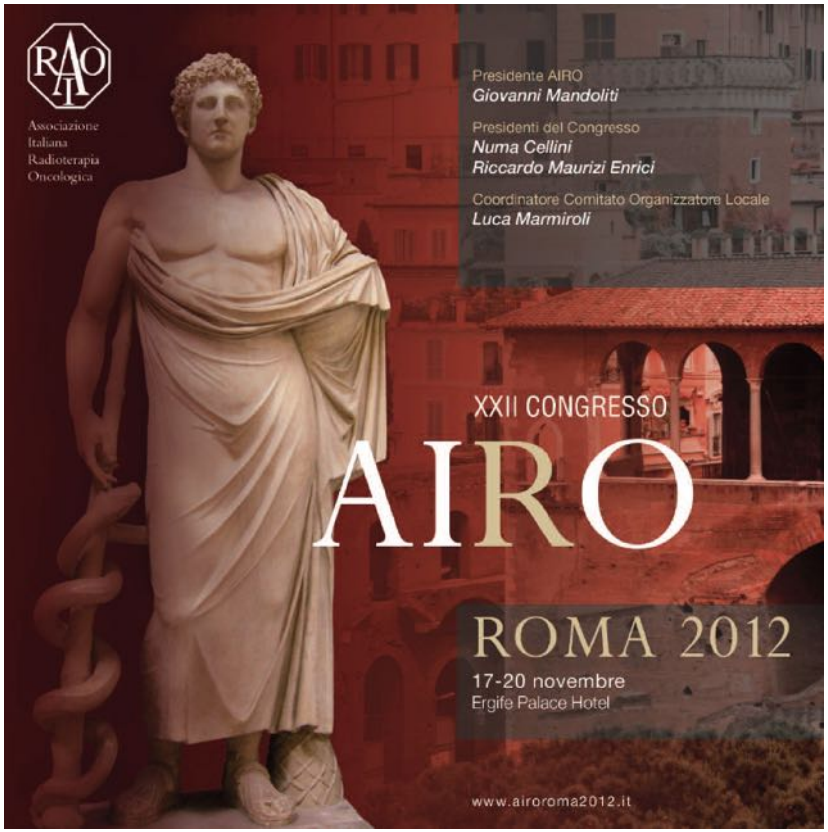


Tossicità tardiva in radioterapia: ipofrazionamento versus frazionamento convenzionale

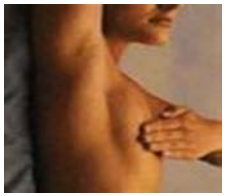
L'esperienza clinica nella mammella

Marina Guenzi
Genova

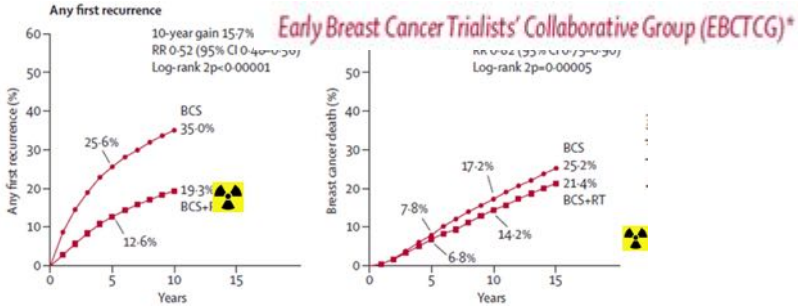
Considerazioni….

35.000
nuovi casi
annui

incidenza delle neoplasie mammarie

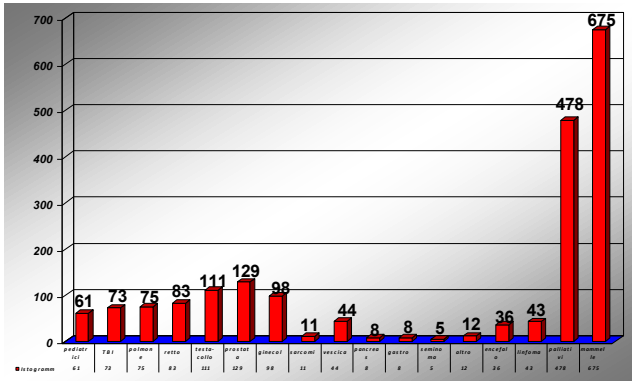


riscontro di forme early



indicazioni alla RT

80% delle pazienti afferisce ai Centri RT



qualità di vita

Desiderio di introdurre metodiche che consentano di "alleggerire" il trattamento e l'impatto che questo ha sulla vita delle donne, consentendo di ottenere analoghi risultati in termini di controllo di malattia

L'ipofrazionamento riducendo gli accessi

migliora la qualità di vita della paziente trattata

consente un ottimale utilizzo delle risorse dei centri RT

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 674–681, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.11.077

CLINICAL INVESTIGATION **Breast Cancer**

PATIENT PREFERENCES AND PHYSICIAN PRACTICE PATTERNS REGARDING BREAST RADIOTHERAPY

David J. Hoopes, M.D.,* David Kaziska, Ph.D.,† Patrick Chapin, Ph.D.,† Daniel Weed, M.D.,‡ Benjamin D. Smith, M.D.,‖ E. Ronald Hale, M.D., M.P.H.,¶ and Peter A. Johnstone, M.D.‡

A total of 1,807 women (36%) and 363 physicians (17%) provided usable responses.

Patient preferences were:

hypofractionated whole breast irradiation (HF-WBI) 62%,
partial breast irradiation (PBI) 28%
conventionally fractionated whole breast irradiation (CF-WBI) 10%.

Physicians preferences were:
82% of physicians use CF-WBI for more than 2/3 of women
56% never use HF-WBI.

And so → Hypofractionated Radiotherapy….

As fraction size increases…… total dose must be reduced in order to maintain the same level of antitumor or normal tissue effect.

It should now be clear that it is always possible to identify a hypofractionated schedule equivalent to a conventionally fractionated regimen in terms of a specific late adverse effect.

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right)$$

Tossicità tardiva in radioterapia: Ipofrazionamento versus frazionamento convenzionale L'esperienza clinica nella mammella

mancato controllo locale
fibrosi, retrazione, teleangiectasie mammarie
tossicità polmonare
tossicità cardiaca
plessopatia brachiale

Table 1. Randomized clinical trials testing fraction size in adjuvant external beam radiotherapy

Trial year range	Test schedule (total dose/fraction no./treatment time (weeks) (fraction size))	No. of patients	% of patients undergoing breast-conserving surgery	% of patients prescribed a boost dose	Median follow up (months)
RMH/GOC 1986–1998	39.0/13/5.0 (3.0) 42.9/13/5.0 (3.3)	1,410	100	74.5	116
Ontario 1993–1996	42.5/16/3.2 (2.66)	1,234	100	0	> 132
START A 1999–2002	39.0/13/5.0 (3.0) 41.6/13/5.0 (3.2)	2,236	85	60.6*	61
START B 1999–2001	40.0/15/3.0 (2.67)	2,215	92	42.6*	72

Data compare designs of randomized clinical trials testing fraction size in adjuvant external beam radiotherapy to whole breast after local excision of early breast cancer. All trials used a control arm delivering 50 Gy in 25 fractions over 5 weeks.

* Breast conservation patients only.

Yarnold J, 2011

Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial

John Yarnold[a,*], Anita Ashton[b], Judith Bliss[c], Janis Homewood[c], Caroline Harper[c], Jane Hanson[a], Jo Haviland[c], Søren Bentzen[d], Roger Owen[b]

Radiotherapy and Oncology 75 (2005) 9-17

Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC)

1410 pts

50 Gy / 25 fr (2.0 Gy/fr) / 5 weeks
39 Gy / 13 fr (3.0 Gy/fx) / 5 weeks
42.9 Gy / 13fr (3.3 Gy/fx) / 5 weeks

75% of pts →electron boost to the lumpectomy cavity
20% of pts → regional lymph nodes RT
14% of pts→ received CMF chemotherapy

Radiotherapy and Oncology 75 (2005) 9-17

Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC)

The primary endpoint was late normal tissue effects……..

The results were consistent with **breast cancer** having a **similar sensitivity** to fraction size as the **late-reacting healthy tissues.**

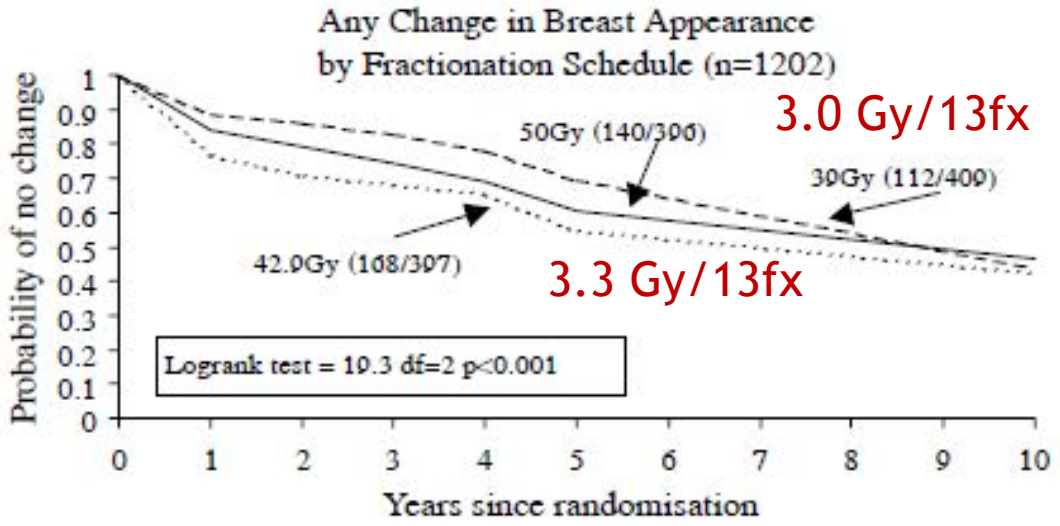


Fig. 2. Probability of any change in breast appearance late radiation effect ten years after radiotherapy by fractionation schedule.

Radiotherapy and Oncology 75 (2005) 9-17

The α/β ratio for any change in breast → 3.6 Gy

The Lancet, 2006

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, Soren M Bentzen, John R Yarnold

In 2006, the investigators reported the results of the trial in terms of local breast recurrence.

The risk of local recurrence at 10 years was

12.1% for 50.0 Gy,

9.6% for 42.9 Gy

14.8% for 39.0 Gy.

No statistical differences

the α/β ratio for local recurrence → 4.0 Gy.

The Lancet, 2008

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*

Between 1998 and 2002, 2236 women with early breast cancer (pT1-3a pN0-1 M0) at 17 centres in the UK were randomly assigned after primary surgery to receive

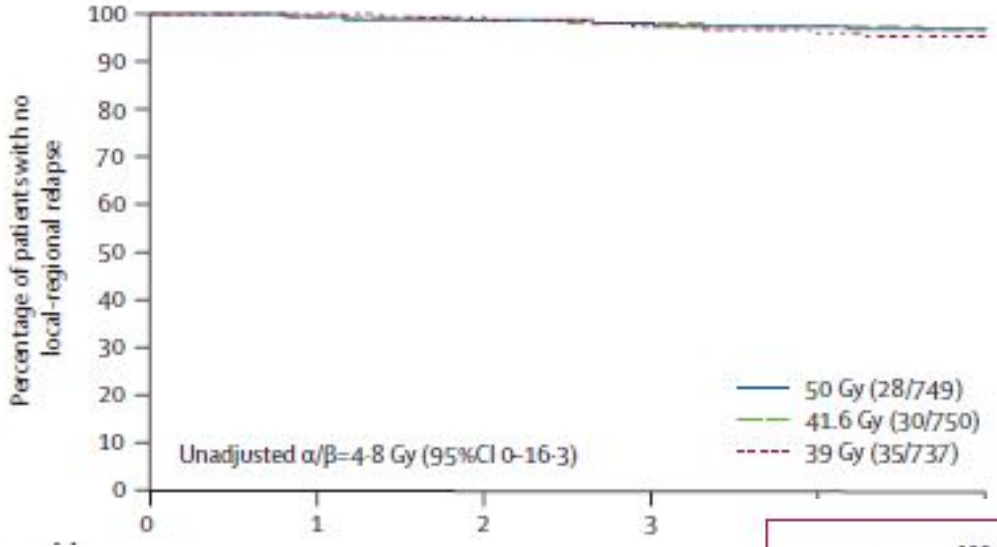
50 Gy in 25 fractions of 2.0 Gy
41.6 Gy in 13 frations of 3.2 Gy
39 Gy in 13 fractions of 3.0 Gy

5 weeks.

The protocol-specific principal endpoints were
- local-regional tumour relapse
- normal tissue effects
- quality of life

the rate of local-regional tumour relapse at 5 years

START A 2008



3.6% after 50 Gy,
3.5% after 41.6 Gy,
5.2% after 39 Gy.

no change in the breast

Photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy than with 50 Gy,

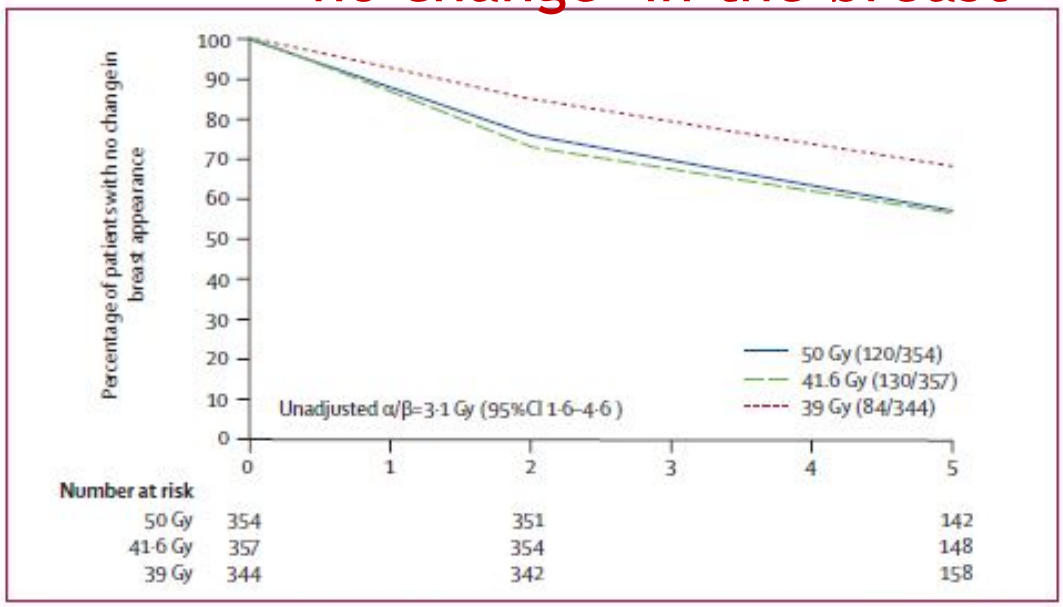


Figure 3: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 1055 patients with breast conserving surgery

START A

	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**

The incidence of ischaemic heart disease, symptomatic rib fracture and symptomatic lung fibrosis was **low** at this stage during follow-up, and **balanced between the schedules**

START A

The results of START Trial A are consistent with the hypothesis that breast cancer is as sensitive to fraction size as the normal tissues.

In START Trial A, 41,6 Gy in 13 fractions (3.2Gy x fr) was **similar** to the control regimen of 50 Gy in 25 fractions in terms of normal tissue effects and also in terms of local tumour control

50 Gy	in 25 fractions of 2.0 Gy
41.6 Gy	in 13 frations of 3.2 Gy
39 Gy	in 13 fractions of 3.0 Gy

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

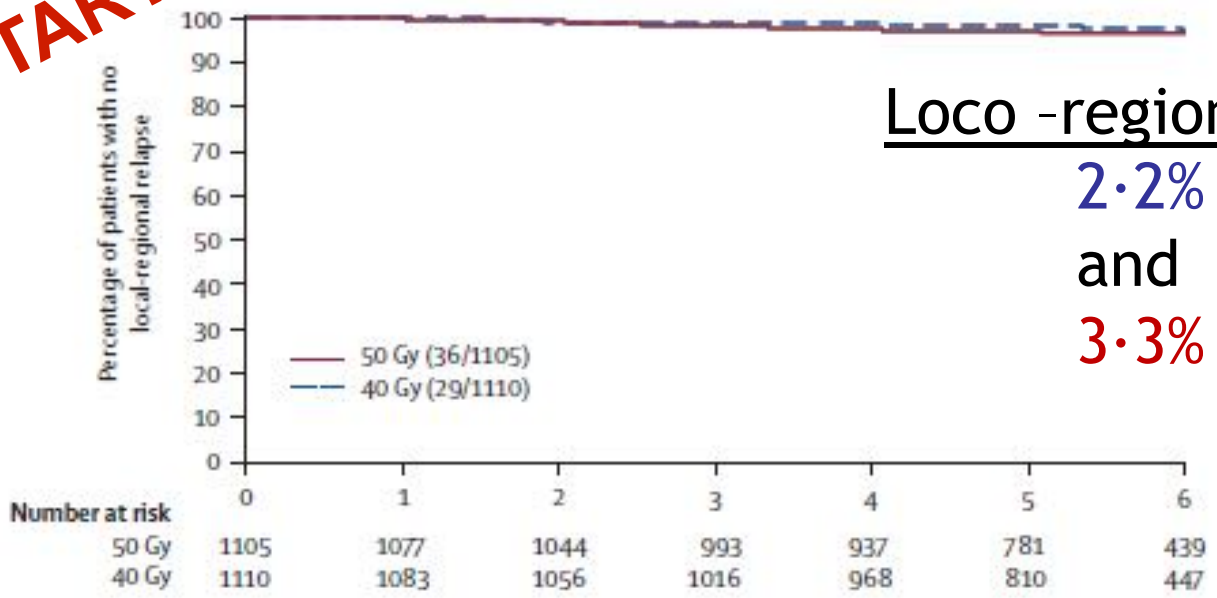
*The START Trialists' Group**

Lancet 2008; 371: 1098–107

Between 1999 and 2001, 2215 women with early breast cancer (pT1-3a pN0-1 M0) at 23 centres in the UK were randomly assigned after primary surgery to receive

50 Gy in 25 fractions of 2·0 Gy over 5 weeks
or
40 Gy in 15 fractions of 2·67 Gy over 3 weeks.

START B



Loco –regional relapse

2·2% in the 40 Gy pts

and

3·3% in the 50 Gy pts,

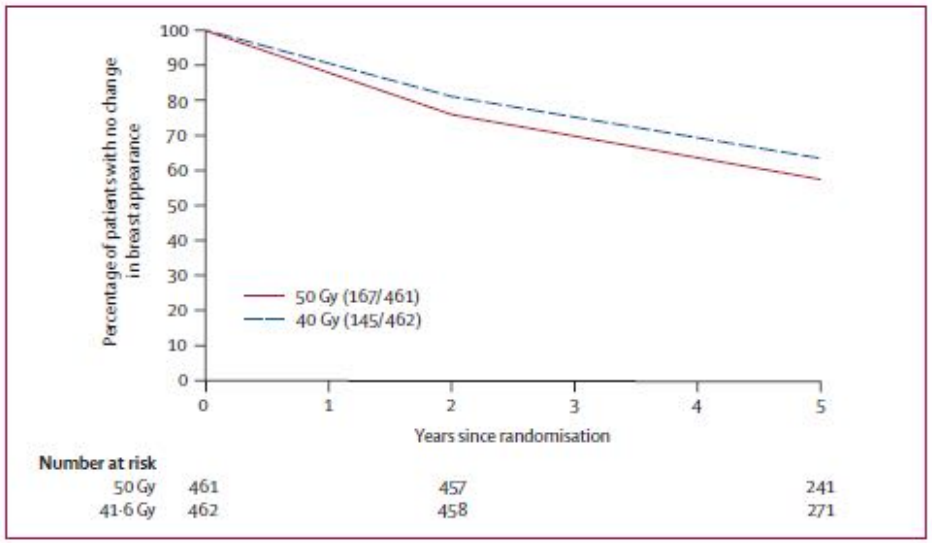


Figure 4: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 923 patients with breast conserving surgery

Mild/marked change in breast appearance

START B

	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**

The incidence of ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis was **low** at this stage during follow-up, and **balanced** between the schedules

START B

Interpretation

A radiation schedule delivering 40 Gy in 15 fractions (2.67 Gy) over 3 weeks seems to offer rates of local-regional tumour relapse and late adverse effects at least **as favourable as the standard** schedule of 50 Gy in 25 fractions.

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 362;6 NEJM.ORG FEBRUARY 11, 2010

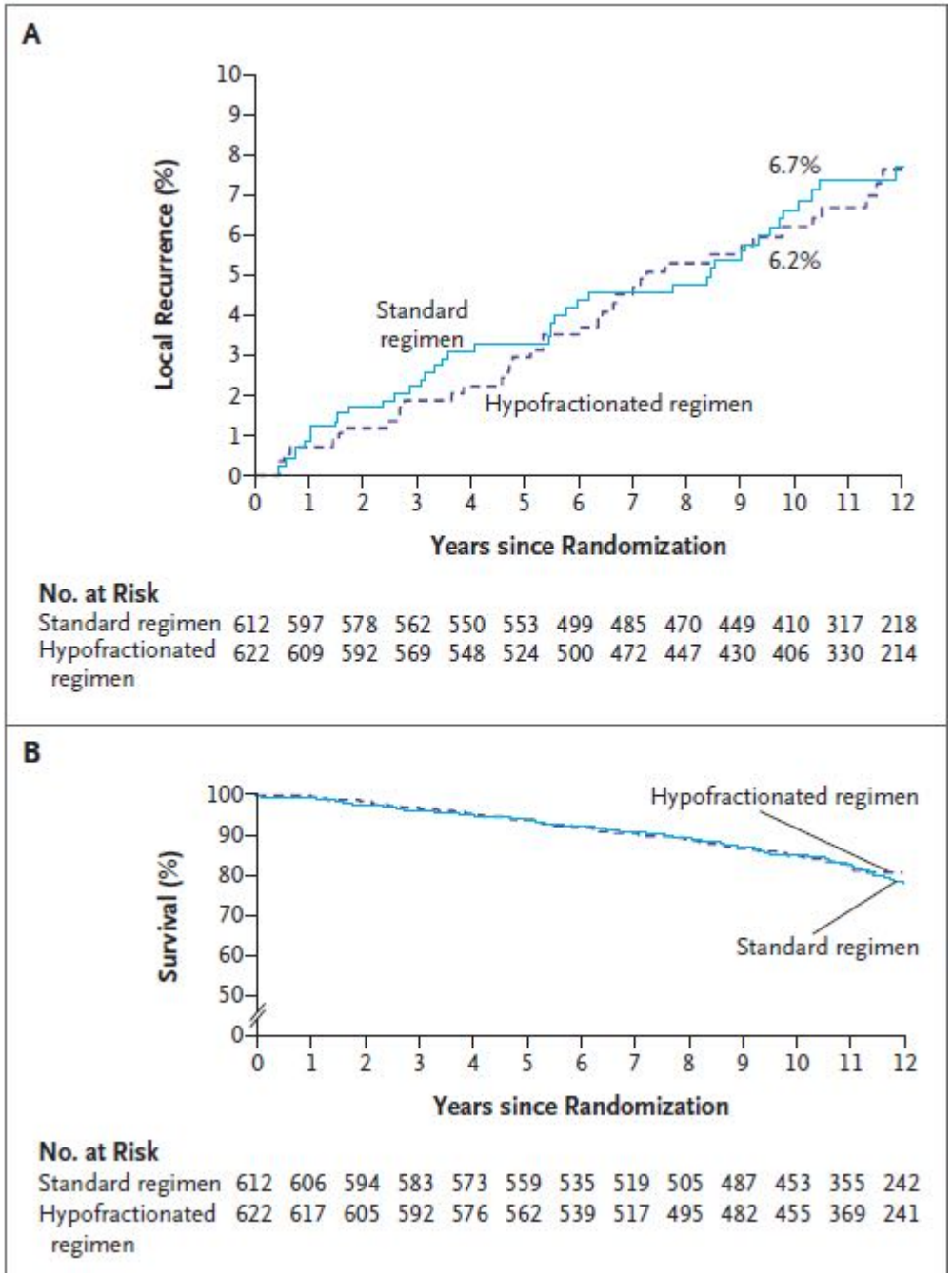
ORIGINAL ARTICLE

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.

612 pts assigned to standard irradiation (50 Gy/25 fr)

622 pts assigned to the hypofractionated regimen (42.5/16 fr)



At 10 years, 71.3% of women in the control group as compared with 69.8% of the women in the hypofractionated-radiation group had a good or excellent cosmetic outcome

Tossicità tardiva in radioterapia:
Ipofrazionamento versus frazionamento convenzionale
L'esperienza clinica nella mammella

mancato controllo locale
fibrosi, retrazione, teleangiectasie mammarie
tossicità polmonare
tossicità cardiaca
plessopatia brachiale

HYPOFRACTIONATED WHOLE-BREAST RADIOTHERAPY FOR WOMEN WITH EARLY BREAST CANCER: MYTHS AND REALITIES

JOHN YARNOLD, F.R.C.R.,* SØREN M. BENTZEN, D.Sc.,† CHARLOTTE COLES, PH.D.,‡ AND JOANNE HAVILAND, M.Sc.¶

Trial	Dose schedule (total dose/fraction no./treatment time (weeks) (fraction size))	5-year rate for: Any change in breast appearance (%)	5-year rate for: Local tumour relapse (%)
RMH/GOC	50.0/25/5.0 (2.0)	35.4	12.1
1986–1998	39.0/13/5.0 (3.0)	27.4	14.8
	42.9/13/5.0 (3.3)	42.3	9.6
Ontario	50.0/25/5.0 (2.0)	–	3.2†
1993–1996	42.5/16/3.2 (2.66)	–	2.8†
START A	50.0/25/5.0 (2.0)	42.9	3.2
1999–2002	39.0/13/5.0 (3.0)	32.1	4.6
	41.6/13/5.0 (3.2)	43.6	3.2
START B	50.0/25/5.0 (2.0)	42.2	3.3
1999–2001	40.0/15/3.0 (2.67)	36.5	2.0

Hypo in 5 wks

Hypo in 3 wks

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 1–9, 2011

Table 1. Randomized clinical trials testing fraction size in adjuvant external beam radiotherapy

Trial year range	Dose schedule (total dose/fraction no./treatment time (weeks) (fraction size))	No. of patients	% of patients undergoing breast-conserving surgery	% of patients prescribed a boost dose	Median follow up (months)
RMH/ICR 1986–1998	39.0/13/5.0 (3.0) 42.9/13/5.0 (3.3)	1,410	100	74.5	116
Ontario 1993–1996	42.5/16/3.2 (2.66)	1,234	100	0	> 132
START A 1999–2002	39.0/13/5.0 (3.0) 41.6/13/5.0 (3.2)	2,236	85	60.6*	61
START B 1999–2001	40.0/15/3.0 (2.67)	2,215	92	42.6*	72

Data compare designs of randomized clinical trials testing fraction size in adjuvant external beam radiotherapy to whole breast after local excision of early breast cancer. All trials used a control arm delivering 50 Gy in 25 fractions over 5 weeks.

* Breast conservation patients only.

Postmastectomy RT

.In our view, hypofractionation trials based predominantly on patients undergoing breast conservation surgery are informative for postmastectomy radiotherapy.

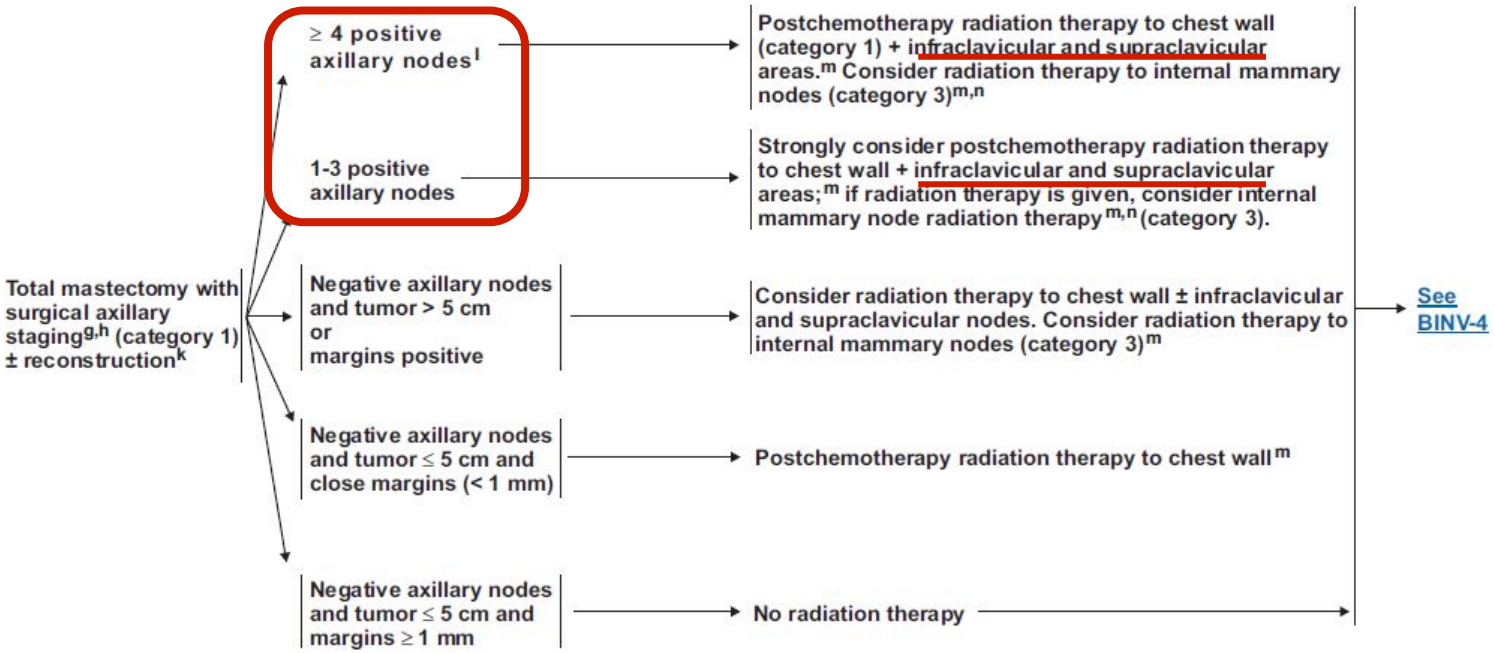
Yarnold J, 2011

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Invasive Breast Cancer

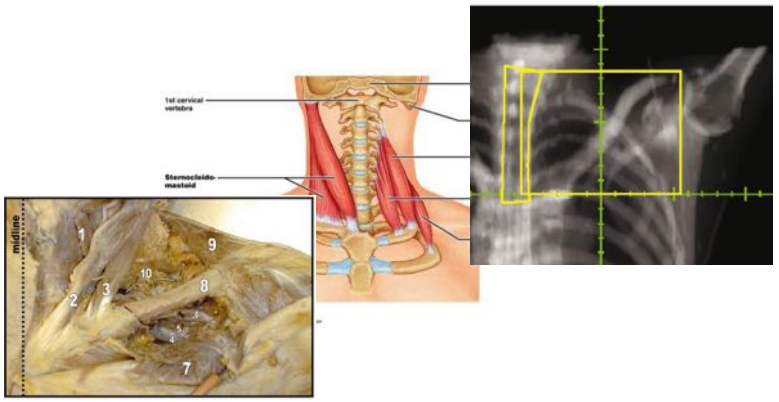
NCCN Guidelines Index
Breast Cancer Table of Contents
Staging, Discussion

LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0



Tossicità tardiva in radioterapia: Ipofrazionamento versus frazionamento convenzionale L'esperienza clinica nella mammella

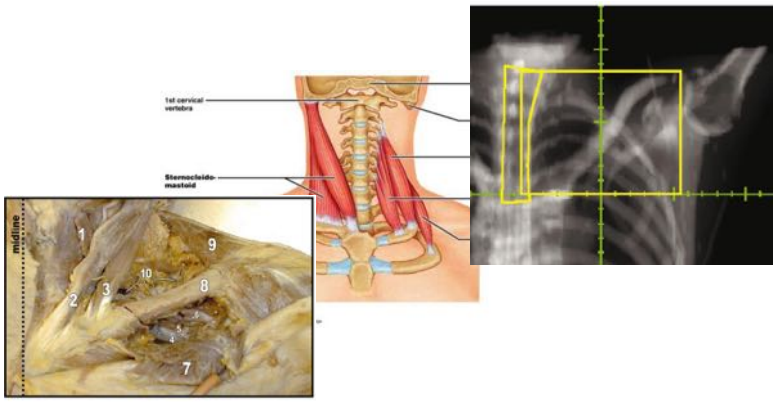
mancato controllo locale
fibrosi, retrazione, teleangiectasie mammarie
tossicità polmonare
tossicità cardiaca
plessopatia brachiale



After irradiation of the axilla and/or supraclavicular fossa, there were **no cases of brachial plexopathy** recorded in 82 patients given 40 Gy in 15 fractions in the START B trial at a median follow-up of 6.0 years

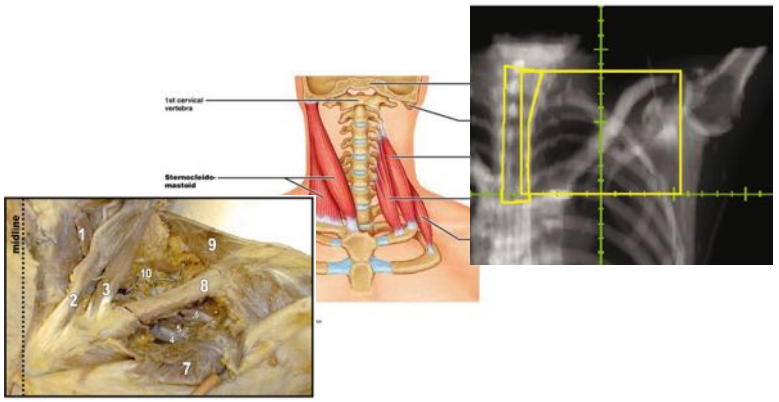
The regimen is equivalent to 47 Gy in 2.0-Gy fractions if the a/b value for brachial plexus is 2.0 Gy or to 49 Gy in 2.0-Gy fractions, if a/b = 1.0 Gy.

Yarnold, 2011



If radiotherapy centers are confident that their technique is safe when prescribing 50 Gy in 25 fractions, there will be no excess risk after 40 Gy in 15 fractions by using the same treatment position, field arrangement, dosimetry, and reference point.

Yarnold, 2011



Tossicità tardiva in radioterapia: Ipofrazionamento versus frazionamento convenzionale L'esperienza clinica nella mammella

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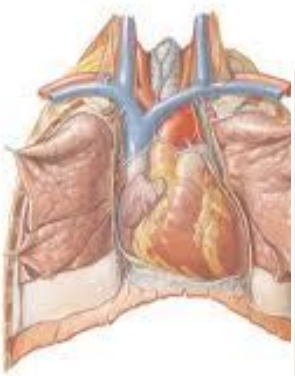
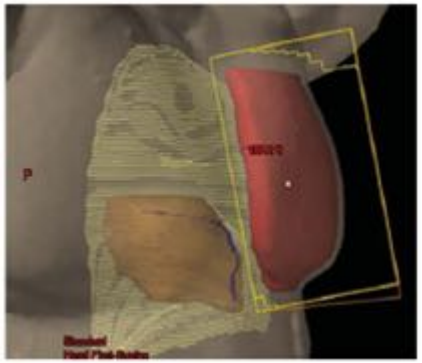




The sensitivity of lung tissue to larger fractions is a concern, but lung doses delivered by tangential fields exceed tolerance in whatever fractionation schedule is used.

START A

	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]

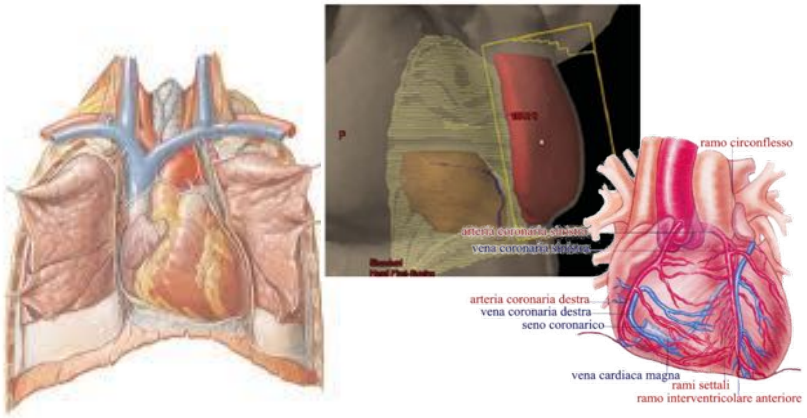
START B

	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]

A median follow-up of 5 years (START A) is too short to allow assessment of all the potential late normal tissue effects such as cardiac damage.

…….

However, the RMH/GOC pilot data (median follow-up 10 years) showed that the relative effects of different fractionation schedules remain unchanged over time.



15–20 years of follow-up will be needed to reliably measure cardiac effects.

The short-term **priority is to protect the heart** from exposure to radiotherapy, regardless of radiation schedule, since there appears to be no safe lower dose limit, however fractionated ; something that is now possible with advanced radiotherapy technologies

Tossicità tardiva in radioterapia: Ipofrazionamento versus frazionamento convenzionale L'esperienza clinica nella mammella

mancato controllo locale
fibrosi, retrazione, teleangiectasie mammarie
tossicità polmonare
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plessopatia brachiale

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0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.04.042

CLINICAL INVESTIGATION

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

BENJAMIN D. SMITH, M.D.,* SOREN M. BENTZEN, PH.D., D.SC.,† CANDACE R. CORREA, M.D.,‡ CAROL A. HAHN, M.D.,§ PATRICIA H. HARDENBERGH, M.D.,¶ GEOFFREY S. IBBOTT, PH.D.,‖ BERYL MCCORMICK, M.D., FACR.,# JULIE R. MCQUEEN, CHES., RHED.,** LORI J. PIERCE, M.D.,†† SIMON N. POWELL, M.D., PH.D.,# ABRAM RECHT, M.D.,§§ ALPHONSE G. TAGHIAN, M.D., PH.D.,¶¶ FRANK A. VICINI, M.D., FACR.,‖‖ JULIA R. WHITE, M.D.,## AND BRUCE G. HAFFTY, M.D.***

Treated with breast-conserving surgery
Age ≥50 years
pT1–2
pN0
Chemotherapy not used
Central axis inhomogeneity −7% to +7%

RMH/GOC 1986–1998

Ontario 1993–1996

START A 1999–2002

START B 1999–2001

but….
treatment planning
boost
chemotherapy

homogeneity of the dose distribution (ICRU) verify only on central axis plane

two-dimensional planning techniques without tissue heterogeneity corrections

As optimizing the homogeneity of dose in the offaxis planes as well as the central-axis plane reduces acute and late toxicities……..

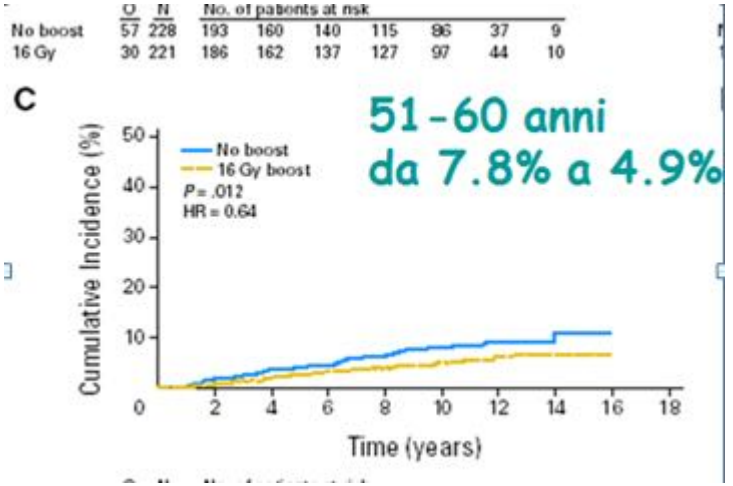
the **task force encourages** the use of **three-dimensional planning techniques** in all patients to minimize dose inhomogeneity and reduce toxicity

Smith BD, 2010 ASTRO

Boost

There were **few data** to define the indications for and toxicity of a tumor bed boost in patients treated with HF-WBI

In the Canadian study, none of the patients received a tumor bed boost, but the risk of IBTR at 10 years was only 7.5%, suggesting that potential benefit of a tumor-bed boost is likely to be small



There are no data to define the results in other study in which included patient treated with boost (RMH/START)

Smith BD, 2010 ASTRO

Boost

the ASTRO task force was **unable** to reach consensus **on the integration of** a tumor-bed boost and HF-WBI in clinical practice.

There was general agreement that the indications for when to use a boost are likely to be similar regardless of the WBI fractionation scheme employed.

The **majority** of the task force membership **supported using a tumor-bed boost in conjunction with HF-WBI** when a boost is indicated, but a minority favored using only CF-WBI in this setting.

Smith BD, 2010 ASTRO

Chemotherapy

65%–90% of patients in these trials did not receive CT

anthracyclines and taxanes were used very infrequently during the era in which those trials were conducted

Retrospective studies have not shown that chemotherapy increased the risk of side effects attributable to HF-WBI, but the numbers of patients in these studies were small and follow-up limited

The **majority** of the task force members reported that they **commonly use HF-WBI following anthracycline- or taxane-based chemotherapy in their clinical practice**

Smith BD, 2010 ASTRO

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CLINICAL INVESTIGATION

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

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Treated with breast-conserving surgery
Age ≥50 years
pT1–2
pN0
Chemotherapy not used
Central axis inhomogeneity –7% to +7%

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.

Recent randomized trials justify the routine use of modest hypofractionation for adjuvant whole-breast radiotherapy in women with early breast cancer.

The standard UK schedule of 40 Gy in 15 fractions is gentler on normal tissues than 50 Gy in 25 fractions, without evidence of inferior local tumor control.

This schedule, or 42.5 Gy in 16 fractions, can be recommended as safe and effective alternatives to 50 Gy in 25 fractions for whole-breast or postmastectomy chest wall radiotherapy.

It is unlikely that a 15- or 16-fraction regimen represents the limits of hypofractionation for whole-breast RT

Yarnold, 2011

Radiotherapy and Oncology 100 (2011) 93–100

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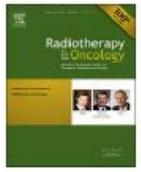


Phase III randomised trial

First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015)

The FAST Trialists group[1]

Women aged >50 years with node negative early breast cancer were randomly assigned after microscopic complete tumour resection to 50 Gy in 25 fractions versus 28.5 or 30 Gy in 5 once-weekly fractions of 5.7 or 6.0 Gy, respectively, to the whole breast.

The primary endpoint was 2-year change in photographic breast appearance.

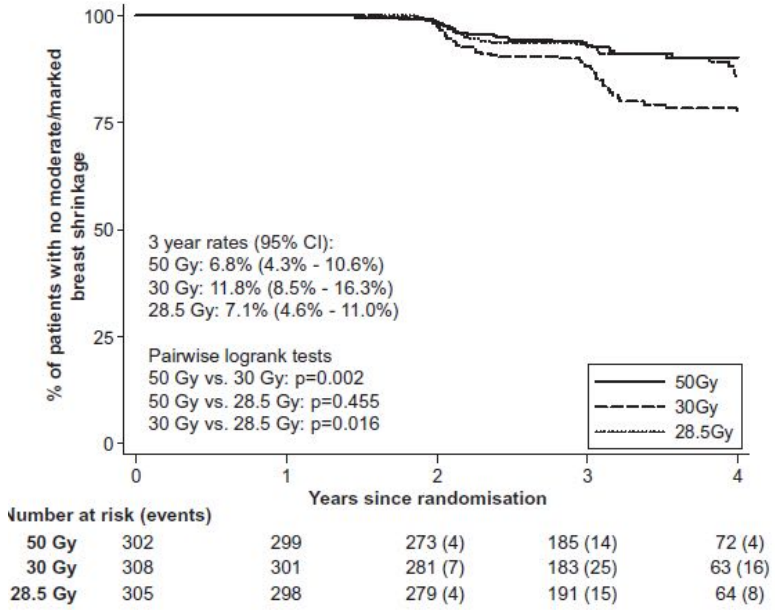
950 women were recruited from 2004 to 2007.
729 patients had 2-year photographic assessments.

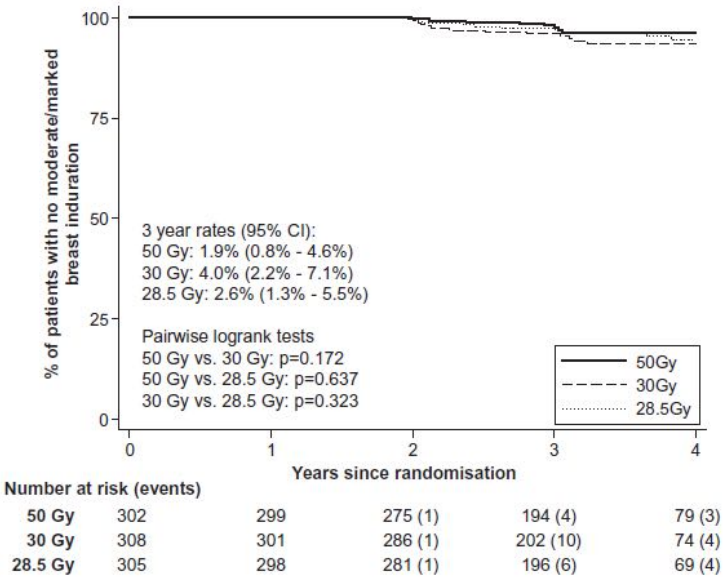
Three-year rates of physician-assessed moderate/marked adverse effects in the breast were

17.3% (13.3–22.3%, p < 0.001) for 30 Gy (6Gyx5)

11.1% (7.9–15.6%, p = 0.18) for 28.5 Gy (5.7x5)

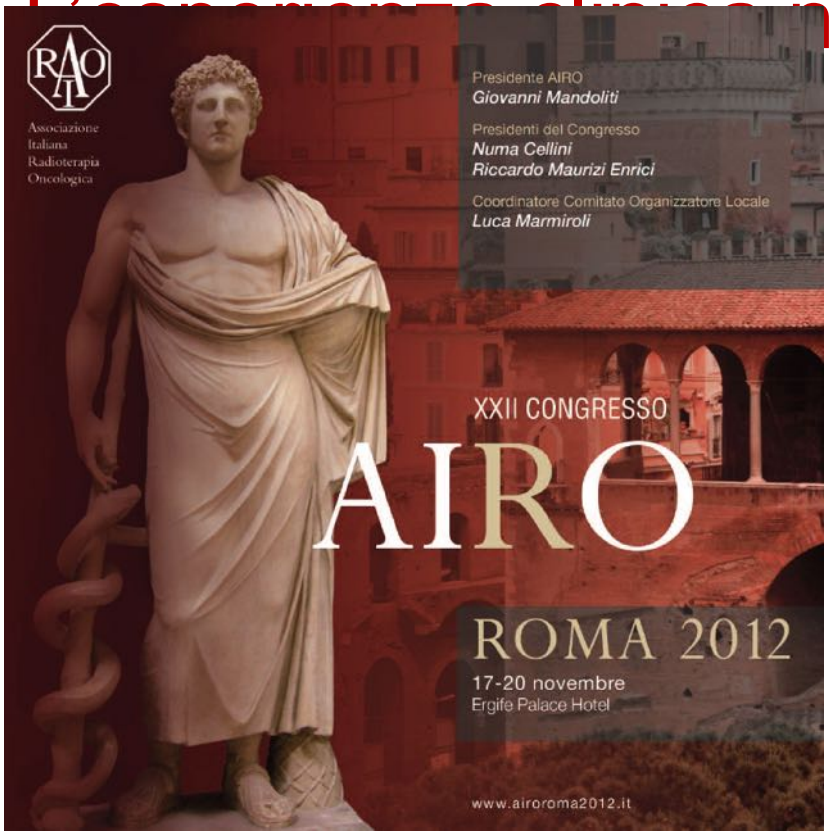
9.5% (6.5–13.7%) after 50 Gy. (2Gyx25)





Tossicità tardiva in radioterapia: ipofrazionamento versus frazionamento convenzionale

L'esperienza clinica nella mammella …….



- risultati soddisfacenti in controllo locale e risultato estetico-funzionale
- accurata definizione dello schema (BED)
- accurata pianificazione

Marina Guenzi
Genova