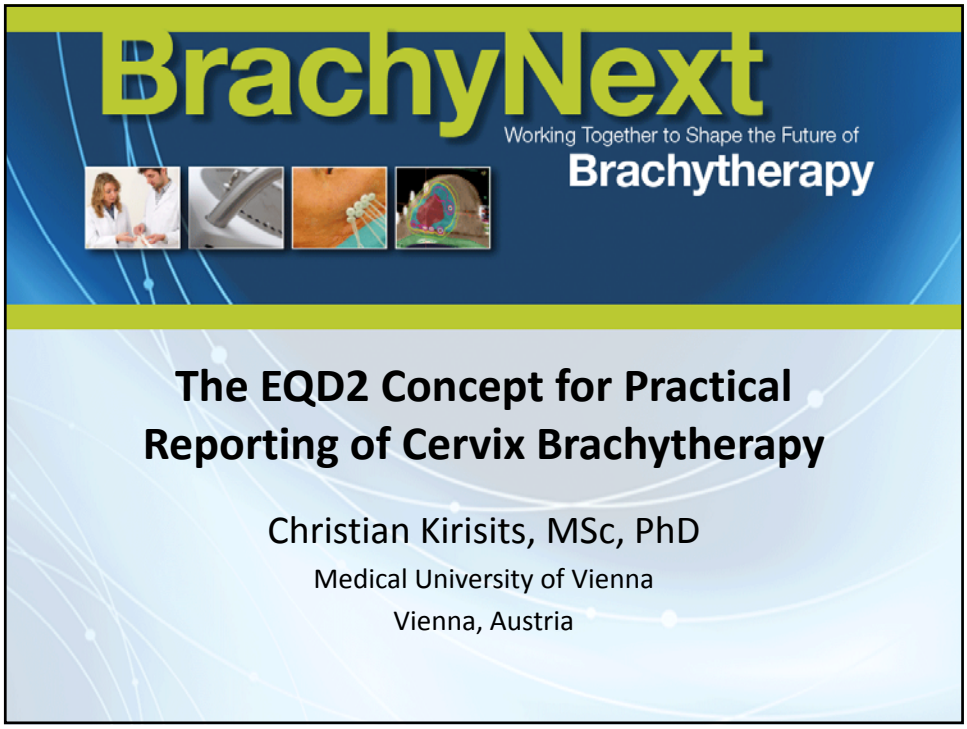

The EQD2 Concept for Practical Reporting of Cervix Brachytherapy

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Disclosures

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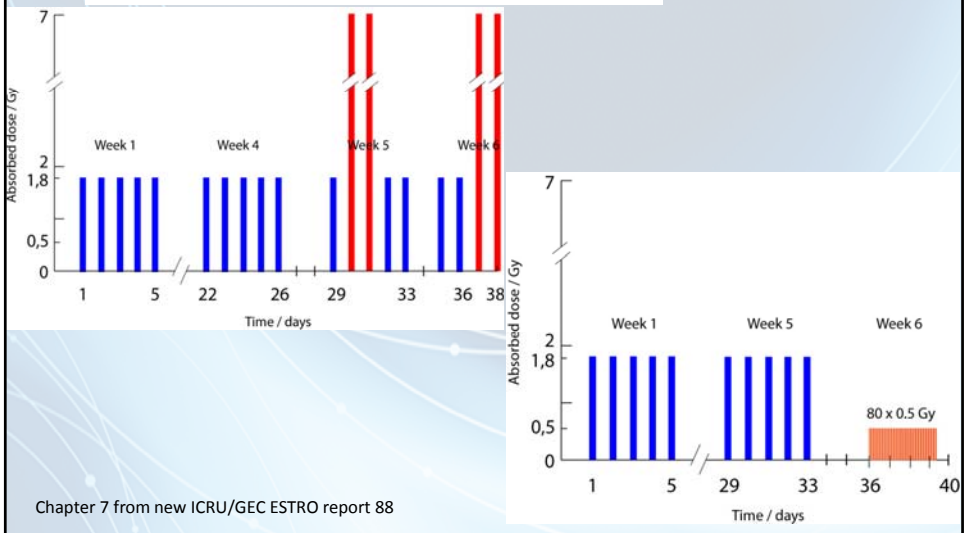
Radiobiology: Time-Dose Pattern

Various patterns of response-guided adaptive CTV



Chapter 7 from new ICRU/GEC ESTRO report 88

General Principles for Assessment and Reporting of Physical and Equieffective EBRT and BT Dose (All Reporting Levels)

Physical dose and number of fractions is assessed for target, OARs, dose points:

- BT
- EBRT

Total equieffective dose (EQD2) is calculated according to the linear quadratic model through the following steps:

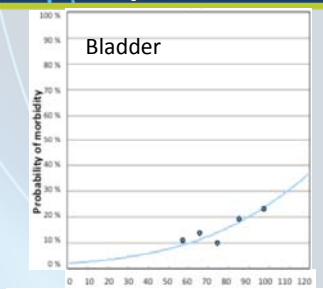
- BT EQD2 for each fraction
- Total BT EQD2
- Total EBRT EQD2
- Accumulated total EBRT+BT EQD2*

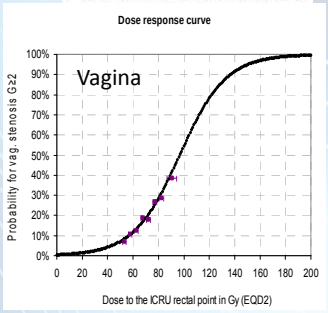
**Based on current assumptions outlined in chapter 9*

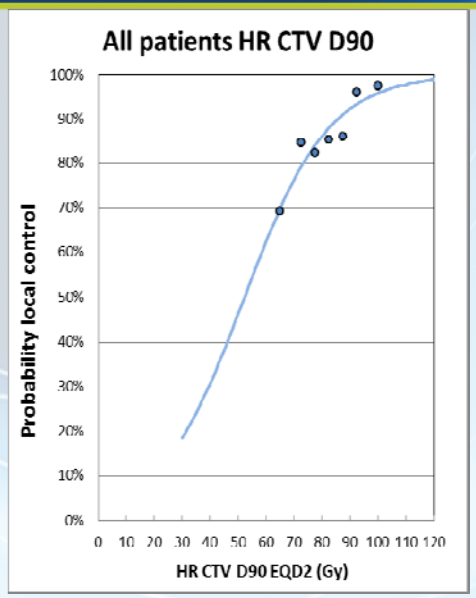
Reporting of radiobiological parameters:
a/b values for tumor and OARs*
In addition $T_{1/2}$ and recovery model for LDR and PDR treatments*
*At present: a/b=3 Gy for late effects in OAR and 10 Gy for tumor, and $T_{1/2}$=1.5h

Chapter 7 from new ICRU/GEC ESTRO report 88

Dose Response Studies
Examples From EMBRACE and RetroEMBRACE

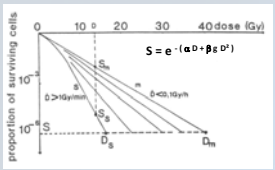






Radiobiological Considerations
Linear - quadratic model for incomplete monoexponential sublethal (DNA) damage repair

- **Biologically Effective Dose:**
- **BED = nd [1 + g d / (α/β)]**



The Role of Dose Rate in Brachytherapy (J. Dutreix) In: A Practical Manual of Brachytherapy (Pierquin / Marinello, Medical Physics Publishing)

- **BED ... virtual dose value that produces the same biological effect as the physical dose with an infinite low dose rate**

n ... number of equal fractions
d ... dose per fraction

tissue-dependent parameters:

α/β ...parameter describing lethal/sublethal lesions
g ... repair function depending on - half time for cell repair $T_{1/2}$
- fractionation

Mathematical Description

External beam radiotherapy and HDR brachytherapy:

- **No repair during irradiation (min)**
  repair function g = 1

LDR, MDR brachytherapy:

- **Repair during irradiation (hours - days) is significant**

$$g(LDR, MDR) = \frac{2}{\mu t}\left[1 - \frac{1 - e^{-\mu t}}{\mu t}\right] \qquad \mu = \frac{\ln 2}{T_{1/2}}$$

m … repair rate
$T_{1/2}$ … half time for repair
t … irradiation time

Mathematical Description

PDR brachytherapy:

- **Repair between successive pulses (hours) and during the whole fraction (hours - days) is significant**

$$g(PDR) = \frac{2}{\mu t}\left[1 - \frac{ny - sy^2}{n\mu t}\right] \qquad s = \frac{nk - k - nk^2 e^{-\mu t} + k^{n+1} e^{-\mu n t}}{\left(1 - ke^{-\mu t}\right)^2}$$

$$\mu = \frac{\ln 2}{T_{1/2}} \qquad y = 1 - e^{-\mu t} \qquad k = e^{-\mu x}$$

μ … repair rate
$T_{1/2}$ … half time for repair
t … irradiation time for each pulse
x … time between pulses without irradiation
n … number of equal pulses

Values of Biological Parameters

- Tumor and early reacting normal tissue:

$\alpha/\beta \sim 10$ Gy	7–20 Gy for most tumors 9–10 Gy for cervix carcinoma
$T_{1/2} \sim 1.5$ hours	0.5–1.5 hours

- Late reacting normal tissue:

$\alpha/\beta \sim 3$ Gy	0.5–6 Gy 3–4 Gy for bladder, rectum, sigmoid
$T_{1/2} \sim 1.5$ hours	1–2 hours

Clinical and experimental experience

Mathematical Description

- LQ model gives biological equivalence for

1. Classical LDR brachytherapy (50 cGy/h) and
2. Conventional external beam therapy (2 Gy/fraction) with $T_{1/2} = 1.5$ hours (clinical experience, ICRU 38, ICRU 88)

- Calculated BED values are normalized to conventional EBT with 2 Gy/fraction (reference schedule):

$$BED = D_{IsoE} [1 + 2 / (\alpha/\beta)]$$

$$D_{IsoE} = BED / [1 + 2 / (\alpha/\beta)] \quad = EQD2$$

"isoeffective dose" = "equivalent dose in 2 Gy fractions"

- To calculate the total isoeffective dose D_{IsoE} of a combined treatment, all isoeffective doses D_{IsoE} are added up:

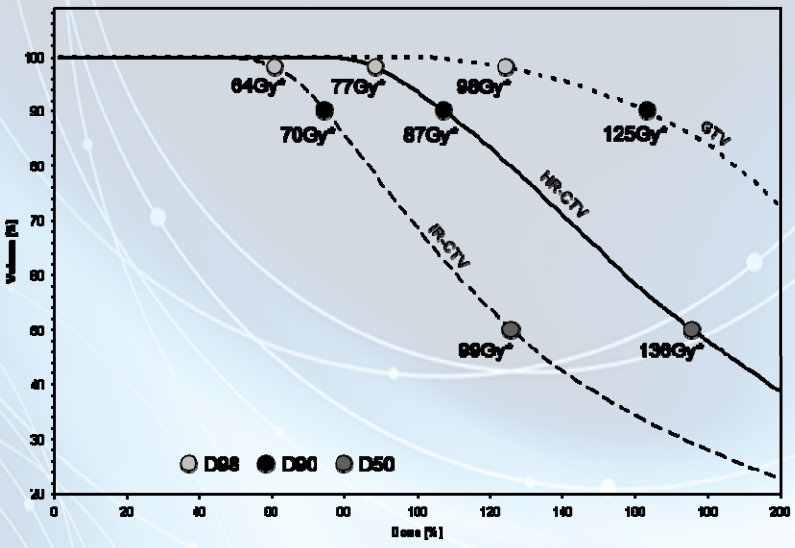
$$D_{IsoE,TOTAL} = D_{IsoE,EXTERNAL} + D_{IsoE,BRACHY}$$

Application of Biological Model to Clinical Situation

Assumptions:

- Time between fractions is long enough to enable full sublethal damage repair (min. ~ 8-12 hours)
- All investigated points and volumes from BT receive full EBT dose
- In fractionated treatments the investigated points or volumes represent the same anatomical position throughout the whole treatment (static situation assumption)
- The same absorbed dose and time-dose pattern of EBT and BT produces the same biological effect
  ATTENTION: dose and dose rate inhomogeneity within BT volume

DVH for Target Volumes



Chapter 8 from new ICRU/GEC ESTRO report 88

Different Fractionation Schedules (examples HDR)

Point A

- 45 Gy EBT + 4 x 7 Gy
- 45 Gy EBT + 4 x 6 Gy
- 50 Gy EBT + 2 x 8.5 Gy

EQD2 total dose?

Organs at Risk (ICRU point)

- 45 Gy EBT + 4 x 5 Gy Rectum, 6 Gy Bladder
- 45 Gy EBT + 4 x 4.5 Gy Rectum, 5 Gy Bladder
- 50 Gy EBT + 2 x 6 Gy Rectum, 7 Gy Bladder

intercomparison?

Different Fractionation Schedules (examples HDR)

Point A

- 45 Gy EBT + 4 x 7 Gy ~ 84 Gy $EQD2_{10}$
- 45 Gy EBT + 4 x 6 Gy ~ 76 Gy $EQD2_{10}$
- 50 Gy EBT + 2 x 8.5 Gy ~ 76 Gy $EQD2_{10}$

Organs at Risk (ICRU point)

- 45 Gy EBT + 4 x 5 Gy Rectum ~ 75 Gy $EQD2_3$; 6 Gy Bladder ~ 86 Gy $EQD2_3$
- 45 Gy EBT + 4 x 4.5 Gy Rectum ~ 70 Gy $EQD2_3$; 5 Gy Bladder ~ 75 Gy $EQD2_3$
- 50 Gy EBT + 2 x 6 Gy Rectum ~ 72 Gy $EQD2_3$; 7 Gy Bladder ~ 78 Gy $EQD2_3$

Example: HDR Brachytherapy for Cervical Carcinoma

α/β = 10 Gy for cervical tumor
α/β = 3 Gy for OAR (bladder, rectum, sigmoid)

Point A	Physical dose		Total dose
External beam	25 x 1.8 Gy =	45 Gy	44 Gy $EQD2_{10}$
Brachytherapy	4 x 7.0 Gy =	28 Gy	40 Gy $EQD2_{10}$
Total dose		73 Gy	84 Gy $EQD2_{10}$

OAR brachy dose to OAR 70% of dose to point A

External beam	25 x 1.8 Gy =	45 Gy	43 Gy $EQD2_3$
Brachytherapy	4 x 4.9 Gy =	20 Gy	31 Gy $EQD2_3$
Total dose		65 Gy	74 Gy $EQD2_3$

Example: LDR/PDR Brachytherapy for Cervical Carcinoma

α/β = 10 Gy for cervical tumor
α/β = 3 Gy for OAR (bladder, rectum, sigmoid)
$T_{1/2}$ = 1.5 h for cervical tumor and OAR

Brachytherapy treatment time: 80h (PDR: pulse time = 15 min, interval = 1h)

Point A	Physical dose		Total dose
External beam	25 x 1.8 Gy =	45 Gy	44 Gy $EQD2_{10}$
Brachy 0.5 Gy/h	40 Gy =	40 Gy	40 Gy $EQD2_{10}$
Total dose		85 Gy	84 Gy $EQD2_{10}$

OAR brachy dose to OAR 70% of dose to point A

External beam	25 x 1.8 Gy =	45 Gy	43 Gy $EQD2_3$
Brachy 0.35 Gy/h	28 Gy =	28 Gy	25 Gy $EQD2_3$
Total dose		73 Gy	68 Gy $EQD2_3$

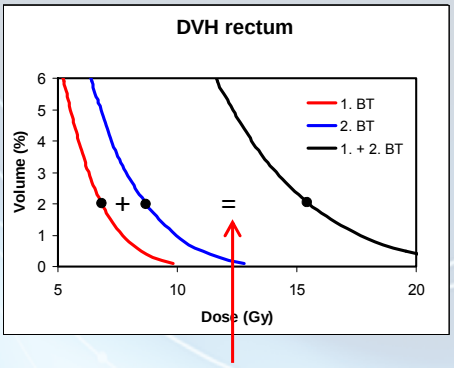
Total Dose Values (EQD2) for 2 HDR Fractions

EBRT	25 x 1.8 Gy	25 x 1.8 Gy
BT	4 x 7 Gy	5 x 5.5 Gy
D90 HR CTV (α/β = 10 Gy)	84 Gy	80 Gy
D_{2cc} rectum (e.g., ~ 70% of D90 α/β = 3 Gy)	74 Gy	70 Gy
D_{2cc} bladder (e.g., ~ 90% of D90 α/β = 3 Gy)	90 Gy	83 Gy

Treatment Planning Documentation of Fractionated Gynecological BT (HDR)

BRACHYTHERAPY	F1	F2	F3	F4	F5	F6		
date							dose values in Gy	
physicist								
MR / CT							TOTAL BT	TOTAL BT + EBT
applicator(s): type								
applicator(s): dimensions								
eval plan, remarks							*mean*	*stddev*
TRAK [cGy at 1m]							0,00	
Planning aim for D_{90} CTV $_H$	7	7	7	7				
planning aim $EQD2_{10}$	9,9	9,9	9,9	9,9	0,0	0,0	39,7	**83,9**
volume of 7 Gy [cm^3]							*#DIV/0!*	*#DIV/0!*
volume of 14 Gy [cm^3]							*#DIV/0!*	*#DIV/0!*
dose to + A left	6,6	6,6	6,4	6,4				
A_{left} $EQD2_{10}$	9,1	9,1	8,7	8,7	0,0	0,0	35,8	**80,0**
dose to - A right								
A_{right} $EQD2_{10}$	0,0	0,0	0,0	0,0	0,0	0,0	0,0	**44,3**
dose to A mean		3,3	3,2	3,2	0,0	0,0		
A_{mean} $EQD2_{10}$	0,0	3,7	3,5	3,5	0,0	0,0	10,7	**54,9**

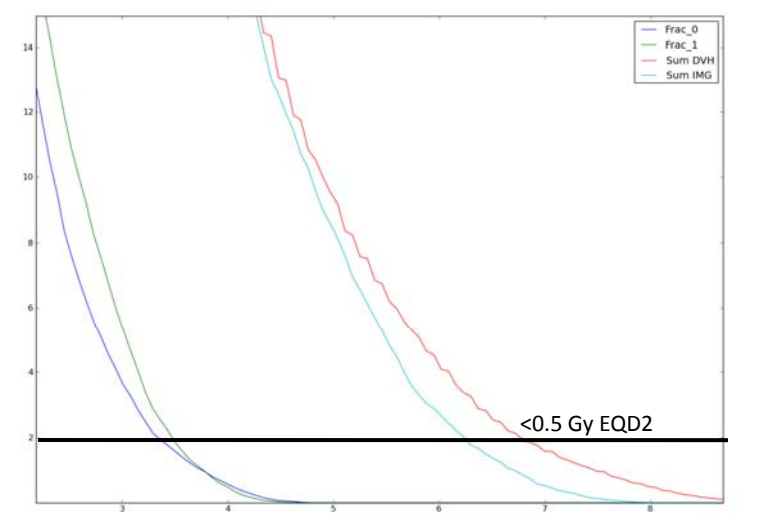
Calculation of DVH for Several Fractions



Approximation
Worst case assumption

Provided by K Tanderup

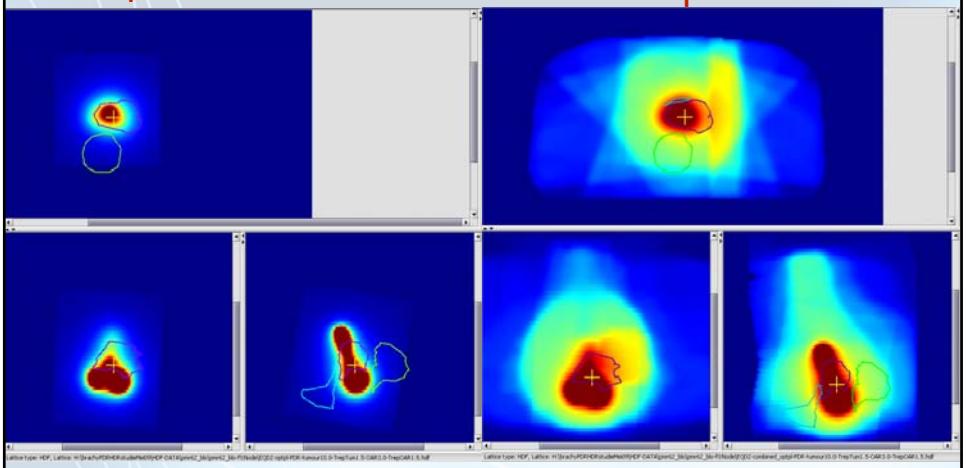
Rectum Wall DVH in EQD2
2.5-cm Longitudinal Shift of Whole Organ



Combination of EBRT and BT

2xF1 optimized PDR

EB + Node Boost
2xF1 optimized PDR



Provided by Astrid de Leeuw /van de Kamer et al. Radiother Oncol 2010

Differences Between 2 Methods
"Adding 3D Distributions" vs. "Adding Parameters"

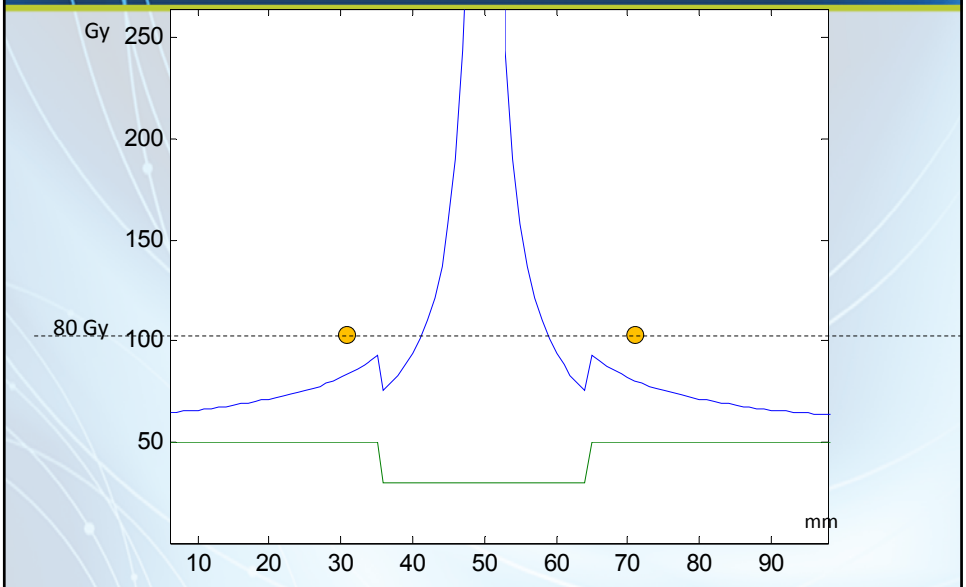
	HR-CTV		Bladder		Rectum	
	without	with paraBoost	without	with paraBoost	without	with paraBoost
PDR						
avg	**1.5%**	**9.1%**	**-0.5%**	**2.4%**	**-0.2%**	**0.8%**
SD	**1.7%**	**6.2%**	**1.0%**	**3.3%**	**0.6%**	**1.0%**

Is adding parameters a valid approximation?

Yes, provided no EB boost!

Provided by Astrid de Leeuw/van de Kamer et al. Radiother Oncol 2010

3-cm Shielding After 30 Gy AP/PA



Conclusion

- EQD2 concept is reproducible and able to compare different dose rate and dose fractionation schedules
- Has to be used within comparable settings (similar EBRT concept, chemotherapy…)
- Final parameters will be determined in dose response analysis performed within large multicenter trials

Thanks for your attention!