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ORIGINAL ARTICLE

Multiple myeloma survival in New South Wales, Australia, by treatment era to 2020

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ABSTRACT

Objective: Australia has relatively high multiple myeloma (MM) incidence and mortality rates. Advancements in MM treatment over recent decades have driven improvements in MM survival in high-income countries; however, reporting in Australia is limited. We investigated temporal trends in population-wide MM survival across 3 periods of treatment advancements in New South Wales (NSW), Australia.

Methods: Individuals with an MM diagnosis in the NSW Cancer Registry between 1985 and 2015 with vital follow-up to 2020, were categorized into 3 previously defined treatment eras according to their diagnosis date (1985–1995, chemotherapy only; 1996–2007, autologous stem cell transplantation; and 2008–2015, novel agents including proteasome inhibitors and immunomodulatory drugs). Both relative survival and cause-specific survival according to Fine and Gray's competing risks cumulative incidence function were calculated by treatment era and age at diagnosis.

Results: Overall, 11,591 individuals were included in the study, with a median age of 70 years at diagnosis. Five-year relative survival improved over the 36-year (1985–2020) study period (31.0% in 1985–1995; 41.9% in 1996–2007; and 56.1% in 2008–2015). For individuals diagnosed before 70 years of age, the 5-year relative survival nearly doubled, from 36.5% in 1985–1995 to 68.5% in 2008–2015. Improvements for those > 70 years of age were less pronounced between 1985–1995 and 1996–2007; however, significant improvements were observed for those diagnosed in 2008–2015. Similar overall and age-specific patterns were observed for cause-specific survival. After adjustment for gender and age at diagnosis, treatment era was strongly associated with both relative and cause-specific survival ($P < 0.0001$).

Conclusions: Survival of individuals with MM is improving in Australia with treatment advances. However, older age groups continue to experience poor survival outcomes with only modest improvements over time. Given the increasing prevalence of MM in Australia, the effects of MM treatment on quality of life, particularly in older age, warrant further attention.

KEYWORDS Multiple myeloma; cancer epidemiology; survival analysis; competing risk analysis; Australia

Introduction

Multiple myeloma (MM), the second most common type of blood cancer, tends to be diagnosed at older ages, among men, or among people with a family history of MM[1]. Global MM trends have shown increasing incidence rates and decreasing mortality rates over the past several decades, with improving survival outcomes in high-income countries[2-5]. Similar trends have been observed in Australia[6], which has one of the world's highest MM incidence and mortality rates: 2,663 people were diagnosed with MM, and 1,180 MM deaths occurred in 2023[7,8]. Similarly, the 5-year survival increased from 27.3% in 1990–1994 to 57.6% in 2015–2019[8]. Survival outcomes are expected to continue to improve in Australia, thus leading in part to the projected doubling in 30-year prevalence from 2018 to 2043[6].

Historically, chemotherapeutic drugs were the recommended treatment for MM[9]. Internationally, MM treatment advancements, which extend quality of life and prolong survival, have partially driven improvements in survival outcomes[9,10]. The introduction of the stem cell transplantation (SCT) in the 1990s marked one of the most important changes to MM treatment[11]. In Australia, SCT has traditionally been recommended for individuals younger than 65 years with

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acceptable levels of organ reserves and performance status[12]; however, emerging research now indicates benefits for older individuals[13]. More recently, novel chemotherapeutic treatment agents have entered the market, including 2nd generation protease inhibitors, immunomodulatory drugs, and chimeric antigen receptor T cell therapies from the mid-2000s[9,10,12,14].

Reporting of the effects of treatment advancements on MM survival has been limited in the Australian context. One study has reported higher 5-year overall survival in people diagnosed with MM between 2002–2005 in the state of New South Wales (NSW) who received SCT compared with those who did not (62% *vs.* 54%, respectively)[15]. A more recent study in the state of Queensland has reported changes in survival according to diagnosis date over 3 study-defined treatment eras, and has found a significant improvement in 5-year relative survival, from 30% (1982–1995; chemotherapy regimens only) to 43% (1996–2007; introduction of SCT) to 53% (2008–2014; introduction of novel agents)[16]. However, large population-based studies reporting changes in MM survival over various periods of treatment advancements have not been replicated in other Australian regions.

Considering age at diagnosis, international studies have reported less pronounced improvements in MM survival for older age groups compared to younger age groups[3,17,18]. In contrast, a Queensland-based study has reported significant improvements in survival from 1982–1995 to 1996–2007 to 2008–2014 among older age groups[16]. Understanding age differences in MM survival in the Australian context is key to enabling comparisons across health systems and populations.

Our study was aimed at quantifying the temporal trends in population-wide survival in individuals diagnosed with MM in 3 treatment eras from 1985 to 2015 in NSW, Australia, and differences by age group.

Patients and methods

We performed a retrospective cohort analysis of individuals diagnosed with MM (ICD-O-3 morphology code 973, equivalent to ICD-10 code C90.0) who were residents of NSW, Australia, between 1985 and 2015, with mortality follow-up to December 2020, thus allowing for a minimum of 5 years of follow-up. Individuals were identified from the NSW Cancer Registry, to which reporting of cancer diagnosis is a statutory requirement.

Individuals' vital status data were obtained through routine annual linkage of cancer records with death records (the NSW Registry of Births Deaths and Marriages and Australian National Death Index, and the Cause of Death Unit Record File) until December 31, 2020. Probabilistic linkage was performed by the Centre for Health Record Linkage through a privacy-preserving approach and a matching process known to be highly accurate (false-positive and false negative rates < 0.4%).

Individuals first diagnosed at death were excluded, as were very young (< 20 years) or old individuals (90 years or older). Individuals were categorized into 3 previously defined treatment eras according to their diagnosis date[16]: 1985–1995 (chemotherapy only), 1996–2007 (autologous stem cell transplant), and 2008–2015 (novel agents: proteasome inhibitors and immunomodulatory drugs). Additionally, individuals were categorized into 3 broad age groups according to ages at diagnosis of 20–69, 70–79, or 80–89 years.

Statistical analysis

The baseline characteristics in the 3 treatment eras were compared with chi-squared tests.

Survival was measured from the date of diagnosis to the date of death, 5 years after diagnosis, or the study end date (December 31, 2020), whichever came first. Those alive at the end of follow-up were censored. Relative survival, the ratio of the observed proportion surviving in a group of individuals with MM to the expected proportion that would have survived in a comparable group of individuals from the general population[19], was calculated because this method is preferred for measuring cancer survival at a population level[20] and is robust to inaccuracies in causes of death in population-based data collection[21]. The cohort method was used, because this study was designed to assess temporal trends in survival[22]. Observed survival was estimated with the life table method[23], and expected survival was calculated with the Ederer II method[24], on the basis of NSW life tables stratified by gender, age, and calendar year.

To assess differences in survival over time, we conducted 2 types of analysis. First, we fitted a relative survival regression model for excess deaths from MM[25,26]. In this analysis, numbers of death were modeled as a function of year of follow-up, gender, age group, and treatment era through Poisson regression with the logarithm of the person-years at risk as the offset. This model quantified the extent to which the excess risk of death in each treatment era differed from that in the reference era (1985–1995), after controlling for the factors included in

the model. Relative excess risks (RERs) and their 95% confidence intervals (CIs) were calculated with the estimated coefficients and standard errors from the Poisson model.

Second, we estimated cause-specific survival with Fine and Gray's competing risks cumulative incidence function and subdistribution hazard model[27] to adjust for other factors, as recommend by Lau et al.[28]. In this analysis, MM, as the underlying cause of death, was treated as the primary event of interest, and death due to other causes was treated as a competing risk. Cox proportional hazards regression was used for fitting the subdistribution hazard model[28,29]. All significance tests with P-value < 0.01 were considered to indicate statistical significance. All analyses were conducted in SAS version 9.4.

This analysis received ethical approval for the Cancer Institute NSW's Enduring Cancer Data Linkage (also known as CanDLe) initiative from the NSW Population and Health Services Research Ethics Committee (Approval No. 2019/ETH12584). Data were stored in the Secure Unified Research Environment facility, a remote access computing environment to which authorized researchers were given encrypted access with strong authentication.

Results

A total of 11,591 individuals 20–89 years of age diagnosed with MM between 1985 and 2015 were included in the study. The median age at diagnosis of the cohort was 70 years, and the interquartile range was 61–78 years; 57.4% were men. The distribution by age group showed a shift toward older age at diagnosis in the more recent cohort, with an increasing proportion of individuals 80–89 years of age over the study period (15.3% in 1985–1995 *vs*. 20.5% in 2008–2015) (**Table 1**).

Relative survival

Relative survival improved over the 36-year study period; the largest increase was observed in the third treatment era. The 5-year relative survival over the treatment eras increased from 31.0% in 1985–1995, to 41.9% in 1996–2007, and 56.1% in 2008–2015 (**Table 1** and **Figure 1**). The improvement in survival over time was observed for all age groups (**Figure 1**). For individuals younger than 70 years at diagnosis, the 5-year relative survival nearly doubled, from 36.5% in 1985–1995 to 68.5% in 2008–2015 (**Figure 1**). Less improvement was observed for those 70–79 years of age, whereas little improvement was found for those 80–89 years of age between the first 2 treatment eras. In contrast, significant improvements in relative survival were observed for individuals > 70 years of age in 2008–2015. Similar trends in relative survival were observed between men and women (data not shown).

In the multivariable analysis, RERs due to diagnosis of MM were significantly lower (P < 0.0001) for individuals diagnosed

Table 1 Baseline characteristics of individuals diagnosed with multiple myeloma, and relative survival (%) by treatment era, New South Wales, Australia, in 1985–2015 with 5-year follow-up (to 2020)

Item	Total *n* (%)	1985–1995	1996–2007	2008–2015	*P*-value*
Number of cases	11,591	2,826	4,708	4,057	
Gender					< 0.0001
Male	6,658 (57.4%)	1,560 (55.2%)	2,662 (56.5%)	2,436 (60.0%)	
Female	4,933 (42.6%)	1,266 (44.8%)	2,046 (43.5%)	1,621 (40.0%)	
Age group					< 0.0001
20–69 years	5,649 (48.7%)	1,477 (52.3%)	2,167 (46.0%)	2,005 (45.4%)	
70–79 years	3,748 (32.3%)	918 (32.5%)	1,608 (34.2%)	1,222 (30.1%)	
80–89 years	2,194 (18.9%)	431 (15.3%)	933 (19.8%)	830 (20.5%)	
Relative survival (%)					< 0.0001
1-year (95% CI)	78.9 (78.1–79.7)	74.0 (72.2–75.7)	77.3 (76.0–78.5)	84.1 (82.9–85.3)	
2-year (95% CI)	67.1 (66.2–68.0)	59.5 (57.5–61.4)	65.0 (63.5–66.5)	74.8 (73.3–76.2)	
5-year (95% CI)	44.3 (43.3–45.4)	31.0 (29.0–32.9)	41.9 (40.4–43.5)	56.1 (54.4–57.9)	

*From chi-squared test.

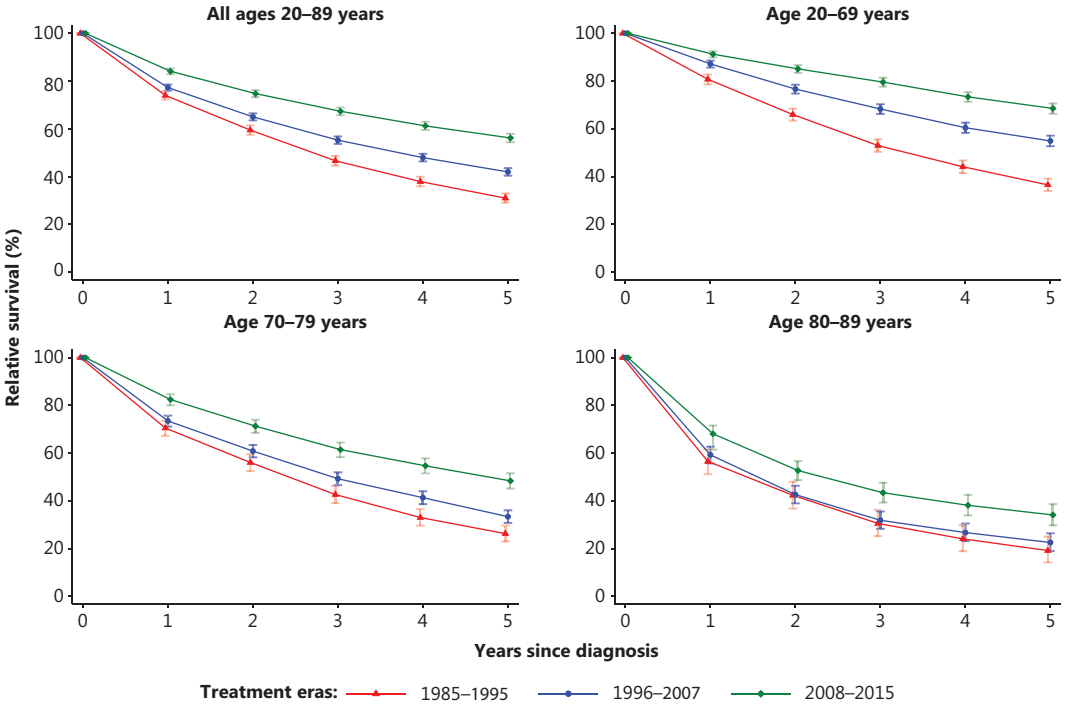

Figure 1 Five-year relative survival among individuals diagnosed with multiple myeloma, by age at diagnosis in different treatment eras, New South Wales, Australia.

in 1996–2007 (RER = 0.73, 95% CI: 0.69–0.78) and 2008–2015 (RER = 0.48, 95% CI: 0.45–0.52) than in 1985–1995 (**Table 2**). Age at diagnosis was a significant prognostic factor: older individuals had higher excess death (RER = 1.71 and 2.76 for those 70–79 and 80–89 years of age, respectively) than younger individuals (< 70 years of age). RERs decreased with year of follow-up, thereby indicating a progressively lower excess risk of death for people with prevalent MM.

Cause-specific survival

Cumulative incidence curves of death due to MM by treatment era are presented in **Figure 2**. The cumulative incidence significantly decreased over time (Gray's test $P < 0.0001$), and the 5-year cumulative incidence of death due to MM was much higher among those diagnosed in 1985–1995 (0.58, 95% CI: 0.57–0.60) than in 1996–2007 (0.47, 95% CI: 0.46–0.49) or 2008–2015 (0.37, 95% CI: 0.36–0.39) (**Table 3**).

The estimated hazard ratios (HRs) by treatment era are reported in **Table 3**. After adjustment for gender and age at diagnosis, treatment era was a significant prognostic factor ($P < 0.0001$): HRs were significantly diminished in the later 2 eras (HR = 0.87, 95% CI: 0.81–0.92 for 1996–2007 and HR = 0.69, 95% CI: 0.64–0.73 for 2008–2015).

Table 2 Relative excess risk of death (RER) due to diagnosis of multiple myeloma by treatment era in New South Wales, Australia, in 1985–2015 with 5-year follow-up (to 2020)

Item	RER	95% confidence interval	*P*-value
Treatment era			< 0.0001
1985–1995	1.00		
1996–2007	0.73	(0.69–0.78)	
2008–2015	0.48	(0.45–0.52)	
Gender			0.27
Female	1.00		
Male	1.03	(0.98–1.09)	
Age group (years)			< 0.0001
20–69	1.00		
70–79	1.71	(1.61–1.82)	
80–89	2.76	(2.57–2.96)	
Year of follow-up			< 0.0001
1	1.00		
2	0.70	(0.65–0.76)	
3	0.71	(0.66–0.77)	
4	0.64	(0.59–0.70)	
5	0.62	(0.56–0.68)	

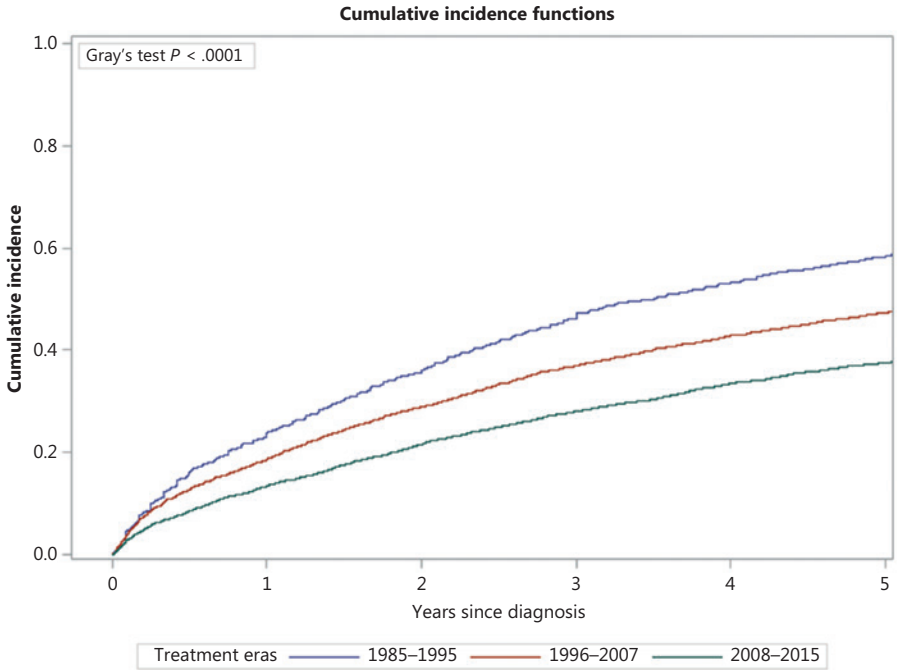

Figure 2 Cumulative incidence of death due to multiple myeloma among individuals diagnosed in different treatment eras, New South Wales, Australia.

Table 3 Five-year cumulative incidence of multiple myeloma death by treatment era, and hazard ratio (HR) from a subdistribution hazard model for death from multiple myeloma in New South Wales, Australia, in 1985–2015 with 5-year follow-up (to 2020)

Item	5-year cumulative incidence and 95% confidence interval		HR* and 95% confidence interval		*P*-value†
Treatment era					< 0.0001
1985–1995	0.58	(0.57–0.60)	1.00		
1996–2007	0.47	(0.46–0.49)	0.87	(0.81–0.92)	
2008–2015	0.38	(0.36–0.39)	0.69	(0.64–0.73)	

*Adjusted for gender and age group at diagnosis in the subdistribution hazard model.
†*P*-value for Gray's test for equality of cumulative incidence between treatment eras, or the type 3 test for treatment era from the subdistribution hazard model.

Discussion

Our study is the largest population-based analysis of MM survival in Australia to date, involving more than 11,000 individuals with MM. We observed a shift toward older age at diagnosis over time and an improvement in relative survival over the treatment eras, from 31.0% in 1985–1995 to 56.1% in 2008–2015, similarly to previous studies[16,18]. In the analysis adjusting for competing risk, the cumulative incidence of MM mortality was higher for those diagnosed in the 1985–1995 era than the later 2 eras. Over the 36-year study period, the excess mortality increased with increasing age at diagnosis, and the adjusted HR indicated that treatment era was a significant prognostic factor for MM.

Treatment era

Treatment options have been an important focus of MM management, given that MM is considered an incurable disease, and appropriate treatment can prolong life[10]. The treatment advancements in Australia from 1985 to 2020 have been previously outlined[12,30]. Briefly, the progression from chemotherapy alone to SCT to novel agents has introduced more options for the increasing number of individuals diagnosed and living with MM[6,30]. From the 1990s, SCT was heralded as a breakthrough in MM treatment, with evidence of improved 5-year overall survival in individuals with MM who received SCT compared with those who did not receive SCT in Australia[15]; however, improvements were generally seen in younger individuals (under 70 years of age)[16]. In our study, relative survival increased in the 1996–2007 era, aligning with the availability

of SCT. The improvement in relative survival continued in the 2008–2015 treatment era, thus reflecting the introduction of novel agents in Australia. Evidence has indicated that SCT, compared with conventional therapies, has resulted in improvements in overall survival[31,32]. Although not directly comparable, a Chinese hospital-based study[32] has found that people with MM who received SCT had significantly higher survival than those who did not receive SCT (similarly to our comparison of the first 2 treatment eras). In the same study, novel-agent-based regimens were associated with improved survival for people with MM[32], similarly to our observations in the first and third treatment eras in this study. The use of combinations of novel agents or younger age at treatment (< 70 years) have also demonstrated more pronounced improvements in overall survival[33,34]. The improvements in 5-year relative survival across the treatment eras observed in our study were similar to those in a study by Harwood et al.[16] reporting rates of 30% (1982–1995), 43% (1996–2007), and 53% (2008–2014).

Age group

Our findings showed improvements in relative survival across treatment eras by age group and gender. In older age groups (≥ 70 years), survival improved across the treatment eras, from 26% to 48% in people 70–79 years of age and, to a lesser extent, from 19% to 34% in people ≥ 80 years of age. Although many studies have reported improved survival outcomes over time for all age groups, the increase has commonly been less pronounced in older age groups compared to in younger age groups[17,18,35], as observed in those > 70 years of age between 1985–1995 and 1996–2007. An improvement was also seen in Harwood et al.[16] but was less pronounced in people ≥ 80 years of age, in whom the relative survival was 23% in 2008–2014. More recently, improvements in all age groups have become more evident[3,16-18,35]. The observation of less pronounced improvements in survival among older age groups until more recently is attributable to the lack of treatment options before the introduction of novel agents, given that Australian guidelines regarding SCT eligibility for people > 65 years of age have only recently changed, and that poorer disease biology and/or other comorbidities are associated with older age[12,15,36].

Strengths, limitations, and suggestions for future research

This study has several notable strengths. First the study included a substantially larger sample than previous Australian studies. Moreover, it captured all individuals with MM in the chosen population (NSW), unlike randomized controlled trials or other commonly used treatment efficacy study designs, which tend to involve strict recruitment selection criteria. Furthermore, we used triangulation within methods to increase study validity, and we observed a temporal survival improvement with 2 different analytical approaches: relative and cause-specific survival.

Although robust, our study is not without limitations. Given that comprehensive treatment information was not available, the exact treatment regimens in the cohort are unknown. The treatment eras were used as proxies for the treatment provided, in line with previous studies[16]. Furthermore, individuals were categorized into treatment eras according to their diagnosis date; however, although the date of diagnosis determined the number and choice of treatment options available to an individual, it did not indicate that the individual actually received the newest type of treatment available or even any treatment at all. For example, an individual diagnosed with MM between 2008 and 2014 (the "novel agent" treatment era) might have received SCT; however, the 5-year survival outcomes were calculated as part of the third treatment era. This approach might have overestimated the survival benefits attributed to treatment available at the time, because the survival improvements might potentially have been due to treatment regimens from earlier eras or other unknown lifestyle or biological factors. Although our relative survival analysis considered this possibility by using calendar-specific lifetables from the general population, such biases cannot be completely eliminated when long-term historical data are used.

As costly new MM therapies emerge, demonstrating the efficacy of MM treatments in terms of not only survival but also quality of life outcomes will become increasingly important, to ensure that treatments extend life without sacrificing quality of life. This aspect represents an important gap in the current MM literature: recent Australian research has reported that MM is associated with the highest levels of psychological distress, disability, and pain among all cancer types, as well as the lowest likelihood of continuing in the workforce, thus resulting in high indirect costs[37-39].

Conclusions

Our study demonstrated improvements in survival from 1985 to 2020 in a cohort of more than 11,500 people with MM in Australia. MM treatment advancements over multiple decades

in Australia corresponded to the survival improvements identified, thus probably reflecting the effects of the introduction of SCT and novel agents (proteasome inhibitors and immunomodulatory drugs) into routine clinical practice in Australia. Although, in more recent years, older age groups have started to experience significant improvements in survival with treatment advancements, MM remains more commonly diagnosed at older than younger ages, when survival improvements are poorer and treatment options are unclear, owing to a lack of evidence. Given the increasing prevalence of MM in Australia, the aging population and late-age at diagnosis, the effects of MM treatment on survival and quality of life, particularly in older age, warrants further attention.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceptualization, and Writing—original draft, and preparation of the Introduction and Discussion: Eleonora Feletto.
Conceptualization, Methodology, Statistical analysis, and Writing—original draft, and preparation of the Methods and Results; had full access to all data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis: Xue Qin Yu.
Writing—Critical revision of the manuscript for important intellectual content, and review and editing: Eleonora Feletto, Qingwei Luo, Anna Kelly, Marianne Weber, David Goldsbury, Katherine Barron, Karen Canfell, Xue Qin Yu.

Data availability statement

The data cannot be made available by the authors. These third party data are not owned or collected by the authors, and on-provision by the authors is not permitted by the relevant data custodians (NSW Ministry of Health), as it would compromise the participants confidentiality and privacy. The data contain potentially identifying and sensitive patient information. However, the data are available from the data custodians for approved research projects. Data access enquiries can be made to Cancer Institute NSW (https://www.cancer.nsw.gov.au/research-and-data/cancer-data-and-statistics/data-available-on-request/candle-program). Other researchers may be able to access these data through the same process followed by the authors.

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