Defining targets for brachytherapy

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Thanks to Ryan Tierney, MD for GEC ESTRO slides

Outline

- Anatomy review
- CT vs MRI for target delineation
- Historical background
- GEC ESTRO guidelines
- Clinical impact

Importance of brachytherapy

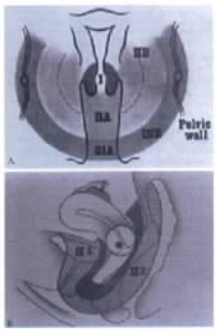
- Brachytherapy is part of the standard of care!
- Patterns of Care studies have shown declining use
- Han et al 2009 SEER database - 1988 – 2009
  - Declining use of brachytherapy – 83% 1988 to 58% 2009
  - Patients treated with brachytherapy higher SURVIVAL
  - Both CSS and OS
- Tanderup et al 2014 editorial
  - increased use of IMRT and SBRT in lieu of brachytherapy
  - decreased local control and increased toxicities

Gill et al 2014

- National Cancer Database – 7654 pts
- 2004 – 2011
  - Brachytherapy use declined 96.7% to 86.1%
  - IMRT and SBRT boost increased 3.3% to 13.9%
  - Older age, IVA, small tumors, low volume centers
  - IMRT/SBRT boost inferior OVERALL SURVIVAL (HR 1.86, 95% CI 1.35-2.55, P<.01) vs brachytherapy
  - Boost modality bigger impact than chemotherapy!

What is the target????

FIGO stage	Description
I	Tumor confined to cervix
IA IA1 IA2	Microscopic invasive tumor Stromal invasion ≤3 mm; width ≤7 mm Stromal invasion >3 mm but ≤5 mm; width ≤7 mm
IB IB1 IB2	Clinically visible invasive tumor or preclinical tumors > stage IA Tumor ≤4 cm Tumor >4 cm
II	Invasion beyond uterus but not to pelvic sidewall or lower third of vagina
IIA IIA1 IIA2	No parametrial invasion, upper two-thirds of the vagina Tumor ≤4 cm Tumor >4 cm
IIB	Parametrial invasion
III	Tumor extends to pelvic sidewall and/or involves the lower third of vagina
IIIA	Tumor extends to lower third of vagina but not to pelvic sidewall
IIIB	Extension to pelvic sidewall and/or hydronephrosis or nonfunctioning kidney
IV	Tumor extends outside true pelvis or invades bladder or rectal mucosa
IVA	Invasion of bladder or rectal mucosa
IVB	Distant metastasis



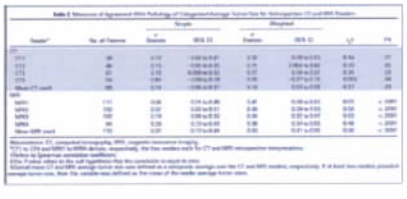
Anatomy

CT vs MRI

- ACRIN 6651/GOG183
- MRI, CT and exam performed prior to radical hysterectomy
- 25 centers, 208 patients, 10 blinded radiologists
- Involvement of cervical stroma, uterine body and tumor diameter measurement

Mitchell, DG et al, JCO 2006

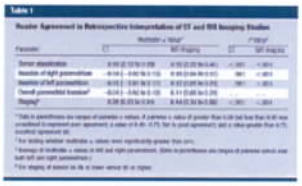
ACRIN 6651/GOG183



Mitchell, DG et al, JCO 2006

CT vs MRI

- ACRIN/GOG – comparative study of diagnostic performance and inter-observer variation
  - 4 radiologists, 146 CTs
  - 4 radiologists, 152 MRIs
  - >IB cancer



Hricak, H et al, 2007

Imaging the target

- MRI is better than CT for imaging the target
- MRI has better overlap with FDG-PET volumes which we know are important clinically (Jackie's talk)
- FDG-PET is not practical for repetitive imaging and brachytherapy planning
- MRI is now the method of choice...

Historical Perspective

- 1903 – Stockholm and Paris - mg-hrs
- 1938 - Manchester System – Point A
- 1953 - Point A revisions
- 1985 – ICRU 38
- 1987 – more Point A revisions...

Historical Perspective

- Point based precription
- 2D – relies upon orthogonal X rays for calculation and prescription
- Assumes all tumors have the same anatomy
- Cannot define OAR on 2D film
- Point estimates of dose to bladder and rectum ICRU38

3D image-guided brachytherapy

- 2000 – GEC-ESTRO supported the development of IGBT in cervical cancer
  - D90, D100 for dose prescription
  - D2cc bladder, rectum and sigmoid (OAR)
- 2004 – GTV and CTV delineation (MRI)
- Concept of HR-CTV and IR-CTV
- 2005 GEC ESTRO recommendations for IGBT
  - Pretreatment MR imaging to define the target

GEC-ESTRO working group recommendations

- "GEC-ESTRO decided in 2000 to support and promote 3D imaging based 3D treatment planning approach in cervix cancer BT"
- "In promoting research and development of 3D image based BT, historical difficulties in communicating results in cervix cancer BT ('mgh'-, 'point A'-, 'reference volume'-traditions) should be overcome by using one terminology based on well-understood concepts and terms from the beginning"
- Groups involved in creation: Institut Gustave Roussy (Villejuif, France), Vienna, Leuven, Oslo, Southampton

Haie-Meder C et al, Radiother Oncol 2005.

GEC-ESTRO – GTV defined by MRI

- Gross Tumor Volume (diagnosis) (GTV_D) – Macroscopic tumor extension at diagnosis as detected by clinical examination and as visualized on MRI
  - MRI: high signal intensity mass(es) at fast spin echo (FSE) sequences T2 in cervix/corpus, parametria, vagina, bladder, and rectum
- Gross Tumor Volume (brachy) (GTV_{B1} GTV_{B2} GTV_{B3} etc) – Macroscopic tumor volume at time of brachy as detected by clinical examination and as visualized on MRI.

Haie-Meder C et al, Radiother Oncol 2005.

GEC-ESTRO – HR CTV

- High risk CTV ($HR\ CTV_{B1}$, $HR\ CTV_{B2}$, $HR\ CTV_{B3}$, etc) – Includes GTV_{Bx}, the whole cervix, presumed extra-cervical tumor spread
- includes MRI "grey zones"
- Represents *macroscopic* tumor load

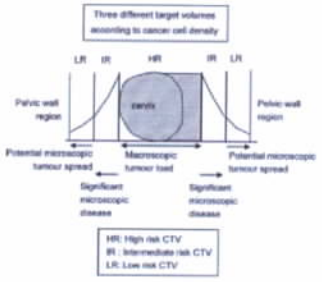
Haie-Meder C et al, Radiother Oncol 2005.

GEC-ESTRO – IR CTV

- Intermediate Risk CTV ($IR\ CTV_{B1}$, $IR\ CTV_{B2}$, $IR\ CTV_{B3}$, etc) – supposed to represent areas carrying a significant *microscopic* tumor load
- High-risk CTV + 5-15 mm margin
  - Limited disease (<4 cm): $IR\ CTV_B$ = HR CTV+margins:
    - AP: 5 mm, craniocaudal 10 mm, lateral 10 mm. If endocervical or lateral macroscopic tumor growth noted, add 5 mm margin in direction of potential spread
  - Extensive disease: Based on GTV_D, superimposed on imaging obtained at time of brachytherapy

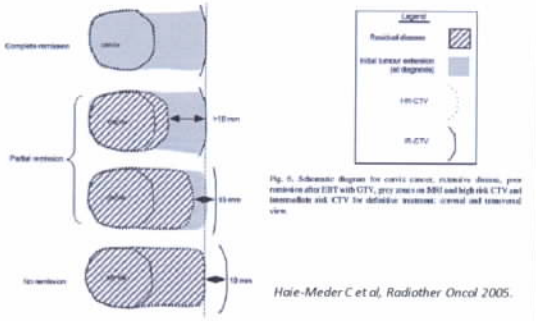
Haie-Meder C et al, Radiother Oncol 2005.

GEC-ESTRO – Target volumes



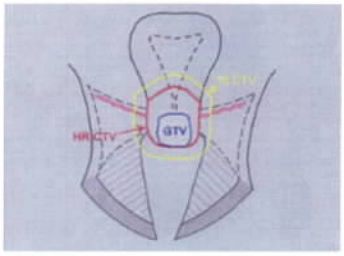
Low-risk CTV: Treated with EBRT or surgery

GEC-ESTRO – volumes after EBRT



Haie-Meder C et al, Radiother Oncol 2005.

GEC-ESTRO – Target volumes

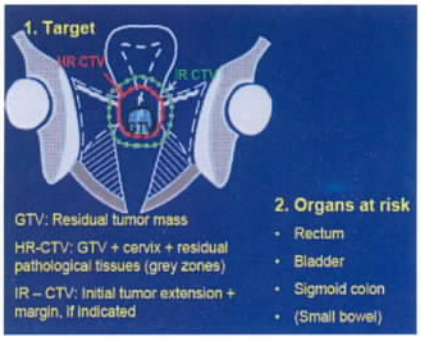


Haie-Meder C et al, Radiother Oncol 2005.

GEC-ESTRO – Dose

- According to the working group, the high-risk CTV should receive the prescription dose of ~85 Gy
- The intermediate-risk CTV should a dose appropriate for microscopic disease, ~60 Gy
- Problem: LDR? HDR? PDR brachytherapy? How to report dose?

Haie-Meder C et al, Radiother Oncol 2005.



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The biologically effective dose BED according to the LQ model is given by

$$BED = Nd\left(1 + g\frac{d}{\alpha/\beta}\right), \text{ while } g(LDR) = \frac{2}{\mu t}\left[1 - \frac{1 - e^{-\mu t}}{\mu t}\right] \text{ and } \mu = \frac{\ln 2}{T_{1/2}}$$

g: repair function. 1 for EBRT and HDR brachytherapy

Haie-Meder C et al, Radiother Oncol 2005.

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The equivalent external beam therapy dose using conventional fractionation of 2 Gy per day EQD_2 [34] is calculated as $EQD_2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$

GEC-ESTRO – Dose

- **The EQD_2 is to be equivalent to the "historical" LDR dose of 50cGy/h**
- **Must recalculate EBRT dose if fractionation schedule is not 2Gy/d**
- **Sum EQD_2 from EBRT and brachytherapy, with the assumption that POI of brachytherapy receive the full EBRT dose – "worst case" assumption**
- **For fractionated treatment (brachy and EBRT), this parameter works for evaluation after the last fraction, as it uses summed doses of all fractions.**

Pötter R et al, Radiother Oncol 2006.

GEC-ESTRO – Dose Reporting

- **Record and report- their recommendations:**
  - **D100, D90 for GTV, HR CTV, IR CTV**
  - **Dose at point A (right, left, mean)**
  - **Dose to bladder and rectum for ICRU reference points**
  - **D0.1cc, D1cc, D2cc for organs at risk (rectum, sigmoid, bladder)**
  - **Complete description of time-dose pattern: physical and biologically weighted doses**

Pötter R et al, Radiother Oncol 2006.

GEC-ESTRO – OAR

- Typical brachy adverse effects (local inflammation, fibrosis, telangiectasis, ulceration, necrosis, fistula formation) occur mainly in limited volumes adjacent to the applicator irradiated with high doses
- Most of these organs are hollow: Filling status is important
- Their recommendation: The *minimum* dose in the most irradiated tissue volume adjacent to the applicator
  - 0.1cc, 1cc, 2cc, and 5cc volumes
  - Corresponds to "wall planes" of 5x4 mm to 3.3 x 3.3 cm

GEC-ESTRO – OAR

Pötter R et al, Radiother Oncol 2006.

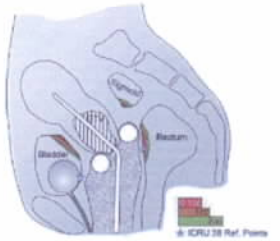


Fig. 6. Schematic anatomical diagram (sagittal view) indicating the most irradiated tissue volumes adjacent to the applicator for rectum, sigmoid and bladder: 0.1, 1, and 2 cm^3 (identical patient as in Figs. 1 and 2, dose volume parameters for this schematic patient example can be taken from Fig. 5).

GEC-ESTRO – Example

Pötter R et al, Radiother Oncol 2006.

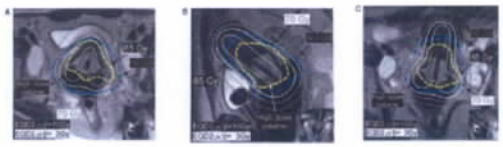


Fig. 3. MR based 3D treatment plan with relevant dose volume parameters for GYN, HR-MR CTV and OAR (at time of brachytherapy applans), Fig. 1). Pelvic MR at time of brachytherapy and treatment plan in (a) transverse, (b) paresagittal, and (c) paracoronal orientation with MR compatible applicator in place (vaginal packing with diluted gadolinium (1:1), rectal tube, bladder balloon with diluted gadolinium (1:10) and defined bladder filling (50 cm^3)). Tumour and cervix have shrunk significantly (for details compare Fig. 1) after combined radiochemotherapy (I) evenly with a residual tumour mass (high signal intensity) of 3.9 cm width x 3.5 cm height x 3 cm thickness (= 12 cm^3) and some grey zone in the left proximal parametrium corresponding to findings from clinical examination, after laparoscopic lymph node sampling there are lymphocytes in both obturator regions. GTV, HR CTV, IR CTV, and OAR (bladder, rectum, sigmoid) are contoured. Isodose lines are given for the total dose of IM $D_{90(EQD2)}$ (α/β = 10 Gy), the prescribed dose (PD) for the HR CTV, for 70 Gy(α/β = 3 Gy) as a significant dose for rectum and sigma, for MR $D_{90(EQD2)}$ (α/β = 10 Gy) related to the HR CTV and for 2000 cm^3 of the brachytherapy dose representing the high dose volume.

Clinical impact of IGBT

- Potter et al – MR-based brachy 145 patients
- 2 treatment periods 1998-2000 and 2001-2003
  - better plan optimization, needles
- 20% improvement in local control tumors > 5 cm
  - (64% to 82%)
- 30% improvement in overall survival
  - (28% to 58%)
- G3/4 late GU and GI toxicity reduced 10% to 2%

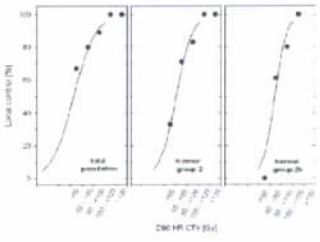
Potter, R et al *Radiother Oncol* 2007

Clinical impact of IGBT

- Potter et al – 156 patients 2001-2008
  - D90 > 85 Gy
  - D2cc rectum/sigmoid < 75 Gy
  - D2cc bladder < 90 Gy
- Local control 98 % 2-5 cm, 92% > 5 cm
- Overall survival 72% 2-5 cm, 65% > 5 cm
- 11 Grade 3 or 4 toxicities
- 70% relative reduction in pelvic recurrence with significant decrease in morbidity

Potter, R et al *Radiother Oncol* 2011

Dose response relationships



EMBRACE trial

- BT treatment planning will be based on **MRI imaging with the applicator in situ** according to the GEC-ESTRO guidelines and additional criteria for MRI sequencing, contouring, applicator reconstruction, and dose optimization. **The intention is to treat the whole cervix and the remaining residual tumour tissue at the primary site at time of BT (high risk-clinical target volume, HR-CTV) to a dose level analogue to the dose level previously prescribed for point-A.**

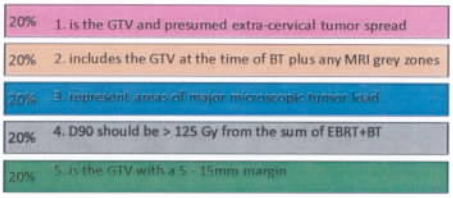
But really...
What is the target????

References

- Dimopoulos, JCA, et al. Intercbserver comparison of target delineation for MRI-assisted cervical cancer brachytherapy: application of GYN GEC-ESTRO recommendations. Radiotherapy Oncol 2009 [91:166-72.
- Dimopoulos, JCA et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. Radiotherapy and Oncology 2008 [83]:113-15.
- Dimopoulos, JCA, et al. Recommendations for Gynaecological (GYN) GEC-ESTRO Working Group IV: basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. Radiotherapy Oncol 2012 103(1): 113-122.
- Gill, BS et al. National Cancer Data Base Analysis of Radiation Therapy Consolidation Modality for Cervical Cancer: The Impact of New Technological Advancements. IJROBP 2014 90(5): 1083-1090.
- Haie-Meder, C et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group I: concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiotherapy Oncol 2005 74: 235-45.
- Han, K et al. Trends in the utilization of brachytherapy in the United States. IJROBP 2013 87(1):111-119.
- Hricak, Het al. Early Invasive Cervical Cancer: CT and MR Imaging in Preoperative Evaluation—ACRIN/GOG Comparative Study of Diagnostic Performance and Interobserver Variability. Radiology 2007 245(2):491-498.
- Mitchell, DG et al. Early Invasive Cervical Cancer: Tumor Delineation by MRI, CT and Clinical Examination, verified by Pathologic results in the ACRIN 6651/GOG 183 study. J Clin Oncol 2008 26(36):5687-5694.
- Potter, R et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group II: concepts and terms in 3D image-based treatment planning in cervical cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiotherapy and Oncol 2006 [78]: 67-77.
- Potter, R et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy for locally advanced cervical cancer. Radiotherapy Oncol 2007 83(2):148-55.
- Potter, R et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiotherapy Oncol 2011 100(1):116-23.
- Rijkmans, EC et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. Gyn Oncol 2014 135: 231-238.
- Tanderup, K et al. Curative radiation therapy for locally advanced cervical cancer: brachytherapy is NOT optional. IJROBP 2014 88(3): 537-9.

Questions

As defined by GEC-ESTRO, the high risk CTV (HR-CTV)



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As defined by GEC-ESTRO, the high risk CTV (HR-CTV)

2 - includes the GTV at the time of brachytherapy plus any MRI grey zones.

The HR CTV includes the whole cervix and presumed extracervical spread. An MRI is performed at the time of brachytherapy to define the GTV and MRI grey zones, which are both included in the HR CTV. The HR CTV is thought to represent macroscopic tumor load and as such should receive doses > 85 Gy. Recent dose volume analyses have suggested a D90 HR-CTV goal of > 87 Gy.

As defined by GEC-ESTRO, the intermediate risk CTV (IR-CTV)

20% 1. For limited disease, is the HR-CTV plus a margin

20% 2. For extensive disease, is the HR-CTV plus a margin

20% 3. Is thought to represent macroscopic tumor load

20% 4. D90 should be > 87 Gy from the sum of EBRT + BT

20% 5. Includes any MRI grey zones

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As defined by GEC-ESTRO, the intermediate risk CTV (IR-CTV)

1 - IR-CTV for limited disease is the HR-CTV plus a margin.

For extensive disease, this volume is based on the GTV at the time of diagnosis. The IR CTV is thought to represent microscopic disease, and as such should receive 60 Gy.

Implementing image guided brachytherapy using GEC-ESTRO guidelines has been shown to

20% 1. Reduce local control for tumors < 5 cm

20% 2. Improve local control for tumors > 5 cm

20% 3. Increase Grade 4 treatment related GU/GI toxicity

20% 4. Increase Pelvic Recurrence

20% 5. Prevent the use of IMRT boosts

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Implementing image guided brachytherapy using GEC-ESTRO guidelines has been shown to

2 - Improve local control for tumors > 5cm.

Implementation of IGBT using GEC-ESRO guidelines has been shown to improve local control for tumors of any size, improve overall survival for patients and reduce toxicity