Hypofractionated Radiotherapy

Frank Lohr

Department of Radiation Oncology, Chairman Prof. F. Wenz
Ludwig Seitz (1872-1961)

Hermann Wintz (1887-1947)

β) Bestrahlungsprinzipien bei den blastomatósen und hyperplastischen Erkrankungen.

1. Bestrahlungsmethoden, die den Zellfaktor berücksichtigen.

a) Die einzelne Bestrahlung.

Die Einzelbestrahlung.

Von

H. Wintz.

Absicht der Kongrüssleitung war es, in Einzelreferaten einen Überblick über die derzeitigsten Methoden der Strahlenbehandlung der Karzinome zu geben; daher wurde nur die Aufgabe gestellt, über die Einzelbestrahlung zu sprechen.

Seit mehr als 20 Jahren habe ich dem Prinzip der Einzelbestrahlung des Karzinoms geblieben; meine Technik und ihre Begründung sind in einer großen Anzahl Veröffentlichungen bereits niedergelegt.

Neue Ergeb

Methoden

Wenn ich die auf den anderen überwiegend unangenehmsten Fälle einbeziehen will, erhalten wir die Erfahrung, daß die Bestrahlung in der Regel eine Verteilung der Strahlen auf den gesamten Kanalanteil des Karzinoms bedingt.

Zunächst ist der Eindruck der Tatsache, daß die einheitliche und gleichmäßige Verteilung der Strahlen auf die ganze Ausdehnung der Geschwulst die beste Möglichkeit bietet, die Bestrahlung des Karzinoms zu verbessern. Dieser Eindruck ist durch die Erfahrungen der Praxis bestätigt worden.

Die Einzelbestrahlung hat sich als die beste Methode zur Behandlung der Karzinome erwiesen. Sie ermöglicht eine genauere, gleichmäßige Verteilung der Strahlen auf die ganze Ausdehnung der Geschwulst und ist daher die Methode der Wahl zur Behandlung der Karzinome.
Die Röntgenbehandlung der epithelialen Krebse der Tonsillengegend.

Von

H. Coutard, Leiter der Röntgenabteilung.

Von 1920—1925 wurden 46 Fälle von Epithelkrebs der Tonsillengegend mit Röntgenstrahlen in meiner Abteilung am Radiuminstitut der Pariser Universität behandelt.

I. Anatomisch-klinische Definition.

Da dieser Krebs gewöhnlich wenig schmerzhaft ist, kommen die Kranken meistens spät zur Untersuchung. 25mal erreichte der Tonsillektomie das Velum und die Üntula; 21 mal war er bis zum Sphen palatinus und Sphen pharyngeus vorgedrungen, wobei er bis an die Epiglotte reichte; in 15 Fällen war die Zange einzubringen; 7 mal der Mandibulak beitfiel; in 5 Fällen führte die Kranke aus die Symptome des Venenbläns ein aus.

Häufig ist es die Drüsenschwellung, welche die Kranken zum Arzt bringt, denn sie kommt sozusagen beständig vor und tritt frühzeitig auf: 14 Kranken zeigten eine einseitige Retromandibular- und (auskultobzw. der männlichen Seite von der Zunge); in 15 Fällen war der Umfang der Tubenbildung bedeutend größer. In 12 Fällen waren die Supraclaviculardrüsen infiltriert, oder es bestanden beiderseitig Drüsen.

II. Statistik und Einteilung der Resultate.

1. Mißerfolge:

84 Kranke sind gestorben oder sterben voraussichtlich in kurzer Zeit; sie verteilten sich folgendermaßen:

2 waren unerreichbar behandelt.

1 war in einem anderen Institut röntgenbehandelt und sein Krebsstrahleninmunus geworden.

3 hatten wiederholte Krebs, welcher sich auf einen großen Teil der Zange oder des Mandibulums ausgezücht hatte (einer dieser 2 Kranken 17°)

Henri Coutard
1876-1950
1951: Presentation of Concept of Radiosurgery

1967: First Treatment with Gammaknife (Thalamotomy, 180 Gy)

1969: First Treatment of an Acoustic Neuroma

1970: First Treatment of AVM (Leksell and Steiner)

Lars Leksell
1907-1986
Two paradigms that have to be discussed separately and that have different rationales:

1. Ablative Therapy („Radiosurgery“)
   -> relatively sharp interface between Tumor and Normal Tissue
   Rationale: **BECAUSE YOU CAN DO IT** and when it was started, a lot of effort went into precision-> you wouldn’t want to do that 30 times(and there might be some other beneficial effects........)

2. Nonablative Therapy („Radiotherapy“)
   -> area of overlap between Tumor and Normal Tissue
   Rationale: **Inverse Ratio of alpha/beta between Tumor and Normal Tissue**
Lung Cancer
Prostate Cancer
Breast Cancer
Lung Cancer
(also applies to Liver Lesions)
FIGURE 3. Local tumor control rate for 2 different radiation dose groups.

FIGURE 4. Local tumor control rate for 2 different tumor volume groups.

Hof et al., Cancer, 2007
Early Stage Lung Cancer

LC at 3 years: 88.1%

Fig. 1. Kaplan-Meier analysis of overall survival for all patients (N = 70). Median survival, 32.4 months (95% CI, 24.1–41.6 months). Three-year survival estimate, 42.7% (95% CI, 31.1–54.3%).

Fig. 2. Actuarial local control in an assessable patient.

Fig. 3. Actuarial survival for all patients.

Fig. 6. Cause-specific survival. Three-year survival estimate, 81.7% (95% CI, 70.0–93.4%).

Denver, Lung Metastases
Rusthoven, JCO, 2009

Indiana, Primary Lung Tumors
Fakiris, IJROBP, 2009
Fig. 9. Selection of number of fractions and dose per fractions based on the constraint models biologically effective dose (BED)_{10} > 100 Gy_{10} and local damage BED_3 < BED_{10}. Our proposed curves for estimating schedules, which will deliver chosen amounts of late biologic BED in Gy_3 (thin curves) and chosen levels of tumor BED in Gy_{10} (thick curves). Figures 9 and 10 are specific for our local method of dose delivery and are examples only, not to be generalized.

Fowler et al., IJROBP, 2004
Liver Tumors

Figure 1. The Lyman NTCP model depicting 5% risk isotherm curve, with 0.6 confidence limits, for patients with liver metastases. Effective volume (the region volume that is included to the prescribed dose uniformly would be associated with the same NTCP as the nonuniform dose distribution) versus normalized dose (prescribed dose normalized to 1 Gy per fraction)."^^\(^1\)"

Fig 1. Dose, effective liver volume irradiated (\(V_{\text{eff}}\)), liver toxicity risk levels, and patient treated tumor Response Evaluation Criteria in Solid Tumor response at ast follow-up. Dose was based on the risk level curves shown, with up to 3 Gy nore permitted as long as patient calculated risk was maintained and lower loses if required because of nonhepatic limits. PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease.

Dawson et al.,
Sem. Rad Oncol. 2005
Acta Oncol 2006
JCO, 2009
Liver Tumors

**Figure 4.** Tumor control rate using cumulative incidence analysis for competing risks of death.

**Figure 2.** Overall survival of (A) all patients and (B) by diagnosis.
Advanced Stage Lung Cancer

Jin, IJROBP, 2009

“Hypofractionation was preferred for small tumors and higher NTDs, and conventional fractionation was better for large tumors and lower NTDs. Hypofractionation might be beneficial for intermediate-sized tumors when NTD = 80–90 Gy, especially if the DL50 is small (20 Gy).”

See also: Atkison, TCRT, 2008
Kepka, J Thorac Oncol, 2009
Immunological Effects of RT

Radiation may render Tumor Cells (more) immunogenic

This may lead to an „Abscopal Effect“

Upregulation of Antigens, depending on Tumor line (Dose-Response-Relationship not completely clear)

Facilitation of Cross Priming/DC Maturation

Changes in Cytokine Profile (Micromilieu)

Cell Migration
Irradiated Tumor Cells may be Immunogenic

Lugade et al., J Imm, 2005
Migration of T-cells
in 4T1 Breast Cancer Cells after RT
(2 x 12 Gy)

Not an in-situ model, but otherwise highly relevant!!
Response modulated by iNKT cells
Dewan et al., Clin Canc Res, 2009

-> Doses of ~10 Gy may be optimal to elicit an immune response
Immunotherapy finally works!

**IMPACT Overall Survival: Primary Endpoint Intent-to-Treat Population**

- **P = 0.032 (Cox model)**
- **HR = 0.775 [95% CI: 0.614, 0.979]**
- **Median Survival Benefit = 4.1 Mos.**

**PROVENG (n = 341)**
- **Median Survival: 25.8 Mos.**

**Placebo (n = 171)**
- **Median Survival: 21.7 Mos.**
Summary Lung (Liver) Tumors

Small, early stage peripheral Lung (Liver) Cancer can properly be treated with hypofractionated RT.

For larger N0-Tumors (although this is a rare situation), particles would be beneficial

The Situation is unclear/problematic for large tumors/mediastinal involvement. Multiple Organs at risk (Heart, Esophagus) with unclear response to large single doses.

Large single doses may play an increasing role in the combination of RT and immunotherapy
FRACTIONATION AND PROTRACTION FOR RADIOTHERAPY OF PROSTATE CARCINOMA

DAVID J. BRENNER, D.Sc.,* AND ERIC J. HALL, D.Sc.**
Center for Radiological Research, Department of Radiation Oncology, Columbia University, New York, NY

DIRECT EVIDENCE THAT PROSTATE TUMORS SHOW HIGH SENSITIVITY TO FRACTIONATION (LOW α/β RATIO), SIMILAR TO LATE-RESPONDING NORMAL TISSUE

DAVID J. BRENNER, PH.D., D.SC.,* ALVARO A. MARTINEZ, M.D., F.A.C.R.,†
GREGORY K. EDMUNDS, M.Sc.,† CHRISTINA MITCHELL, R.N., B.S.N.,† HOWARD D. THAMES, PH.D.,†
AND ELWOOD P. ARMOUR, PH.D.†
*Center for Radiological Research, Department of Radiation Oncology, Columbia University, New York, NY; †Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI; ‡Department of Biostatistics, M. D. Anderson Cancer Center, Houston, TX

THE PROSPECTS FOR NEW TREATMENTS FOR PROSTATE CANCER

JACK F. FOWLER, D.Sc., PH.D.,* RICK J. CHAPPELL, PH.D.,† AND MARK A. RITTER, M.D., PH.D.**
Departments of *Human Oncology and †Biostatistics and Medical Informatics, University of Wisconsin-Madison, Madison, WI

UMM
UNIVERSITÄTSMEZIN
MANNHEIM

PTCOG 48, Heidelberg, 2009
FIGURE 1. Increasing therapeutic advantage with increasing hypofractionation. The equivalent total doses if delivered in 2 Gy fractions for prostate tumor (α/β = 1.5) and normal tissue late effects (α/β = 3) are shown versus fraction size-number combinations that preserve similar late effect levels, as would be predicted by the linear quadratic model. A reduction in total dose is required with increasing hypofractionation to maintain similar predicted late effects. The difference between the solid lines and dotted extensions on the right indicate in nonquantitative fashion a potential, over-prediction of biologic effect by the linear quadratic model for very large fraction sizes.

Ritter et al., Cancer J, 2009
The large randomized trials

55 Gy in 20# / 28d
Hoskin et al., Radiother Oncol, 2007

936 Patienten mit T1/T2 Tumoren
66 Gy in 33# / 45d vs.
52,5 Gy in 20# / 28d
The experience with moderate Hypofractionation

100 Patienten

70 Gy in 28# / 5,5 w

Fig. 1. Biochemical relapse-free survival for all 100 patients treated with high-dose hypofractionated radiotherapy. Both biochemical failure definitions were used. Symbols represent censored patients.

Fig. 3. Biochemical relapse-free survival (ASTRO definition) for the 310 patients treated with three-dimensional conformal radiotherapy with the conventional schedule of 78 Gy at 2 Gy per fraction (median follow-up of 71 months). The outcomes are displayed by low-, intermediate-, and high-risk groups. Symbols represent censored patients.

Fig. 4. Late rectal toxicity rates (RTOG Grades 2 and 3). (a) The Grade 3 only vs. the combined Grades 2 and 3 late rectal toxicity events. (b) All Grades 2 and 3 late rectal toxicity events vs. the Grade 2 or 3 events that were still persistent at last follow-up (i.e., 3% were still actually experiencing Grade 2 or 3 toxicity). Symbols represent censored patients.
Actuarial disease-free survival
49 pts, 60/2 Gy + 15/3 Gy

Kosakowski et al., in preparation

for the whole group (a), for patients with low (1)-, intermediate (2)- and high-risk group (3)(b) and for patients with or without androgen deprivation (c)
Actuarial incidence of late toxicity: erectile dysfunction (a), rectal bleeding (b) and incontinence (c) for the whole population.
The most recent data

60/3 or 63/3.15
Med. Follow up 49 Mo

Leborgne/Fowler, IJROBP, 2009

Table 3. Five-year actuarial rates of bNED

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Hypo (n = 89)</th>
<th>Standard (n = 130)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>96% (CI 0.932–0.994), n = 29</td>
<td>98% (CI 0.969–0.995), n = 56</td>
<td>0.64</td>
</tr>
<tr>
<td>Medium risk</td>
<td>84% (CI 0.767–0.924), n = 45</td>
<td>84% (CI 0.708–0.985), n = 66</td>
<td>0.75</td>
</tr>
<tr>
<td>High risk</td>
<td>85% (CI 0.711–0.993), n = 15</td>
<td>87% (CI 0.740–0.999), n = 8</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Abbreviations: bNED = biochemical control; CI = 95% confidence interval; Hypo = hypofractionation.

The rate of rectal Grade 2–4 complications was 5.5% in both treatment groups and of urinary Grade 2–4 complications was 5.6% in the Hypo and 3% in the standard group (p = 0.36)

King et al, IJROBP, 2009

36.25 Gy/7.25 Gy
Only low risk tumors
No relapse at 33 mo

Table 3. Late urinary and rectal toxicity on the RTOG scale after prostate SBRT

<table>
<thead>
<tr>
<th>RTOG grade</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary, late toxicity</td>
<td>30% (11)</td>
<td>41% (15)</td>
<td>24% (9)</td>
<td>5% (2)</td>
<td>—</td>
</tr>
<tr>
<td>Rectal, late toxicity</td>
<td>51% (20)</td>
<td>33% (13)</td>
<td>15% (6)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: RTOG = radiation therapy oncology group; SBRT = stereotactic body radiotherapy.
Studies under way:

As reviewed by Ritter et al.:

RTOG 0415 (70/2.5 vs. 73.8/1.8)
Fox Chase, and several Ultrahypo# trials
A few words of caution........

Several prostate hypofractionation trials using 20 fractions 3.0 Gy in 4 weeks are in progress (11–14). Their predicted acute mucosal EQD is 53.1 Gy, just above the 52.5-Gy EQD top of the recommended oral grey zone (1). Do these 5-fractions-per-week treatments (in 25 days) need changing to 4 fractions per week in 5 weeks (32 days)? The resulting 48.5-Gy EQD2 would be much safer, but present clinical reports do not complain about excess acute toxicity.

Leborgne and Fowler (14) changed their 20-fraction prostate schedule from 3.0 to 3.15 Gy per fraction because it seemed so safe, with a predicted rise of acute mucosal EQD2 from 48.5 Gy (“safe”) to 52.5 Gy (“upper border”). They then observed an increase in RTOG acute Grade 3 rectal reactions from 1 of 22 (4.5%) to 10 of 34 (29%, p = 0.05)

Fowler, IJROBP, 2009
Summary Prostate Cancer

Moderate Hypofractionation for Prostate Cancer with nominal doses >70 Gy seems to be safe with regard to rectal/bladder toxicity and seems to be effective for all risk groups -> Pending results of RTOG 0415

The perfect regimen for aggressive hypofractionation is still elusive, but regimens $<60 \text{ Gy TD and } <3 \text{ Gy SD}$ seem to be ineffective. 60 Gy/3Gy seems to be safe with a f/u of ~3 years.
Breast Cancer
The UK experience: The START A&B Trials

<table>
<thead>
<tr>
<th>Total dose (Gy)</th>
<th>Dose/fraction</th>
<th>Number of fractions</th>
<th>Weeks</th>
<th>5-year LRR (%)</th>
<th>10-year BRR (%)</th>
<th>p</th>
<th>5-year DM (%)</th>
<th>5-year OM (%)</th>
<th>p (DM/OM)</th>
<th>Breast changes*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMH/GOC (N=1410)*</td>
<td>50</td>
<td>2</td>
<td>25</td>
<td>5</td>
<td>7.9</td>
<td>12.1</td>
<td>NR</td>
<td>NR</td>
<td>--</td>
<td>6.4%†</td>
<td>3.6-9.2%</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>3</td>
<td>13</td>
<td>5</td>
<td>9.1</td>
<td>14.8</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3.9%</td>
<td>1.8-6.1%</td>
</tr>
<tr>
<td></td>
<td>42.9</td>
<td>3.3</td>
<td>13</td>
<td>5</td>
<td>7.1</td>
<td>9.6</td>
<td>0.027‡</td>
<td>--</td>
<td>--</td>
<td>11.2%</td>
<td>7.8-14.7%</td>
</tr>
<tr>
<td>START A (N=2236)*</td>
<td>50</td>
<td>2</td>
<td>25</td>
<td>5</td>
<td>3.6</td>
<td>--</td>
<td>9.8</td>
<td>11.1</td>
<td>--</td>
<td>15</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>41.6</td>
<td>3.2</td>
<td>13</td>
<td>5</td>
<td>3.5</td>
<td>--</td>
<td>9.5</td>
<td>11.3</td>
<td>--</td>
<td>1.09</td>
<td>0.85-1.40</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>3</td>
<td>13</td>
<td>5</td>
<td>5.2</td>
<td>--</td>
<td>NS</td>
<td>11.9</td>
<td>10.7</td>
<td>0.69</td>
<td>0.52-0.91</td>
</tr>
<tr>
<td>START B (N=2215)*</td>
<td>50</td>
<td>2</td>
<td>25</td>
<td>5</td>
<td>3.3</td>
<td>--</td>
<td>10.2</td>
<td>11</td>
<td>--</td>
<td>15</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>2.67</td>
<td>15</td>
<td>3</td>
<td>3.5</td>
<td>7.6</td>
<td>8</td>
<td>0.01/0.03</td>
<td>0.83</td>
<td>0.66-1.04</td>
<td></td>
</tr>
</tbody>
</table>

RMH=Royal Marsden Hospital. GOC=Gloucestershire Oncology Centre. LRR=locoregional recurrence rate. BRR=breast recurrence rate. DM=distant metastasis. OM=overall mortality. N=study size. NR=not reported. NS=not statistically significant. *Breast appearance assessed by photographs. Marked changes for RMH/GOC trial and mild plus marked changes for START trials. †5-year rates. ‡Difference between 39 Gy and 42.9 Gy groups. $Hazard ratio.

Table: Summary of results of UK randomised trials of hypofractionated radiotherapy in breast cancer

START Trials as reviewed by Bartelink/Arriagada
Lancet, 2008
A few relevant single center experiences

Greece (Plantaniotis, Breast Cancer, 2009): 339 pts, 42.5 Gy/16 fractions
f/u 2 years, locoregional control 99.5%, no conclusive data on cosmesis

NY (Constantine/Formenti, Clin Breast Cancer, 2009): 15 x 2.8 (42 Gy), 3 wks
„Among the patients with ≥ 3 years of follow-up, cosmesis was scored as good to excellent in 21 patients (91%) and fair in 2 patients (9%)“

France (Kirova, IJROBP, 2009): 25 x 2 Gy vs. 5 x 6.5 Gy, 1x/wk
„Late complications such as LENT-SOMA (late effects normal tissue-subjective, objective, management, analytic) Grade 1-2 fibrosis developed in 15% of the NF-RT and 33% of the HF-RT group.“ -> Reporting time not specified
Single center experiences: IORT as Boost

Fig. 1. Cosmetic evaluation after 6, 12, 18, 24, and 36 months on a score of 1 to 4. *One patient with a poor cosmetic result was treated with mastectomy because of marked fibrosis of the entire breast 12 months after intraoperative radiotherapy (IORT), and 1 patient was evaluated as having “fair” cosmetic outcome during further follow-up.

Kraus-Tiefenbache, IJROBP, 2006
Long term F/U data is necessary

- postop RT 1992, Co60
- 56 Gy TD/ 2 Gy SD in Prescription Plane
- in plane Maximum 109%
- off plane Maximum ???
- Capecitabine 2007-2009, after initiation started retraction of the breast

Lawton, IJROBP, 2007
Long Term F/U data exist in Sweden

Figure 3. Time from therapy to onset of symptoms. Time from end of therapy to onset of symptoms (latency). The diagram points to the fallacy of the use of truncated observation periods, i.e. 5 years. Injuries may appear many years later. Patients in this study with late appearing injuries were often disbelieved and discarded by the medical profession, stating that side effects could not appear after so many years. The diagram can give the visual impression that 100% of the women treated by hypofractionation are injured. It is the other way round: our study population is selected on the basis of known injuries.

Friberg and Ruden, Acta Oncol, 2009
Accelerated Partial Breast
38.5 Gy in 3.85 Gy/fraction, bid.

Table 4. Cosmetic results over time

<table>
<thead>
<tr>
<th>Cosmetic result</th>
<th>All patients (n = 90)</th>
<th>&gt;12 months follow-up (n = 80)</th>
<th>&gt;24 months follow-up (n = 80)</th>
<th>&gt;36 months follow-up (n = 80)</th>
<th>&gt;48 months follow-up (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>44 (49%)</td>
<td>44 (49%)</td>
<td>44 (51%)</td>
<td>43 (54%)</td>
<td>35 (59%)</td>
</tr>
<tr>
<td>Good</td>
<td>35 (38%)</td>
<td>35 (38%)</td>
<td>34 (36%)</td>
<td>27 (34%)</td>
<td>17 (30%)</td>
</tr>
<tr>
<td>Total excellent</td>
<td>79 (88%)</td>
<td>79 (88%)</td>
<td>75 (87%)</td>
<td>70 (88%)</td>
<td>50 (89%)</td>
</tr>
<tr>
<td>Fair</td>
<td>11 (12%)</td>
<td>11 (12%)</td>
<td>11 (13%)</td>
<td>10 (13%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Poor</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 7. Partial breast irradiation studies using external beam radiation

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. Cases</th>
<th>Follow-up (months)</th>
<th>Fractionation scheme</th>
<th>IBTR</th>
<th>Cosmetic result (good/excellent)</th>
<th>≥ Grade 3 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>William Beaumont Hospital, current study (27)</td>
<td>94</td>
<td>50 (median)</td>
<td>340 or 385 cGy × 10  (b.i.d.)</td>
<td>1.1%</td>
<td>89%</td>
<td>4%</td>
</tr>
<tr>
<td>New York University/Keck School of Medicine (28)</td>
<td>10</td>
<td>36 (minimum)</td>
<td>500, 550, or 600 cGy × 5 (10 days)</td>
<td>0%</td>
<td>100%</td>
<td>ns</td>
</tr>
<tr>
<td>Fomenti (11)</td>
<td>47</td>
<td>18 (median)</td>
<td>600 cGy × 5 (10 days)</td>
<td>0%</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Christie Hospital/Holt Radium Institute (26)</td>
<td>353</td>
<td>96 (mean)</td>
<td>500–531 cGy × 8 (10 days)</td>
<td>25%</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>National Institute of Oncology, Hungary (Phase III Trial)</td>
<td>40</td>
<td>86</td>
<td>200 cGy × 25</td>
<td>2.5%</td>
<td>70%</td>
<td>ns</td>
</tr>
<tr>
<td>Rocky Mountain Cancer Center (9)</td>
<td>55</td>
<td>34</td>
<td>385 cGy × 10 (b.i.d.)</td>
<td>0%</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Harvard (8)</td>
<td>99</td>
<td>36</td>
<td>3200 cGy 4 GY/b.i.d.</td>
<td>2%</td>
<td>97%</td>
<td>ns</td>
</tr>
<tr>
<td>RTOG 0319 (25)</td>
<td>53</td>
<td>—</td>
<td>385 cGy × 10 (b.i.d)</td>
<td>6%</td>
<td>ns</td>
<td>4%</td>
</tr>
<tr>
<td>Tufts University Brown University (22)</td>
<td>64</td>
<td>15</td>
<td>385 cGy × 10 (b.i.d)</td>
<td>ns</td>
<td>81.7%</td>
<td>8.3%</td>
</tr>
<tr>
<td>University of Michigan (21)</td>
<td>34</td>
<td>&gt;24</td>
<td>385 cGy × 10 (b.i.d)</td>
<td>ns</td>
<td>79.5%</td>
<td>ns</td>
</tr>
<tr>
<td>NSABP B39/RTOG 0413 Trial</td>
<td>3200</td>
<td>19.4</td>
<td>385 cGy × 10 (b.i.d)</td>
<td>ns</td>
<td>ns</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Abbreviations: b.i.d. = twice daily; ns = not stated; NSABP = National Surgical Adjuvant Breast and Bowel Project; RTOG = Radiation Therapy Oncology Group.

* Partial breast irradiation patients had a greater incidence of fibrosis, telangiectasias, and fat necrosis.

1 Personal communication.

Chen/Vicini et al, IJROBP, 2009
...and too much of a good thing......

Patients received 38.5 Gy in 3.85 Gy fractions bid

Fig. 2. Isodose distributions achieved in 3 patients. Both cases illustrate the surfactancy of the treatment. The cases differ with respect to the volume of the tumouric cavity and the proportion of normal breast irradiated.

Fig. 4. Distribution of the proportion of the breast reference volume in each case receiving 50% of prescribed dose (V50), by cosmetic outcome, among patients with good or excellent cosmetic at baseline.

Fig. 3. Visible impairment in cosmesis observed in 3 patients deemed to have unacceptable cosmesis after treatment.

Jagsi et al., IJROBP, 2009
Summary Breast Cancer

Partial Breast Hypofractionation seems to be safe and effective in a selected patient subset, confirmation pending. Meticulous Patient selection mandatory!!

Total breast Hypofractionation accepts small (based on current follow up) reductions in effectiveness and cosmetic outcome, yielding (almost) comparable to Normofractionation. Long term F/U pending !!!!
Conclusion

Hypofractionation has made its way (back) into Photon Radiotherapy. It is reasonably safe and effective for small tumors with clear interfaces to normal tissues (such as in Lung or Liver). It may have systemic effects not seen with fractionated RT.

Moderate Hypofractionation for Prostate Cancer seems to be safe and effective, the perfect regimen for aggressive hypofractionation is still elusive.

Partial Breast Hypofractionation seems to be safe and effective in a selected patient subset, confirmation pending. Total breast Hypofractionation accepts small reductions in effectiveness and cosmetic outcome, yielding (almost) comparable to Normofractionation. Long term F/U pending !!!!