Morbidities of Hypofractionation: Management

Dr. Naveen P Kumar

- What is the relevance of this topic?

- Why are we interested in the toxicity of hypofractionated regimen???

- Acute vs late reactions

Early reactions	Late reactions
Expressed in weeks or up to a few months after exposure	expressed months to years after exposure
damage to parenchymal cells	damage to connective tissue cells and supporting tissues
usually seen in cell-populations with a high cell turn over, such as mucosal membranes, skin	Seen in cell populations with low rates of cell turnover like the nervous tissues
usually heal rapidly and completely	Late effects are chronic, and usually progressive

- Hypofractionated regimens have more of late effects..

- Why??
- LQ model - > β kill , low α/β ratio
- Lower a/b ratios imply a greater change in EQD2 through hypofractionation

- Threaten the therapeutic ratio..
- Jeopardize the benefits of hypofractionation!!

- Hence need to understand toxicity, ways to minimize it, recognize it early and manage it so that it doesn’t affect the quality of life of the patient

General considerations

- Patient selection-Justify the use of hypofractionated regimens- knowledge of radiobiology, tumour biology

- Better immobilization and adherence to standard contouring guidelines
- Peer review of contours, help of radiologists
- Better motion management strategies
- Use conformal and better techniques of planning and evaluation.

- AAPM TG-101
- UK SABR consortium guidelines 2017 and 2022
- HyTEC (High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic)
- ICRU Report 91

•

The concept of biologically normalized dose !!

- Normal tissue tolerance doses with conventional fractionation cannot be extrapolated to hypofractionated regimens
- Prospective data is sparse

- Use bio effect measures.
- Convert the physical dose distribution to a biologically normalized dose distribution and to find out dose that produce the same biological effect.
  - BED (Biological Effective Dose)
  - NTD (Normalised Tumour Dose)
  - EUD (Equivalent Uniform Dose)

- Every dose regimen has early effects and late effects
- Early effects -> total dose and total duration of treatment
- Late effects -> dose per fraction

Hypofractionation and Acute Toxicity

- Overall treatment time (OTT)
  - Assuming the use of daily fractions, a hypo fractionated regimen OTT will be shorter than its conventionally fractionated comparator, potentially worsening acute toxicity

- Equivalent Dose in 2 Gy fraction
  - Hypofractionated regimens designed for isoeffectiveness to an end point with a low a/b ratio (e.g. late toxicity) will have a lower EQD2 for acute toxicity (a lower total dose).

- Hypofractionation therefore typically produces two competing effects on acute toxicity:
  - increasing it through acceleration
  - decreasing it through lower EQD2

- The volume treated
  - Larger normal tissue volumes irradiated = more acute toxicity

Hypofractionation and late toxicity

- EQD2 for late reactions
  - Late toxicity end points, often dose-limiting, are characterised by lower a/b ratios than acute toxicities.
  - Small changes in dose /# can significantly increase the EQD2 for late toxicity.

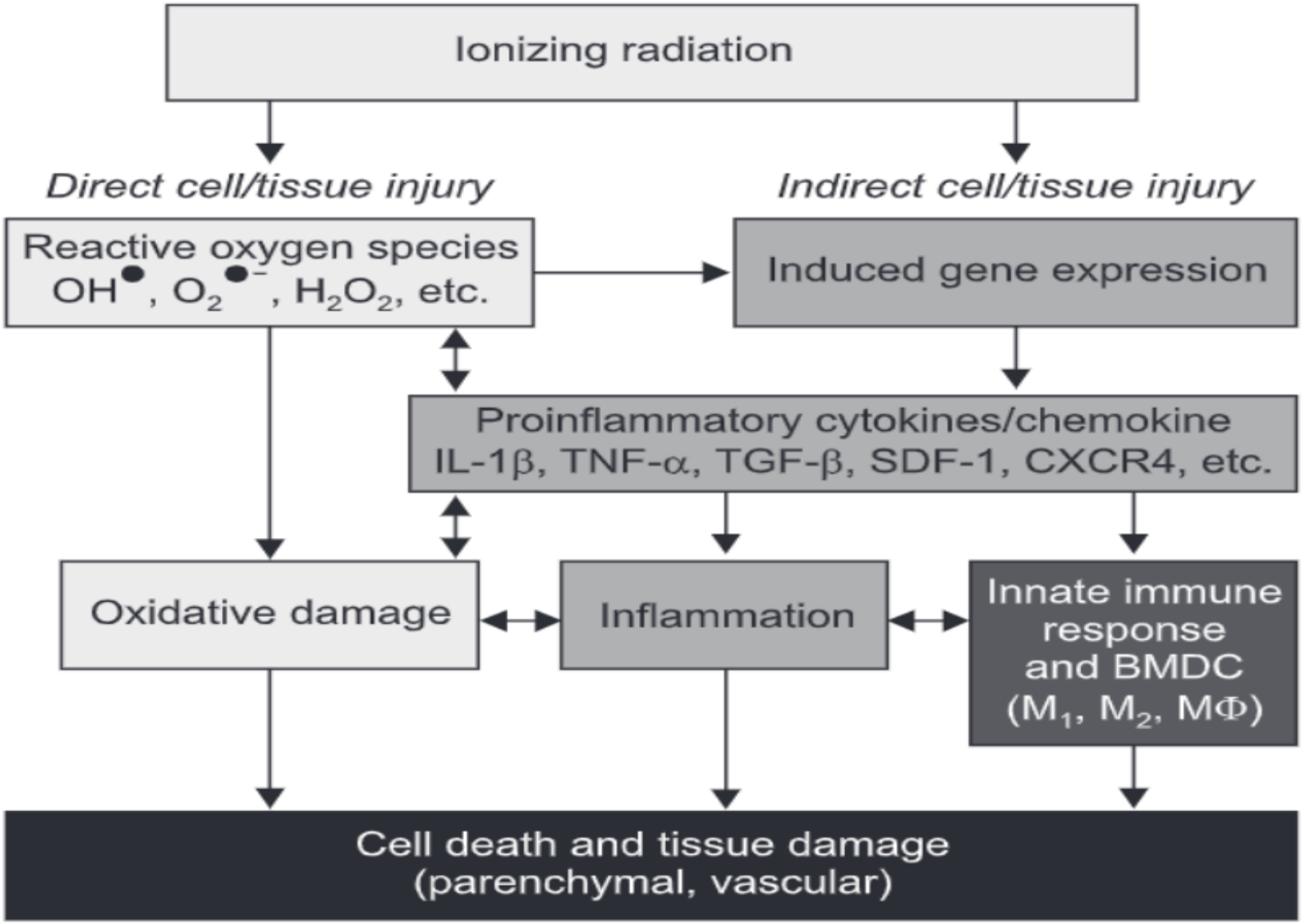
- Time to repair
  - Adequate time between fractions should be given to ensure adequate repair of the tissues.
  - Fast and slow component of repair

- Volume of normal tissue irradiated
  - Similar to acute toxicity, the volume of irradiated normal tissue is important in determining late toxicity.
  - Primarily affecting parallel architecture organs, rather than serial organs

- Genetic predisposition to late toxicity
  - Genomic sequencing:
    - **Radiogenomics Consortium (RGC)**
    - **REQUITE**
  - Identifying genetic polymorphism like single nucleotide polymorphisms (SNPs) that modulate late reaction

Mechanism of cellular damage

- Excessive production of ROS after RT- direct cell death
- Excessive Production of Cytokines and Chemokines- IL-1, IL-6, TNF-alpha, TGF-beta, VEGF- edema, endothelial damage, fibrosis
- Recruitment of BMDCs and macrophages- further inflammatory response and fibrosis


Ionizing radiation
Direct cell/tissue injury
Indirect cell/tissue injury
Reactive oxygen species
$OH^{\bullet}$, $O_2^{\bullet -}$, H_2O_2, etc.
Induced gene expression
Proinflammatory cytokines/chemokine
IL-1β, TNF-α, TGF-β, SDF-1, CXCR4, etc.
Oxidative damage
Inflammation
Innate immune response and BMDC
(M_1, M_2, MΦ)
Cell death and tissue damage
(parenchymal, vascular)

Skin

- Acute- depopulation of the acutely responding basal epithelial cells.
- manifested by early erythema and dry or moist desquamation
- General skin care including cleansing and avoidance of irritation.
- Steroid creams (eg, mometasone) were found in a randomized trial to decrease moist desquamation by approximately one-third.
- Adhesive silicone dressings and silver sulfadiazine are also effective in decreasing and managing moist desquamation,

- The long-term results of START trials A and B demonstrated that hypofractionation, did not worsen breast cosmesis or increase the risk of complications in arm or shoulder

Dermatitis	Acute	• Dry and avoid irritation; steroid creams (for high risk: mometasone 0.1% bid from RT start), aloe, corn starch, nystatin powder; adhesive silicone, silver sulfadiazine, opiates for severe moist desquamation
Fibrosis	Late	• Pentoxifylline (400 mg bid-tid) and vitamin E (400 IU qd) for 6 mo starting 2-4 wk after RT (eg, for RT after postmastectomy reconstruction)
Lymphedema	Late	• Physical therapy (manual lymphatic drainage), compression devices/garments, complete decongestive therapy

Lung

- Toxicity
  - Acute to subacute radiation pneumonitis
  - Progressive, late alveolar fibrosis
- Clinical severity correlates with volume of the irradiated lung (Parallel Organ)
- Levels of the glycoprotein Krebs von den Lungen-6 (KL-6) and surfactant protein D are predictive of severe radiation pneumonitis after SBRT
- Pre-existing interstitial lung disease may increase the risk of pulmonary toxicity from RT 5-fold to 10-fold.

- The reported rates of symptomatic RP after SBRT range from 9% to 28% from various studies

- Grade 3 RP was observed in 3.6% of the overall patients in RTOG 0236- Timmerman et al

- Pathophysiology
  - Effects are caused by endothelial damage and congestion of delicate alveoli, impairing gas exchange, along with an exudative, inflammatory cascade of cytokine-mediated fibroblast proliferation and fibrosis

- Treatment
  - High-dose steroids (40-60 mg prednisone tapering over 4-8 weeks).
  - Nintedanib- TKI- being evaluated

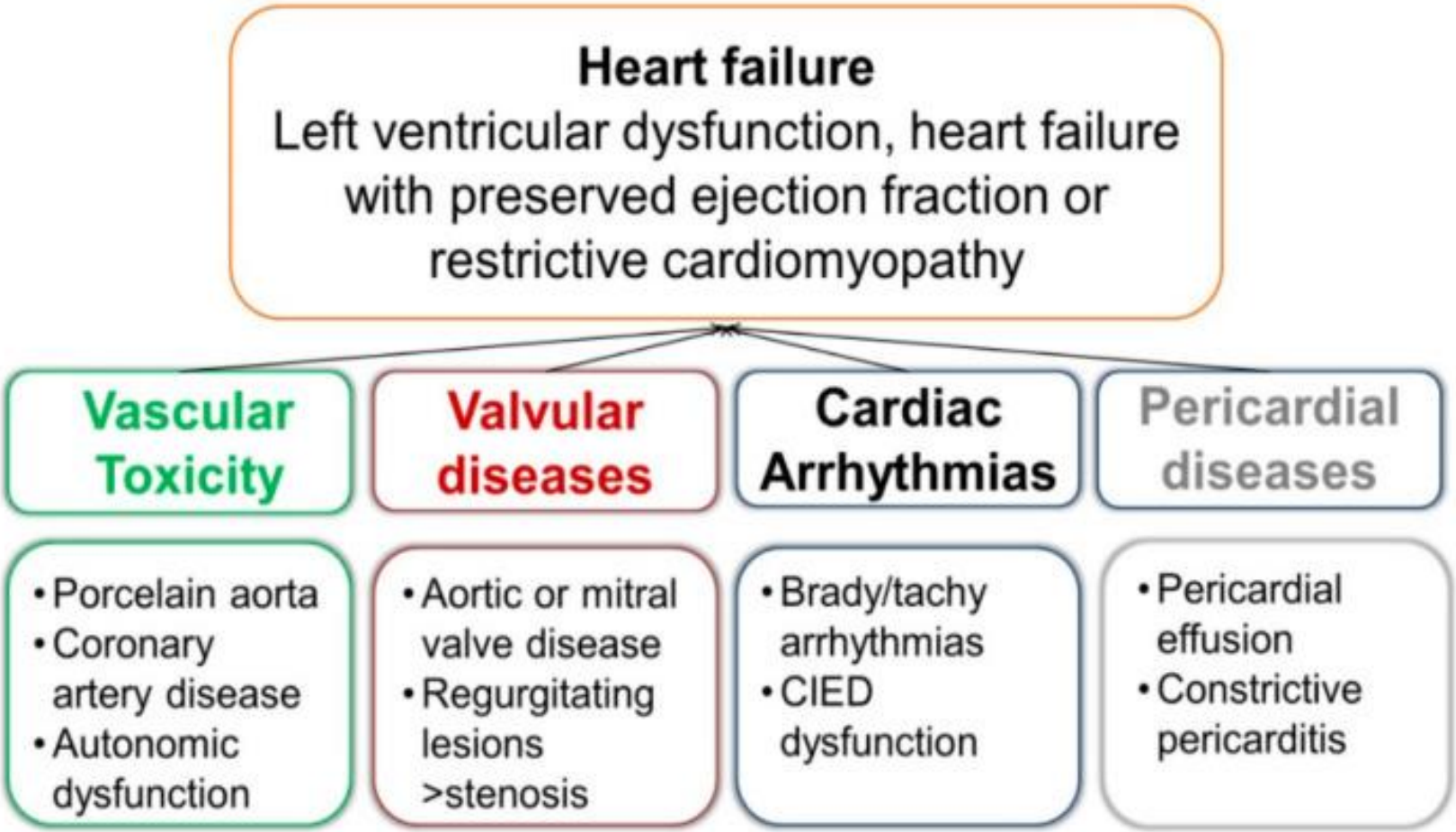
- High doses of RT to the proximal bronchial tree severe bronchial or vascular injury (Serial Organ)
- These include hemorrhage, bronchial stenosis, and fistula

- Be wary of the “no fly zone”- Timmerman et al especially the ultracentral areas

Heart

- Acute – pericarditis
- Late- Ischemic heart disease and myocardial infarction, valvular disease, arrythmias, peridardial disease

Chronic Radiation Induced Heart Disease



PHYSIOPATHOLOGY OF HEART DAMAGE INDUCED BY RADIATION

RADIATION

- Δ TNF
- Δ IL-1
- Δ IL-6
- Δ PLATELET DERIVED GROWTH FACTOR
- Δ MONOCYTES CHEMOTACTIC FACTOR
- Δ PLATELET - DERIVED GROWTH FACTOR (PDGF)
- Δ TRANSFORMING GROWTH FACTOR (TGF)-B

- Δ MYOCARDIAL DAMAGE
- Δ VALVULAR DISEASE
- Δ PERICARDIAL DAMAGE
- Δ MICRO AND MACROVASCULAR DISEASE
- Δ CONDUCTION DITURBANCES

- Δ INFLAMMATION
- Δ VASOCONSTRICTION
- Δ PROTHROMBOSIS
- Δ VENTRICULAR REMODELING
- Δ FIBROSIS

- Δ DNA DISRUPTION
- Δ OXIDATIVE STRESS
- Δ LIPIDIC PEROXIDATION

THORACIC ONCOLOGY ■

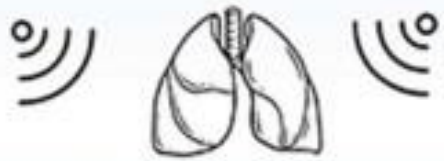
Does the Long-Term Risk of Cardiovascular Outcomes for Patients With Early-Stage NSCLC Differ by Tumor Laterality?

CHEST

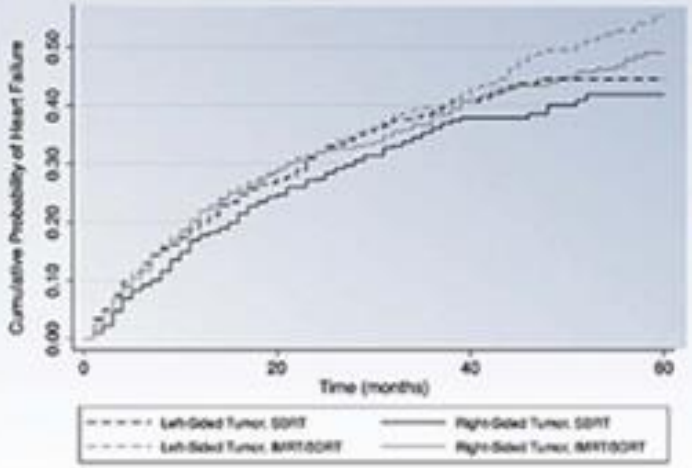
STUDY DESIGN

Used SEER Registry to examine **3,256 adults** with **node-negative stage I or IIA non-small cell lung cancer (NSCLC)** and who received stereotactic body radiation therapy (**SBRT**) or three-dimensional conformal radiation therapy/intensity-modulated radiation therapy (**3DCRT/IMRT**)

Compared left-sided tumors/radiation with right-sided tumors/radiation



RESULTS



No difference for patients who received SBRT by laterality

Patients who received 3DCRT/IMRT with **LEFT-SIDED** tumors had greater risk of:

- **Congestive heart failure** (HR 1.23; 1.01-1.48)
- **Percutaneous coronary artery intervention** (HR 2.24; 1.12-4.47)

Patients with left-sided NSCLC had higher rates of select cardiac events when treated with 3DCRT/IMRT compared with those with right-sided NSCLC, while those treated with SBRT showed no difference.

Liu BY, et al. *CHEST.* June 2022 | @Journal_CHEST | https://doi.org/10.1016/j.chest.2021.12.667

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†*

10 years of follow-up of START trials have not found evidence for an increased cardiac ischemic risk compared with CFRT

	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

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.

In the control arm, 9 were related to cardiac disease (1.5%), In the hypofractionated-radiation arm, 12 were related to cardiac disease (1.9). No significant differences were detected between the groups (P=0.56).

Liu *et al. Radiation Oncology* (2020) 15:17
https://doi.org/10.1186/s13014-020-1463-1

Radiation Oncology

REVIEW Open Access

Comparing hypofractionated to conventional fractionated radiotherapy in postmastectomy breast cancer: a meta-analysis and systematic review

Lei Liu†, Yongqiang Yang†, Qi Guo†, Bixin Ren, Qiliang Peng, Li Zou, Yaqun Zhu and Ye Tian*

Late Cardiac Related Toxicity: Six studies reported late cardiac related toxicity in 1677 patients, and results showed no significant difference between the two groups (OR = 1.17, 95% CI = 0.82 - 1.65, P = 0.39).

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

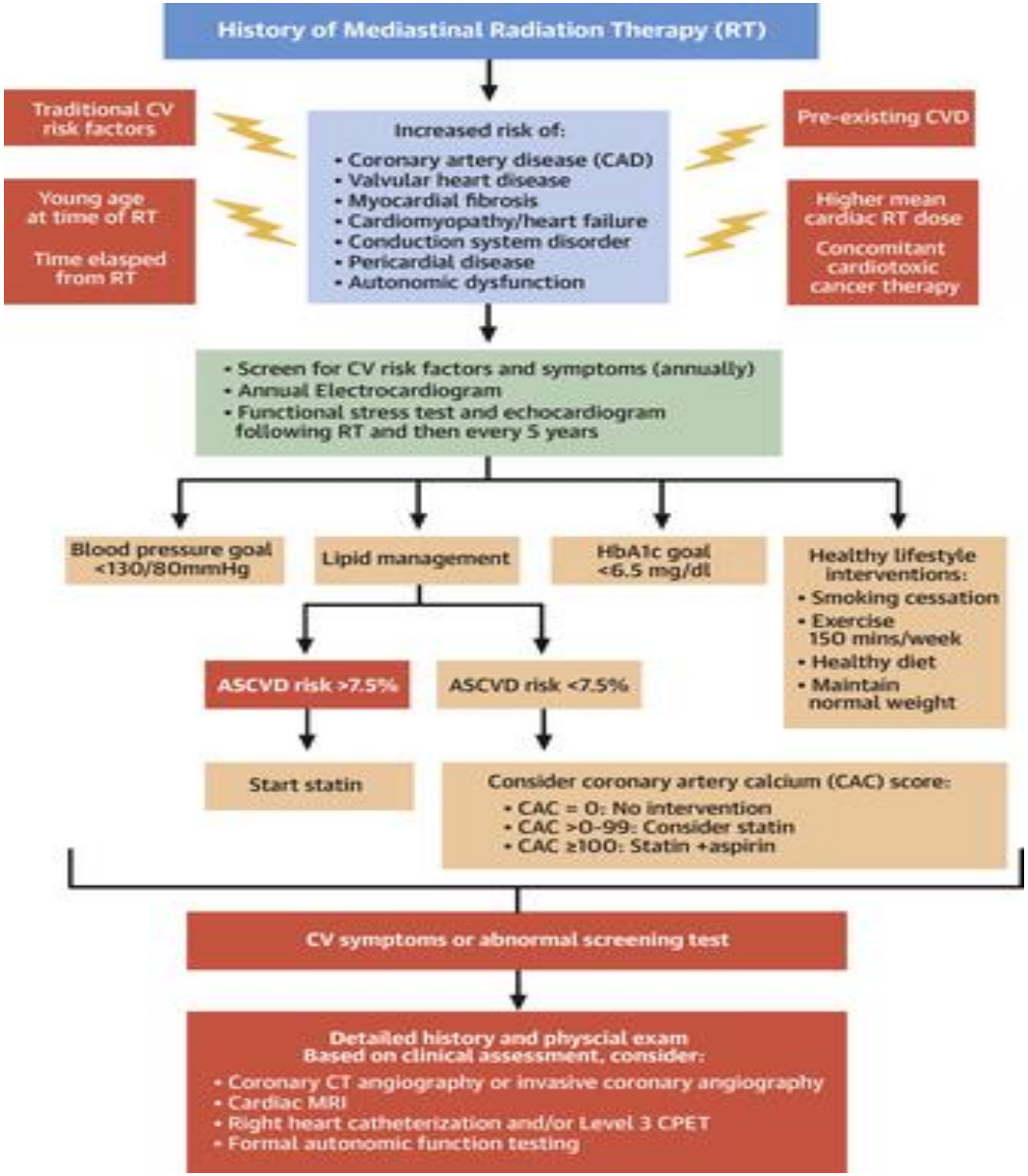
Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer

Adrian Murray Brunt, FRCR[1]; Joanne S. Haviland, MSc[2]; Mark Sydenham, BSc Hons[2]; Rajiv K. Agrawal, FRCR[3]; Hafiz Algurafi, FRCR[4]; Abdulla Alhasso, FRCR[5]; Peter Barrett-Lee, FRCR[6]; Peter Bliss, FRCR[7]; David Bloomfield, FRCR[8]; Joanna Bowen, FRCR[9]; Ellen Donovan, PhD[10]; Andy Goodman, FRCR[11]; Adrian Harnett, FRCR[12]; Martin Hogg, FRCR[13]; Sri Kumar, FRCR[14]; Helen Passant, FRCR[6]; Mary Quigley, FRCR[15]; Liz Sherwin, FRCR[16]; Alan Stewart, FRCR[17]; Isabel Syndikus, FRCR[18]; Jean Tremlett, MSc[8]; Yat Tsang, PhD[19]; Karen Venables, PhD[19]; Duncan Wheatley, FRCR[20]; Judith M. Bliss, MSc[2]; and John R. Yarnold, FRCR[21]

No significant differences were observed to suggest any increased risk of RIHD or death from cardiac causes attributable to treatment with any of the schemes used

- Preventive strategies
  - Conformal planning
  - Prone position
  - Breath hold techniques
  - APBI
  - Proton therapy

- Management
  - Close follow up for occurrence and daignosis
  - Drugs
  - Surgical
  - Cardiac rehabilitation and lifestyle changes



Sarju Ganatra et al. *J Am Coll Cardiol CardioOnc* 2020; 2:655-660.

JACC CardioOncology
An Open Access Journal

Gastrointestinal and Genitourinary

– Acute- include nausea/ vomiting, diarrhea, increased stool frequency, decreased food intake, fluid and electrolyte loss, and abdominal and rectal pain and tenesmus

– Chronic- Changes in the bowel habit, diarrhea, fecal incontinence, pain and blood loss, malabsorption, anal stenosis and fecal incontinence from sphincter dysfunction.

- Pathophysiology of GI toxicity
  - Acute: Microvascular injury, injury mediated by endothelial apoptosis, crypt abscess formation.
  - Late: Vascular ischemia contributes to secondary enterocyte depletion, mucosal barrier breach, bacterial translocation, and structural damage of the intestine

- Nausea and vomiting which is specific to stomach is due to release of factors, including 5-hydroxytryptamine- 3, serotonin, neurokinin- 1, and dopamine, that act on central receptors

- Bladder toxicity (radiation cystitis)
  - Acute: irritative symptoms include frequency, urgency, dysuria, and spasmodic pain
  - Late: Hemorrhagic cystitis (<5%), contracted, nonfunctional bladder, persistent incontinence; fistula formation; necrosis

- Pathophysiology of bladder toxicity
  - occurs through direct urothelial damage, along with effects on urinary sphincter and detrusor muscle from fibrosis and vascular ischemia.

Genitourinary		
Obstructive urinary symptoms	Both	• Avoid fluids before sleep, minimize caffeine and alcohol; α-blockers (eg initiate/increase tamsulosin dose for 3-6 mo after RT); steroids if severe
Cystitis	Both	• Rule out urinary tract infection; phenazopyridine for dysuria; antimuscarinics (eg, oxybutynin, solifenacin) for severe frequency, urge incontinence, and/or bladder spasms
Sexual		
Female	Late	• Topical estrogens, regular vaginal dilator usage, pelvic floor physical therapy
Male	Late	• Phosphodiesterase inhibitors (eg, sildenafil), vacuum devices, urologic interventions

Late toxicity management

- Fistula formation usually requires surgical intervention
- Endoscopic injection sclerotherapy is used in intractable hemorrhagic cystitis.
- Hyperbaric oxygen (HBO) therapy

10-Year efficacy and co-morbidity outcomes of a phase III randomised trial of conventional vs. hypofractionated high dose intensity modulated radiotherapy for prostate cancer (CHHiP; CRUK/06/016).

Journal of Clinical Oncology 41, no. 6_suppl (February 20, 2023) 304-304.

With a median follow-up of 12 years, incidence of late grade III GI and GU toxicity ie bowel stricture, ureteric obstruction, bowel strictures, trans-urethral resection of prostate, urethrotomy, urethral dilatation or long term catheterisation and treatment of proctopathy with steroid, sucralfate, formalin, laser coagulation or rectal diversion was low <1 %.

Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial

Shafak Aluwini, Floris Pos, Erik Schimmel, Stijn Krol, Peter Paul van der Toorn, Hanja de Jager, Wendimagegn Ghidey Alemayehu, Wilma Heemsbergen, Ben Heijmen, Luca Incrocci

Cumulative grade 3 or worse late genitourinary toxicity was significantly higher in the hypofractionation group than in the standard fractionation group (19·0% [95% CI 15·2–23·2] *vs* 12·9% [9·7–16·7], respectively.

There was no significant difference between cumulative grade 3 or worse late gastrointestinal toxicity (2·6% [95% CI 1·2–4·7]) in the standard fractionation group and 3·3% [1·7–5·6] in the hypo fractionation group; p=0·55).

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

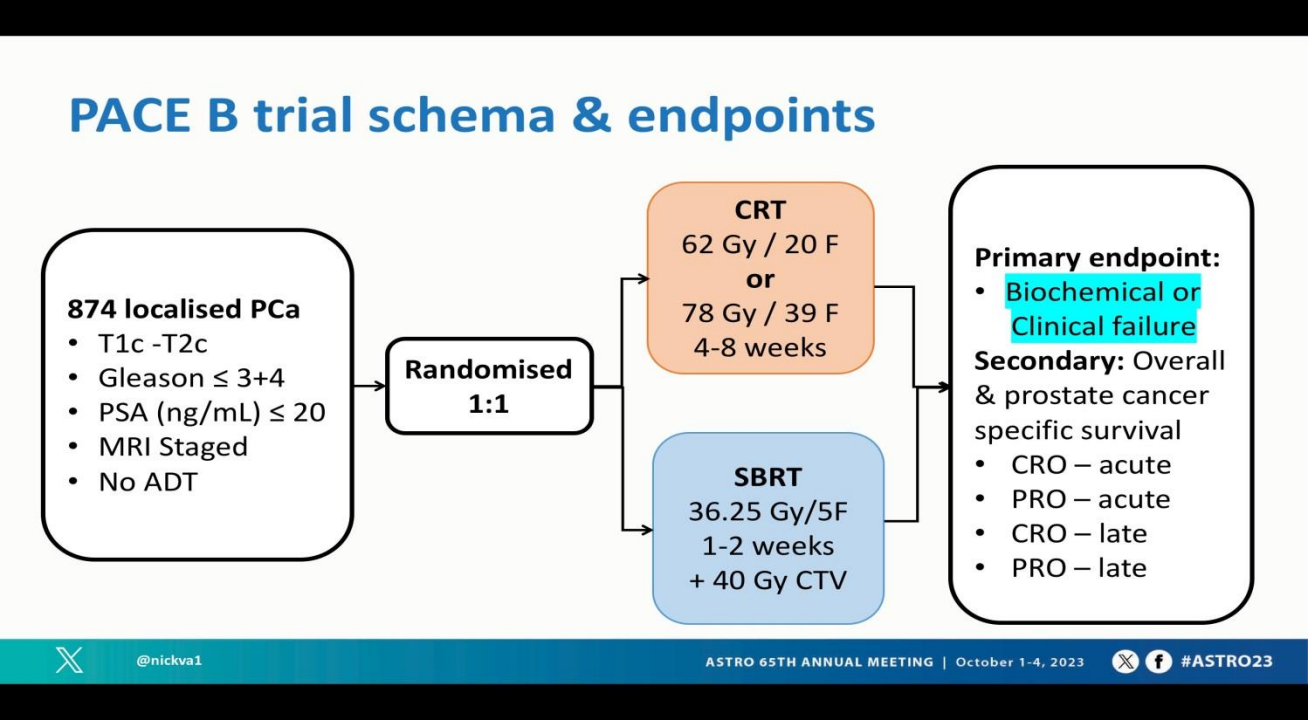
Review Article

Acute and late toxicity patterns of moderate hypo-fractionated radiotherapy for prostate cancer: A systematic review and meta-analysis

F. Sinzabakira [a,b,*], V. Brand [a], W.D. Heemsbergen [a], L. Incrocci [a]

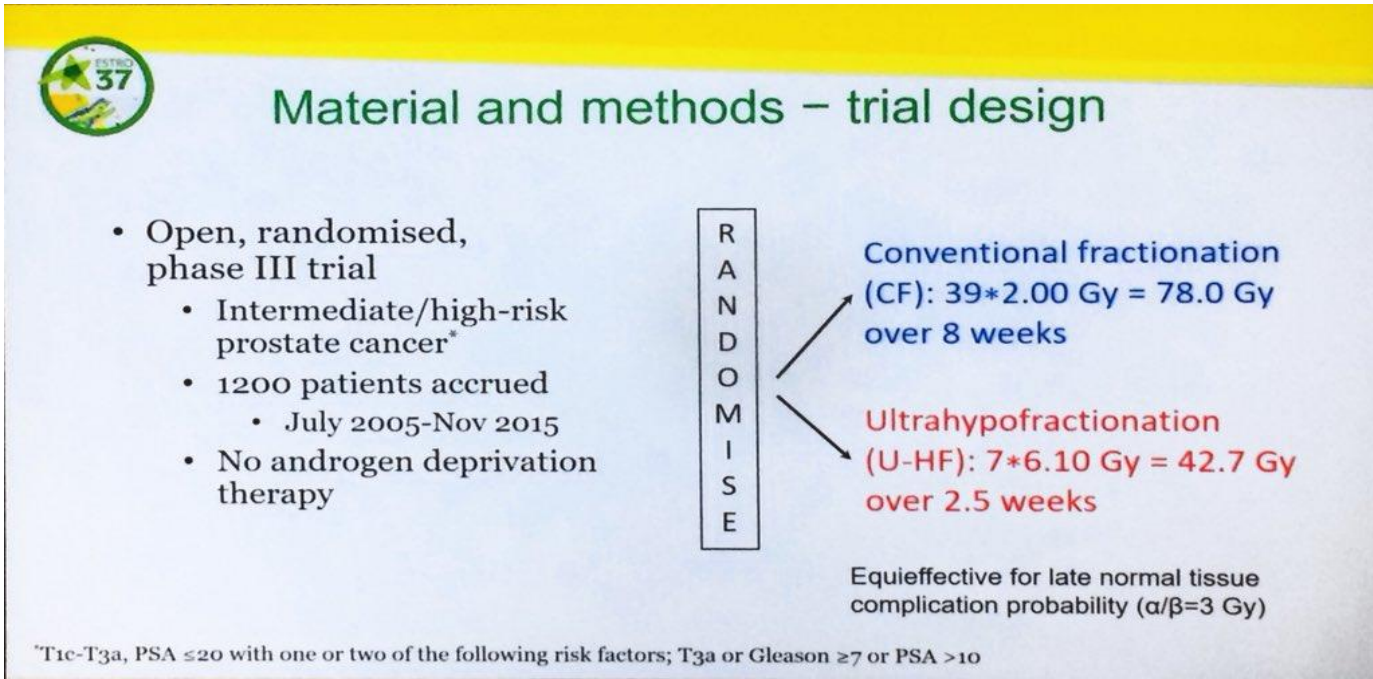
Acute grade ≥ 2 gastro-intestinal (GI) toxicity was increased by 6.3 % (95 % CI for risk difference = 2.0 %–10.6 %) for HF vs SF. Acute grade ≥ 2 Genito-urinary (GU) was not significantly increased. Pooled late GI and GU toxicity showed similar levels for SF and HF.

- What about ultra-hypofractionation (> 5Gy/#) for Ca prostate??
- Data from two trials-
  - PACE-B
  - HYPO-RT-PC
- The Hypo-RT-PC and PACE-B reported a similar late GI and GU toxicity between arms.



PACE-B trial

HYPO-RT-PC trial



- Toxicity (HYPO-RT-PC)
  - Acute patient-reported urinary and bowel toxicities in UF-RT were significantly worse at treatment completion and remained significantly worse three months after treatment and grade ≥2 GU toxicity at one year was significantly greater with UF-RT arm (6% vs. 2%, P=0.0037)
  - The 5-year cumulative incidence of grade ≥2 GU and toxicity (18% vs. 17%) and GI toxicity (10% vs. 10%) were similar.
  - Grade ≥3 GU and GI toxicities were low across both arms (4.2% vs. 4.7% for GU and 1.7% vs. 1.9% for GI).
  - Erectile function worsened from 70% at baseline to 35% at 5 years in both arms.

Toxicity (PACE –B)

- Grade 2 or more severe gastrointestinal toxic events in 12% CH or MH group versus 10% in the SBRT group (95% CI −6·2 to 2·4; p=0·38).

- Grade 2 or worse GU toxicity was reported in 27% patients CH or MH group versus 23% in SBRT group, (95% CI −10·0 to 1·7; p=0·16).
- The 2 year update also did not show any difference

Gastrointestinal

Esophagitis	Acute	• Soft/liquid diet; antacids, viscous lidocaine (before swallowing), and/or opiates (before meals); fluconazole for empiric treatment of candida esophagitis
Nausea	Acute	• Antacids, prn ondansetron or prochlorperazine (both tid and alternating if severe)
Gastritis/ulceration	Both	• Avoid gastric irritants; antacids and prolonged course of proton pump inhibitors; formalin for refractory bleeding, coagulation if severe
Enteritis	Both	• Low fiber/residue/fat diet; loperamide (qd/bid prn) and/or diphenoxylate/atropine; subcutaneous octreotide (100 μg tid for 3-5 d) if refractory with dehydration
Proctitis	Both	• Steroid creams; for late hematochezia, sucralfate enema, formalin, and coagulation

- Central Nervous System
  - Extremely sensitive to total dose, dose/# and volume and region of brain irradiated
  - Radiation-induced brain injury is described in three phases:
    - Acute (within days to weeks after irradiation)
    - Early-delayed (within 1–6 months post irradiation)
    - Late (> 6 months post irradiation)

- Pathophysiology
- Combination of mitotic death and subcellular alterations
- Oxidation of the lipid bilayer, changes in microvascular permeability, cell-cell junctional complex rearrangements, and mitochondrial alterations inducing additional oxidative stress

- Radiation primarily causes coagulation necrosis of the white matter tracts and cerebral vasculature by axonal demyelination and damage to vascular endothelial cells.
- Leukoencephalopathy occurs from the overproduction of myelin in oligodendrocytes and occurs as a late toxicity .
- Astrocytes may undergo reactive gliosis.
- Radionecrosis – inflamatory response

- The RTOG 90–05 series reported an 11% rate of radionecrosis at 2 years.
- Roa et al- 60Gy/30#s vs 40Gy/15#s- lesser corticosteroid requirement with 40Gy/15#
- Perry et al: Quality of life was similar in the two trial groups.

- Management
  - Medical- Steroids, Memantine, Donepezil,
  - Non-pharmacological strategies, such as exercise-induced stimulation of hippocampal neurogenesis, cognitive therapies and mesenchymal stem cell replacement

CNS edema/radiation necrosis	Both	• Dexamethasone 2-16 mg qd for ≥1-4 wk based on severity, with GI prophylaxis and steroid taper for longer courses; bevacizumab/surgery for refractory necrosis
Cognitive	Late	• Before RT: Memantine 5-10 mg qd, increasing to 20 mg by 4 wk, total 24 wk; after RT: donepezil 5 mg qd for 6 wk, 10 mg qd for 18 wk

Thank you