.94)	p=0.0006
Cancer									
Order of lung cancer									
First cancer	3,121	93.6	1,301	98.4	1820	90.4	1		
Second or subsequent cancer	214	6.4	21	1.6	193	9.6	5.17	(3.20-8.37)	p<0.0001
Histological subtype§									
Squamous	994	29.8	409	30.9	585	29.1	1		
Adenocarcinoma	746	22.4	305	23.1	441	21.9	1.12	(0.90-1.39)	
Large Cell	1,144	34.3	473	35.8	671	33.3	0.98	(0.80-1.19)	
Other	451	13.5	135	10.2	316	15.7	1.29	(0.98-1.70)	p=0.1318
Method of diagnosis									
Cytology	478	14.3	147	11.1	331	16.4	1		
Clinical	407	12.2	137	10.4	270	13.4	1.23	(0.89-1.70)	
Histology hospital	1,307	39.1	555	42.0	752	37.4	0.88	(0.68-1.14)	
Histology by cancer registry staff	1,143	34.2	483	36.5	660	32.8	0.87	(0.67-1.14)	p=0.0599
Treatment factors									
Period of diagnosis									
2000-2004	1,455	43.6	855	64.7	600	29.8	1		
2005-2008	1,880	56.4	467	35.3	1413	70.2	4.08	(3.46-4.74)	p<0.0001

For patients not admitted to hospital after diagnosis the information for COPD, smoking and comorbidity has been obtained from admissions two months or more prior to their date of diagnosis and is not contemporaneous.
†Smoking codes (diagnosis codes Z86.43, Z72.0, Z71.6,F17)
‡Chronic obstructive Pulmonary Disease (diagnosis codes J41.0,J41.1,J41.8,J42.0,J42,J43,J43.1,J43.2,J43.8,J43.9,J44.0,J44.1,J44.8,J44.9
§Non small cell lung cancer=squamous (80503-80783),large cell carcinoma 80353,83103,80103-80123,80143-80313, Sarcoma'88003,88013,88023,88053,88103,88113,88303,88903,89203,90403,90413,91203,91333,91503,95403,88403-89213,89903-89913,91203-91333,95403-95813,88303,91503Adenocarcinoma 82303-82313, 82503-82603, 81403, 82113,83233,85763,8246Other =80003-80053

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7.8. Acceptance of this manuscript in the Australian New Zealand Journal of Surgery

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8. Survival of Australian lung cancer patients and the impact of distance from and attendance at a thoracic specialist centre: A data linkage study

Chapter 8 is a paper that has been published online first

Tracey E, McCaughan B, Badgery-Parker T, Young J, Armstrong B. Survival of Australian lung cancer patients and the impact of distance from and attendance at a thoracic specialist centre: a data linkage study. *Thorax.* July 29, 2014. 0:1–9. doi:10.1136/thoraxjnl-2014-205554.

8.1. Abstract

Lung cancer patients have better survival when treated in thoracic surgical (specialist) centres. **Aims**: To determine, whether, outcome of non-small cell lung cancer (NSCLC) patients is poorer with increasing distance to the nearest accessible specialist hospital (NASH). **Methods** We linked cancer registry, hospital and death records of 23,871 NSCLC patients; 3,240 localised, 2,435 regional and 3,540 distant stage patients hospitalised within 12 months of diagnosis were analysed. Distance from patients' residences to the NASH was measured using geographical coordinates. Cox proportional hazards models examined predictors of NSCLC death. **Results:** Having a resection of the cancer, which admission to a specialist hospital made more likely, substantially reduced hazard of NSCLC death. Distance influenced hazard of death through both these variables; a patient was less likely to be admitted to a specialist hospital than a general hospital and less likely to have a resection the further they lived from the NASH. However, patients who lived distant from the NASH and were admitted to a specialist hospital were more likely to have a resection and less likely to die from NSCLC than patients admitted to a specialist hospital and living closer to the NASH. These patterns varied little with lung cancer stage. **Conclusions** NSCLC outcome is best when patients are treated in a specialist hospital. Greater distance to the NASH can affect its outcome by reducing the likelihood of being treated in a specialist hospital. Research is needed into patient and health service barriers to referral of NSCLC patients for specialist care.

8.2. Introduction

Surgical resection is recommended for early stage non small lung cancer patients; with lobectomy the preferred type of surgery.[1] Depending on the location of the tumour, surgery may also be appropriate for patients with up to stage IIIa tumours.[2] Post-operative mortality is lower and survival longer when patients are treated by thoracic surgeons in high volume centres probably because these surgeons are most likely to adhere to established practice standards.[3, 4]

Distance to specialist centres is hypothesised to be a barrier to access to specialised medical care.[5, 6] Most studies of the effects of distance to specialist care on treatment of NSCLC have been done in the UK. The majority of these studies have shown that patients' access to surgical treatment is influenced by distance; and by clinician specialty and hospital of treatment.[5-8] These studies generally could not take account of effects of lung cancer stage on their conclusions.

New South Wales (NSW) Central Cancer Registry based patterns of care studies have shown that probability of no surgical treatment varies by a patient's area of residence.[9-11] The five year relative excess risk of death for NSW lung cancer patients was found to be significantly higher for patients living in accessible and moderately accessible areas regardless of stage.[12] A NSW GP or specialist can refer a patient to hospital as a planned admission, or patients can themselves present to the emergency department and be admitted directly to hospital. The commonest non-emergency pathway is probably referral by a GP to a specialist and referral by the specialist to a hospital for treatment under their care. Chemotherapy and radiotherapy are usually provided in outpatient settings.

In this study, we investigate whether increasing distance to the nearest accessible specialist hospital (NASH), the nearest public hospital with a thoracic surgical serviceis associated with poorer survival for patients with localised, regional and distant stage primary lung cancer after adjusting for potentially confounding variables.

8.3. Methods

The NSW CCR was the primary data source.[13] The study population was all patients with NSCLC (International Classification of Disease (ICD) topography codes C33–C34 excluding morphology codes M80413–M80453, M82463) diagnosed in NSW between 2000 and 2008 and followed up to the end of 2008. Cancer registry coders based on pathology reports, doctor's letters and other notifications determine stage at diagnosis. It is grouped into four categories: localised (confined to the organ of origin), regional (invasion of adjacent organs and proximal lymph nodes), distant (invasion distant lymph nodes or distant organs) and unknown (not recorded because pathology information was not available). Previous studies have shown these extent of disease categories to provide broadly comparable information to other methods of staging.[14, 15]

A total of 23,871 patients were potentially eligible for this study. Of these, 22,997 patients whose CCR[13] record linked to one or more records in the NSW APDC, which details diagnosis and surgical treatment for all separations from NSW public and private hospitals, [16] were considered for the analysis. The combined automated and manual record linkage process had an estimated false positive rate of 0.4%.[17] Patients were excluded if they were diagnosed by death certificate only (707) were not admitted to hospital after diagnosis (10,684), or were admitted more than 12 months after diagnosis (459); which left 11,147 patients. Inpatient staging procedures could not have occurred and hospital risk factor and treatment information was not available for the patients not admitted to hospital after diagnosis.We also excluded (1,932) unknown stage patients except in a sensitivity analysis. This left 9,215 in the main analysis. Of these patients, 3,240 patients had localised stage, 2,435 had regional stage and 3,540 had distant stage cancer.

8.3.1. Distance

Distance to the NASH was obtained for each patient by using the geographical coordinates of the patient's address and the NASH, and the "Great Circle Distance Calculator", a (SAS) programme. This algorithm calculates the shortest distance between two points on Earth, treating it as a sphere. [18] We considered this distance to be a measure of access to best care because it encompasses both distance to and affordability of care; all Australians are entitled to treatment free-of-charge in public hospitals. Distance to a patient's actual hospital of

treatment as an alternative measure of access may be biased because patients that are more mobile may be referred to hospitals that are more distant. In addition, it can only apply to those who received treatment.[6] UK studies using travel time and straight-line distance [19] have found them to be highly correlated (R = 0.856).

Patients were grouped into three categories of distance: 0–39 km, 40–99 km and ≥100 km. The ≥100km category was made the most distant category because patients living this distance from required care in NSW can obtain financial support for travel and accommodation through the Isolated Patient Travel, Accommodation and Assistance Scheme.[20] Patients' place of residence was also classified broadly as metropolitan, outer metropolitan and rural, based on the 2010 boundaries of NSW Local Health Districts.

8.3.2. Hospitals

Eleven public specialist hospitals were identified using Canrefer, [21] a Cancer Institute NSW web directory of cancer services. We grouped hospitals in which patients were treated as specialist (public and private hospitals with a thoracic surgery service) or general hospitals (public and private hospitals without a thoracic surgery service). We selected the hospital of treatment as the hospital where patients received their most invasive procedure; in the absence of any procedure we selected the first hospital to which the patient was admitted after diagnosis.

Because there was structural correlation between distance to the NASH and the type of hospital in which a patient was treated (the specialist hospitals were in Sydney or a large city while the general hospitals were distributed more widely throughout the State) we created a six category variable of hospital type in two categories, specialist and general, by distance from the NASH in three categories, 0–39 km, 40–99 km, ≥100 km. Other covariates are described in Appendix 1 Tables 1 and 2.

8.3.3. Surgery

Whether or not patients had their primary cancer treated surgically by lobectomy, segmental resection or pneumonectomy (referred to hereafter as a resection) was determined from hospital procedure codes in APDC records covering the period a month before diagnosis to 12 months after diagnosis. Other characteristics of patients are found in Appendix 1.

8.3.4. Statistical analysis

Stata 12.1 was used for the statistical analysis. We described cause specific survival from NSCLC and its predictors using Kaplan–Meier curves. Univariable Cox proportional hazards regression models were fitted for each covariate. Proportionality was examined and time varying components were retained if proportionality assumptions failed. Interactions were included on an a priori basis. Independent determinants of cause specific survival were identified by backward elimination from a full Cox proportional hazards model. A p value less than 0.05 in the likelihood ratio test was used to determine whether a variable was retained in the final model. Sex, age, comorbidity and history of chronic obstructive pulmonary disease were retained in the final model, regardless of their statistical significance, because of their clinical importance. The combination of type of hospital and distance from the NASH were similarly retained because investigation of the effects of distance was the main objective of this study. For all other variables, nested maximum likelihood ratio tests compared two models with and without the covariate. We checked model fit by comparing unadjusted Kaplan Meier survival curves with adjusted curves for each covariate after redoing the model using the Royston and Palmer `stpm2` [22] command and the Predict command in Stata 12.1 (Appendix 1 Figure 1). This model was the source of the adjusted survival curves in Figures 1 and 2. A sensitivity analysis was done by repeating the Cox modelling after imputing values for unknown stage (data available on request).

8.4. Results

Most NSCLC patients were male and Australian born. The mean age was 70 years in males and 69 years in females. There was a lower proportion in the highest socioeconomic status (SES) group than is found in the general Australian population. Seventy-two per cent were recorded as being current or previous smokers, 31% had chronic obstructive pulmonary disease and 35% one or more comorbid conditions (Appendix 1 Table 1).

Of the 3,240 patients with localised cancer, 59.2% (95% CI 57.5–60.9) had resections. A lower proportion of patients who lived 100 km or more from the NASH had a resection (49.4%, 95% CI 45.8–53.1) compared to patients living 0–39 km (62.5%, 95% CI 60.3–64.4) or 40–99 km from it. Conversely, for patients who attended a specialist hospital there was a greater likelihood of resection with increasing distance to the NASH (69.7% at 0–39 km,

91.6 at 40–99 km and 94.6 at ≥100 km) (Table 1).For patients with regional stage cancer the proportion attending a general hospital also increased with distance from the NASH: 14.8% at 0–39 km to 51.2 at ≥100 km for localised stage, 15.3% at 0–39 km to 54.4% at ≥100 km. Much higher proportions of patients with distant stage than localised or regional stage attended general hospitals (Table 1). Overall, there were 3,517 surgical resections, or 16% of total NSCLC patients, 95% occurred in specialist hospitals, while only 5% occurred in general hospitals (Table 1).

Chapter 8 Table 1 The proportional breakdown of NSCLC patients by distance from the NASH by their hospital of treatment whether they had major surgery by stage category, NSW, 2000-2008

Distance from the NASH by stage at diagnosis		Hospital of treatment					Had surgical resection				
		Specialist		General		Total	Specialist		General		Total
		n	%	n	%	n	n	%	n	%	n
Localised stage	0-39 km	1,757	85.2	306	14.8	2,063	1,225	69.7	63	20.6	1,288
	40-99 km	263	63.2	153	36.8	416	241	91.6	13	8.5	254
	100+	371	48.8	390	51.2	761	351	94.6	25	6.4	376
Regional stage	0-39 km	1,244	84.7	224	15.3	1,468	836	67.2	46	20.5	882
	40-99 km	208	64.0	117	36.0	325	191	91.8	5	4.3	196
	100+	293	45.6	349	54.4	642	267	91.1	10	2.9	277
Distant stage	0-39 km	1,539	70.5	644	29.5	2,183	166	10.8	7	1.1	173
	40-99 km	85	19.5	351	80.5	436	24	28.2	0	0	24
	100+	131	14.2	790	85.8	921	46	35.1	1	0.1	47
		5,891	63.9	3,324	36.1	9,215	3,347	95.2	170	5.1	3,517

There was substantial variation in unadjusted survival of NSCLC patients depending on type of hospital of treatment and distance from the NASH (Figures 1a-c). Patients attending specialist hospitals had better survival while patients attending general hospitals had poorer survival for each stage category. Most of these differences, however, diminished greatly on adjustment of the survival curves for the covariates that were retained in the backward elimination Cox models of hazard of death from NSCLC (Figure 1b).

Consistently with Figures 1d-f, the fully adjusted, stage specific hazard ratios for death from lung cancer did not vary greatly by distance and hospital type particularly in patients with regional and distant stage cancer (Table 2). To the extent that individual hazard ratios were materially above unity, these increases appeared more consistent with an independent effect of hospital type than an independent effect of distance from the NASH, with the poorer outcome in patients treated in general hospitals.

However, since there are strong relationships between distance and hospital type, and hospital type and having a lung resection (Table 1), it is likely that resection, which reduced the hazard of death from NSCLC (Figure 2, Table 2), mediates most of the effects that distance and hospital have on the hazard of death, because only 170 of the 3,517 resections were undertaken in general hospitals (Table 1). To explore this possibility, we examined the impact of removing resection from the fully adjusted model on the associations of distance and hospital type with death from NSCLC (Table 3). With resection excluded from the model, there was a strong association with distance from the NASH and a reduced hazard of death for patients treated in a specialist hospital regardless of cancer stage.

Because, with increasing distance from the NASH, patients underwent a resection when they attended a specialist hospital (for localised patients 91.6% at 40-99, and 94.6 at 100+Table 1). Conversely, patients who attended a general hospital were more likely to die from their cancer; this increased risk varied little, by the distance patients lived, from the NASH. This poorer relative outcome in general hospitals was similar for all stage categories (Table 3).

Resection was strongly associated with a lower risk of lung cancer death in all three stage categories, and this was true for each type of resection – pneumonectomy, lobectomy and

segmental resection (Figure 2, Table 2). For localised and regional cancer, this impact appeared greater at one year after diagnosis than at five years.

Women had a lower risk of death for all stage categories (Table 2). As expected, increasing age, one or more comorbid conditions, having squamous cell carcinoma and having only a clinical diagnosis of lung cancer were strong predictors of a poor outcome. Except for comorbidity, these associations appeared weaker with regional and distant disease. Previous smokers had a lower risk of death than non smokers or current smokers regardless of stage; this might be a consequence of smoking cessation preparatory to resection. Similarly, patients with a history of COPD had a better outcome, particularly if they had localised disease, perhaps because of better recording of medical history in patients considered for resection. Patients with localised disease who had an emergency admission had a higher hazard of death at one year (HR 1) than patients who had planned admissions (HR 0.75). Patients admitted for resection 2-12 months after diagnosis had a hazard of death at five years that was more than double that in patients admitted within a month of diagnosis, and an even greater relative hazard if they had distant disease (Table 2). Most patients who had resection were admitted to hospital within a month of diagnosis (80.2%).

The stage specific results in Table 2 were similar when stage was imputed for patients with unknown stage (data available on request).

Chapter 8 Table 2 Hospital of treatment, distance from the NASH and other variables independently associated with hazard of death from localised, regional and distant primary NSCLC in NSW in 2000-2008

	Localised					Regional					Distant				
	One year[1]		Five years[1]			One year[1]		Five years[1]			One year[1]		Five years[1]		
	HR	95% CI	HR	95% CI	P value	HR	95% CI	HR	95% CI	P value	HR	95% CI	HR	95% CI	P value
Hospital of treatment and distance from the NASH															
Specialist hospital 0-39.9	1		1			1		1			1		1		
Specialist hospital 40-99.9	1.32	(0.96-1.82)	1.32	(0.96-1.82)		0.99	(0.79-1.23)	0.99	(0.79-1.23)		0.92	(0.71-1.18)	0.92	(0.71-1.18)	
Specialist hospital 100 plus	0.96	(0.72-1.28)	0.96	(0.72-1.28)		0.93	(0.76-1.13)	0.93	(0.76-1.13)		0.77	(0.62-0.95)	0.77	(0.62-0.95)	
General hospital 0-39.9	1.28	(1.00-1.65)	1.28	(1.00-1.65)		0.92	(0.77-1.10)	0.92	(0.77-1.10)		1.12	(1.01-1.24)	1.12	(1.01-1.24)	
General hospital 40-99.9	1.57	(1.14-2.18)	1.57	(1.14-2.18)		1.03	(0.82-1.30)	1.03	(0.82-1.30)		1.09	(0.96-1.24)	1.09	(0.96-1.24)	
General hospital 100 plus	1.02	(0.80-1.29)	1.02	(0.80-1.29)	p<0.022	0.84	(0.71-0.99)	0.84	(0.71-0.99)	p=0.2494	1.10	(0.99-1.22)	1.10	(0.99-1.22)	p=0.0097
Sex															
Males	1		1			1		1			1		1		
Females	0.84	(0.75-0.94)	0.84	(0.75-0.94)	p<0.0019	0.90	(0.80-1.00)	0.90	(0.80-1.00)	p< 0.0187	0.80	(0.75-0.87)	0.80	(0.75-0.87)	p<0.0001
Age at diagnosis															
50-69 years	1		1			1		1			1		1		
60-69 years	1.31	(1.10-1.55)	1.31	(1.10-1.55)		1.12	(0.97-1.29)	1.12	(0.97-1.29)		1.13	(1.03-1.24)	1.13	(1.03-1.24)	
70 -79 years	1.51	(1.29-1.77)	1.51	(1.29-1.77)		1.44	(1.24-1.66)	1.44	(1.24-1.66)		1.32	(1.20-1.45)	1.32	(1.20-1.45)	
80 plus years	1.91	(1.58-2.30)	1.91	(1.58-2.30)	p<0.0064	1.62	(1.32-1.99)	1.62	(1.32-1.99)	p<0.0001	1.51	(1.32-1.73)	1.51	(1.32-1.73)	p<0.0001
Country of birth															
Australian born	1		1			1		1			1		1		
English speaking	0.99	(0.81-1.20)	0.99	(0.81-1.20)		1.00	(0.82-1.22)	1.00	(0.82-1.22)		1.10	(0.96-1.27)	1.10	(0.96-1.27)	
Non English speaking	0.87	(0.76-0.99)	0.87	(0.76-0.99)		0.85	(0.75-0.96)	0.85	(0.75-0.96)		0.81	(0.74-0.88)	0.81	(0.74-0.88)	
Unknown	0.58	(0.40-0.83)	0.58	(0.40-0.83)	p<0.0001	0.51	(0.36-0.73)	0.51	(0.36-0.73)	p<0.0002	0.76	(0.60-0.96)	0.76	(0.60-0.96)	p<0.0001
Comorbidity															
No comorbidity	1		1								1		1		
Comorbidity	1.15	(1.01-1.29)	1.15	(1.01-1.29)	p<0.0258	1.13	(1.00-1.28)	1.13	(1.00-1.28)	p=0.0443	1.16	(1.07-1.26)	1.16	(1.07-1.26)	p=0.0005
Chronic obstructive Pulmonary disease															
No COPD	1		1								1		1		
COPD	0.85	(0.75-0.96)	0.85	(0.75-0.96)	p=0.0110	0.99	(0.87-1.12)	0.99	(0.87-1.12)	p=0.8356	0.91	(0.83-1.01)	0.91	(0.83-1.01)	p=0.0874
Smoking[3]															
No smoking	1		1			1		1			1		1		
Previous smoking	0.86	(0.75-0.99)	0.86	(0.75-0.99)		0.84	(0.73-0.97)	0.84	(0.73-0.97)		0.89	(0.81-0.97)	0.89	(0.81-0.97)	

Current smokers	0.97	(0.83-1.13)	0.97	(0.83-1.13)	p=0.0596	0.91	(0.78-1.05)	0.91	(0.78-1.05)	p=0.0607	0.93	(0.85-1.02)	0.93	(0.85-1.02)	p=0.0367
Method of diagnosis															
Cytology	1		1			1		1			1		1		
Clinical	1.65	(1.25-2.19)	1.65	(1.25-2.19)		1.21	(0.88-1.66)	1.21	(0.88-1.66)		1.17	(1.01-1.35)	1.17	(1.01-1.35)	
Histologically verified	0.97	(0.79-1.10)	0.97	(0.79-1.10)	p<0.0001	0.78	(0.64-0.96)	0.78	(0.64-0.96)	p< 0.0013	0.79	(0.72-0.88)	0.79	(0.72-0.88)	p<0.0001
Histology[4]															
Squamous	1		1			1		1			1		1		
Adenocarcinoma	0.89	(0.77-1.03)	0.89	(0.77-1.03)		1.20	(1.05-1.38)	1.31	(1.02-1.68)		0.94	(0.80-1.11)	1.02	(0.75-1.39)	
Large cell	1.04	(0.89-1.20)	1.04	(0.89-1.20)		1.31	(1.12-1.54)	1.02	(0.76-1.37)		1.03	(0.86-1.22)	0.85	(0.62-1.18)	
Other	0.47	(0.37-0.61)	0.47	(0.37-0.61)	p<0.0001	0.93	(0.72-1.19)	0.63	(0.41-0.98)	p<0.0001	1.00	(0.80-1.25)	0.86	(0.57-1.31)	p<0.0001
Type of admission															
Emergency	1		1			1		1			1		1		
Planned	0.75	(0.64-0.87)	0.75	(0.64-0.87)		0.85	(0.72-1.00)	1.34	(0.99-1.80)		1.00	(0.89-1.13)	1.66	(1.32-2.09)	
Other	0.93	(0.67-1.30)	0.93	(0.67-1.30)	p<0.0001	0.97	(0.68-1.38)	0.99	(0.52-1.88)	p<0.0001	1.16	(0.89-1.51)	1.34	(0.83-2.17)	p<0.0001
Major surgery[5]															
No resection	1		1			1		1			1		1		
Pneumonectomy	0.35	(0.25-0.50)	0.74	(0.44-1.25)		0.42	(0.34-0.53)	0.60	(0.40-0.90)		0.28	(0.18-0.42)	0.16	(0.07-0.35)	
Lobectomy	0.14	(0.11-0.17)	0.32	(0.23-0.44)		0.31	(0.26-0.37)	0.54	(0.40-0.73)		0.34	(0.27-0.45)	0.32	(0.19-0.54)	
Segmental resection	0.18	(0.15-0.23)	0.37	(0.25-0.54)	p<0.0001	0.32	(0.26-0.40)	0.60	(0.41-0.87)	p<0.0001	0.36	(0.25-0.51)	0.24	(0.13-0.48)	p<0.0001
Time to surgery															
At diagnosis	1		1			1		1			1		1		
2-3 months	0.96	(0.77-1.19)	1.67	(1.12-2.47)		0.97	(0.82-1.14)	1.51	(1.11-2.04)		1.71	(1.43-2.04)	4.63	(3.23-6.64)	
3-6 months	0.67	(0.50-0.90)	1.74	(1.02-2.96)		1.14	(0.93-1.39)	2.99	(2.01-4.44)		1.44	(1.19-1.76)	7.58	(4.82-11.92)	
7 to 12 months	1.15	(0.97-1.38)	1.74	(1.27-2.37)	p<0.0001	0.65	(0.50-0.85)	2.00	(1.25-3.20)	p<0.0001	0.89	(0.70-1.13)	12.44	(7.01-22.07)	p<0.0001

[1]Hazard ratios at one and five years after diagnosis are presented because the effects of some variables in the model were time varying.
[2]Chronic obstructive pulmonary disease (diagnosis codes J41.0,J41.1,J41.8,J42.0,J42,J43,J43.1,J43.2,J43.8,J43.9,J44.0,J44.1,J44.8,J44.9
[3]Smoking codes (diagnosis codes Z86.43, Z72.0, Z71.6,F17)
[4]Cancer codes: ICD0-3 morphology codes: Squamous 80503-80783, Large cell 80353, 83103,80103-80123,80143-80313, Adenocarcinoma 82303-82313, 82503-82603, 81403, 82113, 83233, 85763, 82463 Other 80003-80053, 88003, 88013, 88023, 8053 88113, 88303, 88903, 89203, 90403, 90413, 91203, 91333, 91503, 95403, 88403-89213, 89903-89913, 91203-91333, 95403-95813, 88303, 91503.
[5]Procedure codes Lobectomy (38438-01, 38441-00), Resection (38438-00, 38440-00, 38440-01, 90169-00,90181-00, Pneumonectomy (38441-01,38438-02).

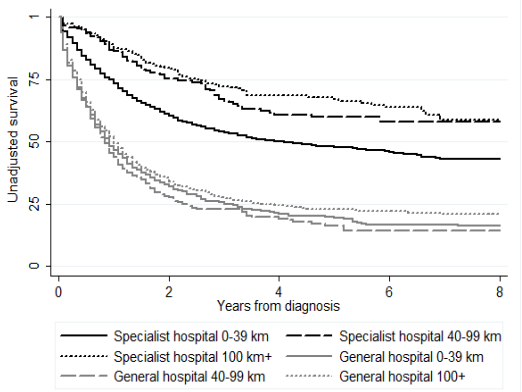
Chapter 8 Table 3 Effect of presence or absence of surgery on associations of hospital of treatment and distance from a NASH with hazard of death from NSCLC in patients with localised, regional and distant stage disease

	HR	95%CI	P value	HR	95%CI	P value
Hospital of treatment and distance from a NASH						
	Multivariable model including surgery*			Multivariable model excluding surgery*		
Localised NSCLC patients (n=3240)						
Specialist hospital 0-39.9	1			1		
Specialist hospital 40-99.9	0.82	(0.64-1.05)		1.32	(0.96-1.82)	
Specialist hospital 100 plus	0.64	(0.51-0.81)		0.96	(0.72-1.28)	
General hospital 0-39.9	1.69	(1.43-2.00)		1.28	(1.00-1.65)	
General hospital 40-99.9	2.01	(1.63-2.48)		1.57	(1.14-2.18)	
General hospital 100 plus	1.82	(1.55-2.13)	p<0.0001	1.02	(0.80-1.29)	p<0.022
Regional NSCLC patients(n=2,435)						
Specialist hospital 0-39.9	1			1		
Specialist hospital 40-99.9	0.82	(0.66-1.01)		0.99	(0.79-1.23)	
Specialist hospital 100 plus	0.77	(0.63-0.93)		0.93	(0.76-1.13)	
General hospital 0-39.9	1.24	(1.04-1.47)		0.92	(0.77-1.10)	
General hospital 40-99.9	1.58	(1.26-1.98)		1.03	(0.82-1.30)	
General hospital 100 plus	1.23	(1.04-1.45)	p<0.0001	0.84	(0.71-0.99)	p=0.2494
Distant NSCLC patients(n=3,540)						
Specialist hospital 0-39.9	1			1		
Specialist hospital 40-99.9	0.82	(0.64-1.06)		0.92	(0.71-1.18)	
Specialist hospital 100 plus	0.65	(0.52-0.80)		0.77	(0.62-0.95)	
General hospital 0-39.9	1.18	(1.06-1.30)		1.12	(1.01-1.24)	
General hospital 40-99.9	1.21	(1.07-1.38)		1.09	(0.96-1.24)	
General hospital 100 plus	1.23	(1.11-1.36)	p<0.0001	1.10	(0.99-1.22)	p=0.0097

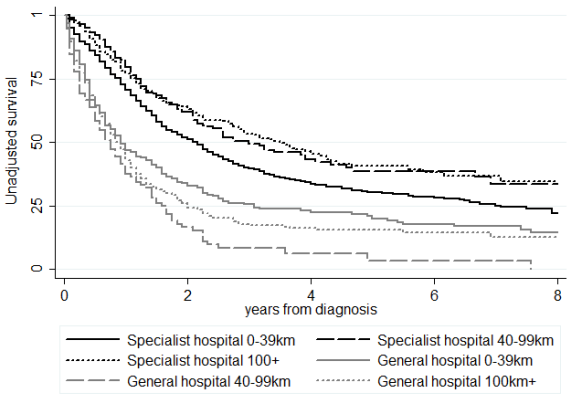
*Adjusted for hospital of treatment and distance from a NASH, sex, age at diagnosis, country of birth, comorbidity, COPD, smoking, method of diagnosis, histology, type of admission, and time to diagnosis

Chapter 8 Figure 1 Kaplan Meier survival curves by hospital of treatment and distance from the nearest accessible specialist hospital (NASH) for patients with primary non small cell lung cancer by stage unadjusted and adjusted for confounding variables, New South Wales (NSW), 2000-2008

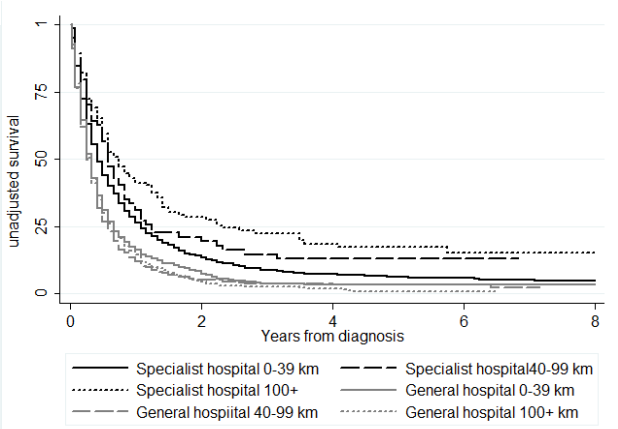
A. Localised stage patients (n=3,240)



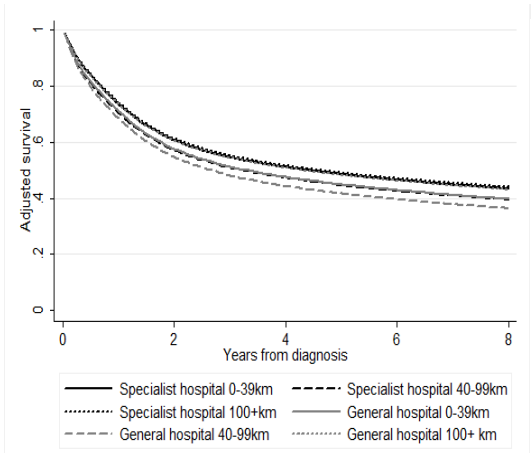
B. Regional stage patients (n=2,435)



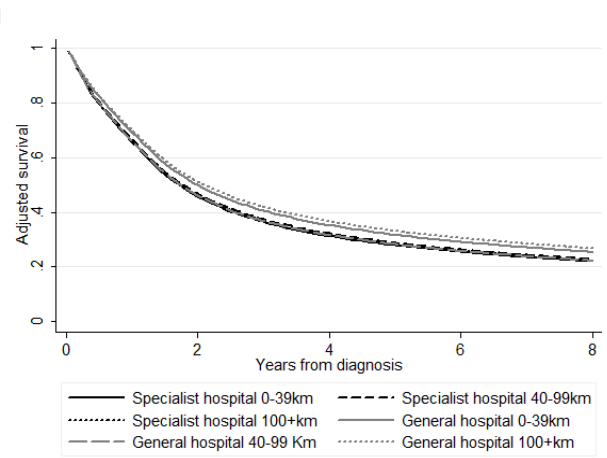
C. Distant stage patients (n=3,540)



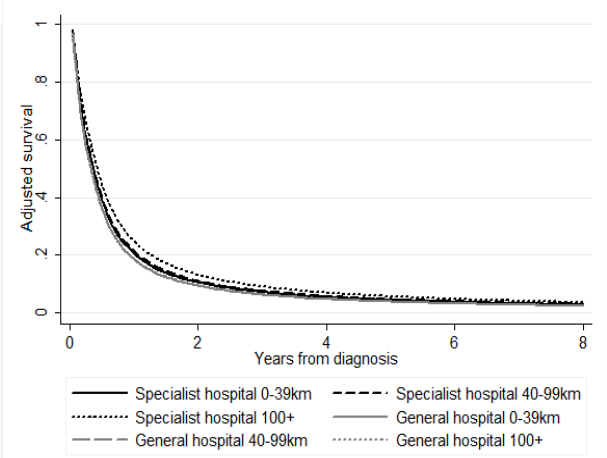
D. Localised stage patients (n=3,240)



E. Regional stage patients (n=2,435)



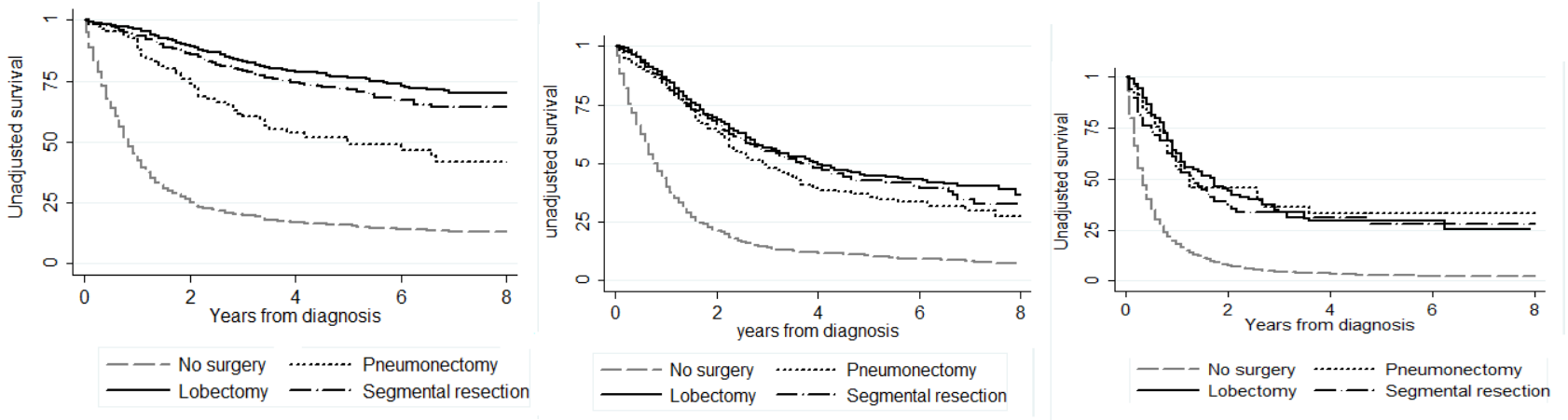
F. Distant stage patients (n=3,540)



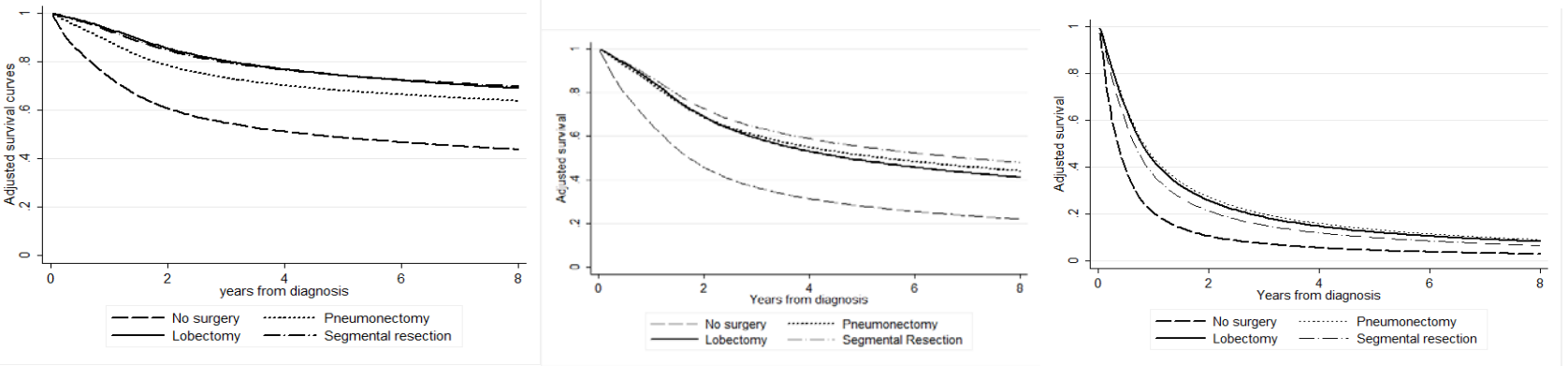
*Adjusted for sex, age at diagnosis, country of birth, comorbidity, chronic obstructive pulmonary disease, smoking, method of diagnosis, histology, type of admission, major surgery and time to diagnosis – the effects of age and time to diagnosis were time varying.

Chapter 8 Figure 2 Kaplan Meier survival curves by surgery for patients with primary non small cell lung cancer by stage unadjusted and adjusted for confounding variables, NSW, 2000-2008

A. Localised stage (NSCLC) patients (n=3,240) **B. Regional stage (NSCLC) patients (n=2,435)** **C. Distant stage (NSCLC) patients (n=3,540)**



D. Localised stage (NSCLC) patients (n=3,240) **E. Regional stage (NSCLC) patients (n=2,435)** **F. Distant stage (NSCLC) patients (n=3,540)**



*Adjusted for hospital of treatment and distance from the NASH, sex, age at diagnosis, country of birth, comorbidity, chronic obstructive pulmonary disease, smoking, method of diagnosis, histology, type of admission, and time to diagnosis

8.5. Discussion

Two factors most influenced the hazard of death: attendance at a specialist hospital and having a resection of the lung cancer. Both were associated with a lower hazard of death. With increasing distance from the NASH, a patient was less likely to be admitted to a specialist hospital and therefore less likely to have a resection. To add to the complexity, when patients who lived further from the NASH were admitted to a specialist hospital, they were more likely to have a resection, probably because patients referred over long distances were more carefully selected for operability. Either way, distance and hospital type appeared as important determinants of having a resection and, therefore, of outcome of NSCLC.

We found as have others[23, 24] in a number of UK[5-7, 25] and US studies[26, 27] that patients living in proximity to a specialist hospital attended one. In addition, we found this pattern of attendance was similar regardless of the stage at diagnosis with 85% of localised and regional and 70% of distant stage patients attending specialist hospitals if they lived within 0-39 km of one. There is evidence, too, that the proximity to hospital and specialty of the referring doctor is important. In a study of US SEER registered lung cancer patients with linked Medicare records, patients were more likely to attend a NCI Centre if they lived within 30 minutes of one and had care from a specialist doctor in the preceding six months.[24]

We found that if a patient attended a general hospital, their survival was poorer, because they were less likely to have a resection of their cancer. Crawford [7] in a UK registry study also found that lung cancer patients whose closest hospital was district hospital were significantly less likely to have thoracic surgery than those whose closest hospital was a cancer centre. Other, studies of lung cancer patients in the north of England found that both distance from a cancer centre and deprivation reduced the likelihood of surgery, and treatment in a cancer centre reduced the likelihood of death. [5-7] More recently, the UK lung cancer audit found that NSCLC patients first seen at thoracic surgical centres were 51% more likely to have resection than those seen in other centres (adjusted OR 1.51, 95% CI 1.16–1.97).[8] A recent UK study also found better survival in hospitals with higher resection volumes even for patients who were older, had lower socioeconomic status or had comorbidities.[28] We found as have others that regardless of stage at diagnosis and after adjustment for other factors

having any resection (pneumonectomy, lobectomy or segmental resection) was the single most important factor in reducing the hazard of death. [8, 24]

Most studies of the efficacy of surgical resection of early stage NSCLC have been observational, based on routinely collected data or audits.[29] However, both US[30] and Australian [1] guidelines recommend that stage I to stage IIIa NSCLC patients with potentially resectable disease have a lung resection, subject to staging that includes systematic lymph node sampling or mediastinal lymph node dissection. We could not determine if formal staging was undertaken. However, NSW lung cancer patterns of care studies [9-11] report that 89% of lung cancer patients saw a specialist at some time in their care, with 54% initially referred to a respiratory physician. Of these, 90% were referred to either an oncologist or cardiothoracic surgeon. Vinod et al.[11] found that 49% of stage I patients, 24% of stage II, and 4% of stage III NSCLC patients would have expected to have their lung cancer resected.

The outcomes for surgically treated patients we observed are similar to those of Rich et al., [8] who examined the outcomes for 34,513 NSCLC patients in a lung cancer audit. They found that potentially curative surgery was the most powerful overall determinant of survival. Relative to patients who did not have surgery, patients who had surgery had an HR of 0.41 (95%CI 0.39–0.44) after adjusting for age, sex, performance status, stage and comorbidity.

Apart from the increased likelihood of having a resection, patients referred to specialist centres would have access to lung cancer specialists for all their care, PET for operative pre-staging, guideline based lung cancer treatment,[23] and a reduced likelihood of developing complications.[3] A recent lung cancer audit in Victoria, Australia, found that multidisciplinary team management of lung cancer patients, which is most likely to be available in specialist centres, was an independent predictor of receiving guideline based treatment and of a lower hazard of death.[31] Specialised facilities and practices are less likely to be available in general hospitals, which tend to be outer urban or rural and to serve smaller, less dense populations.[32]

We found, as have others, consistently lower hazard of death in women [5, 8] and a higher hazard of death with increasing age. [5, 7, 8] Unlike others[5, 6] but consistent with some NSW studies [10, 33] but not all, [34] we did not find that socioeconomic status affected the hazard of

dying from lung cancer. We also found, as have other Australian [9-11, 31] and UK studies,[7] that there were higher hazards of death in patients with any comorbidity[8], those without histological confirmation[35] and patients who were admitted through the emergency department.[36]

8.5.1. Limitations and strengths

This study was limited to surgical treatment. Other studies have shown that, as for surgery, there is lower use of radiotherapy, [6 37] chemotherapy [7 37] and combined treatment [37] with increasing distance to a specialist centre. Our study used a cancer registry based definition of localised, regional and distant stage; while TNM definitions would have been preferable, they were not available. Cancer registry summary staging categories, however, are routinely used for international comparisons of survival.[14] A recent comparison of lung cancer summary staging and TNM staging showed that whereas all metastases are grouped into T4 category with summary staging extension to adjacent organs (mediastinum, great vessels, trachea, oesophagus or carina) is categorised as regional stage.[14] However, we do not believe that staging error will have an effect on our main findings because results for hospital of treatment and distance to the NASH were similar in each stage category.

The major strengths of our study are its coverage of the whole population and our ability to link cancer registry and hospital separation records, both public and private, include routinely recorded measures of cancer stage (albeit imperfect), and use geocoded data to provide precise measures of distance between patients' residences and distance to the NASH.

If patients were being referred to specialist hospitals based on appropriateness for resection then the proportion of patients so referred would not vary by distance from the NASH. A better understanding of physician referral patterns is needed. A greater understanding of patient factors influencing travel to specialist care is also required.

8.6. Appendix 1 online text - methods

8.6.1. Other characteristics of patients

The following variables were obtained from cancer registry records: sex; age at diagnosis (grouped into four categories: 15–59, 60–69, 70–79 and ≥80 years); country of birth

(grouped as Australian born, born in an English speaking country, born in a non English speaking country and unknown country of birth); socioeconomic status (allocated in five categories using the Australian Bureau Statistics' Index of Relative Socioeconomic Disadvantage based on the 2001 or 2006 Census depending on the period of diagnosis[38]) and year of diagnosis (grouped as 2000–2004 and 2005–2008).

Additional variables obtained from APDC records were: smoking status (non smoker, past smoker, current smoker based on ICD-10 codes Z86.43, Z72.0, Z71.6, F17 in any hospital admission record); any or no comorbidity (any condition in the Charlson index[39], except secondary cancer coded as a primary or other diagnosis in any record, or no condition); and any or no history of chronic obstructive pulmonary disease (based on relevant four-digit ICD-10 codes in the range J41.0–J44.9 in any separation record). Because of its relevance to which hospitals a person might have access to, patients' financial status at admission, as recorded in the APDC, was also included in the analysis, grouped into three categories: public patient in a public hospital, private patient in a private hospital and private patient in a public hospital.

8.6.2. Stage, pathology and treatment

Summary stage at diagnosis was classified, based on the extent of disease notified to, or inferred by, the CCR, as localised, regional, distant or unknown[40]. Histological subtype of cancer was coded by the CCR from pathology reports using the ICD-O version 3 morphology codes[41], which were grouped in accord with Cancer Incidence in Five Continents Vol IX[42]. Method of diagnosis, clinical, cytology or histopathology, which is recorded by the CCR, was also included because a number of studies have reported it to be a reliable indicator of lack of investigation.[35] Time to surgery was recorded in months from diagnosis to the procedure.

8.6.3. Statistical methods: sensitivity analyses

Sensitivity analyses were conducted by modelling factors associated with the hazard of death for patients with unknown stage and those not admitted to hospital after diagnosis. A complete analysis was undertaken of all non small cell lung cancer (NSCLC) patients and we

applied multiple imputation using the "ice" (imputation by chained equations) command in Stata 12.1[43] to impute unknown stage, creating 10 imputed datasets.(Available on request).

8.6.4. Determining model fit

To determine model fit we plotted the unadjusted Kaplan Meier survival curves and the adjusted survival curves predicted from our `stpm2`model after using the Predict command. We found very little difference between the survival curves within each of the covariates indicating good model fit.

Chapter 8 Appendix 1 Table 1 New South Wales, NSCLC patients diagnosed between 2000-2008 distributed by patient, tumour and treatment factors

Characteristics	N	%
Total	23,871	100
Hospital of treatment distance from the NASH[1]		
Specialist hospital 0-39.9	8,247	34.5
Specialist hospital 40-99.9	769	3.2
Specialist hospital 100 plus	1,029	4.3
General hospital 0-39.9	4,837	20.3
General hospital 40-99.9	2,364	9.9
General hospital 100 plus	5,573	23.3
No hospital[2]	1,022	4.3
Index of remoteness		
Accessible	23,051	96.6
Not accessible	802	3.4
Area of residence		
Urban	8,572	35.9
Outer metropolitan	6,493	27.2
Rural	8,788	36.8
Sex		
Males	15,053	63.1
Females	8,800	36.9
Age at diagnosis		
15-59 years	4,244	17.8
60-69 years	6,143	25.77
70 -79 years	8,418	35.31
80 plus years	5,036	21.12
Country of birth		
Australian born	15,675	65.7
Born in an English Speaking country	1,760	7.4
Born in a Non English speaking country	5,393	22.6
Unknown country of birth	1,025	4.3
Socioeconomic status		
Lowest SES	4,917	20.6
Second lowest SES	4,383	18.4
Middle SES	5,404	22.6
Second highest SES	4,904	20.5
Highest SES	4,233	17.7
Period of diagnosis		
2000-2004	9,849	41.3
2005-2008	14,004	58.7
Comorbidity		
No comorbidity	15,611	65.4
Comorbidity	8,242	34.6
Smoking status[3]		
Non smoker	6,547	27.4
Previous smoker	8,755	36.7
Current smoker	8,551	35.8
Chronic obstructive pulmonary disease[4]		
no COPD	16,495	69.2
COPD	7,358	30.8
Method of diagnosis[5]		
Cytology	3,355	14.1
Clinical	3,587	15.0
Histology coded by hospital	6,730	28.2
Histology coded by cancer registry	9,474	39.7
Discovered at autopsy	51	0.2
Death certificate only	656	2.8
Order of lung cancer		
First cancer	22,336	93.6
Second or subsequent cancer	1,517	6.4
Histology[6]		
Squamous	4,808	20.2
Adenocarcinoma	7,596	31.9

Large cell	7,760	32.6
Other	3,677	15.4
Stage		
Localised	5474	22.9
Regional	4156	17.4
Distant	8105	34.0
Unknown	6136	25.7
Emergency presentation		
Emergency	10,495	44.0
Planned admission	12,626	52.9
Other	750	3.1
Major surgery for the primary cancer[7]		
No admission to hospital[2]	1,022[2]	4.3
Admitted to hospital for diagnostic purposes only	5,912	24.8
No cancer procedure	13,185	55.3
Lobectomy	2,224	9.3
Segmental resections	1,122	4.7
Pneumonectomies	388	1.6
Time from diagnosis to surgery or admission		
At diagnosis	8,607	36.1
2-3 months	1,287	5.4
3-6 months	782	3.3
7 to 12 months	525	2.2
More than 12 months	459	1.8
Admission to hospital before diagnosis	11,189	46.9
No admission[2]	1,022	4.3
Financial status		
Public financial status treated in public hospitals	14,231	59.69
Private financial status treated in private hospitals	5,811	24.37
Private financial status treated in public hospitals	2,777	11.65
No admission to hospital	1,022	4.29

[1]Nearest accessible specialist hospital.

[2]These patients were a combination of New South Wales patients that did not have any hospitalisations because they did not link or were patients who were death certificate or autopsy notifications

[3]Smoking codes (diagnosis codes Z86.43, Z72.0, Z71.6,F17)

[4]Chronic obstructive Pulmonary Disease (diagnosis codes J41.0,J41.1,J41.8,J42.0,J42,J43,J43.1,J43.2,J43.8,J43.9,J44.0,J44.1,J44.8,J44.9

[5]Histology by cancer registry staff means the record is coded using a pathology report notified to the registry. Histology hospital means that hospital staff have coded records from a pathology report. When the cancer registry sights the histology report, coding of diagnosis is likely to be more accurate than when it does not.

[6]Cancer codes: ICD0-3 morphology codes: Squamous 80503-80783, Large cell 80353, 83103,80103-80123,80143-80313, Adenocarcinoma 82303-82313, 82503-82603, 81403, 82113, 83233, 85763, 82463 Other 80003-80053, 88003, 88013, 88023, 8053 88113, 88303, 88903, 89203, 90403, 90413, 91203, 91333, 91503, 95403, 88403-89213, 89903-89913, 91203-91333, 95403-95813, 88303, 91503. There are two main morphology codes responsible for 81% of the 15.4% of "other" these are morphology code 80003 Neoplasm not otherwise specified (1,375 or 37% of "other") and 80463 non small cell carcinoma not otherwise specified (1,609 or 44% of "other").

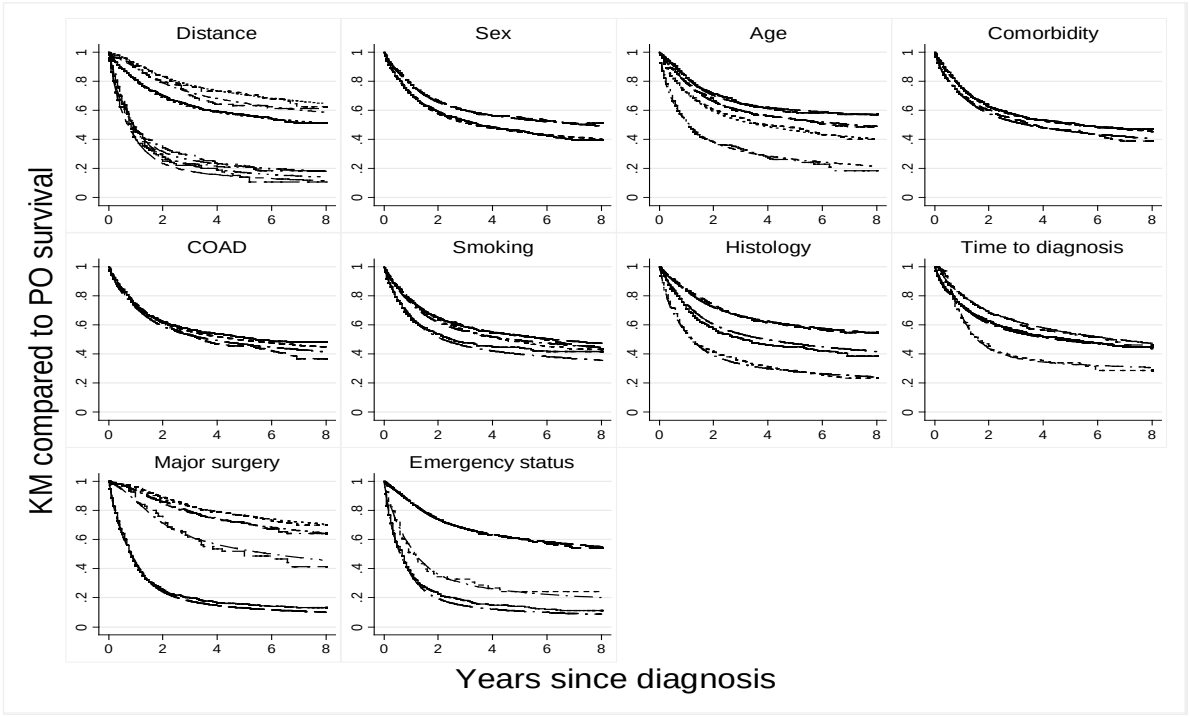
[7]Procedure codes Lobectomy (38438-01, 38441-00), Resection (38438-00, 38440-00, 38440-01, 90169-00, 90181-00, Pneumonectomy (38441-01, 38438-02).

Chapter 8 Appendix 1 Table 2 New South Wales, NSCLC patients diagnosed between 2000-2008 and admitted to hospital within 12 months of diagnosis by patient, tumour and treatment factors and localised, regional and distant stage

	Localised stage patients				Regional stage patients				Distant stage patients			
		%	Died	%		%	Died	%		%	Died	%
Hospital of treatment and distance from the NASH	3,240	100	1,384	100	2,435	100	1,461	100	3,540	100	3087	100
Specialist hospital 0-39.9	1,757	54.2	628	19.4	1,244	51.1	703	48.1	1,539	43.5	1,313	42.5
Specialist hospital 40-99.9	263	8.1	71	2.2	208	8.5	100	6.8	85	2.4	67	2.2
Specialist hospital 100 plus	371	11.5	86	2.7	293	12.0	134	9.2	131	3.7	97	3.1
General hospital 0-39.9	306	9.4	210	6.5	224	9.2	171	11.7	644	18.2	574	18.6
General hospital 40-99.9	153	4.7	116	3.6	117	4.8	98	6.7	351	9.9	323	10.5
General hospital 100 plus	390	12.0	273	8.4	349	14.3	255	17.5	790	22.3	713	23.1
Sex												
Males	2,005	61.9	927	28.6	1,527	62.7	965	66.1	2,221	62.7	1,953	63.3
Females	1,235	38.1	457	14.1	908	37.3	496	33.9	1,319	37.3	1,134	36.7
Age at diagnosis												
50-69 years	662	20.4	225	6.9	606	24.9	342	23.4	1,053	29.7	895	29.0
60-69 years	970	29.9	368	11.4	825	33.9	463	31.7	1,123	31.7	979	31.7
70 -79 years	1,176	36.3	528	16.3	792	32.5	505	34.6	990	28.0	877	28.4
80 plus years	432	13.3	263	8.1	212	8.7	151	10.3	374	10.6	336	10.9
Country of birth												
Australian born	2,094	64.6	924	66.8	1,557	63.9	946	64.8	2,223	62.8	1,965	63.7
English speaking	232	7.2	113	8.2	164	6.7	114	7.8	254	7.2	223	7.2
Non English speaking	772	23.8	315	22.8	626	25.7	369	25.3	970	27.4	826	26.8
Unknown	142	4.4	32	2.3	88	3.6	32	2.2	93	2.6	73	2.4
Comorbidity												
No comorbidity	2,035	62.8	831	60.0	1,633	67.1	974	66.7	2,498	70.6	2,169	70.3
Comorbidity	1,205	37.2	553	40.0	802	32.9	487	33.3	1,042	29.4	918	29.7
Smoking												
Non smoker	720	22.22	349	25.22	529	21.7	353	24.2	1,065	30.1	934	30.3
Previous smoker	1,371	42.31	557	40.25	986	40.5	580	39.7	1,209	34.2	1,040	33.7
Current smoker	1,149	35.46	478	34.54	920	37.8	528	36.1	1,266	35.8	1,113	36.1
Chronic obstructive pulmonary disease												

no COPD	2,147	66.3	864	62.4	1,712	70.3	1,013	69.3	2,953	83.4	2,562	83.0
COPD	1,093	33.7	520	37.6	723	29.7	448	30.7	587	16.6	525	17.0
Method of diagnosis												
Cytology	164	5.1	107	3.3	150	6.2	122	8.4	498	14.1	452	14.6
Clinical	144	4.4	100	3.1	78	3.2	63	4.3	412	11.6	378	12.2
Histologically verified	2,932	90.5	1,124	93.7	2207	90.6	1276	87.3	1,241	35.1	1,121	36.3
Histology[3]												
Squamous	962	29.7	459	14.2	658	27.0	380	26.0	446	12.6	390	12.6
Adenocarcinoma	1,214	37.5	394	12.2	1,051	43.2	588	40.2	1,393	39.4	1,169	37.9
Large cell	692	21.4	431	13.3	522	21.4	383	26.2	1,288	36.4	1,162	37.6
Other	372	11.5	100	3.1	204	8.4	110	7.5	413	11.7	366	11.9
Type of admission												
Emergency	730	22.5	558	17.2	566	23.2	455	31.1	2,215	62.6	1,983	64.2
Planned	2,440	75.3	778	24.0	1,804	74.1	961	65.8	1,157	32.7	958	31.0
Other	70	2.2	48	1.5	65	2.7	45	3.1	168	4.7	146	4.7
Major surgery												
No surgery	1,322	40.8	994	30.7	1,080	44.4	885	60.6	3,296	93.1	2,940	95.2
Pneumonectomy	113	3.5	50	1.5	219	9.0	113	7.7	46	1.3	27	0.9
Lobectomy	1,185	36.6	211	6.5	812	33.3	318	21.8	119	3.4	74	2.4
Segmental resection	620	19.1	129	4.0	324	13.3	145	9.9	79	2.2	46	1.5
Time to diagnosis												
At diagnosis	2,600	80.2	1,090	78.8	1,831	75.2	1,107	75.8	2,899	81.9	2,546	82.5
2-3 months	409	12.6	152	11.0	344	14.1	177	12.1	373	10.5	314	10.2
3-6 months	154	4.8	92	6.6	168	6.9	110	7.5	179	5.1	150	4.9
7 to 12 months	77	2.4	50	3.6	92	3.8	67	4.6	89	2.5	77	2.5

Chapter 8 Appendix 1 Figure 1 Testing model fit: a comparison of unadjusted Kaplan Meier survival curves with adjusted survival curves using `stpm2` for primary localised NSCLC treated within 12 months of diagnosis, New South Wales, 2000-2008



When the unadjusted Kaplan Meier curve and the adjusted survival curve obtained from the model show little difference to one another then this variable is considered to have good fit

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Cc: Lim Eric; Elizabeth Tracey; Claire Weinberg; Ian Pavord
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9. Discussion

9.1. Discussion

This thesis has presented a series of studies that have examined the impact of distance to surgical care on cancer survival after adjusting for patient, tumour and treatment factors. First, an overview of the international literature highlighted the relationship between increasing distance from services and poorer patient outcomes. Varying results in outcome in the non-cancer setting depends on the type of presenting problem and the availability or otherwise of a service. Distance from outpatient care, the type of service and compliance with treatment were important for patients with mental health, drug abuse, depression and eating disorders. - For patients with myocardial infarction results were mixed with some finding no effect because services were in close proximity while others found poorer survival was due to less intensive treatment and reduced access to expert care.

In the particular context of cancer care, previous studies of straight line distance have been dominated by studies in women with breast cancer. A consistent pattern of mastectomy instead of breast conserving surgery was found with increasing distance to radiotherapy services. In many - Scottish and UK studies, for the majority of cancer sites examined, the hazard of death increased with increasing straight-line distance to a cancer centre. Depending on the cancer site and factors examined, a number of studies have found that attendance at a cancer centre rather than distance explained the hazard of death. Most studies were undertaken to appreciate the policy impact of the specialisation and centralisation of cancer services on access for people who live more remotely. In Australia, most services are located in cities, and distances travelled are greater than the international studies examined. With increasing trends towards sub-specialisation and greater centralisation of cancer services in NSW, the further investigation of the relationship between distance from specialist cancer surgical services and outcome, as undertaken in this thesis, could inform policy development in this area.

The early part of this thesis focused on issues of measurement, including measures of distance (Chapter 2) and cancer survival (Chapter 3). The remaining chapters (4-8) discuss the findings of studies that use linked cancer registry and hospital data and apply the distance and cause specific survival methods previously validated in chapters 2 and 3.

Bladder cancer was the first study in this thesis to use the cause specific survival method and to measure distance to actual surgical care in patients undergoing a cystectomy or bladder resection while adjusting for a wide range of patient, tumour and treatment factors (Chapter 4). The study of distance from and access to specialist hospitals for women diagnosed with ovarian cancer also investigated predictors of general hospital care and the receipt of surgery (Chapter 5). The three remaining chapters investigated the impact of distance to the nearest accessible specialist hospital (NASH) and hospital of treatment for patients with non small cell lung cancer (NSCLC) living in New South Wales (NSW) after adjusting for patient tumour and treatment factors. The first study of NSCLC examines predictors of advanced or unknown stage (Chapter 6), the second, predictors of no surgery (Chapter 7) and finally cancer survival (Chapter 8). This final chapter summarises the unique contributions of this thesis to the literature previously discussed in detail in the earlier chapters. Emphasis is given to common findings for bladder, ovarian and lung cancers. Possible reasons for disparities observed in this thesis are discussed, along with limitations, strengths and key implications of the research for future research. Recommendations for changes in clinical practice provide a consolidated understanding of the impact of distance to specialist care in NSW.

9.2. Unique contributions of this thesis to the literature

9.2.1. Measuring distance

Reporting and explaining variability in patterns of cancer incidence, mortality and survival by time at diagnosis for small geographic areas is common to all cancer registries and necessary for evaluating cancer control efforts. The NSW Central Cancer Registry (CCR) was geocoded to replace the current method (National Locality Index (NLI) encoder) of allocating geographic regions in the CCR. However, validating whether this new method produced the same results as the old method was necessary. One benefit of geocoded address data is that an algorithm called the Great Circle Distance Calculator could be applied to geocoded coordinates to measure straight line distance. This algorithm was applied to all patient's addresses on the CCR (living within an LGA) to a designated hospital (RPA) to measure the straight-line distance (in kilometres). This method had not been used in NSW, before. Therefore, checking whether the distances calculated were correct and consistent

with known distances was necessary. The number of cancer cases associated with each geocoded LGA compared to the number of cases allocated using the NLI coder was similar providing reassurance the new method produced the same result. Furthermore, the distance in kilometres for every case of cancer used to calculate the median value of distance from the LGA to a single hospital RPA was plausible, therefore, providing further reassurance that distance was being calculated correctly (Chapter 2).

9.2.2. Measuring survival

A comparison of different methods of measuring cancer survival, the primary outcome of interest, and, therefore, central to this thesis, was undertaken to determine whether cause specific was a practical alternative to the more traditional relative or the new net survival methods. Three methods of survival were calculated for two registry populations (the NSW CCR and the Northern and Yorkshire Registry) for cancers of the lung, breast, prostate and colorectal cancer. In NSW, regardless of survival method, cancer survival at monthly intervals, up to one year and yearly intervals, up to eight years after diagnosis, for each cancer site, produced almost identical results. This finding was important to this thesis because it provided reassurance that cause specific survival in NSW was an acceptable method to undertake the subsequent analyses in chapters 4 to 9. Cause specific survival depends on the quality of the cause of death data used to determine the final cause of death. This study allocated the cause of death to Northern and Yorkshire registry subjects using NSW rules. For the good survival cancers of prostate and breast similar survival estimates were obtained for cause specific survival compared to other survival methods. However, cause specific survival estimates of lung cancer and bowel cancer in Northern and Yorkshire were 2.3% and 3.8% higher than the relative or net survival estimates. There was little difference between cause specific, relative, and net survival estimates when addition cancer specific deaths mentioned in part two of the death certificate were included in the final determination of cause of cancer death. In NSW, the cause of death is more likely to be correct as all notifications determine the final cause of death. The second aim of this study investigated differences in survival rates for each cancer site between NSW and Northern and Yorkshire. Survival estimates in NSW were 5-10% higher than Northern and Yorkshire (depending on the site) even after taking account of the cause of death allocation. Therefore,

the higher survival estimates in NSW, routinely reported in International studies of cancer survival, would appear to be real and not related to the methods used to calculate survival or differences in allocating the cause of death (Chapter 3).

9.2.3. Bladder cancer survival and distance to surgical care

This study of people diagnosed with bladder cancer between 2000 and 2008 and living in NSW was the first study in this thesis to use linked cancer registry and hospital data. In addition, distance and cause specific survival methods were applied. This study extended previous analyses of predictors of bladder cancer survival and further examined why survival was poorer in women[1] and considered whether distance to the hospital of surgical treatment was a predictor of survival after cystectomy or surgical resection. After adjustment for a wide range of variables, there was little impact on women's higher risk of death from bladder cancer following cystectomy. The variable(s) principally contributing to the weakening of the association of female sex with risk of death in cystectomy patients were in order of strength: summary stage, age at diagnosis, distance from treatment facility, the presence of haematuria, country of birth and time to cystectomy. With increasing distance from a person's home to their hospital of cystectomy, people with bladder cancer were less likely to die. As this study was the first in this thesis to examine the distance to surgical care in retrospect, it may have been preferable to group hospitals into specialist and non-specialist rather than public and private. However, many urologists operate in the private sector and in the absence of guidelines for bladder cancer this approach seemed reasonable. It is most likely that patients who travelled further, and who underwent a cystectomy were receiving their care in specialist hospitals. The most significant finding in this study, however, was the interaction of sex with a history of cystitis in influencing death after cystectomy: Hazard Ratio (HR) was 1.55, 95% CI 1.15-2.10, in women with a history of cystitis. No such interaction was evident in women who underwent resection.

9.2.4. Ovarian cancer survival and distance to specialist care

Australian,[2] NSW [3] and International Guidelines[4, 5] recommend that women with epithelial ovarian cancer should undergo optimal surgical debulking by gynaecological oncologists

and be treated in specialist centres. Long term survival from ovarian cancer depends strongly on whether residual disease remains after surgery.[6 7, 8]

The most important finding of the paper presented in Chapter 5, was that women were more likely to be admitted to a general hospital for their care and less likely to have surgery with increasing distance to a Gynaecological Oncology Surgical (GOS) hospital. There was an increasing trend in the unadjusted risk of death due to distance from the GOS hospital, however, after adjustment for patient, tumour and treatment factors distance to the GOS hospitals was no longer significant because of the strong association of distance with type of treating hospital. Women treated in general hospitals were less likely to have surgery and more likely to die.

In contrast, women treated in GOS hospitals (public and private) or private general hospitals were 30-50 per cent less likely to die. Furthermore, women who had surgery for their ovarian cancer also had a 65 per cent lower hazard of death at five years after adjustment for hospital type and other factors.

Campbell, [9] in Scotland, used straight-line distance to treatment and found the hazard of death for women with ovarian cancer was greater with increasing distance to a cancer centre. Whereas distance from a woman's home to her closest hospital or family doctor examined in UK registry studies [10 11] did not appear to be important; only treatment in a cancer centre showed a significant reduction in the hazard of death after adjustment for age and deprivation. A higher proportion of unknown stage at diagnosis for women treated in general hospitals and a lower likelihood for those in specialist hospitals suggests selection of patients is occurring with increasing distance. Others have found that women with unstaged disease were less likely to receive care from a gynaecological oncologist or to receive recommended treatment. [12]

The results reported in Chapter 5 are similar to other large registry based studies of ovarian cancer survival. Women treated in teaching hospitals were found to have a lower risk of death than women treated in non teaching (general) hospitals, [10, 13]even after adjusting for extensive surgery and chemotherapy. [14]

9.2.5. Predictor of advanced or unknown stage NSCLC with increasing distance from the NASH

The findings in the next three papers on lung cancer in NSW extend and build on the work undertaken for ovarian cancer. Lung cancer, similar to ovarian cancer, is a poor survival cancer, usually detected at a late stage. In contrast, provided the tumour is located in a part of the lung that is operable and the tumour is localised to the lung, surgery can be curative in lung cancer patients. Australian[15] and International[16] guidelines recommend surgery for patients with localised NSCLC and for some later stage patients with survival better for those treated in a specialist centres.

The key question of interest in this study was whether people who lived further from the NASH were more likely to have advanced or unknown stage NSCLC at diagnosis or not when admitted to hospital within 12 months of diagnosis. People who lived 100km or more from the NASH were less likely to have localised stage and more likely to have advanced (regional and distant stage) or unknown stage at diagnosis. After adjustment for other factors, the likelihood of presenting with advanced stage was significantly higher in people who lived 100 km from the NASH relative to those who lived less than 39 kilometres from the NASH. When factors subsequent to diagnosis of stage (e.g. hospital of treatment, histological verification, type of admission), were added to the model, people treated in general hospitals had higher odds of advanced stage or unknown stage cancer regardless of distance from the NASH. In contrast, a lower likelihood of advanced or unknown stage NSCLC was observed among people who attended a specialist hospital with increasing distance from the NASH.

This study illustrates three important issues. Firstly, patient selection would appear to be occurring for people with lung cancer in NSW. With increasing distance from the NASH patients attended general hospitals for their care, which was associated with a greater likelihood of advanced or unknown stage. Secondly, the determination of advanced stage suggests that some diagnostic investigations had occurred, with patients with advanced stage considered unsuitable for surgery and therefore admitted to a general hospital. However, a person having a tumour of unknown stage suggests that full diagnostic assessment with clinical, radiological and histological assessment had not occurred. Thirdly, people who

attended specialist hospitals were significantly less likely to have advanced or unknown stage with increasing distance from the NASH, suggesting some diagnostic investigation and suitability for surgery had occurred prior to referral and staging that was more extensive after admission to hospital.

A plausible explanation could be that with increasing distance from the NASH perhaps stabilisation of symptoms or assessment of suitability for surgery (in patients who had some staging) influenced the referral to specialist hospitals. In NSW, lung cancer patterns of care studies report that 83 per cent of patients see at least one specialist[17-20] [21] at some time for their care indicating that most patients would have had some opportunity for investigation. However, it may be that patients who live more remotely delay visiting their GPs and thereby present at an advanced stage reducing treatment opportunities. Well documented in NSW are the low GP to population ratios found in rural areas [22, 23] and limited after hour services. [24, 25] Studies of lung cancer patients living in Western Australia (WA) report that rural patients took longer to consult their GPs, presented with more symptoms and had longer waits for specialist consultation.[26] More generally, a lack of awareness of the importance of symptoms may also be a factor causing delay. [27]

This study (Chapter 6) is only the second study of straight line distance to examine predictors of advanced and unknown stage NSCLC. The greater likelihood of advanced and unknown stage NSCLC with increasing distance from the NASH combined with a reduced likelihood of histopathological diagnosis, and higher likelihood of an emergency admission or attendance at hospital six or more months suggests a pattern of disadvantage.

9.2.6. Predictors of no NSCLC surgery with increasing distance from the NASH

This study focused on people diagnosed with localised NSCLC admitted to hospital within 12 months of diagnosis and investigated whether they were less likely to receive surgery with increasing distance from the NASH. Australian[15] and International[16] guidelines are unequivocal in recommending curative surgery as the best treatment option for this group. The most significant finding of this study was that with increasing distance to the NASH, patients with localised NSCLC were more likely to attend general hospitals for their care and not have potentially curative surgery. In contrast, patients who did travel longer

distances to attend a specialist hospital had a lower likelihood of not receiving surgery than patients who lived closer to the NASH. These findings are consistent with the findings in the previous study (Chapter 6); that is, with increasing distance from the NASH people referred to a specialist hospital are less likely to have tumours of advanced or unknown stage and more likely to have curative surgery (Chapter 7). Two factors explained much of the variation in receipt of surgical resection, namely the hospital of treatment and admission via the emergency department rather than a planned admission. Most studies of the effects of distance to specialist care on surgery of NSCLC have been done in the UK. The majority of them have shown that patients' access to surgical treatment is influenced by distance, clinician specialty and hospital of treatment. [10, 11, 28, 29] Emergency admissions appear to put patients on a sub-optimal care pathway. Others have reported that lung cancer patients who attended emergency departments without a diagnosis or without a chest x-ray were less likely than other patients to receive specialist care (62% vs 94%),[30] or to have their lung cancer confirmed pathologically.[31]

9.2.7. Lung cancer survival in people with NSCLC and distance from the NASH

The final study of lung cancer in NSW examined distance from the NASH, hospital of treatment and cancer survival by stage at diagnosis. With increasing distance from the NASH, the univariable hazard of death increased in people treated in general hospitals and declined for those treated in specialist hospitals. After adjustment, having surgery for lung cancer was the most significant predictor and thoroughly explained the survival advantage regardless of the stage at diagnosis. With increasing distance from the NASH, NSCLC patients were admitted to a general hospital and when so admitted were less likely to undergo surgery. Therefore, attendance at a specialist hospital determined whether surgery occurred. People with localised NSCLC, who had surgery (lobectomy, pneumonectomy or resection), relative to those that did not, had 60-80 per cent reduction in the hazard of death at one year and 26-68 per cent reduction at five years (depending on the surgical procedure). Similar risk of death reductions occurred for people diagnosed with regional and distant stage NSCLC who had surgery.

Potentially curative surgery has been found to be one of the best determinants of cancer survival with a recent UK lung cancer audit of 34,513 NSCLC patients reporting a HR of 0.41 (95%CI 0.39-0.44) in patients who underwent surgery relative to those who did not after adjusting for age, sex, performance status, stage and Charlson index of comorbidity.[29] NSCLC patients have better survival if they are treated in high volume surgical centres, even if they are older, of low socioeconomic status, or have comorbidities.[32] This study and the UK lung cancer audit have shown strong evidence of the survival benefits of potentially curative lung cancer surgery. It is of concern that people who live more than 100km from the NASH are more likely to attend general hospitals for their care be diagnosed with advanced stage, have double the likelihood of being unstaged and therefore not receive potentially curative surgery.

9.3. Common findings in this thesis

With increasing distance from the nearest specialist hospital, admission to a general hospital was more likely for both women diagnosed with ovarian cancer and people diagnosed with lung cancer. Attendance at a specialist hospital and undergoing major surgery independently reduced the likelihood of death for women with ovarian cancer. Furthermore, having surgery for NSCLC (that only occurred if admitted to specialist hospitals) explained the better survival outcomes for patients regardless of the stage at diagnosis. Therefore, what are the common factors?

Women with ovarian cancer and people with lung cancer treated in general hospitals were more likely to be emergency department admissions and to have a reduced likelihood of histological verification. Increasing age at diagnosis, any comorbidity and no histological verification were factors, which increased the risk of death in people with bladder, ovarian and lung cancer.

These findings are consistent with other studies that have found that the hazard of death increases with age, comorbidity[29] and in those without histological confirmation. [33] Patients admitted via the emergency department are also less likely to receive specialist care. [34] Alternatively, a lack of histological confirmation could perhaps indicate poor general health or comorbidity. The patient may not be well enough to undergo the further tests and

biopsies, or their general health was too poor for cancer surgical treatment; therefore, histological verification of stage may not have affected their management. Recent lung cancer guidelines for GPs recommend that a patient is immediately referred to the emergency department if they have symptoms indicative of advanced stage that is massive haemoptysis (coughing up blood) or stridor (difficult noisy breathing). [35]

Another common finding was the reduced likelihood of advanced stage and particularly unknown stage, the greater likelihood of for women with ovarian cancer and people diagnosed with lung cancer who attended specialist hospitals.

The considerable survival advantage conferred by surgical resection for women with ovarian cancer and people with lung cancer relative to other factors was also a common finding in this thesis further highlighting the importance of diagnosis and referral to a specialist hospital. Women undergoing surgery for ovarian cancer were 65 per cent less likely to die at five years. To our knowledge, this is the first population based study to report survival due to surgical resection while adjusting for patient, tumour and treatment factors. In addition, to our knowledge, this is the first study to provide survival estimates for people with NSCLC by type of lung surgery, for each category of stage and to have used cause specific rather than all cause or relative survival.

Histological subtypes within each cancer significantly affected survival with a higher hazard of death observed in bladder cancer patients with transitional cell carcinoma, women diagnosed with serous epithelial ovarian carcinoma and people diagnosed with adenocarcinoma and large cell NSCLC. These findings are also consistent with the literature previously discussed in the introduction to this thesis. While it is not possible to modify a person's prognosis due to the histological subtype, molecular profiling, may provide opportunities for targeted therapies in the future.

The time from diagnosis to surgery or hospital admission for those who did not have surgery was relatively short for most patients. The majority or 75 per cent of NSW patients who had a cystectomy did so within the recommended three-month or 12 weeks from diagnosis. Most women (86 per cent) diagnosed with ovarian cancer were treated within six months of

diagnosis. About 10 per cent were admitted to hospital seven months or more after diagnosis. Similarly, admission to hospital within a month of their date of diagnosis (80.2 per cent) occurred for most people with NSCLC. It would appear that time from diagnosis to surgery or admission was short for most patients. However, a higher hazard of death occurred in patients with increasing time from diagnosis to hospitalisation for all three cancer sites.

These results suggest differential referral of patients to specialist hospitals, with those with earlier stage disease (i.e., most amenable to treatment) more likely referred. However, a more standardised approach, particularly given the high proportion of patients with unstaged cancer, is required to ensure equity of access for all who may be suitable for curative surgery.

Presented below are potential reasons for the disparities observed in this thesis, factors that may explain a delay between symptom awareness and diagnosis, potential risk prediction tools and referral pathways (Multidisciplinary Team Meeting (MDTs) and Cancer Care Coordinators (CCC) that may assist to ensure that all patients have access to early diagnosis, appropriate staging and specialist care.

9.4. Possible reasons for disparities observed in this thesis

Common to all three types of cancer studied in this thesis was the inability to measure the time from symptom awareness to diagnosis. Given, that most bladder, ovarian and lung cancer patients were treated within a relatively short time after diagnosis, it is possible, that the delay is occurring between symptom awareness and attending the GP. This could explain why, with increasing distance, patients are presenting with advanced or unknown stage attending general hospitals for their care and missing out on surgery.

Recently UK and Denmark have initiated strategies[36 37 38] that focus on reviewing factors that cause a delay in diagnosis. Two factors best indicated delay; these were the number of days from symptom onset to diagnosis and the proportion of patients diagnosed with late stage. The National Awareness and Early Diagnosis Initiative[36] was introduced in 2008 in the UK to examine pathways to a delayed diagnosis of cancer. A risk factor for delay

identified across all cancer types was non-recognition of the seriousness of symptoms. Patients who adopted a wait and see attitude often contributed to delay. Not associated with delay were lower levels of social support, low socioeconomic status or age at diagnosis were. [36]

9.4.1. Factors associated with delay in people diagnosed with bladder cancer

The most common presenting symptom of people diagnosed with bladder cancer is painless haematuria (blood in the urine). Other less common symptoms include urgency, dysuria (pain on urination) and in, more advanced tumours, pelvic pain and symptoms related to urinary track obstruction. [39] Recently, the American Urological Society has published guidelines that anyone with microscopic haematuria (defined as three or more blood cells) should be followed up clinically and subsequently with a biopsy because approximately 5% of patients will have a urinary tract malignancy.[40]

Factors associated with delays prior to diagnosis for bladder cancer include female sex and non-white ethnic origin. Compared to men, delayed diagnosis is more common in women who have haematuria because other factors like post menopausal bleeding are often investigated first.[41] Delay was shorter in men who presented with bleeding and longer with pain or when symptoms were vague or non-specific. [36] Haematuria in men [42] and cystitis in women[43] were factors that reduced delay. Practitioner delay was shorter for younger urological patients and increased when health symptoms not related to cancer were present. Therefore, risk prediction tools in a general practice setting would be welcomed in an Australian context particularly given the poorer survival in women compared to men.[36] It is unknown whether GPs or urologists use risk prediction tools to assist them to diagnose people suspected of bladder cancer in NSW.

9.4.2. Factors associated with delay in women diagnosed with ovarian cancer and potential risk prediction tools

Reasons given for the delay in diagnosing women suspected of ovarian cancer, range from the misattribution of symptoms, due to stress or menopause, or attributing symptoms to previously benign conditions, for example, irritable bowel syndrome. [46] Presenting symptoms of women influence GP referral patterns. GPs referred women with

gastrointestinal symptoms to a gastroenterologist while women who presented with bleeding to a gynaecologist.[44, 45]Currently, there is no screening test to detect ovarian cancer. [46]

Women eventually diagnosed with ovarian cancer often present with suspicious ovarian masses; a definitive diagnosis may not be possible, until a tumour is removed, and histopathology undertaken. A risk of malignancy index may be calculated that takes into account a woman's menopausal status, ultrasonic scan and CA125 levels which collectively can be used to triage and refer women suspected of ovarian cancer to a gynaecological oncologist.[47]

In Australia where large distances to specialist centres occur, triaging is particularly important.[47] Jacobs[48] who first reported this index in 1990 recorded a sensitivity of 85% and specificity of 97% in differentiating malignant from benign disease. More recently, the sensitivity and specificity of a symptom index developed by Goff [49] and Rossing [50] was applied to age specific numbers of patients with confirmed ovarian cancer identified through the Australian Epithelial Ovarian Patterns of Care Study.[51] This study calculated a positive symptom index (based on numbers of symptoms, clinical history and risk factors) of between four and 16 times in women with confirmed ovarian cancer. The authors concluded that while not adequate as a screening tool, it may be a useful risk prediction tool to prompt referral for diagnostic testing. [51]

9.4.3. Factors associated with delay in people diagnosed with NSCLC and risk prediction tools to assist with earlier diagnosis

Most people with lung cancer present at a late stage with survival differences varying greatly internationally by stage at diagnosis.[52, 53] A lung cancer tumour can take up to 8-10 years to be clinically detectable.[54] People with lung cancer may not recognise their symptoms or ignore them for a variety of reasons including stigma and high psychosocial distress.[55]

Recently, a number of risk prediction tools have been developed that may assist GPs to detect lung cancer. The CAPER studies[56] developed in the UK examined the risk of detecting lung cancer using combinations of symptoms. Haemoptysis in combination with weight loss had a PPV of 9.2%. However, the model was more predictive when stratified by

patient age ranging from 8.4% in those aged less than 55 to 20% for those aged 85 years or older.[56] Another model called the Q Cancer lung model[57] included risk factors as well as symptoms. This model found that haemoptysis, appetite loss, weight loss, cough, body mass index, deprivation score, smoking status, chronic obstructive airways disease, anaemia and prior cancer (females only) explained 72% of the variation in the model. The 10% of patients with the highest predicted risks included 77% of all lung cancers diagnosed over the subsequent 2 years.[57]

Delays in diagnostic testing were found to occur for rural lung cancer patients in WA leading to more advanced stage at diagnosis and limited opportunity for surgery. [26] According to Salomaa, a multidisciplinary approach and rapid access to carefully planned investigations[58] increases the likelihood of timely diagnosis in lung cancer patients. In addition, multidisciplinary team review was found to be an independent predictor of lung cancer survival in the recent Victorian patterns of care study.[21]

9.4.4. Availability of primary care in rural areas

Improving rural patients access to primary care is currently a National Priority.[59] Patients who live in rural areas or further from specialist hospitals could be presenting at an advanced stage or unknown stage because of their limited access to primary care physicians. Patients living in rural areas in Australia[22] and the US [60] have a reduced number of primary care physicians per head of population. In a US study that considered predictors of unknown stage lung cancer, people were more likely to have their cancer unstaged if they were older and resided in low income rural areas with fewer primary care physicians per 10,000 population.[60] In Australia, the average ratio of full-time equivalent doctors to patients is 0.71 per 1000[61] with ratios below this found in rural and remote areas and outer metropolitan areas in capital cities. In addition, Brown et al. [62] reported that women who live in rural and remote areas had significantly fewer visits to GPs and specialists ($P < 0.001$) than women living in urban areas.

9.4.5. Multidisciplinary team review

Lack of multidisciplinary team (MDT) participation in rural areas (41%) was nominated by the Clinical Oncological Society of Australia as an issue that required specific attention. people living in rural areas.[63] MDTs may be seen as part of the cancer coordination pathway or may exist alone.

Specific issues identified in patients from rural and remote populations were a lack of available specialist health care. This is seen as a major factor in delayed diagnosis. [64]Inconsistent, delayed or incomplete communication particularly between family physicians and specialists inhibit the delivery of coordinated care for patients.[64] A number of success factors of MDTs and referral pathways were identified as part of a literature review commissioned by Cancer Australia. These were, determining a clear vision, developing a statement of purpose , a structure and strategy for linking with existing organisations, consideration of geographic and demographic issues, governance models as well as tracking and measuring of outcomes.[65] To date the effectiveness of the CanNet (Cancer network strategy) mainly relates to process measures. Those include the service directory, Canrefer, (developed in NSW and used to identify specialist hospitals in this thesis) the monitoring of the number and specialty of MDTs, the funding of clinical nurse consultants and the education sessions provided to clinical staff.

A number of CanNet pilot projects in NSW aim to improve referral patterns for cancer patients in rural areas. However, these projects are in progress and are yet to report. One project developed referral pathways between the Northern Sydney, Central Coast, Hunter New England and North Coast Area Health Services. [65] The second project commissioned by the Cancer Institute NSW as part of phase 2 of the CanNET project is developing primary care referral guides.[66] Lastly, Cancer Australia has funded a Lung Cancer Demonstration Project run by Catalyst and based at Sydney LHD and Lifehouse. [67]This project aims to document pathways from Orange and Dubbo to RPA and St Vincent's. Memorandums of Understanding (MOU) will be eventually be signed by all participants in this referral pathway. [67]

9.4.6. Cancer care coordination

Few studies have examined the effectiveness of cancer care coordination (CCC) on patient outcomes. A literature search of the term "cancer care coordination" revealed there were eight studies, [64, 68-73] of these, three were undertaken in NSW.[64, 69, 70] One study evaluated a questionnaire [70], another attempted to define cancer care coordination and concluded that there was not an agreed definition[69] and the last study was a small qualitative study (n=20 patients and 29 clinicians) that considered barriers.[64] Only one study evaluated the timeliness of care [68] and this study had its limitations: it was small (n=352); a single health facility and a retrospective cohort. However, after establishment of CCC, the proportion of early stage non-small lung cancer patients increased from 32% to 48% (p=0.006).[68] No studies have evaluated the impact of cancer care coordination on outcome.

The Cancer Institute NSW funded a number of CCC positions and undertook an evaluation of the program in 2011. In urban areas most cancer care coordinators where tumour specific whereas most rural cancer care coordinators were community based and worked across multiple tumour streams including palliative care.[64] Cancer care coordinators in urban areas also reported seeing more than 80% of tumour specific patients, whereas regional and rural coordinators only saw between 20 to 46%.[74] The main barriers reported include lack of time, lack of administrative and IT support, limited links to metropolitan specialist centres and the private sector.

Most CCCs expressed difficulty in obtaining referrals from surgeons and GPs. An increase in GP referrals and CCC had occurred in those who sent letters to the GPs and updated them on the progress of their patients. Some of the CCCs had developed proformas to inform GPs about the MDT discussions and the patient's treatment plan. In addition, CCCs in rural areas had developed referral pathways to CCCs in metropolitan hospitals.[74]

Most patients (88%) believed that CCCc were an essential part of cancer care and those who received assistance (86%) from a CCC were satisfied with the communication and information provided on their care from the MDT. [74] Patients also reported that they were also more likely have their support needs assessed such as transport and be referred to psychosocial and other support services.[74]

The Cancer Council, NSW has also recommended in the 2014 budget estimates document that additional CCCs, palliative care physicians and nurses be funded for people in rural areas.[75]

9.4.7. Cost of transport and out of pocket expenses

The only proxy that related to cost in this thesis were the studies undertaken on lung cancer where factors predictive of advanced and unknown stage, no surgery and survival for NSCLC who lived 100km or more from the NASH. .

In NSW, patients who have a car and travel over 100 kilometres are partly subsidised and can apply for Isolated Patient Transport and Accommodation Scheme (IPTAAS) funding to cover transport and accommodation costs. This policy does not include the expense of meals and incidentals (road tolls, parking, booking fees) which are not reimbursable and other out of pocket items.[76]

In a study of out of pocket expenses in Queensland, cancer patients who live more than 100km from a specialist hospital had five times the out of pocket expenses ($7,752 compared to $1,481) compared to those that lived less than 100km. Not surprising, out of pocket costs increased with distance. [77] Therefore, travel burden and cost may be influencing the hospital of treatment. Travel burden, cost and employment status predicted whether NSW and Victorian patients travelled and lived away for their cancer treatment. People in the paid workforce were half as likely (OR=0.48) to live away for treatment, than those who were retired or were pensioners. [78]

Currently there are a number of budget initiatives that the Cancer Council has suggested for inclusion in the NSW State budget for 2014/2015 that will have a direct impact on access to specialist care for cancer patients.[75] Specifically, these included the increase in funding for the transport for health program to $11.4 million annually as well as amending the IPTAAS scheme to cover travel and accommodation for patients who participate in clinical trials.[75]

9.4.8. Characteristics of rural patients

In NSW in 2006, the percentage of households with gross weekly income less than $500 per week increased with remoteness, while the percentage of households earning at least $2,000 per week decreased with increasing rurality and remoteness. In major cities, 10.7% of households reported gross weekly income of less than $500 compared with 17.7% of outer regional and remote households. In contrast, 25.6% of households in major cities reported gross weekly income of at least $2,000 compared with only 9.1% of households in outer regional and remote areas. [24]

Regional Australians reported substantially lower levels of private health fund membership. In 2001, 50.2% of people living in capital cities were covered by private health insurance compared with 43.5% living outside capital cities. [79]

In NSW, a significantly higher proportion of adults in 2012 in rural health areas (33 %) than urban health areas (11.7 %) experienced difficulties getting access to health care in the past 12 months with the proportion increasing since 2002 (24.8% Rural and 9.3% Urban). [24] Furthermore, people in rural NSW present with more complex medical conditions and comorbidities due to stoicism and reluctance to ask for help.[80, 81]

A systematic review examined the psychosocial well-being and supportive care needs of cancer patients living in urban and rural areas and found that rural patients had higher psychosocial morbidity and poorer quality of life.[81] Phone based counselling or internet chat rooms may overcome barriers to the provision psychosocial help. [81] Most of the studies in the review were breast cancer patients with more research recommended in other areas. Other barriers included travelling daily and staying away from home. Families reported financial, emotional and relationship issues associated with travel. The Australian Longitudinal Study of Women's Health also reported higher hazards of death particularly for women with lung cancer and chronic obstructive pulmonary disease, with little or no difference in smoking rates.[82]

According to Underhill, access may not be the only explanation for rural disparities because some patients may choose not to have treatment, but improvement in access is still required.

[83]The new regional cancer centres of excellence will provide MDT, support, educational services and mentoring by major metropolitan centres as well as links to smaller more remote areas. Coordination of government funded travel and accommodation schemes as well as telemedicine is important if this initiative is to work.[83]

9.5. Strengths of the studies in this thesis

Major strengths of the studies in this thesis include factors relating to the design of studies, as well as the methods and measures used. Each of these issues in discussed below.

All studies undertaken in this thesis were population based with very few cases that did not link to the APDC. In addition, inclusion and exclusion criteria were identified and explained. Furthermore, patients with unknown stage at diagnosis were included in the analysis of predictors of advanced and unknown stage NSCLC (Chapter 6). Few cancer registry studies include patients with unknown stage at diagnosis, because of their concerns about data quality or lack of follow up. However, because notification to the registry is mandatory in NSW, and registry staff follow up missing or discrepant stage information, missing stage is most likely due to a lack of investigation rather than a data quality issue. US studies of distance were limited to categories of patients.

To be consistent with other survival analyses for ovarian cancer patients, unknown stage was excluded in this study and a complete analysis undertaken. However, a sensitivity analysis was undertaken where the analysis was repeated after imputing unknown stage. Similarly, multiple imputation was also undertaken as a sensitivity analysis for predictors of advanced and unknown stage (Chapter 7) and lung cancer survival (Chapter 8).

Cause specific survival estimates in NSW produced similar results to those of the more widely accepted relative survival and newly developed net survival method. Modelling of cause specific cancer survival was possible after adjustment for a wide range of patient, tumour and treatment factors. Most US and UK studies of distance to cancer treatment could not measure stage, comorbidity or measure cause specific survival. Those that did measure survival used all cause survival instead of cause specific survival because the cause of death was not available.

This thesis compared existing methods of modelling survival, for example, Cox proportional regression modelling with new methods of survival analysis such as `stpm2.` The inclusion of time-varying effects and directly adjusted survival curves to the studies in this thesis is novel. The comparison of covariate-adjusted survival curves with unadjusted Kaplan-Meier survival curves using the `stpm2` method of survival allowed determination of model fit.

Unique to this thesis is was the measure of straight line distance to hospital of surgical treatment (bladder) and distance to specialist care (ovary and lung) which provided a measure of access to specialist cancer care. Previous studies of distance in Australia have used the Accessibility and Remoteness index of Australia (ARIA) that considers distance to generic service centres based on the size of the population only.

There has been no investigation in Australia previously of distance to specialist care and survival outcomes by hospital of treatment and surgery. Selection of specialist hospitals occurred from a directory of cancer services reviewed and regularly updated. The studies in this thesis also considered Australian and NSW clinical and service guidelines that documented management of people with lung and ovarian cancer.

9.6. Limitations of the studies in this thesis

There are a number of limitations to the work in this thesis. In particular, no information on the impact of costs was available apart from taking account of the IPTAAS for the analysis of distance to specialist care for patients with lung cancer. No information was available on access to primary care or specialists. However, for the ovarian and lung cancer studies undertaken in this thesis a number of comparisons with NSW patterns of care were possible. Similar numbers of women were referred to gynaecological oncologists as those who presented at specialist hospitals.[45] Although, unknown, is whether the specialists were the most appropriate or whether patients had a multidisciplinary review. No information on why proximity to a hospital influenced choice of hospital, although distance to a specialist hospital, as well as care from a specialist doctor, were found to be issues with lung cancer patients.[84]

We had no information on whether patients received chemotherapy or radiotherapy as these services are provided in outpatient cancer care centres and we did not have access to this data. However, other studies have shown that, like surgery, there is lower use of radiotherapy,[11 85, 86] chemotherapy[28 85] and combined treatment[85] with increasing distance to specialist treatment with greater access in specialist hospitals.[28 11]

Not investigated, in this thesis, was the competing risk method of survival analysis. More recently, a number of studies have suggested that competing risks analyses[87] may be an alternative to the cause specific hazard analysis combined with the cumulative incidence function[88] (the probability of failure from a particular cause). However, one study compared the "cause specific" failure rate, the "relative" failure rate, and the cumulative incidence in the presence of competing risks at five years for the same dataset of colorectal cancer patients and found identical failure rates regardless of the method used.[89] Therefore, a similar result would have most been likely in the studies in this thesis.

9.7. Key implications of the research for future research

People who live in rural and remote areas of NSW will continue to need to travel to specialist surgical care for cancers of the bladder, ovary and lung, which is appropriate if they are to receive the best care. The physical size and population of NSW does not support specialist centres in rural areas. Therefore, the studies in this thesis support the literature that access to appropriate staging, multidisciplinary review, and surgical treatment by specialists in specialist centres will result in the best survival outcomes for everyone regardless of where they live.

The main implication for bladder cancer patients in NSW is an urgent need to consolidate urological surgical services. The reduction in the hazard of death with increasing distance for patients undergoing cystectomy suggests that bladder cancer patients were attending specialist hospitals. Only one study, (US linked Surveillance Epidemiology and End Results (SEER) and Medicare data) has examined increasing distance to specialist care for bladder cancer patients who had a cystectomy. [90] Longer distance to an available surgeon resulted in a decreased odds of having surgery and overall survival was higher for those who had a cystectomy compared to those who did not. Currently, 27 hospitals in NSW provide

urological surgery. Treatment is recommended in a smaller number of specialised centres.[91] Organised referral pathways, MDT review and CCC involvement would also be of benefit to rural patients. The poorer survival from bladder cancer in women remains largely unexplained. That a history of cystitis in women diagnosed with bladder cancer and treated by cystectomy may contribute to this poorer outcome merits further investigation.

Considerable debate exists as to whether the histological subtype of ovarian cancer or the extensive surgical removal of all residual tumour most influences ovarian cancer survival.[6] The reality is that extensive surgical debulking is the only factor within the surgeon's control. Therefore, the significant survival advantage of attending a specialist GOS hospital is demonstrated in this thesis as providing women with the best chance of survival.

Provision of specialist care to all women diagnosed with ovarian cancer is essential regardless of where they live. To achieve timely diagnosis and surgery for women who live more remotely, development of strategies for each barrier is required. Documented barriers for women suspected of ovarian cancer include recognising symptoms and the influence of the type of presenting symptom on GP referral patterns.

According to the Australian ovarian cancer patterns of care study 60 per cent of Australian women were eventually referred to a gynaecologist or gynaecological oncologist.[45] Unknown is whether gynaecologists on-refer patients to gynaecological oncologists. The only prognostic factor that a surgeon can alter for women with ovarian cancer is the amount of residual disease that remains after surgery. Cytoreductive surgery to less than 1.0 cm of residual disease undertaken by gynaecological oncologists has been shown to confer a greater survival advantage in a number of single institution studies than cytoreductive surgery with more than 1.0cm of residual disease.[6] It was clear from the study in this thesis that surgery and treatment in either a public or private gynaecological oncology centre confers a considerable survival advantage. Therefore ensuring that women themselves are aware of this finding is necessary. Most recently, Cancer Australia have published information for women called "Five things you should know about ovarian cancer." The fourth thing and the most important piece of information for women is that they should be referred to a gynaecological oncologist to obtain the best surgical outcomes.[92]

The main implications for lung cancer patients who live further from specialist centres is to develop strategies to encourage presentation at an early stage to increase the likelihood of surgery in specialist centres. In the last few years in Australia and NSW a number of initiatives and strategies have been developed that should increase community and GP awareness of lung cancer. The recent Cancer Australia guidelines for general practitioners were developed to assist GPs detect symptoms of lung cancer and to provide them with information on appropriate referral. [35] The Cancer Institute NSW has also developed treatment algorithms for the management of lung cancer that are stage specific. [93] The most important pre-treatment assessment is to confirm the stage, assess the patient's fitness for treatment by undertaking a multidisciplinary team (MDT) assessment (that includes at least a surgeon and a respiratory physician) and stabilise other conditions first. Recommended is a clinical cancer care coordinator or lung cancer nurse to ensure that a treatment plan and access to surgery is organised and communicated. In addition, a video translated into a number of different languages provides people with practical advice on symptoms. [94] There is enough evidence for all these suggestions, with MDT review found to be an independent predictor of cancer survival.[21, 95]

It is noteworthy that the proportion of NSCLC patients undergoing lung cancer surgery in Australian cancer registry studies is similar with 20% reported in WA in 1996,[96] and 21% in 2007,[97] 19.1% in Victoria,[21] and 20% in 1996 and 19% in 2002 in NSW.[17] However, this proportion varies between regions, 17% to 26% in NSW,[18] when three areas are compared and as this thesis has found depends on whether the patient lived in proximity to a specialist hospital. Therefore, the challenge is to ensure that everyone has the same opportunities. Compared to SEER data for the same region more localised stage and better survival occurred after implementing a community-based lung cancer program. This program included weekly MDT meetings, nurse coordinators, thoracic surgeons skilled in VATs surgery, treatment guidelines and CT screening of former smokers. Cancer survival in the community based program increased steadily from 15% in 1983 to 30% in 2006.[95] Therefore, monitoring the proportion of people diagnosed with early stage lung cancer should increase the proportion of patients who have potentially curative surgery.

9.8. Recommendations for changes in clinical practice

The NSW Surgical Services Taskforce developed a strategic plan for surgery in Greater Sydney[91] and for Rural Surgery for the period 2011-2021. [98] The emphasis of these plans is the development of concentration of surgical centres particularly for cardiothoracic, gynaeconcology and urology. The plan recommends consolidation of existing specialist cardiothoracic surgical units to fewer units than currently available. Recommendations for gynaecological surgery include reducing the number of specialist centres to ensure that an experienced MDT supports all women.

Co-located, high volume, comprehensive services with experienced staff with the intent of improving clinical outcomes for patients is the vision articulated in the most recent NSW Surgery Futures plan for Greater Sydney. [91] Comprehensive services include a full range of surgery, oncology, radiotherapy, specialised nursing and allied health. Currently, the Cancer Institute NSW is reviewing surgical procedures and outcomes for the upper Gastro Intestinal (GI) cancers (pancreatectomy and oesophagectomy) to ensure that only specific centres can perform these procedures.[99, 100]

However, for other types of cancer it is said that "further planning for cancer surgery needs to be undertaken with the Cancer Institute and the Cancer plan before these changes can be fully implemented." [91]

The Rural Surgery Futures plan has identified a number of key recommendations. The first recommendation suggested networking of small hospitals around a major regional or base hospital and improved access to specialist clinics in specialist hospitals. Rural clinicians have expressed concern that timely access to specialist clinics in specialist hospitals is only possible when a surgical specialist provides outreach to the local town. [98, 101]

Another recommendation is to link long-term clinical service plans in rural areas to capital works programs. Rural clinicians are often uncertain about the long term future of their service or hospital. Other barriers include the difficulty in attracting and retaining experienced clinical staff, the shortage of GP proceduralists, and the lack of access to ongoing education and training for perioperative nursing, the deficiencies in succession

planning and the lack of support from specialist hospitals. [53] Credentialing or the formal process of ensuring clinical staff have the relevant training and experience could be more efficient. Currently, there are separate processes required between towns and clinical services. Identified as a barrier to diagnosis was the limited access to new technologies, radiology and pathology services. The majority of pathology service providers in rural areas were from the private sector. Rural health staff were concerned about the cost to patients and the variable quality of providers. [53] Furthermore, a number of rural hospitals did not have access to cytology or frozen sections, which is obviously essential, for pathological investigation and diagnosis of a suspected tumour. Lack of access to histopathology may explain the increased likelihood of unstaged NSCLC with increasing distance from the NASH.

Furthermore, a survey of NSW staff working in rural areas reported that 43% did not have access to the system to plan surgery, which may explain the high proportion of emergency admissions for people with NSCLC. Most identified that advanced imaging and interventional radiology to assist with diagnosis were the most important future investments in rural areas. [98, 101]

Recommended also is the development of Australian clinical practice guidelines for bladder cancer and the consolidation of urological services into specialist centres. The 55 per cent greater hazard of death from bladder cancer in women who had a history of cystitis needs to be investigated further using clinical trial data.

Regardless of distance to a specialist hospital, referral of all women suspected of ovarian cancer should occur to enable surgical treatment by a gynaecological oncologist in a specialist hospital so that MDT review is available. Clearly, if appropriate referral to specialist hospitals was occurring, then the proportion of patients would not vary by distance to specialist care. Further understanding of other patient factors apart from cost[78] is required to determine why some patients decide not to travel to specialist care.

Clinicians need to refer and patients need to be encouraged to attend specialist thoracic hospitals to ensure that appropriate staging and treatment options are available to all lung

cancer patients regardless of where they live. Importantly, all patients regardless of where they live should be treated in accordance with the recently updated National Health and Medical Research Council (NHMRC) lung and ovarian cancer guidelines.

Outlined in the National Strategic Framework for Rural and Remote Health were systemic issues that require attention to improve health outcomes for rural and remote Australians. Issues identified include access, appropriate models of care, sustainable workforce, development of collaborative partnerships and strong leadership and performance.[65, 102]

In the 2009/2010 Australian Federal budget 560 million dollars[103] was provided to build ten regional cancer centres. The new or enhanced services ranged from radiotherapy bunkers, linear accelerators, Computer Assisted Topography (CAT), MRI and Positive Emission Topography (PET) scanners. Funded also is much needed additional patient accommodation in three NSW regional cancer centres.[104] These centres are in the process of being built and will provide much needed diagnostic services and will improve the provision of chemotherapy and radiotherapy locally. However, surgery in specialist centres will continue to be a requirement for most cancer patients. Therefore, it is important that people who live more remotely have equal access to specialist surgical care.

9.9. References

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