Rural residency and prostate cancer specific mortality: results from the Victorian Radical Prostatectomy Register

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Abstract

Objective: To present long-term survival data from the Victorian Radical Prostatectomy Register (VRPR), 1995-2000, and analyse the effect of rural residence on survival.

Methods: Men who underwent open radical prostatectomy (RP) in Victoria from 1995 to 2000 were recorded in a population register co-ordinated by the Victorian Cancer Registry and Cancer Council Victoria. Baseline clinical, pathological and demographic information such as location were recorded and linked to mortality and recurrence data. Men who had neoadjuvant therapy or missing data for socioeconomic status (SES), tumour grade and stage were excluded leaving 1984 patients in the analyses (92.1% of total register).

Results: Follow-up concluded in 2009 with 238 deaths observed, of which 77 were prostate cancer (PCa) specific. Cox and competing risk regressions were used for analysis. Living in a rural area was associated with higher odds of PCa specific mortality after RP (trend $p<0.001$) and a higher hazard of PCa death, the discrepancy rising up to four-fold (SHR=4.09, $p=0.004$) with increasing remoteness of residence. This effect is apparent after adjustment for SES, age, private or public hospital treatment, PSA level and tumour-specific factors.

Conclusion: Rural men in Victoria have a shorter time to PCa death following definitive treatment, even after adjustment for SES and adverse tumour characteristics.

Implication: Rural men are faring worse than their urban counterparts following the same cancer treatment.

Key words: prostate cancer, rural health, population study

Prostate cancer (PCa) is the most commonly diagnosed malignancy in Australian males and causes the second-highest number of cancer-related deaths, behind lung cancer, with 3,235 deaths in 2010.[1] Australian men from regional areas have a 20% higher PCa mortality rate than those residing in a major city which corresponds to 182 'excess' deaths per year (reporting period 2002-04).[2] This disparity is also evident in population-wide surveys in the United States[3] and Canada,[4] with mortality rate increases of 6% and 9% respectively for the rural relative to the urban population.

Several plausible explanations have been put forward to account for this difference. The published SPCG-4 randomised controlled trial has shown the superiority of radical prostatectomy (RP) as a curative treatment for early stage PCa,[5] and Australian rural patients have had comparatively fewer RPs since the treatment became commonplace:[6] in 2007-08, there was a difference of 57/100,000 men in the age-standardised rate of RP.[7] Additionally, prostate-specific antigen (PSA) testing is lower, with the rural:urban rate ratio of 0.93 reported in 2008-09 and a PSA screening specific ratio of 0.86.[7] Furthermore, a link between low socioeconomic status (SES) and adverse PCa specific outcomes has been reported in other countries[8-10] and, in our sample, Australian rural men are over-represented in the lowest quintiles of national SES.

While rural residency appears to affect the choice of treatment[11] or perhaps its timing, it is unknown whether rural men do worse than urban counterparts following definitive treatment for localised PCa. We sought to identify if rural residency is a risk factor for PCa specific mortality using outcomes data from the Victorian RP register (VRPR), a whole of population series of men from both urban and rural areas of Victoria who have all undergone treatment by open RP.

Methods

The VRPR is a prospective whole of population series of all men who underwent open RP for the treatment of localised prostate adenocarcinoma between 1995 and

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2000 in Victoria, Australia. It was established within the Victorian Cancer Registry (VCR), which documents all cancer cases in the state, excluding non-melanoma skin cancer. The VCR is managed by The Cancer Council of Victoria and the VRPR was approved by the Cancer Council of Victoria's Human Research Ethics Committee and established within the VCR. Further details regarding patient registration and data collection have been previously described.[12]

Rural status was defined using the Australian Bureau of Statistics (ABS) remoteness structure, part of the 2001 Australian Standard Geographical Classification. This categorised census collection districts for Victoria into four classifications: Major cities, Inner regional, Outer regional and Remote.[13] The subjects in our register were geocoded with latitude and longitude co-ordinates accurate to five decimal places. Mapping of subjects to the ABS classifications was performed using the open source geographic information system QGIS. Only four subjects were classified as 'Remote' so 'Outer regional' and 'Remote' patients were combined for the analysis. This created three classifications: 'Major Metropolitan' which encompasses metropolitan Melbourne and Geelong and two rural subgroups: 'Inner regional', which includes Ballarat, Bendigo and Shepparton, and 'Outer regional/Remote', which includes towns such as Portland, Mansfield and Bairnsdale.

Socioeconomic status was defined by the ABS Socioeconomic index for areas (SEIFA) 'Index of relative disadvantage' score.[14] This score is based on census-derived data with each postcode's score re-evaluated at each census date. Men in our series who had surgery prior to 30 June 1998 were coded with data from the 1996 census year, men who had surgery on or after this date were coded with the index score corresponding to the 2001 census year. These scores are then transformed into quintiles with 'Quintile 1' being the most disadvantaged and 'Quintile 5' being the least disadvantaged.

All subjects had a recorded PSA test prior to surgery and operative histology reports plus follow-up PSA testing histories were obtained by record linkage to the pathology laboratories, with staging based on prostate specimen histology. Biochemical recurrence post RP was defined as two consecutive PSA values ≥0.2 ng/mL as per the American Urological Association guidelines[15] and the latter date taken as the time of recurrence.

Deaths were recorded by the VCR as either prostate cancer death, other cancer death or death from another cause. Subjects exited the study at the date of death or 1 January 2009, whichever occurred first. Men who had neoadjuvant therapy were excluded from the multivariable analyses.

Baseline data between the urban and rural cohorts were compared with chi-square tests, Kruskal-Wallis tests and the Wald test from linear or logistic regressions. A multivariable Cox regression model was fitted to analyse all-cause mortality. Competing risks regression based on the Fine and Gray method[16] was fitted to analyse prostate specific mortality with other cause mortality as the competing hazard. Covariates were selected for the model *a priori* as those that were thought to be associated with survival. Socioeconomic status was included as it has, by definition, an association with our rural groupings as both are defined by location. Formal statistical testing of the proportional hazards assumption was performed by analysing Schoenfeld residuals for the Cox regressions and interacting covariates with a time variable for the competing risks regression. In both cases the assumption was not violated. In the two regressions, time from surgery was set as the time axis, covariates were entered simultaneously and biochemical failure included as a time varying covariate. Post prostatectomy follow up comparisons were adjusted for socioeconomic status by its inclusion in a multivariable model with rural residence. All tests were two sided and significance level set at $p \leq 0.05$.

Analyses were performed with Stata 12.1 SE (Statacorp, College Station, TX, US).

Results

During the accrual period 2,154 men underwent RP. Follow-up information was available for 2,115 men. Men who had neoadjuvant therapy were excluded (n=50) as were men with missing data for SES status, grade and stage. There were 1,984 patients (92.1% of total) available for the analyses, 348 of whom were classified 'Inner regional' (17.5%) and 72 'Outer regional/Remote' (3.6%). The median time of follow-up was 10.3 years (range 0.3-13.5 years). Demographic characteristics and prostate cancer status of these men at RP are shown in Table 1. Figure 1 shows the geographic distribution of patient origin and Figure 2 the SES distribution.

There were 238 deaths observed in this sample (180 'Major metropolitan', 47 'Inner regional', 11 'Outer regional/Remote'). This included 77 PCa specific deaths ('Major metropolitan' 50 deaths, 3.20% of this classification, 'Inner regional' 21 deaths, 6.03%; 'Outer regional/Remote' 6 deaths, 8.33%), score test for trend in odds, $p<0.001$.

In this whole-of-population-based series, 35% of men were from the most advantaged quintile of SES and in excess of 95% of this subgroup was urban based. Four hundred and thirty-one (431) RPs were done in the public health system and 1,533 in the private system. Significant differences were present between urban and rural subgroups in regard

Table 1: Baseline data for covariates entered into multivariable models according to residence. The *p*-value indicates overall difference between the three groups.

	Major metropolitan N=1564	Inner regional N=348	Outer regional / Remote N=72	*p*-value (difference between groups)
Age at surgery, years: median (IQR)	62.0 (57.1 – 65.9)	61.5 (57.1 – 65.4)	62.1 (58.3 – 65.5)	0.582
PSA prior to RP, ng/mL: median (IQR)	7.9 (5.7 – 11.8)	8.8 (6.1 – 13.4)	8.2 (5.4 – 12.8)	0.029
% PSA>10 ng/ml	33.8%	40.5%	36.1%	0.056
Private system: %	81.4%	66.1%	69.4%	<0.001
Gleason score: %				
6 or less	58.6%	57.8%	54.2%	0.490
7 (3+4)	25.3%	25.9%	23.6%	
7 (4+3)	9.7%	8.3%	9.7%	
8 or greater	6.4%	8.1%	12.5%	
Tumour stage: %				
T2	74.6%	74.7%	77.8%	0.299
T3a	15.1%	17.0%	8.3%	
T3b	7.9%	7.5%	11.1%	
T4	2.4%	0.9%	2.8%	

IQR = interquartile range

to median PSA values prior to surgery and whether they were treated in the private system OR 0.43 (95%CI 0.34-0.56, $p<0.001$). The percentage with PSA>10 ng/mL prior to surgery was higher in the rural subgroups, almost reaching significance, $p=0.056$. Tumour stage, grade and age at surgery were not significantly different between groups.

Living in a rural area was observed to confer a greater hazard of prostate cancer specific mortality and increasing remoteness amplified this, 'Inner regional' subdistribution hazard ratio (SHR) = 1.64, p=0.154, 'Outer regional/Remote' SHR = 4.09, $p=0.004$. This result is after adjustment for individual patient and tumour factors and socioeconomic status. There was not a significantly greater hazard for overall mortality in men who underwent RP. Table 2 demonstrates the results of the regressions for the urban and rural groups described above with hazard ratios, subdistribution hazard ratios, confidence intervals and associated *p*-values presented. The cumulative incidence plot for this increased risk of PCa specific mortality in rural men treated by RP is shown in Figure 3. There is a clear and continuing separation of the plots with the curve for the most remote classification noticeably divergent from the urban plot.

Tumour grade and stage were both observed to be associated significantly with PCa mortality shown in Table 2. In our study, there was a clear difference between men with Gleason 7 disease when separated according to dominant pathological pattern. Men with Gleason grade 3+4 did not have a significantly different SHR than those with grade 6 or less (SHR 1.08, 95%CI 0.55-2.13) while men with 4+3 disease had SHR = 3.21 (95%CI 1.65–6.23) compared to Gleason grade 6 or less. For overall mortality, T4 stage disease did not reach significance probably due to the low numbers of subjects with this classification in the sample (n=42) and deaths (n=7). We note that men who underwent RP at an older age were more likely to die sooner than younger men from competing causes but age at surgery did not significantly predict PCa specific mortality (SHR 0.98 95%CI 0.94–1.02). Biochemical recurrence was significantly associated with a higher hazard of both overall and PCa specific mortality.

Further comparisons between urban and rural cohorts after adjusting for SEIFA are presented in Table 3. Men in urban areas were significantly more likely to be operated

Figure 1: Location of VRPR cohort. Each yellow dot represents the location of residence of a patient who underwent radical prostatectomy in Victoria from 1995-2000. The shaded areas grow darker with increasing remoteness, as defined by the Australian Bureau of Statistics in 2001. (Created with the open source software QGIS).

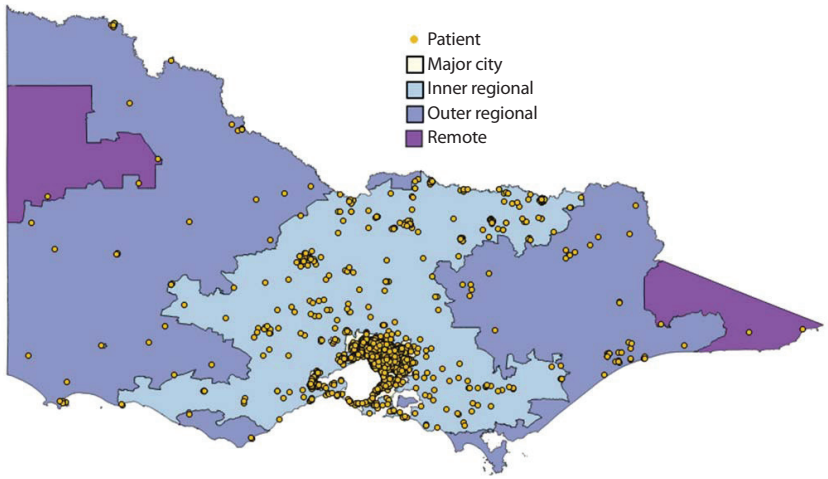


Figure 2: Distribution of SEIFA quintiles by residence. Socioeconomic index for areas scores were divided into fifths. Quintile 1 represents the fifth of all patients with the lowest (SEIFA) score, indicating most disadvantaged. The coloured areas, blue for major metropolitan, red for inner regional and green for outer regional/remote represent the absolute numbers of patients in each fifth.

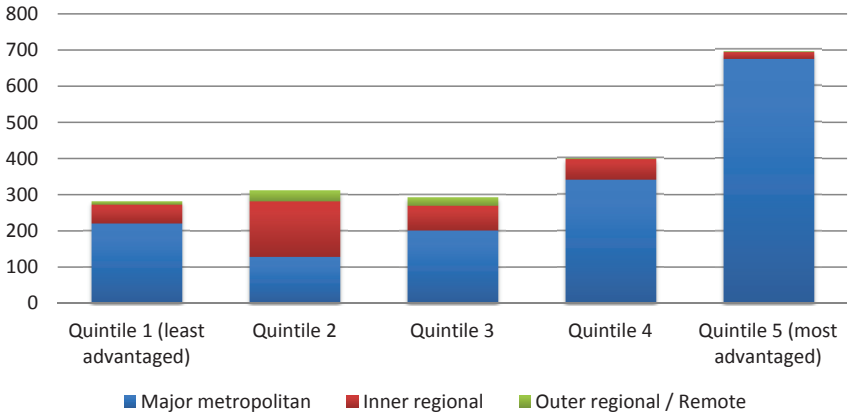
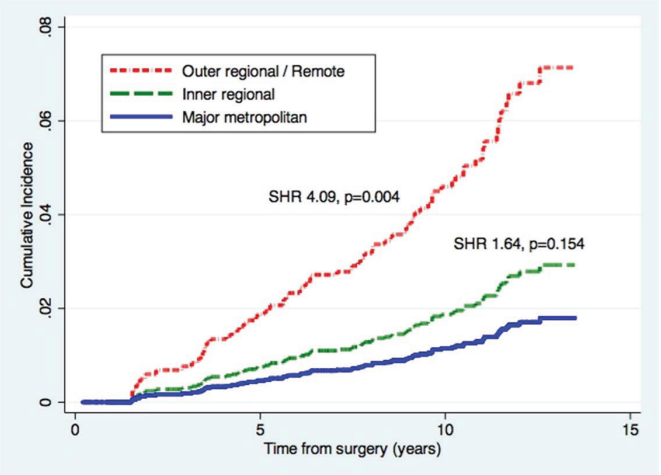


Figure 3: Cumulative incidence plots of prostate cancer specific mortality (PCSM). The plots represent incidence of PCSM, cumulative over the follow-up period and adjusted for all other variables in the multivariable model. The red line represents outer regional/remote men, the green line inner regional and solid blue line, major metropolitan. The subhazard ratios (SHR) and associated p-values are for each rural group relative to major metropolitan.



on by an experienced surgeon, defined as one who had contributed more than 50 cases to the registry. In a univariable analysis, however, surgeon experience alone did not significantly predict PCa mortality (SHR 0.74, p=0.177). The follow-up PSA measures only include men who were alive at the conclusion of the study. Rural men were observed to be followed less closely with repeat PSA measurements and that both the overall number and time between tests differ significantly. Fifty-one (51) men had only one recorded follow-up PSA; proportionately more of these were rural men. There was also a longer lag time between confirmatory biopsy date and date of RP for rural men though this did not reach significance and in univariable analysis, lag time was not predictive of PCa specific mortality (p>0.20).

Table 2: Multivariable analysis: Cox regression and competing-risks regression. N indicates the number of deaths (overall or prostate cancer specific) for each category of the variable. The p-value is in reference to the base case for categorical variables of for each unit increase in continuous variables.

	Overall mortality			Prostate cancer specific mortality		
	N	HR (95% CI)	P-value	N	SHR (95% CI)	P-value
Location of residence						
Major metropolitan	180	1.0		50	1.0	
Inner regional	47	1.09 (0.75-1.57)	0.659	21	1.64 (0.83-3.23)	0.154
Outer regional / Remote	11	1.34 (0.70-2.57)	0.382	6	4.09 (1.56-10.7)	0.004
SEIFA						
Quintile 1 (least advantaged)	39	1.0		15	1.0	
Quintile 2	50	1.05 (0.67-1.64)	0.846	22	1.01 (0.46-2.22)	0.972
Quintile 3	28	0.73 (0.45-1.20)	0.214	9	0.69 (0.28-1.69)	0.417
Quintile 4	39	0.79 (0.51-1.24)	0.312	8	0.55 (0.22-1.38)	0.204
Quintile 5 (most advantaged)	82	0.88 (0.59-1.31)	0.530	23	0.90 (0.45-1.82)	0.776
Private system (vs. public)	188	0.97 (0.70-1.35)	0.859	56	0.65 (0.37-1.16)	0.144
Age at surgery (per year)		1.07 (1.04-1.09)	<0.001		0.98 (0.94-1.02)	0.376
PSA at RP (per 5 ng/ml)		0.99 (0.94-1.05)	0.824		1.01 (0.93-1.10)	0.845
Gleason score						
Less than 6	107	1.0		18	1.0	
7 (3+4)	53	0.93 (0.66-1.31)	0.668	14	1.08 (0.55-2.13)	0.828
7 (4+3)	37	1.44 (0.95-2.16)	0.083	20	3.21 (1.65-6.23)	0.001
Equal or greater than 8	41	1.94 (1.28-2.98)	0.002	25	3.48 (1.79-6.78)	<0.001
Tumour stage						
T2	144	1.0		25	1.0	
T3a	39	1.11 (0.77-1.60)	0.583	17	2.43 (1.27-4.62)	0.007
T3b	48	1.83 (1.24-2.72)	0.003	31	4.62 (2.52-8.47)	<0.001
T4	7	1.26 (0.58-2.73)	0.551	4	3.69 (1.29-10.6)	0.015
Biochemical recurrence (yes vs. no)	120	2.41 (1.81-3.21)	<0.001	58	5.33 (3.00-9.45)	<0.001

HR = hazard ratio, SHR = subdistribution hazard ratio, ng/ml = nanogram/millilitre

Table 3: Comparison of lag time to surgery, surgeon experience and follow-up PSA testing post radical prostatectomy. PSA follow-up variables exclude men who had died from any cause. *P*-values are for comparison to metropolitan men.

	Major metropolitan	Inner regional	Outer regional / Remote
Time between biopsy and surgery dates, days: median (IQR)	54 (39 – 76)	59 (42 – 83) p=0.199[b]	65 (42 – 83) p=0.121[b]
Delay >100 days	12.5%	15.3% p=0.190	15.5% p=0.466
High volume surgeon, >50 cases in our cohort (%)	72.2%	44.0% p<0.001	51.4% p=0.017
Mean number of PSA follow-ups	7.33	5.49 p<0.001	5.0 p<0.001
Mean length of PSA follow-up (years)[a]	6.38	6.09 p=0.125	5.76 p=0.076
Pt. with only a single follow-up PSA (%)	2.47%	5.41% p=0.068	4.92% p=0.569
Ave. time between PSA readings (years)	1.13	1.35 p<0.001	1.45 p=0.003

a In men with more than one follow-up PSA.
b following log transformation

Discussion

In our state-wide, population-based series of men who underwent RP between 1995 and 2000, we found an association between patients who lived in a rural location and PCa specific mortality even after adjustment for socioeconomic status, age at surgery, private or public hospital treatment and biochemical (PSA) and tumour factors (Gleason grade and tumour stage). Previously published studies[6,8,17] have noted rural men are less likely to be screened as often and/or undergo RP. To our knowledge, this is the first population-wide study that demonstrates rural disadvantage persists even after definitive treatment and that it affects PCa specific mortality. The register incorporates a heterogeneous patient and urologist population, with 54 surgeons contributing data. This further removes any outcomes bias associated with a more highly selected patient cohort or the absence of a learning curve in a high-volume, single-institution series.

Baseline characteristics show significant differences only in median PSA prior to surgery and whether the patient was treated in the private or public health system. The higher median PSA and greater percentage of men with PSA > 10ng/mL may indicate a later presentation or be a consequence of less frequent screening leading to rural men having a slightly higher value when plans for definitive treatment are initiated. The difference is, however, unlikely to be clinically significant as the pre-operative PSA value was not shown to predict overall or PCa specific mortality between these groups in the regression analyses. The percentage of Gleason 8-10 tumours in rural men was slightly higher, the reason for this is unclear, though this has been adjusted for in the multivariable regressions.

For biopsy-confirmed PCa, the time from biopsy to surgery is comparable for both groups though there is a small difference in medians. There was a greater percentage, around 3% more, of rural men with long delays (>100 days) to surgery. This is in

contrast to an American study that showed distance from treating hospital to be predictive of shorter time to surgery,[18] although our data does not specifically include information about distances from hospital. The distinction between treatment in private and public health care facilities also did not reach significance in predicting mortality in keeping with a recent Australia-wide breast cancer study.[19] Tumour factors have been shown in other prospective studies to be predictive of mortality[20,21] and it is also true in our series, but no baseline differences between the groups were observed and even after adjustment for these factors, the rural effect remained. Age at surgery was not observed to be associated with PCa mortality after RP. This suggests RP remains an effective treatment for men of advanced age. In our registry, 31% of men were aged over 65 with 5.2% over 70.

The frequency of PSA testing following RP was significantly less for rural men. However the consequence of this is unclear. There is some controversy about how often men should be tested after RP, Ciezki et al[22] found that lower testing intensity is associated with clinical failure while another study suggests no survival benefit[23] and that clear, evidence based guidelines are lacking. In our study, full follow-up information on PSA testing, despite the best efforts of investigators may be differentially incomplete for rural men due to logistical problems in obtaining the data.

A limitation of our study is the method of capturing SES. The SEIFA metric uses postcodes, which do not account for the heterogeneity of the population within a postcode area. As a consequence, there is also a correlation between SEIFA quintile and rural status. This is adjusted for in the regressions and we found no significant evidence for heterogeneity of the effect of rural status on PCa-specific mortality across the SES quintiles (data not shown). Co-morbidities have not been recorded and these may be higher in the rural population. Our results suggest overall mortality to be not significantly different between rural and urban cohorts. We would expect a much larger hazard ratio, closer to the cancer specific figure, if co-morbidities alone explained the poorer PCa survival statistic for rural men. Salvage treatments were also not recorded in our register. Inadequate access to radiotherapy (RT) centres may account for the relative increased mortality.

An Australian survey[24] noted the paucity of rural medical and radiation oncological services, multidisciplinary clinics and access to psychosocial care. But this in itself should not necessarily lead to worse outcomes. In Canada[25] radiotherapy rates did not differ between urban/rural patients for treatment of PCa (though they did for breast and lung cancer). In Scotland,[26] a study describes minimal, if any impact of distance to RT centre for lung and colorectal cancer. In eight states of the United States[27] rural/urban differences in RT utilisation were observed only for breast cancer with no difference for lung, cervical, anal and rectal cancer. It has been observed that rural Australian patients are reluctant to travel to urban centres for treatment[28] and the current paradigm of rural health service delivery is to place high quality services closer to the rural populace.[29] However, it is also noted that evidence that this leads to improved cancer outcomes is lacking.[29]

The management of prostate cancer has changed somewhat in the years since our study period. The percentage of Victorian men with PCa undergoing RP has increased from 13.5% in 1993 to 43.9% in the period 2008-2011.[30] A considerable amount of patient follow-up is done by their general practitioner (GP) and the distribution of GPs over Victoria has altered minimally from 1999-2000 to 2011-2012. The percentage of total full-time workload equivalents done in the 'Inner regional' category of Victoria increased from 15.6% to 18.9% and from 4.19% to 4.35% in the 'Outer regional' category.[31] It is our experience that the distribution of consultant urologists has also changed minimally over the same period. As the number of operations increases while the allocation of the medical workforce over the state remains constant, it is likely our findings remain valid in a contemporary context.

In conclusion, this population-wide study has demonstrated men from rural areas who have undergone open RP for localised PCa have a shorter time to PCa-specific mortality than urban men, even after adjustment for SES and individual tumour factors. This effect is more pronounced with greater remoteness from major metropolitan centres. The precise reasons for this result remain unclear though it is certain a co-ordinated response across surgical, oncological, general practice and allied health disciplines is required.

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