Clinical Oncology 35 (2023) e469–e477

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Locoregional control and toxicity following high-dose hypofractionated and accelerated palliative radiotherapy regimens in breast cancer

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Abstract

Aims: For patients with locally advanced primary/recurrent breast cancer, radiotherapy is an effective treatment for locoregional control. 36 Gy in 6 Gy once-weekly fractions is a commonly used schedule, but there are no data comparing local control and toxicity between 36 Gy delivered once-weekly versus accelerated schedules of multiple 6 Gy fractions per week. This retrospective study compared local control rates and acute and late toxicity in patients undergoing 30–36 Gy in 6 Gy fractions over 6 weeks versus more accelerated schedules over 2–3 weeks for an unresected breast cancer.

Materials and methods: Patients who received 30–36 Gy in 6 Gy fractions to an unresected breast cancer ± involved lymph nodes between December 2011 and August 2020 were identified. Patients were grouped into once-weekly versus accelerated fractionation schedules. Response rates, local control and toxicity data were analysed.

Results: In total, 109 patients were identified. The median follow-up duration was 46 months. Forty-seven patients (43%) received once-weekly fractions and 62 patients (57%) received accelerated fractionation schedules. There were no significant differences in baseline tumour characteristics between the groups. Eighty-seven per cent of patients had an objective (complete or partial) response (81% in the once-weekly group; 91% in the accelerated group). The median time to local progression was 23.5 months overall (95% confidence interval 17.8–29.2); 23.5 months (95% confidence interval 18.8–28.1) in the once-weekly group and 19.0 months (95% confidence interval 7.0–31.1) in the accelerated group ($P = 0.99$). Acute toxicity of any grade occurred in 75% of patients (76% in the once-weekly group; 74% in the accelerated group) and grade 3 toxicity occurred in 7% of patients (7% in the once-weekly group; 8% in the accelerated group). There were no associations between the groups and acute or late toxicity grade ($P = 0.78$ and $P = 0.26$, respectively), although one grade 4 late toxicity (skin radionecrosis) occurred in a patient who received five fractions a week and therefore this regimen is not recommended. Study limitations included a lack of statistical power analysis, the necessary grouping of all accelerated patients for analysis and a high rate of censored data.

Conclusion: There were no apparent differences in response rate, time to local progression or toxicity between patients who received 30–36 Gy in 6 Gy fractions once-weekly compared with twice-weekly as palliative treatment for locally advanced breast cancer. This regimen appears to be a safe alternative and may be preferred by patients.

Keywords: Breast cancer; Hypofractionation; Palliative radiotherapy

Introduction

Radiotherapy for breast cancer is most commonly delivered adjuvantly (following surgery to remove the primary tumour) for microscopic residual disease, using hypofractionated daily doses established from trials such as START (40 Gy in 15 fractions of 2.67 Gy) and FAST-Forward (26 Gy in five fractions of 5.2 Gy) [1–3]. However, for newly diagnosed patients of poor performance status or with metastatic disease, an initial surgical approach may not be appropriate. Without surgery, these patients are at high risk of suffering local progression of the unresected breast primary should there be loss of breast tumour control during systemic therapy. Additionally, patients presenting with unresectable primary/recurrent breast cancer may not be suitable for systemic therapies. For these patients, radiotherapy offers an alternative to achieve local control and reduce the risk of pain, bleeding, infection and the associated psychological

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https://doi.org/10.1016/j.clon.2023.06.006

distress from tumour fungation. There are several palliative radiotherapy regimens in common use, without systematic evaluation of the most appropriate schedule for long-term control with minimal toxicity.

Radiotherapy has been given for local tumour control of the breast for decades, and several large studies have shown that local control is dependent on tumour size and total dose [4–6]. Total doses of more than 60 Gy using conventional fractionation of 2–2.5 Gy daily produce significantly better local control rates at 5 years than lower total doses. For patients with a poor performance status or metastatic disease, with limited life expectancy, conventional fractionation with daily trips to hospital for several weeks may not be acceptable. Hypofractionation, with fewer, larger doses per fraction is attractive in this context and has the added radiobiological advantage in breast cancer of a low α/β ratio (3.5 Gy, 95% confidence interval 1.2–5.7) for tumour control radiotherapy [7].

In the palliative setting, the regimen of 36 Gy in once- (or twice-) weekly fractions of 6 Gy is commonly used for locoregional control in many tumour types [8–10]. Once-weekly regimens have been assessed in the locally advanced and/or metastatic breast cancer setting for locoregional control upfront with concurrent first-line hormones [11,12]. Assuming an α/β ratio of 3.5, 36 Gy in six fractions delivers around 62 Gy in equivalent 2 Gy per fraction to breast tumours (ignoring the effects of overall treatment time). Based on the above trials, this indicates an adequate total dose for locoregional tumour control, with the assumption that acute toxicity is kept at manageable levels by reducing the total dose and prolonging the overall treatment time.

36 Gy in six once-weekly fractions has been the standard high-dose palliative radiotherapy regimen at The Royal Marsden Hospital (Sutton, UK). Since 2011, an accelerated schedule of 36 Gy in 6 Gy fractions two or three times a week (over 3 or 2 weeks, respectively) has been offered to patients. In 2016, Haviland *et al.* [13] looked at the effect of overall treatment time on locoregional control using data from the START trials and estimated that 0.6 Gy per day was rendered ineffective due to tumour cell repopulation with prolongation of treatment time. This lends support to the accelerated schedules, but there are limited data evaluating the effectiveness or toxicity of accelerated high-dose palliative regimens in locally advanced breast cancer. An abstract published by Dulley *et al.* [14] of 35 patients who received either 36/30 Gy in 6 Gy fractions weekly or twice-weekly reported that both schedules were well-tolerated, with an overall median local progression-free survival of 18 months in the 22 patients for whom follow-up data were available.

In this retrospective single-institution study we compared local control rates and acute and late toxicity in patients undergoing 30–36 Gy in 6 Gy fractions over 6 weeks versus more accelerated schedules over 2–3 weeks for an unresected breast cancer.

Materials and Methods

All patients treated with 30 or 36 Gy in five or six fractions (6 Gy/fraction) to the breast/chest wall ± locoregional lymph nodes between 1 December 2011 and 1 August 2020 were identified from The Royal Marsden Hospital's electronic patient database. Patients who received this regimen in the adjuvant setting were excluded. Approval to carry out data collection and analysis was obtained from the Clinical Audit Committee at The Royal Marsden Hospital. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Radiotherapy was delivered as per standard practice at our institution. In brief, patients were positioned supine on an angled breast board with both arms abducted in arm rests. Computed tomography scanning and tattoos were performed for localisation. The clinical target volume comprised the whole breast ± involved lymph nodes, with or without a 6 Gy boost to the affected tumour quadrant (total dose not exceeding 36 Gy). Brachial plexus tolerance was respected by not exceeding 30 Gy in five fractions to the supraclavicular fossa (SCF; EQD2 60 Gy, assuming an α/β of 2 for the brachial plexus). Tangential fields were used, with or without a direct anterior field to cover nodal disease. A wax bolus was applied to the breast or chest wall where there was evidence of skin involvement. All patients were treated with three-dimensional conformal radiotherapy or simple forward planned intensity-modulated radiotherapy with dosimetry conforming to International Commission on Radiation Units and Measurements (ICRU) recommendations.

Acute and late toxicity were defined by the Radiation Therapy Oncology Group (RTOG) grading system. Acute toxicity was assessed during and 3 weeks after the completion of radiotherapy. Late toxicity was defined as toxicity present from 6 months after the completion of radiotherapy. Tumour response was ideally captured at the $\geq$3 months post-radiotherapy review. Any clear responses prior to this were accepted in the absence of documentation beyond 3 months. A change in concurrent systemic treatment was defined as starting a new systemic treatment within 6 weeks either side of radiotherapy.

Statistical Methods

Local control, overall survival and progression-free survival were measured using the Kaplan–Meier method, performed using R v4.1.0. Local control was defined as the absence of progression (clinical or radiological) within the radiotherapy field. Progression-free survival encompassed both local and distant progression and death from any cause. The follow-up duration was defined as the time from the radiotherapy start date to death or last follow-up at the time of data collection. The median follow-up duration was calculated using reverse Kaplan–Meier methodology. For the purposes of statistical analysis, patients were grouped

into once-weekly versus accelerated fractionation schedules. Exploratory analyses for group comparisons and toxicity data including independent *t*-test, Log-rank, chi-squared and Mann-Whitney U testing were carried out using SPSS v26.

This retrospective dataset was not assessed for power to detect true differences between the groups and therefore all analysis is exploratory.

Results

Baseline Patient Characteristics

In total, 109 patients were identified (108 women and one man). The median age of the patients was 81 years (range 37–100). The reason for heavily hypofractionated treatment was documented as poor performance status in 55 patients (50.4%) and metastatic/locally advanced disease in 54 patients (49.6%). Most patients had locally advanced disease; T-stage was documented for 104 patients and 80/104 (76.9%) had T4 disease. The average tumour size was 50 mm (range 17–150 mm). Nodal staging was documented for 103 patients; 70/103 (68.0%) were node positive (Table 1).

The median number of lines of previous treatment was 2 (interquartile range 2 (1,3), range 0–6). Most patients (80/109, 73.4%) were offered radiotherapy for progressive local disease and did not have a change in systemic treatment planned at the time of radiotherapy. Of the 29/109 patients (26.6%) who did have a concurrent change in systemic treatment, 4/29 patients (13.8%) received radiotherapy and first-line hormone therapy upfront at the time of diagnosis and all others had progressed on at least one previous systemic treatment. Most patients (69/102; 67.7%) received no subsequent systemic treatments following radiotherapy (median number of treatments received 0, (interquartile range 1 (0,1), range 0–4).

Radiotherapy Details

Most patients (76/109; 69.7%) received a total dose to the breast of 36 Gy in six fractions; 33/109 patients (30.3%) received 30 Gy in five fractions. Forty-seven of 109 patients (43.1%) were treated weekly, 26/109 patients (23.9%) were treated twice-weekly, 24/109 patients (22%) were treated three times a week and 12/109 patients (11%) were treated on consecutive weekdays. The documented reasons for patients receiving consecutive daily treatment included minimising interruption of systemic therapy, patient convenience and rapidly progressive disease.

Sixty-three of 109 patients (57.8%) received radiotherapy to the breast alone, whereas 46/109 (42.2%) received radiotherapy to regional lymph nodes. Seventy-seven of 109 patients (70.6%) were treated with tangential fields only. Of these, 14 patients had documented axillary disease. Eleven patients had level I axillary disease encompassed by standard tangential fields and three patients were treated with 'high' tangential fields (elevation of the superior border of the fields to cover part of axillary level II in addition to level I). Twenty-seven patients were treated with an anterior field in addition to tangential fields to cover the SCF and mid/upper axilla. One patient was treated with an additional posterior field to cover deeper axillary nodes. Three patients were treated with an anterior field to cover nodal disease only (having previously received radiotherapy to the breast or chest wall). One patient was treated with volumetric modulated arc therapy to chest wall, axilla and SCF.

There were no significant differences in tumour characteristics at baseline between patients in the once-weekly versus accelerated treatment group, although there were non-significant trends towards a larger tumour size (65 mm versus 52 mm, $P = 0.07$) and higher nodal stage in the accelerated treatment group ($P = 0.06$). Patients in the accelerated treatment group also trended towards being more heavily pretreated (median 2 versus 1, $P = 0.07$). There was no difference in the proportion of patients with a concurrent change in systemic treatment at the time of radiotherapy between the groups ($P = 0.51$) and no difference in the number of subsequent systemic treatments received ($P = 0.66$). There was a slight trend towards a higher proportion of metastatic patients in the accelerated treatment group (35/62, 56.5% versus 19/47, 40.4%; $P = 0.10$) (Table 1).

Patients who had nodal irradiation appeared more likely to have received only 30 Gy to the breast in line with dose to the nodes [17/46 (37.0%) versus 16/63 (25.4%)] and to have received accelerated treatment [30/46 (65.2%) versus 32/63 (50.8%)]. However, neither group difference was significant ($P = 0.13$ and $P = 0.20$, respectively). There were no other differences in radiotherapy received (total dose, proportion of patients receiving nodal irradiation) between the once-weekly and accelerated groups.

Outcome Data (Local Control, Overall Survival, Progression-free Survival)

The median follow-up duration was 46.0 months (95% confidence interval 31.3–60.7). The median time to local progression was 23.5 months (95% confidence interval 17.7–29.2). At 1 year, the local control rate was 75.3%, which dropped to 44.1% by 2 years. The median overall survival was 11.4 months (95% confidence interval 8.7–14.1) (Table 2 and Figure 1a–c).

On exploratory analysis there did not appear to be a difference in the time to loss of local control between patients in the once-weekly and accelerated treatment groups; median 23.5 months (95% confidence interval 18.8–28.1) and 19.0 months (95% confidence interval 7.0–31.1), respectively ($P = 0.99$) (Figure 2). There was also no difference in progression-free survival or overall survival ($P = 0.28$ and $P = 0.39$, respectively) between the groups. Of note, the median follow-up durations between the two groups differed, with significantly longer follow-up in those who received weekly treatment (median 98.7 months versus 35.0 months, $P = 0.01$).

Table 1
Baseline tumour characteristics by radiotherapy schedule (once-weekly fractionation versus accelerated fractionation schedules)

Tumour characteristics		No. patients (%)	Once weekly (%)	Accelerated (%)	*P*-value†
T-stage $n = 100$*	T1/T2	15 (15.0)	8 (18.6)	7 (12.3)	$P = 0.877$
	T3/T4	85 (85.0)	35 (81.4)	50 (87.7)	
N-stage $n = 103$*	N0	33 (32.0)	17 (37.8)	16 (27.6)	
	N1	40 (38.9)	19 (42.2)	21 (36.2)	$P = 0.06$
	N2	17 (16.5)	6 (13.3)	11 (19.0)	
	N3	13 (12.6)	3 (6.7)	10 (17.2)	
Grade $n = 92$*	1	1 (1.1)	1 (2.5)	0 (0)	
	2	42 (45.7)	17 (42.5)	25 (48.1)	$P = 0.958$
	3	49 (53.2)	22 (55.0)	27 (51.9)	
ER $n = 102$*	ER positive	70 (68.6)	30 (66.7)	40 (70.2)	$P = 0.705$
	ER negative	32 (31.4)	15 (33.0)	17 (29.8)	
HER-2 $n = 98$*	HER-2 positive	20 (20.4)	12 (27.9)	8 (14.6)	$P = 0.103$
	HER-2 negative	78 (79.6)	31 (72.1)	47 (85.4)	

ER, oestrogen receptor; HER-2, human epidermal growth factor-2. *Denotes number included, as each category had missing data: T-stage = 9 patients; N-stage = 6 patients; Grade = 17 patients; ER status = 7 patients; HER-2 status = 11 patients. †**Group comparison was performed using χ2 and χ2 for trend as appropriate.**

During the follow-up period, 32 patients progressed locally. Twenty-seven patients had progression in the breast/chest wall alone, two patients progressed in both the breast and axilla, and three patients progressed in nodal regions alone (two in axilla, one in SCF). There was no difference in the time to local progression between patients who received nodal irradiation and those who did not [median 23.9 months (95% confidence interval 10.8–37.0) and 21.0 months (95% confidence interval 14.0–28.0), respectively ($P = 0.87$)]. There was also no difference in the time to local progression by total dose received [median 23.5 months (95% confidence interval 18.7–28.2) for 36 Gy, 19.0 months (95% confidence interval 0–46.5) for 30 Gy ($P = 0.91$)].

Overall Best Response

A clearly documented overall best response assessment (progressive disease; stable disease; partial response; complete response) was available in 78 patients. Eight of 78 patients (10.3%) experienced a complete response, 60/78 (76.9%) demonstrated a partial response and stable disease was observed in 9/78 (11.5%). One patient (1.3%) progressed during radiotherapy and the last fraction of treatment was withheld (30 Gy received).

Twenty-six of 32 patients (81.3%) experienced an objective response (partial response and complete response combined) in the once-weekly group compared with 42/46 (91.3%) in the accelerated treatment group. There was no association between the two groups and overall best response ($P = 0.43$)/objective response ($P = 0.20$) (Figure 3).

Acute Toxicity

Clear documentation regarding acute toxicity was available in 98 patients. Twenty-five of 98 patients (25.5%) experienced no toxicity, 35/98 (35.7%) experienced grade 1 toxicity, 31/98 (31.6%) experienced grade 2 toxicity and 7/98 (7.1%) experienced grade 3 toxicity. No grade 4 toxicity was reported. Grade 1 and 2 toxicity reflected skin toxicity and fatigue. Grade 3 toxicity was exclusively skin related.

There was no association between the groups and acute toxicity grade ($P = 0.78$) (Figure 4a). Thirty-four of 45 patients (75.6%) experienced any grade of acute toxicity in the once-weekly group, compared with 39/53 (73.6%) in the accelerated group. Grade 3 toxicity was reported in 3/45 (6.7%) and 4/53 (7.5%) patients in the once-weekly and accelerated groups, respectively. Interestingly, all four patients who experienced a grade 3 acute skin reaction in the accelerated group had been treated with a wax bolus, compared with none of the three patients in the once-weekly group.

Late Toxicity

Late toxicity was documented in 48/109 patients (44%). Overall, 20/48 patients (41.7%) experienced no toxicity, 20/48 (41.7%) reported grade 1 toxicity and 7/48 (14.6%) experienced grade 2 late toxicity. No patients experienced grade 3 late toxicity, but one patient experienced grade 4 toxicity (skin radionecrosis). This patient had received 30 Gy in five fractions to the breast, axilla and SCF using tangents and an anterior field, with no bolus, treated on consecutive weekdays (five fractions a week). The patient had undergone a palliative axillary debulking procedure 8 weeks before radiotherapy due to rapid tumour growth and developed a seroma that did not require drainage. She developed erythematous changes in the irradiated field 6 months after radiotherapy, followed by recurrent infections and pain in the axilla. Tumour recurrence with skin radionecrosis and a fistulating axillary wound was documented by an oncology consultant 15 months after radiotherapy.

The other late toxicities reported from most to least common were breast distortion/asymmetry, skin thickening/fibrosis/induration, telangiectasia, oedema of the breast, skin dryness and rib pain with no documented

Table 2
Median time to loss of local control, overall survival and progression-free survival and percentage of patients without event(s) at 6 months, 1 year, 2 years and 3 years. The median duration of local control appears longer than overall survival due to the fact that patients who died with no local progression were censored at the last follow-up (an 'event' constituted local progression only). These results indicate that most patients died without having progressed locally.

	Median in months (95% confidence interval)	6 months	1 year	2 years	3 years
Local control	23.5 (17.7–29.2)	89.4%	75.3%	44.1%	33.1%
Overall survival	11.4 (8.7–14.1)	77.9%	47.9%	25.1%	21.4%
Progression-free survival	7.1 (5.5–8.7)	58.7%	32.7%	13.7%	9%

fracture. One patient experienced grade 1 changes in the lung.

Overall, there was no association between the groups and late toxicity grade ($P = 0.26$) (Figure 4b). However, a separate examination of the consecutive weekday group revealed that of 12 patients, late toxicity was documented for six, five of whom (83.3%) experienced late toxicity (grade 1 in two patients, grade 2 in two patients and grade 4 in the patient above). There was more frequent documentation of late toxicity in the accelerated treatment group [30/62 patients (48.4%) versus 18/47 patients (38.3%) in the once-weekly group].

Discussion

This retrospective dataset was not assessed for power to detect true differences between the groups and therefore all analyses are exploratory and hypothesis-generating. Further limitations include the necessary grouping of all patients receiving multiple fractions a week into one category, to increase numbers for statistical analysis. Despite this, the relatively small numbers of patients in each group meant that true differences in patient and tumour characteristics between the groups and breast cancer and toxicity outcomes may not have been detected. Additionally, there was a high rate of censored data, reflecting the fact that studying elderly patients at a tertiary radiotherapy centre may be challenging, as patients are discharged to local centres for patient convenience.

Despite the above limitations, the radiotherapy regimen of 36/30 Gy in 6 Gy fractions appears to provide a reasonable duration of local control for an unresected breast tumour in patients with/without metastatic disease who are unsuitable for surgery. Most patients in our study had advanced disease, had already progressed through several systemic treatments at the time of radiotherapy and received no further systemic treatments following radiotherapy. Nevertheless, 87% of patients had a response to radiotherapy, and given that a number of patients were discharged or died within a year of treatment, this value may be an underestimation, as breast tumours may continue to shrink up to 6–12 months after radiotherapy [15]. Patients receiving nodal irradiation did not experience worse tumour control outcomes, and although the numbers are very small there did not appear to be a propensity for progression in these nodal regions compared with in the breast, despite the often lower total dose to nodes. Most patients did not start a new systemic treatment at the time of or following radiotherapy, and so the tumour responses and local control probably reflect radiotherapy effects, although in some patients with metastatic disease local control may have been prolonged by subsequent lines of treatment for progression at other sites.

Three-quarters of evaluable patients remained free of local progression 1 year after radiotherapy, with most patients dying without further local progression. However, local control had dropped to 44% by 2 years. Local progression following radiotherapy is often difficult to manage and distressing for the patient as the tumour may fungate and cause pain, bleeding, odour and infections, significantly impacting on quality of life. Following loss of local control after radiotherapy, in our dataset, the median survival was around 5 months. With the increasing number of systemic therapies available and improving survival in metastatic breast cancer in recent decades [16–18], patients with an *in situ* breast cancer are more likely to be troubled at some point by local progression. Although the regimen of 36 Gy in 6 Gy fractions may be sufficient for lifelong control of local disease in most patients, in those with a better life expectancy, further strategies are warranted to improve the efficacy of radiotherapy.

There did not appear to be a difference in tumour response or time to local progression between patients receiving once-weekly or accelerated treatment schedules. From the Haviland data, we hypothesised that the reduction of overall treatment time from 6 weeks to $\leq$3 weeks may have improved local control [13], but in our small dataset this did not appear to be the case. There were indications that the accelerated treatment group had a higher burden of disease, including trends towards a larger tumour size, higher nodal staging (and consequent higher proportion of patients treated with nodal radiotherapy), more prior lines of therapy and a higher likelihood of having metastatic disease. This may have masked potential improvements in local control outcomes in the accelerated group. Prior to 2015, the vast majority of patients received once-weekly radiotherapy (only 1/38 patients received accelerated treatment) and from 2015 onwards most received accelerated treatment (61/71 patients), leading to a significant

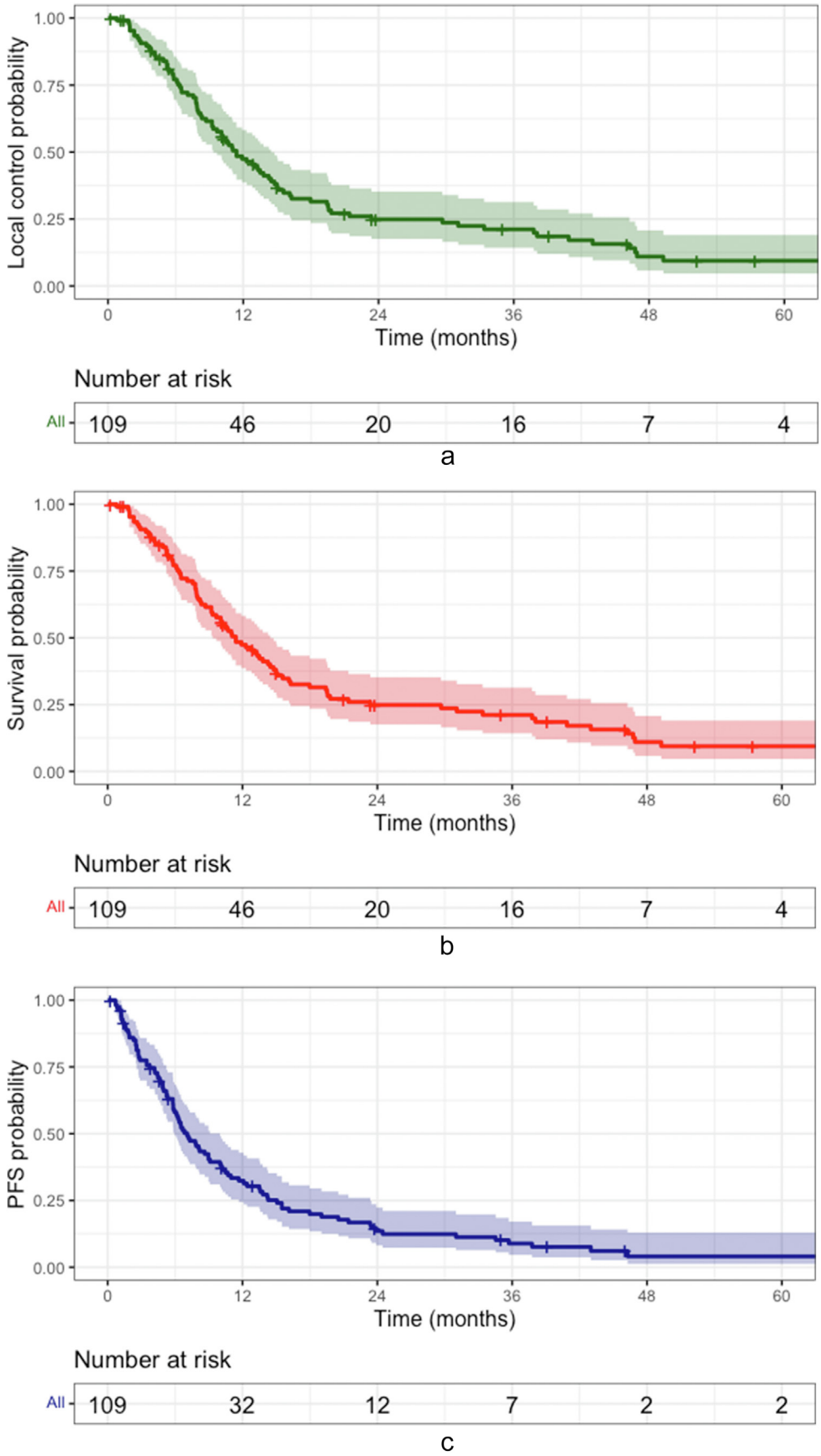

Fig 1. Kaplan-Meier curves revealing: (a) local control, (b) overall survival and (c) progression-free survival following radiotherapy in all patients. Shading denotes the 95% confidence interval.

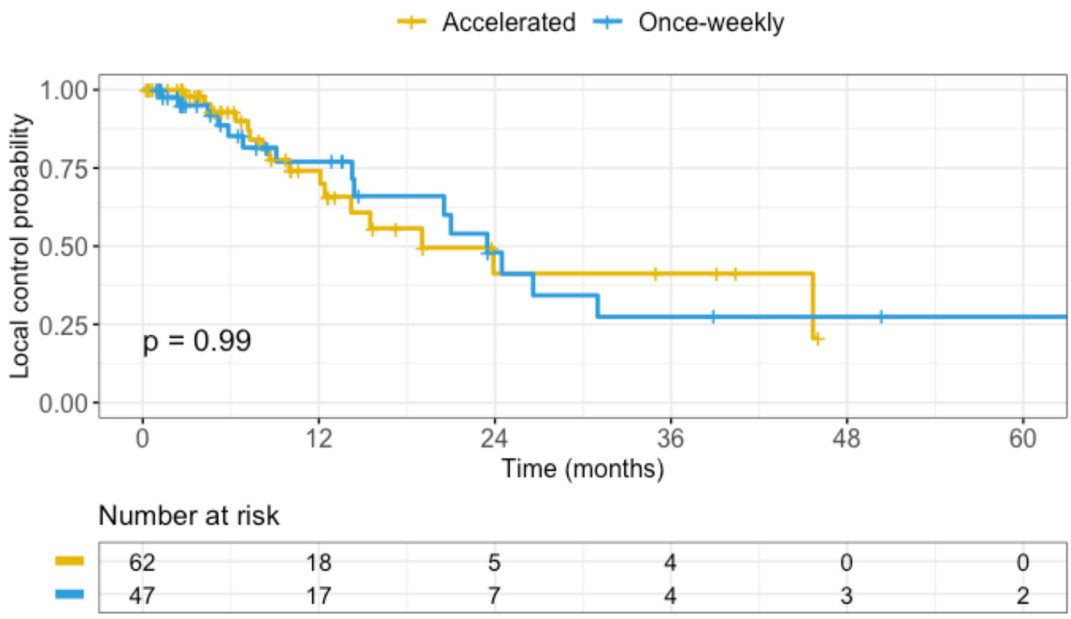

Fig 2. Kaplan-Meier curves for local control stratified by treatment schedule (once-weekly versus accelerated fractionation schedules) (P = 0.99).

difference in the median follow-up time between the two groups. We are therefore comparing two populations – patients treated from 2011 to 2015 and patients treated 2015 onwards – and given the ever-changing nature of breast cancer management, this must be borne in mind when comparing outcomes, although there was no difference in the number of systemic treatments received following radiotherapy between the groups.

Given that accelerated tumour cell repopulation is assumed to begin around 21 days from the start of radiotherapy [19,20], there should, in theory, be no additional benefit from treatment three times a week or consecutive daily treatment over a twice-weekly regimen for local tumour control. A very short overall treatment time may increase toxicity due to incomplete repair of normal tissues between fractions. Our data did not reveal worse acute or late toxicity with a reduction in overall treatment time to 2–3 weeks. However, the occurrence of a grade 4 late toxicity in the consecutive weekday group, as well as a very high overall late toxicity rate, means that we do not recommend this regimen. On balance, the twice-weekly regimen may be the most appealing, in which treatment is completed before the predicted onset of accelerated repopulation, but allows for more time between fractions for both acute and late-responding normal tissue recovery.

Due to the retrospective nature of the data we were unable to compare the speed of resolution of acute toxicity between once-weekly and accelerated treatment regimens. This is of paramount importance, particularly in patients with a limited life expectancy, as a grade 3 skin reaction (confluent moist desquamation) lasting many months would have much more of an impact on quality of life than a grade 3 skin reaction that resolves very quickly.

Inadequate documentation meant long-term toxicity was only evaluable in 48 patients. Another limitation of the late toxicity data is that the comparison between once-

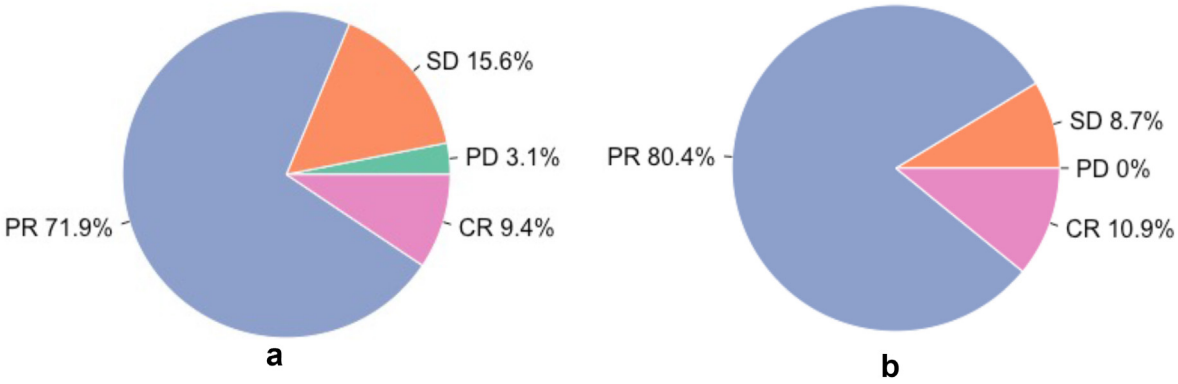

Fig 3. Overall best response in (a) the once-weekly group and (b) the accelerated group. PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response. Evaluable patients in the once-weekly group, n = 32; evaluable patients in the accelerated group, n = 46.

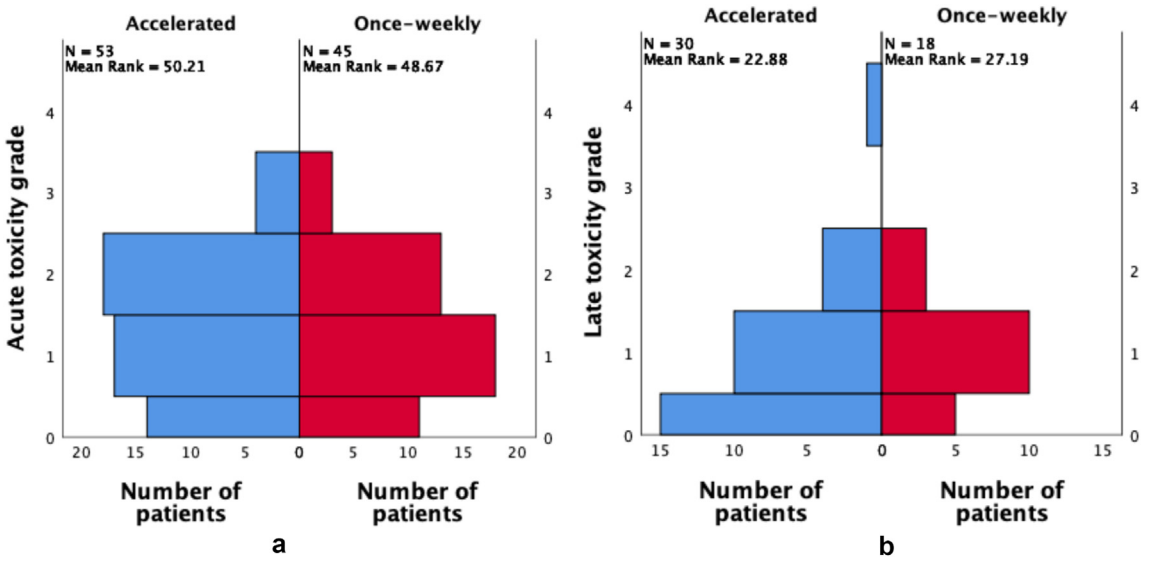

Fig 4. Distribution of patients experiencing each grade of (a) acute and (b) late toxicity between once-weekly and accelerated fractionation schedules. Mann-Whitney U testing revealed no significant association between the groups and acute or late toxicity grade ($P = 0.78$ and $P = 0.26$, respectively). One patient in the accelerated group experienced a grade 4 late toxicity (skin radionecrosis).

weekly and accelerated treatment groups may have been influenced by better documentation of toxicity, including of no toxicity, in the accelerated treatment group. The consecutive daily group had worse late toxicity outcomes and will have negatively influenced the overall late toxicity in the accelerated group. Nevertheless, it was reassuring that the overall rate of grade 2 or higher late toxicity in our cohort was just under 17%, which is comparable with the 18% 'moderate or marked late effects' seen at 5 years in the arm of the FAST trial that evaluated 30 Gy in once-weekly 6 Gy fractions in the adjuvant setting [21]. Another adjuvant study focusing on elderly patients treated with once-weekly hypofractionated radiotherapy (total dose 30–37.5 Gy) reported any grade of chronic skin impairment in 30.9% of patients, with grade $\geq$2 fibrosis in 8.6% [22]. It may have been expected that the rates in our retrospective study would be higher, due to selective examination and documentation if a patient reported symptoms.

Conclusion

The radiotherapy regimen of 36 Gy in 6 Gy for breast cancer patients with advanced local disease is an effective treatment and provides a reasonable duration of local control, with acceptable acute toxicity. There did not appear to be a difference in local control rates or toxicity between patients receiving once-weekly fractions or two/three fractions a week. Importantly, the shorter overall treatment time did not appear to increase toxicity in these regimens. However, the consecutive 6 Gy daily fractionation group had a higher rate of late toxicity, including one grade 4 late toxicity, and therefore this regimen is not recommended. From a radiobiological standpoint, twice-weekly fractionation is compelling for both local control and allowing sufficient normal tissue recovery between fractions. The twice-weekly regimen appears to be a safe alternative to the more commonly used once-weekly schedule and may be attractive to patients who would like their treatment completed in a shorter overall time. The accelerated schedule also minimises interruptions to any concurrent systemic therapy.

Author Contributions

KW and **NS** are the guarantors of integrity of the entire study. **KW**, **NS**, **AK** and **IL** were responsible for study concepts and design. **KW** and **NS** carried out the literature research. **KW** was responsible for the experimental studies/data analysis. **KW** and **KM** carried out the statistical analysis. **KW** and **LG** prepared the manuscript. **KW**, **NS**, **LG**, **KM**, **AK** and **IL** edited the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgements

We are extremely grateful to Jo Deubert and David Taylor, from the Hospital Information System team at The Royal Marsden NHS Foundation Trust, for helping us identify all the patients for this analysis. Dr Douglas Brand helped put this proposal through The Royal Marsden NHS Foundation Trust's audit review committee for approval. We would also like to thank Dr Gill Ross and Professor John Yarnold for allowing us to include their patients in this analysis. We acknowledge funding to the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London. N. Somaiah and A.

Kirby are supported by a Cancer Research UK Radiation Research Centre of Excellence at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust (grant ref: A28724).

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