Defining targets for brachytherapy

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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% in 1988 to 58% in 2009
  - Patients treated with brachytherapy higher SURVIVAL
    - Both C55 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???
Anatomy

Pelvis: Vagina and Proximal of Female
Midopened Section

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
  - >18 cancer

![Image](Hribal.pdf)

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 prescription
- 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

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) \( (GTV_{br}, GTV_{br}, GTV_{br} \text{ etc}) \) – Macroscopic tumor volume at time of brachy as detected by clinical examination and as visualized on MRI.


GEC-ESTRO – HR CTV

- High risk CTV \( (HR \text{ CTV}_{HR}, HR \text{ CTV}_{HR}, HR \text{ CTV}_{HR} \text{ etc}) \) – includes GTV\(_{HR} \), the whole cervix, presumed extra-cervical tumor spread
  - Includes MRI "grey zones"
  - Represents macroscopic tumor load


GEC-ESTRO – IR CTV

- Intermediate Risk CTV \( (IR \text{ CTV}_{IR}, IR \text{ CTV}_{IR}, IR \text{ CTV}_{IR} \text{ etc}) \) – supposed to represent areas carrying a significant microscopic tumor load
  - High-risk CTV + 5-15 mm margin
    - Limited disease (<4 cm): IR CTV\(_{IR} = HR \text{ CTV} + \text{margins}:
      - AP: 5 mm, cranio-caudal: 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\(_{HR} \), superimposed on imaging obtained at time of brachytherapy

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?


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The biologically effective dose B(ED) according to the LQ model is given by

\[
B(ED) = D \left[ 1 + \frac{d}{2(\alpha/\beta)} \right]
\]

while \(g(\text{BED}) = \frac{2^m - 1}{m} \frac{1 - e^{-m}}{m} \) and \( m = \frac{1.1 T}{\alpha} \)

\( g \) repair function, 1 for EBRT and HDR brachytherapy

GEC-ESTRO – Dose

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• Problem: LDR? HDR? PDR brachytherapy? How to report dose?

The biologically effective dose (BED) according to the EQ model is given by

\[
BED = N \left( 1 + \frac{d}{d_{EQ}} \right), \quad \text{while} \quad d_{EQ} = \frac{d}{1 - e^{-d/T}}
\]

\(N\) repair function, 1 for EBRT and HDR brachytherapy.

The equivalent external beam therapy dose using conventional fractionation of 2 Gy per day (EQD):

\[
EQD = \frac{R(\alpha/\beta)}{1 + \frac{R(\alpha/\beta)}{d}}
\]

\(R\) calculated as \(R(\alpha/\beta) = 1 + \frac{\alpha}{d} d/\beta\)

GEC-ESTRO – Dose

• The EQD 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 from EBRT and brachytherapy, with the assumption that both of brachytherapy receive the full EBRT dose – "worst case" assumption
• For nonfractionated treatment (brachy and EBRT), this parameter works for evaluation after the last fraction, as it uses summed doses of all fractions.


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

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


Fig. 6. Schematic anastomosis diagram (posterior view) indicating the most irradiated tissue volumes adjacent to the applicator for rectum, sigmoid and bladder (0.1, 1, and 2 cm² identical phantom as in Figs. 1 and 2). (See appendix for this schematic phantom example can be drawn from Fig. 2.

GEC-ESTRO – Example


Fig. 7. ATP post-B treatment with rectal dose volume isosurfaces. Near the rectum, the high-dose (100%) isosurfaces are surrounded by a large volume of dose intermediate (50% to 150%) and low dose (10% to 50%). This figure demonstrates the impact of the rectal dose on the surrounding normal tissue.

Fig. 8. ATP post-B treatment with rectal dose volume isosurfaces. The figure shows the dose distribution in the rectum and surrounding tissue, highlighting the importance of dose planning in rectal surgery.

Fig. 9. ATP post-B treatment with rectal dose volume isosurfaces. The figure illustrates the relationship between the dose distribution and the surrounding critical structures, demonstrating the need for precise dose management.
Clinical impact of IGBT

- Potter et al – MR-based brachy 145 patients
  - 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 Radiat 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 Radiat Oncol 2011

Dose response relationships

![Dose response graphs](image)
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

Questions

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

- 20% 1. Is the GTV and presumed extracervical tumor spread
- 20% 2. Includes the GTV at the time of BT plus any MRI grey zones
- 20% 3. Opposite cervix or major microscopic involved area
- 20% 4. D90 should be > 125 Gy from the sum of EBRT+BT
- 10% 5. In the CTV with ± 1.5 cm margin

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)

1. For limited disease, is the HR-CTV plus a margin
2. For extensive disease, is the HR-CTV plus a margin
3. Incl. any microscopic tumor-bed
4. D90 should be >87 Gy from the sum of EBRT + BT
5. Incl. any MRI gray zones

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

1. Reduce local control for tumors < 5 cm
2. Improve local control for tumors > 5 cm
3. Increase Grade 4 toxicity related to GU/GI toxicity
4. Increase Pelvic Recurrence
5. Prevent Use of MWA as boost
Implementing image guided brachytherapy using GEC-ESTRO guidelines has been shown to

2 - Improve local control for tumors > 5 cm.

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