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der Universität Heidelberg

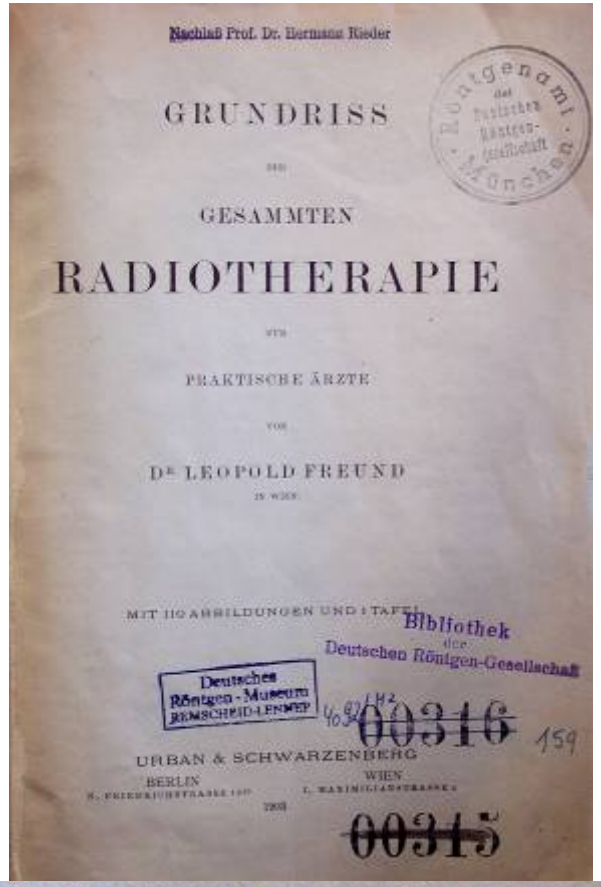
Universitätsklinikum Mannheim

Hypofractionated Radiotherapy

Frank Lohr

Department of Radiation Oncology, Chairman Prof. F. Wenz

Leopold Freund 1868-1943



[1]) Wiener med. Wochenschr., 1897, Nr. 10. Die von Prof. Dr. *E. Schiff* in letzter wiederholt publicirte Angabe, ich hätte diese Versuche unter seiner Controle gemacht, entspricht nicht den Thatsachen. Dieselben wurden von mir ganz selbstständig in der k. k. graphischen Lehr- und Versuchsanstalt in Wien ausgeführt; Herr Hofrath Director Dr. *J. M. Eder* allein stand mir damals in den rein physikalischen Fragen als Berather zur Seite.

Ludwig Seitz (1872-1961)

β) Bestrahlungsprinzipien bei den blastomatösen und hyperplastischen Erkrankungen.

1. Bestrahlungsmethoden, die den Zeitfaktor berücksichtigen.

a) Die einzeitige Bestrahlung.

Die Einzeitbestrahlung.

Von

H. Wintz.

Absicht der Kongreßleitung war es, in Einzelreferaten einen Überblick über die derzeitigen Methoden der Strahlentherapie des Karzinoms zu geben; daher wurde mir die Aufgabe gestellt, über die Einzeitbestrahlung zu sprechen.

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

Gesamtdosis den durch die Erholungsfähigkeit bedingten Verlust wieder

34a*

Hermann Wintz (1887-1947)

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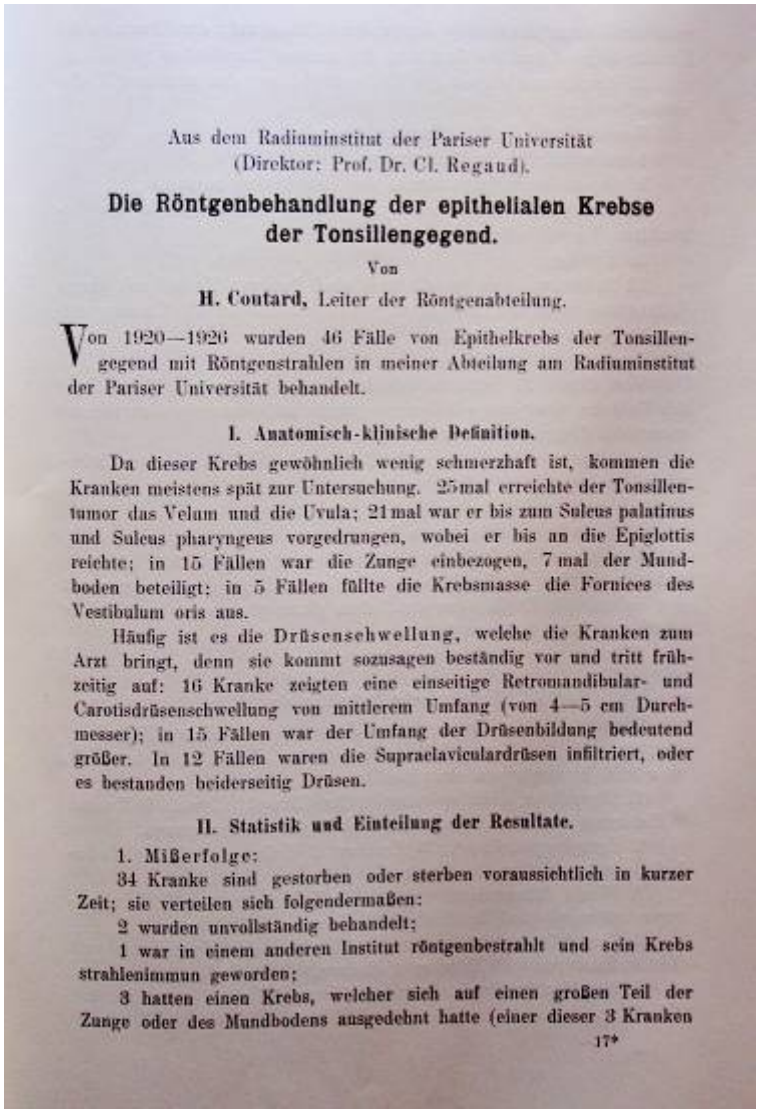
Henri Coutard
1876-1950



Aus dem Radiuminstitut der Pariser Universität
(Direktor: Prof. Dr. Cl. Regaud).

Die Röntgenbehandlung der epithelialen Krebse der Tonsillengegend.

Von

H. Coutard, Leiter der Röntgenabteilung.

Von 1920—1926 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 Tonsillentumor das Velum und die Uvula; 21mal war er bis zum Sulcus palatinus und Sulcus pharyngeus vorgedrungen, wobei er bis an die Epiglottis reichte; in 15 Fällen war die Zunge einbezogen, 7mal der Mundboden beteiligt; in 5 Fällen füllte die Krebsmasse die Fornices des Vestibulum oris aus.

Häufig ist es die Drüsenschwellung, welche die Kranken zum Arzt bringt, denn sie kommt sozusagen beständig vor und tritt frühzeitig auf: 16 Kranke zeigten eine einseitige Retromandibular- und Carotisdrüsenschwellung von mittlerem Umfang (von 4—5 cm Durchmesser); in 15 Fällen war der Umfang der Drüsenbildung bedeutend größer. In 12 Fällen waren die Supraclaviculardrüsen infiltriert, oder es bestanden beiderseitig Drüsen.

II. Statistik und Einteilung der Resultate.

1. Mißerfolge:

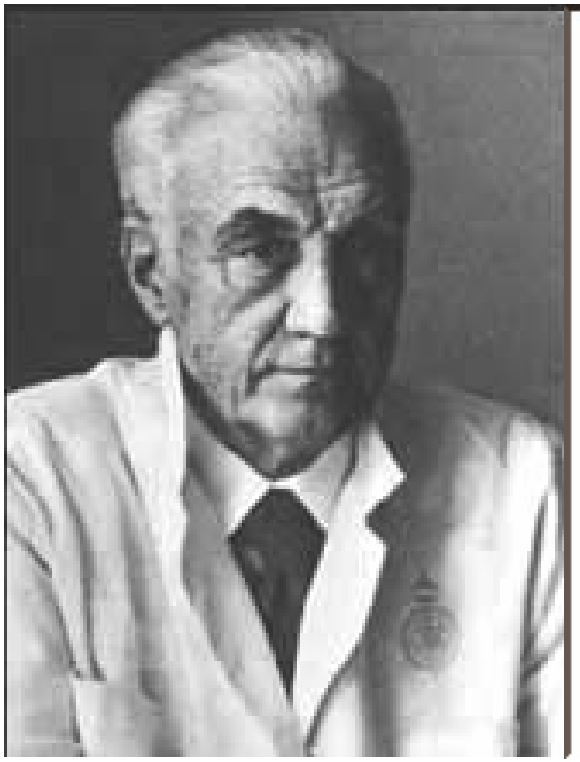
34 Kranke sind gestorben oder sterben voraussichtlich in kurzer Zeit; sie verteilen sich folgendermaßen:

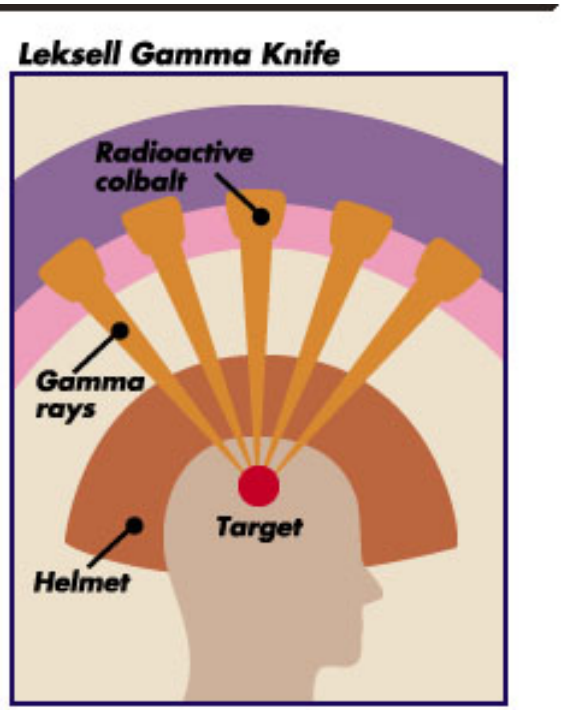
2 wurden unvollständig behandelt;

1 war in einem anderen Institut röntgenbestrahlt und sein Krebs strahlenimmun geworden;

3 hatten einen Krebs, welcher sich auf einen großen Teil der Zunge oder des Mundbodens ausgedehnt hatte (einer dieser 3 Kranken

17*





Lars Leksell
1907-1986

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)

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)

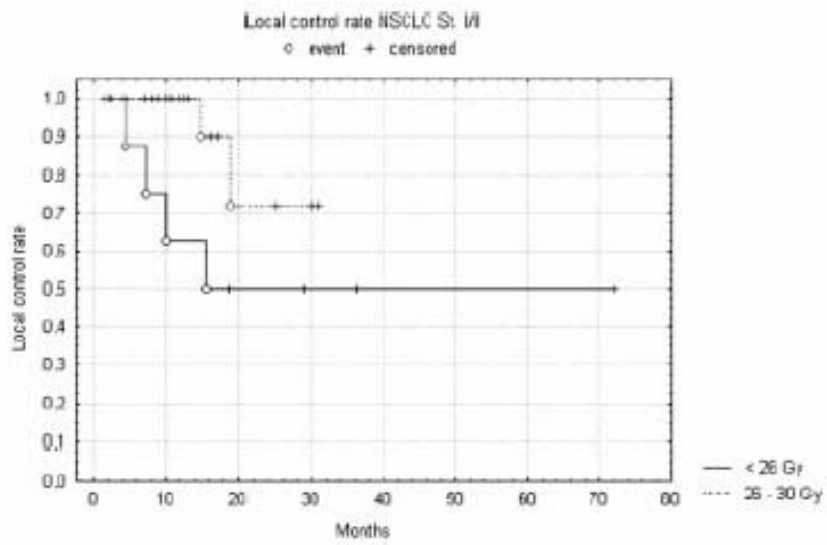


FIGURE 3. Local tumor control rate for 2 different radiation dose groups.

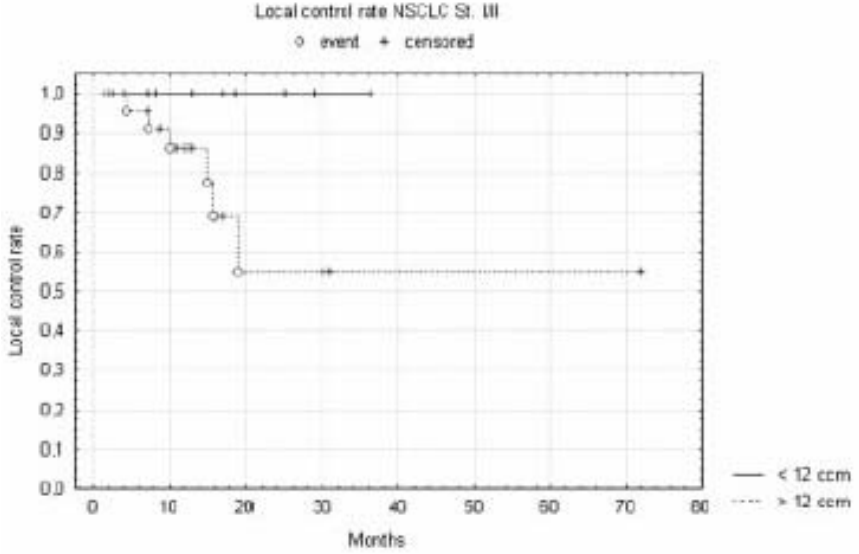


FIGURE 4. Local tumor control rate for 2 different tumor volume groups.

Hof et al., Cancer, 2007

Early Stage Lung Cancer

Denver, Lung Metastases
Rusthoven, JCO, 2009

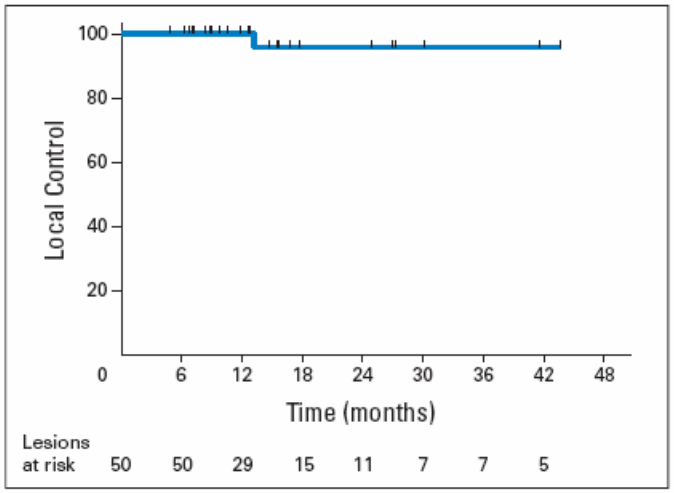


Fig 2. Actuarial local control in an assessable patient.

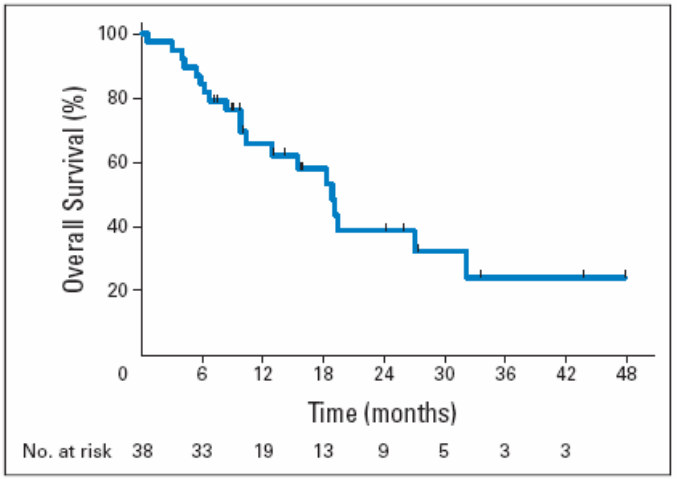


Fig 3. Actuarial survival for all patients.

Indiana, Primary Lung Tumors,
Fakiris, IJROBP, 2009

LC at 3 years:
88,1%

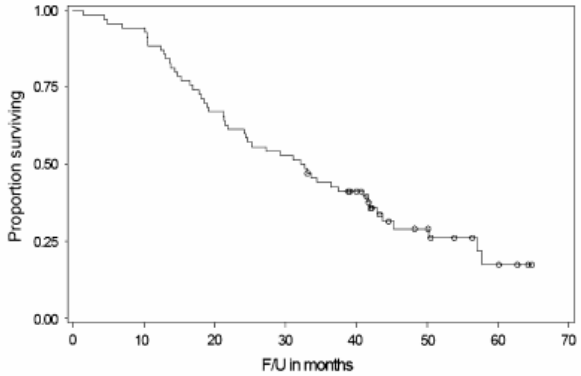


Fig. 1. Kaplan-Meier analysis of overall survival for all patients (N = 70). Median survival, 32.4 months (95% CI, 24.1–41.6 months). Three-year survival estimate, 42.7% (95% CI, 31.1–54.3%).

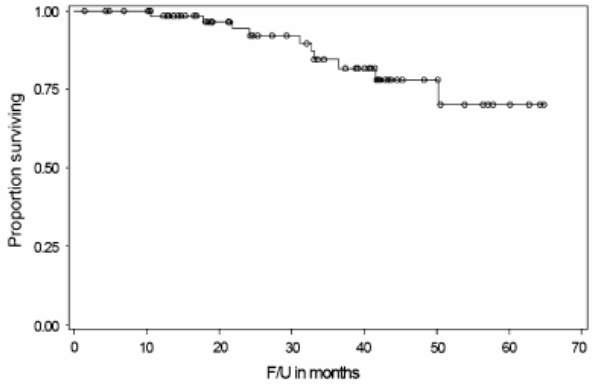


Fig. 6. Cause-specific survival. Three-year survival estimate, 81.7% (95% CI, 70.0–93.4%).

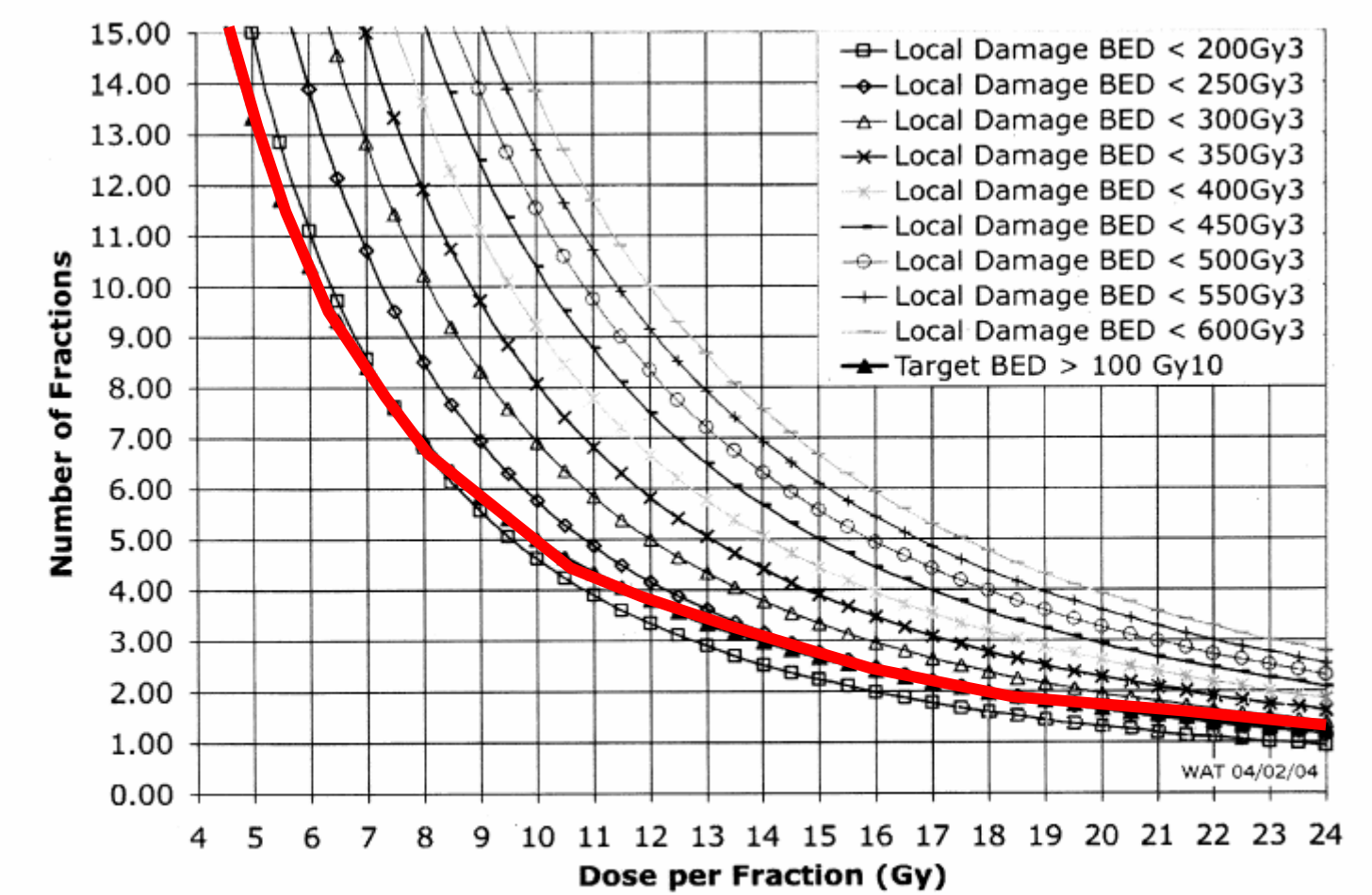


Fig. 9. Selection of number of fractions and dose per fractions based on the constraint models biologically effective dose $(BED)_{10} > 100\ Gy_{10}$ and local damage $BED_3 < BED_{ref}$. Our proposed curves for estimating schedules, which will deliver chosen amounts of late biologic BED in Gy_3 (thin 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

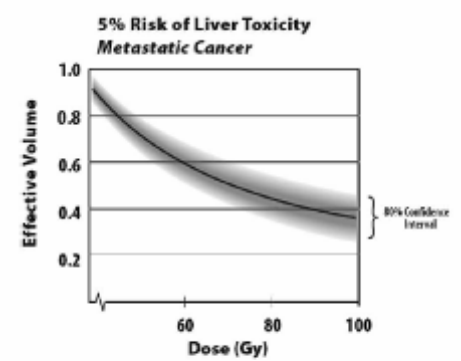


Figure 1 The Lyman NTCP model displaying 5% iso-NTCP curves, with 80% confidence limits, for patients with liver metastases. Effective volume (the organ volume that if irradiated to the prescribed dose uniformly would be associated with the same NTCP as the nonuniform dose distribution) versus normalized dose (prescribed dose normalized to 1.5 Gy twice a day).[11]

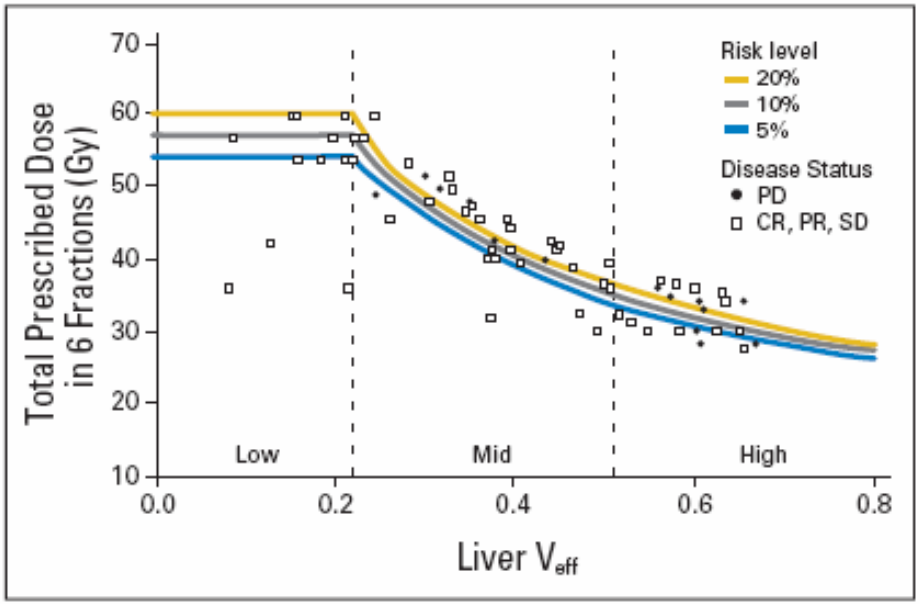


Fig 1. Dose, effective liver volume irradiated (V_{eff}), liver toxicity risk levels, and patient treated tumor Response Evaluation Criteria in Solid Tumor response at ast follow-up. Dose was based on the risk level curves shown, with up to 3 Gy nore permitted as long as patient calculated risk was maintained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

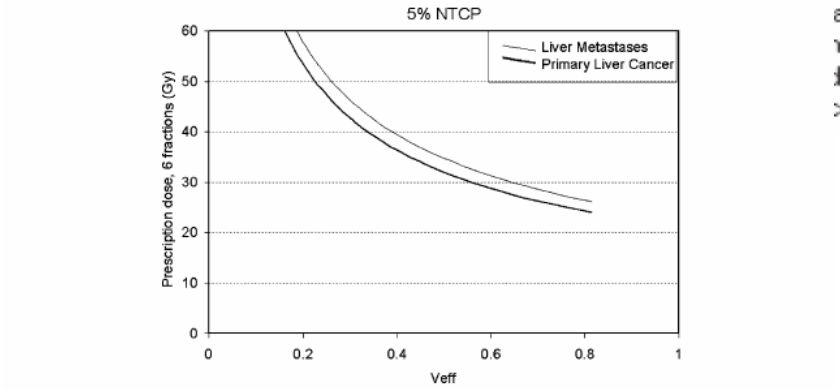


Figure 4. Dose- effective liver volume (V_{eff}) curve associated with a 5% risk of radiation induced liver disease for patients with liver metastases (thin line) and primary liver cancer (thick line).

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

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Liver Tumors

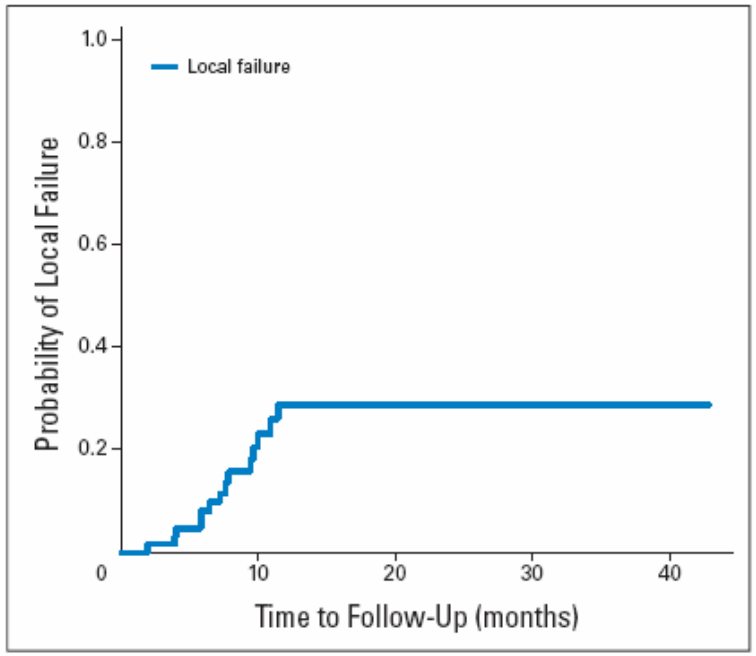


Fig 4. Tumor control rate using cumulative incidence analysis for competing risks of death.

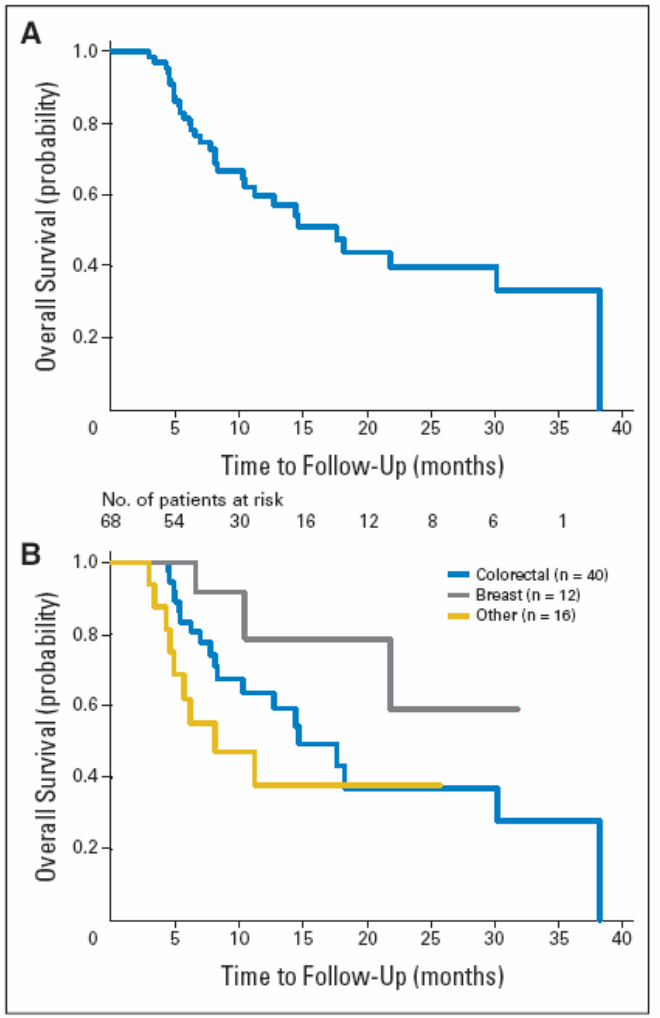


Fig 2. Overall survival of (A) all patients and (B) by diagnosis.

Advanced Stage Lung Cancer

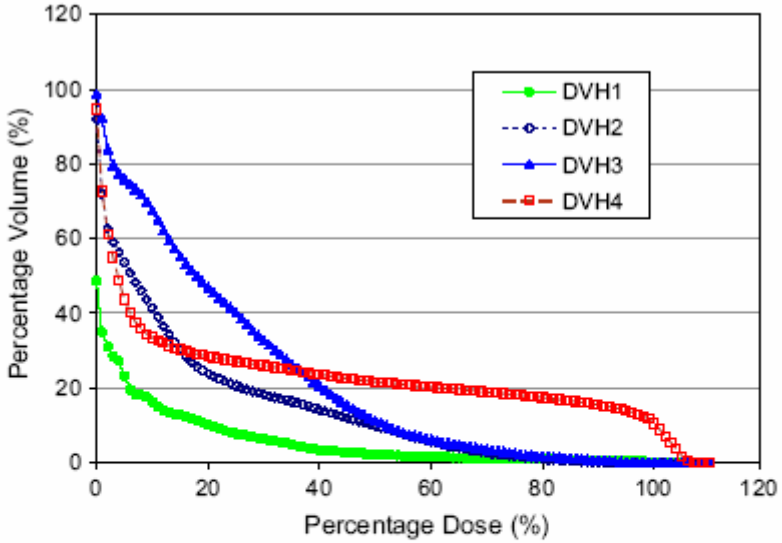


Fig. 1. Four representative dose–volume histograms (DVHs) used for the analysis. DVH1 was from a stereotactic body radiotherapy plan of a small gross tumor volume (GTV) (11 cm^3). DVH2 was from a similar hypothetical seven-field intensity-modulated radiotherapy plan of a relatively large peripheral tumor (GTV = 224 cm^3). DVH3 was from a seven-field plan of a large central lesion (GTV = 266 cm^3). DVH4 was from an anteroposterior/posteroanterior plan of the same large central lesion.

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“

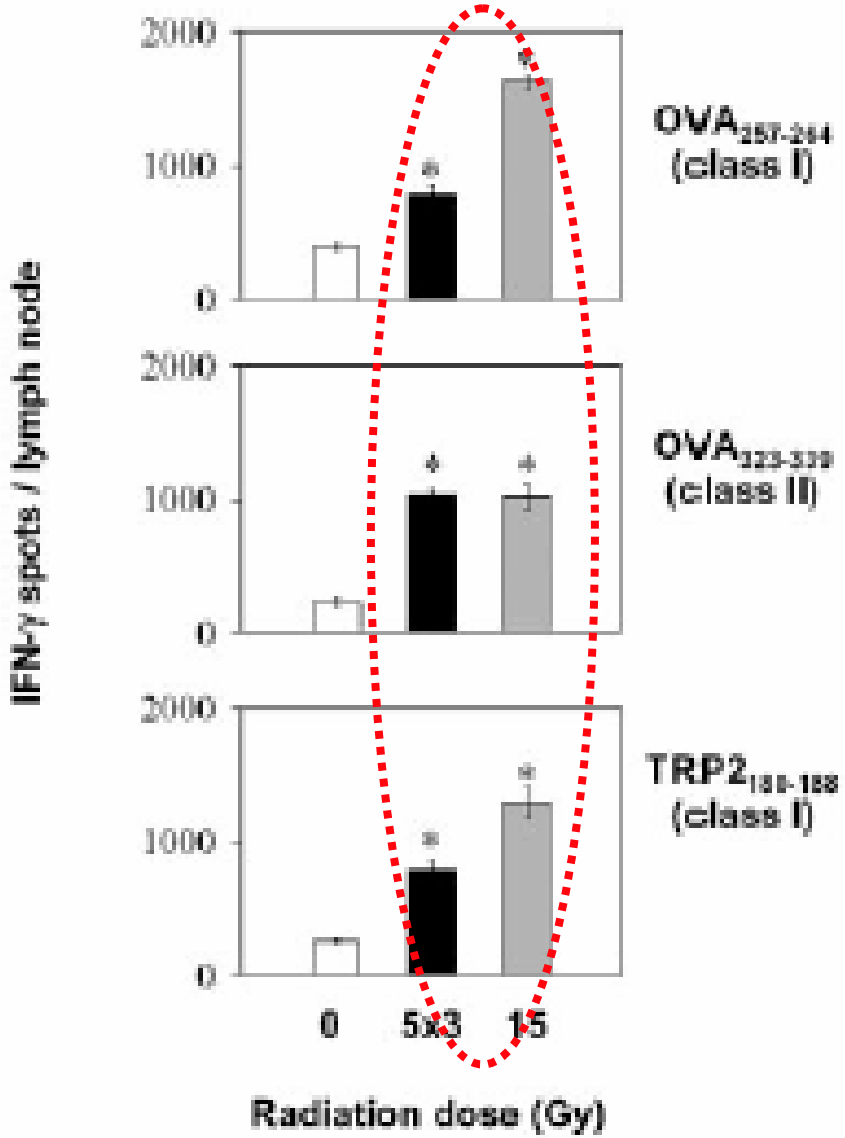
Upregulation of Antigens, depending on Tumor line (Dose-Response-Relationship not completely clear)

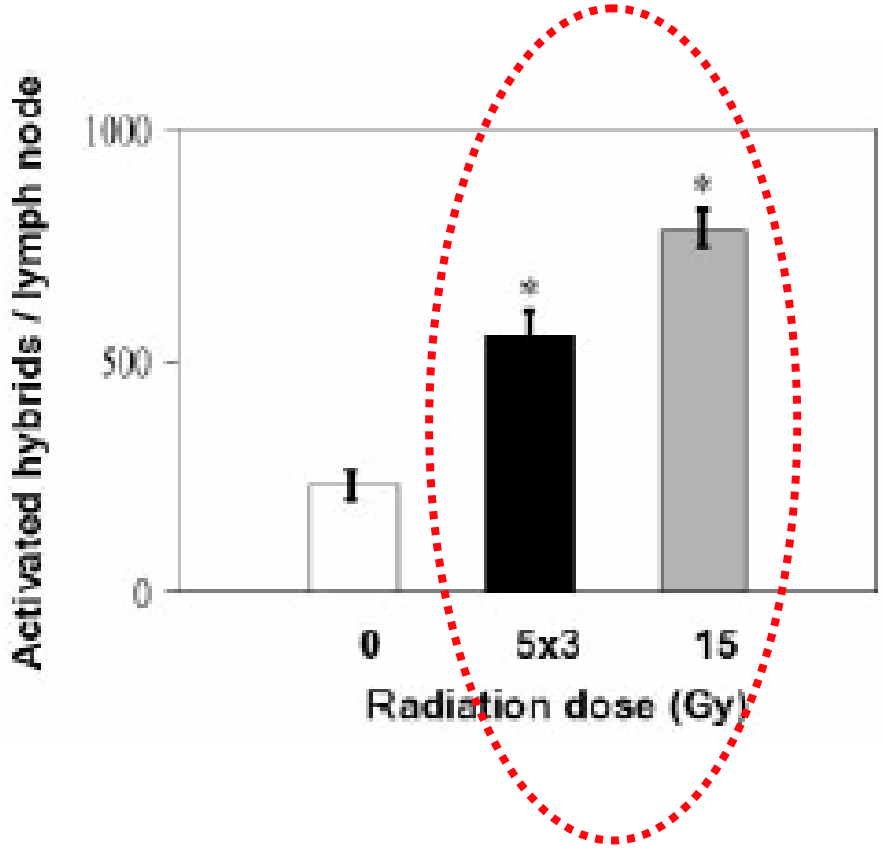
Facilitation of Cross Priming/DC Maturation

Changes in Cytokine Profile (Micromilieu)

Cell Migration

Irradiated Tumor Cells may be Immunogenic

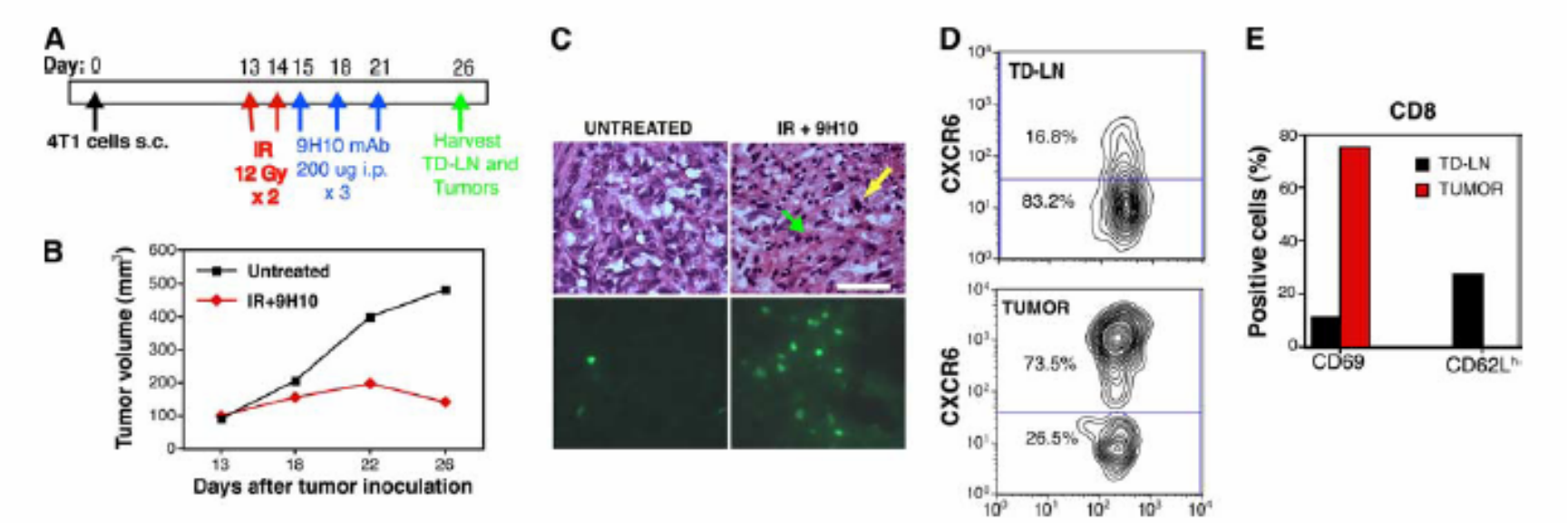




Lugade et al., J Imm, 2005

Migration of T-cells in 4T1 Breast Cancer Cells after RT (2 x 12 Gy)

Matsumura/Formenti/Demaria et al., J Imm, 2008
Pilones/Demaria/Formenti et al. Clin Cancer Res, 2009



Not an in-situ model, but otherwise highly relevant !!
Response modulated by iNKT cells

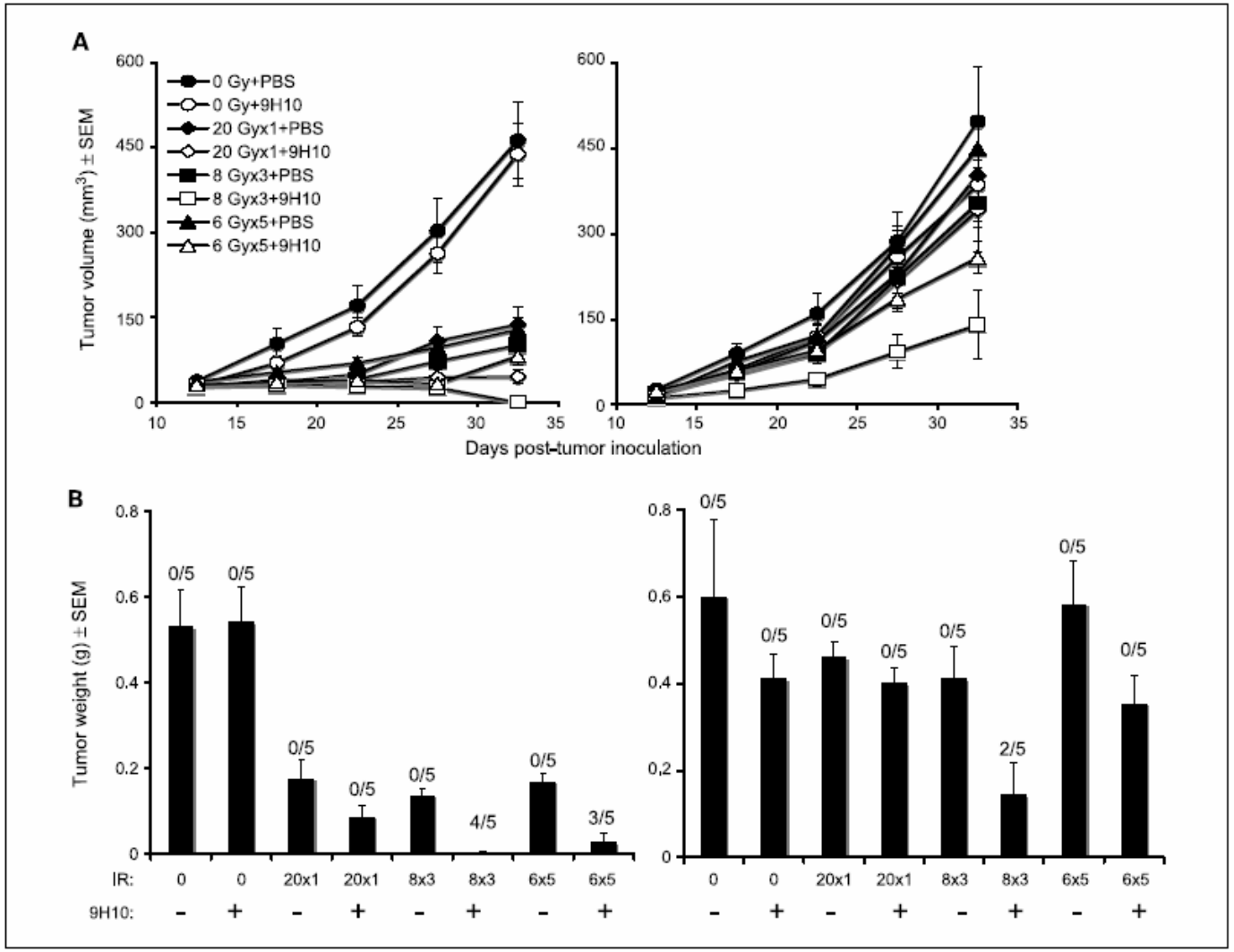
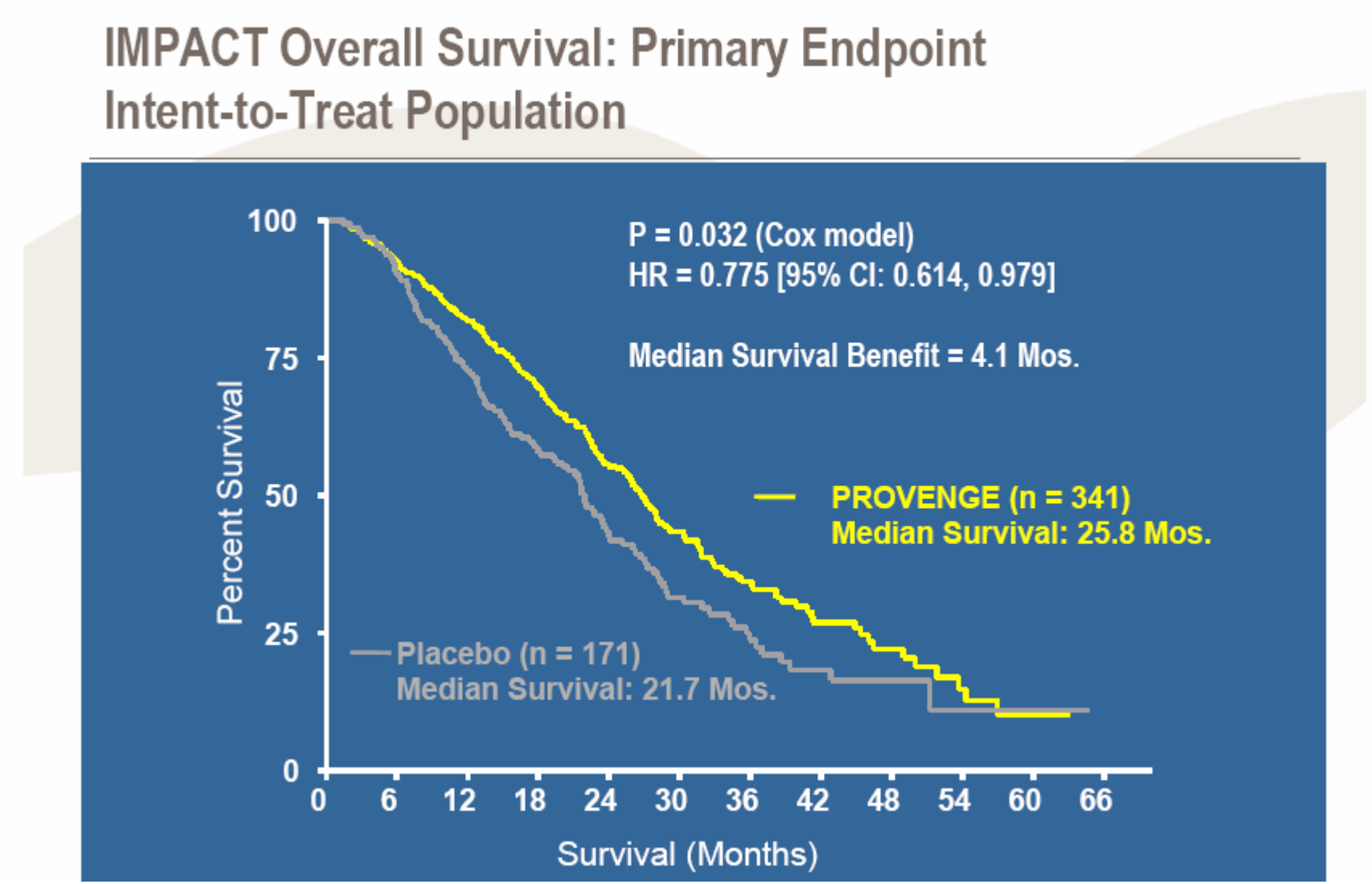


Fig. 2. The abscopal effect is induced in TSA tumor-bearing mice by fractionated radiation in combination with anti–CTLA-4 antibody. *A*, tumor growth delay of primary irradiated tumors (*left*) and secondary nonirradiated tumor (*right*) in mice treated with PBS (*closed circles*), 9H10 (*open circles*), 20 Gy × 1 + PBS (*closed diamonds*), 20 Gy × 1 + 9H10 (*open diamonds*), 8 Gy × 3 + PBS (*closed squares*), 8 Gy × 3 + 9H10 (*open squares*), 6 Gy × 5 + PBS (*closed triangles*), or 6 Gy × 5 + 9H10 (*open triangles*). 9H10 was given on days 14, 17, and 20. Data, mean ± SE of five mice per group. *B*, tumor weight of primary (*left*) and secondary (*right*) tumors at day 35. Data, mean ± SE from one of two independent experiments with similar results. The number of mice with complete tumor regression over the total number of mice per group is indicated.

Dewan et al., Clin Canc Res, 2009

-> Doses of ~10 Gy may be optimal to elicit an immune response

Immunotherapy finally works!



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

Prostate Cancer

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. EDMUNDSON, 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 Biomathematics, 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

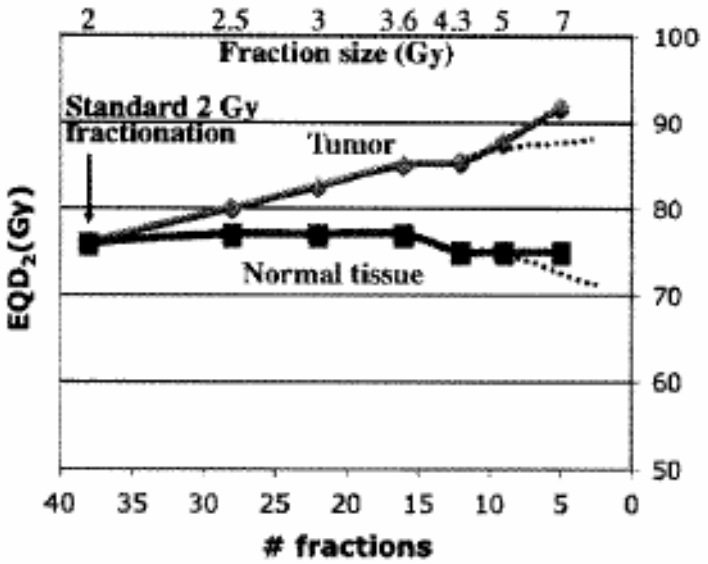


FIGURE 1. Increasing therapeutic advantage with increasing hypofractionation. The equivalent total doses if delivered in 2 Gy fractions for prostate tumor ($\alpha/\beta = 1.5$) and normal tissue late effects ($\alpha/\beta = 3$) are shown versus fraction size-number combinations that preserve similar 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

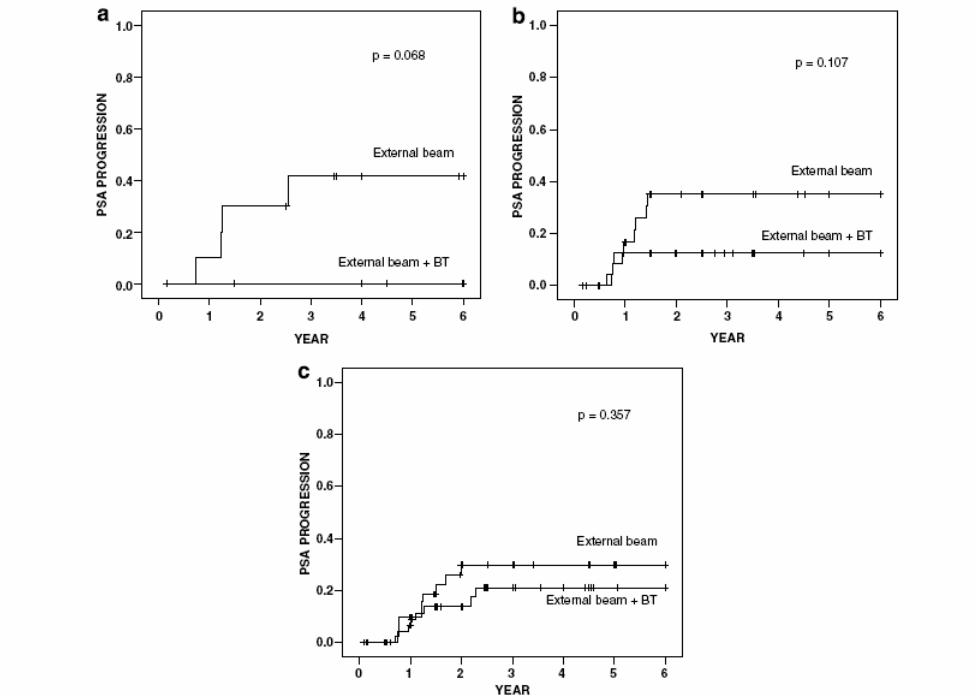


Fig. 3. Biochemical response by risk group. (a) Risk Group 1, PSA <10 ng/ml, Gleason 6 or less and Stage T2b or less. (b) Risk Group 2, neither Group 1 or 3. (c) Group 3, PSA >10 ng/ml, Gleason >6 and Stage T2c or higher.

55 Gy in 20# / 28d

Hoskin et al., Radiother Oncol, 2007

Randomized Trial Comparing Two Fractionation Schedules for Patients With Localized Prostate Cancer

Hirnu Lukka, Charles Hayter, Jim A. Julian, Padraig Warde, W. James Morris, Mary Gospodarowicz, Mark Levine, Jinka Sathya, Richard Choo, Hugh Prichard, Michael Brundage, and Winkle Kwan

J Clin Oncol 23:6132-6138. © 2005 by American Society of Clinical Oncology

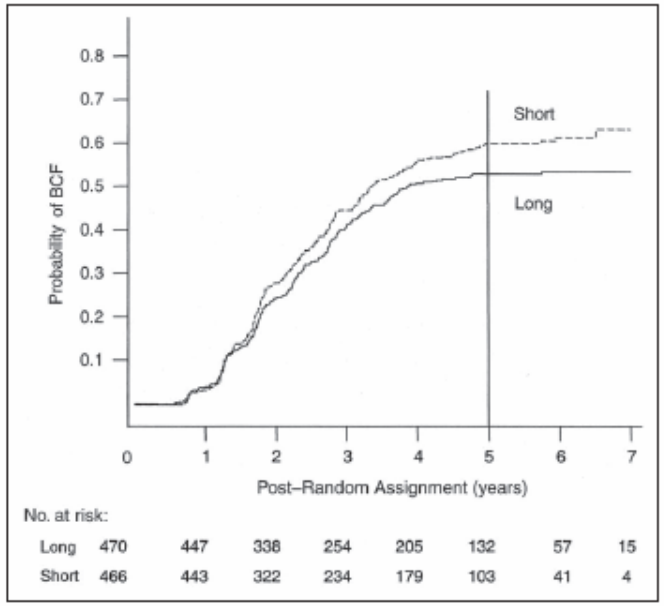


Fig 1. Biochemical or clinical failure (BCF) by randomized treatment arm.

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

The experience with moderate Hypofractionation

HYPOFRACTIONATED INTENSITY-MODULATED RADIOTHERAPY (70 GY AT 2.5 GY PER FRACTION) FOR LOCALIZED PROSTATE CANCER: LONG-TERM OUTCOMES

PATRICK A. KUPELIAN, M.D.,* VIPUL V. THAKKAR, M.D.,† DEEPAK KHUNTIA, M.D.,‡ CHANDANA A. REDDY, M.S.,† ERIC A. KLEIN, M.D.,§ AND ARUL MAHADEVAN, M.D.†

Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 5, pp. 1463–1468, 2005

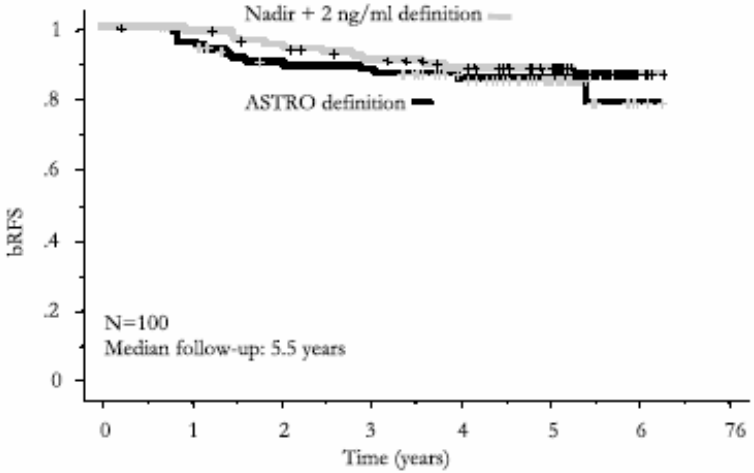


Fig. 1. Biochemical relapse-free survival for all 100 patients treated with high-dose hypofractionated radiotherapy. Both biochemical failure definitions were used. Symbols represent censored patients.

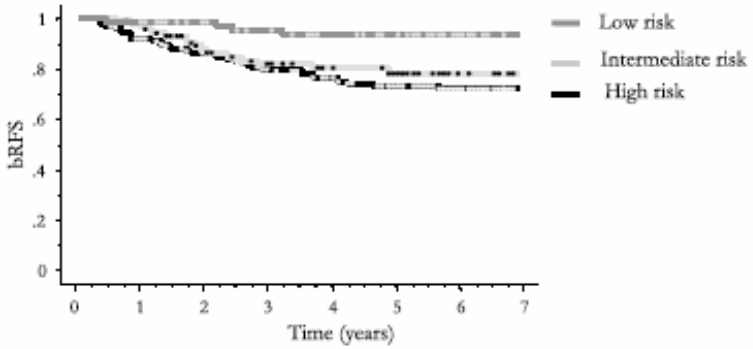


Fig. 3. Biochemical relapse-free survival (ASTRO definition) for the 310 patients treated with three-dimensional conformal radiotherapy with the conventional schedule of 78 Gy at 2 Gy per fraction (median follow-up of 71 months). The outcomes are displayed by low-, intermediate-, and high-risk groups.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

100 Patienten

70 Gy in 28# / 5,5 w

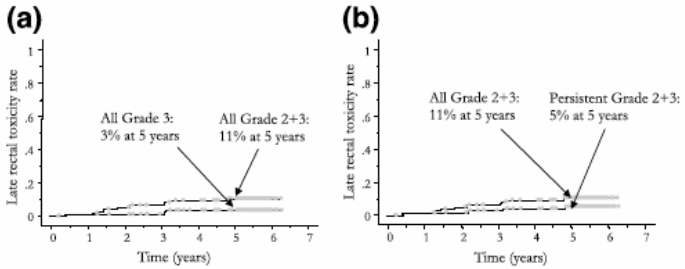
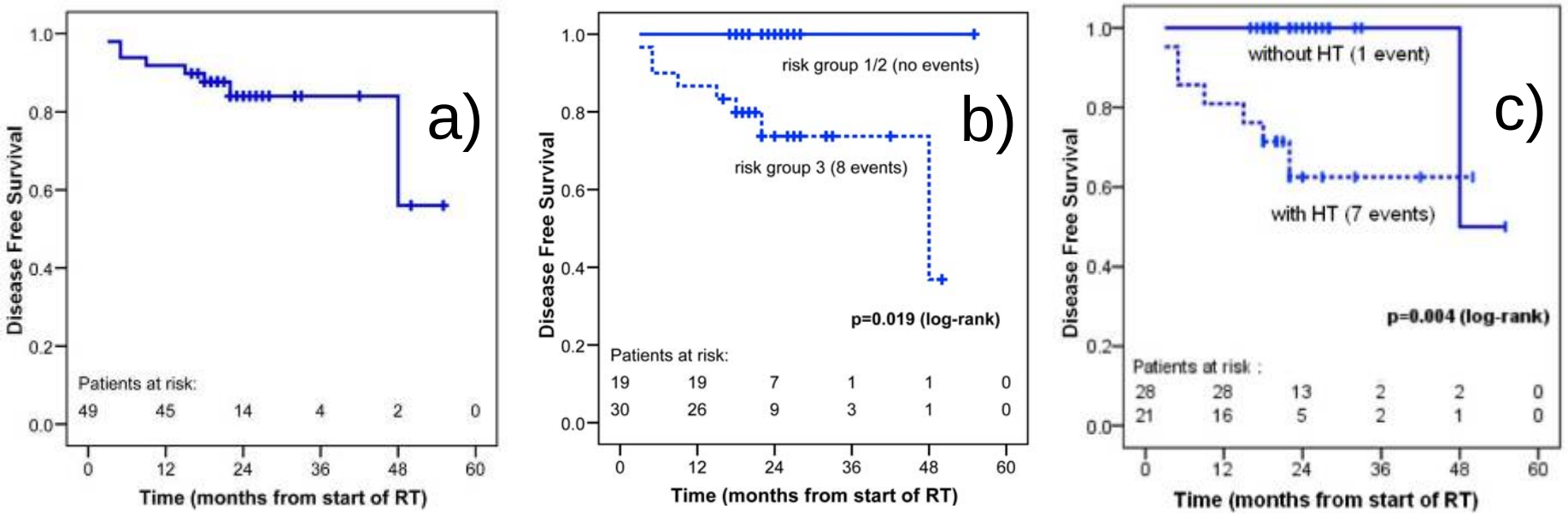


Fig. 4. Late rectal toxicity rates (RTOG Grades 2 and 3). (a) The Grade 3 only vs. the combined Grades 2 and 3 late rectal toxicity events. (b) All Grades 2 and 3 late rectal toxicity events vs. the Grade 2 or 3 events that were still persistent at last follow-up (i.e., 5% were still actually experiencing 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

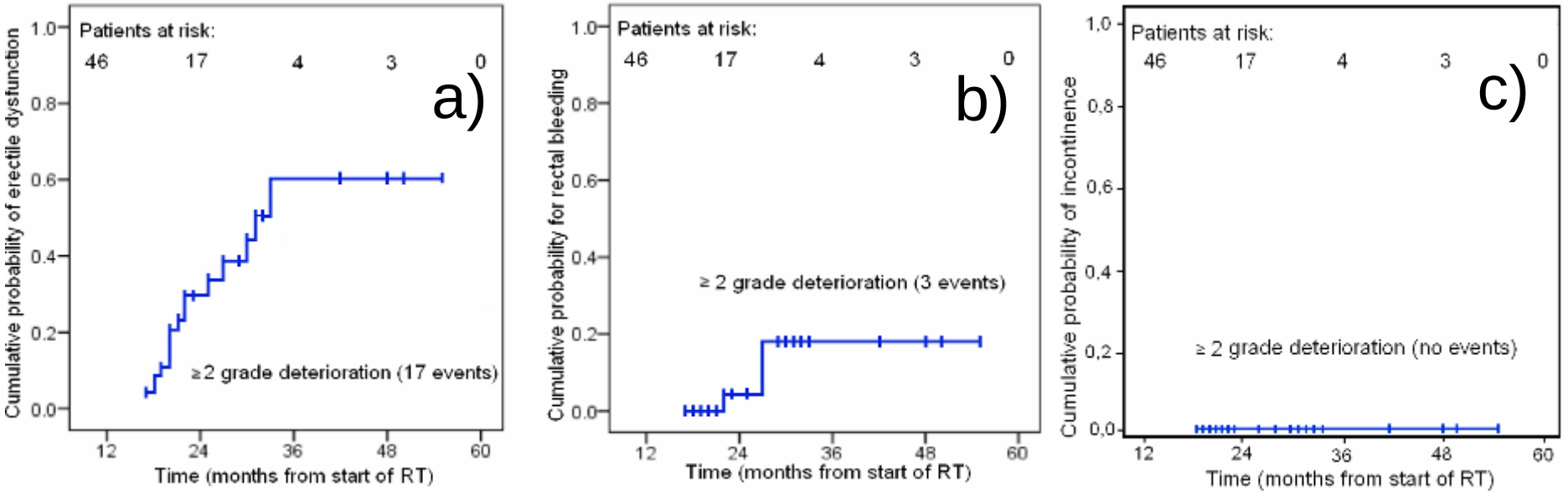


Actuarial disease-free survival
for the whole group (a), for patients with low (1)-, intermediate (2)- and high-risk group (3)(b) and for patients with or without androgen deprivation (c)

Actuarial incidence of late toxicity

49 pts, 60/2 Gy + 15/3 Gy

Kosakowski et al., in preparation



Actuarial incidence of late toxicity:
erectile dysfunction (a), rectal bleeding (b) and incontinence (c) for the whole population.

The most recent data

Leborgne/Fowler, IJROBP, 2009

60/3 or 63/3.15

Med. Follow up 49 Mo

Table 3. Five-year actuarial rates of bNED

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

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

	RTOG grade				
	0	I	II	III	IV
Urinary, late toxicity % (no. patients)	30% (11)	41% (15)	24% (9)	5% (2)	—
Rectal, late toxicity % (no. patients)	51% (20)	33% (13)	15% (6)	—	—

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……

Table 1. Head-and-neck schedules that were originally too hot and had to be moderated

Schedule*	Treatment given: Total dose (Gy)	Treatment given: Overall time (d)	Tumor time, corrected: EQD2 (Gy)†	Tumor time, corrected: Log_{10} cell kill†	Late complications EQD2 (Gy) (aim, <70 Gy)†	Acute mucosal EQD2 (Gy) (aim, < 52.5 Gy)†‡
Gortec 1: 2 Gy × 32 fx	64	22	63.6	11.6	64.1	54.1
Gortec 2: 1.75 × 36 fx	63	24	60.8	11.1	60.0	51.2
Cair 1: 2 Gy × 35 fx	70	34	63.1	11.5	70(+?)	52.2
Cair 2: 1.8 Gy × 39 fx	70.2	38	59.8	10.9	67.2	48.6
Harde 1: 1.2 + 1.3 + 1.5 + 2 Gy	76	33	65.1	11.9	67.2	54.5
Harde 2: 1.2 + 1.5 Gy	73.2	32	60.3	11.0	63.6	49.3
Leborgne: 1.6 Gy × 42 fx	67.2	25	62.8	11.5	61.8	53.1
in longer Overall Time	67.2	29	60.6	11.1	61.8	50.4
Sanguinetti: 1.3 Gy × 60 fx	78	39	63.6	11.6	67.0	52.3
in longer Overall Time	78	42	61.9	11.3	67.0	50.3

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 Gy TD* ***and*** *<3 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

Total dose (Gy)	Dose/ fraction	Number of fractions	Weeks	5-year LRR (%)	10-year BRR (%)	p	5-year DM (%)	5-year OM (%)	p (DM/OM)	Breast changes*	95% CI
RMH/GOC (N=1410)^[4]											
50	2	25	5	7·9	12·1	..	NR	NR	..	6·4%†	3·6–9·2%
39	3	13	5	9·1	14·8	..	..	..	..	3·9%	1·8–6·1%
42·9	3·3	13	5	7·1	9·6	0·027‡	..	..	..	11·2%	7·8–14·7%
START A (N=2236)[1]											
50	2	25	5	3·6	..	..	9·8	11·1	..	1§	..
41·6	3·2	13	5	3·5	..	..	9·5	11·3	..	1·09	0·85–1·40
39	3	13	5	5·2	..	NS	11·9	10·7	NS/NS	0·69	0·52–0·91
START B (N=2215)[2]											
50	2	25	5	3·3	..	..	10·2	11	..	1§	..
40	2·67	15	3	2·2	..	0·35	7·6	8	0·01/0·03	0·83	0·66–1·04

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

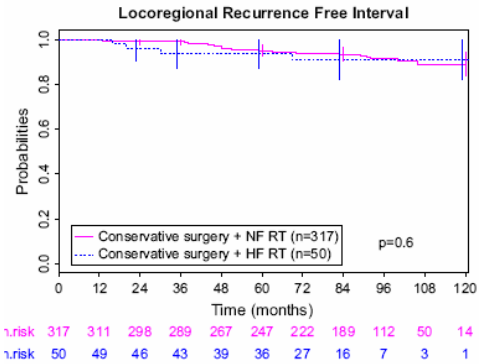


Fig. 2. Locoregional recurrence-free Kaplan-Meier survival curves in elderly patients receiving either normofractionated radiotherapy or hypofractionated radiotherapy.

ASCO '09, Heidelberg, 2009

„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

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Single center experiences: IORT as Boost

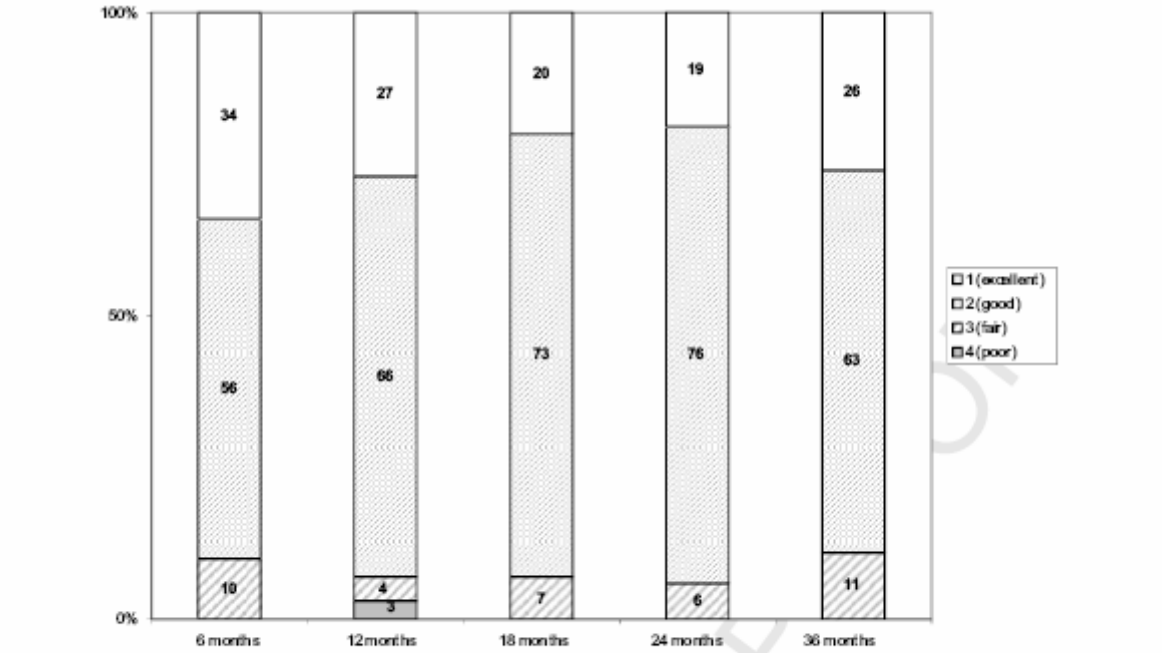


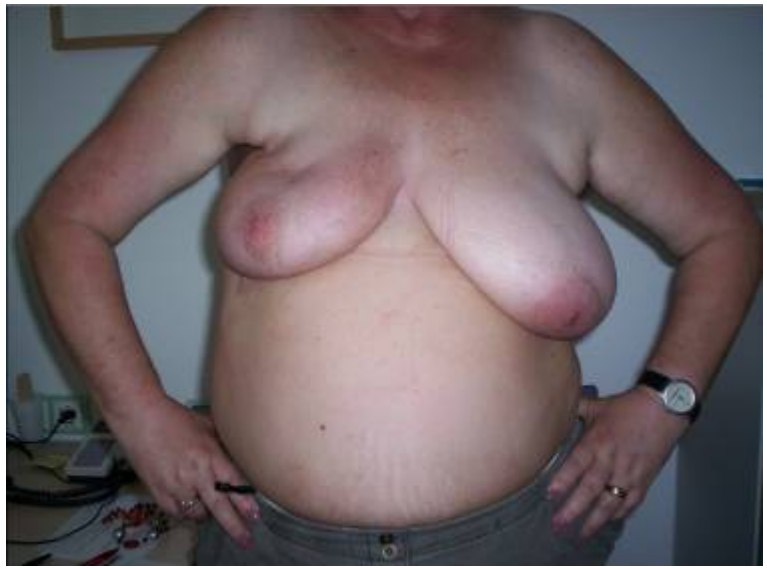
Fig. 1. Cosmetic evaluation after 6, 12, 18, 24, and 36 months on a score of 1 to 4. *One patient with a poor cosmetic result was treated with mastectomy because of marked fibrosis of the entire breast 12 months after intraoperative radiotherapy (IORT), and 1 patient was evaluated as having "fair" cosmetic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

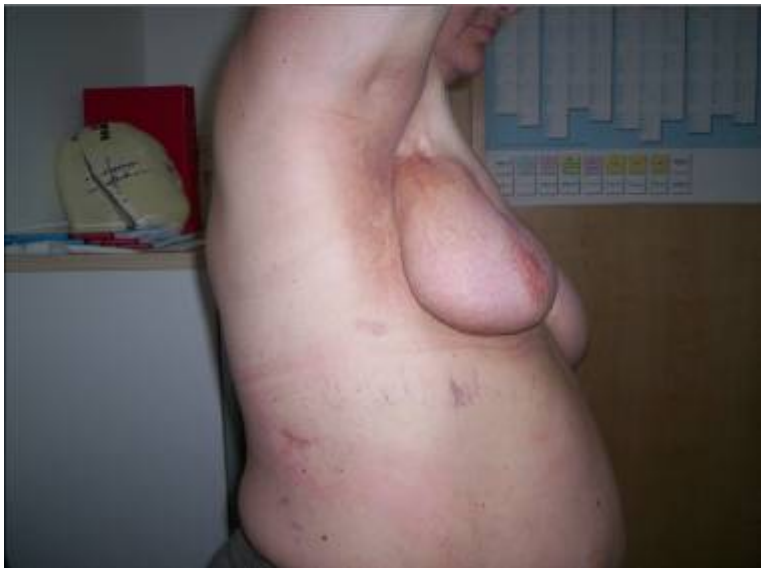
20 Gy SD at Applicator Surface

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

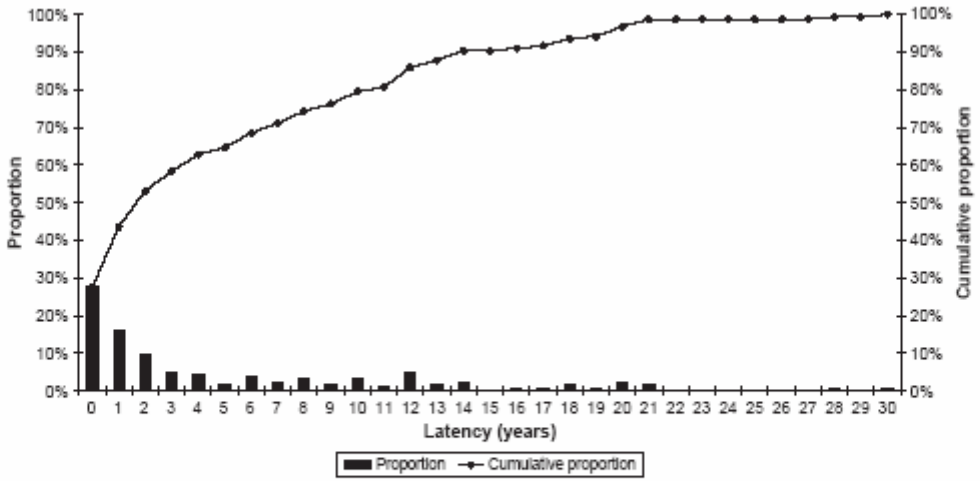


Figure 3. Time from therapy to onset of symptoms Time from end of therapy to onset of symptoms (latency). The diagram points to the fallacy of the use of truncated observation periods, i.e. 5 years. Injuries may appear many years later. Patients in this study with late appearing injuries were often disbelieved 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

Cosmetic result	All patients ($n = 90$)	>12 months follow-up ($n = 90$)	>24 months follow-up ($n = 86$)	>36 months follow-up ($n = 80$)	>48 months follow-up ($n = 56$)
Excellent	44 (49%)	44 (49%)	44 (51%)	43 (54%)	33 (59%)
Good	35 (39%)	35 (39%)	31 (36%)	27 (34%)	17 (30%)
Total excellent/good	79 (88%)	79 (88%)	75 (87%)	70 (88%)	50 (89%)
Fair	11 (12%)	11 (12%)	11 (13%)	10 (13%)	6 (11%)
Poor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 7. Partial breast irradiation studies using external beam radiation

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

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, telengiectasias, and fat necrosis.

† Personal communication.

Chen/Vicini et al, IJROBP, 2009

….and too much of a good thing……

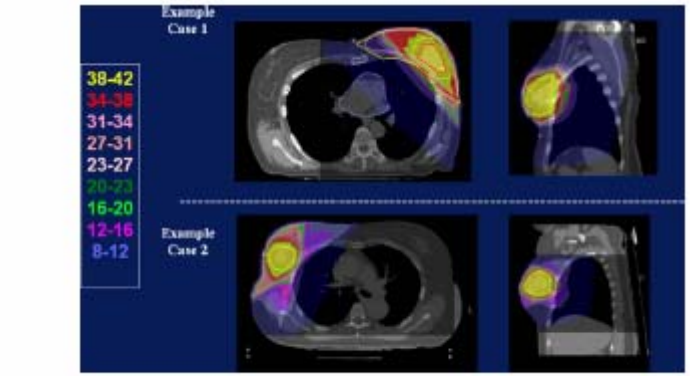


Fig. 2. Isodose distributions achieved in 2 patients. Both cases illustrate the conformality of the treatment. The cases differ with respect to the volume of the lumpectomy cavity and the proportion of normal breast irradiated.

Patients received 38.5 Gy in 3.85 Gy fractions bid

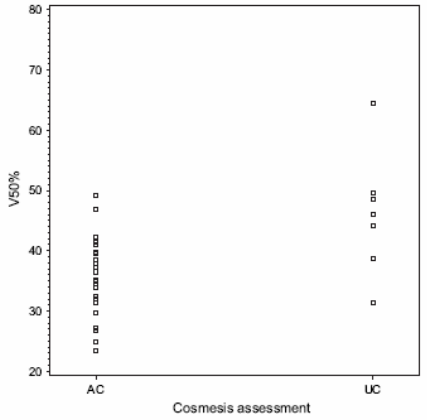


Fig. 4. Distribution of the proportion of the breast reference volume in each case receiving 50% of prescribed dose (V50), by cosmetic outcome, among patients with good or excellent cosmesis at baseline.

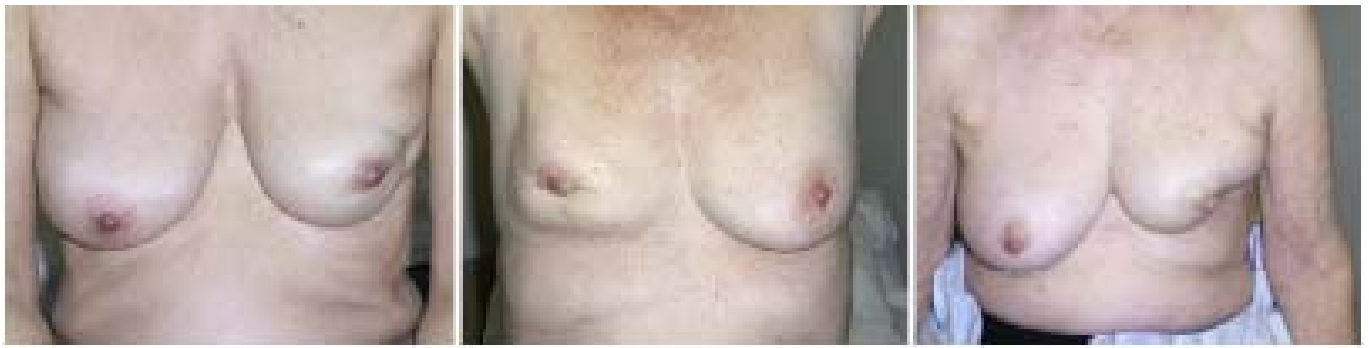


Fig. 3. Visible impairment in cosmesis observed in 3 patients deemed to have unacceptable cosmesis after treatment.

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 !!!!