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TITLE PAGE

Do Indigenous patients in Australia's Northern Territory present with more advanced colorectal cancer? A cohort study based on registry data

Running Head: Colorectal Cancer in Indigenous Austrians

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Manuscript not submitted or published elsewhere

Figures = 1

Tables = 3

Abstract word count = 245

Text word count = 2168

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/ans.15376](https://doi.org/10.1111/ans.15376)

ABSTRACT

Background: Previous studies show that Indigenous Australians (IndA) of the Northern Territory (NT) present later and have lower survival for colorectal cancer (CRC) compared with Non Indigenous (NI) Territorians. This study compared the odds of presenting with advanced-stage CRC between IndA and NI adjusted for demographic, histopathological and surgical features.

Methods: A cohort study of NT Cancer Registry (NTCR) CRC cases from 2005-2014. All persons (667) notified to the Northern Territory Cancer Registry with a new diagnosis of colorectal cancer were included, of which 504 had sufficient data for analysis. The NTCR was used for case identification and linked to available hospital clinical data. The principal exposure was IndA compared with NI and the principal outcome was odds of presenting with advanced-stage tumour (III, IV) compared with early-stage (I, II). Univariable and multivariable logistic regression were performed on all relevant variables.

Results. Univariable logistic regression found no difference in the odds of advanced CRC between IndA and NI (OR =0.99; 95% CI: 0.56 – 1.76; P = 0.982). This effect remained insignificant adjusted for the effects of sex, tumour position, remoteness and time period (OR = 0.85, 95% CI: 0.47 – 1.55; P = 0.606) and when adjusted for tumour grade, lympho-vascular invasion, lymph node harvest and emergency status (OR =1.39; 95% CI: 0.64 – 3.03, P = 0.401).

Conclusions: In distinction from previous studies, there was no evidence that IndA of the NT presented with later stage CRC in 2005-14. Other factors (incomplete treatment or comorbidity) may be responsible for the continued observed survival disparity.

Introduction

Indigenous Australians (IndA) face multiple geographical, cultural and linguistic barriers to accessing health care and have a life expectancy approximately ten years lower than Non-Indigenous Australians (NI)¹. Although the incidence of many cancers is lower in Indigenous persons, mortality is higher, with reduced screening, more comorbidity, a predilection for poorer prognosis cancers and less access to and completion of treatment thought to contribute². In the Northern Territory (NT), colorectal cancer (CRC) incidence is lower for Indigenous persons (IndA 18.9 vs NI 59.6 /10⁵) but five year survival is inferior (IndA 41.9%, NI 60.3%)³. There is evidence for a later stage at presentation and less completion of treatment for IndA treated in the in the NT in the 1990's but nothing more contemporaneous⁴.

This study examined demographic, tumour and surgical factors which may contribute to this survival disparity. The specific aim of this study was to compare the odds of presenting with advanced-stage CRC between IndA and NI patients, using data from the Northern Territory Cancer Registry (NTCR), over a 10-year period.

Methods

Study design: A cohort study using retrospective analysis of prospectively collected registry data of patients with colorectal adenocarcinoma.

Setting: The NT of Australia differs from the rest of the nation, in that it has a relatively small population (250,000) over a vast geographical area of 1.4 million km². Approximately 25% of the NT population is Indigenous (compared with 3% of Australia), who are more likely to live remotely⁵. Hospital care is centralized, with two tertiary referral hospitals: The Royal Darwin Hospital (RDH) and Alice Springs Hospital (ASH). Most oncology services are delivered as a public/private collaboration. There is a single private hospital (Darwin Private (DPH)) which is co-located with RDH and shares oncology services. Complex elective colorectal surgical problems, such as low rectal cancer, are usually referred interstate.

Participants: All persons reported to NTCR with CRC identified by ICD10a (International Classification of Disease) administrative data codes: C18, C19 and C20, from the years 2005-2014. The NTCR collects data on all persons diagnosed with cancer in the NT. Exclusion criterion for this study were: colorectal tumours other than adenocarcinoma, carcinoma in a polyp and recurrent CRC. For synchronous tumours, the lower stage tumour was excluded.

Variables and Data sources: Demographic variables included age at diagnosis, sex and Indigenous status. Remoteness was measured by the Australian Statistical Geography Standard (ASGS) Remoteness Structure⁶. Indigenous status was defined by patient self-nomination and included both Australian Aboriginal persons and Torres Strait Islanders.

Tumour variables included histological grade, anatomical site of tumour, TNM stage as per American Joint Committee on Cancer (AJCC) 8th edition⁷ (ref) and lympho-vascular invasion (LVI). Tumour site was grouped as right (including caecum to splenic flexure), left (descending colon to recto-sigmoid) and rectum.

Surgical variables included emergency status based on evidence of perforation or obstruction. Surrogate measures of quality of surgical care included lymph node harvest and circumferential resection margin (CRM). The median lymph node (LN) harvest was calculated as per the method described in the Bi-National Colorectal Cancer Audit (BCCA) report, capped at 30⁸. A positive rectal CRM was defined as a margin less than 1mm.

An assessment of the treatment intent was made (by a single observer) as curative, palliative or patient-refused treatment from a combination of pathology reports, multidisciplinary meeting reports and patient medical letters.

The NTCR provided all demographic information, tumour grade, site and NT Health hospital record number (HRN). With the latter, synoptic pathology reports and electronic medical records (patient letters, multidisciplinary meeting outcomes) were accessed where possible, facilitated by the fact that all persons have a single HRN that covers all public hospitals in the NT.

Records for patients operated upon in other hospitals (DPH or interstate) were often available via the NT health medical oncology and radiotherapy service, which is run as a public/private collaboration.

Ethics: Ethics approval was obtained from Menzies School of Health Research Human Research Ethics Committee, reference 2017-2976.

Statistical analysis: Statistical analysis was performed with Stata 15.0 (College Station, Texas, USA). Categorical variables were presented as counts and percentage. Continuous variables were presented as median and inter-quartile range (IQR). The principal exposure of interest was IndA compared with NI and the principal outcome of interest was odds of presenting with advanced tumour stage (III and IV) compared with early tumour stage (I and II). Several categorical variables were grouped as dichotomous variables for simplicity of

presentation and biological plausibility. Univariable logistic regression was performed on most baseline variables except treatment-intent; staging was only represented by AJCC stage. Multivariable logistic regression was performed with Indigenous status remaining the principal exposure of interest and adjusting for those variables from the univariable analysis which had a greater or less than 10% change in odds ratio from the null value. Because of missing data concerning aspects of histopathology and emergency status, the logistic regression has been presented in 2 forms. To maximize data-use, a first analysis utilized the largest cohort but with fewer variables. A second complete-case analysis has also been presented utilizing all variables but with a smaller cohort. Effect modification due to remoteness was examined by using likelihood ratio testing to compare logistic regression models with and without an indicator variable for remoteness.

Results: A total of 753 persons were identified from NTCR as potentially eligible. Figure 1 describes the case flow. Sixty-six were excluded as they were non-adenocarcinoma (e.g. lymphoma, carcinoid), carcinoma in a polyp, recurrences or second primaries. This resulted in 677 subjects with information concerning demographics, remoteness, tumour grade and site of primary. Of these, 10 had no medical record in the NT, and 146 had records, but insufficient to assign staging, treatment intent or other pathological variables. Adequate data for staging was available for 504 patients.

Baseline data were listed in Table 1. Of the 677 participants, 67 identified as Indigenous. Most baseline variables were similar between the 2 groups but a higher percentage of IndA lived remotely. There was a differing distribution of cancers; IndA had more rectal cancers and fewer right-sided cancers compared with NI. Regarding the surrogate indices of surgical quality, lymph node harvest was similar between groups. A higher percentage of positive rectal CRM was found with IndA but case numbers were very small.

Univariable logistic regression found no difference in the odds of presenting with advanced CRC between IndA and NI (OR =0.99, 95% CI: 0.56 – 1.76, P-value = 0.982). In the larger cohort analysis, adjusted for the effects of sex, tumour position, remoteness and time period, there remained no evidence of an association between indigenous status and advanced tumour (OR = 0.85, 95% CI: 0.47 – 1.55, P-value = 0.606) (Table 2). In the smaller, complete-case analysis, adjusted for the previous variables but also for tumour grade, LVI, lymph node harvest and emergency status, the odds of advanced tumour associated with IndA were increased nearly 40% but with a wide confidence interval and high P-value, there was no evidence that this result was not due to random chance (OR =1.39, 95% CI: 0.64 – 3.03, P-value = 0.401) (Table 3). Testing was performed looking for varying effects in the differing zones of remoteness and no evidence of effect modification was found.

Discussion

In the NT, Indigenous persons have a lower incidence of and survival from CRC, although both have increased over the last two decades³. The improved survival has been interpreted as an improvement of health care service delivery, and the increased incidence a result of IndA in the NT changing from a traditional existence to a more westernised diet and lifestyle⁹. We hypothesized that IndA presented with more advanced-stage CRC than NI but this study has found no evidence of this. Univariable logistic regression shows almost identical odds of advanced stage at presentation for both groups. Adjusted for the effects of demographic factors and remoteness in the larger cohort, the odds were still similar. In the smaller cohort, complete-case analysis, however, where there was additional adjustment for features of tumour histology and emergency status, there was a slightly larger but still insignificant effect of Indigeneity. These findings are in contrast to earlier NT studies from the 1990's⁴, but are similar to a more contemporaneous study from North Queensland¹⁰. Whether this represents

an improvement of health care service delivery, an evolving different epidemiology or both is speculative.

Case identification was from NTCR database, which has legislation directing the notification of all new cancers (excluding SCC and BCC's) diagnosed in the NT by pathology providers and hospitals, and from the registry of births, deaths and marriages when a death certificate mentions cancer. Data concerning NT residents diagnosed with cancer interstate would also be captured, as the NTCR is routinely notified by the relevant interstate cancer registry. It is likely that a proportion of the cases in this series that were identified by the NTCR but had no clinical information in NT Department of Health records were part of the 1.5 million tourists the NT receives per annum¹¹.

Three administrative data codes were used for initial case finding. A study of coding accuracy in the state of Victoria has found ~70—90% accuracy for these codes¹² so some cases of CRC in the NT may have been missed. The fact that NTCR cases link to a common patient record number in the NT was advantageous for case finding in this study but despite a starting cohort of 743 patients, there was only sufficient detail to perform AJCC staging for 504. In the 146 cases with incomplete pathology data for whom Indigenous status was available, 92.47% were NI, similar to the percentage NI in the initial 677 cohort (90.10%) and in the univariable regression cohort of 504 (89.48%), suggesting that missing data were evenly distributed between the groups. The low number of IndA requires some caution with interpretation particularly when specific subsets are considered, for example, rectal cancer. The accuracy of staging is believed to be reliable, as median LN harvest for resected cases was 14, comparable to the published data from a contemporaneous period (BCCA median LN harvest 15, annual range 13-17)⁸.

Whilst this study has adjusted for several potential confounding variables, two areas of interest were not available for examination: comorbidity and incomplete treatment. IndA have been described as having a higher burden of comorbidity^{9,13}, and this may impact upon survival. The importance of comorbidity has been highlighted in data from the NT Audit of Surgical Mortality¹⁴, which showed no difference in the surgeon reported quality of care, but a greater burden of comorbidity was present in IndA. A study comparing survival for CRC in Maori and Non-Maori persons came to a similar conclusion; comorbidity and healthcare access rather than tumour factors were responsible for Maori survival disadvantage¹⁵.

The second unexamined, potential confounding variable is incomplete treatment, as a result of poor health service performance for IndA. It is known from previous studies that IndA have less completion of cancer treatment in the NT, particularly those for whom an Indigenous dialect is their primary spoken language¹⁶. This suggests a suboptimal addressing of communication and cultural issues by the health service, particularly as increasing remoteness was not shown to be a factor in this study. Less than five persons in both cohorts had evidence of refusal of treatment, although this study assessed the initial surgical treatment rather than adjuvant and neoadjuvant treatment; the later having been shown to be more often refused by IndA¹⁶. There was no appreciable difference between groups in the two available markers of surgical quality: LN harvest and rectal cancer CRM positivity, although the limited available data for the later means that only a cautious statement of equivalency can be made. Although these results may be interpreted as a useful step forward in 'closing the gap', survival is still inferior, and evidence of suboptimal health service performance for IndA with respect to CRC still exists, notably a much inferior rate of uptake for screening for CRC (IndA 19.5% versus NI 42.7%)¹⁷. How CRC screening would contribute to the survival disparity is uncertain, as this study did not show more advanced stage of disease at presentation.

One unexpected finding in this study was that there was a difference in distribution of primary tumour site, with IndA having more rectal and less right-sided cancers. Right-sided CRC has been described as having a poorer prognosis than left and rectal cancer¹⁸, so it is uncertain how this may relate to the survival disparity. This may allude to a biological difference not yet measured by available techniques. Further interrogation of molecular features such as MSI or BRAF mutations is a potential area of future interest.

Conclusion

The results of this study shows that Ind of the NT no longer present with more advanced stage of CRC. Therefore, features other than advanced tumour stage are responsible for current survival disparity. Comorbidity or incomplete treatment, particularly adjuvant, could be in part responsible. There is a difference in anatomical distribution of colorectal cancers, which may allude to a difference in tumour biology not measured by this methodology. Addressing low rates of screening, high medical comorbidity, and continuing to improve the delivery of care in a collaborative, culturally sensitive fashion are recommended priorities for the future.

Conflict of Interest. The authors have no actual or potential conflicts of interest to declare

Acknowledgments. The authors wish to acknowledge the assistance of the Northern Territory Cancer Registry, ad the Surgeons of the NT who contributed patients.

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Figure legends

Figure 1: Case acquisition and flow

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Table 1: Sample description

	n		Indigenous n (%)	Non Indigenous n (%)
Total	677		67 (9.9)	610 (90.1)
Sex	677	Male	43 (64.2)	379 (62.1)
		Female	24 (35.8)	231 (37.9)
Age	677	median (IQR)	56 (47-66)	63 (55-72)
Remoteness	677	RA 2	24 (35.8)	423 (69.3)
		RA 3	15 (22.4)	148 (24.3)
		RA 4	28 (41.8)	39 (6.4)
Year of diagnosis	677	2005-2009	32 (47.8)	275 (45.1)
		2010-2014	35 (52.2)	335 (54.9)
Tumour Site	657	Right	14	396 (64.9)
		Left	22	50 (8.2)
		Rectum	28	164 (26.9)
Grade	607	Well differentiated	5 (8.8)	47 (8.6)
		Moderately Differentiated	43 (75.4)	421 (76.5)
		Poorly or Undifferentiated	9 (15.8)	82 (14.9)
Tumour size		mm, median, IQR	32.5 (45- 60)	40 (30-50)
T stage*	407	T0	1 (2.2)	10 (2.4)
		T1	4 (8.9)	20 (4.7)
		T2	7 (15.6)	65 (15.3)
		T3	27 (60.0)	288 (67.8)
		T4	6 (13.3)	42 (9.8)
N stage	411	N0	21 (47.7)	194 (53.2)
		N1	9 (20.5)	95 (26.0)
		N2	14 (31.8)	76 (20.8)
M stage	500	M0	39 (73.6)	347 (77.6)
		M1	14 (26.4)	100 (22.4)
AJCC Stage*	504	0	1 (1.9)	3 (0.7)
		I	10 (18.9)	61 (13.5)
		II	12 (22.6)	131 (29.0)

		III	16 (30.2)	156 (34.6)
		IV	14 (26.4)	100 (22.2)
LVI positivity	341	+ve	9 (23.7)	71 (23.4)
		-ve	29 (78.3)	232 (76.6)
Obstruction or perforation	381	no	34 (82.9)	288 (84.7)
		yes	7 (17.1)	52 (15.3)
Treatment intent	517	Curative	40 (70.2)	356 (77.4)
		Palliative	14 (24.6)	103 (22.4)
		Refusal	3 (5.2)	1 (0.2)
Rectal cancer circumferential resection margin	63	CRM >1mm	8 (80.0)	48 (90.6)
		CRM < 1mm	2 (20.0)	5 (9.4)
LN harvest	299	Median (IQR)	14 (10-17.5)	14 (10-18)

*includes stage post neoadjuvant treatment

Table 2. Indigenous status and advanced tumour stage
Smaller cohort: complete-case analysis

	Univariable logistic regression				Multivariable logistic regression			
Variable	n=	Odds Ratio of advanced tumour	95% confidence interval	P-value	n=	Odds Ratio of advanced tumour	95% confidence interval	P-value
Indigenous status compared with non-indigenous status	504	0.99	0.56 to 1.76	0.982	320	1.39	0.64 to 3.03	0.401
Sex: male compared with female	504	1.36	0.95 to 1.96	0.094	320	1.24	0.76 to 2.04	0.393
Tumour position: right compared with left	495	0.74	0.51 to 1.07	0.112	320	0.78	0.46 to 1.32	0.351
Remoteness: remote compared with urban	504	1.26	0.86 to 1.83	0.234	320	1.03	0.60 to 1.77	0.917
Time period: year 2010-14 compared with 2005-09	504	0.83	0.58 to 1.19	0.310	320	0.75	0.45 to 1.26	0.281
Age at diagnosis: per 1 year increase	504	0.99	0.97 to 1.00	0.127	320			
Tumour grade: poor undiff. compared with mod/welldiff.	474	2.44	1.42 to 4.19	0.001	320	1.85	0.87 to 3.89	0.106
Lymphovascular invasion (LVI) compared with no LVI	339	7.70	4.20 to 14.11	<0.001	320	7.06	3.75 to 13.27	<0.001
Nodal harvest: 12+ nodes compared with 1-11 nodes	368	1.15	0.76 to 1.75	0.518	320	1.09	0.64 to 1.86	0.757
Emergency compared with non-emerg.	377	1.99	1.13 to 3.51	0.018	320	1.87	0.93 to 3.74	0.078

Indigenous status and advanced tumour stage Larger cohort (fewer datafields)								
	Univariable logistic regression				Multivariable logistic regression			
Variable	n=	Odds Ratio of advanced tumour	95% confidence interval	P-value	n=	Odds Ratio of advanced tumour	95% confidence interval	P-value
Indigenous status compared with non-indigenous status	504	0.99	0.56 to 1.76	0.982	495	0.85	0.47 to 1.55	0.606
Sex: male compared with female	504	1.36	0.95 to 1.96	0.094	495	1.31	0.90 to 1.89	0.156
Tumour position: right compared with left	495	0.74	0.51 to 1.07	0.112	495	0.77	0.53 to 1.12	0.165
Remoteness: remote compared with urban	504	1.26	0.86 to 1.83	0.234	495	1.23	0.83 to 1.82	0.298
Time period: year 2010-14 compared with 2005-09	504	0.83	0.58 to 1.19	0.310	495	0.82	0.57 to 1.18	0.282
Age at diagnosis: per 1 year increase	504	0.99	0.97 to 1.00	0.127

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Date:

2019-10

Citation:

Read, D. J. & Hayes, I. (2019). Do Indigenous patients in Australia's Northern Territory present with more advanced colorectal cancer? A cohort study based on registry data.. ANZ J Surg, 89 (10), pp.1296-1301. <https://doi.org/10.1111/ans.15376>.

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