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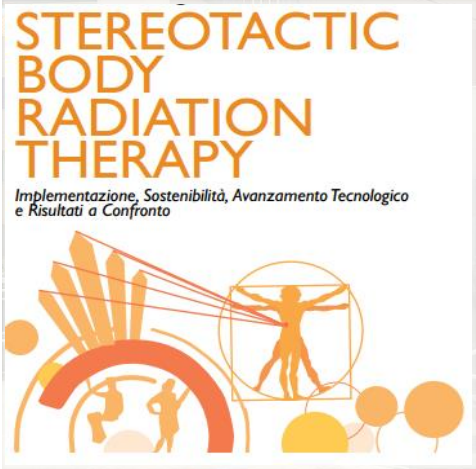

Controlli di qualità in SBRT

Carmelo Marino

24/25 OTTOBRE 2014
Università degli studi di Milano

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Quality Assurance of Radiotherapy in Cancer Treatment: Toward Improvement of Patient Safety and Quality of Care

Satoshi Ishikura

Outreach Radiation Oncology and Physics, Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Chuo-ku, Tokyo, Japan

Jpn J Clin Oncol. 2008 Nov;38(11):723-9. doi: 10.1093/jjco/hyn112.

"…Each step in the integrated process of RT needs quality control and quality assurance (QA) to prevent errors and to give high confidence that patients will receive the prescribed treatment correctly".

"…As new technologies are introduced, such as Stereotactic Body Radiation Therapy (SBRT), the number and sophistication of possible activities, tests and measurements required to maintain quality also increase".

SBRT

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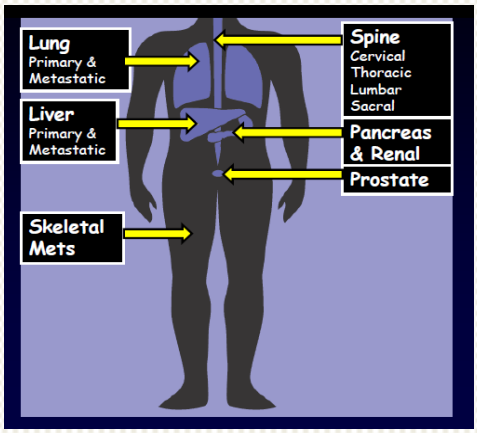
- Large doses in a few fractions high BED.
- Rapid fall off doses away from the target.

Current SBRT protocols generally involve **3-5 treatments with a dose of 6-25 Gy per fraction** to sites such as the spine, liver, and lung.



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Simulation imaging:

- Precise delineation of patient anatomy, targets……
- CT + MR + PET/CT
- Scan length: at least 5-10 cm superior and inferior..
- CT slice thickness: 1-3 mm.
- 4DCT or breath-hold techiniques.

Treatment planning:

- ICRU 50 and 62 definitions for GTV, CTV, PTV and OAR.
- Use of multiple non overlapping beams: … IMRT, VMAT.
- 6 MV photon beam…beam penetration and penombra
- 5 mm MLC leaf width is adequate for most applications.

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Calculation grid size and algorithm:

- Use of an isotropic grid of 2 mm o finer.
- Use of convolution/superposition algorithms. No Pencil Beam!

Patient positioning, immobilization:

- Body frames and fiducial systems, abdominal compression…
- Image guided localization: ..Epid, 3D kV CBCT, ultrasound ecc.
- Respiratory motion management.

Normalization/Prescribing Dose:

- Various options are available:

  Isocenter , %IDL: 80%, 65%, 60%, 50%, PTV periphery …

AAPM TG#

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TG 106 Accelerator beam data commissioning equipment and procedures (2008)

TG 142 Quality assurance of Medical Accelerators (2009)

TG 53 Quality assurance for clinical radiotherapy treatment planning (1998)

TG 166 The use and QA of Biologically Related Models for Treatment Planning (2012)

TG 82 Guidance document on delivery, treatment planning, ... of IMRT (2003)

TG 119 IMRT commissioning: Multiple institution planning and ..... (2009)

TG 179 Quality assurance for image-guided ..... CT-based technologies (2012)

TG 76 The management of respiratory motion in radiation oncology (2006)

TG 101 Stereotacticbody radiation (2010)

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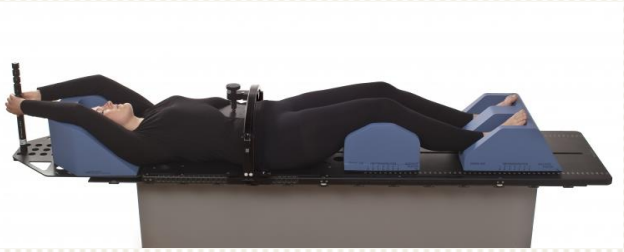
- **Comprehensive QA Program for SRS and SBRT:**

Patient-specific QA procedures for SRS/SBRT should be developed as an integrated part of a comprehensive ongoing QA program in the clinic: **immobilization systems, localization systems, and on-board imaging systems.**

Immobilization Systems
- Stereotactic body frame.
- Paddle used to induce shallow breathing.
- Limitations of body anatomy.
- Pneumatic Compression Belt.



Internal fiducial markers

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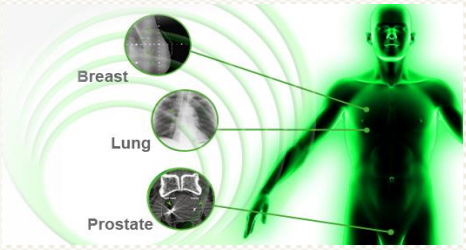

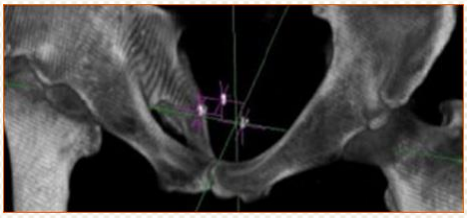

Image-guided localization is best achieved by utilizing **implanted fiducials**.

Two main categories:

- **Bone markers** are pure gold spheres. They are used in cranial and spinal applications. They image clearly on EPID. The markers are typically placed in a small hole in the bone, and bone wax is used to ensure that they stay in place.
- **Soft tissue markers** are cylindrical so that they can be easily inserted using a needle. The markers have been through a special knurling procedure so that the surface is cross-cut to inhibit migration once the marker is placed.

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TABLE IV. Achievable accuracies reported in the literature categorized by body site and immobilization/repositioning device.

Author, year	Site	Immobilization/repositioning	Reported accuracy
Lax, 1994[a]	Abdomen	Wood frame/stereotactic coordinates on box to skin marks	3.7 mm Lat, 5.7 mm Long
Hamilton, 1995[b]	Spine	Screw fixation of spinous processes to box	2 mm
Murphy, 1997[c]	Spine	Frameless/implanted fiducial markers with real-time imaging and tracking	1.6 mm radial
Lohr, 1999[d]	Spine	Body cast with stereotactic coordinates	≤3.6 mm mean vector
Yenice, 2003[e]	Spine	Custom stereotactic frame and in-room CT guidance	1.5 mm system accuracy, 2–3 mm positioning accuracy
Chang, 2004[f]	Spine	MI™ BodyFix with stereotactic frame/linac/CT on rails with 6D robotic couch	1 mm system accuracy
Tokuuye, 1997	Liver	Prone position jaw and arm straps	5 mm
Nakagawa, 2000[g]	Thoracic	MVCT on linac	Not reported
Wulf, 2000[h]	Lung, liver	Elekta™ body frame	3.3mm lat,4.4 mm long
Fuss, 2004[i]	Lung, liver	MI™ BodyFix	Bony anatomy translation 0.4, 0.1, 1,6 mm (mean X,Y,Z); tumor translation before image guidance 2.9, 2.5, 3.2 mm (mean X,Y,Z)
Herfarth, 2001[j]	Liver	Leibinger body frame	1.8–4.4 mm
Nagata, 2002[k]	Lung	Elekta™ body frame	2 mm
Fukumoto, 2002[l]	Lung	Elekta™ body frame	Not reported
Hara, 2002[m]	Lung	Custom bed transferred to treatment unit after confirmatory scan	2 mm
Hof, 2003[n]	Lung	Leibinger body frame	1.8–4 mm
Timmerman, 2003[o]	Lung	Elekta™ body frame	Approx. 5 mm
Wang, 2006[p]	Lung	Medical Intelligence body frame stereotactic coordinates/CT on rails	0.3 ± 1.8 mm AP, -1.8 ± 3.2 mm Lat, 1.5 ± 3.7 mm SI

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Initial 3D set-up errors obtained by image guidance for mask immobilization : further results

Study	Type of image guidance	Immobilization type	3D mean±SD (mm)
Guckenberger et.al. IJROBP(2007)	KV-CBCT	Scotch-cast mask	3.0±1.7
		Thermoplastic mask	4.6±2.1
L.Masi et.al IJROBP (2008)	KV_CBCT	TPmask + bite block	2.9±1.3
		Thermoplastic mask	3.2±1.5
E. Tryggestad et.al. IJROBP (2011) (*)	KV-CBCT	TPmask + bite block	2.1 (1.0)
		Thermoplastic mask	2.3 (1.5)
T. Gevaert et.al IJROBP (2011) (*)	Novalis (exatrac+ stereoscopic kV images)	Brainlab frameless Mask	1.91 (1.25)

(*) Frameless just from the start

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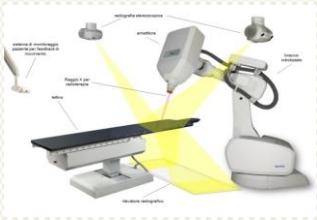
The purpose of **IGRT** : to place the clinical target in the high dose volume, fraction after fraction, day after day.

In-Room Imaging 3D

OBI KV Cone Beam

Mvision MV Cone Beam

Cyber Knife



XVI KV Cone Beam

Tomo MV CT

Exac Trac

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TABLE VI. Imaging.

Procedure	Application-type tolerance: non-SRS/SBRT	Application-type tolerance: SRS/SBRT
Daily[a]		
Planar kV and MV (EPID) imaging		
Collision interlocks	Functional	Functional
Positioning/repositioning	≤2 mm	≤1 mm
Imaging and treatment coordinate coincidence (single gantry angle)	≤2 mm	≤1 mm
Cone-beam CT (kV and MV)		
Collision interlocks	Functional	Functional
Imaging and treatment coordinate coincidence	≤2 mm	≤1 mm
Positioning/repositioning	≤1 mm	≤1 mm
Monthly		
Planar MV imaging (EPID)		
Imaging and treatment coordinate coincidence (four cardinal angles)	≤2 mm	≤1 mm
Scaling[b]	≤2 mm	≤2 mm
Spatial resolution	Baseline[c]	Baseline
Contrast	Baseline	Baseline
Uniformity and noise	Baseline	Baseline
Planar kV imaging[d]		
Imaging and treatment coordinate coincidence (four cardinal angles)	≤2 mm	≤1 mm
Scaling	≤2 mm	≤1 mm
Spatial resolution	Baseline	Baseline
Contrast	Baseline	Baseline
Uniformity and noise	Baseline	Baseline
Cone-beam CT (kV and MV)		
Geometric distortion	≤2 mm	≤1 mm
Spatial resolution	Baseline	Baseline
Contrast	Baseline	Baseline
HU constancy	Baseline	Baseline
Uniformity and noise	Baseline	Baseline
Annual (A)		
Planar MV imaging (EPID)		
Full range of travel SDD	±5 mm	±5 mm
Imaging dose[e]	Baseline	Baseline
Planar kV imaging		
Beam quality/energy	Baseline	Baseline
Imaging dose	Baseline	Baseline
Cone-beam CT (kV and MV)		
Imaging dose	Baseline	Baseline

On-going QA

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- Mechanical and radiation isocenter verification
- MV and kV isocenter coincidence verification
- AAPM TG-142, 2009 for other routine linac tests

Aim of **WINSTON-LUTZ TEST:**

- To measure the size of the MV isocenter (which is the intersection of the radiation isocenter and the couch isocenter) for a range of gantry and couch angles;
- To measure the difference between the MV isocenter and the KV isocenter.

The front pointer is attached to the couch and lined up with the room lasers
A small MV field is used to image the ball bearing with the portal imager or a film.
Images are collected for a range of gantry and couch angles.

W. Lutz, K. R. Winston, and N. Maleki, "A system for stereotactic radiosurgery with a linear accelerator," Int. J. Radiat. Oncol., Biol., Phys. **14**, 373–381 1988.

On-going QA

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Cumulative system accuracy can be characterized through an end-to-end test using phantoms with measurement detectors and imaging.

This test demonstrates the agreement between the image-guidance system's positioning and beam delivery at isocenter.

The phantom should be positioned with known error and then the IGRT system is used to correct them.

A simulation CT scan of the phantom is used to position the fields that irradiate the targets in the phantom.

J. P. Bissonnette, "Quality assurance of image-guidance technologies," Semin. Radiat. Oncol. **17**, 278–286 2007.

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TABLE V. Summary of published QA recommendations for SBRT and SBRT-related techniques.

Source	Purpose	Proposed test	Reported achievable tolerance	Proposed frequency
Ryu *et al.*, 2001[a]	End-to-end localization accuracy	Stereo x ray/DRR fusion	1.0 to 1.2 mm root mean square	Initial commissioning and annually thereafter
Ryu *et al.*, 2001[a]	Intrafraction targeting variability	Stereo x ray/DRR fusion	0.2 mm average, 1.5 mm maximum	Daily (during treatment)
Verellen *et al.*, 2003[b]	End-to-end localization accuracy	Hidden target (using stereo x ray/DRR fusion)	0.41 ± 0.92 mm	Initial commissioning and annually thereafter
Verellen *et al.*, 2003[b]	End-to-end localization accuracy	Hidden target (using implanted fiducials)	0.28 ± 0.36 mm	Initial commissioning and annually thereafter
Yu *et al.*, 2004[c]	End-to-end localization accuracy	Dosimetric assessment of hidden target (using implanted fiducials)	0.68 ± 0.29 mm	Initial commissioning and annually thereafter
Sharpe *et al.*, 2006[d]	CBCT mechanical stability	Constancy comparison to MV imaging isocenter (using hidden targets)	0.50 ± 0.5 mm	Baseline at commissioning and monthly thereafter
Galvin *et al.*, 2008[e]	Overall positioning accuracy, including image registration (frame-based systems)	Winston–Lutz test modified to make use of the in-room imaging systems	≤2 mm for multiple couch angles	Initial commissioning and monthly thereafter
Palta *et al.*, 2008[f]	MLC accuracy	Light field, radiographic film, or EPID	<0.5 mm (especially for IMRT delivery)	Annually
Solberg *et al.*, 2008[g]	End-to-end localization accuracy	Hidden target in anthropomorphic phantom	1.10 ± 0.42 mm	Initial commissioning and annually thereafter
Jiang *et al.*, 2008[h]	Respiratory motion tracking and gating in 4D CT	Phantoms with cyclical motion	N/A	N/A
Bissonnette *et al.*, 2008[i]	CBCT geometric accuracy	Portal image vs CBCT image isocenter coincidence	±2 mm	daily

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Respiratory motion

For SBRT (high doses and few fractions) **Target Miss** during RT (even during a single fraction) could be devastating.

- Most prominent in lung and liver
- Traditionally (planning and delivery):

large margins to account for motion

A variety of techniques for accounting for tumor motion within the PTV have been described and are summarized in the report of
AAPM task group 76.

Respiratory motion

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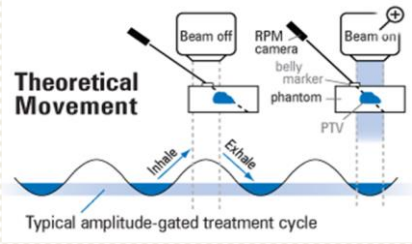
- Forced shallow breathing techniques (Compression Paddle, Pressure Belt)
- Respiratory Gated CT and 4D-CTs
- Free Breathing and Slow CT-Scanners
- Free Breathing and Fast CT-Scanners
- Breath-Hold (BH) CT-Scans



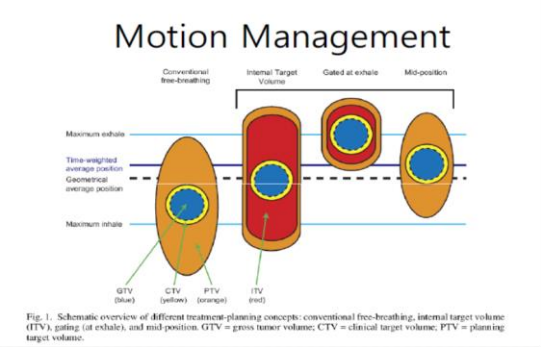


Fig. 1. Schematic overview of different treatment-planning concepts: conventional free-breathing, internal target volume (ITV), gating (at exhale), and mid-position. GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume.

The efficacy of many of these techniques can vary on a patient-specific basis and therefore require patient-specific QA procedures to verify their appropriateness in any given situation.

TG-142 Linac QA Example

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Monthly

Respiratory gating	
Beam output constancy	2%
Phase, amplitude beam control	Functional
In-room respiratory monitoring system	Functional
Gating interlock	Functional

Annual

Respiratory gating	
Beam energy constancy	2%
Temporal accuracy of phase/amplitude gate on	100 ms of expected
Calibration of surrogate for respiratory phase/amplitude	100 ms of expected
Interlock testing	Functional

Dosimetry of small/narrow field geometry : Detectors

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CI

- Volume Averaging: understimate of the actual dose for the output measurements.
- Polarity effect.
- Energy response: the central electrode (high Z material) causes significant sensitivity variations with field size and deph.
- Stem effect: Irradiating a portion of the ionization chamber stem (cable or holder) can induce leakage current and this will perturb the collected charge.

Diodes detectors

- Very small active volumes and high sensivity to radiation.
- Orientation and temperature dependence.
- Greater sensitivity to low-energy photons: overstimate for the output measurements.
- Long-term irreversible radiation damage that changes the sensitivity over time.

Diamond detectors

- High resolution (1 mm).
- Soft tissue equivalence in terms of atomic composition.
- Small directional dependence.
- Good mechanical stabilitity.
- Dose-rate dependence

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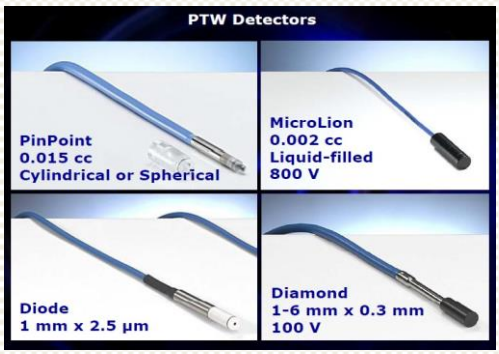
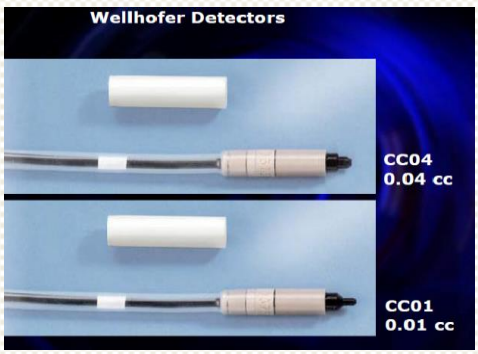
- **Dosimetry of small/narrow field geometry** (less than 10 mm): measurement of small photon beams is complicated by the loss of lateral electronic equilibrium, volume averaging, detector-interface artifacts, collimator effects, and detector position effects.

  The maximum inner diameter of a detector should be less than half the FWHM of the smallest beam measured in order for the deconvolution of the detector-size effect to work properly.





PRE-TREATMENT QA

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Med Phys. 2011 Feb;38(2):553-5.

Point/counterpoint. It is still necessary to validate each individual IMRT treatment plan with dosimetric measurements before delivery.

Smith JC[1], Dieterich S, Orton CG.

Med Phys. 2013 Jul;40(7):070601. doi: 10.1118/1.4794929.

Point/Counterpoint. Patient-specific QA for IMRT should be performed using software rather than hardware methods.

Siochi RA[1], Molineu A, Orton CG.

WORKFLOW PRE-TREATMENT QA

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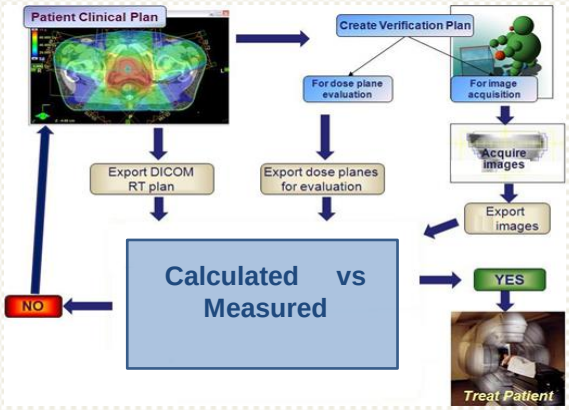
1. Creation of Patient Treatment
2. Creation of Verification Plan in a Phantom (preferably in 3D)
3. Execution of treatment in Phantom
4. Matching Calculated - Measured

Desiderable independent secondary TPS calculation!



2D – Radiochromic Films

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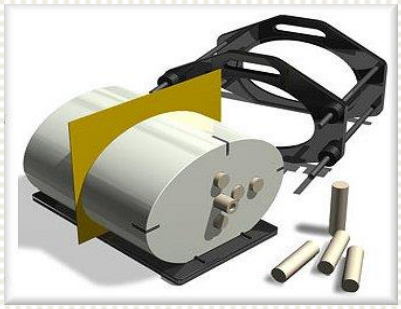
- High spatial resolution
- Weak energy dependence
- Near tissue equivalence
- Insensitive to visible light
- Do not require chemical processing
- No dose rate dependence
- Handling → AAPM TG-55 report
- Achievable accuracy levels:
  1,3 % (1 SD)



2D – EPID

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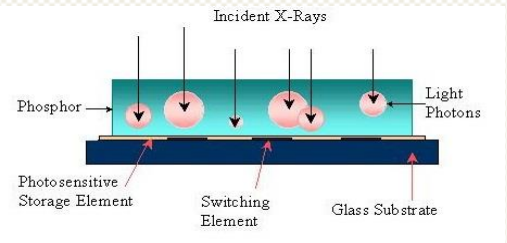
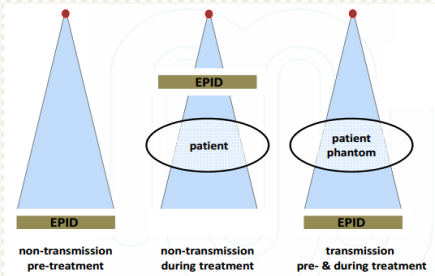
- High spatial resolution 0,8-1,0 mm
- Over – response to low energy photons
- Field size and dose rate dependence
- High dose rates of unflattened beams may lead to saturation
- Reduced off-axis signal variation
- Possibility of in-vivo dosimetry





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2D/3D – Detector Array

- Ionization chamber arrays or Diode arrays
- Immediate results – Convenient and efficient
- low spatial resolution – impairs measurements at high dose gradients and in small beams
- well prepared cross-calibration procedures
- software provided by manufacturer :
  - ✓ γ-index analysis
  - ✓ DVH comparisons
  - ✓ machine related QA tools

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Gamma Analysis

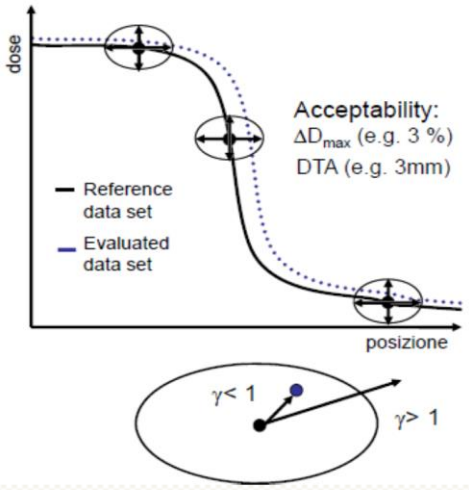
Gamma Index method (Low)

How it works

- dose difference (%) for low gradients
- Distance To Agreement (DTA in mm) per high gradients

$$\gamma = \min \sqrt{\frac{\Delta D^2}{\Delta D_{max}{}^2} + \frac{\Delta d^2}{DTA^2}}$$

Acceptability if $\gamma < 1$



Dose-Difference criterion of 3% and a DTA criterion of 3 mm.

Gamma Analysis

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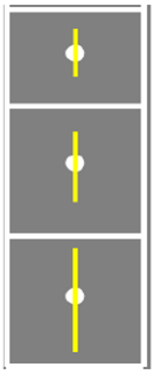
Local Gamma vs Global Gamma

Local gamma (Low, standard approach -intercomparison point by point)

Global gamma (Van Dick)

- $D_{prescribed}$/die
- D_{MAX}/die



Variable error bar as a function of punctual dose

Fixed global error bar, calculated as a percentage of the dose (prescribed or max)

Global Gamma is less restrictive than Local in low - dose areas

Gamma Analysis

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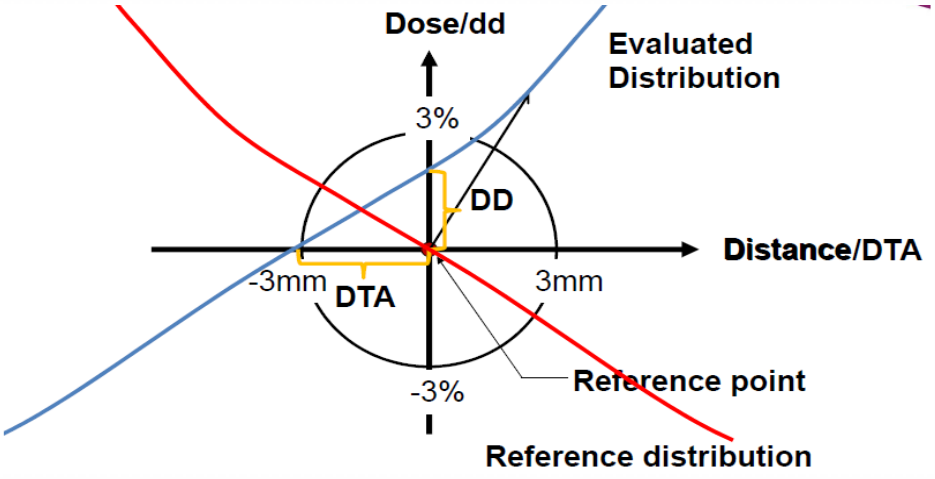

The angle that gamma vector makes to the DD axes can be used to determine whether its discrepancy is due to a spatial or dose error.

BOOKLET N.9 ESTRO

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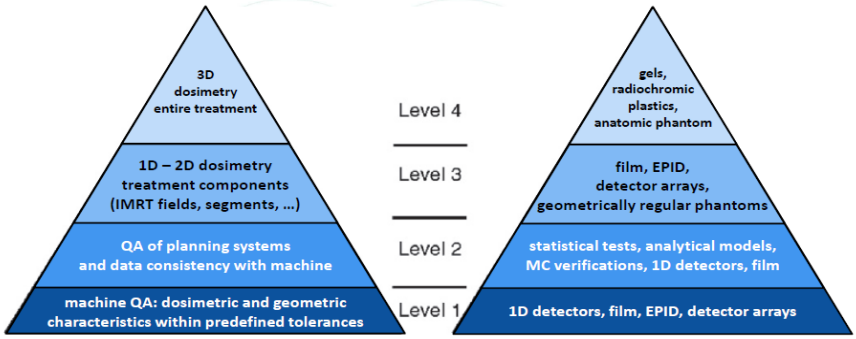

adapted from: De Wagter. J Conf Ser 3 (2004) / Estro Booklet Nb. 9

Table 7.5 Criteria for acceptability of gamma evaluations of pre-treatment verification of IMRT beams (from Stock *et al.*, 2005).

Approach	*Average gamma*	*Maximum gamma*	$P_{>1}$
Acceptable	< 0.5	< 1.5	0 – 5%
Need further evaluation	0.5 – 0.6	1.5 – 2.0	5 – 10%
Not acceptable	> 0.6	> 2.0	> 10%

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Med Phys. 2011 Feb;38(2):1037-44.

Per-beam, planar IMRT QA passing rates do not predict clinically relevant patient dose errors.

Nelms BE[1], Zhen H, Tomé WA.

Attention to the false positives or false negatives in a gamma analysis!!!

"..There is a lack of correlation between conventional IMRT QA performance metrics (Gamma passing rates) and dose differences in critical anatomic regions-of-interest. The most common acceptance criteria and published actions levels therefore have insufficient, or at least unproven, predictive power for per-patient IMRT QA".

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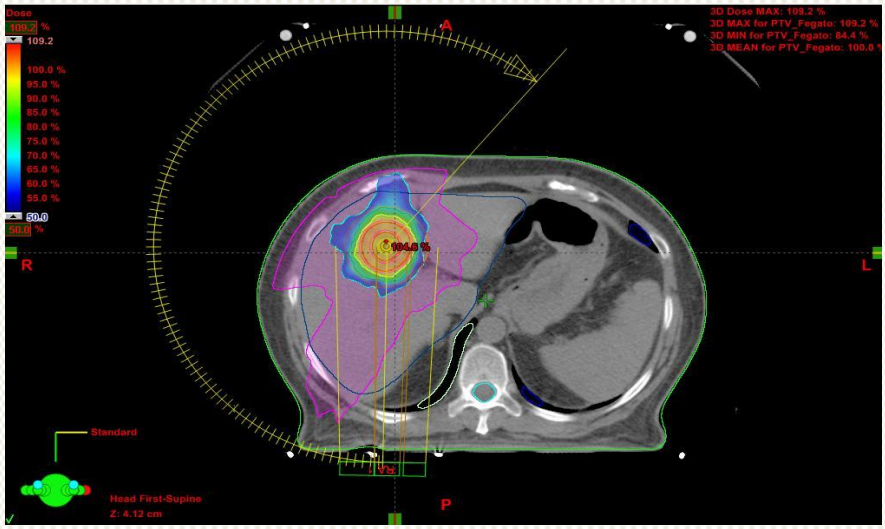
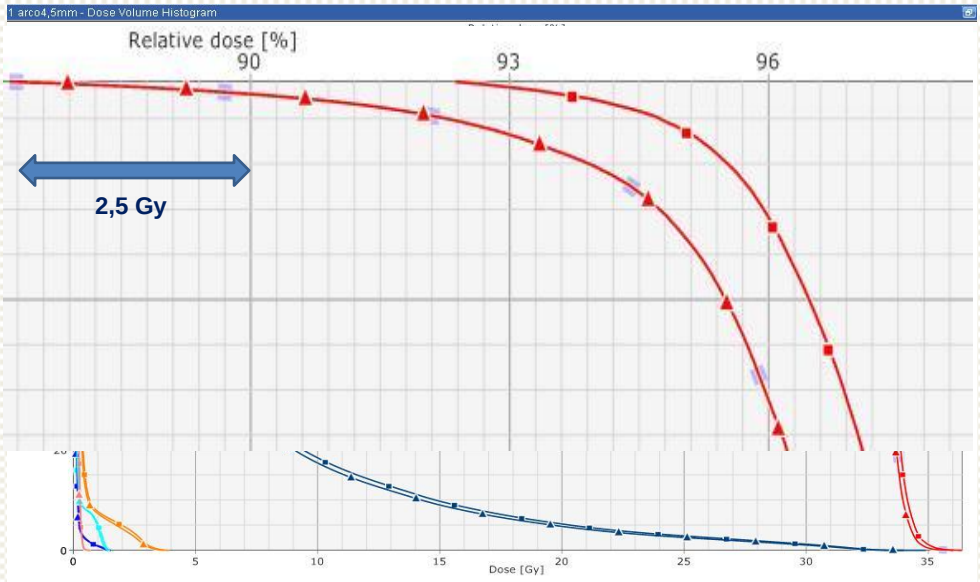
SBRT LIVER 10GyX3
Field 5X5 Isodose Prescription : 90%



Errors in Jaws (from 1,5 to 6,5mm) and MLC Positions (from 2 to 5mm and leaf in filed)

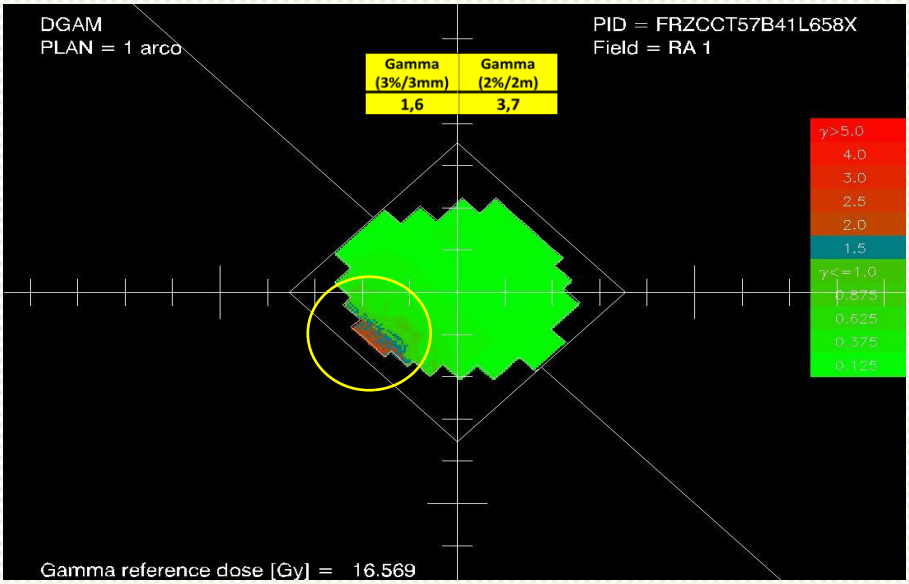
HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

ECLIPSE DVH
REFERENCE PLAN vs PLAN WITH 4.5mm JAW ERROR



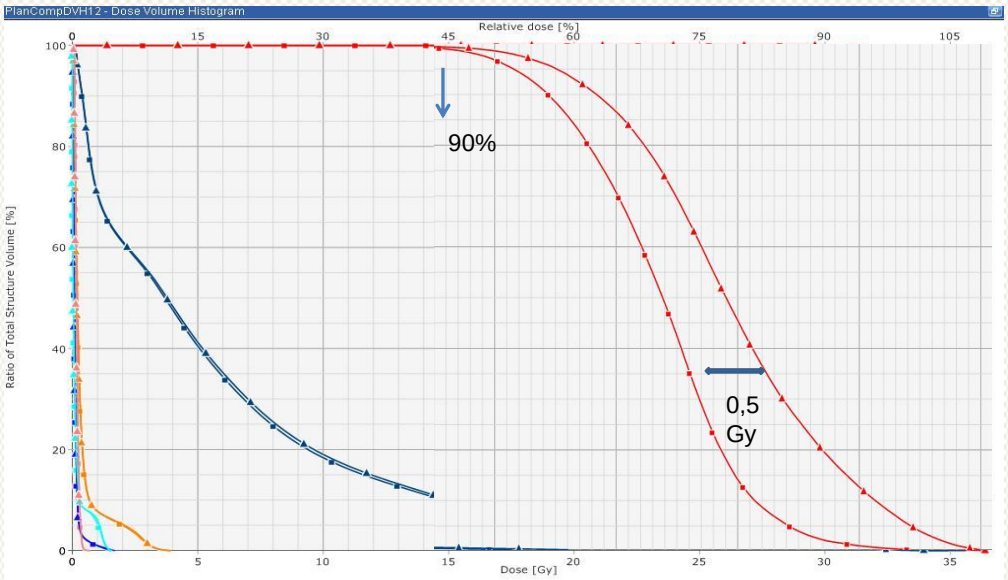
HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

ECLIPSE Evaluatin
REFERENCE PLAN vs PLAN WITH 4.5mm JAW ERROR



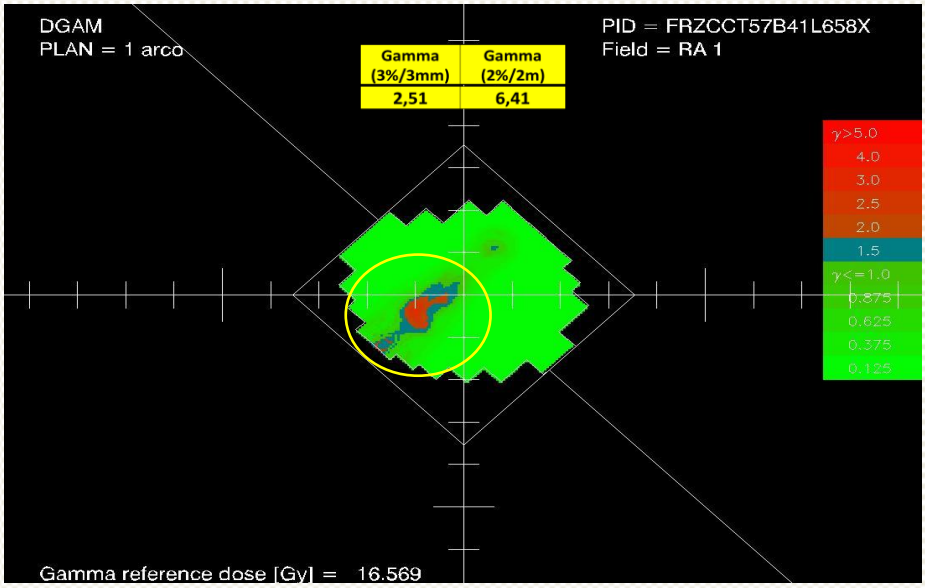
HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

ECLIPSE DVH
REFERENCE PLAN vs PLAN WITH 3mm MLC ERROR



HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

ECLIPSE DVH
REFERENCE PLAN vs PLAN WITH 3mm MLC ERROR



HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

GAMMA RESULTS	TPS vs TPS		EPID vs EPID	
PIANI	Gamma (3%/3mm)	Gamma (2%/2m)	Gamma (3%/3mm)	Gamma (2%/2m)
reference	0,17	2,14	0,17	2,14
1arco 1,5 mm	0	0,16	0	0
1arco 3,5 mm	0,13	1,51	0	0,18
1arco 4,5 mm	1,6	3,7	0,17	1,29
1arco 6,5 mm	6,52	9,52	6,88	9,61
2mmMLC	0,35	2,17	0,86	2,2
3mmMLC	2,51	6,41	2,42	5,19
4mmMLC	4,49	8,75	5,21	8,7
5mmMLC	5,7	9,79	5,39	8,86
MLCin field	9,35	16,48	9,58	14,51

HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

Med Phys. 2013 Nov;40(11):111722. doi: 10.1118/1.4826166.

Evaluating IMRT and VMAT dose accuracy: practical examples of failure to detect systematic errors when applying a commonly used metric and action levels.

Nelms BE[1], Chan MF, Jarry G, Lemire M, Lowden J, Hampton C, Feygelman V.

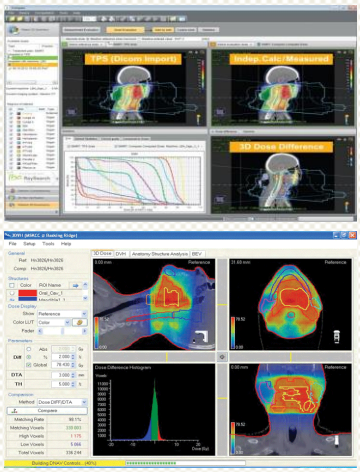
"..Removing systematic errors should be a goal not only of commissioning by the end users but also product validation by the manufacturers. For any systematic errors that cannot be removed, detecting and quantifying them is important as it will help the physicist understand the limits of the system and work with the manufacturer on improvements. In summary, IMRT and VMAT commissioning, along with product validation, would benefit from the retirement of the 3%/3 mm passing rates as a primary metric of performance, and the adoption instead of tighter tolerances, more diligent diagnostics, and more thorough analysis".

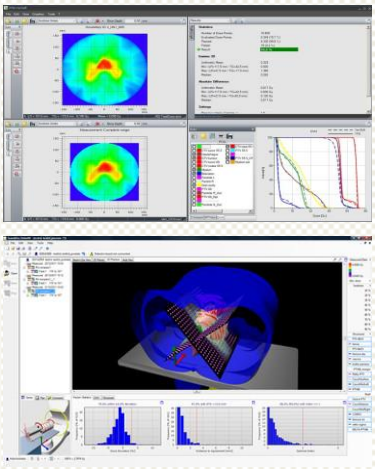
Patient DVHs

HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

Verify the patient plan based on a complete understanding of the clinical relevance of dose discrepancies and necessary corrective action via an independent dose engine.

Comparison of DVH calculated – measured of Target and OAR.





Patients IVD

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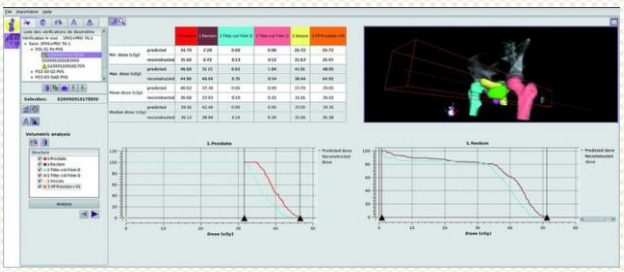
CENTRO CATANESE DI ONCOLOGIA



HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

AAPM Task Group 101 Reccomendations

".....The complexity, variation in individual practice patterns, and continued evolution of SBRT-related technology can render a static, prescriptive QA paradigm insufficient over time. Recommendation: A vital component of any comprehensive QA strategy should be to regularly review existing QA procedures with the objective to assess and critique the current QA practice in the context of current and proposed equipment....."

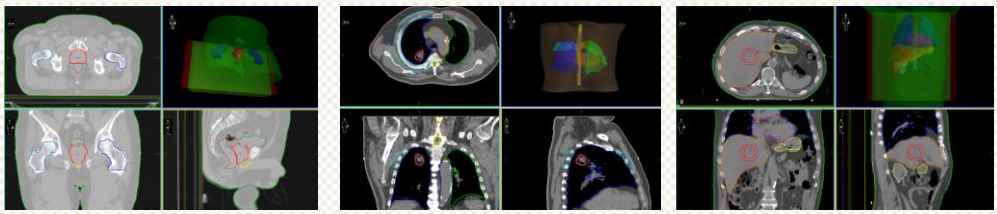
SBRT is a continuously evolving therapy.

MULTICENTER studies are important to share knowledge and to provide GUIDELINES for clinical activities.

GdL SBRT

Multicentrico Pre-trattamento

PROSTATA **POLMONE** **FEGATO**



Pre-Treat

*Campo obbligatorio

Sigla Identificativa *
Usare la stessa sigla identificativa del multiplanning

Strumentazione di Verifica *
Specificare marca e modello

Nome e Versione del Software di analisi utilizzato *

Verifica dose all'Isocentro con Camera a Ionizzazione ? *
Se "Si" specificare il tipo di camera utilizzata in "eventuali precisazioni"
- ○ Si
- ○ No

Valutazione Gamma Index *
- ☐ Gamma Locale
- ☐ Gamma Globale

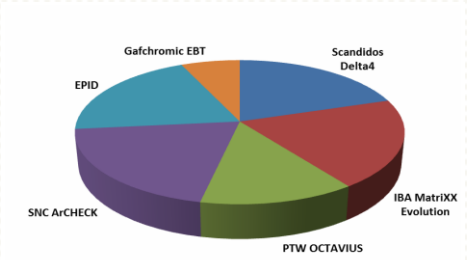
Threshold DTA/DA utilizzati *

Risultato/i Paz. 1 Prostata (GAMMA ed eventuale differenza % Dose I

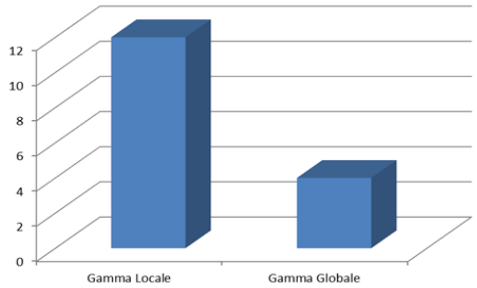
Piano clinicamente erogabile ?
Indicare se, sulla base dei risultati dell Verifica pre-trattamento, il pianno sa trattamento
- ☐ Si
- ☐ No

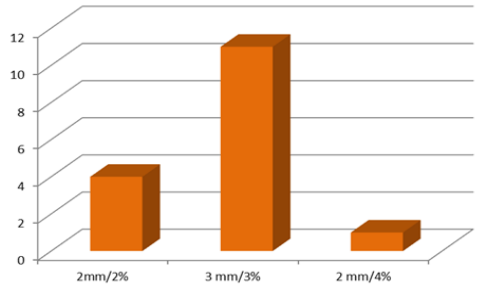
Strumentazione

GdL SBRT



Gamma Criteria

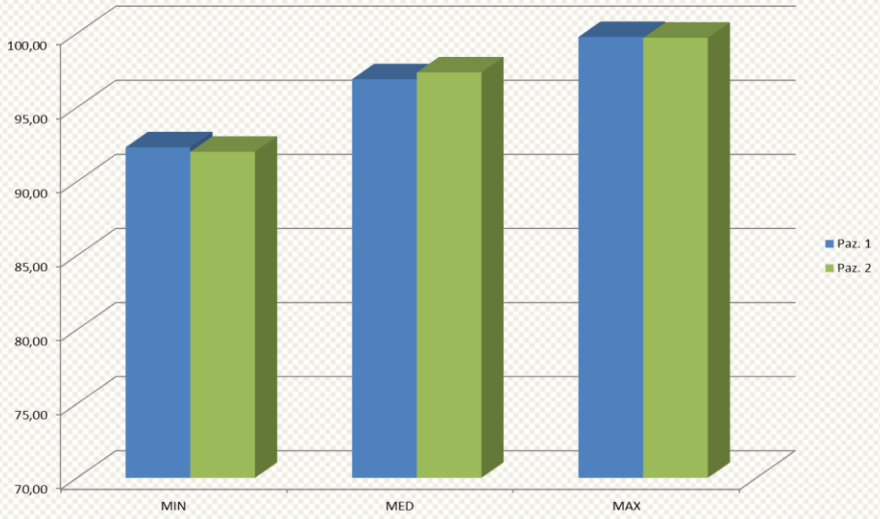




Risultati GAMMA distretto Prostata - 11 Centri

GdL SBRT

Piani Clinicamente Erogabili

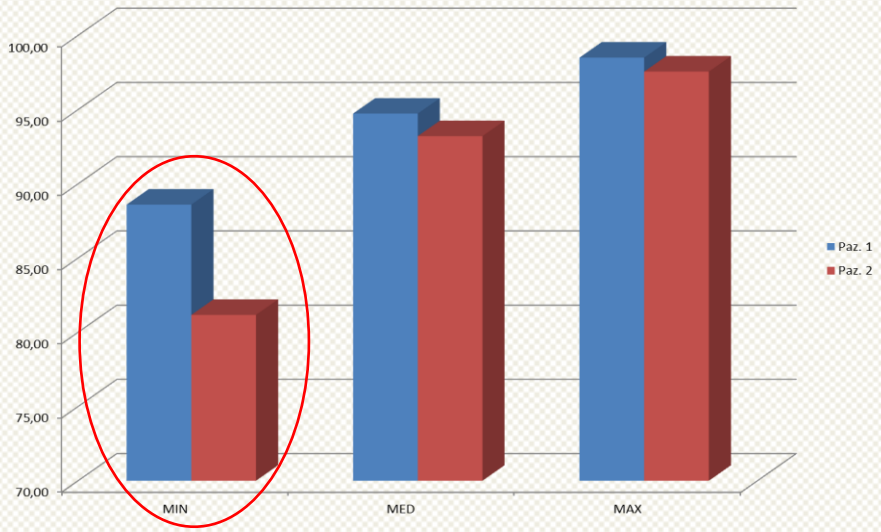


N. 4 Centri Dose Isocentro : Max DD% = 5,9 %

Risultati GAMMA distretto Fegato 7 Centri

GdL SBRT

N. 2 Piani Clinicamente NON Erogabili

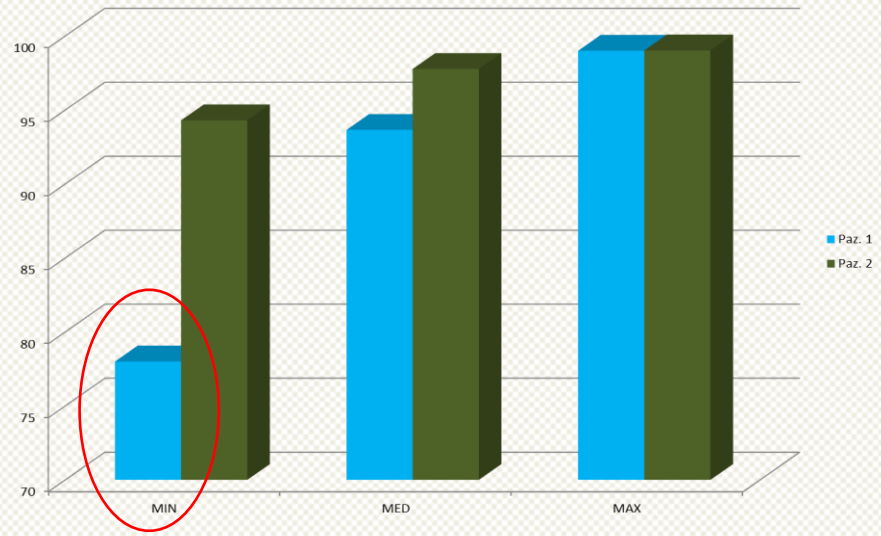


N. 1 Centri Dose Isocentro : DD% = 2,7 %

Risultati GAMMA distretto Polmone - 12 Centri

GdL SBRT

N. 1 Piani Clinicamente NON Erogabili



N. 2 Centri Dose Isocentro : MAX DD% = 9,6 %

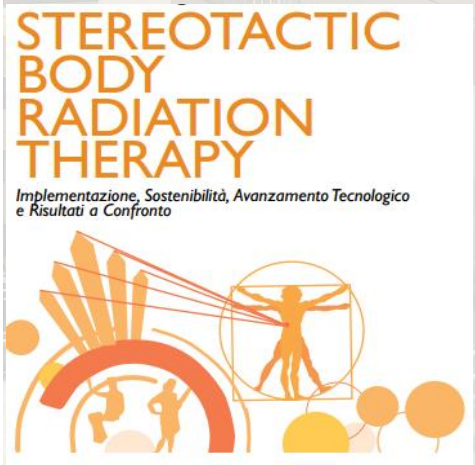
GdL SBRT

Multicentrico Pre-trattamento Futuro :

Ulteriore verifica con errori volontari ?

Individuazione di un rivelatore di riferimento ..?

HUMANITAS
CENTRO CATANESE DI ONCOLOGIA



GRAZIE

Carmelo Marino

24/25 OTTOBRE 2014
Università degli studi di Milano