Moderatori:
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Ipofrazionamento:standard attuali
D. Cante

THE PRINCIPLES OF TREATMENT BY RADIOTHERAPY IN BREAST CARCINOMA.

R. McWHIRTER.

From the Department of Radiotherapy, Royal Infirmary, Edinburgh.

Received for publication November 21, 1950.

In only a minority of cases is the disease still confined to the breast by the time the patient is referred to a large general hospital. The surgical results are good so long as the disease is confined to the breast, but immediately the disease extends beyond the breast the results become much poorer. Axillary spread is, of course, common and, in the past, surgical efforts have been concentrated on this route of spread. That this is not the only route of spread, however, has been clearly demonstrated by Handley and Thackray (1947), who have shown that in a high proportion of cases where there is axillary involvement there is also involvement of the glands along the internal mammary artery. Treatment of this route of spread by surgery is not at present possible. In addition the supraclavicular glands are involved in 33 per cent of the cases where the axillary glands are involved and, while surgical removal of the supraclavicular glands may be attempted, the value of this procedure is extremely doubtful. For the majority of cases of breast carcinoma it therefore follows that surgery is unlikely to be successful unless supplemented by radiotherapy.

Success in radiotherapy is dependent on the sensitivity of the tumour to radiation. Unfortunately breast carcinoma is only moderately sensitive, and improved results can only be expected if the radiotherapy is carefully planned.

It is not the purpose of this paper to give a detailed account of the treatment of a patient by radiotherapy, but rather to emphasize the main principles in the treatment of breast carcinoma by radiotherapy. There are five main principles:

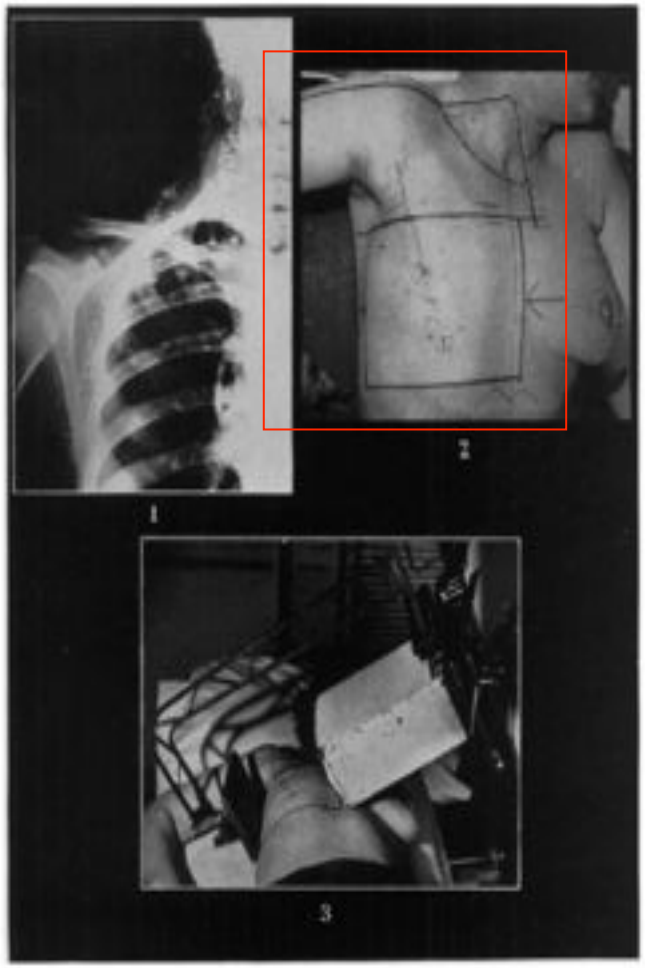
1. *The axillary and supraclavicular glands must be treated as one continuous chain.*

In the past it has been customary to regard the supraclavicular glands as being somewhat separate and distinct from the axillary glands. I believe the supraclavicular glands are best regarded as representing the proximal group of glands which accompany the axillary vessels.

If a finger is placed in the apex of the axilla at the time of a radical operation, it can be easily demonstrated that the apex in fact lies almost deep to the supraclavicular region.

In tuberculosis the disease may readily spread from the neck glands to the axillary glands, as is demonstrated in Fig. 1. This radiograph shows the two main groups of glands in the neck—the carotid chain accompanying the carotid vessels and the posterior cervical chain which lies along the anterior border of the trapezius. It will be noted that both chains are continuous with the glands of the axilla, and that the medial group of supraclavicular glands form the proximal group of the axillary chain.

Further proof of the continuity of the neck and axillary glands is shown in



carcinoma of the thyroid, for if the glands in the neck are involved it is common to find that there is also axillary involvement.

Continuity with the posterior cervical chain is readily demonstrated in patients suffering from carcinoma of the nasopharynx where the posterior cervical chain is commonly involved. If the lower glands of the posterior cervical chain are involved there is nearly always involvement of the axilla.

In the above examples spread downwards has occurred, but it may be assumed that if downward spread can take place the reverse is also possible. As has already been mentioned when the glands in the axilla are involved in breast carcinoma the supraclavicular glands are involved in 33 per cent of cases, and there can be little doubt that in a proportion of cases the supraclavicular glands have become involved by upward spread from the axilla.

It follows therefore that the axillary and supraclavicular glands must be treated as one continuous chain of glands, and the only satisfactory method of doing so is by the use of two directly opposed fields—one field placed in front and the other placed posteriorly as in Fig. 2.

Irradiation of the axilla by a field applied to the base of the axilla and irradiation of the supraclavicular glands by a separate field is unlikely to meet with success because the intervening glands are not treated. It has been stated by some workers that it is difficult to irradiate the supraclavicular region successfully. I believe that in many cases the reappearance of glands in the supraclavicular region has not been due to any difficulty in treating this area, but is due to reinfection of the supraclavicular glands from involved glands high up in the axilla which received no radiation at all.

2. *The internal mammary glands must be treated in continuity with the chest wall.*

This is best done by glancing fields so as to avoid lung damage. The medial glancing field should be placed beyond the midline so as to include within the irradiated area the glands along the internal mammary artery on the side affected (Fig. 3). By using large fields the dose distribution over the area can be made fairly uniform. The use of bolus further assists in obtaining a homogeneous distribution.

The usual separation between the glancing fields is 16 cm., and in radical treatment it is rarely necessary to exceed this distance. If the skin involvement is more extensive and all the diseased area cannot be satisfactorily included within those limits, only palliative treatment is indicated.

It will have been noted that the total area requiring irradiation has been divided into two sections. Every effort is made to avoid a gap between the two sections, and experience has shown that it is uncommon for recurrence to take place along the line of junction. Ideally, of course, it would be better to irradiate the whole of the area to be treated without any division. Unfortunately this cannot be achieved because the axillary and supraclavicular glands cannot be satisfactorily treated except by means of directly opposed fields. (Carcinomata of the axillary tail of the breast do, however, call for some modification of the usual technique.)

3. *Hard quality radiation is essential.*

With radiation of long wave-length much more energy is absorbed by bone than by soft tissue. Not only may this result in bone necrosis, but any tumour

cells situated in the path of the beam distal to the bone will receive less dosage than might be expected from isodose curves obtained by measurements taken in a uniform medium.

In Edinburgh we use a beam generated at 250 kV. constant potential and filtered by a "triple" Thoraeus filter (1·0 mm. steel (tube window), 1·5 mm. tin, 1·0 mm. aluminium), giving a half value layer of 3·7 mm. copper. Further proof of the value of this quality of radiation was demonstrated during a breakdown of the main apparatus, when it became necessary to treat patients on a 220 kV. pulsating tension apparatus with only 1 mm. copper filtration. The half value layer was 1·6 mm. copper. Axillary glands, palpable before treatment was commenced, did disappear, but as a general rule the disappearance was only temporary, and recurrence took place in a high proportion of these cases at about six months after treatment had been given.

4. *Adequate dosage must be delivered throughout the whole of the treated area.*

We aim at a minimum tumour dose of 2750 r in three weeks. The maximum dose varies according to the thickness of the patient, but is not allowed to exceed a maximum of 4500 r. On this account if a patient is stout and the minimum tumour dose cannot readily be achieved it is better to carry out a radical operation.

5. *Only one course of treatment should be given.*

Repeated courses of treatment at intervals of three to six months are quite illogical if the intention is to give radical treatment. Repeated courses imply that malignant cells are deliberately left behind for further treatment at a later date.

TABLE I.—*Total Cases referred* 1941–45 = 1345.

Operable 60 per cent.		Inoperable (radical operation) 40 per cent.	
Axillary glands negative	Axillary glands positive	Advanced locally	Distant metastases
24 per cent	36 per cent	21 per cent	15 per cent
Axillary dissection unnecessary	Disputed group	Radical mastectomy contra-indicated	Radical mastectomy contra-indicated
Simple mastectomy + X-rays	Simple mastectomy + X-rays	Simple mastectomy + X-rays or X-rays alone	No treatment or palliative treatment
5 year Survival rate 69 per cent	5 year Survival rate 44 per cent	—	—
All operable cases (537) 5 year survival rate 62 per cent		All locally advanced cases (280) 5 year survival rate 29 per cent	—
All cases without evidence of distant metastases (1140) 5 year survival rate 50·5 per cent			
Every case (treated and untreated) coming to the hospital (1345) 5 year survival rate 43·7 per cent			


Why
not?

STUDI PROSPETTICI RANDOMIZZATI HYPO RT

Author/Publication	Schedule	Dosage	Selection	N°pz (BCT)
Whelan *JNCI 2002*	Standard HYPO	25x2 Gy 16x2,66 Gy	T1-2, N0 only; BCT only	612 622
Owen RMH/GOC *Lancet Oncol 2006*	Standard HYPO HYPO	25x2 Gy 13x3,3 Gy 13x3 Gy	T1-3; N-/(+ max 1 LK), BCT only	470 466 474
Bentzen/Yarnold START A *Lancet Oncol 2008*	Standard HYPO HYPO	25x2 Gy 13x3,2 Gy 13x3 Gy	T1-3; N-/+, R0 (>1mm); BCT and ME	749 (631) 750 (641) 737 (628)
Bentzen/Yarnold START B *Lancet Oncol 2008*	Standard HYPO	25x2 Gy 15x2,66 Gy	T1-3; N-/+, R0 (>1mm); BCT and ME	1105 (1020) 1110 (1018)

Randomized Trial of Breast Irradiation Schedules After Lumpectomy for Women With Lymph Node-Negative Breast Cancer

Timothy Whelan, Robert MacKenzie, Jim Julian, Mark Levine, Wendy Shelley, Laval Grimard, Barbara Lada, Himu Lukka, Francisco Perera, Anthony Fyles, Ethan Laukkanen, Sunil Gulavita, Veronique Benk, Barbara Szechtman

Journal of the National Cancer Institute, Vol. 94, No. 15, August 7, 2002

1993-1996

1234 pz pT1-T2, p N0, M0

F-UP mediano: 69 mesi

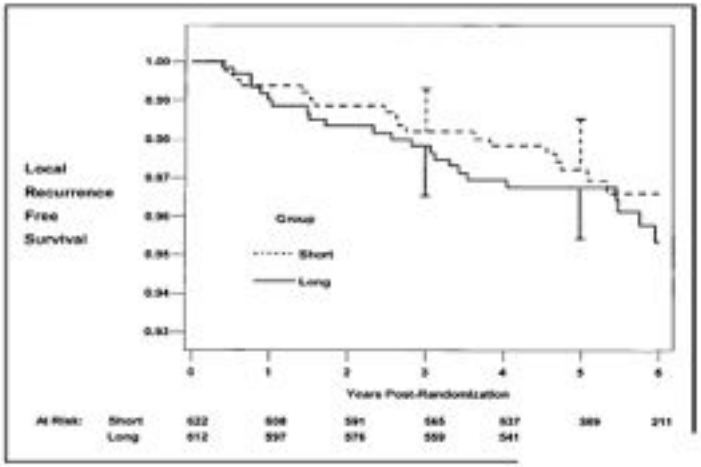
- No N+
- No boost
- No mastectomia

622 pz: 42,5 Gy in 16 fr

612 pz : 50 Gy in 25 fr

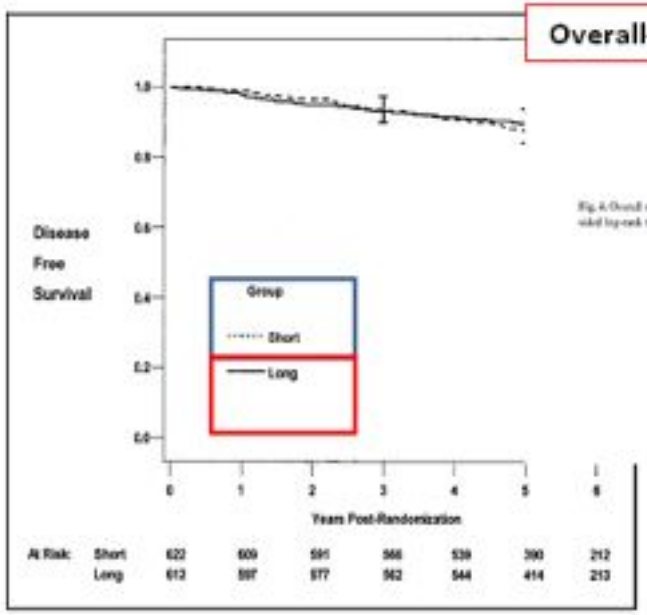
Sopravvivenza libera da recidiva locale

Fig. 2. Local recurrence-free survival in the study groups. The hypothesis that the short arm is worse than the long arm by 5% or more at 5 years is rejected ($P<.001$).



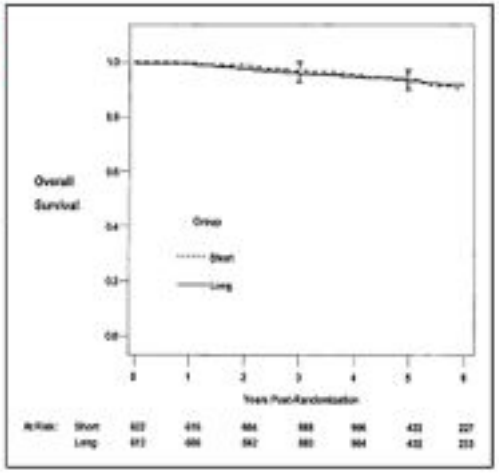
Sopravvivenza libera da malattia

Fig. 3. Disease-free survival in the study groups (two sided log-rank test, $P = .37$).



Overall-survival

Fig. 4. Overall survival in the study groups (two-sided log-rank test, $P = .70$).



TOSSICITA'

Table 3. Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) late radiation morbidity (grade %) by site and time

Site	Grade	% at 3 y		% at 5 y	
		Short arm (n = 515)	Long arm (n = 492)	Short arm (n = 394)	Long arm (n = 358)
Skin	0	90	87	87	82
	1	8	11	10	15
	2/3	2	2	3	3
Subcutaneous tissue	0	69	63	66	60
	1	27	32	29	33
	2/3	4	5	5	7

Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial

J Roger Owen, Anita Ashton, Judith M Bliss, Janis Homewood, Caroline Harper, Jane Hanson, Joanne Haviland, Sarah Bliss, John R Yarnold

1410 Pz (42.9 Gy: 466 pz, 39 Gy: 474 pz, 50 Gy: 470 pz)

Standard: 50 Gy, fx 2 Gy in 25 fr

Ipofrazionato I: 42,9 Gy, fx 3,3 Gy in 13 fr

Ipofrazionato II: 39 Gy, fx 3 Gy in 13 fr

Boost (75%): 14 Gy, fx 2 Gy in 7 fr con elettroni

•Risultati

GRUPPO STANDARD: LRR a 10 aa: 12.1% (ad un anno 1.20%)

GRUPPO IPOFRAZ. I: LRR a 10 aa: 9.1% (ad un anno 0.9%)

GRUPPO IPOFRAZ. II: LRR a 10 aa: 14.8% (ad un anno 1.5%)

The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

The START Trialists' Group*

Lancet Oncol 2008; 9: 331-41

1998-2002

2236 pz (pT1-T3, N0-N1,M0)

5 settimane

750 pz: 41.6 Gy in 13 fr- 3.2 Gy/fr

749 pz: 50 Gy in 25 fr

737 pz: 39 Gy in 13 fr-3 Gy /fr

F-UP mediano:5.1 anni
Età> 18 aa
No ricostruzione immediata

End-points:
- **Recidiva locoregionale**
- **Tossicità tardiva dei tessuti sani**
- **Qualità di vita**

α\β tumore: 4.6 Gy – α\β tox tardiva 3.6 Gy

	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	Wald test p value*
Local relapse†				
50 Gy	25/749 (3·3)	3·2 (1·9–4·6)	1	-
41·6 Gy	28/750 (3·7)	3·2 (1·9–4·5)	1·09 (0·64–1·88)	0·74
39 Gy	31/737 (4·2)	4·6 (3·0–6·2)	1·25 (0·74–2·12)	0·40
Local-regional relapse				
50 Gy	28/749 (3·7)	3·6 (2·3–5·1)	1	-
41·6 Gy	30/750 (4·0)	3·5 (2·1–4·3)	1·05 (0·63–1·75)	0·86
39 Gy	35/737 (4·7)	5·2 (3·5–6·9)	1·26 (0·77–2·08)	0·35
Distant relapse				
50 Gy	73/749 (9·7)	9·8 (7·5–12·0)	1	-
41·6 Gy	69/750 (9·2)	9·5 (7·3–11·7)	0·92 (0·66–1·28)	0·64
39 Gy	93/737 (12·6)	11·9 (9·5–14·4)	1·29 (0·95–1·76)	0·10
Any breast cancer-related event‡				
50 Gy	102/749 (13·6)	13·6 (11·0–16·2)	1	-
41·6 Gy	91/750 (12·1)	12·0 (9·6–14·5)	0·87 (0·65–1·15)	0·33
39 Gy	115/737 (15·6)	15·2 (12·5–17·9)	1·14 (0·87–1·49)	0·33
All-cause mortality				
50 Gy	84/749 (11·2)	11·1 (8·7–13·4)	1	-
41·6 Gy	89/750 (11·9)	11·3 (8·9–13·7)	1·04 (0·77–1·40)	0·81
39 Gy	83/737 (11·3)	10·7 (8·3–13·1)	1·00 (0·74–1·36)	0·99

*p value from Wald test comparing each schedule with 50 Gy. †Local relapse defined as ipsilateral local tumour relapse in breast parenchyma / breast skin / chest wall skin. ‡Breast cancer-related events: local, regional, or distant relapse, breast cancer death, contralateral breast cancer (disease-free survival).

Table 2: Survival analyses of relapse and mortality according to fractionation schedule in START Trial A

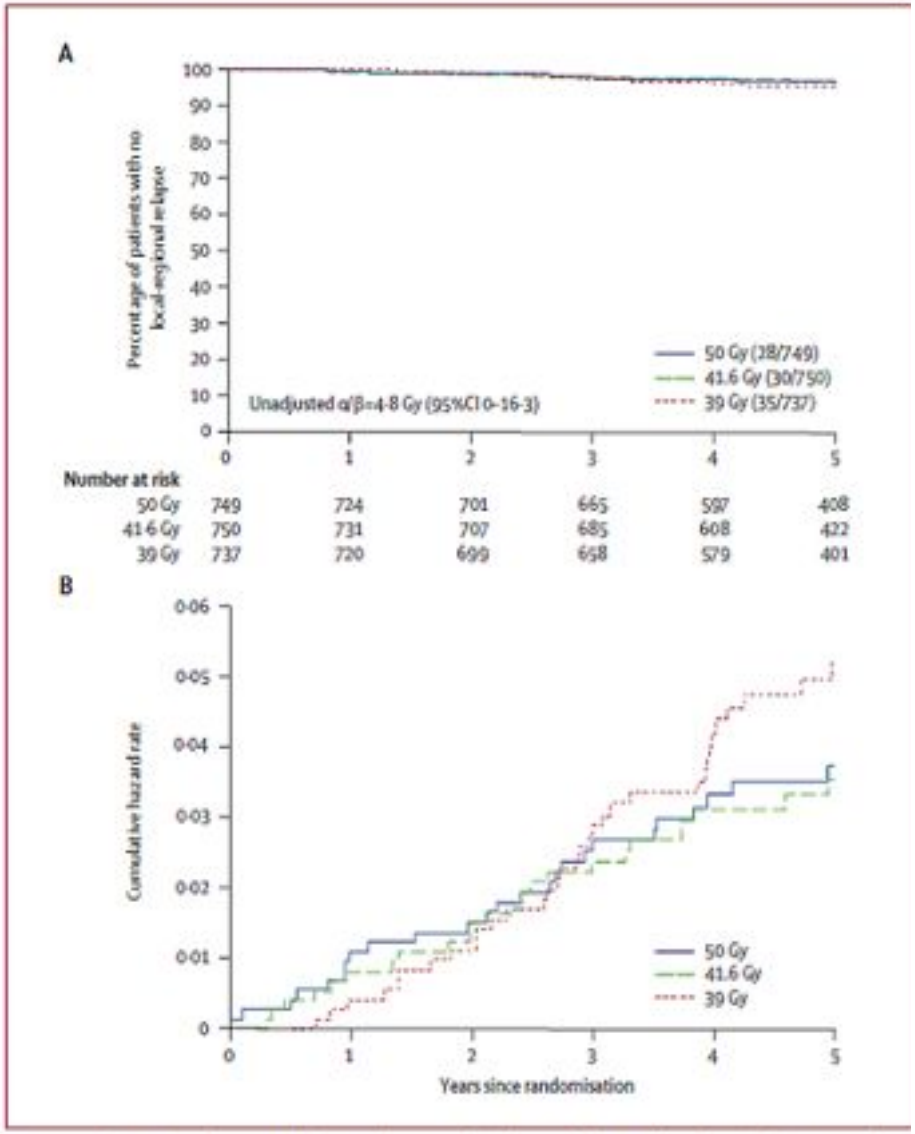


Figure 2: Kaplan-Meier plot (A) and Nelson-Aalen cumulative hazard plot (B) of local-regional tumour relapse in 2236 patients

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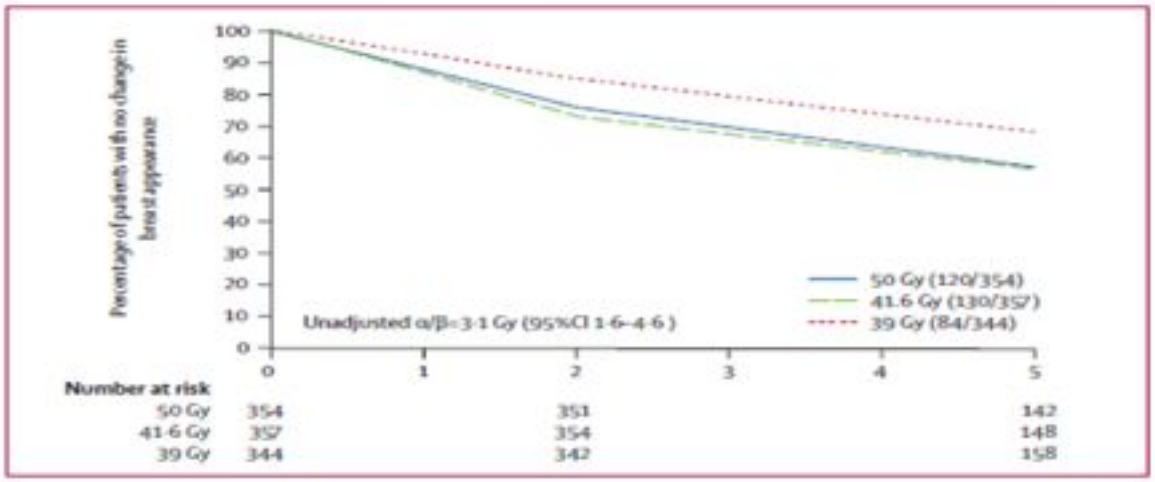


Figure 3: **Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 1055 patients with breast conserving surgery**

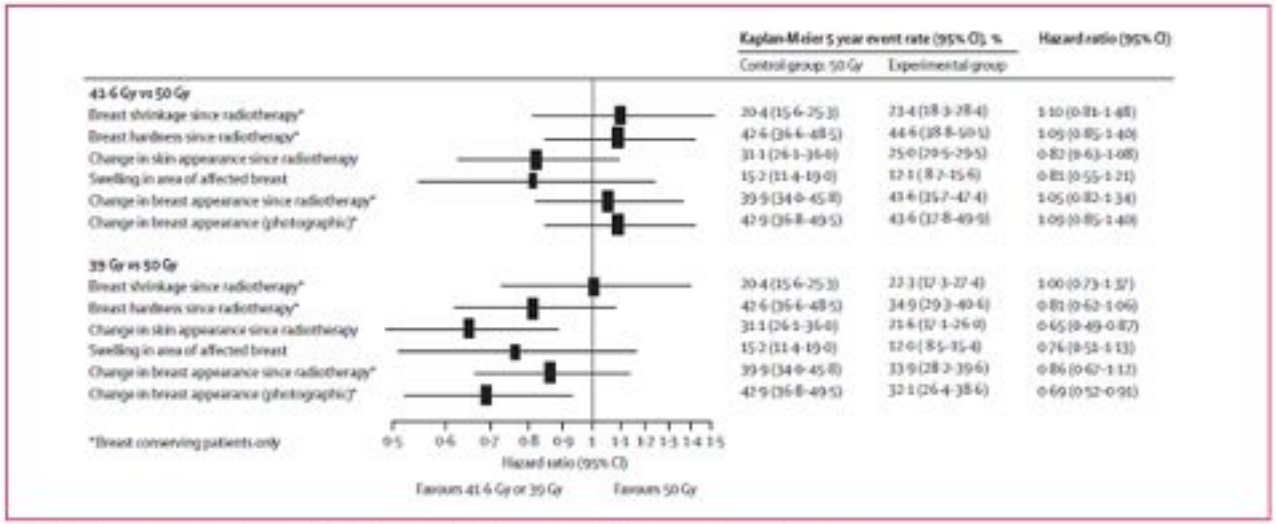


Figure 4: **Forest plot of late normal tissue effects assessed as moderate/marked by patients and mild/marked from photographs**

	Fractionation schedule			Total n=2236 (%)
	50 Gy n=749	41·6 Gy n=750	39 Gy n=737	
Ischaemic heart disease*				
Reported	12 (1·6)	7 (0·9)	8 (1·1)	27 (1·2)
Confirmed† [left-sided]‡	3 (0·4) [1]	2 (0·3) [0]	5 (0·7) [4]	10 (0·4) [5]
Symptomatic rib fracture§				
Reported	8 (1·1)	9 (1·2)	10 (1·4)	27 (1·2)
Confirmed†	1 (0·1)	2 (0·3)	1 (0·1)	4 (0·2)
Symptomatic lung fibrosis				
Reported	5 (0·7)	6 (0·8)	7 (0·9)	18 (0·8)
Confirmed†	0 (0)	2 (0·3)	1 (0·1)	3 (0·1)

Data are n (%). *18 patients had pre-existing heart disease at randomisation and were excluded. †Cases confirmed after imaging and further investigations. ‡Confirmed cases of ischaemic heart disease in patients with left-sided primary tumours. §Reported cases include three with rib fracture after bone metastases and nine after trauma.

Table 3: **Incidence of ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis according to fractionation schedule**

TOSSICITA'

The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

The START Trialists' Group*

1999-2001

2215 pz (pT1-T3, N0-N1,M0)

1105 pz: 50 Gy in 25 fr

5 settimane

1110 pz: 40 Gy in 15 fr-2.67 Gy /fr

3 settimane

F-UP mediano: 6.0 anni
Età> 18 aa
No ricostruzione immediata

End-points:
- Recidiva locoregionale
- Tossicità tardiva dei tessuti sani
- Qualità di vita

α\β tumore: 4.6 Gy – α\β tox tardiva 3.6 Gy

	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	Log-rank test p value
Local relapse*				
50 Gy	34/1105 (3·1)	3·3 (2·2–4·4)	1	
40 Gy	25/1110 (2·2)	2·0 (1·1–2·8)	0·72 (0·43–1·21)	0·21
Local-regional relapse				
50 Gy	36/1105 (3·2)	3·3 (2·2–4·5)	1	
40 Gy	29/1110 (2·6)	2·2 (1·3–3·1)	0·79 (0·48–1·29)	0·35
Distant relapse				
50 Gy	122/1105 (11·0)	10·2 (8·4–12·1)	1	
40 Gy	87/1110 (7·8)	7·6 (6·0–9·2)	0·69 (0·53–0·91)	0·01
Any breast cancer-related event†				
50 Gy	164/1105 (14·8)	14·1 (12·0–16·2)	1	
40 Gy	127/1110 (11·4)	10·6 (8·7–12·4)	0·75 (0·60–0·95)	0·02
All-cause mortality				
50 Gy	138/1105 (12·5)	11·0 (9·1–12·9)	1	
40 Gy	107/1110 (9·6)	8·0 (6·4–9·7)	0·76 (0·59–0·98)	0·03

*Local relapse defined as ipsilateral local tumour relapse in breast parenchyma/breast skin/chest wall skin. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer ("disease-free survival").

Table 2: Survival analyses of relapse and mortality according to fractionation schedule

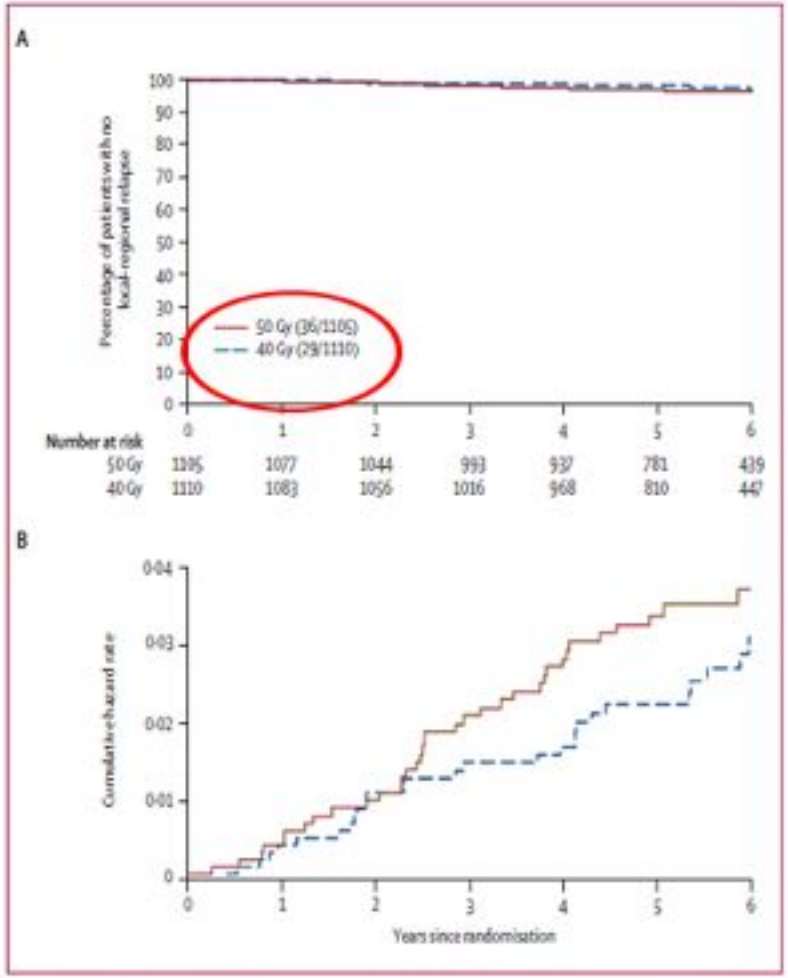


Figure 2: Kaplan-Meier plot (A) and Nelson-Aalen cumulative hazard plot (B) of local-regional tumour relapse in 2215 patients

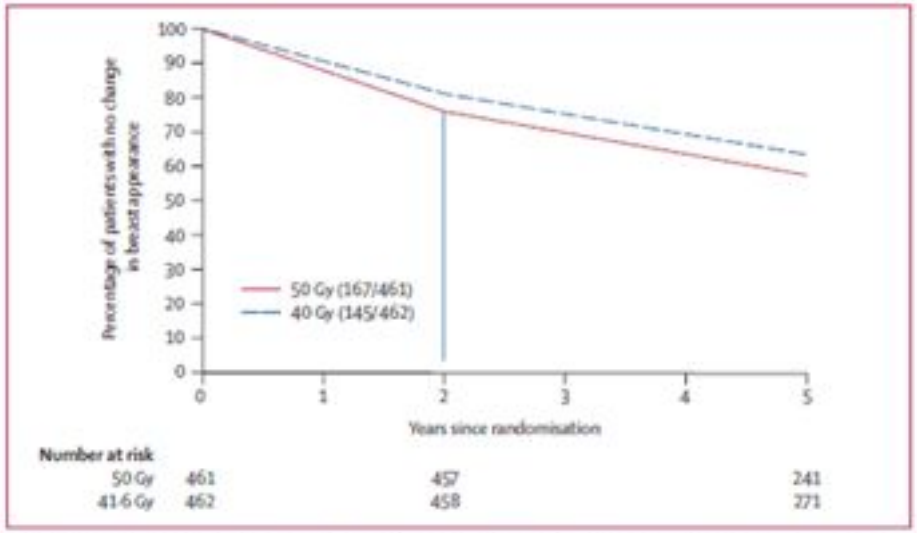


Figure 4: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 923 patients with breast conserving surgery

TOSSICITA'

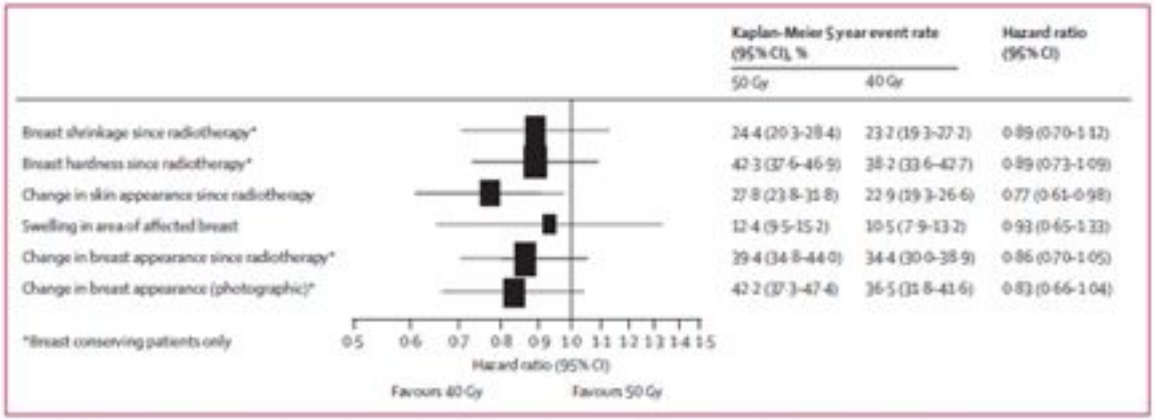


Figure 5: Forest plot of late normal tissue effects assessed as moderate/marked by patients and mild/marked from photographs

	Fractionation schedule		Total n=2215
	50 Gy n=1105	40 Gy n=1110	
Ischaemic heart disease*			
Reported	19 (1·7)	15 (1·3)	34 (1·5)
Confirmed† [left-sided]‡	12 (1·1) [4]	7 (0·6) [3]	19 (0·9) [7]
Symptomatic rib fracture§			
Reported	17 (1·5)	16 (1·4)	33 (1·5)
Confirmed†	2 (0·2)	2 (0·2)	4 (0·2)
Symptomatic lung fibrosis			
Reported	15 (1·4)	16 (1·4)	31 (1·4)
Confirmed†	1 (0·1)	3 (0·3)	4 (0·2)

Data are n (%) unless otherwise stated. *11 patients had pre-existing heart disease at randomisation and were excluded. †Cases confirmed following imaging and further investigations. ‡Confirmed cases of ischaemic heart disease in patients with left-sided primary tumours. §Reported cases include four with rib fracture after bone metastases and three after trauma.

Table 3: **Incidence of ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis according to fractionation schedule**

TOSSICITA'

Lancet Oncol 2013; 14: 1086–94

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

Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss*, John R Yarnold*, on behalf of the START Trialists' Group†

	Events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Local relapse					
50 Gy	40/749 (5·3%)	3·4% (2·3–5·1)	6·7% (4·9–9·2)	1·00	–
41·6 Gy	37/750 (4·9%)	3·1% (2·0–4·7)	5·6% (4·1–7·8)	0·90 (0·57–1·40)	0·63
39 Gy	47/737 (6·4%)	4·4% (3·1–6·2)	8·1% (6·1–10·7)	1·20 (0·79–1·83)	0·39
Local-regional relapse					
50 Gy	45/749 (6·0%)	4·0% (2·8–5·7)	7·4% (5·5–10·0)	1·00	–
41·6 Gy	42/750 (5·6%)	3·8% (2·6–5·5)	6·3% (4·7–8·5)	0·91 (0·59–1·38)	0·65
39 Gy	52/737 (7·1%)	5·1% (3·7–7·1)	8·8% (6·7–11·4)	1·18 (0·79–1·76)	0·41
Distant relapse					
50 Gy	100/749 (13·3%)	9·8% (7·9–12·3)	14·7% (12·2–17·7)	1·00	–
41·6 Gy	110/750 (14·7%)	9·5% (7·6–11·9)	16·8% (14·0–20·0)	1·08 (0·82–1·41)	0·58
39 Gy	121/737 (16·4%)	11·8% (9·7–14·4)	18·0% (15·1–21·2)	1·24 (0·95–1·61)	0·11
Any breast cancer-related event†					
50 Gy	154/749 (20·6%)	14·0% (11·6–16·7)	22·6% (19·5–26·1)	1·00	–
41·6 Gy	149/750 (19·9%)	11·7% (9·5–14·2)	22·7% (19·5–26·3)	0·94 (0·75–1·17)	0·57
39 Gy	163/737 (22·1%)	15·5% (13·0–18·3)	24·3% (21·1–28·0)	1·08 (0·87–1·35)	0·48
All-cause mortality					
50 Gy	130/749 (17·4%)	10·5% (8·5–13·0)	19·8% (16·8–23·2)	1·00	–
41·6 Gy	128/750 (17·1%)	10·7% (8·7–13·2)	18·4% (15·7–21·6)	0·96 (0·75–1·22)	0·74
39 Gy	134/737 (18·2%)	9·9% (8·0–12·4)	20·3% (17·3–23·7)	1·05 (0·82–1·34)	0·69

*Assessed with Wald test comparing each schedule with 50 Gy. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer.

Table 3: Relapse and mortality according to fractionation schedule in START-A

START A

	Events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Local relapse					
50 Gy	50/1105 (4·5%)	3·3% (2·4–4·6)	5·2% (3·9–6·9)	1·00	–
40 Gy	36/1110 (3·2%)	1·9% (1·2–3·0)	3·8% (2·7–5·2)	0·70 (0·46–1·07)	0·10
Local-regional relapse					
50 Gy	53/1105 (4·8%)	3·5% (2·5–4·8)	5·5% (4·2–7·2)	1·00	–
40 Gy	42/1110 (3·8%)	2·3% (1·5–3·4)	4·3% (3·2–5·9)	0·77 (0·51–1·16)	0·21
Distant relapse					
50 Gy	158/1105 (14·3%)	10·5% (8·8–12·5)	16·0% (13·8–18·5)	1·00	–
40 Gy	121/1110 (10·9%)	7·5% (6·0–9·2)	12·3% (10·3–14·6)	0·74 (0·59–0·94)	0·014
Any breast cancer-related event†					
50 Gy	222/1105 (20·1%)	14·3% (12·3–16·5)	22·2% (19·7–25·0)	1·00	–
40 Gy	182/1110 (16·4%)	10·4% (8·7–12·4)	18·3% (16·0–20·9)	0·79 (0·65–0·97)	0·022
All-cause mortality					
50 Gy	192/1105 (17·4%)	10·9% (9·1–12·9)	19·2% (16·8–21·9)	1·00	–
40 Gy	159/1110 (14·3%)	7·9% (6·4–9·6)	15·9% (13·7–18·4)	0·80 (0·65–0·99)	0·042

*Assessed with log-rank test compared with 50 Gy. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer.

Table 4: Relapse and mortality according to fractionation schedule in START-B

START B

	Moderate or marked events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Breast shrinkage†					
50 Gy	165/616 (26·8%)	14·1% (11·5–17·2)	34·2% (29·8–39·2)	1·00	–
41·6 Gy	168/627 (26·8%)	17·8% (14·9–21·1)	31·4% (27·2–36·0)	0·98 (0·79–1·21)	0·83
39 Gy	140/617 (22·7%)	14·7% (12·0–18·0)	30·0% (25·7–34·8)	0·86 (0·69–1·08)	0·19
Breast induration (tumour bed)†					
50 Gy	142/616 (23·0%)	18·5% (15·6–21·9)	27·1% (23·3–31·3)	1·00	–
41·6 Gy	150/627 (23·9%)	18·9% (16·0–22·3)	28·2% (24·2–32·7)	1·01 (0·80–1·27)	0·95
39 Gy	110/617 (17·8%)	15·0% (12·3–18·3)	21·6% (18·1–25·7)	0·76 (0·59–0·98)	0·034
Telangiectasia					
50 Gy	42/730 (5·7%)	4·3% (3·0–6·1)	7·2% (5·2–9·8)	1·00	–
41·6 Gy	43/733 (5·9%)	4·9% (3·5–6·8)	7·1% (5·2–9·5)	1·00 (0·65–1·53)	0·99
39 Gy	18/723 (2·5%)	1·3% (0·6–2·5)	3·0% (1·8–5·0)	0·43 (0·25–0·75)	0·003
Breast oedema†					
50 Gy	78/616 (12·7%)	12·1% (9·7–15·0)	13·5% (10·9–16·6)	1·00	–
41·6 Gy	67/627 (10·7%)	9·2% (7·1–11·7)	11·8% (9·3–14·8)	0·82 (0·59–1·14)	0·24
39 Gy	43/617 (7·0%)	7·3% (5·5–9·7)	7·3% (5·5–9·7)	0·54 (0·37–0·78)	0·001
Shoulder stiffness‡					
50 Gy	14/117 (12·0%)	8·8% (4·7–16·4)	17·5% (10·2–29·1)	1·00	–
41·6 Gy	10/95 (10·5%)	7·1% (3·3–15·2)	14·8% (8·0–26·6)	0·85 (0·38–1·90)	0·69
39 Gy	8/92 (8·7%)	7·5% (3·4–16·0)	11·0% (5·6–21·0)	0·74 (0·31–1·76)	0·49
Arm oedema‡					
50 Gy	15/117 (12·8%)	12·8% (7·6–21·2)	16·3% (9·9–26·2)	1·00	–
41·6 Gy	16/95 (16·8%)	11·9% (6·6–21·0)	22·5% (14·1–34·7)	1·31 (0·65–2·66)	0·45
39 Gy	6/92 (6·5%)	6·4% (2·7–14·7)	8·2% (3·7–17·6)	0·50 (0·20–1·30)	0·16
Other					
50 Gy	18/729 (2·5%)	1·3% (0·7–2·6)	3·4% (2·1–5·4)	1·00	–
41·6 Gy	20/733 (2·7%)	2·0% (1·2–3·4)	3·7% (2·3–6·1)	1·09 (0·58–2·06)	0·79
39 Gy	24/724 (3·3%)	2·3% (1·4–3·8)	3·9% (2·6–5·9)	1·37 (0·74–2·52)	0·31

*Assessed by Wald test, comparing each schedule with 50 Gy. †Only assessed in women who had breast-conserving surgery. ‡Restricted to women who received lymphatic radiotherapy (to axilla or supraclavicular fossa).

Table 2: **Physician-assessed normal tissue effects by fractionation schedule in START-A**

TOSSICITA'

	Moderate or marked events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Breast shrinkage†					
50 Gy	256/1003 (25·5%)	15·8% (13·6–18·3)	31·2% (27·9–34·9)	1·00	..
40 Gy	221/1006 (22·0%)	11·4% (9·5–13·6)	26·2% (23·1–29·6)	0·80 (0·67–0·96)	0·015
Breast induration (tumour bed)†					
50 Gy	153/1003 (15·3%)	12·1% (10·2–14·4)	17·4% (14·9–20·3)	1·00	..
40 Gy	129/1006 (12·8%)	9·6% (7·9–11·6)	14·3% (12·1–16·9)	0·81 (0·64–1·03)	0·084
Telangiectasia					
50 Gy	52/1081 (4·8%)	3·8% (2·8–5·2)	5·8% (4·4–7·7)	1·00	..
40 Gy	34/1094 (3·1%)	1·8% (1·1–2·8)	4·2% (2·9–5·9)	0·62 (0·40–0·96)	0·032
Breast oedema†					
50 Gy	86/1003 (8·6%)	8·1% (6·6–10·1)	9·0% (7·3–11·0)	1·00	..
40 Gy	49/1006 (4·9%)	4·7% (3·5–6·2)	5·1% (3·9–6·7)	0·55 (0·39–0·79)	0·001
Shoulder stiffness‡					
50 Gy	4/73 (5·5%)	2·9% (0·7–11·0)	8·2% (2·9–21·8)	1·00	..
40 Gy	3/81 (3·7%)	3·1% (0·8–11·9)	3·1% (0·8–11·9)	0·76 (0·17–3·39)	0·71
Arm oedema‡					
50 Gy	7/73 (9·6%)	6·0% (2·3–15·3)	13·5% (6·4–27·0)	1·00	..
40 Gy	3/81 (3·7%)	2·8% (0·7–10·7)	4·7% (1·5–14·0)	0·42 (0·11–1·63)	0·21
Other					
50 Gy	77/1082 (7·1%)	5·6% (4·3–7·2)	8·1% (6·5–10·2)	1·00	..
40 Gy	53/1095 (4·8%)	3·3% (2·4–4·6)	6·4% (4·8–8·4)	0·65 (0·46–0·93)	0·018

*Assessed by Wald test compared with 50 Gy. †Only assessed in women who had breast-conserving surgery. ‡Restricted to women who received lymphatic radiotherapy (to axilla or supraclavicular fossa).

Table 5: Physician-assessed normal tissue effects by fractionation schedule in START-B

TOSSICITA'

	START-A				START-B		
	50 Gy (n=749)	41·6 Gy (n=750)	39 Gy (n=737)	Total (n=2236)	50 Gy (n=1105)	40 Gy (n=1110)	Total (n=2215)
Symptomatic rib fracture*							
Reported	5 (0·7%)	8 (1·1%)	9 (1·2%)	22 (1·0%)	17 (1·5%)	24 (2·2%)	41 (1·9%)
Confirmed†	0	0	1 (0·1%)	1 (<0·1%)	3 (0·3%)	3 (0·3%)	6 (0·3%)
Symptomatic lung fibrosis							
Reported	6 (0·8%)	9 (1·2%)	8 (1·1%)	23 (1·0%)	19 (1·7%)	19 (1·7%)	38 (1·7%)
Confirmed†	0	2 (0·3%)	1 (0·1%)	3 (0·1%)	2 (0·2%)	8 (0·7%)	10 (0·5%)
Ischaemic heart disease‡							
Reported	14 (1·9%)	11 (1·5%)	8 (1·1%)	33 (1·5%)	23 (2·1%)	17 (1·5%)	40 (1·8%)
Confirmed†							
Total	7 (0·9%)	5 (0·7%)	6 (0·8%)	18 (0·8%)	16 (1·4%)	8 (0·7%)	24 (1·1%)
Left sided	4 (0·5%)	1 (0·1%)	4 (0·5%)	9 (0·4%)	5 (0·5%)	4 (0·4%)	9 (0·4%)
Brachial plexopathy	0	1 (0·1%)	0	1 (<0·1%)	0	0	0

Data are n (%). *Reported cases include seven after trauma (five in START-A, two in START-B), and ten after metastases (five in START- A and five in START-B). †After imaging and further investigations. ‡26 patients in START-A and 22 in START-B had pre-existing heart disease at enrolment and were excluded.

Table 3: **Incidence of other late adverse effects according to fractionation schedule**

schedule group. A meta-analysis of many thousands of patients would be needed to assess individual prognostic subgroups more precisely. One exclusion criterion from the START trials was immediate breast reconstruction, and a conservative approach might be to defer from using a 15 fraction regimen in such patients, despite the very high likelihood, in our opinion, that the 15 fraction schedule would reduce normal tissue effects and provide equivalent local-regional control. Treatment of the supraclavicular fossa and axilla is another aspect that is often approached conservatively, despite the fact that even a dose of 40 Gy in 15 fractions at the level of the brachial plexus delivers the equivalent of 46·7 Gy, 47·6 Gy, and 48·9 Gy in 2·0 Gy equivalents, assuming α/β values of 2·0 Gy, 1·5 Gy, and 1·0 Gy, respectively.[5] In other words, 40 Gy in 15 fractions is less damaging to the brachial plexus than is 50 Gy in 25 fractions, even under extreme assumptions about the fractionation sensitivity of the nervous system. Although only a small proportion of women in the START trials received lymphatic radiotherapy, the assessments of arm and shoulder effects showed no evidence of a detrimental effect for the hypofractionated schedules. Finally, concerns have been raised about doses to the heart with hypofractionated schedules.[3] Our results showed that although follow-up was still short for cardiac events, there was no major difference between the schedules for the number of cases of heart disease in women with left-sided primary tumours. Some research suggests that hypofractionated breast radiotherapy might be safer for the heart than are conventional regimens.[6] Although such findings are reassuring, the heart is sensitive to radiation whatever fractionation is used, with no lower dose threshold for adverse effects.[7] Thus, the heart should be protected irrespective of the dose fractionation regimen used.

Other ongoing or planned trials of hypofractionation for whole breast radiotherapy aim to validate the findings from the START trials in different populations. Mean-

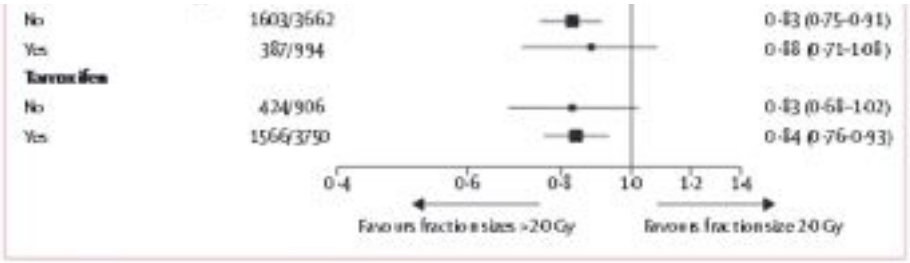


Figure 5: **Meta-analysis of any moderate or marked physician-assessed normal tissue effects in the breast comparing hypofractionated regimens versus 50 Gy in 25 fractions**
Includes 4672 patients from START pilot trial, START-A, and START-B. *Assessed from baseline photographs.

Panel: Research in context

Systematic review

The START trials began with the pilot study in 1986, at which time there was no evidence available from randomised trials comparing alternative fractionation schedules for breast cancer radiotherapy. Alternative shorter fractionation schedules were in use at some UK centres and in Canada, but the only evidence available for these schedules was from case series and cohort studies. The need for the START trials was shown by a survey of fractionation practices done by the UK Royal College of Radiologists in 1993. A similar trial to START-B began in Ontario in 1993. 5-year results of the START trials were published in 2008, and in 2002 for the Ontario trial, which suggested that the hypofractionated regimens were as safe and effective as the historical standard control schedule of 50 Gy in 25 fractions. However, confirmation after long-term follow-up was needed, especially because late normal tissue effects continue to occur for many years after radiotherapy. 10-year follow-up results of the Ontario trial were published in 2010, and an updated Cochrane systematic review was published in 2010.

Interpretation

Following publication of 5-year results from the Ontario and START trials, long-term follow-up was needed to confirm the safety and efficacy of the hypofractionated schedules. The 10-year START trial results presented here, together with the long-term results of the Ontario trial, confirm the earlier findings and strengthen the evidence in favour of using hypofractionated schedules for breast cancer radiotherapy. They support the continued use of 40 Gy in 15 fractions as the UK standard of care as recommended by the National Institute for Health and Care Excellence, and contribute further to the worldwide debate about breast cancer radiotherapy hypofractionation.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

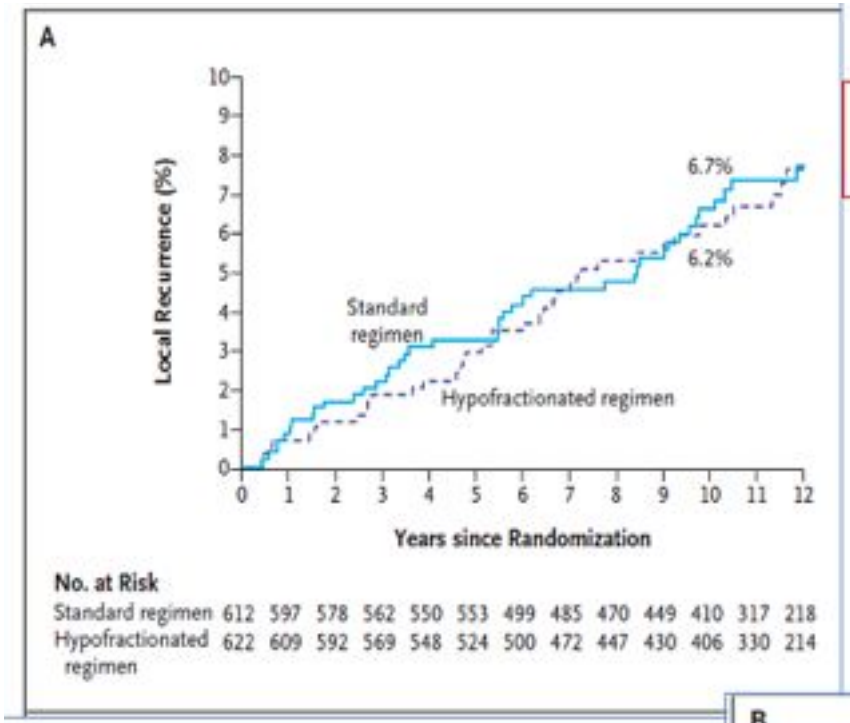
Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, M.D., Jim A. Julian, Ph.D., Robert MacKenzie, M.D., Sameer Parpia, M.Sc., Wendy Shelley, M.D., Laval Grimard, M.D., Julie Bowen, M.D., Himu Lukka, M.D., Francisco Perera, M.D., Anthony Fyles, M.D., Ken Schneider, M.D., Sunil Gulavita, M.D., and Carolyn Freeman, M.D.

F-UP MEDIANO: 12 AA

END-POINT PRIMARIO:

- **Recidiva locoregionale**

Recidiva locale
Incidenza cumulativa



Sopravvivenza

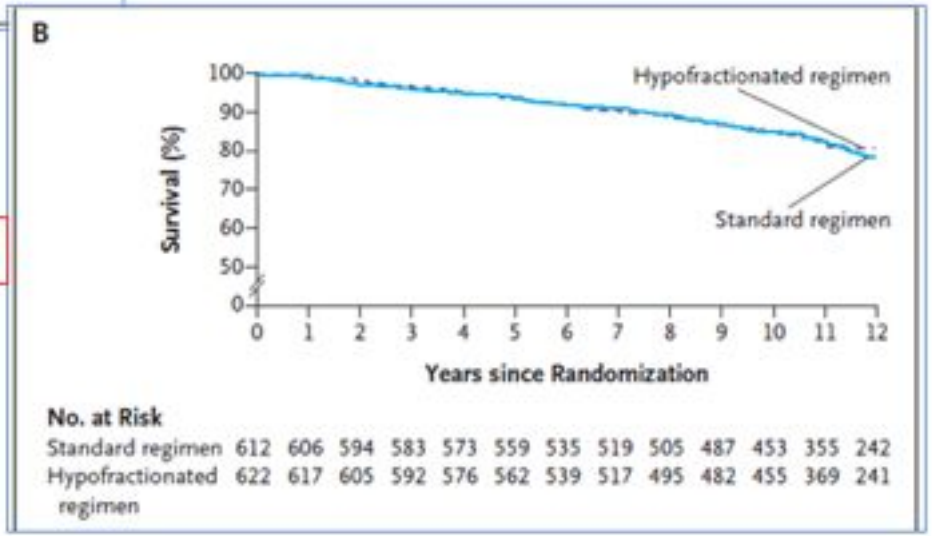


Table 1. Late Toxic Effects of Radiation, Assessed According to the RTOG–EORTC Late Radiation Morbidity Scoring Scheme.*

Site and Grade	5 Yr		10 Yr	
	Standard Regimen (N=424)	Hypofractionated Regimen (N=449)	Standard Regimen (N=220)	Hypofractionated Regimen (N=235)
	percent of patients			
Skin				
0†	82.3	86.1	70.5	66.8
1	14.4	10.7	21.8	24.3
2	2.6	2.5	5.0	6.4
3	0.7	0.7	2.7	2.5
Subcutaneous tissue				
0‡	61.4	66.8	45.3	48.1
1	32.5	29.5	44.3	40.0
2	5.2	3.8	6.8	9.4
3	0.9	0.9	3.6	2.5

* Effects of radiation therapy on skin and subcutaneous tissue were graded on a scale of 0 to 4 (with 0 indicating no toxic effects and grade 4 indicating skin ulceration or soft-tissue necrosis). RTOG–EORTC denotes the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer.

† The absolute difference at 5 years was −3.8 percentage points (95% confidence interval [CI], −8.7 to 1.0), and at 10 years the absolute difference was 3.7 percentage points (95% CI, −4.9 to 12.1).

‡ The absolute difference at 5 years was −5.4 percentage points (−11.9 to 0.9), and at 10 years the absolute difference was −2.8 percentage points (−11.7 to 6.5).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Tumori, 94:706-711, 2008

Weekly concomitant boost in adjuvant radiotherapy for patients with early breast cancer: preliminary results on feasibility

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ABSTRACT

Aims and background. Recent advances in the management of patients with breast cancer are focused toward the reduction of overall treatment time of radiotherapy by delivering a dose biologically equivalent to a standard schedule. The aim of the present study was to evaluate the feasibility and preliminary toxicity of a moderately hypofractionated whole breast irradiation schedule with the addition of a concomitant boost delivered to the tumor bed once-a-week in patients with early breast cancer submitted to conservative surgery.

Materials. We selected patients with pT1c and pT2N0/N+M0 carcinoma of the breast with negative surgical margins. The basic course consisted of 4800 cGy prescribed to the ICRU 50 reference point dose and delivered in 20 fractions, 4 times a week for 5 weeks. Once a week, immediately after whole breast irradiation, a concomitant photon boost of 120 cGy was delivered to the lumpectomy area. Overall, according to the linear-quadratic model, the schedule provides a biologically equivalent dose of 87 Gy for breast tumor (assuming α/β = 4 Gy), of 66 Gy for acute responding normal tissues (assuming α/β = 10 Gy), and 99 Gy for late responding normal tissues (assuming α/β = 3 Gy). Biologically, the schedule compares favorably with the 6-week conventional regimen consisting of 50 Gy, 2 Gy/fraction, followed by a 10 Gy boost (BED_{tumor} 90 Gy; $BED_{acute\ effects}$ 72 Gy, and $BED_{late\ effects}$ 100 Gy).

Results. From November 2004 to April 2007, we tested this radiotherapy schedule in 178 patients. All enrolled patients had achieved a minimum follow-up of 6 months and were considered in detail for the evaluation of feasibility. Three clinical examinations were performed by a group of independent physicians at treatment end, after 1 month and after 6 months. According to the RTOG/EORTC Toxicity Criteria, of the 178 assessable patients at the end of radiotherapy, 58% showed grade 0-1 skin toxicity, 30% grade 2 and 12% grade 3. At one month of follow-up, grade 0 toxicity was observed in 47% of cases, grade 1 in 46% and grade 2 in 7%. At 6 months, late (skin and subcutaneous tissue) toxicity was assessed with the following scores: grade 0 in 68%, grade 1 in 28% and grade 2 in 4% of the patients. At 6 months, cosmesis was excellent, good and fair in 71%, 24% and 5% of patients, respectively.

Conclusions. The explored adjuvant schedule planned to intensify the radiotherapy course for patients with early breast cancer by adding a weekly concomitant boost appears to be feasible and provides low local toxicity and excellent to good short-term cosmetic results.

Table 1 - Radiotherapy schedule with weekly concomitant boost (W-CB)

Week	1		2		3		4		5		
WBI	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	
Dose (Gy)	2.3 2.3	2.3 2.3 ↑	2.3 2.3	2.3 2.3 ↑	2.3 2.3	2.3 2.3 ↑	2.3 2.3	2.3 2.3 ↑	2.3 2.3	2.3 2.3 ↑	46 Gy ↑
W-CB		-		-		-		-		-	
Dose (Gy)		1.2		1.2		1.2		1.2		1.2	6 Gy

WBI, whole breast irradiation.

Table 2 - Biological comparison between standard adjuvant radiotherapy schedule and explored W-CB schedule

Adjuvant radiotherapy	Basic course and boost delivery	BED Late effects (α/β= 3 Gy)	BED Acute effects (α/β= 10 Gy)	BED Tumor control (α/β= 4 Gy)
Standard schedule 50 Gy/ 25 fx/5 w	WBI basic course: 50 Gy in 25 fx over 5 weeks + Sequential boost: 10 Gy in 5 fx over 1 week	100	72	90
Explored W-CB schedule 52 Gy/20 fx/5 w	WBI basic course: 46 Gy in 20 fx over 5 weeks + Weekly concomitant boost: 1.2 Gy, one-a-week for 5 weeks	99	66	87
Difference in dose		-0.01%	-8%	-4%

BED, biologically effective dose; w, weeks; WBI, whole-breast irradiation; W-CB, weekly-concomitant boost; fx, fractions.

Table 4 - Assessment of acute skin morbidity, late skin and subcutaneous tissue morbidity and cosmesis in 178 patients treated with the W-CB schedule

Morbidity score	Time of clinical assessment	Patients (%)
RTOG/EORTC acute toxicity*	At the last fraction of radiotherapy	
Grade		
0		28 (16)
1		74 (42)
2		53 (30)
3		21 (12)
RTOG/EORTC acute toxicity*	One-month after completion of radiotherapy	
Grade		
0		83 (47)
1		81 (46)
2		12 (7)
3		–
RTOG/EORTC skin/subcutaneous late toxicity*	Six-months after completion of radiotherapy	
Grade		
0		120 (68)
1		46 (26)
2		10 (6)
3		–
Cosmesis score*	Six-months after completion of radiotherapy	
Excellent		125 (71)
Good		42 (24)
Fair		9 (5)
Poor		–

ANTICANCER RESEARCH 30: 4749-4754 (2010)

Adjuvant Hypofractionated Radiotherapy with Weekly Concomitant Boost for Women with Early Breast Cancer: The Clinical Experience at Genoa University

RENZO CORVÒ[1,3], FRANCESCO RICCHETTI[1], DANIELA DEINO[3], PAOLO TORIELLI[3], STEFANO AGOSTINELLI[2], FRANCESCA CAVAGNETTO[2], FLAVIO GIANNELLI[1], ALESSIA D'ALONZO[1], STEFANO VAGGE[1], LILIANA BELGIOIA[3] and MARINA GUENZI[1]

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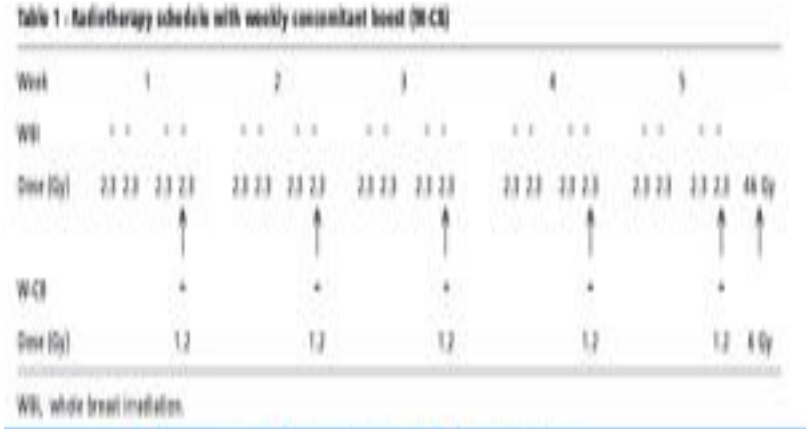
Abstract. *The aim of this investigation was to evaluate the feasibility of a shortened whole-breast irradiation schedule with a concomitant boost delivered to the tumor bed once-a-week in patients with early breast cancer submitted to conservative surgery. Patients and Methods: Patients with pT1 and pT2 M0 carcinoma of the breast were selected. The basic course consisted of 4600 cGy to the whole breast in 20 fractions, 4 times a week, for 5 weeks. Once a week, a concomitant boost of 120 cGy was delivered to the lumpectomy area. Results: From March 2007 to August 2008, we assessed this radiotherapy schedule in 377 patients. According to the RTOG/EORTC Toxicity Criteria, at treatment completion, 85% of patients showed G0-1, 12% G2 and 3% G3 skin toxicity. At 24 months, late toxicity was G0 in 92%, G1 in 7% and G2 in 1%; cosmesis was excellent or good in 95% of patients. To date, at a median follow-up of 33 months, no patient has yet experienced local relapse. Conclusion: A shortened whole-breast irradiation schedule with a weekly concomitant boost may be an alternative option with acceptable toxicity and excellent cosmesis.*

radiotherapy delivery include external 3-D conformal treatment, interstitial or endocavitary brachytherapy or intraoperative radiotherapy (3, 4). Traditionally, external RT consists of two planned courses: 50 Gy or an equivalent biological dose is delivered to the whole breast (WBI) in 25 fractions over 5 weeks (5 fractions per week) followed by 10-16 Gy delivered in 5-8 fractions over 1-2 weeks to the surgical site of tumor removal (3). In an attempt to intensify treatment especially when RT is delivered sequentially to chemotherapy several months after surgery a simultaneous boost has been introduced in clinical practice by using 3-D conformal radiotherapy or intensity-modulated RT (5,6). Preliminary results from experiences where a boost dose was delivered either daily after WBI (6) or weekly on Saturday as a sixth fraction (7) appear interesting, with a good feasibility in terms of acute toxicity. Since November 2004, we have proposed a concomitant boost technique delivered once a week (W-CB) during a moderately hypofractionated WBI course; compared to the daily-boost regimen (6) this W-CB schedule has practical advantages such as a very limited number of boost delivery sessions in an overall



377 pazienti

Analisi della tossicità tardiva a 24 mesi:

G0 = 92%

G1 = 7%

G2 = 1%

Cosmesi:

Eccellente/buona = 95 %

Guenzi et al. Radiation Oncology 2010, 5:111
http://www.ro-journal.com/content/5/1/111

RADIATION ONCOLOGY

RESEARCH Open Access

A biologically competitive 21 days hypofractionation scheme with weekly concomitant boost in breast cancer radiotherapy feasibility acute sub-acute and short term late effects

Marina Guenzi[1†], Stefano Vagge[1*†], Ngwa Che Azinwi[1†], Alessia D'Alonzo[1], Liliana Belgioia[1], Stefania Garelli[2], Marco Gusinu[2], Renzo Corvò[1,2,3]

65 Pz 39 Gy, fx 3 Gy in 13 fr

Boost: 9 Gy in 3 frazioni (concomitant boost)

•Risultati

TOSSICITA' ACUTA

Fine RT: **G0: 52%** **G1: 39%** **G2: 9%**

TOSSICITA' SUB-ACUTA

6 mesi: **G1: 34%** **G2: 6%**

TOSSICITA' TARDIVA

12 mesi: **G1: 39% G2: 9%** **fibrosi** **G1: 5%** **iperpigmentazione**

24 mesi: **fibrosi G2: 3%**

Conclusioni:

Trattamento fattibile con bassa tossicità tardiva a 2 anni

Deantonio et al. Radiation Oncology 2010, 5:112
http://www.ro-journal.com/content/5/1/112

RADIATION ONCOLOGY

RESEARCH Open Access

Hypofractionated radiotherapy after conservative surgery for breast cancer: analysis of acute and late toxicity

Letizia Deantonio[1], Giuseppina Gambaro[1], Debora Beldì[1], Laura Masini[1], Sara Tunesi[2], Corrado Magnani[2], Marco Krengli[1*]

155 Pz (45 Gy, fx 2,25 Gy: 85 pz, 50 Gy, fx 2 Gy: 70 pz

Boost: 9 Gy in 3 frazioni (entrambi i gruppi) Sequenziale con e-

Table 2 Acute radiation reactions (RTOG scale)

Grade	Hypofractionation		Conventional fractionation		p
	No	%	No	%	
0	13	16	3	4	< 0.001
1	51	60	34	49	
2	19	22	29	41	
3	2	2	4	6	

Table 3 Late radiation reactions (RTOG scale).

Grade	Hypofractionation		Conventional fractionation		p
	No	%	No	%	
0	68	90	57	85	0.4
1	8	10	10	15	
2	0	0	0	0	
3	0	0	0	0	

Conclusioni:

Utilizzo dell'ipofrazionamento nella pratica clinica

The Breast Journal

ORIGINAL ARTICLE

Accelerated Hypofractionated Adjuvant Whole Breast Radiotherapy with Concomitant Photon Boost after Conserving Surgery for Early Stage Breast Cancer: A Prospective Evaluation on 463 Patients

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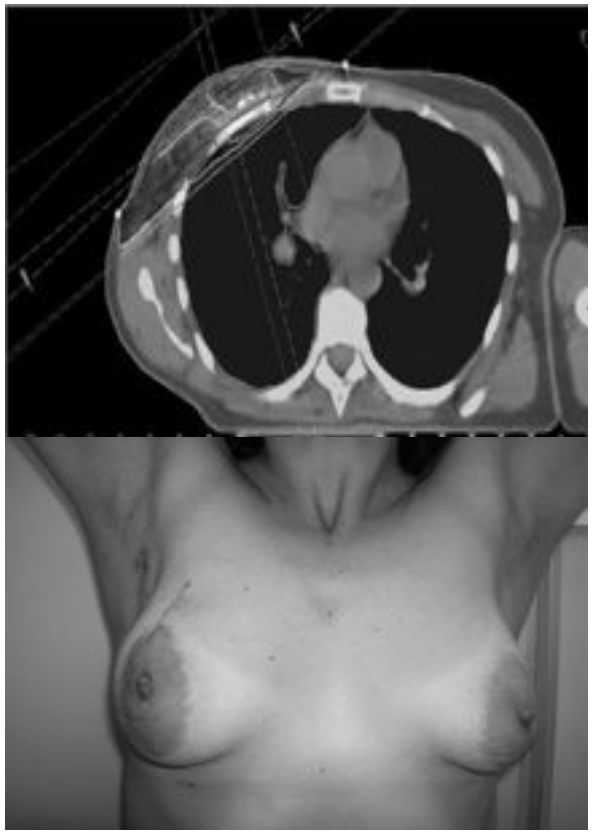
■ **Abstract:** The current standard therapeutic option for early stage breast cancer (EBC) employs a multimodality treatment approach including conservative surgery, radiotherapy, chemotherapy, and hormone therapy. The most common adjuvant radiotherapeutic strategy consists of external beam radiation therapy (EBRT) delivered to the whole breast using 1.8–2 Gy fractions given five times a week, up to a total dose of 45–50 Gy over a period of 5 weeks. In recent years, altered schedules employing larger dose per fraction delivered in fewer treatment sessions over a shorter overall treatment time began to be explored. We herein present clinical data on accelerated hypofractionated adjuvant whole-breast radiotherapy delivered on a daily basis for a total treatment time of 20 fractions. Between February 2005 and June 2009, a total of 463 patients underwent hypofractionated accelerated adjuvant radiation after conservative surgery for early breast cancer (pathological stage pTis, pT1 or pT2, pN0-N1). The basic course of radiotherapy consisted of 45 Gy, to the whole breast in 20 fractions with 2.25 Gy/fraction; an additional daily boost dose of 0.25 Gy was concomitantly delivered, to the lumpectomy cavity, for an additional total dose of 5 Gy. The cumulative nominal dose was 50 Gy. At follow-up, patients were examined at 3 and 6 months after the end of radiotherapy and twice a year afterward. Toxicity was scored according to the Common Terminology Criteria for Adverse Events, using the Radiation Therapy Oncology Group /European Organization for Research and Treatment of Cancer toxicity scale. Cosmetic results were assessed in agreement with the Harvard criteria. All the 463 patients treated with the accelerated hypofractionated adjuvant whole-breast radiotherapy schedule achieved at least 6 months' follow-up and subsequently were considered for the present analysis. With a median follow-up of 27 months, 5-year DFS is 93.1%. Only three patients experienced disease recurrence: two of them with an axillary nodal relapse; one patient with systemic spread. No local relapse occurred. No major toxicities (grade 3 or more) were detected during follow-up. Only 2% of the patients experienced grade 3 skin toxicity at the very end of the radiotherapy course. Cosmetic result was assessed and scored at 6 months, 1 year, 2 years: 100% of patients showed excellent or good cosmetic result. The explored accelerated hypofractionated adjuvant radiotherapeutic approach for early breast cancer with concomitant photon boost seems to be feasible providing consistent clinical results with excellent short-to-medium-term toxicity profile. ■

Key words: breast cancer, concomitant boost, hypofractionation, radiotherapy



463 pazienti

CDI + DCIS

45 Gy, fx 2.25 sulla mammella + concomitant daily boost fx 0.25 con dose totale 50 Gy.

Follow up mediano di 27 mesi:

DFS = 93.1 %

Solo 3 pazienti sono recidivate, 2 linfonodi ascellari e una mts polmonari.

No tossicità > G2

Med Oncol (2013) 30:518
DOI 10.1007/s12032-013-0518-7

ORIGINAL PAPER

Five-year results of a prospective case series of accelerated hypofractionated whole breast radiation with concomitant boost to the surgical bed after conserving surgery for early breast cancer

Domenico Cante · Pierfrancesco Franco · Piera Sciacero · Giuseppe Girelli · Anna Maria Marra · Massimo Pasquino · Giuliana Russo · Valeria Casanova Borca · Guido Mondini · Ovidio Paino · Roberto Barmasse · Santi Tofani · Gianmauro Numico · Maria Rosa La Porta · Umberto Ricardi

Received: 22 January 2013 / Accepted: 18 February 2013

Abstract Accelerated hypofractionation (HF) using larger dose per fraction, delivered in fewer fractions over a shorter overall treatment time, is presently a consistent possibility for adjuvant whole breast radiation (WBRT) after breast-conserving surgery for early breast cancer (EBC). Between 2005 and 2008, we submitted 375 consecutive patients to accelerated hypofractionated WBRT after breast-conserving surgery for EBC. The basic course of radiation consisted of 45 Gy in 20 fractions over 4 weeks to the whole breast (2.25 Gy daily) with an additional daily concomitant boost of 0.25 Gy up to 50 Gy to the surgical bed. Overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS) and local control (LC) were assessed. Late toxicity was scored according to the CTCAE v3.0; acute toxicity using the RTOG/EORTC toxicity scale. Cosmesis was assessed comparing treated and untreated breast. Quality of life (QoL) was determined using EORTC QLQ-C30/QLQ-BR23 questionnaires. With a median follow-up of 60 months (range 42–88), 5 years OS, CSS, DFS and LC were 97.6, 99.4, 96.6 and 100 %, respectively. Late skin and subcutaneous toxicity was generally mild, with few events > grade 2 observed. Cosmetic results were excellent in 75.7 % of patients, good in 20 % and fair in 4.3 %. QoL, assessed both through QLQ-C30/QLQ-BR23, was generally favorable, within the functioning and symptoms domains. Our study is another proof of principle that HF WBRT with a concurrent boost dose to the surgical cavity represents a safe and effective postoperative treatment modality with excellent local control and survival, consistent cosmetic results and mild toxicity.

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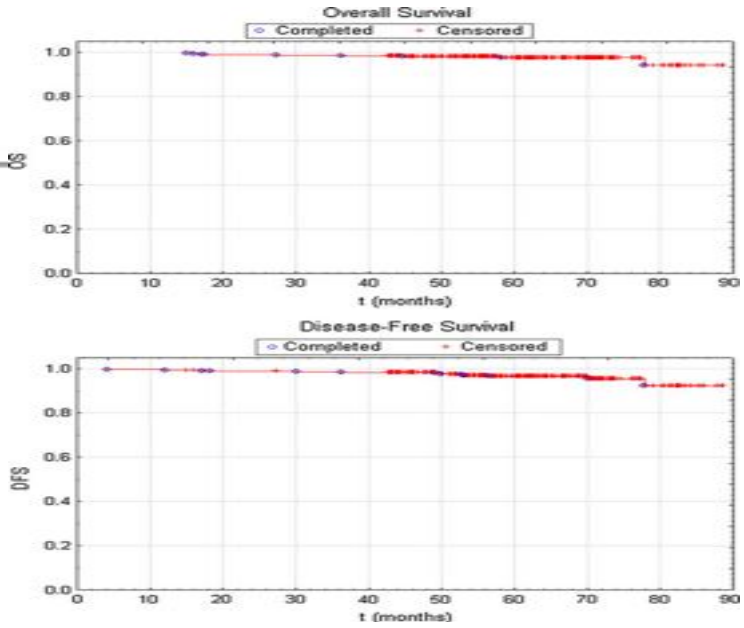

375 pazienti

Follow up di 60 mesi:

Risultati a 5 anni:

OS = 97.6%

CSS = 99.4%

DFS = 96.6%

LC = 100%

13 pazienti recidivate, 9 mts distanza e 4 a livello linfonodale (2 ascellare e 2 scl)

9 pazienti sono decedute, 3 per cancro mammario e 6 per altre cause non correlate

QoL (QLQ-C30 e QLQ-BR 23) = favorevole

No tossicità > G2

J Cancer Res Clin Oncol
DOI 10.1007/s00432-013-1560-8

ORIGINAL PAPER

Intensity-modulated and hypofractionated simultaneous integrated boost adjuvant breast radiation employing statics ports of tomotherapy (TomoDirect): a prospective phase II trial

Pierfrancesco Franco · Michele Zeverino · Fernanda Migliaccio · Domenico Cante · Piera Sciacero · Valeria Casanova Borca · Paolo Torielli · Cecilia Arrichiello · Giuseppe Girelli · Maria Rosa La Porta · Santi Tofani · Giannauro Numico · Umberto Ricardi

Received: 12 September 2013 / Accepted: 20 November 2013

Abstract

Purpose To report the 1-year outcomes of a prospective phase II study on hypofractionated whole-breast intensity-modulated radiotherapy (IM-WBRT) with a simultaneous integrated boost (SIB) to the tumor bed delivered with static ports of tomotherapy (TomoDirect) (TD).

Methods A prospective cohort of 82 patients was enrolled between 2011 and 2012. Treatment schedule consisted of 45 Gy/20 fractions to the whole breast and 50 Gy/20 fractions to the surgical bed delivered concomitantly with TD over 4 weeks. A one-armed optimal two-stage Simon's design was selected to test the hypothesis that treatment modality under investigation would decrease acute skin toxicity over historical data using conventional fractionation and sequential boost. Primary endpoint was acute skin toxicity. Secondary endpoints included late toxicity, cosmesis, quality of life and local control.

Results Median follow-up was 12 months (range 6–18). Maximum detected acute skin toxicity was G0 41 %; G1 53 %; G2 6 %; G3 <1 %. With two G2–G3 acute skin toxicity events in the first stage and four in the second, the study fulfilled the requirements for the definition of the treatment approach under investigation as promising. Late skin toxicity was mild with no >G2 events. Cosmesis was good/excellent in 91 % of patients and fair/poor in 9 %. Quality of life was preserved over time, with the exception of fatigue, which was transiently increased.

Conclusions Hypofractionated IM-WBRT with a SIB to the tumor bed delivered with TD provides consistent clinical results and it is able to reduce acute skin toxicity rate over conventionally fractionated and sequential boost tomotherapy-based IM-WBRT.

Keywords IMRT · IGRT · SIB · Adjuvant breast radiotherapy · Breast cancer · Tomotherapy · TomoDirect · Simultaneous integrated boost

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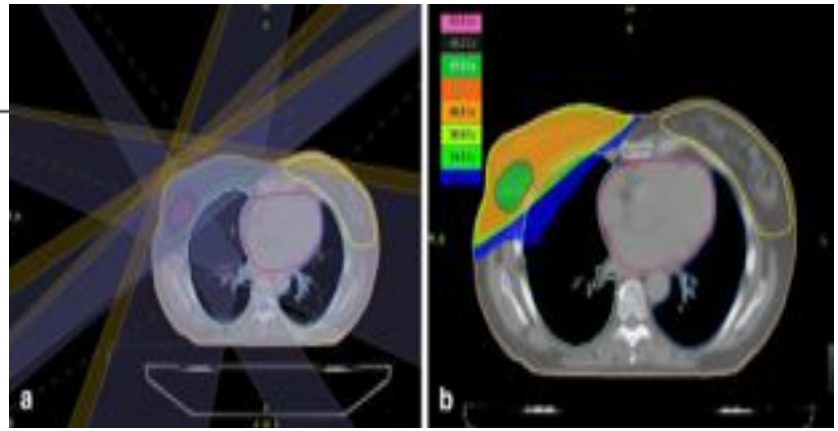
Background

The standard combination therapy after conserving surgery (BCS) for early-stage breast cancer (EBC) includes adjuvant whole-breast radiotherapy (WBRT), which decreases the rate of local recurrence and increases overall survival (Poortmans 2007; Early Breast Cancer Trialists' Collaborative Group 2005). Boosting the tumor bed (TB) further raises local control (Bartelink et al. 2007). The most common radiotherapy schedule employs conventional frac-



TomoDirect:

82 pazienti

Risultati a 1 anno

Tossicità acuta:

G0 = 41%

G1 = 53%

G2 = 6%

G3 = < 1%

Tossicita tardiva:

No tox > G2

Cosmesi:

Eccellente/buona = 91%

Sufficiente/insuff = 9%

Ottimi risultati dosimetrici:

V105% basso

V110% non valutabile

Ciammella et al. Radiation Oncology 2014, 9:97
http://www.ro-journal.com/content/9/1/97

RADIATION ONCOLOGY

RESEARCH Open Access

Toxicity and cosmetic outcome of hypofractionated whole-breast radiotherapy: predictive clinical and dosimetric factors

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Abstract

Purpose: The objective of this study is to evaluate toxicity and cosmetic outcome in breast cancer patients treated with adjuvant hypo fractionated radiotherapy to the whole breast, and to identify the risk factors for toxicity.

Methods and materials: Two hundred twelve women with early breast cancer underwent conserving surgery were enrolled in the study. The patients received 40.05 Gy in 15 daily fractions, 2.67 Gy per fraction. The boost to the tumor bed was administered with a total dose of 9 Gy in 3 consecutive fractions in 55 women. Physician-rated acute and late toxicity and cosmetic outcome (both subjective and objective) were prospectively assessed during and after radiotherapy.

Results: In our population study the mean age was 63 with the 17% (36 pts) of the women younger than 50 years. The median follow-up was 34 months. By the end of RT, 35 patients out of 212 (16%) no acute toxicity, according to the RTOG criteria, while 145 (68%) and 31 patients (15%) developed grade 1 and grade 2 acute skin toxicity, respectively.
Late skin toxicity evaluation was available for all 212 patients with a minimum follow up of 8 months. The distribution of toxicity was: 39 pts (18%) with grade 1 and 2 pts (1%) with grade 2. No worse late skin toxicity was observed.
Late subcutaneous grade 0-1 toxicity was recorded in 208 patients (98%) and grade 2 toxicity in 3 patients (2%), while grade 3 was observed in 1 patient only. At last follow up, a subjective and objective good or excellent cosmetic outcome was reported in 93% and 92% of the women, respectively. At univariate and multivariate analysis, the late skin toxicity was correlated with the additional boost delivery ($p=0.007$ and $p=0.023$). Regarding the late subcutaneous tissue, a correlation with diabetes was found ($p=0.0283$).

Conclusion: These results confirm the feasibility and safety of the hypofractionated radiotherapy in patients with early breast cancer. In our population the boost administration was resulted to be a significant adverse prognostic factor for acute and late toxicity. Long-term follow up is need to confirm this finding.

f acute skin toxicity

RTOG	Total patients
Toxicity grade	**N (%)**
G0	35 (16%)
G1	144 (68%)
G2	32 (15%)
G3	1 (1%)

f late skin toxicity

RTOG	Total patients
Toxicity grade	**N (%)**
G0	171 (81%)
G1	39 (18%)
G2	2 (1%)
G3	0 (0%)

Two Different Hypofractionated Breast Radiotherapy Schedules for 113 Patients with Ductal Carcinoma *In Situ*: Preliminary Results

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Abstract. *Aim: To assess local control and cosmetic outcomes for two different hypofractionated radiotherapy schedules after breast-conserving surgery for ductal carcinoma in situ (DCIS). Patients and Methods: A total of 113 conservative-operated patients with DCIS were treated from August 2006 to August 2011: 41 women received 46 Gy in 20 fractions of 2.3 Gy four times a week, for five weeks; the other 72 patients received 39 Gy in 13 fractions of 3 Gy four times a week for 3.5 weeks. Both schedules involved a concomitant boost to the tumor bed, with dose according to the surgical margins. Results: The median follow up is 30.5 months. Overall, the treatments were well tolerated. The most common acute effect was erythema: grade 1 in 56.1% and 31.9% in the longer and in the shorter hypofractionated treatment, grade 2 in 9.8% and 0% respectively. Late toxicity of fibrosis occurred at grade 1 in 19.6% and 15.3% respectively and at grade 2 in 0% and 2.8%. Conclusion: These results suggest that patients with DCIS can be safely treated with a shorter radiotherapy regimen.*

Screening mammography has increased the diagnosis of ductal carcinoma *in situ* (DCIS) from 3-5% in the 1970s and 1980s to 25-30% today (1). Randomised clinical trials demonstrated that adjuvant breast radiotherapy (RT) reduces the risk of recurrence in DCIS following breast-conserving surgery (BCS) (3, 4). The standard radiation treatment is administered in 25 fractions over five weeks and such a number of visits to the RT center can impact the quality of life of patients. Moreover, this prolonged schedule does not allow the optimum use of human and technological resources of the center. Recent randomized trials justify the routine use of hypofractionation for adjuvant whole-breast radiotherapy in women with early breast cancer, but there are currently no prospective data addressing this schedule for DCIS (5). At our center, all patients with breast cancer receive hypofractionated radiotherapy (HFRT). In this analysis, we review preliminary data for local control and cosmetic outcomes for a cohort of patients treated with two different HFRT schedules in routine use at our center following BCS for DCIS.

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Key Words: Breast cancer, ductal carcinoma in situ, hypofractionated radiotherapy.

Patients and Methods

We analyzed a sample of 113 breast cancer patients treated with BCS then treated at our Department from August 2006 to August 2011 with two different adjuvant RT schedules for DCIS. The median age was 67 (range=35-85) years. The patient and tumor characteristics are listed in Table I. Surgery consisted in a wide excision. In cases of occult invasion risk, high-grade lesions, palpable node or extended microcalcifications, sentinal lymphnode biopsy was implemented (6, 7). Margins were microscopically evaluated and scored as free when exceeding a tumor-free width of 2 mm and as involved when less. DCIS was graded into three categories (well, intermediately, and poorly differentiated). The patients were evaluated and classified according to the presence of comedo subtype with or without necrosis. Intraoperative specimen X-rays were performed to confirm complete excision of micro-calcifications.

We used two different RT to progressively introduce shorter HFRT schedules, starting with the older women (over 60 years) and extending to the younger patients. In addition we used four fractions per week to administer palliative single doses, to perform weekly dosimetry and other technical requirements on the fifth day (Wednesday). According to clinical characteristics (performance status, age, breast volume and shape), after primary surgery, the appropriate schedule was selected for each patient: 41 women, younger than 60 years, were assigned to receive 46 Gy in 20 fractions of 2.3 Gy four times a week for five weeks. The remaining

0250-7005/2013 $2.00+.40

ANTICANCER RESEARCH
International Journal of Cancer Research and Treatment

August 2013 vol. 33 no. 8 3503-3507

DCIS

113 pazienti

-41 pz: 46 Gy, fx 2.3 Gy in 20 fr

-72 pz: 39 Gy, fx 3 Gy in 13 fr

(Concomitant boost in base allo stato dei margini)

Tossicità acuta:

G1 = 56.1 % --- 31.9 %

G2 = 9.8% --- 9%

Tossicità tardiva:

G1 = 19.6% --- 15.3%

G2 = 0% --- 2.8%

Med Oncol (2014) 31:838
DOI 10.1007/s12032-014-0838-2

ORIGINAL PAPER

Hypofractionation and concomitant boost to deliver adjuvant whole-breast radiation in ductal carcinoma in situ (DCIS): a subgroup analysis of a prospective case series

Domenico Cante · Pierfrancesco Franco · Piera Sciacero · Giuseppe Girelli · Anna Maria Marra · Massimo Pasquino · Giuliana Russo · Valeria Casanova Borca · Guido Mondini · Ovidio Paino · Gianmauro Numico · Santi Tofani · Maria Rosa La Porta · Umberto Ricardi

Received: 17 November 2013 / Accepted: 4 January 2014

Abstract To report the four-year outcomes of accelerated hypofractionated whole-breast radiotherapy (WBRT) with a concomitant boost (CB) to the tumor bed in ductal carcinoma in situ (DCIS), we performed a subgroup analysis of 103 patients affected with DCIS within a cohort of 960 early breast cancer patients treated with breast conservation and hypofractionated WBRT. Prescription dose to the whole breast was 45 Gy (2.25 Gy/20 fractions) with an additional daily CB of 0.25 Gy to the surgical cavity (2.5 Gy/20 fractions up to 50 Gy). With a median follow-up of 48 months (range 12–91), no local recurrence was observed. Maximum detected acute skin toxicity was as follows: G0 in 35 % of patients, G1 in 54 %, G2 in 9 % and G3 in 2 %. Late skin and subcutaneous toxicity were generally mild with only 1 % of patients experiencing ≥G3 events (telangiectasia). No major lung and heart toxicity were detected. Cosmetic results were excellent in 50 % of patients, good in 37 %, fair in 9 % and poor in 4 %. Quality of life had a generally favorable profile both within the functioning and symptoms domains. The present result supports the hypothesis that DCIS patients could be safely treated with a hypofractionated schedule employing a CB to the lumpectomy cavity.

Keywords Ductal carcinoma in situ (DCIS) · Breast cancer · Hypofractionated adjuvant whole-breast radiotherapy · Concomitant boost · Hypofractionation · Simultaneous-integrated boost (SIB)

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Introduction

Adjuvant whole-breast radiation (WBRT) after conservative surgery (BCS) is a standard option for early breast cancer (EBC), as it decreases local recurrence, with a benefit on overall survival [1, 2]. Adding a boost dose to the tumor bed (TB) further raises local control (LC) [3]. Traditionally, WBRT has been delivered over 5 weeks

DCIS

103 pazienti

Risultati a 5 anni:

Tossicità acuta

G0 = 35%

G1 = 54%

G2 = 9%

G3 = 2%

Tossicità tardiva

Solo 1% dei pazienti G3

Cosmesi:

Eccellente 50%

Buona 37%

Sufficiente 9%

Insufficiente 4%

Associazione Italiana
di Radioterapia Oncologica
Gruppo di lavoro AIRO per la Patologia Mammaria

La Radioterapia dei Tumori della Mammella

Indicazioni e Criteri Guida

2013

2.4 FRAZIONAMENTI E DOSI

Dopo chirurgia conservativa il trattamento standard prevede la somministrazione di 50,0-50,4 Gy in regime di frazionamento convenzionale (1,8-2 Gy/die, in 5 frazioni settimanali).
Poiché la maggior parte delle recidive locali è documentata in corrispondenza o nelle immediate vicinanze del letto tumorale, al fine di ridurne l'incidenza, l'erogazione di un sovradosaggio al letto operatorio (boost) è pratica routinaria presso la maggior parte dei centri di radioterapia (46,47). Di norma sono previste dosi totali al letto operatorio (irradiazione del corpo mammario e sovradosaggio) di 60,0 Gy in caso di margini di resezione istologicamente negativi. In presenza di margini non negativi è indicata la somministrazione di una dose più elevata, come indicato nel paragrafo 2.8.3. Sono in corso esperienze che valutano l'impiego del boost integrato o concomitante con diverse modalità esecutive (48-50). La somministrazione del boost può impattare sull'insorgenza di effetti collaterali e determinare un peggioramento del risultato cosmetico. Per ridurre il rischio sono stati individuati sottogruppi di pazienti che possono trarre beneficio dalla sua erogazione (pazienti giovani o con fattori di rischio per recidiva locale, quali margini di resezione non negativi, alto grading, positività linfonodale, elevato indice proliferativo, presenza di estesa componente intraduttale e infiltrazione linfovascolare, recettori ormonali negativi) e sottogruppi a basso rischio, nei quali l'incremento di dose al letto tumorale potrebbe essere omesso (51,52).
Per ridurre la durata totale del trattamento, sono stati sperimentati schemi alternativi che prevedono, rispetto al frazionamento convenzionale, l'impiego di dosi singole più elevate somministrate in un tempo totale più breve con dose nominale inferiore ma radiobiologicamente equivalente (ipofrazionamento della dose) (53). Il razionale dell'ipofrazionamento è la dimostrazione che il valore del rapporto α/β per il tumore della mammella è vicino a 4Gy, analogo a quello dei tessuti sani a risposta lenta (54). L'ipofrazionamento è quindi attrattivo sia per la logistica delle pazienti che per l'ottimizzazione dell'utilizzo delle risorse dei centri di radioterapia (riduzione del numero degli accessi in ospedale e dei costi diretti ed indiretti del trattamento) (55).
I dati provenienti dalla pubblicazione dei risultati di studi randomizzati (56-60) hanno dimostrato che dosi di 40 Gy in 15 frazioni e 42.5 Gy in 16 frazionari hanno sicurezza e efficacia comparabili al frazionamento convenzionale. Sulla base di questi dati l'ipofrazionamento è considerato uno standard nelle linee guida di paesi anglosassoni (18,61).
I primi risultati di un ulteriore studio randomizzato (62) che compara il trattamento convenzionale con due regimi ipofrazionati più spinti (5 frazioni settimanali di 5.7 Gy fino 28.5 Gy o 6 Gy fino a 30 Gy) evidenziano a 3 anni risultati peggiori per lo schema 30 Gy in 5 frazioni.
A tutt'oggi non sono disponibili dati sufficienti a chiarire alcuni interrogativi legati all'impiego dell'ipofrazionamento:

- in pazienti sottoposte a chirurgia conservativa per carcinoma duttale in situ
- relativamente all'eventuale esecuzione di un sovradosaggio (boost)
- all'associazione dell'ipofrazionamento con schemi di chemioterapia adiuvante

poiché le pazienti con tali caratteristiche incluse negli studi sono numericamente insufficienti ad ottenere un elevato livello di raccomandazione.
Sulla base di questi dati, nonostante i dubbi relativi ai rischi per gli OR, alla possibile presenza di hot spot interni al volume mammario e alle problematiche radiobiologiche (54) non sembrano esistere giustificate preoccupazioni tali da scoraggiare nella routine clinica l'adozione di schemi di trattamento ipofrazionati. Evidenze di livello I permettono di applicare un modesto ipofrazionamento in sottogruppi di pazienti candidabili alla irradiazione mammaria postoperatoria dopo chirurgia conservativa cui questi schemi devono essere riservati.
Precauzionalmente, in linea con le linee-guida dell' ASTRO (63), si devono valutare le seguenti possibili cause di esclusione:

- stadi localmente avanzati (pT3-4);
- interessamento linfonodale (pN+);
- età inferiore a 50 anni;
- istologia di carcinoma duttale in situ;
- volume mammario importante definito come distanza tra gli ingressi dei due campi tangenziali maggiore di 25 cm, a causa della difficoltà ad ottenere una distribuzione omogenea della dose e conseguente maggiore probabilità di tossicità;
- piano di trattamento non conforme ai limiti di dose (da valutare dopo elaborazione del piano di trattamento) quali la presenza di aree di parenchima mammario in cui la dose supera il 107% della dose stabilita;
- precedenti trattamenti di RT sugli stessi volumi per altre patologie, ad esempio linfoma;
- trattamento concomitante di schemi di chemioterapia contenenti antracicline o taxani, ma anche CMF per il rischio di un aumento della tossicità acuta cutanea;

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0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.04.042

CLINICAL INVESTIGATION **Breast**

FRACTIONATION FOR WHOLE BREAST IRRADIATION: AN AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) EVIDENCE-BASED GUIDELINE

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Purpose: In patients with early-stage breast cancer treated with breast-conserving surgery, randomized trials have found little difference in local control and survival outcomes between patients treated with conventionally fractionated (CF-) whole breast irradiation (WBI) and those receiving hypofractionated (HF-)WBI. However, it remains controversial whether these results apply to all subgroups of patients. We therefore developed an evidence-based guideline to provide direction for clinical practice.

Methods and Materials: A task force authorized by the American Society for Radiation Oncology weighed evidence from a systematic literature review and produced the recommendations contained herein.

Results: The majority of patients in randomized trials were aged 50 years or older, had disease Stage pT1-2 pN0, did not receive chemotherapy, and were treated with a radiation dose homogeneity within ±7% in the central axis plane. Such patients experienced equivalent outcomes with either HF-WBI or CF-WBI. Patients not meeting these criteria were relatively underrepresented, and few of the trials reported subgroup analyses. For patients not receiving a radiation boost, the task force favored a dose schedule of 42.5 Gy in 16 fractions when HF-WBI is planned. The task force also recommended that the heart should be excluded from the primary treatment fields (when HF-WBI is used) due to lingering uncertainty regarding late effects of HF-WBI on cardiac function. The task force could not agree on the appropriateness of a tumor bed boost in patients treated with HF-WBI.

Conclusion: Data were sufficient to support the use of HF-WBI for patients with early-stage breast cancer who met all the aforementioned criteria. For other patients, the task force could not reach agreement either for or against the use of HF-WBI, which nevertheless should not be interpreted as a contraindication to its use.

Breast cancer, Hypofractionation, Evidence-based guideline, Breast conserving therapy.

GUIDELINE ASTRO

42.5 Gy/16 fr

No boost

> 50 anni
pT1-2 pN0
No chemioterapia
Omogeneità di dose 7%

Table 4 Criteria for Treatment With Hypofractionated Breast Radiation, Based on ASTRO 2011 Consensus Guidelines and Update of the START Trials[23]

Factors	Appropriate	Cautionary	Unsuitable
Patient factors			
Age	≥ 50 yr < 50 yr with boost	< 50 yr (without boost)	
Pathologic factors			
T stage	T1–2	T3	T4
N stage	N0	N1	N2+
Margins	Negative		
Grade	1–2 3 (with boost)	3 (without boost)	
Receptor status	ER/PR-positive/negative	HER2-positive Triple-negative	HER2-positive (with concurrent trastuzumab)
Histology	Invasive carcinoma	DCIS	Inflammatory
Treatment factors			
Surgery	Breast-conserving	Mastectomy	Breast reconstruction
Chemotherapy	None	Neoadjuvant Adjuvant	Concurrent
Dose inhomogeneity	≤ ±7% MP	±7% MP to ± 10% 3D	Concurrent

3D = three-dimensional conformal therapy; ASTRO = American Society for Radiation Oncology; DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor type 2; MP = at midplane; PR = progesterone receptor; START = Standardisation of Breast Radiotherapy trial.

Hypofractionation for Breast Cancer: Lessons Learned From Our Neighbors to the North and Across the Pond

Review Article | *June 15, 2014* | *Oncology Journal*, *Breast Cancer*, *Radiation Oncology*
By Michael J. Eblan, MD, Noam A. VanderWalde, MD, Elaine M. Zeman, PhD, and Ellen Jones, MD, PhD

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Original article

Long-term mortality from cardiac causes after adjuvant hypofractionated vs. conventional radiotherapy for localized left-sided breast cancer

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Background and purpose

Ongoing concern remains regarding cardiac injury with hypofractionated whole breast/chest-wall radiotherapy (HF-WBI) compared to conventional radiotherapy (CF-WBI) in left-sided breast cancer patients. The purpose was to determine if cardiac mortality increases with HF-WBI relative to CF-WBI.

Materials and methods

Between 1990 and 1998, 5334 women with early-stage breast cancer received post-operative radiotherapy to the breast/chest wall alone. A population-based database recorded baseline patient, tumor and treatment factors. Baseline cardiovascular risk factors were identified from hospital administrative records. A propensity-score model balanced risk factors between radiotherapy groups. Cause of death was coded as breast cancer, cardiac or other cause. Cumulative mortality from each cause after radiotherapy was estimated using a competing risk approach.

Results

For left-sided cases, median follow-up was 14.2 years. 485 women received CF-WBI, 2221 women received HF-WBI. There was no difference in 15-year mortality from cardiac causes: 4.8% with HF-WBI and 4.2% with CF-WBI ($p = 0.74$), even after propensity-score adjustment ($p = 0.45$). There was no difference in breast cancer mortality or other cause mortality. For right-sided cases, there was no difference in mortality for the three causes of death.

Conclusions

At 15-years follow-up, cardiac mortality is not statistically different among left-sided breast cancer patients treated with HF-WBI or CF-WBI.

Breast Care

Review Article

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Tumor Bed Boost Integration during Whole Breast Radiotherapy: A Review of the Current Evidence

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Keywords
Adjuvant whole breast radiotherapy · Concomitant boost · IMRT · IGRT · Hypofractionation · Simultaneous integrated boost · Breast cancer

Summary
Radiation therapy delivered with hypofractionation, which involves the delivery of a higher dose per fraction in fewer fractions (generally with a lower total nominal dose) over a shorter overall treatment time, is an established therapeutic option at least for a selected group of early breast cancer patients after breast-conserving surgery. Optimal delivery of the tumor bed boost dose in terms of timing, fractionation, and total dose whenever a hypofractionated schedule is employed has yet to be established. We herein present a review of the current evidence on the role of boost integration in whole breast radiotherapy.

Introduction

Combining breast-conserving surgery (BCS) and radiation therapy (RT) is a mainstay option in the multimodality treatment of breast cancer with optimal long-term local control, mild toxicity, good cosmetic outcome, and survival rates comparable to mastectomy [1]. Adjuvant whole breast radiotherapy (WBRT) yields a local failure rate of 3–15% depending on the patient cohort and variables such as intrinsic risk factors, type of surgery, and follow-up time [2]. However, in recent years, substantial improvements in the fields of early diagnosis, clinical selection, surgery, RT technology, and systemic treatments have led to an increase in local control, with higher rates than those observed in early randomized trials [3]. It has been demonstrated that good local control translates into improved overall survival (OS) [4]. The rationale for delivering an adjunctive radiation dose boosting the lumpectomy cavity is derived from several considerations: First, the radiobiological observation of a dose-response relationship for breast cancer; second, the pathological evidence of a higher microscopic tumor burden in proximity to the site of lumpectomy; and third, the clinical observation of the local pattern of failure close to the primary tumor location [5–7]. Randomized phase III trials exploring the role of boosting the tumor bed demonstrated a relative reduction in local failure in the range of 20–50%, depending on risk factors of the patient cluster analyzed [2]. However, in spite of this substantial clinical benefit, in several countries there has been a tendency to omit adjuvant WBRT after BCS, especially in women over 70–80 years, but also in younger patients, maybe due to the extended overall treatment time using a conventionally fractionated schedule and sequential boost approach [8]. Hypofractionation (HF) (delivery of a larger dose per fraction in shorter overall time) and concurrent boost (delivery of a synchronous adjunctive dose to the tumor bed) represent a useful option to optimize treatment both for patients and healthcare providers [9].

Boosting the Tumor Bed

Local Control and Cosmetic Outcome

A boost dose to the lumpectomy cavity can be delivered with external photon beam RT, external electron beam RT, and high-dose brachytherapy employing an after-loading system administered either intraoperatively or after WBRT. Boosting the tumor

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Vantaggio in termini di riduzione del tempo totale di trattamento e dosimetrico

The Breast Journal

ORIGINAL ARTICLE

Hypofractionated Radiation Therapy for Early Stage Breast Cancer: Outcomes, Toxicities, and Cost Analysis

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■ **Abstract:** A French prospective randomized trial comparing whole breast radiotherapy with 45 Gy in 25 fractions versus 23 Gy in four fractions demonstrated equivalent 5-year local control and survival. On the basis of this data, we offer the hypofractionated regimen to women who refuse to undergo standard radiotherapy. We report our outcomes and a cost analysis. Between 2000 and 2012, 84 patients participated in this IRB-approved study and underwent whole breast radiation to 23 Gy in four fractions. Local control and survival were analyzed using the Kaplan-Meier method. Acute toxicities and overall long-term cosmetic results were assessed. Costs were estimated from 2012 Medicare reimbursement data and compared to costs from standard courses of 25 and 16 fractions. All 84 patients are included in this report. Median age was 83 (range 42-96). Most patients had stage I (80%), hormone receptor positive (90%) breast cancer. Fifty-eight patients (69%) were treated prone and 26 (31%) supine. At a median follow-up of 3 years, one local recurrence has occurred, of ductal carcinoma in situ histology. Among the 13 patients deceased, two died of metastatic breast cancer. Five-year actuarial local control is 99%, breast cancer-specific survival is 98%, and overall survival is 79%. Toxicities were limited to grade 1 dermatitis in 32 patients (38%) and grade 2 fatigue in three (4%). Sixty-three patients (75%) reported good or excellent cosmetic outcome at their last follow-up. Collected Medicare reimbursement was $4,798 for the hypofractionated course. Compared to the projected reimbursement of standard regimens, $10,372 for 25 fractions and $8,382 for 16 fractions, it resulted in a difference of $5,574 and $3,584, respectively. At a follow-up of 3 years, this hypofractionated regimen appears to be a promising approach, primarily for elderly women who are unable to undergo longer treatment courses but have indications for whole breast radiotherapy. ■

Key Words: Breast cancer, hypofractionated radiotherapy

Baillet et al. conducted a randomized trial evaluating whole breast hypofractionated radiotherapy. In their study, breast cancer patients were randomly assigned to a classical course of 45 Gy in 25 fractions over 33 days or a hypofractionated course of 23 Gy in four fractions over 17 days; fractions 1 and 2 were given on days 1 and 3, and fractions 3 and 4 were given on days 15 and 17. With a median follow-up of

Costo: 4,798 $

Baillet, IJROBP 1990:
23 Gy, 4 fr, →
2 fr 5 Gy (gg 1; 3) + 2 fr 6,5 Gy (gg 15; 17)

radiotherapy. Whelan et al. reported the results of the Ontario Clinical Oncology Group randomized trial with a follow-up of 10 years. They compared a total dose of 42.56 Gy given in 16 daily 2.66 Gy fractions five times a week to a standard dose of 50 Gy given in 25 daily 2 Gy fractions five times a week. Eligibility

Costo: 8,382 $

five times a week to a standard dose of 50 Gy given in 25 daily 2 Gy fractions five times a week. Eligibility

Costo: 10,372 $

CONCLUSIONI

Hypofractionation for Breast Cancer: Lessons Learned From Our Neighbors to the North and Across the Pond

ONCOLOGY

Review Article | June 15, 2014 | Oncology Journal, Breast Cancer, Radiation Oncology

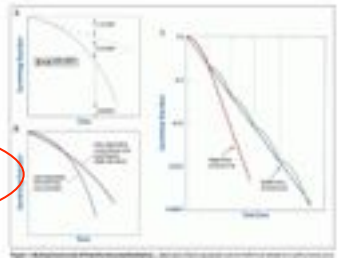
By Michael J. Eblan, MD, Noam A. VanderWalde, MD, Elaine M. Zeman, PhD, and Ellen Jones, MD, PhD

Adjuvant whole breast irradiation was established within the standard of care for breast-conserving therapy in the early 1980s, following the results of major randomized trials comparing mastectomy vs breast-conserving surgery and radiation. Since that time, techniques and treatment strategies have evolved, but one major thread that carries forward is the need to balance cost, efficacy, complications, and convenience. Fortunately, data from randomized trials conducted in Canada and Great Britain provide a solid framework for the consideration of hypofractionated radiation in the treatment of breast cancer. In this review we discuss the rationale and underlying radiobiologic concepts for hypofractionation, and review the clinical trials and American Society for Radiation Oncology (ASTRO) guidelines supporting this approach. We also review the practical considerations for treatment planning, including dosimetric criteria and how to approach treatment of the node-positive patient. In the current era of healthcare reform and cost awareness, thoughtful utilization of hypofractionation may offer considerable savings to individual patients and the healthcare system—without compromising clinical outcomes or quality of life.

Reviews

Fractionation in Breast Cancer Radiotherapy for Conservative Treatment: Are We Really Done Learning?

Consider a Single Intraoperative Fraction for Patients Eligible for Hypofractionated Regimens?



In questo momento di difficoltà del Sistema Sanitario e di attenzione ai costi, l'utilizzo dell'ipofrazionamento potrebbe rappresentare una risorsa preziosa per il paziente, per i centri di radioterapia e per il Sistema Sanitario

GRAZIE