RADIATION ONCOLOGY—ORIGINAL ARTICLE

Variations in whole brain radiation therapy fractionation for brain metastases in Victoria

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Abstract

Introduction: We aim to evaluate the use of different whole brain radiation therapy (WBRT) fractionation schedules for brain metastases (BM) in Victoria, and the factors associated with it.

Methods: This is a population-based cohort of patients who received radiation therapy for BM between 2012 and 2017, as captured in the Victorian Radiotherapy Minimum Dataset. We excluded patients with primary brain tumour and those who had 'prophylactic' intent treatment. The Cochran–Armitage test was used to evaluate changing trend in WBRT fractionation. Multivariate multinomial logistic regressions were used to evaluate factors associated with WBRT fractionation.

Results: Of the 3111 patients who had WBRT, 1048 (45%), 1291 (42%) and 312 (13%) had ≤5, 6–10 and >10 fractions WBRT respectively. There was progressive increase in ≤5 fractions WBRT use over time, from 37% in 2012 to 50% in 2017 (P-trend < 0.001). In multivariate analyses, increasing age, patients with gastrointestinal cancer, patients living in remote/regional areas and more recent treatment were associated with the use of shorter WBRT fractionation (≤5 fractions), while patients who had WBRT plus stereotactic radiosurgery, and those treated in private institutions were associated with the use of prolonged WBRT fractionation (≥6 fractions). Three hundred eighty-nine (13%) patients died within 30 days of WBRT, of which 241 (64%), 119 (32%) and 17 (5%) had ≤5, 6–10 and > 10 fractions WBRT respectively.

Conclusion: We observed large variations in WBRT fractionation that are associated with patient, tumour, treatment and institutional factors. It is important to continuously monitor and benchmark our practice in order to reduce potentially unwarranted variations.

Key words: brain metastases; whole brain radiation therapy.

Introduction

Brain metastases (BM) are common, particularly in patients with lung cancer, breast cancer and melanoma.[1] The exact incidence of BM, while unknown, is reported to be increasing,[2] in part due to advancement in brain imaging and patients living longer due to effective systemic therapies. Nonetheless, outcomes of patients with BM remain poor, and most treatments aim to provide intracranial control and to maintain or slow the worsening in neurological symptoms and quality of life, rather than cure.

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Historically, whole brain radiation therapy (WBRT) is the conventional treatment option for patients with multiple BM.[3] There is a wide range of dose-fractionation schedules for WBRT, with five to ten fractions being the most commonly prescribed.[4] Several randomised trials, albeit older trials, have looked at different dose-fractionation schedules, but none have been shown to be superior in terms of survival.[5–9] Given the limited survival following WBRT for BM, the goal is to mitigate the decline in quality of life. It is however challenging to balance the potential clinical benefits from WBRT versus its neurocognitive toxicities.[10,11] In situations where WBRT is clinically justified, the aim is to ensure that the shortest and most effective treatment is delivered, so that patients do not spend prolonged periods receiving treatment, especially at the very end of life (EOL). In patients with a very poor prognosis, evidence from the QUARTZ trial in non-small cell lung cancer cohort has shown that optimal supportive care with omission of WBRT is a reasonable option.[12]

A recent study from New South Wales has reported large, and potentially unwarranted, variations in the WBRT fractionations used.[13] There is however limited similar data in Victoria. The aim of the current study is to utilise the Victorian population-based administrative database to evaluate the variations in WBRT fractionation use in Victoria.

Methods

Study population

This is a Victorian population-based cohort of patients with solid tumour (ICD-10 codes: C00-C80), who received radiation therapy (RT) to the brain between January 2012 and December 2017. Patients were identified from the Victorian Radiotherapy Minimum Data Set (VRMDS), a state-wide administrative healthcare dataset, which captures all episodes of RT delivered in both public and private RT facilities in Victoria. To restrict the cohort to patients who received palliative RT for brain metastases, we excluded patients with primary CNS malignancies (ICD-10 code: C69-72), and those whose RT intention was documented as 'prophylactic'. Data from VRMDS were linked with the Victorian Cancer Registry (VCR) and the Registry of Births, Deaths and Marriages (BMD), which capture data on death in Victoria. The study was approved by our institutional Human Research Ethics Committee (LNR/18/34).

Primary outcomes and covariables

The primary outcomes were proportion of different WBRT fractionations used, which was divided into three ordinal fractionation categories: ≤5 fractions, 6–10 fractions and >10 fractions. Data on the number of fractions were available in VRMDS, but information on dose-per-fraction was not available for the study period. RT techniques documented in VRMDS included 3D conformal RT (3DCRT), intensity-modulated RT (IMRT), volumetric modulated arc therapy (VMAT), stereotactic RT (SRT) and stereotactic radiosurgery (SRS). Consistent with earlier VRMDS study,[14] we used the following definition to operationally distinguish WBRT from SRS—any IMRT/VMAT/SRT treatment of not more than 4 fractions were classified as SRS, given the unavailability of information on dose-per-fraction in VRMDS, and the potential coding inconsistencies in RT techniques in VRMDS for the study period. We further analysed WBRT fractionation in a subset of patients who had WBRT at the EOL, defined as those who died within 30 days of WBRT. The covariables of interest adjusted in the analyses were age at WBRT, sex, primary cancer type, the use of SRS in combination with WBRT, socioeconomic status (divided into quintiles), remoteness of area of residency (major cities vs. regional/remote), treatment institution type (public vs. private) and location (metropolitan vs. regional) and year of WBRT.

Statistical analyses

Differences in characteristics between patients who had different WBRT fractionation categories were evaluated using Pearson's chi-squared test. The Cochran–Armitage test for trend was used to evaluate the change in trend for each fractionation categories over time. Multinomial logistic regressions were used to evaluate factors associated with prolonged fractionation (separately for 6–10 fractions and >10 fractions), with ≤5 fractions as reference group. For patients who died within 30 days of WBRT, logistic regressions were used to evaluate factors associated with prolonged fractionation (≥6 fractions). Covariables with $P < 0.1$ in univariable analyses were included in multivariable analyses. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using STATA/SE17 (StataCorp, College Station, TX, USA).

Results

There were 3961 patients who had radiation therapy for BM between 2012 and 2017 in Victoria. Overall, 3111 (78%) had WBRT, and the proportion who had WBRT decreased from 82% in 2012 to 69% in 2017 (P-trend < 0.001) (Fig. 1). Of the 3111 patients who had WBRT and were included in this study, 2845 (91%) had WBRT alone, while 266 (9%) had SRS in combination with WBRT (Table 1).

WBRT fractionation

There were 1408 (45%) patients who had ≤5 fractions WBRT, 1291 (42%) had 6–10 fractions, and 312 (13%) had >10 fractions (Table 1). Older patients were more

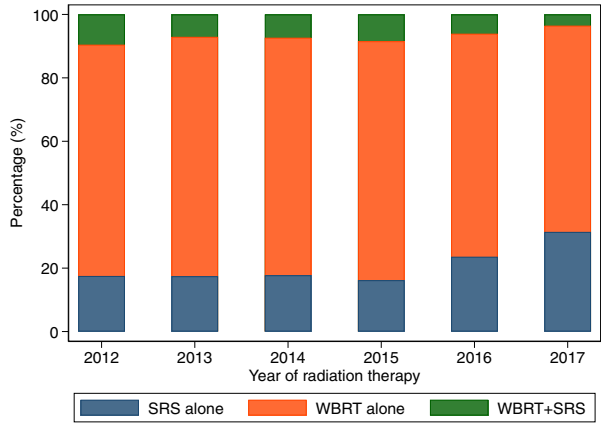

Fig. 1. Trend in the use of stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT) from 2012 to 2017 (n = 3961).

likely to have ≤5 fractions WBRT—54% in patients >75 years old vs. 38% in patients <55 years old ($P < 0.001$). There was also higher proportion of ≤5 fractions WBRT in patients with gastrointestinal cancer (56%) compared with other cancers ($P < 0.001$). Patients who had WBRT in combination with SRS were more likely to have 6–10 fractions (53%) compared with those who did not have SRS (40%) ($P < 0.001$). There was higher proportion of shorter fraction (≤5 fractions) WBRT delivered in public institutions (54%), whereas prolonged fractionation WBRT was more commonly delivered in private institutions (52% were 6–10 fractions and 15% were > 10 fractions; $P < 0.001$). There was progressive increase in ≤5 fraction WBRT use over time from 37% in 2012 to 50% in 2017 (P-trend < 0.001), with corresponding decrease in 6–10 fraction WBRT use, from 50% in 2012 to 38% in 2017 (P-trend < 0.001) (Fig. 2).

In multivariate analyses, patients' age, primary cancer type, combination of SRS, area of residence, treatment institution type and year of treatment were independently associated with the use of a different WBRT fractionation (Table 2). Compared with ≤5 fraction WBRT, for every year increase in age, there was a lower likelihood of being treated with 6–10 fractions (OR = 0.98; 95% CI = 0.97–0.99; $P < 0.001$) or > 10 fractions (OR = 0.97; 95% CI = 0.96–0.98; $P < 0.001$) WBRT. Compared with lung cancer patients, patients with gastrointestinal cancers were less likely to have 6–10 fractions WBRT (OR = 0.64; 95% CI = 0.48–0.63; $P = 0.003$). Patients who had SRS in combination with WBRT were 1.6 times (95% CI = 1.2–2.2; $P < 0.001$) more likely to have 6–10 fraction WBRT instead of ≤5 fraction WBRT. Patients who lived in regional or remote area were less likely to be treated with 6–10 fraction WBRT compared with those who live in major city (OR = 0.80; 95% CI 0.64–0.99; $P = 0.04$). Patients treated in private institutions were more likely to be treated with prolonged fractionation (OR = 2.7, 95% CI = 2.3–3.2; $P < 0.001$ for 6–10 fractions and OR = 2.6; 95% CI = 2.0–3.3; $P < 0.001$ for >10 fractions). More recent year of treatment was associated with lower likelihood of prolonged fractionation for WBRT ($P < 0.001$).

WBRT at the EOL

There were 389 (13%) patients who died within 30 days of WBRT, with approximately half died within 2 weeks of WBRT. Of these 389 patients, 241 (64%), 119 (32%) and 17 (5%) had ≤5, 6–10 and > 10 fractions WBRT respectively (Table 3). There was a non-statistically significant increase in the use of shorter course of WBRT (≤5 fractions) at the EOL over time—from 57% in 2012 to 69% in 2016 (P-trend = 0.08). In multivariate analyses, time-to-death and treatment in private institutions were independently associated with the use of prolonged fractions (≥6 fractions) at the EOL (Table 4). Compared with those who died within 1-week of WBRT, those who died 15–30 days post-WBRT were 1.8 times (95% CI = 1.1–2.9; $P = 0.03$) more likely to have prolonged fractionation. Those treated in private institutions were 2.5 times (95% CI = 1.6–3.8; $P < 0.001$) more likely to be treated with prolonged fractionation.

Discussion

This is the first population-based study on the pattern of WBRT fractionation in Victoria. There are very few similar population-based studies in the literature reporting on the different WBRT fractionation used.[13,15,16] Our findings are similar to an earlier study from New South Wales, whereby approximately half of WBRT episodes were short-course RT (≤5 fractions), and only approximately one-in-ten were prolonged fractionation (>10 fractions).[13] This pattern of WBRT fractionation use was also similar to a registry-based study in Ontario, Canada, whereby 60% of WBRT delivered between 1998 and 2007 were 20 Gy in 5 fractions.[15] However, the practice in the United States is markedly different, with a study using the US National Cancer Database reporting that 57% of WBRT delivered between 2010 and 2015 were 30 Gy in 10 fractions.[16]

A major strength of the current study is that it is based on actual delivered RT courses, and hence reflect a true state-wide practice, rather than what clinicians would theoretically do as reported in a pattern of practice survey.[4] Nonetheless, it is reassuring that in an international survey conducted by the American Society for Radiation Oncology (ASTRO), European Society for Therapeutic Radiology and Oncology (ESTRO), Canadian Association of Radiation Oncology (CARO) and Royal Australian and New Zealand College of Radiologists (RANZCR), the survey responses by Australian and New Zealand clinicians were consistent with the actual clinical practice in Victoria—whereby 57% and 36% of survey respondents reported routinely using 20 Gy in 5 fractions and 30 Gy

Table 1. Baseline characteristics of patients who received different fractionation of whole brain radiation therapy (WBRT)

	All patients (*N* = 3111)	≤5 fractions (*N* = 1408, 45%)	6–10 fractions (*N* = 1291, 42%)	>10 fractions (*N* = 312, 13%)	*P*-value**
Age at WBRT					
Mean (SD) (years)	64.8 (12.5)	66.5 (12.2)	64.1 (11.4)	61.4 (15.6)	<0.001
<55 y/o	632 (20%)	243 (38%)	287 (45%)	102 (16%)	<0.001
55–59 y/o	368 (12%)	146 (40%)	166 (45%)	56 (15%)	
60–64 y/o	464 (15%)	212 (46%)	183 (39%)	69 (15%)	
65–69 y/o	532 (17%)	232 (44%)	235 (44%)	65 (12%)	
70–74 y/o	484 (16%)	235 (49%)	195 (40%)	54 (11%)	
≥75 y/o	631 (20%)	340 (54%)	225 (36%)	66 (10%)	
Sex					
Male	1490 (48%)	705 (47%)	576 (39%)	209 (14%)	0.008
Female	1621 (52%)	703 (43%)	715 (44%)	203 (13%)	
Primary cancer					
Lung cancer	1439 (46%)	684 (48%)	604 (42%)	151 (10%)	<0.001
Breast cancer	573 (18%)	224 (39%)	280 (49%)	69 (12%)	
Melanoma	342 (11%)	155 (45%)	150 (44%)	37 (11%)	
Gastrointestinal cancer	255 (8%)	144 (56%)	87 (34%)	24 (9%)	
Genitourinary cancer	197 (6%)	97 (49%)	75 (38%)	25 (13%)	
Other	305 (10%)	104 (34%)	95 (31%)	106 (35%)	
RT techniques					
WBRT alone	2845 (91%)	1311 (46%)	1150 (40%)	384 (14%)	<0.001
WBRT + SRS	266 (9%)	97 (36%)	141 (53%)	28 (11%)	
Socioeconomic status					
1st quintile (lowest)	660 (21%)	317 (48%)	256 (39%)	87 (13%)	0.63
2nd quintile	546 (18%)	250 (46%)	221 (40%)	75 (14%)	
3rd quintile	626 (20%)	267 (43%)	279 (45%)	80 (13%)	
4th quintile	668 (21%)	297 (44%)	276 (41%)	95 (14%)	
5th quintile (highest)	611 (20%)	277 (45%)	259 (42%)	75 (12%)	
Remoteness classification					
Major city	2131 (69%)	951 (45%)	914 (43%)	266 (12%)	0.04
Regional/Remote	980 (31%)	457 (47%)	377 (38%)	146 (15%)	
Treatment institution type					
Public	1829 (59%)	990 (54%)	625 (34%)	214 (12%)	<0.001
Private	1282 (41%)	418 (33%)	666 (52%)	198 (15%)	
Treatment institution location					
Metropolitan	2281 (73%)	1004 (44%)	979 (43%)	298 (13%)	0.026
Regional	830 (27%)	404 (49%)	312 (38%)	114 (13%)	
Year of BM treatment					
2012	312 (10%)	114 (37%)	155 (50%)	43 (14%)	
2013	370 (12%)	139 (38%)	172 (46%)	59 (16%)	
2014	468 (15%)	197 (42%)	192 (41%)	79 (17%)	
2015	694 (22%)	306 (44%)	291 (42%)	97 (14%)	
2016	678 (22%)	359 (53%)	255 (38%)	64 (9%)	
2017	589 (19%)	293 (50%)	226 (38%)	70 (12%)	
P-trend*		<0.001	<0.001	0.005	

***P*-value based on Pearson's chi-squared test.

**P*-trend based on Cochran–Armitage test for trend.

in 10 fractions for WBRT respectively.[4] The international survey, however, highlighted marked international variations in practice, with only 6% of US clinicians and 35% of European clinicians routinely using 20 Gy in 5 fractions for WBRT.[4]

We observed increasing use of shorter fractionation WBRT (≤5 fractions) over time, from 37% in 2012 to 50% in 2017, with proportional decrease in the use of prolonged fractionation WBRT (6–10 fractions), from 50% in 2012 to 38% in 2017 (Table 1). This is likely attributable to the changing philosophy in the management of BM over the years in the past, patients with limited BM, good extracranial control and favourable prognoses were often treated with prolonged fractionation WBRT of lower dose-per-fraction to minimise the risk of late treatment-related toxicities. However, there is now an increasing interest and shift towards the use of SRS alone, and to avoid or delay WBRT in this group of

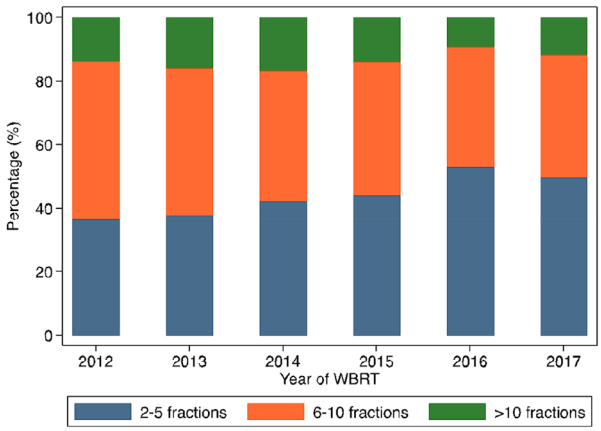

Fig. 2. Trend in different fractionation for whole brain radiation therapy from 2012 to 2017 (n = 3111).

patients.[16-19] Reflecting this, a recent study has suggested that even in patients with up to ten BM lesions, SRS alone without WBRT may be an appropriate treatment option without compromising outcomes.[20] A recent study from Victoria has reported an increasing the use of SRS from 27% in 2012 to 35% in 2017 (P-trend < 0.001) among all patients who had radiation therapy for BM.[14] In the current study, we also observed a decrease in proportion of patients who were treated with WBRT (Fig. 1). However, some patients may still be treated with combination of SRS and WBRT. In our study, patients who had SRS in combination with WBRT were more likely to have prolonged WBRT fractionation—53% received 6–10 fractions and 11% received >10 fractions—compared with those who had WBRT alone. It is of interest to note that the multiple randomised trials that showed improved intracranial control benefits with the combination of SRS and WBRT had consistently used ten to fifteen fractions of WBRT.[21-24] These data may have influenced the use of longer fractionation WBRT with SRS as observed in our study. This pattern was also observed in the aforementioned pattern of practice survey, whereby 80% of Australia and New Zealand clinicians reported using ten or more fractions WBRT when used in combination with SRS.[4]

We reported large variations in practice and identified several patient, tumour and institutional factors that were associated with different WBRT fractionation use. It is also important to acknowledge that not all variation is

Table 2. Factors associated with each fractionation schedule in univariate and multivariate multinomial logistic regressions (≤5 fractions was used as reference group)

	Univariate analyses				Multivariate analyses			
	6–10 fractions		>10 fractions		6–10 fractions		>10 fractions	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age at RT	0.98 (0.97–0.99)	<0.001	0.97 (0.96–0.98)	<0.001	0.98 (0.97–0.99)	<0.001	0.97 (0.96–0.98)	<0.001
Sex (male vs. female)	1.25 (1.07–1.45)	0.004	0.97 (0.78–1.21)	0.8	1.02 (0.86–1.23)	0.8	0.81 (0.62–1.06)	0.1
Primary cancer								
Lung cancer	Reference		Reference		Reference		Reference	
Breast cancer	1.41 (1.15–1.74)	0.001	1.40 (1.02–1.94)	0.04	1.12 (0.89–1.43)	0.3	1.14 (0.80–1.63)	0.5
Melanoma	1.09 (0.85–1.40)	0.5	1.09 (0.73–1.62)	0.7	1.09 (0.83–1.42)	0.5	1.01 (0.66–1.53)	0.9
Gastrointestinal cancer	0.68 (0.51–0.91)	0.009	0.76 (0.48–1.21)	0.3	0.64 (0.48–0.86)	0.003	0.68 (0.43–1.10)	0.1
Genitourinary cancer	0.87 (0.63–1.20)	0.4	1.18 (0.73–1.89)	0.5	0.90 (0.64–1.27)	0.5	1.14 (0.69–1.88)	0.6
Other	1.03 (0.77–1.39)	0.8	4.65 (3.36–6.42)	<0.001	0.99 (0.73–1.35)	0.9	4.09 (2.92–5.71)	<0.001
RT techniques (WBRT alone vs. WBRT + SRS)	1.66 (1.26–2.17)	<0.001	0.99 (0.64–1.53)	0.9	1.63 (1.22–2.18)	0.001	1.01 (0.64–1.58)	0.9
Socioeconomic status								
1st quintile (lowest)	Reference		Reference		Reference		Reference	
2nd quintile	1.10 (0.86–1.40)	0.5	1.08 (0.76–1.53)	0.7	1.08 (0.84–1.39)	0.5	1.08 (0.75–1.56)	0.7
3rd quintile	1.29 (1.02–1.64)	0.03	1.09 (0.77–1.54)	0.6	1.20 (0.94–1.54)	0.1	1.04 (0.72–1.50)	0.9
4th quintile	1.15 (0.91–1.45)	0.2	1.17 (0.84–1.62)	0.4	0.97 (0.76–1.24)	0.8	1.08 (0.76–1.55)	0.6
5th quintile (highest)	1.16 (0.91–1.47)	0.2	0.99 (0.70–1.40)	0.9	1.03 (0.80–1.34)	0.8	1.01 (0.69–1.49)	0.9
Remoteness classification (Major city vs. regional/remote)	0.86 (0.73–1.01)	0.07	1.14 (0.91–1.44)	0.3	0.80 (0.64–0.99)	0.04	1.09 (0.81–1.47)	0.6
Treatment institution type (public vs. private)	2.53 (2.16–2.96)	<0.001	2.18 (1.74–2.73)	<0.001	2.73 (2.29–3.24)	<0.001	2.57 (1.99–3.31)	<0.001
Treatment institution location (metropolitan vs. regional)	0.79 (0.67–0.94)	0.009	0.94 (0.74–1.20)	0.6	1.21 (0.96–1.52)	0.1	1.25 (0.90–1.73)	0.2
Year of BM treatment	0.88 (0.84–0.92)	<0.001	0.86 (0.80–0.92)	<0.001	0.91 (0.86–0.95)	<0.001	0.89 (0.83–0.95)	0.001

Table 3. Characteristics of patients of patients who died within 30 days of whole brain radiation therapy for brain metastases (n = 389)

	All patients (N = 389)	≤5 fractions (N = 247, 64%)	6–10 fractions (N = 125, 32%)	>10 fractions (N = 17, 5%)	P-value**
Time from last WBRT treatment to death					
0–7 days to death	112 (29%)	78 (70%)	29 (26%)	5 (4%)	0.2
8–14 days to death	85 (22%)	57 (67%)	23 (27%)	5 (6%)	
15–30 days of death	192 (49%)	112 (58%)	73 (38%)	7 (4%)	
Age at WBRT					
Mean (SD) (years)	66.8 (12.1)	66.8 (12.7)	66.9 (10.8)	66.6 (13.3)	0.9
<55 y/o	65 (17%)	44 (68%)	18 (28%)	3 (5%)	0.9
55–59 y/o	43 (11%)	25 (58%)	18 (41%)	0 (0%)	
60–64 y/o	47 (12%)	31 (66%)	13 (28%)	3 (6%)	
65–69 y/o	74 (20%)	45 (61%)	25 (34%)	4 (5%)	
70–74 y/o	57 (15%)	36 (63%)	19 (33%)	2 (4%)	
≥75 y/o	103 (26%)	66 (64%)	32 (31%)	5 (5%)	
Sex					
Male	215 (55%)	129 (60%)	72 (33%)	14 (7%)	0.04
Female	174 (45%)	118 (68%)	53 (30%)	3 (2%)	
Primary cancer					
Lung cancer	191 (49%)	122 (64%)	61 (32%)	8 (4%)	0.05
Breast cancer	45 (12%)	30 (67%)	14 (31%)	1 (2%)	
Melanoma	38 (10%)	20 (53%)	17 (45%)	1 (3%)	
Gastrointestinal cancer	48 (12%)	34 (71%)	14 (29%)	0 (0%)	
Genitourinary cancer	28 (7%)	16 (57%)	7 (25%)	5 (18%)	
Other	39 (10%)	25 (64%)	12 (31%)	2 (5%)	
RT techniques					
WBRT alone	270 (95%)	238 (64%)	117 (32%)	15 (4%)	0.2
WBRT + SRS	19 (5%)	9 (47%)	8 (42%)	2 (11%)	
Socioeconomic status					
1st quintile (lowest)	97 (25%)	59 (61%)	34 (25%)	4 (4%)	0.5
2nd quintile	54 (14%)	34 (63%)	17 (31%)	3 (6%)	
3rd quintile	82 (21%)	54 (66%)	22 (27%)	6 (7%)	
4th quintile	81 (21%)	54 (67%)	27 (33%)	0 (0%)	
5th quintile (highest)	75 (19%)	46 (61%)	25 (33%)	4 (5%)	
Remoteness classification					
Major city	279 (72%)	174 (62%)	95 (34%)	10 (4%)	0.3
Inner regional	110 (28%)	73 (66%)	30 (27%)	7 (6%)	
Treatment institution type					
Public	233 (60%)	168 (72%)	55 (24%)	10 (4%)	<0.001
Private	156 (40%)	79 (51%)	70 (45%)	7 (4%)	
Treatment institution location					
Metropolitan	287 (74%)	176 (61%)	100 (34%)	11 (4%)	0.1
Regional	102 (26%)	71 (70%)	25 (25%)	6 (6%)	
Year of BM treatment					
2012	30 (8%)	17 (57%)	13 (43%)	0 (0%)	
2013	70(18%)	39 (56%)	28 (40%)	3 (4%)	
2014	76 (20%)	50 (66%)	18 (24%)	8 (11%)	
2015	97 (25%)	61 (63%)	32 (33%)	4 (4%)	
2016	116 (30%)	80 (69%)	34 (29%)	2 (2%)	
P-trend*		0.08	0.1	0.5	

BM, brain metastases; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

***P*-value based on Pearson's chi-squared test

**P*-trend based on Cochran–Armitage test for trend.

unwarranted.[25] Older patients were more likely to be treated with shorter fractionation (≤5 fractions). Increasing age is generally considered poor prognostic factor for many cancers, and it is an important factor incorporated in the Graded Prognostic Assessment (GPA) for BM.[26] However, the observed association between age and shorter WBRT fractionation use could also be due to other considerations such as the patient's performance status, mobility and inconvenience for multiple visits for elderly patients. We also observed differences in WBRT

Table 4. Factors associated with prolonged fractionation (≥6 fractions) WBRT within 30 days of death in univariate and multivariate logistic regressions

	Univariate analyses		Multivariate analyses	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Time from last WBRT treatment to death				
0–7 days to death	Reference		Reference	
8–14 days to death	1.13 (0.61–2.07)	0.7	1.19 (0.64–2.23)	0.6
15–30 days of death	1.64 (1.00–2.69)	0.05	1.75 (1.05–2.91)	0.03
Age at WBRT	1.00 (0.98–1.02)	0.9	–	–
Sex (male vs. female)	0.71 (0.47–1.08)	0.1	–	–
Primary cancer				
Lung cancer	Reference		–	–
Breast cancer	0.88 (0.44–1.76)	0.9	–	–
Melanoma	1.59 (0.79–3.21)	0.3	–	–
Gastrointestinal cancer	0.73 (0.37–1.45)	0.6	–	–
Genitourinary cancer	1.33 (0.59–2.96)	0.3	–	–
Other	0.99 (0.48–2.03)	0.9	–	–
RT techniques (WBRT alone vs. WBRT + SRS)	2.00 (0.79–5.05)	0.1	–	–
Socioeconomic status				
1st quintile (lowest)	Reference		–	–
2nd quintile	0.91 (0.46–1.81)	0.8	–	–
3rd quintile	0.81 (0.44–1.48)	0.5	–	–
4th quintile	0.78 (0.42–1.44)	0.4	–	–
5th quintile (highest)	0.98 (0.53–1.82)	0.9	–	–
Remoteness classification (major city vs. regional/remote)	0.84 (0.53–1.34)	0.5	–	–
Treatment institution type (public vs. private)	2.52 (1.65–3.85)	<0.001	2.46 (1.59–3.81)	<0.001
Treatment institution location (metropolitan vs. regional)	0.69 (0.43–1.13)	0.1	–	–
Year of BM treatment	0.87 (0.74–1.02)	0.08	0.92 (0.78–1.09)	0.3

BM, brain metastases; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

fractionation by primary cancer type, whereby patients with gastrointestinal cancers were significantly less likely to be treated with prolonged fractionation. This most likely reflects the overall poorer prognosis in these patients. In the pooled analyses from eleven multinational institutions, the median overall survival for patients with gastrointestinal cancer and BM were among the lowest at 5.4 months (95% CI = 4.3–6.3) compared with other primary cancers.[26]

We observed that patients who lived in regional or remote area were less likely to be treated with prolonged fractionation. It is likely that these patients required longer daily travel distance to RT facilities, or required accommodation arrangements closer to RT facilities for the course of treatment, and hence influencing the prescription of a shorter course of WBRT for patients' convenience. While we did not observe differences in WBRT fractionation use by patients' socioeconomic status, there were marked differences in WBRT fractionation use for patients treated in public vs private institutions. Patients treated in private institutions were 1.2 times more likely to be treated with prolonged fractionation (≥6 fractions) WBRT (Table 2). A higher proportion of prolonged RT fractionation use in private institutions has been also observed in the use of RT for bone metastases in earlier study.[27] There may be a combination of reasons for this observation in the current study. First, this could be due to differences in patient population seen in public versus private institutions, such that patients treated in private institutions may have more favourable prognoses that clinically justify prolonged fractionation WBRT. Second, it could be due to differences in radiation therapy techniques used in public and private institutions, such as SRS and hippocampal-avoidance WBRT (HA-WBRT). A previous Victorian study has reported higher proportion of SRS use in public institutions,[14] and hence those patients who would have otherwise been treated with SRS in public institutions may have been treated with prolonged fractionation WBRT in private institutions. In regard to HA-WBRT, the evidence is largely based on 30 Gy in 10 fractions of WBRT,[28,29] with a lack of evidence-based guidelines on hippocampal dose constraints for 5-fraction WBRT. A possibility is that a more rapid uptake of HA-WBRT in private institutions may have partly accounted for their higher proportion of prolonged fractionation use, but this remains only a conjecture as we are not able to identify the use of HA-WBRT from the VRMDS dataset. However, even among patients who had WBRT at EOL (i.e. those unlikely to benefit from HA-WBRT), private institutions were more than 2 times more likely to use prolonged fractionation (≥6 fractions) WBRT (Table 4). Possible reasons for this may include suboptimal patient selection for prolonged fractionation WBRT, or remuneration-related, given that

the current Medicare Benefits Schedule (MBS) reimbursement is based on number of fractions delivered.

Another important finding in our study is that approximately one-in-eight patients who had WBRT died within 30 days of treatment. Any death within 30 days of any treatment is generally considered a poor quality of care,[30,31] and the WBRT delivered in this cohort of patients may potentially be futile treatment. In fact, there is evidence from randomised trial that optimal supportive care is a reasonable option for these patients, although the trial was limited to patients with non-small cell lung cancer.[12] An earlier study from the Southern California Cancer Registry between 2007 and 2011 has also reported that 12% and 23% of lung cancer patients who had WBRT died within 14 and 30 days of treatment respectively.[32] One of the limitations of the current study using administrative dataset is that we do not have detailed clinical information to comment on appropriateness of WBRT and fractionation used in individual patients' clinical situation. It is important to acknowledge that prognostication at the EOL can be challenging and clinicians may over-estimate the benefits of WBRT in some of the cases.

In conclusion, in this population-based study in Victoria, we report marked variations in WBRT fractionation use that is associated with various factors such as age, primary cancer type, combination treatment with SRS, area of residence and institutional practice. Nonetheless, the reporting and publications of these findings are important in raising awareness of these variations in current practice. Moving forward, as the management of BM continues to evolve, it is important that clinical practice is being continually monitored and benchmarked to ensure alignment with contemporary best evidence-based practice.

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Data availability statement

The data presented in this study are available on request to the corresponding author.

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