

Advancing Care Through Teamwork

How Medical Physicists and Medical Doctors Can Work Together to Create Change.

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Disclosures

Clinical Educator and Consultant to Isoray Medical, INC.

Consultant to Radiadyne, LLC

Objectives

Review epidemiology of Gynecologic Cancers including treatment

Discuss the role of complex brachytherapy procedures

Discuss Permanent Interstitial Brachytherapy (PIB)

Describe the team process for adapting new therapies using PIB as an example

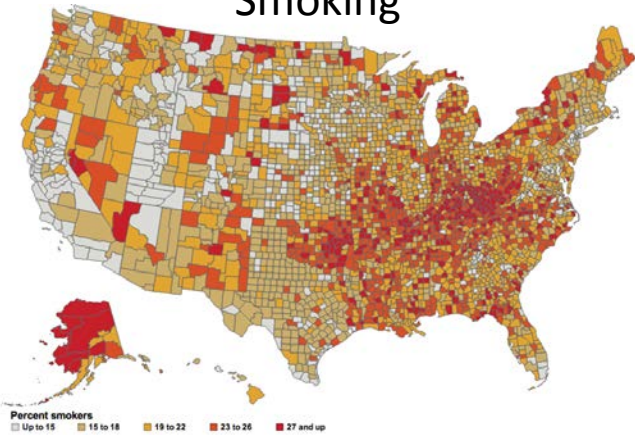
- Discuss initial isotope selection for PIB
- Applicability and selection of patients for PIB
- Review our personal experience with Cesium-131 PIB
 - Curative treatment of recurrent disease
 - Integration of PIB into initial therapy for complex cases
- Suggest how to incorporate new modalities into your current brachytherapy program

Kentucky – what do we do well?

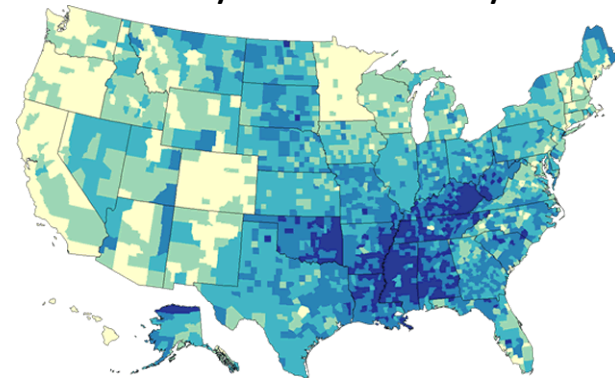


Kentucky – what do we also do well?

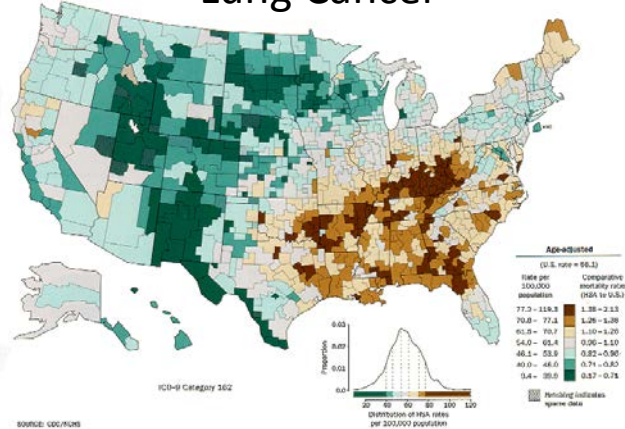
Smoking



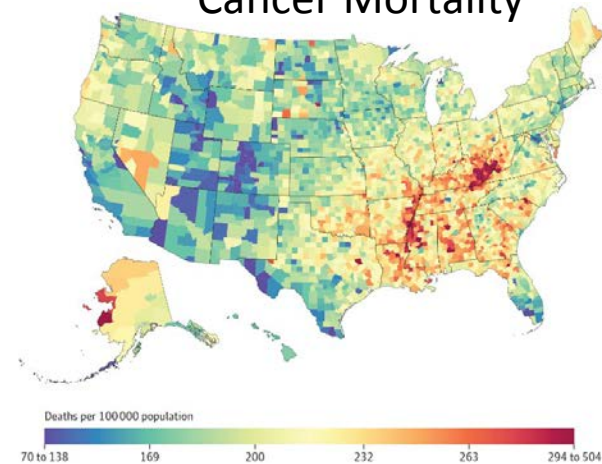
Physical Inactivity



Lung Cancer



Cancer Mortality



Risk Factors for Gynecologic Cancers

Ovarian Cancer – familial and sporadic cancers

Uterine Cancer – obesity

Cervical Cancer, Vaginal Cancer, & Vulvar Cancer – Human papilloma virus (HPV)



Gynecologic Cancer Treatment

Uterine Cancer

- Early stage = surgery then external radiation \pm brachy
- Advanced stage = surgery then external radiation + brachy

Cervical Cancer

- Early stage = surgery then external radiation \pm brachy
- Advanced stage = external radiation + brachy

Vaginal Cancer

- Early stage = surgery then external radiation \pm brachy
- Advanced stage = external radiation + brachy

Vulvar Cancer

- Early stage = surgery then external radiation \pm brachy
- Advanced stage = external radiation + brachy

Improvements in Gynecologic Cancer Treatment in last 20yrs

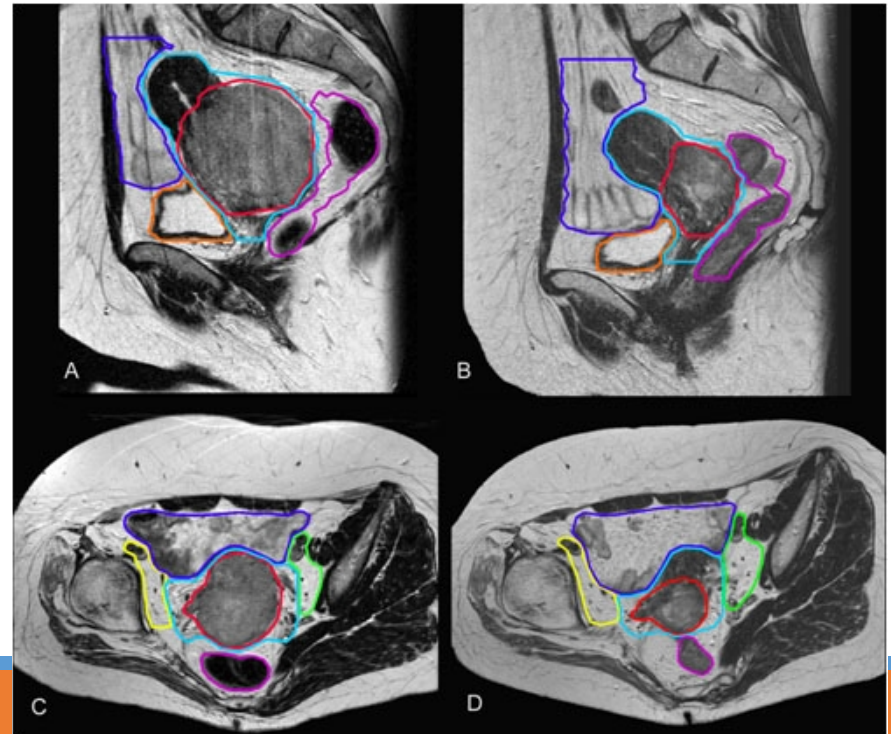
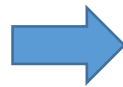
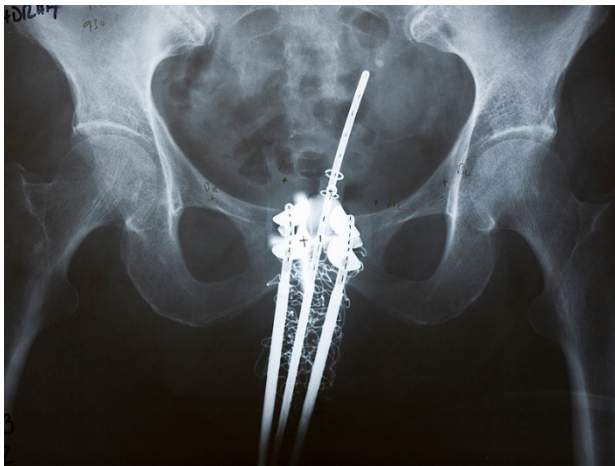
- Addition of chemotherapy to pelvic radiation therapy results in 5% improvement in overall survival for Cervical Cancer
- Transition from low dose rate (LDR) brachytherapy to high dose rate (HDR) brachytherapy resulting in improved patient quality of life (QOL), reduced exposure to radiation staff, and reduce cost for care
- Use of Intensity Modulated Radiation Therapy (IMRT) for post-operative gynecologic cancers resulting in significant reduction in acute and late GI toxicities
- Advent of image-guided brachytherapy

Image Guided Brachytherapy

Improved delineation of gross disease and target volumes

Improved identification of organs at risk

Ability to identify changes between brachytherapy fractions and optimize treatments accordingly



Brachytherapy is Imperative!

Most important component of radiation therapy for gynecologic cancers

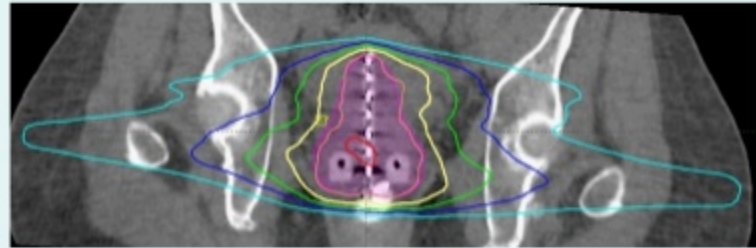
- Superior survival outcomes seen with use of brachytherapy in cervical cancer and vaginal cancer
- Benefits cannot be replaced with advanced techniques such as Intensity modulated radiation therapy (IMRT) or stereotactic body radiotherapy (SBRT)
- Omission of brachytherapy has been associated with as much as a 30% decrease in cancer-specific survival

Despite the proven benefits, there has been a consistent decline in brachytherapy utilization since 1998

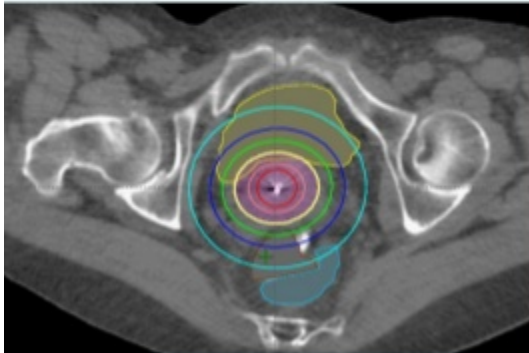
HDR



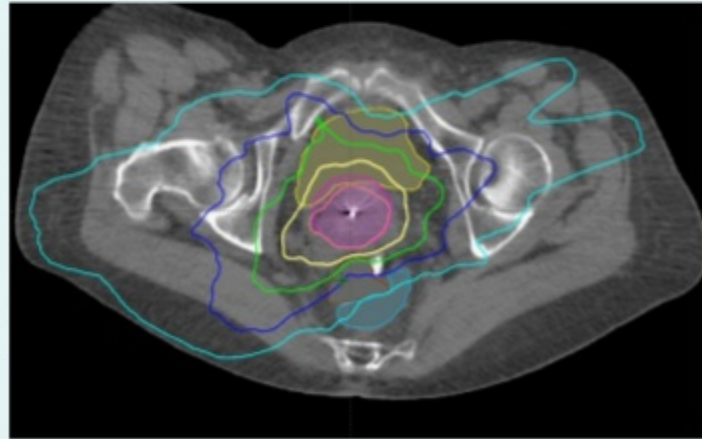
SBRT



HDR



SBRT



Images courtesy of A. Damato

Question #1

In a recent Surveillance, Epidemiology, and End Results (SEER) registry trial by Orton et al., what was the benefit observed with the use of brachytherapy in women with any stage of primary vaginal cancer?

- a) The use of brachytherapy significantly reduces the risk of death from vaginal cancer regardless of the stage of tumor
- b) Brachytherapy can be replaced by advanced radiation techniques such as SBRT, IMRT, etc.
- c) Brachytherapy only benefits women with larger tumors
- d) None of the above are TRUE.

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Reference: Orton A, Boothe D, Williams N, Buchmiller T, Huang YJ, Suneja G, Poppe M, Gaffney D. Gynecol Oncol. (2016) June; 141 (3): 501-6.

Common Barriers to Performing Brachytherapy

Physician training and experience

Facility expenses, equipment, and maintenance

Appropriate physics support

Medical knowledge

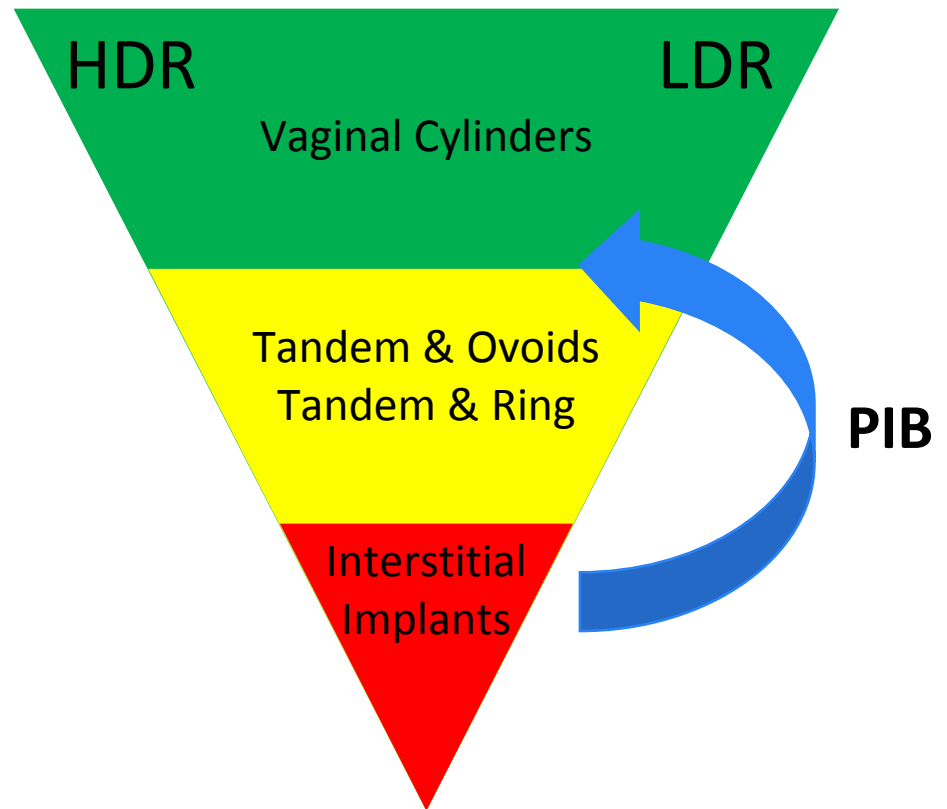
Patient health and performance

Tumor related

Increased utilization of other radiation techniques: IMRT, SBRT

Brachytherapy Options

Radiation
Oncologist's
Comfort Zones
(most Radiation Oncologists)



Question #2

Which of the following are common reasons that the utilization of brachytherapy has declined in recent years?

- a) Increased utilization of non-invasive radiation techniques such as SBRT and IMRT
- b) Inadequate training of Radiation Oncology residents in brachytherapy techniques and skills
- c) Facility limitations and cost for purchasing and maintaining brachytherapy equipment
- d) All of the above are cited reasons for the declining use of brachytherapy.

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Reference: Gill BS, Lin JF, Krivak TC, et al. National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements. Int J Radiat Oncol Biol Phys 2014 Dec 1;90(5): 1083-90.

My 1st Medical Event for Brachytherapy

October 8, 2014 – 2:08 am

The Problem = Complex Interstitial Implants

Awful procedure for patients

- Morbid concept
- Long process

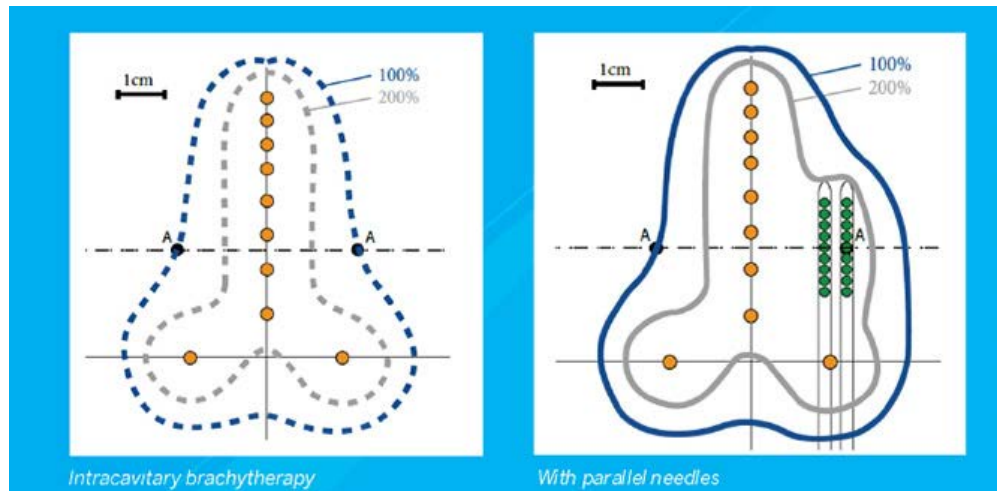
Many variables capable of going wrong:

- LDR – no routine re-imaging to assess for needle migration
- HDR – able to re-optimize plans in the event of migration, but ability to readjust needles is somewhat limited

Complex Interstitial Implants are necessary in certain situations¹:

- Bulky tumors not adequately covered by intracavitary techniques
- Large tumor size
- Involvement of the lower vagina, urethra, and/or rectovaginal septum

Hybrid Applicators – a partial solution



Question #3

What are the common clinical indications where an interstitial implant should be considered for women with gynecologic cancers?

- a) Large tumor size
- b) Involvement of the lower vagina and/or urethra
- c) Inability to appropriately cover a tumor using intracavitary techniques
- d) All of the above are indications for interstitial brachytherapy

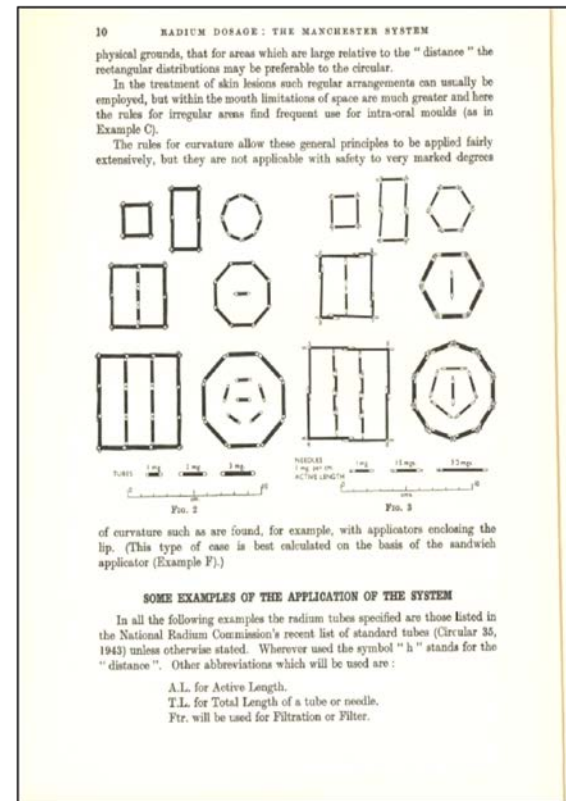
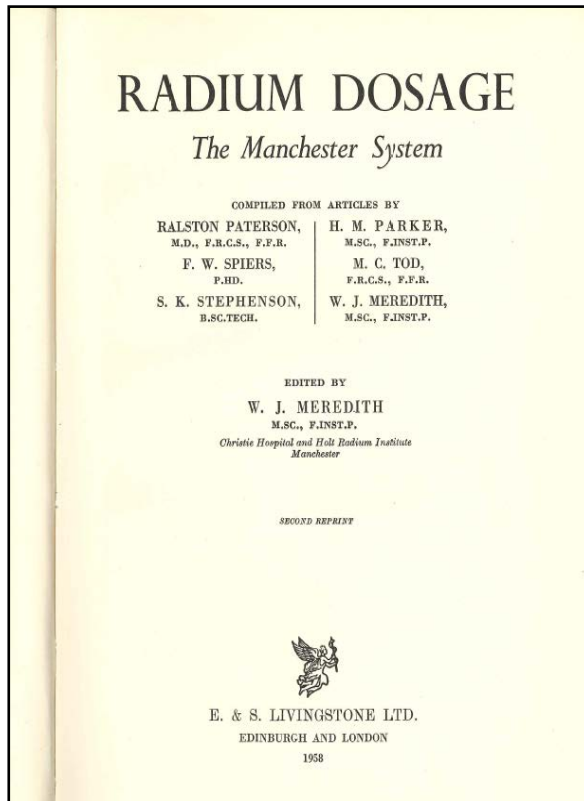
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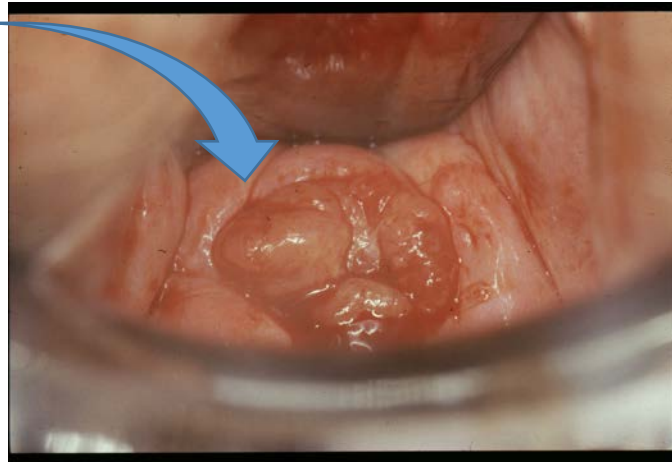
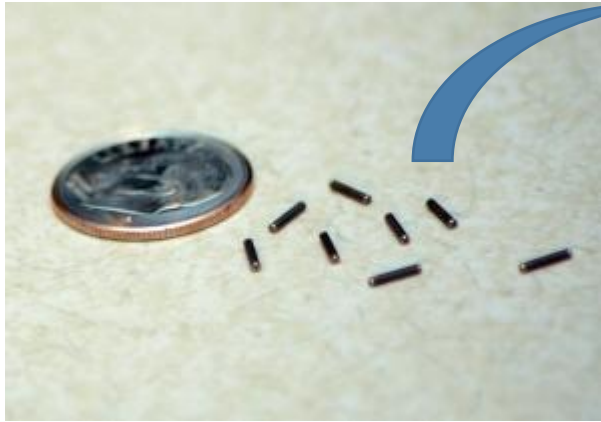
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Reference: Viswanathan AN, Thomadsen BC. American Brachytherapy Society cervical cancer recommendations, American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. Brachytherapy. 2012;11:33-46.

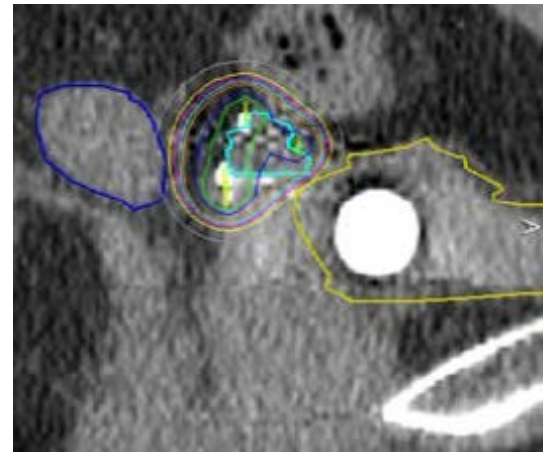
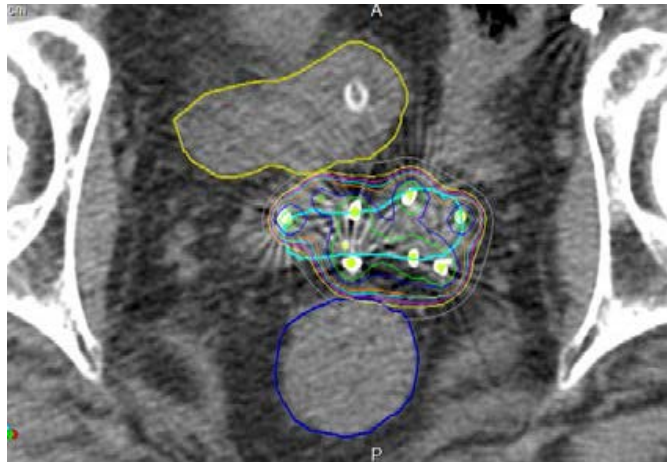
The Manchester System of Brachytherapy



"Non-uniform placement of sources to create a uniform dose distribution."



Single outpatient procedure
55 Gy to 5mm
Curative



Permanent Interstitial Brachytherapy

Ideal strategy for treating small volume disease

- High cumulative radiation dose
- Tightly conformal volumes
- Reduced toxicity compared to external RT
- Single application that can be done as an outpatient

What really makes PIB appealing?

Single treatment capable of delivering curative doses (> 50 Gy)

Ability to generate very tight dose distribution

No hospitalization required

Need for indwelling applicators for a few days was not necessary

Relatively straightforward regarding resources

Hand-calculations or using existing software (Prowess, Variseed, etc.)

Low toxicity rates and high curative potential

Initial Experience with Interstitial Re-irradiation (IRI) using Au-198

7 permanent seed implants (5 Au-198, 2 Pd-103)

6 temporary implants (LDR Ir-192, SNIT)

Mean and median implanted volumes: 14.3, 12 cc

9/13 (69%) had CR

6/14 (46%) NED 24-71 months later

Median f/u = 58 months

Only 1 possible complication: R-V fistula 22 months following SNIT, in presence of recurrent dz

IRI Favorable Prognostic Factors

Cervical and vaginal > endometrial

Squamous > adenocarcinoma

Smaller tumor volumes

Higher RT doses (≥ 50 Gy)

Permanent implants > temporary (SNIT)

Vaginal wall/suburethra > vaginal cuff

Longer disease-free intervals

Randall ME, Evans L, Greven KM, et al. Interstitial Reirradiation for Recurrent Gynecologic Malignancies: Results and Analysis of Prognostic Factors. *Gyn Oncol* (1993) 48: 23-31.

UK Experience with Permanent Isotopes in Gynecologic Cancers

30 year experience with permanent Au¹⁹⁸, particularly in gynecologic cancers (Randall)

No known experience to evaluate the safety/efficacy of Cs¹³¹ in gynecologic malignancies

Hypothesized Cs¹³¹ efficacy would be at least equivalent to Au¹⁹⁸ with the added benefit of lower radiation exposure for occupationally exposed personnel in 2010

Based on 6+ years of experience, UK is exclusively utilizing Cs¹³¹ for permanent interstitial brachytherapy for gynecologic malignancies

Brachytherapy Isotopes

Isotope	Half-Life	Mean Energy
Au-198	2.7 days	411.8 KeV
Cs-131	9.7 days	30.4 KeV
Pd-103	17 days	20.8 KeV
I-125	60.2 days	28 KeV

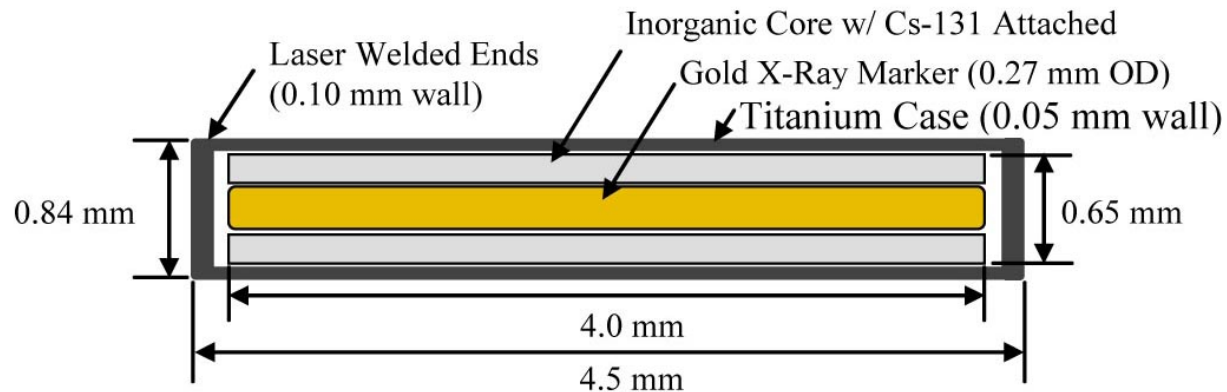
- Au-198 dosing is essentially equivalent to External Beam radiation therapy dosing
e.g. 50 Gy EBRT = 50 Gy Au-198 =

Favorable properties of Cesium-131

Short $\frac{1}{2}$ life translates into high initial dose rate (9.7 days vs. 2.7 days for Au-198)

Lower energy (30.4 KeV vs 411 KeV for Au-198) translates into adequate dose distribution with better radiation safety*

Relative equivalence to Au¹⁹⁸ facilitating clinical dosing/conversions



UK Dosimetric Modeling Studies for ^{131}Cs

Multiple Monte Carlo simulations to evaluate optimal distribution of activity

- Essentially comparing Quimby vs Manchester rules
- Goal of adequate coverage and homogeneity of dose distribution.

Determined that optimal planning was based on Paterson-Parker (Manchester) rules for permanent implants (uneven distribution of activity to create more homogeneity)

To determine doses, used BED formalism to estimate, then adopted correction factor (compared to Au^{198}) based on clinical experience = 1.1

UK Initial Experience using Cs-131

14 patients treated with a total of 17 Cs-131 permanent implants

- 10 implants for recurrent gynecologic cancers
- 7 implants for definitive treatment, and used as a boost

Included spectrum of gynecologic sites and pathologies for primary and recurrent cancers

UK Initial Experience using Cs-131

Actuarial local control at 12 months = 84.4%

Two local failures occurred 5 and 7 months after the implant

One patient was able to gain local control through re-implantation

The second received a dose of 44 Gy to largest implant area of 17.5 cm³

Probability of tumor control correlated most closely with Doses > 45 Gy and Small Tumor Size

Question #4

What prescription dose for permanent interstitial brachytherapy using Au-198 or Cs-131 appears to be a threshold for controlling gross disease?

- a) 25 Gy
- b) 35 Gy
- c) 45 Gy
- d) 55 Gy
- e) 65 Gy

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References:

Randall ME, Evans L, Greven KM, McCunniff AJ, Doline RM. Interstitial reirradiation for recurrent gynecologic malignancies: results and analysis of prognostic factors. *Gynecologic oncology*. 1993;48:23-31.

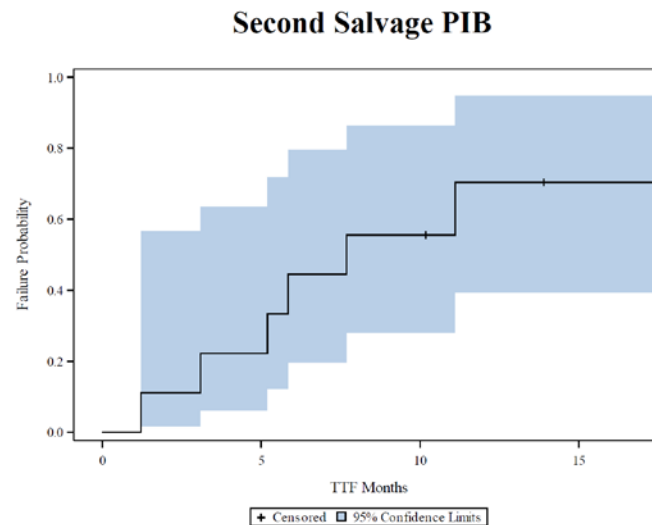
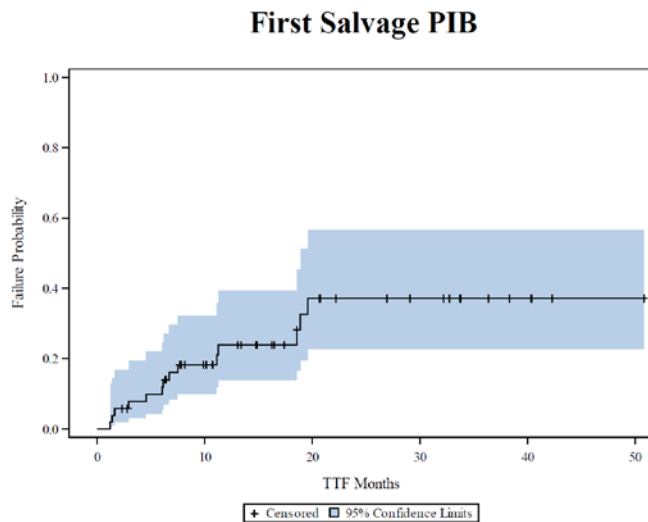
Wooten CE, Randall M, Edwards J, et al. Implementation and early clinical results utilizing Cs-131 permanent interstitial implants for gynecologic malignancies. *Gynecol Oncol*. 2014; 133 (2): 268-73.

Updated UK Experience for Re-Irradiation

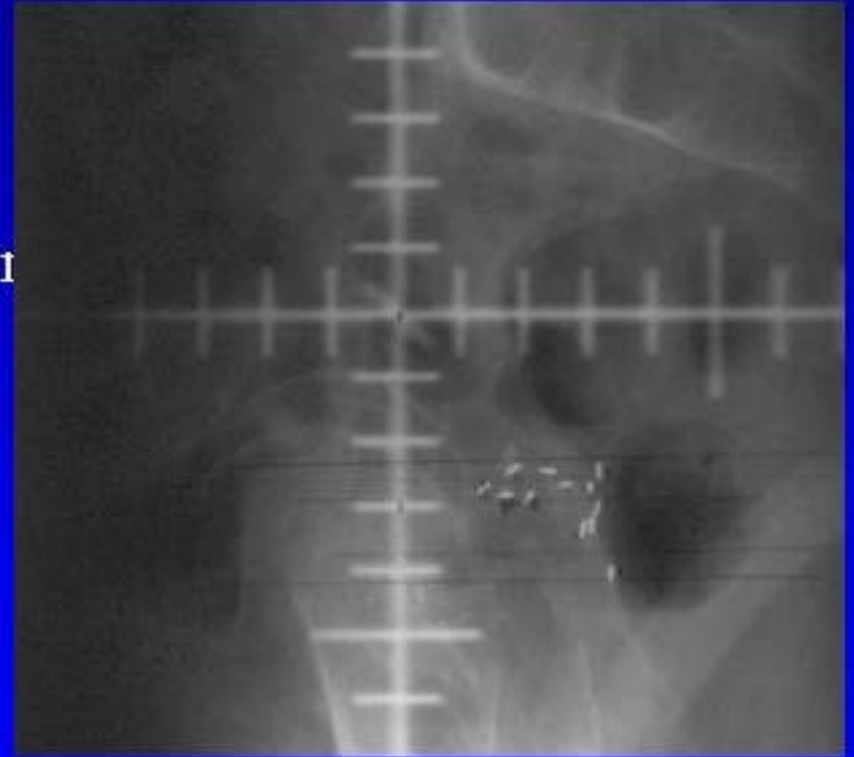
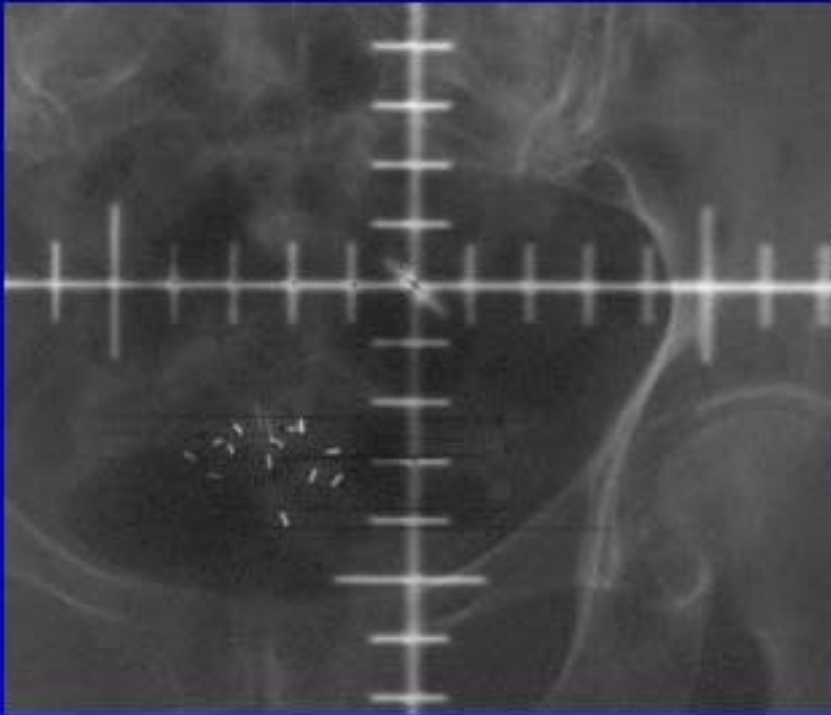
61 PIB implants performed for re-irradiation of a pelvic malignancy

Median F/U 14.6 months

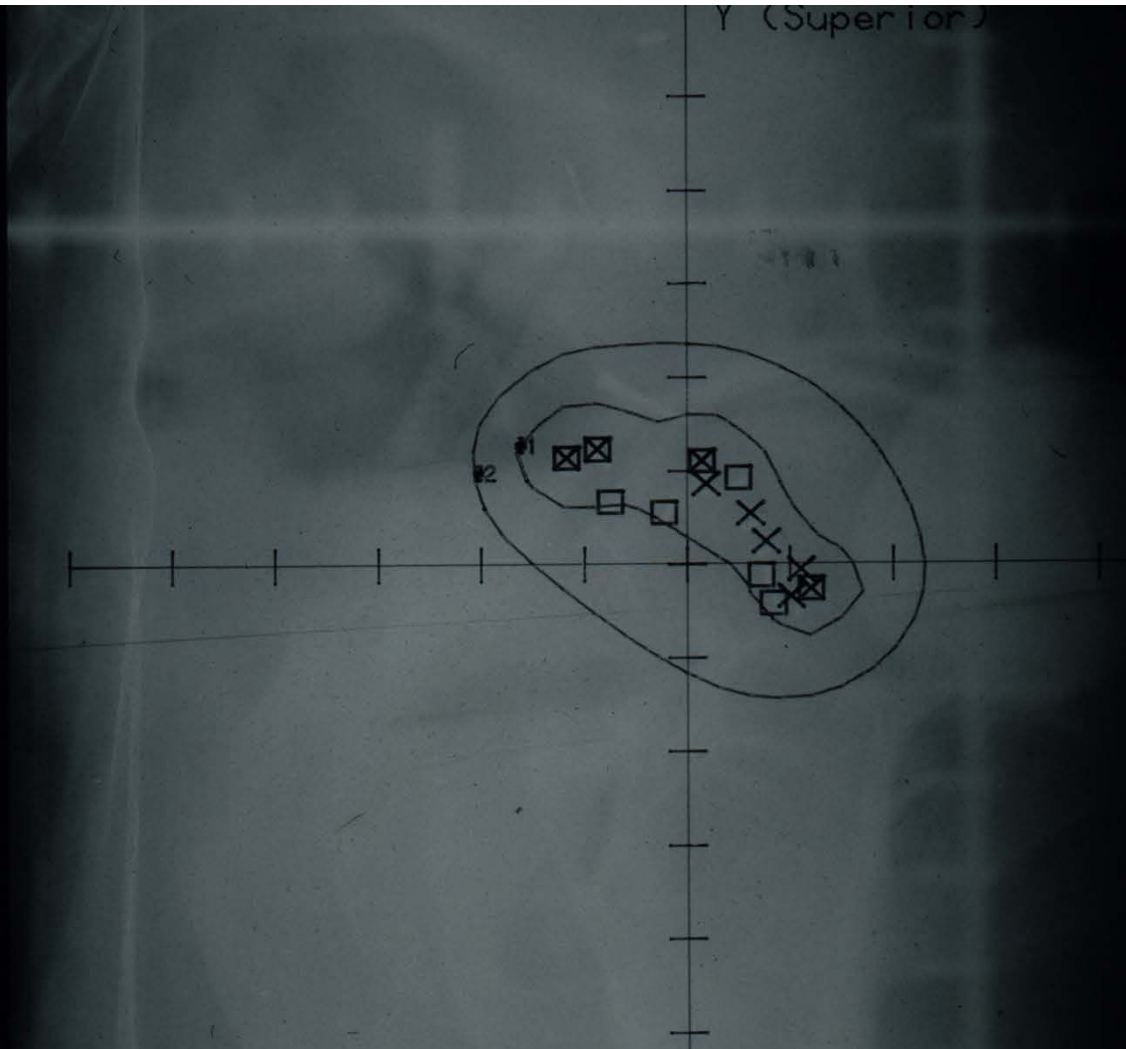
- Median time to failure was not reached for 1st attempt at salvage
- Median time to failure was more than 8 months for 2nd attempt at salvage




Orthogonal Radiographs of an Interstitial Au-198 Implant of a Vaginal Cuff Recurrence



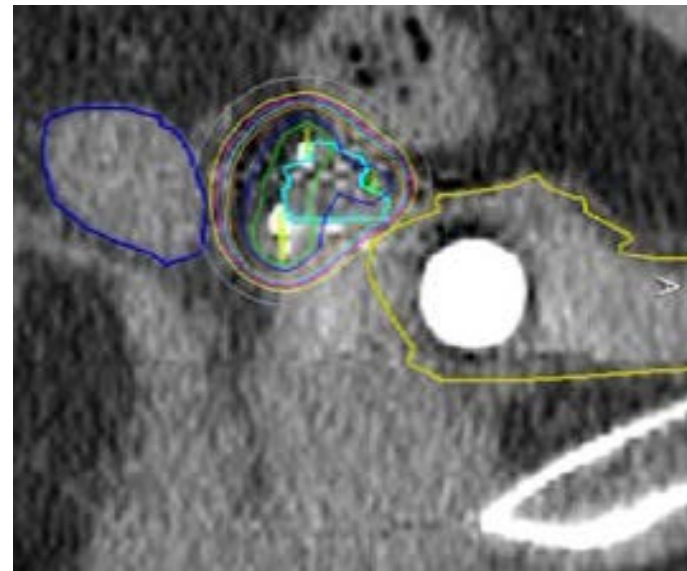
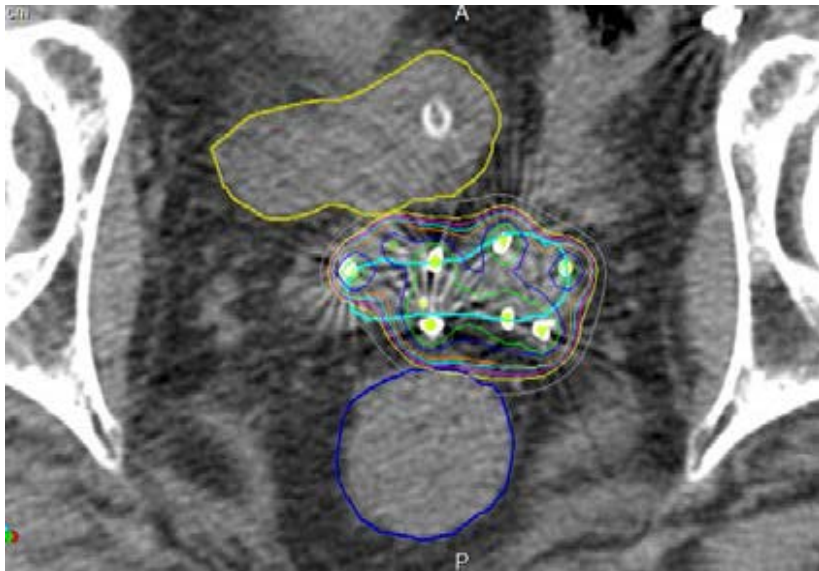
Reconstructed 50 Gy Dose Cloud



Improving Workflow

 HealthCare Department of Radiation Medicine Cesium-131 Seed Strength Calculation		Patient Name: _____ Hospital Number: _____ Date of Birth: _____
Cs-131 Prescription Dose (Gy)=	<input type="text"/>	Number of Seeds= <input type="text"/> <input type="text"/>
BED Equivalent Au-198 (Gy) ¹	0	<small>¹W. Luo et al., "Determination of prescription dose for Cs-131 permanent implants using the BED formalism including re-sensitization correction," Med. Phys. 41, (2014)</small>
Treatment Distance (cm)=	<input type="text"/>	
Treatment Length (cm)=	<input type="text"/>	
Treatment Width (cm)=	<input type="text"/>	
Treatment Area (cm ²)=	0	
Activity in RaEq/10Gy=		
Activity in Au198 (mCi) =	0.00	
Conversion to Cs131 (mCi) ¹	0.00	
Activity per Seed (mCi)=	#DIV/0!	
Air Kerma Strength per Seed (U)=	#DIV/0!	
Radiation Oncologist:	_____	
Medical Physicist:	_____	

Migration to CT Planning PIB



Or at least CT post-planning

Why not use our experience
with small volume PIB to
revamp Complex Interstitial
Implants?

Why use PIB with Cs-131 in definitive therapy?

Template-guided interstitial implants are not ideal*

- Prolonged bedrest
- Hospitalization
- Patient limitations
- Practice limitations

Intracavitary techniques are often not acceptable

Hybrid applicators are not always available and have limitations

Conventional interstitial techniques can be overkill

Relative ease of calculating dose (multiply EBRT dose X 1.1)

Radiobiologic benefits of low dose rate brachytherapy is suggested to result in lower rates of late toxicity

Interstitial Implants = Torture (well some are...)

Typical LDR Implant

2-3 days bedrest

Epidural pain pump

Inability to appropriately use the bathroom

Risks for:



We Can Do Better

Long term... patients have post-traumatic stress disorder (PTSD)

What about HDR?

- Same overall process, but without isolation
- Multiple fractions
- Ability to optimize dwell positions, so better plans

Potential Risks of Permanent Template Guided Implants

High risk to patient if needles placed inappropriately

- “Once you put radiation in, you can’t take it back”
- Very high reliance on image-guided therapy

Due to decay characteristics of Cs-131 compared to Ir-192 – in certain cases, more needles may be required to generate equivalent plans

Strands migrate according to location to the pelvic diaphragm...

How did the first PIB Syed Happen?

Patient with recurrent endometrial cancer despite chemotherapy and previous radiation x2

Medically unfit to undergo a multiple day implant

Lived in another state so unable to undergo multiple fractions

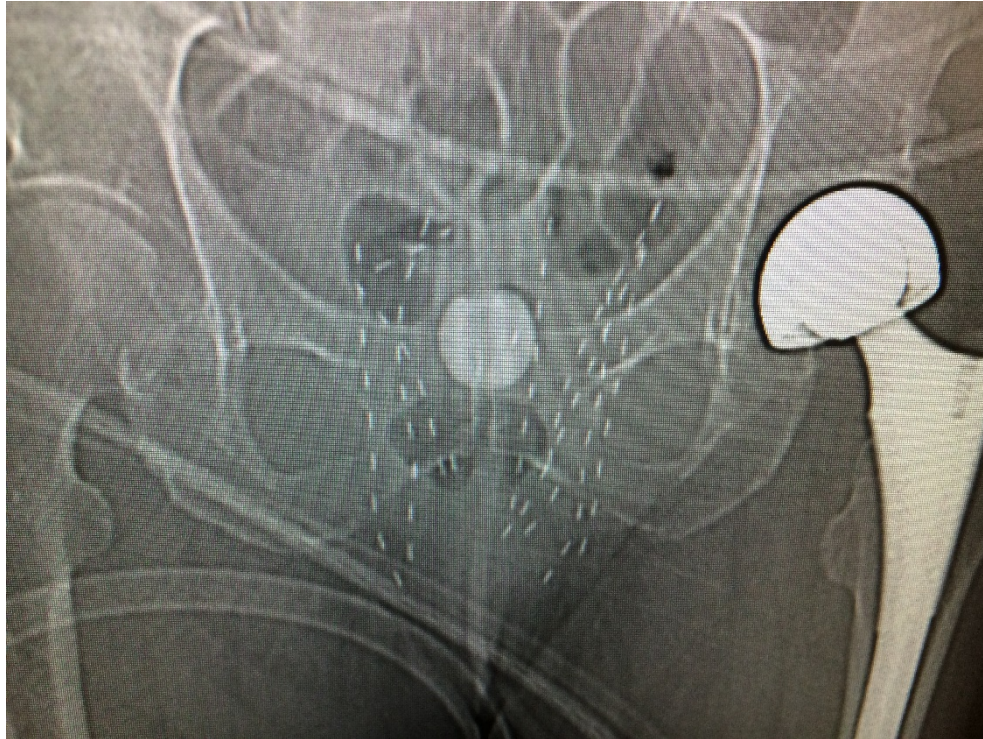
Extensive discussion and planning with brachytherapy physicist

- Graph paper
- Prowess
- Hand calcs
- Proposed workflow (next slide)

Revised Workflow for Cesium-131 Template-Guided Implants

1. All needle positions pre-planned
2. Patient enters the procedure suite
3. Exam performed and template sutured to perineum
4. Needles advanced based on pre-planned arrangement and distances obtained from diagnostic imaging
5. Once all needles have been placed, patient awakens from anesthesia
6. Transfer patient to the CT simulator
7. Needles adjusted and unsheathed incrementally using CT
8. Patient completes recovery and is discharged home

1st PIB Syed



What did we learn from our first PIB Syed?

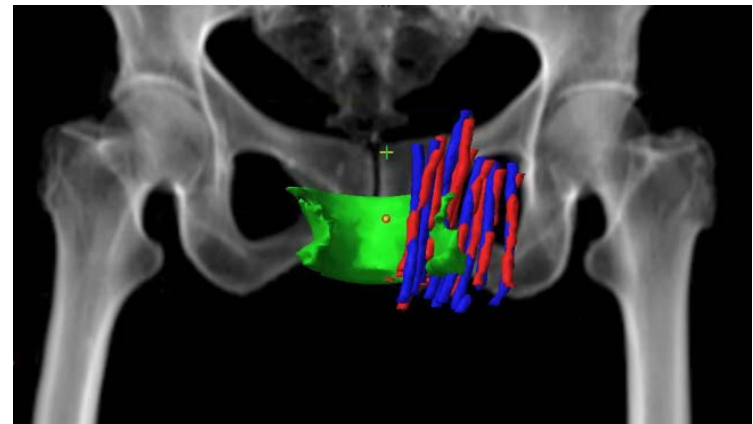
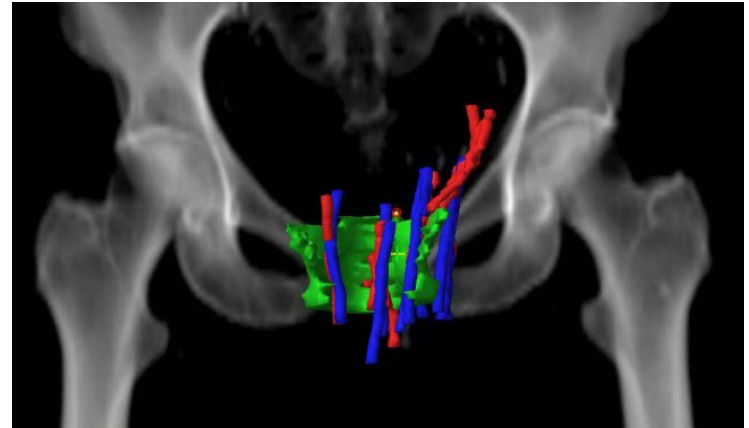
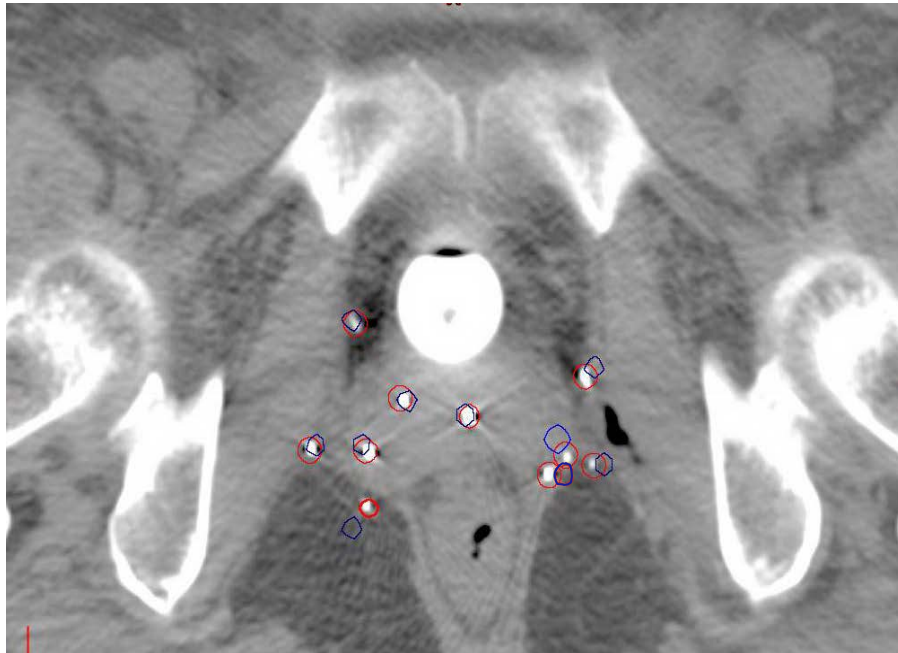
1. The Procedure room and CT simulator doesn't fit a lot of people
2. Needle insertion is not perfect and not as accurate as what you plan
3. Some patients awake from anesthesia quite rapidly
4. After recovering for 5-10min, patients can only really tolerate a few needle adjustments, and with small increments
5. When placing 15+ needles... its really hard to look at axial or sagittal CT slices, and pick out the exact 3 needles and run and adjust it and be correct
6. Plan ahead the an artificial hip is going to make needle identification difficult

First 5 Patients Treated with a Permanent Template-Guided Interstitial Implant

Cesium-131 PIB performed as salvage re-irradiation without any other treatment

- 3 Vaginal Recurrences of Endometrial Cancer with Side Wall Extension
- 2 Vulvar Recurrences with extension into the Vagina & PSW
- A total of 40 needles were placed:
 - Patients 1 & 2 utilized stranded sources
 - Patients 3-5 utilized a combination of stranded & unstranded sources
- Overall Results:
 - Well tolerated - No significant acute toxicities
 - 4/5 patients were discharged to home within 3 hours of Cs-131 Syed
 - 1st patient admitted for 23hr observation – nothing happened
- Strand/seed positions were re-evaluated 2-3 weeks later with a repeat CT

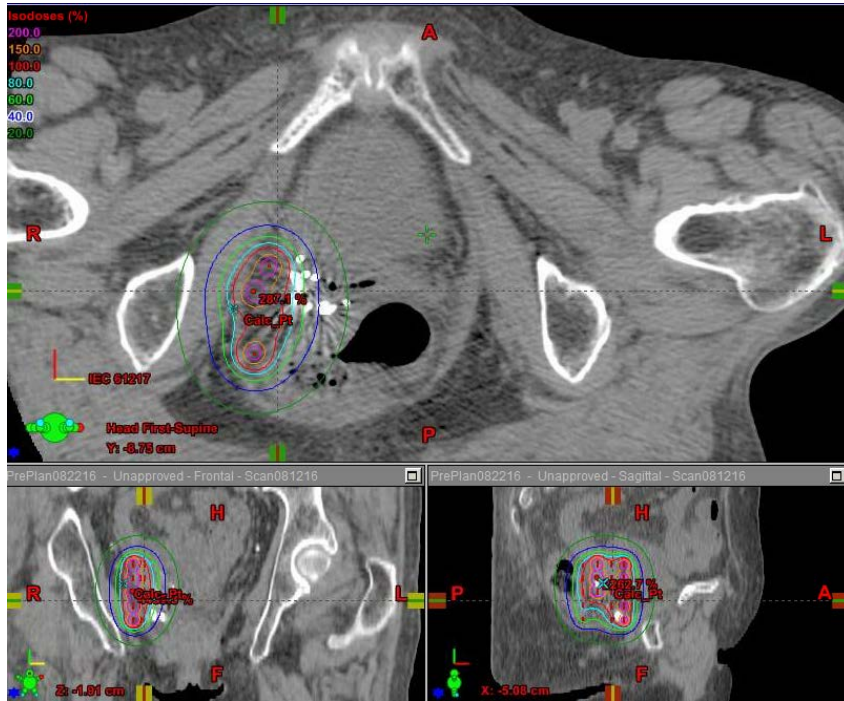
Strand Migration



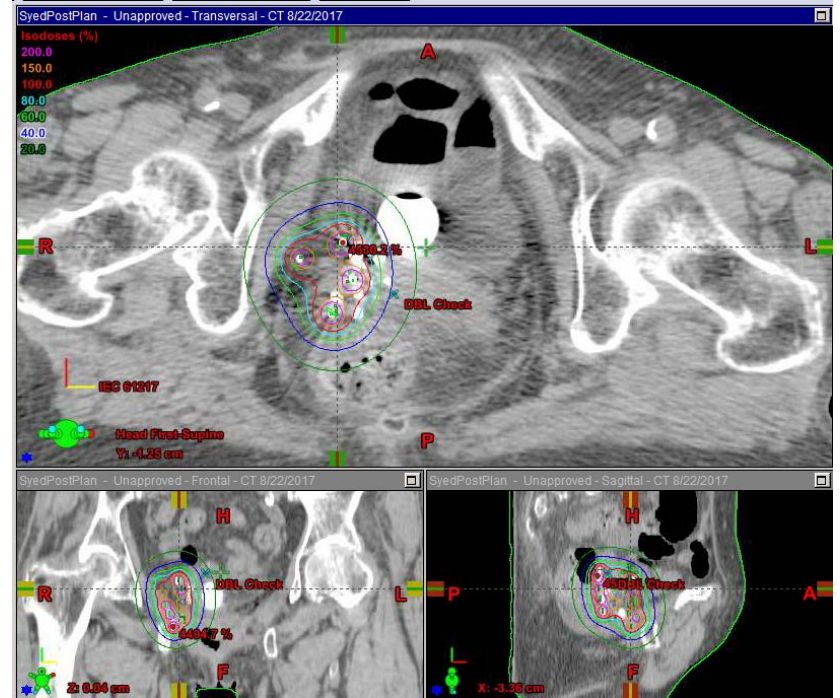
Making changes and improving the process

1. Structured templates for needle positions
2. Input coordinates for needle positions into Eclipse Brachyvision and all interstitial plans are now pre-planned
 - Able to use CT or MRI
 - Improved needle placement and spacing
 - Revise our active lengths according to organs at risk
 - Gain a better insight into the source strengths and dose
3. Incorporation of Image-guidance – combinations of ultrasound, fluoroscopy, and CT
4. Manipulation of existing equipment

Pre-Plan



Actual Implant



Revised Workflow for Cesium-131 Template-Guided Implants

1. Modify the template prior to procedure to enable use of trans-rectal ultrasound
2. Patient enters the procedure suite
3. Exam performed, TRUS positioned, and template sutured to perineum
4. Needles advanced based on pre-planned arrangement and distances obtained from diagnostic imaging under direct-ultrasound guidance
5. Needles adjusted and unsheathed visually using ultrasound; template removed
6. Patient awakes from conscious sedation
7. Transferred to CT Simulator for confirmatory imaging
8. Patient completes recovery and is discharged home

UK PIB Syed Experience

Since 2014, more than n=32 permanent interstitial procedures have been performed with at least 6 months follow-up

- Median PTV volume: 36.4 cm³ (14-128 cm³)
- Average source strength: 1.8 u/seed
- Median # Needles: 8 (5-21)
- Median Active Length: 5cm (3-11cm)

- Control rate 77%
- Only 2 patients have experienced a grade 2+ toxicity as a result of the permanent implant

- Only one patient has been admitted for an overnight hospital stay (#1)

Question #5

What makes permanent interstitial brachytherapy an ideal treatment approach in cases where re-irradiation is necessary?

- a) A curative dose of radiation can be delivered in a single procedure and limited to only the area of interest
- b) Treatment can be delivered between multiple fractions thereby minimizing toxicity
- c) The delivery of radiation using low dose rate techniques may potentially reduce the rate of late toxicities
- d) A and B are correct
- e) All of the above are correct

Question #5

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Reference: Wooten CE, Randall M, Edwards J, et al. Implementation and early clinical results utilizing Cs-131 permanent interstitial implants for gynecologic malignancies. *Gynecol Oncol.* 2014; 133 (2): 268-73.

Final Thoughts Regarding PIB

“Another tool in the shed”

- Cs-131 dose characteristics very appealing
- Relatively easy, Clinical brachytherapy procedure
- Capable of delivering therapeutic doses in a single implant
- Low Cost
- Multiple different treatment applications & potential

How did this work?

Hard-headed physician

Right patient population

Hard-working and very smart physicists

- One perfectionist
- One quiet and extremely diligent at doing long, complex equations
- One determined to make the process more straightforward, reproducible, and accurate

Supportive staff

Special Thanks

Marcus Randall, MD

Prakash Aryal, PhD

Wei Luo, PhD

Dennis Cheek, PhD

Dave Lockhart

Penny Ross, RN

Laura Reichel, RN