

Definition of target volumes and organs at risk



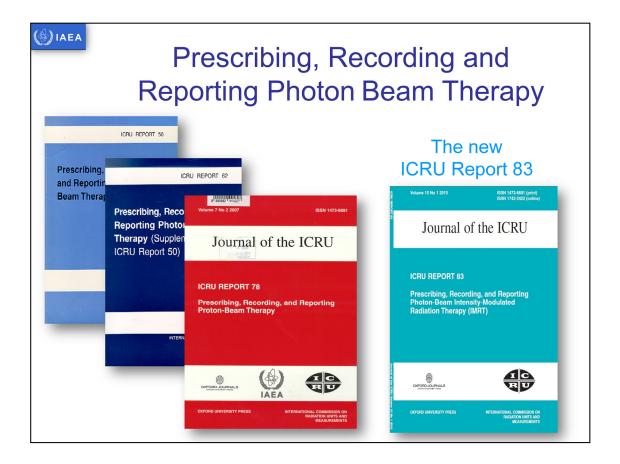
Aim

To introduce target volumes and organ at risk concepts as defined by ICRU

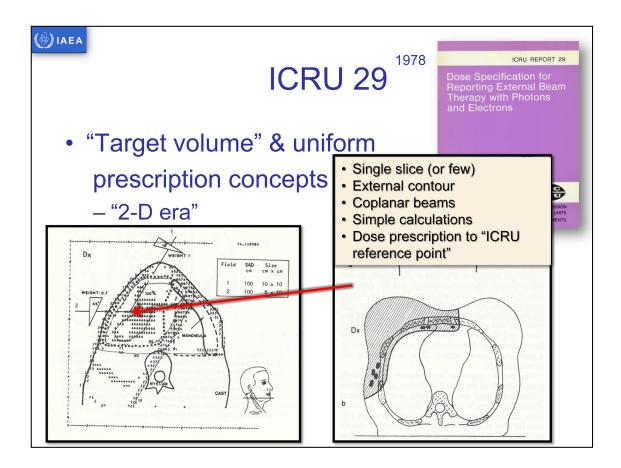


Specific Learning Objectives

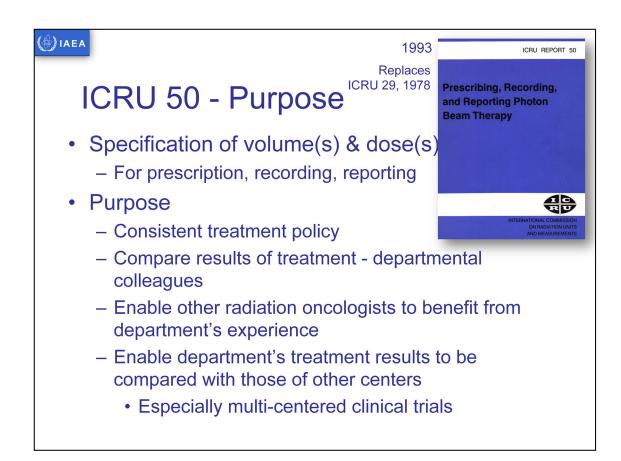
- Distinguish the various target volume definitions of ICRU Reports (GTV, CTV, and ITV)
- Determine how these elements are part of a global planning target volume (PTV) construction
- Describe the elements that influence the definitive shape and volume of the PTV and OAR



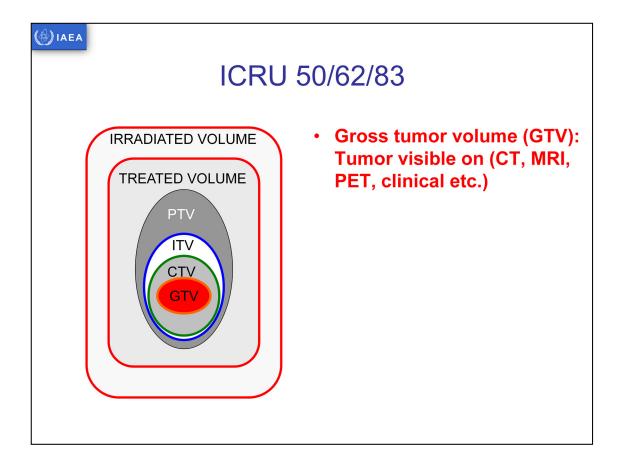
There has been several ICRU reports on photon beam prescription and reporting. The earliest report was ICRU Report 29.



ICRU 29 first described the concept of target volume and uniform dose prescription. This was in 2D with simple mainly manual planning.

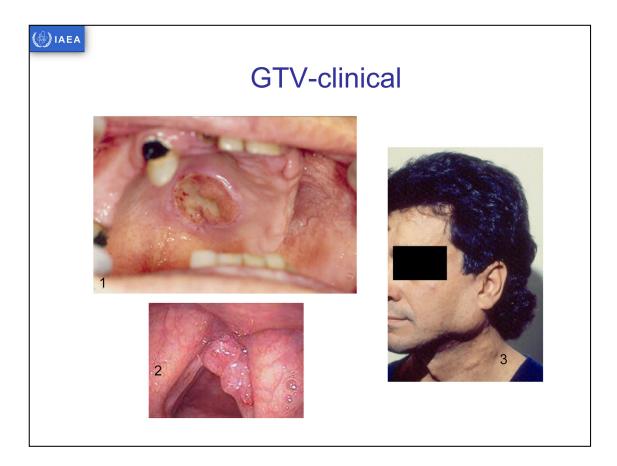


The ICRU Report 50 replaces report 29.



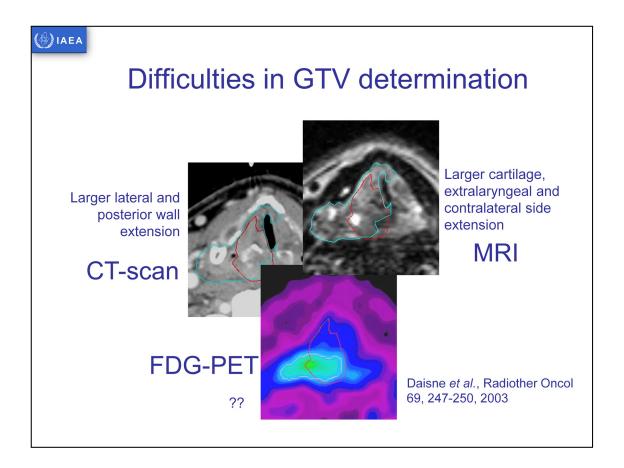
The most obvious volume is the Gross Tumour Volume (GTV), i.e. the volume that can be seen by eye (or palpation) either on the patient himself, or with the help of imaging (plain RX, CT scan, MRI, FDG-PET, etc). This volume follows *strictly* what is actually seen, without adding any margin for possible extension. This is important, as margins for possible microscopic extension constitute a different volume, the Clinical Target Volume or CTV (see further).

In postoperative radiotherapy (breast cancer, limb sarcoma, etc), the gross tumour volume has been removed by the surgeon. The GTV no longer exist and should therefore (and logically) not be contoured.

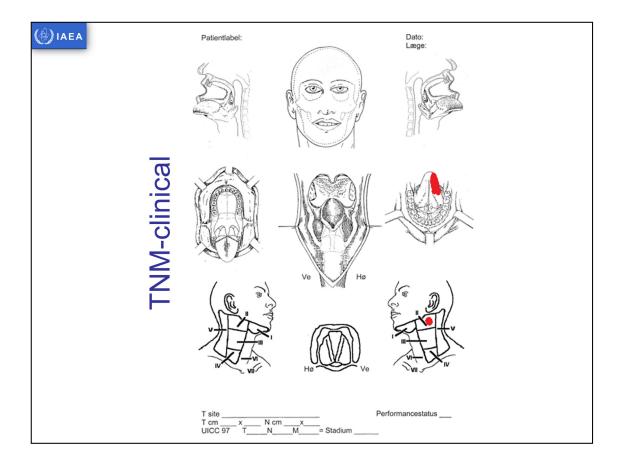


These are examples of Head and Neck cancer patients. On each picture, the tumour is clearly visible. Panel 1: tumour on the left side of the hard palate. Panel 2: tumour of the right vocal cord that invades the anterior commissura. Panel 3: enlarged lymph node (adenopathy) of the neck on the left side, zone II. The GTV is clearly identified by direct inspection, at least for its external (visible) part. The view is bi-dimensional. Infiltration in the depth can only be determined by palpation or additional imaging, in order to create a complete volumetric image of the tumour beyond its visible side.

Additional imaging would normally include a CT scan and if appropriate/feasible MRI, FDG-PET or other images (f.i. ultrasound, although of lesser reproducibility).

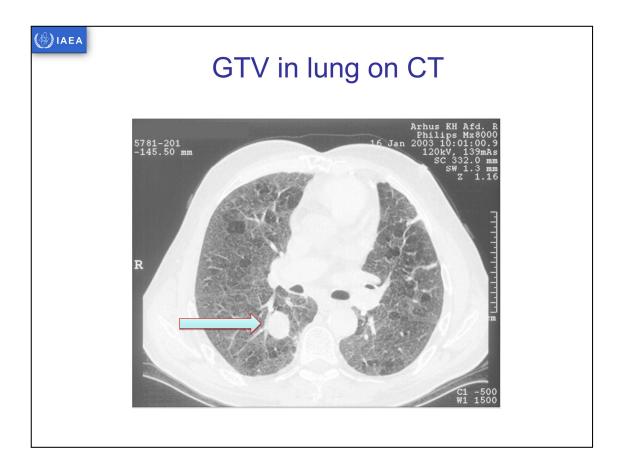


The determination of the GTV is not always straightforward. Different imaging modalities might show different tumour shape and/or volume. Limitations exist for several tumour sites that must be understood and remembered. Ideally, specific clinical studies are required for validating imaging modalities in their ability to precisely reproduce the exact shape and volume. In the example above, the same tumour (infiltrating larynx cancer) has been imaged with CT, MRI and FDG-PET. Surprisingly, the 3 modalities suggest 3 different volumes and even location of the tumour. Histological verification in this case has shown that FDG-PET volume was close to reality.

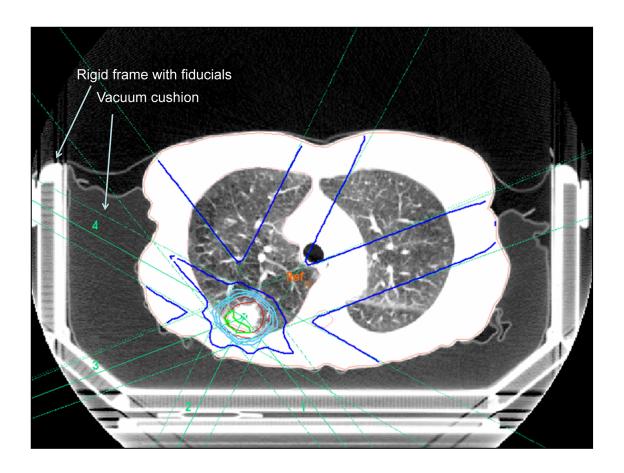


Once the visible tumour has been identified, it should be given a "stage" according to UICC guidelines (TNM classification system) or other accepted guidelines (FIGO, Ann Arbor...). TNM staging helps in 2 ways:

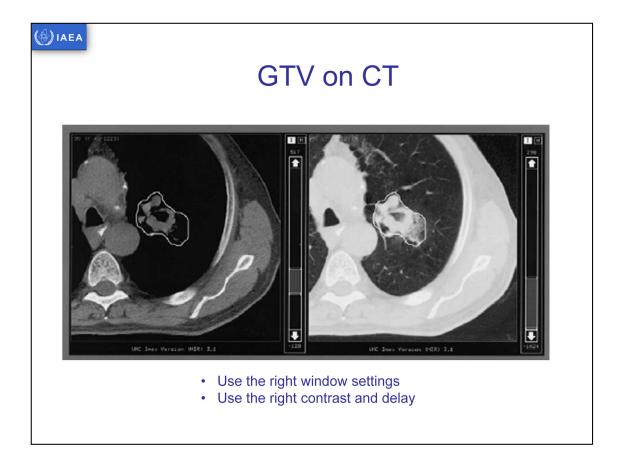
- 1.Most treatment guidelines have been developed for specific stages. In particular, dose level and fractionation depends on the tumour stage. A T1 larynx cancer does not require the same dose of radiation than a T3 of the hypo pharynx. Staging correctly a patient helps to select the appropriate treatment.
- 2.Consistency within the same practice and between different hospitals requires a common language for the description of tumours. It is a powerful tool for communication and benchmarking of results.



A right lung image of density higher than he background lung tissue, very suspect of cancer. The image alone is of course not sufficient, the complete clinical history of the patient is also important and helps to understand the CT image.

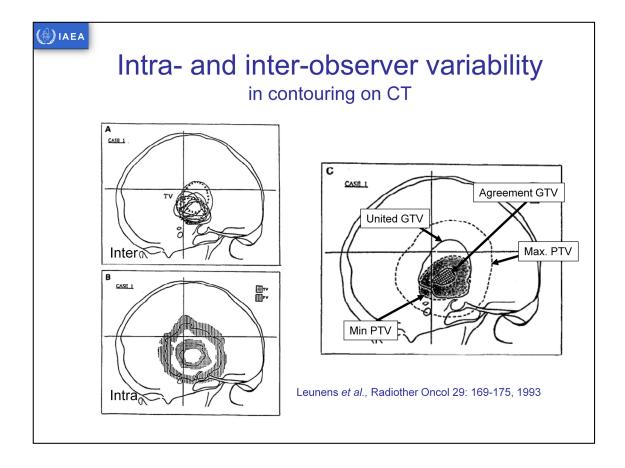


This is a CT section in the lung of a patient with a peripheral tumour, taken during simulation.



Because the lung is filled with air, its CT density is much lower than other soft tissues. The exact contours of the tumour can only be seen with the appropriate window setting. The use of infusion contrast medium can be discussed.

- 1.On the left panel, the window level is set on the mediastinum. There is clear contrast gradient between muscle, bone and fatty subcutaneous tissue. However, some peripheral part of the tumour is not visible because it is of lower density.
- 2.On the right panel, a window setting for lung parenchyma reveals the entire contour of the tumour. With this setting, details of the lung structure are seen, whereas the contrast gradient between bones, muscles and fatty tissue is greatly attenuated.



A correct identification of tumour boundaries requires a long training, even for its visible part (GTV). It is not uncommon that some lack of agreement exists between clinicians (inter observer variability) and even for the same clinician contouring the same tumour at different occasions (intra observer variability). In the example above, a series of confirmed oncologists (radiotherapy, surgeons and radiologists) were asked to contour a glioblastoma, back projected from the CT on a lateral planar schema. The cumulated zone of agreement was less than 10% of the entire volume. However, this is now an old publication (1993).

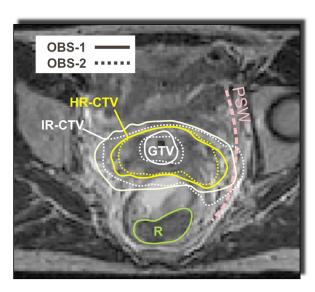
This lack of consistency has been observed in other tumour sites. It is caused by a series of factors:

- 1.Different background: surgeons, radiologists and radiation oncologists come with different backgrounds and tend to contour differently.
- 2. Capacity of a given imaging method to clearly indicate the macroscopic extension of a tumour (see slide 6).
- 3.Image quality plays also an important role (slice thickness, patient motion during acquisition, equipment characteristics...).
- 4. There is a long learning curve before a radiation oncologist becomes consistent with himself and with colleagues.

5.	Advanced imaging appeared first, then MD's learned how to read images (it could not have been the other way around!).



Inter-observer variation in GTV and CTV delineation of cervix cancer



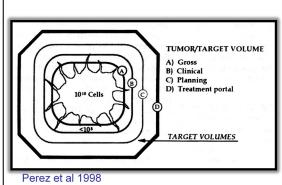
Dimopoulos et al., Radiother Oncol 89: 164-171, 2008

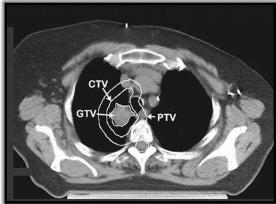
Another example of the difficulty to agree between two experienced radiation oncologists trying to identify the tumour in a women with cervix carcinoma. However, this is a recent exercise (2008) and the level of disagreement is far less than in the previous example. Still, it will take some more time and training before volumes will be defined unambiguously. This has become today a major part of the curriculum of residents. Also, consensus meetings organised at regional or national levels are of great help to homogenise target definition and delineation.

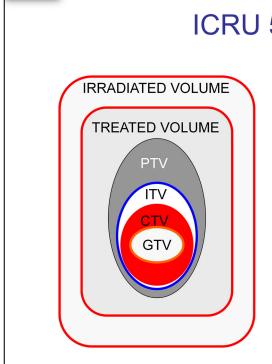


Clinical Target Volume (CTV)

- Contains GTV and/or subclinical microscopic malignant disease, which has to be eliminated.
 - This volume needs to be treated adequately to achieve cure or palliation







(🖃) IAEA

- ICRU 50/62/83
 - Gross tumor volume (GTV): Tumor visible
 - Clinical target volume (CTV): GTV and microscopic tumor

Beyond the GTV, there is often some further microscopic spread, too tiny to be visible (microscopic indeed), but that can be the source of treatment failure if not accounted for. It can be a direct spread around the tumour, or in draining lymphatic vessels and nodes. Knowledge on microscopic spread is often based on statistics of distant invasion, gathered through careful analysis of surgical series. Because microscopic spread is probabilistic, the choice of irradiating or not area of possible cancer spread is based on judgment of appropriateness. A volume likely to contain microscopic tumour deposits is called a Clinical Target Volume (CTV).

Under ICRU 50 CTV is defined as:

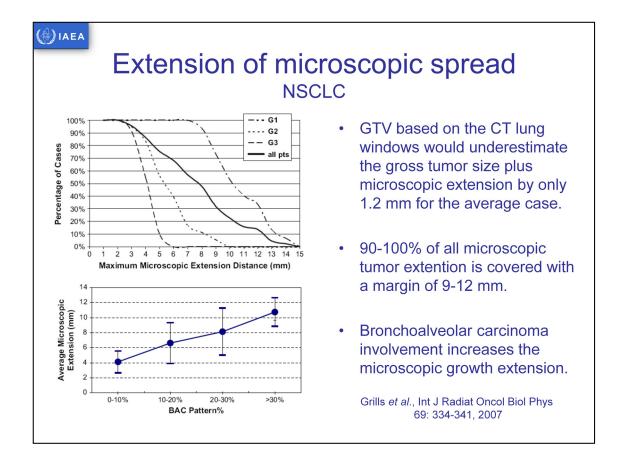
The CTV is a tissue volume that contains a GTV and/or subclinical microscopic malignant disease, which has to be eliminated. This volume has to be treated adequately in order to achive the aim of the therapy: cure or palliation

Opinions may vary between oncologists as to the need or not to irradiate such and such structure. Two examples are discussed further: microscopic spread around a visible lung tumour, and lymph node irradiation in NO head and neck cancer patients.

Other examples exist, like in prostate cancer, where knowledge about the clinical stage (T), the Gleason score, the PSA blood level and age help to predict the probability of capsular invasion beyond the prostate, of seminal vesicle invasion or distant lymph node spread (see f.i. www.prostatecalculator.org). Data to support these predictions have been collected from surgical series.

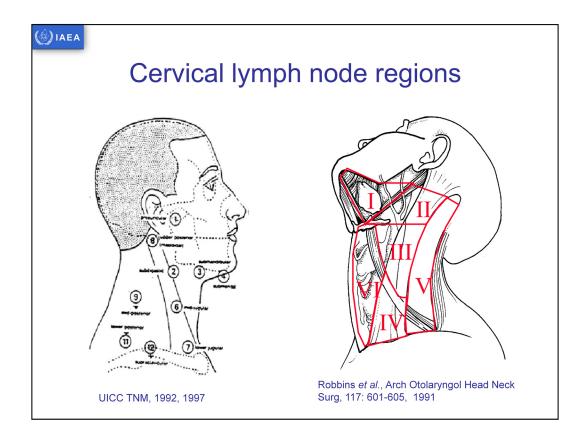
As surgical data become more and more available, uncertainties regarding the CTV is

decreasing steadily. Several consensus papers have been published that help the individual radiation oncologist to make choices based on evidence rather than opinion (head and neck cancer, cervix cancer, rectum cancer, prostate cancer...).

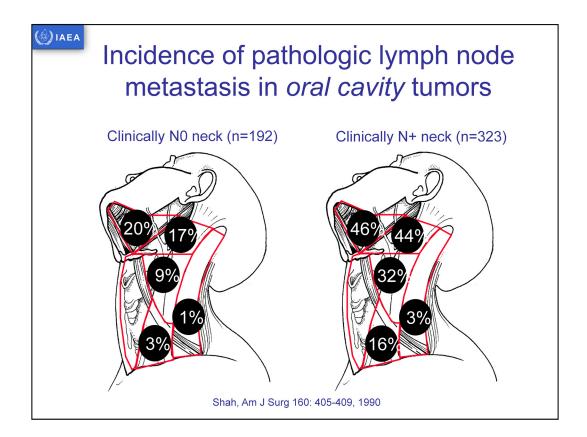


This paper discusses the margin of microscopic spread around a non-small cell lung cancer, according to the tumour grade (well, moderately, poorly differentiated) from a series of patients treated by surgery. It shows that the margin is variable among patients. To avoid the risk of leaving microscopic deposits outside the irradiated region, it is necessary to expand the GTV by a few millimeters. By doing so, some patients are treated appropriately, and some are over-treated. In the absence of better imaging capacity, it is advised to apply the same margin to all patients. Thus the CTV is the GTV expanded by an isotropic margin of 9 mm of one wishes to treat at least 90% of patients correctly, or by 12 mm if one wishes to cover 100% of patients.

Broncho-alveolar cancer has a more distant spread, but it is not an usual indication for radiotherapy.



Lymph node regions of the neck have been classified some 20 years ago by distinct zones that are more or less at risk of invasion, depending on the siteof the primary. Originally, this classification has been developed by surgeons for surgeons.



Further to the classification of lymphatic zones in the neck, the frequency of nodal invasion, zone per zone, has been derived from surgical series, stratified by the site of the primary. The example above demonstrates the frequency of nodal invasion for an oral cavity primary, in clinically N0 and clinically N+ patients. The series is large, including 515 patients treated at the Memorial Sloan Kettering Cancer Centre in New York city.

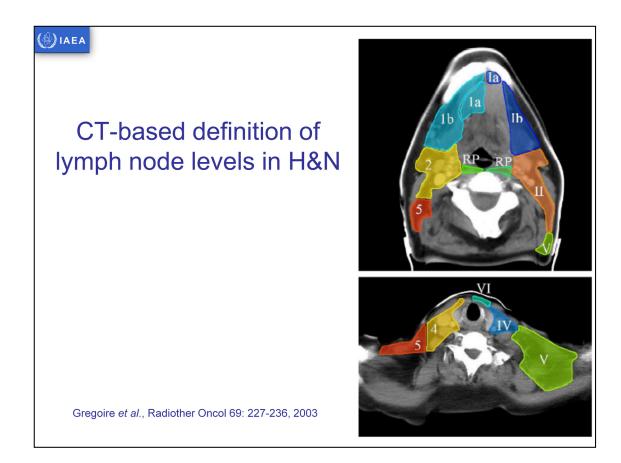
Clinically NO patients can be found to have invaded nodes that are neither palpable nor visible on CT or MR imaging. The invaded nodes are most often those at the first level next to the oral cavity, i.e. zone I and II.

Clinically N+ patients have a much larger frequency of invaded nodes, although some of the nodes might be infectious rather than tumoural, even at distance from the primary.

In the former case, one might discuss the need for nodal irradiation at all (consensus meetings have been organised, see next slide). In the latter case, it is probably wise to always irradiate the lymphatic regions (except zone V), even if it means overtreatment for a proportion of patients.

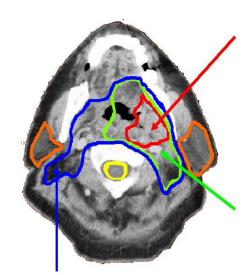
This latter remark is fundamental. Because the CTV is probabilistic, the decision to treat implies overtreatment for a fraction of patients. Conversely, refraining from irradiating results in under treatment for another fraction. Which one is better, which one is worse is a matter of debate, with the first principle of medicine in mind: "Thou shall not harm". Although the principle itself is not debatable, both under and overtreatment can be considered as harmful.

Sound judgment therefore needs to be applied, and consensus must be reached so that as much homogeneity is obtained as is possible for a given cancer at a given stage.



The figures on the previous slides are of little help for the radiation oncologist that has to delineate lymphatic CTV on a series of CT slices. Therefore, a detailed atlas has been produced by a group of radiation oncologist, anatomist, radiologist and surgeon to translate on cross-sectional anatomical images the zones defines earlier by surgeons. Unambiguous definitions have been offered regarding the exact boundaries of the 6 zones.





GTV: Macroscopic (gross) tumor in T and N position

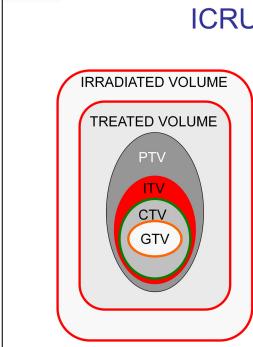
CTV-T: Region with known macroscopic tumor, R1-R2 areas, or regions with extranodal extension

CTV-E high risk: Regions close to GTV/CTV-T determined from experience, e.g. first echelon and R0-operated tumor area

CTV-E standard risk: GTV+1 cm minimum and regions with risk of subclinical spread, e.g.elective nodal areas.

An example of GTV and CTV contours in head and neck cancer from the Danish Head And Neck Cancer (DAHACA) collaborative group. An agreement on CTV definitions was necessary for the multicentric group to carry clinical trials in which a perfect homogeneity existed regarding volume definitions.

In this way, an important source of statistical noise was removed, that had possibly blurred the difference between the various treatments that were tested.



(🖃) IAEA

ICRU 50/62/83

- Gross tumor volume (GTV): Tumor visible
- Clinical target volume (CTV): GTV and microscopic tumor
- Internal tumor volume (ITV): CTV including internal movement

In radiotherapy, patients breath freely during irradiation (with very few exceptions today). GTV's and CTV' belonging to mobile organs will thus move during exposure following the respiratory cycle. The frequency of these movements is on average16 cycles/min. Other organs are mobile on a slower time scale, like the small bowel in which the lower jejunum and ileum loops roll continuously and change position. The filling of the rectum or of the urinary bladder varies during the day, and create both a continuous change in volume and shape. The larynx structure moves vertically by a few centimetre at each deglutition. There are numerous examples.

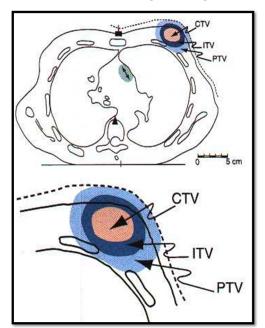
Because imaging for planning is usually done in a few seconds (multislice CT), these movements are not accounted for when delineating the GTV, CTV and organs at risk (OAR) volumes. It is therefore necessary to add a margin around these structures that accounts for the variation of position, volume and/or shape during a multifraction treatment.

This new volume is called the ITV, obtained by adding a margin to the CTV. In the current state of radiotherapy (2010), this concept is still a matter of research and there is no unambiguous answer to the problem. Possible solutions are discussed in a different chapter/lecture.

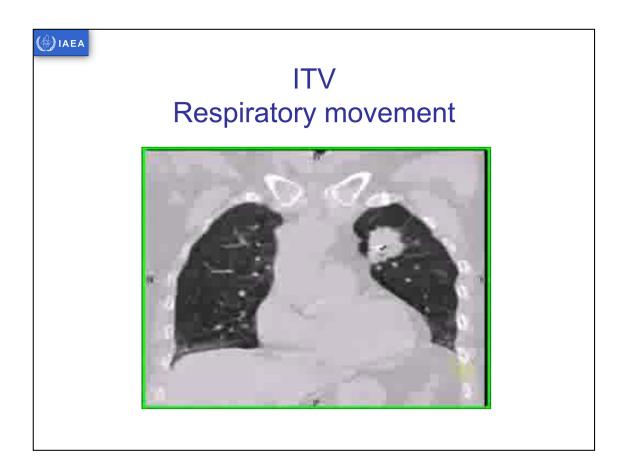


Internal Target Volume (ITV)

- ITV = CTV + IM
- Geometric
 - ITV accounts for motion of CTV in the patient
 - Does not account for setup uncertainties



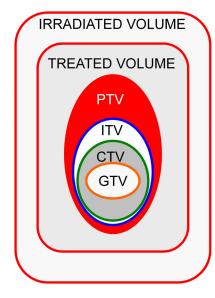
ITV is defined by ICRU 62. ITV accounts for motion of CTV in the patient but does not account for setup uncertainties



Images created with a 4D CT that demonstrate the variation in position of a lung tumour during the respiratory cycle. If the patient is irradiated while breathing freely, the volume to treat must be slightly larger than the tumour (GTV + CTV) itself in order to cover all its successive positions. More of the healthy lung will then be exposed, which is the cost to pay to cover the mobile tumour at all time. Alternatively, ways can be developed to fix the tumour for a few second (10-20 sec) during irradiation (breath hold), or to allow the beam only at a specific phase of the respiratory cycle (gating), or to have the beam following the tumour during its movements (tracking).



ICRU 50/62/83



- Gross tumor volume (GTV): Tumor visible
- Clinical target volume (CTV): GTV and microscopic tumor
- Internal tumor volume (ITV): CTV including internal movement
- Planning tumor volume (PTV):
 ITV including geometric uncertainties in daily set-up and machine tolerances

When all the volumes have been defined, appropriate beam sizes can be selected that cover adequately the tumour (GTV), the microscopic spread (CTV) and the dynamic volume that accounts for CTV movements (ITV).

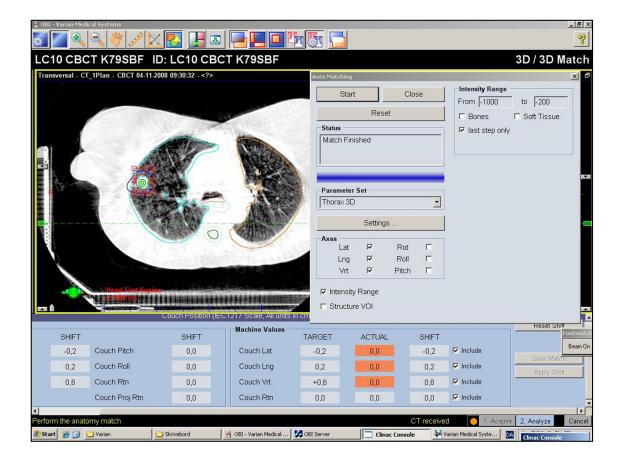
However, there is an additional source of uncertainty: the reproducibility of the patient positioning, and the mechanical accuracy of the equipment = set-up errors

- 1.Patient positioning: day after day after day, the patient is put back in its treatment position by the RTT's, with as much care as possible. Still, despite RTT's skills, there might be small daily variations in the patient set-up. The magnitude of the variation will vary with the RTT's skill, in the first place, and also with the type of fixation and accessories that are used in a given department, for a given tumour site. To avoid the danger that mispositioning by a few mm will carry the CTV-ITV out of the beam, an additional volume is defined, the Planning Target Volume (PTV), by adding the appropriate margin to the CTV-ITV.
- 2.Modern equipment have a good mechanical stability. Typically, linacs have an isocentre contained in a sphere of 1-2 mm diameter when rotating 360°. This adds to the uncertainty of daily positioning and must be accounted for in the PTV (as any other equipment-related uncertainties).



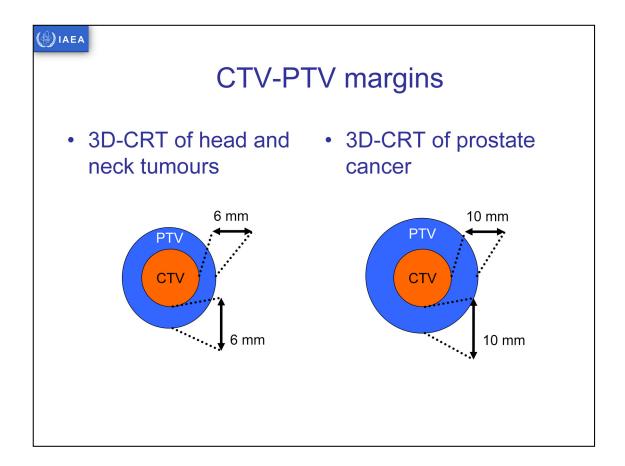
Modern radiotherapy equipment comes with some sort of portal imaging device. Newer machines have CT-scan like capability called cone beam CT.

Using these images prior to treatment, correction to errors in positioning can be made prior to treatment.



This figure shows a cross-section of the chest in a patient treated for lung cancer, acquired with a cone-beam CT (an advanced imaging equipment embarked on the linac). It also shows the contours of the OAR and the CTV of the original planning image in overlay.

On the lower panel, the software gives the deviations in all direction of space between the two images (see lung contours). A correction of the treatment couch position according to these parameters will bring the patient closer to the initial position. By this mean, the PTV around the tumour and the amount of irradiated healthy lung can be significantly reduced.



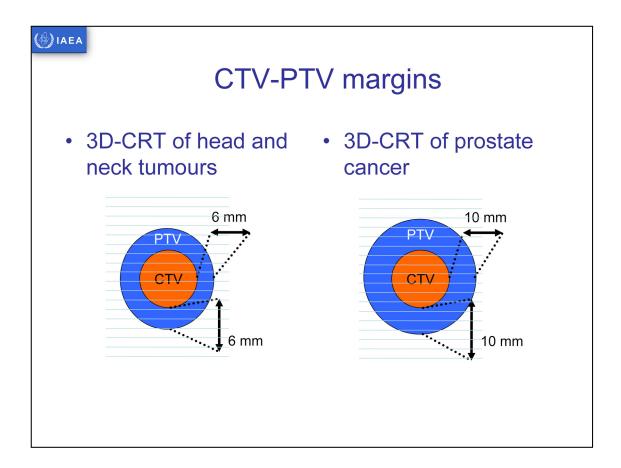
Patients treated for head and neck cancer are commonly immobilised with a thermoplastic mask (or other similar devices), because the head and the neck have considerable degrees of movement liberty. The mask greatly restricts the day-to-day variation of position. Therefore, the margin to be added to the CTV can be limited to a few millimetre. In a detailed study by Gilbeau et al, it was found that a PTV created by an expansion of the CTV by 6 mm would cover 95% of the variation in patient setup. The margin was based on a study of over 915 portal images in about 100 patients. Whether this finding is relevant to other radiotherapy department is debatable, as the level of skill of RTT's, the setup accuracy and reproducibility, the type of fixation vary from place to place. In an ideal world, the PTV should be defined per department, and revised each time modifications are made to the setup technique.

[Gilbeau et al, Radiother Oncol, 2001].

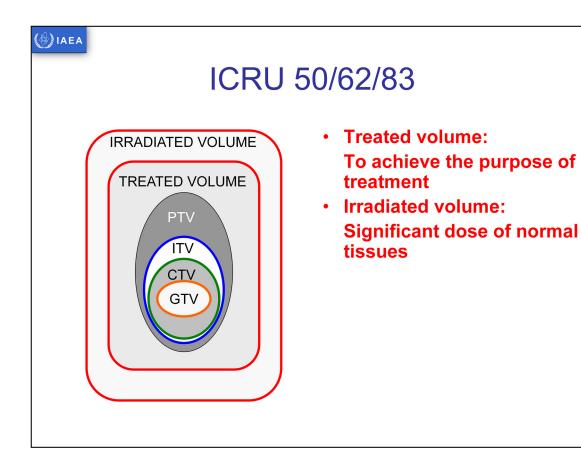
Patients treated for prostate cancer also need that a PTV be defined. However, this part of the body moves differently than the head and neck region (usually less). Nevertheless, the prostate itself has a position that is influenced by the level of bladder and rectal filling. Respiratory movements are only tiny in the pelvis, but the filling level of both organs has a major influence. Logically, the PTV must be larger than in the head and neck region. In a similar study, Van Herck et al advised a PTV of 1 cm (at least) around the prostate to accommodate for the prostate movements in the pelvis and the body setup variation.

[Van Herck et al, Radiother Oncol, 1999]

These two examples are by no means recommendations for PTV size in H&N or prostate cancer since, again, such volume depends on local practice and accessories.



When entering the 3D world, it is important to realise that all definitions are volumetric. Therefore, the CTV does not only expand radially, in the plane of the cross-section containing the GTV, but also axially, cranial and caudal from the GTV. The same is true for the PTV.



An homogeneous irradiation of the PTV is obtained by the appropriate sizing and shaping of the collimator for each radiation beam. It is not uncommon that the prescribed dose to the PTV is actually delivered to a larger volume, especially when the PTV is not a simple geometric figure (concave, asymmetrical, etc). The region receiving the prescribed dose is called the Treatment Volume. In an ideal situation, it would perfectly fit with the PTV, but more often than not it doesn't.

Therefore, to give a representative account of a treatment, a clear description of the Treatment Volume is required.

Regions of lower doses, around the Treatment Volume, still receive a significant amount of radiation energy. What is significant varies from tissue to tissue but, again, a clear account of all parts irradiated significantly is necessary for a clear reporting. This Irradiated Volume.

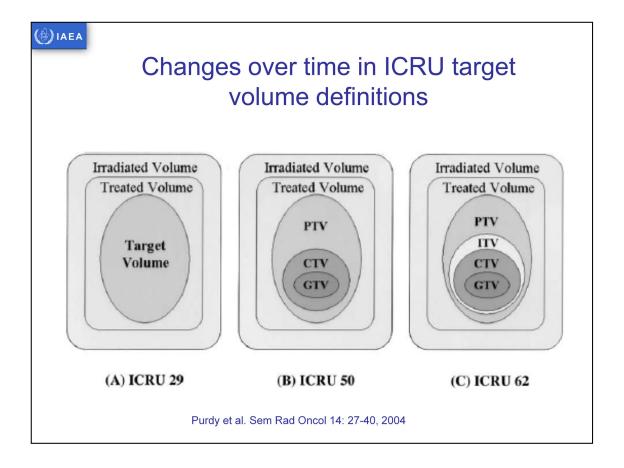


Conformity index

- Defined as: V_{90%}/PTV,
- Ideally = 1.00
- In SRT
 - Should be less than 2.00
 - Preferable between 1.00 and 1.50



The Conformity Index (CI) is a way to report on the difference between the PTV and the Treated Volume. It is usually expressed as a ratio of volumes. Ideally, the CI is 1.00 meaning that all parts of the PTV and no part outside the PTV receive the nominal dose. It requires specific software to be able to calculate this ratio. Some treatment planning systems (TPS) offer this function, but not all. If the CI is too high, then the treatment plan might need further optimisation for beam size, shape and/or weight.



ICRU 29 defined: Target volume, Treated Volume (TV) and Irradiated Volume (IR)

Treated Volume is the volume enclosed by an isodose surface, selected and specified by the radiation oncologist as being appropriate to achive the purpose of treatment (e.g., tumor eradication, palliation). This volume should encompass the PTV.

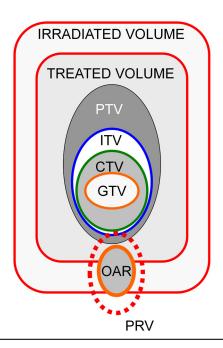
Irradiated Volume is that tissue volume which receives a dose that is considered significant in relation to normal tissue tolerance. This will differ between different tissues eg lung will have lower tolerance to radiation compared to muscle.

ICRU 50 introduced GTV, CTV and PTV which we have gone through

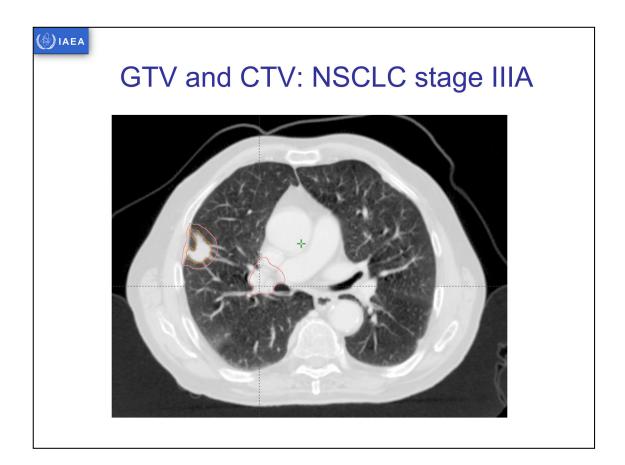
ICRU 62 introduced ITV to account for organ movements.



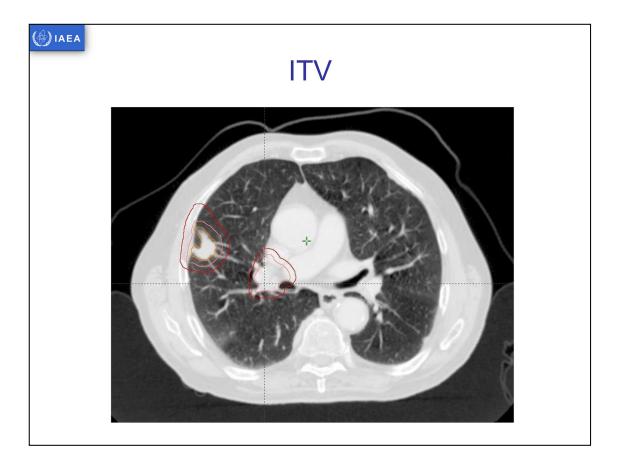
ICRU 50/62/83



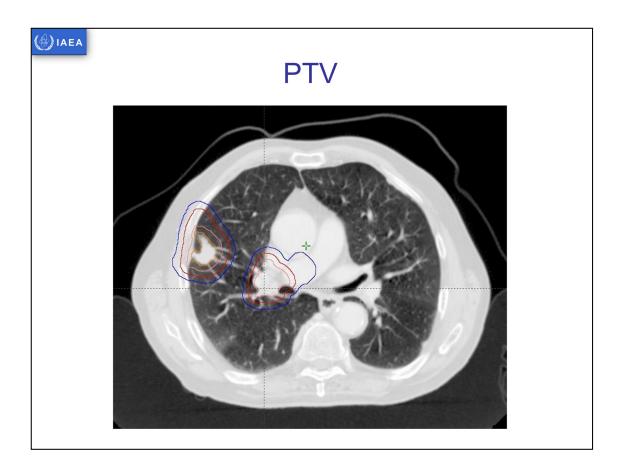
- Organ at risk (OAR): Organ whose radiation sensitivity is such that the dose received by the treatment may be significant compared to its tolerance.
- OARs may significantly influence treatment planning and/or prescribed dose.
- PRV: Includes margin around the OAR to compensate for changes in shape and internal motion and for setup variation.



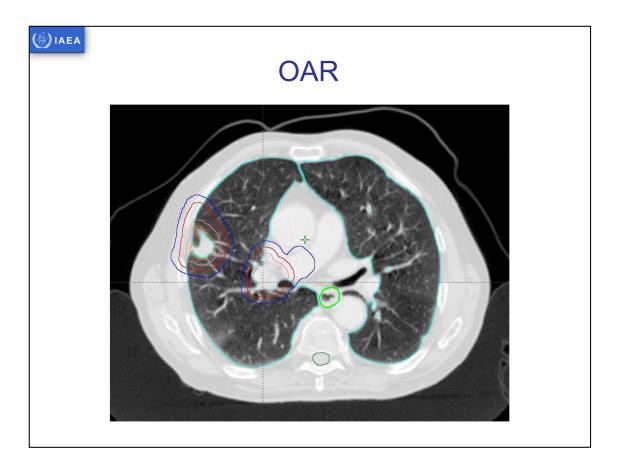
Figures 28 to 33 illustrate the construction of the successive volumes in a lung cancer patient. On this slide, the GTV is delineated around the tumour (peripheral, close to the chest wall), already with the CTV. This has two parts: the microscopic extension around the macroscopically visible tumour and the next lymph node station that is likely to be invaded.



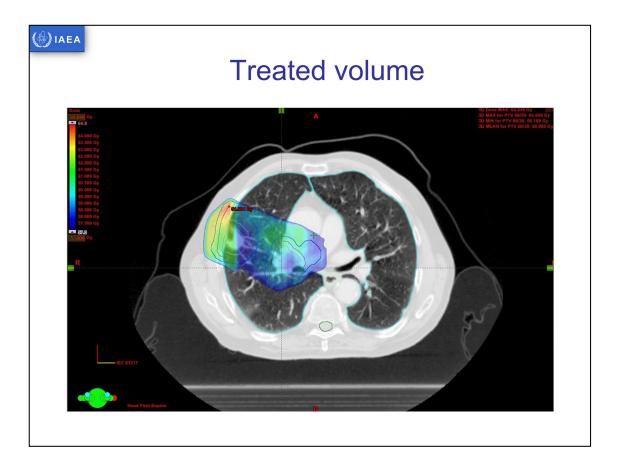
An ITV is added to account for the CTV movement during free respiration.



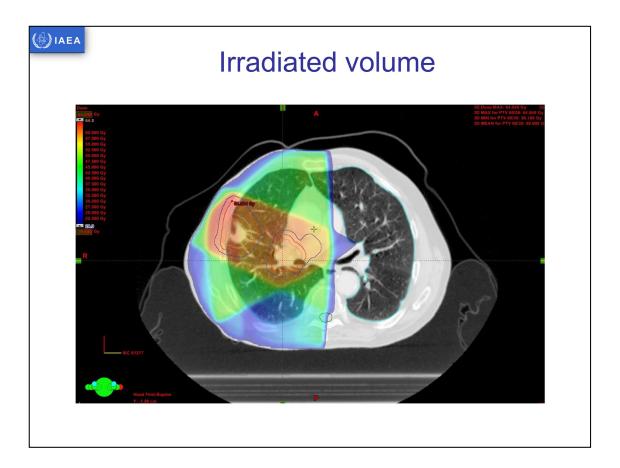
Further, a PTV is delineated to account for daily setup variation.



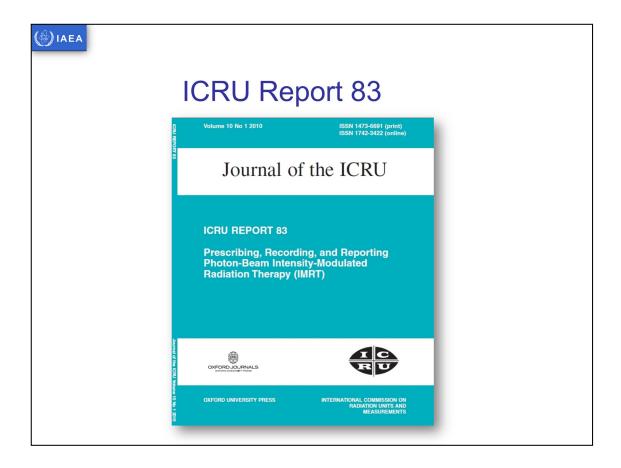
Lastly, the Organs At Risk (OARs) are also delineated. On this cross-section, the lungs, spinal cord and the oesophagus



The slide shows the treated volume (TV) for this patient. Note that is should encompass the \mbox{PTV}



The Irradiated volume is much larger especially in the context of lung and spinal cord tolerance.



ICRU 83 is a new report which updates some dose reporting concepts.



ICRU 83- Purpose

- Irradiation techniques have advanced
 - 3-D CRT to IMRT
 - More availability of CT
 - Additional imaging CT + MRI, PET, PET/CT, functional
 - Improved conformality
 - Reduced doses to normal tissues
 - More detailed dose-volume information on TPS
 - Use of dose-volume constraints
 - Automated optimization, IMRT



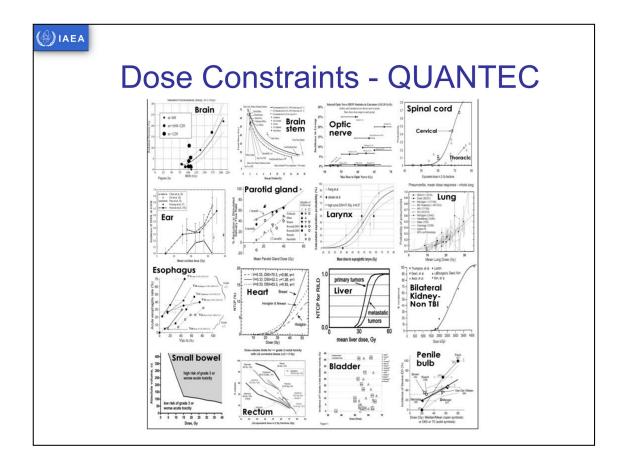


ICRU 83



- Dose reporting adapted to IMRT
 - Use of DVH
 - No D_{min} or D_{max} , instead ...
 - $-D_{98\%}$ and $D_{2\%}$
 - Specify median dose, $D_{50\%}$
 - Close to "old" ICRU reference dose at "ICRU reference point"

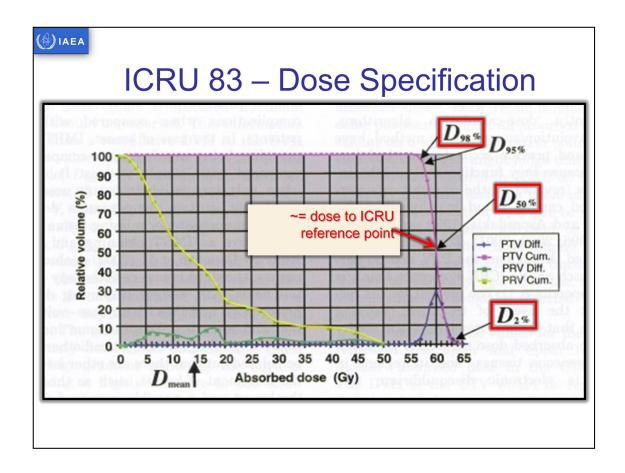
ICRU recommends reporting of DVH and dose volumes. However this system has yet to be used in many centres.



The ICRU Report is more important with the publication of new dose constraint limit delineated by the QUANTEC paper. This paper details out the volume, tolerance doses and risk of injury to various organs with radiation.

Use Of Normal Tissue Complication Probability Models In The Clinic Lawrence B. MARKS Et Al

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S10-S19, 2010



This is an example of a DVH showing the relevant dose point. The mean dose is reported as per "old" ICRU dose point eg isocentre



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Remaining Volume at Risk (RVR)

- The RVR is defined by the difference between the volume enclosed by the external contour of the patient and that of the CTVs and OARs on the slices that have been imaged
- The RVR is of importance in evaluating plans; if not specifically evaluated, there could be unsuspected regions of high absorbed dose within the patient that would otherwise go undetected

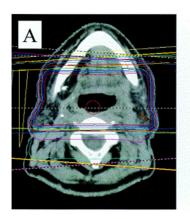
A new concept introduced is the RVR

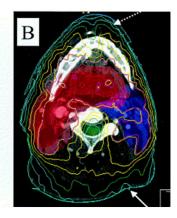
The absorbed dose in the RVR might also be useful in estimating the risk of late effects, such as carcinogenesis. Therefore, contouring the RVR is especially important for younger patients who can expect a long life span.

The RVR could also be relevant in IMRT as with less meticulous contouring, there could be "dose dumping" by the program to area not countoured as at risk.



Importance of RVR





Dose distribution for conventional beam (A) and IMRT (B) treatment of an oropharyngeal tumour. The patient experienced a lip desquamation (dashed arrow) and hair loss in the occipital/posterior area (solid arrow), which are not expected with conventional bilateral opposing beams (Zhen et al., Med. Dos. 27, 155-159, 2002)

This is an example of dose dumping and RVR where the plan increased dose distribution to the lips which would not usually be in the field for 2D or 3DCRT.



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And Jake Van Dyke







References

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