THE AGE OF RADIATION IN ADVANCED ENDOMETRIAL CANCER IS OVER?

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WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

NCI
Designated
Comprehensive
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DISCLOSURES

EMORY UNIVERSITY SCHOOL OF MEDICINE
Department of Gynecology and Obstetrics

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

Dr. Modesitt receives a stipend as Editor-in-Chief for *Gynecologic Oncology Reports*

Dr. Remick has no disclosures

LEARNING OBJECTIVES

1. Review the etiology and risk factors for endometrial cancer;

2. Understand the historical data/outcomes for chemotherapy and radiation in advanced endometrial cancer;

3. Debate the data to omit or add radiation;

LEADING SITES OF NEW CANCER CASES AND DEATHS IN US WOMEN-2023

Breast	297,790	31%
Lung & bronchus	120,790	13%
Colon & rectum	71,160	8%
Uterine corpus	66,200	7%
Melanoma of the skin	39,490	4%
Non-Hodgkin lymphoma	35,670	4%
Thyroid	31,180	3%
Pancreas	30,920	3%
Kidney & renal pelvis	29,440	3%
Leukemia	23,940	3%
All sites	**948,000**	

Female

Lung & bronchus	59,910	21%
Breast	43,170	15%
Colon & rectum	24,080	8%
Pancreas	23,930	8%
Ovary	13,270	5%
Uterine corpus	13,030	5%
Liver & intrahepatic bile duct	10,380	4%
Leukemia	9,810	3%
Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	7,970	3%
All sites	**287,740**	

- Uterine corpus cancer has been increasing 2% per year in women under 50 and 1% per year for women over 50
- Mortality continues to increase since 1990 with a 0.7% annual increase from 2016-2020
- 70% due to excess body weight and inadequate exercise
- Profound racial disparities
  - Five-year survival 84% in non-Hispanic White vs. 64% in Non-Hispanic black
  - Advanced stage at presentation 44% in non-Hispanic White vs. 29% in Non-Hispanic black

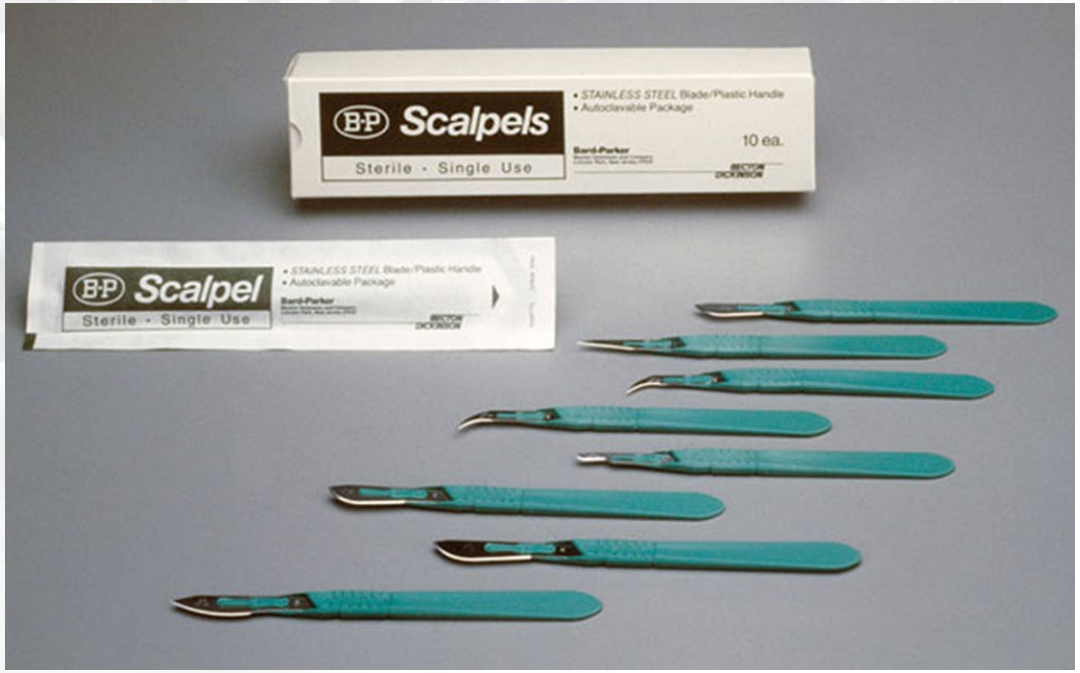
American Cancer Society Cancer Facts & Figures 2023

CASE PRESENTATION

- Ms. X is a 72 year-old patient who underwent a robotic assisted TLH/BSO and sentinel node dissection for a grade 3 endometrioid endometrial cancer. Final pathology showed a positive node and disease in the ovary and the tumor is MMR deficient. No other disease on imaging. Your treatment recommendation is which of the following?
  - A. Vaginal brachytherapy
  - B. External beam radiation therapy
  - C. Chemoradiation with cisplatin
  - D. Paclitaxel/carboplatin
  - E. Paclitaxel/carboplatin and radiation of some flavor
  - F. Paclitaxel/carboplatin and PDL-1 inhibitor
  - G. No freaking idea (or something else TBD after this debate)

ENDOMETRIAL CANCER INITIAL TREATMENT OPTIONS

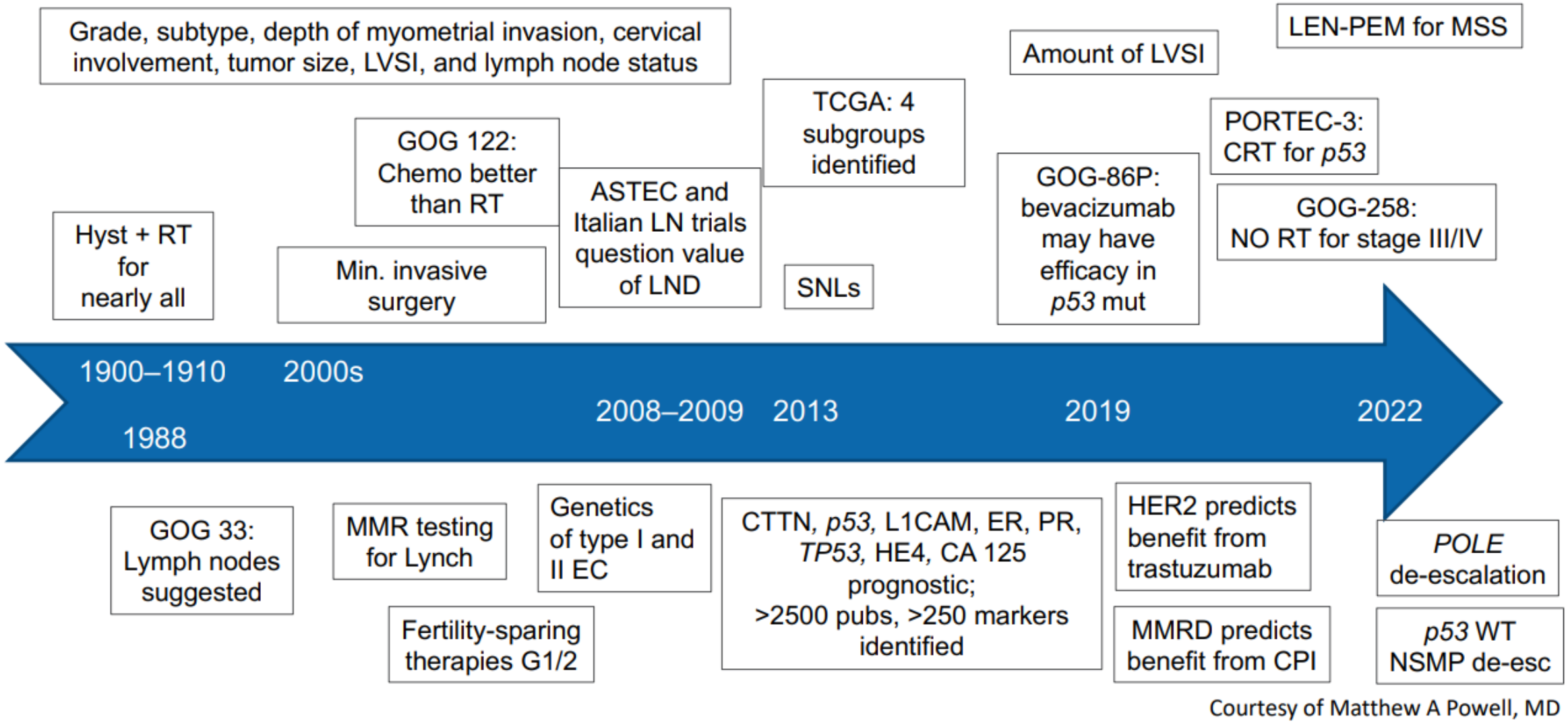
- Surgery
- Radiation
- Chemotherapy*



Surgery: A chance to cut is a chance to cure

***Includes standard cytotoxic chemotherapy, hormones, targeted therapy, immunotherapy etc.**

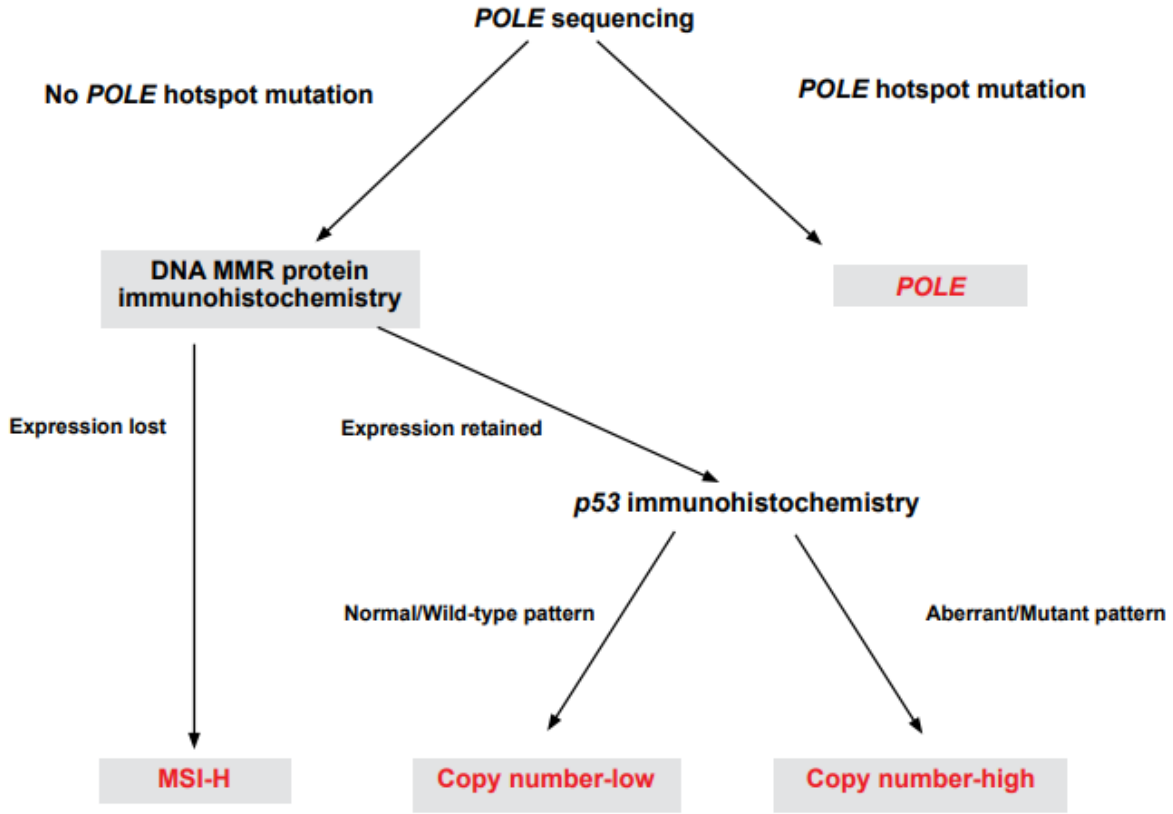
History of Management of Endometrial Cancer: Journey From Prognostic to Predictive Markers



Courtesy of Matthew A Powell, MD

PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA
(The decision to use molecular testing/classification depends on the availability of resources and the multidisciplinary team of each center)[f,g]



[f] Adapted with permission from Murali R, Delair DF, Bean SM, et al. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Nat Compr Canc Netw 2018;16:201-209.
[g] Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas.

TYPES OF ENDOMETRIAL CANCER: BEYOND BASIC HISTOLOGY

Endometrial cancer sequencing with the TCGA identified 4 molecular subtypes

1. POLE (polymerase epsilon) ultra-mutated
   - ***BEST*** clinical prognosis
2. Microsatellite High
   - intermediate prognosis
3. Copy number high* (p53 mutant)
   - ***WORST*** clinical prognosis
4. Copy number low*
   - Associated with intermediate prognosis

Further Classifications (PORTEC)

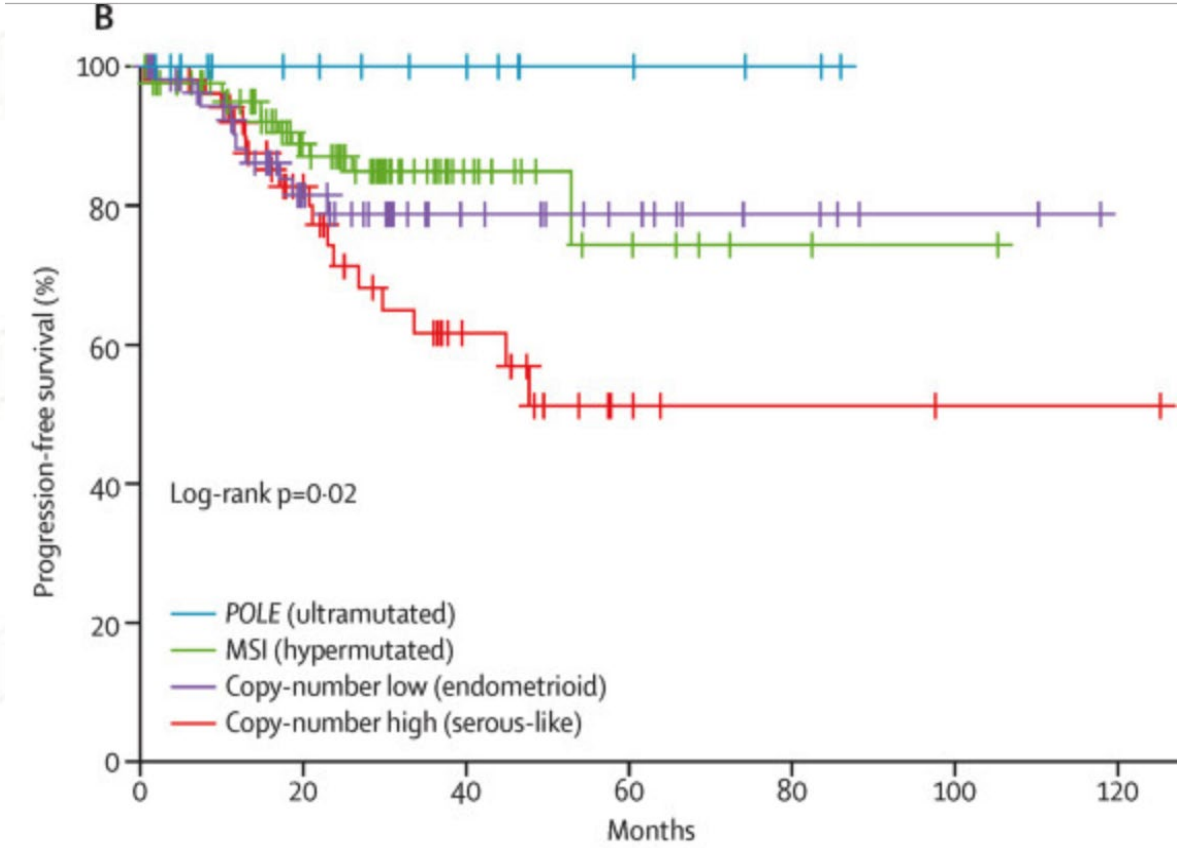
1. DNA POLE (polymerase epsilon)
   - ***BEST*** clinical prognosis
2. MMR deficient
   - Akin to MSI--intermediate prognosis
3. P53 abnormal*
   - Copy number high-***WORST*** clinical prognosis
4. P53 wildtype
   - Copy number low—intermediate prognosis
5. No specific molecular subtype (NSMP)
   - Associated with intermediate prognosis

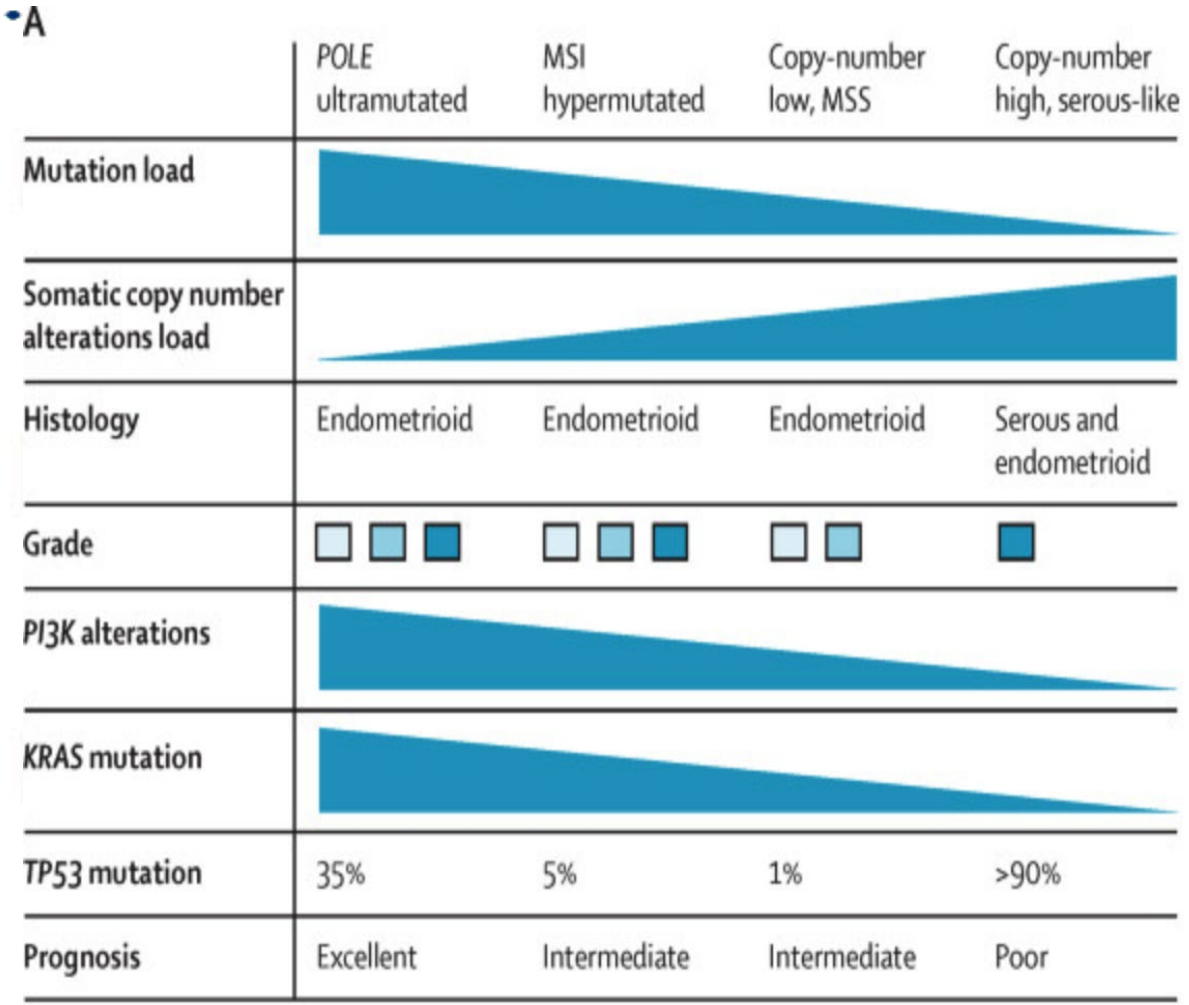
ARTICLE

OPEN
doi:10.1038/nature12113

Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*





Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.

NCCN Guidelines Version 2.2023
Endometrial Carcinoma

All staging in guideline is based on updated FIGO staging. (See ST-1)

CLINICAL FINDINGS
(Endometrioid Histology)[a]

ADJUVANT TREATMENT[g,h]

Of note, about 50% of endometrial cancer are advanced stage at diagnosis with 5 year survival rates of 10-19% *

Surgically staged[e]:
Stage III, IV[r] → **Systemic therapy**
± EBRT[s]
± vaginal brachytherapy[s]

*Rubenstein M et al. *Gynecol Oncol* 167:540-6, 2022

S-Combination therapy depends on assessment of both locoregional and distant metastatic risk. Consider combination therapy for stage IIIB and IIIC disease.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

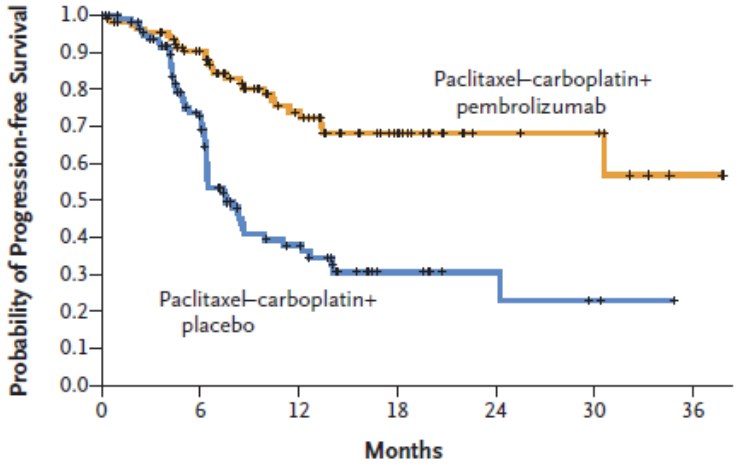
Primary or Adjuvant Therapy (Stage I-IV)	
Chemoradiation Therapy	**Systemic Therapy**
Preferred Regimens • Cisplatin plus RT followed by carboplatin/paclitaxel[1,2]	**Preferred Regimens** • Carboplatin/paclitaxel[3] • Carboplatin/paclitaxel/pembrolizumab (for stage III-IV tumors, except for carcinosarcoma) (category 1)[a,b,4] • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III-IV tumors) (category 1)[b,c,5] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[d,e,6] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma) (category 2B)[d,e,6]

ADJUVANT SYSTEMIC TREATMENT FOLLOWING SURGERY

- Surveillance for early stage and low-grade cancers
- Adjuvant chemotherapy for high grade/stage
  - First **SURVIVAL** advantage for chemotherapy over radiation seen with doxorubicin/cisplatin in GOG 122
  - Paclitaxel/carboplatin shown to be equivalent and less toxic
  - Addition/approval of trastuzumab for Her-2- neu positive serous cancers
- Two groundbreaking Phase III trials published 3/27/23 with marked improvement with addition of PDL-1 inhibitors to chemo: NRG GY 18 and RUBY trials

NRG GYN 18: PACLITAXEL/CARBOPLATIN +/- PEMBROLIZUMAB

A dMMR Cohort



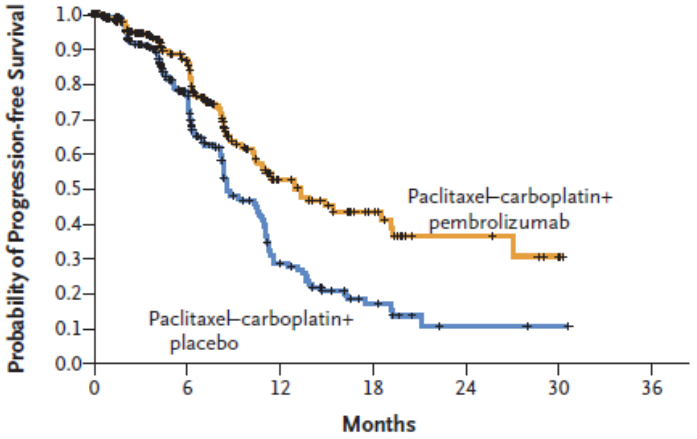
	No. of Events	No. of Patients	Median Progression-free Survival (95% CI)
			mo
Paclitaxel–Carboplatin+ Pembrolizumab	26	112	NR (30.6–NR)
Paclitaxel–Carboplatin+ Placebo	59	113	7.6 (6.4–9.9)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.19–0.48)

No. at Risk

Paclitaxel–carboplatin+ pembrolizumab	112	80	44	22	9	8	2
Paclitaxel–carboplatin+ placebo	113	62	24	8	4	2	0

B pMMR Cohort



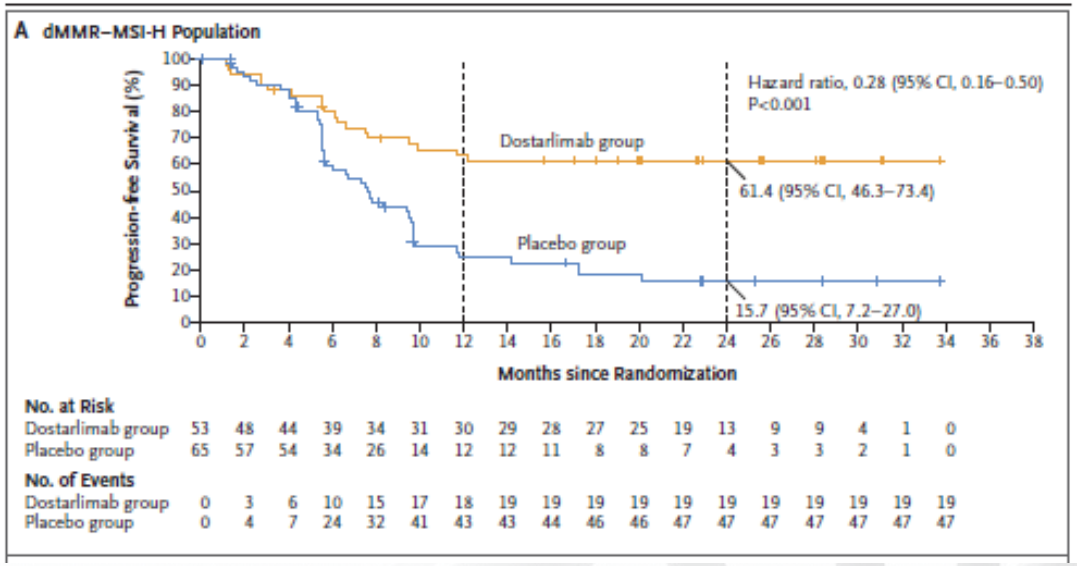
	No. of Events	No. of Patients	Median Progression-free Survival (95% CI)
			mo
Paclitaxel–Carboplatin+ Pembrolizumab	89	290	13.1 (10.5–18.8)
Paclitaxel–Carboplatin+ Placebo	133	292	8.7 (8.4–10.7)

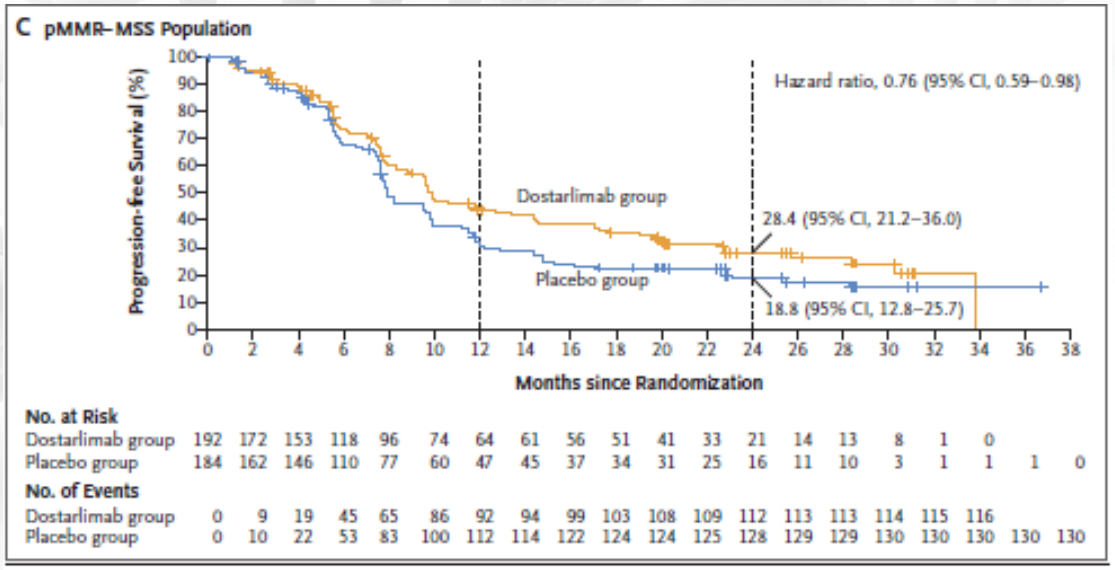
Stratified hazard ratio for disease progression or death, 0.54 (95% CI, 0.41–0.71)

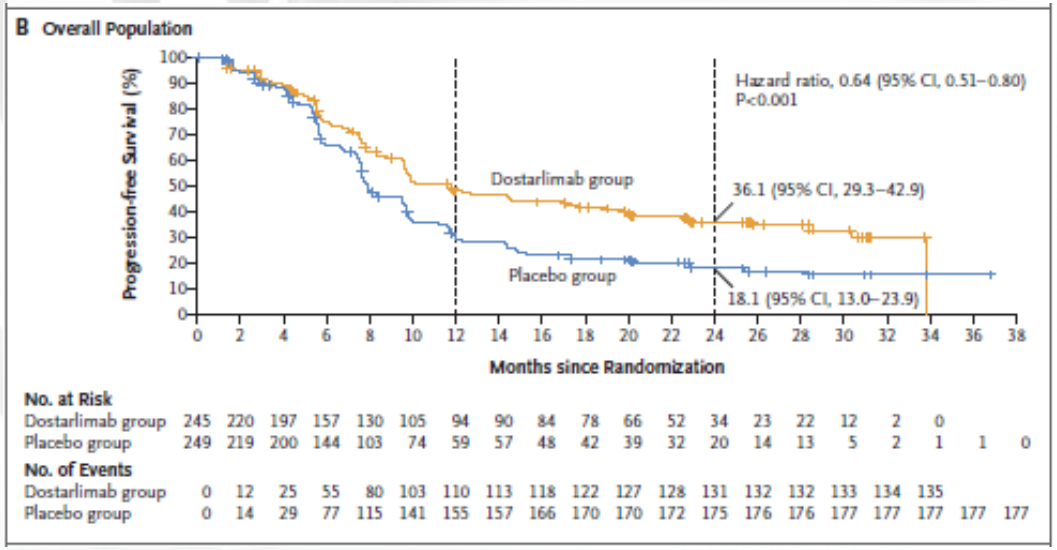
No. at Risk

Paclitaxel–carboplatin+ pembrolizumab	290	150	45	20	7	3	0
Paclitaxel–carboplatin+ placebo	292	129	33	10	2	1	0

RUBY TRIAL: PACLITAXEL/CARBOPLATIN +/- DOSTARLIMAB



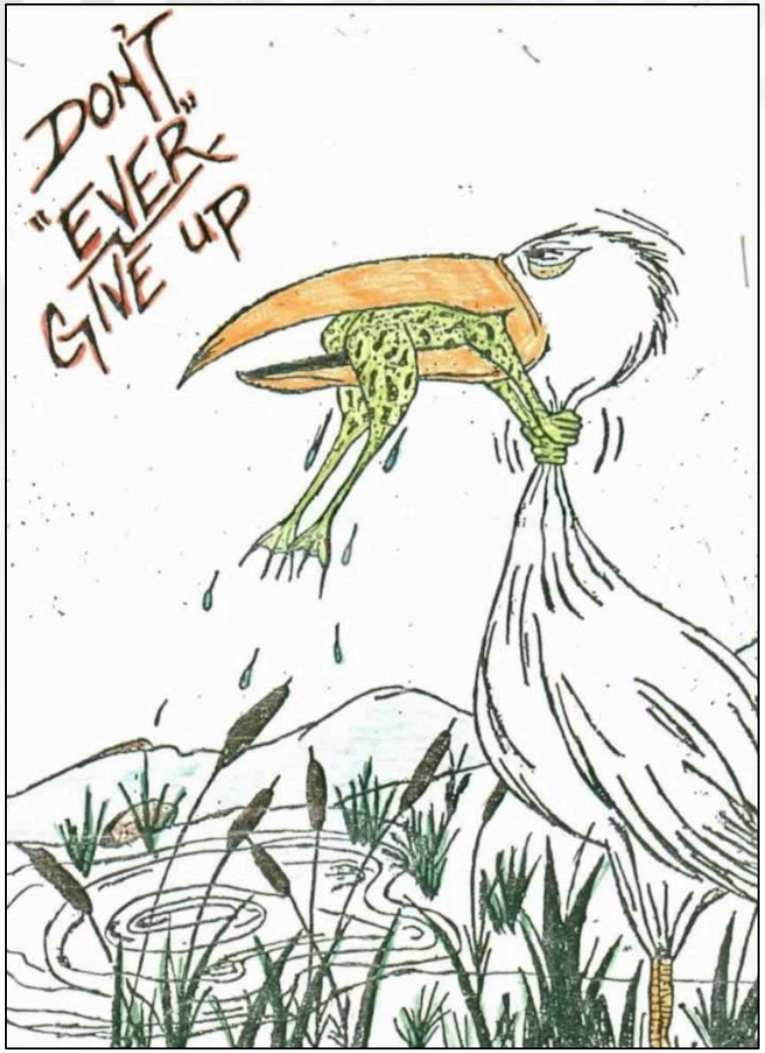




ONLY CHEMOTHERAPY HAS EVER PROVEN SURVIVAL BENEFIT IN ENDOMETRIAL CANCER

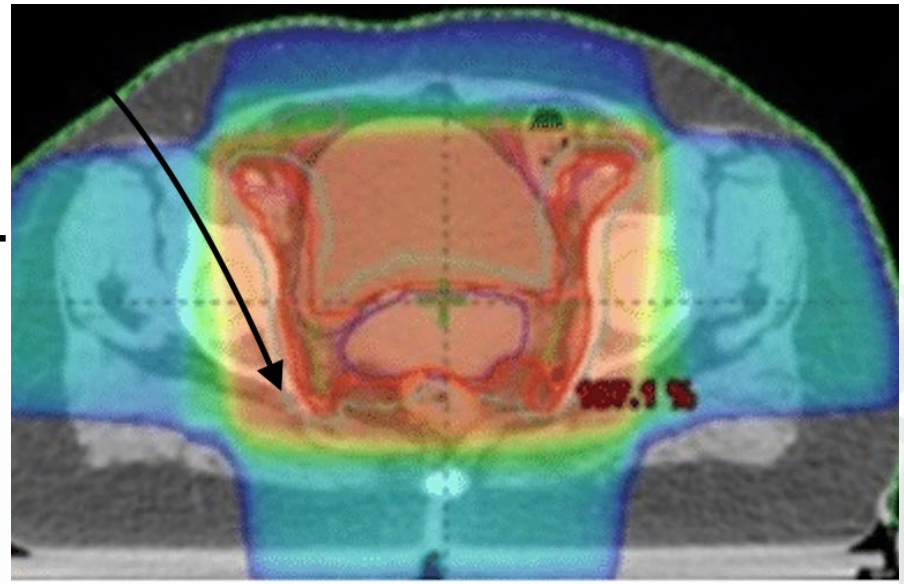
- Vast majority (80%) of advanced endometrial cancer won't have regional/local recurrence and won't derive any benefit from radiation
- Survival is unchanged with addition of radiation
- Costs of radiation are not insignificant
  - Actual monetary costs
  - Time: 4-5 weeks of daily treatment
  - Side effects

ROLE FOR ADJUVANT RADIATION IN ADVANCED ENDOMETRIAL CANCER?

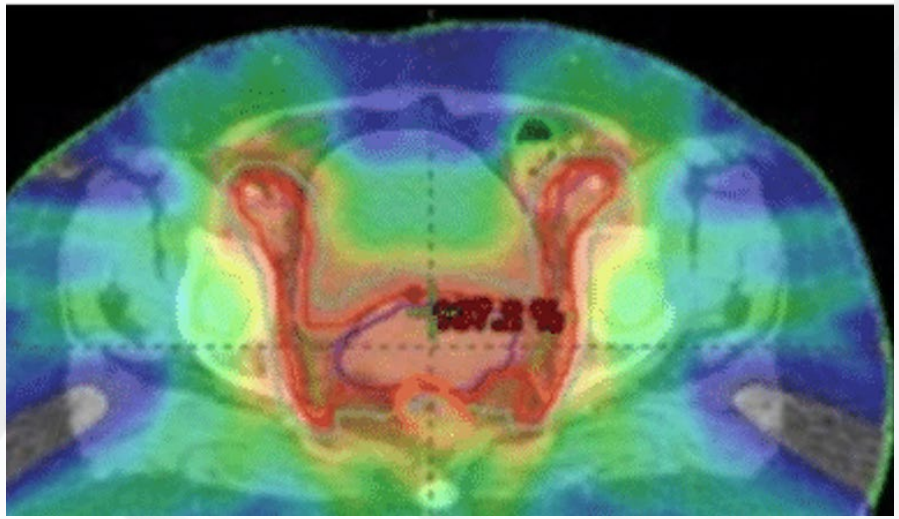


WHAT IS PELVIC RADIATION THERAPY (RT)?

3DCRT



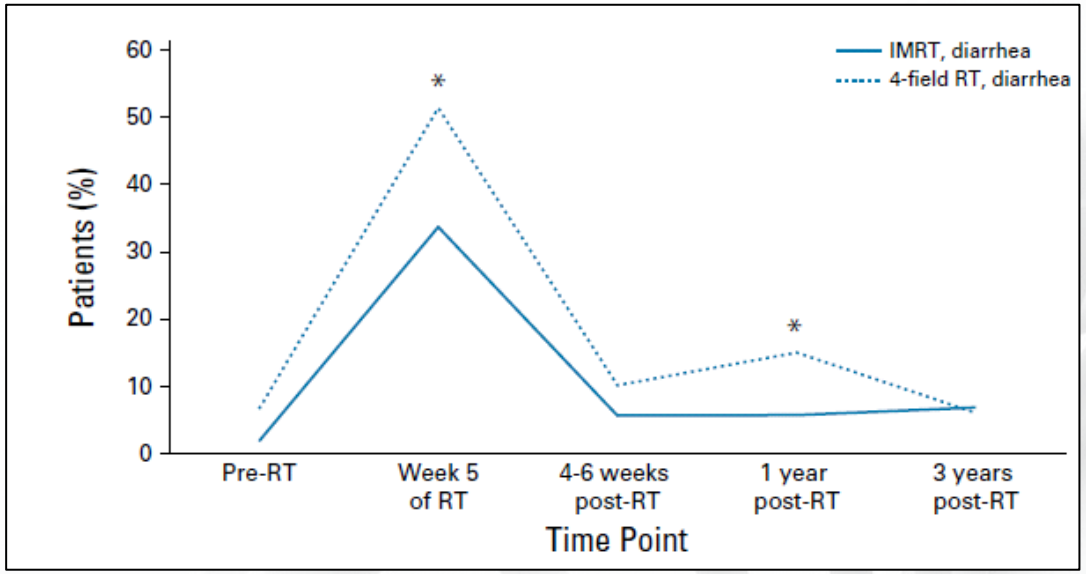
IMRT



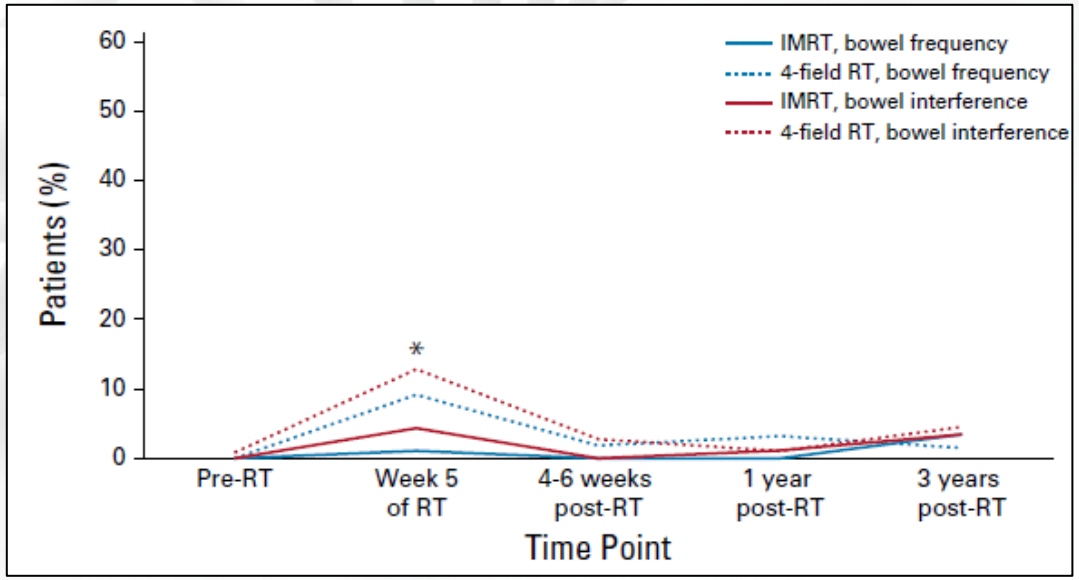
- Intensity-modulated radiation (IMRT) is standard of care
- Standard fractionation: 45Gy/25 fractions (5 weeks)
- Toxicity
  - Acute: fatigue, diarrhea, dysuria, abdominal pain/cramping, incontinence, cytopenias.
  - Late: vaginal stenosis, changes in bowel/urinary habits, incontinence (≤10%).

PATIENT REPORTED OUTCOMES WITH PELVIC RT (RTOG 1203)

Severe (G3+) diarrhea



Severe (G3+) fecal incontinence



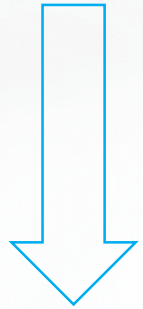
Yeung et al JCO 2020.

EVOLUTION OF RT IN ADVANCED ENDOMETRIAL CANCER

US Standard of Care:
Chemotherapy alone
GOG 122 Randall et al 2006

Regional recurrences - 20%

European Standard of Care:
WPRT alone
Italian Study Maggi et al 2006
JGOG 2033 Susumu et al 2008



Distant recurrence ~25-30%

RT IN ADVANCED ENDOMETRIAL CANCER

GOG 258

Eligibility:
- Stage III-IVA
- Stage I-II serious or clear cell AND positive peritoneal histology **(<5%)**
- < 2cm residual disease
- s/p TAH/BSO, LND optional (**94%**)

PORTEC-3

Eligibility:
-Stage IA G3 with LVSI; Stage IB G3
-Stage II-IIIC EC
-Stage IA-III serous or clear-cell histology **(25%)**
-s/p TAH/BSO, LND optional (58%)

Arm 1:
Experimental

Concurrent CRT (cisplatin) → Adjuvant chemo (Carbo/Taxol x 4c)

Arm 2:
Standard

Chemo Alone
(Carbo/Taxol q3wks x 6c)

RT alone
(48.6Gy/27 Fxs +/- VBT)

GOG 258 RESULTS

- No difference in RFS or OS, no subgroup benefit
- 2023 update at SGO: still no benefit

- **CRT arm less likely to complete all chemo cycles due to toxicity (75% vs 85%).**
- **More distant recurrences (25% vs 20%)in CRT arm which drove survival.**
- **However…..majority treated with 3DCRT!**

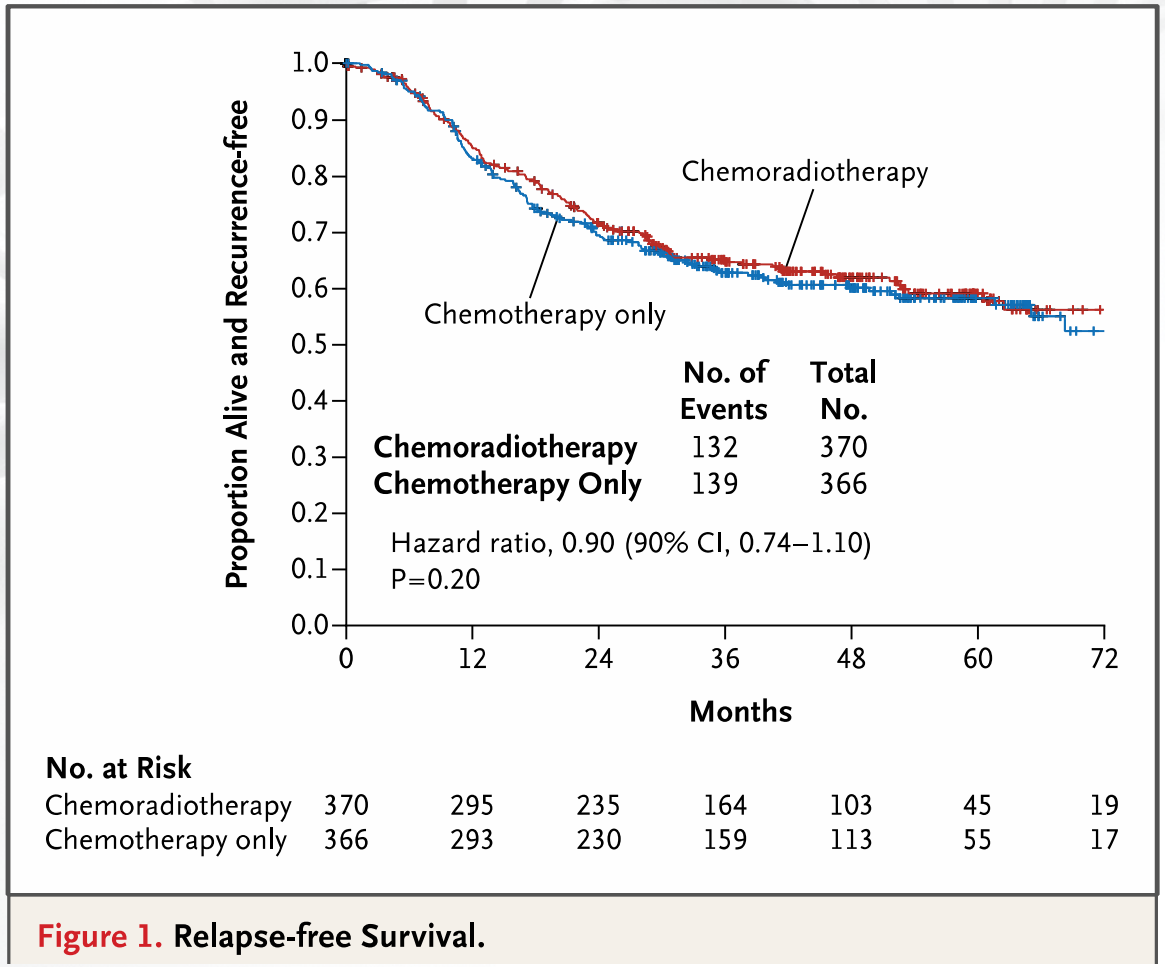
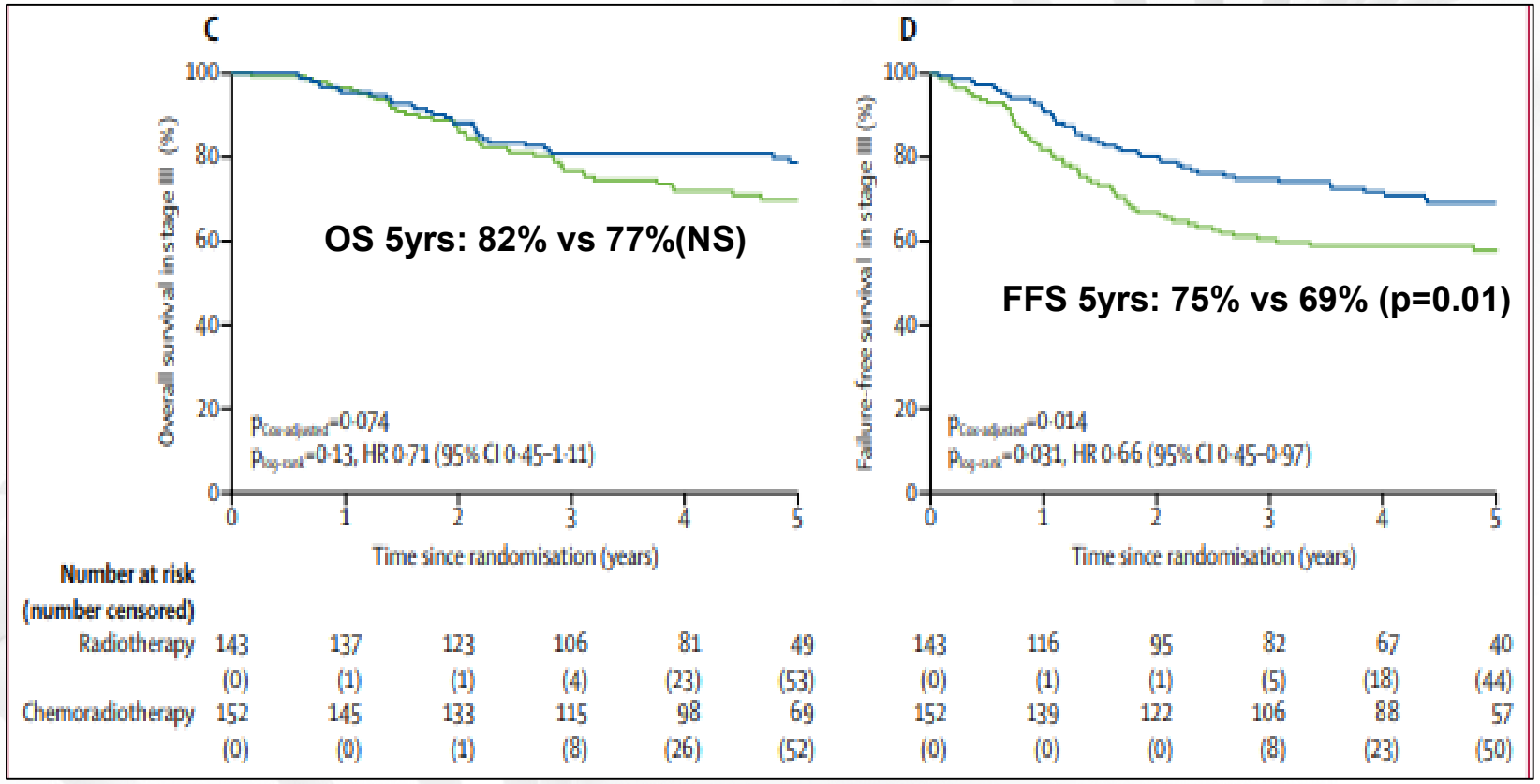


Figure 1. Relapse-free Survival.

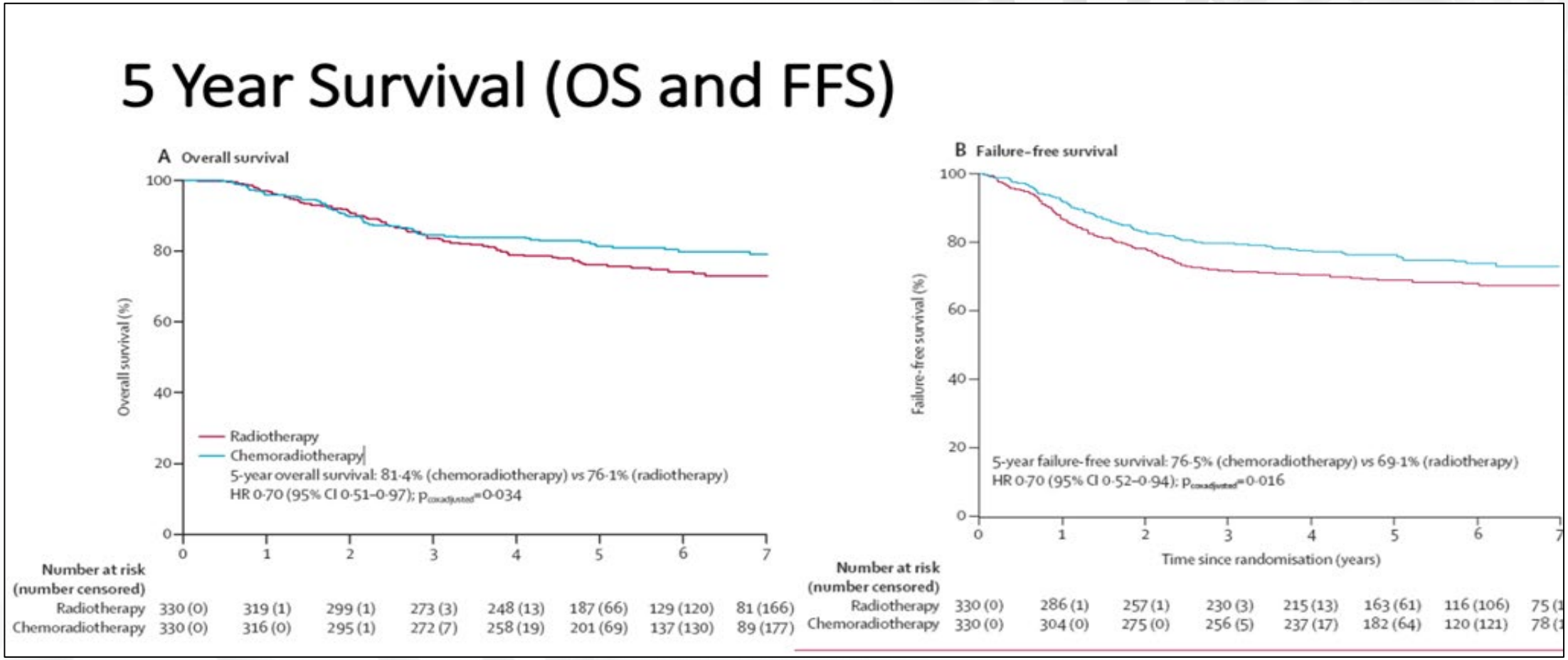
Matei et al. NEJM 2019

PORTEC-3 RESULTS



De Boer et al Lancet 2018

PORTEC-3 POST-HOC ANALYSIS



- Subgroups with largest OS benefit:
  - -Stage III (78% vs 68%)*
  - -Serous cancers (71% vs 53%)*

De Boer et al Lancet 2019

CONCLUSIONS

GOG-258
- CRT does not improve outcomes compared to chemotherapy alone

PORTEC 3
- CRT improves outcomes (FFS and OS) compared to radiation alone (greatest benefit in Stage III disease or serous cancers)

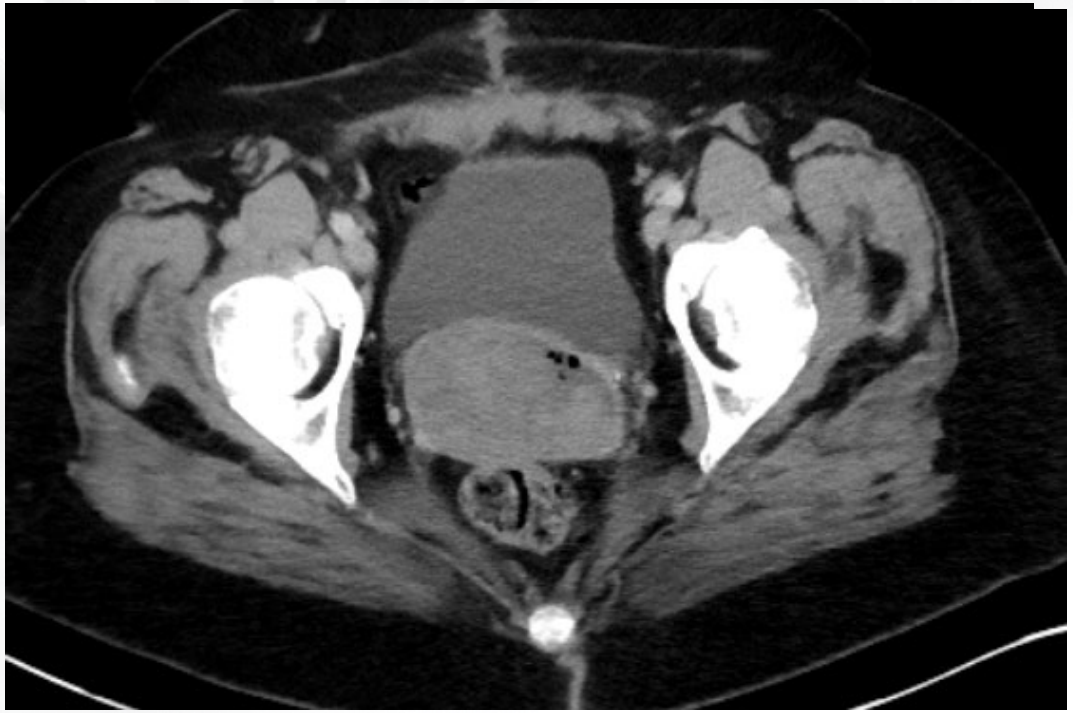
NCCN Guidelines:

Surgically staged:[e] Stage III, IV[u]	**Systemic therapy ± EBRT ± vaginal brachytherapy[v]**

SEQUENTIAL APPROACH: Chemotherapy → Re-scan → Pelvic Radiation

LOCOREGIONAL CONTROL IS IMPORTANT FOR GYNECOLOGIC CANCERS!

- Adjuvant RT with modern radiation techniques (IMRT) is well-tolerated with low risk of serious acute and long term toxicity (RTOG 1203).
- RT in adjuvant setting is aimed to reduce risk of locoregional recurrence, which can be very symptomatic.
  - Locoregional recurrence is 25-30% with systemic therapy alone (GOG-258)
  - As systemic therapy improves, local control will become more important.
- Chemo-IO trials required measurable disease up front and majority were recurrent and/or metastatic:
  - GY018: ~40% received prior RT
  - RUBY: 48% recurrent, 30% metastatic



MODESITT RATIONALE FOR NO RADIATION

- ChemoXRT arm superior to XRT arm (PORTEC-3)
- Chemo alone arm equivalent to chemoradiation arm (GOG 258)
- All the groups showing benefit in the Chemo XRT arm in PORTEC-3 were eligible for GOG 258
- No survival benefit for pelvic radiation even before impressive results from the addition of immunotherapy to chemotherapy

CASE PRESENTATION REVISITED

Ms. X is a 72 year-old patient who underwent a robotic assisted TLH/BSO and sentinel node dissection for a grade 3 endometrioid endometrial cancer. Final pathology showed a positive node and disease in the ovary and the tumor is MMR deficient. No other disease on imaging. Your treatment recommendation is which of the following?

A. Vaginal brachytherapy
B. External beam radiation therapy
C. Chemoradiation with cisplatin
D. Paclitaxel/carboplatin
E. Paclitaxel/carboplatin followed by radiation of some flavor
F. Paclitaxel/carboplatin and PDL-1 inhibitor
G. Still no freaking idea (was on my phone throughout the presentation)

QUESTIONS AND DISCUSSION

GYNECOLOGIC ONCOLOGY

“IF YOU ARE GOING DOWN, TAKE EVERYONE WITH YOU”

Dr. Butch Fowler, UNC