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Large variation in radiation therapy fractionation for multiple myeloma in Australia

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Abstract

Aim: To evaluate the patterns of use of different radiation therapy (RT) fractionation for multiple myeloma (MM) bone disease.

Methods: This is a population-based cohort of patients with MM who had RT between 2012 and 2017 as captured in the statewide Victorian Radiotherapy Minimum Data Set in Australia. Data linkage was performed to identify subsets of RT delivered within 3 months of death. RT fractionation was classified into four groups: single-fraction (SFRT), 2–5, 6–10, and > 10 fractions. Changes in RT fractionation use over time were evaluated with the Cochran–Armitage test for trend. Factors associated with RT fractionation were evaluated using multivariate logistic regressions.

Results: Nine hundred and sixty-seven courses of RT were delivered in 623 patients. The proportion of SFRT, 2–5, 6–10 and > 10 fractions RT was 18%, 47%, 28%, and 7%, respectively. There was an increase in the use of 2–5 fractions, from 48% in 2012 to 60% in 2017 (p-trend < .001), with corresponding decrease in the use of 6–10 fractions, from 26% in 2012 to 20% in 2017 (p-trend = .003). Nine percent (40/430) of RT courses at private institutions were SFRT, compared to 25% (135/537) in public institutions ($p < .001$). In multivariate analyses, treatment in private institution was the strongest predictor of multifraction RT use. SFRT use was more common closer to the end of life––18%, 14%, and 33% of RT within 2–3, 1–2, < 1 month of death, respectively.

Conclusion: There is increasing use of shorter course RT (2–5 fractions) for MM over time. SFRT use remains low, with large variation in practice.

1 | INTRODUCTION

Bone involvement is common in patients with multiple myeloma (MM), with up to 80% of patients with newly diagnosed MM presenting with osteolytic lesions, with high risk of skeletal-related events, such as pathological fractures and spinal cord compression.[1] Radiation therapy (RT) is an effective treatment modality for symptom management of these bony lesions,[2] and evidence-based modeling estimated that approximately two in five patients with MM should receive at least one course of RT over the course of their disease.[3]

RT fractionation for bone metastases is an area that has been extensively investigated in the past. Meta-analyses of multiple randomized trials have consistently shown that single fraction RT (SFRT) is as effective as multifraction RT for symptom management for uncomplicated bone metastases.[4] However, few of these studies have specifically looked into the MM cohort. A randomized prospective trial comparing 30 Gy in 10 fractions to 8 Gy in 1 fraction for symptomatic bone lesions in 101 patients with MM showed no differences in symptom response.[5] In the setting of MM-related bone disease with spinal cord compression, in a large international multicenter retrospective pooled analysis, Rades et al. reported that long-course RT (10–20 fractions) resulted in better functional improvement compared to short-course RT (1–5 fractions).[6]

Based on the available evidence, several international guidelines and recommendations specifically on the management of MM-related bone disease have been developed by the International Myeloma Working Group[1] and International Lymphoma Radiation Oncology Group (ILROG).[2] The ILROG consensus guidelines recommend that 8 Gy in 1 fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions were all reasonable options for symptom control, but 8 Gy in 1 fraction is preferred for patients with poor prognosis.[2] In situations where there is spinal cord compression or bulky disease where durable control is desired, however, 30 Gy in 10–15 fractions is preferred.[2]

Despite these evidence and guidelines, it is unclear as to the actual pattern of practice of RT fractionation for MM in Australia. Earlier Victoria statewide population studies had evaluated the use of SFRT for the management of bone metastases,[7] but these were restricted to patients with solid tumors, excluding patients with hematological cancers, such as MM. It was unclear as to the proportion of patients with MM in a separate population-based study in the state of New South Wales in Australia.[8] The aim of this study is to evaluate the RT fractionation schedule used in the management of MM-related bone disease in Victoria, and to identify factors associated with multifraction RT.

2 | MATERIALS AND METHODS

2.1 | Study population

This study comprised a population-based cohort of patients with MM (ICD10: C90.0) who received RT between 2012 and 2017, as captured in the statewide Victorian Radiotherapy Minimum Data Set (VRDMS). VRDMS is an administrative dataset maintained by the Victorian Department of Health. Patients with plasma cell leukemia (ICD10: C90.1), extramedullary plasmacytoma (ICD10: C90.2), and solitary plasmacytoma (ICD10: C90.3) were excluded. We only included RT courses where the target site of RT was documented as bone. Data from VRMDS were linked with the Victorian Cancer Registry and the Registry of Births, Deaths and Marriages to capture data on death. We further analyzed a subset of RT delivered at the end of life (EOL), defined as at least one fraction palliative RT courses delivered within 90 days of death. The study was approved by our institutional Health Human Research Ethics Committee (LNR/18/34).

2.2 | Primary outcomes and covariables

The primary outcome was the different RT fractionations used, categorized into four ordinal groups: SFRT, 2–5 fractions, 6–10 fractions, and >10 fractions. Information on radiation dose was not available in VRMDS for the study period. Factors evaluated for association with different fractionations were: age at time of RT, sex, site of treated lesion (spine or non-spine), socioeconomic status, remoteness of residency (major cities, or regional/remote), treatment center type (public or private) and location (metropolitan or regional), and year of RT. Socioeconomic status was determined based on residential postcode using the Socio-Economic Indexes for Areas index for Relative Socio-Economic Disadvantage based on the Australian Bureau of Statistics data (i.e., based on 2011 Australian census data for patients treated in 2012 and 2013, and Australian census 2016 data for patients treated in 2014–2017); this was further subdivided into quintiles based on the Victorian general population. The area of residence was also dichotomized as major city or regional/remote using the Australian Statistical Geographical Standard remoteness structure. It is important to note that VRMDS does not capture information on MM-related prognostic factors, as well as information on systemic therapy that patients received.

2.3 | Statistical analyses

Variables associated with different RT fractionations were evaluated using Pearson's chi-squared test for categorical variables, and Kruskal–Wallis test for continuous variables. The Cochran–Armitage test for trend was used to evaluate the changes in different fractionation use over time. Multinomial logistic regression was used to assess the factors associated with different fractionations, with SFRT as the reference group. For the subset of RT courses delivered at the EOL, multivariate logistic regression was used to evaluate factors associated with SFRT. All multivariable analyses employed the robust standard errors, with analyses clustered on patient identifiers to allow for clustering of multiple courses of RT given to the same patient. A two-sided p-value of $< .05$ was considered to indicate statistical significances. All statistical analyses were performed using STATA/SE 17 (STATA Corp, College Station, TX, USA).

3 | RESULTS

A total of 967 courses of RT were delivered in 623 patients for MM between 2012 and 2017. The mean age at RT was 69.7 (SD = 11.7). Approximately two-third of the RT target sites were spine. The use of advanced RT techniques, such as intensity-modulated RT, volumetric-modulated arc therapy, or stereotactic RT, was rare (4%). Majority of RT

TABLE 1 Baseline characteristics and different fractionation for radiation therapy for multiple myeloma

Number of fractions	1 175 (18%)	2–5 452 (47%)	6–10 275 (28%)	>10 65 (6%)	*p*-value[#]
Age at RT					
Mean (SD)	69.2 (13.6)	70.2 (11.3)	69.3 (11.3)	69.8 (11.0)	
<60	49 (25%)	81 (42%)	54 (28%)	10 (5%)	.001
60–69	36 (13%)	137 (50%)	83 (30%)	18 (7%)	
70–79	41 (14%)	132 (45%)	96 (33%)	26 (9%)	
≥80	49 (24%)	102 (50%)	42 (21%)	11 (5%)	
Sex					
Male	107 (19%)	255 (46%)	148 (27%)	43 (8%)	.2
Female	68 (16%)	197 (48%)	127 (31%)	22 (5%)	
Target site of radiation therapy					
Non-spine	83 (24%)	140 (41%)	100 (29%)	22 (6%)	.002
Spine	92 (15%)	312 (50%)	175 (28%)	43 (7%)	
RT techniques					
3D CRT	172 (19%)	429 (46%)	265 (29%)	63 (7%)	.3
Advanced RT[a]	3 (8%)	23 (61%)	10 (26%)	2 (5%)	
Socioeconomic status					
First quintile (most disadvantaged)	41 (19%)	111 (51%)	49 (23%)	15 (7%)	.2
Second quintile	30 (21%)	64 (44%)	45 (31%)	5 (3%)	
Third quintile	21 (13%)	76 (48%)	52 (33%)	11 (7%)	
Fourth quintile	29 (15%)	85 (43%)	65 (33%)	17 (9%)	
Fifth quintile (least disadvantaged)	54 (22%)	116 (46%)	64 (26%)	17 (7%)	
Remoteness of residence					
Major cities	114 (17%)	311 (46%)	213 (31%)	42 (6%)	.02
Regional/remote	61 (21%)	141 (49%)	62 (22%)	23 (8%)	
Treatment institution type					
Public	135 (25%)	267 (50%)	104 (19%)	31 (6%)	<.001
Private	40 (9%)	185 (43%)	171 (40%)	34 (8%)	
Treatment institution location					
Metropolitan	135 (18%)	344 (45%)	234 (31%)	49 (6%)	.03
Regional	40 (20%)	108 (53%)	41 (20%)	16 (8%)	
Year of RT					
2012	21 (17%)	60 (48%)	32 (26%)	11 (9%)	
2013	38 (21%)	58 (33%)	65 (37%)	16 (9%)	
2014	28 (20%)	58 (41%)	49 (35%)	7 (5%)	
2015	24 (15%)	67 (42%)	53 (34%)	14 (9%)	
2016	36 (18%)	108 (55%)	42 (21%)	11 (6%)	
2017	28 (17%)	101 (60%)	34 (20%)	6 (4%)	
p-trend[*]	.5	<.001	.003	.05	

[a]Advanced RT techniques include intensity-modulated radiation therapy, volumetric-modulated arc therapy, and stereotactic radiation therapy.

[#]*p*-value from Pearson's chi-squared test.

[*]*p*-trend from Cochran–Armitage test for trend.

TABLE 2 Use of different RT fractionation stratified by based on remoteness of residence, stratified by treatment institution type and location

Treatment institution	Remoteness of residence	Number of fractions				
		1	2–5	6–10	>10	*p*-value
Public	Major cities	99 (26%)	175 (46%)	81 (21%)	23 (6%)	.09
(*n* = 537)	Regional/remote	36 (23%)	92 (58%)	23 (14%)	8 (5%)	
Private	Major cities	15 (5%)	136 (45%)	132 (44%)	19 (6%)	<.001
(*n* = 430)	Regional/remote	25 (20%)	49 (38%)	39 (30%)	15 (12%)	
Metropolitan	Major cities	102 (16%)	281 (45%)	204 (32%)	41 (7%)	.04
(*n* = 762)	Regional/remote	33 (25%)	63 (47%)	30 (22%)	8 (6%)	
Regional	Major cities	12 (23%)	30 (58%)	9 (17%)	1 (2%)	.3
(*n* = 205)	Regional/remote	28 (18%)	78 (51%)	32 (21%)	15 (10%)	

courses were delivered in metropolitan centers (79%), while just over half were delivered in public centers (56%).

3.1 | RT fractionation

Approximately one in five RT courses were SFRT, and half were delivered over 2–5 fractions (Table 1). There was higher proportion of SFRT use in patients aged under 60 years (25%) and above 80 years (24%). There was lower proportion of SFRT use for spine (15%) compared to non-spine (24%) sites of disease ($p = .002$). There were no significant differences in fractionation use between the different socioeconomic quintiles ($p = .2$).

Of the patients treated in private institutions, there were differences in RT fractionation use between patients who lived in major cities versus regional/remote areas—20% of RT delivered in those who lived in regional/remote areas was SFRT compared to 5% of RT delivered in those who lived in major cities ($p < .001$) (Table 2). Of patients treated in metropolitan centers, SFRT use was lower in those who lived in the major cities (16%) compared to those who live in regional/remote areas (25%) ($p = .04$) (Table 2).

3.2 | Trend in practice

Overall, there was no significant change in SFRT use over time (*p*-trend = .5) (Table 1). There is, however, a marked increase in the use of 2–5 fraction RT (from 48% in 2012 to 60% in 2017, *p*-trend < .001), with corresponding decrease in the use of 6–10 fraction RT (from 26% in 2012 to 20% in 2017; *p*-trend = .003) and > 10 fraction RT (from 9% in 2012 to 4% in 2017, *p*-trend .05).

This change in fractionation over time was observed when stratified by target site of RT, area of residence, and treatment centers (Figure 1A–H). For RT to non-spine sites, the most marked changes in fractionation were observed for 6–10 fractions, decreasing from 27% in 2012 to 14% in 2017 (*p*-trend = .012) (Figure 1A). For RT to spine, there was marked increase in the use of 2–5 fractions from 50% in 2012 to 62% in 2017 ($p < .001$) (Figure 1B). When stratified by area of residence, the increase in the use of 2–5 fractions was observed in patients who lived in both major cities (from 28% in 2012 to 54% in 2017; $p = .002$) (Figure 1C) and regional/remote areas (from 49% in 2012 to 72% in 2017; $p = .003$) (Figure 1D).

There were no statistically significant changes over time in fractionation in public institutions (Figure 1E). However, in private institutions, there was marked increase in the use of 2–5 fractions (from 38% in 2012 to 62% in 2017; *p*-trend < .001), and corresponding decrease in the use of 6–10 fractions (from 42% in 2012 to 29% in 2017, *p*-trend < .001) (Figure 1F). In metropolitan centers, there was increase in the use of 2–5 fractions (from 43% in 2012 to 56% in 2017; *p*-trend < .001) with corresponding decrease in 6–10 fractions (from 32% in 2012 to 25% in 2017; *p*-trend = .017) (Figure 1G). In regional centers, the use of RT fractionation varied over time, but the overall trend for the different RT fractionations over the 6-year period was not statistically significant (Figure 1H).

3.3 | Multivariate analyses

In multivariate analyses, patient age, target site of RT, area of residence, and treatment centers (type and location) were independently associated with the use of multifraction RT compared to SFRT, after adjusting for the year of treatment (Table 3). Compared to patients aged under 60 years, those aged 60–69 were 2.2 times (95%CI = 1.2–4.0; $p = .01$) more likely to have 2–5 fraction RT (than SFRT), while patients aged above 80 were less likely (OR=0.46; 95%CI = 0.21-0.99; p=0.05) to have 6–10 fraction RT (than SFRT).

Treatment to the spine was more likely to be multifraction RT than SFRT –2.2 times (95%CI = 1.5–3.3; $p < .001$) more likely to be 2–5 fractions, and 1.9 times (95%CI = 1.2–3.0; $p = .01$) more likely to be 6–10 fractions. Compared to patients who lived in major cities, RT delivered to patients who lived in regional or remote centers was less likely to be multifraction RT than SFRT – 47% (95%CI = 2–71%; $p = .04$) relatively less likely to be 2–5 fractions, and 67% (95%CI = 31–84%; $p = .003$) less likely to be 6–10 fractions.

Treatment in private institutions was most strongly associated with multifraction RT use, compared to public institutions – 3.3 times (95%CI = 2.0–5.4; $p < .001$) more likely to be 2–5 fractions, 7.8 times (95%CI = 4.5–13.6; $p < .001$) more likely to be 6–10 fractions, and 5 times (95%CI = 2.2–11.2; $p < .001$) more likely to be > 10 fractions.

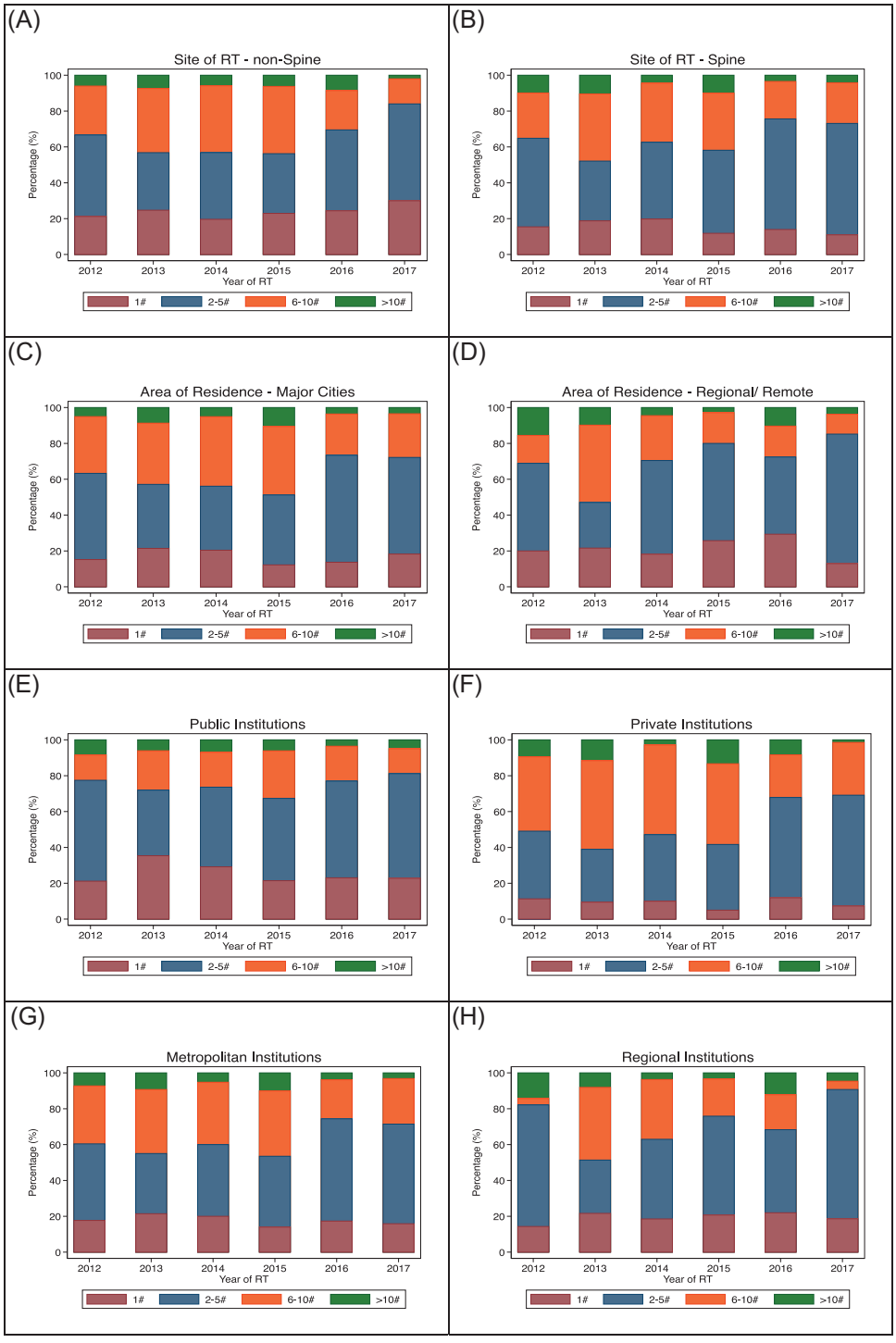

FIGURE 1 Radiation therapy fractionation for multiple myeloma from 2012 to 2017, stratified site of RT (nonspine [A] and spine [B]), area of residence (major cities [C] and regional/remote area [D]), institutional type (public [E] and private [F]), and institutional location (metropolitan [G] and regional [H]) [Colour figure can be viewed at wileyonlinelibrary.com]

3.4 | EOL cohort

There were 122 courses of RT delivered to 59 patients at the EOL, of which only one-quarter of the RT courses was SFRT (Table 4). SFRT was more likely to be given closer to death, comprising 18%, 14%, and 33% of RT courses delivered within 2–3 months, 1–2 months, and < 1 months of death, respectively ($p = .08$). The use of SFRT at the EOL was markedly lower in private institutions (7%) compared to public institutions (41%) ($p < .001$). In multivariate analyses, treatment in private institutions was the only factor indepen-

TABLE 3 Factors associated with different fractionation schedule for multiple myeloma-related bone disease in multivariate analyses (single-fraction RT was used as reference group)

	2–5 fractions		6–10 fractions		>10 fractions	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age at RT						
<60	Reference		Reference		Reference	
60–69	2.17 (1.17–3.98)	.01	1.92 (.95–3.85)	.07	2.37 (.79–7.11)	.1
70–79	1.54 (.82–2.91)	.2	1.57 (.78–3.16)	.2	2.72 (.98–7.51)	.05
≥80	.85 (.45–1.61)	.5	.46 (.21–.99)	.05	.76 (.23–2.48)	.7
Sex (male vs. female)	1.33 (.84–2.09)	.2	1.40 (.83–2.36)	.2	.80 (.39–1.66)	.6
Target site of radiation therapy (nonspine vs. spine)	2.19 (1.45–3.33)	<.001	1.85 (1.15–2.98)	.01	1.97 (.96–4.06)	.07
Socioeconomic status						
First quintile (most disadvantaged)	Reference		Reference		Reference	
Second quintile	.66 (.32–1.34)	.2	.96 (.42–2.21)	.9	.33 (.09–1.17)	.09
Third quintile	1.29 (.61–2.71)	.5	1.79 (.74–4.30)	.2	1.29 (.35–4.79)	.70
Fourth quintile	.91 (.44–1.89)	.8	1.22 (.54–2.80)	.6	1.51 (.55–4.15)	.4
Fifth quintile (least disadvantaged)	.70 (.36–1.33)	.3	.67 (.31–1.43)	.3	.86 (.32–2.36)	.8
Remoteness of residence (major city vs. regional/remote)	.53 (.29–.98)	.04	.33 (.16–.69)	.003	.83 (.35–1.98)	.7
Treatment institution type (public vs. private)	3.29 (2.01–5.38)	<.001	7.82 (4.51–13.57)	<.001	4.98 (2.21–11.24)	<.001
Treatment institution location (metropolitan vs. regional)	1.91 (1.00–3.64)	.05	1.76 (.82–3.80)	.1	1.86 (.65–5.32)	.2
Year of RT						
2012	Reference		Reference		Reference	
2013	.49 (.22–1.12)	.09	.87 (.37–2.09)	.8	.74 (.23–2.40)	.6
2014	.74 (.32–1.68)	.5	1.05 (.42–2.63)	.9	.50 (.13–1.87)	.3
2015	.96 (.43–2.15)	.9	1.33 (.54–3.30)	.5	1.30 (.39–4.32)	.7
2016	1.12 (.52–2.44)	.8	.74 (.30–1.83)	.5	.69 (.18–2.67)	.6
2017	1.28 (.60–2.73)	.5	.79 (.32–1.96)	.6	.42 (.10–1.74)	.2

dently associated with SFRT use (OR = .04; 95%CI = .004–.33; $p = .003$).

4 | DISCUSSION

This is to our knowledge the first Australian population-based study to evaluate the pattern of RT fractionation for MM-related bone disease. We found that SFRT remains a minority of RT fractionation regimens, consistent with the findings of RT for bone metastases in solid tumors.[7–11] A major strength of this study is the use of population-based administrative data, which capture all episodes of RT delivered in Victoria, both in public and private institutions. Thus, the data reflect our statewide practice, allowing us to evaluate any sociodemographic and institutional variations in care, which is not possible using single-institutional studies.

The most common fractionation used in our cohort was 2–5 fractions, and its use has increased over our study period. In contrast, the use of more extended fractionations of 6–10 fractions has decreased. This is in contrast to findings from the only other published population-based series in the literature, using data from the U.S. National Cancer Database (NCDB) between 2004 and 2014, whereby more than half of the RT fractionations for MM were 6–10 fractions.[12] The use of SFRT in our cohort remained low at 18% over the study period, which is similar in the management of bone metastases in solid tumor in Victoria,[7,10,11] but was still much higher than the 2% SFRT use for MM reported in NCDB cohort.[12]

The number of prescribed RT fractions is often guided by the patients' MM disease trajectory and overall prognosis. However, one of the major limitations of this study is the lack of information in some of the important patient factors (e.g., ECOG performance status), tumor-factors (e.g., Revised International Staging System prognostic factors for MM[13]), and treatment factors (e.g., the use of systemic therapy[14]) in administrative databases, such as VRMDS. Hence, we are not able to evaluate the appropriateness of RT fractionation use in each individual patient––a young patient with good performance status early in the

TABLE 4 Factors associated with single fraction radiation therapy (SFRT) in the last 3 months of life ($N = 122$)

	Single fraction $N = 30$ (25%)	Multifraction $N = 92$ (75%)	OR (95% CI)	*p*-value
Age at RT				
Mean (SD)	68.3 (13.7)	72.0 (11.1)		
<60	10 (50%)	10 (50%)	Reference	
60–69	8 (20%)	32 (80%)	.26 (.05–1.33)	.1
70–79	4 (14%)	25 (86%)	.86 (.14–5.13)	.9
≥80	8 (24%)	25 (76%)	.57 (.10–3.40)	.5
Time to death				
<1 month	20 (33%)	40 (67%)	Reference	
1–2 months	3 (14%)	19 (86%)	.43 (.05–3.91)	.5
2–3 months	7 (18%)	33 (82%)	.56 (.12–2.58)	.5
Sex				
Male	21 (27%)	57 (73%)	Reference	
Female	9 (20%)	35 (80%)	.83 (.25–2.79)	.8
Target site of radiation therapy				
Nonspine	12 (30%)	28 (70%)	Reference	
Spine	18 (22%)	64 (78%)	.26 (.06–1.12)	.07
Socioeconomic status				
First quintile (most disadvantaged)	6 (19%)	25 (81%)	Reference	
Second quintile	5 (26%)	14 (74%)	1.74 (.26–11.5)	.6
Third quintile	6 (32%)	13 (68%)	.89 (.17–4.59)	.9
Fourth quintile	2 (11%)	16 (89%)	.47 (.04–5.77)	.6
Fifth quintile (least disadvantaged)	11 (31%)	24 (69%)	2.54 (.37–17.19)	.3
Remoteness of residence				
Major cities	23 (23%)	75 (77%)	Reference	
Regional/remote	7 (29%)	17 (71%)	3.73 (.69–20.1)	.1
Treatment institution type				
Public	26 (41%)	38 (59%)	Reference	
Private	4 (7%)	54 (93%)	.04 (.004–.33)	.003
Treatment institution location				
Metropolitan	27 (25%)	83 (75%)	Reference	
Regional	3 (25%)	9 (75%)	.66 (.07–5.75)	.7
Year of RT				
2012	1 (9%)	10 (91%)	Reference	
2013	8 (26%)	23 (74%)	5.39 (.45–65.0)	.2
2014	7 (25%)	21 (75%)	2.39 (.17–32.8)	.5
2015	9 (33%)	18 (67%)	2.84 (.24–33.2)	.4
2016	5 (20%)	20 (80%)	1.04 (.06–16.9	.9

course of disease with availability of multiple systemic therapy options may warrant higher dose multifraction RT to provide more durable control, and this is different to a frail patient who is refractory to multiple lines of systemic therapy at the EOL. Nonetheless, it is important for radiation oncologists to stay abreast with advancement in systemic therapy options for MM,[15] as new combination systemic therapies (e.g., carfilzomib, daratumumab, and dexamethasone) have been shown to significantly improve outcomes, even in the setting of refractory MM,[16] and this may influence the decision making in RT fractionation prescribed.

There should be less ambiguity in RT fractionation recommendation for patients with limited or poor prognosis at the EOL––ILROG

guidelines recommend that single fraction 8 Gy is the preferred RT fraction for patients with poor prognosis who require RT.[2] In the subset of RT courses delivered within 3 months of death (i.e., at the EOL) in our cohort, the overall SFRT use in our cohort still appears reasonably low at 25%. The underutilization of SFRT at the EOL has been previously reported in the management of bone metastases in solid tumor.[17] This could reflect either a general reluctance for the use of SFRT even at the EOL, or clinicians' overestimation of patients' likely survival.[18]

The RT fractionation used also varied depending on the *target site of treatment*––with lower use of SFRT for spinal disease. ILROG guidelines recommend the use of multifraction RT of 30 Gy in 10–15 fractions in situations where there is epidural disease with spinal cord compression.[2] One limitation of our study is that we do not have detailed clinical information to determine whether the treated spinal disease was associated with spinal instability, pathological fractures requiring surgical interventions, or spinal cord compression, which may justify the need for multifraction RT. We are also unable to account for reirradiation using VRMDS data, which is especially important in spinal disease, given the RT tolerance dose for spinal cord. Given that VRMDS data were only available from 2012 onward, we were not able to confirm if a patient has had RT to the same site prior to 2012. Even when the same target site was irradiated (e.g., spine) on more than one occasion since 2012, we do not have sufficient information to confirm if it was reirradiation of the same level of vertebra, or radiation of another vertebra level, not previously irradiated.

We also evaluated institutional and demographic factors associated with RT fractionation use. One of the most striking findings is that treatment in *private institutions* is the strongest predictor of multifraction RT use. The higher proportion of multifraction RT use persisted even at the EOL and after adjusting for patients' age and target site of RT. A most likely explanation for the differences in RT fractionation use between institutions may be remuneration related. In the current Australian healthcare setting, the Medicare Benefits Schedule (MBS) reimbursement for RT is based on the number of fractions delivered – MBS reimbursement for SFRT, 5-fraction RT, and 10-fraction RT delivered using 3D-conformal technique in Australia was AUD 1320.35–1948.80, AUD 1821.75–2947.35, and AUD 2448.50–4497.60, respectively, depending on the number of organs-at-risks and number of RT fields involved.[19] However, we also could not discount other possible explanations for the observed variations in practice, including differences in patient population seen in public versus private institutions, and possibly resources and capacity constraints in public institutions for delivery of multifraction RT.

We observed no differences in RT fractionation use by patient *socioeconomic status* but there were differences in RT fractionation use depending on patients' *area of residence*––those living in regional or remote areas were less likely to be treated with multifraction RT. This may reflect clinicians' consideration and accommodation of patients' preference to reduce the number of visits for treatment given the long travel distance to and from RT facilities. While remoteness of residence is an indirect measure of access to RT facilities, there is now increasing number of RT facilities being established in regional areas in Australia. A better measure of access would be the travel distance to the nearest RT facility, but these data were not available in our study. This has been assessed in earlier studies,[20,21] which found that increasing distance to the nearest RT facilities was associated with lower likelihood of receiving RT.

Apart from the limitations highlighted above, another inherent limitation with the use of administrative dataset is that it is dependent on accuracy of reporting from each institution, and we cannot discount the possibility of misclassification of variables. This is especially critical in potential miscoding of the diagnosis between MM and solitary plasmacytoma, which will influence the recommended RT fractionation––solitary plasmacytoma is often treated with higher dose and more protracted fractionation.[2]

5 | CONCLUSION

Using an Australian administrative dataset, we observed increasing use of shorter fractionated RT schedules (2–5 fractions) for MM-related bone disease between 2012 and 2017 in a population-based cohort of patients. However, the use of SFRT remained low, even at the EOL. We also observed large variations in RT fractionation use depending on institutional type, with SFRT much more commonly used in public centers. This is an important pattern-of-practice study for MM in Australia as it provides us with a baseline benchmark of the contemporary practice pattern for MM to be measured against (which to date, is not available in any published literature) for future quality improvement initiatives to reduce unwarranted variations in practice.[22] With advancement in systemic therapy for MM and as patients with MM are living longer,[15] we anticipate that the pattern of practice of RT for MM-related bone disease will continue to evolve, not only with respect to RT fractionation, but on the use of advanced RT techniques .[19]

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ETHICS STATEMENT

The study was approved by Austin Health Human Research Ethics Committee (LNR/18/34).

DATA AVAILABILITY STATEMENT

Data will be shared upon reasonable request to the corresponding author.

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