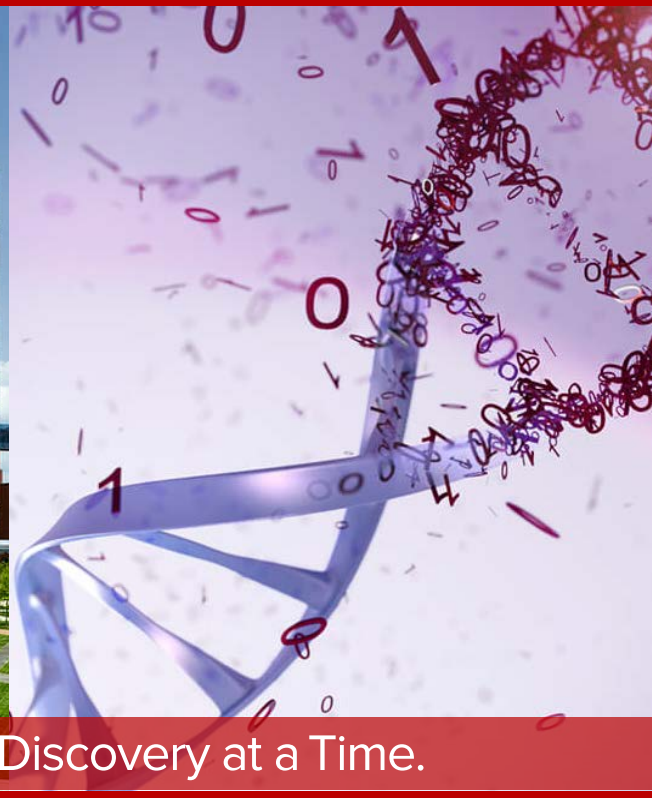

Creating a Cancer-free World. One Person, One Discovery at a Time.

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THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Updates on “the State of the Cervix”

Christa I. Nagel, MD
Associate Professor
Division of Gynecologic Oncology
James Comprehensive Cancer Center

Disclosures

- I have no disclosures

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Objectives

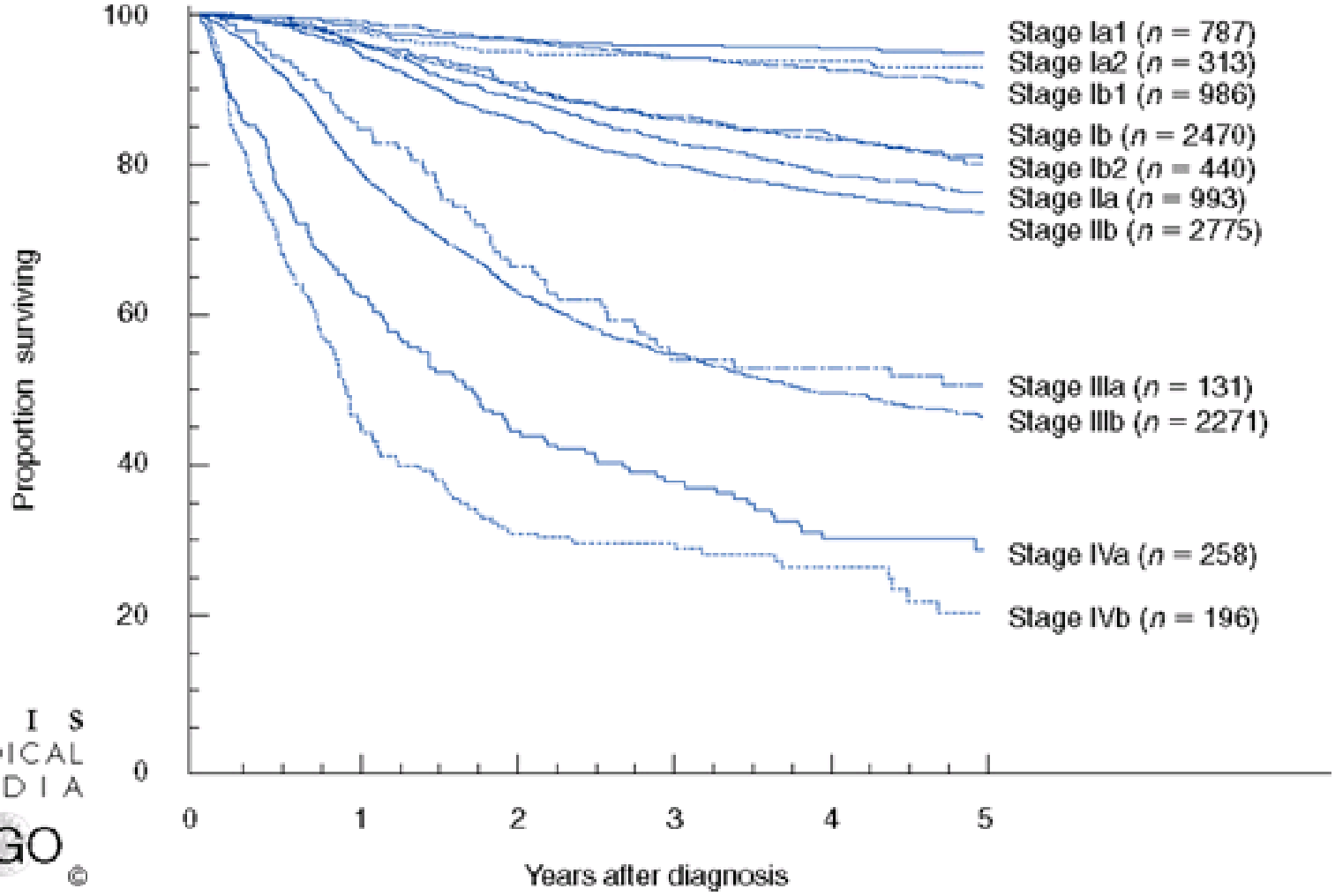
1. Recognize the epidemiology and biology of cervical cancer
2. Discuss screening, prevention, and detection
3. Discuss treatment options for:
   - Primary diagnosis
   - Fertility sparing
   - Recurrent disease

Cervical Cancer Statistics

- Worldwide (4rd most common)
  - 527,600 new cases & 265,700 deaths
  - Second most common cancer in developing world (after breast)
- United States (12th most common)
  - 12,820 new cases & 4,210 deaths (2017)
  - Median age of diagnosis 51
  - 0.1% of cervical cancer cases at age < 21

Siegel and Jemal, Cancer Statistics, 2012; Jemal, Global Cancer Statistics 2012; Cancer Facts & Figures, American Cancer Society 2017)

Cervical Cancer Deaths



I S I S
MEDICAL
M E D I A

FIGO ©

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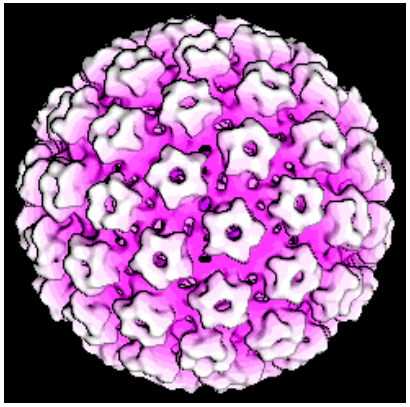
Risk factors for cervical cancer

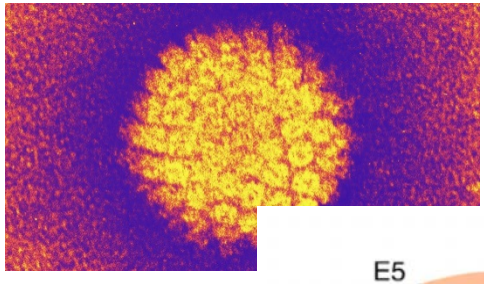
- **HPV exposure**
  - Early onset of sexual activity
  - Multiple partners
  - High risk sexual partners
- Immunosuppression
  - Medications (transplant, autoimmune disease)
  - HIV
- Cigarette smoking
- +/- Other STI's
- +/- OCP's

Human Papillomavirus



- Major role in cervical cancer (>95%)
- HPV 16 (squamous), HPV 18 (adeno-)
  - Cause of 70% of cervical cancers worldwide
- Non-enveloped DNA virus
- Minority of infections lead to cancer
- Promoters
  - Smoking
  - Immune suppression

HPV & Cervical cancer



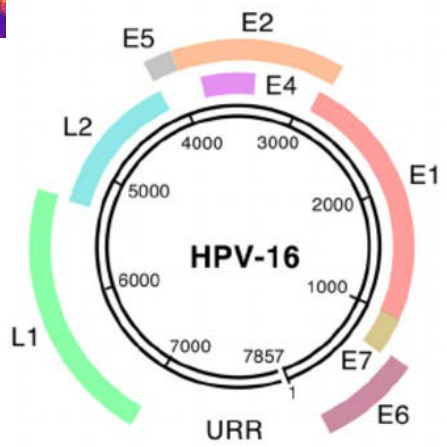


TABLE 1
HPV classification

High-risk	HPV types
Carcinogenic[a]	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably carcinogenic[a]	68
Possibly carcinogenic[a]	26, 53, 66, 67, 70, 73, 82
Tested for in commercially available detection systems	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
Low-risk	6, 11, 40, 42, 43, 44, 54, 61, 72, 81, 89

HPV, human papillomavirus.

[a] Data adapted from Bouvard V, Baan R, Straif K, et al.[23]

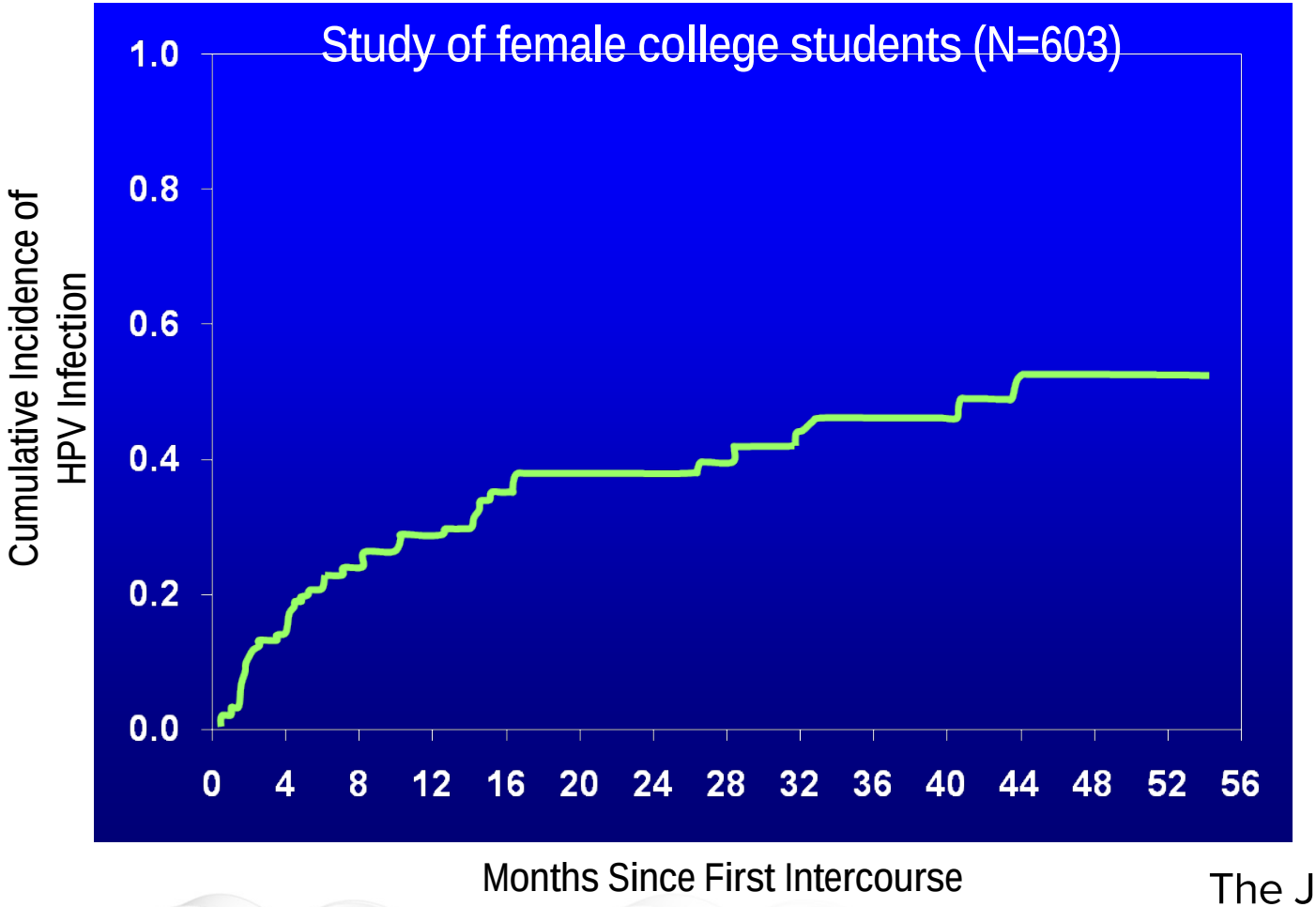
Erickson. HPV review. Am J Obstet Gynecol 2013.

Erickson et al. Am J Obstet Gynecol. 2013

HPV infections

- Each year 14 million people become infected
- Each year 17,600 women and 9,300 men are affected by HPV-related cancers:
  - Genital warts
  - Cervical cancer
  - Penile Cancer
  - Mouth and throat (oropharyngeal/tonsil) cancer
  - Anal cancer
  - Vulva cancer
  - Vaginal cancer

Incidence of HPV Infection From Sexual Debut



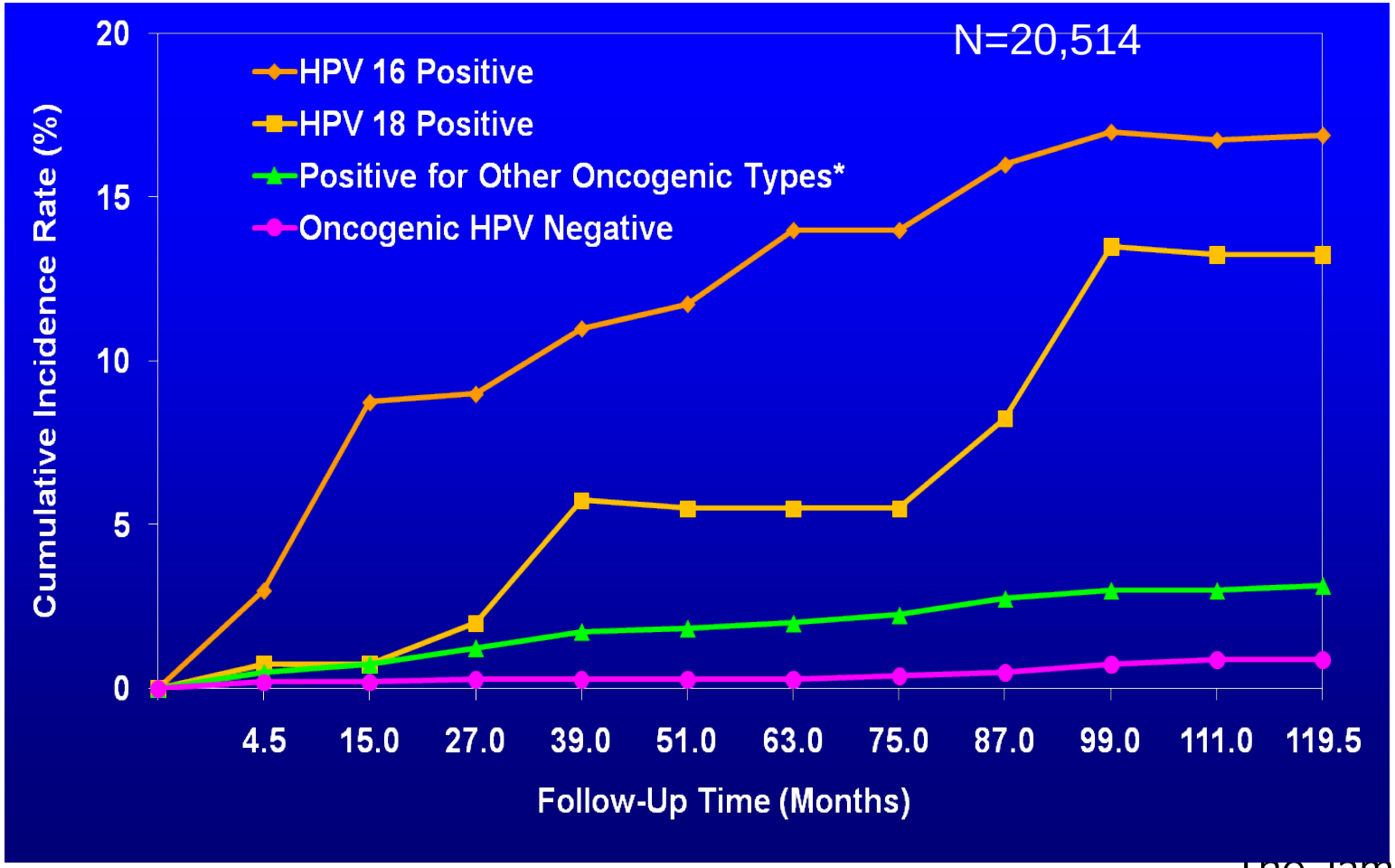
Winer RL. Am J Epidemiol. 2003, with permission of Oxford University Press.

HPV Clearance

- In women 15–25 years of age ~80% of HPV infections are transient.
  - Gradual development of cell-mediated immune response
- 70% of new HPV infections cleared in 1 yr and 91% in 2 yrs
  - Median duration of infection = 8 months
  - Certain HPV types are more likely to persist (HPV 16 and HPV 18)
- In immune-competent women CIN3 clears in 35%

Meijer CJLM. Histopathology. 1998;
Schiffman M. J Natl Cancer Inst Monogr. 2003
Ho GYF. N Engl J Med. 1998

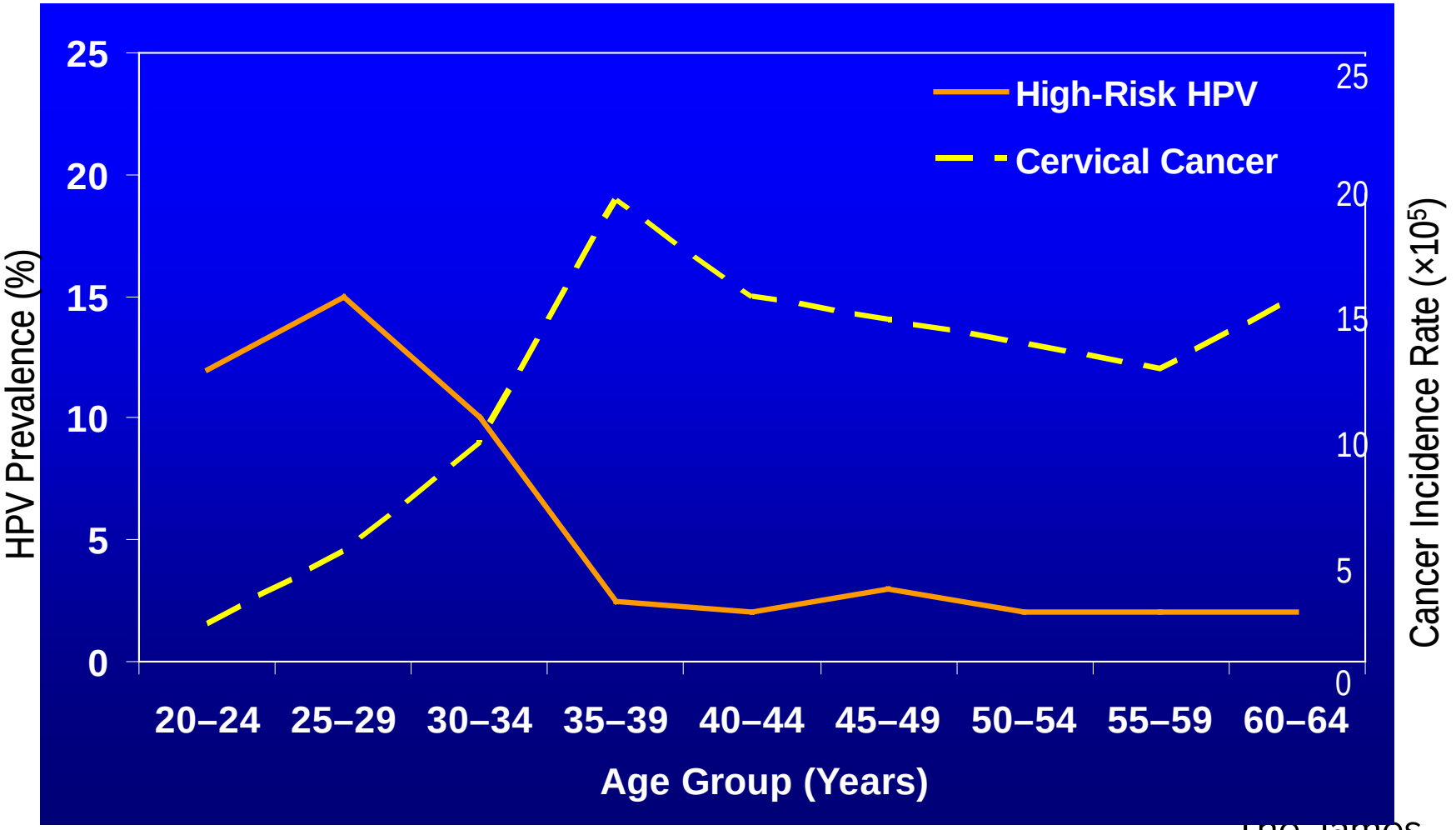
Risk of Cervical Dysplasia and Cancer in Women with HPV 16 or 18



*Positive for the non-HPV 16/18 types in Hybrid Capture 2.

Kahn MJ,*J Natl Cancer Inst*. 2005. Reprinted with permission from Oxford Journals, Oxford University Press.

Age-Specific Rates of HPV Infection and Cervical Cancer

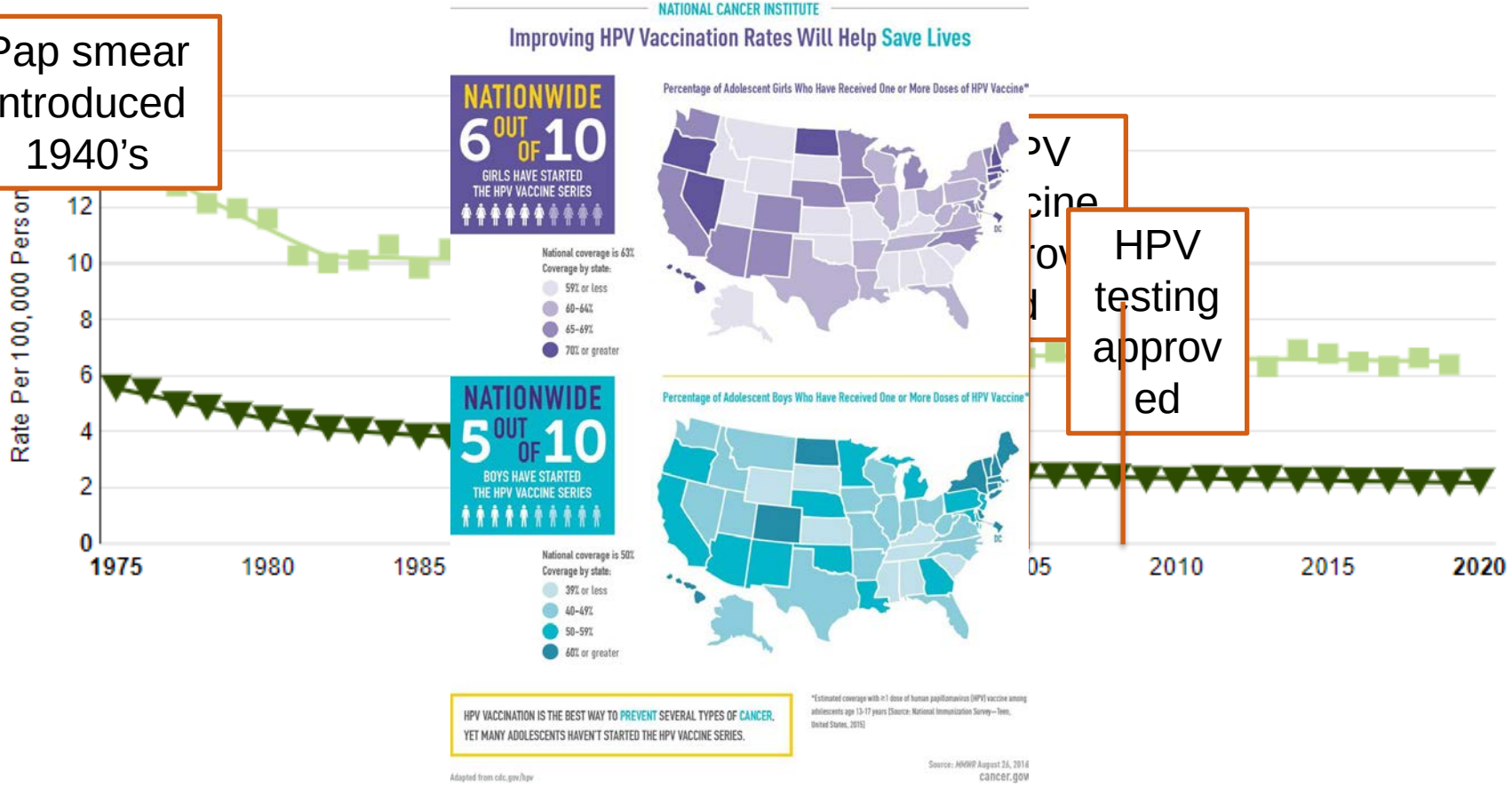


Bosch FX, J Clin Pathol. 2002; Reproduced with permission from the BMJ Publishing Group.

Prevention

- Primary
  - HPV Vaccination
  - (condoms)
- Secondary
  - Screening
    - Pap/HPV testing

Pap smear introduced 1940's

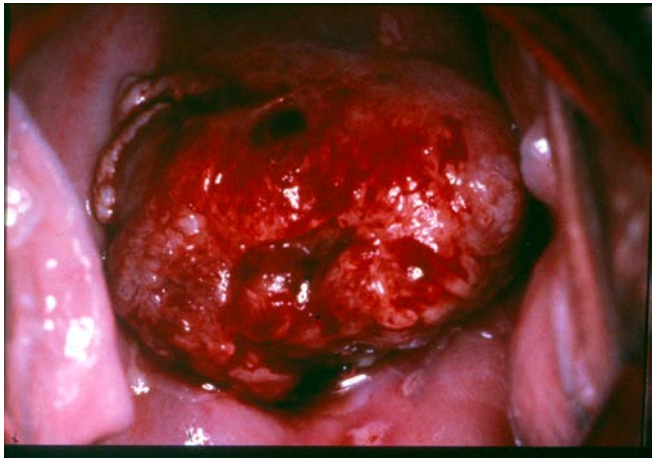


HPV testing approved

https://seer.cancer.gov/statfacts/html/cervix.html

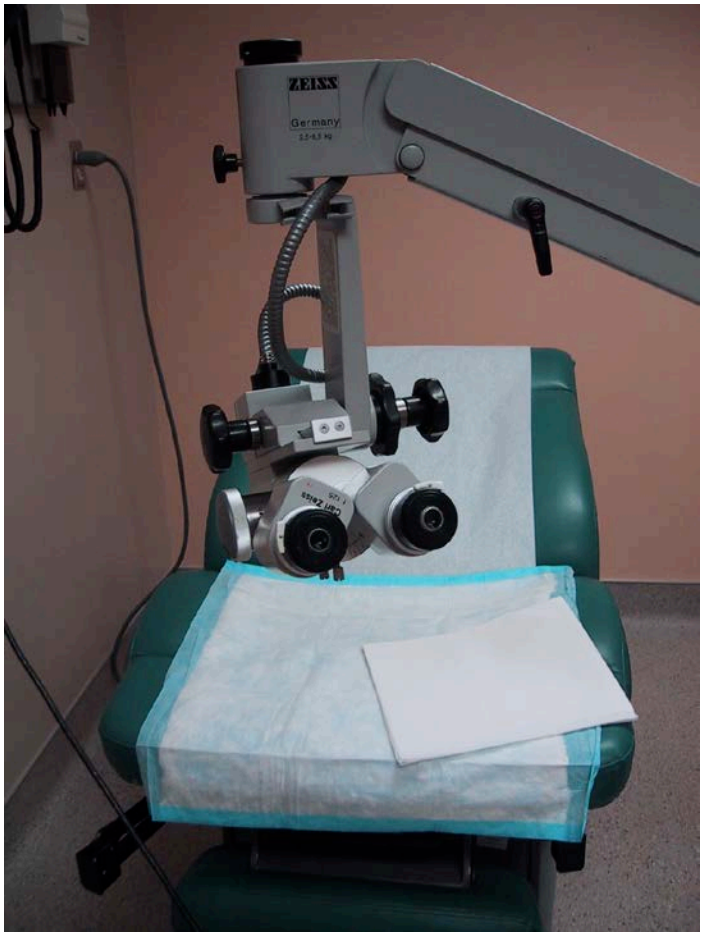
https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-uptake-infographic

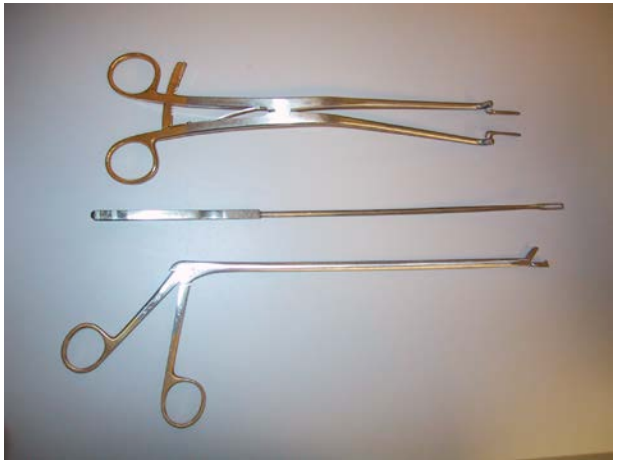
Symptoms and Signs



- Usually asymptomatic
- Abnormal cervical cytology (pap)
- Vaginal bleeding
  - Post-coital (during/after intercourse)
  - Post-menopausal
  - Intermenstrual (in between periods)
- (Copious) vaginal discharge (often malodorous)
- Flank, leg or back pain, leg swelling

Cervical Cancer Diagnosis





Clinical presentation

- Incidental finding on screening evaluation/pelvic examination
- Abnormal uterine bleeding
  - Post-coital bleeding
  - Intermenstrual bleeding
  - Heavy bleeding
- Vaginal discharge (often malodorous)
- Lower back/pelvic pain
- Bowel or urinary symptom

Advanced disease (sidewall involvement):
- Flank pain
- Leg swelling
- Sciatica

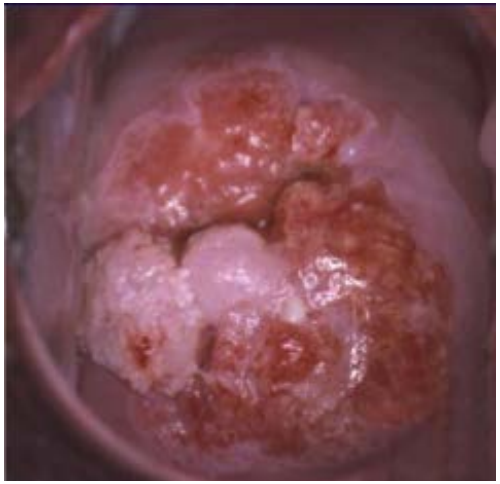
Cervical Cancer Diagnosis

- Pelvic examination
  - Office or operating room
  - ***Clinical*** stage
- Colposcopy (microscopy)
- Biopsy
  - ***Diagnostic*** test
  - NOT A PAP (*screening* test only)

Histology

- Squamous (~80%)
- Adenocarcinoma / Endocervical/ Usual type (~15%)
- Adenosquamous
- Neuroendocrine, Small Cell
- Minimally Deviation Adenoca/ Adenoma Malignum (PJS)
- Clear Cell (DES)
- Serous

Diagnosis

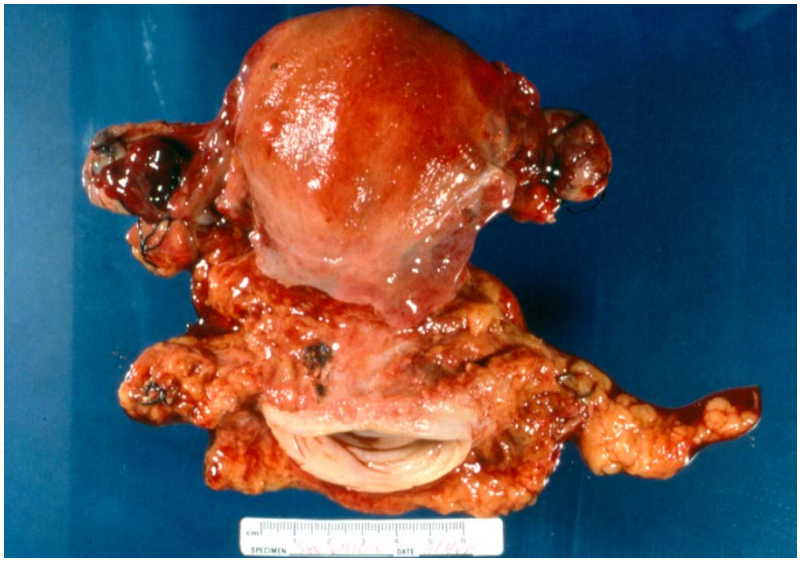


- No visible lesion/no symptoms
  - Pap→
  - Colpo as indicated + biopsy/ECC→
  - Excisional procedure
- Visible lesion
  - Biopsy (do not pass go, do not collect $200, DO NOT DO A PAP)
- Imaging
  - MRI (best for evaluation of cervical lesion)
  - PET (best for evaluation of for metastatic disease)
- Staging New 2018
  - Exam
  - Imaging
  - Surgery

Staging

Stage	Description
I	**Confined to cervix**
IA1	Stromal invasion <3mm
IA2	Stromal invasion ≥3mm and <5mm
IBI	≥5mm DOI, and <2cm
IB2	≥2cm but ≤4cm
IB3	>4cm
II	**Extension to upper 2/3 vagina/parametria**
IIA1	Upper 2/3 vagina, <4cm
IIA2	Upper 2/3 vagina, ≥4cm
IIB	Parametrial involvement (not to sidewall)
III	**Pelvic sidewall, lower vagina, nodes**
IIIA	Lower 1/3 vagina
IIIB	Pelvic sidewall +/- hydronephrosis
IIIC1	Pelvic nodes
IIIC2	PA nodes
IV	**Other organs**
IVA	Adjacent
IVB	Distant

Management



- Considerations prior to treatment
  - Patient factors
    - Age
    - Menopausal status
    - Desires for fertility
    - Medical co-morbidities
  - Disease
    - Stage
    - Histology (Neuroendocrine treated differently)

Early stage disease→ Surgery vs Radiation vs Chemoradiation

Locally advanced disease→ Chemoradiation

Metastatic/recurrent→ Systemic therapy

Management of early stage disease

Stage	Treatment	Fertility sparing option
IAI, no LVSI	Extrafascial hyst	Cone biopsy Trachelectomy (if pos margins
IA2-IB1*	Extrafascial hyst +LN	Cone biopsy + LN Trachelectomy + LN
IA1 with LVSI, IA2	Modified rad hyst + LN EBRT + BT	Radical trachelectomy + LN Cone biopsy + LN
IB1 (not meeting *criteria), IB2, IIA1	Rad hyst + LN EBRT + BT (+/- concurrent chemo)	Radical trachelectomy +LN
IB3, IIA2	chemoRT (EBRT +BT)	Not recommended NACT→ radical trachelectomy +LN

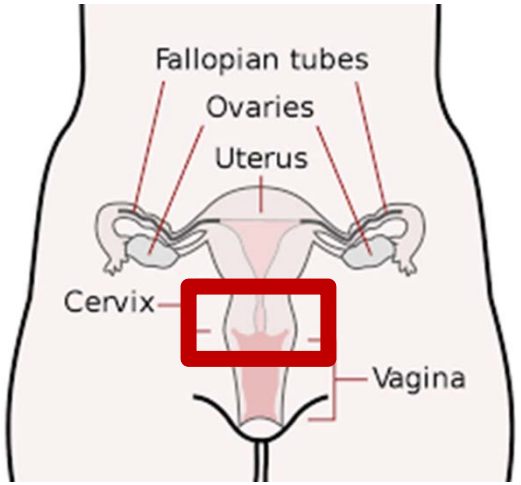
ConCerv Trial
GOG 278
SHAPE Trial
CONTESSA
LACC Trial
ROCC trial
RACC trial

*Based on cone biopsy, no LVSI, neg margins, SCC or usual type adeno g1-2, size ≤2cm, DOI ≤10mm, imaging w/o mets

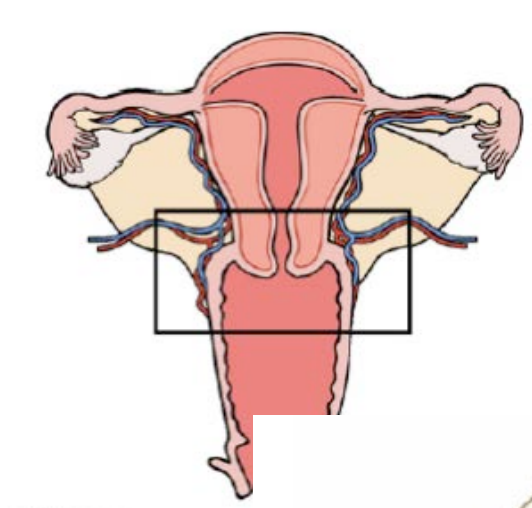
NCCN Guidelines, version 1.2023

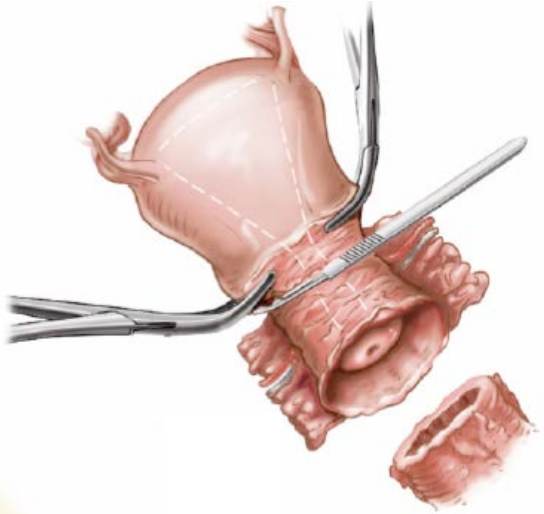
Fertility sparing treatment

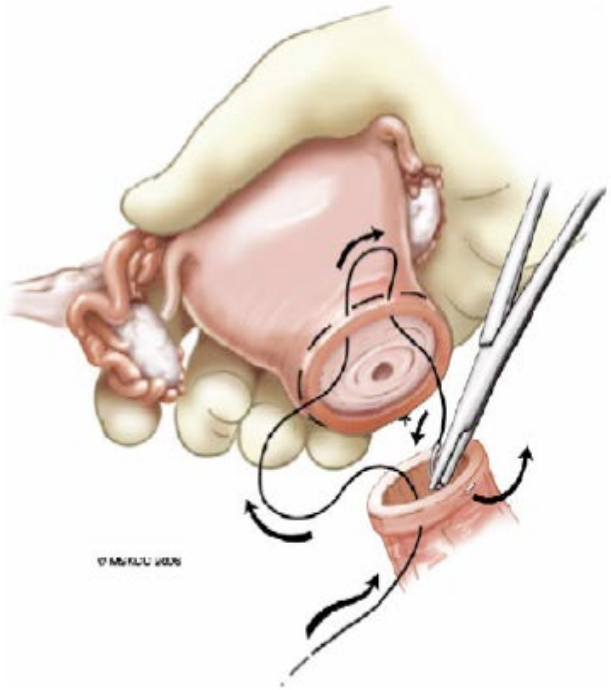
- 10-15% of all cervical cancers occur in women during reproductive years
- Radical trachelectomy and lymph node dissection
  - Removing the cervix only and reconnecting the uterus to the vagina
- Generally must have:
  - desire for fertility preservation
  - small (less than 2 cm) tumor
  - (negative LVSI)
  - no evidence lymph node metastasis
  - no upper endocervical involvement (ECC)



Fertility sparing treatment







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Who needs adjuvant therapy?

- Low risk→ none
- Intermediate risk
  - Sedlis criteria
  - RT
    - Decreased recurrence (30→15%)
    - No difference in survival (but close)
- High risk
  - Peters criteria
  - chemoRT
    - Improved PFS
    - Improved OS

Sedlis Criteria		
LVSI	**Size**	**DOI**
+	Any	Deep 1/3
+	≥2cm	Mid 1/3
+	≥5cm	Sup 1/3
-	>4cm	Deep/mid 1/3

Peters criteria
+nodes
+parametria
+margins

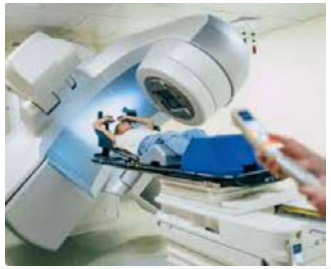
Sedlis et al. Gynecol Oncol. 1999
Peters et al. J Clin Oncol. 2000

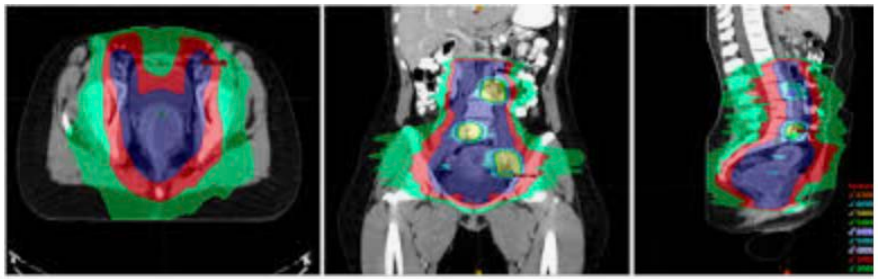
Management of locally advanced disease

- EBRT + BT
  - EBRT 45-50 Gy to primary tumor and regional lymphatics
    - Parametrial/nodal boosts
    - +/-Extended field
  - Primary tumor treated with brachytherapy 30-40Gy
  - Time matters (Goal= complete w/in 56 days)

<u>NCI clinical announcement in 1999: Chemotherapy plus radiation improves survival</u>

- Cisplatin-based regimen reduced the risk of death by 30-50%
- Contemporary regimen: Cisplatin 40mg/m2 weekly during EBRT (x5-6)





But 30-50% of patients recur….

- Adjuvant therapy?
- Additional of immunotherapy to chemoRT?

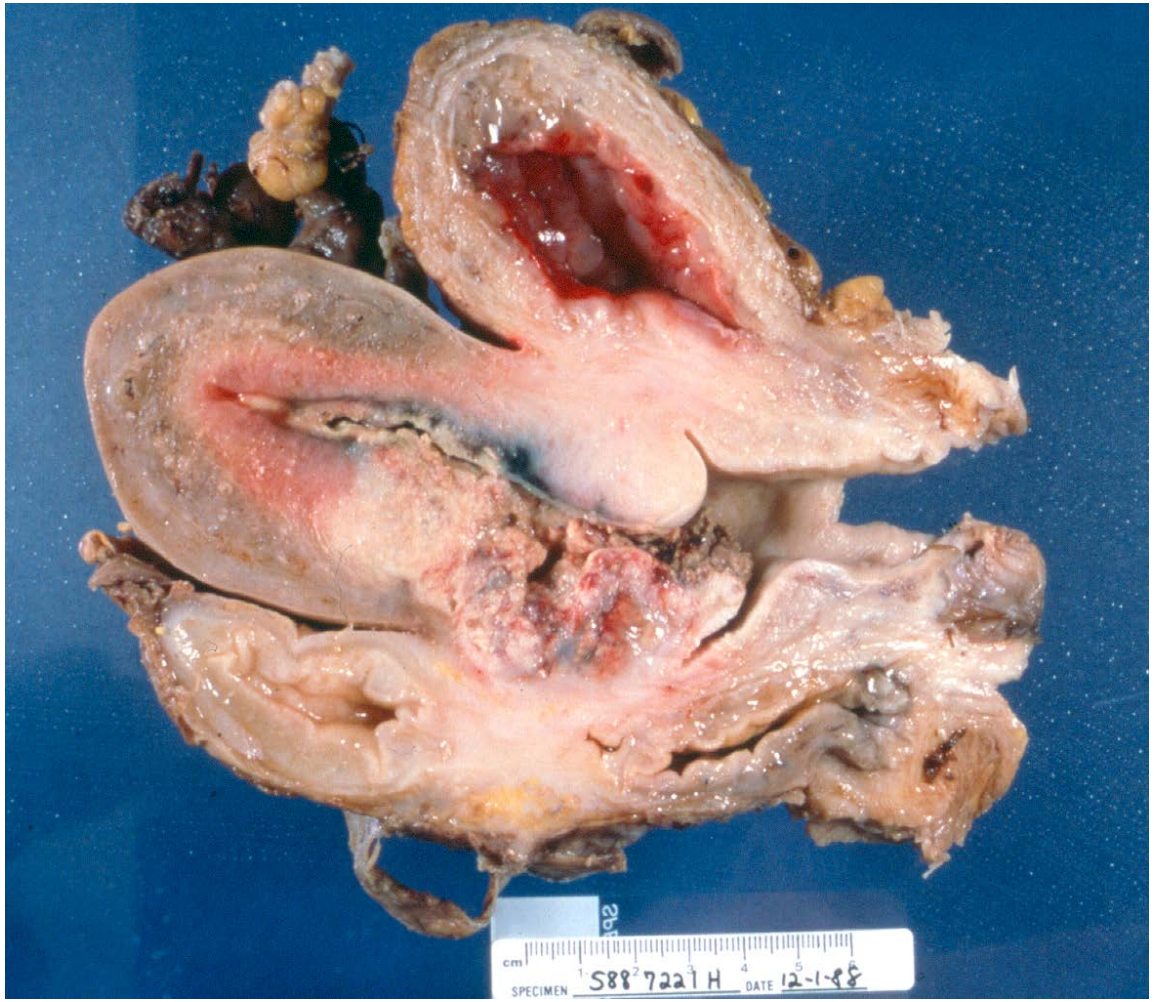
Cervical Cancer treatment

- If metastatic (spread) or recurrent cervical cancer
  - Chemotherapy
- Even with best chemotherapy survival is ~18 months

- Novel treatment / clinical trials
  - Immunotherapy - ~17% overall response rate
  - Tumor vaccines

- Central recurrence
  - Potential for cure
  - Pelvic exenteration – Overall survival 50%

Pelvic Exenteration



- 50% cure rate
- 95% complication rate
- Life altering surgery
  - Permanent colostomy
  - Urinary Conduit
  - Option for vaginal reconstruction

Metastatic/recurrent disease

Predictors of response to therapy:

- Race
- Performance status
- Location of disease
- Prior therapies
- Time to recurrence

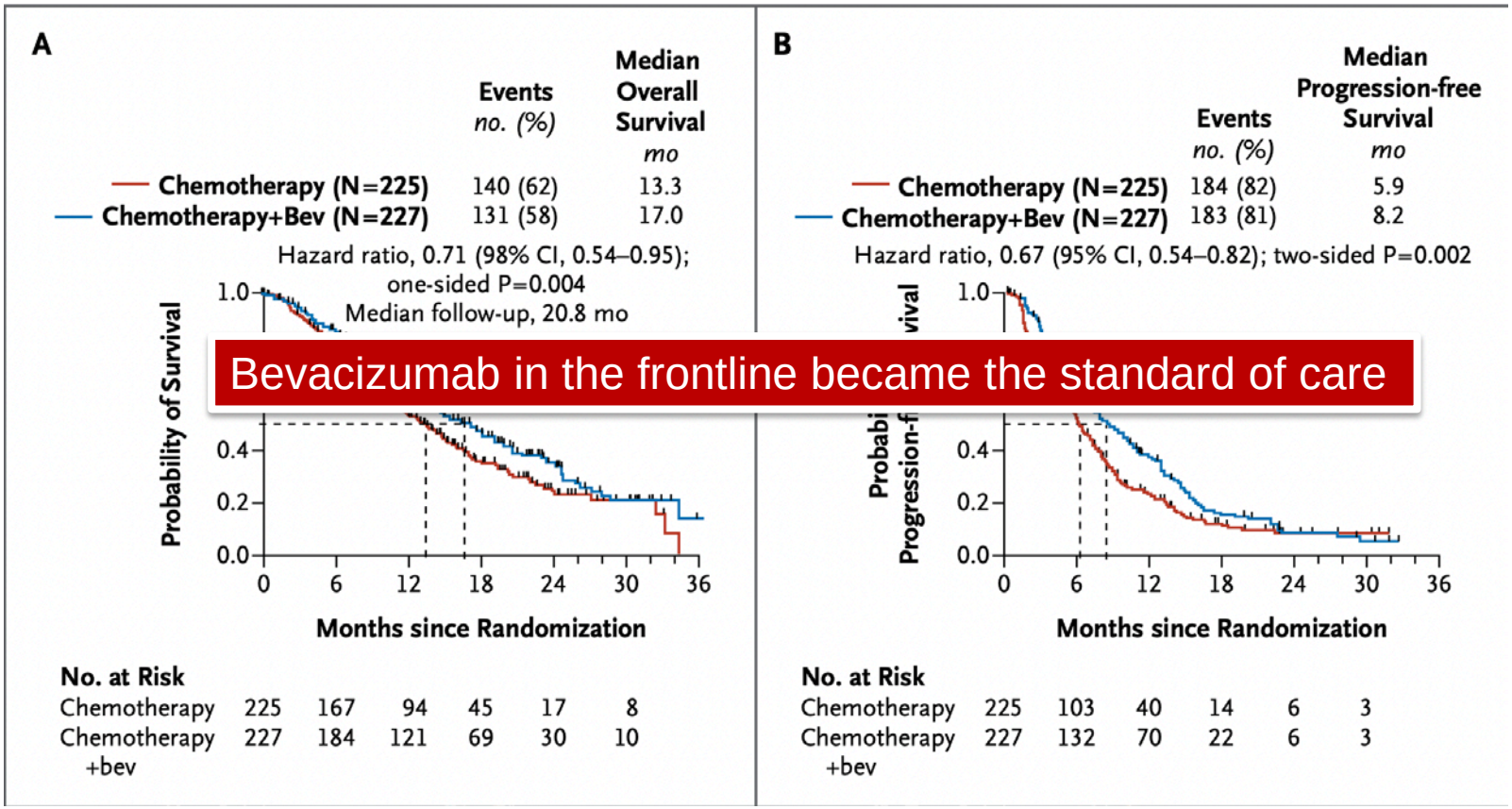
GOG 240

Metastatic, persistent or recurrent disease GOG PS 0-1
Measurable disease
NO prior treatment with chemo for metastatic disease, non-healing wounds, active bleeding conditions, inadequately anticoagulated VTE

Randomized 1:1:1:1

- Cisplatin 50mg/m2 + paclitaxel 135mg OR 175 mg/m2
- Topotecan 0.75mg/m2 (d—3) + paclitaxel 175 mg/m2
- Cisplatin 50mg/m2 + paclitaxel 135mg OR 175 mg/m2 + BEV
- Topotecan 0.75mg/m2 (d—3) + paclitaxel 175 mg/m2 + BEV

Tewari et al. New Eng J Med. 2014



Bevacizumab in the frontline became the standard of care

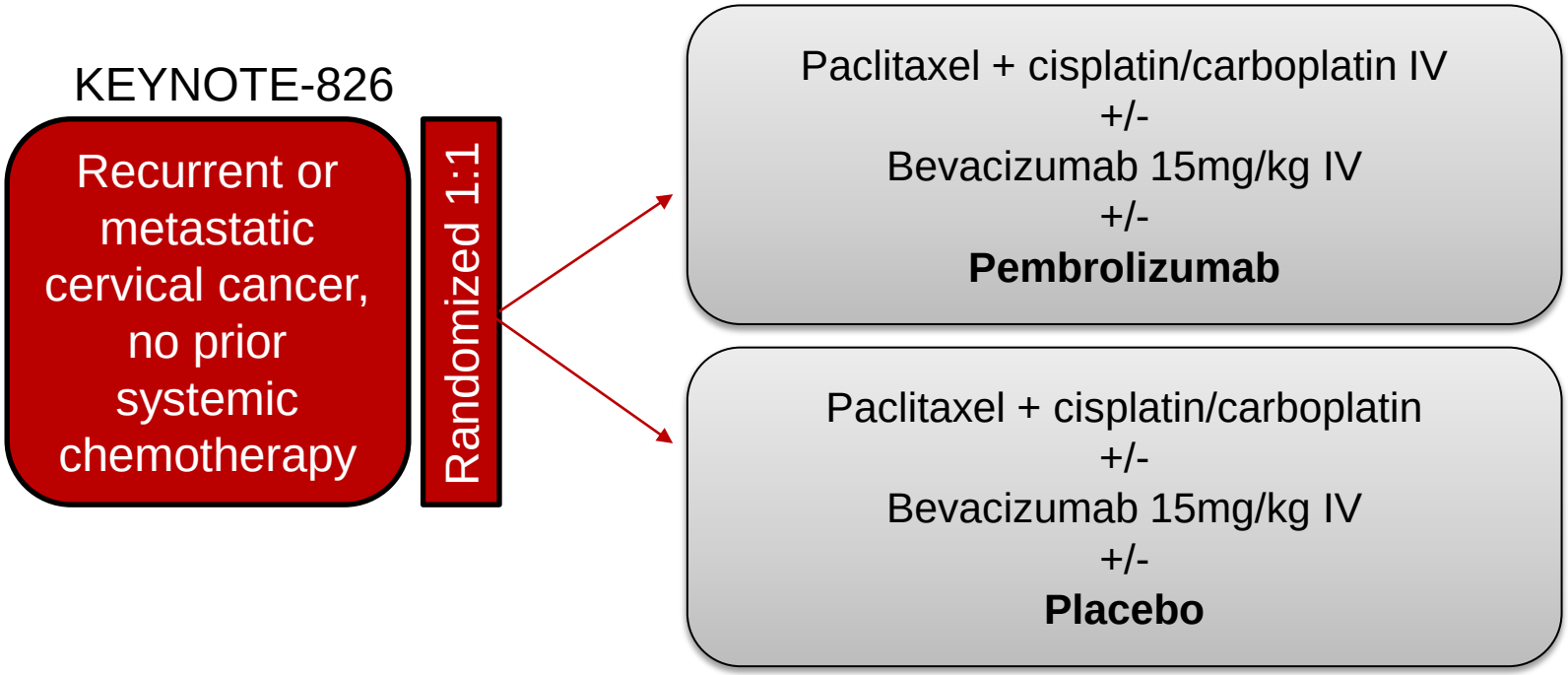
Tewari et al. New Eng J Med. 2014

What about immunotherapy?

- Cervical cancer is a virally-driven cancer (HPV)
- Cervical cancers have increased tumor mutational burden (TMB) rate
- Tumor Infiltrating Lymphocytes (TILs)
- PD-L1 overexpression
  - squamous cell carcinoma (19-88%) and adenocarcinoma (14-65%)

Otter SJ, Clin Oncol (2019)

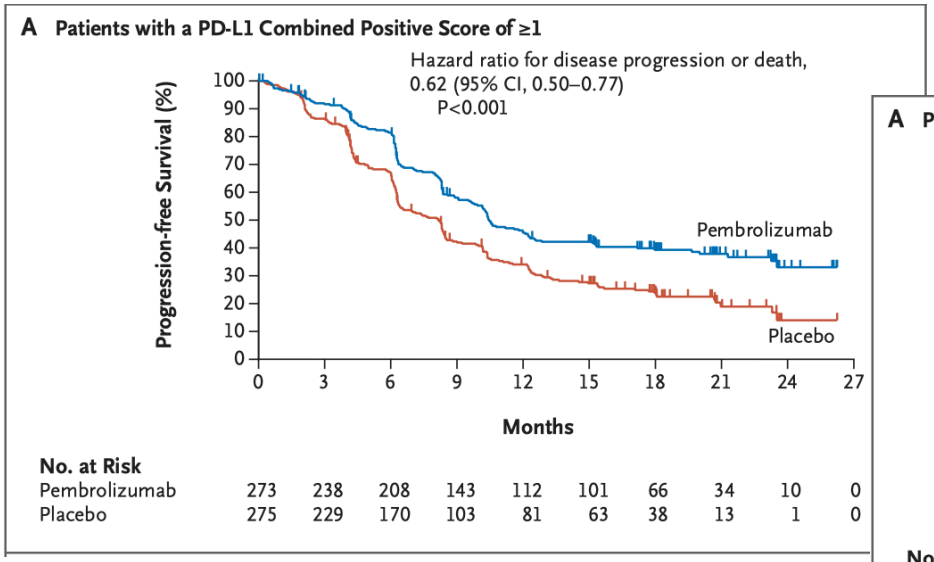
Chemo + immunotherapy in front line?

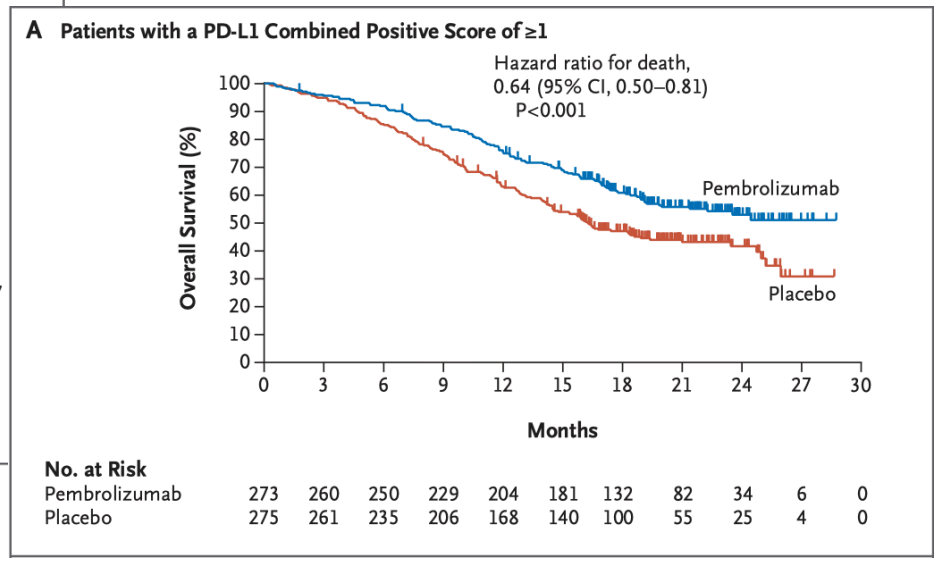


Colombo et al. New Eng J Med. 2021

KEYNOTE-826

New standard





Median PFS 10.4 vs 8.2 months, HR 0.62, p<0.01

Median OS: NR (!!!) vs 16.3 months, HR 0.64, p<0.001

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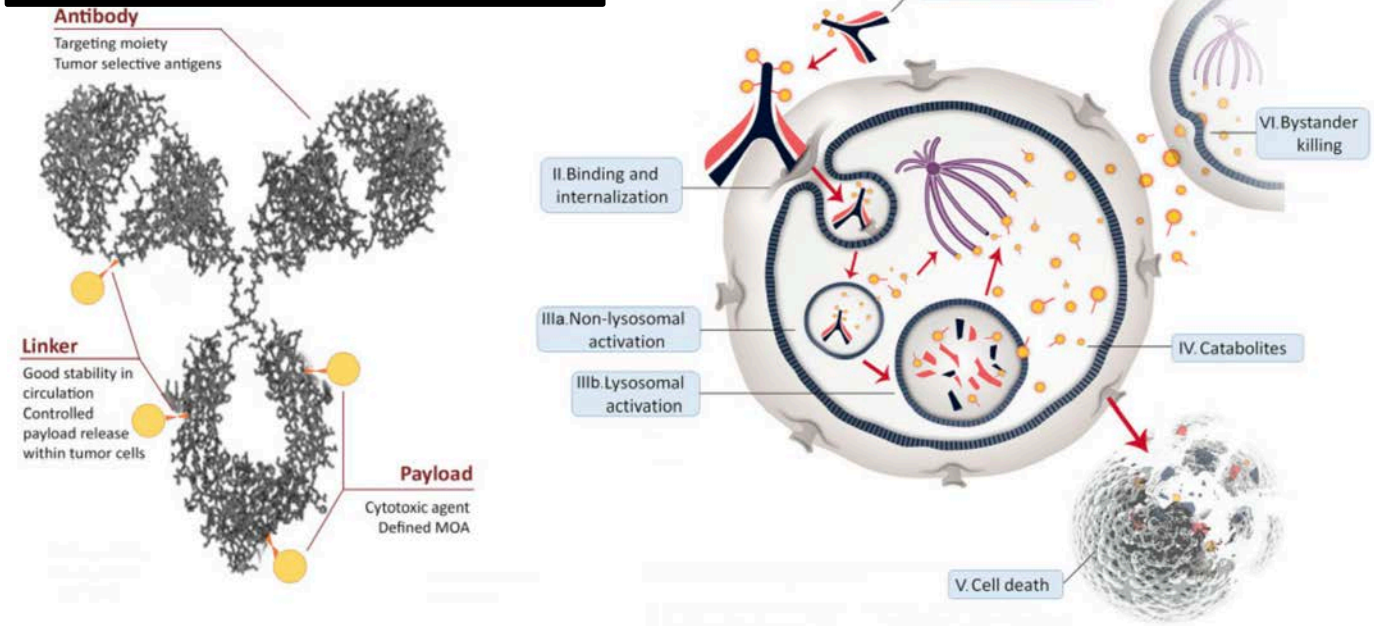
2nd line and beyond

Regimen	ORR (%)	PFS (months)	OS (months)
Topotecan	12.5	2.1	6.6
Vinorelbine	13.7	NS	NS
Pemetrexed	15	3.1	7.4
Docetaxel	8.7	3.8	7.0
Gemcitabine	4.5	2.1	6.5
Abraxane	29	5.0	9.4

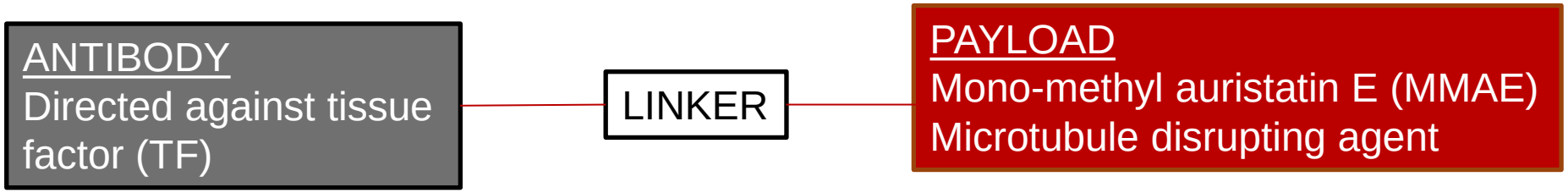
Beyond immunotherapy…

Antibody-drug conjugates



Birrer et al. J Natl Cancer Inst. 2019

Tisotumab Vedotin (TV)



Common toxicities associated with TV

Ocular Toxicity ***BLACK BOX WARNING*** occurs in ~60% pts; onset: ~1.2 months

- Changes in corneal epithelium/conjunctiva--> changes in vision, corneal ulceration
- Conjunctival adverse rxn (40%)
- Dry eye (29%)
- Corneal adverse reactions (21%)
- Blepharitis (8%)

Grade 3 ocular toxicity 3.8%

Peripheral Neuropathy: ~42% pts; onset: ~2.4 months

Hemorrhage: epistaxis (~44%); hematuria (~10%); vaginal hemorrhage (~10%)

Pneumonitis: ~1.3%

Infusion related reactions: ~12%

Summary courtesy of Ambar Khan

EYE CARE	Day of Tisotumab vedotin infusion			Day 2	Day 3	Remainder of cycle (21 day cycle)
	Pre-Infusion	**During Infusion**	**Rest of day**			
Cooling Pads *must remain on each eye for duration of infusion	MUST cover each eye. Apply 5 min prior to infusion	Replace cooling pad after ~20min to maximize optimal eye cooling				
Steroid eye drop (i.e. dexamethasone 0.1%)	1 drop each eye		1 drop each eye x 2 more doses	1 drop each eye three times per day	1 drop each eye three times per day	
Vasoconstrictor eye drop (i.e. brimonidine tartrate 0.2%)	3 drops each eye					
Lubricating eye drop			1-2 drops in each eye as needed for dry eyes			

Baseline ophthalmic exam; *prior to each treatment** and as clinically indicated *(*per package insert)*
Patients should not wear contact lenses for duration of treatment

Summary courtesy of Ambar Khan

Conclusions

- We have come a long way, but have a long way to go
- 1st line of defense is prevention
  - **VACCINATE**
  - **VACCINATE**
  - **VACCINATE**
  - Routine pap smears

Conclusions

- Management pearls:
  - Early Stage:
    - Low Risk: Surgery remains the mainstay of treatment, less radical surgery may be the future
    - Intermediate risk: Adjuvant RT
    - High risk: Adjuvant chemoRT
  - Locally advanced disease:
    - Definitive chemoRT (cisplatin), no role for adjuvant chemo or immunotherapy to date.
  - Metastatic/Recurrent disease:
    - Platinum/taxane + pembro +/- bev is the new standard first line
    - Pembrolizumab approved for PDL1 + (CPS $\geq$1%)
    - Tisotumab vedotin

Conclusions

- What's next:
  - Adjuvant chemoRT for early stage, intermediate risk?
  - Immunotherapy after immunotherapy? Combo strategies (PD1/PDL1, CTLA4)
  - Tisotumab to the front line?
  - TILS (SUPER EXCITING)
  - Vaccines for disease treatment?

Thank You

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