A Century of Cervical Cancer Brachytherapy: Evolving Methods and Practices

Patricia J. Eifel
UT MD Anderson Cancer Center
Houston, Texas

Röntgen ray treatment

- Specialized vaginal intracavitary x-ray tubes by 1905
- Used for several decades because of radium shortage

“Radium is a very convenient substance at a point where the application of X-rays is impossible or exceedingly difficult”

Pusey and Caldwell, 1904

The receptacle: Early applicators

Whickham and Degrais, 1905 (Paris)
Kelly and Burnham, 1915 (Hopkins)

First photo of gynecological radium applicators

Early Intracavitary systems

Stockholm
Paris (Regaud)
Manchester
Early Intracavitary systems

1920s

Stockholm

Forniceal boxes added to increase lateral penetration
Rapid dose rate (22 hrs x 3)
>100 mg of $^{226}$Ra
Complications

1930s

London Curie Clinic

Early Intracavitary systems

1920s

Stockholm

Ernst applicator
(Barnard, St. Louis)

Fixed system, easy to use
Sources close to surface
High complication rates
Abandoned in 1970s

1940s

1990s

Ring applicator

Fixed system, easy to use
Sources close to surface
Early Intracavitary systems

- Designed to improve penetration
  - 2 cm corks – as far lateral as possible
- Low dose rate
  - (~ 60 mg $^{226}$Ra, heavy filtration)
  - Near continuous in one 5-10 d session
  - Total mg-hrs fixed
  - Supplemental parametrial x-rays

The Manchester System Evolves from Paris System

Comparing Paris, Stockholm (MCI), Manchester

- When dose equalized at vaginal surface:
  - Paris, Manchester superior to Stockholm/MCI
- When dose equalized at cervix (Pt C):
  - Paris, Manchester superior to Stockholm/MCI
The Manchester System What Made it Different?

- The applicators
- The dosage system
- Therapeutic techniques
- Attention to
  - Normal tissue tolerance
  - Anatomic variations

The Manchester System: Point A

Detailled studies of the nature and course of RT necrosis

- 1938 hypothesis:
  - Necrosis secondary to damage to paracervical vessels (not direct effect on rectum/bladder)
- Definition of a "paracervical triangle"
- Definition of "Point A" as a "point of limiting tolerance"

Tod and Meredith BJR 11:809, 1938

Anatomical studies of regional spread patterns:
- Broad ligament lymphatics
- Obturator node
- Definition of "point B"

Context: Only 250 KV available for external beam RT

Tod and Meredith BJR 11:809, 1938

Manchester: The dosage system:

"For techniques in general use [Stockholm, Paris], the dose is stated in mg-hrs taking no cognisance of the different arrangements made necessary by variations in size and shape of the organs…"

Tod and Meridith, 1938
The Manchester System: Point A (1938)

Anatomic study of female pelvises (Sandler)
- Variable vaginal capacity

1. Maximize ovoid size
2. Maximize separation
   - Maximize Pt B dose
   - ~ Constant Pt A dose

Manchester – 1953 modifications

- Refined point A definition
- Starting point changed from external os to fornix
- Modified loadings
  - Tandem:ovoids ↑
  - Total Ra (dose rate) ↓

Manchester – 1953 modifications

1938 1953

2 cm (small) ovoids

1938 1953

2.5 cm (med) ovoids
Manchester – 1953 modifications

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- Starting point changed from external os to fornix
- Modified loadings
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2 cm (small) ovoids

The MD Anderson (Fletcher) System

- Non-fixed applicators
  - Individualized positioning
  - Handles improve control

Preloaded Applicators (1953)

- Vaginal applicators
  - Ovoid ➔ "Cylindroid"
  - Internal shields

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Preloaded Applicators (1953)

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- Megavoltage radiation
  - Cobalt
  - Betatron (25 MV)
Applicator selection

- Tandem
  - Uterine length
  - Distribution of disease in cervix/uterus
  - Uterine position/flexion

- Vaginal applicators
  - Size of cervical tumor
  - Vaginal involvement
  - Vaginal capacity

Treatment Specification – Fletcher/MDACC System

- Optimized placement

**Treatment Specification – Fletcher/MDACC System**

- Optimized placement
- Standard loadings/duration
  - Tailored to clinical parameters
  - Control linear intensity in tandem
  - Limit vaginal surface dose
  - Limit integral dose to pelvis
  - 6000–6500 (mg-hrs)
**Treatment Specification – Fletcher/MDACC System**

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  - Control linear intensity in tandem
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  - Limit integral dose to pelvis
    - 6000–6500 (mg-hrs) after 40–45 Gy

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**LDR/PDR radiotherapy: General principles**

- Optimized system geometry
- Optimized source positions/dwell weights
- Loadings that produce an optimal dose rate
  - < 40 cGy/hr to normal tissues
  - 40–50 cGy/hr at Pt A
- Treat to normal tissue tolerance

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**After-loading**

Henschke et al., Radiology 74:834, 1960

- Major advance in radiation safety
- Major deviation from Manchester design
  - Vaginal/uterine sources in parallel
  - Spherical "ovoids"
Remote after-loading
Henschke et al., Cancer 96:45, 1966

“Manchester-style” applicator
The MD Anderson (Fletcher) System
- Megavoltage EBRT
- Novel applicators
  - Flexible
  - Internal shields
  - After-loading (1963)

Fletcher-Suit Applicator (1963)

The MDACC Modification of Manchester
- Megavoltage EBRT
- Novel applicators
  - Flexible
  - Internal shields
  - After-loading (1963)

FSD (Selectron) Applicator (1988)

Fletcher-Williamson applicator: Adaptation of FSD for PDR/HDR
- Vaginal ovoids:
  - Perpendicular vaginal source arrangement
  - Internal shields
- Tandem
  - Continuous curvature
  - Choice of angles
  - Adjustable length
- Adjustable yoke controls relationship between T&Os

Applicator system: Tandem and ring vs. FW
- Ring:
  - No shields
  - Higher VSD
    - Less activity in vagina
    - Lower depth dose
  - Ring tandems:
    - Fixed lengths (2, 4, 6)
    - Straight configuration
The MDACC Modification of Manchester

- Megavoltage EBRT
  - Cobalt, Betatron (1954)
- Vaginal applicators
  - Ovoid → "Cylindroid"
  - Internal shields
- Non-fixed applicators
  - Individualized positioning
  - Handles improve control
- After-loading → RAL


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Central recurrence:
- IB1: 1–2%
- IB2–II: 10–15%
- III: 25–30%

Death from disease:
- IB1: 10–15%
- IB2–II: 30–40%
- III: 50–60%

Overall rate of major (≥ G3) complications in 3489 patients

At 10 years:
- Rectum: 3.3%
- Sigmoid: 0.2%
- Sm Bowel: 4.2%
- Bladder: 3.0%
- All types: 11.2%

Influence of central EBRT dose on DSS and major complications in 907 patients with Stage IIIB Cervical Cancer at MDACC (Logsdon et al. IJROBP 43:763, 1999)
Cervical ICRT applicators – Two major lineages.

Stockholm

Paris

Applicator system:
Tandem and ring vs. FW

Ring applicator
- Fixed geometry
  - Consistent source arrangement
  - Limited customization
  - Sources close to mucosa
    - ↓ depth dose
    - ↑ mucosal dose
    - ↓ surface area exposed
  - No shields

Applicator systems:
Tandem and ring vs. FW

Ring applicator
- Fixed geometry
  - Consistent source arrangement
  - Limited customization
  - Sources close to mucosa
    - ↓ depth dose
    - ↑ mucosal dose
    - ↓ surface area exposed
  - No shields

Applicator system:
Tandem and ring vs. FW

Ring (vs FW):
- No shields
- Higher VSD
  - Less activity in vagina
  - Lower depth dose
- Closer to cervix
- Exposed vaginal surface area may be less
Applicator system:
Tandem and ring vs. mini-ovoids

Similarities:
• Source close to surface
• No shields

Specific to ring:
• Ring source closer to surface than mini-ovoid
• Anterior positions available
  - Rarely used
• Fixed tandem lengths

Loadings: converting LDR to PDR

Tandem:
35–40 mgRaEq in 6–7.5 cm

Ovoids:
Small: 10–15
Medium: 15–20
Minis: 5–10

Similarities between HDR & LDR/PDR

• Pt evaluation and preparation
• Integration with EBRT
• Applicator selection parameters
• Applicator placement
• Treatment planning rules
• Skill set

PDR: Selection of dwell times

Forward planning:
• Dwell times that mimic standard loadings
• Subtle adjustments based on image-based findings
Controlling normal tissue doses

- Be careful of using drag tools to alter reference doses
  - Renormalizes to Pt A
  - Can have unexpected effects on doses beyond reference pts
    - Cervix
    - Sigmoid

Point A - Manchester reference point

- Never meant to be used outside of strict Manchester system rules
  - Bears little relation to tumor
  - Insufficient for dose prescription
- Position varies with applicator placement

Dose specification
ICRU 38 (1985)

- Recommendations for reporting (not prescription)
- Included elements of several systems
  - Manchester (Point A)
    - Recommended for reporting but not prescription
  - Creteil (60 Gy reference volume)
  - TRAK (analogous to mg-hrs)
- Defined normal tissue reference points

So many choices

- Dose rate
- LDR # fxs
- HDR Interval
- Dose rate
- PDR Pulse interval
- PDR Dose/pulse
- Dose specification
- Integratio
- with EBRT
- Chemo-RT
- Loading
- Applicators
- IMRT

How do we choose?
How do we predict outcome?

3D Image-based treatment planning

More U.S. radiation oncologists caring for fewer cervical cancer patients
Facilities with limited experience (PCS1996–99)

- 52% of U.S. facilities treated ≤ 2 cases/yr
- 60% of small facilities that treated CX cancer treated ≤ 2 pts/yr
- 28% of pts were treated in a facility that treated ≤ 2 pts/yr
- 21% of pts had brachy in a facility that treated ≤ 2 pts/yr

Number of Cases of Intact Cervical Cancer Treated in 42 Surveyed Facilities (QRRO 05-07)

- 12% — No Brachy
- 14% — Incomplete RT
- 25% — > 66 d

Treatment vs. facility size (PCS 1996-1999)

- EBRT only
  - < 50/yr: P = 0.0005
  - ≥ 50/yr: P < 0.0001
- RT > 7 days
  - < 50/yr: P = 0.03
  - ≥ 50/yr: None

Recipe for high-quality brachytherapy treatment

- Carefully considered treatment plan
  - Forward planning
- A skillful, dedicated team
- Collaboration
- Communication
- Skill
- Experience
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And that, in simple terms, is how you should cook.

Tools for 3D image-based planning

- Ultrasound
- CT
- MRI

Unsuspected uterine perforation

- Outcome not affected if detected
- Incidence of undetected perforation unknown

Ultrasound guidance
Repositioning after CT evidence of perforation

**Implant Geometry**

Does the tandem bisect the ovoids?
- Goal: center the source on cervix
- Tandem should usually bisect the ovoids
- Posterior displacement can lead to a very high rectal dose superior to the ovoids

**Implant Geometry**

Is the posterior packing adequate?
- Malposition
  - Posterior ovoid displacement
- Inadequate packing
  - Caudad to ovoids
  - Between ovoids

Key to safe HDR: “anatomical advantages of ICRT eliminate the need for LDR”
Key to safe HDR: “anatomical advantages of ICRT eliminate the need for LDR”

18.4 Gy (Pt A)
19 Gy (R 3D Max)
24 Gy (Pt A)
10 Gy (R 3D Max)

HDR vs PDR/LDR?

18.4 Gy (Pt A)
19 Gy (R 3D Max)
24 Gy (Pt A)
10 Gy (R 3D Max)

IGBT – Special problems
- More accurate estimate of tumor dose
- Boost extensive paracervical extension

3D brachytherapy dosimetry
Potter et al. Radiother Oncol 78:67, 2006
**Diagnosis**

MRI 1st fraction

**IGBT — Special problems**

- More accurate estimate of tumor dose
- Boost extensive paracervical extension

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**Boost matched to ICRT distribution**

MR guided interstitial brachytherapy


- Interstitial reconstruction CT vs. MR
  - Patients must be imaged with legs down
  - Protection of bladder or rectum
  - No inadvertent insertion of interstitial catheter into bladder or rectum noted on CT after MR
3D brachytherapy dosimetry

Potter et al. Radiother Oncol 78:67, 2006

Recommendations based on MR-imaging

- GTV – T2 bright areas
- HR-CTV – cervix + visible/palpable disease at brachy
- IR-CTV – 1 cm margin around HR-CTV + initial sites of involvement


Organs at Risk: Bladder, Rectum, Sigmoid

- Point versus volume

GEC ESTRO recommended dose recording

Organs at risk: D0.1cc, D2cc

Target: D90, V100

© 2cm difference ICRU Bladder and D2cc value
Empirical methods of treatment specification (Manchester, Fletcher)

Pros:
- Decades of experience
- Excellent results if used properly

Cons:
- Not well understood
- Difficult to teach
- Often used improperly with potentially disastrous results
- Not well extrapolated to innovative approaches

3D Image-based planning

Pros:
- Improved understanding of dose to critical structures
- Improved basis for comparison of different methods
- Teaching tool

Cons:
- Limited clinical outcome data
- Imperfect understanding of critical tolerance thresholds
- Leads to compromises in application of tried and true methods

Effect of FSD Shields on ICRT dose distribution

- Anterior and posterior shields
- Not modeled in treatment planning software
- Increasingly excluded from "Fletcher-type" applicators

Influence of shielding on ICRT dose to bladder and rectum (Gifford et al.)

- Marked reduction in anterior rectal dose for most cases
- Decreased dose to ICRU point
- Up to 25% reduction in maximum rectal dose
Reduction in overall dose to ICRU rectal reference point with rectal shields in FSD ovoids

- Marked reduction in
  - Contribution from ovoids (up to 40%)
  - Overall dose from ICRT (up to 28%)
- Variable impact

3-D imaging and optimization with shielded ovoids

CT artifact from FSD shields

- Methods of improving safety of ICRT:
  - Internal shields
  - Image guidance

CT artifact from FSD shields

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How to resolve conflicting goals?
Methods of improving safety of ICRT:
- Internal shields
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- Internal shields
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How to resolve conflicting goals?

Conclusions – Image guided brachytherapy
- 3D IGBT should be an important means of improving on past successes
- Image guidance can, at a minimum, reduce the risk of certain disastrous errors (e.g., perforation)
- Dependence on variable CTV/GTV specification in the context of a steep dose gradient can lead to wide variations in applications
- These methods should be employed while retaining a connection with past methods
- Clinical trials are urgently needed

Learning from experience...