London Health Sciences Centre

Radiation Treatment for Gynecological Cancers

David P D'Souza
Chair/Chief of Radiation Oncology
LHSC/Western University

Schulich
MEDICINE & DENTISTRY

- Honorarium/Invited Speaker/Consulting:
- Abbvie, TerSera, Knight, AstraZeneca

- No conflicts of interest relevant to this presentation

My presentation

- Hardest part was determining what to include in a very BROAD topic in a relatively short time

- Case – initial aspects
- Some principles of radiotherapy and its use
- Use of radiotherapy for gynecologic cancers
- Use of brachytherapy for gynecologic cancers
- Case – outcomes and lessons learned

Case History

- 42 year old female presents with gush of vaginal bleeding after lifting weights

Past Medical History

- Known Lynch Syndrome
- Underwent left salpingo-oophorectomy 11 years prior for mucinous adenocarcinoma of ovary (14 cm, Stage 1A, 6 left pelvic and 2 left para-aortic nodes neg)
- 10 months prior underwent lap assisted hysterectomy and RSO as was undergoing fertility treatments and noted to have endometrial thickening – bx: endometrial hyperplasia
- Path: Grade 1 endometrial cancer, 1/9 mm myometrial invasion, LVSI-
- MSH2 and MSH6 deficient on IHC consistent with Lynch
- No further treatment recommended

Exam

- Patient was examined by Gyn Onc with nothing seen
- CT Abdomen/Pelvis clear

- Examined two months later by general gynecologist and noted to have a fungating mass at top of vagina

- On pelvic examination, there is a mass measuring 4 cm from left to right, 3 cm from end to post and approximately 3 cm in height. Left vaginal fornix obliterated, but the right side preserved. No obvious disease coming down the anterior, posterior or lateral walls of the vagina.

- **Microscopic Description (Verified)**

- Sections show an adenocarcinoma. Most of it has the appearance of a conventional endometrioid adenocarcinoma with focal areas of squamous metaplasia. Most of the tumor is consistent with a grade 1 endometrioid adenocarcinoma. Intermixed with this are areas that have a higher grade appearance. In these areas there is significant nuclear pleomorphism, prominent nucleoli and increased mitotic activity.
-
- Immunohistochemistry results:
- Positive: PAX-8, estrogen receptor, progesterone receptor, p53 (in higher grade areas)
- Negative: napsin

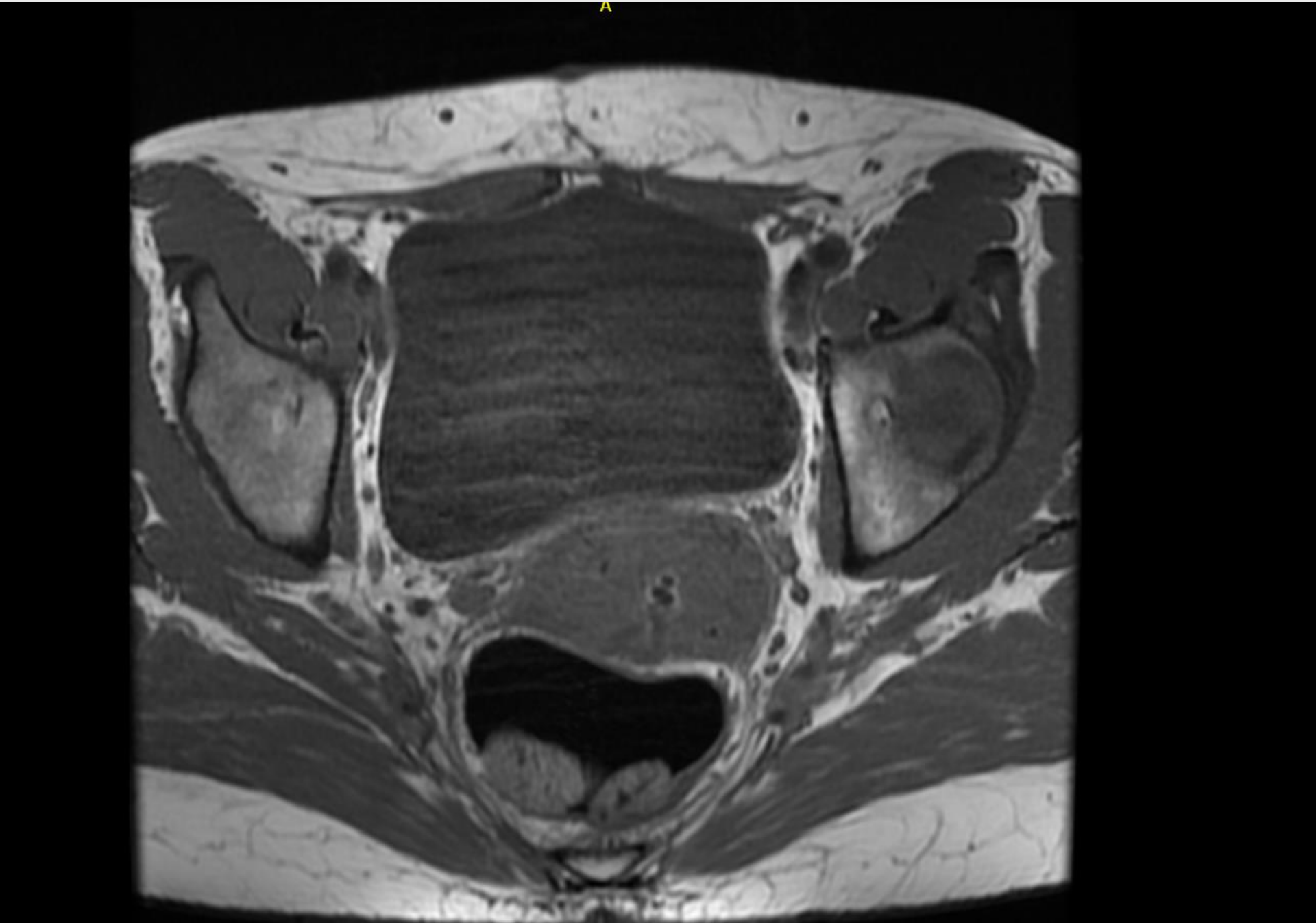
- **Diagnosis (Verified)**

- Vaginal vault biopsies:
- - features consistent with recurrent endometrioid adenocarcinoma, with focal high grade component.

- MR Pelvis

- 5.7 x 6.2 x 4.5 cm mass mid-upper vagina
- Lobulated extensions superiorly involving adjacent loop of sigmoid colon – most likely involving bowel serosa
- Extends to rectovaginal and bladder fat planes
- Abnormal left obturator LN 8.8 mm with similar signal to mass


H
F
13 of 33


A

Radiotherapy

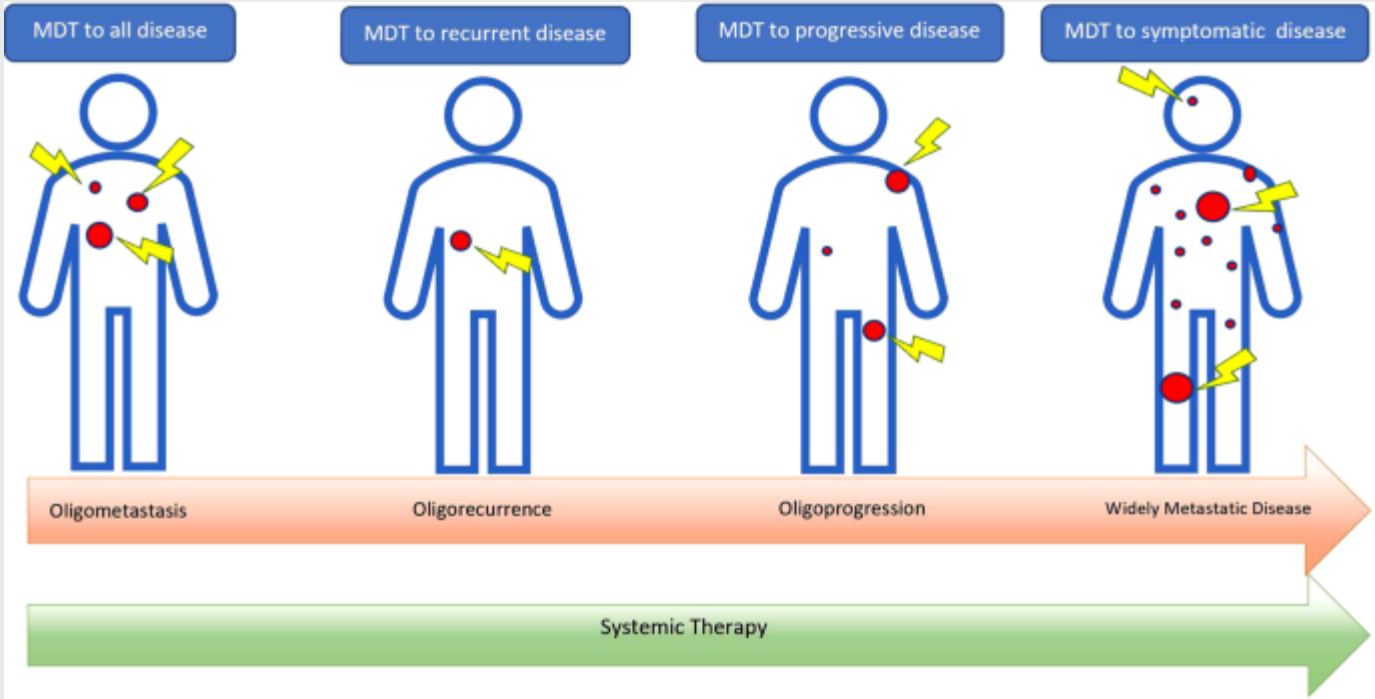
- Delivery of ionizing radiation (machine or radioactive source) to treat cancer (>99% of what is treated)
- Due to the infrastructure needed – specially shielded rooms, equipment (basic radiation machine costs $2.25 million), personnel is placed in regional centers
- That said, it is delivered efficiently in Ontario and remains a cost effective modality for treating cancer and much less than some drugs that may extend life by months and cost >$100k/year
- (bevacizumab $40k/y, pembrolizumab $80k/y)

- Numerous evidence-based indications for radiation – breast cancer, prostate cancer, lung cancer, cervix cancer which you likely are aware of

- Several newer indications that you may not be aware of…

- The term "oligometastatic" refers to the concept that if a patient has a limited number of metastases, they may achieve long-term disease control or even cure if all the sites of disease can be effectively treated

MDT – metastasis directed therapy



- SABR-COMET Trial

- Patients randomized to palliative standard of care or stereotactic ablative radiotherapy (SABR)
- 99 patients; 10 institutions
- Median f/u of 51 months
- 5-year Overall Survival rate 17.1% versus 42.3%
- Treatment did not have detrimental effect on QOL

Palma et al: JCO 2020

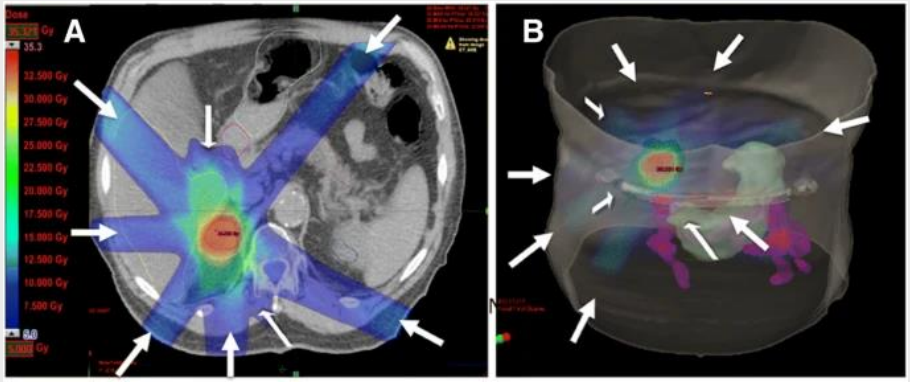
- Another pragmatic question…

- External beam radiation is standard of care (SOC) for pain relief of symptomatic bone metastases
- Question of whether radiating "high-risk" bone mets *prophylactically* reduced skeletal related events (SRE)
- RCT between SOC and radiation
- 78 patients with 122 bone mets at 3 institutions
- SRE: occurred in 29% versus 1.6% at 1 year
- Significantly fewer hospitalized
- Overall survival improved – unclear why

Gillespie et al: JCO 2023

- Additional sites radiated that before wasn't considered possible

- Liver – primary or metastasis
- Kidney cancers – non-operable candidates



Principles of Curative Radiation

- Give a high enough dose of radiation to the target volume to obtain "control" of disease
- Radiation needs to be delivered accurately
- Needs to be safe – acceptable dose to adjacent organs
- Acceptable/reasonable to patient and family in terms of schedule and its effects on QOL (financial, time away from family)

- Example: In some places in the US, treatment of prostate cancer was done over 8 weeks (M–F)

Cancer of the Uterus

- Radiation typically given after surgery with pathology features assessed
- If external beam radiation given it is 5 weeks of treatment
- Looked at delivering radiation using stereotactic approach (1.5 weeks) – initial study done and reported with treatment well tolerated (Sunnybrook & London).
- Second randomized trial close to completion comparing 5 weeks to 1.5 weeks

Leung et al: JAMA Oncol 2022

Gynecologic Oncology in Ontario

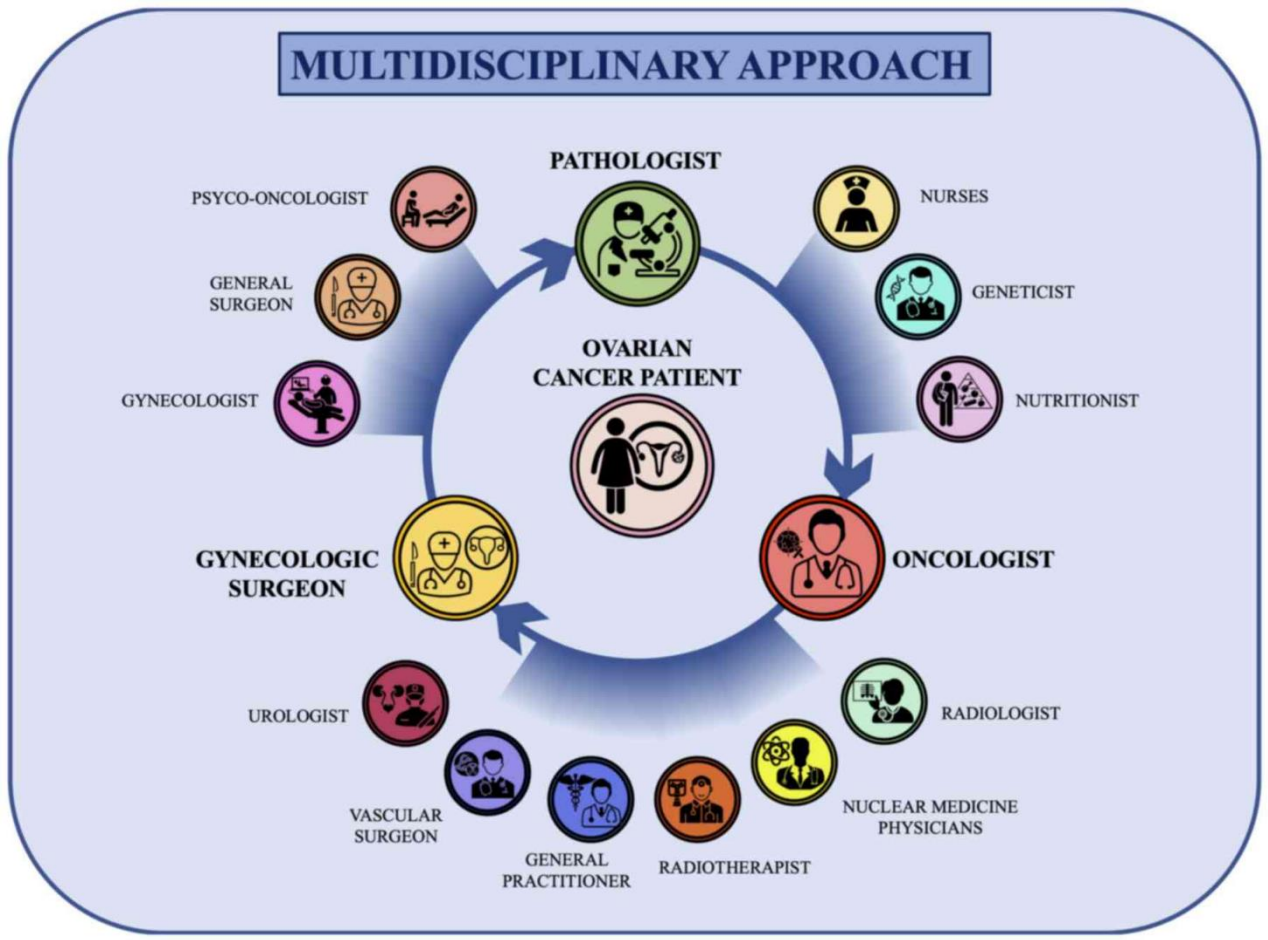
- Care in structured according to CCO guideline from 2013 – "Organizational Guideline for Gynecologic Oncology Services in Ontario"
- Specifies everything from where a patient should be treated for certain cancers, staffing levels and patient volumes
- Aimed to provide:
- Specialized care for patients who need it
- All patients have access to the opinion of experts
- Care should be provided close to home where possible
- Decisions require true multidisciplinary input

Specialized care

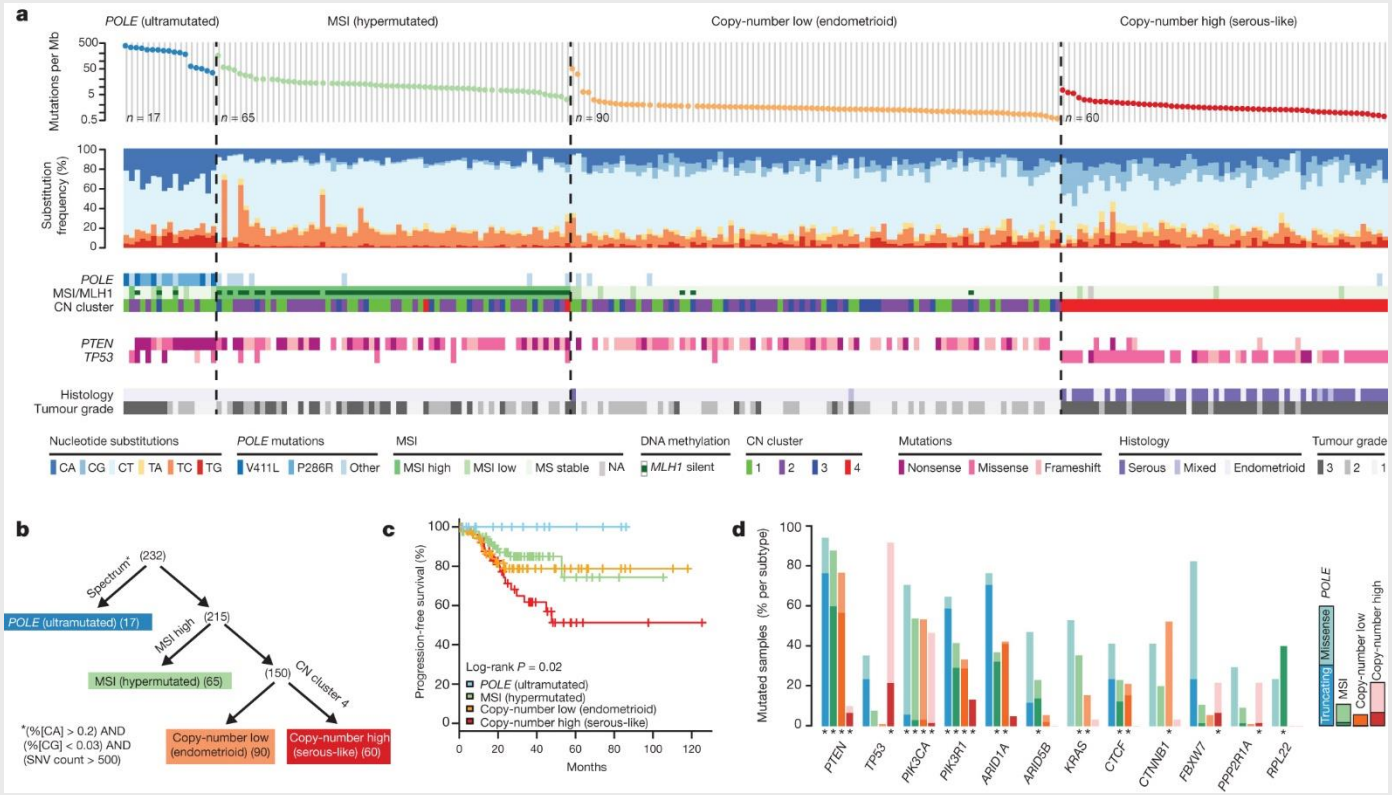
- **Pathologists**
  - Subtle changes in report can influence the need for additional treatment (e.g. months of chemotherapy)

- **Gynecologic oncologists**
  - 2-3 years of extra training
  - High volumes of complicated surgical procedures – outcomes at higher volume centers better for many types of cancers
  - Decision making – cervix cancer patient between cone biopsy, fertility sparing surgery, simple hyst, radical hyst or chemoradiation

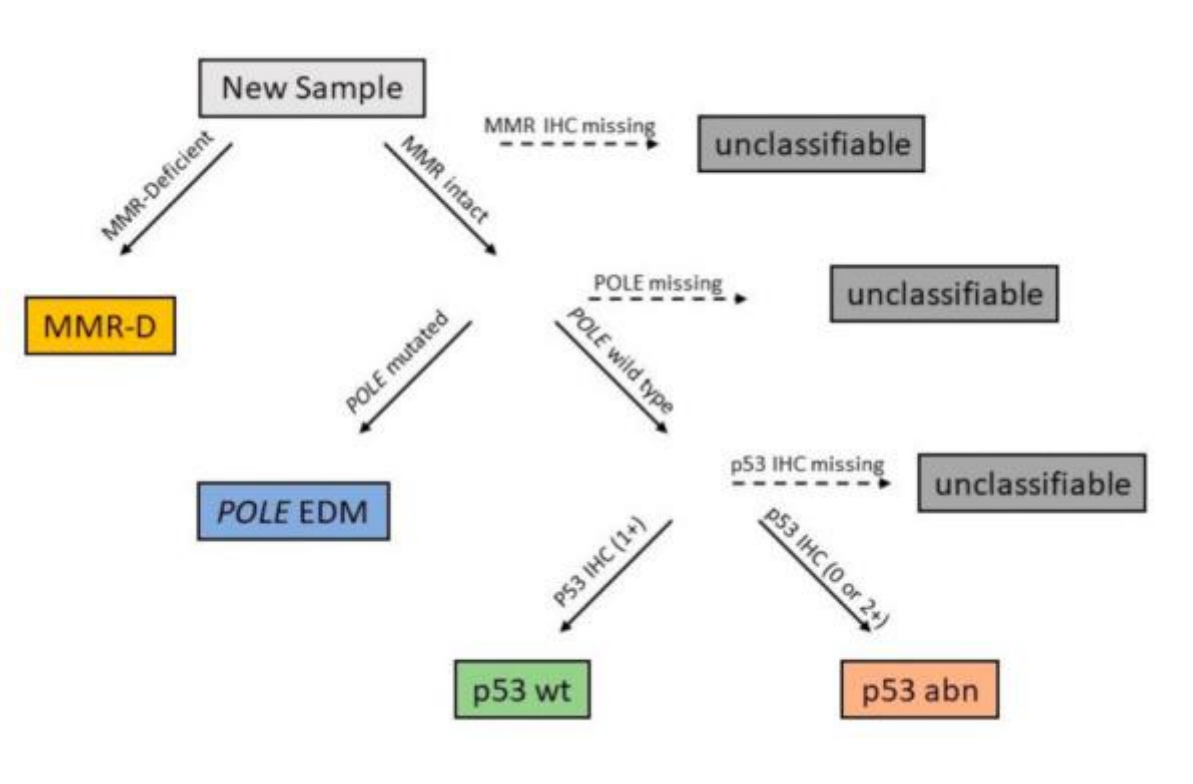
Why Multidisciplinary teams matter



Mutation spectra across endometrial carcinomas



G Getz *et al. Nature* 2013


New Sample
MMR IHC missing
unclassifiable
MMR-Deficient
MMR intact
POLE missing
unclassifiable
MMR-D
POLE mutated
POLE wild type
p53 IHC missing
unclassifiable
POLE EDM
P53 IHC (1+)
p53 IHC (0 or 2+)
p53 wt
p53 abn

2018 FIGO Staging for Uterine Cancer

Table 1. Cancer of the corpus uteri

FIGO Stage	
I [a]	Tumor confined to the corpus uteri
IA [a]	No or less than half myometrial invasion
IB [a]	Invasion equal to or more than half of the myometrium
II [a]	Tumor invades cervical stroma, but does not extend beyond the uterus [b]
III [a]	Local and/or regional spread of the tumor
IIIA [a]	Tumor invades the serosa of the corpus uteri and/or adnexae [c]
IIIB [a]	Vaginal involvement and/or parametrial involvement [c]
IIIC [a]	Metastases to pelvic and/or para-aortic lymph nodes [c]
IIIC1 [a]	Positive pelvic nodes
IIIC2 [a]	Positive para-aortic nodes with or without positive pelvic lymph nodes
IV [a]	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA [a]	Tumor invasion of bladder and/or bowel mucosa
IVB [a]	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes)

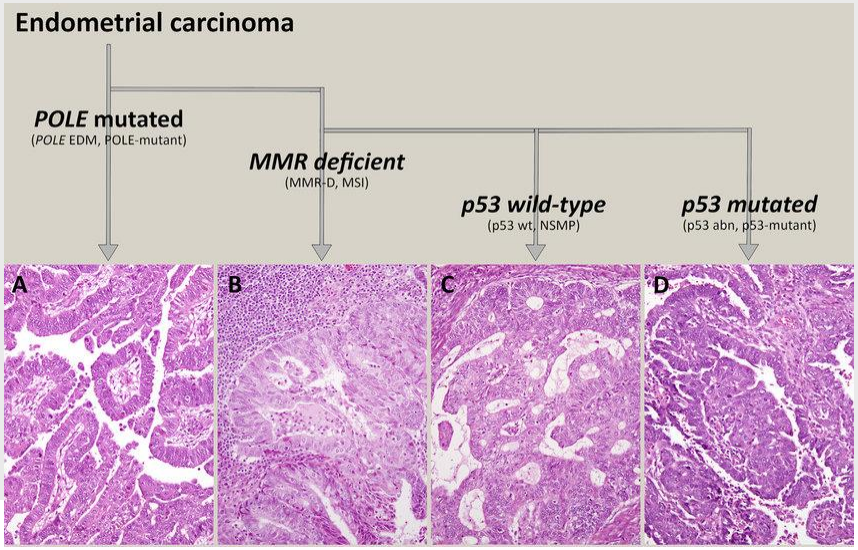
New 2023 FIGO Staging

Stage	Description
I	
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary [c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI [d]
IC	Aggressive histological types [e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI [d] of non-aggressive histological types
IIC	Aggressive histological types [e] with any myometrial involvement

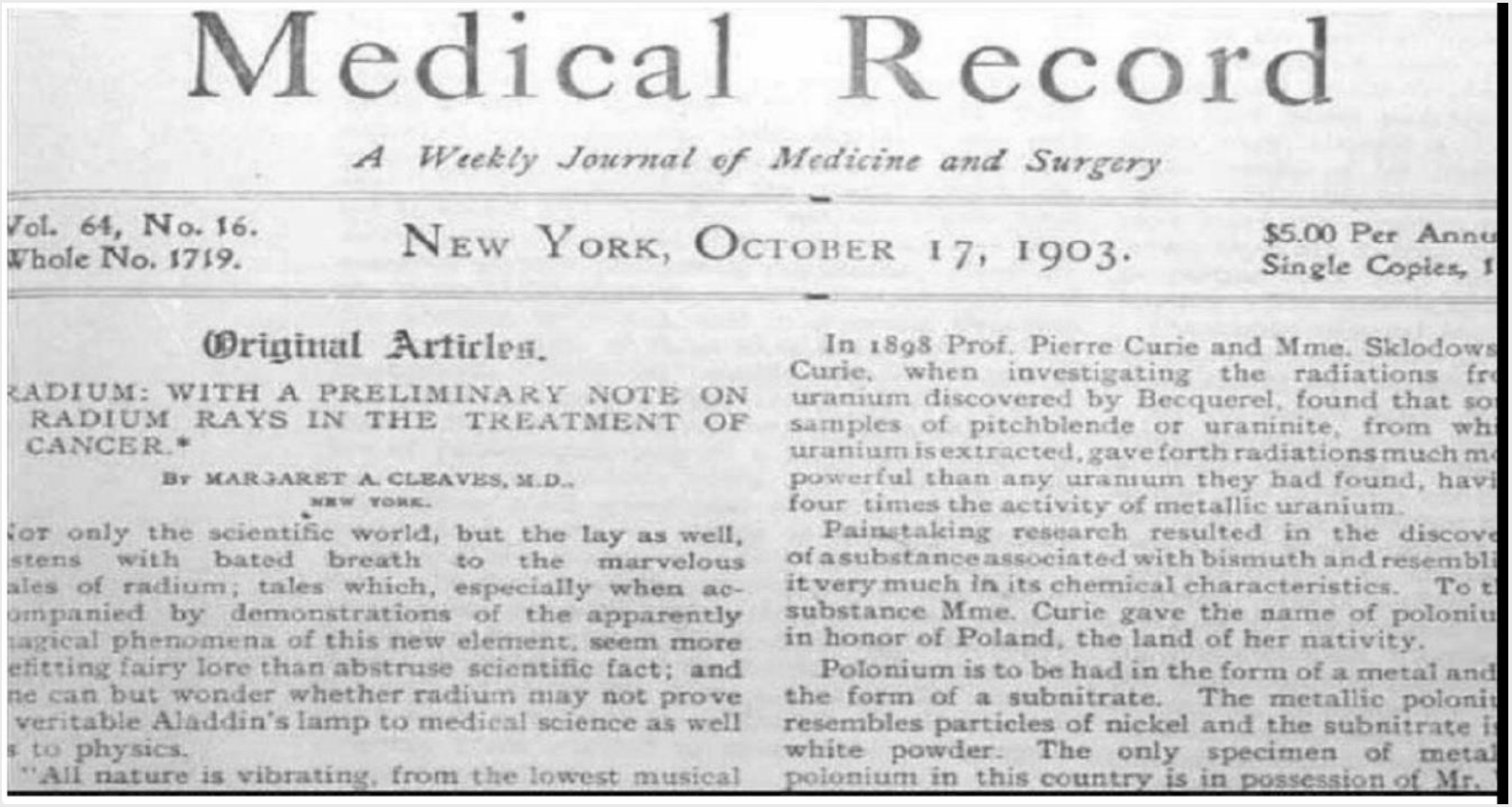
Stage	Description
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria) [c]
	IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria
	IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both [f]
	IIIC1 Metastasis to the pelvic lymph nodes
	IIIC1i Micrometastasis
	IIIC1ii Macrometastasis
	IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
	IIIC2i Micrometastasis
	IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Decisions for treatment evolving

- The most important aspect is COMMUNICATION
- Need to understand specifics of how pathology does their testing
- Important decisions on whether to give radiation, chemotherapy or immunotherapy will rest now not on traditional pathology features but on the molecular/genetic footprint of the tumour



Brachytherapy



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Whole No. 1719.

NEW YORK, OCTOBER 17, 1903.

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Single Copies, 1

Original Articles.

RADIUM: WITH A PRELIMINARY NOTE ON RADIUM RAYS IN THE TREATMENT OF CANCER.*

BY MARGARET A. CLEAVES, M.D.,
NEW YORK.

For only the scientific world, but the lay as well, stens with bated breath to the marvelous ales of radium; tales which, especially when ac- ompanied by demonstrations of the apparently agical phenomena of this new element, seem more efitting fairy lore than abstruse scientific fact; and ne can but wonder whether radium may not prove veritable Aladdin's lamp to medical science as well s to physics.

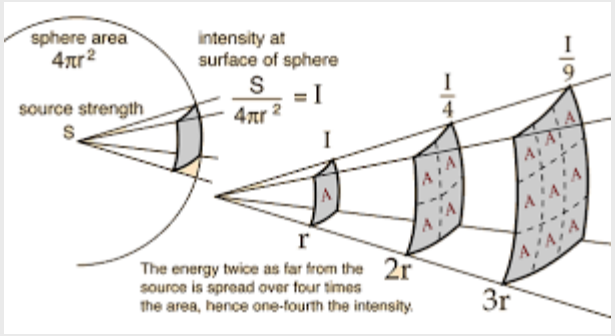
"All nature is vibrating, from the lowest musical

In 1898 Prof. Pierre Curie and Mme. Sklodows Curie, when investigating the radiations fr uranium discovered by Becquerel, found that so samples of pitchblende or uraninite, from wh uranium is extracted, gave forth radiations much m powerful than any uranium they had found, havi four times the activity of metallic uranium.

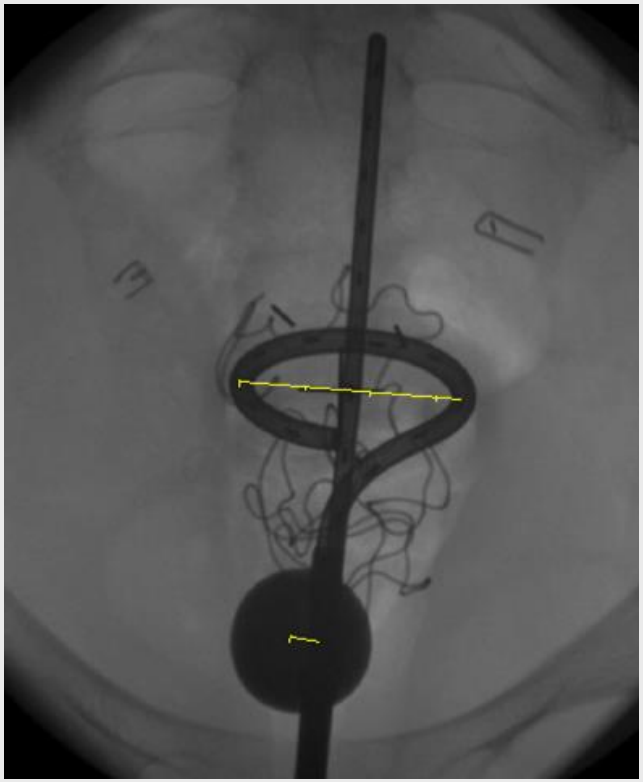
Painstaking research resulted in the discov of a substance associated with bismuth and resembli it very much in its chemical characteristics. To t substance Mme. Curie gave the name of poloniu in honor of Poland, the land of her nativity.

Polonium is to be had in the form of a metal and the form of a subnitrate. The metallic poloni resembles particles of nickel and the subnitrate i white powder. The only specimen of meta polonium in this country is in possession of Mr.

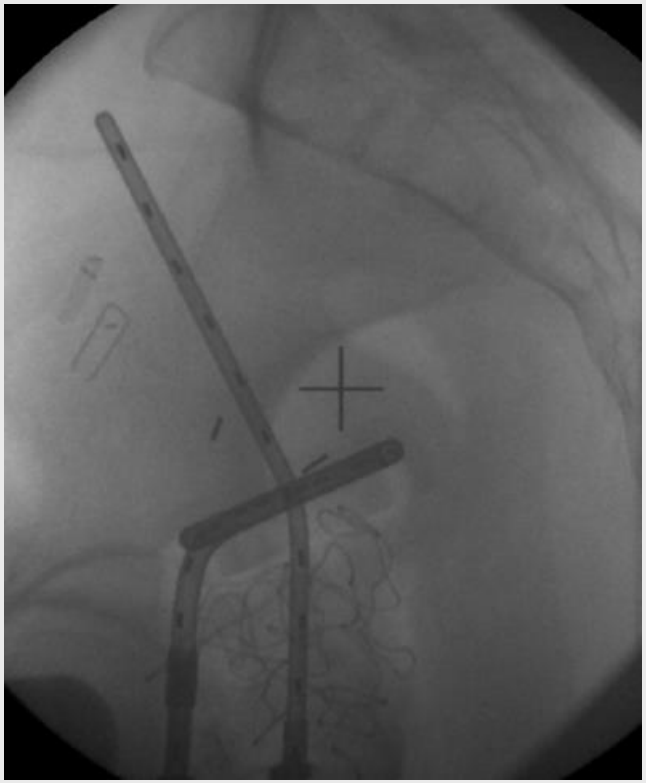
- Use of a radioactive source to deliver ionizing radiation to the target volume
- Can be in a cavity, placed on a surface or within tissue (interstitial)
- Manually loaded radioactive material (EXPOSURE) replaced now mainly with remote afterloading machines
- Takes advantage of inverse square law



Planning with x-rays

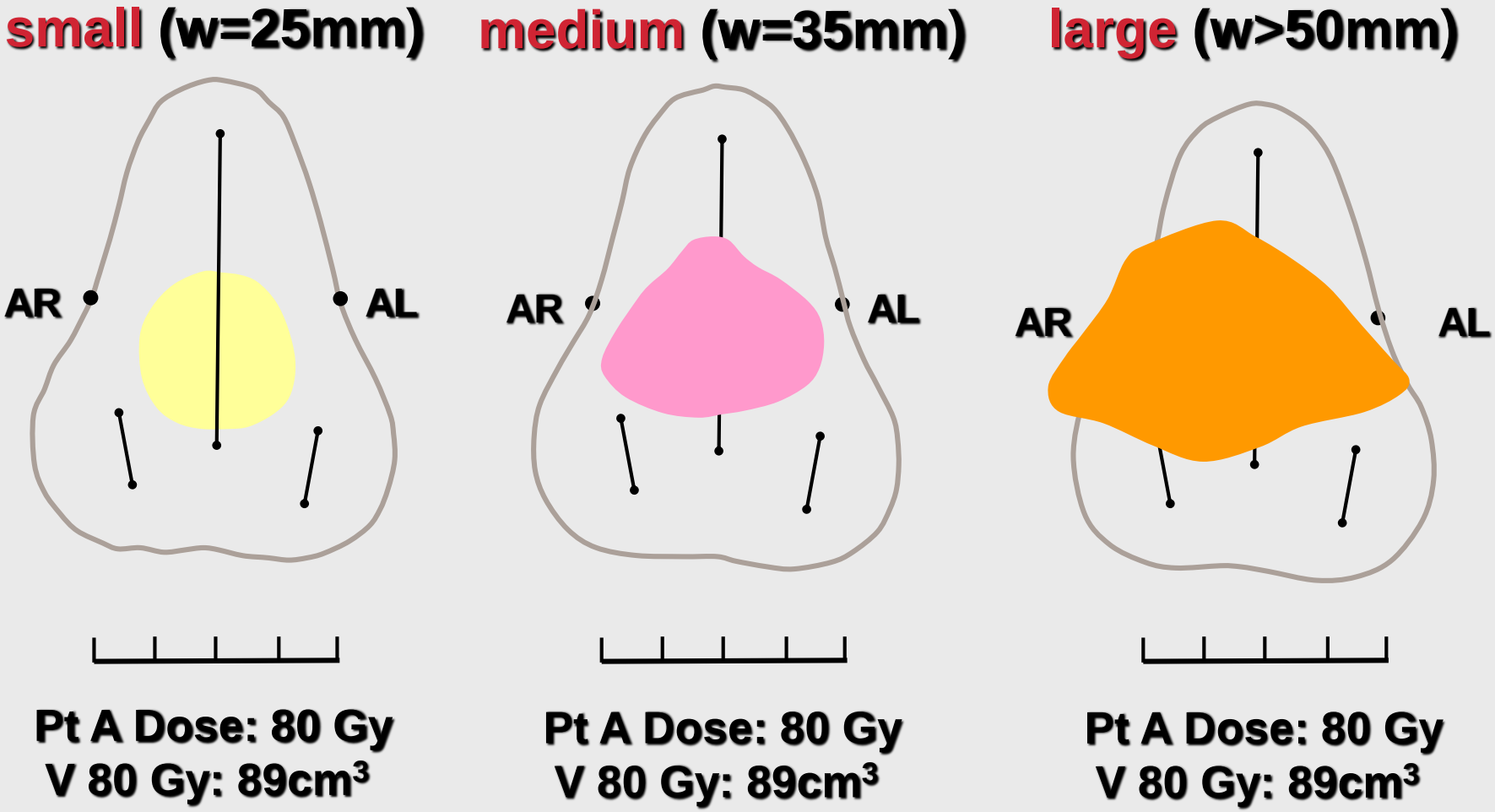


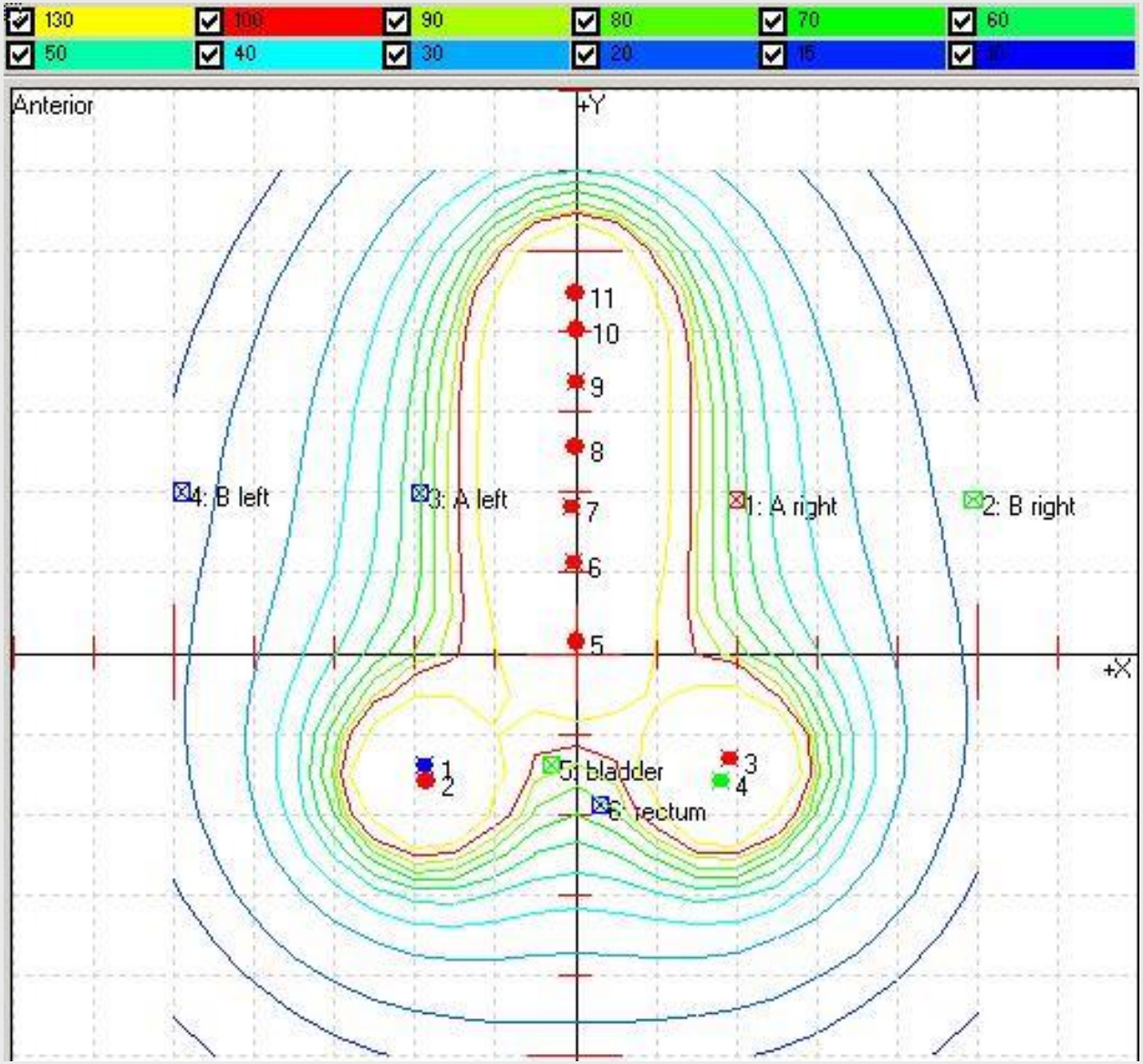
AP



LAT

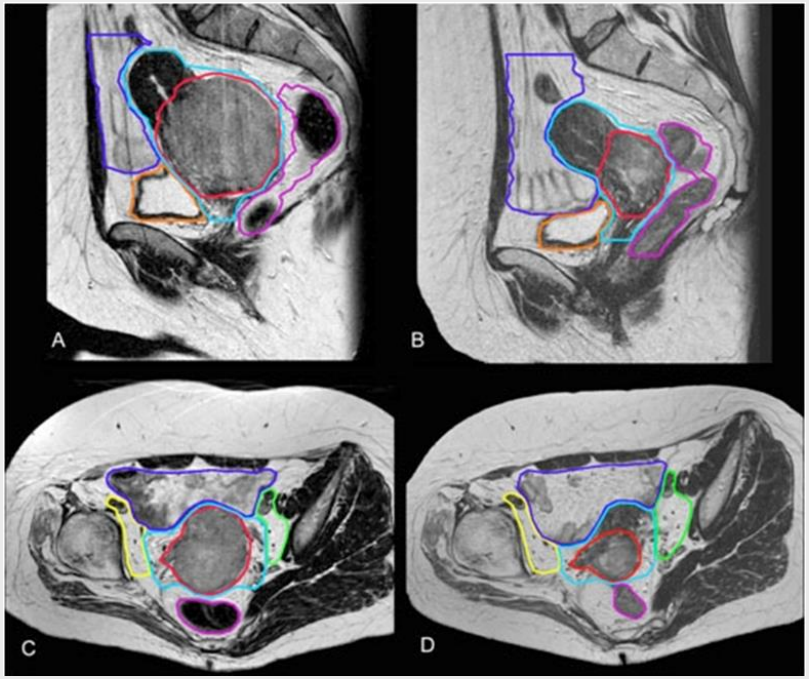
The Standard Pear

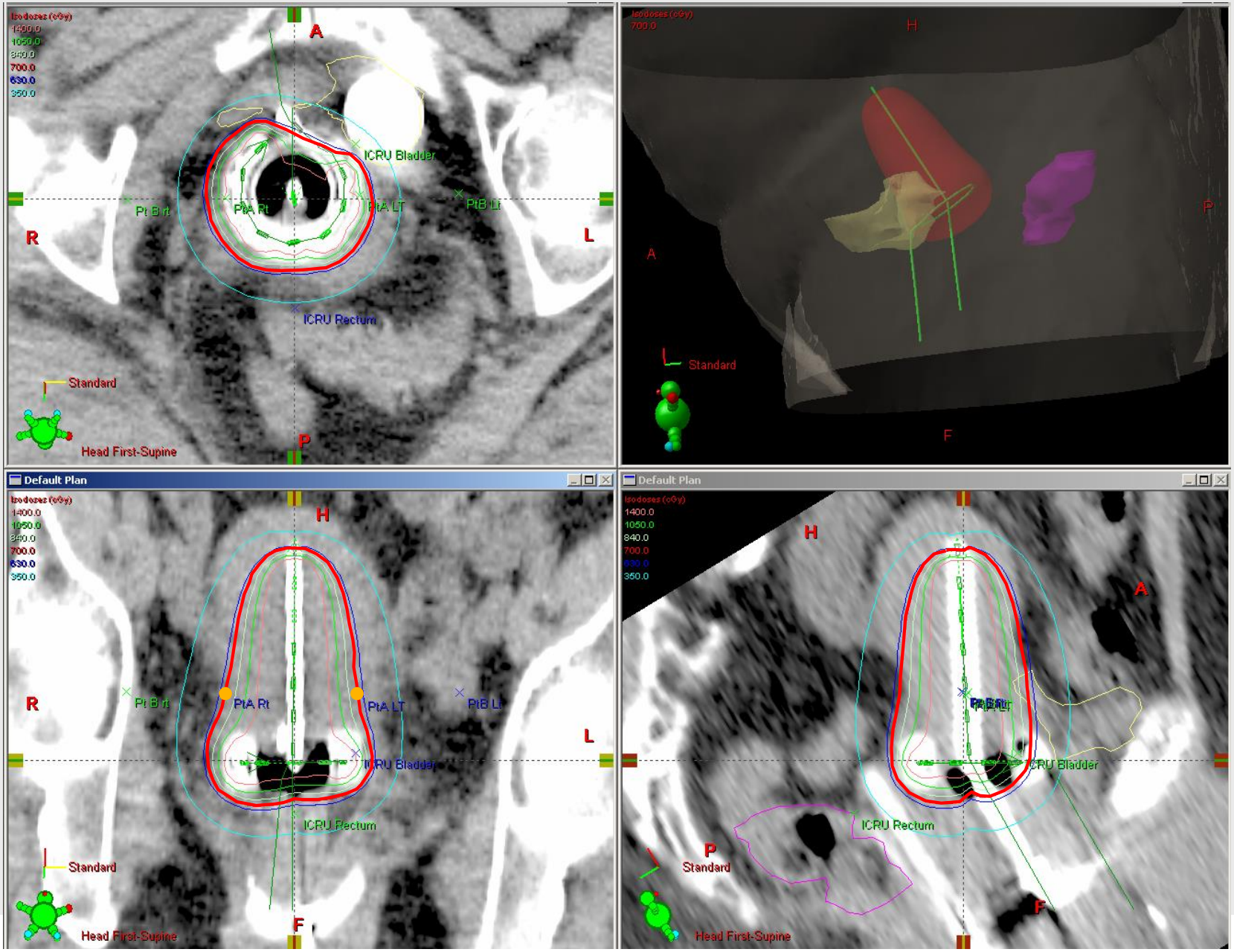



130
100
90
80
70
60
50
40
30
20
10
Anterior
+Y
+X
11
10
9
8
7
6
5
4: B left
3: A left
1: A right
2: B right
1
2
3
4
5: bladder
6: rectum

Transition to 3D planning

- Incorporation of imaging advances into treatment of gynecologic cancers for brachytherapy has taken some time
- Why make the change?
  - Accurately treat the tumor volume
  - Be aware of true dose to adjacent organs and reduce the side effects
  - Tumour can regress/change over course of treatment




A
ICRU Bladder
Pt B Rt
PtA Rt
PtA LT
PtB Lt
R
L
ICRU Rectum
Standard
Head First-Supine
P
H
P
A
Standard
F
Default Plan
Isodoses (cGy)
1400.0
1050.0
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630.0
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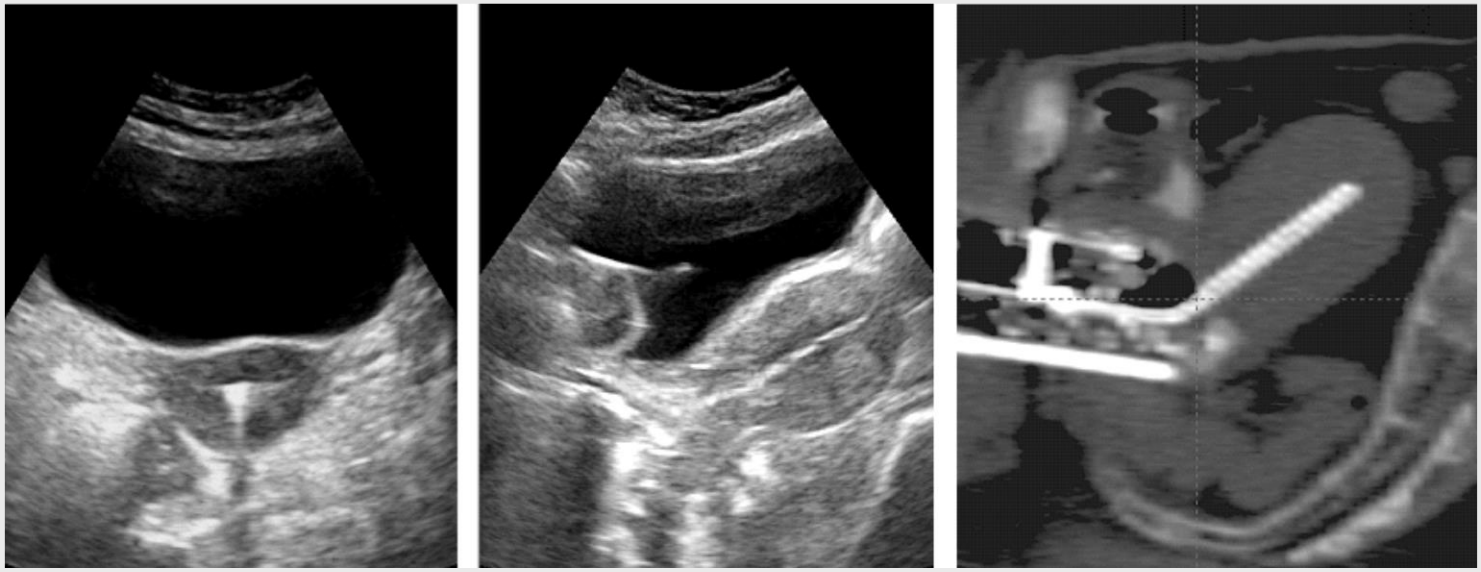
Pt B rt
PtA Rt
PtA LT
PtB Lt
L
ICRU Bladder
ICRU Rectum
Standard
Head First-Supine
F
Default Plan
Isodoses (cGy)
1400.0
1050.0
840.0
700.0
630.0
350.0
H
A
ICRU Bladder
ICRU Rectum
P
Standard
Head First-Supine
F

Use of Intraoperative U/S

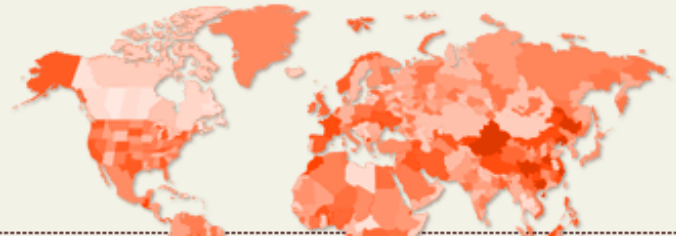
- Done by RT under guidance of RO and physicist
- Allows excellent visualization of tandem placement in uterine canal in *real time*
- Translates into a geometrically favourable implant



Magnetic Resonance Imaging

EMBRACE

An intErnational study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer



- Results of 731 patients from retroEMBRACE (12 institutions)
- 3/5y local control (LC) 91%/89% and low serious morbidity

- EMBRACE ~1300 patients
- 5y LC 92%
- G3+ toxicity – GU 6.8%, GI 8.5% compared to 15-25% historically, (vaginal 5.7% and 3.2% for fistula)

Sturdza A et al. Radiother Oncol Apr 2016
Potter et al. Lancet Onc Apr 2021

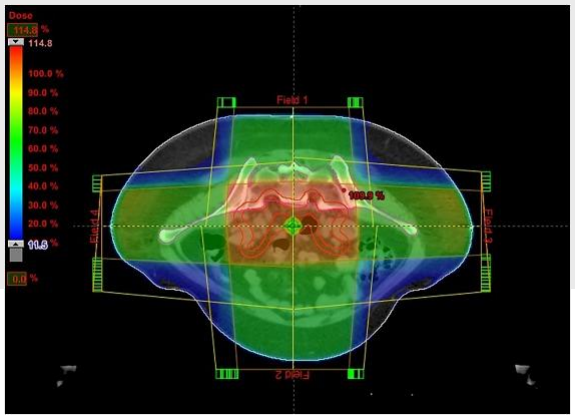
Why add interstitial needles?

- Analysis from retroEMRACE study showed better coverage of the tumour volume to a higher dose without increasing the dose to normal organs
- Improved local control of larger tumours >30cc

Fokdal L et al. Radiother Oncol online Apr 2016

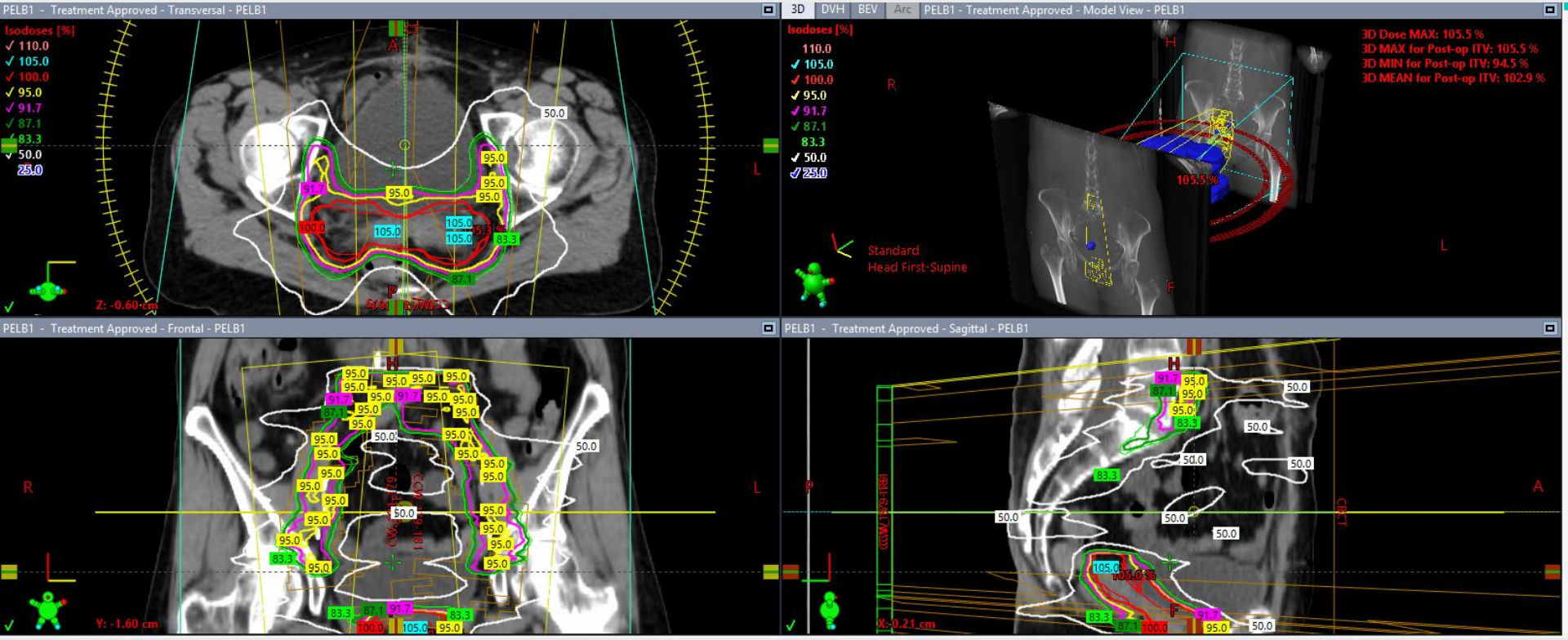
Long lasting effects from radiation

- Depends on type of radiation given (definitive versus adjuvant), the dose delivered, age/health of the patient
- Changes in bowel and bladder function – frequency, urgency, diarrhea where found to affect QOL in terms of social functioning in ~30% of patients
- External beam radiation was previously given by beams from front, back and sides
- Large volumes of small bowel, rectum, sigmoid, bladder received full dose of radiation



Nout et al: Eur J Cancer 2012

SBRT post-op


PELB1 - Treatment Approved - Transversal - PELB1
Isodoses [%]
110.0
105.0
100.0
95.0
91.7
87.1
83.3
50.0
25.0
Z: -0.60 cm
3D
DVH
BEV
Arc
PELB1 - Treatment Approved - Model View - PELB1
3D Dose MAX: 105.5 %
3D MAX for Post-op ITV: 105.5 %
3D MIN for Post-op ITV: 94.5 %
3D MEAN for Post-op ITV: 102.9 %
105.5 %
Standard
Head First-Supine
PELB1 - Treatment Approved - Frontal - PELB1
Y: -1.60 cm
PELB1 - Treatment Approved - Sagittal - PELB1
X: -0.21 cm

Changes in Sexual Function

- Changes from radiation and surgery (if had)
- If have functioning ovaries, removed for uterine cancer and cease function after pelvic radiation for cervix cancer – means dryness, changes in libido
- Foreshortening/narrowing of vagina from fibrosis
- Adhesions of vaginal walls from inflammation
- To prevent "tightening", dilator kits, regular penetrative vaginal intercourse, pelvic physiotherapy

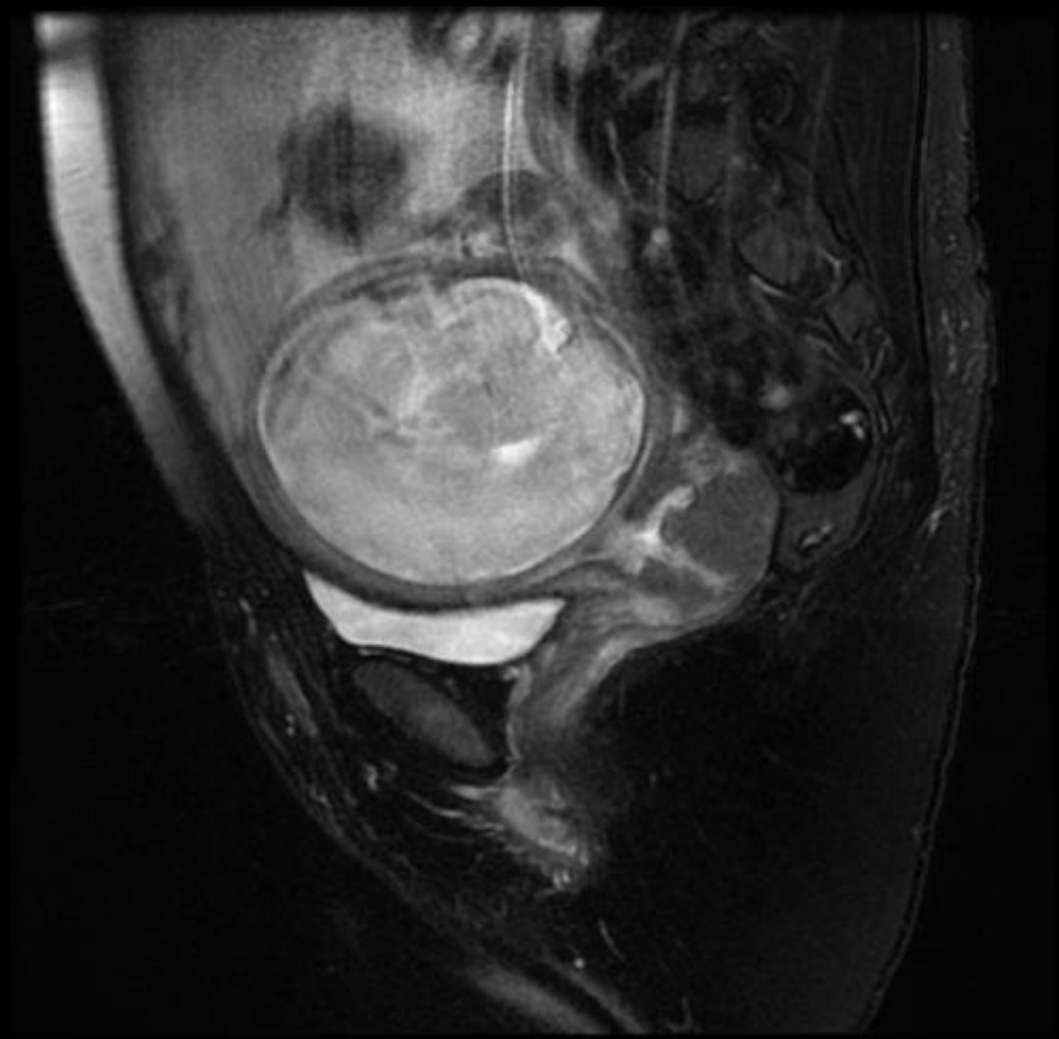
- Currently lack adequate social supports, expertise
- All of this can have significant effects on relationships – either existing or to form new ones

Stigma associated with HPV

- While cervix cancer rates have declined with screening, significant numbers of locally advanced cases occur in Ontario
- Hope for the future with HPV vaccine, HPV testing, we still have a problem
- Almost 1/3rd of women under 50 who received chemoradiation at our institution, had a Pap test done two years or less prior to diagnosis
  - Many do not know signs/symptoms of cervix cancer or what to ask for other than a Pap test
  - Assumptions made of presumed lifestyle and blame for not being screening compliant
  - Reluctance to have a detailed pelvic exam performed

Corkum et al: Cureus 2019

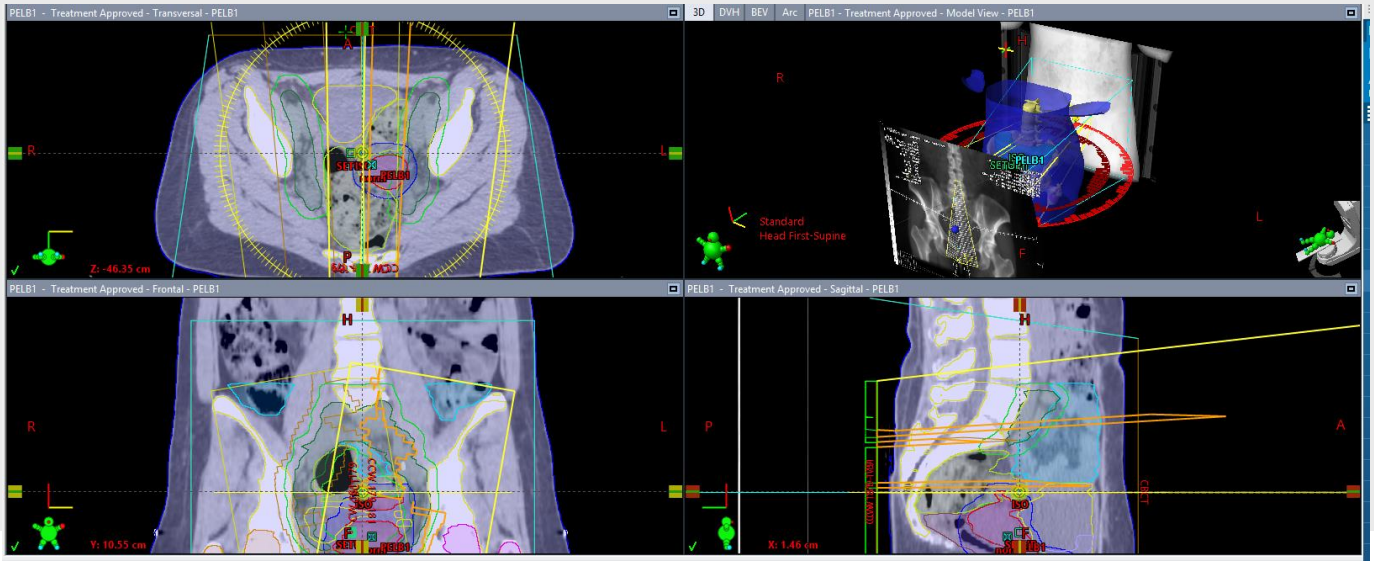
[H]



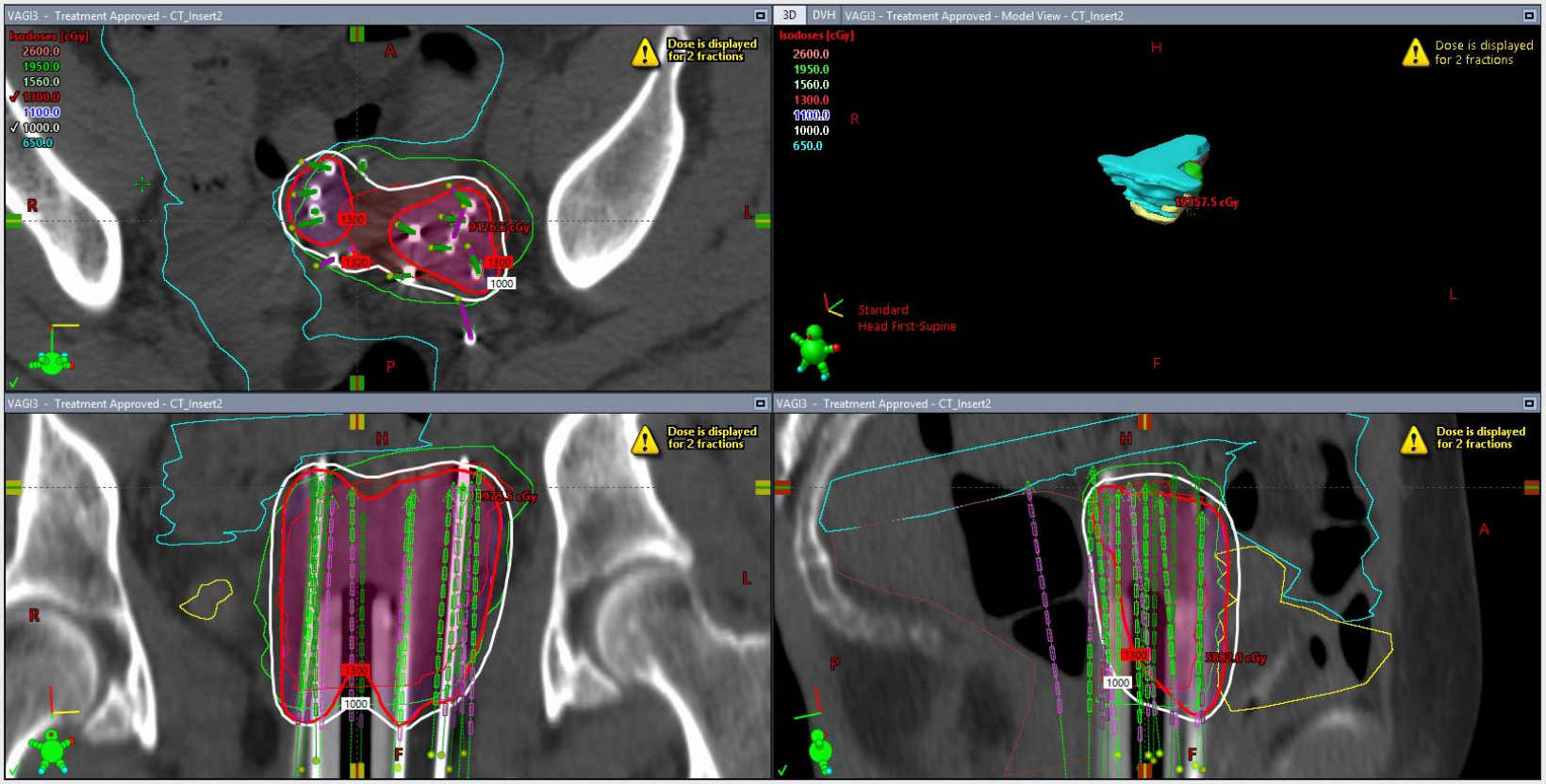
[F]

Back to our case

- 42 yo female with recurrent uterine cancer post hysterectomy
- Has Lynch syndrome
- Received external beam radiation



Interstitial brachytherapy – 2 implants

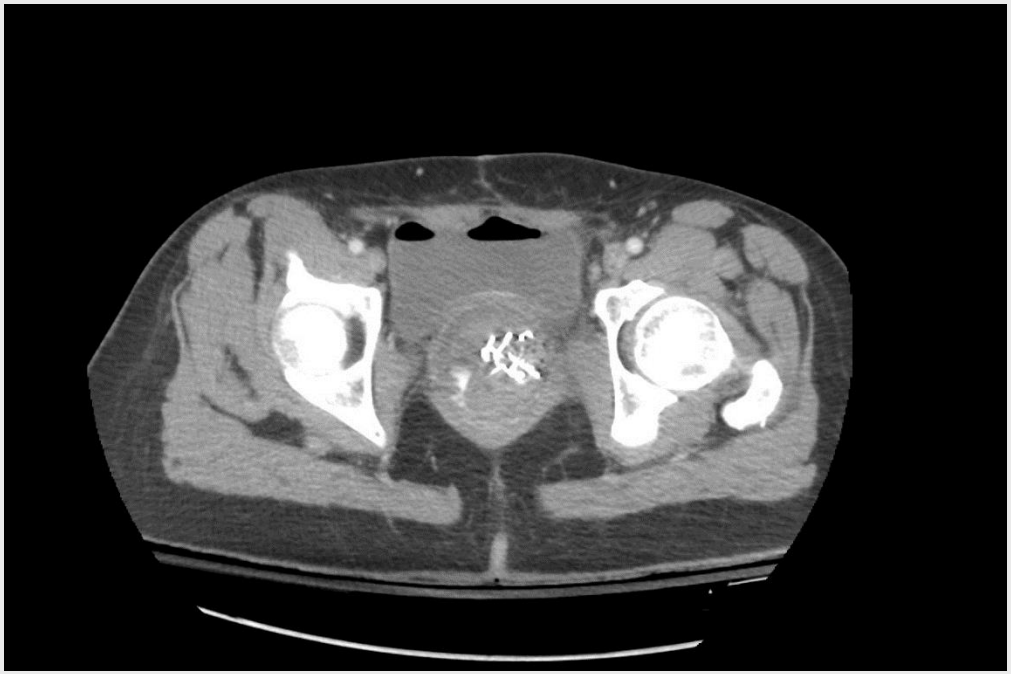


- After patient's second implant and treatments, applicators were removed
- Bleeding noted and persistent
- Packing was inserted
- Gyn Onc was called

- "That blood is bright red – looks arterial to me"

Urgent CT Done

- "Active arterial extravasation along the right lateral wall of the vagina"
- Embolization of right artery with particles effective



- Patient received 6 cycles of chemotherapy
- 3 ½ years post treatment with no evidence of disease
- Taken to the OR earlier this year for lysis of adhesions in vagina to try and improve sexual function

- Followed by GI both for risk of pancreatic and colon cancer

Summary

- The role of radiotherapy is evolving in the treatment of gynecologic cancers
- Care should be provided as part of the multidisciplinary team while aiming to provide the best care for the patient and close to home when possible
- Radiotherapy can be an effective modality of managing cancer – from curative treatments to palliation and should not be overlooked
- There remains room for improving the outcomes of radiotherapy with dedicated resources and better listening to what our patients tell us