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Extreme Hypo Fractionation in Breast Cancer in Older Patients

Blanco Parajón S*

*Department of Radiation Oncology, Hospital Universitario Central de Asturias, Asturias, Spain.

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ABSTRACT

Life expectancy is growing and breast cancer prevalence increases with age. In many cases, the diagnosis is late and they are undertreated based on chronological age. Radiation therapy (RT) is one of the main treatments as adjuvant treatment whenever possible and as definitive if not. Extreme hypo fractionation could be a good treatment schedule compared to daily conventional fractionation, in older women with comorbidities, social problems and who live far from the treatment center. The purpose of this article is to review extreme hypo fractionated schedules in elderly patients published in literature, in terms of loco regional recurrence and side effects. Loco regional recurrences were less of 16% in all series. The number of acute side grade 3 and grade 4 effects was less than 15%. The range of fibrosis as the most significant late side effect was between 15.1% and 39.2%. Extreme hypo fractionated RT seems to be a safe treatment without significant side effects.

Keywords: Aged, Breast neoplasms, Extreme hypo fractionation, Hypo fractionation, Radiotherapy

Life expectancy is growing and breast cancer prevalence increases with age, being the most commonly diagnosed form of cancer and the leading cause of cancer death in women [1]. Although the diagnosis is increasing in older women, in many cases is late and they are undertreated based on chronological age [2]. RT is one of the main treatments and it is absolutely necessary as adjuvant treatment after lumpectomy or after mastectomy when there is node disease, to improve local control, regional control and overall survival [3,4].

The conventional treatment schedule of RT is 50 Grays (Gy), delivered in 25 fractions, 5 days a week during 5 weeks, with or without a subsequent boost. Currently, a moderate hypo fractionated treatment delivered in 15-16 fractions, has been associated with equivalent long-term results than conventional schedule [5], although for the American Society for Radiation Oncology, there is not enough evidence when regional radiation is indicated [6]. Breast cancer would benefit from higher doses per fraction, because its α/β ratio ranges from 3 to 5 Gy, as suggested START A and B studies [5,7]. Shortened treatments can improve the quality of life of elderly patients, who have more problems to receive the best treatment. The purpose of this minireview is to review the results of once-weekly hypo fractionated schedules in elderly patients published in literature, in terms of loco regional recurrence (LRR) and acute and late toxicity.

REVIEW

Currently, there are available data showing that a moderate hypo fractionated RT, delivered in 15-16 fractions during 3 weeks for early stage breast cancer is equivalent than conventional treatment (5 weeks) [5,7,8]. There is a tendency to undertreat elderly women due to different reasons like comorbidities, lack of social support, difficulties to attend the treatment or distance to the treatment center. Extreme hypo fractionation allows shortening treatments and lower spending [9]. The α/β ratio of breast cancer ranges from 3 to 5 Gy, suggested by UK START trials, which implies that breast cancer would benefit from high doses per fraction.

Among published studies, the most important is the UK FAST trial, being the only phase III in the literature. This study compares conventional doses with two equivalent hypo fractionated schedules of 5.7 Gy and 6 Gy, delivered in 5 weekly fractions, in early breast cancer after lumpectomy. It was not the primary endpoint, but at 3 years, local control

Corresponding author: Blanco Parajón S, Department of Radiation Oncology, Hospital Universitario Central de Asturias, Asturias, Spain; Tel: 684075718; E-mail: sonia.bl.pa@gmail.com

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was 99.67%, only two patients developed local recurrence. Hypo fractionation was well tolerated with the vast majority of acute dermatitis grade 1 or less. Cosmetic changes were very similar between arms and a little bit greater in the group that received 6 Gy per fraction than in the group of 5.7 Gy (17.3% Vs 11.1% respectively) [10]. There are six retrospective studies in the literature. Studies published by Rostom et al. [10] and Sanz et al. [11] included patients with all stages, with or without axillary lymph nodes. Patients were treated with lumpectomy, mastectomy and no surgery. The treatment schedules were 39 Gy in 6 weekly fractions of 6.5 Gy including axillary nodes, and some patients received an electron boost to residual tumour with a 3 fraction schedule of 3.2 Gy applied on alternate days in the Rostom et al. and in the Sanz et al. [10,11] firstly 6.25 Gy given in 6 weekly fractions and later 5 Gy schedule given in 6 weekly fractions, with or without a boost of one or two fractions. Nodes were irradiated in 15% patients. LRR was not correctly reported by Rostom et al. [10] while Sanz et al. [11] got at 5 years a local control of 96.5%. Most acute dermatitis was G1-2 in both studies. Late fibrosis and telangiectasia appeared in a few patients and in most of patient's cosmetic was good or excellent. Hyperpigmentation, edema or mastitis were described [11,12].

Two retrospective studies included patients who were not underwent surgery, with all stages. The selected schedule for both studies was a total dose of 32.5 Gy in 5 weekly fractions of 6.5 Gy to the involved breast, followed by one to three weekly fractions as a boost. In both studies, the most selected dose for the treatment of axillary nodes when needed was 27.5 Gy in 5 weekly fractions of 5.5 Gy. Most of patients received hormone therapy. Maher et al. presented 16% developed LRR at 3 years and Courdi et al. 15% LRR at 5 years.
Most acute dermatitis was developed as G1-2. Fibrosis was developed in 39% in the group of Maher and 37.1% in Courdi et al [13,14].

Another two retrospective studies included patients who underwent lumpectomy. Kirova et al. [16] analyzed a group of 50 patients, with stages T1-2 N0-1. Rovea et al. [14] analyzed 291 patients with all stages, although the vast majority was T1 mic, T1 and T2, N0-2. The selected dose in both studies was 32.5 Gy in 5 weekly fractions of 6.5 Gy. After FAST trial, Rovea et al. [14] began to use a schedule of 30 Gy in 5 fractions of 6 Gy. Nodes were not irradiated in any. The results at 5 years were a cancer specific survival of 95% in both. Acute dermatitis was developed as grade 2 or less in most. Fibrosis, telangiectasia, hyperpigmentation and edema were described as late effects [15,16].

The prospective randomized trial published by Baillet et al. [17] and the prospective single-arm study published by Ortholan et al. included patients treated by lumpectomy, mastectomy or nothing. Both have included patients of all stages. Treatment schedule chosen by Baillet et al. [17] was to deliver 23 Gy in 4 fractions of 5 Gy for the first two sessions and another two fractions of 6.5 Gy, administered in 17 days. Forty-five patient treated with lumpectomy, received an additionally brachytherapy boost of 20 Gy. The treatment schedule chosen by Ortholan was a total of 32.5 Gy delivered in 5 weekly fractions of 6.5 Gy each one, followed by a boost of 1 or 2 more fractions in some patients or administered with brachytherapy in 4 patients. Node irradiation was not reported by Baillet et al. [17] and was administered in a 32% by Ortholan et al. At 5 years, LRR was 7% in the Baillet study and 2.3% in the Ortholan study. Acude side effects were less than G2. Fibrosis was the most common late effect. Telangiectasia, brachial lymphoedema and chronic pain were described [17,18].

There are two prospective single arm published studies that included patients after conserving surgery. The schedule selected by both studies was 30 Gy in 5 fractions of 6 Gy. In the Martin et al. [19] study it was delivered twice a week over 15 days. Nodes were negative. On the other hand, Dragun et al. administered it once a week followed by a boost of 1 more fraction of 5.7 or 6 Gy, 8.1 Gy given in 3 fractions or 10 Gy given in 5 fractions. Nodes could be positive or negative, but irradiation was not performed. At 3 years, LRR was 0% and 1.3% in Martin and Dragun studies respectively [19,20]. Acute dermatitis was mild in most of patients with an acute skin reaction greater than G2 in 22.8% reported by Dragun et al. Cellulitis was reported as late effect [19,20].

Globally a total of 87.1 % of lesions were treated with adjuvant RT and 12.9 % as definitive RT, both of them with or without a boost. Only 8.9 % of patients received a boost, 73.3% of patients did not receive a boost and in other 17.7% it was not specified. Summary of results are given in **Table 1.**

The most reported acute side effect was dermatitis, most of them moderate or mild. Acute dermatitis grade 3 decreases with hypo fractionation because a response to lower total dose which reduces late side effects [21-25]. The most collected late side effect was fibrosis followed by hyperpigmentation, telangiectasia, edema or local pain. Several factors such as the age, smoking, post-surgical cosmesis, chemotherapy, breast volume, total radiation therapy dose, technique, fractionation and boost radiation, can influence late effects and these side effects can have a significant physical and psychological impact on patients [26,27].

The studies reviewed collect data similar to historically standard schemes [5,7,8,28]. Results have shown a good loco regional control rates with a small number of LRR and an acceptable chronic toxicity despite being increased. It is necessary to emphasize that the vast majority of patients

were older, most of them with an early stage and therefore a better prognosis and most of them received hormone therapy influencing loco regional control. The worst results in terms of loco regional control are observed in the groups that have not undergone surgery, and followed by patient groups that have not received a boost.

Table 1. Summary of studies done on hypo fractionation in breast cancer.

TRIAL, YEAR	Rostom et al. 1987	Baillet et al. 1990 b	Maher et al. 1995	Ortholan et al. 2005	Courdi et al. 2006	Martin et al. 2008 b	Kirova et al. 2009	FAST Trialist group, 2011
DESIGN	Retrospective	Prospective, randomized	Retrospective	Prospective, single-arm	Retrospective	Prospective, single-arm	Retrospective	Prospective, randomized
ELEGIBILITY CRITERIA	I-IV	T1-4, N-/+	T1-4, N0-2	T1-4, N0-1	T1-4, N0-1	<3cm, N0	T1-2, N0-1	<3cm, N0
AGE	69.2[a]	53[a]	81	78	83	>50	80	62.8
N. PATIENTS/ LESIONS	84 /86	125	70	150/151	115/124	30	50	613
SURGERY	Lumpectomy 13 Mastectomy 18 No surgery 53 2 N.R.	Lumpectomy 45 Mastectomy 52 No surgery 28	No surgery	Lumpectomy 108 Mastectomy 43	No surgery	Lumpectomy	Lumpectomy	Lumpectomy
HT / CHT (%)	HT 4.8 CHT 0	HT N.R. CHT 22.4	HT 100 CHT 0	HT 91.3 CHT 2.7	HT 98.3 CHT 10.4	HT N.R. CHT 0	HT 60-78 CHT 0	HT 88.7 CHT N.R.
DOSE (Gy)	39	23	32.5	32.5	32.5	30	32.5	28.5 30
FRACTIONS (Fx) /N.Patients	6.5 Gy * 6 Fx / 84	5.75 Gy * 4 Fx / 125	6.5 Gy * 5 Fx / 26	6.5 Gy * 5 Fx / 100	6.5 Gy * 5 Fx / 23	6 Gy * 5 Fx / 30	6.5 Gy * 5 Fx / 50	5.7 Gy * 5 Fx / 305 6 Gy * 5 Fx / 308
BOOST / N.Patients	NO	NO	+ 6.5 Gy * 1 Fx / 44	+ 6.5 Gy * 1 Fx / 30 + 6.5 Gy * 2 Fx / 16 + 15 Gy * 1 Fx (BQT) / 4	+ 6.5 Gy * 1 Fx / 7 + 6.5 Gy * 2 Fx/ 69 + 6.5 Gy * 3 Fx / 25	NO	NO	NO
FOLLOW-UP (years)	3	5	3	5	5	3	5	3
Local and Regional Recurrence	N.R.	7%	16%	2.30%	15%	0%	6%	0.33%
DERMATITIS G1-2	45.30%	N.R.	10%	27.80%	27.40%	30%	N.R.	23.20%
DERMATITIS G3-4	3.50%	N.R.	3%	0%	0%	13.30%	0%	0.80%
LATE TOXICITY (fibrosis)	15.10%	11.20%	39%	39.10%	37.10%	N.R.	33%	23.80%

Rovea et al. 2015	Retrospective	T1mic-4, N0-2	80	291/298 [a]	Lumpectomy	HT 77.9 CHT 2.7	30 32.5	6 Gy * 5 Fx / 57 6.5 Gy * 5 Fx / 241	NO	5	2%	27.40%	1.30%	39.20%
Dragun et al. 2017	Prospective, single-arm	0-II, N-/+	59	158	Lumpectomy	HT 73.4 CHT 28.5	28.5 30	5.7 Gy * 5 Fx / 78 6 Gy * 5 Fx / 58	+ 6 Gy * 1 Fx /22 **+ 2.7 Gy * 3 Fx / 3 [c]** **+ 2 Gy * 5 Fx / 3 [c]**	3	1.30%	N.R.	22.8 % [d]	N.R.
Sanz et al. 2018	Retrospective	In situ-IV, recurrence, N-/+	79	486	Lumpectomy 382 Mastectomy 97 No surgery 7	HT 78.6 CHT 13.4	30 37.5	5 Gy * 6 Fx / 45 6.25 Gy * 6 Fx / 441	+ 1-2 Fx / NR	5	3.30%	81.10%	12.80%	27.20%

NR = Not reported; HT = hormone therapy; CHT = chemotherapy; Gy = Gray

a) Age: Median age except average age in studies with a. In the study published by Martin et al. patients were older than 50 years, but median or mean age is NR.

b) Twice-weekly schedules.

c) The group to which the patients who have received boost belong has not been reported.

Acute effects have been reported as grade 2 or greater

CONCLUSION

Extreme hypo fractionation in breast cancer in older women is a well-tolerated and safe treatment, without significant side effects. Surgery is preferable if possible and it is advisable to administer a boost. The delivered of weekly high doses per fraction, could be a good option especially for elderly patients with favorable early stage cancer, in advanced stages who are unfit to receive large daily treatments, or even in patients unfit for surgery despite increasing the risk of recurrence.

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