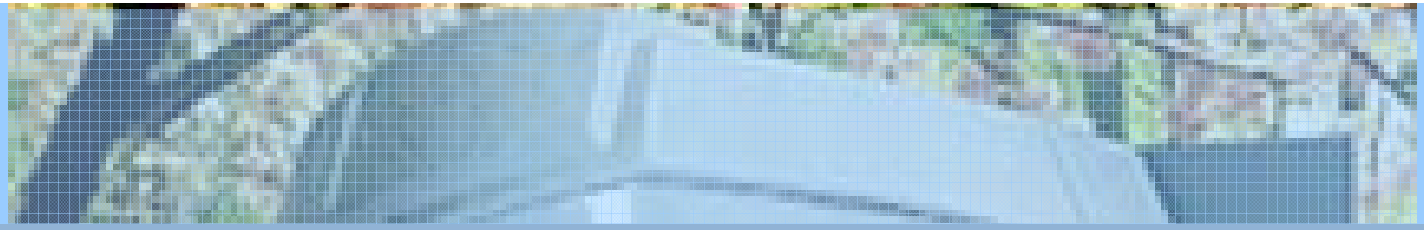


Comparative effectiveness research (CER) and appropriateness

A tool for clinical governance and a responsibility for clinicians

Michael Brada

Brescia

5 October 2012

Particle RT

IGRT

IMRT

SRT

CRT

RT

DXT

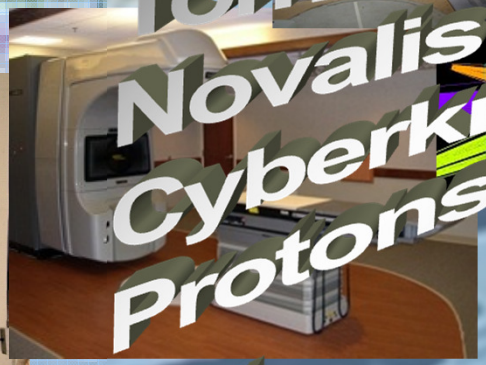
Gamma knife

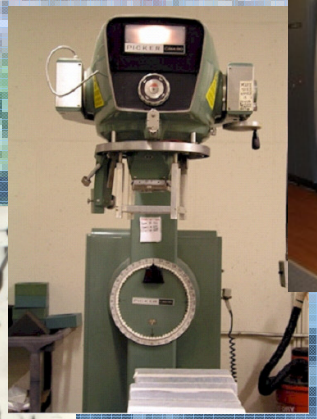
Tomotherapy

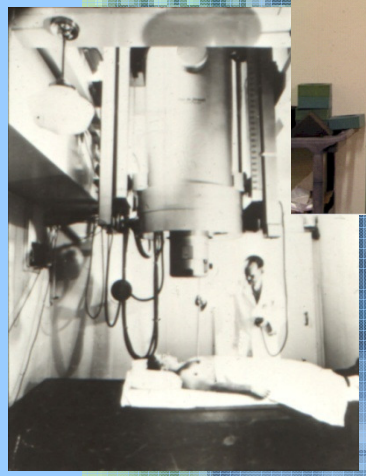
Novalis

Cyberknife

Protons







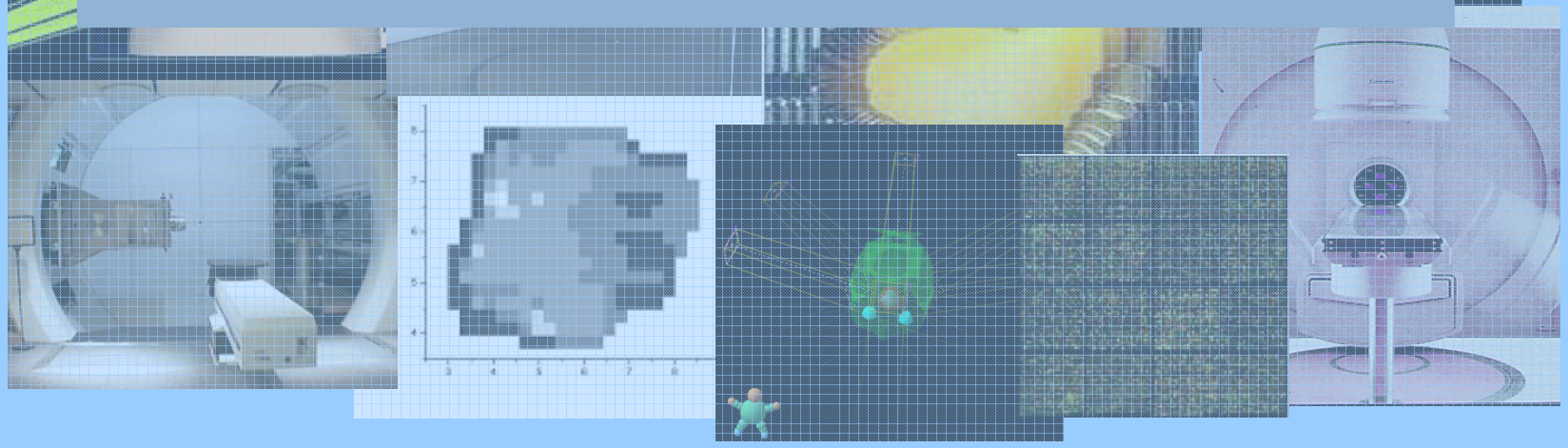
.....

New radiotherapy technology

Introduction of technology into clinical practice

driven by:

- clinical need
- technology

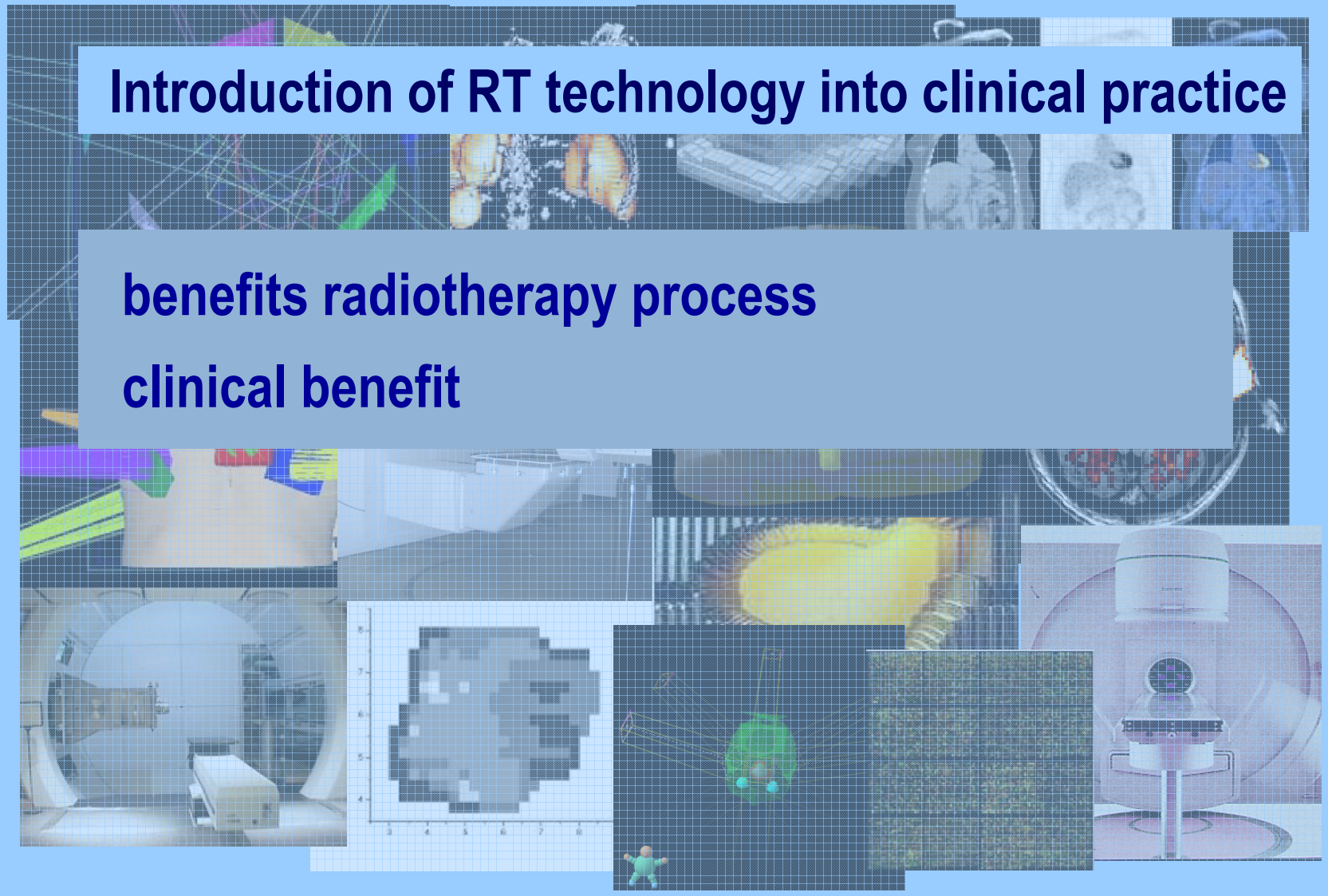


New radiotherapy technology

Introduction of RT technology into clinical practice

benefits radiotherapy process

clinical benefit



New radiotherapy technology

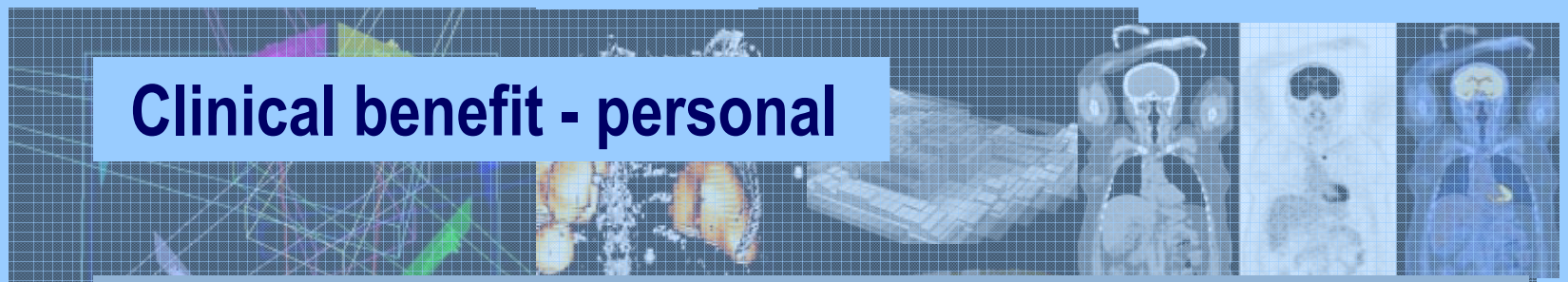
New radiotherapy technology

Clinical benefit - personal

what would you like new technology to achieve

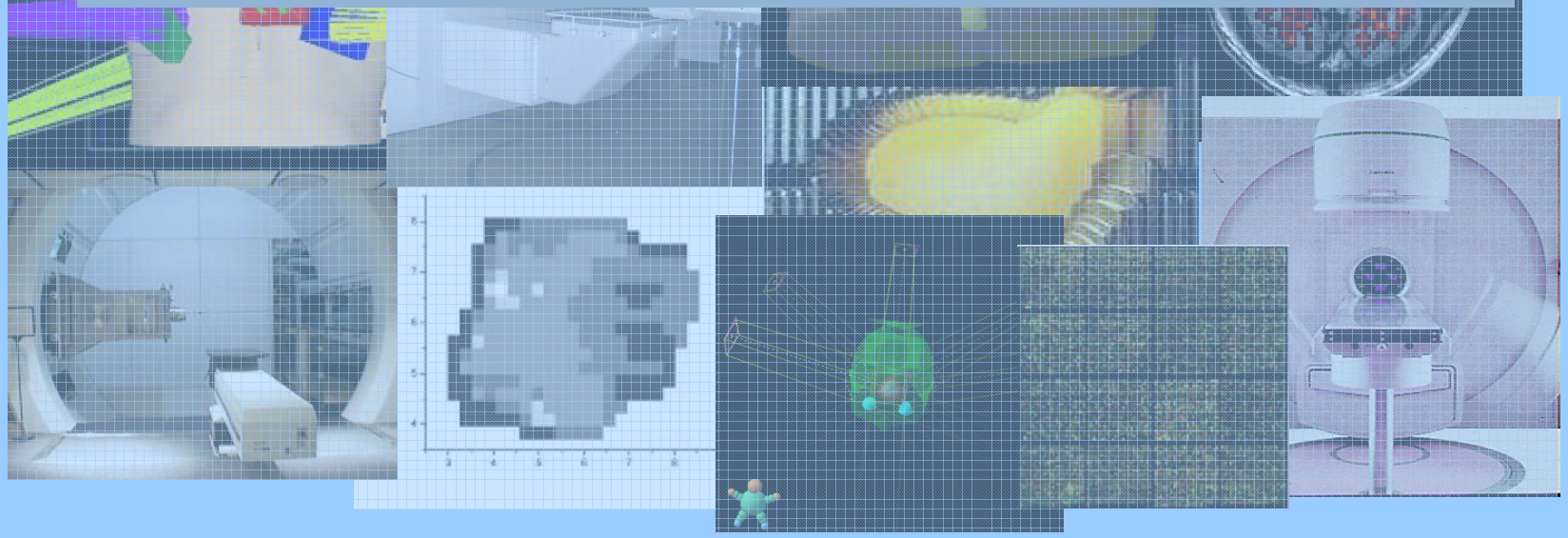
New radiotherapy technology

Clinical benefit - personal



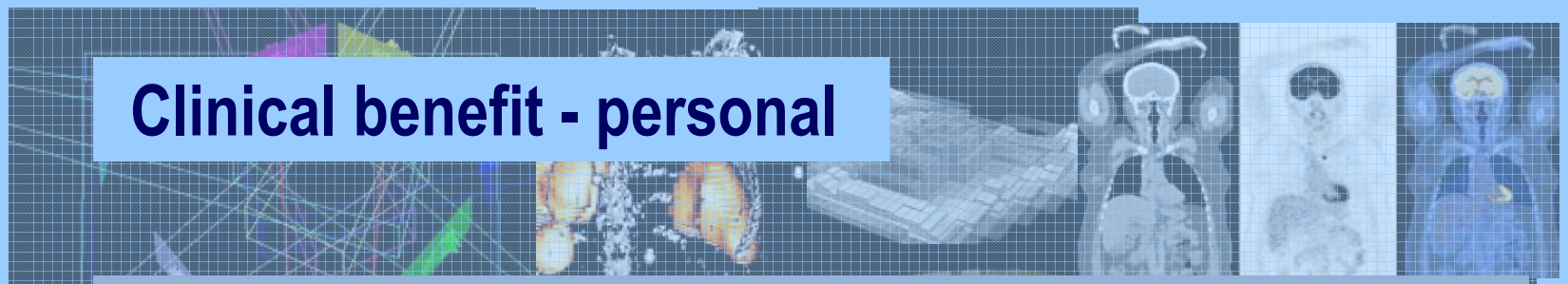
what would you like new technology to achieve

if friend or family need radiotherapy



New radiotherapy technology

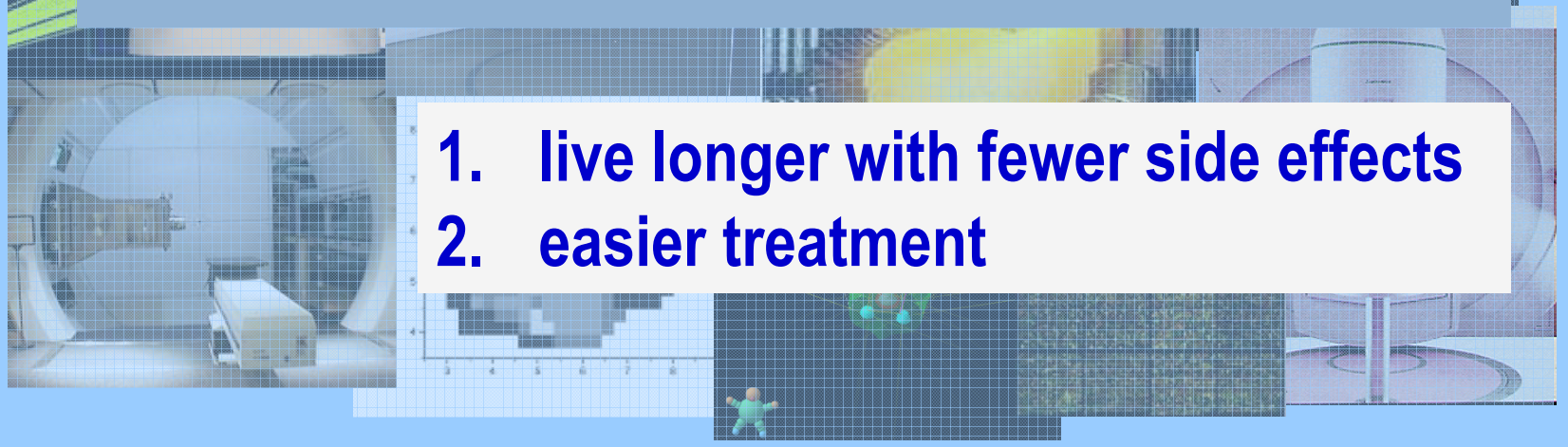
Clinical benefit - personal



what would you like new technology to achieve

if friend or family need radiotherapy

and they have to pay



1. live longer with fewer side effects
2. easier treatment

New radiotherapy technology

Clinical governance & clinician's responsibility

highest standard of clinical care

responsibility & accountability

constant improvement

New radiotherapy technology & clinical governance

Clinical governance & clinician's responsibility

Elements

New radiotherapy technology & clinical governance

Evaluating novel radiotherapy technology

novel RT technologies	methods of evaluation

New radiotherapy technology & clinical governance

Modern technology of radiotherapy delivery

refinements of conformal radiotherapy

conformality

- photons **(IMRT)**
- protons

time factor (4D radiotherapy)

- intrafraction patient and tumour motion
- interfraction changes in tumour & normal tissue

quality assurance

- imaging closer to treatment delivery **(IGRT)**

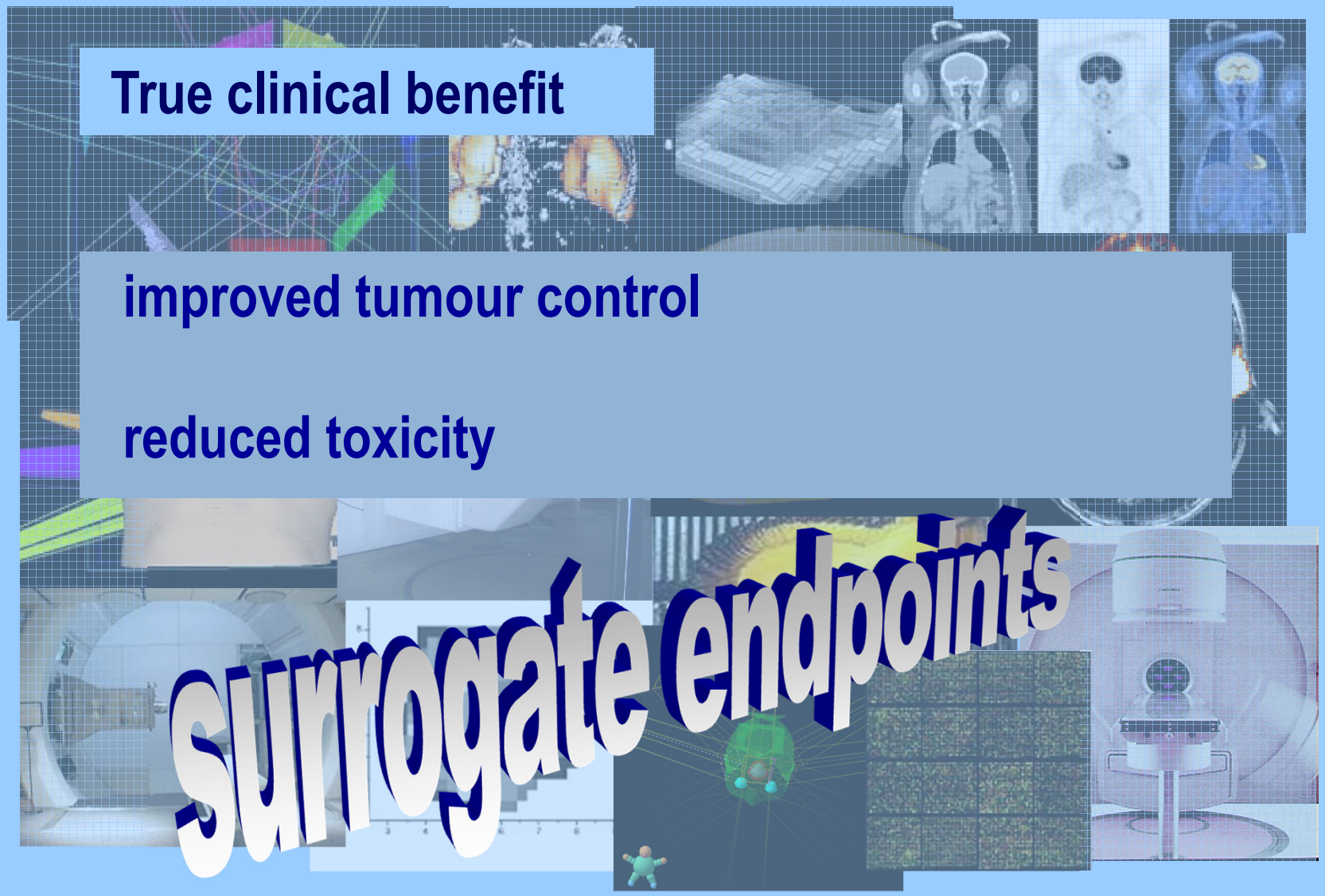
New and emerging radiotherapy technologies

Modern technology of radiotherapy delivery

refinements of conformal radiotherapy

- conformality
  - photons (IMRT)
  - protons
- time factor (4D radiotherapy)
  - intrafraction patient and tumour motion
  - interfraction changes in tumour & normal tissue
- quality assurance
  - imaging closer to treatment delivery (IGRT)

New and emerging radiotherapy technologies



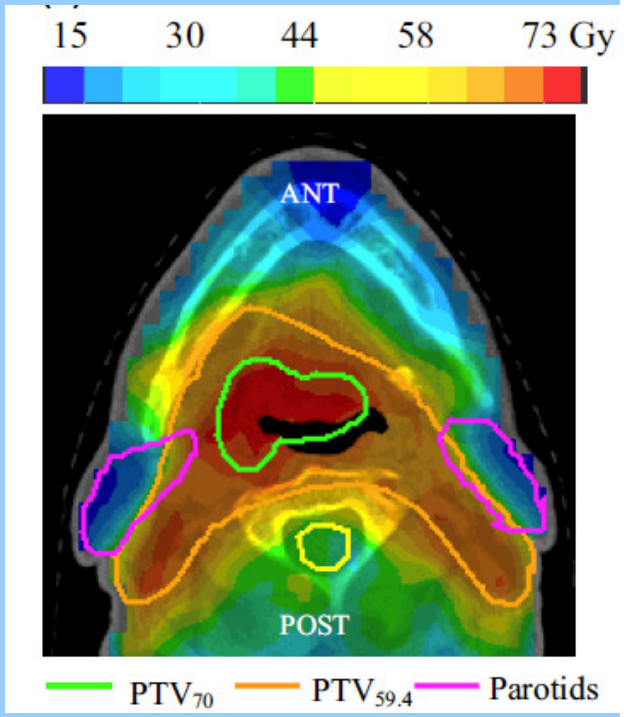
New radiotherapy technology

True clinical benefit

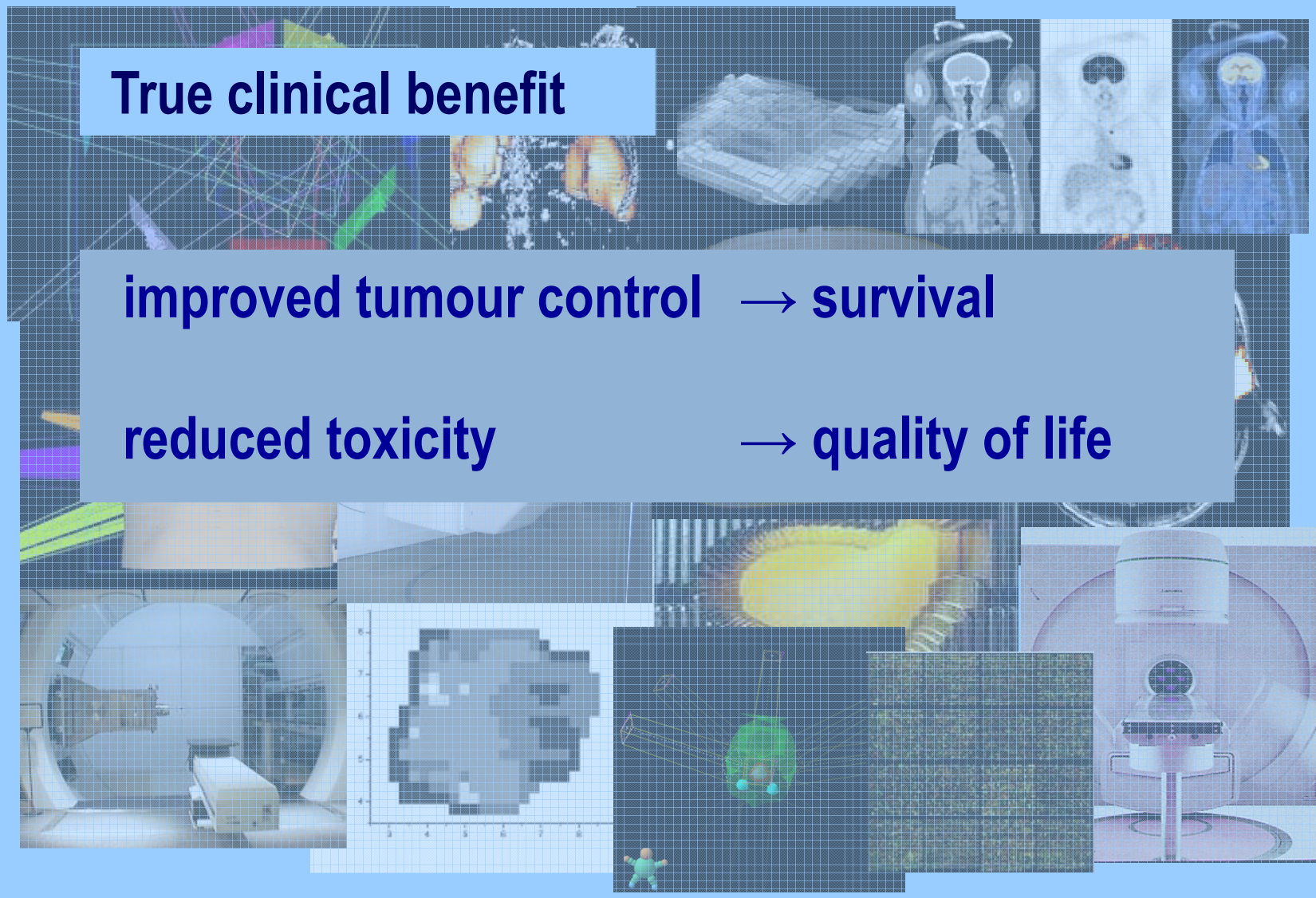
IMRT for parotid sparing

Preserve salivary function

Tumour control …?



New radiotherapy technology



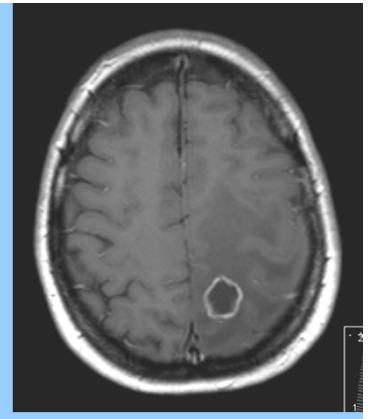
True clinical benefit

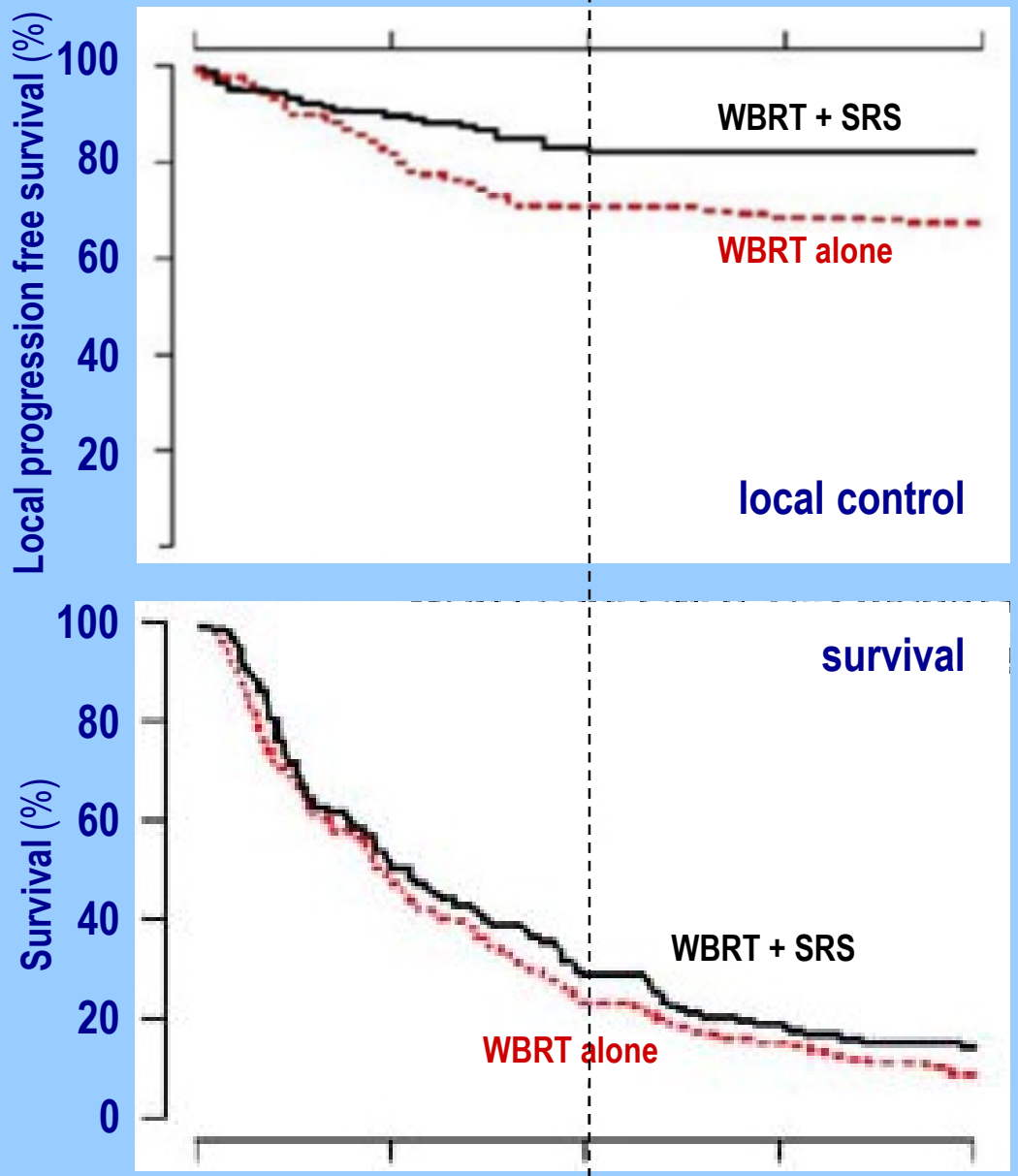
improved tumour control → survival

reduced toxicity → quality of life

New radiotherapy technology

Radiosurgery for brain metastases





Andrews et al 2004 RTOG 9508

WBRT whole brain RT
SRS stereotactic radiosurgery

Introduction of technology into clinical practice

driven by:

technology & commerce

clinical need

- driving forces are difficult to distinguish
- marketing blurs the reality

Introduction of technology into clinical practice

driven by:

- technology & comm
- clinical

Precise
Focused
Image guided
Intensity modulated

- driving forces difficult to distinguish
- marketing blurs the reality

New radiotherapy technology

Introduction into clinical practice

requirements:

technical benefit in clinical setting

- representative series of patients
- clinically relevant endpoint

clinical benefit

- surrogate endpoint (tumour control and toxicity)
- survival and quality of life

Introduction into clinical practice

technical benefit in clinical setting

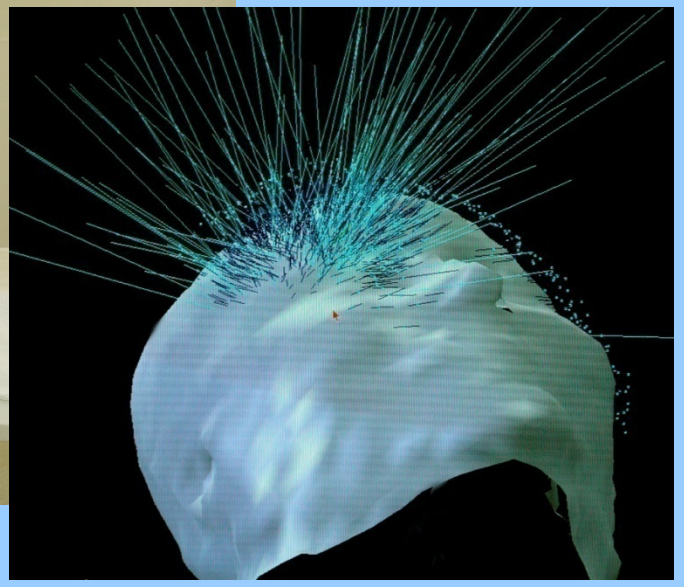
- representative series of patients
- clinically relevant endpoint

clinical benefit

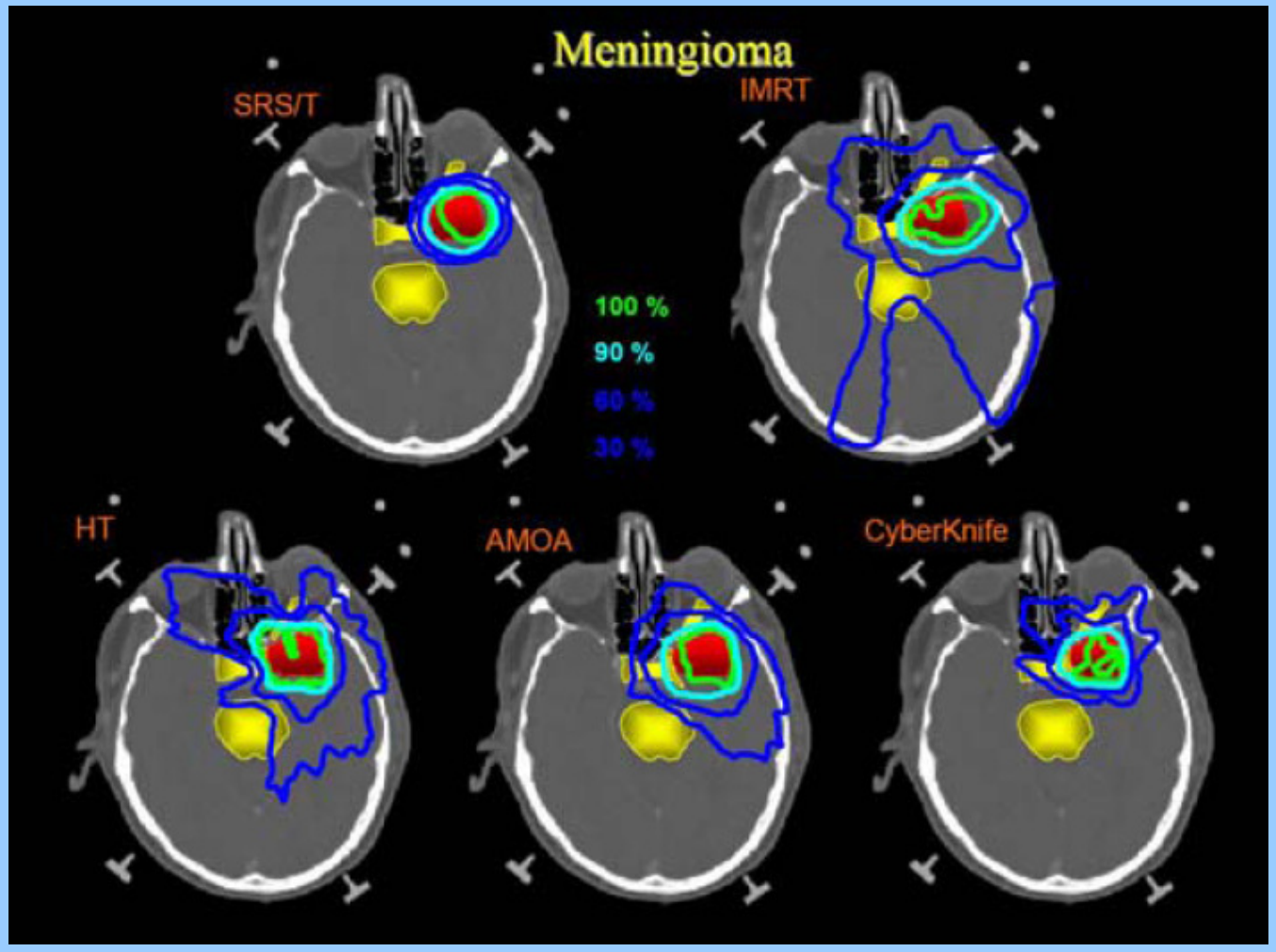
- surrogate endpoint (tumour control and toxicity)
- survival and quality of life

Evaluating new radiotherapy technology

Robotic arm mounted linac (Cyberknife)



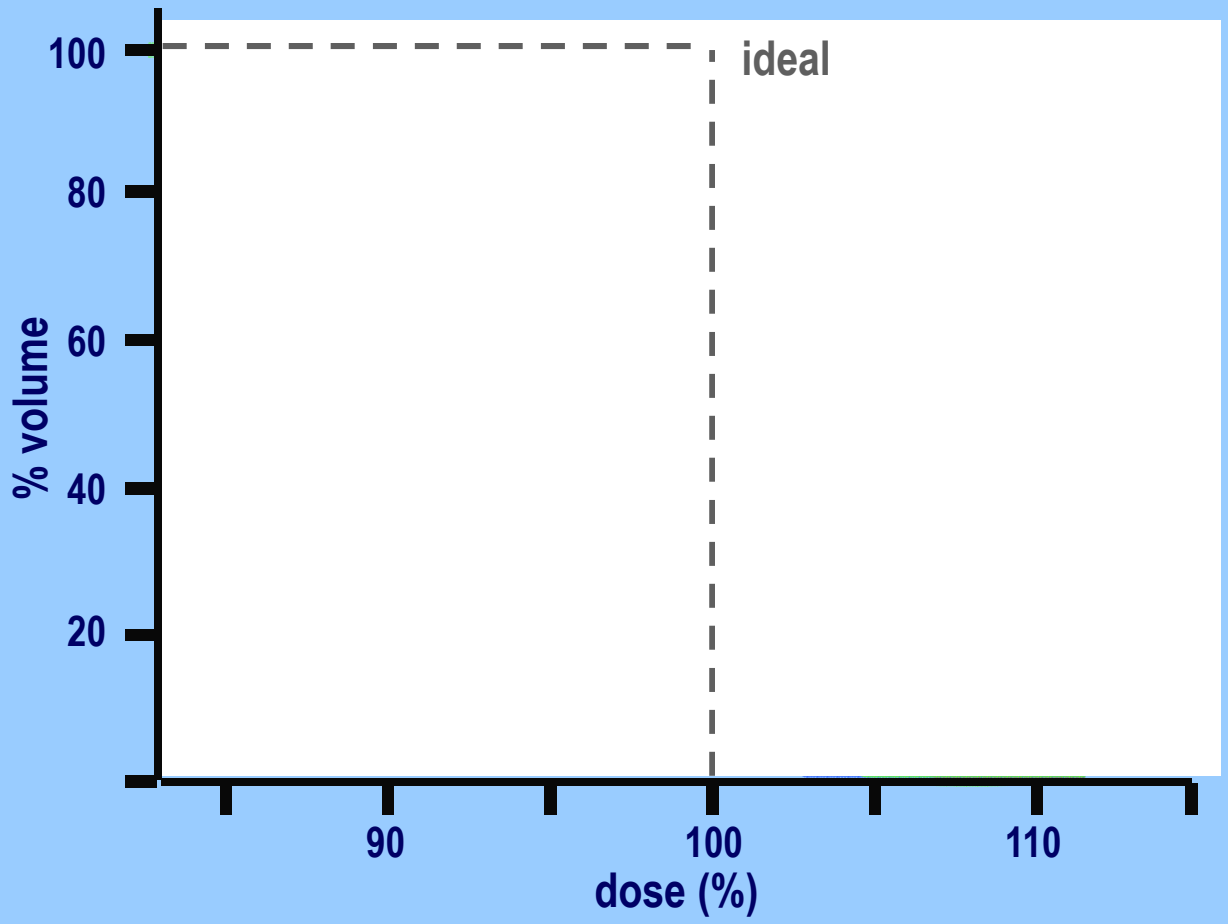
Modern technology of radiotherapy delivery



Comparison of techniques of high precision localised RT

Cozzi et al 2006

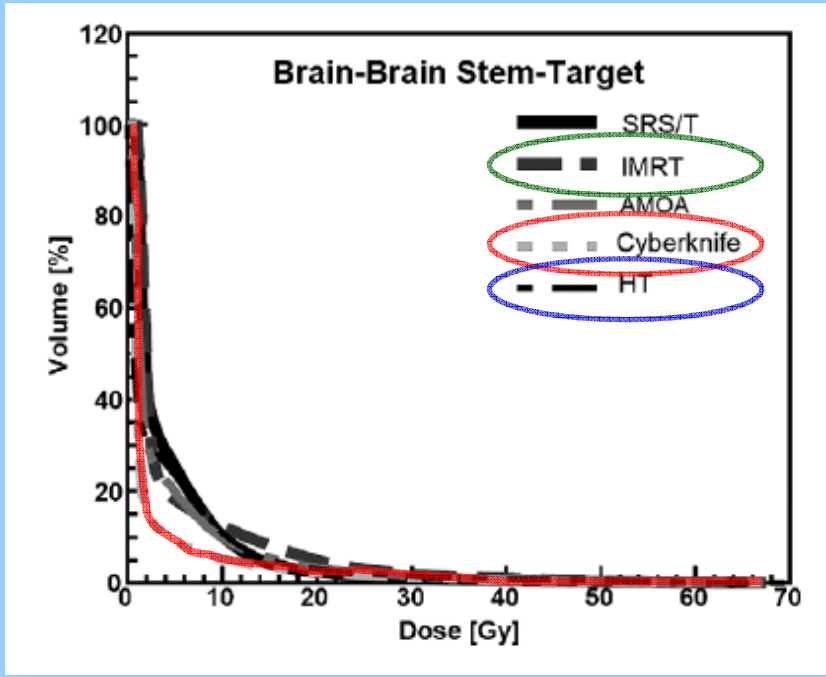
Planning Target Volume (PTV) dose distribution

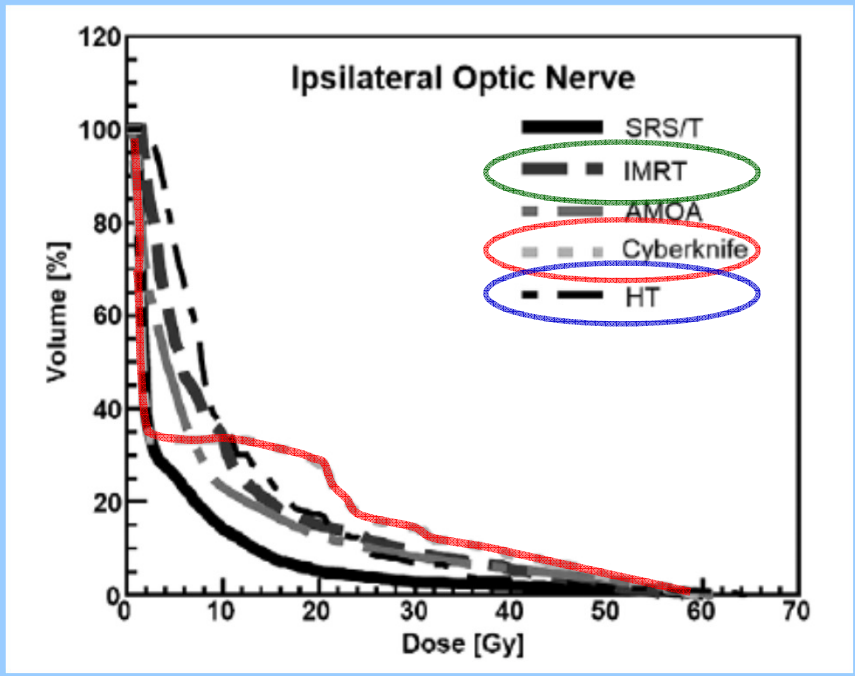


Comparison of techniques of high precision localised RT

Cozzi et al 2006

Normal CNS dose distribution (organs at risk)

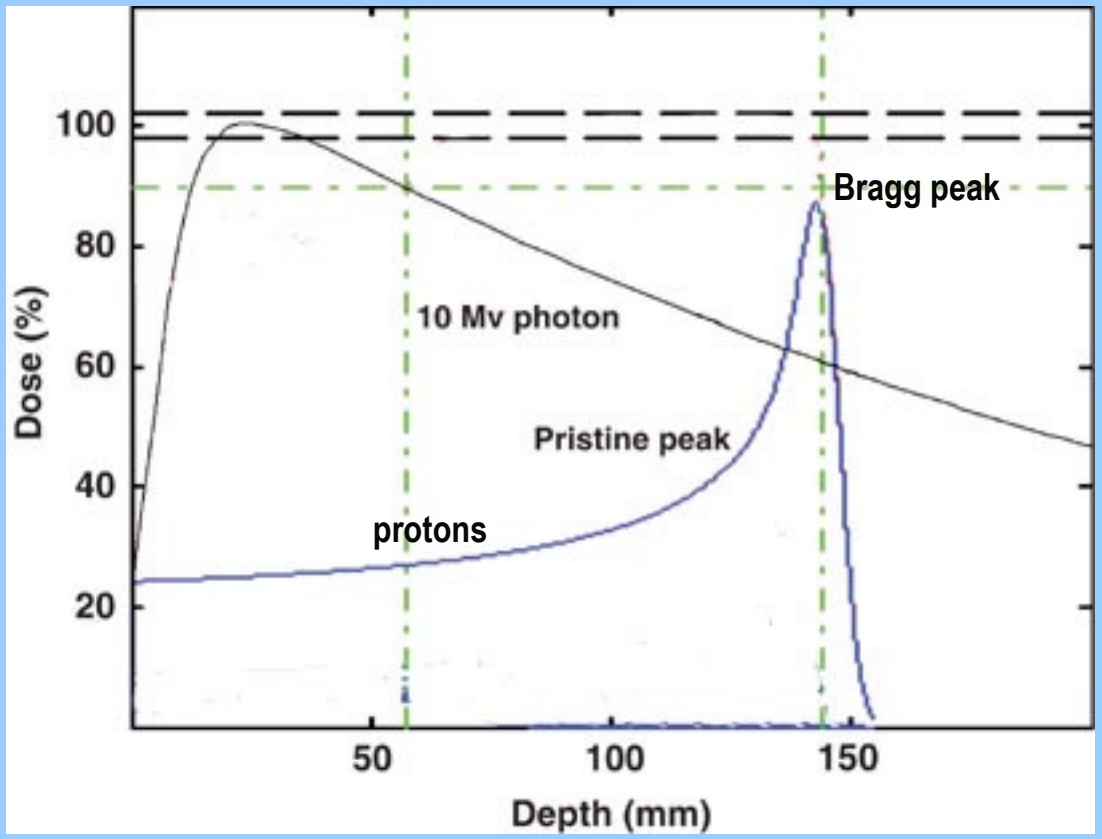




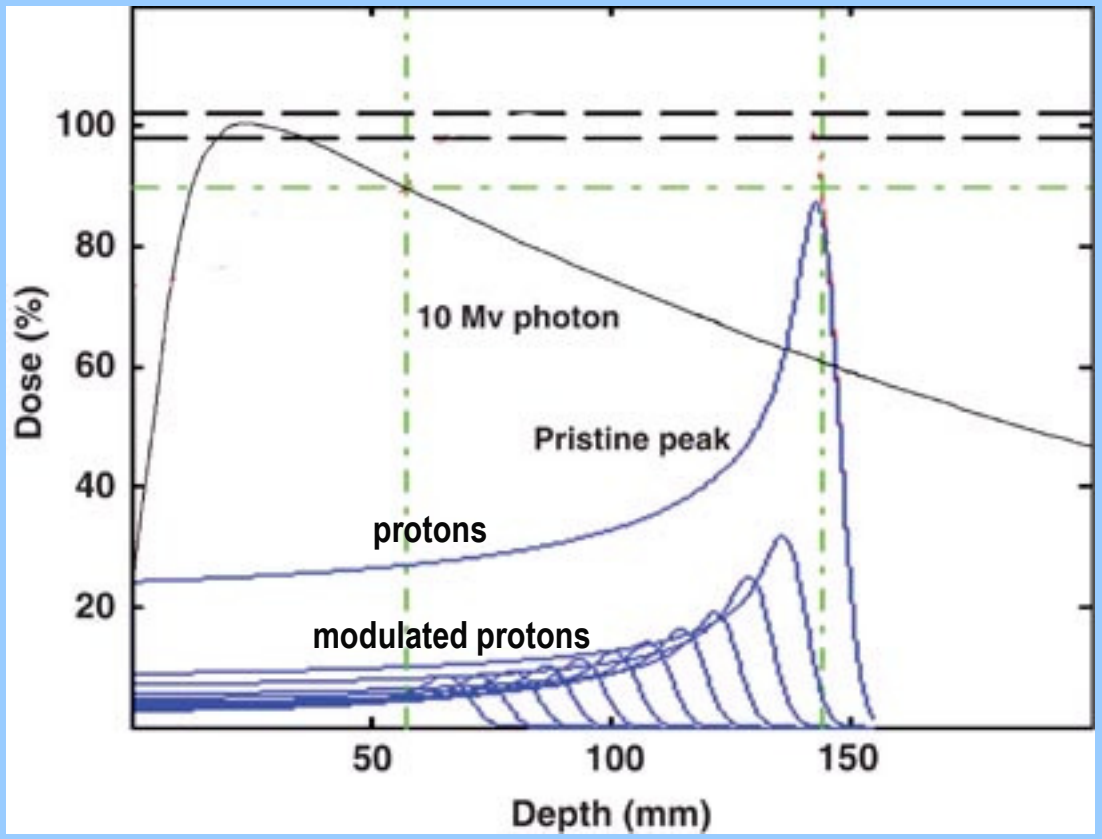
Comparison of techniques of high precision localised RT

Cozzi et al 2006

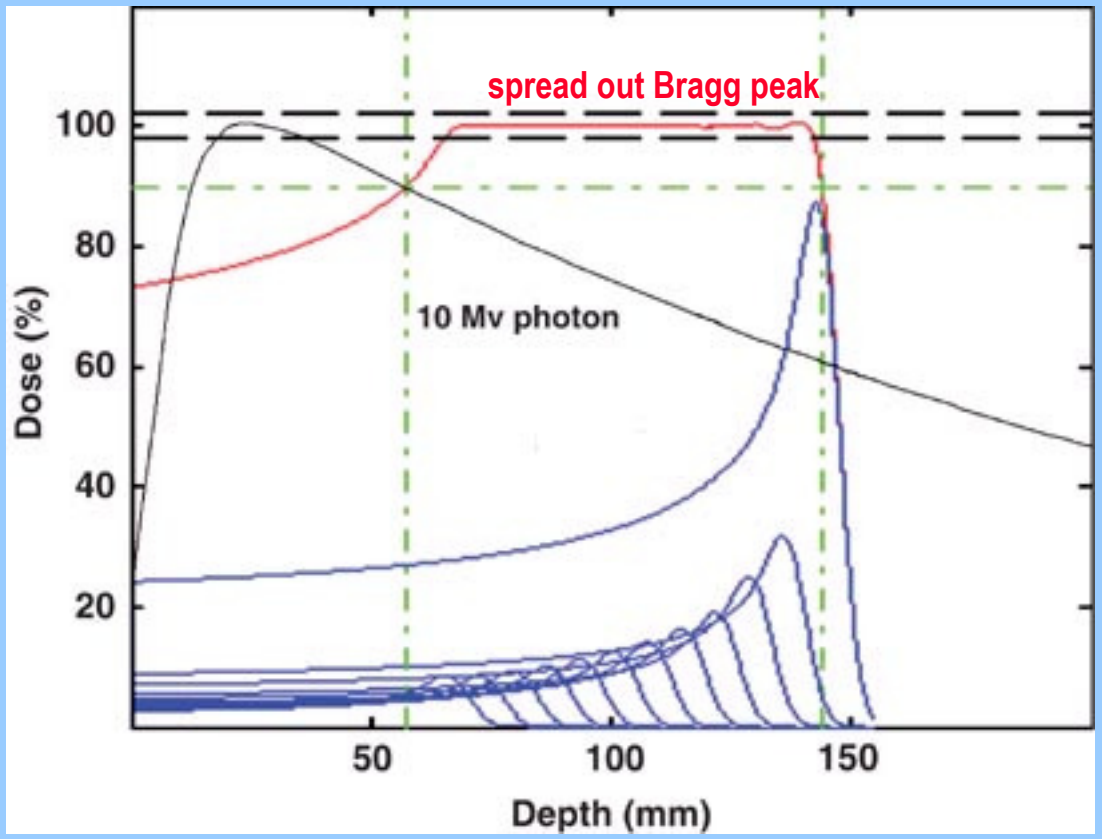
Proton therapy



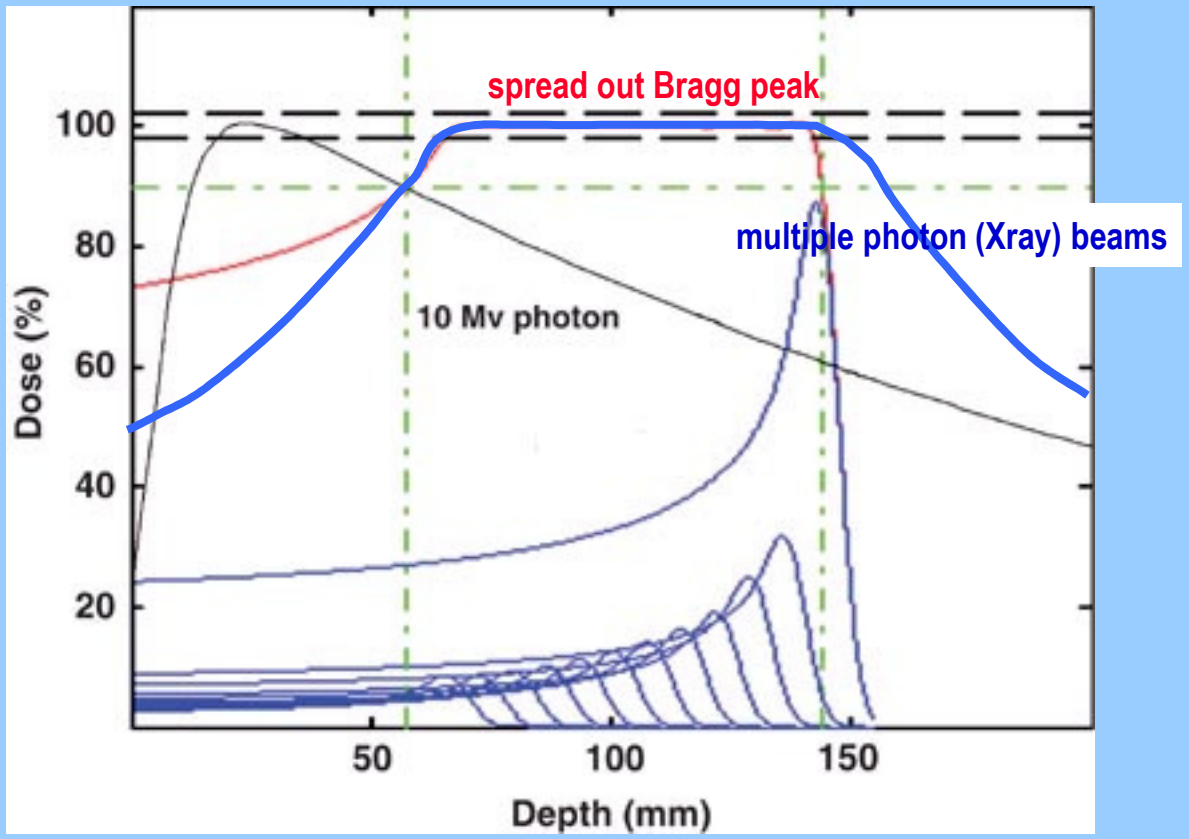
Depth dose distribution of photons and protons



Depth dose distribution of photons and protons



Depth dose distribution of photons and protons



Depth dose distribution of photons and protons

Introduction into clinical practice

technical benefit in clinical setting

- representative set[illegible]s of patients
- cli[illegible]ally relevant endpoints

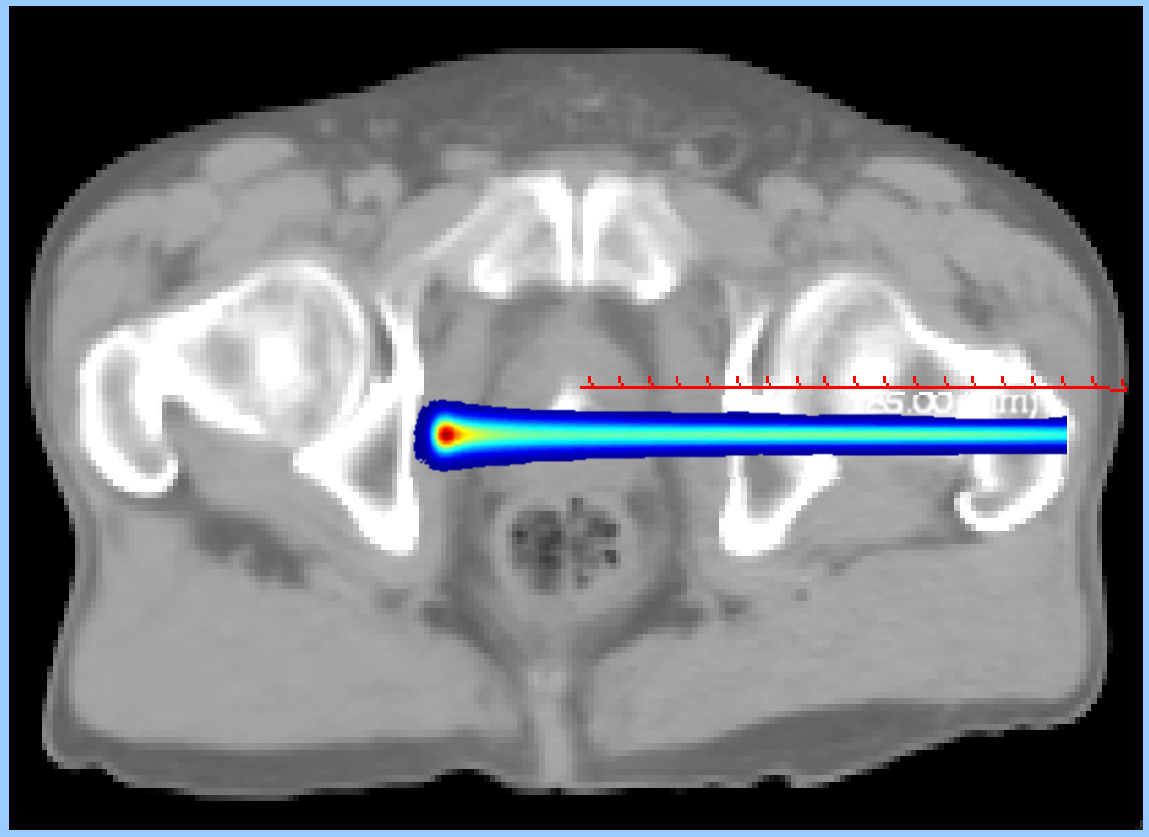
clinical benefit

- surrogate endpoint (tumour control and toxicity)
- survival and quality of life

Potential problems

Evaluating new radiotherapy technology

Range uncertainties due to setup

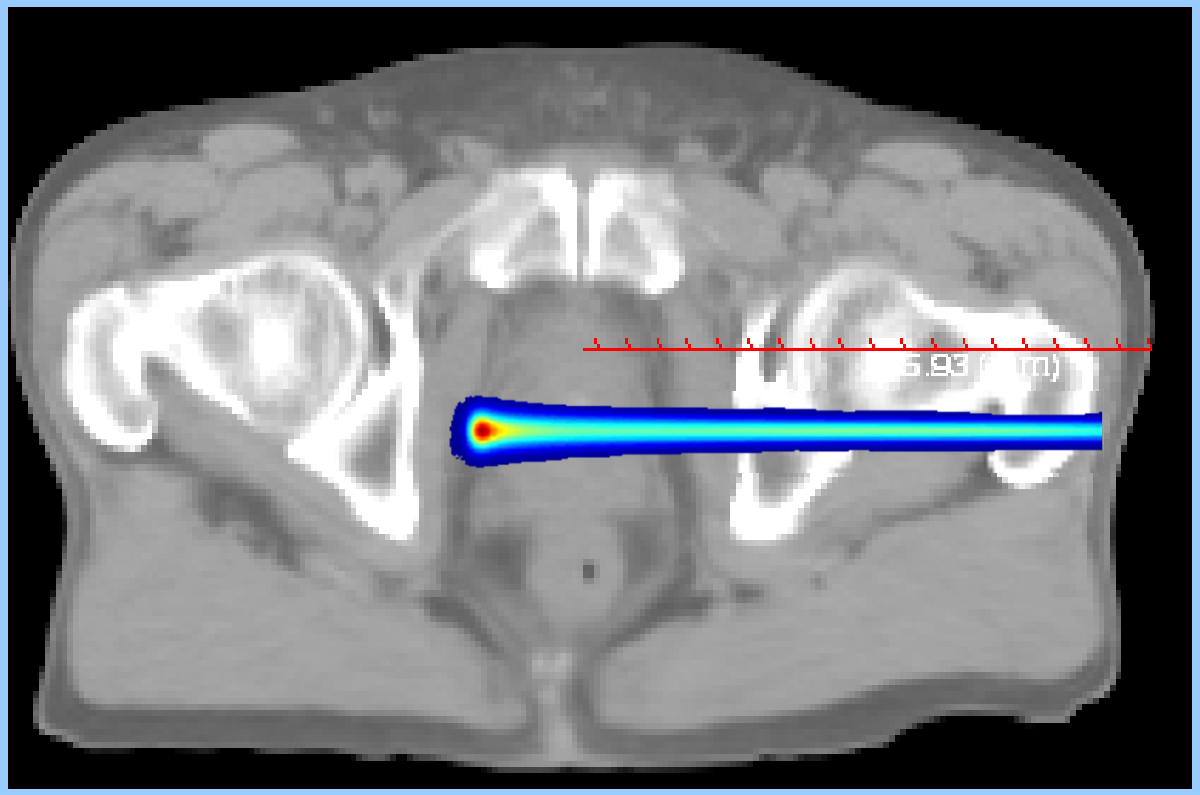


8 Jan

Proton uncertainties

Chen, Rosenthal, et al., IJROBP 48(3):339, 2000

Range uncertainties due to setup



11 Jan

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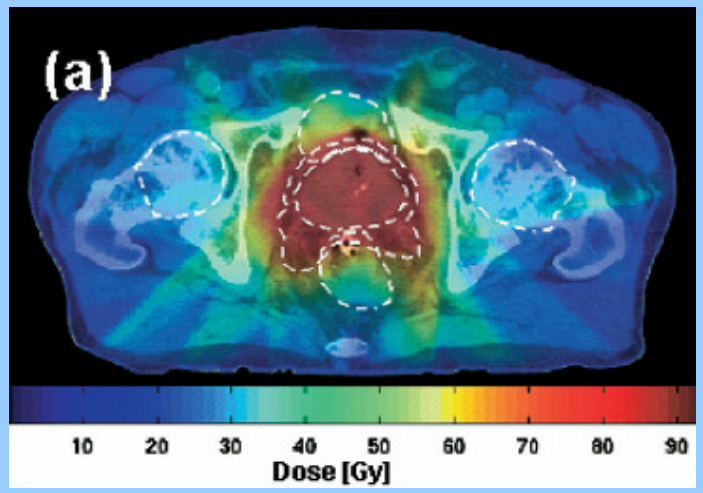
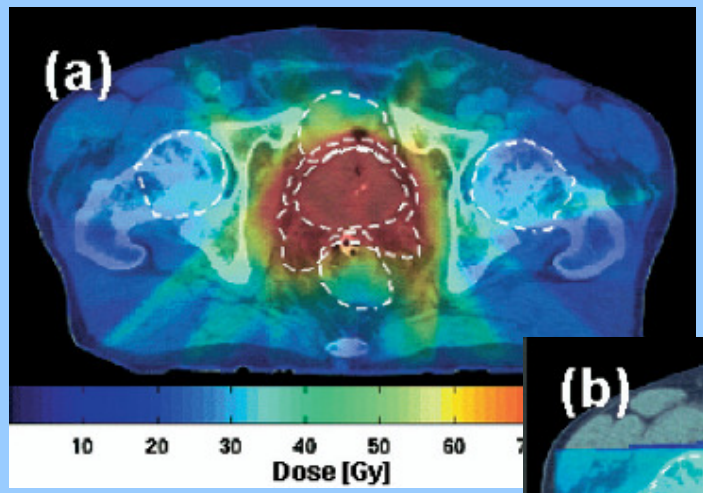


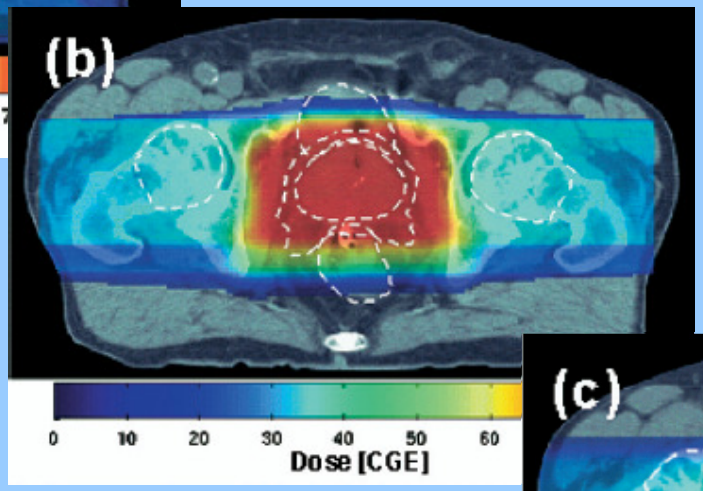
IMRT

Prostate radiotherapy

introducing protons

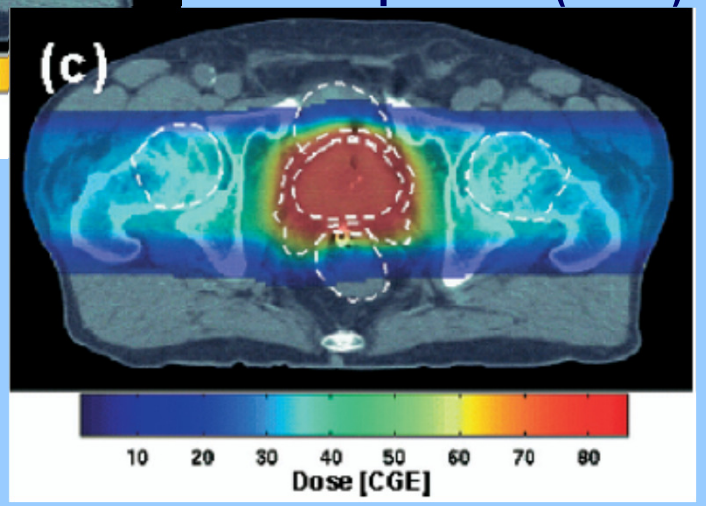


IMRT



conformal protons

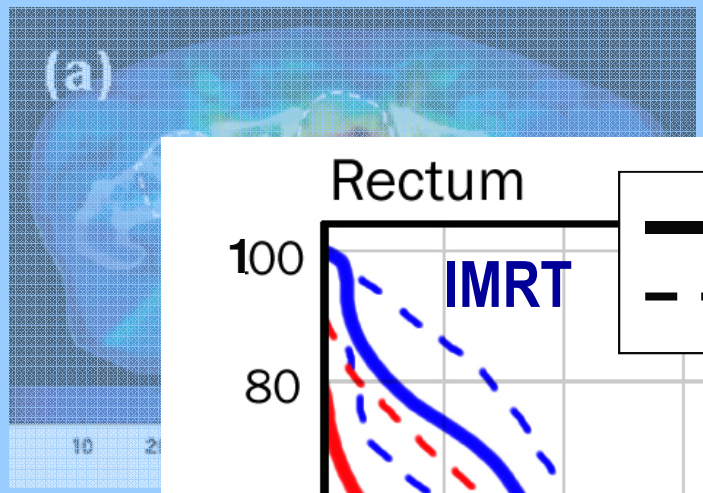
IM protons (IMPT)

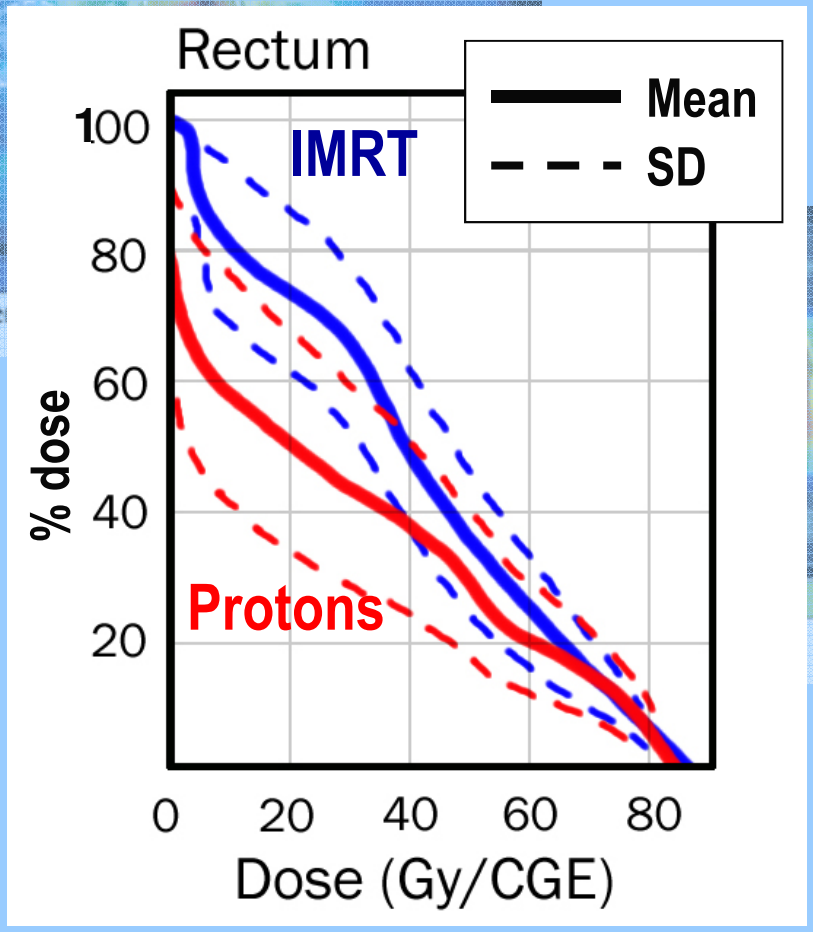


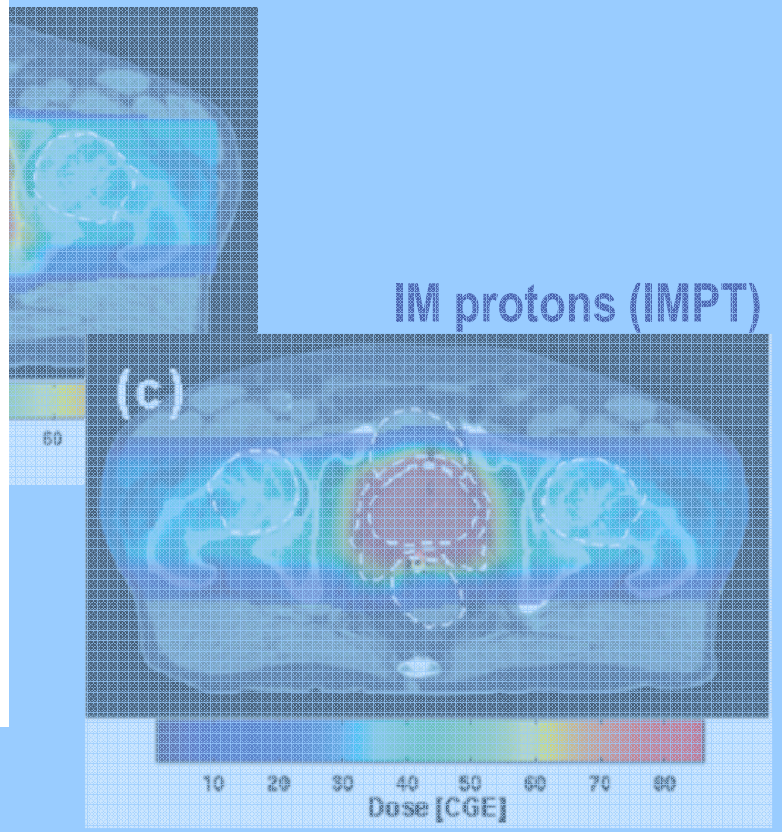
Prostate radiotherapy

Trofimov et al IJROBP (69), 444, 2007

Rectal sparing



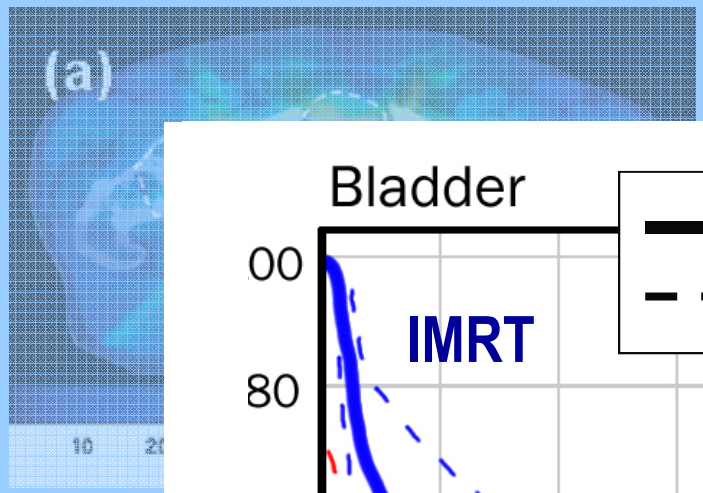




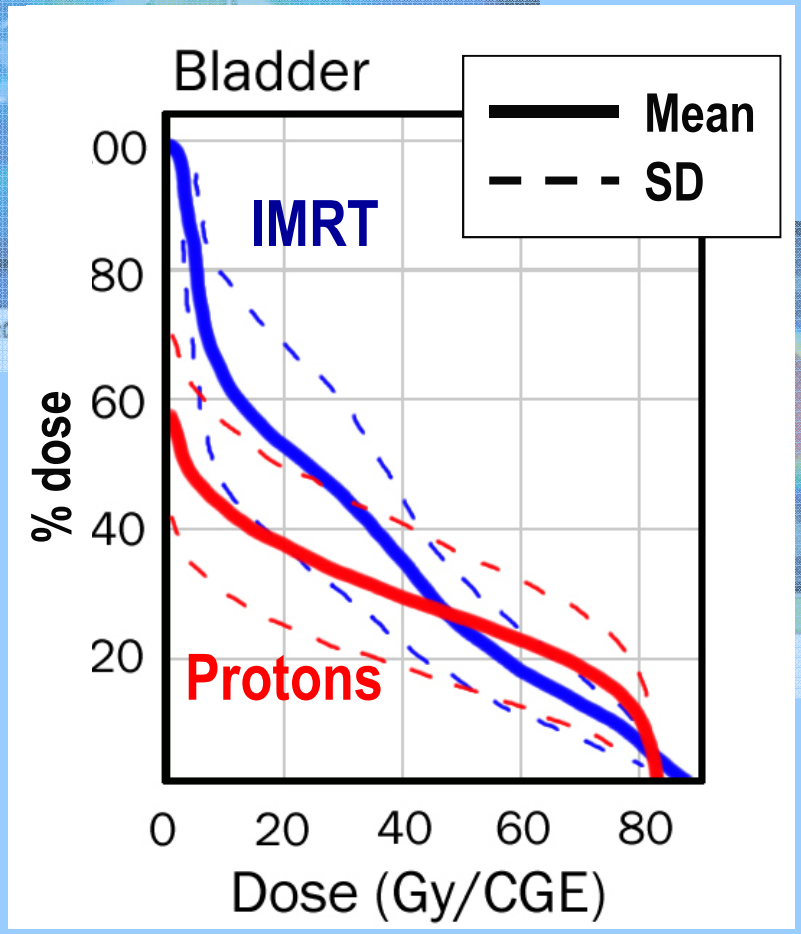
Prostate radiotherapy

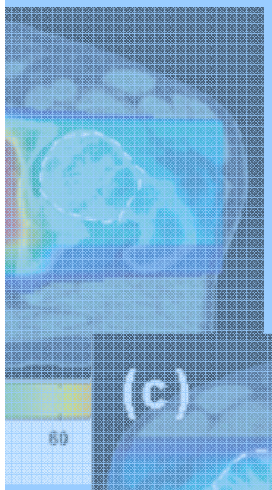
Trofimov et al IJROBP (69), 444, 2007

Bladder sparing

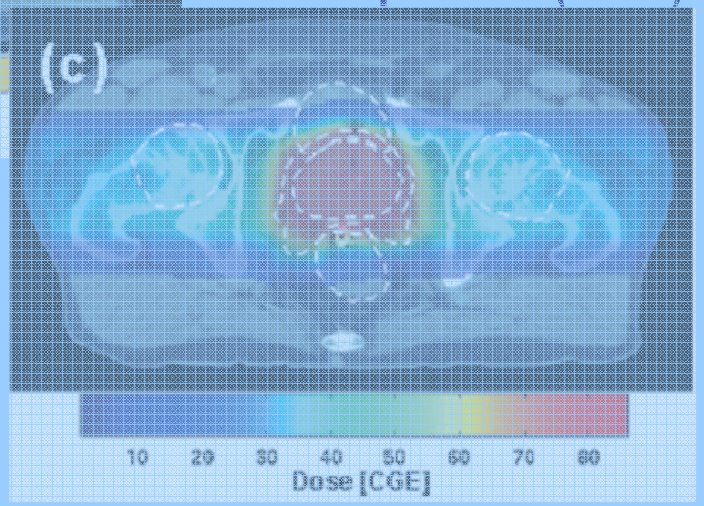


IMRT





IM protons (IMPT)



Prostate radiotherapy

Trofimov et al IJROBP (69), 444, 2007

Introduction into clinical practice

technical benefit in clinical setting

- representative series of patients
- clinically relevant endpoint

clinical benefit

- surrogate endpoint (tumour control and toxicity)
- survival and quality of life

Evaluating new radiotherapy technology

Introduction into clinical practice

technical benefit in clinical setting

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clinical benefit

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Conventional design

to evaluate

Phase I

Phase II

Phase III

model of drug testing

Evidence based medicine

Conventional design

to evaluate

Phase I	clinical pharmacology & toxicity
Phase II	
Phase III	

model of drug testing

Evidence based medicine

Conventional design

to evaluate

Phase I	feasibility & toxicity
Phase II	
Phase III	

model of drug testing

Evidence based medicine

Conventional design

to evaluate

Phase I feasibility & toxicity

Phase II initial investigation of activity

no information on comparative efficacy

Phase III

model of drug testing

Evidence based medicine

Problems of Phase II studies

- **study design** (prospective/retrospective; statistics)
- **patient selection** (performance status, disease status etc)
- **new staging & other treatments**
- **comparative control group**
- **endpoints and methods of assessment**
- **…..**

Evidence based medicine

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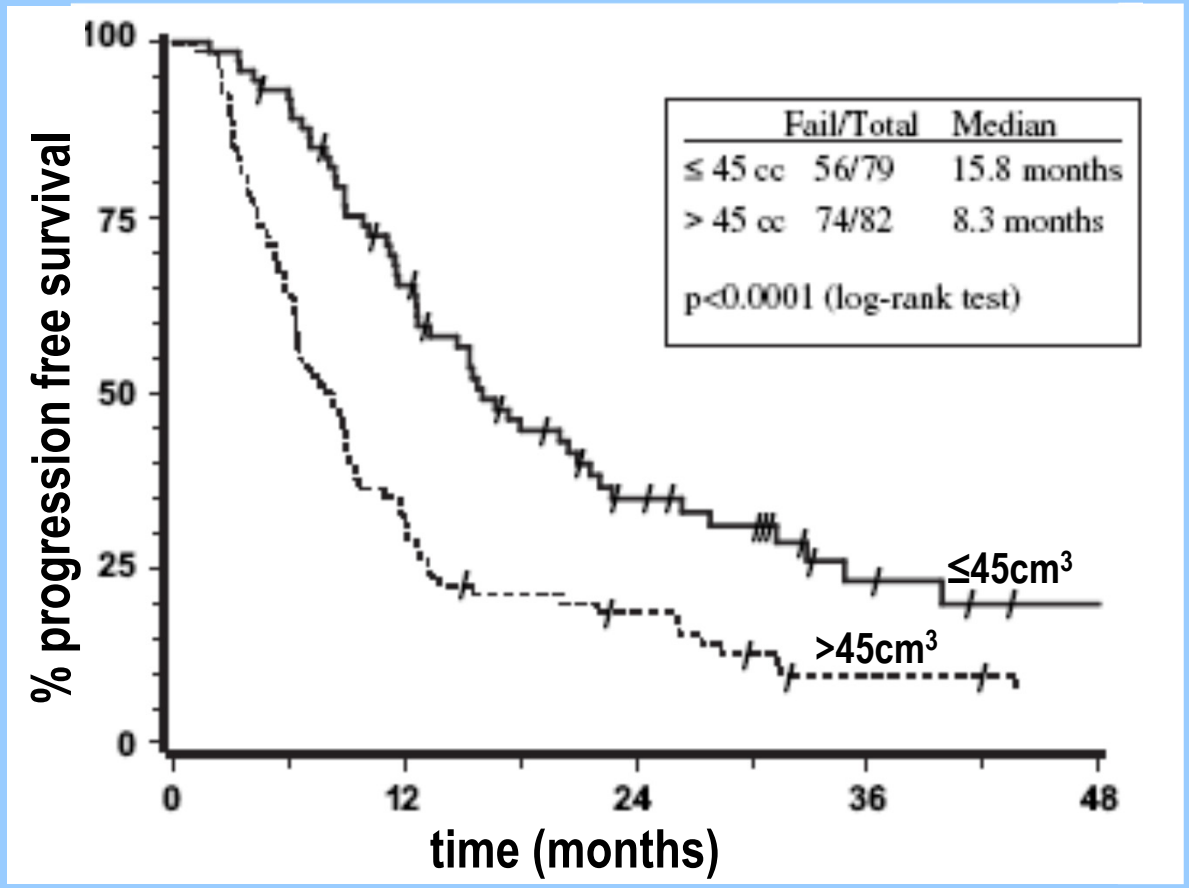
- **endpoints and methods of assessment**
- **…..**

Evidence based medicine

Effect of patient selection on tumour control

RTOG 93-11 Phase I/II dose escalation study in NSCLC



$45cm^3$ ≈ 4.5 cm diameter sphere

Tumour size and disease control

Werner-Wasik et al 2008

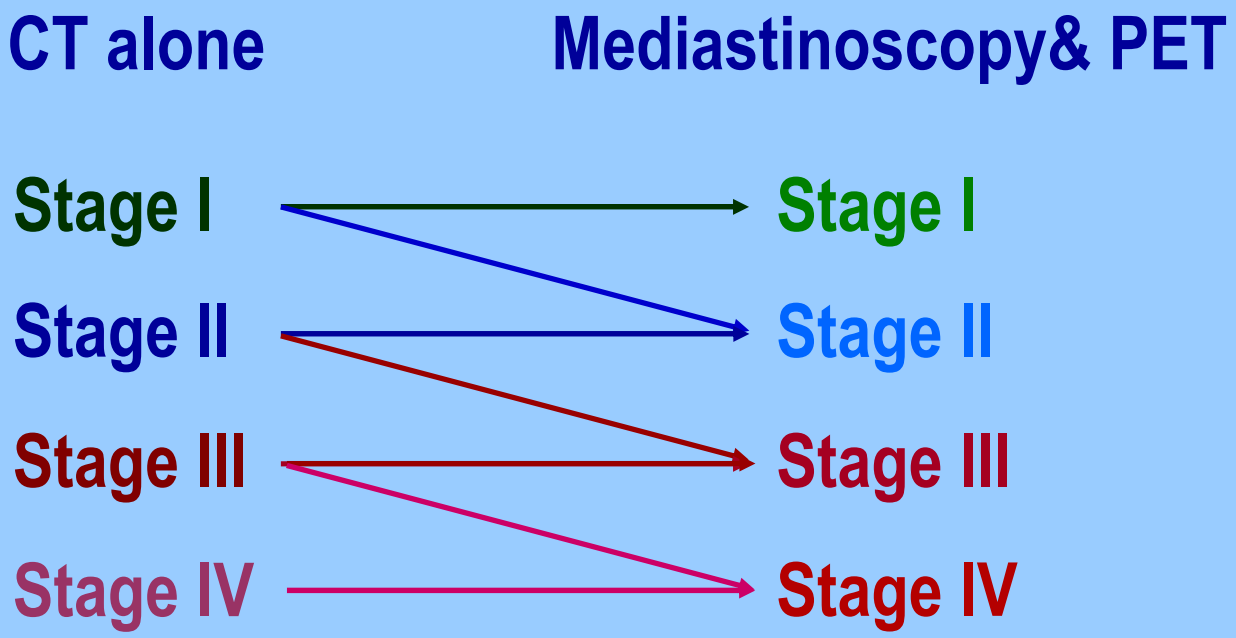
Problems of Phase II studies

- **study design** (prospective/retrospective; statistics)
- **patient selection** (performance status, disease status etc)
- **new staging & other treatments**
- **comparative control group**
- **endpoints and methods of assessment**
- **…..**

Evidence based medicine

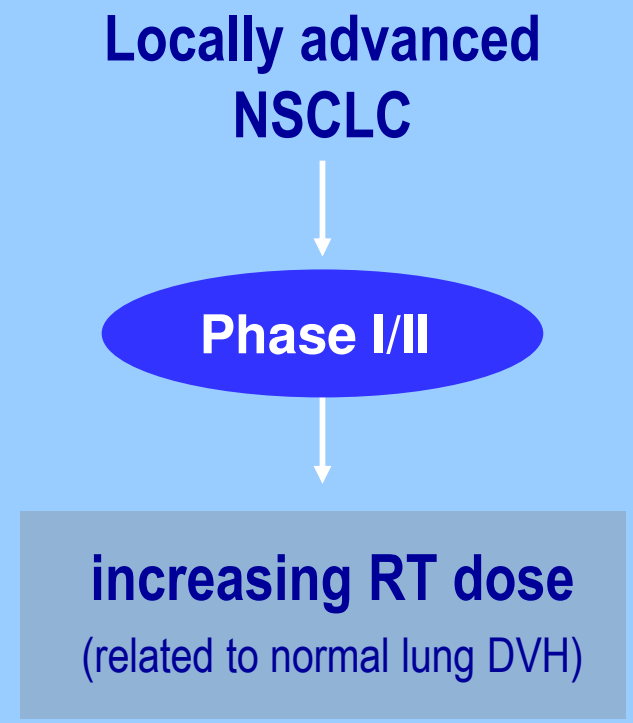
Effect of intensive staging on survival

example of non-small cell lung cancer



Stage migration (Will Rogers phenomena)

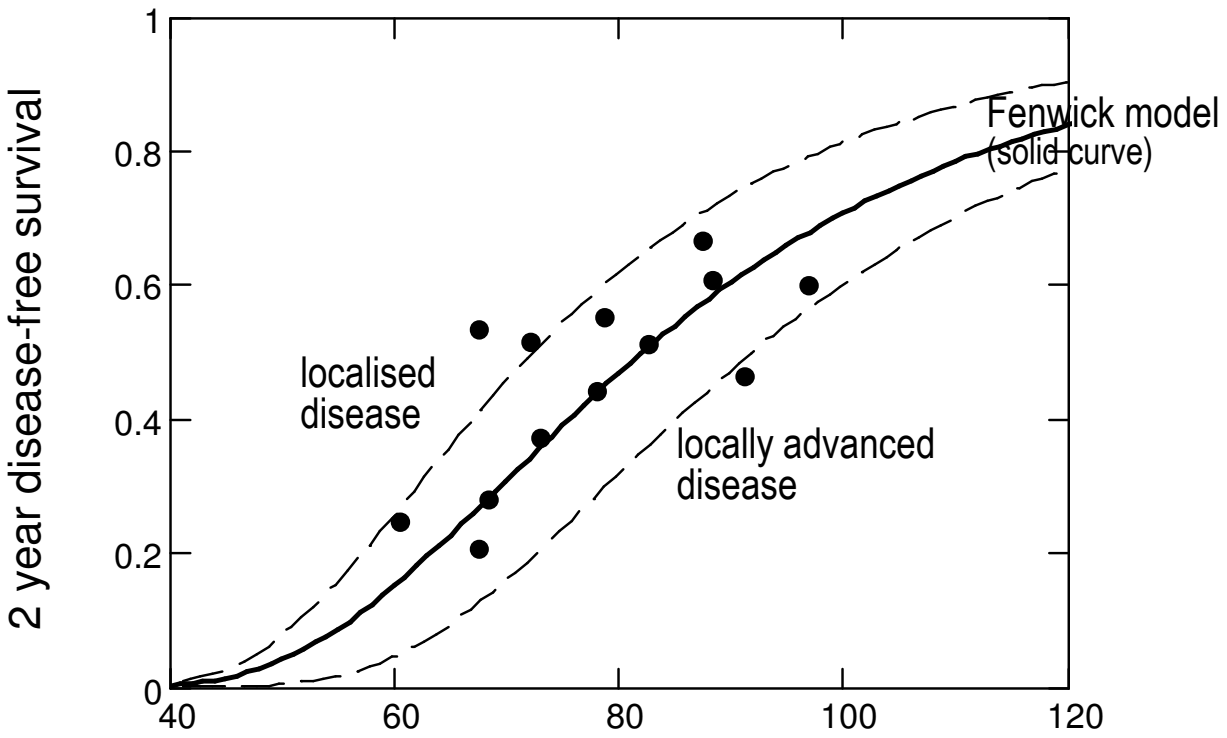
Radical radiotherapy – dose escalation



Improving lung cancer radiotherapy

Summary of published phase I/II studies (1201 patients, 8 publications)

2 year local progression free survival (corrected for stage distribution)

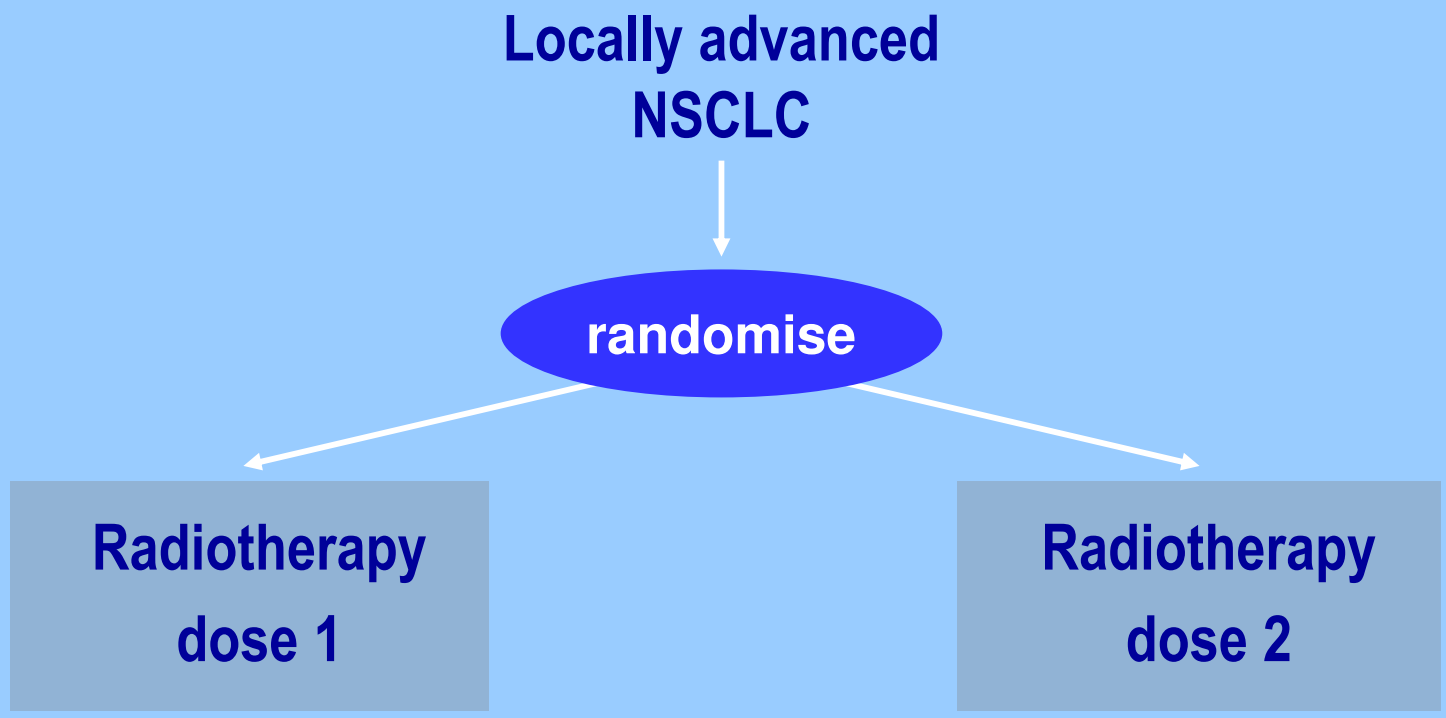


corrected for dose fractionation/time and stage distribution

Dose response in non-small cell lung cancer (NSCLC)

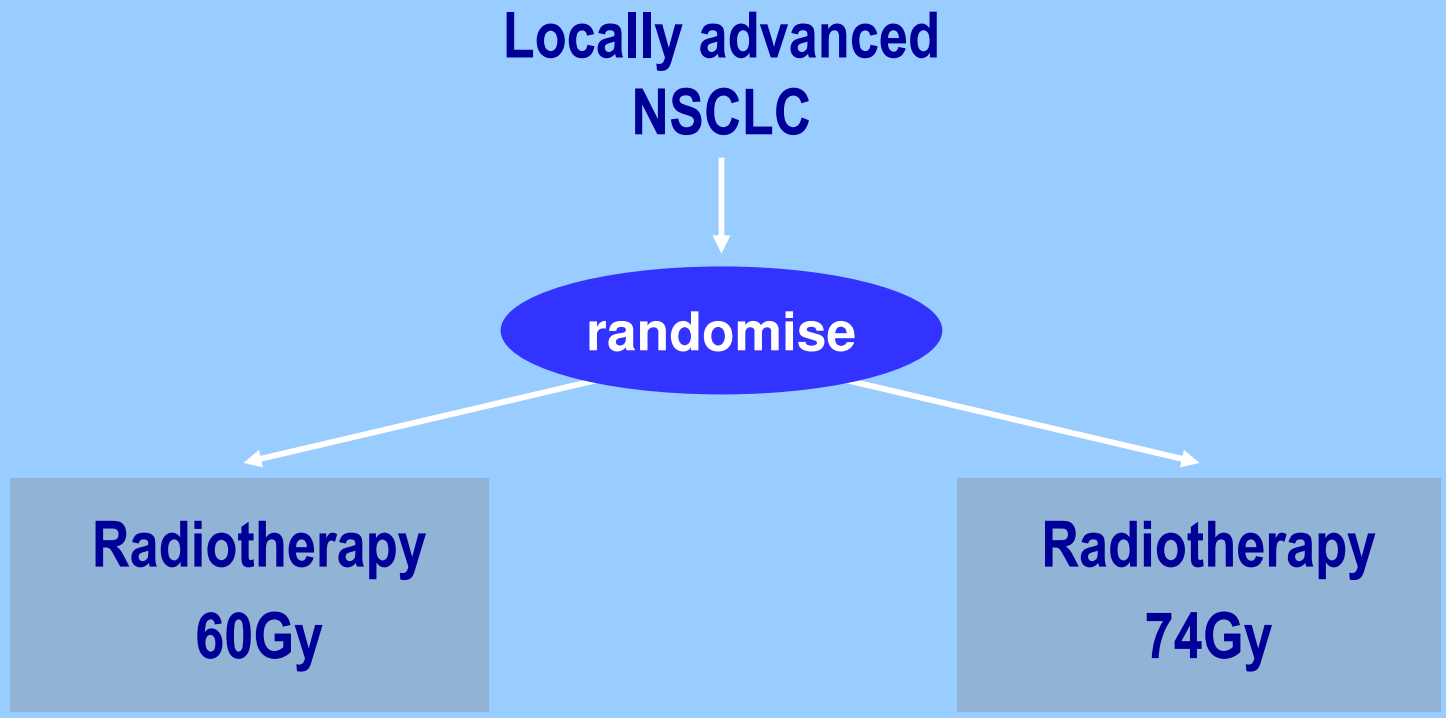
Partridge, Ramos, Sardaro & Brada 2011

Radical radiotherapy – dose escalation



Radical radiotherapy – dose escalation

RTOG 0617

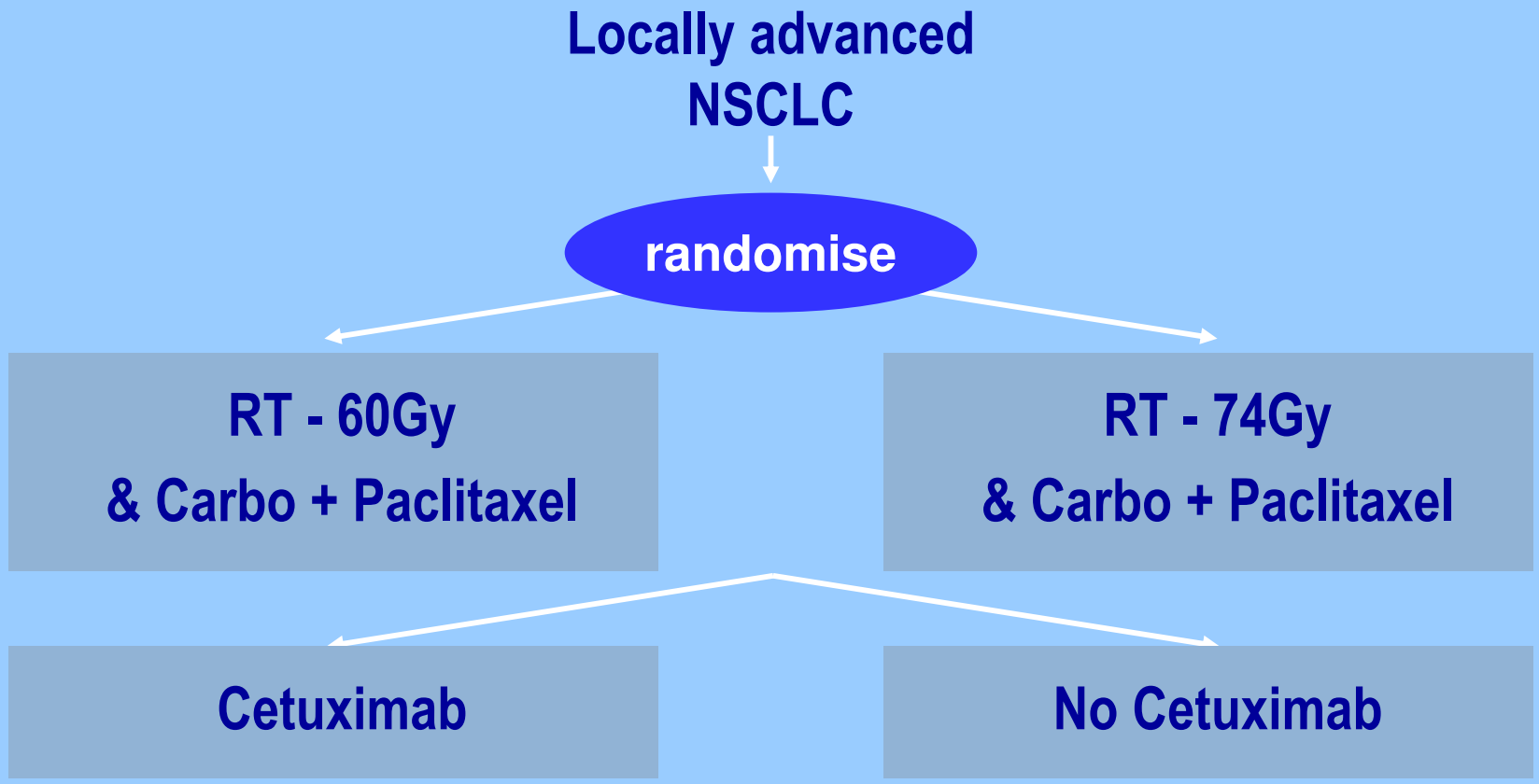


Improving lung cancer radiotherapy

Bradley et al 2011, ASTRO presentation

Radical radiotherapy – dose escalation

RTOG 0617

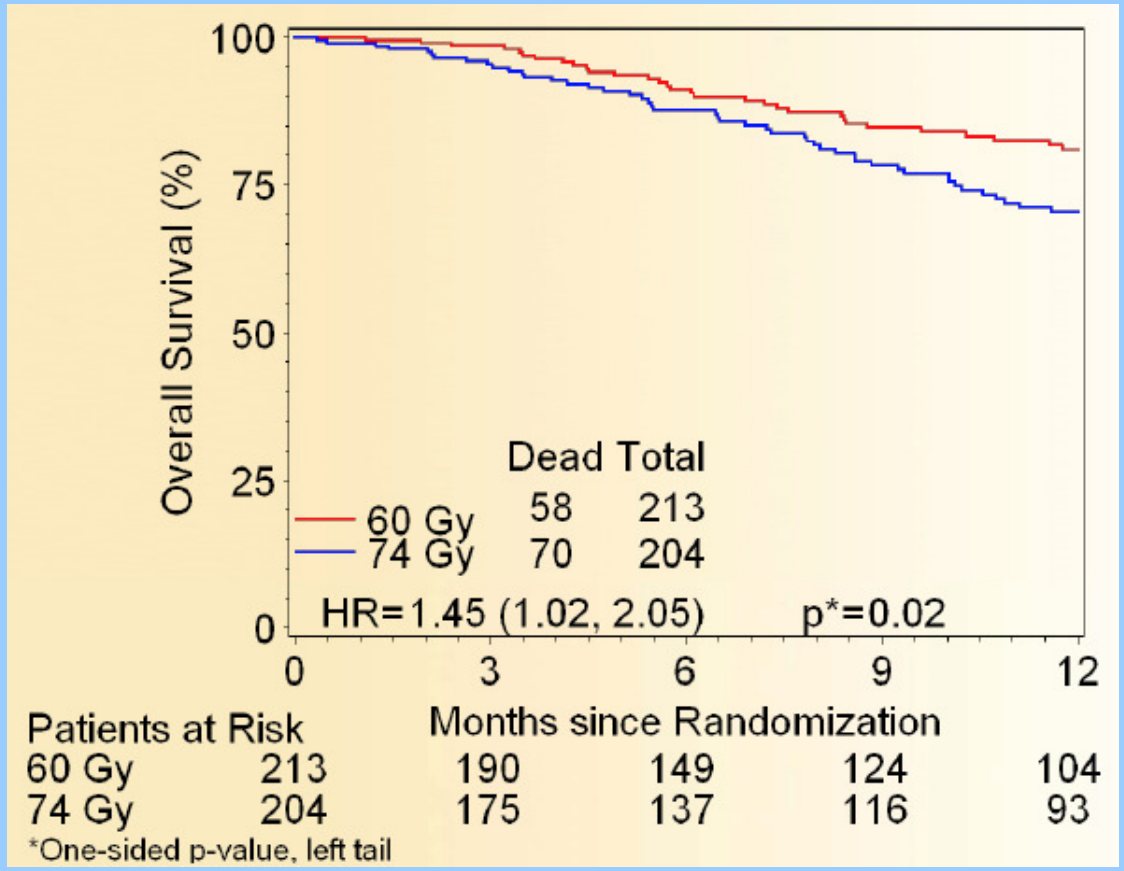


RTOG trial 0617

Bradley et al 2011, ASTRO presentation

Radical radiotherapy – dose escalation

RTOG 0617

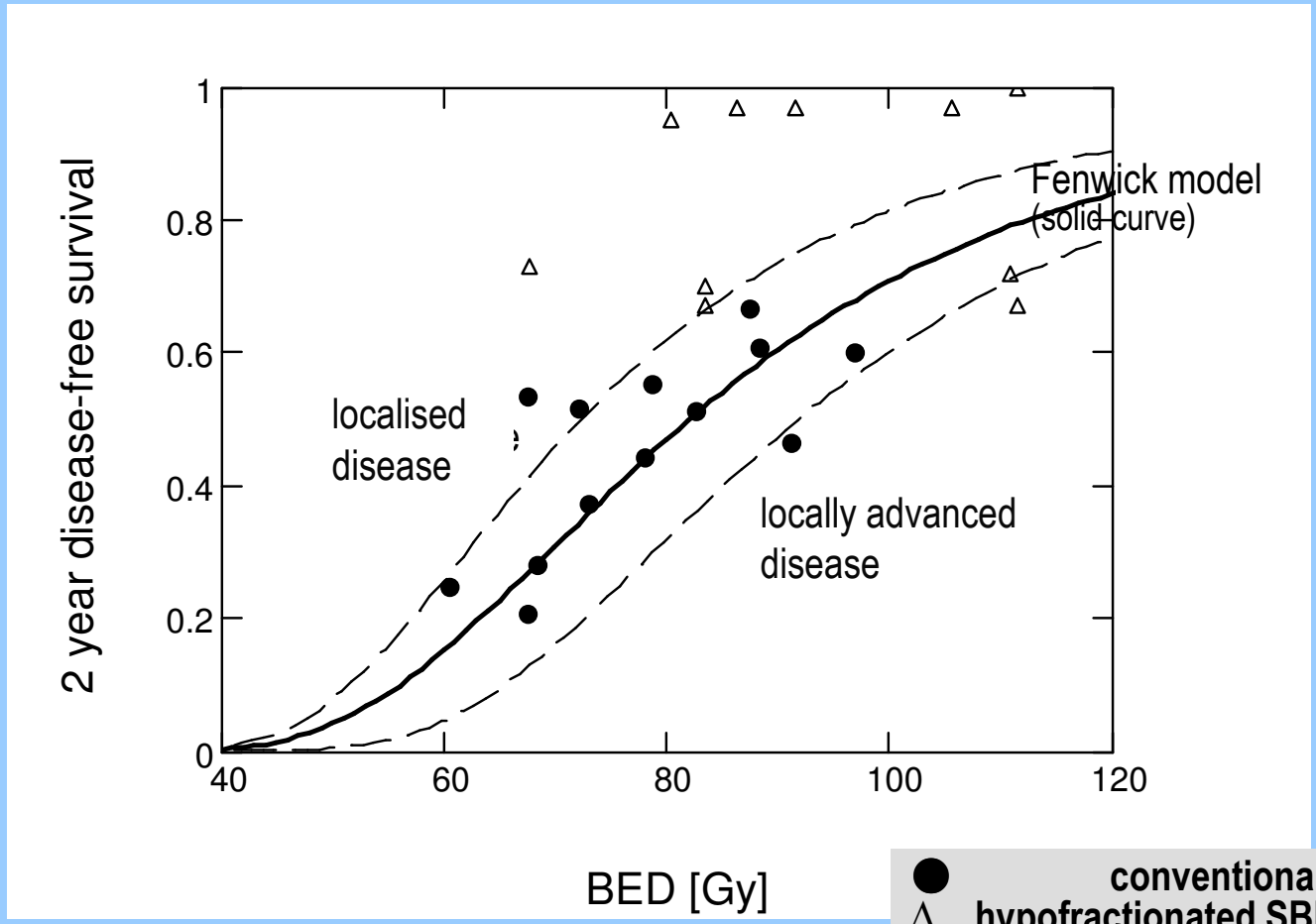


RTOG trial 0617

Bradley et al 2011, ASTRO presentation

Summary of published phase I/II studies including SBRT

2 year local progression free survival



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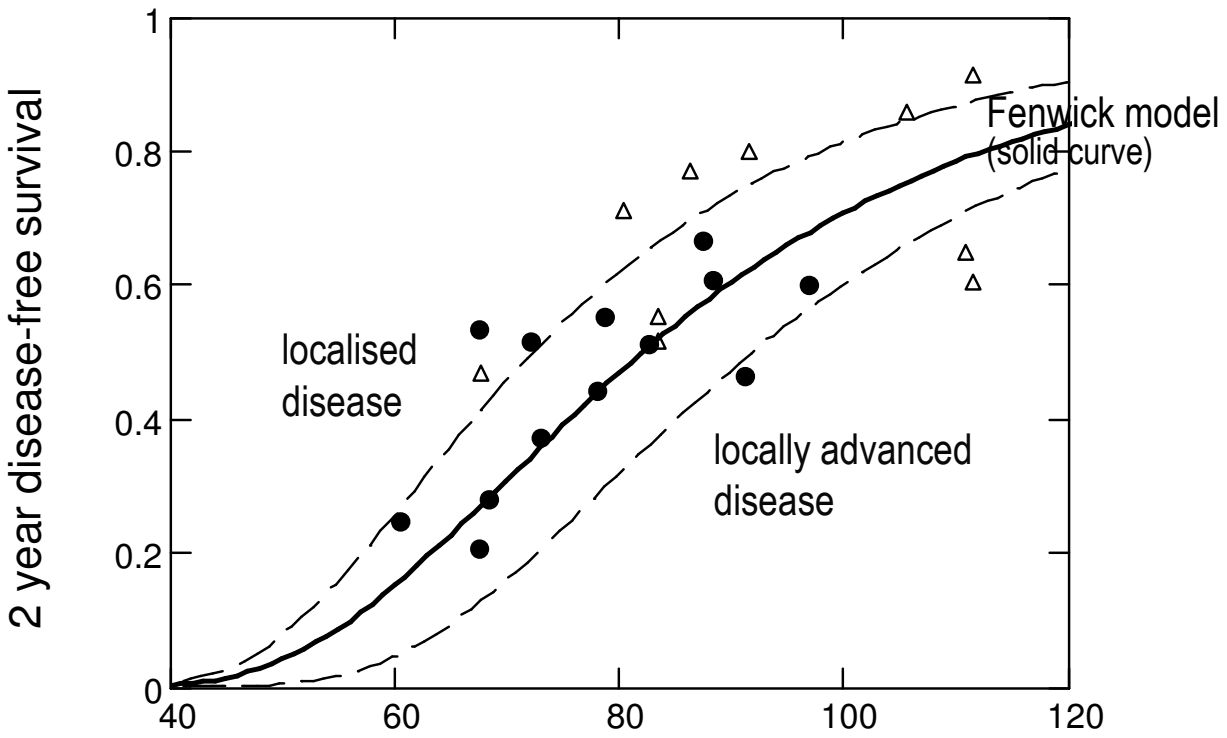
Summary of published phase I/II studies including SBRT

2 year local progression free survival (corrected for stage distribution)

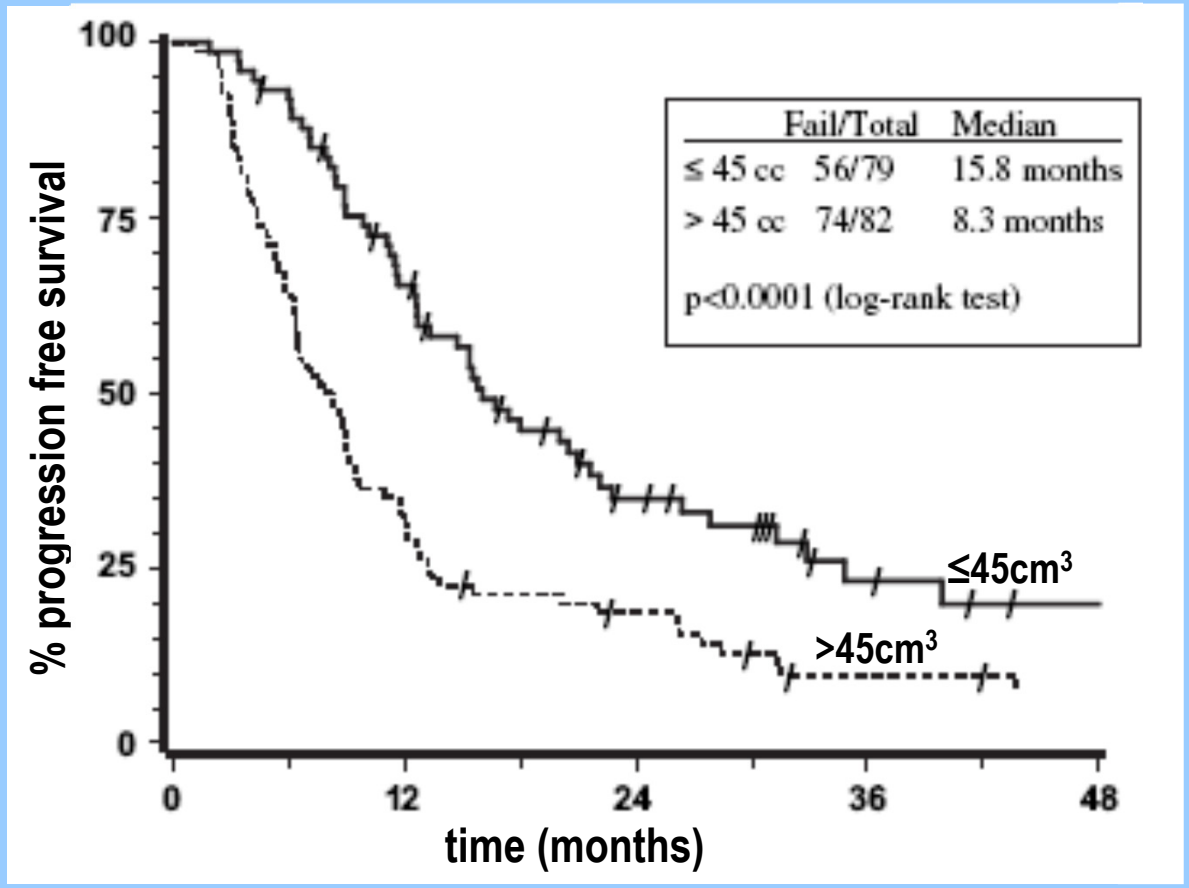


● conventional fractionation
Δ hypofractionated SBRT

Dose response in non-small cell lung cancer (NSCLC)

Partridge, Ramos, Sardaro & Brada 2011

RTOG 93-11 Phase I/II dose escalation study in NSCLC



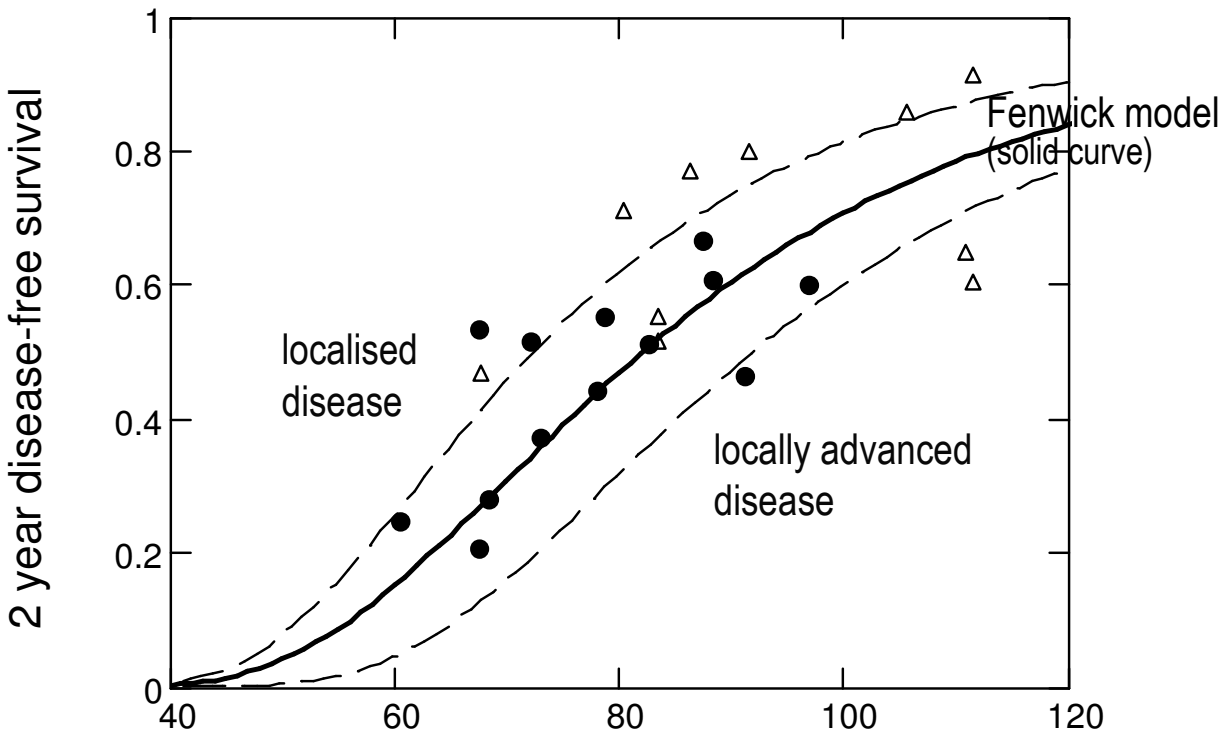
$45cm^3$ ≈ 4.5 cm diameter sphere

Tumour size and disease control

Werner-Wasik et al 2008

Summary of published phase I/II studies including SBRT

2 year local progression free survival (corrected for stage distribution)



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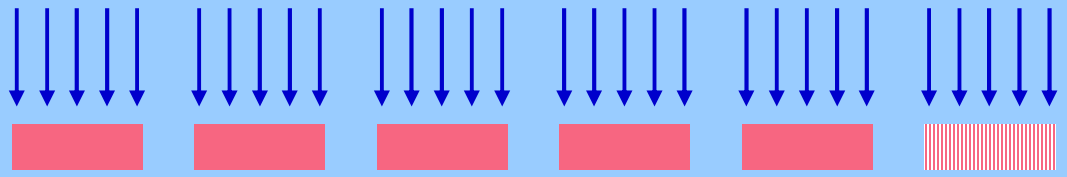
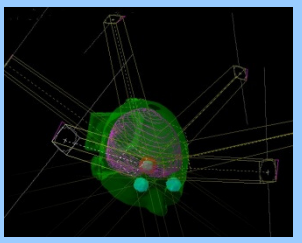
Stereotactic radiotherapy for acoustic neuroma

Fractionated stereotactic radiotherapy

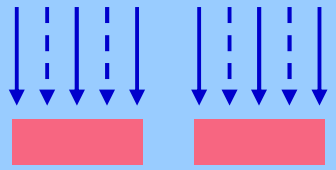


fractions
weeks

45 - 50Gy in 25 - 30 fractions

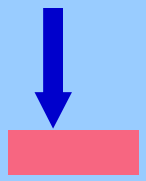


Hypofractionated stereotactic radiotherapy



20 - 30Gy in 6 - 10 fractions

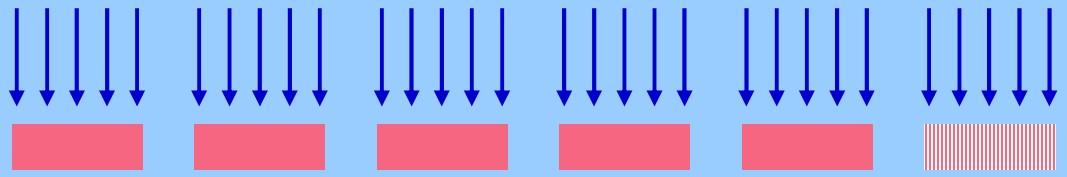
Single fraction radiosurgery



10 - 25Gy in 1 fraction

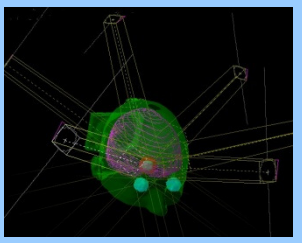
Fractionation in stereotactic radiotherapy

Fractionated stereotactic radiotherapy

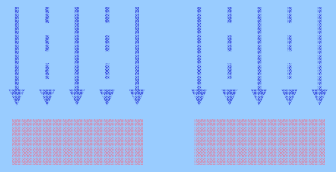


fractions
weeks

45 - 50Gy in 25 - 30 fractions

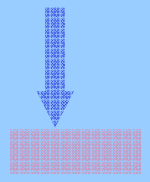


Hypofractionated stereotactic radiotherapy

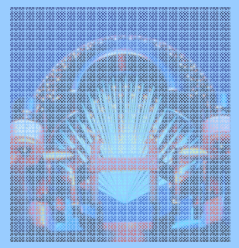


20 - 30Gy in 6 - 10 fractions

Single fraction radiosurgery

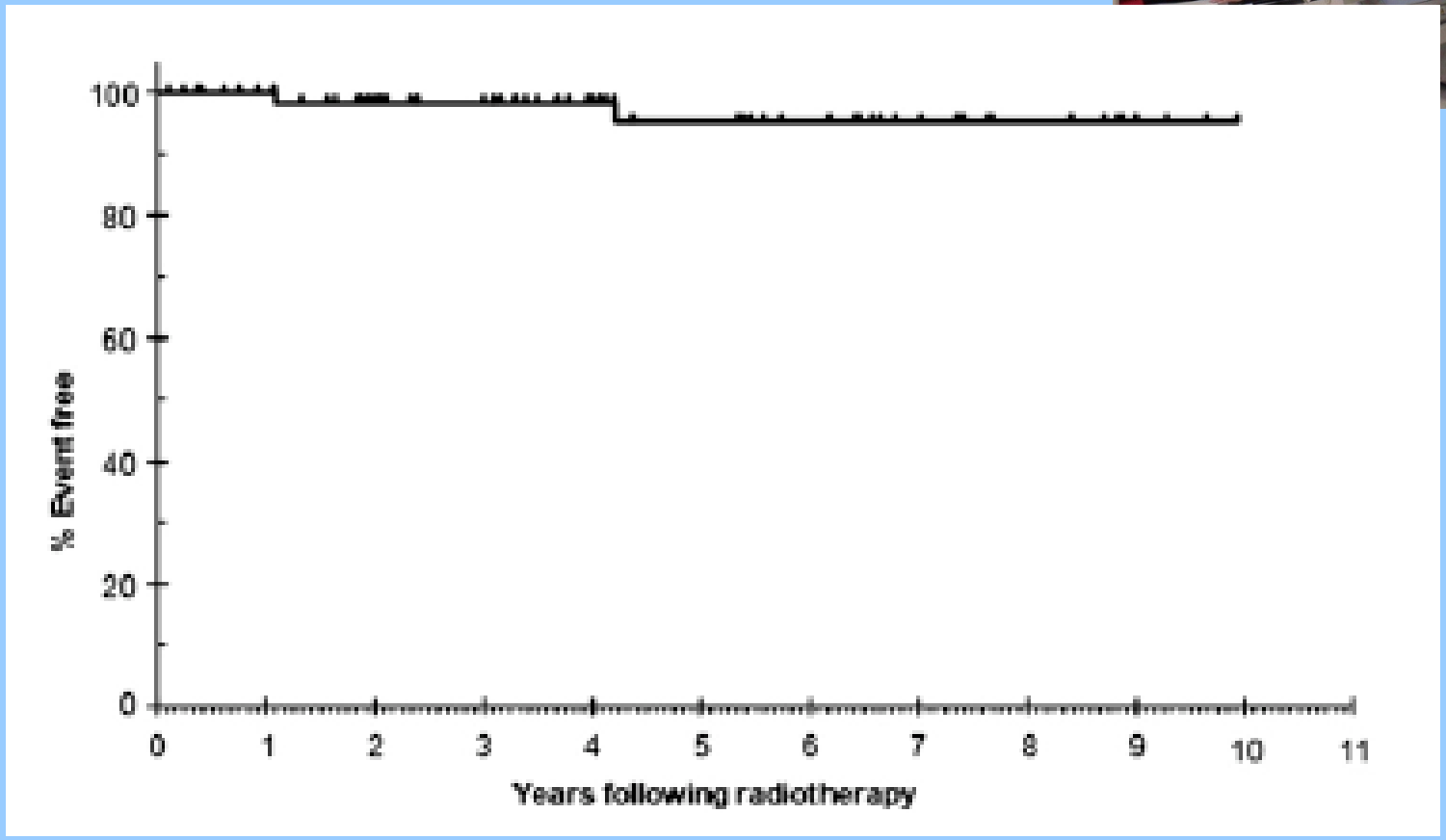


10 - 25Gy in 1 fraction



Fractionation in stereotactic radiotherapy

Tumour control

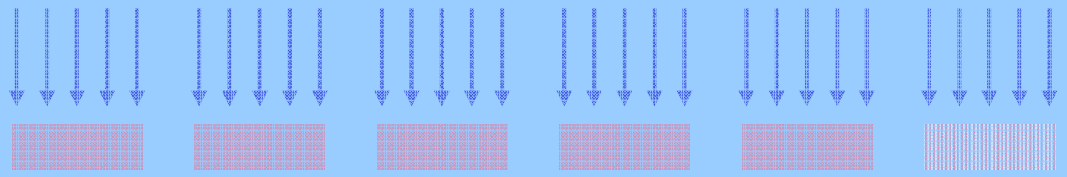


Powell et al 2010 IJROBP
72 patients with acoustic neuroma
Royal Marsden Hospital

Stereotactic RT for acoustic neuroma

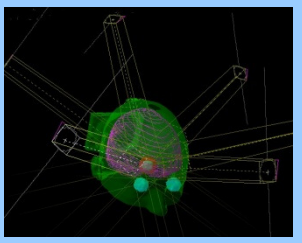
Fractionation in stereotactic radiotherapy

Fractionated stereotactic radiotherapy

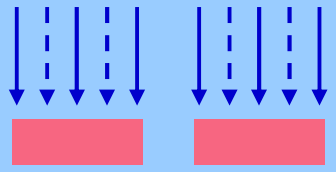


45 - 50Gy in 25 - 30 fractions

fractions
weeks

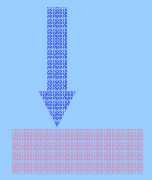


Hypofractionated stereotactic radiotherapy

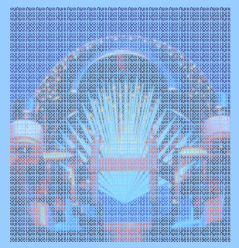


25Gy in 5 fractions
30Gy in 10 fractions

Single fraction radiosurgery

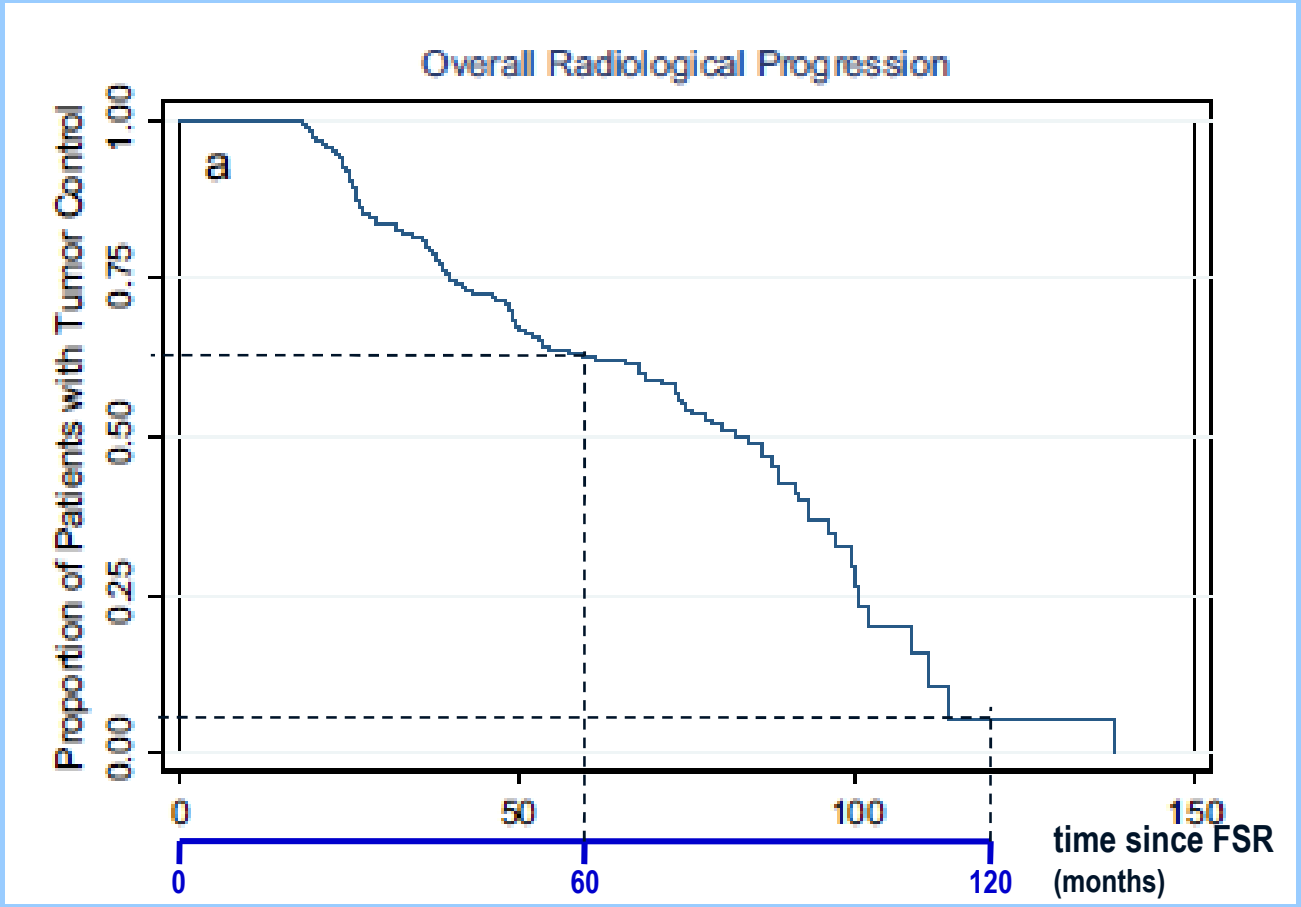


10 - 25Gy in 1 fraction



Kapoor et al 2010, Int J Rad Oncol Biol Phys, Johns Hopkins experience

Tumour control



Fractionated s

Kapoor et al 2010, Int J Rad Oncol Biol Phys, Johns Hopkins experience

Risks from introduction into clinical practice

system problems and complexity

- system errors
- demands on under resourced service

individual patient risks

- reliance on image interpretation
- clinical expertise vs technical prowess
- commercial interests & direct to patient marketing

Conventional design

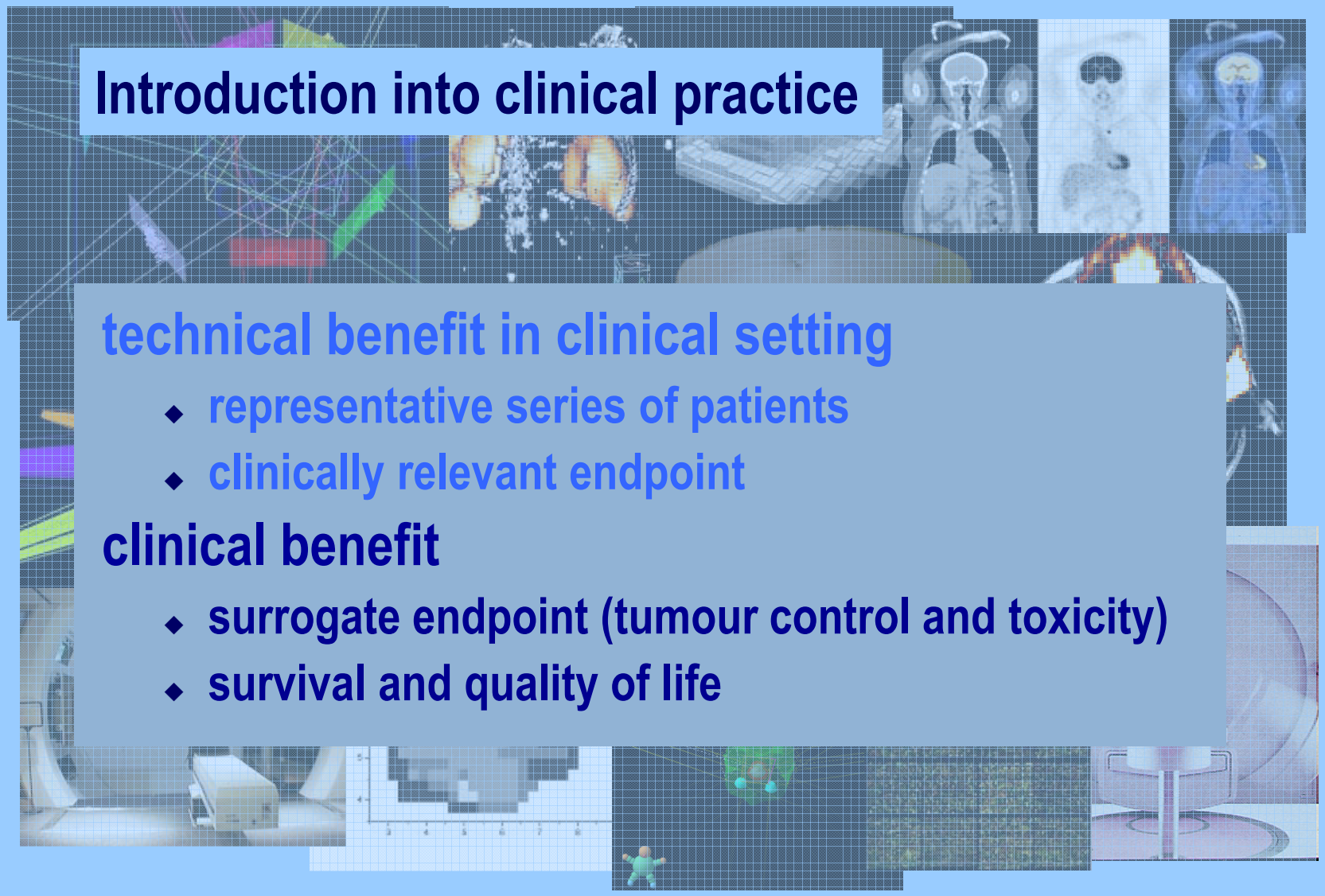
to evaluate

Phase I	feasibility & toxicity
Phase II	initial investigation of activity
Phase III	comparative efficacy

model of drug testing

Evidence based medicine

Introduction into clinical practice



technical benefit in clinical setting

- representative series of patients
- clinically relevant endpoint

clinical benefit

- surrogate endpoint (tumour control and toxicity)
- survival and quality of life

Introduction into clinical practice
Protons

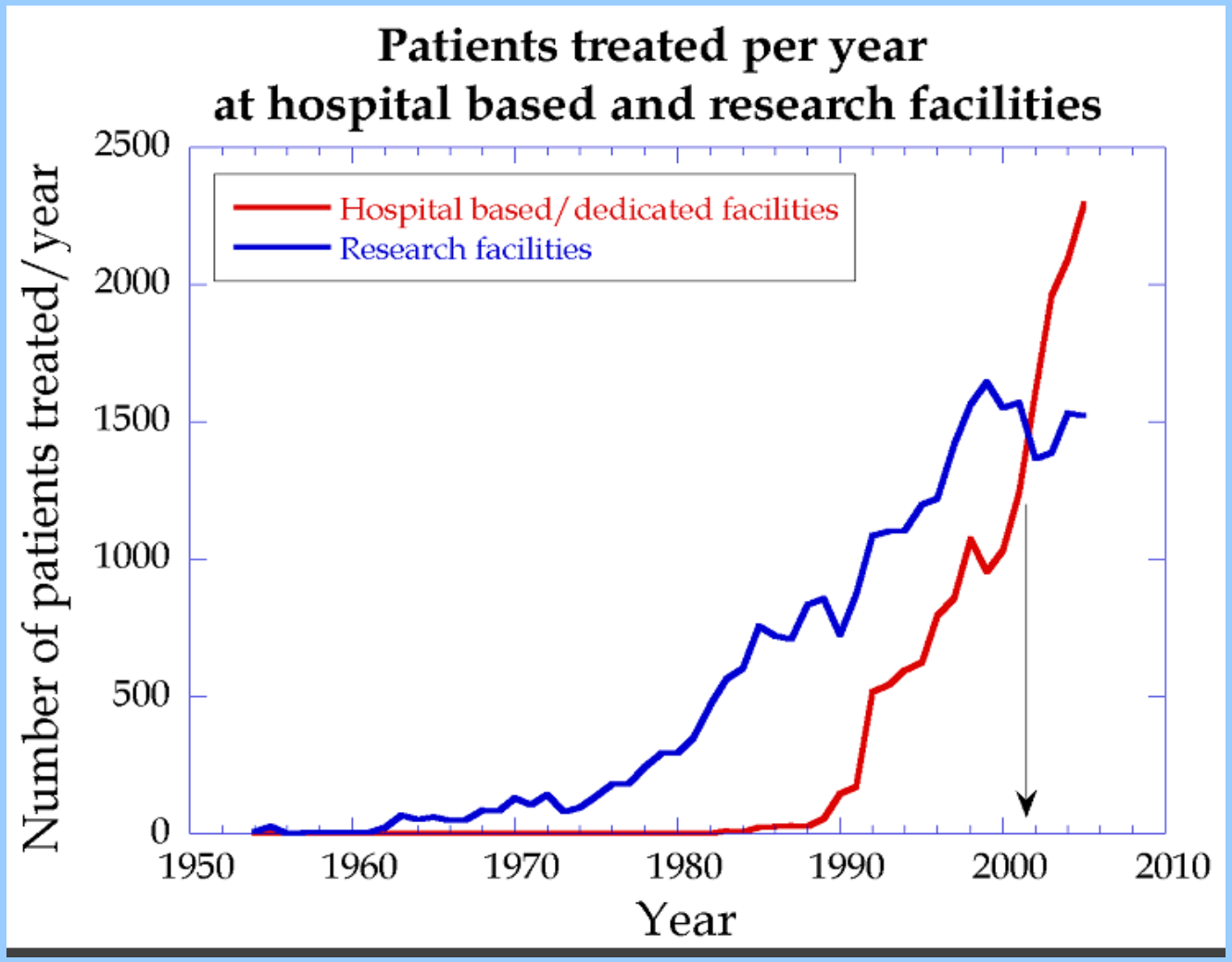
technical benefit in clinical setting

- representative series of patients
- clinically relevant endpoint

clinical benefit

- surrogate endpoint (tumour control and toxicity)
- survival and quality of life

Evaluating new radiotherapy technology



Clinical use of protons

courtesy of Thomas Bortfeld

Clinical evidence for efficacy of protons

Systematic review of published literature

Tumour site	tumour control*	survival*	toxicity*
Head & neck tumours			
Prostate cancer			
Ocular tumours			
Gastrointestinal cancer			
Lung cancer			
CNS tumours			
Sarcomas			
Paediatric tumours			

* benefit compared to
best conventional treatment

Protons in other tumours

Brada et al 2007 JCO, 25 (8), 965-70
Brada et al 2009 Cancer Journal 15 (4), 319 -24

Clinical evidence for efficacy of protons

Systematic review of published literature

Tumour site	tumour control*	survival*	toxicity*
Head & neck tumours	✘	✘	✘
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Ocular tumours	✘	✘	✘
Gastrointestinal cancer	✘	✘	✘
Lung cancer	✘	✘	✘
CNS tumours	✘	✘	✘
Sarcomas	✘	✘	✘
Paediatric tumours	✘	✘	✘

* benefit compared to best conventional treatment

Protons in other tumours

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Conventional design

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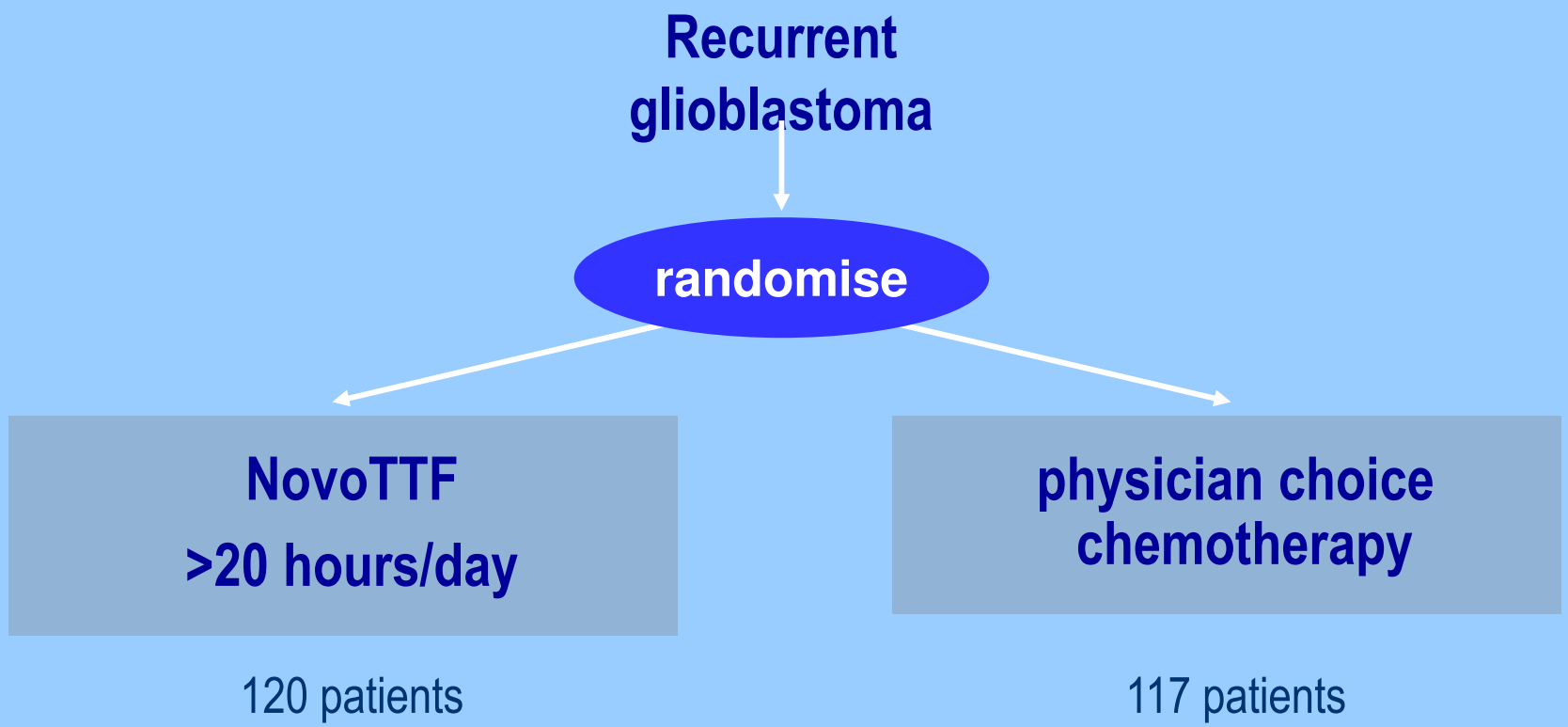
model of drug testing

Evidence based medicine

Successful Phase III Clinical Trial Results Reported For NovoCure's Novel Medical Device For Treatment Of Recurrent Glioblastoma

NovoTTF - 100A

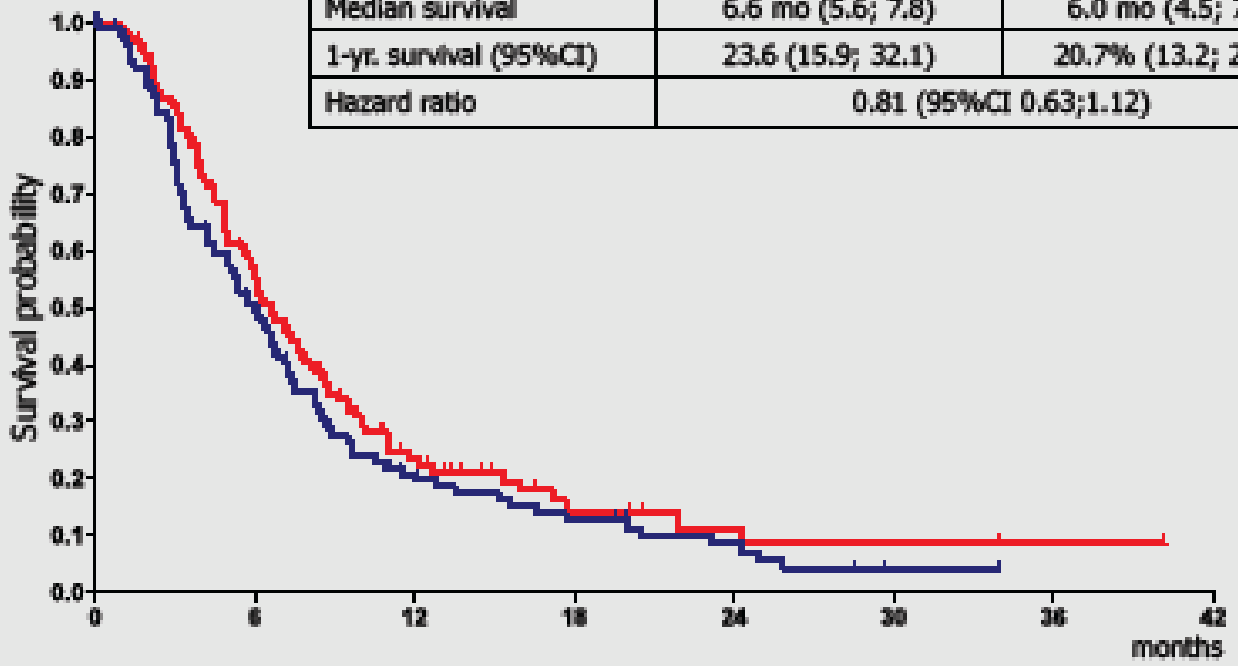
NovoTTF trial



NovoCure trial

NovoTTF trial
Survival by intent to treat (ITT) 237 patients

	Novo-TTF	Physicians Choice
Median survival	6.6 mo (5.6; 7.8)	6.0 mo (4.5; 7.1)
1-yr. survival (95%CI)	23.6 (15.9; 32.1)	20.7% (13.2; 29.4)
Hazard ratio	0.81 (95%CI 0.63;1.12)	

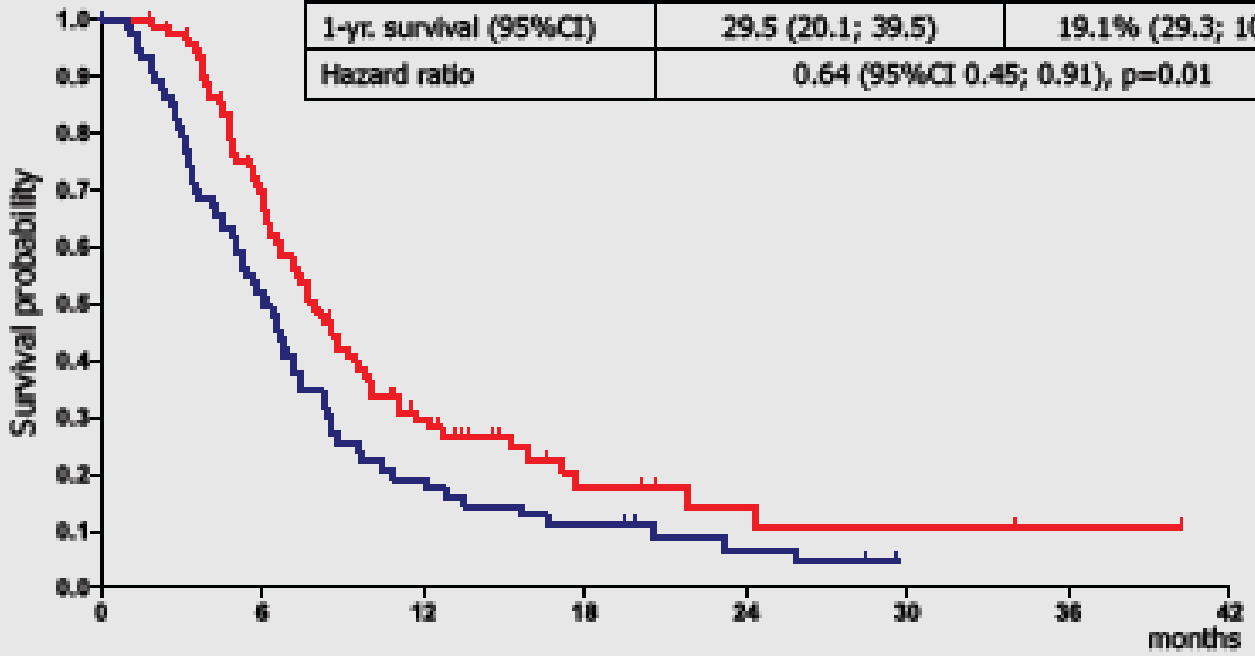


NovoCure trial

Stupp et al ASCO 2010

NovoTTF trial
Survival by treatment per protocol (TPP) 185 patients

	Novo-TTF	Physicians Choice
Median survival	7.8 mo (6.6; 9.4)	6.1 mo (4.8; 7.1)
1-yr. survival (95%CI)	29.5 (20.1; 39.5)	19.1% (29.3; 10.7)
Hazard ratio	0.64 (95%CI 0.45; 0.91), p=0.01	



NovoCure trial

Stupp et al ASCO 2010

Successful Phase III Clinical Trial Results Reported For NovoCure's Novel Medical Device For Treatment Of Recurrent Glioblastoma

Study results show that NovoTTF, a novel, non-invasive, portable medical device, may be as or more effective than the best available chemotherapies for GBM, but without the toxicity usually associated with cytotoxic or targeted treatments.

enterprisepost.com/biomed/bio/
www.news-medical.net/news
www.medicalnewstoday.com
www.thefreelibrary.com
appliedclinicaltrialsonline.findpharma.com/
www.medicalproductguide.com/
www.streetinsider.com/
.....

NovoCure and the web

Press release
Source: NovoCure

Conventional design

to evaluate

Phase I	feasibility & toxicity
Phase II	initial investigation of activity
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Evidence based medicine

Conventional design

to evaluate

Phase I	feasibility & toxicity
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Evidence based medicine

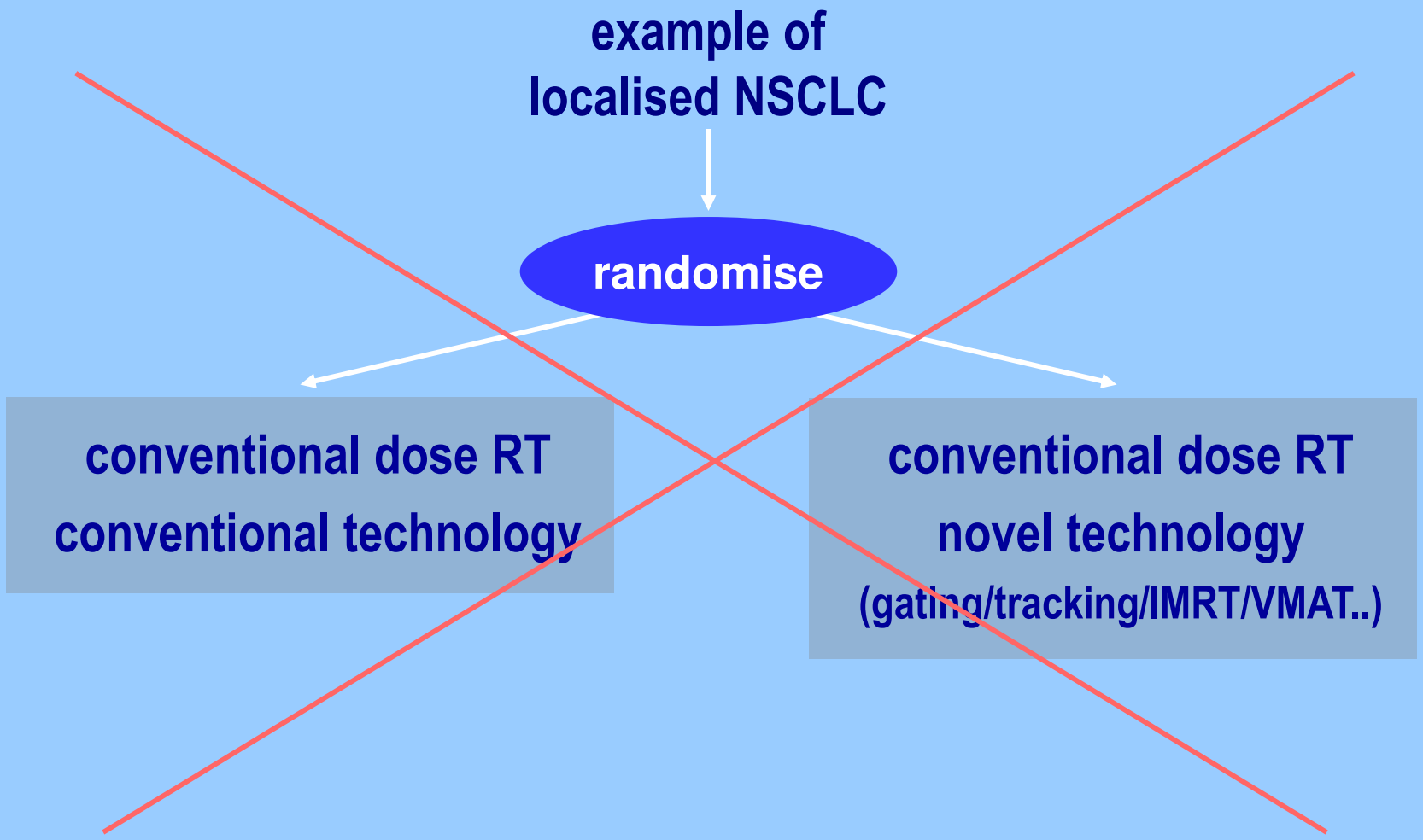
New technology trial

example of
localised NSCLC

conventional dose RT
novel technology
(gating/tracking/IMRT/VMAT..)

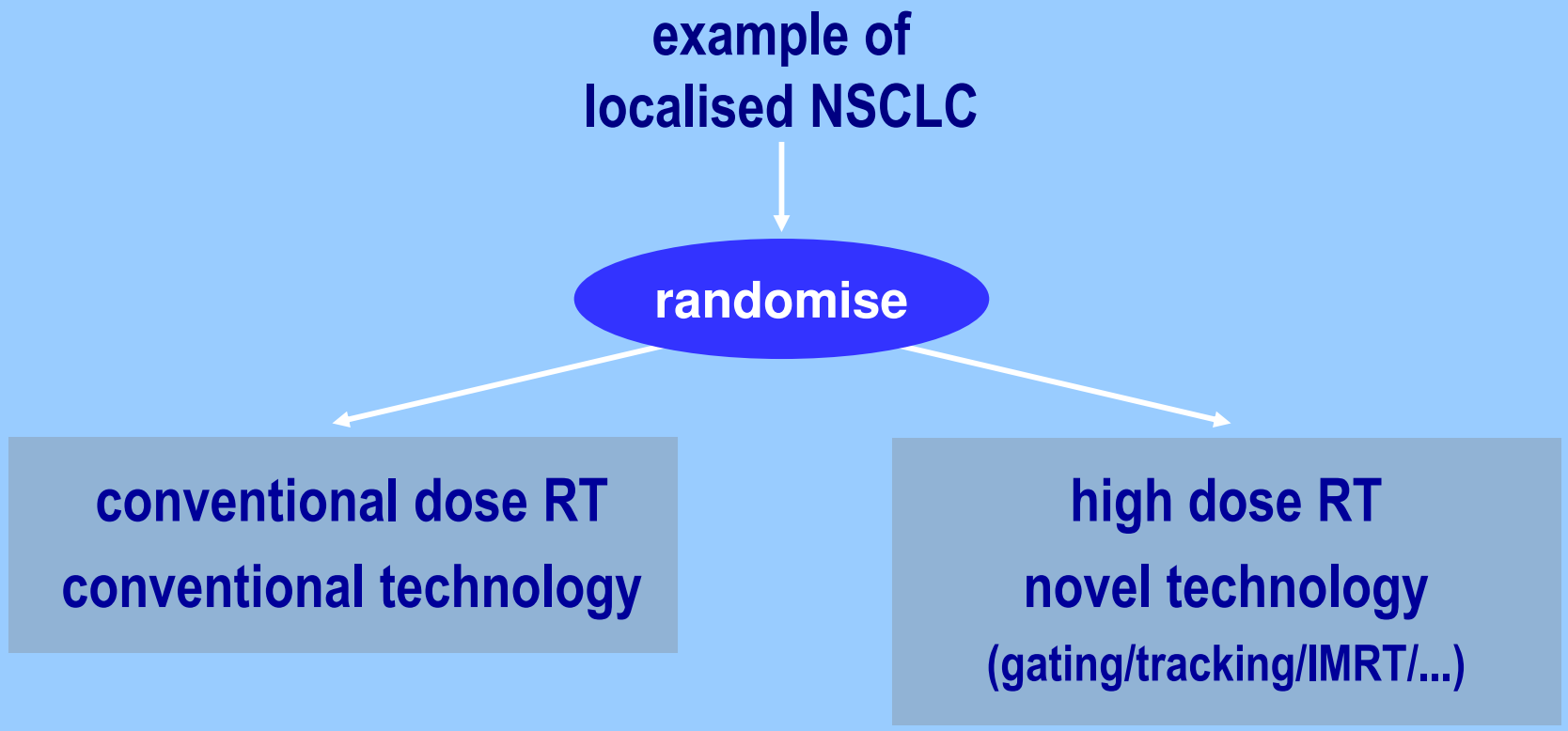
Evaluation of new technology of RT delivery in NSCLC

New technology trial



Evaluation of new technology of RT delivery in NSCLC

Combination of dose escalation with new technology



Evaluation of new technology of RT delivery in NSCLC


Introduction into clinical practice
benefits radiotherapy process
clinical benefit
Demonstrate benefit
in well designed prospective trials
New radiotherapy technology

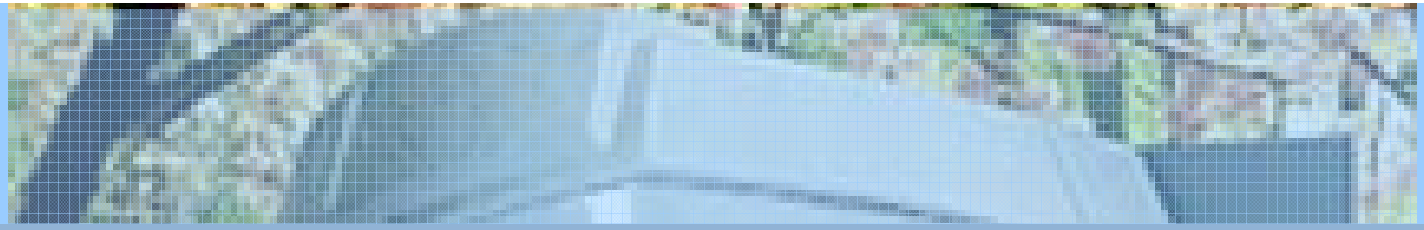
Introduction into clinical practice

benefits radiotherapy process

clinical benefit

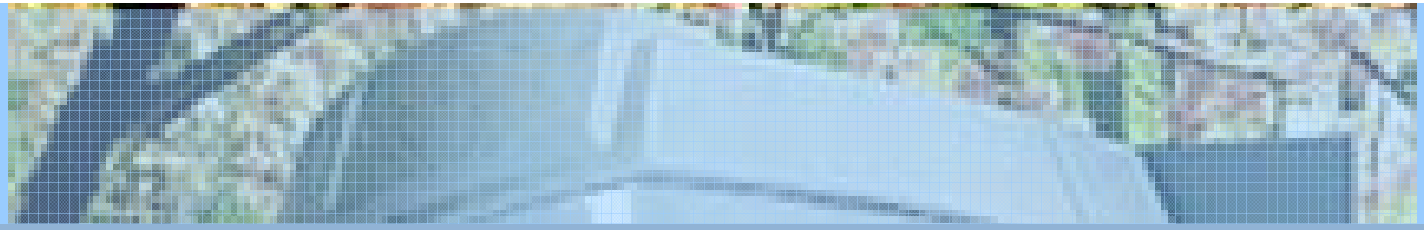
Introduction fuelled by commercial interests and enthusiasm subverts the clinical evaluation process

New radiotherapy technology



Comparative effectiveness research (CER) and appropriateness

A tool for clinical governance and a responsibility for clinicians



Comparative effectiveness research (CER) and appropriateness

A tool for clinical governance and a responsibility for clinicians

University College Hospital, London
Leaders in Oncology Care, London

mbrada@theloc.com

Michael Brada

Brescia

5 October 2012