A prospective comparison of times to presentation and treatment of regional and remote head and neck cancer patients in North Queensland, Australia

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Acknowledgements
We wish to thank our research nurse Jill Matthiesen for her contribution to the study. This project received funding from the Townsville Health Service District Private Practice Study, Research and Education Trust Fund. (Not for Profit Benevolent Trust Fund).
A provisional abstract of this study was presented at ASCO Annual Meeting 2014 (30th May to 3rd June) by Z. Otty. J Clin Oncol 32:5s, 2014 (suppl; abstr 6539)
http://meetinglibrary.asco.org/content/126036-144

There are no relevant conflicts of interest declared for any of the authors

This article has been accepted for publication and 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/imj.13138

Introduction: This study aims to examine differences between outer regional (OR) and remote/very remote (RVR) patients in northern Queensland, Australia, in the times taken to receive various aspects of head and neck cancer management.

Methods: Our study prospectively recruited head and neck cancer patients presenting to three North Queensland regional hospitals from 1/2009 to 1/2011. Data on demographic and cancer specific details, co-morbidities and timing of presentation to various services were collected using a self-administered questionnaire that included two questions in relation to possible reason for delays to health services. Multivariate linear regression analyses were conducted to assess the effects of various demographic characteristics on time delays. Survival and disease recurrence data were analysed in 2014.

Results: 158 patients participated. RVR patients had significantly longer median times between diagnosis and first treatment compared with OR patients (p=0.015). Indigenous patients had significant delays from diagnosis to first treatment (p=0.013) and visit to first specialist and treatment (p=0.031) compared to non-Indigenous patients. Longer median times between symptoms and first treatment associated with low income (p=0.03) and lower education level (p=0.04). Disease recurrence was higher for RVR patients compared with OR patients (p=0.04), without significant differences in overall survival. Possible reasons for delays included patient and professional factors.

Conclusions: Significant delays in various aspects of head and neck cancer management were associated with remoteness, Indigenous and socioeconomic status. While patient and professional factors could be addressed at local levels, it requires a state and national level approach for sustainable improvement in outcomes.

Key words: Head and neck cancer, rural health, diagnosis delay, treatment delay

Abbreviations:
ASGC = Australian Standard Geographical Classification
CI = Confidence Interval
ECOG = Eastern Cooperative Oncology Group
ENT = Ear, Nose and Throat (Otolaryngology) Surgeon
OR = Outer Regional
RVR = Remote / Very Remote
TNM staging = Tumour, Nodes, Metastases staging

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Introduction:

Head and neck cancer describes a range of cancers to the oral cavity, salivary glands, nasal cavity, sinuses, pharynx and larynx [1-4]. The most common histological type is squamous cell carcinoma[1-4]. Despite recent advances in treatment, mortality and morbidity rates continue to be high, particularly for rural and remote patients [3, 5]. These high rates may be due to a number of factors, including delays in diagnosis and treatment [6]. Between 2006-2010, the overall five -year survival rate for head and neck cancer patients in Australia was 68.2%.[3]

People living in regional and remote areas of Australia have poorer health outcomes including lower survival rates when compared to their city counterparts[7-10]. Some of the suggested reasons for this disparity include increased cancer risk factors, including smoking, alcohol consumption and sun exposure amongst people in regional and remote areas[7-10]. Other reasons may include socio-economic factors and poorer access to health care services[8]. The rural/remote disadvantage is particularly evident in Australia with its large geographical

area and relatively small population. Health services are often stretched to the limit in rural and remote areas. North Queensland encompasses a very large geographical area ~740000km2 (~43% of Queensland) but serves a population of only ~600000, (~15% of the total population of Queensland)[11]. This large area is serviced by three tertiary hospitals in Townsville, Cairns, and Mackay, with the main specialist centre in Townsville.

The usual management pathway for head and neck cancer begins with the patient presenting to their general practitioner (primary health care physician) following symptoms[1, 2, 12, 13]. Generally after clinical review, imaging scans are undertaken prior to referral to specialists (e.g. surgeons and/or interventional radiologists) for biopsy and further management. Once a diagnosis is confirmed, the patients are referred to head and neck multidisciplinary meetings and clinics (ENT surgeons, radiation oncologists, medical oncologists) where optimal treatment is planned. Treatments may include surgical excision, radiation therapy, chemotherapy and/or a combination of these [1, 2]. Treatment may be either with curative or palliative (for symptom relief) intent.

Delays in treatment can be classified according to 'patient' or 'professional' delays [6, 13]. Patient delays are where patient factors cause delays from the onset of their first symptoms until presentation to a health care provider for treatment (e.g. patients dismissing their symptoms until at an advanced stage)[6, 13]. Professional delays are those where there are health care provider delays from consultation to diagnosis to treatment [6, 13] (e.g. delay until treatment such as surgery or radiation able to be booked and performed). The average patient delays ranged from 1.0 to 5.4 months and the average professional delays from 3 to 21 weeks [6, 13]. The majority of published studies were retrospective case control studies that aimed to identify risk factors and their impact on stage of disease at presentation [6, 12, 13.]

The identification of specific barriers to health services will inform the development of strategies to improve health outcomes for patients from rural and remote areas. There is a paucity of literature that explores the specific delays patients from rural and remote areas with head and neck cancer experience in the Australian setting. This study aims to examine the differences between patients from outer regional areas and those from remote areas in the time taken to receive head and neck cancer management by the North Queensland Cancer Care Services.

Methods:

Participants and Recruitment

Newly diagnosed head and neck cancer patients presenting to the Townsville, Cairns and Mackay Hospitals were prospectively recruited over a 24-month period from 1/2009 to 1/2011 following identification through specialist outpatient clinics and multidisciplinary head and neck team meetings and informed consent. Ethics approval was granted by the participating health services.

Data Collection

Data was collected through self-administered questionnaires as well as review of medical records, pathology reports and the existing MOSAIQ™ clinical oncology database which is used for integrated cancer services provision. The questionnaire included the following details:

(1) Demographic and socio-economic details such as age, gender, ethnicity, Indigenous status, gross household income, highest level of education, living arrangements, employment, private health insurance and place of residence.

(2) Distance from home to the General Practitioner, local hospital, nearest specialist for surgery, chemotherapy, radiation therapy and palliative care.

(3) Co-morbidities, medications, pre-diagnosis symptoms and performance status.

(4) Dates of first presentation to a general practitioner, investigations, specialist reviews and treatment. Remoteness was classified according to Australian Standard Geographical Classification (ASGC) remoteness classification into outer regional and remote/very remote categories[14].

At the end of the questionnaire, patients were asked to respond to two short answer questions "why was there a delay in reporting your first symptoms to a doctor?" and Why do you think you felt it too difficult to get treatment?". Survival and disease recurrence data was examined at April 2014. Patients were classified as lost to follow up if there was no patient information recorded since September 2013.

Data Analysis

We used the Statistical Package for Social Sciences (SPSS v22) for analysis. Fisher's test was used to identify differences between the outer regional and remote/very remote cohorts. Kruskal-Wallis and Mann-Whitney tests were used to calculate the p-values when examining differences in time delays experienced between stage, Indigenous status, and socio-economic status. Chi squared tests were used for survival and disease recurrence data. Multivariable linear regression analyses were conducted to assess the effects of demographic characteristics (age, gender, Indigenous status, level of education, employment status, living arrangement, number of dependents, private health insurance, synchronous and previous cancer, and income) on time delays. Times were logarithmically transformed to achieve approximate normal distributions. Statistically significant influencing factors were identified using backward and forward modelling processes. Remaining characteristics were checked for potential confounding factors (changes in estimator by at least 5%). Models were adjusted for identified confounders. Data was also analysed according to whether the patient was from Townsville (the main tertiary hospital), Mackay or Cairns (both smaller, hospitals), compared with other remote areas. The stage of head and neck cancer, gender, age (<50, 51 to 70, >70) Indigenous status and socioeconomic status (gross household income, highest level of education) were also examined.

Results:

One hundred and fifty-eight (158) head and neck cancer patients were identified from January 2009 to January 2011 (Table 1). All of these patients had squamous cell carcinomas. The majority of patients had advanced disease, with 33 patients (21%) stage III, and 83 patients (52%) stage IV at the time of diagnosis. In our study group, stage IV head and neck cancers included patients who had locoregionally advanced disease without evidence of distant metastasis and were treated with curative intent. One hundred and eighteen (118) patients (75.3%) received curative intent treatment and 40 patients (25%) received palliative treatment (Table 1). Sites of primary cancer and corresponding patient numbers are as follow: oral cavity 83 (53%), pharynx 30 (19.0%), larynx 26 (15.6%), salivary glands 12 (6.8%) and nasal cavity and paranasal sinus 7 (4.3%). Top five predominant symptoms (with corresponding patient numbers) were pain (99), obvious lump (85), dysphagia (81), voice change (57) and sore throat (54). No differences in the distribution of sites of primary cancer or symptoms were observed between rural and urban groups.

Upon further analysis in 2014, with follow up between 3 – 5 years, overall 83 patients (52.5%) were alive, 10 patients (6.3%) were lost to follow up and 65 patients (41.1%) had died. Of the curative treatment group, 31 patients (26.3%) had died. The median survival time of these 31 deceased patients was 20.5 months (overall median survival not yet reached with >50% alive). Twenty (20) curative intent patients (16.9%) had disease recurrence. The median time to disease recurrence was 9 months (range 4- 43 months).

Ninety-eight patients (62%) were living in outer regional areas and 59 patients (37%) in remote /very remote areas. One patient identified from a metropolitan area. More Caucasians were living in outer regional areas (89.9%), compared to those in remote/very

remote areas (76.3%). There was no significant difference between TNM stage and whether patients were from outer regional or remote/very remote areas. Patients living in remote/very remote areas compared to outer regional areas experienced significantly longer median times between diagnosis and first treatment (p=0.015). There was a significant difference in disease recurrence for patients living in remote/very remote areas with 11/31 (35.5%) compared with patients from outer regional areas 8/56 (14.3%) [Odds ratio 3.30] (CI 1.15 to 9.42, p = 0.04). However, there was no significant difference between mortality for those living in outer regional or remote/very remote locations.

Forty-two (42) patients were identified as living in the Townsville area, forty-one (41) in the Cairns or Mackay area, and 75 in other areas. There was a significant difference in median times between diagnosis and first treatment (36.5 days, vs 40 days vs 55.5 days, p=0.012), and between first specialist visit and first treatment(35.5 days ,vs 42.5 days vs 55 days, p=0.003). There were no significant differences in mortality or disease recurrence between these groups. (See appendix 1 online for table regarding Townsville vs Cairns/Mackay vs Other Areas for more detailed data)

When compared with non-Indigenous patients, Indigenous patients had significant delays from diagnosis to first treatment (p = 0.013) and from their first specialist visit to treatment (p = 0.031) (See Table 2). Sixteen out of twenty-three Indigenous patients (69.6%) presented with Stage IV disease. More Indigenous patients (10/23, 43.5%) had palliative intent treatment compared with non-Indigenous patients (30/135, 22.2%). There were no significant differences in mortality rates between Indigenous and non-Indigenous patients.

There was a statistically significant delay in time between onset of symptoms and first treatment in patients with lower income compared to those with higher incomes (95% CI, 0.785 to 0.036, p = 0.032). Similar results were found in patients with primary or lower level

of education compared to those with higher education levels (95% CI 0.011 to 0.817, p = 0.044). Patients without private health insurance also experienced significant delay in the time between diagnosis and first treatment (95% CI, 1.206 to 0.088, p = 0.024). No significant differences in mortality or disease recurrence between patients of different socio-economic status were found (Table 3).

Analysis based on TNM stage did not find any significant differences between stage and median times between symptoms, first consultation, visit to first specialist, diagnosis and first treatment. Analysis revealed that treatment delays (>30 days) compared to those who had earlier treatment, did not result in significant increased mortality or disease recurrence.

Reason for delays:

71 patients responded to the two questions in relation the reason for delays. Reasons and corresponding patient numbers are outlined as follow:

Presentation to primary care:

Patients had known that there was something serious but presented late due to the hope that it would go away (34), flooding and cyclone (5) and patients attributing their symptoms to other causes (1)

Delay in specialist services:

Delayed referral by general practitioner due to loss of referral (6), patients failing to attend appointments (9), patients undecided about treatment (9), investigation of other co-morbidities (7) and delay in booking surgery (3). No formal comparison between rural and urban patients was conducted due small patient numbers in each subgroup.

Discussion:

We believe this is the first Australian prospective study to examine the differences between regional, and remote/very remote head and neck cancer patients' diagnostic, referral and management pathways. Our study found significantly longer times to first treatment for remote/very remote patients when compared to those in regional areas. Patients from remote locations had a trend to longer median times across all aspects of management of their head and neck cancer, although not all aspects reached statistical significance. The delays in presentation was not reflected by significant differences in stage of cancer at diagnosis. Disease recurrence was significantly greater in the remote/very remote group compared to the outer regional group; however, this finding did not translate to statistically significant differences in survival rates. A larger cohort of patients and longer follow up times may be needed to demonstrate any survival differences.

Although the number of Indigenous patients in our study was small, results indicated that these patients were significantly more likely to receive only palliative treatment. More Indigenous, than non-Indigenous patients, presented with Stage IV disease. Delays to presentation to health services are likely to lead to later stage disease at diagnosis. There appeared to be a trend towards longer median time between symptoms and first consultation, however, this finding did not reach statistical significance. The time between diagnosis and first treatment, and first specialist visit and treatment were statistically significantly longer in this patient cohort. Having palliative treatment only may add to the delay in time to first treatment due to the lack of urgency for palliative treatment.

Indigenous patients have been shown to have poorer health outcomes compared to non-indigenous patients [15, 16]. Indigenous liaison officers help provide support and education to patients but ongoing work is needed to help bridge the gap.

Overall, the patient delays reported in our study at 62 days (with a wide range from 0 to 647 days), were similar to those reported in other studies (1.0 – 5.4 months (ie. 30 – 160 days)) [6, 13]. At least 22% of our patients either assumed that the symptoms would go away or attributed their symptoms to other causes. Our estimated total professional delay from first consultation to first treatment was 94 days (range 2 - 794 days). This delay is consistent with other reports of professional delays of 3 to 21 weeks (i.e. 21 to 147 days)[6, 13]. Once diagnosis was confirmed, the median time to first treatment was 42 days (range 0 to 429 days). In our study, nearly 10% of our patients experienced delays due to loss of referral or failure to attend clinics due to misunderstanding. Longer professional delay may be influenced by patient preferences as well as to when their treatment begins. This issue may be of particular relevance in the case of palliative treatment. Our total median time delay between symptoms and first treatment in our study was 216.5 days.

Delays in treatment are often thought to confer worse outcomes, however, there are some conflicting reports. A Dutch study[17] reported that treatment delay up to 90 days in head and neck squamous cell carcinomas was not associated with worse prognosis in terms of survival or disease recurrence. A recent meta-analysis found that diagnostic delay increased the mortality of head and neck cancer patients by a factor of 1.34 and referral delay increased mortality by three times, although the overall mortality was not significantly increased[6].

As the majority of the patients in our study had advanced disease (stage IV - 52.9%), and we included a variety of tumour sites, our survival rate of 53.5% at 3 years, and disease recurrence rate of 16.9%, appears to be roughly equivalent with other centres. Most studies

however report 5 year survival (not 3 year) and report on specific tumour sites. The Oxford Cancer Intelligence Unit reported the three year survival rate for head and neck cancers in England varied from 33 to 75% depending on tumour site[18].

One of the issues regional and remote cancer patients experience is timely access to specialist treatment. A recent study looked at Head and Neck outcomes in centres with high volumes of patients accrued in clinical trials vs centres with low volumes of patients, and found that overall survival was worse for the centres with low volumes of patients even after adjustment for prognostic factors and radiotherapy compliance[19]. While it is desirable to have treatment at high volume specialist centres, this is not always practical and may further contribute to treatment delays. Townsville is the major head and neck cancer centre for the North Queensland district. The next major referral centre is located in Brisbane approximately 1350km away.

Despite awareness of the rural/remote disparity, there has been little progress in overcoming the rural/remote disadvantage in terms of cancer death rates [7-10]. Various Australian studies, have identified factors contributing to the excessive cancer deaths in regional and remote areas such as higher proportions of Indigenous people, greater economic disadvantage associated with some regional and remote locations, a higher prevalence of cancer risk factors, less cancer screening, delays in seeking medical attention and/or delays in diagnosis, higher prevalence of comorbid conditions and treatment disparities[8]. Some possible strategies to help bridge the rural/regional divide include greater support for regional and remote patients to travel, better managed referral pathways, various specialist outreach models of care such as “fly in fly out” specialists, timely processing of referrals, virtual multidisciplinary teams coordinated by care coordinators, building the capacity of local staff in regional cancer services and telemedicine[8].

Telemedicine is the delivery of medical consultations using videoconferencing and other information and communication technologies. Telemedicine has the advantage of bringing the specialist consultations to the patients in their local communities, allowing the patient to avoid travelling long distances to the centre and allowing them to remain at home with their support network [19]. This may assist with expediting timely diagnosis and treatment and follow up.

Addressing rural healthcare workforce shortages is important in order to bridge the regional/remote divide. Increasing the number of adequately trained medical, nursing and other health care professionals in Australia may translate to more health services for regional, rural and remote communities. Education of primary healthcare workers on head and neck cancers may lead to more timely consultations, diagnosis and treatment

Another area for further study is to examine whether there are differences in the percentage of P16 positivity (Human Papilloma Virus (HPV) associated) head and neck cancers between rural/remote cohorts compared to their metropolitan counterparts. P16 positive head and neck tumours have been found to have better prognostic outcomes [20]. Whether this risk factor/pathogenesis differences between rural/remote cohorts compared to their metropolitan counterparts, accounts for some of the disparities is yet to be explored.

In conclusion, our study demonstrated delays in various aspects of head and neck cancer management associated with geographical remoteness and other socio-economic factors and attempted to identify possible reasons for these delays. While some patient and professional factors could be addressed at local levels, a state-wide or national level approach is needed to achieve sustainable outcomes.

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Table 1. Outer Regional vs Remote/Very Remote

Characteristic	Total N=158	ASGC classification: Outer regional* N=99	ASGC classification: Remote or very remote N=59	p-value**
Demographic				
Male	130 (82.3%)	82 (82.8%)	48 (81.4%)	P=0.832
Mean age (SD)***; range [years]	60.9 (12.4); 26 to 89	61.1 (12.7); 26 to 89	60.7 (12.0); 31 to 89	P=0.852
Caucasian	134 (84.8%)	89 (89.9%)	45 (76.3%)	P=0.037
Born in Australia	131 (83.4%)	80 (80.8%)	51 (87.9%)	P=0.275
Secondary or higher school education; n=121	90 (74.4%)	63 (79.7%)	27 (64.3%)	P=0.140
Employed	77 (48.7%)	46 (46.5%)	31 (52.5%)	P=0.288
Living alone	52 (32.9%)	32 (32.3%)	20 (33.9%)	P=0.207
With dependants	24 (15.2%)	16 (16.2%)	8 (13.6%)	P=0.819
Private health insurance	54 (34.2%)	29 (29.3%)	25 (42.4%)	P=0.260
Income protection cover	2 (1.3%)	2 (2.0%)	0 (0%)	P=0.529
Life insurance	19 (12.0%)	14 (14.1%)	5 (8.5%)	P=0.325
Income less then $20,000; n=107	42 (39.3%)	23 (35.4%)	19 (45.2%)	P=0.320
Diagnosis				
Incidental finding	11 (7.0%)	6 (6.1%)	5 (8.5%)	P=0.748
Squamous cell carcinoma	156 (100%)	98 (100%)	58 (100%)	/
TNM Stage				P=0.304
I	17 (10.8%)	9 (9.1%)	8 (13.8%)	
II	24 (15.3%)	19 (19.2%)	5 (8.6%)	
III	33 (21.0%)	20 (20.2%)	13 (22.4%)	
IV	83 (52.9%)	51 (51.5%)	32 (55.2%)	
Treatment palliative	40 (25.3%)	27 (27.3%)	13 (22.0%)	P=0.571

Time delays experienced				
Median time between symptoms and first consultation (IQR)^; range [days]; n=145	62 (31, 171.5); 0 to 647	61 (31, 153); 0 to 647	90.5 (31, 181.25); 0 to 485	P=0.762
Median time between symptoms and referral to first specialist (IQR); range [days]; n=143	148 (73, 211); 2 to 803	121 (70, 212.75); 2 to 803	168 (96, 201); 13 to 791	P=0.252
Median time between symptoms and visit of first specialist (IQR); range [days]; n=147	155 (88, 155); 5 to 833	132 (81, 235); 5 to 833	181 (99, 213.25); 26 to 831	P=0.298
Median time between symptoms and first treatment (IQR); range [days]; n=140	216.5 (134, 303); 0 to 904	200 (129, 311); 9 to 854	221 (144.75, 302.5); 0 to 904	P=0.441
Median time between diagnosis and first treatment (IQR); range [days]; n=145	42 (26, 66.5); 0 to 429	37.5 (18.25, 62); 0 to 420	53 (33.5, 75.5); 0 to 429	P=0.015
Median time between first consultation and referral to first specialist (IQR); range [days]; n=150	26 (6, 66.75); 0 to 741	24 (6, 62); 0 to 741	30 (10, 72); 0 to 463	P=0.462
Median time between visit of first specialist and treatment (IQR); range [days]; n=145	45 (28.5, 73); 0 to 244	42 (27.25, 59.25); 0 to 223	49 (31, 76.5); 0 to 244	P=0.132
Mortality- overall	65/158(41.1%)	37/99 (37.4%)	28/59 (47.4%)	0.24
Mortality – curative patients	31/118(26.3%)	19/70 (27.1%)	12/49 (24.5%)	0.83
Disease Recurrence - curative patients	20/118(16.9%)	8/56 (14.3%)	11/31 (35.5%)	0.04

*Includes one person from a major city; **p-values are results of Fisher's exact tests, unpaired t-tests, and Mann-Whitney tests; ***SD = standard deviation; ^IQR = inter-quartile range.

^^ Chi squared

Table 2. Indigenous patients

	Indigenous			
Time delays experienced	**No**	**Yes**	**p-value**	**p-value***
	(n=135)	**(n=23)**		
Median time between symptoms and first consultation (IQR)^; range [days]; n=145	61 (31, 155.25); 0 to 485	92 (47.5, 181); 13 to 647	P=0.218	P=0.236
Median time between symptoms and referral to first specialist (IQR); range [days]; n=143	132 (73, 212); 2 to 791	175 (80, 209); 13 to 803	P=0.472	P=0.514
Median time between symptoms and visit of first specialist (IQR); range [days]; n=147	147.5 (87.75, 222.5); 5 to 831	181 (88, 240); 26 to 833	P=0.501	P=0.546
Median time between symptoms and first treatment (IQR); range [days]; n=140	207.5 (129, 293.25); 0 to 904	246.5 (167.25, 327); 96 to 854	P=0.129	P=0.173
Median time between diagnosis and first treatment (IQR); range [days]; n=145	39 (22, 62); 0 to 429	69.5 (35.75, 109); 0 to 420	P=0.013	P=0.027
Median time between first consultation and referral to first specialist (IQR); range [days]; n=150	26 (7, 72); 0 to 741	19 (0, 45.25); 0 to 463	P=0.329	P=0.260
Median time between visit of first specialist and treatment (IQR); range [days]; n=145	42 (27, 66.5); 0 to 244	57 (44.5, 93.5); 1 to 122	P=0.031	P=0.030

Palliative treatment	29/135(21.4%)	10/23 (43.5%)	0.03
Mortality	54/135 (40%)	11/23 (47.8%)	0.5
Disease recurrence	20/99 (20.2%)	0/12	0.12

^IQR = inter-quartile range; *First p-value is result of Mann-Whitney test;** Second p-value excluded 11 patients with incidental findings.

Table 3. Multivariable linear regression analyses

Logarithmic time delays experienced	Influencing factor	Coefficient	95%-confidence interval	p-value
Time between symptoms and first consultation	None			
Time between symptoms and referral to first specialist	None			
Time between symptoms and visit of first specialist	None			
Time between symptoms and first treatment*				
	Income			
	< $40,000	Reference		
	>= $40,000	-0.411	-0.785, -0.036	P=0.032
	Level of education			
	Primary or lower	Reference		
	Secondary level	0.414	0.011, 0.817	P=0.044
	TAFE or tertiary	0.055	-0.504, 0.615	P=0.844
Time between diagnosis and first treatment**				
	Private health insurance			
	No	Reference		
	Yes or DVA	-0.647	-1.206, -0.088	P=0.024
	Remoteness of residence			
	Outer regional	Reference		
	Remote	0.665	0.074, 1.257	P=0.028

	Very remote	0.637	-0.488, 1.762	P=0.264
Time between first consultation and referral to first specialist***				
	Location of residence			
	Townsville	Reference		
	Cairns or Mackay	0.461	-0.260, 1.182	P=0.209
	All other	0.754	0.095, 1.413	P=0.025
Time between visit of first specialist and treatment^				
	Location of residence			
	Townsville	Reference		
	Cairns or Mackay	0.347	-0.069, 0.763	P=0.102
	All other	0.747	0.265, 1.229	P=0.003

*Model based on 81 patients (missing: level of education n=37; income n=51; time delay n=18) ; model was adjusted for the confounding effects of ethnicity, employment status and whether a synchronous cancer was present.

**Model based on 116 patients (missing: level of education n=37; time delay n=13) ; model was adjusted for the confounding effects of ethnicity, and level of education.

***Model based on 150 patients (missing: time delay n=8) ; model was adjusted for the confounding effects of ethnicity and remoteness.

^Model based on 145 patients (missing: time delay n=13) ; model was adjusted for the confounding effects of remoteness.