Altered Fractionation

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Radiation therapy is targeted therapy

- Absolute radioresistance does not exist: treatment failure occurs if and only if...
  - the biologically equivalent dose is not sufficiently high OR ...
  - there is disease outside the high-dose volume

- Normal tissue toxicity arises in irradiated tissues only and shows a dose-volume relationship
The dose-volume trade-off

Geographical miss

Dose-dependent failure

TOXICITY

Dose

Volume
Fractionation sensitivity – human data

- Moist desquamation
- Erythema
- SQCA head and neck
- Telangiectasia
- Frozen shoulder
- Fibrosis

Dose per fraction (Gy)

Dose correction (%)
LQ-model: limits of applicability

Low dose hyper-radiosensitivity (?)

Log-linear dose-effect (?)

Dose per fraction (Gy)

0 1 2 3 4 5 6 7 8 9 10
Dose-distribution \( \nu \) biological advantage

- LE neutrons
- HE neutrons
- IMRT neutrons
- neon ions
- Carbon ions
- Argon ions
- KV XRT
- MV XRT
- Conformal XRT
- stereotactic XRT, IORT, implants
- IMRT
- pions
- protons

increasing physical advantages

increasing RBE

increasing RBE
The “spaghetti” plot
Rib fractures after SBRT

Hodge et al. (in preparation)
Human tumor fractionation sensitivity

- Prostate
  - Bentzen & Ritter 2005

- Breast
  - Owen et al. 2006

- Esophagus
  - Geh et al. 2006
  - Bentzen et al. (in press)

- HNSCC

- Melanoma
  - Bentzen et al. 1989

- Liposarcoma
  - Thames & Suit 1986

- α/β (Gy)
Dose-fractionation effects cannot be analyzed without simultaneous consideration of dose distribution (and combined modalities)
Materials

Virtual clinical trial comparing
6MV IMRT *versus* tomotherapy *versus* proton therapy

15 patients

- 5 HCC
- 5 NSCLC (3 IA, 2 IIIA)
- 3 prostate
- 2 skull base

60 Gy/10F
70 Gy/35F
70 Gy/35F
50.4 Gy/28F

PI: Hidefumi Aoyama
Results of liver cases

General trend in DVHs

Tomotherapy reduced the high dose volume in normal liver.
Proton therapy reduced the low dose volume in normal liver.
Hepato-cellular carcinoma

![Graph showing EUD (Equivalent Uniform Dose) vs. a value for different methods]

- **Pinn**
- **Proton**
- **Tomo**

The graph illustrates the relationship between EUD and a value for various methods.
Skull base tumors: EUD for optic chiasm

The graph shows the values of EUD for different methods: Pinn, Proton, and Tomo. The x-axis represents the value, and the y-axis shows the EUD optic. The graph illustrates the trend of EUD values across different values.
NSCLC

The diagram shows a line graph comparing different methods for treating lung cancer: Pinn, Proton, and Tomo. The x-axis represents the 'a value' ranging from 0.6 to 2.2, and the y-axis represents the EUD lung ranging from 0 to 16. Each method is represented by a different color and line style:

- Blue circles represent Pinn.
- Red circles represent Proton.
- Green circles represent Tomo.

The graph illustrates the relationship between the 'a value' and the EUD lung for each method, showing how the methods perform under varying 'a value' conditions.
Symptomatic Pneumonitis vs. Mean Lung Dose

- MSKCC (10/78)
- Duke (39/201)
- Michigan-1 (17/109)
- MD Anderson (~49/223)
- NKI (17/106)
- WU (52/219)
- Michigan-2 (9/42)
- Heidelberg (10/66)
- Milan (7/55)
- Gyeonggi (12/68)

logistic fit

68% CI

Probability of Pneumonitis

Mean Lung Dose (Gy)
Pneumonitis – Lung bin protocol

Incidence of pneumonitis (%) vs. Lung mean NTD (Gy)

- Dashed line with circles: RT + adj. CT
- Solid line with squares: neo-adj. CT or RT alone

Step 4: Is individualized accelerated radiation possible by using selective mediastinal irradiation and dose prescription on the basis of the MLD? (NCT00573040).

Phase II trial.

De Ruysscher et al. ESTRO 27, 2008
Background. Isotoxic irradiation to a target MLD may lead to the best local tumor control rates vs. toxicity.

MLD scheme, BID
TCP: 34.8%

Gain: 25%

Phase II trial: Radiotherapy

- GTV: primary tumor and the initially PET-positive mediastinal lymph nodes (not anatomical areas) or to the pathological positive nodes to the following MLD:
  - MLD=19 Gy when FeV1 and DLCO > 50 %
  - MLD=15 Gy when FeV1 and/or DLCO 40-49 %
  - MLD=10 Gy when FeV1 and/or DLCO < 40 %
Results

- Median radiation dose: $63.1 \pm 13.9$ Gy ($5.4-79.2$)
- Median fractions: $34.8 \pm 8.5$ (3-44)
- Median overall treatment time: $25.5 \pm 7.2$ days (2-69)
- Median MLD: $13.6 \pm 4.5$ Gy ($2.4-19.9$)
- Median spinal cord dose ($D_{\text{max}}$): $37.6 \pm 17.3$ Gy ($0.7-58.4$)
- Median follow-up: $24.5 \pm 5.6$ months (13.3-34.4)
Local Tumor Progression per stage

- I: 2.3%
- II: 23.2%
- IIIA: 15.5%
- IIIB: 32.4%
Dose limiting toxicity: symptomatic pneumonitis
\( \alpha/\beta = 3.3 \text{ Gy} \)

Reduce number of fractions until iso-MLD reached
CAVEATS

- No consideration of
  - proliferation – may not be too important
  - hypoxia – important??
  - other Organs at Risk – surely important
  - motion and margins

- Iso-dose contours and DVH’s are not surrogate endpoints – not even after having been passed through a TCP/NTCP model

- Clinical benefit is more than local control
Distant Metastases per stage

I: 44.8 %

II: 77.8 %

IIIA: 58.0 %

IIIB: 60.0 %
Lung Ca Treatment Philosophy Needs a Massive Bailout!

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<td>63</td>
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<td>Lung</td>
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<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
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“High-dose” RT
Sequential CRT
Concurrent CRT
Targeted Drugs

Future Solutions?
- Prevention
- Early diagnosis and treatment
Randomizing protons versus photons

- **Equipoise**
  - Collective and Individual equipoise (Freedman)
  - What if $\text{NTCP}_{\text{proton}} << \text{NTCP}_{\text{photon}}$?

The number of degrees of freedom is too high!

Scientific utility?

$\text{NTCP}_{\text{photon}} - \text{NTCP}_{\text{proton}}$
For instance, men with early stage prostate cancer who choose radiation therapy might have no co-payment for 3-dimensional conformal radiation but might have to cover the marginal cost if they want more expensive intensity-modulated radiation therapy. Value-based co-payments would promote high-value interventions and discourage use of marginal medicine. It would help if patients were fully informed and empowered to make decisions they own.

Emanuel and Fuchs, JAMA 299: 2789 (2008)
Assuming the validity of the LQ-model, the following relationship holds up at any response level and irrespective of the exact mathematical form of the dose-response model:

\[
\gamma_N = \gamma_d \cdot \frac{\alpha/\beta + 2 \cdot d_r}{\alpha/\beta + d_r}
\]

Reference:
Bentzen Acta Oncologica 44: 825, 2005
The required accuracy in RT

- Random errors $\sim \frac{1}{\sqrt{N}}$
- Major mis-administrations $\sim \frac{1}{N}$
- Systematic dosimetric errors $\sim \gamma_N$
- Precision in dose/F prescription $\sim \gamma_N$
- Required accuracy increases with decreasing fraction number