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Original Article

Variation in the use of radiotherapy fractionation for breast cancer: Survival outcome and cost implications

Vikneswary Batumalai [a,b,*], Geoff P Delaney [a,b], Joseph Descallar [a], Gabriel Gabriel [a], Karen Wong [a], Jesmin Shafiq [a], Michael Barton [a,b]

[a] Ingham Institute for Applied Medical Research, South Western Clinical School, University of New South Wales; and [b] Department of Radiation Oncology, South Western Sydney Local Health District, New South Wales, Australia

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ABSTRACT

Background and purpose: Substantial variation in the adoption of hypofractionation for breast radiation therapy has been observed, despite the availability of consensus guidelines. This study aimed to investigate the variation in radiation therapy fractionation in breast cancer patients in New South Wales (NSW), Australia, and to estimate survival outcome and cost implications.

Materials and methods: This is a population-based cohort of patients who received radiation therapy for breast cancer (2009–2013), as captured in the NSW Central Cancer Registry. A logistic regression model was used to identify factors associated with fractionation type. Survival outcome was estimated using multivariable Cox proportional hazards model. Cost per treatment and potential cost saving associated with evidence-based fractionation was estimated.

Results: A total of 10,482 patients were available for analysis, divided into 3 cohorts (breast alone: N = 7000; breast + nodes: N = 1119; all chestwall: N = 2363). In multivariable analysis, increasing age, laterality (right), year of treatment (2013), early stage, lower socioeconomic status, and regional area of residence were independent predictors of hypofractionation for breast alone radiation therapy. For the breast + nodes and chest wall cohorts, common factors that predicted the use of hypofractionation were increasing age. In multivariable survival analysis, there was no difference between the fractionation regimens at 5 years. Estimated radiation therapy cost of this cohort approximated $52.1 million, compared with $38.5 million had these patients been treated with evidence-based fractionation. This demonstrated a potential saving of $13.6 million.

Conclusion: Hypofractionation appears underused for breast radiation therapy in NSW over time. This study highlights that evidence-based practice will translate to reduced health care treatment costs.
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Radiation therapy (RT) is an important component in the management of breast cancer. It is recommended that up to 80% of patients with breast cancer should receive RT as part of their treatment [1]. The standard of care for many years has been whole breast irradiation delivered with a long fractionated schedule over 5 to 6 weeks [2]. Hypofractionation (39–42.5 Gy in 13–16 fractions) has been shown in several randomised trials to be equally efficacious when compared with those treated with traditional 5-week RT (45–50 Gy in 25–28 fractions) for patients with early breast cancer [3,4] and is now considered accepted practice [5,6]. In addition to clinical benefits, hypofractionation also offers other advantages including reduced burden of travelling for treatment, convenience, time, cost, quality of life and patient satisfaction.

There is urgency for improving evidence-based practice because of increasing demand for services from an ageing population, medical science developments and cost escalators [7]. Substantial variation in the adoption of hypofractionation for early stage breast cancer has been observed in Australia and internationally [8–12] despite the availability of consensus guidelines. These studies are limited to when the breast alone is treated. There have been no studies that have examined the variation in fractionation in the overall breast cancer population including early and advanced breast cancer, where nodal RT might also be part of the plan. Moreover, patient consequences and financial costs of fractionation variation for this group of patients have yet to be determined either in Australia or internationally. This study aimed to investigate the degree of variation in RT fractionation in a population-

* Corresponding author at: Liverpool Cancer Therapy Centre, Locked Bag 7103, Liverpool 1871, NSW, Australia.
E-mail address: vikneswary.batumalai@health.nsw.gov.au (V. Batumalai).

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based cohort of breast cancer patients in Australia and identify factors associated with the variation, and to estimate survival outcome and cost implications.

Methods and materials

Study population

The cohort comprised all breast cancer patients who received RT in New South Wales (NSW) between 2009 and 2013. Cases were identified from a linked dataset comprising diagnosis data recorded in NSW Central Cancer Registry, the NSW Cancer Institute Electronic RT Oncology Data (extract of RT data from each NSW public and private radiation oncology facility), Admitted Patient Data Collection (APDC), and Registry of Births, Deaths and Marriages (RBDM). Probabilistic data linkage was performed by the Centre for Health Record Linkage (CHeReL). Based on the available datasets, the study period was defined from 2009 to 2013, with the date of last follow up until 2018 providing a minimum of five years potential follow up for survival analysis. The study was approved by the NSW population and health services research ethics committee.

Primary outcomes and covariables

The primary outcome was to identity degree of variation in the use of fractionation in breast RT. For this study, two groups of fractionation regimens were defined; non-hypofractionation (dose per fraction $\leq$2.0 Gy), and hypofractionation (dose per fraction >2.0 Gy).

The analysis was stratified by area of treatment; breast alone, breast + nodes, chest wall alone and chest wall + nodes. Patients were divided into two breast cancer clinical groups according to the evidence-based optimal RT fractionation model [13]; Early (T1-2, N0-1, M0) and Advanced (T3-4, Nx, M0 or Tx, N2-3, M0). In addition to these clinical groups, a third group of patients with missing TNM staging data were also included for analysis. Factors associated with fractionation variation that were evaluated include patients' age at treatment, laterality, year of treatment, local health district (LHD) of residence, socioeconomic status (SES) imputed from area of residence, geographic remoteness of area of residence, and country of birth. Survival outcome was defined as 5 years overall survival.

Cost analysis

The method used to estimate cost per fraction has been previously calculated by our group based on a single RT department as the base case [14]. In this previous study, a hybrid approach that merges features from activity-based costing (ABC) and relative value units costing (RVU) were used to provide cost estimates. ABC methodology was used to allocate costs to all RT activities associated with each patient's treatment course, while the RVUs represent the cost of each RT activity relative to the average cost

Table 1
Logistic regression models to assess factors associated with use of >2 Gy/fraction for breast.

	Breast					
	Frequencies		Univariate analyses		Multivariable analyses	
	>2 Gy/fraction (*N* = 2909, 42%)	$\leq$2 Gy/fraction (*N* = 4091, 58%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at radiation therapy				<0.001		<0.001
<40	33 (14%)	204 (86%)	0.19 (0.13–0.28)	<0.001	0.19 (0.13–0.28)	<0.001
40–49	283 (26%)	808 (74%)	0.41 (0.35–0.48)	<0.001	0.40 (0.34–0.47)	<0.001
50–59	672 (35%)	1262 (65%)	0.62 (0.55–0.71)	<0.001	0.61 (0.53–0.69)	<0.001
60–69	1121 (46%)	1315 (54%)	Reference		Reference	<0.001
70–79	604 (58%)	432 (42%)	1.64 (1.42–1.90)	<0.001	1.68 (1.44–1.96)	<0.001
$\geq$80	196 (74%)	70 (26%)	3.28 (2.47–4.36)	<0.001	3.52 (2.62–4.72)	<0.001
Laterality				0.002		<0.001
Left	1415 (40%)	2142 (60%)	Reference		Reference	
Right	1494 (43%)	1949 (57%)	1.16 (1.06–1.28)	0.002	1.20 (1.08–1.33)	<0.001
Year				<0.001		<0.001
2009	314 (37%)	529 (63%)	Reference		Reference	
2010	549 (37%)	936 (63%)	0.99 (0.83–1.18)	0.9	1.00 (0.83–1.20)	0.9
2011	607 (40%)	894 (60%)	1.14 (0.96–1.36)	0.1	1.07 (0.89–1.29)	0.5
2012	612 (41%)	884 (59%)	1.17 (0.98–1.39)	0.08	1.10 (0.92–1.33)	0.3
2013	827 (49%)	848 (51%)	1.64 (1.39–1.95)	<0.001	1.59 (1.33–1.90)	<0.001
Clinical group				<0.001		<0.001
Early	2097 (45%)	2572 (55%)	Reference		Reference	
Advanced	30 (57%)	23 (43%)	1.60 (0.93–2.76)	0.09	1.42 (0.78–2.57)	0.2
Missing	782 (34%)	1496 (66%)	0.64 (0.58–0.71)	<0.001	0.68 (0.61–0.76)	<0.001
Socioeconomic status				<0.001		<0.001
Most disadvantaged	674 (48%)	717 (52%)	Reference		Reference	
Second quintile	640 (51%)	605 (49%)	1.13 (0.97–13.31)	0.1	1.02 (0.86–1.20)	0.8
Third quintile	615 (40%)	907 (60%)	0.72 (0.62–0.84)	<0.001	0.73 (0.63–0.86)	<0.001
Fourth quintile	582 (42%)	817 (58%)	0.76 (0.65–0.88)	<0.001	0.77 (0.65–0.91)	0.002
Least disadvantaged	398 (28%)	1045 (72%)	0.41 (0.35–0.47)	<0.001	0.43 (0.36–0.51)	<0.001
Remoteness of residency				<0.001		<0.001
Major city	1564 (36%)	2793 (64%)	Reference		Reference	
Inner regional	850 (51%)	826 (49%)	1.84 (1.64–2.06)	<0.001	1.55 (1.37–1.76)	<0.001
Outer regional	484 (52%)	439 (48%)	1.97 (1.71–2.27)	<0.001	1.47 (1.24–1.73)	<0.001
Remote/very remote	11 (25%)	33 (75%)	0.60 (0.30–1.18)	0.1	0.45 (0.22–0.92)	0.03
Country of birth				<0.001		0.1
Australia	1964 (43%)	2586 (57%)	Reference		Reference	
Overseas	945 (39%)	1505 (61%)	0.83 (0.75–0.91)	<0.001	0.91 (0.81–1.02)	0.1

of all activities and were used to achieve a weighted cost allocation. A patient's journey for the financial year was constructed by consolidating all the RT activities and their associated costs, and the average cost per activity (fraction) was determined. For breast cancer, the average cost per fraction was estimated to be AUD $221 per fraction regardless of stage and area of treatment (breast alone, breast + nodes, chest wall alone and chest wall + nodes). Based on this, cost per treatment course for patients in this study population was estimated and potential cost saving associated with evidence-based optimal fractionation was determined. We have previously estimated and reported the evidence-based optimal number of RT fractions for cancer [13,15]. The estimated optimal number of fractions for early and advanced breast cancer were 16.8 and 15.1, respectively [13]. For patients with missing TNM stages, the optimal number of fractions of 16.4 for all breast cancer was used as the model includes all staging groups [15].

Statistical analyses

Logistic regression models were used to analyse factors associated with fractionation variation. The factors included were age, laterality, year of treatment, clinical group, SES, remoteness of residency and country of birth. Kaplan-Meier was used to analyse the association between fractionation regimen and survival on univari-

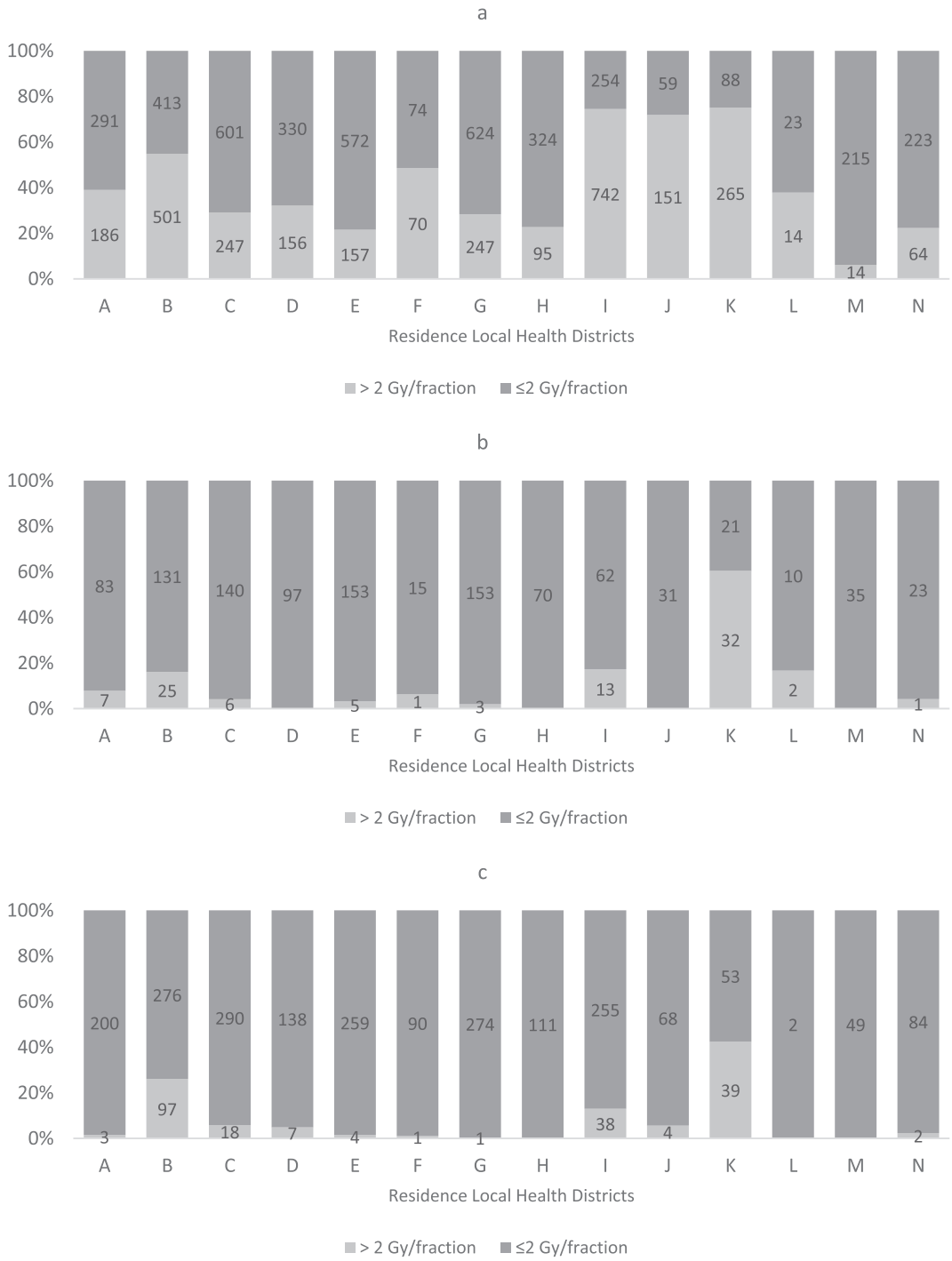

Fig. 1. Variations in fractionation regimen by residence local health districts for (a) breast alone, (b) breast + nodes, and (c) all chest wall.

ate analysis. Multivariable Cox proportional-hazards regression model was used to analyse these patient factors with survival. The adjusting variables included were age, laterality, year of treatment, SES, remoteness of residency and country of birth.

Results

A total of 10,482 patients were available for analysis (Supp Material 1). Results are presented by treatment to the breast, breast + nodes and all chest wall (chest wall alone and chest wall + nodes).

7000 patients received RT to the breast alone. Hypofractionation was more likely to be delivered to older patients: 74% of patients aged ≥80 years, compared with 14% of patients aged <40 years ($P < 0.001$) (Table 1). Patients who received hypofractionation to the right breast (43%) were higher than those that received hypofractionation to the left breast (40%) ($P = 0.002$). The proportion of patients who received hypofractionation increased from 37% in 2009 to 49% in 2013 ($P < 0.001$). Patients in the early stage clinical group (45%) were more likely to receive hypofractionation compared with missing stage (34%) ($P < 0.001$). A higher proportion of hypofractionation was delivered to patients in lower SES regions (48%) compared to those in higher SES regions (28%) ($P < 0.001$). Patients from inner regional and outer regional areas were more likely to receive hypofractionation compared with those from major cities and remote areas ($P < 0.001$). The proportion of hypofractionation delivered to patients born in Australia (43%) was higher compared to those born overseas (39%) ($P < 0.001$). In multivariable analyses, increasing age, laterality (right-sided), year of treatment (2013), early stage, lower SES, and inner/outer regional areas of residence were all independently associated with increased use of hypofractionation. There was a wide range in the proportion of cases who received hypofractionation across the residence LHDS, ranging from 6% to 75% (Fig. 1a).

1119 patients received RT to breast + nodes. Hypofractionation was more likely to be delivered to older patients: 34% of patients aged ≥80 years, compared with 0% of patients aged <40 years ($P < 0.001$) (Table 2). Patients in the advanced stage clinical group were more likely to receive hypofractionation compared with early and missing stage ($P < 0.001$). A higher proportion of hypofractionation was delivered to patients with lower SES (11%) compared to those with higher SES (2%) ($P < 0.001$). Patients from remote/very remote areas were more likely to receive hypofractionation (25%) compared with those from major cities (5%) ($P < 0.001$). In multivariable analyses, increasing age, advanced stage clinical group and remote areas of residence were associated with increased use of hypofractionation. There was a wide spread of hypofractionation used across the LHDS, ranging from 0 to 60% (Fig. 1b).

2363 patients received RT to the chest wall. Hypofractionation was more likely to be delivered to older patients: 21% of patients aged ≥80 years, compared with 6% of patients aged <40 years ($P < 0.001$) (Table 3). Patients in the early stage clinical group were

Table 2
Logistic regression models to assess factors associated with use of > 2 Gy/fraction for breast + nodes.

	Breast + nodes					
	Frequencies		Univariate analyses		Multivariable analyses	
	>2 Gy/fraction (*N* = 95, 8%)	≤2 Gy/fraction (*N* = 1024, 92%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at radiation therapy				<0.001		<0.001
<40	0	104 (100%)	–	–	–	–
40–49	15 (5%)	265 (95%)	0.54 (0.28–1.07)	0.08	0.56 (0.28–1.14)	0.1
50–59	21 (7%)	291 (93%)	0.69 (0.37–1.28)	0.2	0.67 (0.35–1.30)	0.2
60–69	23 (9%)	221 (91%)	Reference		Reference	
70–79	18 (14%)	108 (86%)	1.60 (0.83–3.09)	0.2	1.40 (0.69–2.86)	0.3
≥80	18 (34%)	35 (66%)	4.94 (2.42–10.08)	<0.001	6.21 (2.81–13.75)	<0.001
Laterality				0.6		0.4
Left	52 (9%)	531 (91%)	Reference		Reference	
Right	43 (8%)	493 (92%)	0.89 (0.58–1.36)	0.6	0.81 (0.51–1.30)	0.4
Year				0.7		0.5
2009	13 (11%)	104 (89%)	Reference		Reference	
2010	14 (7%)	193 (93%)	0.58 (0.26–1.28)	0.2	0.48 (0.20–1.16)	0.1
2011	22 (9%)	212 (91%)	0.83 (0.40–1.71)	0.6	0.86 (0.38–1.95)	0.7
2012	23 (9%)	243 (91%)	0.76 (0.37–1.55)	0.4	0.69 (0.31–1.56)	0.4
2013	23 (8%)	272 (92%)	0.68 (0.33–1.39)	0.3	0.65 (0.29–1.44)	0.3
Clinical group				<0.001		<0.001
Early	31 (7%)	399 (93%)	Reference		Reference	
Advanced	47 (16%)	254 (84%)	2.38 (1.47–3.85)	<0.001	2.17 (1.28–3.68)	0.004
Missing	17 (4%)	371 (96%)	0.59 (0.32–1.08)	0.09	0.75 (0.39–1.47)	0.4
Socioeconomic status				<0.001		0.007
Most disadvantaged	25 (11%)	209 (89%)	Reference		Reference	
Second quintile	29 (15%)	159 (85%)	1.52 (0.86–2.70)	0.1	1.18 (0.61–2.30)	0.6
Third quintile	13 (6%)	202 (94%)	0.54 (0.27–1.08)	0.08	0.51 (0.23–1.10)	0.09
Fourth quintile	23 (10%)	204 (90%)	0.94 (0.52–1.71)	0.8	0.95 (0.47–1.91)	0.9
Least disadvantaged	5 (2%)	250 (98%)	0.17 (0.06–0.44)	<0.001	0.25 (0.09–0.70)	0.009
Remoteness of residency				<0.001		<0.001
Major city	34 (5%)	727 (95%)	Reference		Reference	
Inner regional	43 (17%)	203 (83%)	4.53 (2.81–7.29)	<0.001	3.70 (2.10–6.53)	<0.001
Outer regional	17 (16%)	91 (84%)	3.99 (2.15–7.44)	<0.001	3.13 (1.48–6.60)	0.003
Remote/very remote	1 (25%)	3 (75%)	7.13 (0.72–70.32)	0.09	6.90 (0.63–75.43)	0.1
Country of birth				0.4		0.3
Australia	62 (9%)	627 (91%)	Reference		Reference	
Overseas	33 (8%)	*397 (92%)*	0.84 (0.54–1.31)	0.4	1.34 (0.79–2.26)	0.3

more likely to receive hypofractionation compared with advanced and missing stage ($P < 0.001$). A higher proportion of hypofractionation was delivered to patients with lower SES (9%) compared to those with higher SES (3%) ($P < 0.001$). Patients from regional areas ($P < 0.001$) and those born in Australia ($P < 0.001$) were also more likely to receive hypofractionation. In multivariable analyses, increasing age, early stage clinical group, higher socioeconomic status, and regional areas of residence were associated with increased use of hypofractionation. There was a wide spread of hypofractionation used across the LHDS, ranging from 0 to 42% (Fig. 1c).

For early stage, there was no significant difference in the 5-year Kaplan-Meier overall survival estimate; 91.7% for >2 Gy/fraction versus 92.5% for ≤2 Gy/fraction ($P = 0.3$). For advanced stage, the 5-year Kaplan-Meier overall survival estimate was significantly different between the 2 treatment regimens; 64.8% for >2 Gy/fraction and 75.2% for ≤2 Gy/fraction ($P = 0.002$). For missing stage, the 5-year Kaplan-Meier overall survival estimate was 86.5% (>2 Gy/fraction) and 86.0% (≤2 Gy/fraction) with no significant difference ($P = 0.8$) (Fig. 2). In multivariable survival analysis, there was no difference between the two dose regimens for all staging groups at 5 years (Supp Material 2).

An estimated $52.1 million (Early: $27,312,948; Advanced: $6,639,282; Missing: $18,081,336) was spent on this cohort of patients for their breast RT (Table 4). If these patients were treated with optimal number of fractions as per evidence based guidelines [13,15], the estimated cost would be $38.5 million. This demonstrated a potential cost savings of $13.6 million which would be a 26% reduction in breast RT costs for this cohort.

Discussion

This study identified a wide variability in the use of hypofractionation in RT for early and advanced breast cancer in NSW. Factors that affected the use of hypofractionation varied between the clinical groups and whether patients received RT to the breast (±nodes) or chest wall. Factors that correlated with increased use of hypofractionation in breast alone included increasing age, laterality (right-sided), later year of treatment (2013), early stage, lower SES, and inner/outer regional areas of residence. Previous studies in NSW have also identified age, laterality, year, and treating facility as factors that correlated significantly with hypofractionation use in patients with early breast cancer [9,12]. Although our study and previous published studies [8,9,12] showed increase in hypofractionation use over time, this rate of increase is very slow.

There are limited available data regarding the effects of hypofractionated regional nodal RT in breast RT. Reports from a randomised trial [16], registry [17] and institutional [18,19] analyses showed that hypofractionation for nodal RT is safe and effective. In 2013, hypofractionated RT in breast + nodes was only 8%. Similarly, a low rate of hypofractionation (10%) was used for all

Table 3
Logistic regression models to assess factors associated with use of > 2 Gy/fraction for all chest wall.

	All chest wall Frequencies		Univariate analyses		Multivariable analyses	
	>2 Gy/fraction	≤2 Gy/fraction				
	(*N* = 214, 9%)	(*N* = 2149, 91%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at radiation therapy				<0.001		<0.001
<40	14 (6%)	203 (94%)	0.56 (0.30–1.03)	0.06	0.81 (0.42–1.57)	0.5
40–49	47 (8%)	580 (92%)	0.66 (0.44–0.99)	0.04	0.74 (0.48–1.16)	0.2
50–59	35 (6%)	574 (94%)	0.49 (0.32–0.77)	0.002	0.53 (0.33–0.85)	0.009
60–69	54 (11%)	438 (89%)	Reference		Reference	
70–79	40 (13%)	266 (87%)	1.22 (0.79–1.89)	0.4	1.25 (0.77–2.03)	0.4
≥80	24 (21%)	88 (79%)	2.21 (1.30–3.77)	0.004	3.06 (1.66–5.65)	<0.001
Laterality				0.5		0.4
Left	112 (9%)	1074 (91%)	Reference		Reference	
Right	102 (9%)	1075 (91%)	0.91 (0.69–1.21)	0.5	0.88 (0.65–1.21)	0.4
Year				0.6		0.9
2009	13 (7%)	173 (93%)	Reference		Reference	
2010	44 (9%)	420 (91%)	1.39 (0.73–2.65)	0.3	1.22 (0.60–2.46)	0.6
2011	51 (9%)	507 (91%)	1.34 (0.71–2.52)	0.4	1.04 (0.52–2.08)	0.9
2012	45 (8%)	513 (92%)	1.17 (0.62–2.22)	0.6	1.01 (0.50–2.03)	0.9
2013	61 (10%)	536 (90%)	1.51 (0.81–2.282)	0.2	1.08 (0.55–2.14)	0.8
Clinical group				<0.001		<0.001
Early	79 (13%)	539 (87%)	Reference		Reference	
Advanced	115 (13%)	776 (87%)	1.01 (0.74–1.37)	0.9	0.86 (0.61–1.21)	0.4
Missing	20 (2%)	834 (98%)	0.16 (0.10–0.27)	<0.001	0.18 (0.11–0.30)	<0.001
Socioeconomic status				<0.001		<0.001
Most disadvantaged	48 (9%)	474 (91%)	Reference		Reference	
Second quintile	63 (17%)	315 (83%)	1.98 (1.32–2.95)	<0.001	1.23 (0.78–1.92)	0.4
Third quintile	21 (4%)	466 (96%)	0.44 (0.26–0.75)	0.003	0.45 (0.25–0.80)	0.007
Fourth quintile	69 (15%)	404 (85%)	1.69 (1.14–2.50)	0.009	1.74 (1.09–2.80)	0.02
Least disadvantaged	13 (3%)	490 (97%)	0.26 (0.14–0.49)	<0.001	0.43 (0.22–0.84)	0.01
Remoteness of residency				<0.001		<0.001
Major city	47 (3%)	1503 (97%)	Reference		Reference	
Inner regional	122 (22%)	435 (78%)	8.97 (6.30–12.76)	<0.001	7.60 (5.12–11.29)	<0.001
Outer regional	45 (18%)	202 (82%)	7.12 (4.61–11.00)	<0.001	6.07 (3.65–10.07)	<0.001
Remote/very remote	0	9 (100%)	–	–	–	–
Country of birth				<0.001		0.4
Australia	158 (11%)	1346 (89%)	Reference		Reference	
Overseas	56 (6%)	803 (94%)	0.59 (0.43–0.82)	0.001	1.18 (0.82–1.70)	0.4

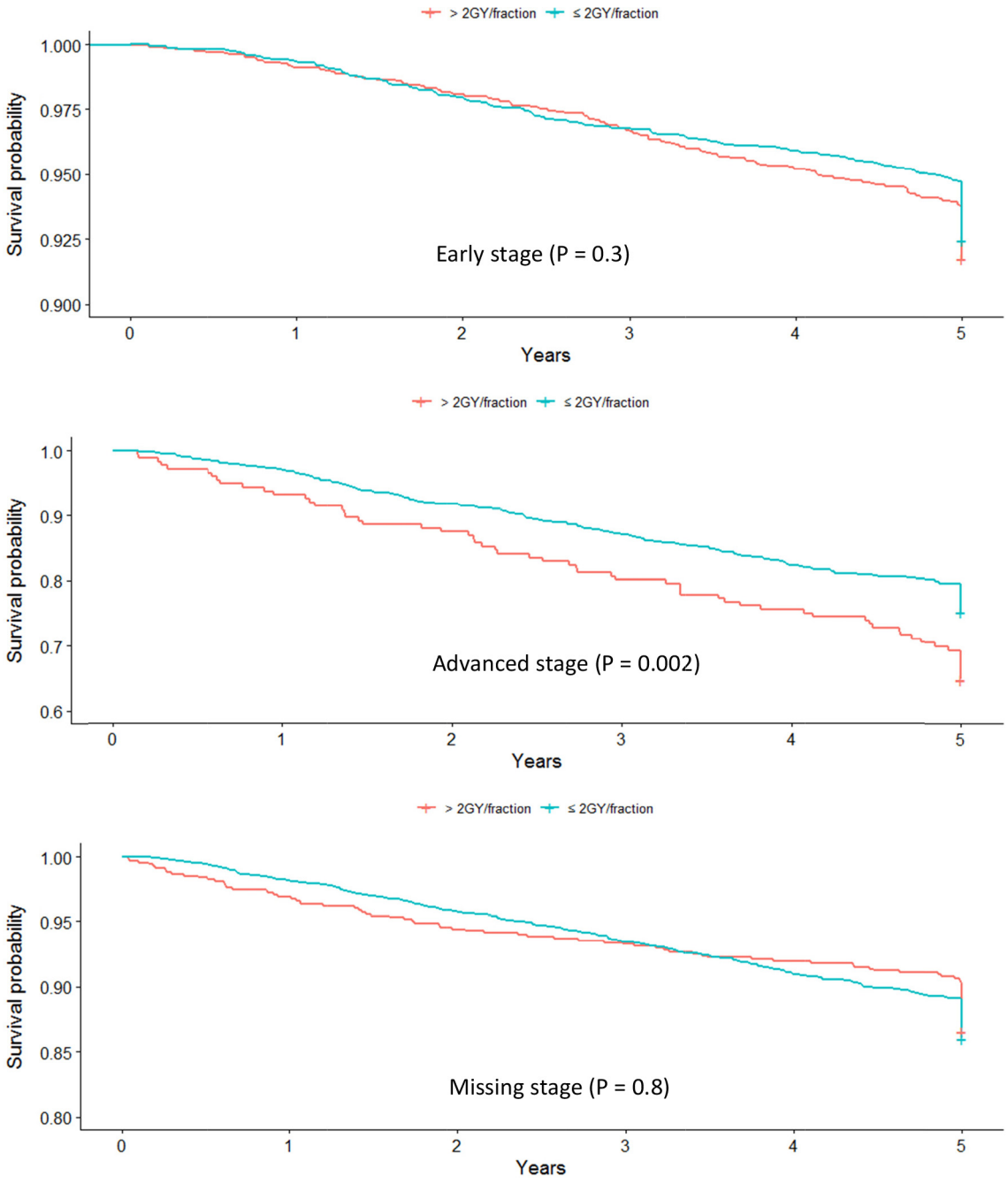

Fig. 2. Kaplan-Meier curves showing the difference in 5-year overall survival between the two fractionation regimens for early, advanced and missing stage.

Table 4
Cost analysis.

	No. of patients (A)	Total no. of fractions treated (B)	Cost per fraction (C)	Estimated cost spent (B*C)	No. of optimal fractions (D)	Optimal cost (A*C*D)
Early stage	5753	123,588	$221	$27,312,948	16.8	$21,359,738
Advanced stage	1259	30,042	$221	$6,639,282	15.1	$4,201,409
Missing stage	3557	81,816	$221	$18,081,336	16.4	$12,891,991
Total				$52,033,566		$38,453,138

chest wall patients, despite evidence from previous studies supporting the use of hypofractionation for postmastectomy breast cancer patients [20,21]. These extreme low rates show lack of progress in the adoption of hypofractionation in these patient groups. Although the rate of hypofractionation in breast alone patients increased from 37% in 2009 to 49% in 2013, this is a small incre-

ment compared to Canadian studies that reported higher rates of adoption (69%–85%) [22]. A possible reason for slow adoption of hypofractionation in Australia may be driven by the remuneration incentives in Australia, which is determined by the number of RT fractions delivered. In Canada, radiation therapy is fully covered by provincial funding and no privately funded or operated radiation treatment facilities are permitted where profit-driven motives may be less influential on clinical decision making [23]. The evidence-based, patient-centered nature of the Canadian system has enabled widespread adoption of hypofractionation [23].

Our study identified that the residence LHD influenced the use of hypofractionation reflecting variation between facilities, and previous studies have identified prescribing radiation oncologist as a factor [9,12,24]. Prades et al [24] suggested two reasons for understanding clinicians' reluctance to adopt hypofractionation regimens; (1) some clinicians perceived newer treatment techniques as 'another layer of complexity' that seemed to slow adoption of hypofractionation, (2) quality of evidence is a necessary but not a sufficient condition determining clinician's behaviour towards hypofractionation including clinical management factors, such as the role of the department head. Efforts are needed to embed a data solution for a clinical quality data repository in RT to systematically identify, interpret and respond to variation in practice. Supporting clinicians to visualise their practice in relation to their peers and evidence base, modify their prescribing habits to adhere to guidelines, and subsequently maintain this change requires effective, reproducible interventions. Evidence shows that facilitated feedback methods and models focussing on changing clinician behaviour are effective to respond to variation [25].

Healthcare is increasingly recognising the relationship between reducing variation, reducing cost and improving outcomes. Leading Better Value Care (LBVC) is one of the programs that aims to accelerate value-based healthcare in NSW. It involves clinicians, networks and organisations working together on high-impact initiatives to improve patient outcomes. One of the initiatives of LBVC program is to reduce variation in the use of hypofractionated breast RT [26]. This will reduce treatment time, reduce cost, improve quality of life for patients, increase RT access, and increase capacity in RT departments. Our study found that a majority of women in NSW received longer and more costly regimen. Overall, only 31% of women in our cohort received the less costly hypofractionated regimen. As expected, the total cost is reduced considerably with the reduction in number of fractions. When considering early breast cancer alone, hypofractionated schedules would have reduced the cost by about 22% compared to non-hypofractionated schedules. For advanced breast cancer, the costs would be reduced by 37% with hypofractionated schedules, while for patients with missing stage, the costs would be reduced by 29%. Treatment with hypofractionation would have resulted in a $13.6 million savings when compared with defaulting to non-hypofractionation treatment in this cohort. Our current results support that significant reductions in cancer-related treatment costs is possible through the practice of evidence-based breast cancer care, and will further support the LBVC initiatives.

More recently, evidence from the FAST-Forward trial showed that 26 Gy in 5 fractions over 1 week is non-inferior to 40 Gy in 15 fractions over 3 weeks for local tumour control, and is as safe in terms of normal tissue effects up to 5 years for patients with early stage breast cancer [27]. The 1-week schedule has major benefits over the 3-week or 5-week regimens in terms of convenience and cost for patients and for health services globally. Will this 1-week regimen also take decades to be fully introduced and practiced widely? The coronavirus disease 2019 (COVID-19) pandemic has brought some challenges to the practice of RT. Measures are now being taken to reduce the flow of patients to cancer centres and hospitals by rapidly adopting hypofractionation regimens including the FAST-Forward regimen [28]. Accelerated partial breast irradiation delivered in 1 to 2 weeks has also been recommended as an effective regimen [29] among appropriately selected patients. Will it take a pandemic to speed up wide adoption of less costly and cumbersome schedules? Is COVID-19 an opportunity to reduce and eliminate low-value practices in RT? It is not certain whether these changes in fractionation will persist if normal service is resumed.

There are several limitations to this study. We were unable to ascertain patients' treatment facilities, therefore LHD of patient residence was used as a surrogate and assumed to be the treatment facility. In reality, a small proportion of patients may have received treatment in a facility outside of their residence LHD. This study also included analyses of patients with missing TNM stage in routinely collected data, likely due to incomplete data received by the registries. As this group of patients accounted for 34% of this study cohort, we included them in this study to provide an overall analysis. It should also be pointed out that the cost per fraction used in this study is the average cost per fraction for breast cancer, regardless of stage and delivery techniques. The costs quoted therefore reflect the average casemix for the NSW population. The cost per fraction also accounts for cost of all activities involved in the treatment preparation and assumes that treatment costs scale linearly with the number of fractions, which may be incorrect. Inclusion of treatment preparation costs into the cost per fraction may give rise to a distortion of the costs of different fractionation schedules [30]. It may be more accurate to calculate the costs incurred in the treatment preparation stage separately, however the approach may be more challenging.

Despite evidence supporting the use of hypofractionation for breast RT, it was underused between 2009 and 2013 in this Australian population-based study. Further work is ongoing to examine more recent rates. This study highlights that evidence-based practice will translate to reduced health care treatment costs. Opportunities exist for patients to receive high-quality breast RT at lower costs, and these options should be encouraged in routine clinical care. Future work is needed to increase the utilisation of hypofractionation and reduce variations in pattern of practice.

Conflict of interest statement

The authors of this paper declare no actual or potential conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.07.038.

References

[1] Delaney G, Barton M, Jacob S. Estimation of an optimal radiotherapy utilization rate for breast carcinoma: a review of the evidence. Cancer 2003;98:1977–86.
[2] Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
[3] Whelan TJ, Pignol J-P, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513–20.

[4] Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086–94.
[5] Smith BD, Bentzen SM, Correa CR, Hahn CA, Hardenbergh PH, Ibbott GS, et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. 2011;81:59-68.
[6] Australia C. Cancer Australia statement. Surry Hills, NSW: Influencing best practice in breast cancer; 2016.
[7] DaSilva P, Gray JM. English lessons: can publishing an atlas of variation stimulate the discussion on appropriateness of care?. Med J Aust 2016;205: S5–7.
[8] Bekelman JE, Sylwestrzak G, Barron J, Liu J, Epstein AJ, Freedman G, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008–2013. JAMA 2014;312:2542–50.
[9] Delaney GP, Gandhidasan S, Walton R, Terlich F, Baker D, Currow D. The pattern of use of hypofractionated radiation therapy for early-stage breast cancer in New South Wales, Australia, 2008 to 2012. Int J Rad Oncol Biol Phys 2016;96:266–72.
[10] Jagsi R, Falchook AD, Hendrix LH, Curry H, Chen RC. Adoption of hypofractionated radiation therapy for breast cancer after publication of randomized trials. Int J Rad Oncol Biol Phys 2014;90:1001–9.
[11] Wang EH, Mougalian SS, Soulos PR, Rutter CE, Evans SB, Haffty BG, et al. Adoption of hypofractionated whole-breast irradiation for early-stage breast cancer: a national cancer data base analysis. Int J Rad Oncol Biol Phys 2014;90:993–1000.
[12] Neville K, Dreosti M, Blakey D, Latham M, Izard M, Young S, et al. Adoption of hypofractionated radiation therapy for early breast cancer in private practice: the GenesisCare experience 2014–2016. J Med Imaging Radiat Oncol 2019;64:127–33.
[13] Wong K, Delaney GP, Barton MB. Estimation of the optimal number of radiotherapy fractions for breast cancer: a review of the evidence. Radiother Oncol 2015;116:174–8.
[14] Batumalai V, Wong K, Shafiq J, Hanna TP, Gabriel G, Heberle J, et al. Estimating the cost of radiotherapy for 5-year local control and overall survival benefit. Radiother Oncol 2019;136:154–60.
[15] Wong K, Delaney GP, Barton MB. Evidence-based optimal number of radiotherapy fractions for cancer: a useful tool to estimate radiotherapy demand. Radiother Oncol 2016;119:145–9.
[16] Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the british columbia randomized trial. J Natl Cancer Inst 2005;97:116–26.
[17] Leong N, Truong PT, Tankel K, Kwan W, Weir L, Olivotto IA. Hypofractionated nodal radiation therapy for breast cancer was not associated with increased patient-reported arm or brachial plexopathy symptoms. Int J Rad Oncol Biol Phys 2017;99:1166–72.
[18] Stokes EL, Tyldesley S, Woods R, Wai E, Olivotto IA. Effect of nodal irradiation and fraction size on cardiac and cerebrovascular mortality in women with breast cancer treated with local and locoregional radiotherapy. Int J Rad Oncol Biol Phys 2011;80:403–9.
[19] Chan EK, Woods R, Virani S, Speers C, Wai ES, Nichol A, et al. Long-term mortality from cardiac causes after adjuvant hypofractionated vs. conventional radiotherapy for localized left-sided breast cancer. Radiother Oncol 2015;114:73–8.
[20] Liu L, Yang Y, Guo Q, Ren B, Peng Q, Zou L, et al. Comparing hypofractionated to conventional fractionated radiotherapy in postmastectomy breast cancer: a meta-analysis and systematic review. Radiat Oncol 2020;15:1–15.
[21] Wang S-L, Fang H, Song Y-W, Wang W-H, Hu C, Liu Y-P, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol 2019;20:352–60.
[22] Ashworth A, Kong W, Whelan T, Mackillop WJ. A population-based study of the fractionation of postlumpectomy breast radiation therapy. Int J Rad Oncol Biol Phys 2013;86:51–7.
[23] Lalani N, Cummings B, Halperin R, Rakovitch E, Brundage M, Vigneault E, et al. The practice of radiation oncology in Canada. Int J Rad Oncol Biol Phys 2017;97:876–80.
[24] Prades J, Algara M, Espinàs JA, Farrús B, Arenas M, Reyes V, et al. Understanding variations in the use of hypofractionated radiotherapy and its specific indications for breast cancer: A mixed-methods study. Radiother Oncol 2017;123:22–8.
[25] Johnson MJ, May CR. Promoting professional behaviour change in healthcare: what interventions work, and why? A theory-led overview of systematic reviews. BMJ Open 2015;5:e008592.
[26] NSW Health. Leading Better Value Care- Hypofractionated radiotherapy for early stage breast cancer. Available from: https://www.health.nsw.gov.au/Value/lbvc/Pages/radiotherapy.aspx.
[27] Brunt AM, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. The Lancet 2020;395:1613–26.
[28] Coles C, Aristei C, Bliss J, Boersma L, Brunt A, Chatterjee S, et al. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. Clin Oncol 2020;32:279–81.
[29] Braunstein LZ, Gillespie EF, Hong L, Xu A, Bakhoum SF, Cuaron J, et al. Breast radiotherapy under COVID-19 pandemic resource constraints–approaches to defer or shorten treatment from a Comprehensive Cancer Center in the United States. Adv Radiat Oncol 2020.
[30] Defourny N, Dunscombe P, Perrier L, Grau C, Lievens Y. Cost evaluations of radiotherapy: what do we know?An ESTRO-HERO analysis. Radiother Oncol 2016;121:468–74.