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Population based analysis of treatment patterns and outcomes for pancreas cancer in Victoria.

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Short running head: *Pancreas Cancer in Victoria*

MINI ABSTRACT

All patients in Victoria with pancreas cancer diagnosed between 2011-2015 were included in this population study. Of most note, 23% of patients treated with intended curative intent never received systemic therapy. Only 1.5% were treated with neoadjuvant therapy and 51% with metastatic disease never received any anti-tumour treatment.

ABSTRACT

Objective: The Victorian Pancreas Cancer summit 2017 analysed state-wide data on management of Victorians with pancreas cancer between 2011-2015 to identify variations in care and outcomes.

Background: Pancreas cancer remains a formidable disease but systemic therapies are increasingly effective. Surgery remains essential but insufficient alone for cure. Understanding patterns of care and identifying variations in treatment is critical to improving outcomes.

Methods: This population-based study analysed data collected prospectively by Department of Health and Human services (Victorian state government). Data were extracted from Victorian Cancer Registry (covering all Victorian cancer diagnoses), Victorian Admitted-Episodes Dataset (all inpatient data), Victorian Radiotherapy Minimum Dataset and Victorian Death Index providing demographics, tumour and treatment characteristics, age-standardised incidence, overall and median survival.

Results: Of 3,962 Victorian patients with any form of pancreatic malignancy, 82% were ductal adenocarcinoma (PDAC), of whom 67% had metastases at diagnosis. One-year overall survival for PDAC was 30% (60% non-metastatic, 15% if metastatic). Median survival with metastases increased from 2.7 to

3.9 months, and from 13.3 to 15.9 months for non-metastatic PDAC between 2011-2015. 31% of non-metastatic patients underwent pancreatectomy. 1.5% were treated with neoadjuvant chemotherapy/chemoradiation. Of patients undergoing intended curative resection, 77% proceeded to adjuvant therapy. 51% of metastatic PDAC patients never received anti-tumour therapy.

Conclusions: Nearly ¼ of surgically-treated patients never received systemic therapy. More than 2/3 of non-metastatic patients never proceeded to surgery. Further consideration of neoadjuvant therapy should be given to borderline resectable patients. Most patients with PDAC still die soon after diagnosis, but median survival is increasing.

INTRODUCTION

Pancreas cancer is the 10th and 9th commonest cancer in Australian males and females respectively, but is the 5th leading cause of cancer death [1]. Pancreas ductal adenocarcinoma (PDAC) is an aggressive pancreatic malignancy, constituting the majority of 'pancreas cancers'. Management of PDAC is complex and challenging and unfortunately viewed by many clinicians with nihilism. However, systemic therapy for PDAC is increasingly efficacious (when administered), and surgery is safer than ever, but increasingly centralised and offered mostly in major urban centres. Regional variations in care may mean patients living outside metropolitan areas are not receiving optimal care and may therefore have poorer cancer outcomes.

Analysing population-level data on all patients, treated at all inpatient institutions in the state provides a real-world snapshot of how patients with pancreas cancer are actually managed in Victoria. This data enables clinicians to provide locally relevant, contemporary and reliable prognostic information to patients. Identifying variations in care highlights areas to focus educational activities, may inform health policy and provides opportunities to improve outcomes by ensuring all patients have access to high-quality care.

The data presented here summarise the analyses prepared for the Victorian State Government Pancreatic Cancer Summit, November 2017. Victorian Cancer Summits are an Integrated Cancer Services (ICS) initiative, delivered in collaboration with Department of Health and Human Services (DHHS) and Cancer Council Victoria (CCV). The ICS comprise clusters of hospitals and associated health services that deliver health services for people with all types of cancers within a geographic area. The Summits are clinician-led, focussing on identifying unwarranted variation in cancer clinical practice or outcomes, establishing priorities for action.

METHODS

Data sources

The Victorian Cancer Registry (VCR) is a population-based registry collecting demographic and tumour details for all Victorians diagnosed with cancer. The Centre for Victorian Data Linkage (CVDL) within the Victorian DHHS perform an annual data linkage between the VCR and administrative datasets including the Victorian Admitted Episodes Dataset (VAED), the Victorian Radiotherapy Minimum Data Set (VRMDS) and the Victorian Death Index (VDI). Linking VCR with VAED provides information on cancer treatment including all surgery and intravenous chemotherapy delivered at inpatient Victorian public and private hospitals and linkage to VRMDS provides information on radiotherapy treatments. Deaths were identified by linkage to the Victorian Death Index. CCV Human Research Ethics Committee provided ethics approval 1412 for this study.

Patients

Victorian residents aged $\geq$18 years with a primary diagnosis of pancreatic cancer between 2011 and 2015 were identified from the VCR. Survival and treatment analyses were restricted to Victorians with pancreatic ductal adenocarcinoma (PDAC) excluding patients diagnosed by death certificate only.

Comorbidities were extracted from diagnosis codes of admitted episodes in the year prior to 7 days after a patient's cancer diagnosis date and classified using the Charlson comorbidity index (CCI) [2]. Comorbidity scores were grouped into three categories of increasing severity (0, 1-2 and 3+).

Patients were considered 'metastatic at diagnosis' if pathology reports received by VCR indicated metastatic disease or if any hospital admission within four months of diagnosis included ICD-10-AM metastatic disease or palliative care codes. No other staging data was available from the VCR.

Socio-economic status (SES) was defined using the Index of Relative Socioeconomic Disadvantage (IRSD). IRSD scores by Statistical Area 1 (SA1; an area with average population size of 400) were obtained from the Australian Bureau of Statistics and assigned using patient's residential address at time of cancer diagnosis. Scores were grouped into quintiles (1-most disadvantaged, 5-least disadvantaged).

Statistical methods

Patient demographics, tumour and treatment characteristics were summarised using descriptive statistics including counts and proportions for categorical variables and mean, standard deviation (SD), median and interquartile range (IQR) for continuous variables.

Age-standardised incidence was calculated for each ICS region of residence and overall by sex, year and SES using the direct method. Rates were standardised to the World Standard Population [3] and expressed as diagnoses/100,000 population. A multivariable negative binomial model was used to determine if age, sex, SES, ICS of residence and year were independent predictors of pancreatic cancer incidence.

Median and overall survival at one-year post diagnosis was estimated using Kaplan-Meier methodology. A Cox proportional hazard model was used to estimate hazard ratios for the association between risk of death and sex, year, SES, ICS of residence, stratified by age, comorbidity score and metastatic status. Survival time was calculated from date of diagnosis to date of death from all causes and was restricted to one year for those who were alive at one-year follow-up. The assumption of proportional hazards was not violated.

All analyses were performed in R (v3.3.2).

RESULTS

Demographics

Between 2011 and 2015 3,962 Victorians were diagnosed with all forms of pancreatic malignancy. Of these 3,262 (82%) were PDAC, forming the cohort described in the remainder of this manuscript, unless otherwise specified. In Victoria, 67% of PDAC were metastatic at diagnosis.

The age-standardised incidence for all pancreatic malignancies was 6.8 (95%CI=6.2–7.3) in 2011 and 7.4 (95%CI=6.8-7.9) cases/100,000 in 2015.

Median age at diagnosis was 73 years, (range 19–102 years). Pancreatic malignancies were slightly more common in males (52%). A quarter of Victorians with pancreatic malignancy were in the most disadvantaged SES quintile. Over half of these Victorians had a CCI of zero.

Multivariable analysis showed age, sex and SES were independent predictors of incidence for all pancreatic malignancies (table 1). There was no evidence of association between incidence and year or ICS of residence.

Survival

One-year overall survival for PDAC diagnosed between 2011 and 2015 was 30% (95%CI=28.1-31.1) overall, 60% (95%CI=56.6-62.5) for non-metastatic and 15% (95%CI=13.7-16.7) for metastatic patients. One-year survival increased from 26% in 2011 to 33% in 2015 (figure S1). Survival was statistically significantly superior for Victorians with PDAC who were diagnosed in more recent years and, who had higher SES (figure 1).

Median survival for patients with metastatic PDAC increased from 2.7 months (95%CI=2.2-3.0m) in 2011 to 3.9 months (95%CI=3.4-4.5m) in 2015, and from 13.3 months (95%CI=11.9-15.2m) to 15.9 months (95%CI=14.0-18.4m) for non-metastatic cases.

Treatment for non-metastatic patients

Treatment for Victorians with non-metastatic PDAC, within one year of diagnosis, is depicted in figure S2.

Of all patients diagnosed as non-metastatic, 31% underwent pancreatectomy. In this time period, there were 1.5% of non-metastatic patients treated with neoadjuvant chemotherapy or chemo-radiation who proceeded to resection. Of patients undergoing intended curative resection, 77% proceeded to adjuvant chemotherapy or chemo-radiation.

A further 34% of patients with non-metastatic PDAC were treated with chemotherapy or chemoradiation alone. There is no data currently collected on a statewide level further characterising whether these patients had upfront-resectable, borderline resectable or locally advanced/unresectable non-metastatic disease.

The remaining 376 patients in this cohort (35% of all Victorian patients diagnosed during this time period with non-metastatic PDAC) did not undergo pancreatectomy, chemotherapy or radiotherapy within one year of diagnosis. Eighty percent (N=300) of these patients were either >80 years, had one or more CCI co-morbidity or died within one month of diagnosis.

Perioperative outcomes

Median length of stay following pancreaticoduodenectomy was 14 days (range=5-91d, IQR=10-20d), and 10 days following distal pancreatectomy (range=4-87d, IQR=7-15d). Thirty and 90-day mortality following any form of pancreatectomy were 2.1% (95%CI=1.0-4.3) and 2.7% (95%CI=1.4-5.0), respectively.

Postoperative mortality following pancreaticoduodenectomy was 2.4% (95%CI=1.2-4.9) and 3.1% (95%CI=1.7-5.8).

Surgery volumes

Median annual surgery volume for Victorian hospitals between 2011 and 2015 was 7 (figure S3). The number of pancreatectomies for all indications conducted in low volume health services decreased over the last three financial years. The number of hospitals performing 3 or fewer pancreatectomies annually has decreased from 10 health services in 2014/2015 performing a total of 17 resections to 4 health services in 2016/2017 performing a total of 6 pancreatic resections. This trend is important as pancreatic surgery should be performed in those centres with higher volume.

Hazard ratio estimates were consistent with better overall survival for patients having surgery in health services with higher volumes, however this was not statistically significant (HR=0.83 [95%CI=0.56-1.23], p=0.363).

Multidisciplinary meeting presentation

There is currently no routine monitoring of discussion of patients at multidisciplinary meetings (MDM) in Victoria. For this analysis, a sample of patients undergoing treatment between 2013-2015 were audited within each ICS. The presence or absence of MDM recommendations in the patient's medical history was used as a measure of whether or not an MDM discussion for that patient had occurred.

The state-wide average for documented MDM discussion was 69% in 2013-15, ranging from 36-96% across ICS. Only 1 of 8 ICS achieved the DHHS target rate of 80%.

Treatment for metastatic patients

Treatment for Victorians with metastatic PDAC is presented in figure S4.

Forty-five percent of patients with metastatic PDAC received chemotherapy and/or radiotherapy, but no surgery. This was mostly chemotherapy alone (84%). It is assumed patients with metastatic disease receiving radiotherapy did so for local indications.

Most of the 51% of metastatic PDAC patients who had no anti-tumour therapy died within one year of diagnosis (N=1077/1124, 96%).

End-of-life care

Of patients with metastatic PDAC, 1515 (69%) received palliative care at an inpatient setting within one year of their cancer diagnosis.

Three quarters of deaths of Victorians with PDAC occurred whilst in Victorian hospitals. In Victoria, 12% of PDAC patients received chemotherapy in the last 30 days of life.

DISCUSSION

Systemic therapy

PDAC is almost always a systemic disease at diagnosis (even in the absence of macroscopic metastases visible on currently available imaging modalities), as evidenced by overall 5-year survival remaining <10% [4]. Autopsy studies have shown following ‘curative surgery’ virtually all patients can be found to have micrometastatic disease [5]. Treatment with curative intent therefore requires administration of systemic therapy. The Victorian Optimal Care Pathway (OCP) states that even if surgery is deemed curable, chemotherapy should be considered. Almost a quarter of patients (23%) who were treated with surgery and curative intent in Victoria between 2011 and 2015 did not receive adjuvant systemic therapy. The reasons for this are unclear and need to be explored, but are almost identical to the number not receiving adjuvant therapy in other states of Australia such as New South Wales and Queensland where the figure is 24% [6].

The currently available state data do not provide sufficient information to discriminate which non-metastatic patients have up-front resectable, borderline resectable or locally advanced PDAC, and this therefore compromises the ability to comment further on the appropriateness of treatment. A previous controversy in pancreas cancer has been agreement on definitions of stages of disease, with multiple competing (yet mostly similar) systems [7-10]. Importantly, published this year is a worldwide consensus on the definition of resectable, borderline resectable and locally advanced disease [11]. It is highly recommended this system is widely adopted and indeed its use will be critical in future publications of outcomes regarding treatment for PDAC. Prospective classification and identification of patients with PDAC into resectable, borderline resectable and locally advanced categories must therefore be a priority to allow future interpretation of data and identification of variations in care.

Regional variation in care and outcomes have previously been reported in the Australian setting [12]. The data presented here similarly show variation in incidence and outcome based on SES, with those more disadvantaged seen to have higher incidence and poorer survival, although this Victorian data does not identify ICS of residence as negative prognostically.

Bilimoria et. al [13] have previously shown that 38% of early stage PDAC in the USA were not offered pancreatectomy without any identifiable contraindication in the years between 1995-2004. This finding is confirmed to likely be the case in the Australian context too, with only 31% of non-metastatic patients in Victoria proceeding to pancreatectomy between 2011-2015. 35% of non-metastatic patients were offered no treatment at all, however 80% of those patients were either over 80 years of age, had one or more significant comorbidity or died within 1 month of diagnosis suggesting surgery was contraindicated in these patients.

More than one third of patients with non-metastatic pancreas cancer were treated with chemotherapy or chemoradiation alone, (not considered curative treatment). However, at least some of these patients will have locally advanced, unresectable (but non-metastatic) disease and will therefore have undergone appropriate treatment. Up to 30% of patients would be expected to have borderline resectable disease [14] and should undergo neoadjuvant therapy prior to surgery according to National Comprehensive Cancer Network guidelines [15]. Upfront resection (surgery first) of borderline resectable pancreas cancer is associated with increased rates of R1 margin positivity compared with resection following neoadjuvant therapy [16]. R1 resections are unequivocally associated with increased risk of death of at least 10% following surgery for PDAC on meta-analysis of 2450 patients [17]. This negative effect on survival is independent on multivariate analysis of receipt of adjuvant therapy [18].

In this cohort virtually no patients who presented with non-metastatic PDAC underwent curative surgery following neoadjuvant therapy (1.5%). Patients with borderline resectable disease were therefore either inappropriately treated with surgery first [14], or received chemotherapy/chemoradiation but did not progress to surgery.

There are no published randomised phase III trials comparing neoadjuvant therapy to no treatment prior to surgery, or comparing neoadjuvant therapy to adjuvant therapy. However, this does not mean there is no evidence regarding neoadjuvant therapy. In fact, a recent systematic review identified over 1000 studies investigating the effect of neoadjuvant therapy on PDAC [16]. Nevertheless, treatment with this intent remains controversial. An Australian Gastrointestinal Trials Group (AGITG) phase II trial examining neoadjuvant therapy for resectable PDAC closed early after interim safety analysis determined the primary endpoint of a difference in R0 resection rate could not be met, perhaps not surprisingly as the patients were by definition resectable upfront (with lower expected R1 rates than borderline resectable). This study did, however, suggest treatment in the neoadjuvant context achieved better compliance than postoperative treatment. In a consensus statement, the AGITG recently acknowledged that neoadjuvant therapy is increasingly recommended for borderline resectable PDAC [10].

MDM recommendations

To ensure consistency of decision making it is imperative all cases be discussed at an MDM [19]. There was variation in documented evidence of MDM recommendations across ICS between 36-96%. PDAC presents with metastases in 67% of cases and it is possible that patients not discussed had metastatic disease. However, the OCP recommends discussion of all cases (including metastatic), and consistent with this, there was strong agreement at the Summit that all PDAC cases should be presented at MDM. Discussion at MDM ensures all treatment options are considered including identifying potential clinical trials and the role of palliative care [19].

Consideration of pancreas-specific MDMs in recognition of the subspecialisation seen in the treatment of PDAC is warranted, but requires additional resources to review additional patients imaging and histology in an appropriate manner as time pressure at MDMs already exists and can negatively affect decision making [20].

Case volume and outcomes

Compared to US and European centres, the majority of health services performing pancreatectomy in Victoria would be considered low volume. Regardless, Victorian hospitals are achieving world-class results with 30 and 90-day mortality rates of 2.1%, 2.7% respectively, particularly relevant when considering a report of >20,000 patients from the US National Cancer Database documented 30-day mortality of 3.7% and 90-day mortality of 7.4% following pancreatectomy, although this did report on an earlier time period (2007-2010) [21]. The results also demonstrate a significant reduction in mortality from an earlier time period in Victoria, where 30-day mortality of 5.3% was published for 73 patients undergoing pancreaticoduodenectomy between 2002 and 2003 [22].

Palliative care

Over half patients diagnosed with metastatic PDAC never received anti-tumour treatment. Of these patients, 84% were >80 and/or with comorbidities. Patients >75 years have poorer adjusted overall survival than younger patients treated with chemotherapy for pancreas cancer [23] suggesting this finding represents appropriate non-treatment.

Patients with PDAC require high levels of supportive care [24]. Data on place of death were used to illustrate possible issues in the use of palliative care services across Victoria. For PDAC, 75% of deaths occurred in hospital, higher than for oesophagogastric (71%) and colorectal (68%) cancers. Timeliness of contact with palliative care should be a focus for action that could reduce the proportion of PDAC patients dying in hospital [25]. The American Society of Clinical Oncology have recently released an updated Clinical Practice Guideline for metastatic pancreas cancer specifying that palliative care should be timely and may require referral at diagnosis [26]. This is especially relevant for PDAC given 67% of patients present with metastases, over half of whom do not proceed to anti-cancer treatment. Twenty-eight percent of all patients with PDAC in this time period were only ever treated by palliative care physicians. These physicians are core members of the team and should be present at MDMs [27]. Similarly, active chemotherapeutic treatment to within 30 days of death may be seen as inappropriate palliative care for patients with terminal disease. Palliative care involvement for PDAC remains low at 7% of contacts nationally in Australia [28].

CONCLUSIONS

Age-standardised incidence of pancreas cancer has remained stable in Victoria, but one-year overall survival has increased. However, most patients with PDAC still die of systemic disease shortly after diagnosis. More than half of patients with metastatic disease never received any anti-tumour treatment. These sobering statistics highlight the importance of early involvement of palliative care physicians, who are an integral part of the MDM.

Treatment pathways for non-metastatic PDAC are roughly evenly split between surgery, systemic therapy alone or no treatment. Very few non-metastatic patients were treated with neoadjuvant therapy demonstrating undertreatment for borderline PDAC by current standards. Almost a quarter of patients undergoing intended curative surgery never received intravenous systemic therapy. All patients who have curative surgery should be treated with adjuvant chemotherapy, or a valid reason documented outlining why this was not the case. Additionally, patients must be prospectively designated as resectable, borderline resectable or locally advanced to guide treatment decisions.

Pancreas cancer remains an aggressive systemic disease in almost all cases, but hope lies in improved efficacy seen with newer chemotherapeutic regimens. It remains an obligation to consider all options for all patients through discussion at MDMs, and consideration of systemic therapy for all patients treated with curative intent.

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LIST OF FIGURES AND TABLES

LIST OF SUPPORTING INFORMATION

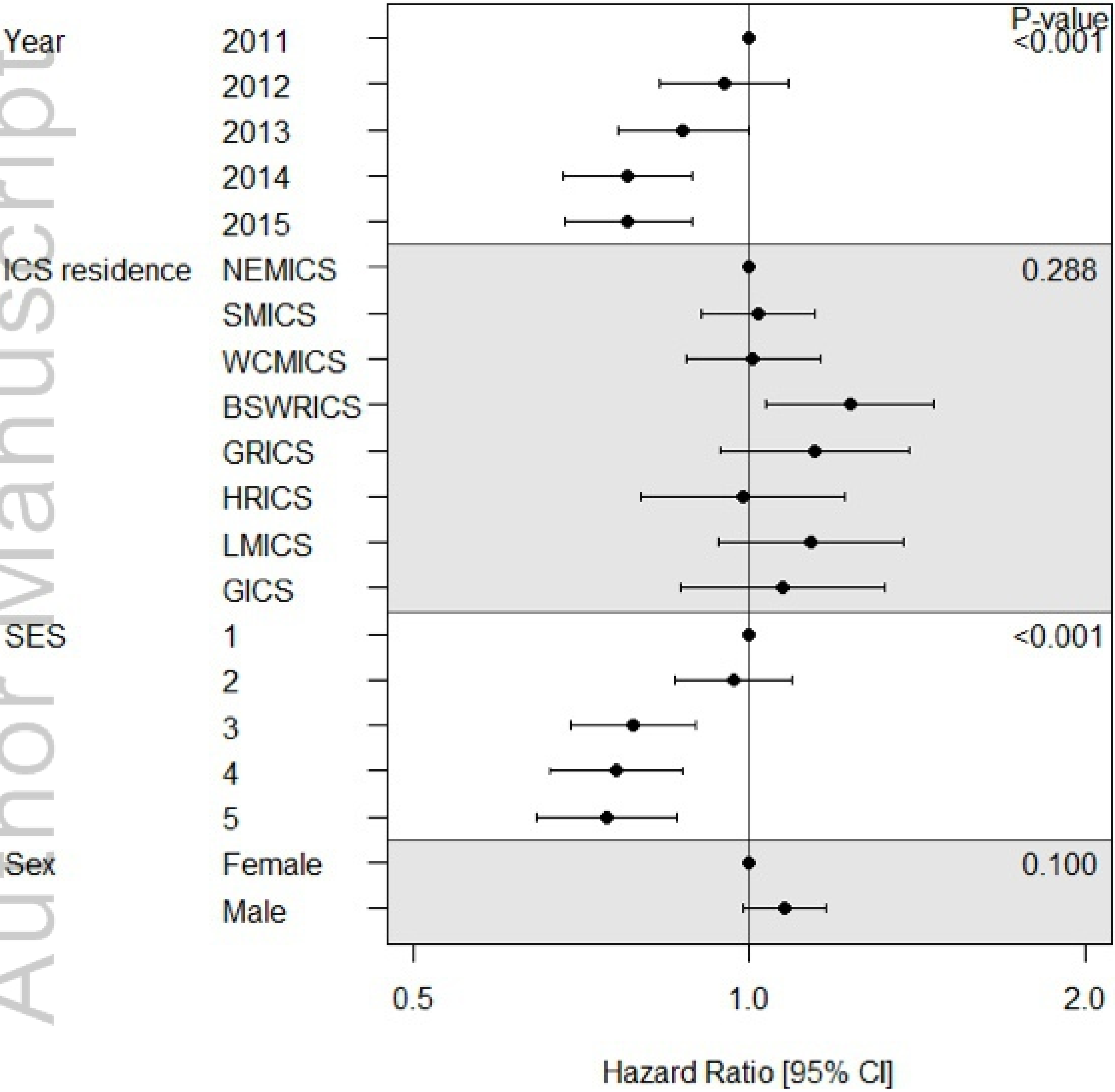

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Figure and Table headings and legends

Table 1: Predictors of pancreatic cancer incidence in Victoria
Year of diagnosis 2011 – 2015

Legend: *Incidence rate ratios (IRR) from a multivariable negative binomial model. NEMICS = North Eastern Metropolitan Integrated Cancer Service (ICS), SMICS=Southern Melbourne ICS, WCMICS=Western and Central Melbourne ICS, BSWRICS=Barwon South Western Regional ICS, GRICS=Gippsland Regional ICS, HRICS=Hume Regional ICS, LMICS=Loddon Mallee ICS, GICS=Grampians ICS. SES=Socioeconomic status. An ICS comprises clusters of hospitals and associated health services that deliver health services for people with all types of cancers within a geographic area.*

Figure 1: Relative risk of death following pancreatic cancer diagnosis
Year of diagnosis 2011-2015

Legend: *Relative risk expressed as hazard ratio from a multivariable Cox proportional hazard model. Bars represent 95% CI. SES = socioeconomic status; ICS = integrated cancer service. NEMICS = North Eastern Metropolitan Integrated Cancer Service (ICS), SMICS=Southern Melbourne ICS, WCMICS=Western and Central Melbourne ICS, BSWRICS=Barwon South Western Regional ICS, GRICS=Gippsland Regional ICS, HRICS=Hume Regional ICS, LMICS=Loddon Mallee ICS, GICS=Grampians ICS. SES=Socioeconomic status. An ICS comprises clusters of hospitals and associated health services that deliver health services for people with all types of cancers within a geographic area.*

Table 1: Predictors of pancreatic cancer incidence in Victoria
Year of diagnosis 2011 – 2015

Variable	Level	Crude incidence per 100,000 population	IRR [95% CI]	P-value
Age	0-59	2.7	1	<0.001
	60-64	25.4	9.29 [8.18 - 10.55]	
	65-69	41.5	15.16 [13.50 - 17.01]	
	70-74	56.3	20.47 [18.24 - 22.97]	
	75-79	77.5	28.27 [25.24 - 31.67]	
	80-84	94.1	34.57 [30.79 - 38.81]	
	85 or over	125.0	46.81 [41.99 - 52.19]	
ICS of residence	NEMICS	14.0	1	0.466
	SMICS	13.5	0.95 [0.87 - 1.04]	
	WCMICS	10.4	0.93 [0.84 - 1.02]	
	BSWRICS	16.2	0.97 [0.85 - 1.10]	
	GRICS	19.5	1.06 [0.92 - 1.22]	
	HRICS	16.2	0.95 [0.82 - 1.11]	
	LMICS	15.6	0.89 [0.77 - 1.03]	
	GICS	16.9	1.02 [0.87 - 1.20]	
SES	1 - most disadv.	17.5	1	0.031
	2	15.4	1.00 [0.91 - 1.10]	
	3	13.1	0.92 [0.84 - 1.02]	
	4	11.6	0.88 [0.79 - 0.97]	
	5 - least disadv.	11.3	0.90 [0.81 - 1.00]	
Sex	Female	13.1	1	<0.001
	Male	14.4	1.29 [1.21 - 1.37]	
Year	Per unit increase	-	1.01 [0.99-1.03]	0.301

Incidence rate ratios (IRR) from a multivariable negative binomial model. NEMICS = North Eastern Metropolitan Integrated Cancer Service (ICS), SMICS=Southern Melbourne ICS, WCMICS=Western and Central Melbourne ICS, BSWRICS=Barwon South Western Regional ICS, GRICS=Gippsland Regional ICS, HRICS=Hume Regional ICS, LMICS=Loddon Mallee ICS, GICS=Grampians ICS. SES=Socioeconomic status.