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Radiotherapy Strategy and Accuracy Requirements

Maria Rosa Malisan
Med.Physicist, Udine, Italy

Outline

- Introduction
- Strategies in Radiotherapy
- Required Accuracy
- Uncertainties in the RT process
- Conclusions

Introduction

- In last century, technical and scientific improvements in radiotherapy (RT) have incessantly occurred, allowing accurate delivery of the ionizing radiation dose, i.e. more precise energy deposition to the tumor while progressively reducing unwanted dose to surrounding normal tissues.
- Over recent years, new RT modalities, such as IMRT, IGRT, VMAT, ART and hadron RT have emerged, each addressing peculiar needs, and are available in many centres all over the world.
- In parallel with these technological advances, new developments have taken place in radiobiology, concerning the understanding of cancer biology in general, and the radiation response in particular.

Introduction

- Such technical and scientific advances have provided the capability to personalize treatments for accurate delivery of radiation dose based on clinical parameters and anatomical information.
- Thus Radiation oncology has now entered the 'precision radiotherapy' era, where the dose to the tumor is allowed to be increased to levels that would be unachievable without precise targeting.
- However, the level I evidence of a survival improvement is still lacking. Only a few randomized trials have validated the benefit of modern irradiation techniques for improving the therapeutic index.

(Chargary et al, Cancer Treat Rev 2016)

Introduction

- *“ The current outcomes of radiation therapy are still far from the high demand of cancer patients for therapy efficacy and quality of life “* (Wang and Lang, Exp. Ther. Med. 2012)
- Although today, tumour control can be achieved in many patients, there remains substantial room for improvement.
- The proportion of in-field recurrences after high-dose radiotherapy, limited by normal tissue tolerance, may still be exceedingly high.
- In other tumours, for which control rates are high, early and late damage to normal tissues may be decreased.

(Baumann et al, NatureRev.Cancer 2016)

Strategies in Radiotherapy

- Two major strategies, acting synergistically, will enable further widening of the therapeutic window of radiation oncology in the era of precision medicine:
  - technology-driven improvement of treatment ***conformity***, (including advanced image guidance and particle therapy)
  - novel ***biological*** concepts for personalized treatment, (including biomarker-guided prescription, combined treatment modalities and adaptation of treatment during its course).

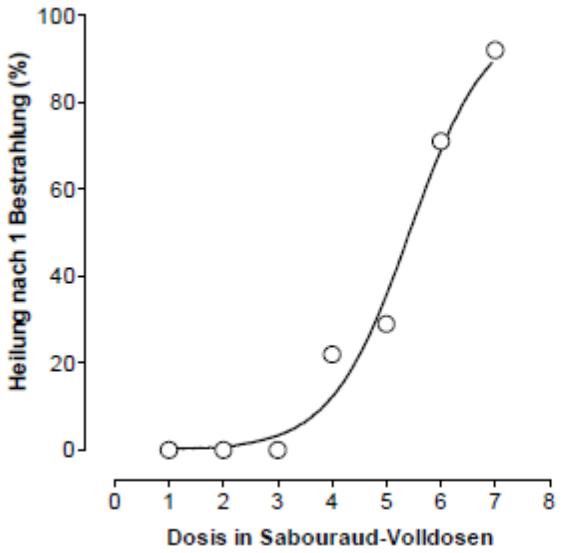
(Baumann et al, Nature Reviews Cancer 2016)

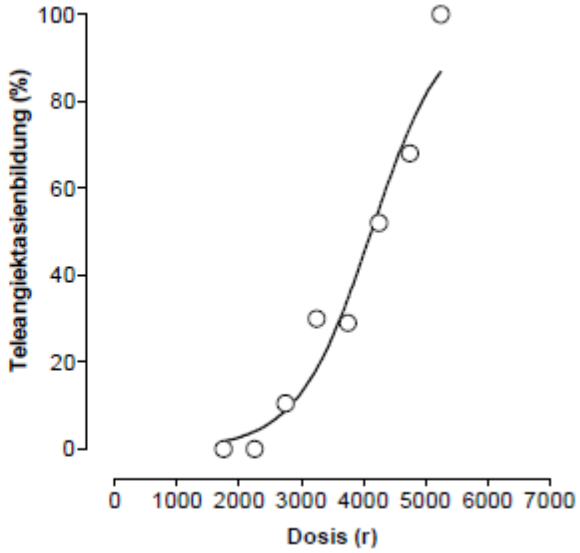
Strategy in Radiotherapy

- RT requires a reasonable *treatment strategy* to gain the best clinical outcome.
- The optimization of the radiation treatment planning includes the dose-fractionation and radiation protection of the normal tissue.
- Many of the crucial concepts of radiobiology and treatment optimization were established ~ 80 years ago by Holthusen.
- Since then, the issue of radiation-induced response has constantly evolved, based on the increasing knowledge of its biological mechanisms and on new techniques for minimizing irradiation of normal tissues.

Strategy in RT

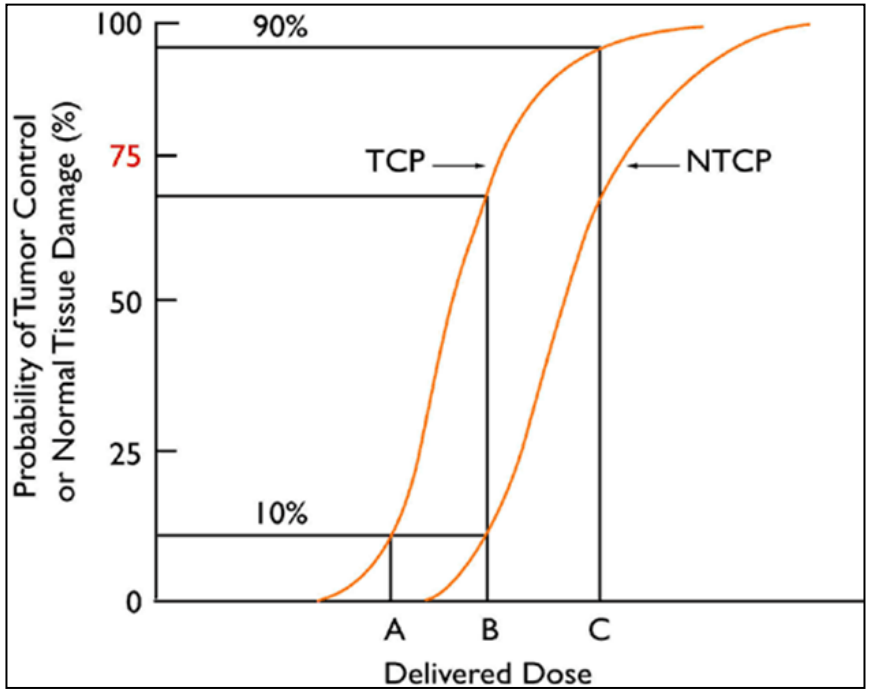
- The aim is to obtain a differential effect of radiation on tumour and normal tissue.
- Dose response curves for tumors and normal tissues have to be considered.
- The first dose response data were reported for skin cancer in 1934.
- From these data, H. Holthusen (1936) constructed the first radiation dose response curves.
- A characteristic sigmoid relationship was observed for both tumor and normal tissue.





Tumor control rate and formation of teleangiectasia. Redrawn from Holthusen (HH. Dübben)

Dose effect curves: TCP & NTCP



TCP = Tumour Control Probability

NTCP = Normal Tissue Complications Probability

- At low doses virtually no tumor is controlled.
- Above a threshold dose TCP increases with dose.
- Theoretically, at sufficiently high doses, 100% TCP may be achieved.
- However, with increasing dose NTCP increases as well.
- For a typical good RT treatment, TCP ≥ 50% and NTCP < 5%.

Uncomplicated Tumor Control

- The dose to the tumour is limited by what can be tolerated by the most at-risk normal tissue.
- Holthusen (1936) was the first to formulate the idea of optimizing the tumor dose applied.
- The probability to achieve tumor control without complications can be calculated:

UCP = TCP*(1-NTCP)

- The 'uncomplicated tumour control' follows a bell-shaped curve.

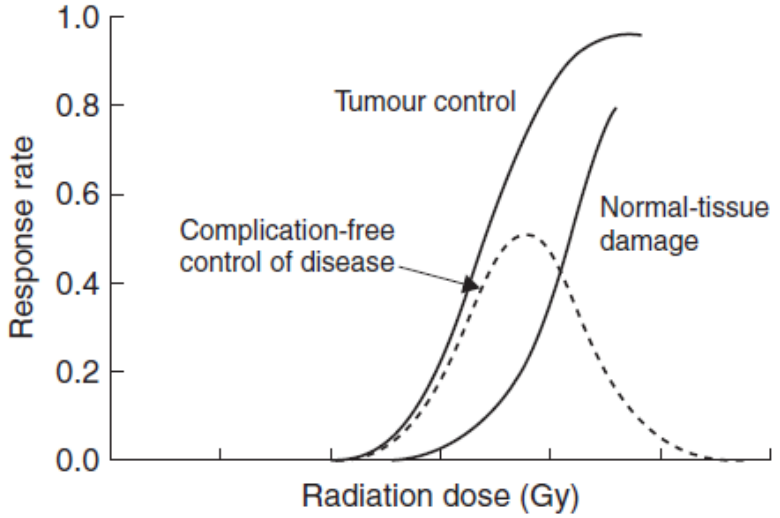


Figure 10.1 Dose–response curves for tumour control and normal-tissue damage. The uncomplicated local tumour control rate initially increases with increasing dose after which it falls again because of a steep increase in the incidence of damage to normal tissue. Adapted from Holthusen (1936).

Uncomplicated Tumor Control

- Once the optimum dose is established, further improvements in UCP can only be achieved by either moving the TCP curve to lower doses, or the NTCP curve to higher doses; the latter is the objective of hyperfractionated schedules
- Conformal RT is another option currently used in dose escalation protocols, reducing the volume of normal tissue irradiated to high dose and therefore also the probability of late normal-tissue damage.

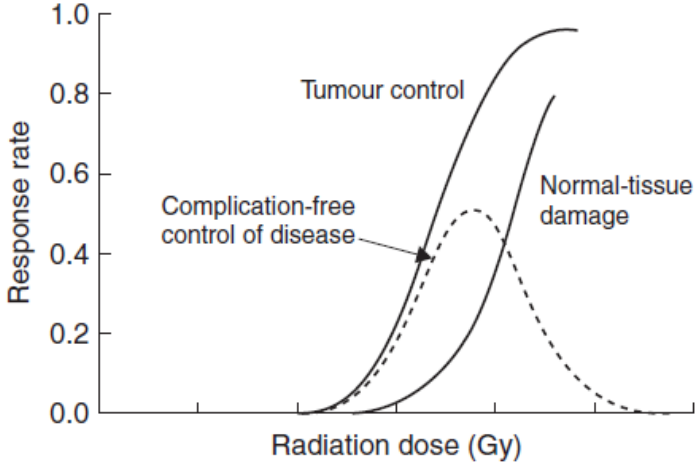


Figure 10.1 Dose–response curves for tumour control and normal-tissue damage. The uncomplicated local tumour control rate initially increases with increasing dose after which it falls again because of a steep increase in the incidence of damage to normal tissue. Adapted from Holthusen (1936).

Radiobiological Optimization

- A major field of research in RT is the exploration of irradiation schedules that are supposed to exploit radiobiological differences between tumor and normal tissue.
- This would yield further separation of the curves of TCP and NTCP, thus leading to a higher maximum for the uncomplicated control rate.
- It is even likely that the expected improvements from technical innovations will reach a limit, and the next breakthroughs will come from biological innovations, such as the application of molecularly targeted drugs in combination with high-precision methods to deliver radiation.

HH Dubben, 2005

Accuracy in Radiotherapy

- Quantification of dose has been an important factor in the development of modern RT.
- Physically based treatment planning, using metrics such as radiation dose, is so successful because this metrics is measurable, and thus the treatment plan is directly verifiable.
- To achieve a good clinical outcome a certain accuracy in the dose delivered to patient is required.

Accuracy in Radiotherapy

- On the other hand, from the prescription to the delivery of RT treatment, a team of professionals from a number of disciplines is involved in a large number of steps.
- Moreover, a treatment is usually delivered with 20 to 40 fractions, each requiring a large number of machine and patient parameters to be set up by the RT technologist.
- Based on these considerations, it is apparent that there is a significant potential for errors and uncertainties, leading to an actual exposure different from the prescribed one.

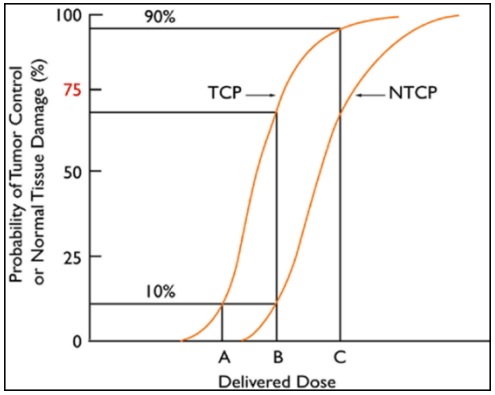
Required dose accuracy based on clinical response: ICRU 24

- In 1976 ICRU Report 24 reviewed the limited information at that time, analysing the clinical evidence of various studies. It concluded that:
- «*although it is too early to generalize, the available evidence for certain tumors points to the need of an accuracy of*

± 5%

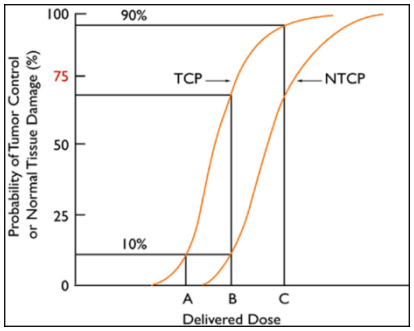
- *in the delivery of an absorbed dose to a target volume if the eradication of the primary tumor is sought.*
- *Some clinicians have requested even closer limits such as ± 2%, but at the present time it is virtually impossible to achieve such a standard.»*

Required accuracy based on clinical response



- The steepness of the given TCP/NTCP curve vs dose defines the change in response expected for a given change in delivered dose.
- Thus uncertainties in delivered dose translate into either reductions in TCP or increase in NTCP from the optimised expected values, both of which worsen the clinical outcome.
- The accuracy requirements are defined by the steepest curves, observed for normal tissue or tumours.
- At the steepest parts of the dose response curves, and for the steepest curves, 5% changes in dose can produce 10-20% changes in TCP and 20-30% changes in NTCP.

Required accuracy based on NTCP

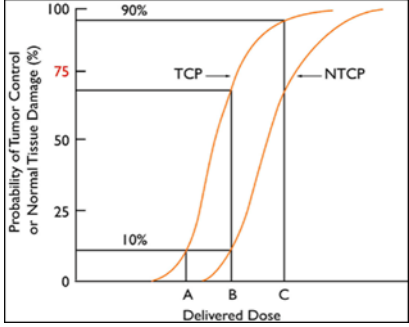


- Mijnheer et al (1987) considered the steepness of NTCP curves in terms of the % increase in absorbed dose to produce a change in the NTCP from 25% to 50% ($\Delta_{25/50}$).
- A representative value of 7% was taken for this relative gradient.
- It was concluded that any transfer of clinical information from one centre to another will involve unacceptable risks of complications for overall dose uncertainty larger than this value.
- This was assigned to the 2 st.dev. level, resulting in a value of

  3.5% as one relative st.dev.

- as the general accuracy requirement on absorbed dose delivery.

Required accuracy based on clinical response: TCP



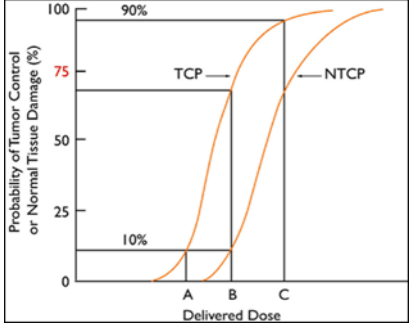
- Effects of dose variation on TCP were considered by Brahme et al (1988), showing that the most critical loss in TCP introduced by dosimetric inaccuracy is found at the highest level of TCP.

- A general figure of

  3% (relative st.dev.)

- on the delivered absorbed dose to the patient was recommended as the tolerance level on accuracy in dose delivery, in order to keep variations in the TCP within acceptable limits.

Required accuracy based on clinical response

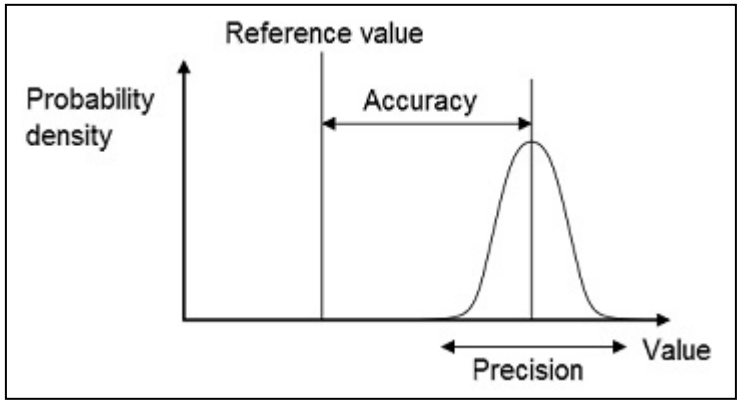


- Thus overall a figure of

3%

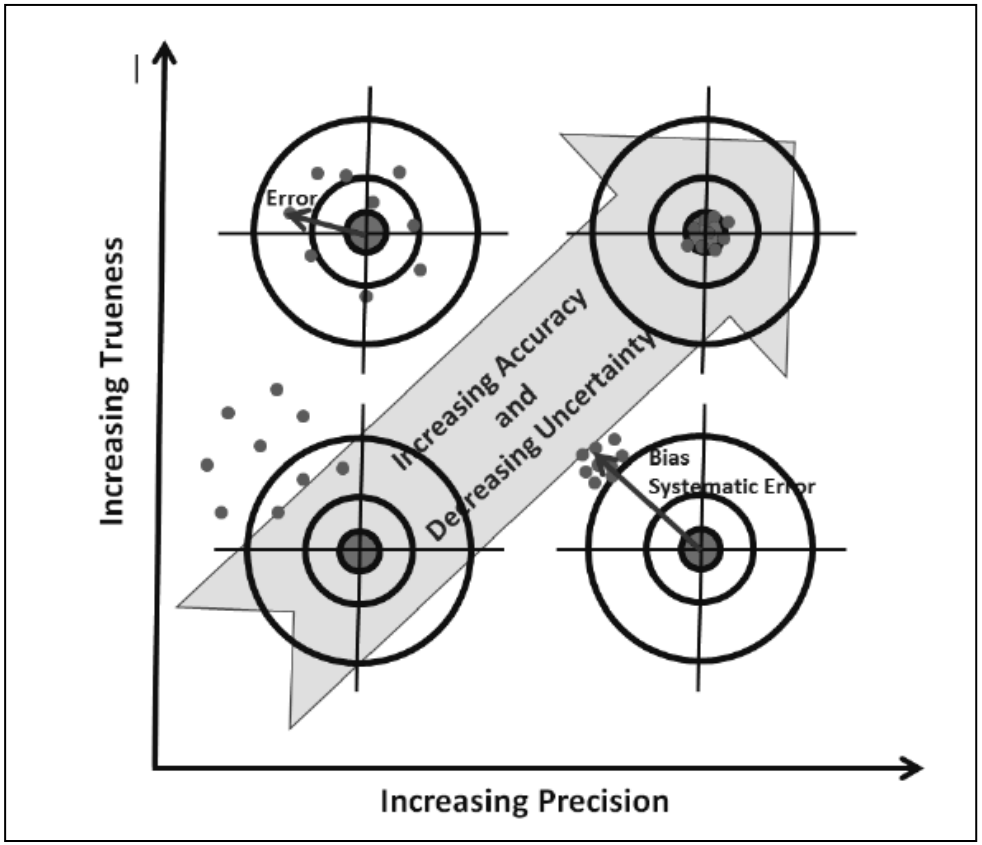
- can be taken as a currently recommended general accuracy requirement, being considered as one relative st.dev., on the value of the dose delivered to the patient at the dose specification point.
- This implies that there is a 95% probability that changes will be clinically observable at twice this level in situations described by the steeper dose-effect relationship.
- This is also consistent with more anecdotal evidence on clinical observations following inadvertent dose changes due to dosimetric errors (Dutreix, 1984).

Accuracy, precision, error, uncertainty



- Accuracy is a measure of how close a result is to the «true value».
- Precision is a measure of the spread of indipendent determinations of the result (generally determined as the st.dev. of the distribution of the results).
- Error is any deviation between the numerical value of a quantity and its «true» value.
- Uncertainty is an estimate of the possible magnitude of the error.

Accuracy /Uncertainty

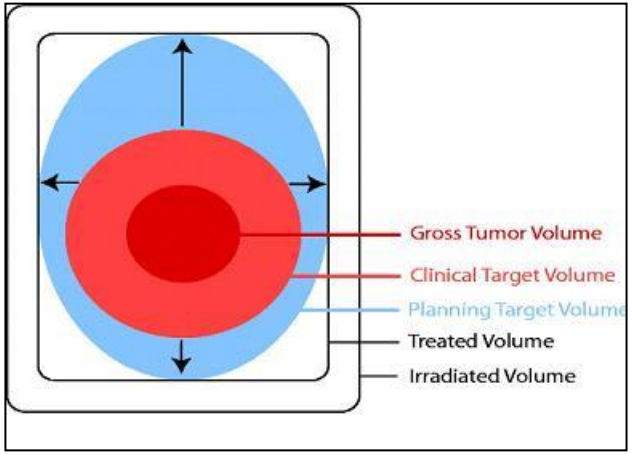


- *Accuracy* is an expression of the lack of errors, both random and systematic.
- *Uncertainty* characterizes the range of values within which the true value is asserted to lie with some level of confidence.
- The upper left quadrant shows large random error.
- The upper right quadrant shows small random error.
- The lower left shows both large systematic error and large random error.

- The lower right demonstrates a large systematic error (or bias) with a small random error.
- With <u>increasing trueness and increasing precision, there is an increase in accuracy</u> and a decrease in uncertainty.

Van Dyk et al, 2011

Geometrical accuracy



- In RT, geometric uncertainties translate to dosimetric uncertainties.
- Geometric uncertainties arise from:
  - treatment machine specifications and tolerances,
  - simulation and treatment set-up,
  - patient or organ movement during treatment,
  - changes of patient shape between fractions.
- In general appropriate margins are defined around the target volume to allow for these uncertainties, so it is difficult to find definitive data on the effect of inaccuracies.
- Geometric miss of tumour/target will obviously decrease TCP, whilst overlap of fields with adjacent normal structures, particularly critical organs, will be detrimental in terms of NTCP.

Geometrical accuracy

- Conventional approaches to this have been to model the effects of overlap onto organs at risk or reduced coverage of target volume or to consider the various sources of uncertainty, combine them to give an overall value
- On this basis, the AAPM TG 24 (1984) arrived at a figure corresponding to

  5 mm, one s.d.

- Mijnheer et al (1987) considered a wider set of data and recommended an accuracy of positioning of field edges and shielding edges of

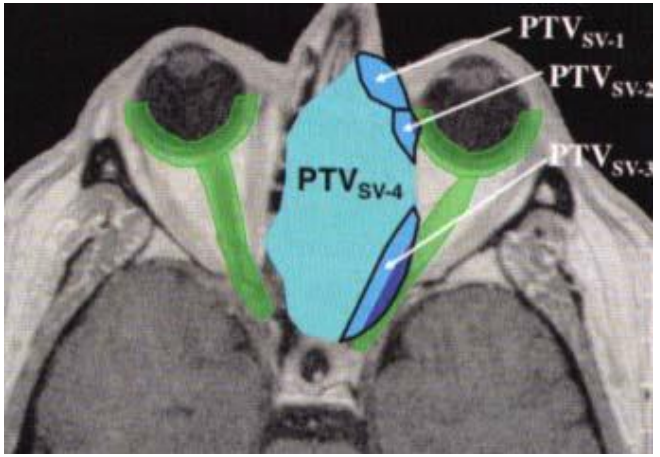
  4 mm, one s.d.

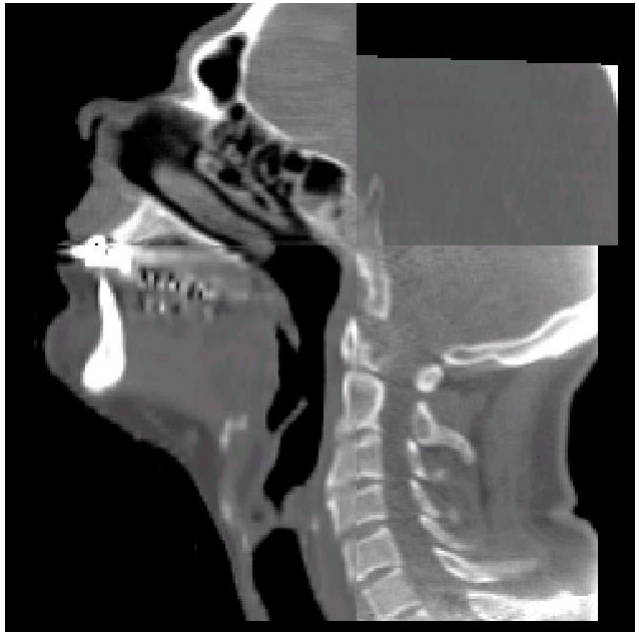
- relative to expected anatomy.

Geometrical accuracy

- However this approach no longer holds so clearly for newer technology/ techniques:

1. geometric uncertainties now affect dose distribution within the target volume for IMRT and not just at the volume edges or interfaces to organs at risk;
2. IGRT, adaptive techniques and motion management techniques have provided the facility to reduce the uncertainties significantly as compared to conventional approaches;
3. the desire to dose-escalate based on these techniques demands greater attention be paid to reducing margins on the boundary between PTV and Organs at Risk , but also taking care not to compromise on TCP.





Geometrical accuracy

- The figure for evidence based geometric precision requirements ranges from sub-mm for the most critical stereotactic cranial treatments to

  2-4 mm

- for other treatments, where the latter is dependent on the site and whether IGRT-based methods are being used.
- For geometric effects on dosimetry within target volumes for IMRT, the recommended tolerances may be considered to be those given for MLC performance in recommendations for IMRT system QA and verification, ie typically

  1 mm or less.

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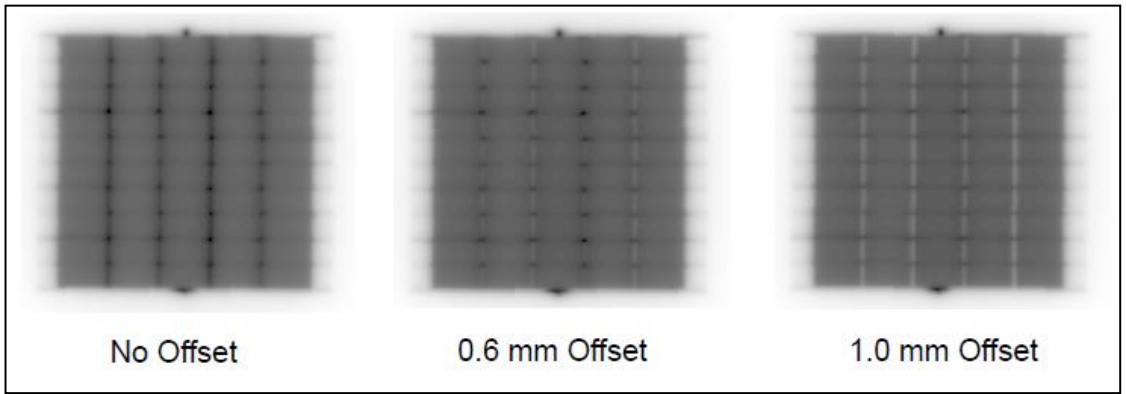
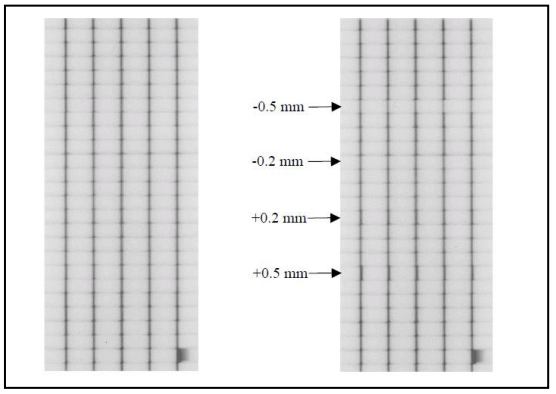
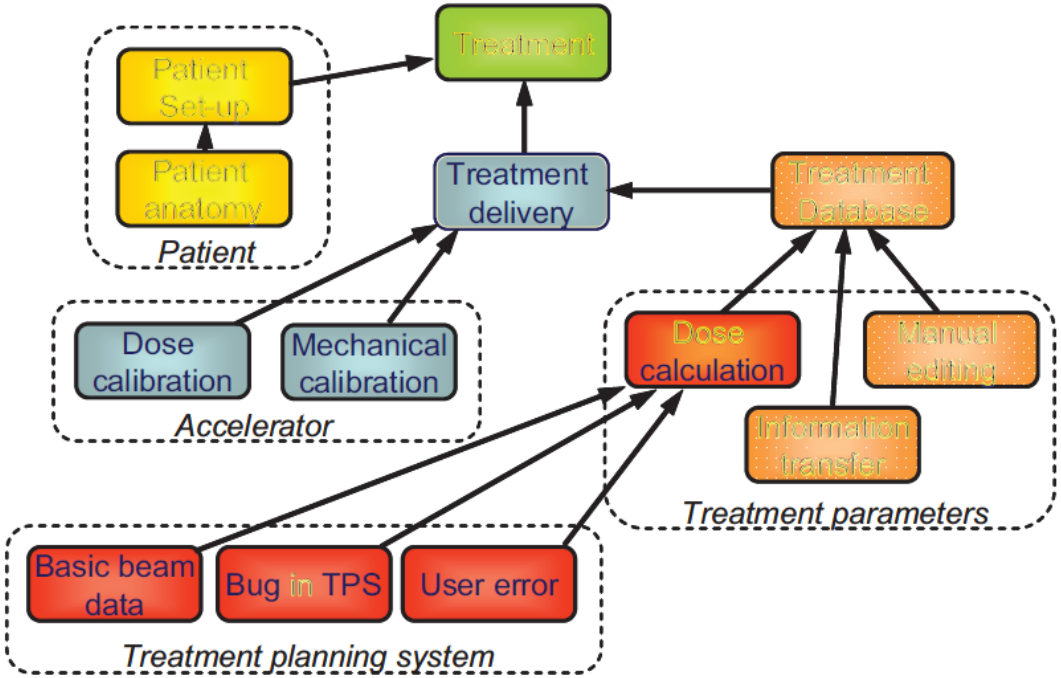




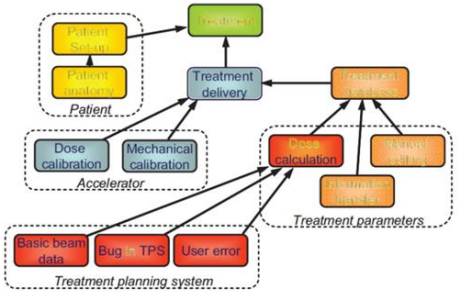
Required accuracy vs overall uncertainty



ESTRO Booklet 10

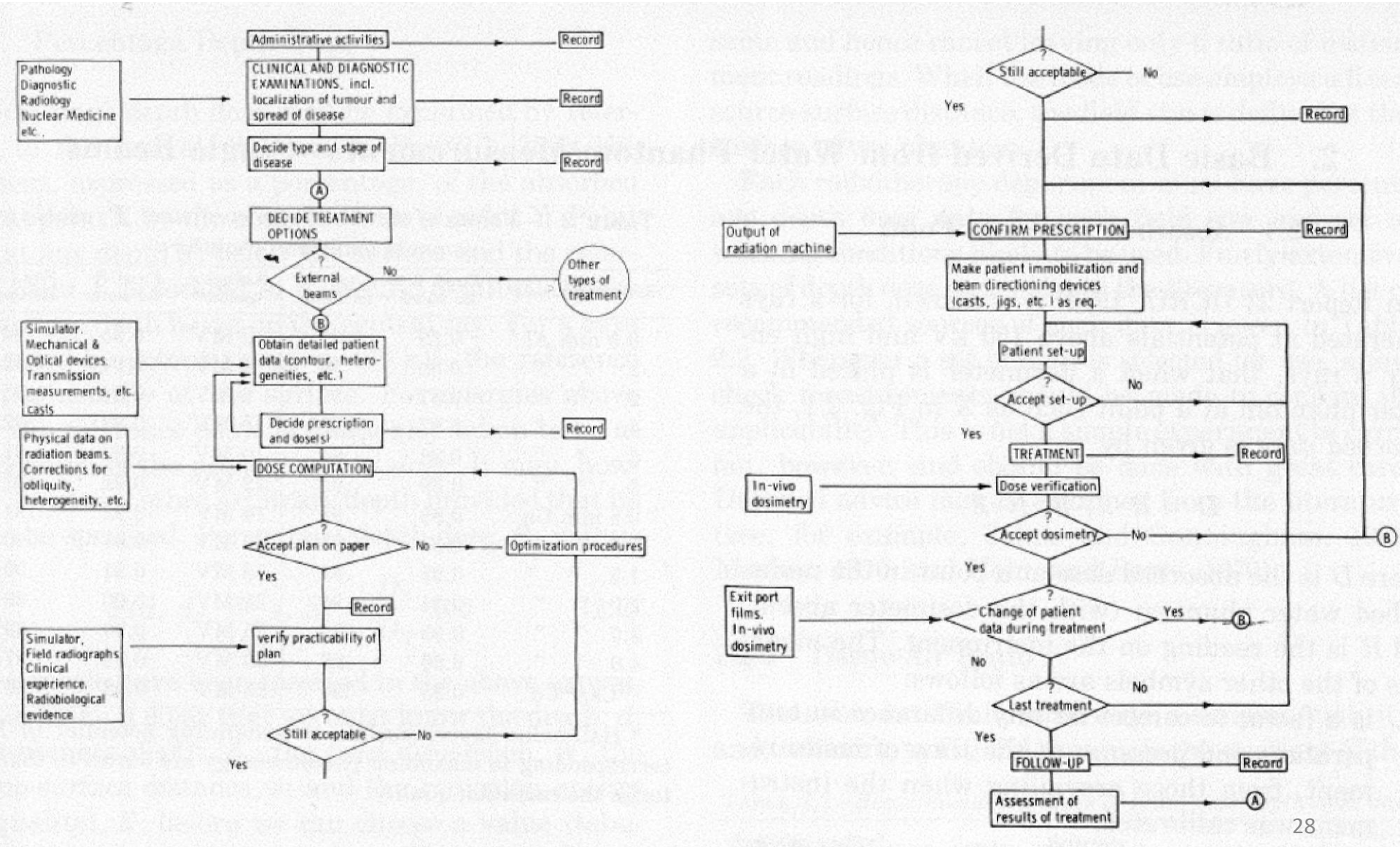
- The 3% figure is a limit on the overall uncertainty, i.e. the sum of both random and systematic uncertainties.
- Moreover, it is on the final dose delivered to the patient!
- To achieve this final value recommended, the accuracy requirement on each part of the whole RT process must be significantly less than the overall recommendation.

RT a complex specialty

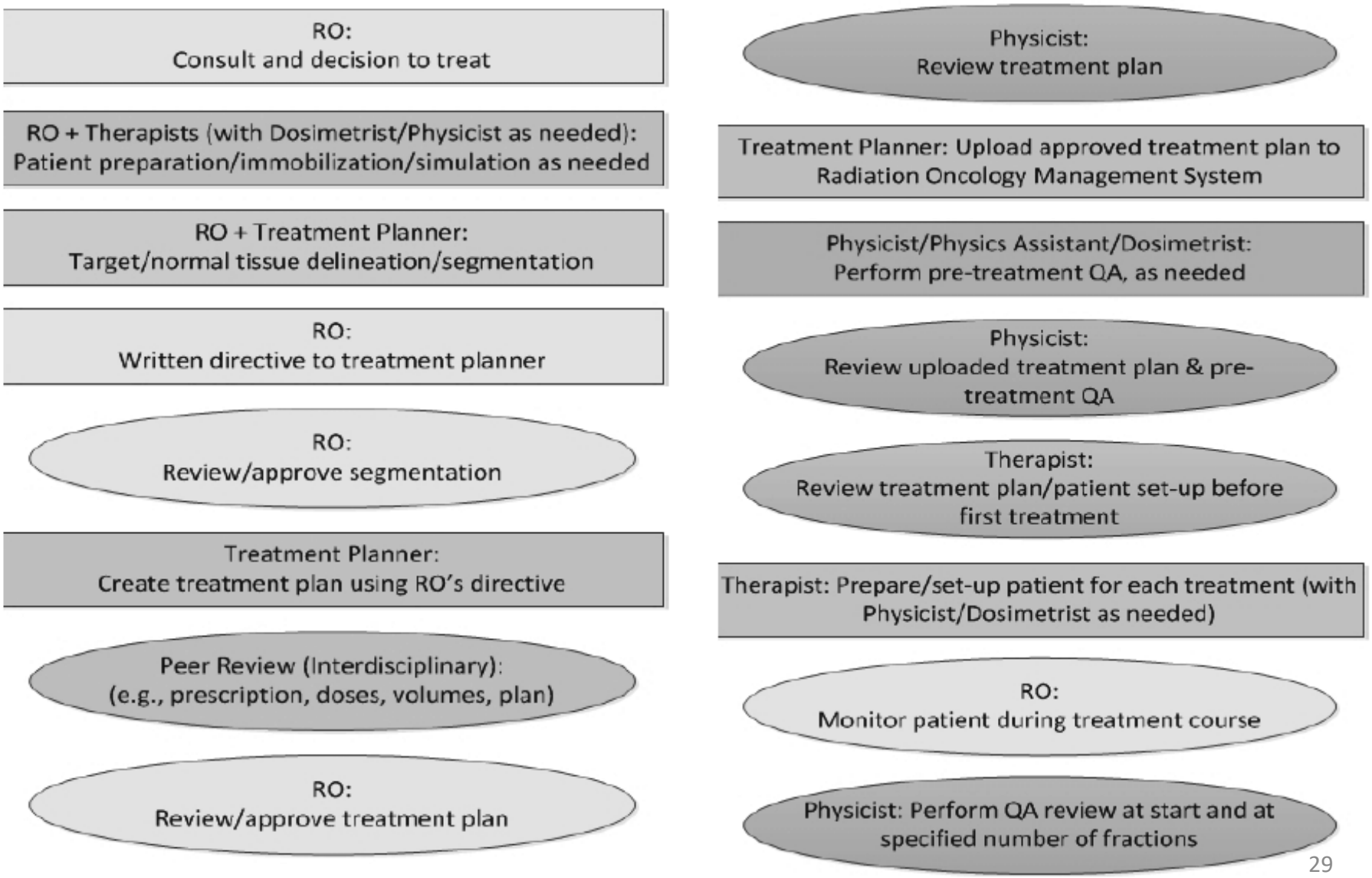


- Each step of the process of radiation treatment involves uncertainties which may compromise the potential advantages of the new technologies.
- Therefore, it is important not only to have a quantitative understanding of uncertainties, but also to consider the propagation of these uncertainties as part of the entire treatment optimization process.
- Ideally, we would all have a clear understanding of the levels of accuracy and uncertainties that exist in our facility for each treatment technique.
- Practically, this is a significant challenge!

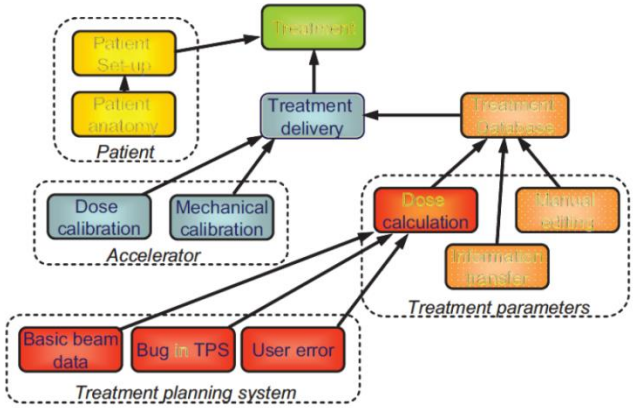
Radiotherapy Flow Chart – ICRU 24 (1976)



RT Flow (Van Dyk et al, 2011)



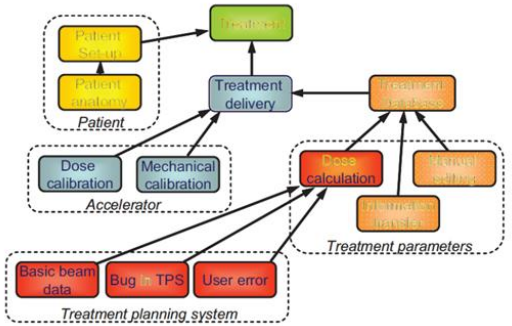
Sources of uncertainty in the RT process



- Two major categories:
  - ***human-related*** *(patient or personnel)* uncertainties
  - ***technology*** **or** ***dose related*** uncertainties.
- Human-related uncertainties can be analyzed by considering the radiation therapy process from a <u>patient's perspective</u> (i.e., patient's-eye view)
- Technology-related uncertainties can be addressed by considering a <u>machine perspective</u> (i.e., machine's-eye view), including dosimetry, commissioning, and quality control processes.

Van Dyk et al, 2011

Sources of uncertainty in the RT process



HUMAN-RELATED UNCERTAINTIES	TECHNOLOGY-RELATED UNCERTAINTIES
Target and organ-at-risk segmentation	Absolute dose determination
Patient repositioning	Machine calibration
Organ/tumour motion	Beam profiles
Interpretation of on-line image matching	Imaging quality/resolution
Deformation	Dose calculation
Couch position	Electron density
Organ full/empty	Beam energy
Weight change	Machine isocentricity
Contour change	Tissue inhomogeneity corrections
Source-to-surface distance	Beam modifiers
Immobilization devices	Leaf transit times
Accuracy of laser setup	Uncertainty in leaf position
Skin tattoo movement	Partial leaf transmission
Breathing motion	Optimization algorithm

Van Dyk et al, 2011

What accuracy is achievable in 3DCRT ?

- Various attempts have been made to analyze the radiotherapy process to obtain cumulative uncertainties on delivered dose .
- Each major step (eg. absorbed dose to a reference point in water, measurement of relative doses and set up of the treatment planning systems, treatment planning and treatment delivery to the patient) has been broken down into sub-steps and best estimates of uncertainty have been assigned at each level for each contributing factor.
- The overall estimated cumulative uncertainties obtained have ranged from 2.5- 8.5%, as one effective st.dev. (Van Dyk).
- A figure of

5%

- (sd) might be representative of these types of estimates, with smaller uncertainties for simpler treatments and larger for more complex.

Accuracy achievable in 3DCRT

7th International Conference on 3D Radiation Dosimetry (IC3DDose) IOP Publishing
Journal of Physics: Conference Series **444** (2013) 012006 doi:10.1088/1742-6596/444/1/012006

Accuracy required and achievable in radiotherapy dosimetry: have modern technology and techniques changed our views?

David Thwaites
Institute of Medical Physics, School of Physics, University of Sydney, Australia

- More recently, uncertainty estimates based on harder evidence from intercomparisons, audits and in vivo dosimetry have been made for external beam MV x-ray treatments, following UK procedures and dosimetry protocols.
- The overall cumulative uncertainties at the specification point are within, or close to, the recommended required values of

  3% (1 sd)

- i.e. the clinical evidence-based requirements can be met on the experimental evidence available.

Optimal uncertainties in 3DCRT dosimetry based on experimental determinations

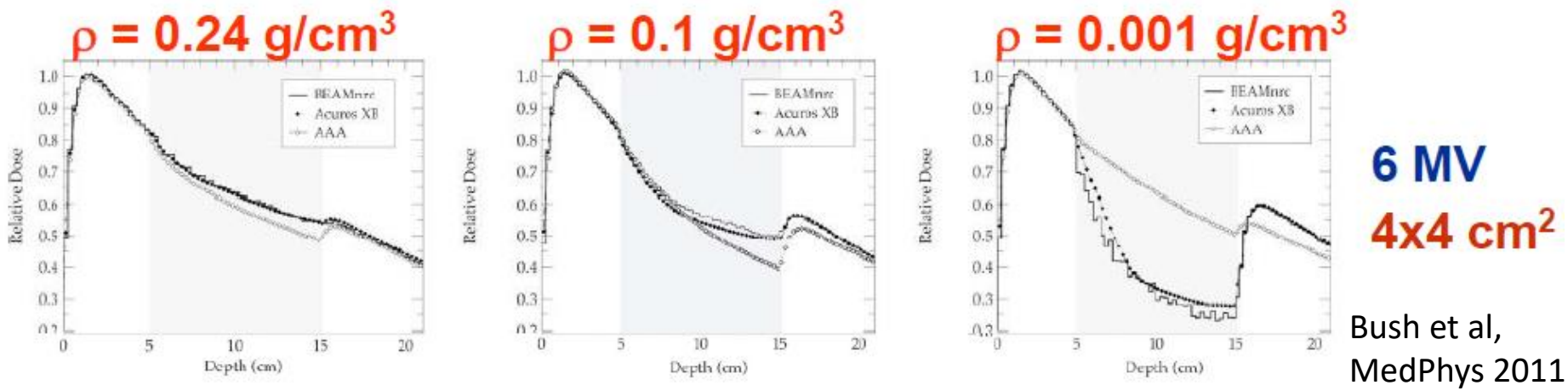
Source/step	*Single centre* (different beams/times)	*Multi-centre*
1. Dose at reference point in water phantom		
1.1. uncertainties quoted on calibration factors by the UK standards lab (NPL) are 0.7% (1 effective sd)	0.7%	0.7 %
1.2. variation in reference dose determination between beams and through time	0.5%	0.7-1%
1.3. combined	0.9%	1.0- 1.2%
2. Dose to phantoms representing various treatment sites (at a range of points within target volumes; given relative to reference dose)	0.8-1.8%	1.1-2.3%
3. Patient dose at specification point (based on estimates from *in vivo* dosimetry; for a wide range of treatment sites and techniques, given relative to reference dose)	1.5-3%	1.6 – 3.2 %
*+ where lung is significantly involved**	*(5%)**	*(5.1%)**
4. Estimated overall cumulative uncertainty on delivered patient dose at the specification point, including standards lab uncertainty	**1.7 – 3.1%**	**1.9 – 3.4%**
(+ where lung is significantly involved*	(5.1%)*	(5.2%)*

- see text for discussion of lung values

D.Twaithes, JoP 2013

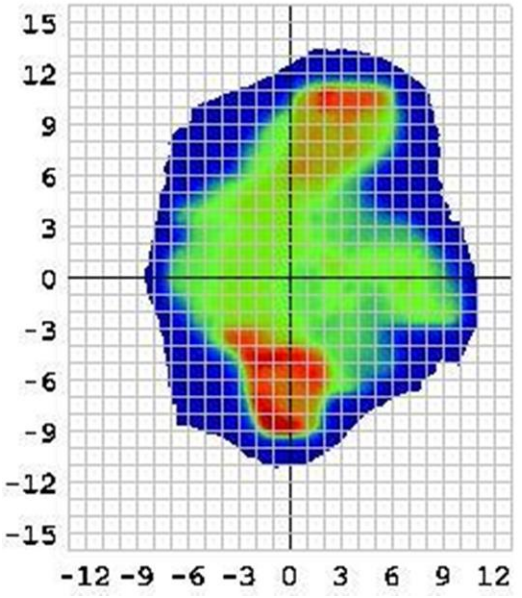
Accuracy achievable in 3DCRT

- The figures given are likely to be representative of fairly optimal situations in normal clinical practice.
- However overall uncertainties will be larger if any steps or sub-steps have larger uncertainties.
- The only exception to the general values are those where there is significant involvement of lung.
- Here the *in vivo* measurements indicate that uncertainties increase, due both to motion and to the ability of TPS's to cope with such situations.



Bush et al, MedPhys 2011

Accuracy achievable in IMRT



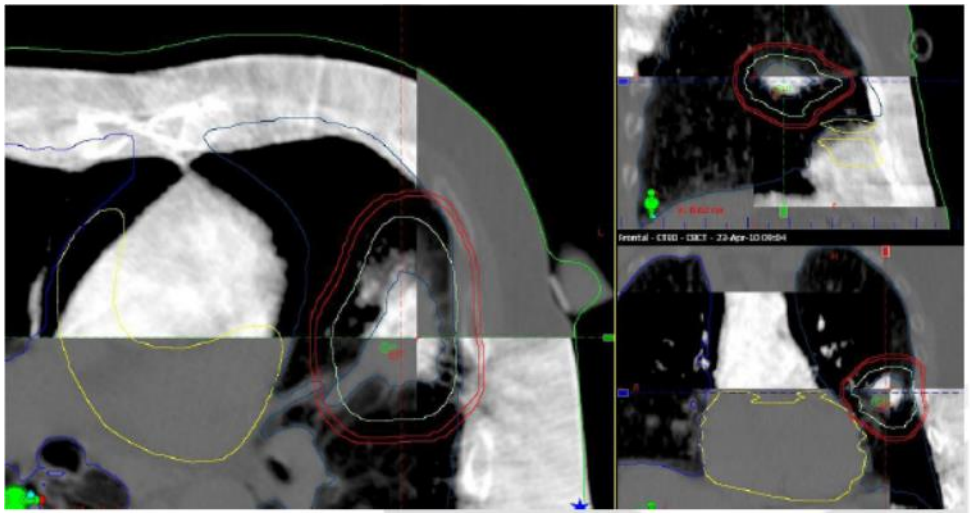
- Overall the results and uncertainties indicated from the European IMRT audits are in line with those for the multi-institution audits for 3DCRT, albeit showing a tendency to shift to rather higher sd.
- There is some evidence that the size of uncertainties achievable may shift upwards in more complex situations.
- The growing evidence from IMRT studies and the growing experience and expertise indicate that almost the same levels of uncertainties as in 3DCRT ought to be achievable for IMRT.
- Overall there is some evidence that they tend to increase, but that similar levels should be achievable.
- Thus it is concluded that those earlier estimates of achievable dosimetric accuracy are still applicable, despite the advances in technology and techniques.

Conclusions on Required Accuracy

- Tumour control and normal tissue complications make strong demands on accuracy and precision of the delivered treatment.

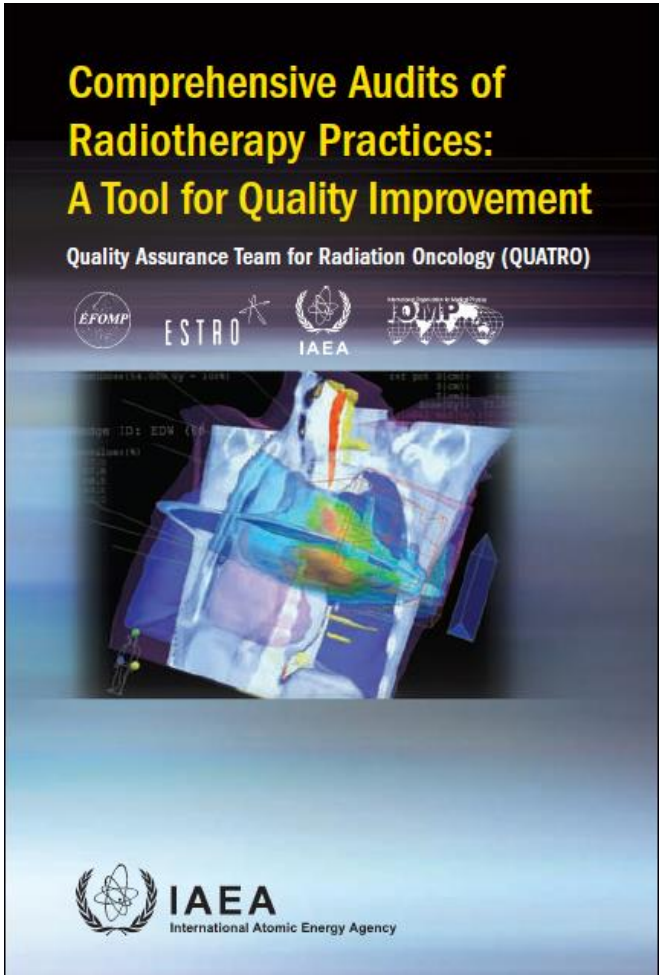
- Clinically-based accuracy requirements have not significantly changed since 1980's, although a greater emphasis on high-precision delivery methods, including Stereotactic RT, and on IMRT has focused attention on reducing geometric uncertainties.

- At the same time the growing use of high-dose-per-fraction hypofractionated treatments, with steeper effective dose-response curves, may imply stricter dose and geometry requirements in these situations.



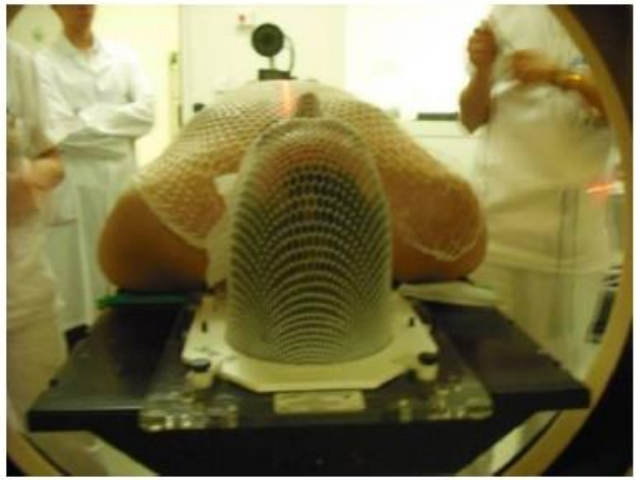
Conclusions: Need of a Quality System

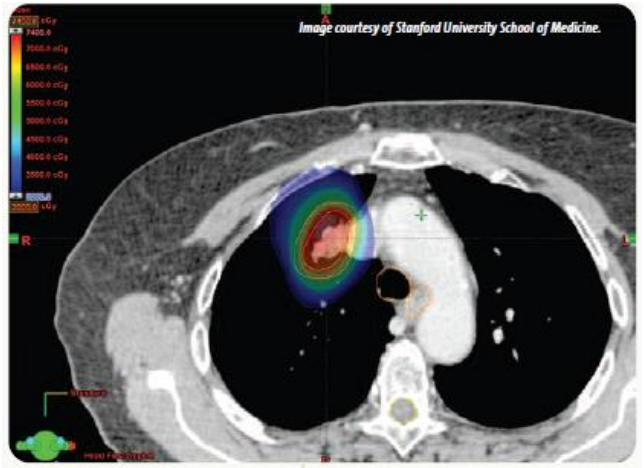
- The accuracies and uncertainties presented here should be achievable, but require optimal approaches throughout, including
  - comprehensive quality systems;
  - attention to detail;
  - safety, quality and accuracy cultures in RT departments;
  - continuing vigilance.
- Practical, accurate, precise dosimeters and dosimetry systems are required to keep pace with the evolving complexity of technology and RT methods, for IMRT, small fields, 4D applications, etc.



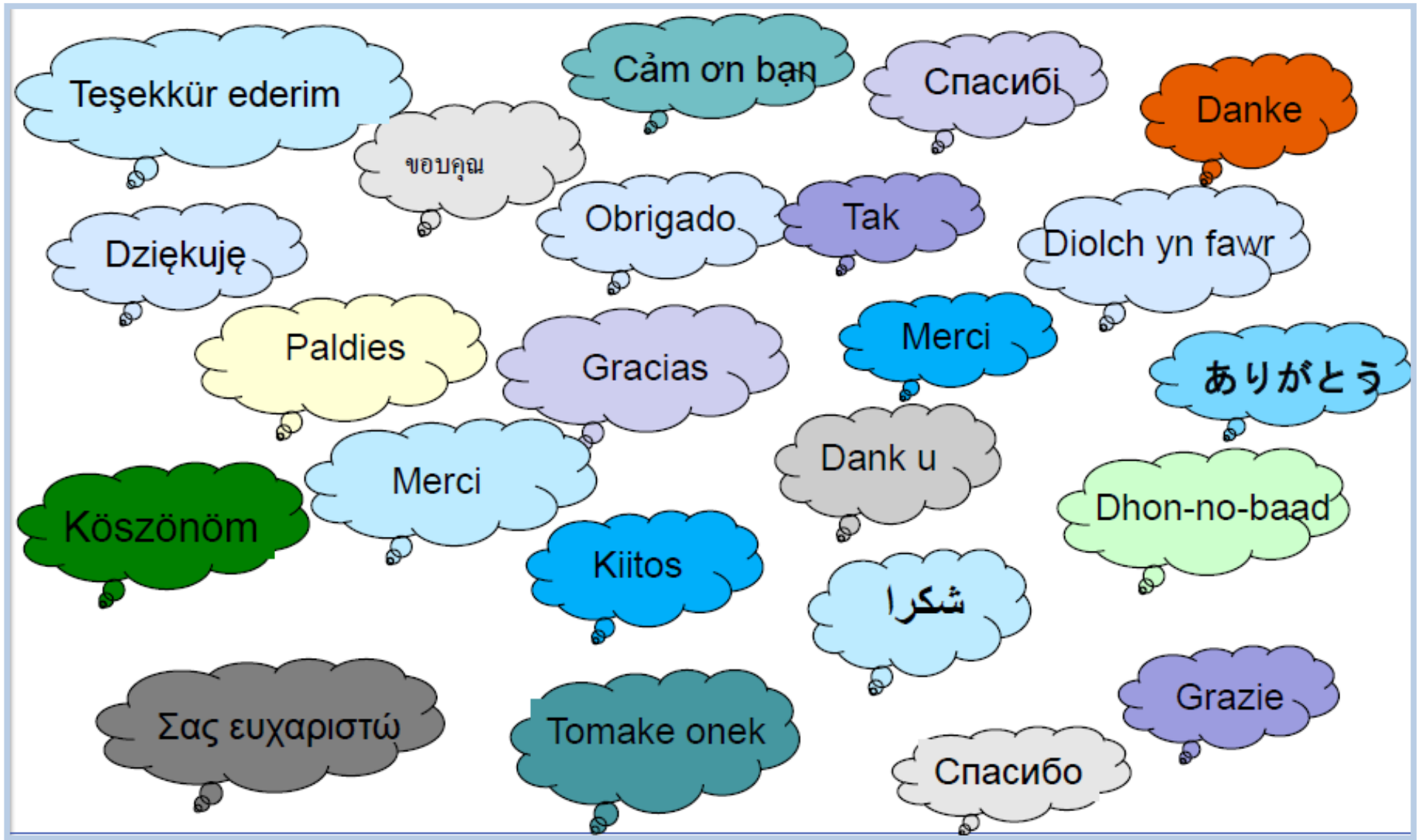
Conclusions: Accuracy & Advanced Techniques

- The more complex the treatments, the greater the potential for problems, so RT must be conducted within a consistent and sustainable quality framework.
- Maintaining and improving dosimetric and geometric accuracy is the key to gain improvements from advancing technology and techniques.
- Outcomes may well be better from high-quality simpler techniques than poorly controlled poor-accuracy advanced techniques.
- Newer techniques are to be implemented in a high quality, safety and accuracy environment to achieve both high precision and high accuracy for all patients.





Thank you for your attention!



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