Report to Waikato Medical Research Foundation

Understanding the importance of tumour biology and socio-demographic difference in cancer stage at diagnosis using the Midland Lung Cancer Register

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Contents

Introduction 3

Methods 4

Data cleaning and verification 4

Combined lung cancer dataset 5

Surgical treatment and survival 6

Results 6

Data cleaning and verification 6

Combined lung cancer dataset 7

Surgical treatment and survival 7

Discussion 8

Conclusion 9

Reference 10

Table 1. Number of cancer cases by year of diagnosis and DHB 11

Figure 1. Comparison of lung cancer and mesothelioma registrations in NZCR and MLCR 11

Table 2. Accuracy of demographic data in NZCR 12

Table 3. Difference between date of diagnosis in NZCR and MLCR 13

Table 4. Comparison of cancer extent in NZCR and cancer stage in MLCR 13

Table 6. Surgical treatment by ethnicity in the MLCR 15

Figure 2. Kaplan-Meier curve for all-cause survival by ethnicity in the NZCR 15

Figure 3. Kaplan-Meier curve for all-cause survival by cell type in the NZCR 16

Figure 4. Kaplan-Meier curve for all-cause survival by gender in the NZCR 16

Figure 5. Kaplan-Meier curve for all-cause survival by ethnicity in the NZCR 17

Table 8. Adjusted hazard ratios of all-cause mortality 18

Introduction

Lung cancer is the leading cause of cancer death in New Zealand with approximately 1500 deaths per year (1). It has a significant impact due to the high rates of morbidity and mortality associated with the disease.(2) Survival from lung cancer in New Zealand is poor with a five year survival of 9.5% for men and 11% for women (3, 4). Māori have a greater incidence of lung cancer with Māori men having 2.0 times the incidence and Māori women having 3.4 times the incidence of Europeans/others (1, 5). The age standardised mortality rate for Māori is 3.5 times that of non-Māori (6). One of the key reasons for the poor prognosis for newly diagnosed patients with lung cancer is that most patients presented with advanced stage disease. Treatment is therefore generally palliative, with few patients being suitable for potentially curative treatment such as surgery and stereotactic ablative body radiotherapy (SABR).(7, 8) Another important influence in patient outcome is the tumour biology, for instance those with small cell lung cancer have a poorer prognosis or non-small cell lung cancer (NSCLC) who are epidermal growth factor receptor (EGFR) positive.(9, 10)

New Zealand Cancer Registry (NZCR) is a population-based tumour registry excluding non-melanoma skin cancers), collecting and storing cancer incidence data. The new cancer registrations were mainly based on the pathology reports sent by reporting laboratories electronically. Other sources s include discharge reports from publicly funded and private hospitals, death certificates and autopsy reports.(11, 12) Data collected in the NZCR includes demographic information (such as date of birth, gender and ethnicity), and tumour information (such as cancer site and extent of disease). The NZCR is the major source of 'information on the incidence of, and mortality from, cancer' and 'a basis for cancer survival studies and research programmes'.(13) Its completeness and accuracy are vital for cancer control in New Zealand.

The completeness and accuracy of registrations in the NZCR were reported to be diverse for different cancers.(12, 14-16) Approximately 88% of the breast cancer cases recorded in the NZCR have information on disease extent with a 94% accuracy rate in those with disease extent,(12) and 96% cases with disease extent and a 87% accuracy rate for colon cancer,(14) compared to only 31% cases with disease extent and a 89% accuracy rate for prostate cancer.(15) An audit was conducted to assess the lung cancer data in NZCR using the data recorded in the Auckland and Northland regional databases in 2004.(16) Of the 565 audit cases, 66 (12%) cases were not included in the NZCR, and 1 duplicate registration and 78 (14%)

ineligible case were identified in the NZCR. Only 58% of the lung cancer cases recorded in the NZCR have information on disease extent with a 79% accuracy rate in those with disease extent.(16) The audit of the lung cancer data in the NZCR was conducted a decade ago, and improvement on data quality may have been achieved. An updated quality assessment on the lung cancer data is needed.

The Midland Respiratory Group have been collecting data on all newly diagnosed cases of lung cancer who are referred to their multidisciplinary review meetings onto an access database: Midland Lung Cancer register (MLCR). It has maintained a register of all patients seen since 2004 and the centre has relatively complete recording of cases for the Midland Cancer Region (Lakes, Waikato and Bay of Plenty District Health Board) since 2007. These three DHBs serve a combined population of 660,000 and generate approximately 300 new cases a year. The region has 27% Māori population and of the over 2000 cases on the register 600 are Māori. The register includes data on date and source of presentation, results of investigations including CT and spirometry, date of diagnosis and pathological reporting. All patients are staged and mode of treatment is then recorded (radiotherapy, chemotherapy or surgery).

This study aims to 1) report the characteristics of newly diagnosed lung cancer cases, 2) compare the data accuracy of registrations in the NZCR with the MLCR, and 3) examine the treatment and survival of these patients.

Methods

Data cleaning and verification

A respiratory nurse specialist validated the MLCR data in 2011-2015 by comparing the clinical records and the data recorded in the MLCR. Lung cancer (ICD code: C33, C34)(17) diagnosed in 2011-2015 were extracted from the NZCR and the MLCR. Approval of accessing these two databases was obtained from the Southern Health and Disability Ethics Committee (reference: 16/STH/167).

Registration duplications were removed from the two datasets. Then they were linked together by the National Health Index (NHI) number, a unique identifier assigned to every person who uses health and disability support services in New Zealand. We classified the cases into three groups: 1) matching cancer cases in both datasets, 2) cancer cases identified in the MLCR only, 3) records identified in the NZCR only. For cancer cases diagnosed in the Waikato DHB and

identified in the NZCR only, clinical records of these patients were examined to verify the diagnosis: 1) lung cancer diagnosed in 2011-2015, 2) lung cancer diagnosed in before 2011 or after 2015, 3) not lung cancer, 4) not in the Midland Cancer Network region, 5) cannot confirm due to insufficient information.

For matching cancer cases in both datasets, we compare the cancer extent/stage, date of diagnosis, DHB, gender and ethnicity (Māori, Pacific, Asian, European and others) to examine the accuracy of demographic data in the NZCR. As demonstrated in the audit(16) on lung cancer data in NZCR in 2004, the difference on date of diagnosis between the NZCR and regional dataset may be due to difference on definition of date of diagnosis. The NZCR may collect the date of diagnosis from 1) date of operation or biopsy, 2) date of admission, 3) date of death if diagnosed at autopsy, or 4) 'approximate time between onset and death' as reported by certifying doctor on the death certificate if the only notification of a cancer comes from the death certificate.(16) However, a regional dataset may record the date of diagnosis from 1) date of issue of the first report confirming malignancy, 2) the date of final report suggesting invasive malignancy, or 3) the first documentation of the diagnosis in the clinical records.(16)

The MLCR records the cancer stage using the Tumour Node Metastases (TNM) staging system,(18) while the NZCR applies the Surveillance Epidemiology and End Results (SEER) programme cancer staging definitions.(19) The TNM classification was updated by the American Joint committee on Cancer. 'T' describes the extent of the primary tumour. 'N' describes the extent of regional lymph node metastasis. 'M' describes the occurrence of distant metastasis.(18) The SEER staging definition was developed by the American National Cancer Institute. Extent at diagnosis in the NZCR is coded as B (limited to organ of origin), C (Extension to adjacent organs), D (Extension to regional lymph nodes), E (distant metastases) and F (unknown).(19). In this study, stage IA and IB in the TNM system were considered to be extent B, stage IIA, IIB, IIIA and IIIB were comparable to extent C and D, and stage IV were extent E.(16)

Combined lung cancer dataset

To have a more complete lung cancer dataset, we created a combined dataset based on the NZCR data and the MLCR data. The combined lung cancer dataset included all cancer cases in the MLCR and the additional cancer cases in the NZCR after excluding the registrations that

were confirmed to be not lung cancer cases or were not diagnosed in 2011-2015. The characteristics of these patients by ethnicity (Māori, Pacific and others) was explored. We have grouped the cancer cell types into six groups: NSCLC, small cell, NSCLC-other, malignant carcinoid, others and unknown.

Surgical treatment and survival

Surgical treatment information was available in the MLCR. Type of surgical treatment (lobectomy, pneumonectomy, segmentectomy, sternotomy, wedge resection and no surgery) was examined in patients identified in the MLCR.

Date of death was recorded in the NZCR with a censor date of 31/12/2016. We explored all-cause survival of patients registered in the NZCR using the Kaplan-Meier method. The survival difference in subgroups was examined by log-rank test. If the p-value of the log-rank test is less than 0.05, the survival difference is considered to be significant. Cox proportional hazards model was used to identify factors that affect the all-cause survival.

Results

Data cleaning and verification

We identified 2126 lung cancer registrations in the NZCR, and 1570 lung cancer registrations in the MLCR (Table 1) in 2011-2015. We found 4 duplicate lung cancer registrations in the NZCR (Figure 1). Of the cancer cases recorded in the MLCR, 1483 (94.5%) lung cancer cases were also registered in the NZCR. There are 639 lung cancer registrations recorded in the NZCR were not identified in the MLCR, including 190 lung cancer registrations in the Waikato DHB. After examining the clinical records of these 200 Waikato patients, 110 (57.9%) were confirmed to be diagnosed with lung cancer in 2011-2015, 10 (5.3%) were diagnosed with lung cancer before 2011 or after 2015, 34 (17.9%) did not have lung cancer, and 36 could not be verified due to lack of information. Of the 87 lung cancer cases recorded only in the MLCR, 43 (49.4%) had clinical diagnosis only without any pathology report.

The demographic data in the NZCR has high accuracy, with 99.0% accuracy for gender, 96.0% for ethnicity, 98.4% for DHB and 99.7% for date of birth among the 1483 matching cancer cases in both datasets (Table 2). For the date of cancer diagnosis, 21.7% of the cancer cases were on

the same date and anther 68.4% were within one month difference (Table 3). However, the recording of cancer extent in the NZCR is poor (Table 4), with 34.8% (516) unknown cancer extent and 51.3% (755) recorded with correct cancer extent.

Combined lung cancer dataset

The combined dataset included 2149 lung cancer cases (Table 5), including 682 (31.7%) Māori patients, 25 Pacific patients and 1442 patients of other ethnicities. Waikato DHB has the largest number of lung cancer cases, followed by Bay of Plenty, Lakes and Tairawhiti DHB. Sixty one percent of patients were diagnosed with metastatic cancer, and 16.7% of patients had small cell lung cancer. Māori patients were more likely to be diagnosed at a younger age (chi-square test: p-value <0.001), more likely to be female (p-value <0.001) and more likely to have small cell lung cancer (p-value <0.001) than others. The difference of having metastatic lung cancer at diagnosis between Māori and others was not significant (p-value =0.138).

Surgical treatment and survival

Of the 1570 patients in the MLCR, 179 (11.4%) had surgery (Table 6). Lobectomy was the most common surgical treatment. There was no significant difference in the surgery treatment between Māori and others (chi-square test: p-value =0.156). Over 50% of patients with stage I lung cancer had surgeries, and 43.6% for patients with stage II cancer (Table 7).

The survival for these cancer patients was poor, with 51.2% of patients surviving 6 months after diagnosis and only around 20.0% survived 2 years. The 2-year survival was 74.5% for stage I cancer, 53.3% for stage II cancer, 25.7% for stage III cancer, and 8.5% for stage IV cancer (Figure 2, log-rank test: p-value <0.001). There was no significant difference in survival between small cell lung cancers and other lung cancers (Figure 3, p-value=0.450). Female patients had a better 2-year survival than male patients (Figure 4, 24.1% vs 16.3%, p-value <0.001). There was no significant difference in all-cause survival between Māori and non-Māori (p-value =0.056). The 6-month and 1-year survival was very similar for Māori and non-Māori. However, the 2-year and 5-year survival was slightly worse for Māori.

After adjustment for other factors including DHB, cell type and year of diagnosis, cancer stage, gender, age and ethnicity all had significant impacts on the all-cause mortality (Table 8). The adjusted hazard ratio for Māori patients and Pacific patients compared to others was 1.28 (95% CI: 1.15-1.42) and 0.61 (95% CI: 0.38-1.00), respectively.

Discussion

Lung cancer in the Midland Cancer Network region is relatively common with over 400 new cases per year. The mortality in this group of patients is poor, with 60% have stage IV disease at diagnosis and 80% have died by 2 years. Prognosis is mainly influenced by cancer stage at diagnosis and to a certain extent by biology. Prognosis is better in female and worse in Māori.

There was some under-reporting in both the NZCR (4%) and the MLCR (15%), and a less than 5% misrecording in the NZCR. The quality of demographic data of the lung cancer registrations in the NZCR is excellent, but the completeness and accuracy of cancer extent has not much improved since 2004: 35% with unknown cancer extent in this study and 42% in the 2004 audit; 79% of accuracy in this study and 77% in the 2004 audit among those with known cancer extent in the NZCR.(16)

Sixty eight percent (1015) of the registrations in the NZCR had a date of diagnosis that were within one month difference compared to the MLCR. Though the definition of date of diagnosis in the MLCR is considered to be more reasonable by clinicians, it is more feasible for NZCR to collect the date of diagnosis based on their definition: 1) date of operation or biopsy, 2) date of admission, 3) date of death if diagnosed at autopsy, or 4) 'approximate time between onset and death' as reported by certifying doctor on the death certificate.(16) For the other 10% registrations whose date of diagnosis in the NZCR was more than one month different from the MLCR, the influence of this discrepancy may be substantial especially when these data are used for survival analysis.

Fifty percent of patients diagnosed with stage I or stage II lung cancer received surgical treatment which is potentially curative. However, only 16% of the new lung cancer cases were stage I and II. Patients diagnosed with stage III and IV lung cancer have four and eight times the risk of dying compared to patients diagnosed with stage I lung cancer. Early diagnosis is the key to improve prognosis for lung cancer patients. Reasons for diagnostic delay in New Zealand are complex and multifactorial.(20) It was demonstrated that patient delay was common but most had seen a general practitioner (GP) before referral. Possible solutions include 'community initiatives to educate and resource at-risk patients to seek help, supporting and resourcing primary care to increase timely referral and implementing strategies to reduce system complexity for GPs and patients, and the employment of care coordinators'.(20)

The difference at risk of having metastatic lung cancer at diagnosis between Māori and others was not significant. However, Māori patients are 1.8 times more likely to have small cell lung cancer than others. Though it was shown that patients with small cell lung cancer have a poorer prognosis than those with non-small cell lung cancer,(9, 10) the difference in all-cause survival between small lung cancers and other types of lung cancers was not significant in this study, as well as the survival difference between Māori and others.

Conclusion

The MLCR provides excellent clinical data on newly diagnosed lung cancer cases. However, there is some under-reporting compared with the NZCR. Combing the two sources of data gives a more complete picture of the incidence of lung cancer in our region.

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Table 1. Number of cancer cases by year of diagnosis and DHB

Categories	MLCR	NZCR
Year of diagnosis		
2011	299	417
2012	293	411
2013	297	398
2014	316	439
2015	365	461
DHB		
Bay of Plenty	402	683
Lakes	223	306
Tairawhiti	85	140
Waikato	860	997
Total	1570	2126

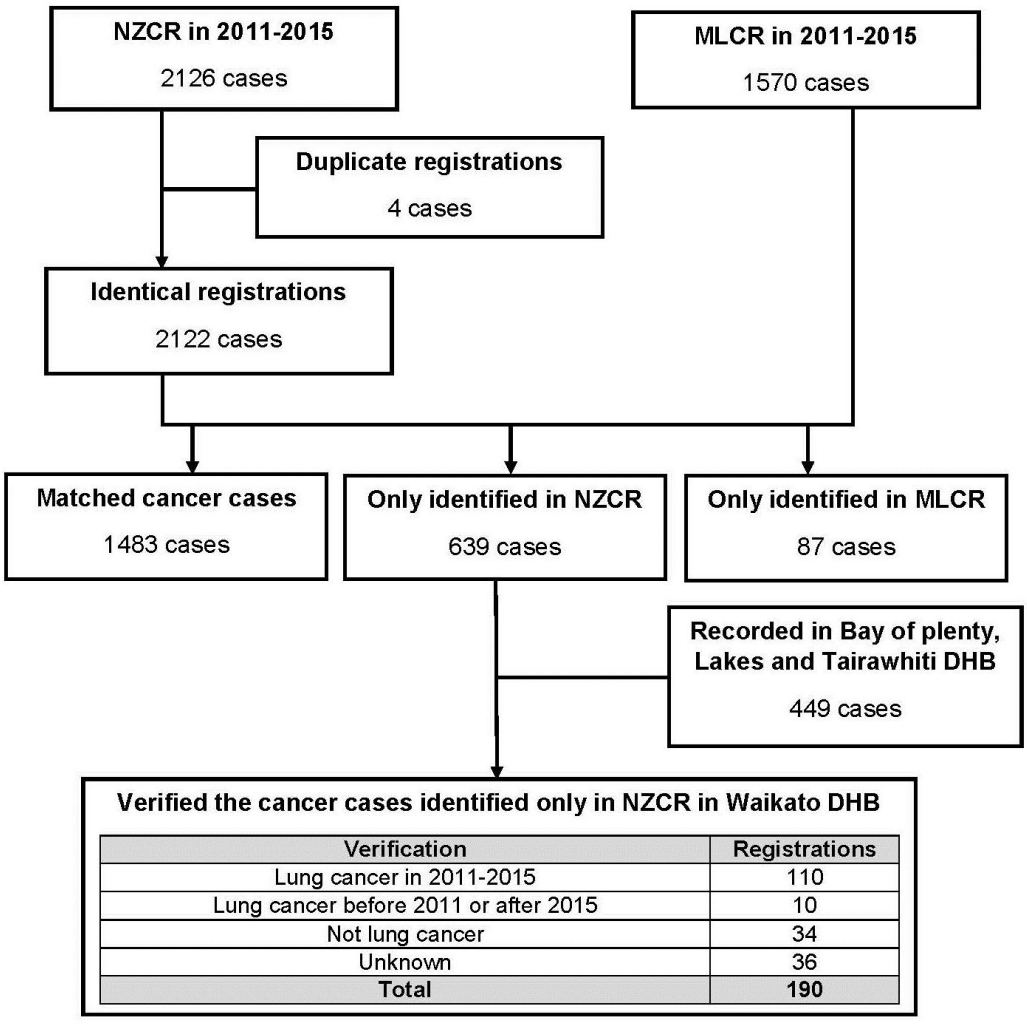

Figure 1. Comparison of lung cancer and mesothelioma registrations in NZCR and MLCR

Table 2. Accuracy of demographic data in NZCR

Demographics	Accuracy	Details

Gender — 99.0%

Gender in NZCR	Gender in MLCR		Total
	Female	Male	
Female	**705**	12	717
Male	3	**763**	766
Total	708	775	1483

Ethnicity — 96.0%

Ethnicity in NZCR	Ethnicity in MLCR						Total
	Māori	Pacific	Asian	European	Others	Unknown	
Māori	479	1		37	1		518
Pacific	2	15	1	2			20
Asian		1	25	1			27
European	6		1	904	1		912
Others				1	1		2
Unknown	1	1		1		1	4
Total	488	18	27	946	3	1	1483

DHB — 98.4%

DHB in NZCR	DHB in MLCR				Total
	Bay of Plenty	Lakes	Tairawhiti	Waikato	
Bay of Plenty	381	11		3	395
Lakes	1	203		3	207
Tairawhiti	1		76		77
Waikato	1	2	2	799	804
Total	384	216	78	805	1483

Date of birth — 99.7%

Differences of date of birth in both dataset	Total
0 day	1479
1 day	1
3 days	1
6 days	1
731 days	1
Total	1483

Table 3. Difference between date of diagnosis in NZCR and MLCR

Number of days: Difference between Date of diagnosis in NZCR and MLCR	Records	Percentage
0 days	322	21.7%
1-30 days	1015	68.4%
31-182 days	119	8.0%
183-364 days	19	1.3%
≥365 days	8	0.5%
Total	1483	

Table 4. Comparison of cancer extent in NZCR and cancer stage in MLCR

Accuracy in cancer stage/extent	Extent in NZCR	Stage in MLCR								
		IA	IB	IIA	IIB	IIIA	IIIB	IV	U	Total
51.3%	Localised to organ of origin	59	17	13	3	2		1	3	98
	Invasion of adjacent tissue or organ	6	8	5	3	6	2	12		42
	Regional lymph nodes	1	3	15	8	62	49	74		212
	Distant	6	3	2	3	25	44	530	2	615
	Unknown	39	26	25	17	119	75	209	6	516
	Total	111	57	60	34	214	170	826	11	1483

Table 5. Characteristics of lung cancer patients by ethnicity in the combined dataset

	Māori		Pacific		Others		Total	
	N	%	N	%	N	%	N	%
Year of diagnosis								
2011	129	18.9%	5	20.0%	285	19.8%	419	19.5%
2012	139	20.4%	3	12.0%	280	19.4%	422	19.6%
2013	129	18.9%	5	20.0%	267	18.5%	401	18.7%
2014	140	20.5%	5	20.0%	287	19.9%	432	20.1%
2015	145	21.3%	7	28.0%	323	22.4%	475	22.1%
Age (years)								
<50	34	5.0%	2	8.0%	44	3.1%	80	3.7%
50-59	160	23.5%	6	24.0%	142	9.8%	308	14.3%
60-69	246	36.1%	11	44.0%	374	25.9%	631	29.4%
70-79	184	27.0%	6	24.0%	498	34.5%	688	32.0%
80+	58	8.5%		0.0%	384	26.6%	442	20.6%
Gender								
Female	377	55.3%	7	28.0%	637	44.2%	1021	47.5%
Male	305	44.7%	18	72.0%	805	55.8%	1128	52.5%
DHB								
Bay of Plenty	198	29.0%	5	20.0%	474	32.9%	677	31.5%
Lakes	134	19.6%	1	4.0%	186	12.9%	321	14.9%
Tairawhiti	85	12.5%	0	0.0%	60	4.2%	145	6.7%
Waikato	265	38.9%	19	76.0%	722	50.1%	1006	46.8%
Cancer stage								
I	58	9.5%	1	4.2%	147	11.4%	206	10.7%
II	31	5.1%	0	-	70	5.4%	101	5.2%
III	151	24.8%	4	16.7%	245	18.9%	400	20.7%
II or III*	10	1.6%	1	4.2%	26	2.0%	37	1.9%
IV	360	59.0%	18	75.0%	807	62.3%	1185	61.4%
Unknown	72		1		147		220	
Cell type								
NSCLC	402	73.2%	19	79.2%	937	84.2%	1358	80.5%
NSCLC-other	8	1.5%	1	4.2%	19	1.7%	28	1.7%
Small cell	131	23.9%	3	12.5%	148	13.3%	282	16.7%
Malignant Carcinoid	0	-	0	-	5	0.4%	5	0.3%
Others	8	1.5%	1	4.2%	4	0.4%	13	0.8%
Unknown	133		1		329		463	
Total	682		25		1442		2149	

* Recorded regional extent in the NZCR, therefore cannot be confirmed stage II or III

Table 6. Surgical treatment by ethnicity in the MLCR

Surgery type	Māori		Pacific		Others		Total	
	N	%	N	%	N	%	N	%
Lobectomy	42	8.2%	1	5.3%	96	9.2%	139	8.9%
Pneumonectomy	0	-	0	-	9	0.9%	9	0.6%
Segmentectomy	0	-	0	-	1	0.1%	1	0.1%
Sternotomy	2	0.4%	0	-	1	0.1%	3	0.2%
Wedge resection	6	1.2%	0	-	21	2.0%	27	1.7%
No surgery	462	90.2%	18	94.7%	911	87.7%	1391	88.6%
Total	512		19		1039		1570	

Table 7. Surgical treatment by cancer stage in the MLCR

Surgery type	Stage I		Stage II		Stage III		Stage IV		Unknown	
	N	%	N	%	N	%	N	%	N	%
Lobectomy	79	40.3%	39	38.6%	17	4.3%	4	0.5%	0	-
Pneumonectomy	3	1.5%	2	2.0%	3	0.8%	1	0.1%	0	-
Segmentectomy	1	0.5%	0	-	0	-	0	-	0	-
Sternotomy	0	-	0	-	0	-	2	0.2%	1	9.1%
Wedge resection	21	10.7%	3	3.0%	2	0.5%	1	0.1%	0	-
No surgery	92	46.9%	57	56.4%	378	94.5%	854	99.1%	10	90.9%
Total	196		101		400		862		11	

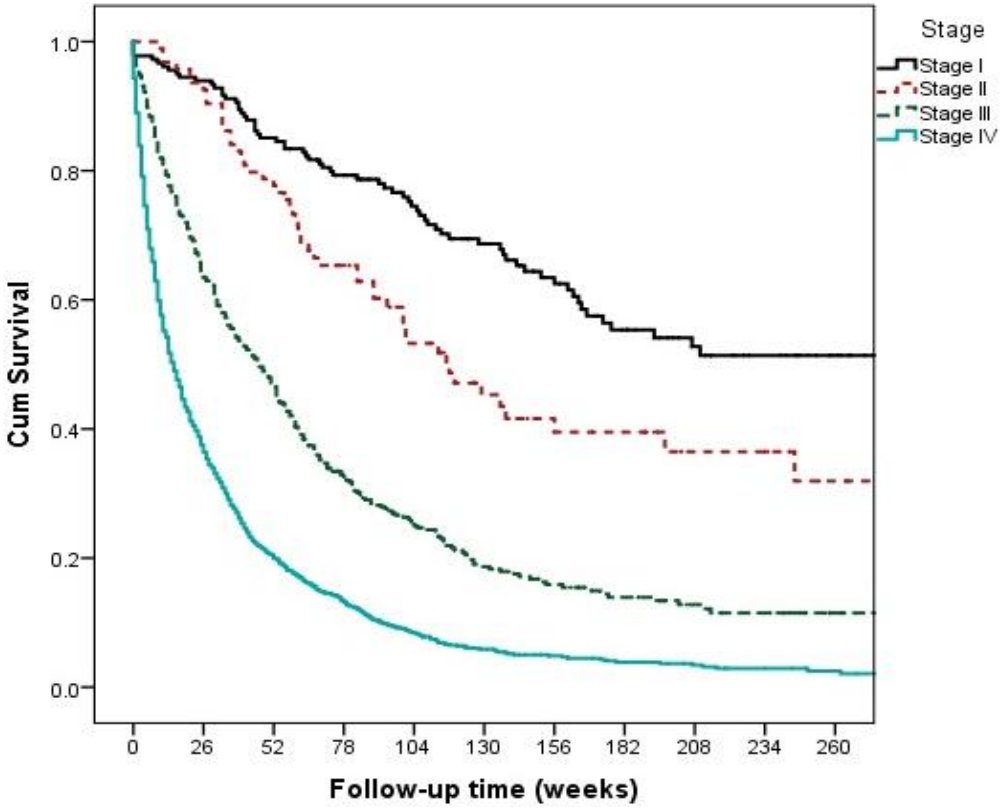

Figure 2. Kaplan-Meier curve for all-cause survival by ethnicity in the NZCR

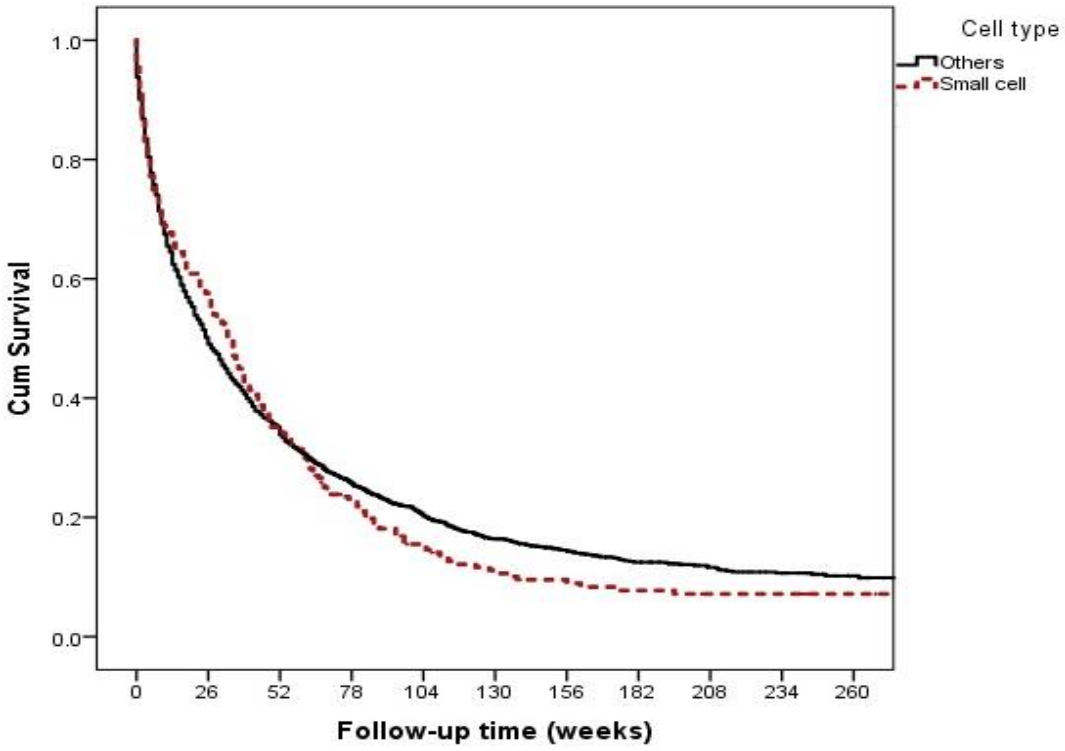

Figure 3. Kaplan-Meier curve for all-cause survival by cell type in the NZCR

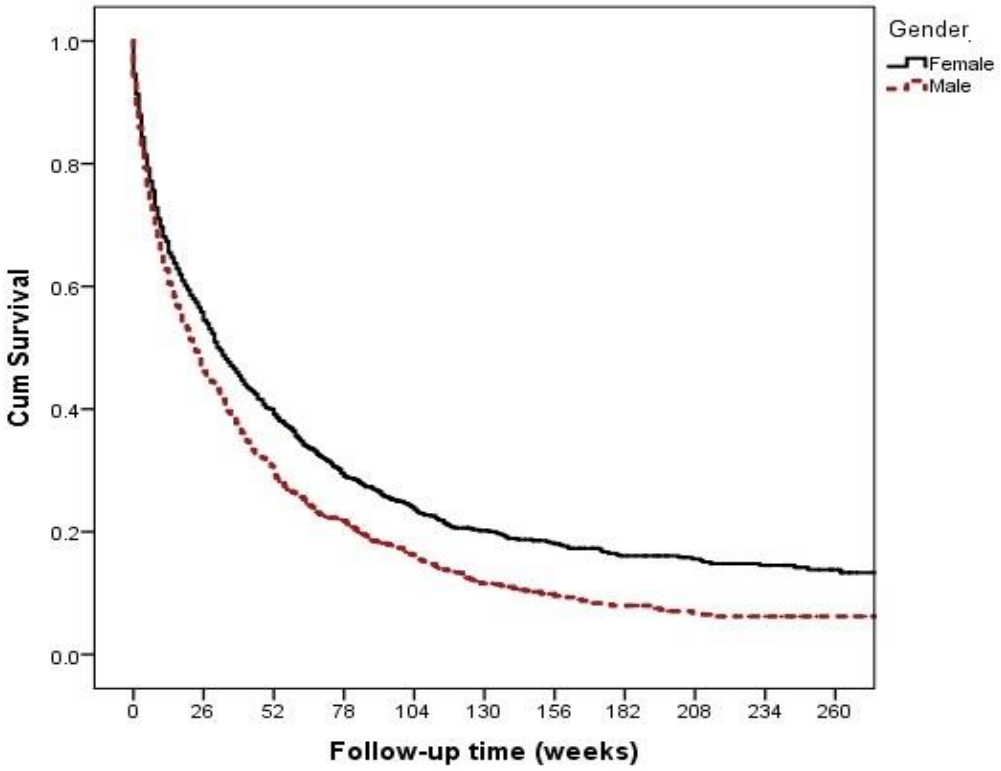

Figure 4. Kaplan-Meier curve for all-cause survival by gender in the NZCR

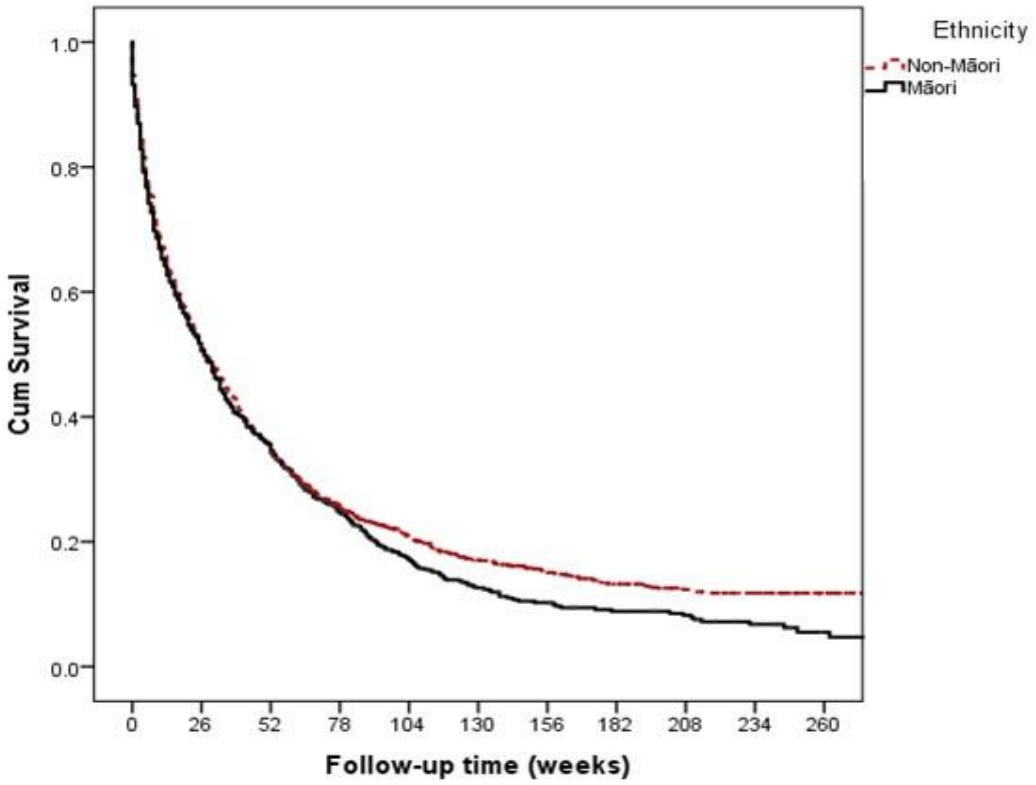

Figure 5. Kaplan-Meier curve for all-cause survival by ethnicity in the NZCR

Table 8. Adjusted hazard ratios of all-cause mortality

Factors	P-value	Hazard ratio (95% CI)
Stage	<0.001	
Stage II vs stage I	0.003	1.74 (1.21-2.50)
Stage III vs stage I	<0.001	4.01 (3.09-5.21)
Stage IV vs stage I	<0.001	7.97 (6.22-10.23)
Cell type: Small cell vs others	0.233	0.92 (0.80-1.06)
Gender: Male vs female	<0.001	1.20 (1.09-1.32)
Age (continuous variable)	<0.001	1.02 (1.02-1.03)
Ethnicity		
Māori vs others	<0.001	1.28 (1.15-1.42)
Pacific vs others	0.048	0.61 (0.38-1.00)
DHB	0.865	
Bay of Plenty vs Waikato	0.517	0.96 (0.86-1.08)
Lakes vs Waikato	0.898	1.01 (0.88-1.16)
Tairawhiti vs Waikato	0.772	1.03 (0.85-1.26)
Year of diagnosis	0.219	
2012 vs 2011	0.171	0.90 (0.78-1.05)
2013 vs 2011	0.792	0.98 (0.85-1.14)
2014 vs 2011	0.037	0.85 (0.74-0.99)
2015 vs 2011	0.541	0.95 (0.82-1.11)