Topics

- The history of fractionation
- The resurgence of hypofractionation
- Theorized risks and benefits of hypofractionation
- Basic radiobiology
- The UK and Canadian experiences
- What about a boost?
- For whom should we consider not using it?
- Current NCCN and ASTRO guidelines/recommendations
The History of Fractionation

- Early understanding of biology was frequently anecdotal but two schools of thought emerged as rivals and have become associated with the locations of their major proponents
  - The German School
  - The French School
The German School

- Primarily seated in Erlangen
- Hermann Wintz and Georg Perthes
- Theorized that radiation would be more effective if given in a single fraction
- Persisted into the 1920’s
Gottwald Schwartz

- Theorized in the mid 1910’s that fractionation might be more effective as cells would be allowed to enter the more sensitive phase of mitosis.
The French School

• Based out of The Radium Institute in Paris
• The external beam and biological branch was headed by Cladius Regaud in the Pasteur Pavilion section.
Sterilization of ram's testis without excessive skin reactions using fractionated radiation (Claude Regaud)
Dr. William D. Coolidge
and his NEW MAGIC RAY

Producing as Many ELECTRONS Every SECOND as a TON of RADIUM

By Robert Merrill

What will it do for Humanity?

Dr. Coolidge, assistant director of the Research Laboratory of the General Electric Company, Schenectady, recently startled scientists by his cathode tube invention which, according to the manufacturer, will have a far-reaching influence on the future development of electrical appliances. The tube, which was created after years of research, is said to be capable of emitting as many as 300,000,000,000 electrons per second, a figure that is far beyond the capabilities of other known tubes. This extraordinary development has the potential to revolutionize the electrical industry, with applications ranging from lighting to communication systems. The tube's ability to produce such high energy levels is attributed to the use of a special cathode material, which has not been disclosed by the manufacturer. The implications of this technology are vast, and it is anticipated that it will be the subject of extensive exploration in the coming months.
Henri Coutard

- Fractionated in part due to the fact that his tubes had to cool between applications.
- His clinical outcomes and experience resulted in an expansion of fractionation at The Radium Institute cementing its place in the 1920’s and 1930’s.
Francois Baclesse

- Successor to Coutard at The Radium Institute
- He developed new fractionation schedules aimed at decreasing mucositis and shrinking fields
Gilbert Fletcher and the US

• Gilbert Fletcher, trained in Paris and influenced by the French School and Baclesse, comes to the US in 1942 and becomes chair at MD Anderson Cancer Center in 1948
• Relationship between Total Dose (TD) and Biological Effective Dose (BED) depends on \textit{dose per fraction}.
  
  – Conceptual understanding for over 100 years.
  – As Fraction size $\uparrow$ total dose must $\downarrow$ to maintain equal...
    • Antitumoral effect
    • Normal tissue detriment

• Ellis Isoeffect Formula (Hypothesis) \( \text{NSD} = \frac{\text{Dose}}{T^{0.11}} N^{0.24} \)
  
  – (Ellis F. Clin Radiol 1969; 20:1-7)
  – \( 50\text{Gy}/25\text{fx} = 45\text{Gy}/15\text{fx} \) for skin reactions

Ellis’ proposal was a **hypothesis** meant to be tested clinically

- Radiation Oncologists applied the formula uncritically in late 70s - early 80s
- Late effects of subcutaneous fibrosis/brachialplexopathy/telangectasia, etc. were more sensitive than acute skin reactions to fraction size
- “Hyopfractionation” fell out of favor due to anecdotal bad experiences

Ellis’ formula insufficient for matching late effects

- Assuming typical $\alpha/\beta$ value of 3.0 for late normal tissue response with linear-quadratic (LQ) model: $45\text{Gy}/3\text{Gy}/fx \mapsto 54\text{Gy}/2\text{Gy}/fx$
  - For tissues like brachial plexus ($\alpha/\beta \sim 2.0$), BED = 56.3Gy
- Reductions in TD Necessary for 15 fraction regimens
  - $42.8\text{Gy}/2.85\text{Gy} \mapsto 50\text{Gy}/2\text{Gy}$
  - $40\text{Gy}/2.67\text{Gy} \mapsto 45.5\text{Gy}/2\text{Gy}$
    - Brachial plexus ~ 47Gy/2Gy
- Ellis formula for isoeffective doses led to overdosing of tissues where late effects are dose limiting

Hypofractionation Compromised

• Historical experience of HF:
  – Inadequate downward adjustment of total dose
  – Poor dosimetry/ high skin doses
  – Low energy beams, non-standard reference points
  – Delivery of medial/lateral tangents on alternate days
  – Failure to detect gross off-axis dose inhomogeneities
Resurgent Hypofractionation

- Melanoma
- Lung
- Prostate
- Metastases
- Breast
Melanoma

• Ang et al 1994  IJROBP Head and neck  30Gy/6fx improved 5 yr LRC and survival – widely extrapolated

• RTOG 83-05 had failed to show a difference in mild hypofractionation 2.5 Gy X 20 vs a more aggressive regimen 8.0 Gy X 4

• Konefal et al 1987  Radiology  ≤5 Gy 9% CR vs 50% with >5 Gy
Lung

- Cheung et al 2002 IJROBP T1/T2N0 4Gy X 12 fx with OS at 46% at 2 years and DFS 40% at 2 years
- Timmerman et al 2010 JAMA RTOG 0236 18Gy X 3fx (after homogeneity corr – rx 20X3) 55 patients with 2 year estimates of LC at 94% OS at 72% and DFS at 66.6%
- Videtic et al 2011 IJROBP Cleveland Clinic 30 Gy X 1 fx 32 lesions (stage I) with LC 100% at 1-2 yrs and median distant DFS 11 months
- Long term results from 0618 and 0813 pending
Prostate

• Cyberknife  Oliai et al 2013  JRO 7.25 X 5 fx  52 pts  27 LR 18 IR 7 HR
  with 1+/-1 failure at median 23 month follow up
• Pollock et al 2013  JCO  2.0 Gy X 38 vs 2.7 Gy X 26 303 pts
  randomized similar control and toxicity excepting those with
  significant pretreatment urinary problems
• Kupelian et al 2007  IJROBP 2.5 Gy X 28  770 pts acceptable control
  and toxicity overall 5 yr BRFS 82%
• RTOG 0938 ongoing phase II  ARM 1  7.25 Gy X 5 fx  ARM 2 4.3 Gy X
  12 fx
Metastases

- Choosing wisely: 8.0 Gy X 1 to 4.0 Gy X 5 for bony metastases and no more than 10 fx routinely.
- Oligometastatic disease in the brain, lungs, and liver may be treated with SRS/SBRT.
- RTOG 79-05 Phase I/II trial for advanced pelvic metastases: 10.0 Gy X 1 for up to 3 courses with Misonidazole then 3.7 Gy BID for 2 days for up to 3 courses without Misonidazole. Better tolerance with the less hypofractionated regimen.
Theorized risks of hypofractionation

- More potential toxicity to sensitive OAR with low $\alpha/\beta$ ratios
- Potential sparing of malignancies with high $\alpha/\beta$ ratios relative to surrounding normal tissue
- Potential diminishment of re-assortment and re-oxygenation
Normal Tissue Complications

• Cosmetic outcome:
  – Photographic change: most commonly atrophy (shrinkage)
    • Edema, retraction, telangectasia also contribute
  – Complex phenotype: pathogenesis?
    • Early induration: fat necrosis
    • Late induration: fibrosis
    • Photographic appearance may not quantify injury to pectoralis muscle, chest wall
      – Patient self-assessment must accompany photographic assessment to obtain whole picture
Normal Tissue Complications

• Lung injury?
  – Lung dose delivered by tangential fields exceeds tolerance no matter the fractionation schedule
    • Volume of lung irradiated in modern era makes pneumonitis rare

• Heart injury?
  – Priority is to protect the organ regardless of dose
    • There is no “safe” dose to the heart, no matter the fractionation
Theorized benefits of hypofractionation

- Convenience
- Cost
- Use of resources
- Biological advantage in less sensitive malignancies
- Potentially fewer late and early effects going against the Regaud model but seen clinically in the Canadian and US breast experience
Radiobiology of hypofractionation

• 4 R’s + 1
  – Repair – may be less important in lesions with a low $\alpha/\beta$
  – Redistribution - favors fractionation
  – Repopulation - favors shorter courses
  – Reoxygenation – FAVORS fractionation
  – + Radioresistance/Radiosensitivity
Response to Fractionation Varies With Tissue

Fractionation spares late responding tissues

\[ \alpha/\beta \text{ is high (>6Gy) when survival curve is almost exponential and low (1-4Gy) when shoulder is wide} \]

Dose (Gy) vs. S.F. for Acute and Late Effects.

- **Acute Responding Tissues**: \( \alpha/\beta = 10\text{Gy} \)
- **Late Responding Tissues**: \( \alpha/\beta = 2\text{Gy} \)

Single Dose Effects:
- **Acute Effects**: \( \alpha/\beta = 10\text{Gy} \)
- **Late Effects**: \( \alpha/\beta = 2\text{Gy} \)

Fractionated Effects:
- **Acute Effects**: \( \alpha/\beta = 10\text{Gy} \)
- **Late Effects**: \( \alpha/\beta = 2\text{Gy} \)
Radiobiology: Dosimetry

• “Double Trouble” (Withers, 1992 PPRO)
  – Significance of a hot spot that not only receives a higher dose, but also a higher dose/fraction
  – Hot spots will be penalized even more severely if using HF: “triple trouble” (Yarnold et al 2011 RO)

<table>
<thead>
<tr>
<th>Dose inhomogeneity</th>
<th>2 Gy</th>
<th>3 Gy</th>
<th>4 Gy</th>
<th>5 Gy</th>
<th>6 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>105%</td>
<td>107.1%</td>
<td>107.1%</td>
<td>108.0%</td>
<td>108.3%</td>
<td>108.5%</td>
</tr>
<tr>
<td>110%</td>
<td>114.4%</td>
<td>115.5%</td>
<td>116.3%</td>
<td>116.9%</td>
<td>117.3%</td>
</tr>
<tr>
<td>115%</td>
<td>121.9%</td>
<td>123.6%</td>
<td>124.9%</td>
<td>125.8%</td>
<td>126.5%</td>
</tr>
</tbody>
</table>

“Triple trouble” describes the relative change in the equivalent dose in 2-Gy fractions as a function of magnitude of hot spot and dose per fraction for hypofractionated schedules that are isoeffective at the 100% reference point. For example, if 2.0 Gy is prescribed to the 100% reference point, a 110% hot spot receives a 14.4% higher dose, so if 25 fractions are prescribed, the 100% hot spot receives 114.4% of 50.0 Gy = 57.2 Gy, α/β = 3 Gy. Original plan was normalized to 2 Gy per fraction at the 100% isodose contour.
Radiobiology of hypofractionation

- A serial organ will be damaged if one of its sub-volumes is damaged – e.g., brain, spinal cord, rectum, bladder
  - Marked dose damage at lower volumes
- A parallel organ will lose function only if all sub-volumes of the organ are damaged – e.g., lung, kidney
  - Less dose damage at lower volumes with a steeper late rise
Radiobiology of hypofractionation

- Owen et al 2006 Lancet and Dewar et al 2007 JCO
  - UK START Trial
    - 50Gy in 25Fx c.w. 39Gy in 13Fx; or 41.6Gy in 13Fx [or 40Gy in 15Fx (3 wks)]
  - Breast Cancer $\alpha/\beta = 4.0\text{Gy (1.0-7.8)}$
  - Breast appearance $\alpha/\beta = 3.6\text{Gy};$ induration $\alpha/\beta = 3.1\text{Gy}$

- Fewer fractions and larger doses can be considered regarding efficacy and possibly safety/late effects when the $\alpha/\beta$ ratios are similar for the malignancy and the surrounding tissue
Randomized Trials

• UK RMH/GOC

• UK START A/B (STAndardization of breast RadioTherapy)

• UK FAST

• Canada/Ontario Clinical Oncology Group
Royal Marsden Hospital / Gloucestershire Oncology Center

- Owen et al 2006 Lancet-Onc
- 1986-1998
- 2 Gy X 25 fx vs 3 Gy X 13 fx vs 3.3 Gy X 13 fx
- 1410 pts
- 10 yr relapse 12.1%(50), 14.8%(39), 9.6%(42.9)
- Cosmesis 39>50>>42.9
- Boosts of 14 Gy/7 fx were used in a substudy
UK Experience

START A

- 2008 Lancet
- 1998-2002 2236 pts randomized median F/U 5.1 yrs
- 2 Gy X 25 fx vs 3 Gy X 13 fx vs 3.2 Gy X 13 fx
- 22.7% under 50, 28.8% node+, 28.1% G3, 35.5% chemo
- Slightly higher 5 yr relapse rate for 39 Gy (5.2% vs 3.6% [50 Gy] and 3.5% [41.6 Gy]) and worse imaged and self scored cosmesis for 41.6 Gy
- 14% were given SCRT and 60.6% boosts of 10 Gy
UK Experience

START B

- 2008 Lancet
- 1999-2001  2215 pts randomized median F/U 6 years
- 2 Gy X 25 fx vs 2.67 Gy X 15 fx
- 20.7% under 50, 22.8% node+, 23.0% G3, 22.2% chemo
- Slightly higher 5 yr relapse rate for 50 Gy (3.3% vs 2.2% [40.05 Gy]) and better imaged and self scored cosmesis for 40.05 Gy
- 7.3% were given SCRT and 42.6% boosts of 10 Gy
Meta-analysis

- Meta-analysis of RMH, START A, START B
  - Hazard Ratios for LR by grade (p=0.12)
    - GRADE 1-2: 1.28 (95% CI: 0.87-1.88)
    - GRADE 3: 0.83 (95% CI: 0.56-1.23)
  - Adjusted α/β ratios:
    - GRADE 1-2: 3.6Gy
    - GRADE 3: 2.2Gy
  - “results suggest that response to radiotherapy fraction size is not affected by tumor grade”

Haviland et al. 2010 NEJM
START 10 yr Data

• Haviland et al 2013 Lancet-Onc

• START A relapses 6.3%(41.6), 7.4(50) and 8.8%(39) with better cosmesis for 39 vs 50 and 41.6

• START B relapses 4.3%(40.05) and 5.5%(50) with better cosmesis for 40.05
### Table: Number of events/patients and Hazard ratio (95% CI)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of events/patients</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>60/343</td>
<td>0.79 (0.47-1.34)</td>
</tr>
<tr>
<td>40-49</td>
<td>116/1046</td>
<td>0.88 (0.60-1.28)</td>
</tr>
<tr>
<td>50-59</td>
<td>154/2226</td>
<td>1.03 (0.74-1.44)</td>
</tr>
<tr>
<td>≥60</td>
<td>114/2246</td>
<td>1.11 (0.75-1.63)</td>
</tr>
<tr>
<td><strong>Primary surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast conservation surgery</td>
<td>409/5348</td>
<td>0.97 (0.80-1.19)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>35/513</td>
<td>0.91 (0.46-1.81)</td>
</tr>
<tr>
<td><strong>Axillary nodes (pN)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>289/4318</td>
<td>1.10 (0.86-1.40)</td>
</tr>
<tr>
<td>Positive</td>
<td>149/1421</td>
<td>0.80 (0.57-1.11)</td>
</tr>
<tr>
<td><strong>Tumour grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41/1213</td>
<td>0.96 (0.51-1.82)</td>
</tr>
<tr>
<td>2</td>
<td>108/2398</td>
<td>1.07 (0.72-1.59)</td>
</tr>
<tr>
<td>3</td>
<td>114/1272</td>
<td>0.86 (0.59-1.25)</td>
</tr>
<tr>
<td><strong>Tumour bed boost radiotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>199/2749</td>
<td>0.99 (0.74-1.32)</td>
</tr>
<tr>
<td>Yes</td>
<td>241/3071</td>
<td>0.99 (0.76-1.29)</td>
</tr>
<tr>
<td><strong>Adjuvant chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>303/4346</td>
<td>1.09 (0.86-1.38)</td>
</tr>
<tr>
<td>Yes</td>
<td>139/1480</td>
<td>0.81 (0.57-1.14)</td>
</tr>
</tbody>
</table>

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HYPOfractionation

- Once or twice-weekly large fractions
- Courdi et al. (2006, RO) France
  - N=115 (1987-1999), Elderly (med 78y); NO SURGERY
  - 6.5Gy X5 fractions, once-weekly
    - Boost (1, 2 or 3 fractions of 6.5Gy)
  - 5y PFS = 78%
  - Late effects: G1 (24%); G2 (21%); G3 (6%)
- Kirova et al. (2009, IJROBP) France
  - N=50, Elderly AFTER SURGERY
  - 6.5Gy X5, once weekly
  - 7y PFS: 91%; G1-2 induration=33%
- 6.5Gy X 5 = 62Gy in 31 Fx (α/β = 3)
HYPOfractionation

• UK Pilot Study
  – Martin et al. (2008, Clin Onc.)
    • N=30; > 50y; pT1-2, No, No Chemo
    • 30Gy/5fx, 15 days
    • Acute Tox: 13% moist desquamation
    • 2y cosmesis: 77%=no change from baseline (photo)
    • 3y PFS: 100%

• UK FAST Trial (2011, RO)
  – N=915; 2004-2007; >50y, pT1-2, No
UK Experience

FAST

• 2 Gy X 25 fx vs 5.7 Gy X 5 fx (1/wk) vs 6 Gy X 5 fx (1/wk)

• 2004-2007 915 pts randomized 3 arm 88% G1/2 89% HR+ (endocrine tx)

• Yarnold et al 2011 RO 2-5 year follow up – 3 yr median
  – > moderate adverse effects 9.5% vs 11.1% vs 17.3%

• Similar fractionation in a Phase II out of Louisville with 1 yr results published by Dragun et al in 2012 IJROBP - acute effects only reported thus far
Table 2
Acute skin reactions during treatment by fractionation schedule.

<table>
<thead>
<tr>
<th>RTOG grade</th>
<th>Fractionation schedule</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 Gy (%)</td>
<td>30 Gy (%)</td>
</tr>
<tr>
<td>0 = No visible change</td>
<td>8 (7.3)</td>
<td>28 (25.2)</td>
</tr>
<tr>
<td>1 = Faint/dull erythema</td>
<td>51 (46.4)</td>
<td>67 (60.4)</td>
</tr>
<tr>
<td>2 = Tender/bright erythema ± dry desquamation</td>
<td>39 (35.5)</td>
<td>13 (11.7)</td>
</tr>
<tr>
<td>3 = Patchy moist desquamation, moderate oedema</td>
<td>12 (10.9)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>4 = Confluent moist desquamation, pitting oedema</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total with known RTOG grade for acute skin reaction</td>
<td>110 (100)</td>
<td>111 (100)</td>
</tr>
<tr>
<td>Not recorded*</td>
<td>187</td>
<td>192</td>
</tr>
<tr>
<td>Not known</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total randomised</td>
<td>302</td>
<td>308</td>
</tr>
</tbody>
</table>

* Acute toxicity data was not collected from the beginning of the trial.

Table 3
Change in photographic breast appearance at 2 years by fractionation schedule.

<table>
<thead>
<tr>
<th>Fractionation schedule</th>
<th>Total, N = 729 (%)</th>
<th>Risk ratio for 30 Gy vs 50 Gy (95% CI), p-value for trend</th>
<th>Risk ratio for 28.5 Gy vs 50 Gy (95% CI), p-value for trend</th>
<th>Risk ratio for 30 Gy vs 28.5 Gy (95% CI), p-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy, N = 239 (%)</td>
<td>189 (79.1)</td>
<td>1, p &lt; 0.001</td>
<td>1, p = 0.26</td>
<td>1, p = 0.002</td>
</tr>
<tr>
<td>30 Gy, N = 248 (%)</td>
<td>160 (64.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.5 Gy, N = 242 (%)</td>
<td>184 (76.0)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

No change

<table>
<thead>
<tr>
<th>Risk ratio for 30 Gy vs 50 Gy (95% CI), p-value for trend</th>
<th>Risk ratio for 28.5 Gy vs 50 Gy (95% CI), p-value for trend</th>
<th>Risk ratio for 30 Gy vs 28.5 Gy (95% CI), p-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, p &lt; 0.001</td>
<td>1, p = 0.26</td>
<td>1, p = 0.002</td>
</tr>
<tr>
<td>1, p = 0.26</td>
<td>1, p = 0.002</td>
<td></td>
</tr>
<tr>
<td>1, p = 0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mild change

<table>
<thead>
<tr>
<th>Risk ratio for 30 Gy vs 50 Gy (95% CI), p-value for trend</th>
<th>Risk ratio for 28.5 Gy vs 50 Gy (95% CI), p-value for trend</th>
<th>Risk ratio for 30 Gy vs 28.5 Gy (95% CI), p-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, p &lt; 0.001</td>
<td>1, p = 0.26</td>
<td>1, p = 0.002</td>
</tr>
<tr>
<td>1, p = 0.26</td>
<td>1, p = 0.002</td>
<td></td>
</tr>
<tr>
<td>1, p = 0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Marked change

<table>
<thead>
<tr>
<th>Risk ratio for 30 Gy vs 50 Gy (95% CI), p-value for trend</th>
<th>Risk ratio for 28.5 Gy vs 50 Gy (95% CI), p-value for trend</th>
<th>Risk ratio for 30 Gy vs 28.5 Gy (95% CI), p-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, p &lt; 0.001</td>
<td>1, p = 0.26</td>
<td>1, p = 0.002</td>
</tr>
<tr>
<td>1, p = 0.26</td>
<td>1, p = 0.002</td>
<td></td>
</tr>
<tr>
<td>1, p = 0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UK FAST Trial

Fig. 2. Kaplan-Meier plot of time to moderate/marked physician assessed breast shrinkage, by fractionation schedule. 95% CI = 95% confidence interval. Events reported at 1 year were excluded from the analysis.

Fig. 3. Kaplan-Meier plot of time to moderate/marked physician assessed breast induration, by fractionation schedule. 95% CI = 95% confidence interval. Events reported at 1 year were excluded from the analysis.
# UK FAST Trial

## Table 5
Relapses, second primary cancers and deaths by fractionation schedule.

<table>
<thead>
<tr>
<th></th>
<th>50 Gy</th>
<th>30 Gy</th>
<th>28.5 Gy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local (breast skin or parenchyma)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Regional (axilla or supraclavicular fossa)</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Distant</td>
<td>5</td>
<td>2</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td><strong>Second primary cancer</strong></td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>6</td>
<td>5</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td><strong>Other cause</strong></td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

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* a Deaths from other causes included 4 cardiac-related events, 2 of which were in patients who received left-sided radiotherapy.
UK guidelines

• 40Gy in 15 fractions/3 weeks is now recommended by the National Institute for Clinical Excellence (NICE) as standard of care for adjuvant breast radiotherapy in the UK
  – No clinical rationale for excluding underrepresented subgroups
  – Breast-conservation or Post-mastectomy
  – DCIS, systemic chemotherapy or premenopausal
  – Regional nodal irradiation or not

Yarnold, IJROBP (2011)79:1; Yarnold, 2012 SABCS, Plenary Session
Canadian Protocol
First report Whelan et al 2002 JNCI

- 1993-1996 - 1234 randomized patients T1/T2,No
- 2.65 Gy x 16 fx vs 2 Gy x 25 fx
- Median F/U 69 mo
- <50 yrs 24.5%, G3 19%, ER- 26.5%, Chemo 11%
- 5 yr recurrences 2.8% (42.5) and 3.2% (50)
- 5 yr EORTC cosmetic score good/excellent 76.8% (42.5) and 77.0% (50)
Canadian Protocol
10 year + data Whelan et al 2010 NEJM

- 10 yr local recurrence 6.2% (42.5) and 6.7% (50)
- G3 subgroup 15.6% (42.5) vs 4.7% (50)
- 10 yr cosmetic score 69.8% (42.5) vs 71.3% (50) No significant difference for age or tumor size between groups
- Discussion did not suggest DCIS could be extrapolated
Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients.
Boost?

• The vast majority of the randomized trials did not routinely utilize a boost but the EORTC data was not available when they were designed.

• Consider it strongly for pts under 50, G3, very close or positive margins, LVSI and other high risk factors.
EORTC 22881-10882
Bartelink et al 2007 JCO

HR = 0.59
99% CI, 0.46 to 0.76
P < .0001
Relative contraindications

• Node positive patients
• Triple negative patients
• Adjuvant chemotherapy patients
• Younger patients
Node positive patients

- Discrete nodal radiation is not currently recommended though node + patients were included in both START trials.
- The HeNRIetta Trial phase II non-randomized trial recruiting SLN positive and ALND patients into a hypofractionationated regimen in 2 separate arms. 50+ yrs opened 2015 VCU/NCI
Triple negative patients

- TNBC are not absolutely contraindicated but are typically found in younger patients receiving chemotherapy which are both currently recommended to have conventional fractionation. Additional study is required. The START and Ontario trials did include "ER-" cancers. Long term results of OCOG showed poorer results with G3.
Adjuvant chemotherapy patients

- Generally felt to increase toxicity both acute and chronic regarding the skin and underlying soft tissues.
- The START and Ontario trials included chemotherapy patients but were not specifically powered to allow subgroup analysis for this issue.
Adjuvant chemotherapy patients

- Hijal et al 2010 Current Onc(McGill) 162 patients (48 chemo) with no appreciable difference in skin toxicity
- Kouloulias et al 2014 WJCC(Greece) 50.54-53.2 Gy in 19-20 fx 116 pts (83 chemo) 27.6% G1, 7.8% G2 and 2.6% G3 skin toxicity (EORTC) all were >25 days post chemotherapy
- Zygogianni et al 2014 Breast J(Greece) found a marked increase in skin toxicity with less than 20 days interval between chemotherapy and HFRT
Large breasts

- Not a contraindication but segmented fields / forward planned modulated fields are useful for minimizing V105 and above.
- Regardless, patients with a separation of >25 cm or a PTV of >2500cc should be counseled to expect more skin reaction than their peers as they should be for any fractionation schedule.
Large breasts

- Randomized trials limited breast size for inclusion ("separation")
- Dorn et al. (2012 IJROBP) U. Chicago
  - N=80, BMI 29.2, Median Vol (~1300cc)
  - 42.5Gy/16
  - Sep >25cm not significant
  - Vol >2500cc ↑ rate of acute skin toxicity (moist desquamation)-27.2% vs. 6.3%
- Hannan et al. (2012 IJROBP) UTSW/Columbia
  - Sep >25cm; Vol >1500cc ↑ rate of acute skin toxicity (moist desquamation)-28% vs. 12%
  - Prone positioning may limit toxicity
- Goldsmith et al. (2011 RadOnc) UK
  - Change in cosmesis in large breast patients can be related to dose inhomogeneity
Younger patients

- Not included in most US guidelines though these patients were included in the randomized trials.
- Their exclusion is often linked to grade, receptor status and chemotherapy.
Older patients

- Generally, the ideal candidate
- May be a candidate for no RT
- May require conventional schedule for aggressive histology or adjuvant chemotherapy
ASTRO guidelines 2011
Smith et al 2011 IJROBP

- Recommendations as published officially expired 12/31/2015 but have not been updated in a published manner
- Age $\geq 50$
- T1 or T2 (DCIS felt to be insufficiently studied)
- Node negative
- No chemotherapy (lack of data, particularly with modern agents, rather than overwhelming negative data)
- Dose +/- 7% on CAX plane
NCCN guidelines

• “Hypofractionation is preferred”
Dose per fraction

- Pick your favorite 265-267 cGy are the most common doses with a range from 225 – 330 cGy.

- The ideal dose has yet to be determined
Thank You