Gemelli Oct 2023

Modern Radiation Oncology. Innovation in personalised oncology: back to the future

Cycles in Radiation Therapy innovations

or

Motus et rondo verticalis et horizontalis Radiotherapeutica

Jens Overgaard

Department of Experimental Clinical Oncology,
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JO-2023-10

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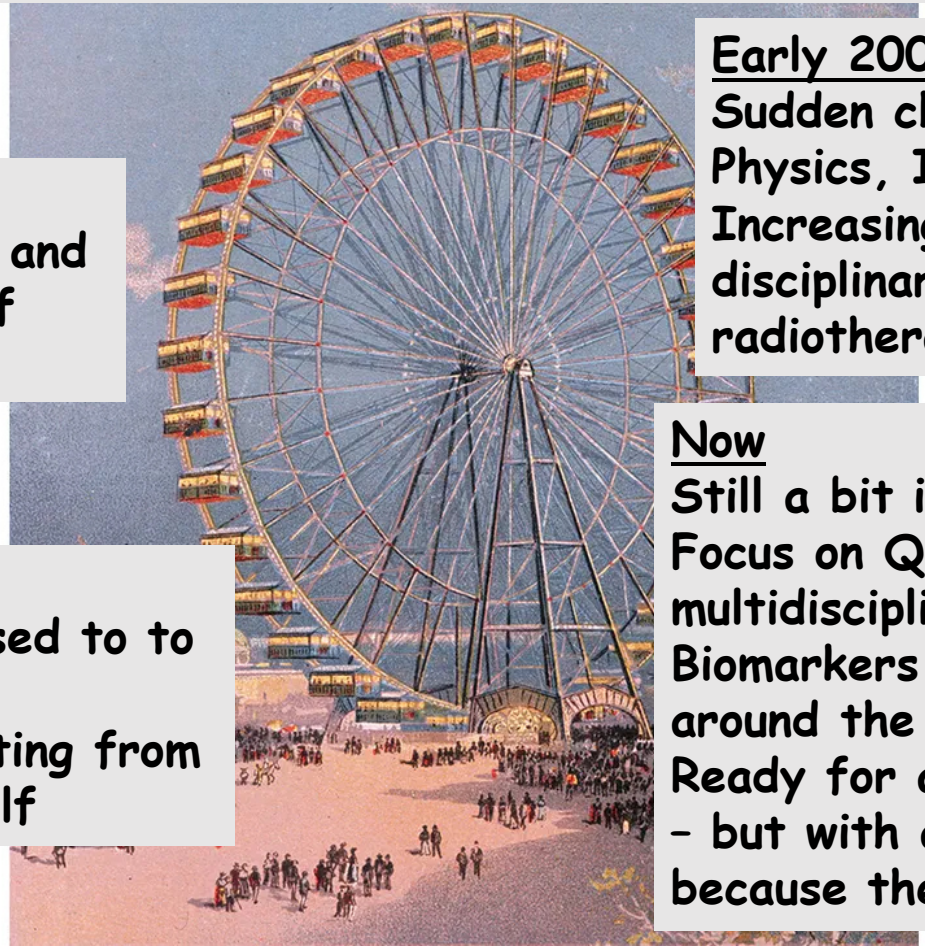
This talk is a '**Message for the future**' to you - the persons who are going to travel into the future - and about what kind of baggage you are (or should be) bringing with.

Motus et rondo verticalis et horizontalis

40 years ups and downs of radiotherapy in a multidisciplinary context

Turn of the millenium (±2000) – At the peak, taking leadership in ECCO – the European multidiciplinary cancer collaboration/congress



1980's
Joining together in Europe and creating ESTRO – ahead of other specialities

Early 2000+
Sudden change!
Physics, IMRT, computer power
Increasingly narcissistic, so multi-disciplinary mean a relation between radiotherapist and physicist.

Late 1970's
Chemotherapy was supposed to to take care of all cancer –
Radiotherapy was separating from radiology and finding itself

Now
Still a bit introvert.
Focus on QA, morbidity, AI, with multidisciplinary site specific activity.
Biomarkers and personal indication around the corner.
Ready for a new spin in the wheel – but with a more humble role, because the world has changed.

The development of radiotherapy has over time been like a pendulum swinging between the clinic and biology, constantly gaining mutual knowledge resulting in improved practice on a biological basis.

This development takes place on a (ever changing) platform of the current technology and multidisciplinary interaction.

The latter may change and create new 'rules for the game' but still it is the clinical-biological interaction which is fundamental. Ignoring that, bring us into trouble.

Biology **Clinic**

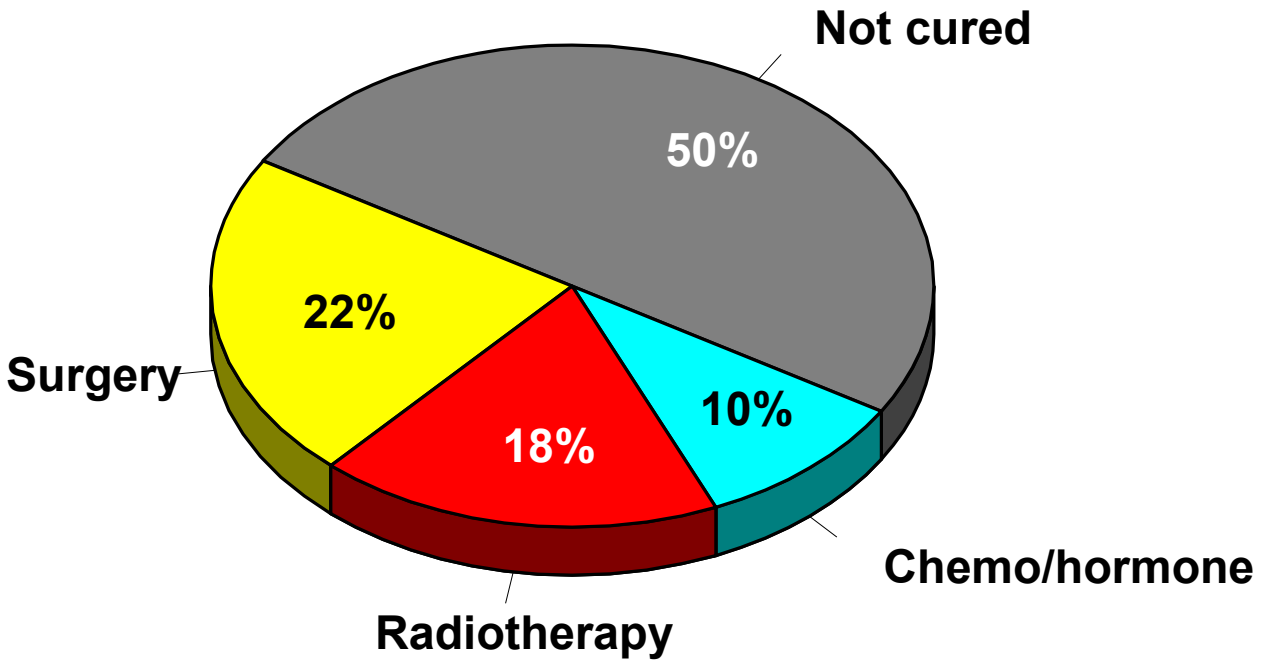
CANCER IN EUROPE (EU) Today (2020+)

4 mio. will get cancer diagnosed.
(70% with loco-regional disease only)

2 mio. will die of cancer.

>16 mio. are alive after cancer therapy.
Of these approx 12 mio. are 'cured'
and 4 mio. alive with disease.

The importance of different therapeutic modalities for the cure of cancer



Modified from: M. Tubiana EJC 1992

ABOUT RADIOTHERAPY

Message for the future:

There is no doubt that radiotherapy will have an even increased role in cancer therapy many years ahead

patients will

The number of p
is likely to increase due to earlier
new indications, and more (elderly) people.


FUTURE
FUTURE
FUTURE


USE ALTERNATE ROUTE
ALTERNATE ROUTE CLOSED
ROAD CLOSED
Way ahead?
DETOUR
MEN WORKING
CONSTRUCTION AHEAD
UNDER CONSTRUCTION

Back to the future !

about 40 years !

40 years ago:
The heyday of (translational) radiobiology

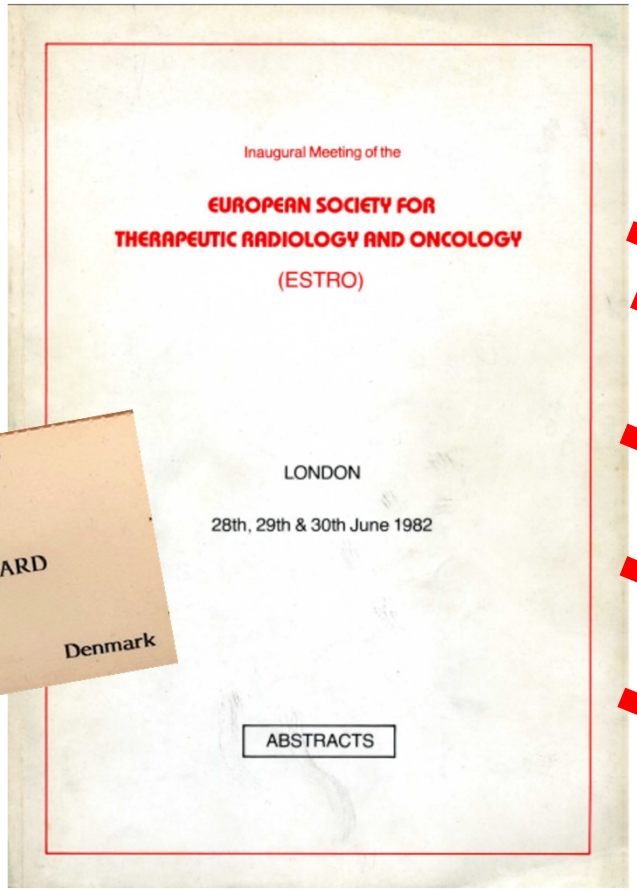


TABLE OF CONTENT

Evidence based radiotherapy

Number of publications (Pubmed Oct 2024) on:

Evidence based "Oncology":	71620	(100%)
Evidence based "Radiotherapy":	8587	(12%)
Evidence based "Radiobiology":	213	(0.3%)

Evidence based radiobiology

The history of radiotherapy is characterized by development based on LACK of evidence.

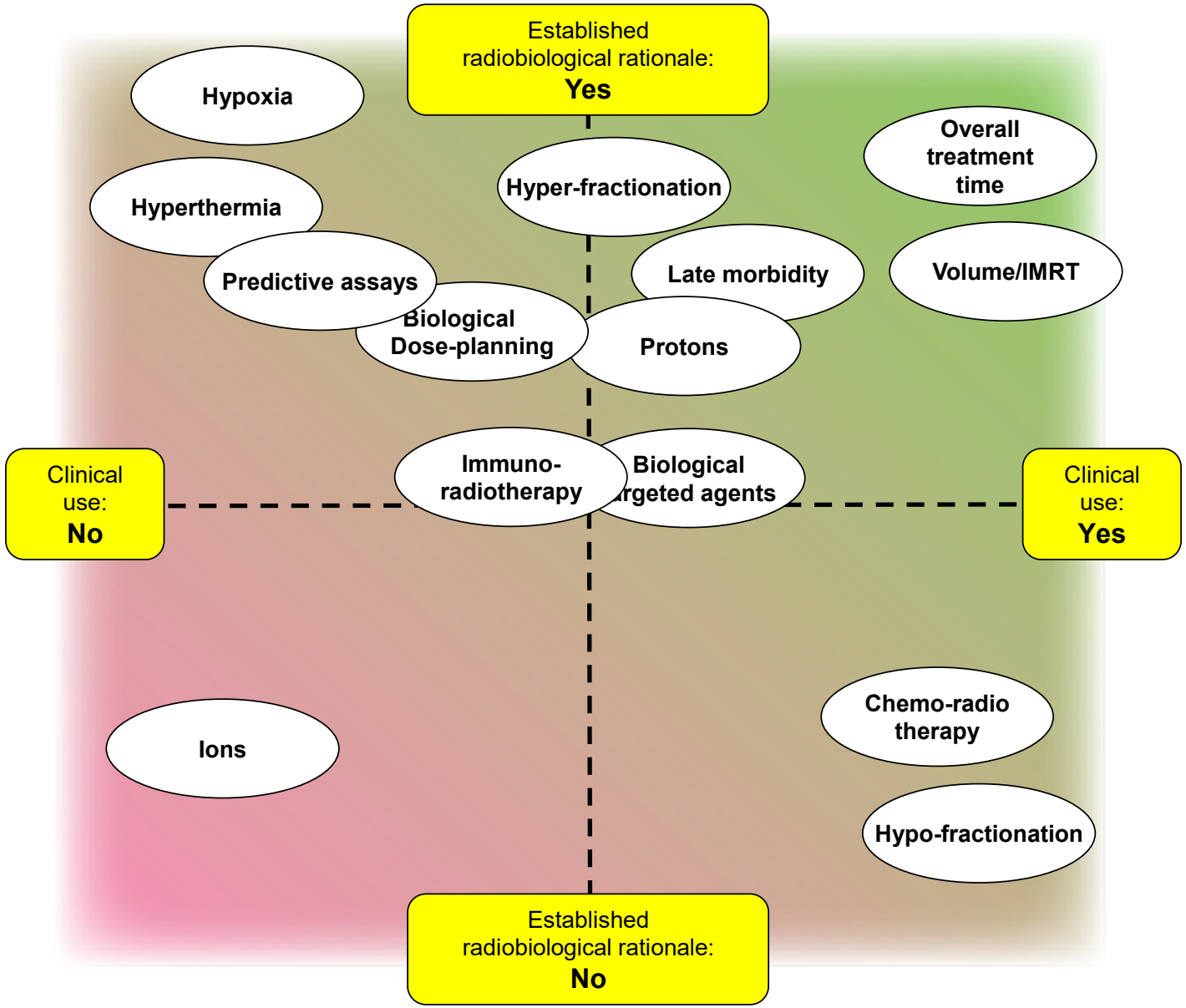
Most of our "progress" are driven by wishes of more precision and better and more focussed delivery (heavy machinery) and biological knowledge derived from past experience (and mistakes)

– all put together by (very elaborate) modelling which often are based on past mistakes and limited retrospective clinical data (not derived for the purpose)

Some important assumptions and information:

The human body has not changed much in the last century – and consequently must biological observations obtained with in that time period be comparable.

By far most of the clinical radiobiological tumor data and information comes from observations of **squamous cell carcinomas** (not least in the head and neck) – other tumor types can not uncritically be assumed to behave in a similar way – although they often does.

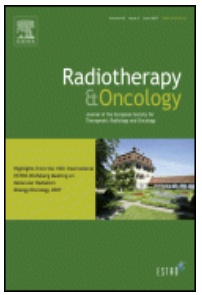

Established radiobiological rationale: Yes
Hypoxia
Hyperthermia
Predictive assays
Biological Dose-planning
Hyper-fractionation
Overall treatment time
Late morbidity
Volume/IMRT
Protons
Clinical use: No
Immuno-radiotherapy
Biological targeted agents
Clinical use: Yes
Ions
Chemo-radio therapy
Hypo-fractionation
Established radiobiological rationale: No

Hypoxia – most cited topic in RT

An overview of the ten most cited original papers in each of the four top ranked international radiotherapy journals showed that:

three out of the four most cited papers in the journals are dealing with hypoxia,

and among the 40 most cited papers 17 (43%) are related to hypoxia and radiation resistance.



First clinical demonstration of hypoxia 1909

"Oxygen Enhancement Ratio"

...dass die Radiosensibilität durchaus kein konstanter faktor ist. Kompressionsanämie der Haut setz die Röntgenempfind lichkeit derselben aus 1/3 herab.

Gottwald Schwarz 1914

(Wiener Medizinische Wochenschrift 64: 2597-98, 1914)


MÜNCHENER
MEDIZINISCHE W HENSCHRIFT.
ISCHE ÄRZTE.
56. Jahrgang.

Gottwald Schwarz

Vienna

1880-1959

Oxygen Concentration and Radiosensitivity

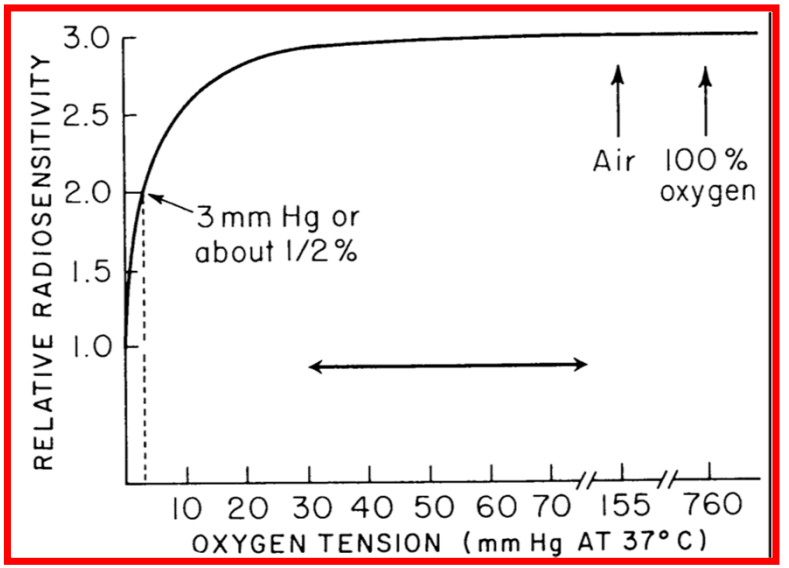
L. Harold Gray
1953

THE CONCENTRATION OF OXYGEN DISSOLVED IN TISSUES AT THE TIME OF IRRADIATION AS A FACTOR IN RADIOTHERAPY

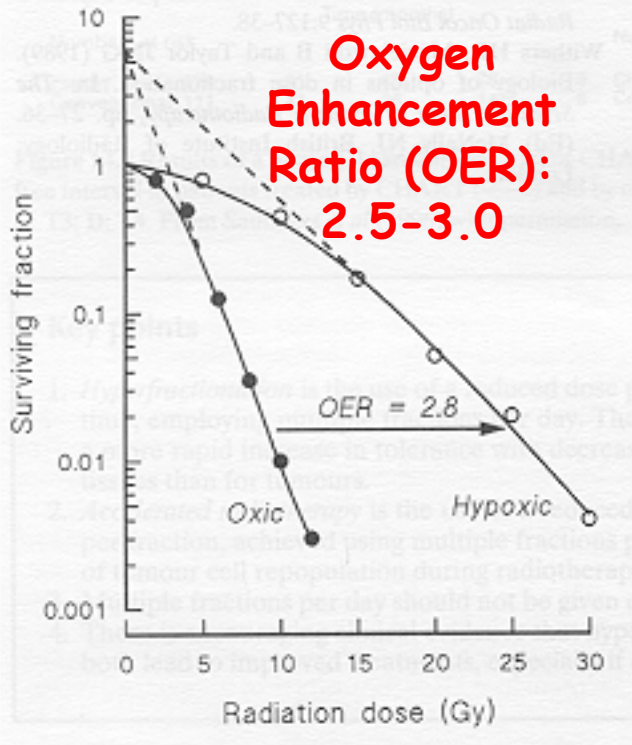
By L. H. Gray, M.A., Ph.D., A. D. Conger, Ph.D., M. Ebert, Dr. Rer. Nat., S. Hornsey, B.Sc., and O. C. A. Scott, M.B., B.Ch.
Radiotherapeutic Research Unit, Hammersmith Hospital, London

(Accepted for publication September, 1953)

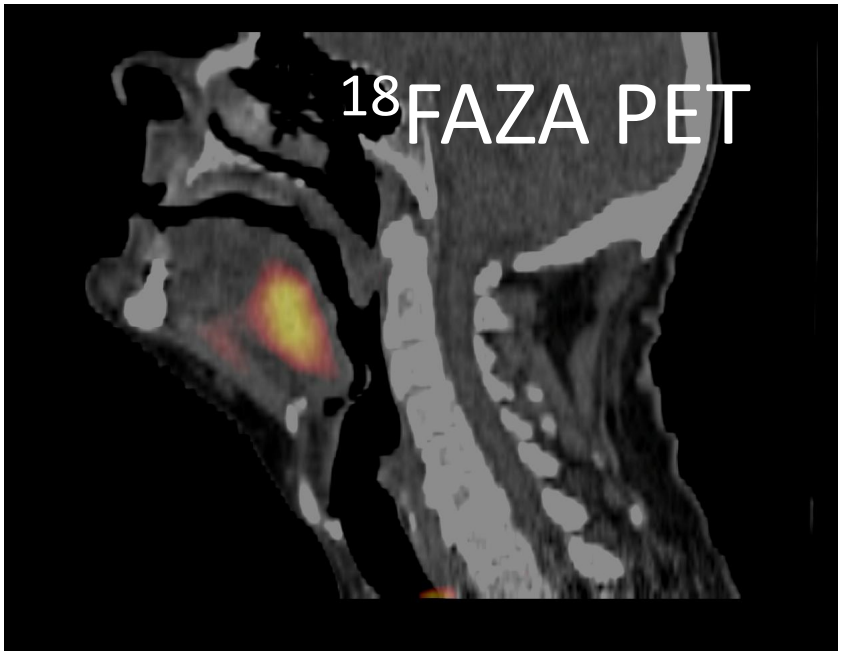
IT has long been known that both normal and cells irradiated *in vitro* have been found (Trowell,



Hypoxic cells are radioresistant



Head and neck tumors are hypoxic



Mortensen et al. Radiother Oncol 2012

Can we modify hypoxic radioresistance in the treatment of SCC?

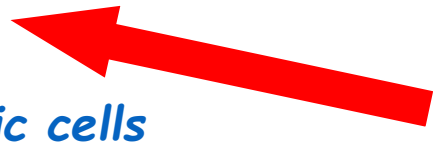
Modification of hypoxic radioresistance

Increased oxygen delivery by the blood

- Hyperbaric oxygen
- Carbogen breathing
- Nicotinamide
- Blood transfusion, Erythropoetin

Mimic of oxygen in the radiochemical process

- Nitroimidazoles



Destruction of hypoxic cells

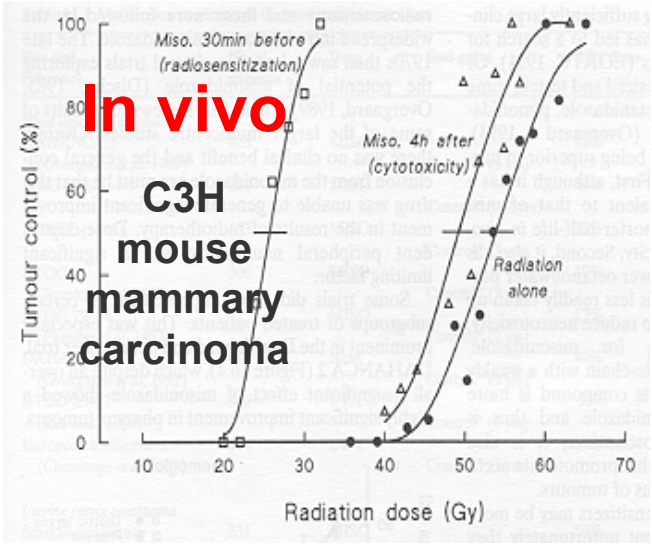
- Hypoxic cytotoxins
- Hyperthermia

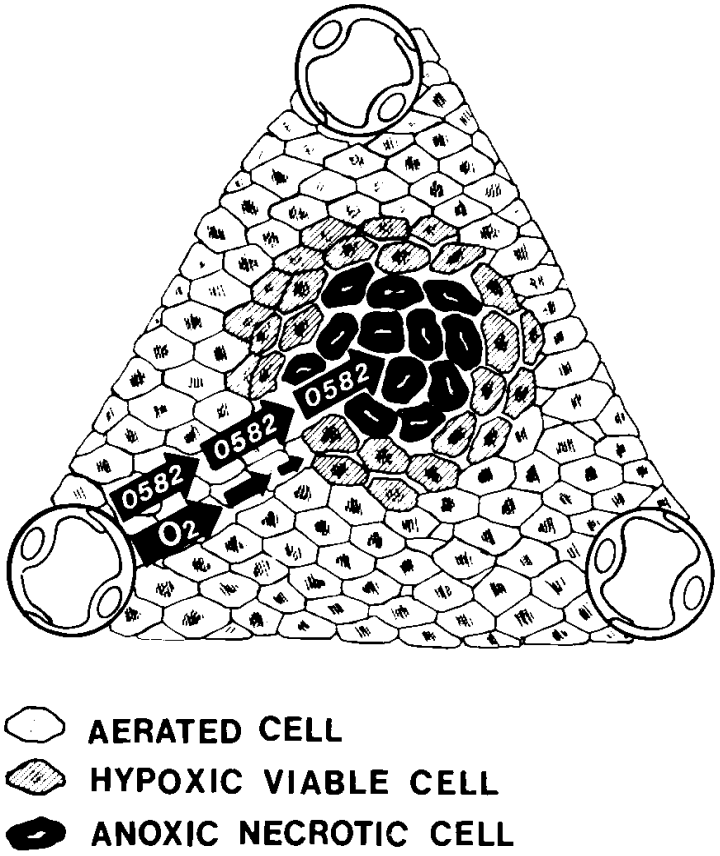
Elimination of OER

- High LET

Hypoxic cell radiosensitizer

Drugs which selectively sensitizes hypoxic cells for RT by mimic of oxygen





DAHANCA 5 (1986-90)

SUPRAGLOTTIC AND PHARYNX - 414 pts.

NIMORAZOLE vs PLACEBO (66 Gy/ 33 fx - 6.5 wk)

STRATIFY:

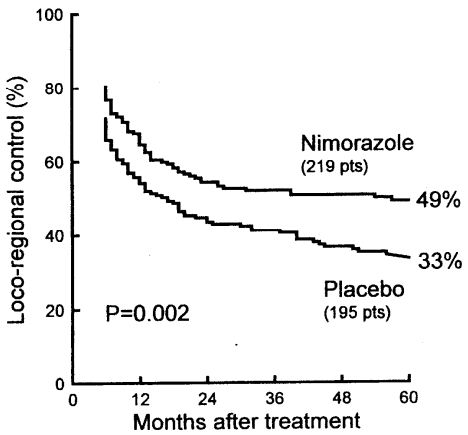
T-size
Region
Sex
Hemoglobin*
Institution

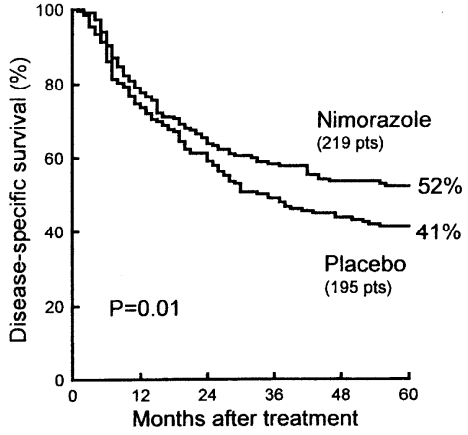
RANDOMIZE

RT + Nimorazole (219 pts)
(NIM: 1.2 g/m2 x 30)
(RT: 66-68 Gy/ 33-34 fx, 5 Fx/wk)

RT + Placebo (195 pts)
(RT: 66-68 Gy/ 33-34 fx, 5 Fx/wk)

*Patients with low hemoglobin are randomized to +/- transfusion before radiotherapy (Low Hb: male < 9, female < 8 mMol/L)

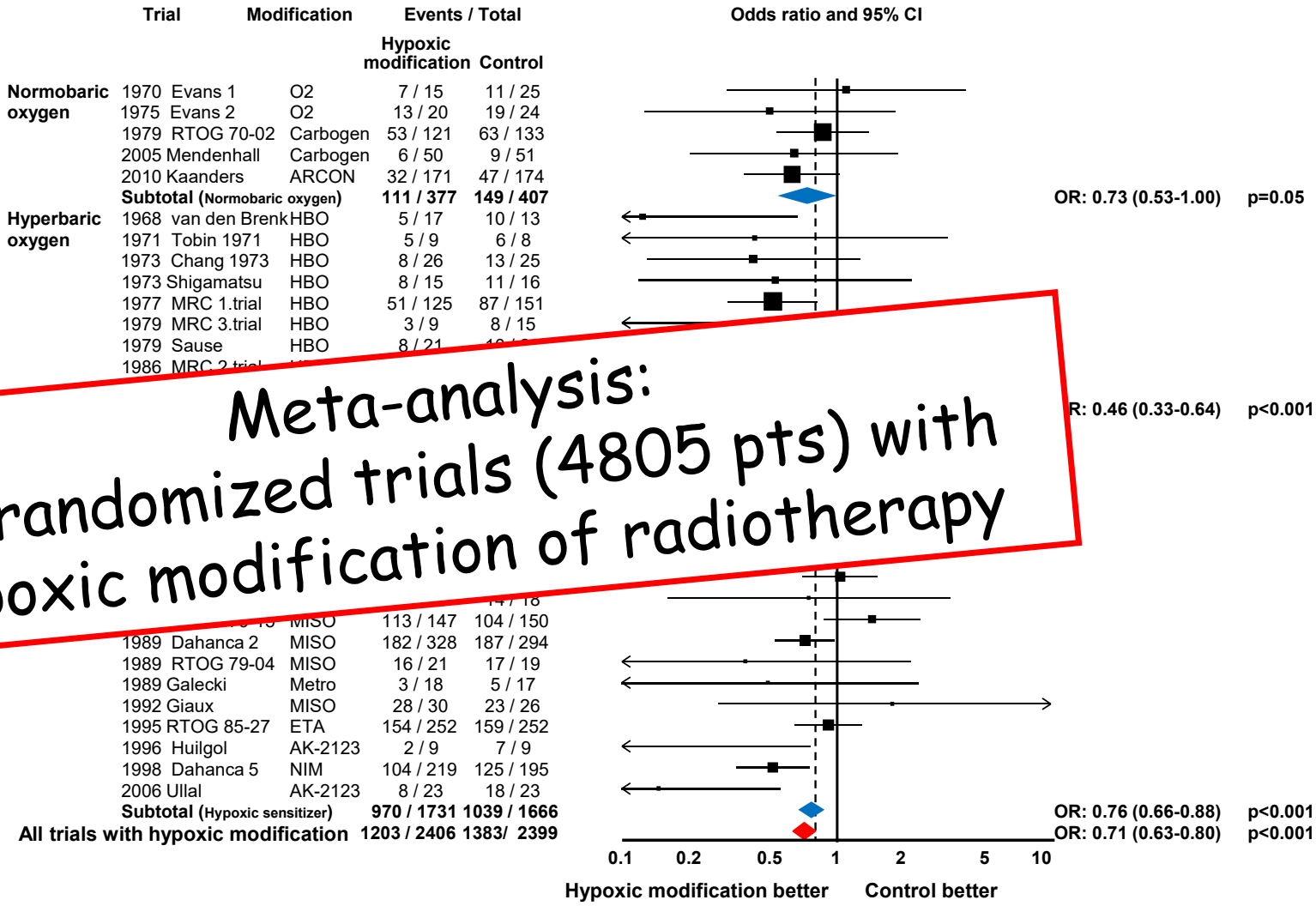




Overgaard et al, Radiother Oncol, 46, 1998.

DAHANCA.dk

Endpoint: Loco-regional failure



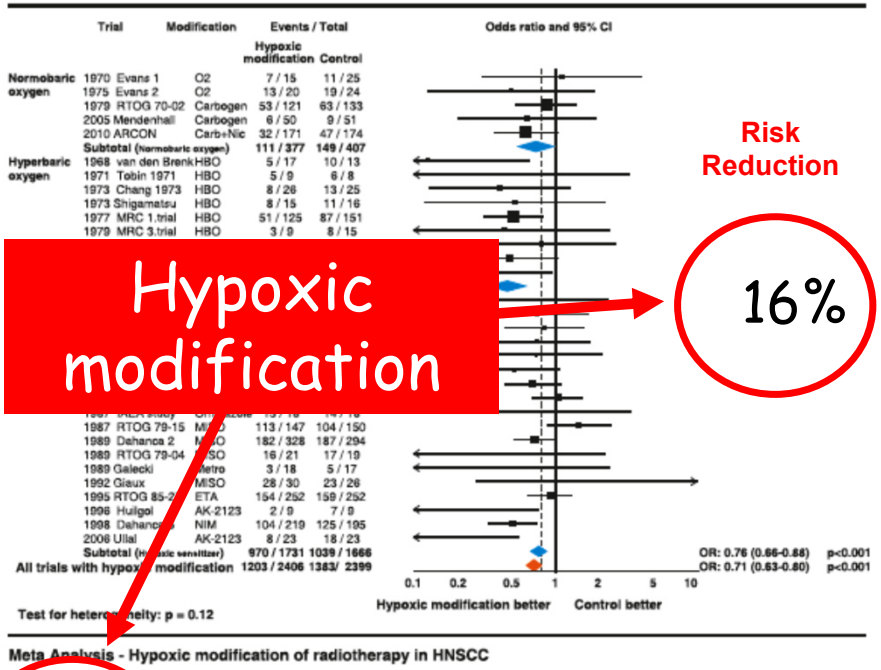
Meta-analysis:
32 randomized trials (4805 pts) with hypoxic modification of radiotherapy

Overgaard Radiother Oncol 2011

Meta-analysis:
Hypoxic modification of radiotherapy in head & neck carcinoma

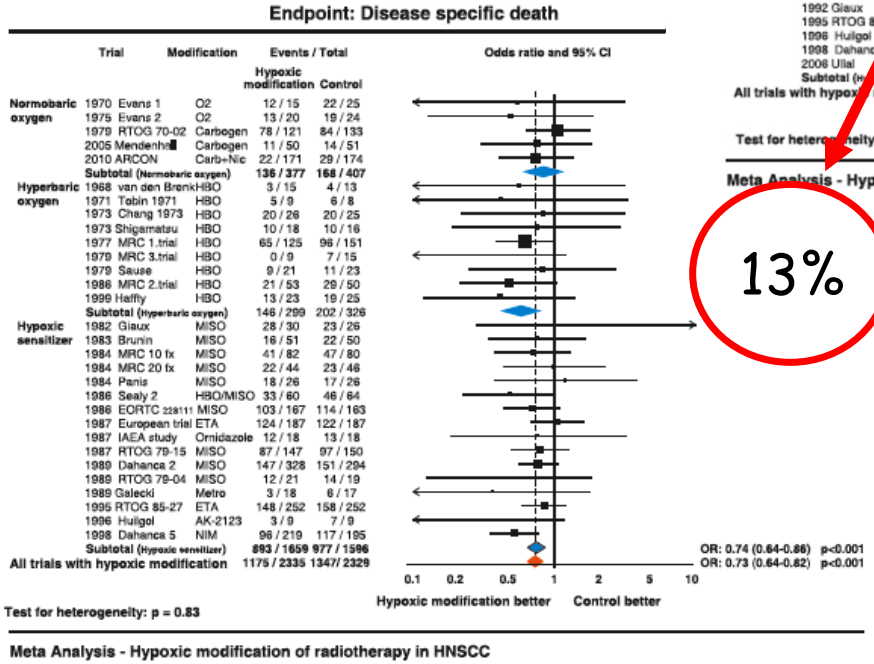
4805 pts in 32 trials

Loco-regional failure



Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

Cancer death



Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

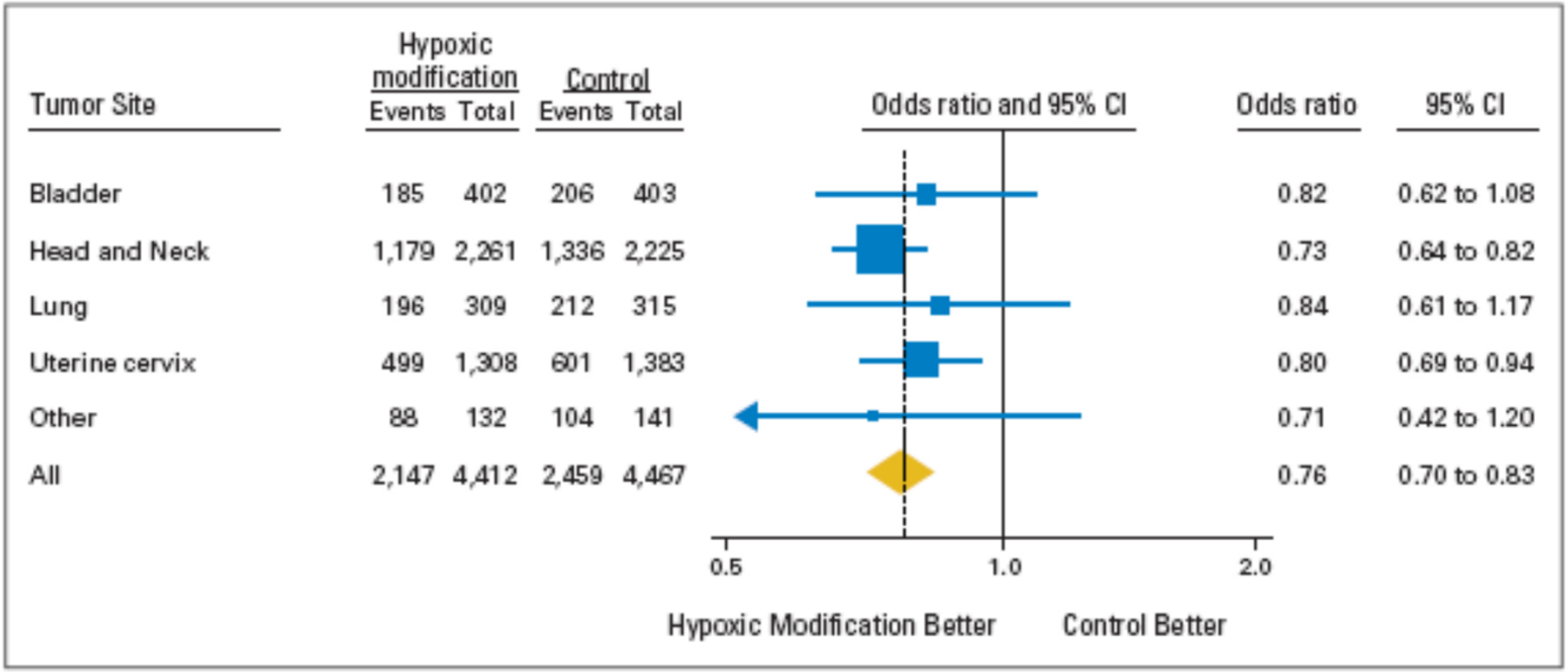
Overgaard Radiother Oncol 2011

Meta analysis

Modification of hypoxia in radiotherapy

Loco-regional control as function of tumor type and localization

Summary of 96 randomized trials with 10108 pts



Overgaard, JCO, 2007

Hypoxia and radiotherapy

The benefit of hypoxia modification is "free".

It
re

Th
in
tu

Hypoxic modification does therefore represent an obvious (evidence based) possibility for improving radiotherapy.

Message for future:

We must learn to acknowledge our achievements.

The purpose of clinical trials are to secure an evidence based platform for improvements (to the patients), and –if successful – the outcome of such trials should be implemented.

The clinical development of radiobiological based treatment strategies (especially hypoxia and fractionation in SCC) followed a distinct pattern with almost parallel randomized trials conducted in:

UK (MRC)

'Europe' (EORTC)

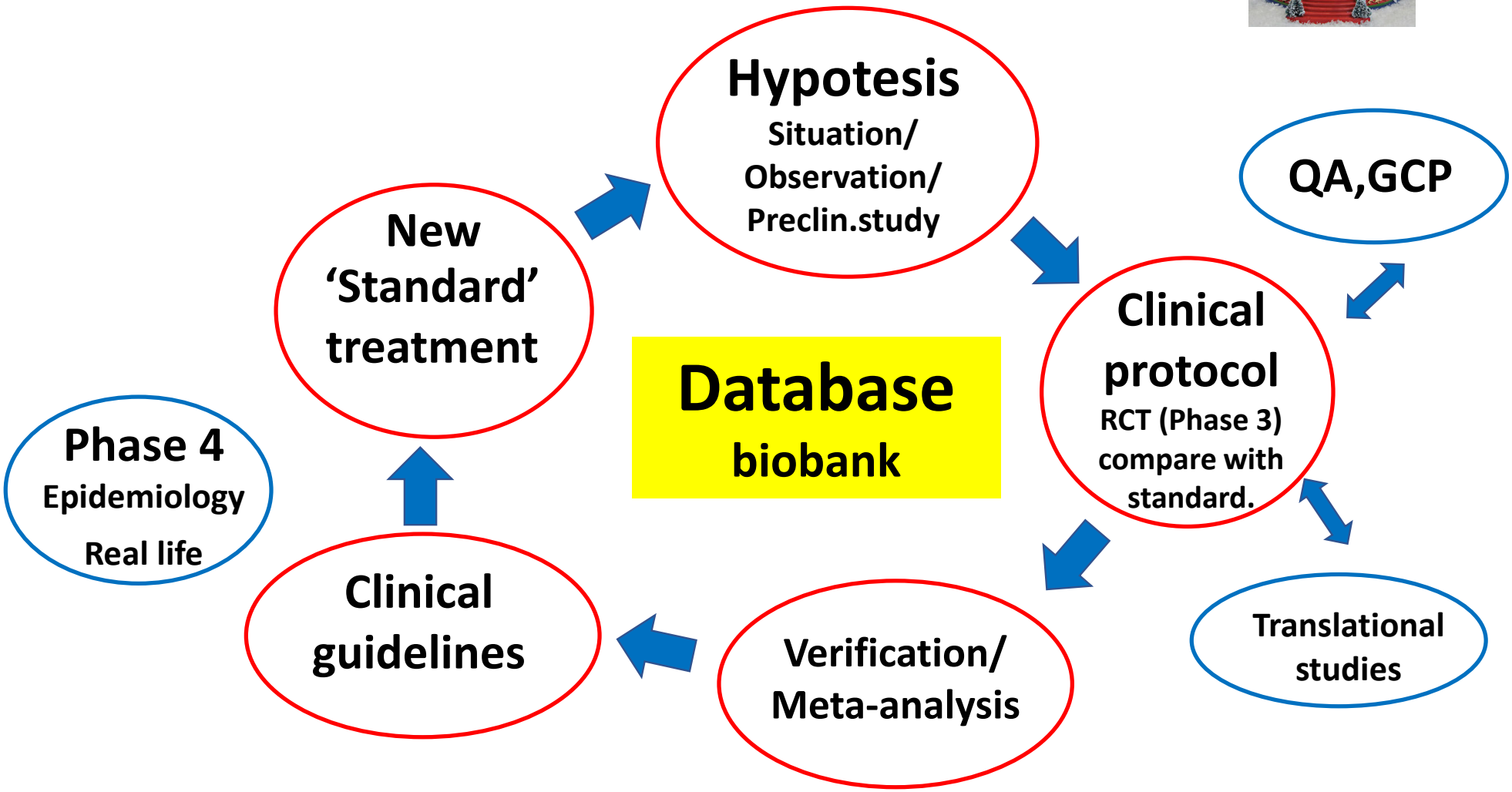
USA (RTOG)

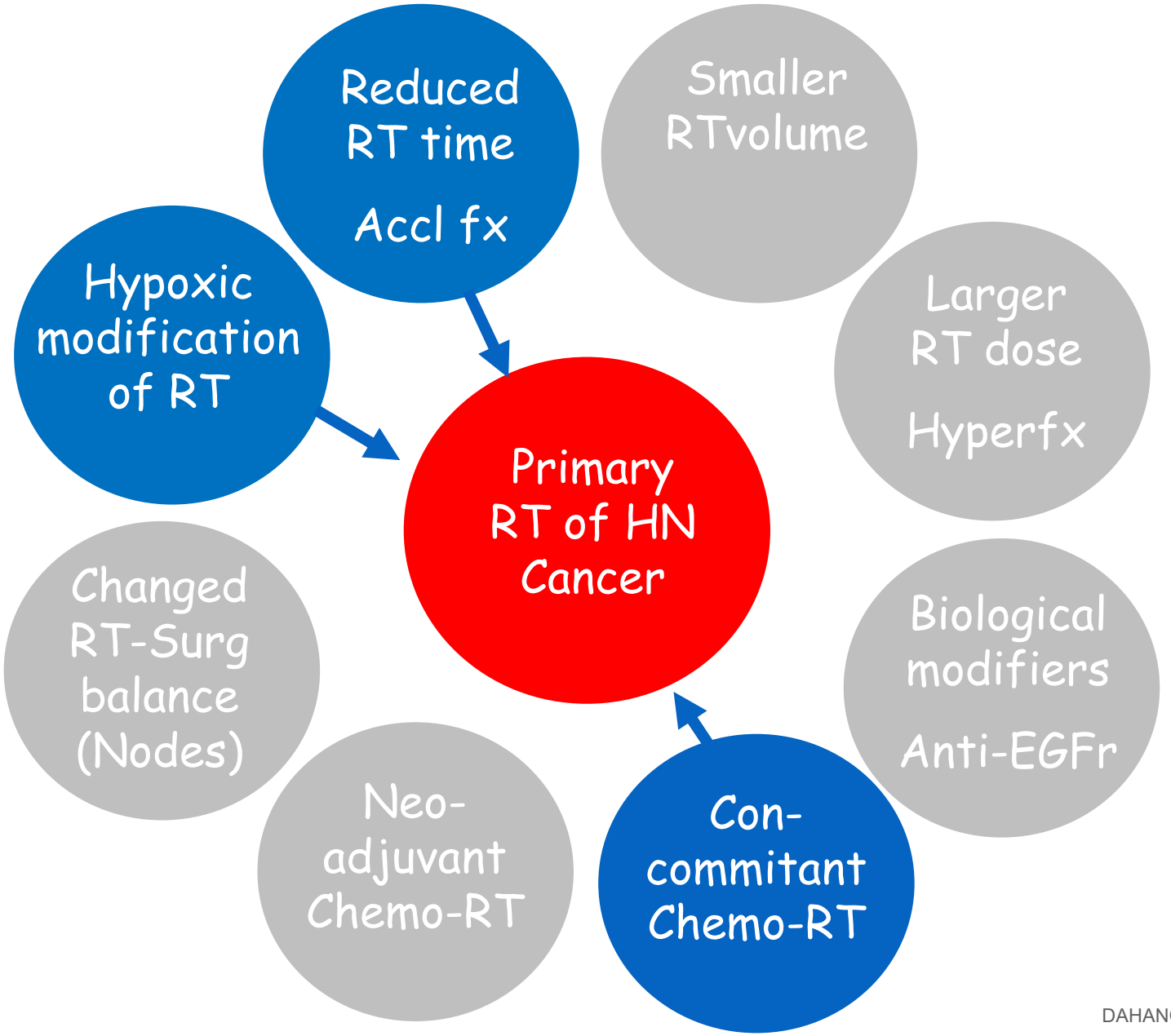
Denmark/Scandinavia

How do we know what we know?

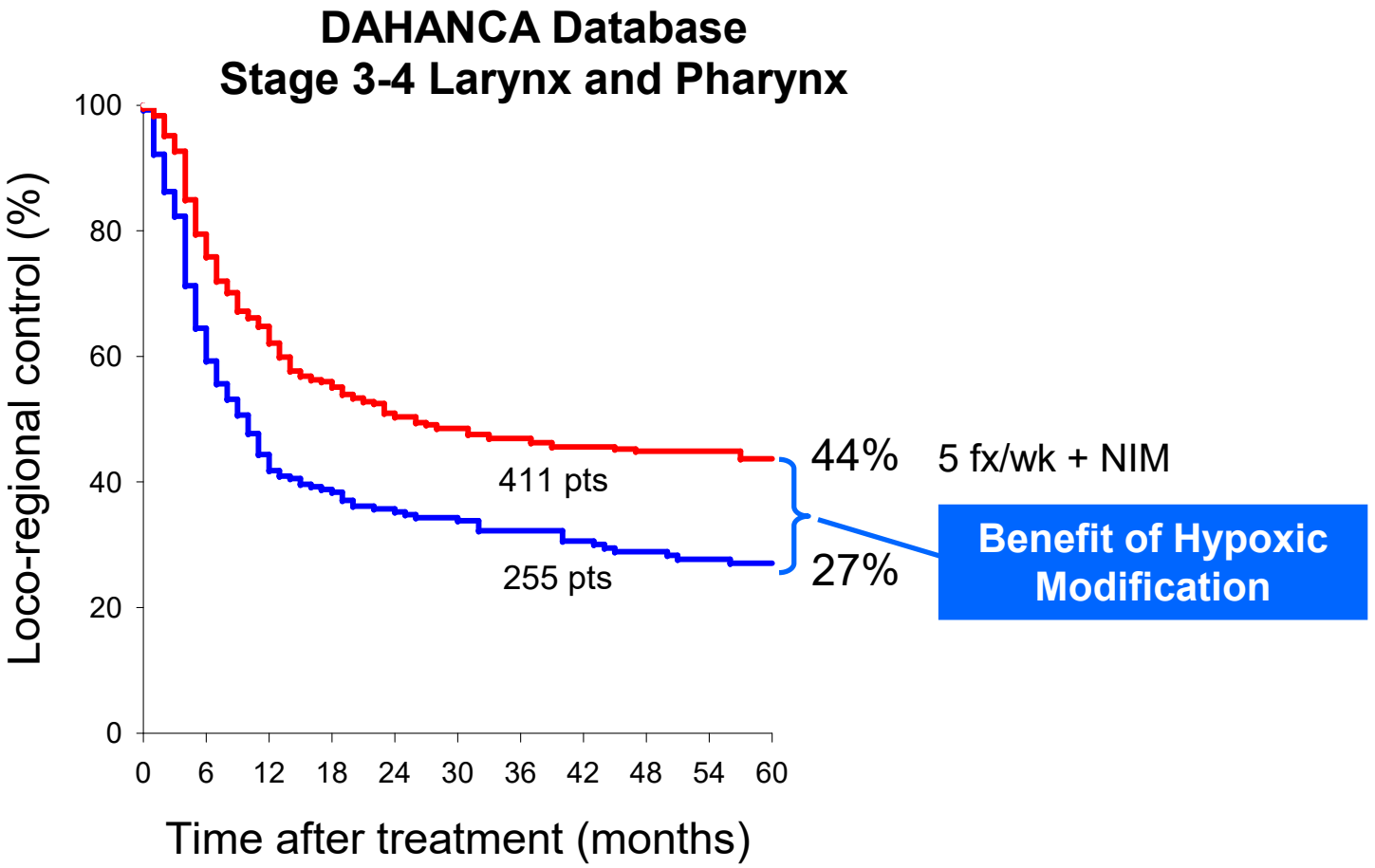
and how do we get more knowledge?

‘La Ronde’
in prospective clinical research




Reduced RT time
Accl fx
Smaller RTvolume
Hypoxic modification of RT
Larger RT dose
Hyperfx
Primary RT of HN Cancer
Changed RT-Surg balance (Nodes)
Biological modifiers
Anti-EGFr
Neo-adjuvant Chemo-RT
Con-commitant Chemo-RT

Radiotherapy of advanced (HN)SCC



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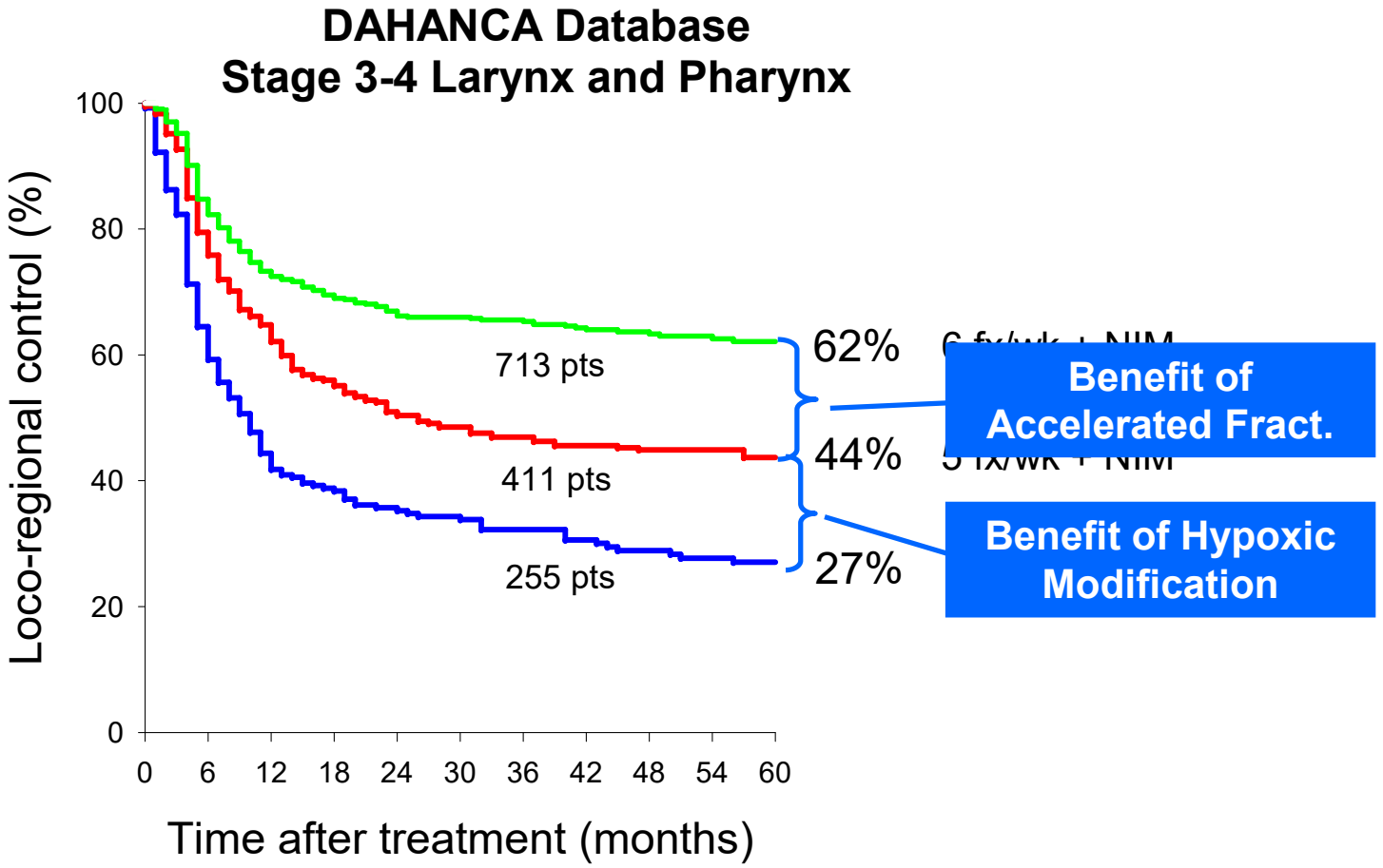
Radiotherapy of advanced (HN)SCC



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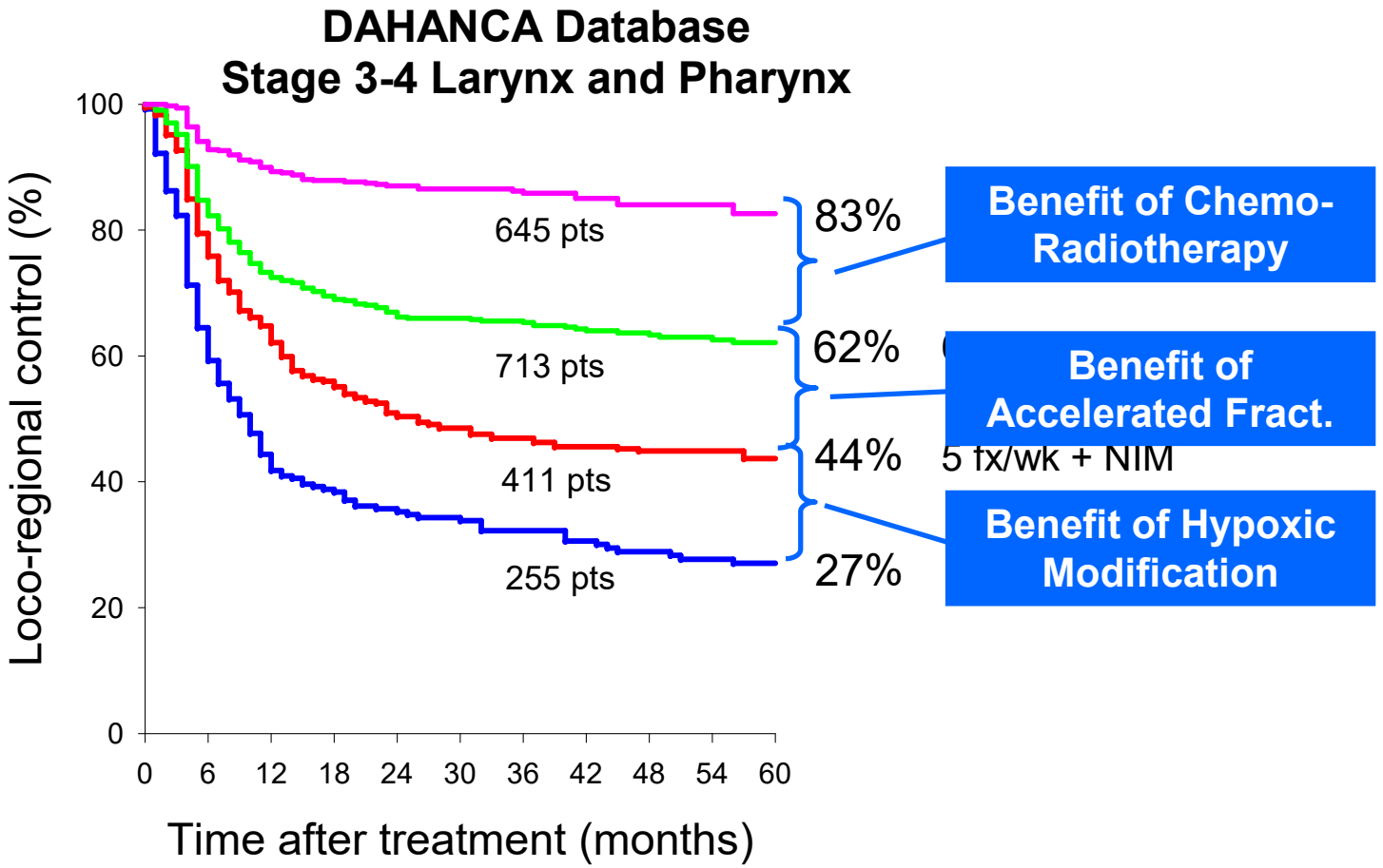
Radiotherapy of advanced (HN)SCC



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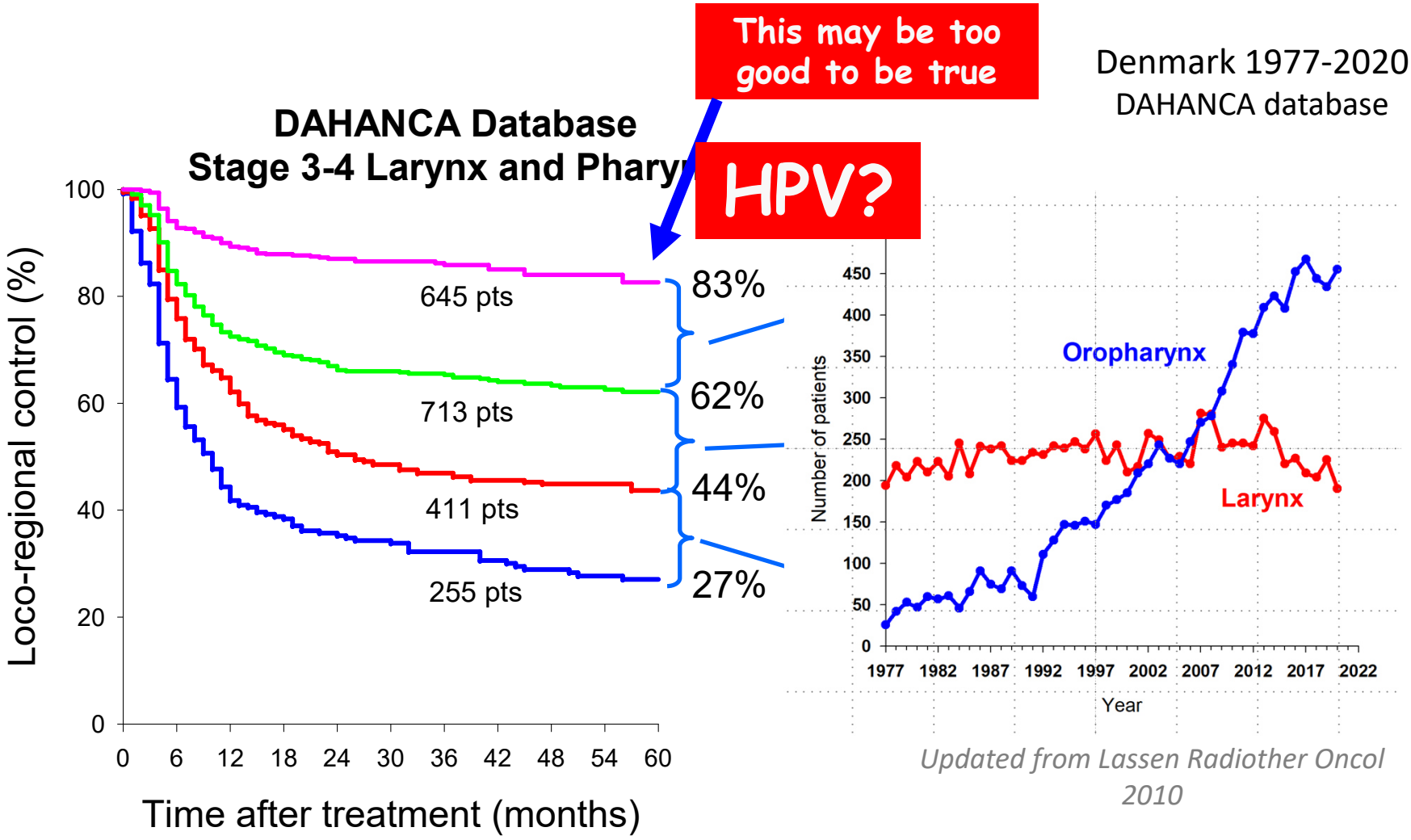
Radiotherapy of advanced (HN)SCC



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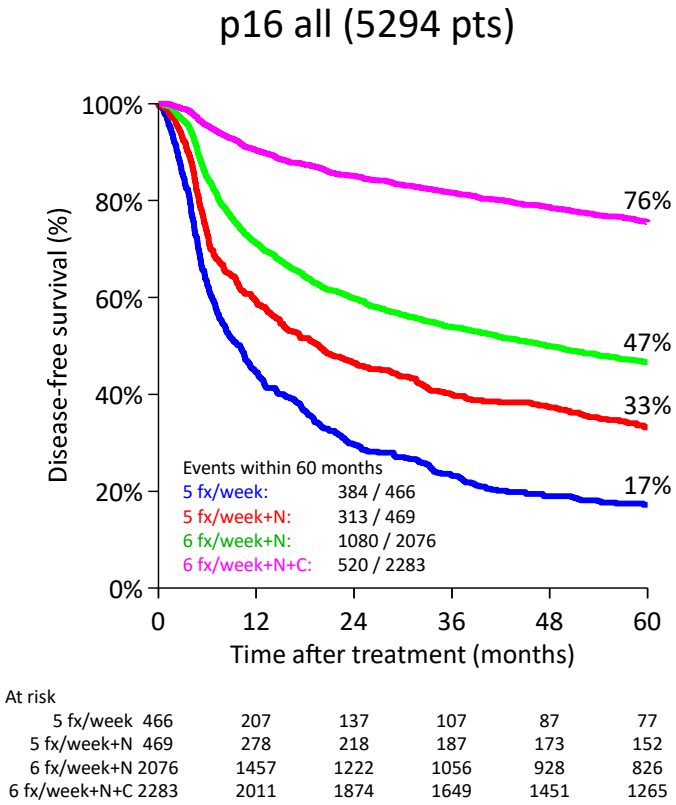
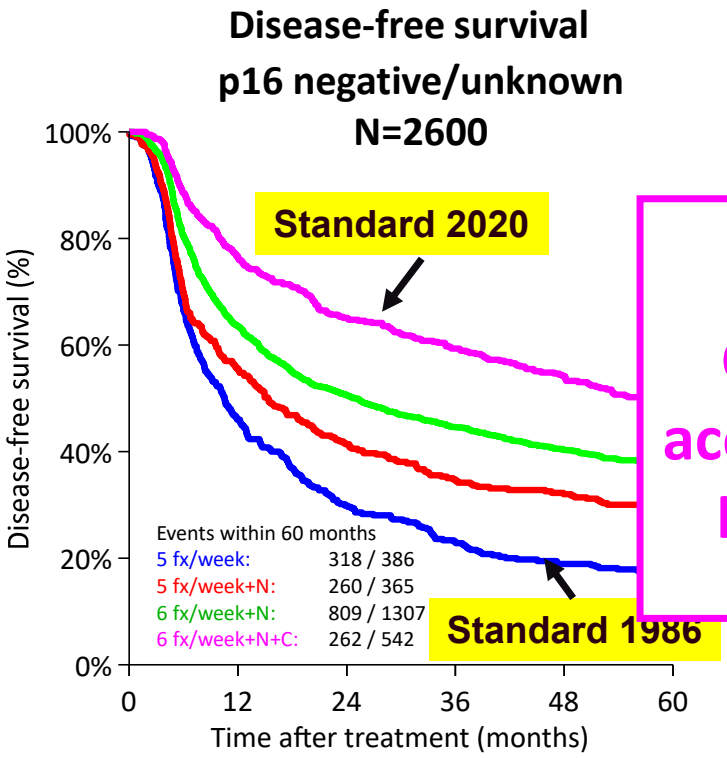
Disease-free survival
Stage III-IV Oropharynx (1986-2020)



'Real life' data
- from the Dahanca national database

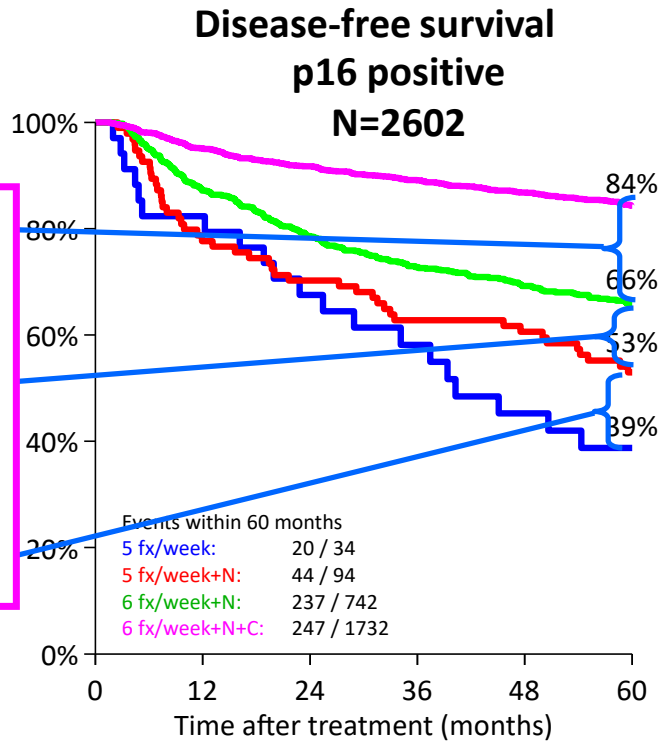
Development in treatment of OPSACC 1986-2020

Stage III-IV Oropharynx Denmark 1986-2020



Current standard of care:

Chemo-radiotherapy
accelerated fractionation
Hypoxic modification



At risk

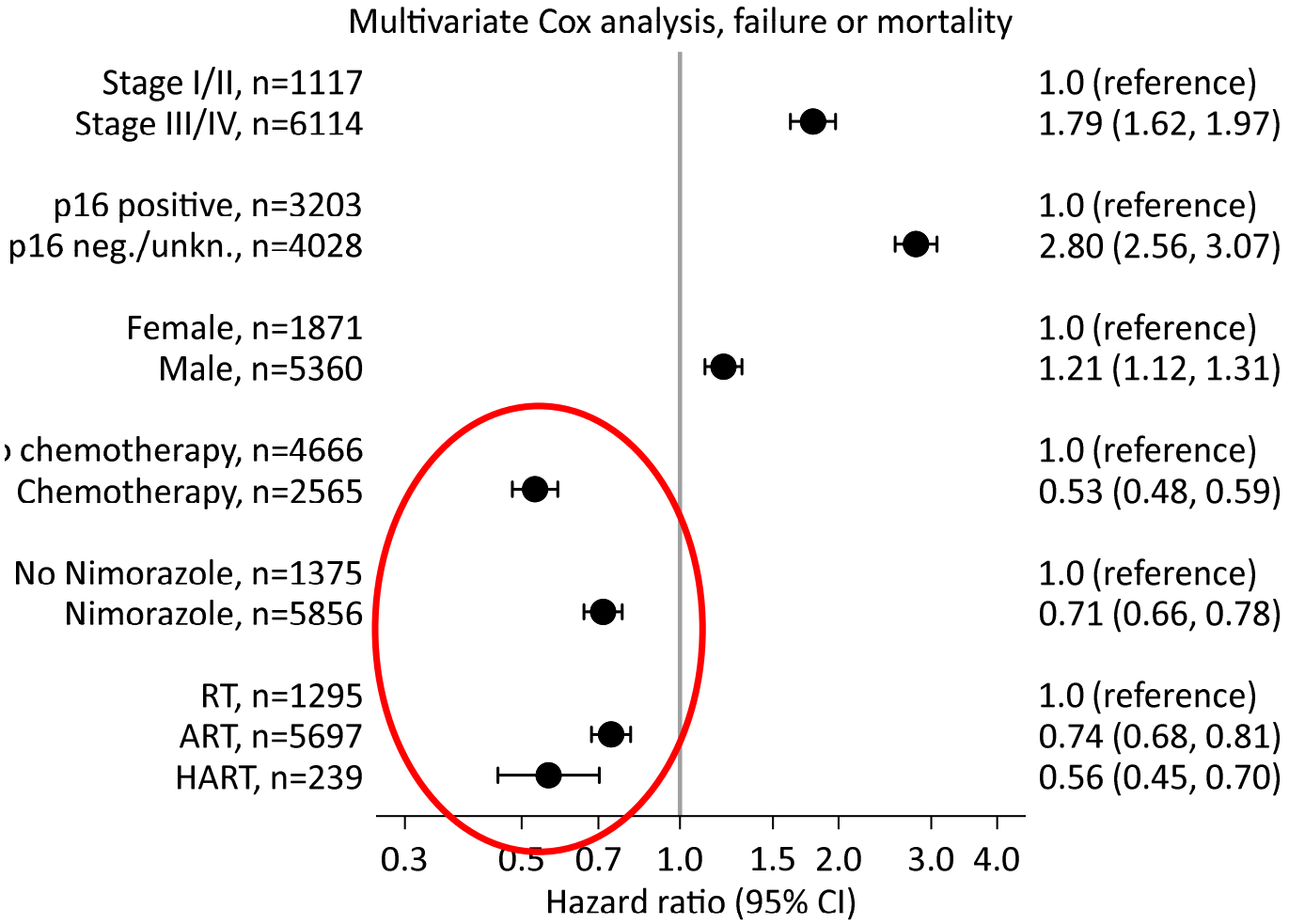
5 fx/week	386	177	115	89	72	66
5 fx/week+N	365	203	151	126	115	103
6 fx/week+N	1307	823	653	571	503	458
6 fx/week+N+C	542	407	341	286	241	198

At risk

5 fx/week	34	28	22	18	14	11
5 fx/week+N	94	73	66	59	57	48
6 fx/week+N	742	633	566	474	413	365
6 fx/week+N+C	1732	1601	1523	1337	1189	1052

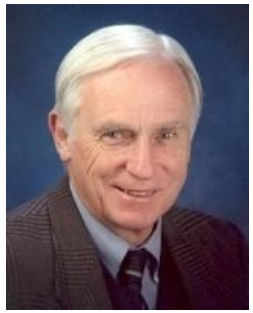
Lassen et al. in prep

Multivariate Cox analysis
Disease-free survival
DAHANCA
Oropharynx
(1986-2020)
Curative intended RT
7231 pts



A word about

Hypofractionation

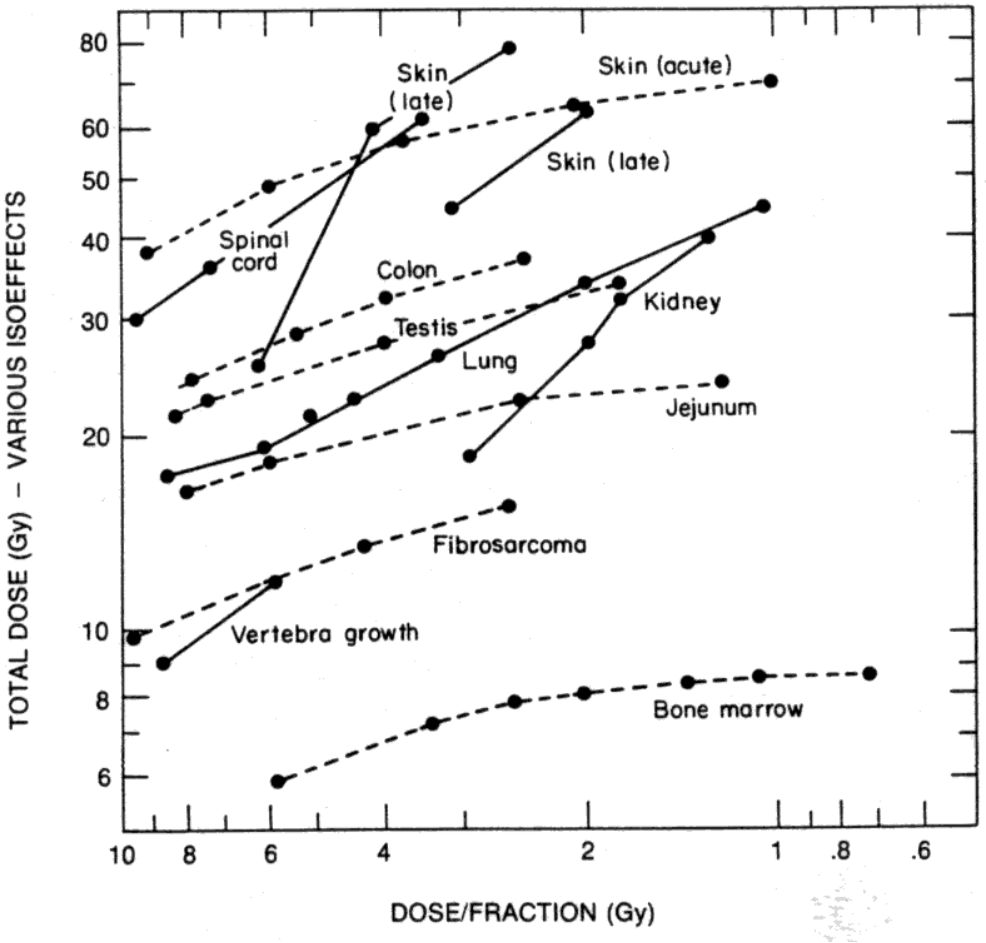


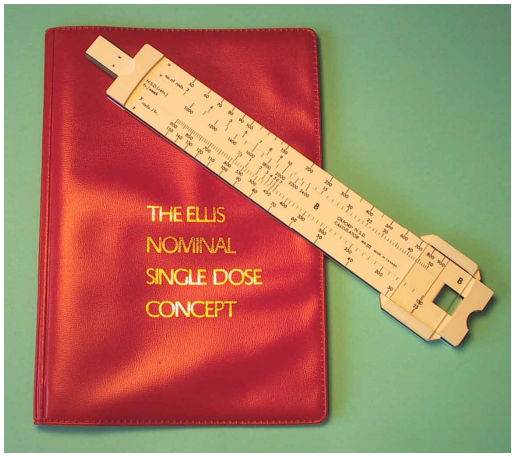
Time, dose and fractionation in radiotherapy

THE "SPAGHETTI" PLOT

Dose per fraction vs total dose. Isoeffect for various tumors, early and late responding normal tissues

H.R. Withers
Cancer 55: 2086, 1985





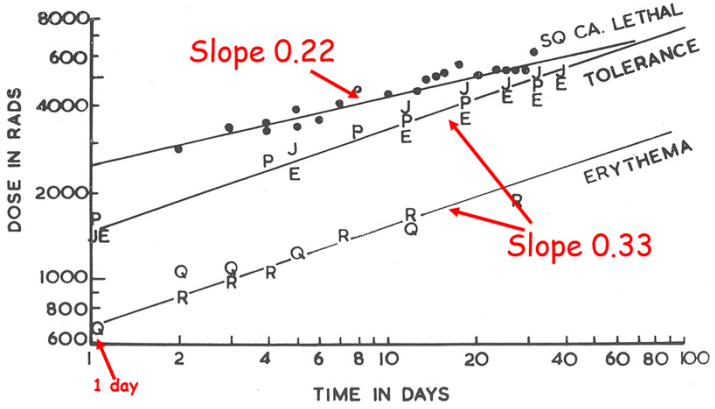


FIG. 4

Iso-effect curves for different fractionation regimes for squamous cell carcinoma, for skin erythema and for normal tissue tolerance. Taken from Cohen (1960).

DOSE, TIME AND FRACTIONATION: A CLINICAL HYPOTHESIS

FRANK ELLIS

From the Radiother

Ellis formula:

Total dose = NSD x N $^{0.24}$ T $^{0.11}$

termed 'Nominal

biological ef

possible to compare various t

different fractionation patterns and various overall treat

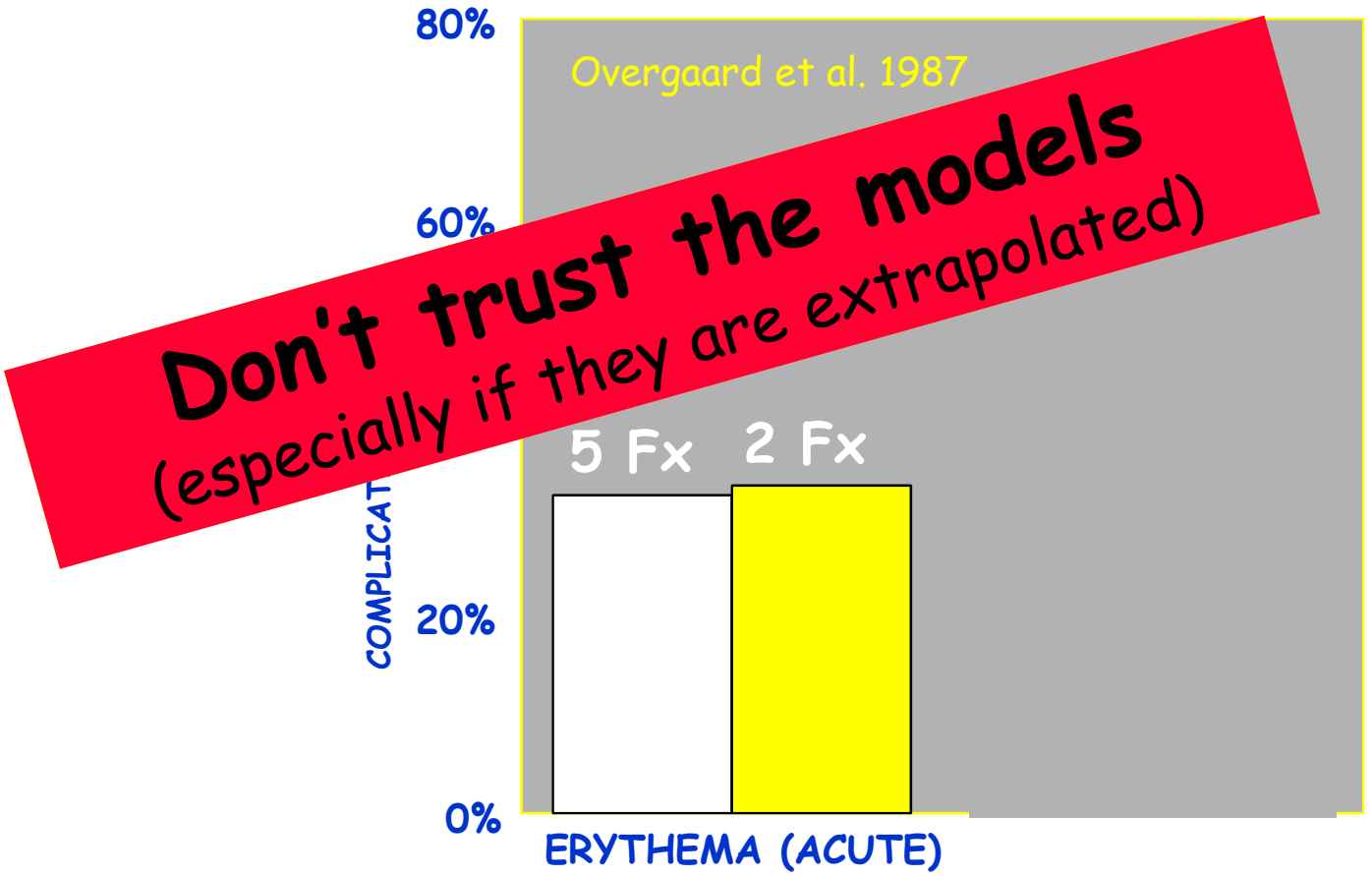
which the idea is based, and also its use in routine clinical practice, are discussed.

Long week-end!

F. Ellis: Clin. Radiol. 1969

High dose per fraction increase late radiation damage

2 vs 5 Fractions/Week (Ellis' NSD equavalent)



Large legal cases are caused by hypofractionation and/or poor radiotherapy technique, such as:

The Norwegian and Swedish

cas

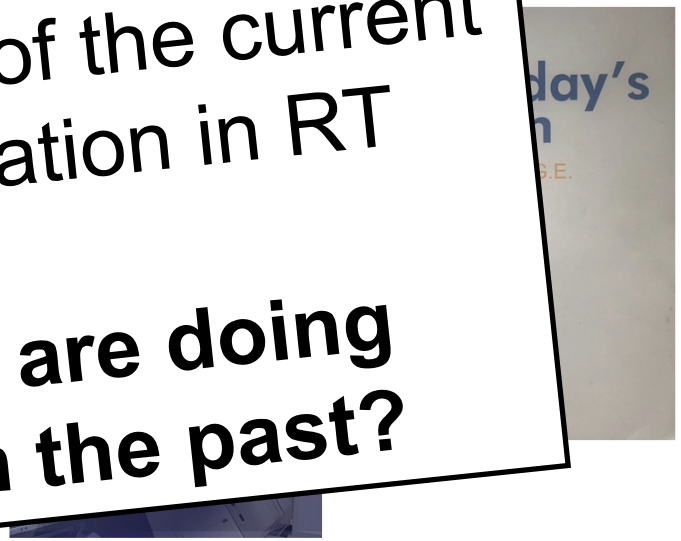
The

The

etc.

With such past history, one can be a bit nervous about the late outcome of the current increased use of hypofractionation in RT

Do we realy know what we are doing – or have we just forgotten the past?



(all attracting major public attention, and resulting in millions of € in compensation to the patients)

Why HYPO-fractionation now

- whats has happened?:

Has human (radio)biology changed?

Has tumor biology changed?

Has radiation oncologists chanced?

Table 1. Isoeffect doses in 2Gy equivalents (EQD_2) comparing the 5F regimens to 40Gy/15F and highlighting the differences. The α/β 3·7Gy (0·3, 7·1) were estimated in the Fast Forward trial for in breast tumour recurrence and α/β 1·7Gy (1·2, 2·3) for late NTE with no correction for treatment time.

	26Gy/5fr	27Gy/5fr	40Gy/15fr	Diff 26Gy vs 40Gy
α/β	EQD_2			
1·7 Gy	48·5 Gy	51·8 Gy	47·2 Gy	+2·8%
3·7 Gy	40·6 Gy	43·1 Gy	44·7 Gy	-9·2%

FAST-Forward

40 Gy/15 fx
vs
26-27 Gy/5 fx

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

Summary

Background We aimed to identify a five-fraction schedule of adjuvant radiotherapy (radiation therapy) delivered in 1 week that is non-inferior in terms of local cancer control and is as safe as an international standard 15-fraction regimen after primary surgery for early breast cancer. Here, we present 5-year results of the FAST-Forward trial.

Methods FAST-Forward is a multicentre, phase 3, randomised, non-inferiority trial done at 97 hospitals (47 radiotherapy centres and 50 referring hospitals) in the UK. Patients aged at least 18 years with invasive carcinoma of the breast (pT1–3, pN0–1, M0) after breast conservation surgery or mastectomy were eligible. We randomly allocated patients to either 40 Gy in 15 fractions (over 3 weeks), 27 Gy in five fractions (over 1 week), or 26 Gy in five fractions (over 1 week) to the whole breast or chest wall. Allocation was not masked because of the nature of the intervention. The primary endpoint was ipsilateral breast tumour relapse; assuming a 2% 5-year incidence for 40 Gy, non-inferiority was predefined as ≤1·6% excess for five-fraction schedules (critical hazard ratio [HR] of 1·81). Normal tissue effects were assessed by clinicians, patients, and from photographs. This trial is registered at isrctn.com, ISRCTN19906132.

Findings Between Nov 24, 2011, and June 19, 2014, we recruited and obtained consent from 4096 patients from 97 UK centres, of whom 1361 were assigned to the 40 Gy schedule, 1367 to the 27 Gy schedule, and 1368 to the 26 Gy

Table 1. Isoeffect doses in 2Gy equivalents (EQD_2) comparing the 5F regimens to 40Gy/15F and highlighting the differences. The α/β 3·7Gy (0·3, 7·1) were estimated in the Fast Forward trial for in breast tumour recurrence and α/β 1·7Gy (1·2, 2·3) for late NTE with no correction for treatment time.

	26Gy/5fr	27Gy/5fr	40Gy/15fr	Diff 26Gy vs 40Gy
α/β	EQD_2			
1·7 Gy	48·5 Gy	51·8 Gy	47·2 Gy	+2·8%
3·7 Gy	40·6 Gy	43·1 Gy	44·7 Gy	-9·2%

Late effects

Tumor

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

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Same treatment?

Offersen and Overgaard, Lancet 2020

The biology is clear and loud:

The use of large doses per fraction has no biological advantage

– but may be acceptable **if the treatment volume is small and only a small amount of (uncritical) normal tissue is exposed.**

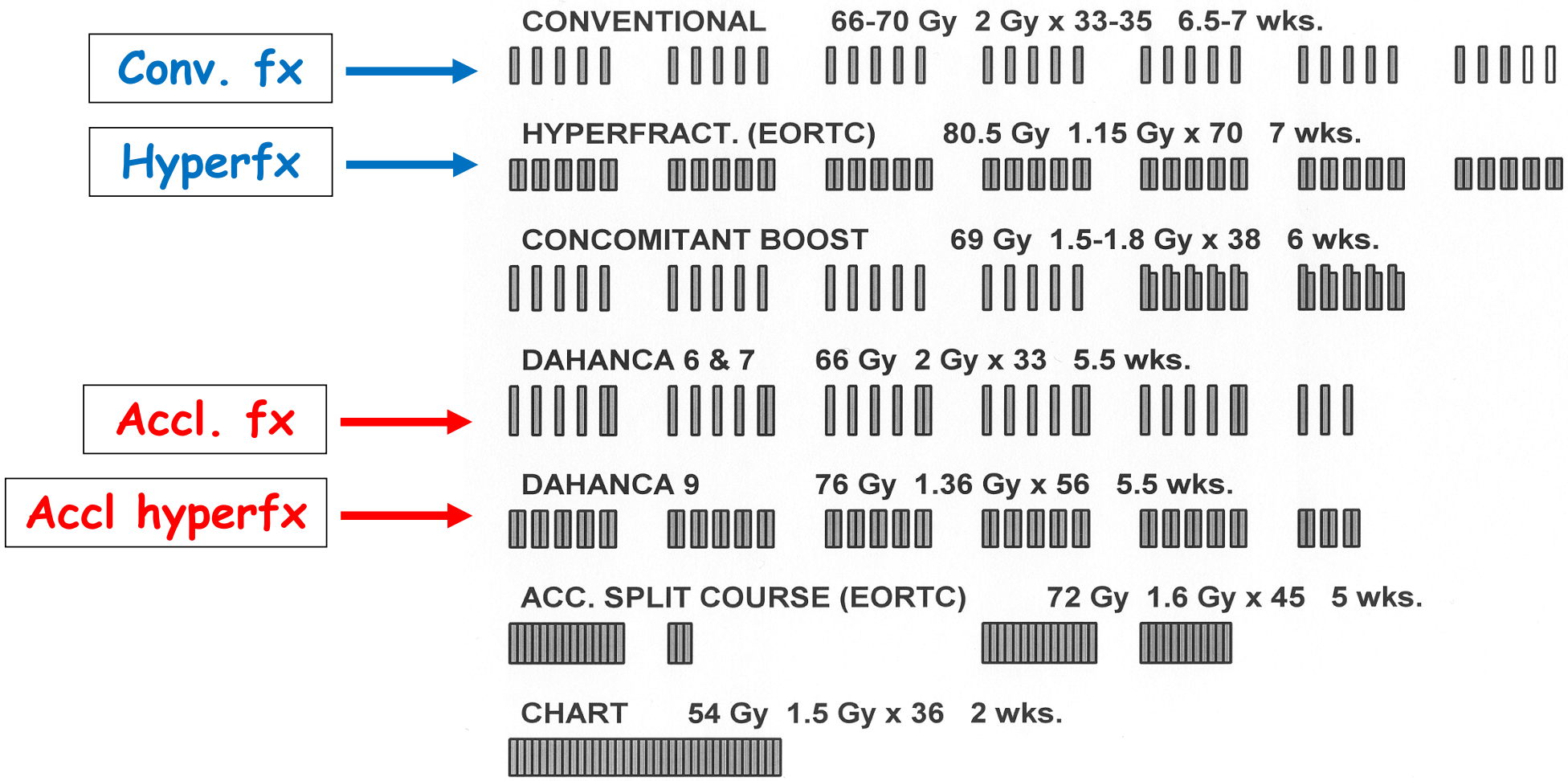
- and if we are willing to **accept a lower tumor control probability** (adjuvant treatment)

Message for future:

Hypofractionation decreases the therapeutic ratio. For equal late morbidly does the effective tumor dose decrease if dose/fx increases - thus, hypofractionation is biologically BAD.

The (inverse) corollary to this is that hyperfrationation is biological advantageous - and that is exactly what it is. - so we are progressing in the wrong direction

FRACTIONATION STUDIES IN HEAD & NECK CANCER



Web-Table 6 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for event-free survival.

Hyperfx chemo-rad

Hazard ratio; global Cochran Q statistic p=0.11, heterogeneity (within design) p=0.05, inconsistency (be

HFCRT (1) 5y-AB: 18.6%				0.81* [0.31-2.06]	0.70 [0.60-0.82]									
0.83 [0.63-1.10]	**IC_{TaxPF}-LRT (2)** 5y-AB: 12.2%						0.73 [0.60-0.88]							
0.84 [0.67-1.04]	1.01 [0.80-1.27]	**ACRT (3)** 5y-AB: 12.5%		1.01 [0.89-1.15]	0.76* [0.62-0.95]			0.84 [0.72-0.98]						
0.90 [0.69-1.18]	1.08 [0.82-1.42]	1.07 [0.87-1.33]	**IC_{TaxPF}-CLRT (4)** 5y-AB: 14.9%	0.94 [0.67-1.33]		0.71* [0.50-1.01]			0.8 [0.67-0.95]					
0.80 [0.65-0.98]	0.96 [0.78-1.18]	0.96 [0.85-1.07]	0.89 [0.74-1.07]	**$CLRT_P$ (5)** 5y-AB: 10.8%	0.76 [0.52-1.12]		0.90 [0.73-1.13]	0.86* [0.71-1.05]	1.04 [0.78-1.38]	0.67 [0.50-0.90]	0.75 [0.70-0.81]			0.78 [0.60-1.00]
0.71 [0.60-0.84]	0.85 [0.68-1.06]	0.84 [0.74-0.97]	0.79 [0.64-0.98]	0.88 [0.79-0.99]	**HFRT (6)** 5y-AB: 6.4%					0.98* [0.85-1.14]	0.82 [0.74-0.91]			
0.67 [0.54-0.84]	0.81 [0.65-1.00]	0.80 [0.69-0.93]	0.75 [0.61-0.91]	0.84 [0.75-0.94]	0.95 [0.83-1.09]	**$CLRT_{noP}$ (7)** 5y-AB: 4.5%					0.89 [0.81-0.97]	0.81* [0.63-1.04]	0.88* [0.68-1.13]	0.86 [0.73-1.02]
0.64 [0.52-0.80]	0.77 [0.64-0.93]	0.76 [0.66-0.88]	0.71 [0.58-0.88]	0.80 [0.72-0.89]	0.90 [0.79-1.04]	0.95 [0.84-1.08]	**IC_{PF}-LRT (8)** 5y-AB: 2.7%				0.94 [0.85-1.03]			
0.67 [0.54-0.84]	0.81 [0.65-1.01]	0.80 [0.70-0.92]	0.75 [0.61-0.93]	0.84 [0.75-0.95]	0.95 [0.82-1.10]	1.00 [0.87-1.15]	1.05 [0.92-1.21]	**VART (9)** 5y-AB: 4.6%			0.90 [0.80-1.02]			
0.72 [0.54-0.97]	0.87 [0.64-1.17]	0.86 [0.67-1.10]	0.80 [0.68-0.94]	0.90 [0.73-1.12]	1.02 [0.80-1.30]	1.07 [0.85-1.35]	1.13 [0.89-1.43]	1.07 [0.84-1.36]	**IC_{PF}-CLRT (10** 5y-AB: 7.0%					
0.67 [0.54-0.82]	0.80 [0.65-0.99]	0.80 [0.70-0.91]	0.74 [0.61-0.91]	0.83 [0.76-0.91]	0.94 [0.84-1.06]	0.99 [0.89-1.11]	1.04 [0.93-1.17]	0.99 [0.87-1.12]	0.93 [0.73-1.17]	**MART (11)** 5y-AB: 4.2%	0.87 [0.79-0.96]			
0.60 [0.49-0.73]	0.71 [0.59-0.87]	0.71 [0.63-0.80]	0.66 [0.55-0.80]	0.74 [0.70-0.79]	0.84 [0.76-0.93]	0.88 [0.81-0.97]	0.93 [0.85-1.02]	0.88 [0.79-0.98]	0.83 [0.66-1.03]	0.89 [0.83-0.96]	**LRT (12)** 5y-AB: ref	1.08 [0.86-1.36]		
0.60 [0.47-0.77]	0.73 [0.57-0.93]	0.72 [0.60-0.86]	0.67 [0.53-0.85]	0.75 [0.65-0.88]	0.85 [0.72-1.02]	0.90 [0.77-1.05]	0.94 [0.80-1.12]	0.90 [0.75-1.07]	0.84 [0.64-1.09]	0.91 [0.77-1.06]	1.02 [0.88-1.1	**LRT-AC (13)** 5y-AB: 0.6%		
0.63 [0.46-0.85]	0.75 [0.56-1.02]	0.75 [0.58-0.97]	0.70 [0.52-0.94]	0.78 [0.62-1.00]	0.89 [0.69-1.14]	0.93 [0.73-1.19]	0.98 [0.76-1.26]	0.93 [0.72-1.20]	0.87 [0.63-1.20]	0.94 [0.74-1.20]	1.05 [0.84-1.33]	1.0 [0.81-1.33]		
0.57 [0.45-0.71]	0.68 [0.54-0.86]	0.68 [0.58-0.79]	0.63 [0.51-0.78]	0.71 [0.63-0.80]	0.80 [0.69-0.93]	0.84 [0.75-0.96]	0.89 [0.77-1.02]	0.84 [0.72-0.98]	0.79 [0.62-1.01]	0.85 [0.75-0.97]	0.95 [0.86-1.07]	0.94 [0.79-1.12]		

Conv.

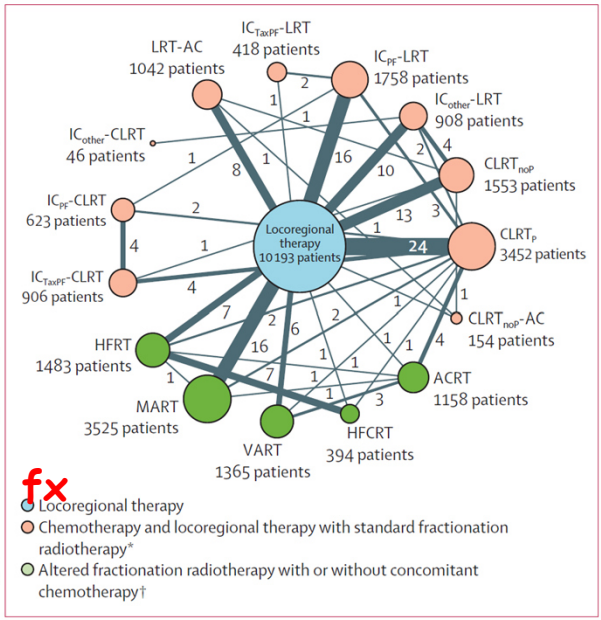
* comparison with only one trial; results are highlighted in grey if they are statistically significant, see web-table 2 for abbreviations and how to re

Chemotherapy and radiotherapy in locally advanced head and neck cancer: an individual patient data network meta-analysis

*Claire Petit, Benjamin Lacas, Jean-Pierre Pignon, Quynh Thu Le, Vincent Grégoire, Cai Grau, Allan Hackshaw, Björn Zackrisson, Mahesh K B Parmar, Ju-Whei Lee, Maria Grazia Ghi, Giuseppe Sanguineti, Stéphane Temam, Maurice Cheugoua-Zanetsie, Brian O'Sullivan, Marshall R Posner, Everett E Vokes, Juan J Cruz Hernandez, Zbigniew Szutkowski, Eric Lartigau, Volker Budach, Rafal Suwiński, Michael Poulsen, Shaleen Kumar, Sarbani Ghosh Laskar, Jean-Jacques Mazeron, Branislav Jeremic, John Simes, Lai-Ping Zhong, Jens Overgaard, Catherine Fortpied, Pedro Torres-Saavedra, Jean Bourhis, Anne Aupérin, Pierre Blanchard, on behalf of the MACH-NC and MARCH Collaborative Groups**

115 RCT with 228987 pts

Petit et al. Lancet Oncol 2021.



Overall message for the future:

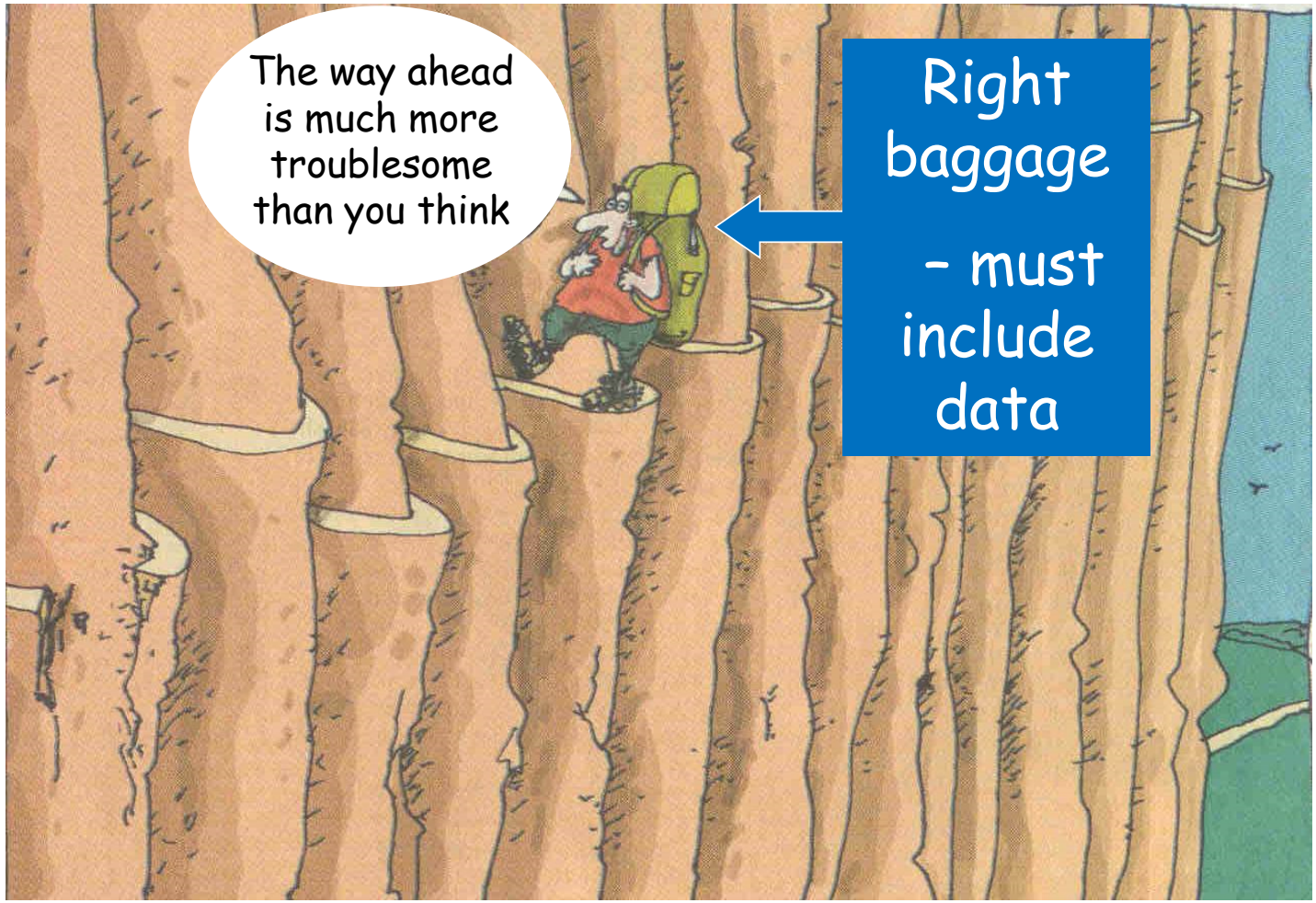
There is strong evidence showing that classical radiobiology (still) is the basis for good radiotherapy.

- and good radiotherapy is needed to secure optimal cancer treatment

– ignoring that may cause trouble.

The future is yours

- but don't forget your historical baggage



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Abstract submission deadline:
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