Hypofractionation: Advantages & Disadvantages

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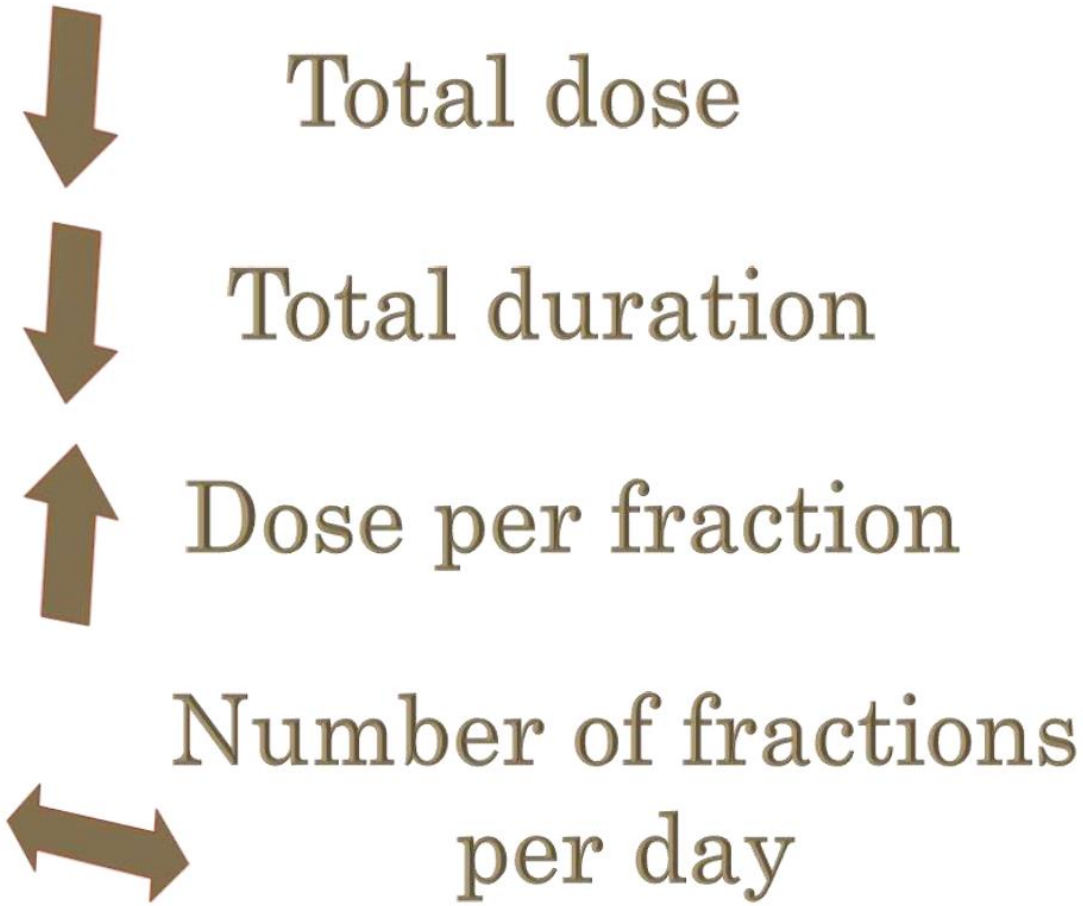
Hypofractionation: Definition

	Fractionation schedule		
	Conventional	Moderate	Extreme
Total dose (Gy)	76–80	57–70.2	38–50
Total treatment duration (weeks)	8–9	4–6	1–2
Number of fractions (n)	38–40	19–30	4–5
Dose per fraction (Gy)	1.8–2	2.4–4	6–10
Interval between fractions (days)	1	1	1–2

Conventional Fractionation

- Conventional fractionation
- It is the application of daily doses of 1.8 - 2 Gy and 5 fractions per week.
- Total dose depends on :
  - tumour
  - histology,
  - tumour
  - size
  - and localization,
  - macroscopic/microscopic disease

Hypofractionation



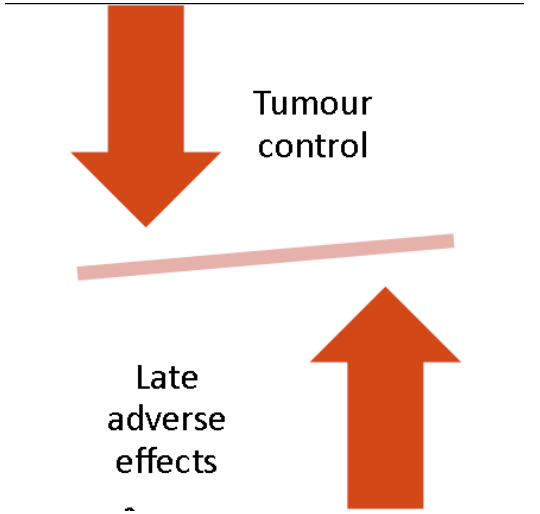
Hypofractionation: History

- Early 1900's: radiotherapy initially delivered in single/few fractions, Popularized by Gosta Forsell (Stockholm method)
- Increased toxicity, limited tumor control
- 1920-1930: experience in France with multiple fractions over longer duration in H&N cancer
- Less toxicity, increased tumor control
- Fractionation of radiation adopted based on empiric observation, Before the era of randomized trials
- Fractionated treatments becoming more popular than hypofractionated , And it was almost abandoned across world as curative treatment

Hypofractionation : Return

- In the early 1950s, the comeback of hypofractionation started quietly and came from Stockholm, the city where hypofractionation was first championed by Forsell ,50 years previously
- Lars Leksell. Leksell had-“stereotaxy.”, Working with a radiation physicist, Borge Larsson
- they created the first Gamma Knife (Elekta AB, Stockholm, Sweden).

Hypofractionation: Rationale



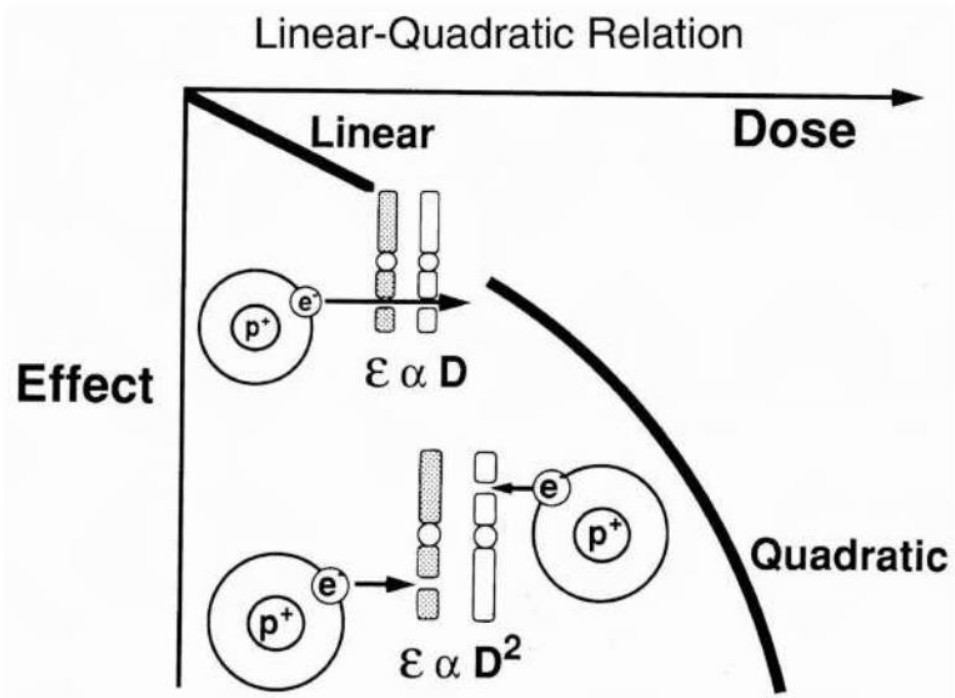
- High dose per fraction = High cell kill
- High dose per fraction = Increase late effects
- But always was preferred in palliative setting - because of logistic reasons
- But as we understand radiobiology better, hypofractionation is back For the tumors with low α/β ratio like Prostate cancer where it is Seen that cell are sensitive to dose per fraction.
- Interest also because of the newer conformal techniques like stereotactic treatments, IMRT : chance of irradiating normal tissues with high dose per fraction is less.

Hypofractionation: Radiobiology

CELL SURVIVAL CURVE

alpha is the log of number of cells sterilized *non-repairable* way per gray of ionizing radiation.

beta is the log of the number of cells sterilized in a *repairable* way per gray squared.



Hypofractionation: Radiobiology

ALPHA/BETA RATIO

- Mathematically, when $\alpha D = \beta D^2$.

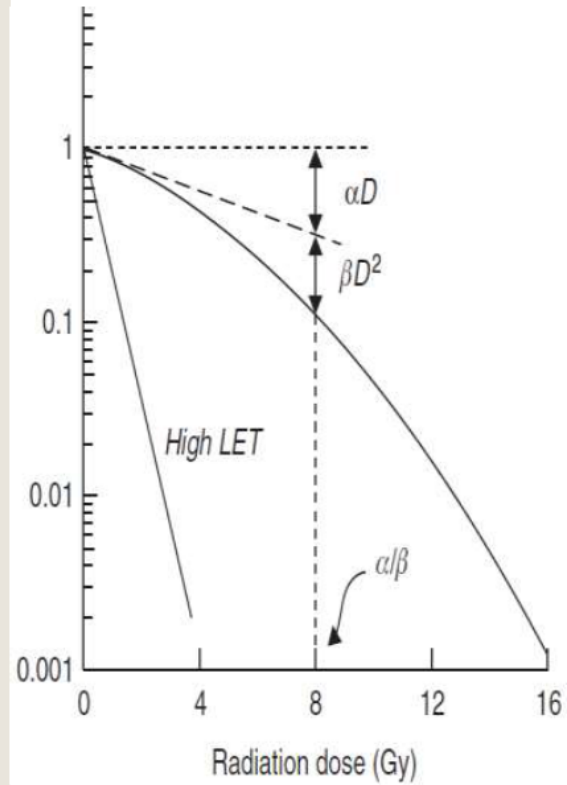
  i.e. when the two components are equally responsible for cell kill, **$D = \alpha/\beta$.**

  i.e. the dose at which the linear and quadratic components of cell killing are equal. (Unit = Gy)

  It is the ratio of "intrinsic radiosensitivity" to "repair capability" of a specified tissue.

- HIGH (>8 Gy) for rapidly proliferating tissues and most tumors (eg HNSCC, mucosa).

- SMALL (<6 Gy) for slowly proliferating tissues, including late normal-tissues and tumours like Ca prostate and Ca breast.



Hypofractionation: Why

- RADIOBIOLOGY
  - Assumption of better tumour control.
  - Alpha/beta-3-5
- LOGISTICS
  - Logistic advantages.
  - Economic favourability
- Better Tumor Imaging (e.g. MRI in prostate) & Radiation delivery (e.g. Stereotactic accuracy)

Hypofractionation: Which cancers?

- Prostate
- Breast
- Glioblastoma Multiforme (GBM)
- Bone
- Glottis

Hypofractionation: Questions for each sites

- Standard Treatment?
- Hypofractionated Treatment?
- Evidence? Quality of Evidence?
  - – ASTRO Guidelines
  - – Outcomes, Side Effects/Toxicity
  - – # of patients, randomized, length of follow-up
- Advantages & Disadvantages, Take homes

PROSTATE : Standard Treatment?

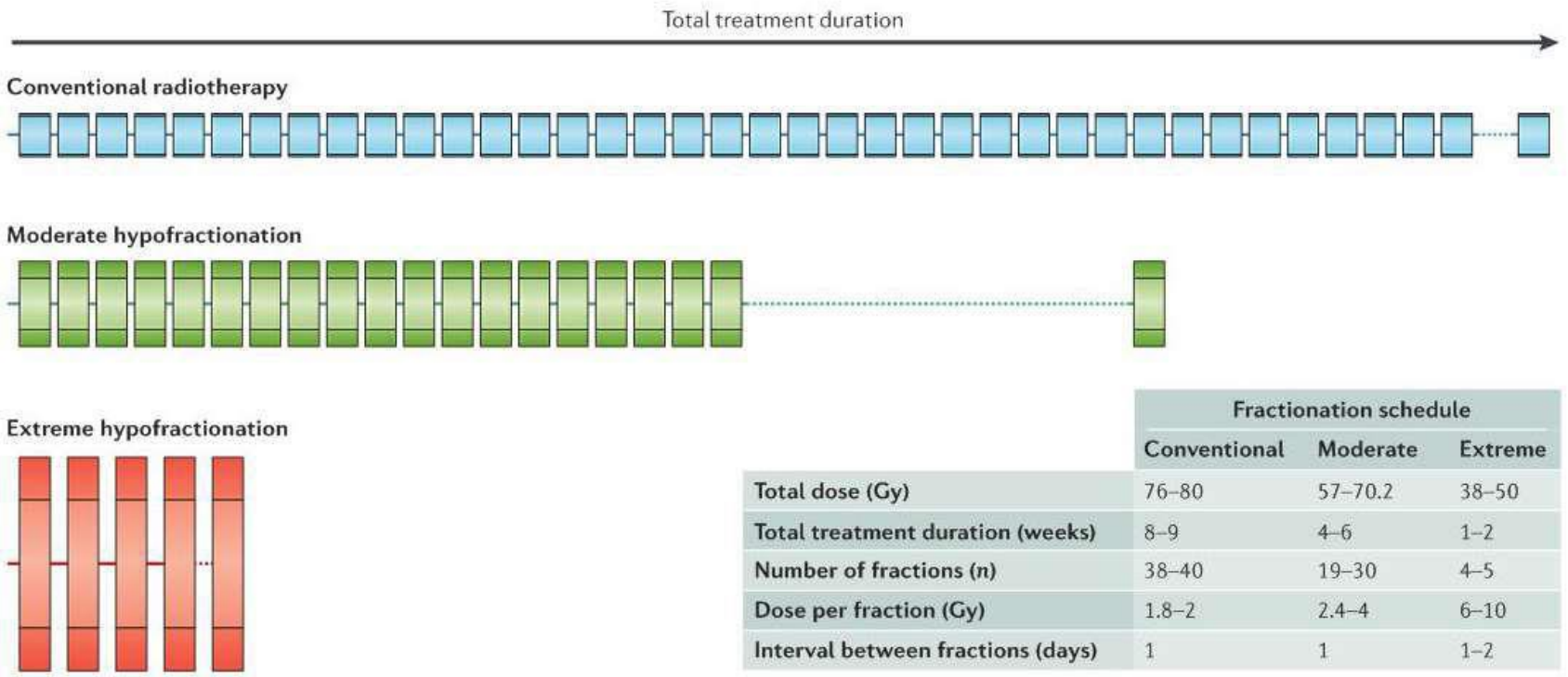


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Figure 1 | **Radiotherapy fractionation schedules for the management of patients with prostate cancer.** Fractionation of a prescribed radiation dose over several treatment sessions is used to protect nonmalignant tissues adjacent to the tumour. Technological developments have improved the precision of radiation delivery, enabling increased fraction doses and shorter treatment schedules without compromising efficacy but increasing patient compliance. Conventionally fractionated radiotherapy is usually delivered in 38–40 sessions of single 1.8–2 Gy fractions, resulting in an 8–9-week treatment duration. In moderate hypofractionation, 19–30 sessions of single 2.4–4 Gy fractions are given over a total of 4–6 weeks. Extremely hypofractionated radiotherapy consists of 4–5 treatment sessions of 6–10 Gy doses each and treatment is usually concluded after 1–2 weeks.

Prostate: Hypofractionated Treatment?

Table 1. Accumulating Evidence From Randomized Trials on Hypofractionated Therapy for Prostate Cancer

Trial, Predominant Risk Group	Conventional Dose, Gy	Hypofractionated Dose	Median Follow-up	Cancer Control Conclusions	Toxicity Comparison
PROFIT[3] (N = 1,206), intermediate risk	78	60 Gy given in 3-Gy fractions	6 years	Moderate hypofractionation noninferior to standard	Overall, no significant differences except that GI toxicity more acute for moderate hypofractionation but more later for standard fractionation
Regina Elena National Cancer Institute[4] (N = 168), mostly high risk	80	62 Gy given in 3.1-Gy fractions	9 years	Moderate hypofractionation not superior to standard	Overall, toxicity similar, but greater macroscopic hematuria for moderate hypofractionation (P = .009)
RTOG 0415[5] (N = 1,115), low to intermediate risk	73.8	70 Gy given in 2.5-Gy fractions	5.8 years	Moderate hypofractionation noninferior to standard	More grade 2 GU and GI late toxicity for moderate hypofractionation but not grade 3
CHHiP[1] (N = 3,216), intermediate risk	74	60 Gy given in 3-Gy fractions and 57 Gy given in 3-Gy fractions	62 months	Moderate hypofractionation given in 3 Gy × 20 fractions is noninferior to standard	Overall, no significant differences in toxicity, although patterns of toxicity different, with more acute toxicity for the hypofractionated group and more later toxicity for the standard fractionated group
HYPRO[6,7] (N = 820), high risk	78	64.6 Gy given in 3.4-Gy fractions in 3 fractions/week	60 months	Moderate hypofractionation not superior to standard	Noninferiority of moderate hypofractionation could not be excluded, and late grade 3 or worse toxicity significantly higher for moderate hypofractionation (P = .021)
FCCC,[8] (N = 303), mostly high risk	76	70.2 Gy given in 2.7-Gy fractions	68.4 months	Moderate hypofractionation not superior to standard	No differences in late toxicity, although for patients with preexisting urinary symptoms, greater incidence of late grade 2 or higher GU toxicity
MD Anderson[9] Cancer Center (N = 203), intermediate risk	75.6	72 Gy given in 2.4-Gy fractions	6 years	Moderate hypofractionation not superior to standard	Nonsignificant increase in late GI toxicity for moderate hypofractionation; toxicity associated with rectal irradiation dose distribution

Abbreviations: CHHiP, Conventional Versus Hypofractionated High-Dose Intensity-Modulated Radiotherapy for Prostate Cancer; FCCC, Fox Chase Cancer Center; GU, genitourinary; HYPRO, Hypofractionated Versus Conventionally Fractionated Radiotherapy for Patients With Localized Prostate Cancer; PROFIT, Prostate Fractionated Irradiation Trial; RTOG, Radiation Therapy Oncology Group.

Prostate: Evidence?

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Prostate: Quality of Evidence?

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Prostate: Quality of Evidence?

- Constraint Planning (RTOG 0415):

73.8 Gy in 41 fx

Arm 1

Normal organ limit	No more than 15% volume receives dose that exceeds	No more than 25% volume receives dose that exceeds	No more than 35% volume receives dose that exceeds	No more than 50% volume receives dose that exceeds
Bladder Constraint	80 Gy	75 Gy	70 Gy	65 Gy
Rectum Constraint	75 Gy	70 Gy	65 Gy	60 Gy
Penile Bulb	Mean dose less than or equal to 52.5 Gy			

70 Gy in 28 fx

Arm 2 (Assumes alpha-beta for rectum bladder is 3)

Normal organ limit	No more than 15% volume receives dose that exceeds	No more than 25% volume receives dose that exceeds	No more than 35% volume receives dose that exceeds	No more than 50% volume receives dose that exceeds
Bladder Constraint	79 Gy	74 Gy	69 Gy	64 Gy
Rectum Constraint	74 Gy	69 Gy	64 Gy	59 Gy
Penile Bulb	Mean dose less than or equal to 51 Gy			

- Constraints at Duke and UAB (70 Gy/28):

Table 3 Duke University current organs-at-risk dose-volume histogram constraints for 70 Gy in 28 fractions of 2.5 Gy

Organ at risk	Dose (Gy)	Volume (absolute or %)
Bladder	70	<10 cm^3
Bladder	65	15%
Bladder	40	35%
Rectum	70	<10 cm^3
Rectum	65	10%
Rectum	40	35%
Left femoral head	40	0%
Right femoral head	40	0%
Penile bulb	Mean dose <50	
Small bowel	40	1%

The clinical target volume is the prostate in low-risk and favorable intermediate-risk patients and includes 10 mm of proximal seminal vesicles in patients with unfavorable intermediate-risk disease. A 3-dimensional expansion of the clinical target volume by 4 to 10 mm is used to create the planning target volume (PTV). A simultaneous boost technique is used to deliver 58.8 Gy in 28 fractions to the PTV including the proximal seminal vesicles. The maximum dose to the PTV cannot exceed the prescription dose by more than 7; up to 10% is a minor, acceptable variation, and >10% is a major, unacceptable variation.

Prostate: Take homes

Advantages

- Prostate hypofractionation is a reasonable treatment option
- Non-Inferior to standard fractionation
- Shorten treatment duration

Disadvantages

- Studies not long enough, Awaiting long-term follow-up :Need 10 year data?
- More side effects with hypofractionation?
- More long-term side effects with standard treatment?

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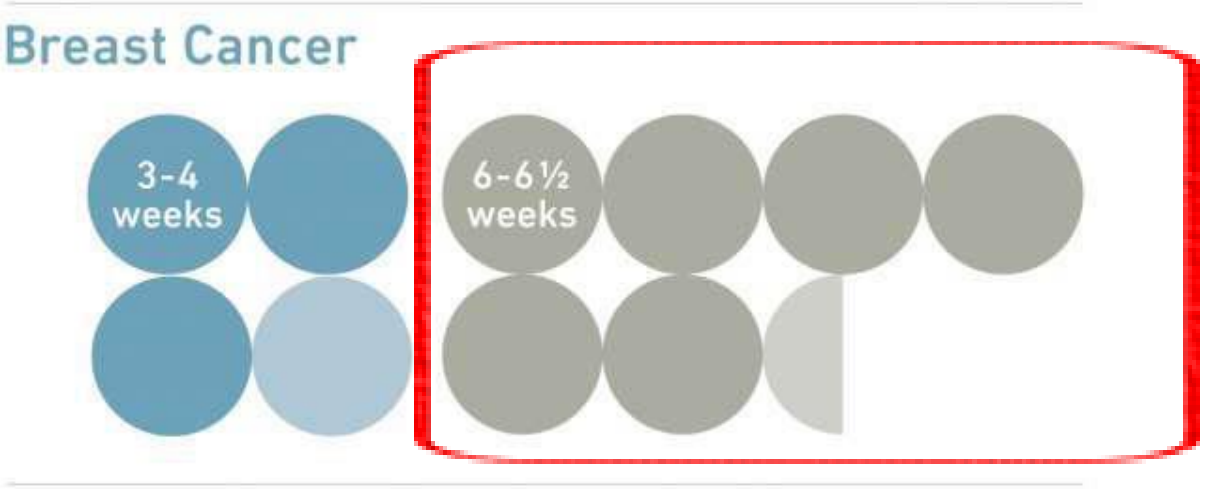
E D I T O R I A L

Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Less Cost at the Expense of More Genitourinary Toxicity Is a Concerning But Testable Hypothesis

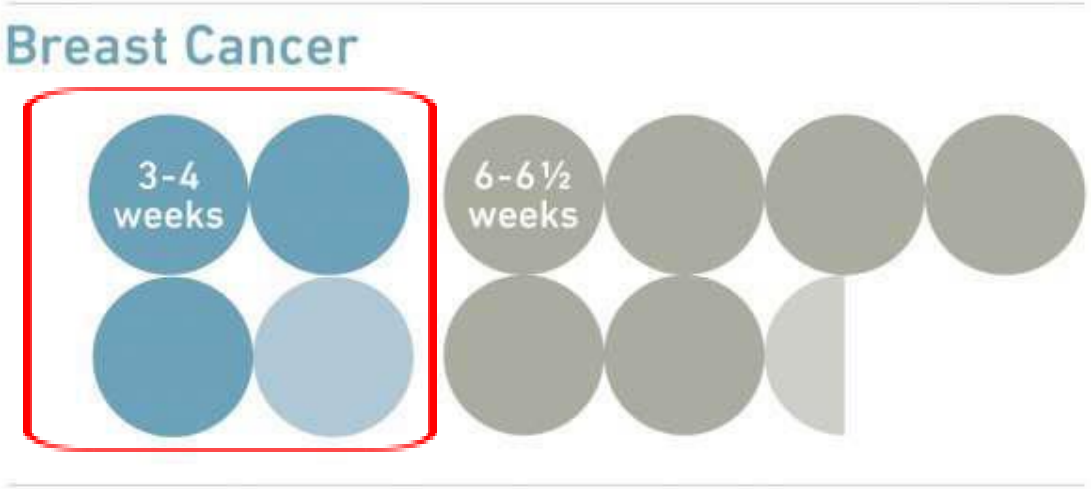
BREAST : Standard Treatment?

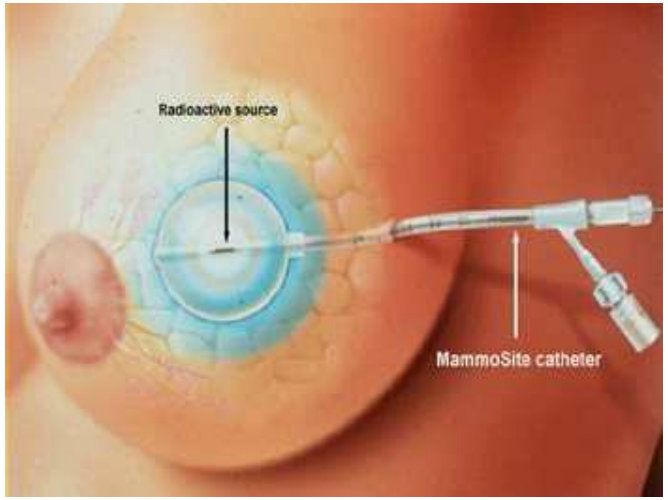
- 23-25 2 Gy fractions to 46-50 Gy, ± 5-8 fraction boost of 10-16 Gy

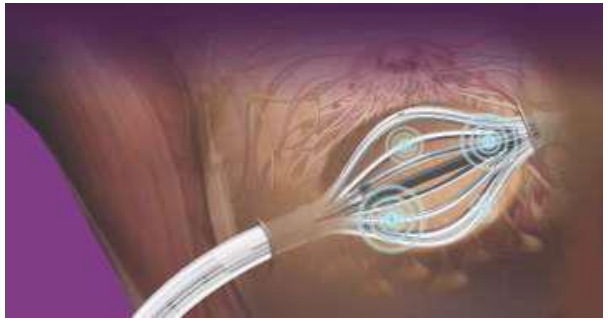


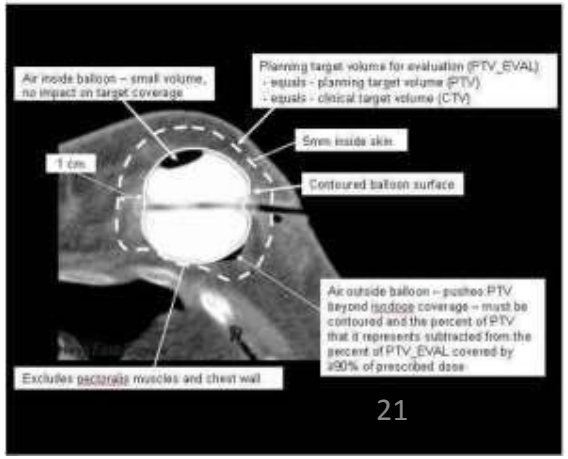
BREAST : Hypofractionated Treatment?

- 40-42.5 Gy in 15/16 fractions (2.66 Gy/fx), ± 4-5 fraction boost of 10-12.5 Gy
- Accelerated Partial Breast Irradiation (APBI): 34 Gy in 10 fractions BID, 1 week









Breast: Evidence?

- EBRT Hypofractionation:

Table 4. Characteristics of patients enrolled on clinical trials comparing hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation

	Canada (18, 19, 21) $N = 1,234$		RMH/GOC (17, 20) $N = 1,410$		START A (10) $N = 2,236$		START B (16) $N = 2,215$	
	n	%	*n*	%	*n*	%	*n*	%
Treated with breast-conserving surgery	1,234	100%	1,410	100%	1,900	85%	2,038	92%
Age ≥50 years	929	75%	987	70%	1,727	77%	1,758	79%
pT1–2	1,234	100%	1,324	94%	Majority		Majority	
pN0	1,234	100%	564	40%	1,547	69%	1,635	74%
Chemotherapy not used	1,098	89%	1,214	86%	1,443	65%	1,724	78%
Central axis inhomogeneity −7% to +7%	1,234	100%	1,410	100%	2,236	100%	2,215	100%
High tumor grade	233	19%			629	28%	509	23%

Abbreviations: CF = conventional fractionation; HF = hypofractionation; RMH/GOC = Royal Marsden Hospital/Gloucester Oncology Center; START = standardization of breast radiotherapy; WBI = whole- breast irradiation.

Breast: Quality of Evidence?

Table 5. Oncologic outcomes for randomized clinical trials comparing hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation

			Arm				IBTR		Local-regional recurrence		Disease-free survival		Overall survival	
Trial	Median Follow- up (years)	Time point for outcome reporting (years)	Dose (Gy)	# Fr	# Days	*N*	%	*p*	%	*p*	%	*p*	%	*p*
Canada (18, 19, 21)	12	10	50	25	35	612	7.5						84.4	
			42.5	16	22	622	7.4	<.001*					84.6	0.79
RMH/GOC (17, 20)	9.7	10	50	25	35	470	12	†						
			42.9	13	35	466	9.6	†						
			39	13	35	474	15	†						
START A (10)	5.1	5	50	25	35	749	3.2		3.6‡		86		89	
			41.6	13	35	750	3.2	0.74	3.5‡	0.86§	88	0.33§	89	0.81§
			39	13	35	737	4.6	0.40	5.2‡	0.35§	85	0.33§	89	0.99§
START B (16)	6.0	5	50	25	35	1105	3.3		3.3‡		86		89	
			40	15	21	1110	2.0	0.21	2.2‡	0.35	89	0.02	92	0.03

Breast: ASTRO Guidelines (2010)

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.

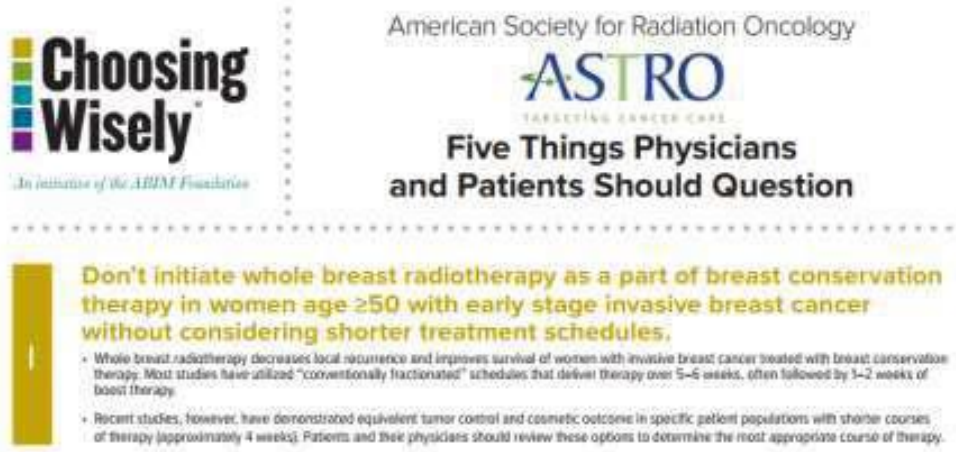
Breast EBRT Hypofractionation: Take Home

Advantages

- Complete RT faster
- Compete with other therapies
- ?Increased compliance

Disadvantages

- Not “tried and true”
- Only certain cases
- Not for post-mastectomy or nodal RT



Breast: APBI Evidence?

TABLE. Key Accelerated Partial-Breast Irradiation Studies

	Study Type	Patients (n)	Median Follow-Up (months)	Technique	Local Recurrence	Toxicity
Interstitial						
National Institute of Oncology, Hungary	Randomized	258	122	HDR (n=88)/ electrons (n=40)	10-year LR (5.1% WBI vs. 5.9% PBI, NS)	Improved excellent/good cosmesis with partial breast 81% vs 63%
GEC-ESTRO	Randomized	1184	78	HDR/PDR	5 year LR (0.9% WBI vs. 1.4% APBI, NS)	Reduced breast pain and trend for reduced grade 2-3 late skin toxicity with APBI
RTOG 9517	Prospective	99	73	HDR (n=66)/ LDR (n=33)	5-year LR 3%/6% (HDR/LDR)	13% grade 3 skin toxicity, 37% skin dimpling, 45% fibrosis, 45% telangiectasias, 15% symptomatic fat necrosis, 66% excellent/good cosmesis
Harvard University	Prospective	50	134	LDR (dose-escalation)	12-year LR 15%	67% excellent/good cosmesis, 35% fat necrosis, 34% telangiectasias, 22% grade 3/4 skin toxicity
William Beaumont Hospital	Matched-Pair Analysis	199	127	HDR	12-year LR (3.8% WBI vs 5% APBI, NS), no difference in RR, DFS, CSS, OS	
Applicator						
MammoSite Initial Trial	Prospective	70 (43 treated)	65 (n=36)	Single-Lumen	5-year LR 0%	9.3% infection, 33% seroma, 12% symptomatic seroma, 4 patients with fat necrosis, 83% excellent/good cosmesis
MammoSite Registry	Prospective	1449	63	Single-Lumen	5-year LR 3.8% (3.7% invasive, 4.1% DCIS)	91% excellent/good cosmesis, 9.6% infection, symptomatic seroma 13%, 13% telangiectasias, 2.5% fat necrosis
External Beam						
NSABP B-39/RTOG 0413; 2011	Randomized	1367	37	3D-CRT		3% Grade 3+ fibrosis
RAPID	Randomized	2135	36	3D-CRT		Increased adverse cosmesis with APBI, Grade 3 toxicity 1.4%, increased grade 1/2 toxicity with APBI
University of Florence	Randomized	520	60	IMRT	5-year IBTR 1.5%, no difference with WBI	Reduced acute and chronic toxicity with APBI, improved cosmetic outcome with APBI
RTOG 0319	Prospective	52	63	3D-CRT	4-year LR 6%	64% excellent/good cosmesis at 3 years, 5.8% grade 3 toxicity
William Beaumont Hospital	Retrospective	192	56	3D-CRT	5-year LR 0%	81% excellent/good cosmesis, 7.5% grade 3 fibrosis, 7.6% telangiectasias
Tufts University	Retrospective	60	15	3D-CRT		8% grade 3/4 fibrosis, 82% excellent/ good cosmesis
University of Michigan	Prospective	34	60	3D-CRT	5-yr LR 3%	73% excellent/good cosmesis, 0% grade 3 fibrosis

Breast: APBI Quality of Evidence

Published randomized trials comparing APBI and WBI

	National Institute of Oncology—Hungary	GEC-ESTRO	University of Florence	Barcelona	RAPID	NSABP B39
Years of accrual	1998–2004	2004–2009	2005–2013	—	2006–2011	2005–2013
Number of patients	258	1184	520	102	2135	4300 (1386 reported on)
Inclusion criteria	pT1, pN0-1mi, Grade ½, nonlobular, negative margins, age >40 y (2001)	pT1-2 (<3 cm), pN0-1mi, margins >2 mm, no LVSI, IDC/ILC/DCIS, age >40 y	pT1-2 (<2.5 cm), negative margins, clips placed in tumor bed, age >40 y	pT1-2 (<3 cm), pN0, Grade ½, negative margins, IDC, age >60 y	pT1-2 (<2 cm), pN0, negative margins, IDC/DCIS, age >40 y	pT1-2 (<3 cm), pN0-1 (no ECE, cN0), negative margins, adenocarcinoma or DCIS, age >18 y
APBI technique	Interstitial/electron	Interstitial	IMRT	3D-CRT	3D-CRT	3D-CRT (for subset analysis)
Dose/fractionation	36.4 Gy/7 fractions (interstitial); 50 Gy/25 fractions (electrons)	32 Gy/8 fractions, 30.2 Gy/7 fractions (HDR)/50 Gy (PDR)	30 Gy/5 fractions	37.5 Gy/10 fractions	38.5 Gy/10 fractions	38.5 Gy/10 fractions (3D-CRT cohort)
Followup (y)	10.2	6.6	5.0	5.0	3.0	3.5
Local recurrence	5.9% APBI vs. 5.1% WBI	1.4% APBI vs. 0.9% WBI	1.5% APBI vs. 1.5% WBI	No local recurrences	NR	NR
Toxicity	Improved cosmesis APBI (81% vs. 63%)	APBI reduced breast pain, trend reduced late Grade 2–3 skin toxicity	Reduced acute/chronic toxicity with APBI, improved cosmesis	Lower rates of late toxicity with APBI, no difference in cosmesis	APBI increased Grade ½ toxicity, adverse cosmesis	Grade 2 fibrosis 12%, Grade 3 3%, no Grade 4/5

GEC-ESTRO = Groupe Europeen de Curietherapie; RAPID = Randomized Trial of Accelerated Partial Breast Irradiation; NSABP = National Surgical Adjuvant Breast and Bowel Project; LVSI = lymphovascular space invasion; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; DCIS = ductal carcinoma in situ; ECE = extracapsular extension; IMRT = intensity-modulated radiation therapy; 3D-CRT = 3-dimensional conformal radiotherapy; HDR = high dose rate; PDR = pulsed dose rate; APBI = accelerated partial breast irradiation; WBI = whole breast irradiation.

Breast: APBI Guidelines

Clinical guidelines for use of AWBI and APBI

	ASTRO	ASTRO	ABS	GEC-ESTRO	ASBS
Technique	AWBI	APBI	APBI	APBI	APBI
Age	50 y or older	60 y or older	50 y or older	50 y or older	45 y or older
Size	pT1-2	pT1	pT1-2 (≤3 cm)	pT1-2 (≤3 cm)	pT1-2 (≤3 cm)
Nodal status	pN0	pN0	pN0	pN0	pN0
Histology	—	IDC/favorable	IDC/ILC/DCIS	IDC	IDC/DCIS
Margins		Negative	Negative	Negative	Negative
Estrogen receptor	—	Positive	Any	Any	—
LVSI	—	Negative	Negative	Negative	—
Chemotherapy	Not receiving chemotherapy	No neoadjuvant	—	No neoadjuvant	—
Endocrine therapy	—	—	—	—	—
Dose	+/−7%	—	—	—	—
Grade	—	Any	—	Any	—

Breast: APBI Take Homes

Advantages

- Breast hypofractionation is a reasonable treatment option for appropriate patients
- • Acute side effects may be better with hypofractionation
- Complete RT in 1 week
- Convenient

Disadvantages

- New Procedure (compared to whole breast irradiation)
- ?Worse cosmesis
- New, not “tried and true”
- Only certain cases (T1, >50 yo, negative margins) Not for advanced cases, e.g. regional nodal RT or post-mastectomy
- Benefit to treatment in this cohort?
- Final RTOG/NSABP results not out

GBM: Standard Treatment?

- 60 Gy in 30 fractions with concurrent TMZ

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

GBM: Hypofractionated Treatment?

- Suggested as option if >60 yo and/or lower KPS
- Various Regimens:
- 3 week regimen: 40 Gy in 15 fractions
- 2 week regimen: 34 Gy in 10 fractions
- 1 week regimen: 25 Gy in 5 fractions

GBM: Evidence?

- 3 week option: 40 Gy x 15 fractions
- >60, KPS >50

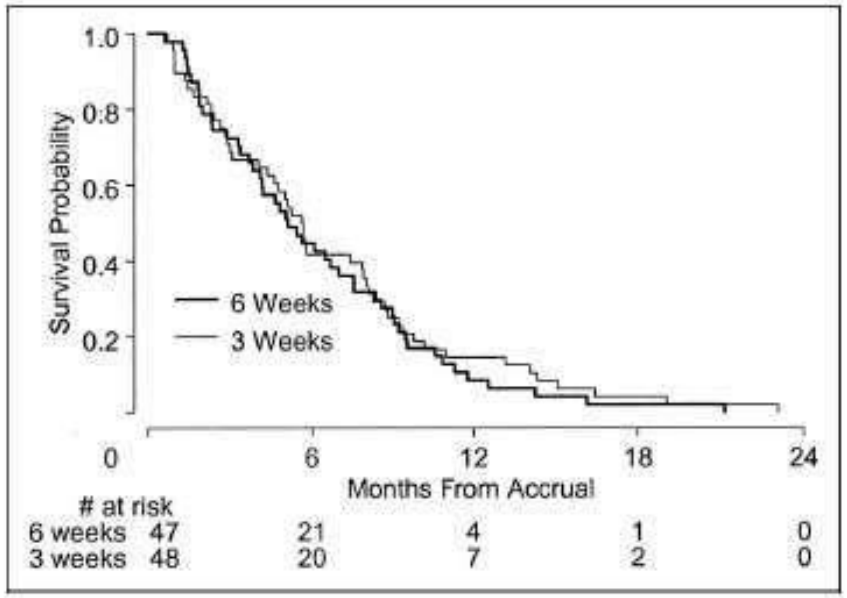


Fig 1. Overall survival from randomization by treatment group. There was no difference in the overall survival between the standard 6-week (thick line) versus abbreviated 3-week (thin line) course of radiation therapy (Log-rank test, $P = .57$).

Results

All patients had died at the time of analysis. Overall survival times measured from randomization were similar at 5.1 months for standard RT versus 5.6 months for the shorter course (log-rank test, $P = .57$). The survival probabilities at 6 months were also similar at 44.7% for standard RT versus 41.7% for the shorter course (lower-bound 95% CI, −13.7). KPS scores varied markedly but were not significantly different between the two groups (Wilcoxon test, $P = .63$). Low completion rates of the FACT-Br (45%) precluded meaningful comparisons between the two groups. Of patients completing RT as planned, 49% of patients (standard RT) versus 23% required an increase in posttreatment corticosteroid dosage (χ^2 test, $P = .02$).

GBM: Evidence?

- 2 week option: 34 Gy x 10 fractions
- – >60, KPS >50

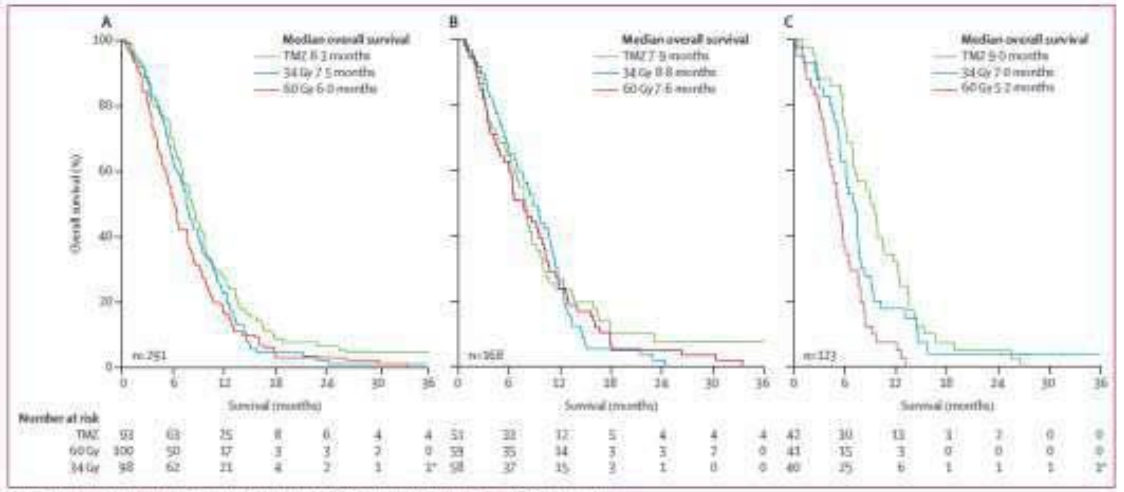


Figure 2: Kaplan-Meier analysis of overall survival in patients randomised across three treatment groups

(A) All patients. (B) Patients aged 60–70 years. (C) Patients older than 70 years. TMZ=temozolomide. 34 Gy=hypofractionated radiotherapy. 60 Gy=standard radiotherapy. *Patient censored at 25 months.

Findings 342 patients were enrolled, of whom 291 were randomised across three treatment groups (temozolomide n=93, hypofractionated radiotherapy n=98, standard radiotherapy n=100) and 51 of whom were randomised across only two groups (temozolomide n=26, hypofractionated radiotherapy n=25). In the three-group randomisation, in comparison with standard radiotherapy, median overall survival was significantly longer with temozolomide (8·3 months [95% CI 7·1–9·5; n=93] *vs* 6·0 months [95% CI 5·1–6·8; n=100], hazard ratio [HR] 0·70; 95% CI 0·52–0·93, p=0·01), but not with hypofractionated radiotherapy (7·5 months [6·5–8·6; n=98], HR 0·85 [0·64–1·12], p=0·24). For all patients who received temozolomide or hypofractionated radiotherapy (n=242) overall survival was similar (8·4 months [7·3–9·4; n=119] *vs* 7·4 months [6·4–8·4; n=123]; HR 0·82, 95% CI 0·63–1·06; p=0·12). For age older than 70 years, survival was better with temozolomide and with hypofractionated radiotherapy than with standard radiotherapy (HR for temozolomide *vs* standard radiotherapy 0·35 [0·21–0·56], p<0·0001; HR for hypofractionated *vs* standard radiotherapy 0·59 [95% CI 0·37–0·93], p=0·02). Patients treated with temozolomide who had tumour *MGMT* promoter methylation had significantly longer survival than those without *MGMT* promoter methylation (9·7 months [95% CI 8·0–11·4] *vs* 6·8 months [5·9–7·7]; HR 0·56 [95% CI 0·34–0·93], p=0·02), but no difference was noted between those with methylated and unmethylated *MGMT* promoter treated with radiotherapy (HR 0·97 [95% CI 0·69–1·38]; p=0·81). As expected, the most common grade 3–4 adverse events in the temozolomide group were neutropenia (n=12) and thrombocytopenia (n=18). Grade 3–5 infections in all randomisation groups were reported in 18 patients. Two patients had fatal infections (one in the temozolomide group and one in the standard radiotherapy group) and one in the temozolomide group with grade 2 thrombocytopenia died from complications after surgery for a gastrointestinal bleed.

GBM: Evidence?

- 1 week option: 25 Gy x 5 fractions
- >60, KPS >50

Patients and Methods

Between 2010 and 2013, 98 patients (frail = age ≥ 50 years and Karnofsky performance status [KPS] of 50% to 70%; elderly and frail = age ≥ 65 years and KPS of 50% to 70%; elderly = age ≥ 65 years and KPS of 80% to 100%) were prospectively randomly assigned to two arms in a 1:1 ratio, stratified by age (< and ≥ 65 years old), KPS, and extent of surgical resection. Arm 1 received short-course radiotherapy (25 Gy in five daily fractions over 1 week), and arm 2 received commonly used radiotherapy (40 Gy in 15 daily fractions over 3 weeks).

Results

The short-course radiotherapy was noninferior to commonly used radiotherapy. The median overall survival time was 7.9 months (95% CI, 6.3 to 9.6 months) in arm 1 and 6.4 months (95% CI, 5.1 to 7.6 months) in arm 2 ($P = .988$). Median progression-free survival time was 4.2 months (95% CI, 2.5 to 5.9) in arm 1 and 4.2 months (95% CI, 2.6 to 5.7) in arm B ($P = .716$). With a median follow-up time of 6.3 months, the quality of life between both arms at 4 weeks after treatment and 8 weeks after treatment was not different.

Conclusion

There were no differences in overall survival time, progression-free survival time, and quality of life between patients receiving the two radiotherapy regimens. In view of the reduced treatment time, the short 1-week radiotherapy regimen may be recommended as a treatment option for elderly and/or frail patients with newly diagnosed glioblastoma.

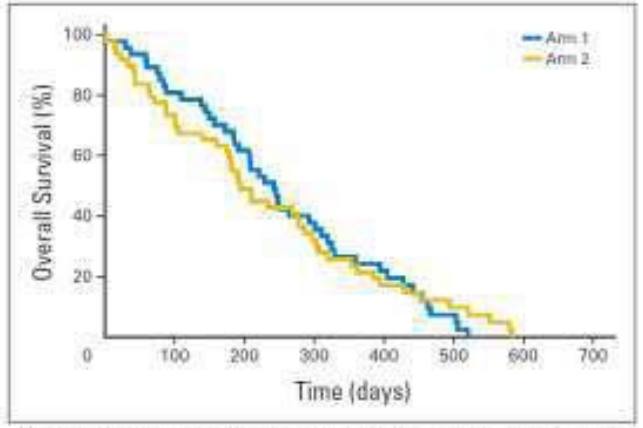


Fig 2. Overall survival (OS). Kaplan-Meier plots of OS according to the treatment arm (arm 1 = short-course radiotherapy: 25 Gy in five daily fractions; arm 2 = commonly used radiotherapy: 40 Gy in 15 daily fractions). Comparison of median OS showed no statistically significant difference between arms (7.9 v 6.4 months in arms 1 and 2, respectively; P = .988).

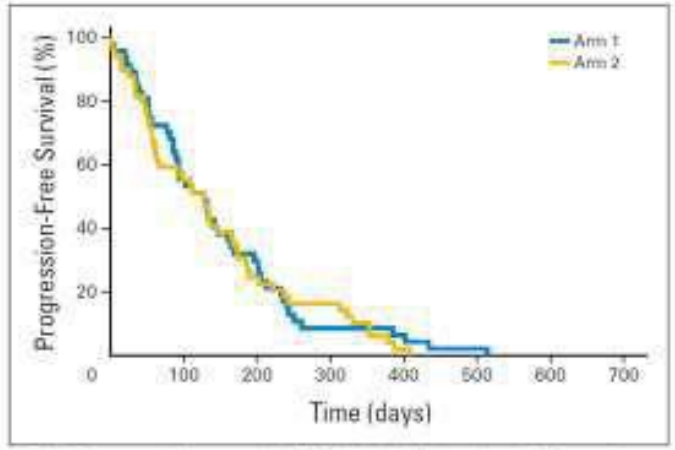


Fig 3. Progression-free survival (PFS). Kaplan-Meier plots of PFS according to the treatment arm (arm 1 = short-course radiotherapy: 25 Gy in five daily fractions; arm 2 = commonly used radiotherapy: 40 Gy in 15 daily fractions). Comparison of median PFS showed no statistically significant difference between arms (4.2 v 4.2 months in arms 1 and 2, respectively; P = .716).

GBM: Quality of Evidence

- 3 randomized trials for each 3-, 2-, and 1-week regimen
- Smaller numbers (n=100, n=342, and n=98)

GBM: Take Homes

Advantages

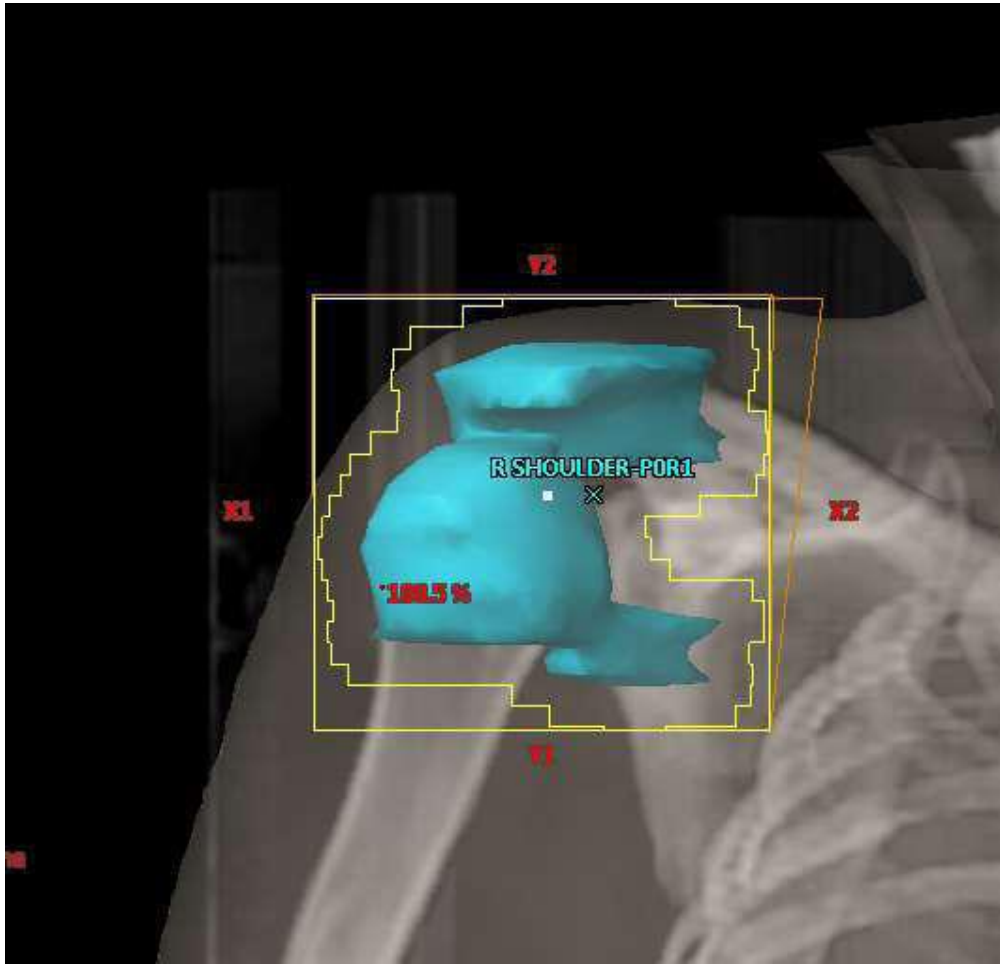
- effective treatment for patients for patients that are not good candidates for 6 weeks of RT
- Allows completion of RT
- Similar outcomes in selected patients
- ?Increased compliance

Disadvantages

- patients may be more frail requiring more assistance with completing treatment
- Potentially undertreating patients
- Age only surrogate for performance status?

Bone Mets: Standard Treatment?

- 30 Gy in 10 fractions
- 20 Gy in 5 fractions



Hypofractionated Treatment?

- 8 Gy x 1 fraction

Bone Mets: Evidence?

- RTOG 9714
- 30 Gy/10 vs 8 Gy/1
- Primary outcome: Pain at 3 mo
- Grade 2-4 acute toxicity:
- 30-Gy arm (17%)
- 8-Gy arm (10%)
- P= 0.002

Table 5. Response to treatment at 3 months, as measured by the Brief Pain Inventory worst pain score, showing the response by treatment arm for each stratification variable

Response by stratification variable	No. of patients (%) 8-Gy arm (n = 288)	30-Gy arm (n = 285)	P*
No. of painful sites			.550
Solitary			
Complete	29 (18)	32 (21)	
Partial	85 (52)	79 (51)	
Stable	40 (24)	33 (21)	
Progressive	11 (7)	12 (8)	
Multiple			
Complete	15 (12)	19 (15)	
Partial	58 (47)	58 (45)	
Stable	34 (28)	36 (28)	
Progressive	16 (13)	16 (12)	
Treatment site			.547
Weight bearing			
Complete	22 (14)	34 (22)	
Partial	80 (50)	74 (47)	
Stable	44 (27)	36 (23)	
Progressive	15 (9)	14 (9)	
Non–weight bearing			
Complete	22 (17)	17 (13)	
Partial	62 (49)	63 (50)	
Stable	30 (24)	33 (26)	
Progressive	13 (10)	14 (11)	
Pretreatment Worst Pain Score			.603
5–6			
Complete	17 (20)	13 (18)	
Partial	28 (34)	28 (38)	
Stable	25 (30)	20 (27)	
Progressive	13 (16)	12 (16)	
7–10			
Complete	23 (12)	36 (18)	
Partial	113 (57)	109 (53)	
Stable	48 (24)	49 (24)	
Progressive	13 (7)	10 (5)	
<5 with ≥60 mg/day morphine			
Complete	4 (50)	2 (25)	
Partial	1 (13)	0	
Stable	1 (13)	0	
Progressive	2 (25)	6 (75)	
Bisphosphonate use			.547
No			
Complete	32 (16)	41 (19)	
Partial	97 (48)	97 (46)	
Stable	53 (26)	51 (24)	
Progressive	21 (10)	22 (10)	
Yes			
Complete	12 (14)	10 (14)	
Partial	45 (53)	40 (54)	
Stable	21 (25)	18 (24)	
Progressive	7 (8)	6 (8)	

*The Wilcoxon–Mann–Whitney test was used for comparison of treatment groups. All statistical tests were two-sided.

Bone Mets: Quality of Evidence?

- RTOG 9714
- Prospective, RCT, 455 patients
- Dutch trial: 1171, similar results

Bone Mets: Take Homes

Advantages

8 Gy x 1 fraction is reasonable option for patients who cannot undergo 10 fractions

– Live far away

– Poor performance status

Quicker

Pain control appears equivalent

Disadvantages:

– Higher re-treatment rate with 8Gy arm (18% v 9%, $p<0.001$)

-May have flair of pain in first few days but should resolve after 1-2 days

CONCLUSIONS

- Use of hypofractionation for each site has its own advantages & disadvantages
- Evidence is rapidly developing in favor of use of hypofractionation in various sites
- Hypofractionation is a well-studied radiation treatment for Prostate, Breast, GBM, and Bone Metastases
- Using hypofractionated radiation depends on appropriate patient selection and patient preference