Radiation Oncology in North Carolina: Updates for 2021

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Learning Objectives

- Describe the utilization and efficacy of hypofractionation
- Discuss methods to improve the anti-tumor effect of radiation, such as the combination of immunotherapy with radiation
- Recognize techniques to limit radiation-induced toxicity

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Radiation Basics

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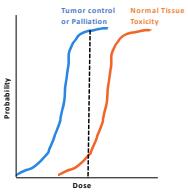
Radiotherapy

- Radiation is a local treatment modality that plays a critical role in the management of >60% of patients with cancer
- Can be delivered with curative/definitive vs palliative intent
- Different types of radiation including Intensity-Modulated and Image-Guided Radiation Therapy (IMRT, IGRT), Stereotactic Body Radiation Therapy (SBRT), Brachytherapy, Intraoperative Radiation Therapy
- Always must think about the therapeutic ratio when deciding to offer radiation
- Units of radiation are Gray (Gy), total dose is delivered in small daily doses called fractions



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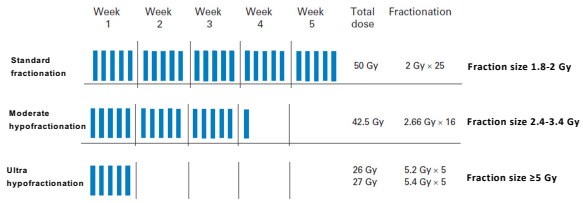
Fractionation Definitions



Adapted from Fisher et al., Clin Onc 2014

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Poll Question 1

- Treatment over multiple weeks with small doses per day (<2 Gy / day) is referred to as
  - Conventional/standard fractionation
  - Moderate hypofractionation
  - Ultra hypofractionation

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Updates in Hypofractionation

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Hypofractionation

- Why hypofractionate?
  - Reduction in total treatment length for patients saves time, energy, & cost (and enhances safety/convenience during COVID)
  - For some tumors like prostate cancer, allows improved therapeutic ratio via enhanced killing of tumor cells while sparing normal cells
- Feasible given improvements in conformality and precision of radiation delivery with IMRT and IGRT
- Which cancers do we routinely consider hypofractionation for now?
  - Prostate, breast, lung (early stage), GI cancers

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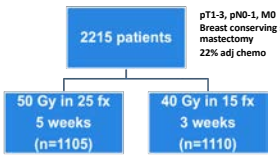
Moderate Hypofractionation: Breast Cancer START B Trial



pT1-3, pN0-1, M0
Breast conserving surgery (BCS) or mastectomy
22% adj chemo

Primary endpoint: Local-regional tumor relapse and late normal tissue effects
Median follow up: 9.9 years

Landmark Study
Haviland et al., Lancet Oncology 2013

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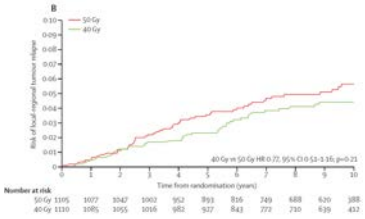
Moderate Hypofractionation: Breast Cancer START B Trial Efficacy



Landmark Study
Haviland et al., Lancet Oncology 2013

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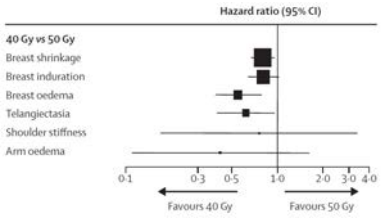
Moderate Hypofractionation: Breast Cancer START B Trial Late Toxicity



Landmark Study
Haviland et al., Lancet Oncology 2013

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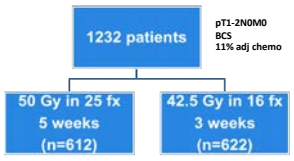
Moderate Hypofractionation: Breast Cancer Canadian Trial



Primary endpoint: Local recurrence
Median follow up: 12 years

Landmark Study
Whelan et al., NEJM 2010

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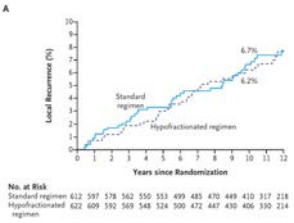
Moderate Hypofractionation: Breast Cancer Canadian Trial Efficacy



Landmark Study
Whelan et al., NEJM 2010

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Moderate Hypofractionation: Breast Cancer Canadian Trial Late Toxicity

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

Landmark Study
Whelan et al., NEJM 2010

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Moderate Hypofractionation: Breast Cancer

ASTRO Guidelines 2018:

"For women with invasive breast cancer receiving WBI with or without inclusion of the low axilla, the preferred dose-fractionation scheme is hypofractionated WBI to a dose of 4000 cGy in 15 fractions or 4250 cGy in 16 fractions." This decision is independent of many factors including tumor grade, prior chemotherapy, breast size, etc.

Smith et al., PRO 2018

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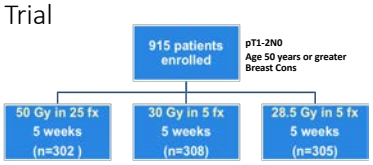
Ultra Hypofractionation: Breast Cancer FAST Trial



Primary endpoint: Change in photographic breast appearance at 2 years
Secondary endpoints:
- Change in photographic breast appearance at 5 years
- Ipsilateral tumor control
- Clinical assessment of late effects

Brunt et al., JCO 2020

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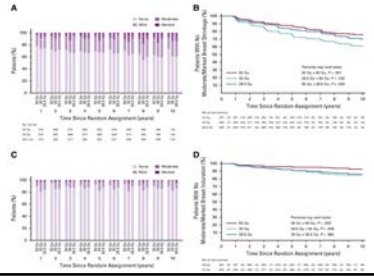
Ultra Hypofractionation: Breast Cancer FAST Trial Results



~28 Gy in 5 fractions appears to equivalent with regard to normal tissue effects as 50 Gy in 25 fractions, but 30 Gy in 5 fractions results in higher toxicity

Brunt et al., JCO 2020

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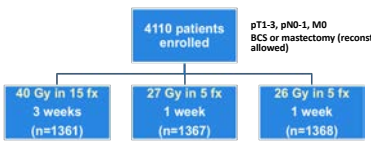
Ultra Hypofractionation: Breast Cancer FAST-Forward Trial



Primary endpoint: Ipsilateral breast tumor recurrence
Median follow-up: 71.5 months

Brunt et al., Lancet 2020

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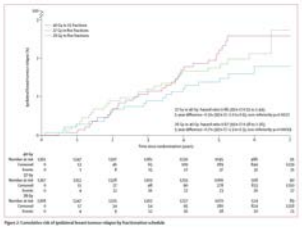
Ultra Hypofractionation: Breast Cancer FAST-Forward Trial Efficacy



40 Gy in 15 fx: 2.1%
27 Gy in 5 fx: 1.7%
26 Gy in 5 fx: 1.4%

Brunt et al., Lancet 2020

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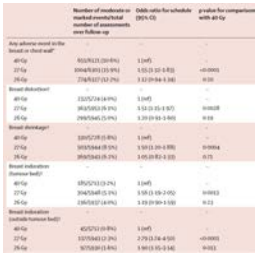
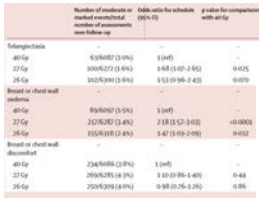
Ultra Hypofractionation: Breast Cancer FAST-Forward Trial Toxicity





Conclusion: *26 Gy in 5 fractions is as effective and safe as 40 Gy in 15 fractions regimen after primary surgery for early stage breast cancer*

Brunt et al., Lancet 2020

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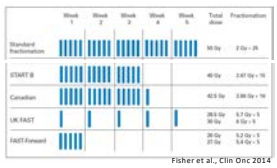
Hypofractionation: Breast Cancer Conclusions

- Moderate hypofractionation is the well accepted standard of care for patients receiving whole breast irradiation
- Moderate hypofractionation is also under investigation for those receiving regional nodal irradiation (RT-CHARM)
- Ultra-hypofractionation regimens like FAST-Forward are being increasingly considered in certain circumstances, with the caveat that we only have 5 year data for the FAST-Forward regimen.



Fisher et al., Clin Onc 2014

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Poll Question 2

- Which of the following is an absolute contraindication to receiving whole breast irradiation with a moderate hypofractionation schedule over 3-4 weeks?
  - Age <50 years
  - Triple negative disease
  - Grade 3 tumor
  - Large chest wall separation (with homogenous dosing achieved)
  - None of the above – moderate hypofractionation can used in any of the above scenarios

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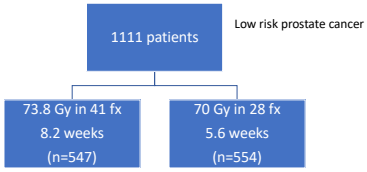
Hypofractionation: Prostate Cancer RTOG 0415



Primary end point: Disease free survival

Median follow up: 5.9 years

Lee et al., JCO 2016

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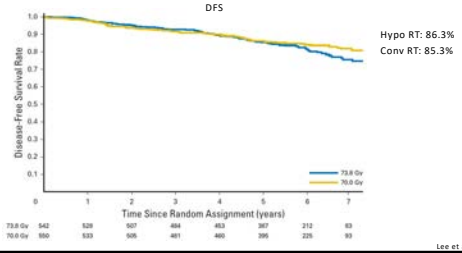
Hypofractionation: Prostate Cancer RTOG 0415 Efficacy



Lee et al., JCO 2016

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Hypofractionation: Prostate Cancer RTOG 0415 Acute Toxicity

Adverse Event Class	3D-CRT/ IMRT 73.8 Gy (n = 534)	3D-CRT/ IMRT 70 Gy (n = 545)	RR (95% CI)*	P
Maximum grade of early GI toxicity				.541†
None reported	327 (61.2)	311 (57.1)		
1	152 (28.5)	176 (32.3)		
2	52 (9.7)	54 (9.9)	1.03 (0.73 to 1.46)	.85
3	3 (0.6)	3 (0.6)	1.31 (0.29 to 5.81)	.72
4	0 (0.0)	1 (0.2)	—	—
Maximum grade of early GU toxicity				.831†
None reported	204 (38.2)	206 (37.8)		
1	185 (34.6)	192 (35.2)		
2	132 (24.7)	129 (23.7)	0.99 (0.82 to 1.21)	.95
3	13 (2.4)	18 (3.3)	1.36 (0.67 to 2.74)	.39
4	0 (0.0)	0 (0.0)	—	—

Lee et al., JCO 2016

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Hypofractionation: Prostate Cancer RTOG 0415 Late Toxicity

Adverse Event Class	3D-CRT/ IMRT 73.8 Gy (n = 534)	3D-CRT/ IMRT 70 Gy (n = 545)	RR (95% CI)*	P
Maximum grade of late GI toxicity				.002†
None reported	350 (65.7)	300 (55.4)		
1	108 (20.3)	121 (22.3)		
2	61 (11.4)	99 (18.3)	1.59 (1.22 to 2.06)	.005
3	13 (2.4)	22 (4.1)	1.55 (0.80 to 2.99)	.19
4	1 (0.2)	0 (0.0)	—	—
Maximum grade of late GU toxicity				.061†
None reported	255 (47.8)	227 (41.9)		
1	157 (29.5)	154 (28.4)		
2	109 (20.5)	142 (26.2)	1.31 (1.07 to 1.61)	.009
3	11 (2.1)	19 (3.5)	1.56 (0.76 to 3.18)	.22
4	1 (0.2)	0 (0.0)	—	—

In men with low-risk prostate cancer, 70 Gy / 28 fractions over 5.6 weeks is non-inferior to 73.8 Gy / 41 fractions over 8.2 weeks.

Lee et al., JCO 2016

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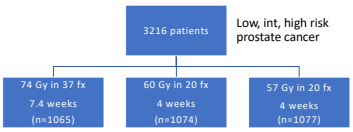
Hypofractionation: Prostate Cancer CHHiP Trial



Primary end point: Biochemical or clinical failure
Median follow up: 62 months

Dearnaley et al., Lancet Oncol 2016

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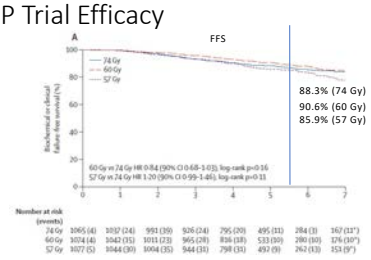
Hypofractionation: Prostate Cancer CHHiP Trial Efficacy



Dearnaley et al., Lancet Oncol 2016

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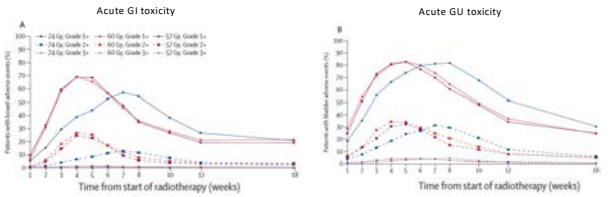
Hypofractionation: Prostate Cancer CHHiP Trial Acute Toxicity



Dearnaley et al., Lancet Oncol 2016

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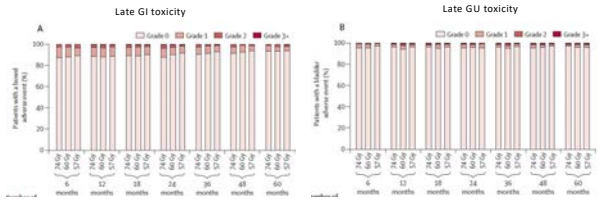
Hypofractionation: Prostate Cancer CHHiP Trial Late Toxicity



Dearnaley et al., Lancet Oncol 2016

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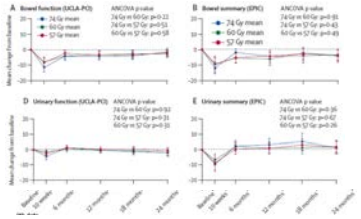
Hypofractionation: Prostate Cancer CHHiP Trial Patient Reported Outcomes



Hypofractionated radiotherapy using 60 Gy in 20 fractions is non-inferior to conventional fractionation using 74 Gy in 37 fractions and is recommended as a new standard of care for external-beam radiotherapy of localized prostate cancer.

Wilkins et al., Lancet Oncol 2015

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Hypofractionation: Prostate Cancer Conclusions

- "Based on high-quality evidence, strong consensus was reached for offering moderate hypofractionation across risk groups to patients choosing external beam radiation therapy." (ASTRO 2018 Guidelines)
- Emerging data that moderate hypofractionation will also be utilized soon in the post-prostatectomy setting
- Ongoing studies looking at ultra-hypofractionation with 5 fractions of stereotactic body radiation therapy for prostate cancer (i.e., NRG-GU005)

Morgan et al., PRO 2018
Buyyounouski et al., ASTRO 2021

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Radiation Efficacy

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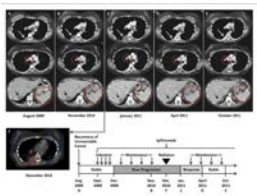
How to make radiation more effective?

- Increase total dose
- Fractionate to take advantage of biologic properties of specific tumors in relation to normal tissue
- Combine with systemic approaches for potential synergy and enhancement of anti-tumor effect (i.e., immunotherapy)



Landmark Study
Postow et al., NEJM 2012

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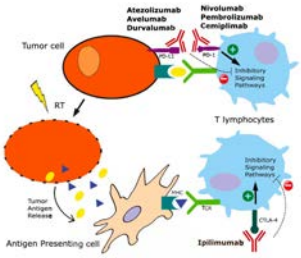
Immunotherapy + Radiation

Multiple potential synergistic effects of radiation combined with immunotherapy



Williamson et al., Cancer 2021

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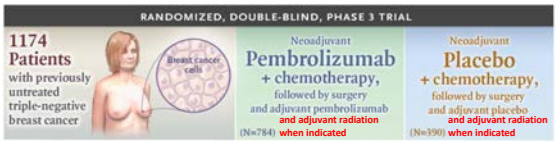
Immunotherapy for Triple Negative Breast Cancer KEYNOTE 522



Schmid et al., NEJM 2020

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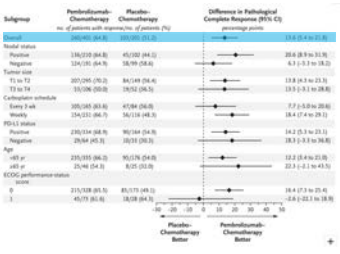
Immunotherapy for Triple Negative Breast Cancer
KEYNOTE 522 Efficacy



Schmid et al., NEJM 2020

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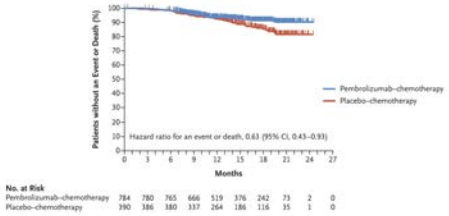
Immunotherapy for Triple Negative Breast Cancer
KEYNOTE 522 Efficacy



Schmid et al., NEJM 2020

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Immunotherapy for Triple Negative Breast Cancer
KEYNOTE 522 Toxicity

7/26/21: FDA approval of pembrolizumab for high-risk, early stage triple negative breast cancer in neoadjuvant setting in combination with chemotherapy and then in adjuvant setting as treatment after surgery (with radiation!).

Schmid et al., NEJM 2020

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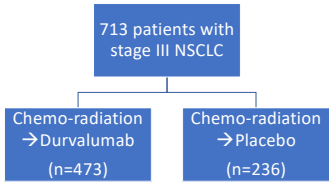
Immunotherapy for NSCLC
PACIFIC Trial



Primary endpoints: Progression free survival and overall survival

Median follow up: 14.5 months

Antonia et al., NEJM 2017

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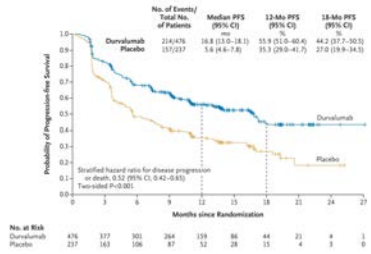
Immunotherapy for NSCLC
PACIFIC Trial Efficacy



Antonia et al., NEJM 2017

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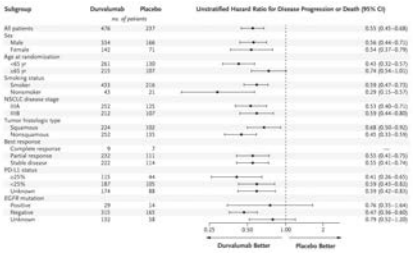
Immunotherapy for NSCLC
PACIFIC Trial Efficacy



Antonia et al., NEJM 2017

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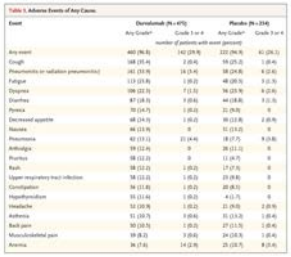
Immunotherapy for NSCLC PACIFIC Trial Toxicity



Antonia et al., NEJM 2017

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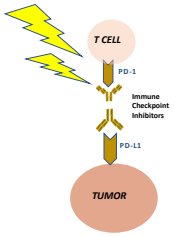
Immunotherapy + Radiation Summary

- Immunotherapy and radiation now play a key role in early stage, high risk triple negative breast cancer and locally advanced NSCLC
- There is likely synergy between radiation and immunotherapy
- Many ongoing studies assessing safety and efficacy of combined immunotherapy and radiation (high grade glioma, head and neck cancer, small cell lung cancer, stage IV cancers, etc.)



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Toxicity Reduction

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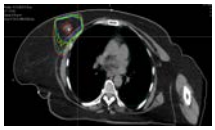
How can we try to reduce toxicity from radiation?

- Omit it altogether!
- De-escalation strategies: decrease dose and/or volume of radiation to normal tissue
  - Accelerated partial breast irradiation (APBI) for breast cancer
  - Hippocampal sparing radiation for whole brain treatment
- Technology to spare normal tissue
  - Protons

APBI



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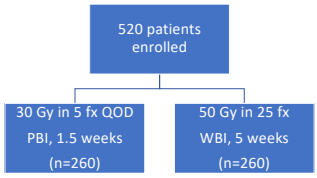
Toxicity Reduction in Breast Cancer APBI-IMRT Florence Trial



Primary endpoint: Ipsilateral breast tumor recurrence

Median follow up: 10.7 years

Meattini et al., JCO 2020

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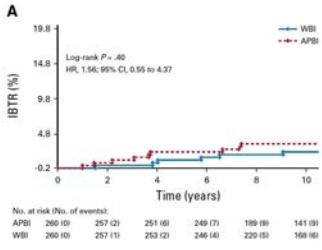
Toxicity Reduction in Breast Cancer APBI-IMRT Florence Trial Efficacy



Meattini et al., JCO 2020

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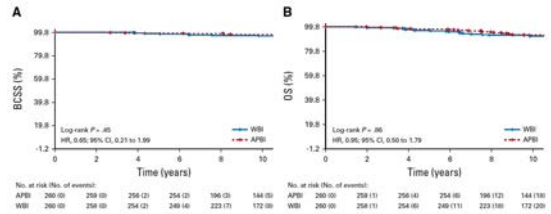
Toxicity Reduction in Breast Cancer
APBI-IMRT Florence Trial Efficacy



Meattini et al., JCO 2020

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Toxicity Reduction in Breast Cancer
APBI-IMRT Florence Trial Toxicity

Assessment	APBI (n = 246)	WBI (n = 260)	P
Acute period adverse events*			
None	194 (78.9)	87 (33.5)	.0001
Yes, any grade	52 (21.1)	173 (66.5)	
Grade 1	47 (19.1)	75 (28.8)	.0001
Grade 2	5 (2.0)	81 (31.2)	
Grade 3	—	17 (6.5)	
Grade 4	—	—	
Grade 0-1	241 (98.0)	162 (62.3)	.0001
Grade ≥ 2	5 (2.0)	98 (37.7)	.0001
Late period adverse events*			
None	235 (95.5)	182 (70.0)	.0001
Yes, any grade	11 (4.5)	78 (30.0)	.0001
Grade 1	11 (4.5)	71 (27.3)	.0001
Grade 2	—	7 (2.7)	
Grade 3	—	—	
Grade 4	—	—	
Grade 0-1	246 (100)	253 (97.3)	.015
Grade ≥ 2	0	7 (2.7)	

Assessment	APBI (n = 246)	WBI (n = 260)	P
Physician-rated cosmesis*			
Excellent	233 (94.7)	189 (72.7)	.0001
Good	13 (5.3)	66 (25.4)	
Fair	—	5 (1.9)	
Poor	—	—	
Patient-rated cosmesis*			
Excellent	44 (17.9)	13 (5.1)	.0001
Good	200 (81.3)	209 (80.3)	
Fair	2 (0.8)	38 (14.6)	
Poor	—	—	

Meattini et al., JCO 2020

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Toxicity Reduction in Breast Cancer
APBI-IMRT Florence Trial Quality of Life

Table 3
Mean values (and SDs of QLQ-C30 scores at T1 according to arm in the series of 205 breast cancer patients: difference of scores between arms, and p-value from Mann–Whitney U test.

Domain	APBI Mean	APBI SD	WBI Mean	WBI SD	Difference of score (95% CI)	p-Value
QL2	86.4	18.8	49.7	18.1	+16.7 (11.6; 21.8)	0.0001
Functional scales						
PF2	86.2	15.2	77.7	17.3	+8.5 (4.6; 13.0)	0.0001
RF2	88.5	19.2	76.8	25.6	+11.7 (6.1; 17.4)	0.0001
EF	78.6	17.6	66.3	24.3	+12.3 (6.5; 18.1)	0.0001
CF	86.8	18.2	81.7	17.8	+5.1 (0.2; 10.1)	0.014
SF	88.9	19.4	82.5	19.5	+6.6 (1.2; 11.9)	0.005
Symptom scales						
FA	25.6	18.7	33.8	21.2	−14.2 (−19.7; −8.7)	0.0001
NV	5.5	9.6	8.8	11.2	−2.8 (−5.6; 0.1)	0.047
PA	13.2	19.3	23.7	19.6	−10.5 (−15.8; −5.1)	0.0001
DY	12.4	21.3	26.3	23.6	−7.9 (−14.1; −1.8)	0.006
SL	19.7	24.8	28.7	25.1	−9.0 (−15.8; −2.1)	0.004
AP	5.7	13.4	20.0	24.2	−14.3 (−19.6; −8.9)	0.0001
CO	15.0	20.4	29.7	25.6	−7.7 (−13.7; −1.6)	0.01
DI	6.8	14.9	5.0	14.5	−0.2 (−4.3; 3.8)	0.88
FI	14.9	31.0	8.0	16.3	+6.9 (0.2; 13.6)	0.67

QL2, global health status; PF2, physical functioning; RF2, role functioning; EF, emotional functioning; CF, cognitive functioning; SF, social functioning; FA, fatigue; NV, nausea+vomiting; PA, pain; DY, dyspnoea; SL, insomnia; AP, appetite loss; CO, constipation; DI, diarrhoea; FI, financial difficulties; APBI, accelerated partial breast irradiation; WBI, whole breast irradiation.
Bold values stand for "reached statistical significance".

Table 4
Mean values of QLQ-BR23 scores at T1 according to arm in the series of 205 breast cancer patients: difference of scores between arms, and p-value from Mann–Whitney U test.

Domain	APBI Mean	APBI SD	WBI Mean	WBI SD	Difference of score (95% CI)	p-Value
Functional scales						
BRBI	86.5	16.5	66.9	24.2	+19.6 (13.9; 25.3)	0.0001
BRSEF	19.2	20.3	21.3	20.5	−2.1 (−7.7; 3.5)	0.46
BRSEE	40.7	21.6	43.9	20.1	−3.2 (−11.2; 4.8)	0.44
BRFU	68.6	27.3	52.7	27.3	+15.9 (8.4; 23.4)	0.0001
Symptom scales						
BRST	14.0	12.7	20.3	11.8	−6.3 (−9.7; −2.9)	0.0001
BRBS	13.0	12.5	32.3	17.0	−19.3 (−23.4; −15.2)	0.0001
BRAS	12.4	13.4	21.8	17.9	−9.4 (−13.7; −5.1)	0.0001
BRHL	42.3	37.2	55.8	29.6	−13.5 (−30.0; −3.0)	0.076

BRBI, body image; BRSEF, sexual functioning; BRSEE, sexual enjoyment; BRFU, future perspective; BRST, systemic therapy side-effects; BRBS, breast symptoms; BRAS, arm symptoms; BRHL, hair loss; APBI, accelerated partial breast irradiation; WBI, whole breast irradiation; SD, standard deviation.
Bold values stand for "reached statistical significance".

Meattini et al., European Journal of Cancer 2017

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ASTRO Guidelines for Eligibility of APBI

Factor	Suitable	Cautionary
Age	> 50 years	40-49 (if other criteria for suitable met)
Tumor size	0-2cm	2.1-3cm
Margins	Negative (with 2mm or more)	Close (<2m)
ER status	Positive	Negative
Multifocality	Clinically unifocal with tumor size less than 2cm	Clinically unifocal with tumor size less than 3cm
Grade	Any	Any
LVSI	None	Limited/focal
Histology	IDC and other favorable types	ILC
Nodes	N0 (i-, i+)	"
BRCA1/2	Not present	"
Pure DCIS	"low risk" – 9804 criteria	3cm or less if other

Correa et al., PRO 2017

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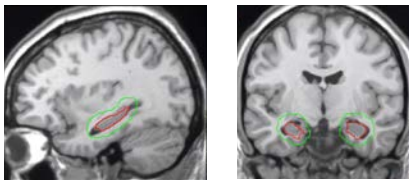
Hippocampal Sparing Whole Brain Radiation

Red: Hippocampus **Green: Hippocampal Avoidance Zone**



MR images from: Holmes CJ, Hoge R, Collins L, et al. "Enhancement of MR Images Using Registration for Signal Averaging" Journal of Computer Assisted Tomography 22, 324-333 (1998)

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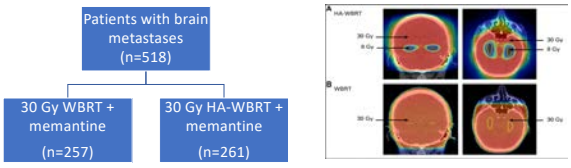
Hippocampal Avoidance Whole Brain Radiation Therapy (HA-WBRT), NRG Oncology CC001



Primary endpoint: Time to neurocognitive failure
Median follow up: 7.9 months (alive patients)

Brown et al., JCO 2020

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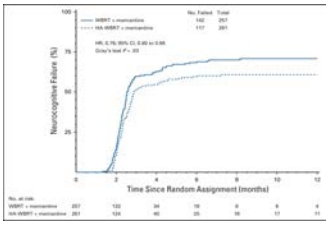
Hippocampal Avoidance Whole Brain Radiation Therapy (HA-WBRT), NRG Oncology CC001



Brown et al., JCO 2020

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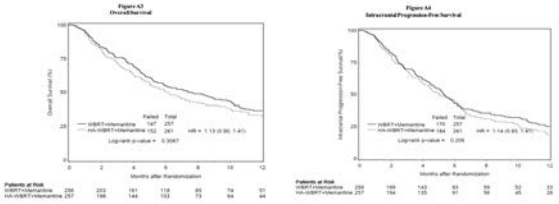
Hippocampal Avoidance Whole Brain Radiation Therapy (HA-WBRT), NRG Oncology CC001



"HA-WBRT should be considered a standard of care for patients with good performance status who plan to receive WBRT for brain metastases with no metastases in the HA region."

Brown et al., JCO 2020

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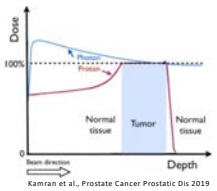
Protons

- Energy deposited at specified depth, followed by rapid energy fall off
- Given improvements in dosimetry, ***potential*** to a) spare side effects via reduction in dose to normal tissues, b) allow for dose escalation in resistant tumors, and c) re-irradiate safely
- Most data is from single center or retrospective series showing safety and efficacy of protons, with very little randomized data comparing protons to photons!



Kamran et al., Prostate Cancer Prostatic Dis 2019

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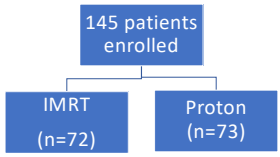
Proton Therapy
Randomized Phase IIB Trial for Esophageal Cancer



Primary endpoint: Total toxicity burden (TTB) and progression-free survival (PFS)
Median follow up: 44 months

Lin et al., JCO 2020

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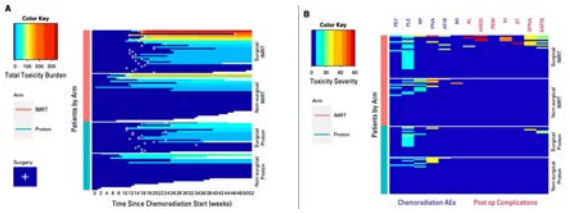
Proton Therapy
Randomized Phase IIB Trial for Esophageal Cancer



Lin et al., JCO 2020

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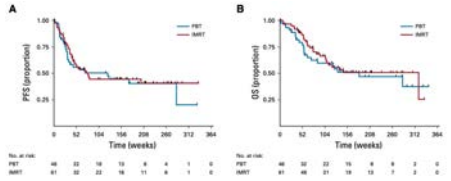
Proton Therapy
Randomized Phase IIB Trial for Esophageal Cancer



First randomized evidence supporting the utility of proton beam radiation to reduce toxicity.

Await ongoing studies evaluating role of protons in lung cancer, gliomas, meningioma, hepatocellular carcinoma, breast cancer, prostate cancer, and head and neck cancer.

Lin et al., JCO 2020

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Poll Question 3

- Which of the following is a technique to decrease radiation induced toxicity?
  - Higher radiation doses
  - Reduced radiation volumes and/or sparing of important normal tissues (i.e., hippocampal avoidance whole brain)
  - Delivery of concurrent immunotherapy
  - Hypofractionation

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Conclusions

- Hypofractionation is now considered standard of care for many cancer types and indications will likely continue to grow
- We must continue to discover ways to improve the therapeutic ratio of radiation
  - Combination strategies to improve anti-tumor effects for those tumors that may benefit from enhanced tumor control
  - Reduction in toxicity from radiation in those tumors with excellent disease control and/or significant morbidity via decreased volume/dose and improvements in technology

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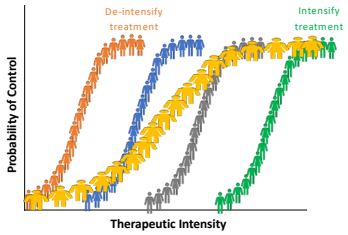
Next Steps for Radiation? Precision Radiation



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