Hypofractionation and positioning in breast cancer radiation

John Hardie, M.D., Ph.D.
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At McFarland/MGMC we treat early stage breast cancer with 42.4 Gy in 16 fractions, in the prone position.

Some Questions:
1. Why?
2. Does it work as well as conventional radiation?
4. Who, exactly, is treated this way?
5. What does all this stuff mean anyway?
A little radiobiology... (try not to snore, please)

Radiation dose is measured in units of GRAY (Gy)

For scale, a chest xray is about 0.0001 Gy
Natural background radiation for 1 year is about 0.003 Gy.
Average CT scan is about 0.01 Gy
Maximum dose for radiation workers in a year is 0.05 Gy
Temporary radiation sickness at 1 Gy (whole body)
LD50 for whole body radiation is 5 Gy.
Invariably fatal whole body dose is 10-12 Gy (death within 2 weeks)
Immediately fatal whole body dose (death within 48 hours) is 30 Gy.

Typical course of radiation therapy is 50 Gy (NOT whole body)
The very early days

• X rays discovered: 1895
• Freund treats hairy nevus – 1896.
• Low output xray tubes (low dose rate).
• Technique: Turn on machine. Check patient occasionally. Turn off. Repeat daily. When skin turns red, or blisters or hair falls out, stop (1).
• Worked for skin cancers.
• Dose not measured – determined by clinical effect.

(1) Radiation Oncology residency was much shorter then...
• 1900 – higher intensity xray tubes.

• Dose not known for treatment effects – done clinically to effect, then dose recorded.

• Initially used a single large dose (10% larger than the amount to cause skin reaction).

• Assumed that organs were equivalent to skin.

• Doses later given in H.E.D. (Haut Erythema Dose), or alternatively in Holzknecht units (1/3 of the H.E.D., about 1 Gy).

It was determined early on that radiation could kill cancer cells at different rates than normal tissue cells. The details took most of a century to begin to be understood.
The cutaneous dose necessary for the healing of these cancers is small, on an average [6000 r (on the skin)], with fields of 50 sq. cm. and a duration of 15–25 days.

X ray treatment of radioresistant cancers of the larynx, which have immobilised the hemi-larynx, infiltrated the muscle, and invaded the cartilage, is generally difficult. In spite of heavy doses these cases are not often cured and accidents may occur. Doses of 7000 to 8000 r or more are required and often constitute the maximum supported by the tissues.

with alternating cutaneous doses which have been able to reach as a maximum in some cases 700 and even 800 r per day, during one, two, or three days; sometimes a dosage of only 200 to 300 r per day has been used, or even

Fractionation: 60-70 Gy in 1.7-2.6 Gy fractions

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### Table I

| Lymphosarcoma of the mouth, tongue, and nasopharynx |
|---------------------------------|--------------|--------------|
| **Cases treated**               | **Survivals** | **Survivals** |
| from 1920 to 1926.              | after 5 years | after 7 years |
| 45                             | 8 (17%)       | 8 (17%)       |

### Table II

| Epithelioma of the tonsillar region |
|------------------------------------|--------------|--------------|
| **Cases treated**                  | **Survivals** | **Survivals** |
| from 1920 to 1926.                 | after 5 years | after 7 years |
| 46                                | 13 (28%)     | 8 (17%)      |

### Table III

| Epithelioma of the larynx         |
|-----------------------------------|--------------|--------------|
| **Cases treated**                 | **Survivals** |
| from 1920 to 1926.                | after 5 years | After 7 years |
| 77                                | 22 (28%)     | 21 (27%)     |

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Coutard, *Principles of X ray therapy of malignant disease*, Lancet 1934
This paper also discusses:

- Treatment over 15-21 days (larynx), 25-31 days (hypopharynx), and 30-40 days (tonsil)
- Doses of 6000-8000 which (when tolerated) cured some cancers but not others.

So they tried dose escalation:
(but were limited by toxicity)

“We next thought it possible to obtain cure in differentiated cancers by increasing the dose. These efforts were fruitless. Under the same conditions of treatment, increasing the dose above 10,000 r up to 12,000 r, and even 15,000 r, never gave us a single case of cure but always aggravated the general condition of the patient; modifications of the vasculo-

They also tried BID hyperfractionation well:
(which worked pretty well, though toxic)

... extended the duration of treatment for certain cancers, ... from 30 to 90 days, by means of weak daily doses (in the order of 175, 200, 225, or 250 r per day), distributed in two seances, without varying the other factors and particularly the size of the fields.
• **Patterson** – 5000 R in 3 weeks (44 Gy/15-21 fx) or 5500 R in 5 weeks for SCC(48Gy/30-35 fx). *(Treatment of Malignant Disease by Radium and X-rays. Williams and Wilkins, 1949)*

• **1940s** – Strandqvist recovery curves used to adjust fractionation schedules for supposedly “equivalent” doses, but frequently resulted in severe complications/adverse events.

• **By mid century** (1950s), data showed
  • Straightforward increase in dose can increase control but also toxicity
  • Longer courses can get equivalent control but require higher total doses and smaller fractions to avoid toxicity.
  • No good theory of tumor response and toxicity.
Survival Curves

\[ S = e^{-aX} \]

Describes the number of items left after some random process.

- \( S \) = surviving fraction (from original population)
- \( a \) = constant to make units and scale work
- \( X \) = number of occurrences of an event which removes members from the population.

Shape of the survival curve gives clues to structure of the underlying physical process.
\[ S = e^{-\alpha d - \beta d^2} \]

Sgouros et al., *Radiobiology and dosimetry of alpha particle emitters for targeted radionuclide therapy*, Journal of Nuclear Medicine, 51 (2) 2010
Linear Quadratic Model

• Cell death caused by double strand break in DNA.
• Two ways to get this lesion
  1. Single photon induces break in both strands.
  2. Two photons induce “close” breaks in single strands without time for repair between the two events.

And now for a handwaving argument....
“Plausibility argument” for LQ model

• To determine cell survival, we need to:
  • Estimate the number of double strand breaks
  • Use this number as the exponent in a survival function.

• The number of double strand breaks will have at least two terms, deriving from
  • A single photon event
  • A two photon event
Single photon event.

The number of double strand breaks by this mechanism depends on:

- The number of photons
- The energy deposited by a photon
- The angles between the photon and the DNA molecule
- The size of the DNA molecule
- The likelihood that a given energy deposition will break a DNA strand

\[ N_1 = k_1 \cdot g_1 \cdot V_{dna} \cdot \frac{d\sigma}{d\Omega} \cdot (E \cdot \frac{d\phi}{dt} \cdot dt) = \alpha d \]

Fudge factor

Factors that depend on the DNA but not the photons

Factors that depend on the photon alone. (e.g. dose)

Double photon event

The number of two photon double strand breaks depends on:

- The number of photons
- The geometry of the DNA
- The energy deposition per photon
- The probability of a single strand break from this energy
- The probability that the two breaks are “close enough” together
- The probability that one of the breaks will be repaired before the second is delivered.

\[ N_2 = k_2 \cdot C_2 \cdot R_2 \cdot \left( g_2 \cdot V_{dna} \cdot \frac{d\sigma_s}{d\Omega} \cdot \left( E \cdot \frac{d\phi}{dt} \cdot dt \right) \right) \cdot \left( g_2 \cdot V_{dna} \cdot \frac{d\sigma_s}{d\Omega} \cdot \left( E \cdot \frac{d\phi}{dt} \cdot dt \right) \right) = \beta d^2 \]

- Close enough
- Not Repaired

First break

Second break
End result, LQ survival model

\[ S = e^{-(\alpha d + \beta d^2)} \]

Single photon event  
Not repairable

Double photon event  
Potentially repairable

Alpha describes the likelihood of a single photon event (aka “instant death”) while beta describes the likelihood of a two photon event (aka “I’m not quite dead yet – and I might get better”)

Also note, that this has been for single fractions only. For multiple fractions the exponent gets multiplied by the number of fractions.

\[ S = e^{-n(\alpha d + \beta d^2)} = e^{-\alpha \cdot n \cdot d \cdot (1 + \frac{d}{\alpha / \beta})} \]

Total dose for treatment course
In the multifraction curve the effect of the quadratic term is diminished and the curve looks closer to a simple exponential. This depends on the a/b ratio and the fraction size.
We would like to be able to compare these

Biological effect depends on:

1. Total dose of radiation given
2. The length of time to deliver the dose (days, weeks, etc.)
3. The size of individual doses (the fraction size)
4. The number of fractions given per unit time

This leads to the concept of “Equivalent Dose”, and to “Biologically Effective Dose”

Models to compute these include all of the above factors.
“Isoeffect” Doses produce the same effect
How do $\alpha$ and $\beta$ relate to early and late effects?

Although the radiosensitivity of the putative target cells determines the severity of an early or late effect in a normal tissue, the “earliness” or “lateness” of the clinical manifestation of that injury is related to the tissue’s proliferative organization (discussed above). The distinction between the radiosensitivity of a tissue’s cells and the radioresponsiveness of the tissue as a whole can be a source of confusion. Bergonié and Tribondeau’s “laws,” for example, confused the concepts of radiosensitivity and radioresponsiveness to some extent, referring to tissues that responded to damage early as “radio sensitive” when this was not necessarily the case.

Gunderson and Tepper, Clinical Radiation Oncology, 3rd edition, Elsevier, p47

Got that?

Very crudely, high $\alpha/\beta$ ratio suggests more single photon DSB than double photon and the target is likely to respond quickly because it can’t recover as well.

Conversely, low $\alpha/\beta$ ratio suggests that the tissue may be able to repair some of the potentially lethal or sublethal damage and show longer term changes in structure or function.

None of this is absolute, of course.
But $\alpha/\beta$ is not the entire story

• Equivalent dose (EQD2) also depends on how quickly the radiation is delivered.

• In the simplest model, longer courses of therapy allow tissues (including tumor) to start to recover, decreasing the effective dose of the treatment.

• Detailed, well justified models from first principles are not well established.

• We will use a simple approximation from Fowler.

Fowler et al., *Loss of biological effect in prolonged fraction delivery*, IJROBP 2004
Suggestions from the model

• Decreasing fraction sizes for fixed EQD2 for tumor will tend to decrease long term side effects. \((cet.\ par.\)\)
• This is partly offset by loss of efficacy from longer radiation course.
• Time effects can be reduced by increasing number of daily fractions.
• Increasing dose per fraction for fixed EQD2 tumor will increase long term effects.

Also, some typical values:  \textit{In general}

\textbf{Tumors} have alpha/beta of about \textbf{8-10}

\textbf{Acute toxicity} in tissues has an alpha/beta of about \textbf{10-15}

\textbf{Late toxicity} in tissues has an alpha/beta of about \textbf{3-5}
A little more explanation of confusing graphs.
40/15 for Low alpha/beta value for tumor

Number of fractions vs. Fraction size (Gy)

- 40/15
- Late Toxicity
- Tumor Control
- Acute Toxicity
- 40/15 No Repop Effects
It’s a nice theory – but does it work?
Some very complex measurements led to...

• An estimate that prostate cancer has an alpha/beta ratio between 1 and 3.

• An estimate that breast cancer has an alpha/beta ratio between 3 and 5.

• The normal tissues surrounding both have alpha/beta values of about 10 for acute effects and about 3 for late effects.
• For tumors with low alpha/beta ratios, the clinical benefit occurs with larger fraction sizes and smaller number of fractions.

• This is the part of the graph where the tumor control isoeffect curve lies above the late toxicity isoeffect curve.

• Moving this direction leads to equivalent tumor control with less long term toxicity.

• This leads to hypofractionated regimens for both prostate cancer and breast cancer.

• And to SBRT (or SBRT-like) regimens for both.

• Let’s take a look at some of them for breast cancer...
Multiple Breast fractionation regimens compared to 40/15

- Late Toxicity
- Tumor Control
- Acute Toxicity
- 50/25 Conv. No Boost
- 60/30 Conv. Boost
- EORTC Boost conv arm, 50/25
- EORTC Boost exp arm, 66/33
- Canadian trial 42.6/16
- START B 40/15
- START A 41.6/13 in 5wk
- FAST-Forward trial 27/5
- Mayo APBI 21.9/3
- ABS APBI HDR 34/10 BID
Based on equivalence analysis, we expect to see

- All of the hypofractionated regimens should be very similar.
- They all should have essentially the same late toxicity as conventional radiation without boost, and less than conventional radiation with boost.
- They should all have equivalent tumor control as conventional fractionation.
- They should (maybe) have better acute toxicity than conventional radiation.
Results: Canadian trial.... (Whelan et al, NEJM 2010)

• 1234 participants, early stage cancer, breast conserving surgery, negative nodes, tumor < 5 cm in size, negative margins, randomized to 42.4/16 or 50/25 fractionation. This was a noninferiority trial.

• At 10 years of follow up, there was no difference in local control, distant recurrence, locoregional recurrence.

• No difference in skin or subcutaneous long term toxicities.

• No difference in cosmetic outcome at 5 or 10 years.

• Conclusion: Hypofractionation is noninferior to conventional radiation for both tumor control and toxicity in this population of patients.
Results: START trials (Haviland et al., Lancet Oncol 2013)

• (Will cover START B only – START A similar).
• 2215 patients, early stage, node negative or N1 only, invasive carcinoma, completely excised, age > 18. Randomized to 50 Gy/25 fractions or 40.05 Gy/15 fractions, no boost.
• Median follow up of 9.9 years.
• No difference in local relapse, statistically, but probably not clinically better distant relapse and all cause mortality for hypofractionated regimen.
• Significantly decreased long term toxicity for breast shrinkage, induration, edema, telangiectasia. Other toxicities equivalent.
• Conclusion: Hypofractionation is at least as good as standard fractionation in this population, and may have better toxicity profile.
What about DCIS?

• The initial trials of hypofractionation did not include DCIS alone.
• However, there was no expectation that there should be a difference between IDC and DCIS, so it was done almost immediately.
• Recently, starting to see some study results for DCIS.
• For example: *Isfahanian et al., Clin Breast Cancer 2016.*
• Reviewed 348 patients with DCIS treated with either conventional radiation or hypofractionated.
• Found, at 64 months median follow up, that there was no difference in recurrence rate, or toxicity between the two regimens.
Another issue... Darby et al., NEJM 2013

• Case control study looking at coronary events in women treated for breast cancer.
• Found a 7% relative risk increase in cardiac events per gray of mean heart dose.
• While size of effect varied somewhat, the result was confirmed in other studies.
• Most used cohorts of patients treated well before the use of modern treatment planning. Mean heart doses were 4-8 Gy in general, depending on treatment given.
• This is a toxicity that is difficult to avoid with the kinds of dose adjustments we’ve been talking about.
• The solution is to get the heart out of the way of the beams.
Conventional tangent radiation for breast cancer

Heart is clipped by radiation fields without some changes to treatment planning.
Several techniques were tried

- **Supine with deep inspiration breath hold**
- **Prone positioning**
- Lateral decubitus positioning
- IMRT or other more conformal beam design techniques

All had advantages and disadvantages. All reduce heart dose, but

- Breath hold requires additional monitoring, practice, and prolongs treatment times.
- Prone requires different setup, equipment, and planning techniques
- Lateral decubitus is more complicated to set up and difficult to reproduce
- IMRT is more complex, more expensive, and requires longer treatments.
DIBH with supine positioning...

Heart falls away from chest wall on deep inspiration. Marker on chest is tracked by accelerator. Beam shuts off when patient exhales. Reduces mean heart dose to about 1 Gy.
Prone positioning

Heart moves closer to chest wall, but there is less motion of heart and chest wall, stabilizing posterior edge of radiation field. Also, gravity pulls the breast tissue anterior and away from chest wall allowing separation between beam edge and chest cavity while still covering breast tissue. Mean heart dose about 1 Gy, lower in some patients.
Does this make a difference? Maybe.

- Boero et al., IJROBP 2016
- Retrospective study of patients treated between 2000 and 2009 with modern planning techniques (not all had heart sparing techniques, all had modern 3D planning).
- Found that patients getting radiation on the left had 5.5% cumulative incidence of PCI, compared to 4.5% for treatment on the right.
- The increase risk was only apparent in the subgroup of patients with previous significant cardiac disease.
- The increased cardiac risk is not completely attributable to radiation as there was some difference in chemotherapy as well between groups.
- Of note, only diagnosis of CAD had an association with laterality (1.04 HR favoring right sided). - this is a 4% relative risk increase in patients with significant history of coronary disease prior to radiation.
Metaanalysis by Taylor and Kirby Clin Onc 2015

• Analysis of multiple evaluations of cardiac toxicity vs mean heart dose, modeling total cardiac risk as a function of baseline cardiac risk factors and radiation dose to the heart.

• Found that, for patients with heart sparing radiation and mean heart doses less than 2 Gy, the absolute increase in cardiac risk at 20 years (risk for death from ischemic heart disease) is <0.1% in patients with no cardiac risk factors (and baseline risk of 0.5%) and is 0.2% for patients with cardiac risk (baseline risk of 0.9%).

• On the other hand, for patients who did not have heart sparing techniques, the absolute increase in risk at 20 years is 0.3% with no cardiac history and 0.7% for patients with cardiac history.
Incidentally, there is no difference in cardiac toxicity between conventional and hypofractionated treatment:

- Chan et al, IJROBP 2013
- Retrospective study of 5334 patients, < 80 years old, postoperative radiation to breast or chest wall alone. Median follow up 13.2 years. 485 left breast patients treated with conventional radiation, 2221 with hypofractionation.
- There was no difference in cardiac related hospitalization or cardiac morbidity/mortality between the two cohorts.
- Conclusion: the more rapid delivery of radiation with hypofractionated approaches does not increase the cardiac risk.
Conclusions

1. Hypofractionated radiation provides equivalent disease control, less long term toxicity and, perhaps, less acute toxicity.
2. It is more convenient for the patients since it takes about half the time to complete treatment.
3. It is less expensive, also by about half.
4. We use prone positioning to reduce heart dose for these patients with left sided breast cancer.
5. We treat patients with right sided disease in the prone position also. No probable change in heart dose, but lung doses are better.
6. Use of prone positioning (and decreased heart dose) decreases long term risk of cardiac events in patients who are likely to be cured of their cancer (and who will therefore be exposed to the cardiac risk for a prolonged period)
Questions?