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Title Page

Title

Impact of hospital geographic remoteness on overall survival after colorectal cancer resection using state-wide administrative data.

Short running head

OS post CRC resection in Victoria

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Abstract

Purpose

This study aimed to use administrative data (AD) linked to the Victorian Death database (VDI) to report on overall long-term survival following colorectal cancer (CRC) surgery, comparing regional to metropolitan hospitals.

Methodology

A retrospective cohort study using prospectively-gathered AD linked to VDI.

The primary outcome was overall survival (OS).

Outcomes were adjusted for potential confounders via multivariable Cox proportional hazard regression analysis.

Results

Total of 17533 patients: 12879 metropolitan patients, 3835 inner regional patients and 719 outer regional patients.

Multivariable Cox regression, adjusted for the effects of age, ASA score, Charlson score, position of tumour, mode of access, admission type, lymph node metastases, distant metastases, return to theatre, Length of stay, HDU admission and discharge destination showed no difference in OS comparing CRC resection patients from inner or outer regional hospitals to metropolitan ((HR 1.02, 95%CI 0.95 – 1.09, p=0.59) and (HR 0.97, 95%CI 0.85 – 1.11, p=0.68) respectively).

Conclusion

This is the largest and most detailed study concerning OS after CRC resection involving Victorian public hospitals.

There was no difference in overall survival following CRC resection when inner or outer regional hospitals were compared to metropolitan hospitals in Victoria.

The study demonstrated the utility of AD with validated algorithms, linked to death data for reporting CRC survival outcomes.

Keywords: Colorectal neoplasm, overall survival, administrative data, data linkage

Introduction

Background

This study reports overall survival (OS) after colorectal (CRC) resection in the state of Victoria over a ten-year period. In a previous study we used validated algorithms of administrative data (AD) to report on short-term outcomes following resection for CRC in Victoria. It showed that outcomes from regional hospitals were similar to, and in some cases better, than metropolitan hospitals.

AD, used alone, can only report on short-term outcomes because it only collects inpatient data and thus not long-term out-of-hospital survival outcomes¹. To report on OS required linkage to a dataset that contains out-of-hospital mortality data.

Data linkage is a process whereby datasets are combined using personal identifiers present in both datasets, such as date of birth and Medicare number. In this way, variables relating to an individual can be collected across datasets and combined. For this study, linkage of Victorian Admitted Episodes Dataset (VAED) and the Victorian Death Index (VDI) was performed by the Centre for Victorian Data Linkage (CVDL). The VAED is a central repository of all AD in Victoria has access to all recorded inpatient AD for the state. The VDI contains death data collected from death certificates of people who have died in Victoria. Combining these two datasets allowed us to report on OS whilst adjusting for potentially confounding variables accessible through VAED.

We compared regional to metropolitan hospitals in this study to address whether centralisation of CRC operations might result in better long-term survival outcomes, as postulated by other studies,²⁻⁴ but not yet demonstrated for the state of Victoria.

Objectives

The aim of this study was to use validated coding algorithms applied to the VAED linked to the VDI to report on hazard of long-term mortality following major resection for CRC, comparing regional to metropolitan hospitals.

A further important objective was to examine the potential of data linkage to enable long-term survival analysis based on AD.

Method

Study Design

This is a retrospective cohort study using prospectively gathered AD stored in the VAED and prospectively gathered mortality data from VDI.

This study was performed and reported in accordance with the STROBE statement on reporting observational studies in epidemiology⁵.

Ethics approval for this study was granted by the Human Research and Ethics Committee (HREC), National Health and Medical Research Council of Australia (HREC reference number HREC/52415/MH-2019).

Participants

The algorithms created in a previous study were applied to the VAED to facilitate case finding and improve accuracy⁶. These algorithms were based on comparing clinical notes with AD and using this information to construct combinations of administrative codes to improve the clinical relevance of AD. These algorithms stratified CRC based on anatomical location into right, left and rectum. Right

colon was defined as extending to and including the splenic flexure, left colon comprised the descending colon and sigmoid colon and rectum included recto-sigmoid and rectum. The algorithms combined the code for 'tumour location' with the code for 'type of operation' to eradicate illogical combinations thereby increasing accuracy¹. (An example of an illogical combination is a tumour location code in the ascending colon but with an operative code of a high anterior resection). When compared to clinical notes, the accuracy of validated algorithms of AD was 93%, 89% and 88% for right, left and rectum respectively. To create our study population, these algorithms were applied to the VAED to gather all patients undergoing resection for CRC in Victoria from 2008 to 2018. Data from VAED is de-identified for patient and hospital name. However, data can be requested by categories such as hospital location, case-volume etc.

Patients less than 10 years old were excluded from the analysis. Patients with metachronous cancers were also excluded from the analysis as it would be difficult to determine which operation affected patient survival.

Exposure and Control

The principal exposure of interest was geographic location of hospital. Patients having major resection for CRC (adenocarcinoma) in regional public hospitals were compared with similar patients from metropolitan public hospitals (control) in the state of Victoria, Australia.

To define the geographical location of hospitals, the Accessibility/Remoteness Index of Australia (ARIA+) was used. ARIA+ is a nationally recognised index for defining geographical remoteness based on accessibility to services. It divides Australia into five categories (S1)¹. All Victorian hospitals reside in major cities, inner regional and outer regional zones. To give examples: Melbourne and Geelong

are defined as metropolitan, Ballarat is Inner regional and Horsham is outer regional (see map, supplement).

The control group was metropolitan hospitals and was compared separately to inner regional and outer regional hospitals.

Potential Confounders

Details on patient demographics, comorbidities ((Charlson Comorbidity Index score⁷ (CCI) and American Society of Anaesthesiologists (ASA) score)), mode of surgery (open or laparoscopic approach) and pathological details of the tumour were recorded. Although AD does not record the TNM stage of the tumour, it does report on the presence of lymph node metastases (92% accuracy) and distant metastases (88% accuracy)⁶.

Hospitals data was recorded on case volume (high volume ≥ 50 cases per year, low volume < 50 cases per year) and Colorectal Surgical Society of Australia and New Zealand (CSSANZ) status. CSSANZ hospitals are those with the volume and expertise to achieve accreditation for teaching specialty colorectal surgery to post-fellowship surgeons. Victorian CSSANZ hospitals are Alfred Hospital, Austin Hospital, Box Hill Hospital, Dandenong Hospital, Royal Melbourne Hospital, St Vincent's Hospital and Western Hospital (all metropolitan). Although Peter MacCallum Cancer Centre is not a CSSANZ hospital, it was included in this group because of its case load, surgeon experience and research.

ASA was defined categorically: low for ASA 1-2, high for ASA 3-5. A further category was assigned 'grade not recorded' if an anaesthetic code had been used without an ASA grade. This was done to avoid data restriction in the final multivariable analysis.

CCI score was also categorical as 0, 1 or 2. This is because any CCI score greater than or equal to 2 confers a high chance of mortality. The diagnostic categories used to calculate CCI were those validated for use in ICD-10-AM⁷. This categorisation has been used in other studies in this area⁷⁻¹⁰.

Surgical mode of access was defined as laparoscopic or open. An operation was defined as laparoscopic if it had a unique code for a laparoscopic colorectal surgical operation or had an open code combined with the code of 'diagnostic laparoscopy' or 'laparoscopic division of adhesions.' Codes for unique laparoscopic colorectal operations only came into effect after 2013. The overall accuracy of coding for laparoscopic operations is 76% in our institution.

Length of stay (LOS) was defined as the discharge date minus the admission date. Prolonged LOS was defined as >14 days and expected ≤14 days.

RTT was defined as an unplanned operation following the initial CRC resection. The algorithm used to extract this information was described in a previous study⁶.

Discharge destination was defined in a binary fashion as home or other.

The composite variable HDU+ was a composite variable signifying patients that required more than simple ward care. It represents all patients requiring any period of postoperative mechanical ventilation and/or a monitored bed including ICU, CCU or HDU.

HDU+ was also dichotomised as requiring these measures or not.

It should be noted that AD does not report on outpatient treatments such as chemotherapy or radiotherapy and does not record outpatient follow up.

Outcome

The outcome of interest was overall survival which in this study equates with hazard of death. There are two methods to link AD with mortality data: deterministic and probabilistic¹¹. Deterministic linkage is when patient identifiers (such as name) match exactly across cohorts. This ensures 100% specificity in the matched dataset. Probabilistic linkage is not as exact and allows matching of patient identifiers with different spellings or combinations of words. This results in a greater number of matched data but with decreased specificity. The linkage for this study used deterministic data linkage using the Victorian Linkage Map V1812.

Overall survival was determined from this matched data. A patient was censored either on the date of death as per the VDI data or the date of last inpatient follow-up. Those without a date of death according to the VDI records were assumed to have survived. Their date of last clinical follow-up was defined as the discharge date of their last in-patient admission.

Statistical analysis

Data was analysed using Stata version 15.0 (College Station, Texas, USA) statistical software.

Baseline data were presented as absolute numbers with percentages.

A univariable Cox regression analysis assessing hazard of death was performed for each baseline variable. Multivariable Cox regression analysis was then performed retaining geographical location as the principal exposure of interest. Co-variables from the univariable analysis which were associated with a greater than 10% change in hazard ratio were included in the multivariable Cox regression analysis. The co-variables, CSSANZ-status and Case-volume were not included in the multivariable analysis because CSSANZ hospitals were all metropolitan and there were no high-

volume hospitals in the outer regional zone. Separate analysis was performed comparing each of the two regional zones to control.

The proportional hazard assumption was tested using Schoenfeld residuals complemented by visual assessment of cumulative hazard graphs.

Sample size was not calculated for this study as the database was a fixed available sample.

A priori, it was determined that rectal cancer, high ASA score and modality of surgery (laparoscopic versus open) were potential effect modifiers. That is, the effect of a rectal cancer, high ASA score or mode of surgery might be different in a regional compared with a metropolitan setting. Testing for effect modification was performed on the primary outcome by using likelihood ratio testing to compare the original regression model with a further regression model including the variable of concern as an indicator variable. Where evidence of effect modification was found, that co-variable was included as an indicator variable in the final multivariable model.

If patients had missing data, they were identified and excluded from the analysis.

Results

Data extracted from the VAED included 75,460 patients totalling 1,623,753 admissions. Of the 75,460 patients, 60,819 had major colorectal resections (not necessarily for cancer). After applying the algorithms described above to improve the accuracy of the database, 33,275 patients were found who had major colorectal resections for CRC stratified by tumour position. Patients aged less than 10 years were also excluded (five patients) as were patients operated on in private hospitals leaving 18479. Nine duplicates were excluded leaving 18470 patients for analysis. Patients who had illogical death dates (i.e. death before admission) were also excluded (169). After exclusion of

metachronous tumours (768) there were 17533 patients: 12879 from metropolitan hospitals, 3835 from inner regional hospitals and 719 from outer regional hospitals (S2). Data from all admissions involving these patients were used for follow-up. This dataset had very little missing data; only 1% of ASA score and 2% of discharge destination had missing data. The distribution of missing data was similar across cohorts.

Baseline characteristics were similar across cohorts (Table 1). Median follow-up time was 2.64 years (interquartile range (IQR) 1.02 – 5.42 years)) and follow-up time was similar across cohorts: metropolitan hospitals median 2.65 years (IQR 1.03 – 5.45 years), inner regional hospitals median 2.60 years (IQR 0.98 – 5.31 years), outer regional hospitals median 2.64 years (IQR 1.04 – 5.34 years). During the follow-up period, 32% of metropolitan patients, 35% of inner regional patients and 34% of outer regional patents died (Figure 1).

Univariable Cox regression analysis showed an 11% decreased long-term hazard of death from all causes for patients who had their CRC resection in inner regional hospitals compared to metropolitan hospitals (HR 1.11, 95%CI 1.05 – 1.18, $p=0.001$). There was no difference in survival between patients from outer regional hospitals compared with those from metropolitan hospitals (HR 1.09, 95%CI 0.96 – 1.24, $p=0.20$). Multivariable Cox regression, adjusted for the effects of age, ASA score, CCI score, position of tumour, mode of access, admission type, lymph node metastases, distant metastases, return to theatre, LOS, HDU+ and discharge destination showed no difference in overall survival comparing CRC resection patients from inner or outer regional hospitals to metropolitan ((HR 1.02, 95%CI 0.95 – 1.09, $p=0.59$) and (HR 0.97, 95%CI 0.85 – 1.11, $p=0.68$) respectively) (Table 2).

CSSANZ status and hospital volume were not included in the multivariable Cox analysis as these variables were not represented in all geographical zones. Their effects were analysed from their respective univariable Cox analyses. CSSANZ hospital-status decreased the hazard of death by 14% (HR 0.86, 95%CI 0.81 – 0.90, $p < 0.001$). High volume hospitals were also associated with improved overall survival by a lesser degree (HR 0.93, 95%CI 0.87 – 0.98, $p = 0.01$).

No evidence of effect modification was found. This suggests that the subgroups of patients having high ASA score, rectal surgery or laparoscopic surgery in regional centres did not have different overall survival compared with metropolitan centres.

There was no evidence of violation of the proportional hazards assumption.

Discussion

Having adjusted for a large number of potentially confounding variables, we found no difference in OS between regional hospitals and metropolitan hospitals after major resection for CRC. This study has also highlighted the potential utility of data linkage by creating one of the largest Australian studies to report on OS after CRC resection.

Because it is not randomised, the methodology of this study does not account for the inherent biases in current practice such as patterns of referral to metropolitan hospitals, case selection by regional surgeons and which patients choose to have surgery at their regional hospital. However, these results support the current practices in surgical treatment of CRC across the state of Victoria. Whilst there are many potential sources of variance which could contribute to differing outcomes for CRC resection between regional and metropolitan centres, this study, using detailed information from validated algorithms of AD, has allowed us to adjust for the confounding effects of many co-

variables. One might hypothesise that patients in the country are not as comorbid or that surgeons do fewer rectal resections. However, the method has adjusted for such variables to ensure our final result takes those differences into account.

Although CSSANZ and high-volume hospitals were associated with improved OS, this analysis was unadjusted. In support of the overall findings of the study is the observation that those variables which would be expected to have an association with poorer prognosis such as age, comorbidity, right sided cancers, open surgery, emergency surgery, return to theatre, prolonged LOS, ICU admission, discharge destination other than home, lymph node and distant metastases, did have reduced OS.

A limitation of AD is its accuracy. Clinical databases with prospectively-gathered, detailed clinical data are the most accurate of the surgical databases. The largest CRC database in Australia in the Bi-National Colorectal Cancer Audit (BCCA). However, The BCCA only captures 15-20% of CRC resections and most data are from metropolitan teaching hospitals¹². BIOGRID, the other large clinical database with colorectal patients, only has three public sites in Victoria that contribute to its database¹³. We have used validated algorithms of AD codes to achieve accuracies approaching that of a clinical database but with the benefit of much broader population coverage than clinical databases.

Several Australian studies have previously used AD to report on CRC outcomes in Australia^{10,14-24} however these studies have used unmodified AD with untested accuracies. Of those that did report on OS, their findings were in keeping with this study^{16,25}. This has also been substantiated internationally in a Canadian study²⁶ and the USA^{27,28}.

This study did not report on disease free survival and cancer-specific survival. Although potentially achievable, when CRC was listed in death certificate data as a significant contributing factor to death, it was difficult to determine if the cancer was pre-existing or recurrent. We decided that overall survival was a more reliable measurement.

This study has not recorded deaths that occurred outside Victoria. However, 5 year survival in this study was around 60%, which is similar to other states in Australia^{15-17,29,30} and first world countries.³¹, suggesting that this study does not have large numbers of missing death data. In terms of follow-up data for those who survived, we only had objective follow-up data based on re-admissions to a Victorian Hospitals as outpatient data (such as clinic or private room consultations) does not form part of AD. A future direction for improved indirect follow-up data would include linkages to other datasets such as electoral roles and Medicare billing. However, such linkages were outside the scope of the current project.

Conclusion

After adjustment for confounding variables, this study showed that inner and outer regional hospitals have similar OS after resection for CRC compared with metropolitan hospitals in the state of Victoria.

Also highlighted is the potential of data linkage, in particular using validated AD and linking this to a death index to report on survival outcomes. This methodology facilitates reporting on survival after resection for CRC at a population level.

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Figure Legends

Figure 1: Kaplan-Meier Graph: Overall Survival

Supplementary Figure legend

S1: ARIA+ remoteness classification.

S2: Study population selection flow diagram

S3: Algorithms to improve cohort accuracy

		Metropolitan n=12879 (73%)	Inner Regional n=3935 (23%)	Outer Regional n=719 (4%)
Age, deciles (years) (%total)	10-19	11 (0.1%)	1 (0.0%)	0 (0.0%)
	20s	96 (0.8%)	9 (0.2%)	1 (0.1%)
	30s	326 (2.5%)	46 (1.2%)	8 (1.1%)
	40s	864 (6.7%)	181 (4.6%)	23 (3.2%)
	50s	2020 (15.7%)	517 (13.1%)	88 (12.2%)
	60s	3257 (25.3%)	918 (23.3%)	171 (23.8%)
	70s	3940 (30.6%)	1339 (34.0%)	248 (34.5%)
	80s	2355 (18.3%)	924 (23.5%)	180 (25.0%)
	90+	10 (0.1%)	0 (0.0%)	0 (0.0%)
Sex M:F (Male%)		7220:5659 (56.1%)	2121:1814 (53.9%)	383:336 (53.3%)
ASA score	Grade not recorded	2260 (17.6%)	604 (15.4%)	165 (23.0%)
	1	679 (5.3%)	214 (5.4%)	43 (6.0%)
	2	4507 (35.0%)	1318 (33.5%)	232 (32.3%)
	3	4441 (34.5%)	1381 (35.1%)	243 (33.8%)
	4	833 (6.5%)	338 (8.6%)	29 (4.0%)
	5	32 (0.3%)	21 (0.5%)	2 (0.3%)
	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	127 (1.0%)	59 (1.5%)	5 (0.7%)
CCI score	0	11791 (91.6%)	3585 (91.1%)	662 (92.1%)
	1	985 (7.7%)	317 (8.1%)	53 (7.4%)
	2	59 (0.5%)	23 (0.6%)	3 (0.4%)
	3	18 (0.1%)	8 (0.2%)	1 (0.1%)
	4	18 (0.1%)	1 (0.0%)	0 (0.0%)
	5	1 (0.0%)	1 (0.0%)	0 (0.0%)
	6	7 (0.1%)	0 (0.0%)	0 (0.0%)
Year *	2007	720	257	45
	2008	1,012	362	67
	2009	1,071	321	62
	2010	1,088	339	51
	2011	1,086	335	63
	2012	1,041	335	68
	2013	1,070	333	55
	2014	1,054	329	67
	2015	1,128	329	57
	2016	1,063	306	54
	2017	1,162	309	65

	2018	1,188	332	54
	2019	196	48	11
Admission type	Elective	10834 (84.1%)	3265 (83.0%)	559 (77.8%)
	Emergency	2045 (15.9%)	670 (17.0%)	160 (22.3%)
Side of operation	Right	5494 (42.7%)	1986 (50.5%)	386 (53.7%)
	Left	3045 (23.6%)	843 (21.4%)	171 (23.8%)
	Rectum	4340 (33.7%)	1106 (28.1%)	162 (22.5%)
Mode of access	Laparoscopic	5578 (43.3%)	997 (25.3%)	64 (8.9%)
	Open	7301 (56.7%)	2938 (74.7%)	655 (91.1%)
Lymph nodes Metastases	Present	9048 (70.3%)	2687 (68.3%)	526 (73.2%)
	Absent	3831 (29.8%)	1248 (31.7%)	193 (26.8%)
Distant metastases	Present	1726 (13.4%)	445 (11.3%)	89 (12.4%)
	Absent	11153 (86.6%)	3490 (88.7%)	630 (87.6%)
Return to theatre	No	12180 (94.6%)	3703 (94.1%)	685 (95.3%)
	Yes	699 (5.4%)	232 (5.9%)	34 (4.7%)
HDU+ required	No	8959 (69.6%)	1997 (50.8%)	373 (51.9%)
	Yes	3920 (30.4%)	1938 (49.3%)	346 (48.1%)
Length of stay	Expected	10012 (77.7%)	3235 (82.2%)	556 (77.3%)
	Prolonged	2867 (22.3%)	700 (17.8%)	163 (22.7%)
Discharge destination	Home	11003 (86.8%)	3143 (81.3%)	566 (79.9%)
	Other	1667 (13.2%)	723 (18.7%)	142 (20.1%)

Table 1: Baseline characteristics

*2017 & 2019 are included in this table as patients have fallen within this timeframe due to patient dates being moved forward and backwards by fixed amounts by VAED to protect confidentiality.

		Univariable						Multivariable				
		No. total	no. of deaths	HR	95% CI		p-value	n=	HR	95% CI		p-value
ARIA	Inner v Metro	3935 v 12879	1361 v 4072	1.11	1.05	1.18	0.001	17055	1.02	0.95	1.09	0.59
	Outer v Metro	719 v 12879	245 v 4072	1.09	0.96	1.24	0.199	17055	0.97	0.85	1.11	0.676
CSSANZ Hospital	Yes v No	9046 v 8487	2689 v 2989	0.86	0.81	0.90	<0.001					
Case Volume	≥40 cases/year vs <40 cases/year	13514 v 4019	4251 v 1427	0.93	0.87	0.98	0.012					
Age	>70 v <70	8996 v 8537	3674 v 2004	2.03	1.92	2.14	<0.001	17055	1.72	1.62	1.82	<0.001
Sex	Male v Female	9724 v 7809	3240 v 2438	1.05	1.00	1.11	0.05					
Year	2007-2013 v 2014 - 2019	9781 v 7752	4348 v 1330	0.93	0.87	0.99	0.031					
ASA score	High vs Low	7320 V 6993	2930 v 1579	2.23	2.09	2.37	<0.001	17055	1.55	1.45	1.65	<0.001
	NR vs Low	3029 v 6993	1103 v 1579	1.64	1.52	1.78	<0.001	17055	1.39	1.29	1.51	<0.001
CCI score	1 vs 0	1355 v 16038	360 v 5249	1.12	1.01	1.25	0.032	17055	1.07	0.96	1.20	0.215
	≥2 vs 0	140 v 16038	69 v 5249	2.03	1.60	2.57	<0.001	17055	1.03	0.78	1.37	0.828
Position	Left vs Right	4059 v 7866	1291 v 2769	0.81	0.76	0.87	<0.001	17055	0.86	0.80	0.92	<0.001
	Rectum vs Right	5608 v 7866	1618 v 2769	0.70	0.66	0.75	<0.001	17055	0.90	0.84	0.96	0.001
Mode of access	Laparoscopic v Open	6639 v 10894	1450 v 4228	0.61	0.58	0.65	<0.001	17055	0.87	0.82	0.93	<0.001
Admission type	Emergency/Elective	2875 v 14658	1496 v 4182	2.38	2.25	2.53	<0.001	17055	1.45	1.35	1.55	<0.001
Lymph nodes	Positive v Negative	5272 v 12261	2339 v 3339	1.93	1.83	2.03	<0.001	17055	1.75	1.65	1.85	<0.001
Distant metastases	Positive Negative	2260 v 15273	1458 v 4220	4.17	3.92	4.43	<0.001	17055	3.97	3.71	4.23	<0.001
Return to theatre	Yes v No	965 v 16568	411 v 5267	1.53	1.38	1.69	<0.001	17055	0.85	0.75	0.95	0.006
HDU+ required	Yes v No	6204 v 11329	2665 v 3013	1.80	1.71	1.90	<0.001	17055	1.18	1.12	1.26	<0.001
Length of stay	Prolonged v Expected	3730 v 13803	1755 v 3923	1.90	1.79	2.01	<0.001	17055	1.20	1.13	1.29	<0.001
Discharged destination	Other v Home	2532 v 14712	1392 v 4021	2.70	2.54	2.87	<0.001	17055	1.80	1.68	1.92	<0.001

Table 2: Univariable and multivariable Cox regression analysis – overall survival

HR = Hazard ratio

Kaplan-Meier survival estimates

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