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Clatterbridge Centre for Oncology NHS
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Lo stato della modellistica in radioterapia

Alan E. Nahum PhD
Physics Department
Clatterbridge Centre for Oncology, Bebington,
Wirral CH63 4JY UK
(alan.nahum@ccotrust.nhs.uk)

Convegno Fisica e Radioterapia, NUOVE FRONTIERE TRA HI-TECH E POST GENOMICA, 2 luglio 2010
Convento di S. Francesco del Monte, Monteripido (PERUGIA).

What do we do with all the sophisticated radiotherapy equipment?

- Individualisation of beam shapes, beam weighting, sometimes non-uniform beam intensities (IMRT), according to the tumour shape and patient anatomy (3D planning, ”inverse” planning)

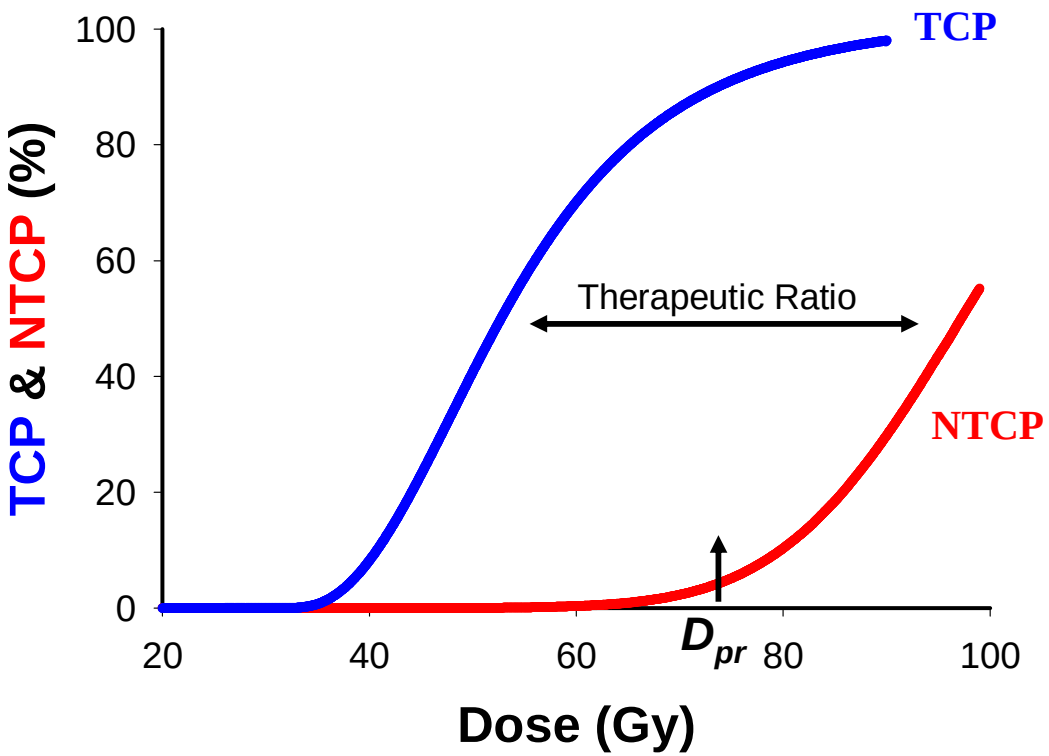
BUT

- “Rigid” protocols for prescribing tumour dose and number of fractions

THIS DOES NOT ACHIEVE THE HIGHEST PROBABILITY OF “SAFE” TUMOUR LOCAL CONTROL

Treatment plan “optimisation”

For a given fraction size



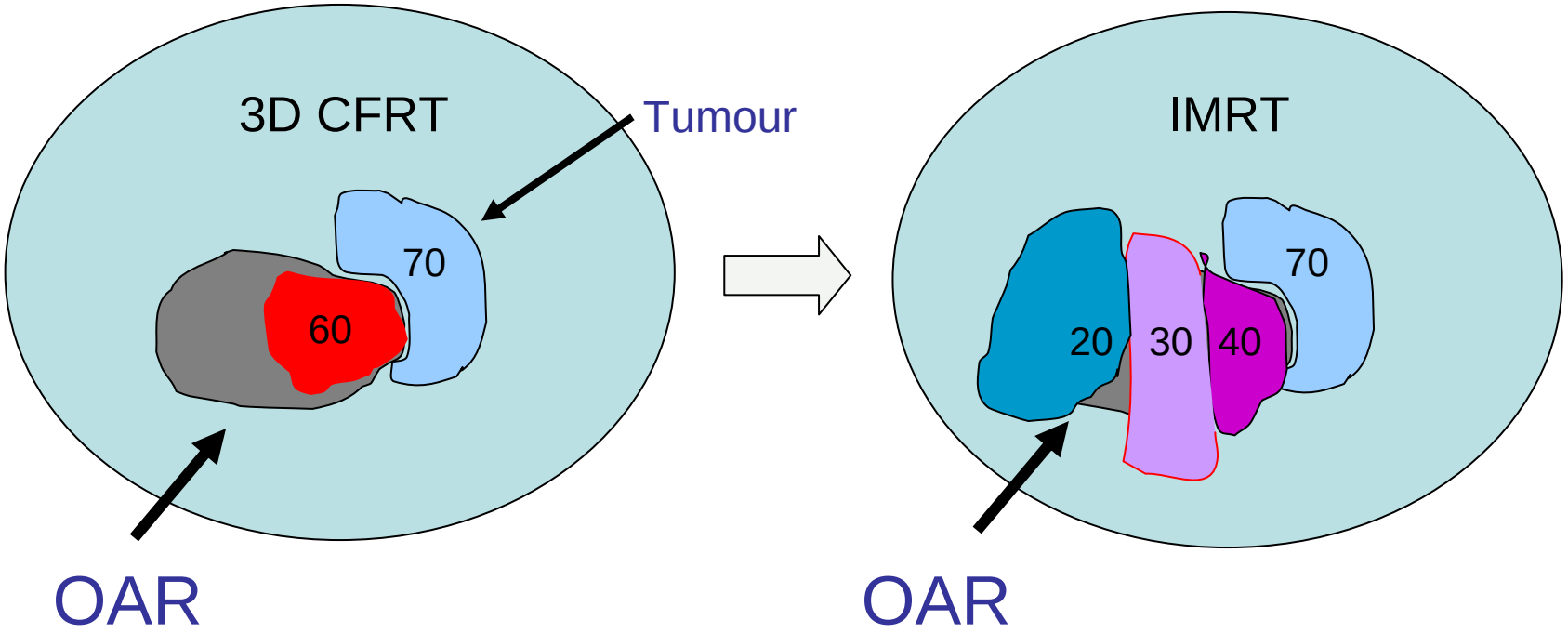
I will assume that you are familiar with these models

e.g. the ”Marsden” TCP model based on linear-quadratic cell killing and population-variation in radiosensitivity; the Lyman-Kutcher-Burman (LKB) NTCP model (quasi-empirical; *n* – volume effect etc).

What does IMRT really do?

Volume close to the tumour irradiated to high dose

LARGER volume, receiving a **LOWER** dose



IMRT *redistributes* the energy; the mean dose outside the tumour remains ≈ the same

D_{mean} = Total Energy/mass of the body ≈ constant (∝ integral dose)

What are the variables?

- Beam modality (photons, electrons, protons...)
- Beam number and directions
- Beam modulation (IMRT)

DOSE DISTRIBUTION

- Number of fractions
- Overall time (once a day, twice a day.....)

What are the input data?

- Patient anatomy
- Structures: Tumour, OARs
- Individual Patient “Biology” (if available):

  $\vec{\alpha}(r)$, $\vec{\beta}(r)$

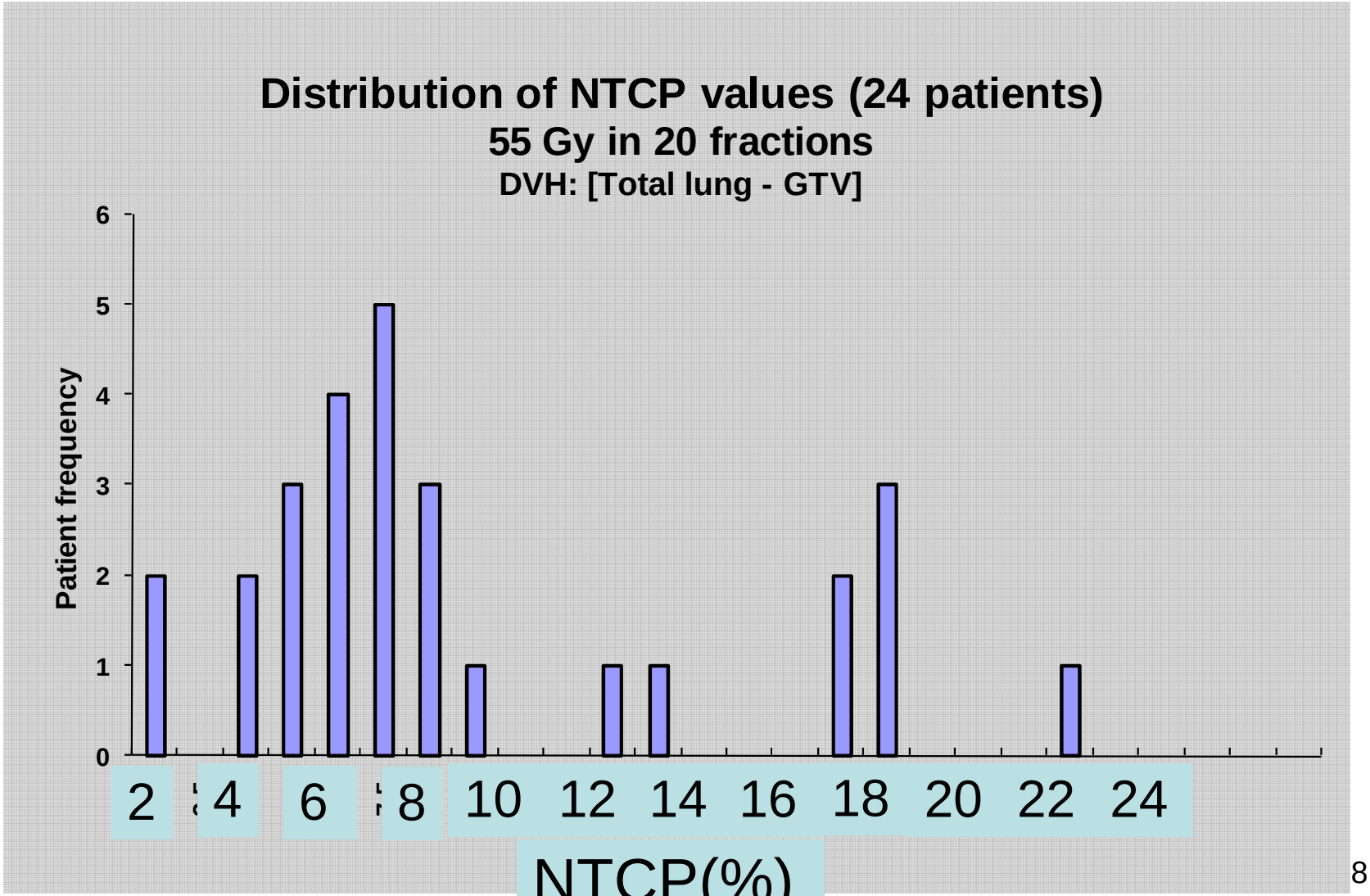
  Co-morbidities

  Concomitant/sequential biological-chemo agents
- NTCP for each OAR (f’n of dose distribution incl. fractionation)
- TCP (fn. of dose distribution incl. fractionation)

Using TCP and NTCP models to improve treatment outcome/therapeutic ratio

I. Iso-NTCP prescription-dose customisation

The distribution of NTCP values (grade 2 pneumonitis) estimated for around 25 CCO patients all given 55 Gy in 20 fractions; the extremely wide variation in NTCP is simply a reflection of the wide variation in tumour sizes, tumour position and hence volume of lung in the radiation fields.

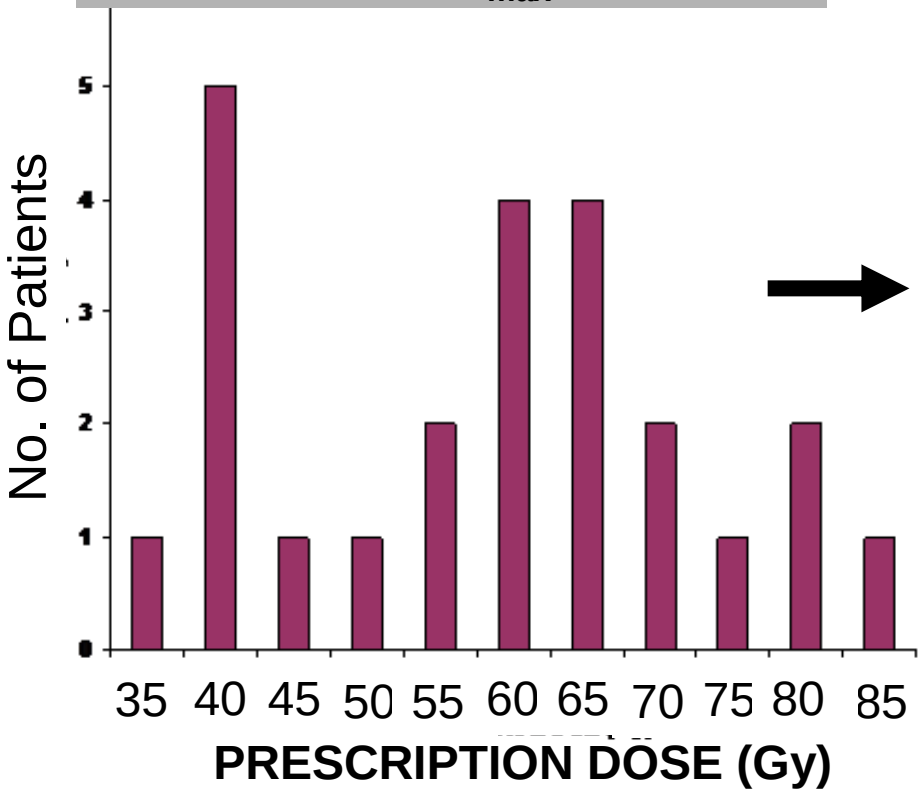


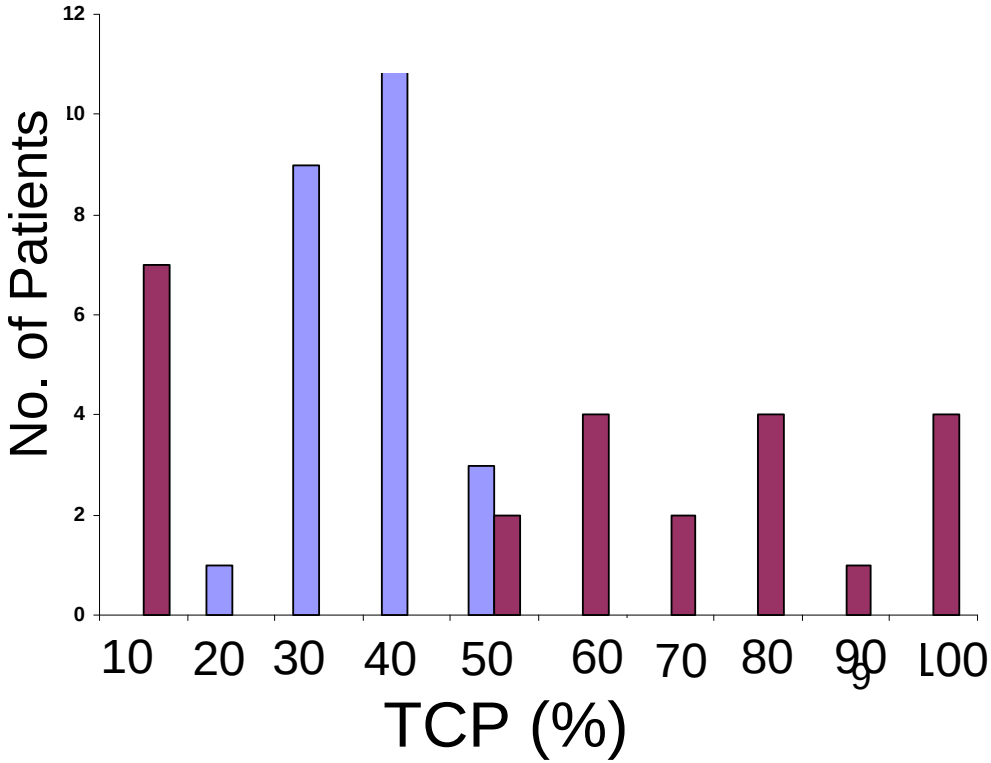
The *individualisation* of D_{presc} based on normal-tissue constraints; the example in the figure is for a so-called *isotoxic* (NTCP=10%) lung-tumour protocol where a spectrum of doses is applied (left figure). On the right are shown the changes in TCP which are estimated to result from changing from 55 Gy in 20 fractions to these individualised doses, and individualised fraction sizes (as the number of fractions is kept equal to 20). The wide variation in GTV volumes is also reflected in these TCP 'spectra'.

DOSE INDIVIDUALISATION

For NTCP = 10% or TCP = 99% or oesophagus D_{max} = 63 Gy

TCP (20 fractions)	**Mean**
i)55 Gy - blue	**35.8%**
ii)Customised D_{presc}	**52.7%**





IDEAL-CRT lung tumour Dose-Customisation Protocol (UK)

David Landau, oncologist (St. Thomas', London)

John Fenwick, physicist/modeller (Clatterbridge)

30 fractions, one per day (no weekends)

Prescription Doses chosen according to $rNTD_{mean}$ such that risk of grade 3-4 pneumonitis <= 10%.

Concurrent chemo.

HAS STARTED

No lower than 62 Gy for large tumours

No higher than 73 Gy for small tumours

I-START lung tumour Dose-Customisation Protocol (UK)

Jason Lester, oncologist (Velindre, Cardiff)

Zaf Malik, oncologist (Clatterbridge, Merseyside)

Nazia Mohammed, oncologist (Beatson, Glasgow)

Alan Nahum, physicist/modeller (Clatterbridge)

20 fractions, one per day (no weekends) **NATIONALLY APPROVED**

Prescription Doses according to $NTCP_{LKB}$ = 10% (pneumonitis grade 2)

Radiotherapy alone. No lower than 55 Gy for large tumours.

Fraction size?

- What is the scope for increasing the therapeutic ratio by changing the fraction size? (depends on the α/β ratio)
- Is there a connection between the degree of conformality of the treatment and the ‘fractionation sensitivity’?

The well-known "Withers" iso-effect formula (e.g. The Steel ESTRO radiobiology book):

$$EQD_X = D\ [d + (\alpha/\beta)_{OAR}]\ /\ [X + (\alpha/\beta)_{OAR}]$$

converts a total dose *D* given in fractions of size *d* into a total dose EQD_X given in X-Gy fractions (assuming complete repair of sub-lethal events between fractions).

a. Withers formula has nothing to say about dose distributions – conventionally one uses the prescription dose, D_{presc}

b. Use of D_{presc} only makes sense if

EITHER 100% of the NT receives this dose

OR Complication probability is wholly determined by the volume of the NT receiving this dose i.e. a ”serial” organ.

c. But if the organ in question responds in terms of <u>mean</u> dose, say, and receives a heterogeneous dose distribution??? E.g. normal lung.

Much more logical to use an 'effective dose per fraction' in the OAR defined such that

$$d_{OAReff} = d_{tumour} \times k_{OAR}$$

where $k \approx 1$ **for "Series" organs (e.g. rectum)**

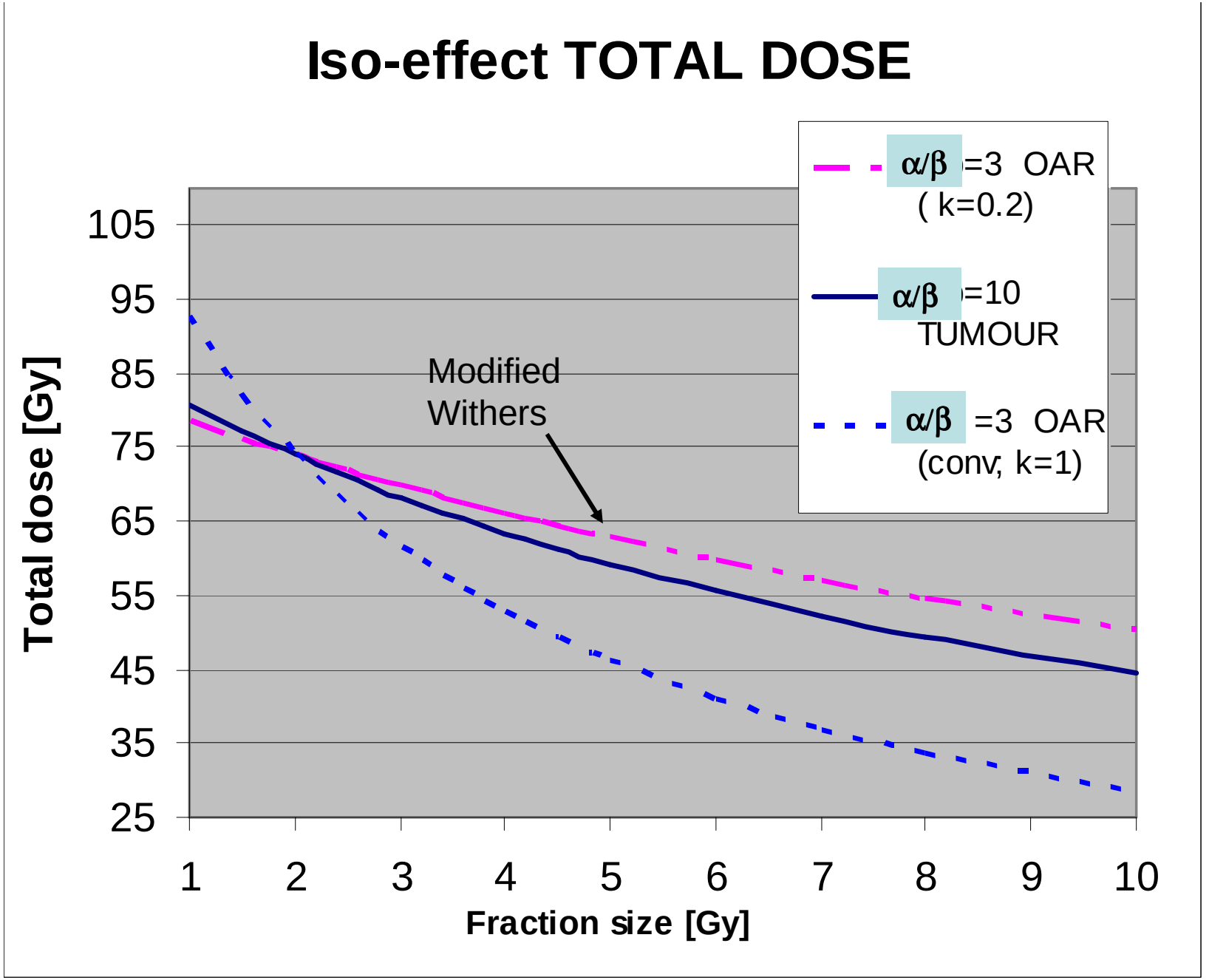
$k \approx D_{mean} / D_{presc}$ **for "Parallel" organs (e.g. lung)**

k **= an intermediate value for "intermediate" organs**

Thus the factor relating the two total doses becomes

$$[\, d \times k_{OAR} + (\alpha/\beta)_{OAR} \,] \; / \; [\, 2 \times k_{OAR} + (\alpha/\beta)_{OAR} \,]$$

LET'S SEE WHAT EFFECT THIS HAS…….


Iso-effect TOTAL DOSE
Total dose [Gy]
105
95
85
75
65
55
45
35
25
1
2
3
4
5
6
7
8
9
10
Fraction size [Gy]
Modified
Withers
α/β =3 OAR
(k=0.2)
α/β =10
TUMOUR
α/β =3 OAR
(conv; k=1)

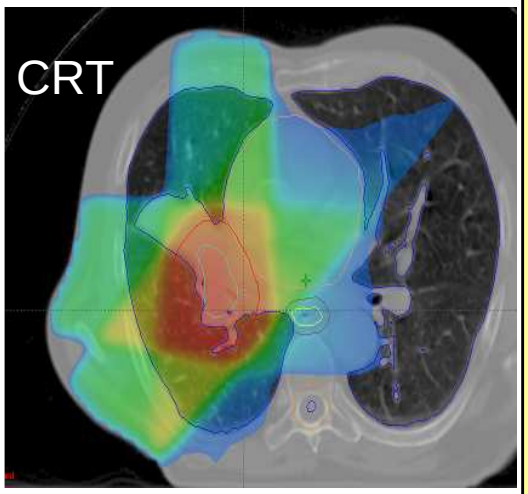
Immediately we see that the fractionation sensitivity is MUCH reduced in organs such as lung.

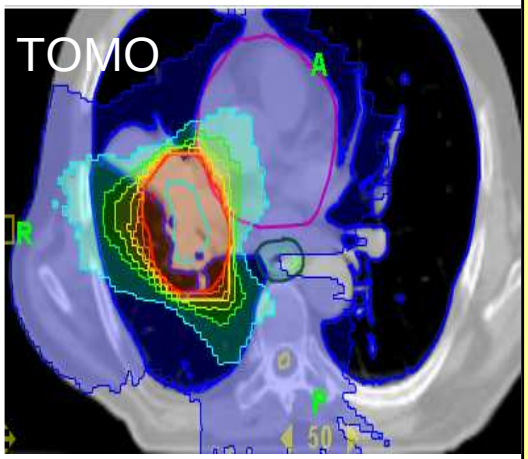
What consequences might this have?

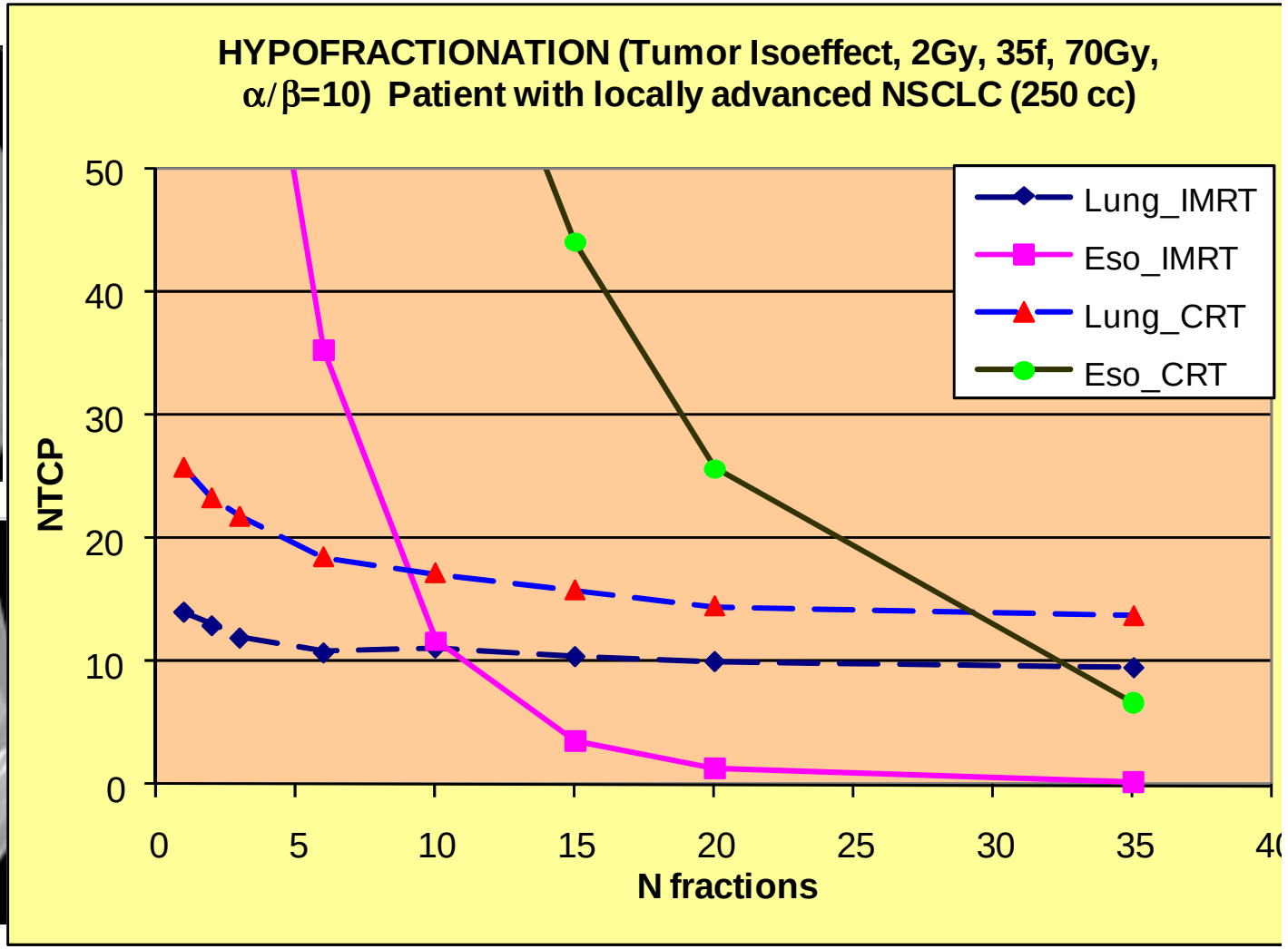
External-beam radiotherapy involving “parallel” or “quasi-parallel” OARs could be treated with much larger fraction sizes / HYPOfractionation

SOME RADIOBIOLOGICAL CONSIDERATIONS ON THE POTENTIAL OF IMRT IN NON-STANDARD FRACTIONATION

R. Calandrino[1], S.Broggi[1], G.M. Cattaneo[1], C. Fiorino[1], A.E. Nahum[2], F. Fazio[3]







SBRT – an NTCP analysis

ACKNOWLEDGEMENTS: Andrea Filippi, Riccardo Ragona, Umberto Ricardi (Department of Radiotherapy, University of Turin, S Giovanni Battista Hospital, Torino, Italy) – for kindly making available DVH data from some of their SBRT treatments.

3 fractions of 15 Gy, prescribed at the 80% isodose, 8 fields

L-K-B parameters: TD_{50}= 29.2 Gy; m = 0.45; n = 1 (De Jaeger *et al* 2003)

[DVHs converted to 2-Gy iso-effective total doses using $\alpha/\beta = 3$]

PATIENT nr.	GTV/CTV (cm3)	[TOTAL LUNG-GTV/CTV] D_{mean}(Gy)	NTCP(L-K-B)
2	2.46	2.1	0.028
3	7.08	2.6	0.031
8	7.86	5.5	0.080
13	14.72	6.2	0.106
6	19.54	7.0	0.189

Mean NTCP for these 5 patients **0.071** or **7.1**%

Conclusion: The L-K-B NTCP model makes reasonable predictions for these extremely hypofractionated regimens

Customising both Dose and fraction number/size using *BIOSUITE*

TCP parameters (*Marsden* model)*:*

Lung tumours

$N_o = 10^7$ clngns.cm^{-3} ; $\alpha = 0.31$ Gy^{-1}, $\sigma_\alpha = 0.062$ Gy^{-1},

$\alpha/\beta = 10$ Gy; $T_{dbl} = 3$ days; T-delay $= 21$ days

NTCP parameters (L-K-B model)

Lung (grade-2 pneumonitis)

$\alpha/\beta = 3$; $TD_{50} = 24.5$ Gy*;* $m = 0.37$, $n = 1$

Oesophagus

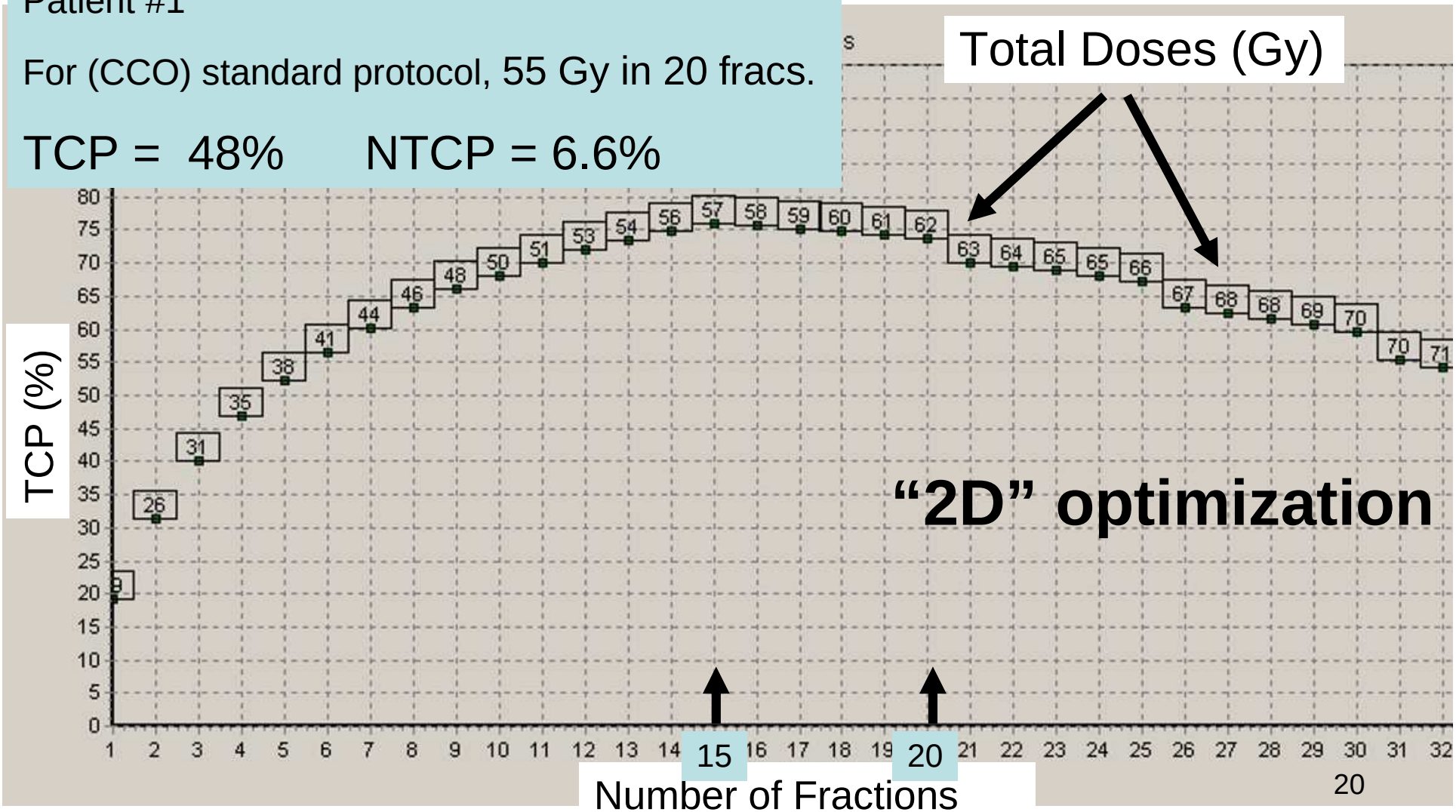
$\alpha/\beta = 1.7$, $m = 0.1$, $n = 0.1$

TCP at (iso)NTCP = 10% for variable fraction number

Patient #1

For (CCO) standard protocol, 55 Gy in 20 fracs.

TCP = 48% NTCP = 6.6%



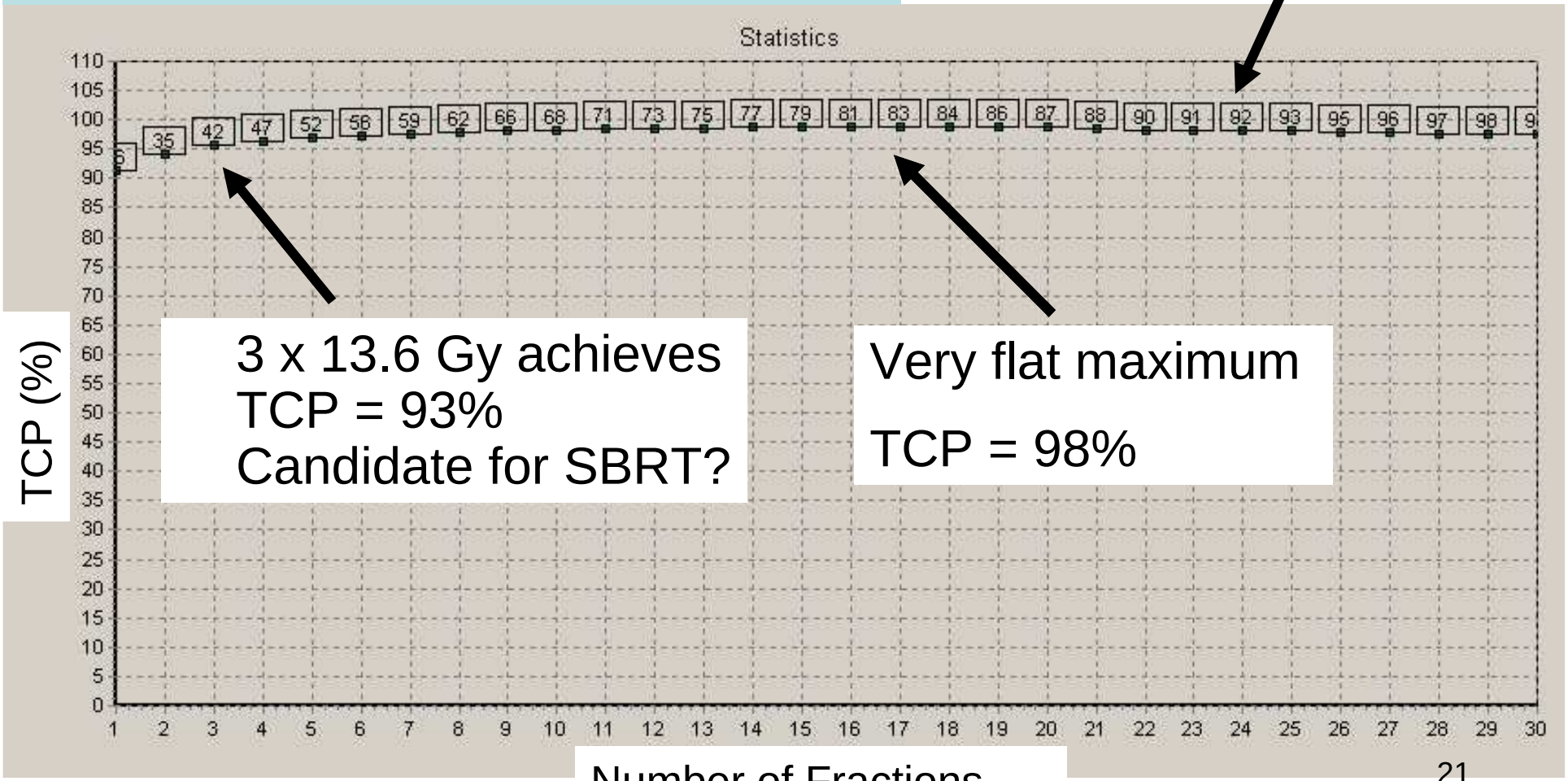
Computations using BIOSUITE (Julian Uzan, CCO)

TCP at (iso)NTCP = 10%

Patient #9

For (CCO) standard protocol : 55 Gy in 20 fracs.

TCP = 50.4% NTCP = 4.3%



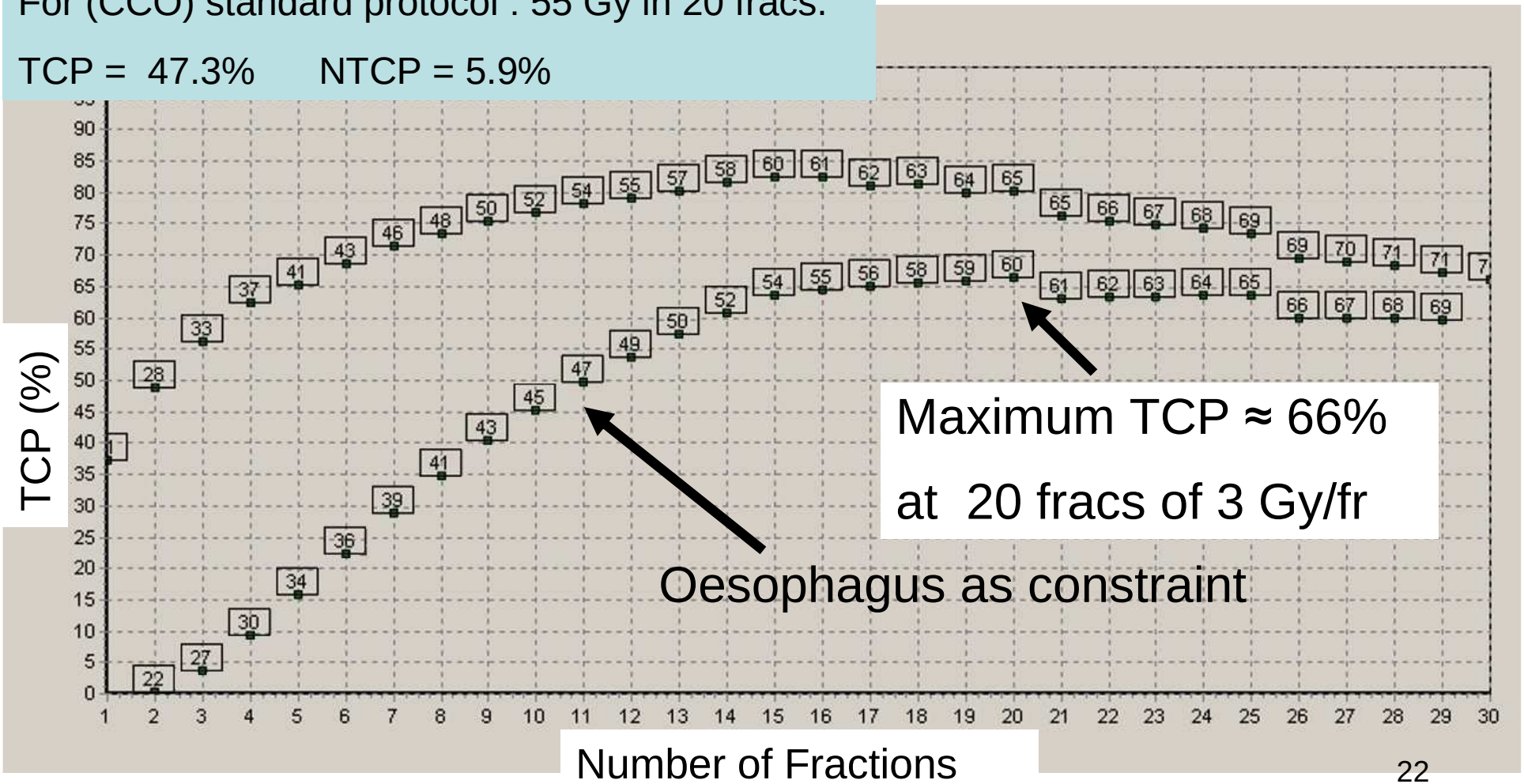
Computations using BIOSUITE (Julian Uzan, CCO)

TCP at (iso)NTCP = 10%

Patient #13

For (CCO) standard protocol : 55 Gy in 20 fracs.

TCP = 47.3% NTCP = 5.9%



Computations using BIOSUITE (Julian Uzan, CCO)

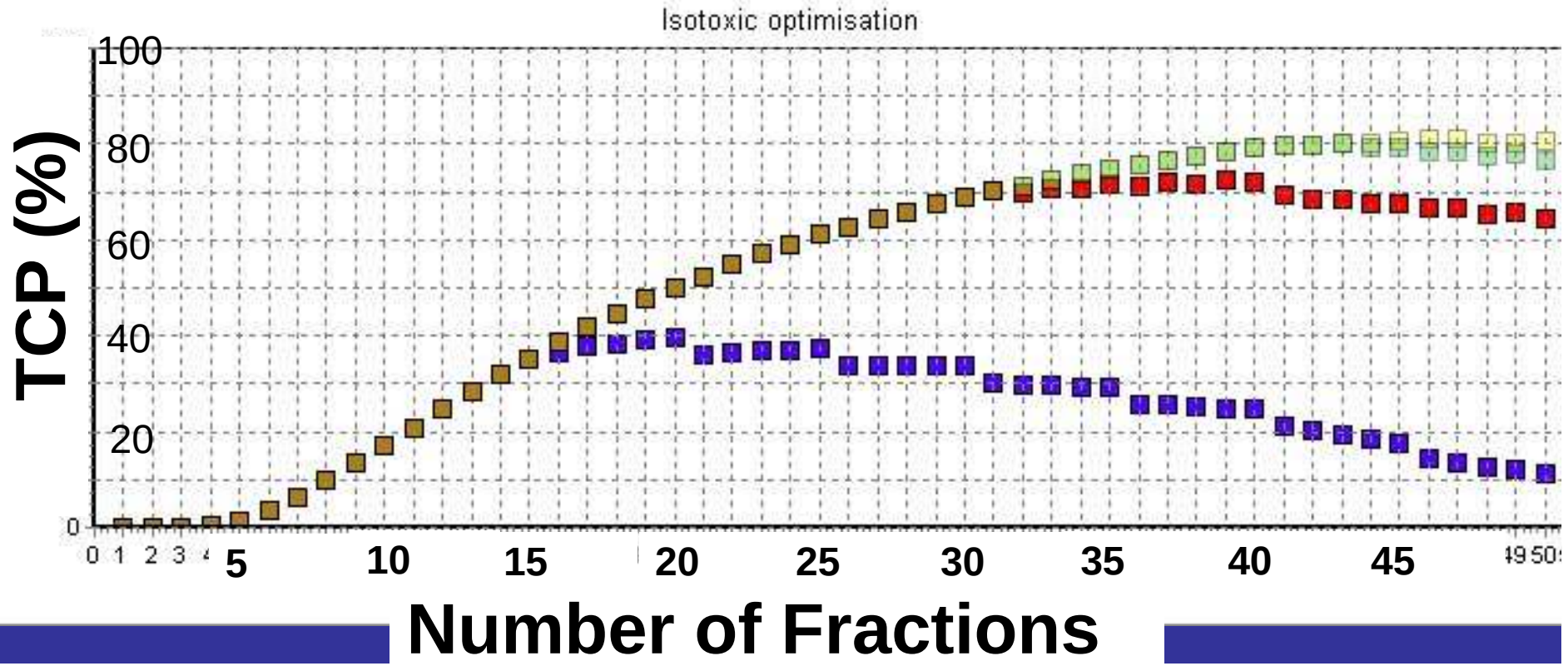
More than one fraction per day?

NTCP = 10% - grade-2 pneumonitis [DVH: Totallung-GTV]

BLUE – one fraction/day TCP_{max} = **40%** **(20 x 2.9 Gy)**

RED - twice per day TCP_{max} = **72.5%** **(39 x 1.9 Gy)**

GREEN- twice a day+no wkd. break TCP_{max} = **80%** **(43 x 1.8 Gy)**

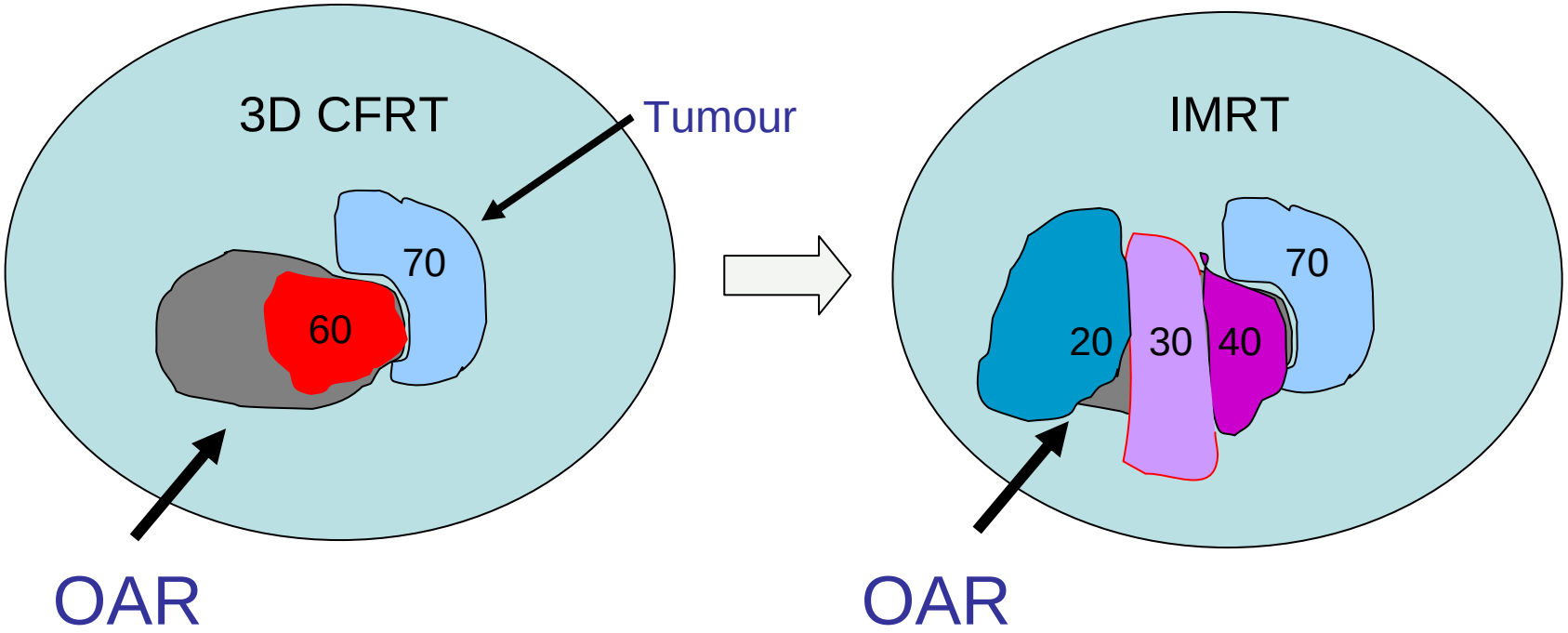


Is it enough just to play around with the prescription dose (or the number of fractions)?

What does IMRT really do?

Volume close to the tumour irradiated to high dose

LARGER volume, receiving a **LOWER** dose



IMRT *redistributes* the energy; the mean dose outside the tumour remains ≈ the same

D_{mean} = Total Energy/mass of the body ≈ constant (∝ integral dose)

LEVEL-II OPTIMISATION

‘*Biologically motivated’ optimization*:

Use expressions for NTCP and TCP directly in the ‘objective function’ of the inverse-planning process, thus allowing the mathematical and radiobiological properties of the models to drive the search for the optimum plan (e.g. Hoffmann, Larsson *et al* 2004; Peñagarícano *et al* 2005; Kim and Tome 2007; Alber etc.).

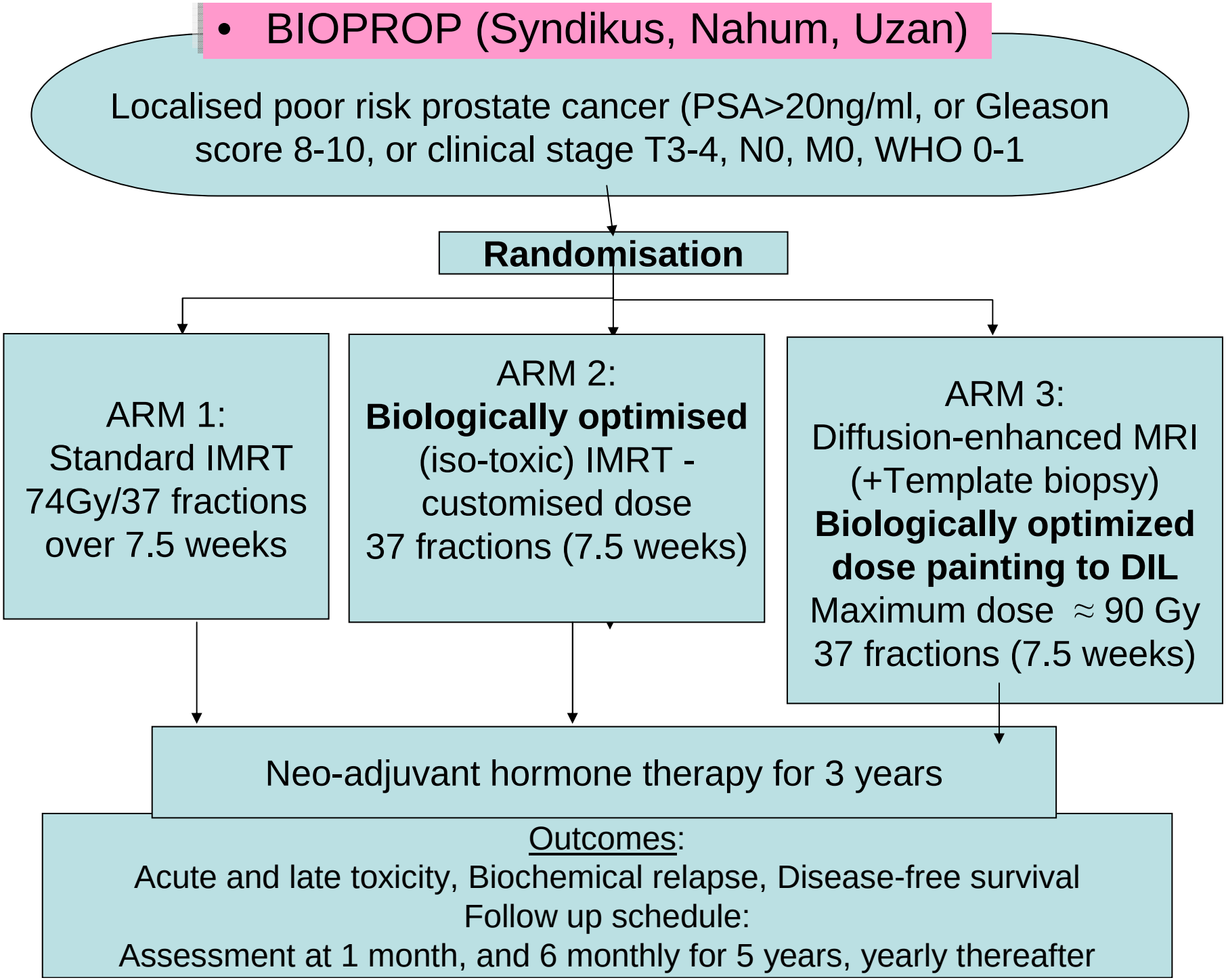
“3D” optimization

What should the objective be?

Maximise *TCP* for fixed *NTCP e.g. 4%*

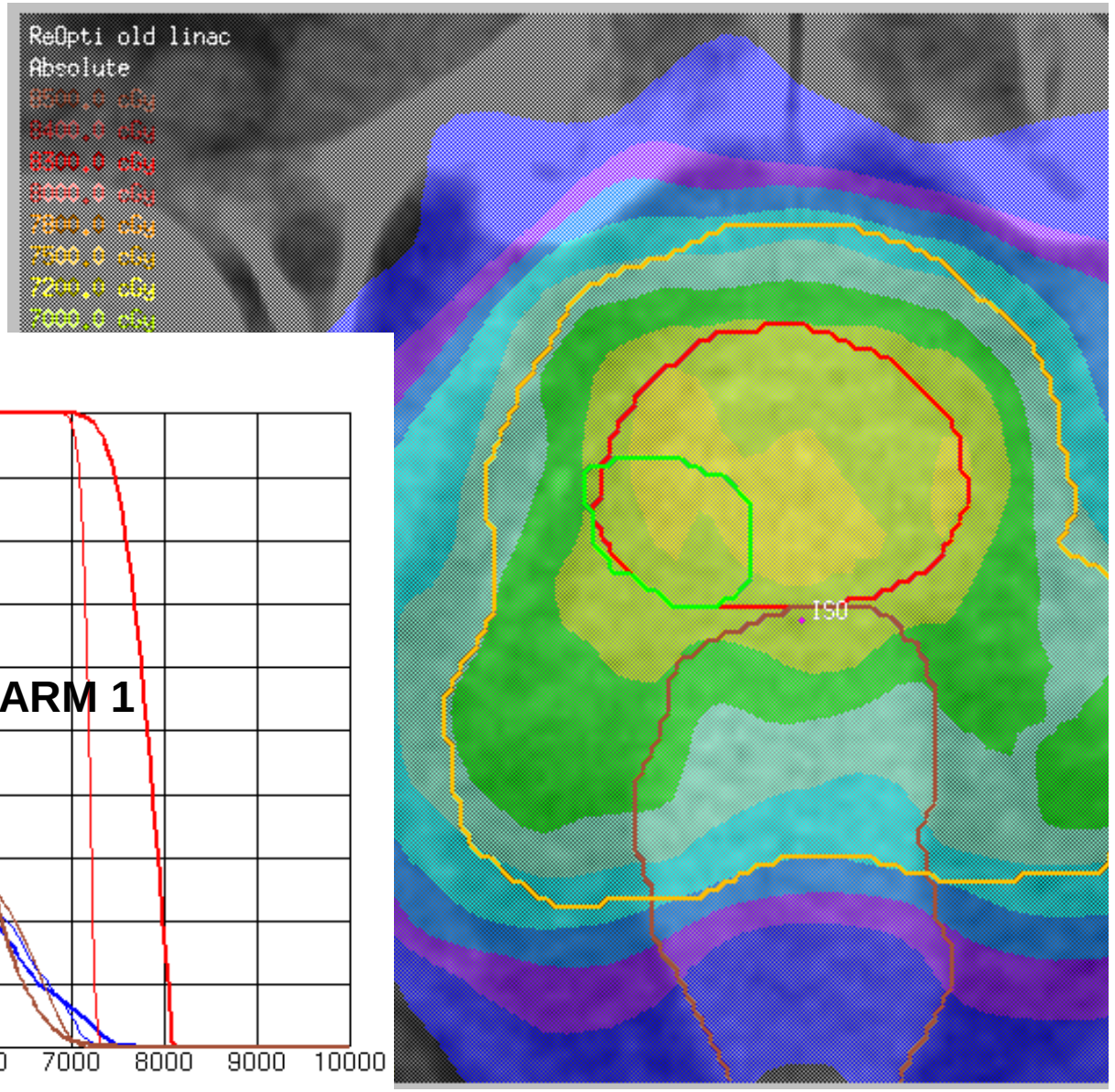
OR

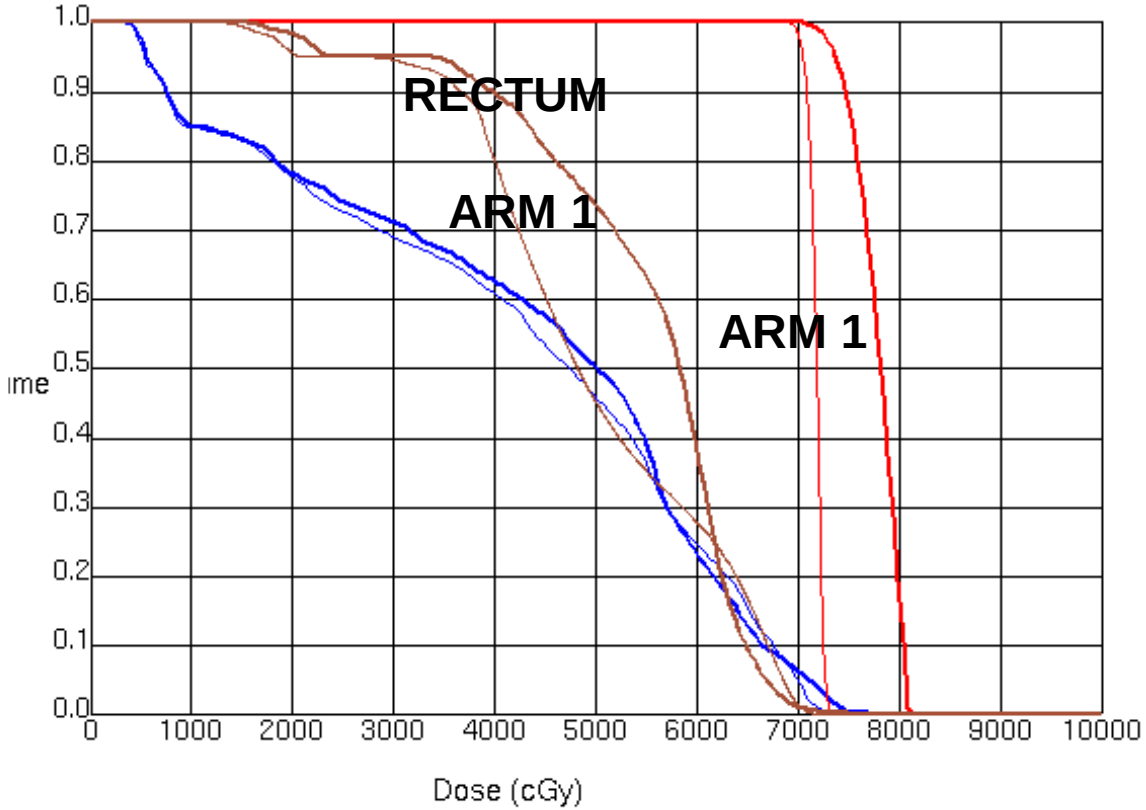
Minimise *NTCP* for fixed *TCP e.g. 95%*,


• BIOPROP (Syndikus, Nahum, Uzan)
Localised poor risk prostate cancer (PSA>20ng/ml, or Gleason score 8-10, or clinical stage T3-4, N0, M0, WHO 0-1
Randomisation
ARM 1: Standard IMRT 74Gy/37 fractions over 7.5 weeks
ARM 2: Biologically optimised (iso-toxic) IMRT - customised dose 37 fractions (7.5 weeks)
ARM 3: Diffusion-enhanced MRI (+Template biopsy) Biologically optimized dose painting to DIL Maximum dose ≈ 90 Gy 37 fractions (7.5 weeks)
Neo-adjuvant hormone therapy for 3 years
Outcomes:
Acute and late toxicity, Biochemical relapse, Disease-free survival
Follow up schedule:
Assessment at 1 month, and 6 monthly for 5 years, yearly thereafter

Standard IMRT Plan

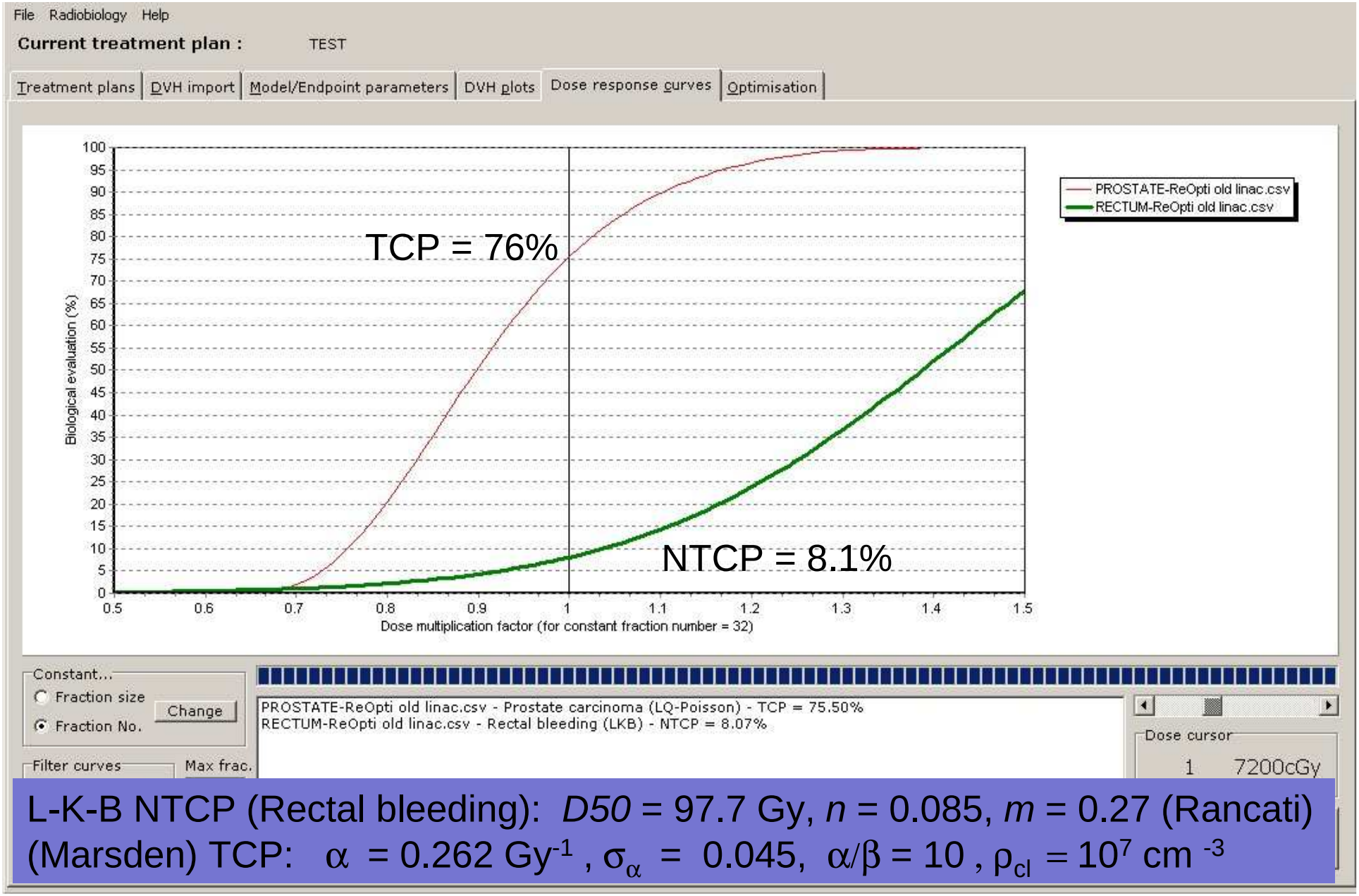
Pinnacle “Research Interface”





TCP, NTCP (Rectal Bleeding) vs Prescription Dose STANDARD IMRT PLAN

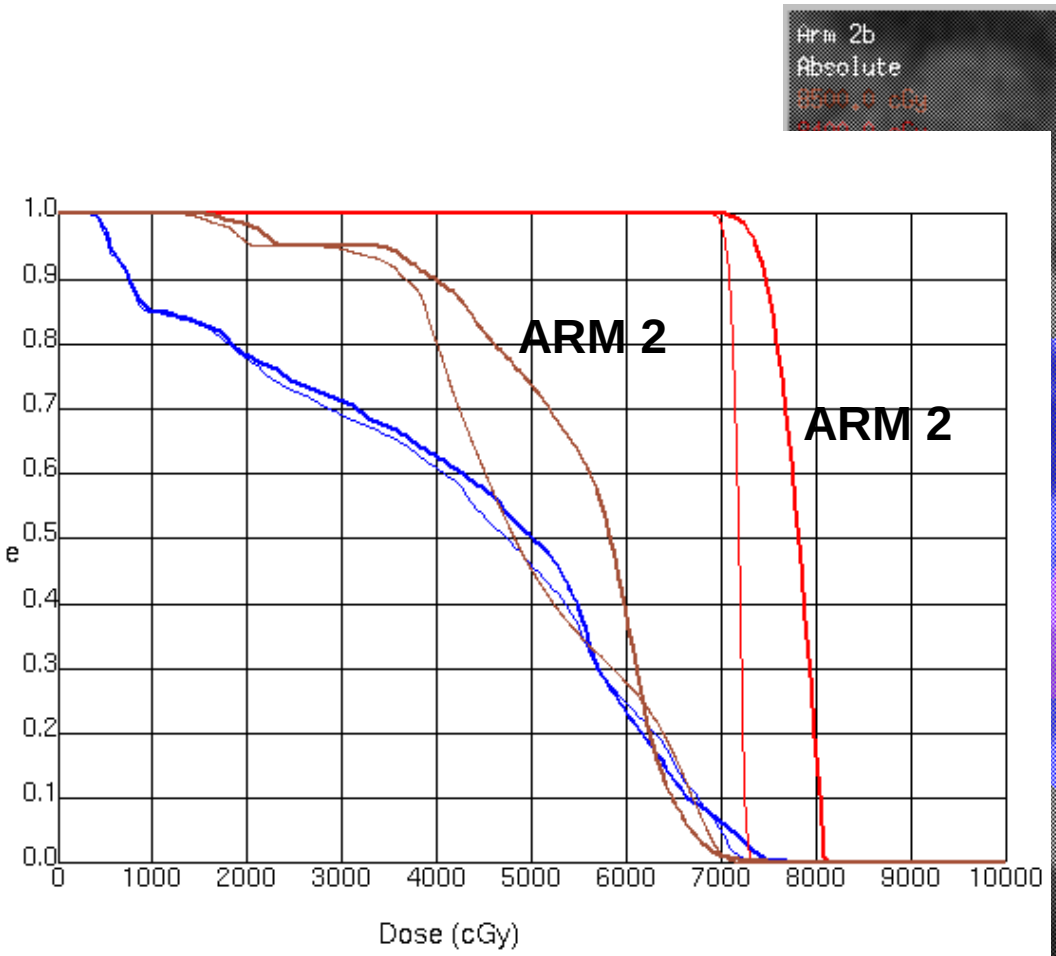
72 Gy in 32 Fractions *BioSuite* (J. Uzan)

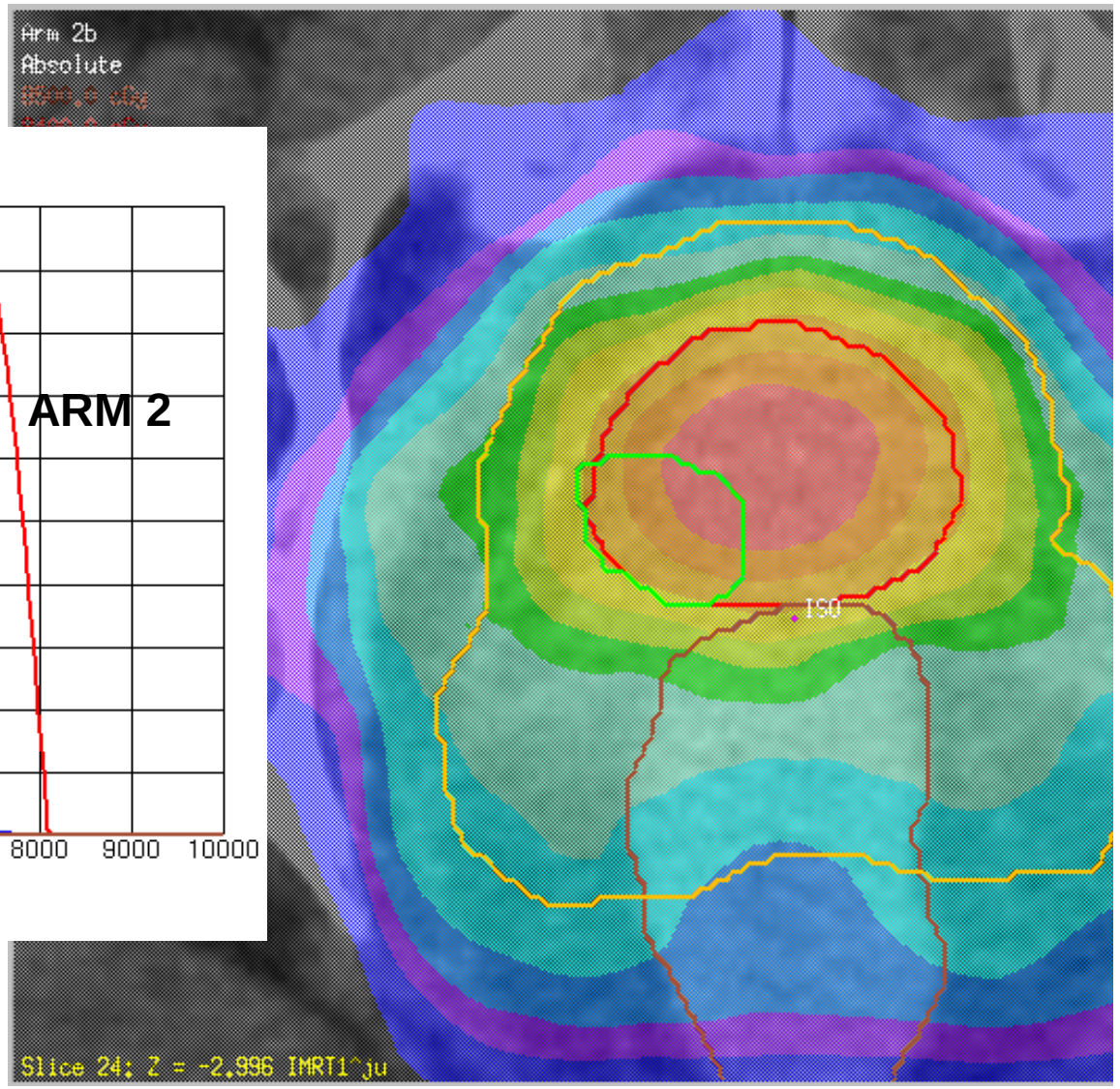


L-K-B NTCP (Rectal bleeding): *D50* = 97.7 Gy, *n* = 0.085, *m* = 0.27 (Rancati)

(Marsden) TCP: $\alpha = 0.262\ Gy^{-1}$, $\sigma_\alpha = 0.045$, $\alpha/\beta = 10$, $\rho_{cl} = 10^7\ cm^{-3}$

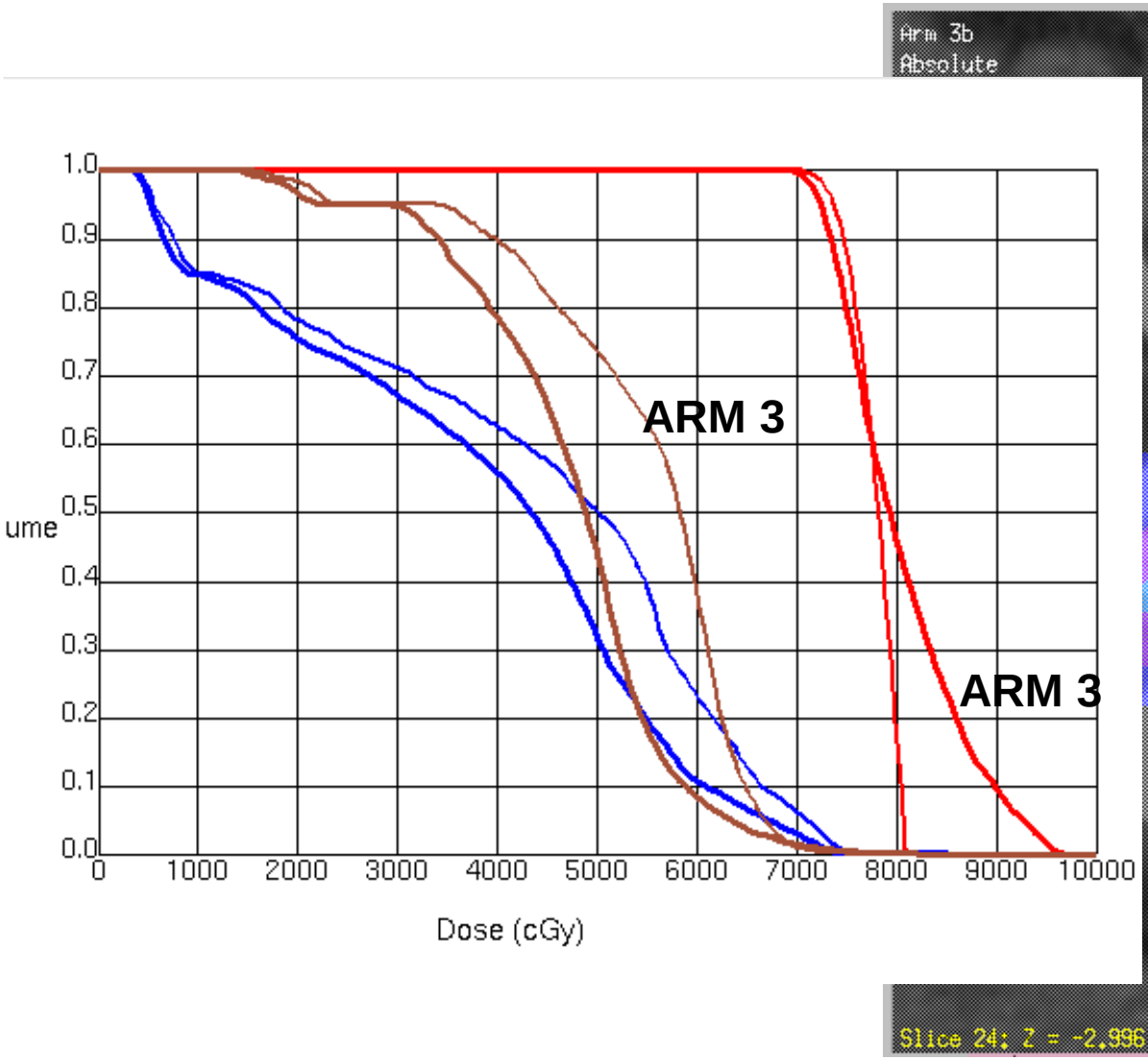
ARM 2: Iso-toxic IMRT

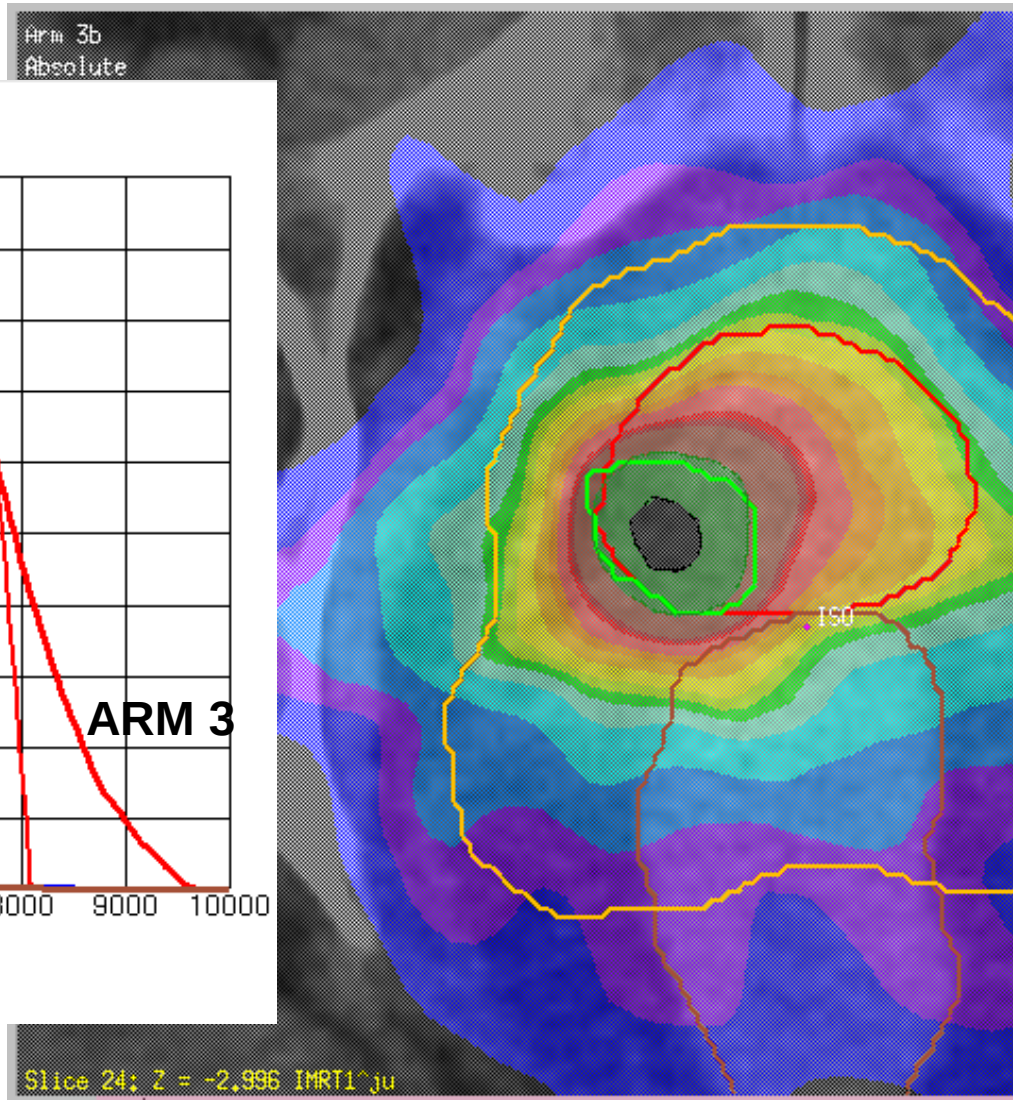




TCP = **84**%, NTCP = 8.1% (by definition)

ARM 3 – Biological dose-painting





- TCP = **90**%, NTCP = 8.1% (by definition)

SUMMARY/CONCLUSIONS:

Modern radiotherapy contains a large number of *degrees of freedom*: beam-shaping, beam energy and modality (photons vs protons vs carbon ions), intensity modulation – BUT currently individualisation is restricted to ”anatomy”; the same dose (and fraction size) given to the tumour according to rigid protocols. THIS IS NOT OPTIMAL.

”Iso-toxic” Prescription-dose *individualisation* under TCP-model guidance is a promising strategy e.g. lung tumours (**1D optimisation**)

Customisation of fraction number/size under isotoxicity will yield significant therapeutic gains especially for proliferating tumours surrounded by ”parallel” OARs. (**2D optimisation**).

Radiobiologically-guided inverse planning has the potential to significantly increase tumour local control through the exploitation of *volume effects* in organs at risk e.g. *maximise TCP for fixed NTCP*. (**3D optimisation**)

Information on clonogen density and hypoxia in tumour subvolumes obtained from functional imaging (PET, MR) will increase the gains from inverse radiobiological optimisation through "dose painting".

WHAT IS LACKING -

Developments in the *radiobiological functionality* of (commercial) Treatment Planning Systems are required urgently – TCP, NTCP, intelligent optimisation algorithms e.g. *CMS Monaco; VARIAN Eclipse (now includes radiobiological inverse planning - RaySearch)*

Better validation of NTCP modelling for certain OARs (post-*QUANTEC*)

Effect of "individual patient biology/genomics" on NTCP predictions (e.g. Valdagni et al, Milan)

The effect on TCP and NTCP of combined chemo/biological therapies

Second cancer induction probabilities – can now be estimated with reasonable confidence – should be put inside the TPS.

Dose accumulation algorithms & 4DCT e.g. Respiratory motion.

Databases containing both treatment plan information and outcomes: e.g. VODCA-Bio (Gianolini-Henggeler), DREES (El Naqa-Deasy)

*BioSuite**

Freeware, runs on PCs (developed at CCO)

Calculates (from e.g. from *Pinnacle*, *Eclipse* DVHs) :

i. *TCP (Marsden) and NTCP (LKB & RS) as a function of (total) dose*

ii. *Iso-NTCP customised prescription doses* (incl. *TCP <= e.g. 99%)*

iii. *TCP at iso-NTCP for **variable number of fractions***

Available from: **julien.uzan@ccotrust.nhs.uk**

*Manuscript about to be submitted

Improving patient care Nucletron

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Radiobiology & Radiobiological modelling in Radiotherapy

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Information also at:
http://www.wirral.nhs.uk/uploads/documents/CCORBLGYCOURSEFLYERApril09.pdf

The course provides the background to understand both the basis of radiation treatment for cancer and the use of radiobiological models in the evaluation and optimisation of radiotherapy treatment plans. It is suitable for anyone involved in Radiotherapy: Radiation Oncologists (especially those in training for (UK) FRCR part I), Physicists, Therapy Radiographers, Researchers and University Teachers. Days 1 and 2 will cover fundamentals – clonogenic assays, cellular response to radiation, the effect of doserate, radiation quality (LET), cell-cycle effects, the influence of oxygen, the linear-quadratic (LQ) formula and its limitations, the 5 Rs of Radiotherapy, the principles of fractionation and specific considerations in LDR and HDR brachytherapy. Days 3 and 4 are dedicated to the basis and use of radiobiological models (TCP, NTCP, EUD) in both the evaluation and optimisation of radiotherapy treatment plans. This is the first-ever course giving extensive coverage, including hands-on practice, to these modeling tools, which are beginning to be available in commercial treatment planning systems.

The teaching faculty is composed of Radiobiologists, Radiation Physicists and Radiatic Oncologists who are internationally known for their research and are experienced teachers of various aspects of Radiobiology and its application to Radiotherapy.

Students are encouraged to bring with them, in poster format, presentations of Radiobiological Modelling work from their own departments; these will be displayed during the course.

VENUE

All the lectures and practical sessions will take place at **The Chester Grosvernor and Spa**, Eastgate, Chester CH1 1LT, Cheshire, UK (www.chestergrosvenor.com). The Chester Grosvenor is in the heart of the old Roman city of Chester, some 25 miles from Liverpool, and within reach of both Manchester and Liverpool airports.

By arrangement, it will be possible to view the spacious and modern Radiotherapy facilities at the Centre, which include the UK's only proton-therapy facility as well as *cone-beam* and 4D CT.

Course Organisers: *Prof. Alan E. Nahum and Alistair Pooler, Physics dept., Consultant Dr. Pooja Jain, Radiotherapy Dept., Clatterbridge Centre for Oncology*
alan.nahum@ccotrust.nhs.uk; tel: +44 (0)151 334 1155 extn. 4169
pooja.jain@ccotrust.nhs.uk; tel: +44 (0)151 334 1155 extn. 5915.

Grazie per la vostra attenzione