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UHN Princess Margaret Cancer Centre

Toward Personalized Risk-Adapted Therapy for Oropharynx Cancer

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Princess Margaret Cancer Centre & U of Toronto

August 7, 2019

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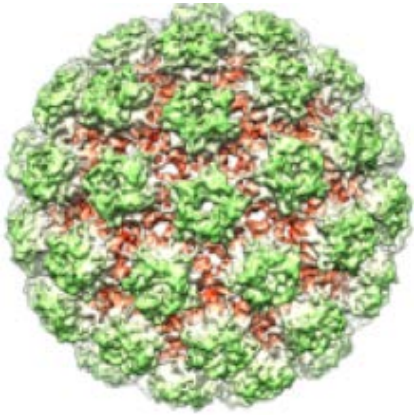
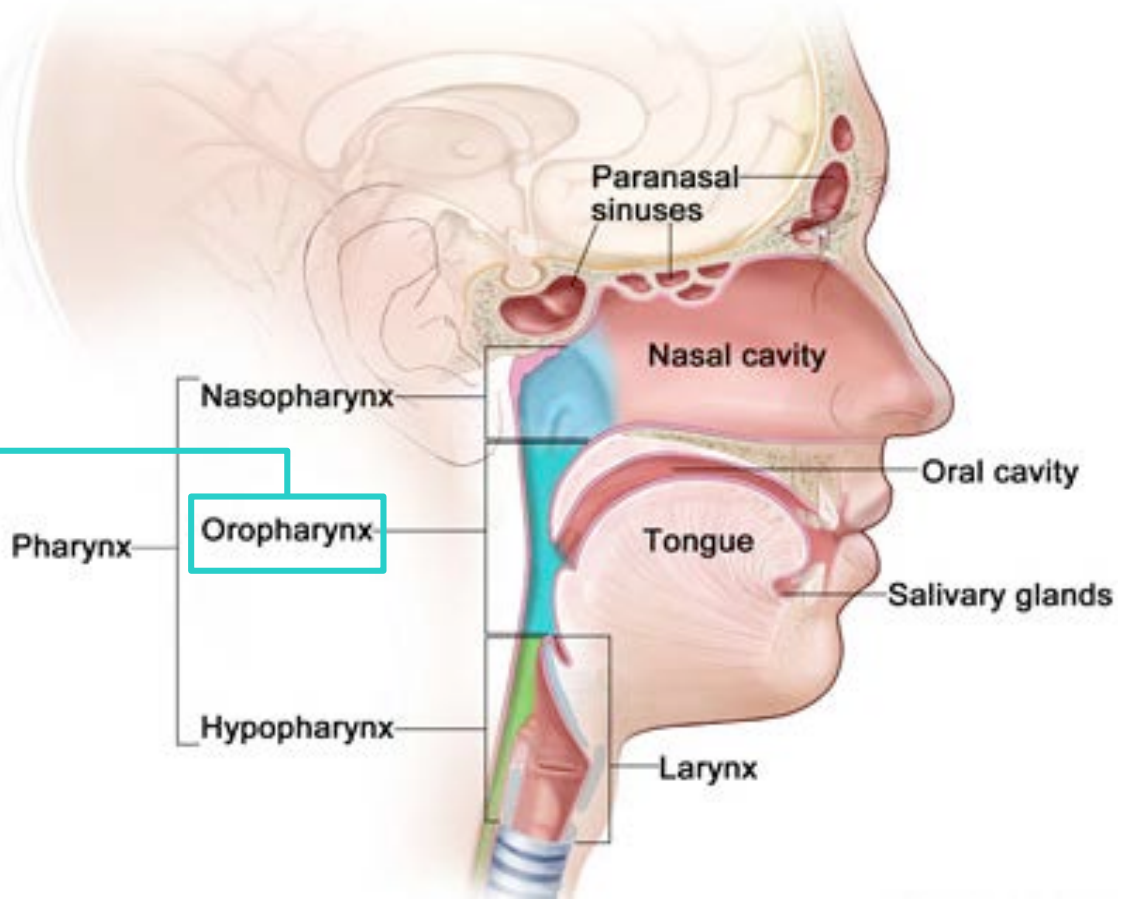
Disclosures:

- Co-inventor of patent relating to ctDNA detection technology licensed to Roche Molecular Diagnostics

HPV and Oropharynx Cancer (OPSCC)

Human Papillomavirus (HPV)

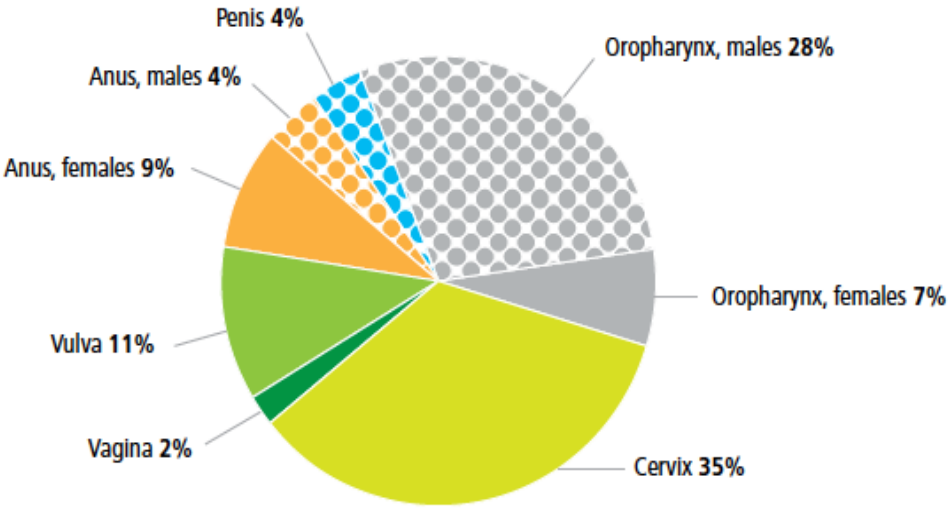




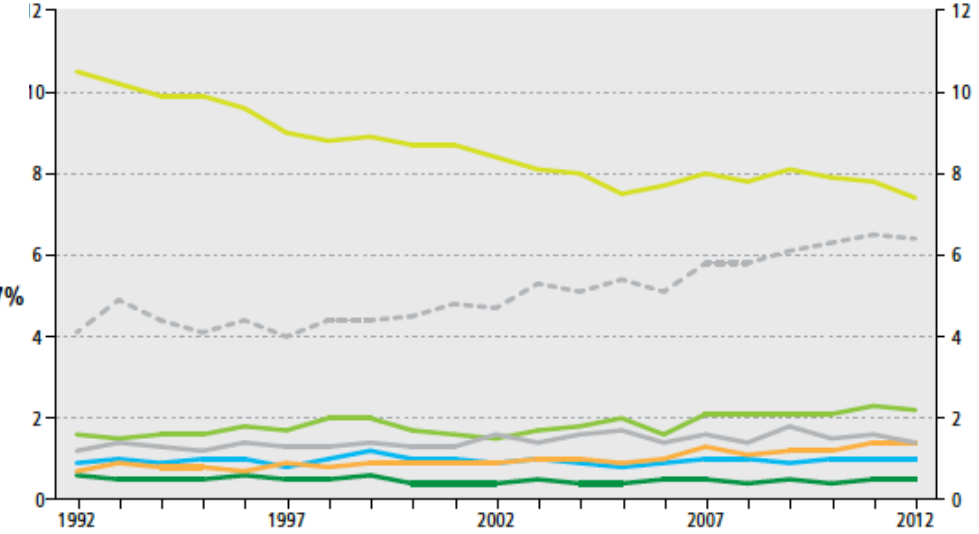
Burden of OPSCC in Canada

- HPV+ OPSCC: the most common type of HN cancer in Canada
- >1,300 cases diagnosed annually in Canada

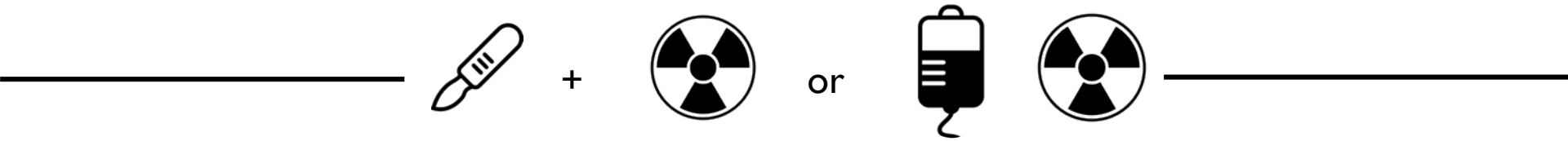
New HPV+ Cancers in Canada, 2012



Age-Standardized Incidence Rates



Standard Treatment for OPSCC



LIMITATIONS

High treatment-related toxicities

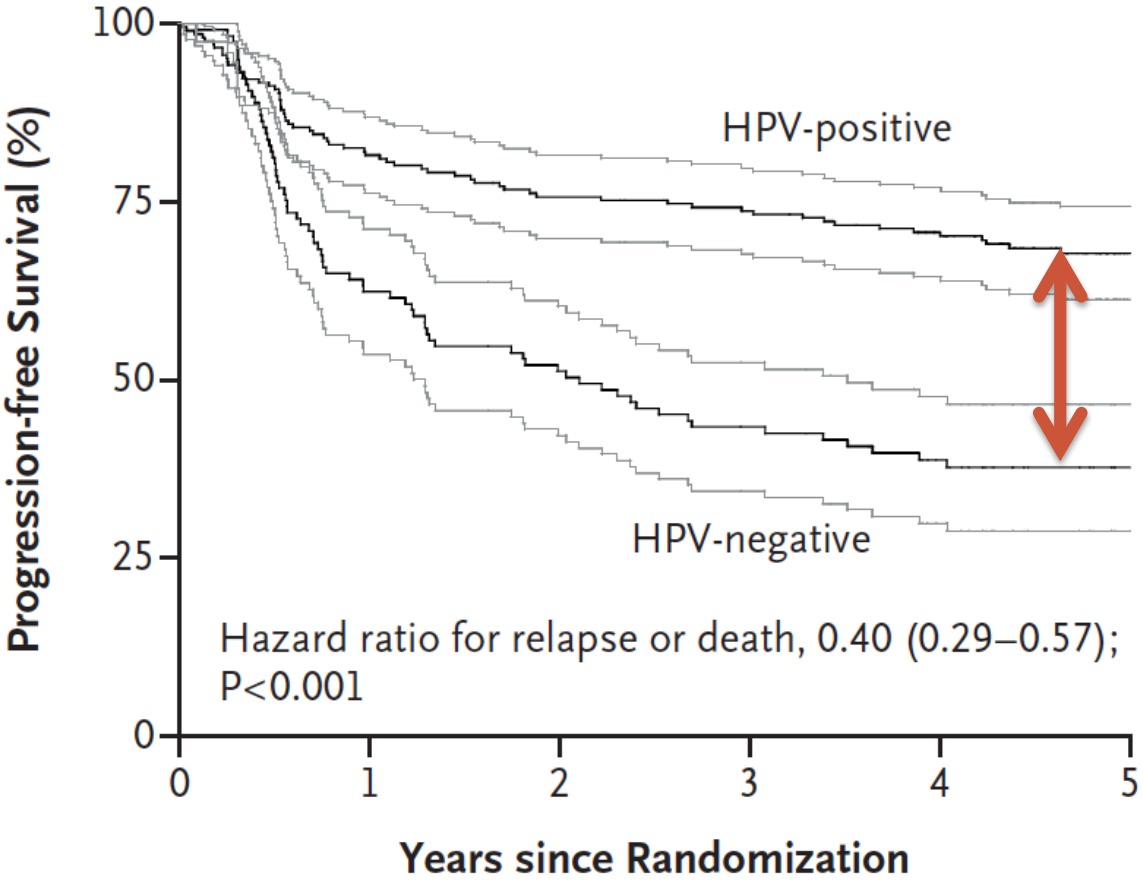
Heterogeneous response outcomes

Narrow therapeutic index

- Risk stratification for clinical trials
- De-escalation for low-risk HPV+ OPSCC
- Circulating biomarkers for adaptive therapy

- **Risk stratification for clinical trials**
- De-escalation for low-risk HPV+ OPSCC
- Circulating biomarkers for adaptive therapy

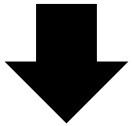
HPV Status and Survival in OPSCC



Ang et al. N Engl J Med 2010;363:24-35

HPV Status and Survival in OPSCC:
Rationale for Distinct Disease Entities

HPV-negative



Poor prognosis

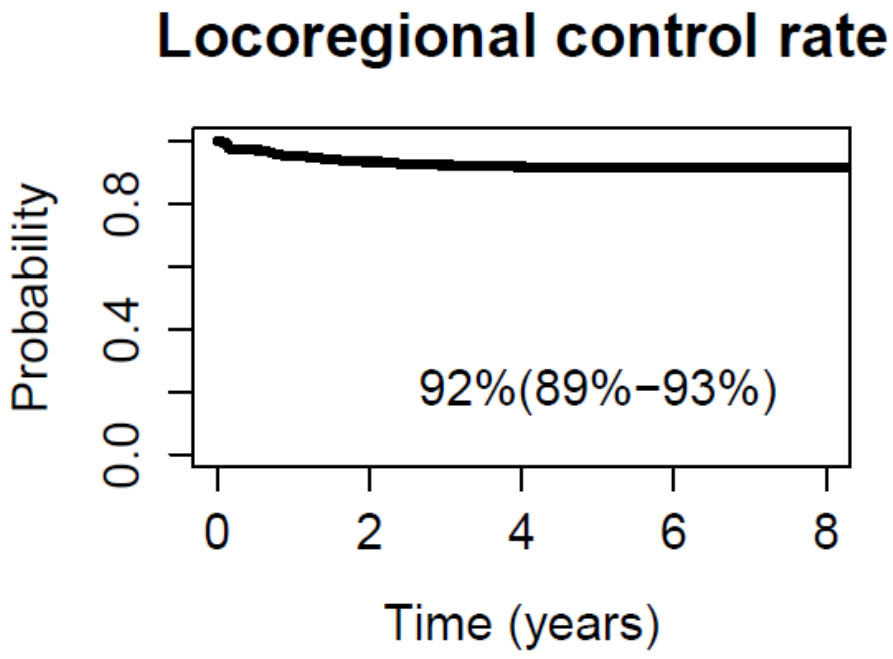
Risk factors
Mutational profiles

HPV-positive

Favourable prognosis

Rationale for De-Escalated Treatment for HPV+ OPSCC

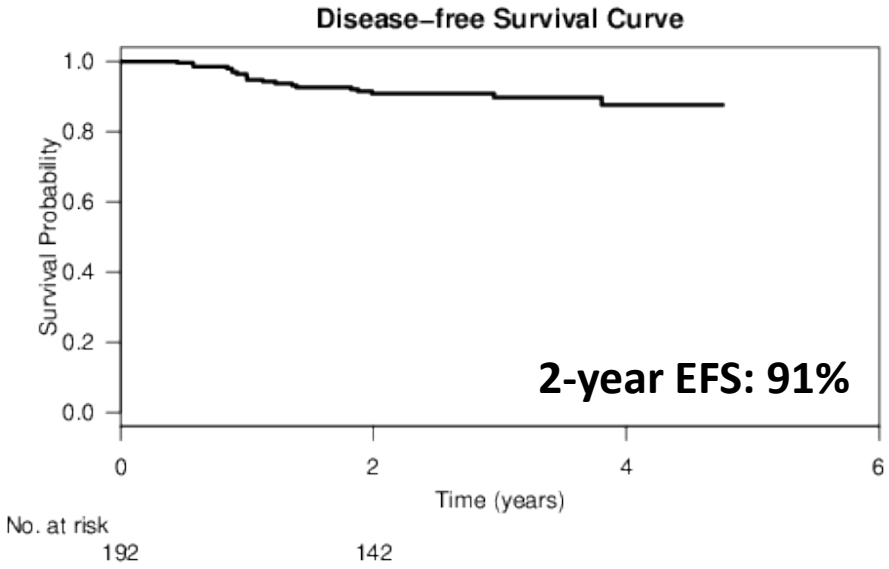
- Disease control of HPV+ OPSCC is favourable
- Many patients are being over-treated

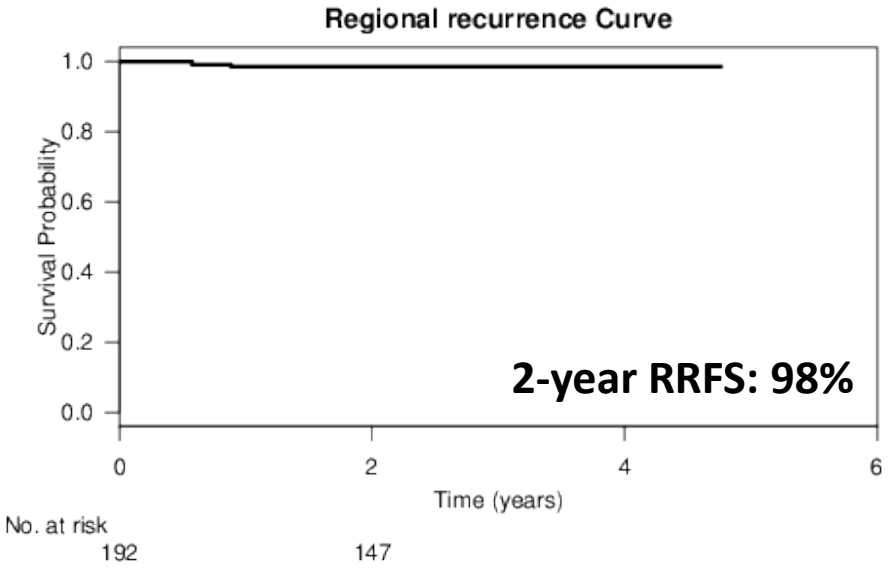


O'Sullivan et al., CARO 2015

Risk Stratification for De-Escalation

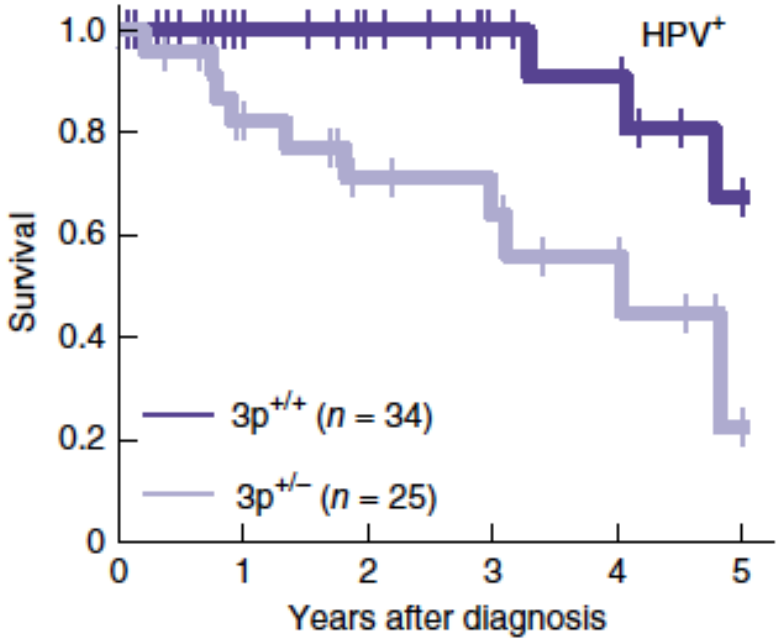
- Anatomic features associated with prognosis
  - Favourable risk: T1-3 N0-1 (8th Ed. UICC/AJCC) HPV+ OPSCC





Risk Stratification for De-Escalation

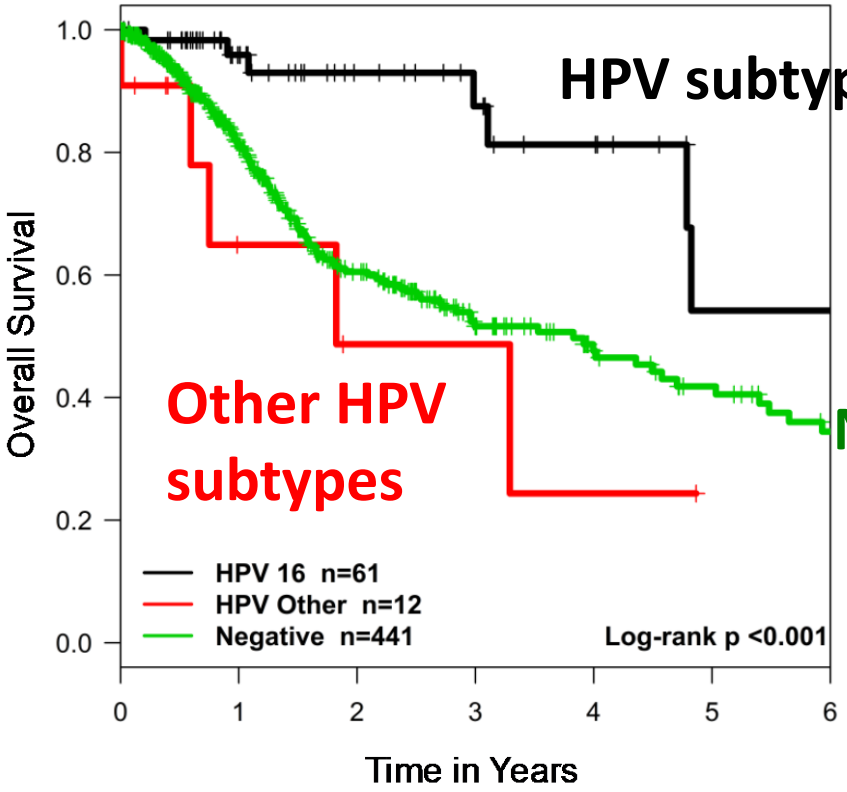
- Genomic features associated with prognosis
  - Chromosome 3p loss
  - Mutations in TP53, Nrf2 pathway?



Gross et al. Nat Genet 2014

Risk Stratification for De-Escalation

- Different HPV subtypes associated with prognosis
  - HPV-16 is associated with better survival



Bratman et al. JAMA Oncology 2016

Risk Stratification for De-Escalation

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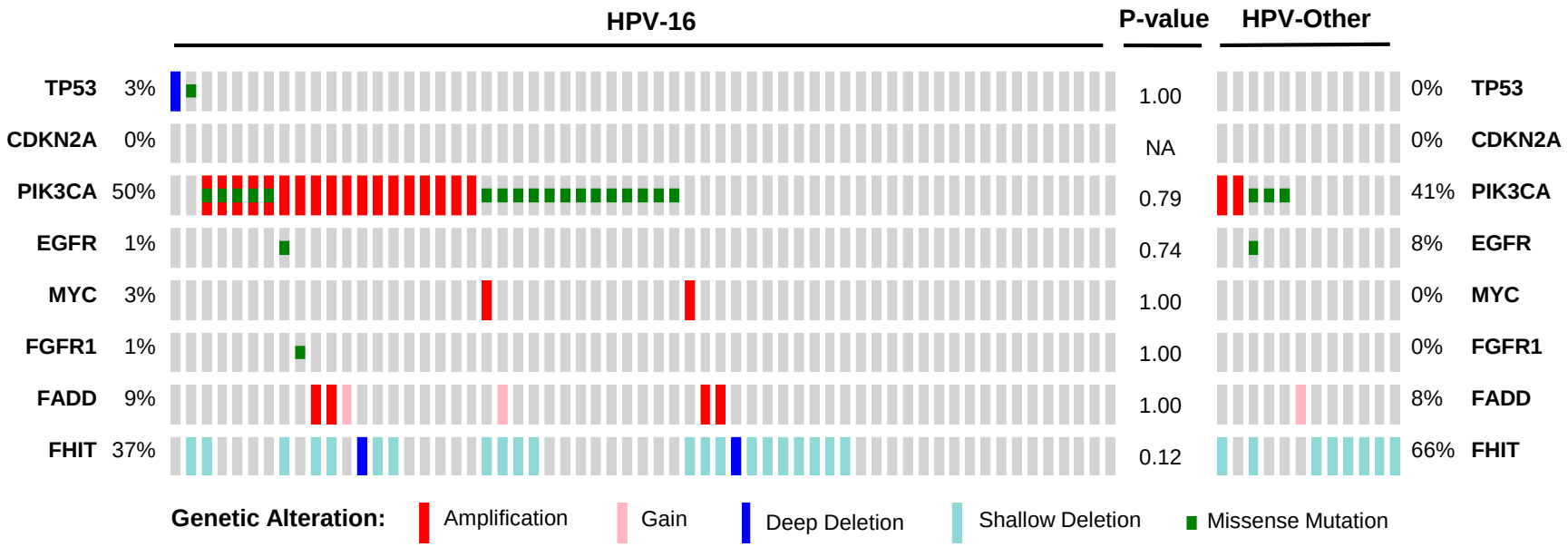
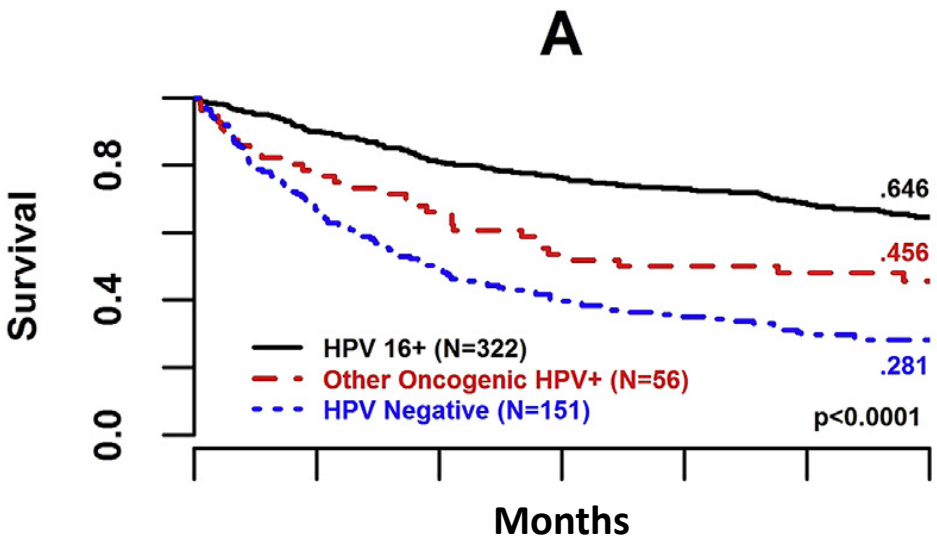


No difference in known prognostic genomic factors

Bratman et al. JAMA Oncology 2016

Risk Stratification for De-Escalation

- Different HPV subtypes associated with prognosis
  - HPV-16 is associated with better survival

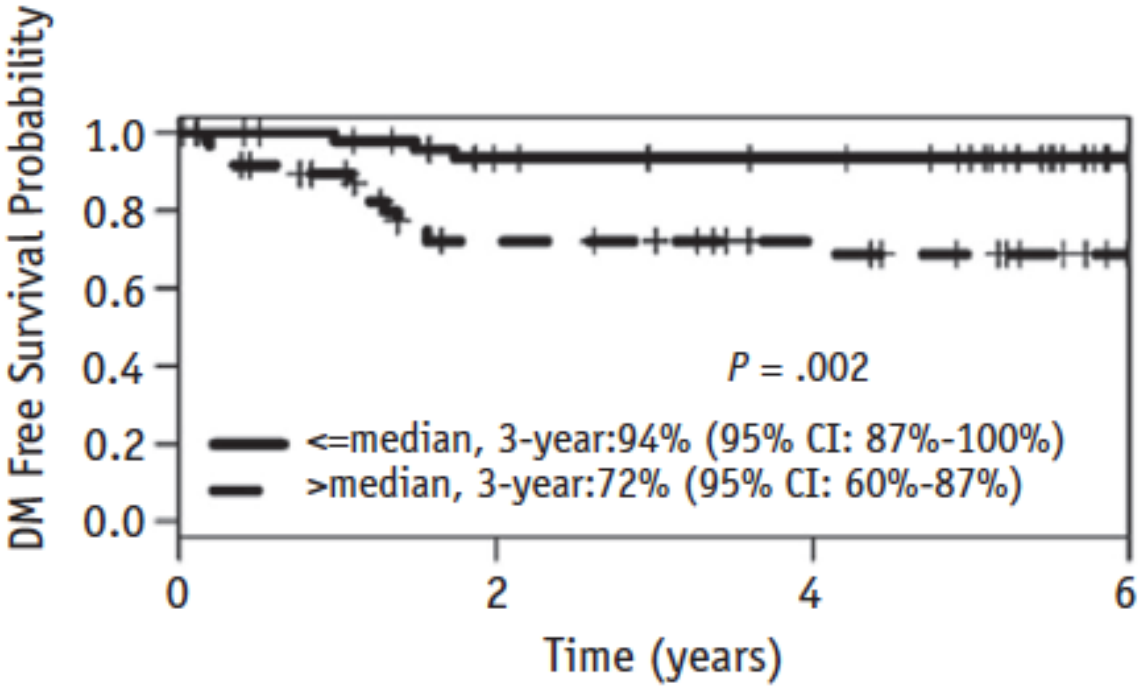


Independently validated in USA SEER data

Goodman et al Eur J Cancer, 2015

Risk Stratification for De-Escalation

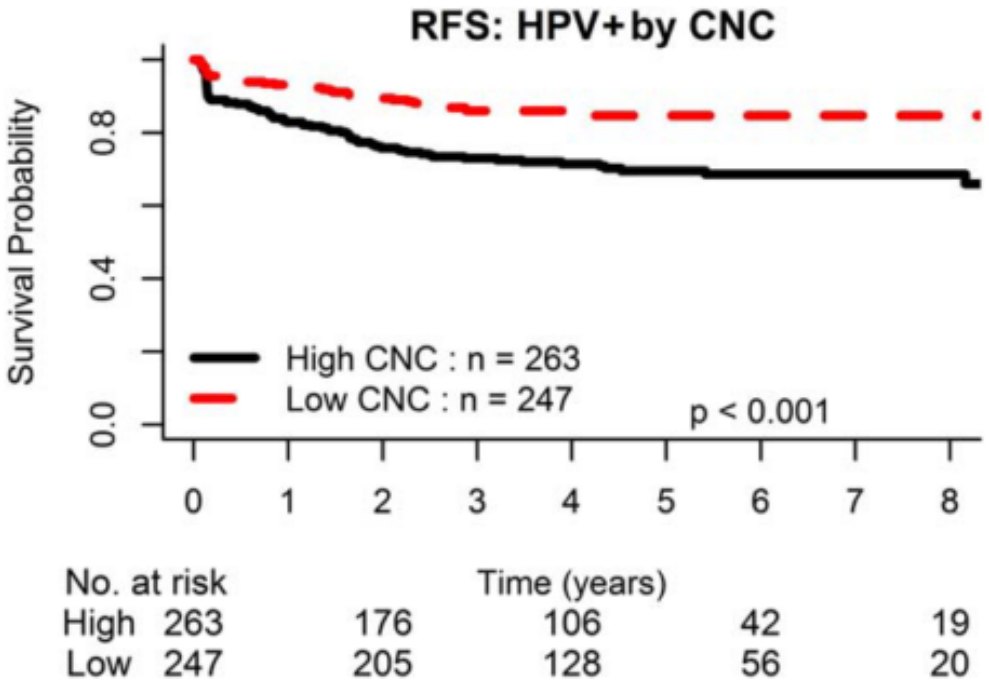
- Imaging features associated with prognosis
  - Radiologic extranodal extension
  - High-risk radiomic features



Kwan et al IJROBP 2018

Risk Stratification for De-Escalation

- Circulating neutrophil count (CNC) associated with prognosis

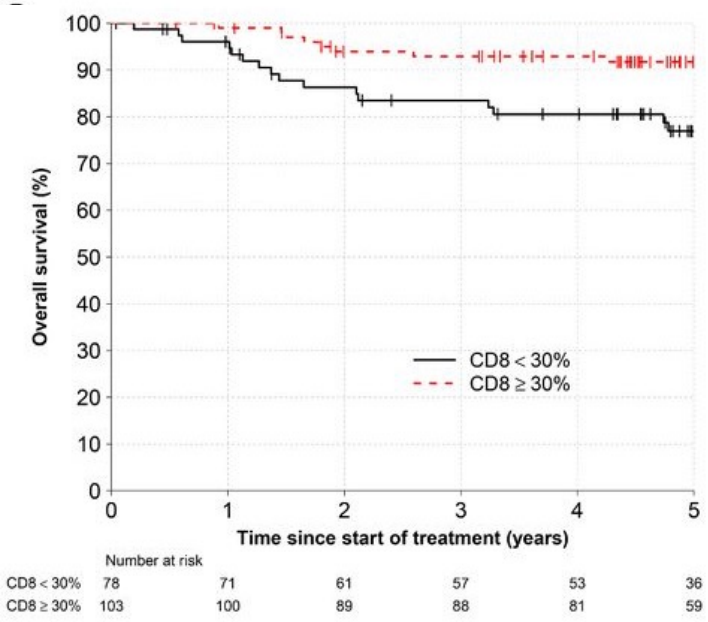


Huang et al. Cancer. 2015;121:545-55

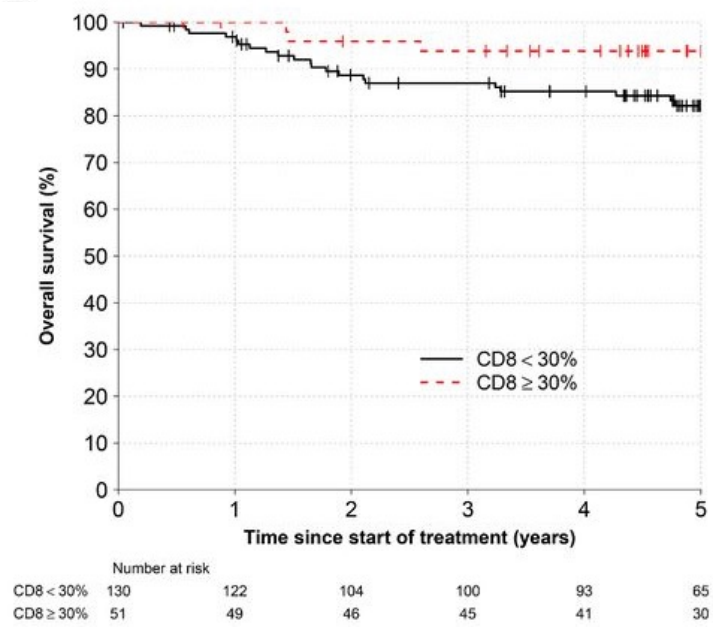
Risk Stratification for De-Escalation

- Immune cell infiltrates associated with prognosis

Stromal



Intra-tumoural



Solomon et al Cancer Immunol Res 2018

Risk Stratification for De-Escalation

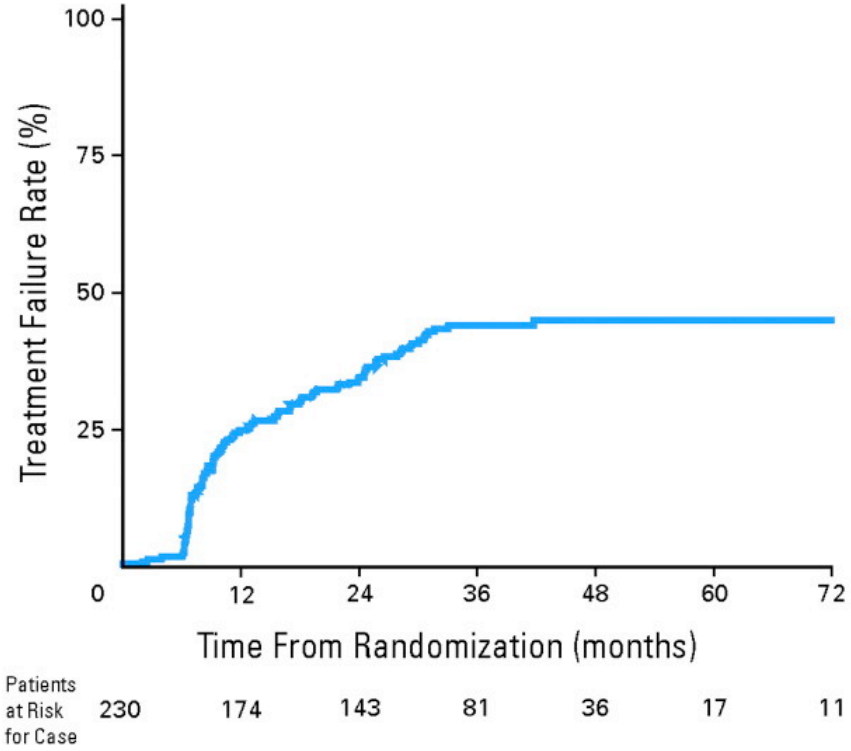
- Many putative baseline prognostic features
- No current system for combining into risk groups
- Eligibility on trials may be affected

- Risk stratification for clinical trials
- **De-escalation for low-risk HPV+ OPSCC**
- Circulating biomarkers for adaptive therapy

Burden of Over-Treatment for OPSCC

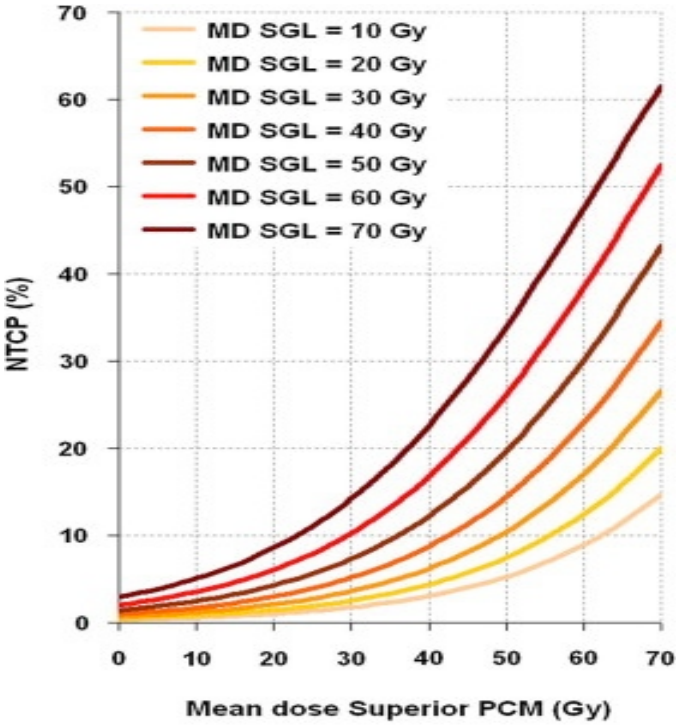
- Treatment-related toxicities impact quality of life and resource utilization

Grade ≥3 Swallowing Toxicity in RTOG H&N Trials



Machtay et al J Clin Oncol 2008

Risk of Swallowing Toxicity Related to RT Doses



Christianen et al Radiother Oncol 2012

Landscape of De-Escalation Trials

- Systemic therapy de-escalation
  - Replace cisplatin with cetuximab (RTOG 1016, De-ESCALaTE-HPV)
  - Replace cisplatin with immune checkpoint inhibitor (**CCTG HN.9**)
- Radiation dose de-escalation
  - Reduction of gross disease and/or elective doses (**HN002**, **HN005**)
  - Response-based reduction of dose (E1308)
  - Risk stratification and dose reduction based on path findings (E3311, **ORATOR I/II**)
- Radiation volume de-escalation
  - Reduction or elimination of CTV margins (Wisconsin)
  - Response-based reduction of volume (Chicago)
  - Omission of nodal levels based on staging, anatomy, and/or drainage patterns (**CCTG HN.10**)

NRG HN002

PATIENT POPULATION

Oropharyngeal squamous cell carcinoma; p16 positive by immunohistochemistry; ≤ 10 pack-year history of smoking; T1-T2, N1-N2b or T3, N0-N2b

REGISTRATION

***Mandatory p16 analysis (central review)**

STRATIFICATION

RT Planning: Unilateral vs. Bilateral

RANDOMIZATION

Arm 1

60 Gy (2.0 Gy/fraction) in 6 weeks+ Cisplatin, 40 mg/m^2 weekly for 6 weeks

Arm 2

60 Gy (2.0 Gy/fraction) in 5 weeks using 6 fractions per week

- To select the arm(s) achieving a 2-year PFS ≥85% without unacceptable swallowing toxicity at 1 year
- Last patient on Feb 2017
- Final analysis pending (fall 2019)

"Canada" Arm

PI: Sue Yom (UCSF)

Co-PI: John Waldron (PMH)

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NRG HN005: A Randomized Phase II/III Trial of De-intensified Radiation Therapy for Patients with Early Stage, p16-Positive, Non-Smoking-Associated Oropharyngeal Cancer

Eligibility

- Oropharynx SCCA
- p16+
- ≤10 pack-yr
- T1-2N1 or T3 N0-1

Randomized Phase II

N = 399 (133/arm)
Non-inferiority margin HR=2.4; 9-mo PFS=96.5%
Primary endpoint: PFS.
"Go/No-Go" decision based on PFS and futility analysis for QOL (MDADI global score)

RANDOMIZE

- 70 Gy in 6 weeks + cisplatin 100 mg/m2 x 2 cycles
- 60 Gy in 6 weeks + cisplatin 100 mg/m2 x 2 cycles
- 60 Gy in 5 weeks + nivolumab 240 mg x 6 cycles

Phase III continuation

N = 104 additional pts PER ARM (total of 237/arm)
Nested co-primary endpoints: PFS and MDADI
Non-inferiority margin HR=1.75
2-yr PFS = 92.3%

RANDOMIZE

- 70 Gy in 6 weeks + cisplatin 100 mg/m2 x 2 cycles
- *1 or 2 experimental arms*

N = 474 if 2 arms go forward
N = 711 if 3 arms go forward
(QOL N = 378 per 2-arm comparison)

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PI: Yom (UCSF) Co-PI: Waldron (PMH)

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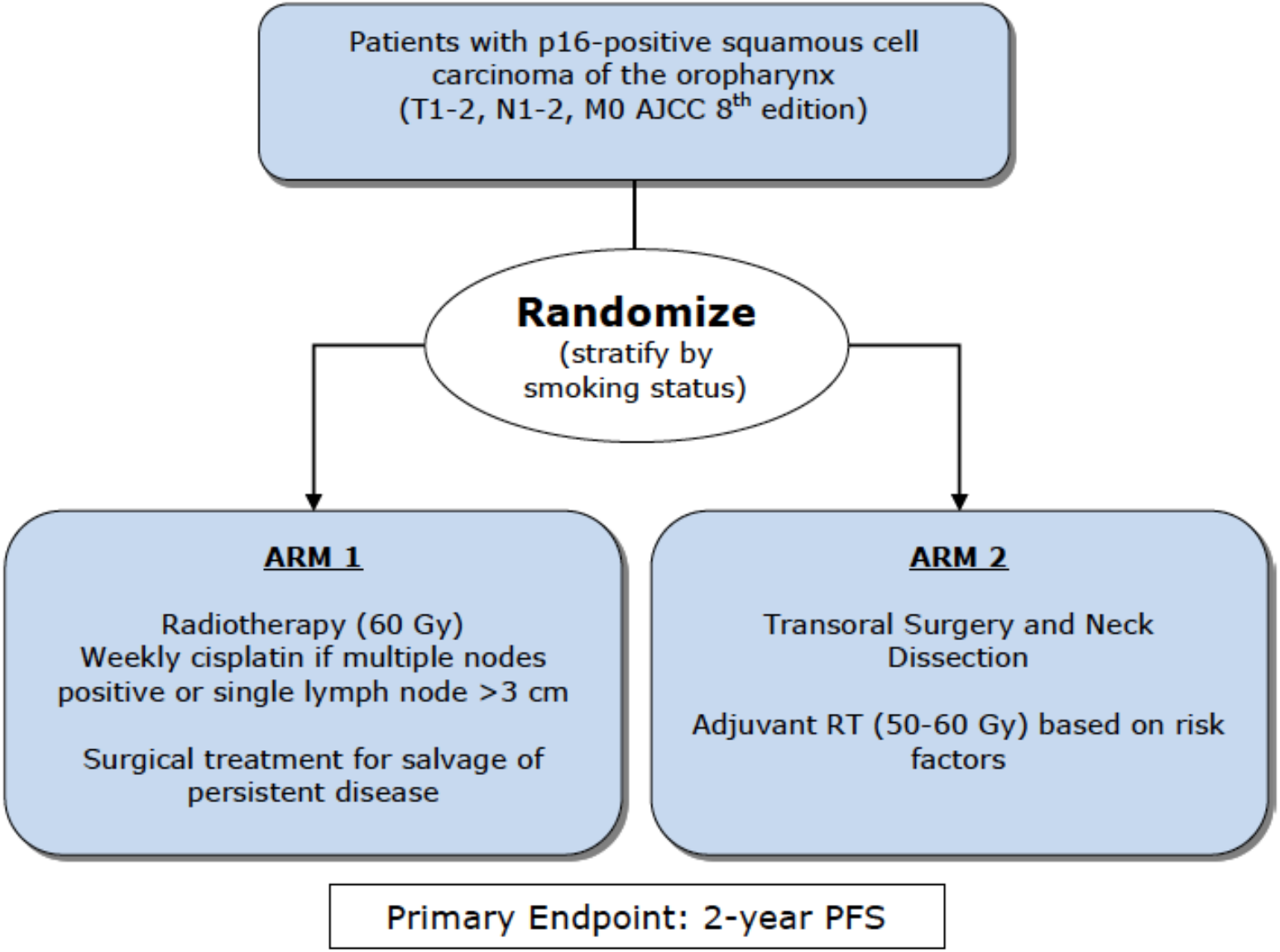
ORATOR II



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PI: Nichols/Palma

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CCTG HN.10

A phase II single arm trial of Elective Volume Adjusted De-Escalation Radiotherapy (**EVADER**) in patients with low-risk HPV+ OPSCC

HN.10 Study Team

Study Chair:	Scott Bratman
Trial Committee:	Eric Berthelet Jim Butler John de Almeida Irene Karam Ur Metser Robert Olson Craig Pochini John Waldron Eugene Yu
Senior Investigator:	Wendy Parulekar
Biostatistician:	Bingshu Chen
RT Physics and QA Coordinator:	Andrea McNiven
Quality of Life Coordinator:	Winson Cheung
Health Economics Coordinator:	Marc Gaudet
Study Coordinator	Sarah Hunter
Regulatory Sponsor:	CCTG
Trial Type:	Co-operative group, single-arm phase II
Supported by:	CIHR, CCSRI

Objective and Endpoints

- **Objective:** To evaluate the efficacy and safety of primary definitive RT or CRT utilizing volume-reduced ENI in patients with low-risk HPV-related OPSCC.
  - Primary endpoint: 2-year EFS
  - Secondary endpoints: Out-of-field regional control, local control, regional control, distant metastasis-free survival, cancer-specific survival, and overall survival; early and late toxicities of treatment; swallowing and salivary related QOL; overall QOL; resource utilization; tumour, germ line, radiomic, and blood biomarkers for prognosis and toxicity.
  - Tertiary endpoints: Assemble an imaging and biospecimen bank for future research that could improve risk stratification and patient selection for volume-reduced ENI.

HN.10 Schema

Pathologically-proven OPSCC **p16+ or HPV+** **Clinical stage** **T1-3 N0-1 M0** **(UICC/AJCC 8th Ed.)** **No prior radiotherapy or chemotherapy**	**R E G I S T E R**	**Option #1:**	**<u>Radiotherapy (Standard Fractionation)</u>:** **Reduced ENI Volumes** **35 fractions, 5/wk, 7 wks** **70Gy/56Gy** **<u>Cisplatin</u>:** **100 mg/m^2 on day 1, 22, and 43** **or** **40 mg/m^2 /wk for 7 wks** (Allowed for T3 N0-1, T2 N1, and T1 N1 with single node >3cm or multiple ipsilateral nodes)
		Option #2:	**<u>Radiotherapy Alone (Accelerated Fractionation)</u>:** **Reduced ENI Volumes** **35 fractions, 6/wk, 6 wks** **70Gy/56Gy** (Mandatory for T1-2 N0 and for T1 N1 with single node ≤ 3 cm; allowed for other patients who are not eligible for cisplatin)

N = 100

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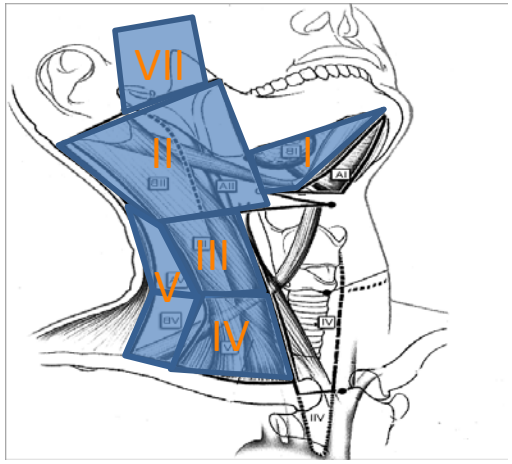
Base-of-tongue

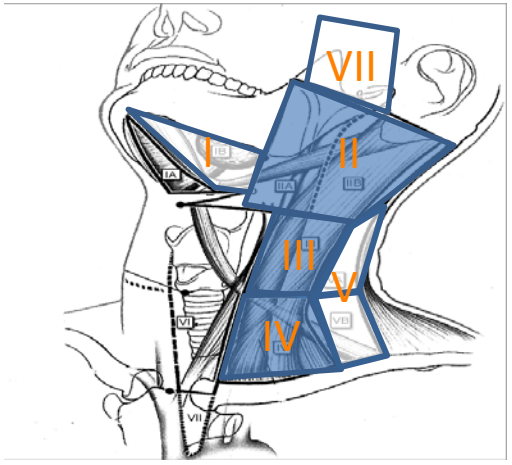
T1-2 N1

Current

Ipsilateral

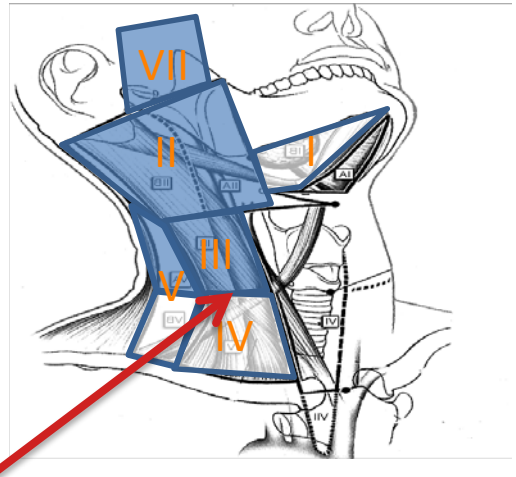


Contralateral

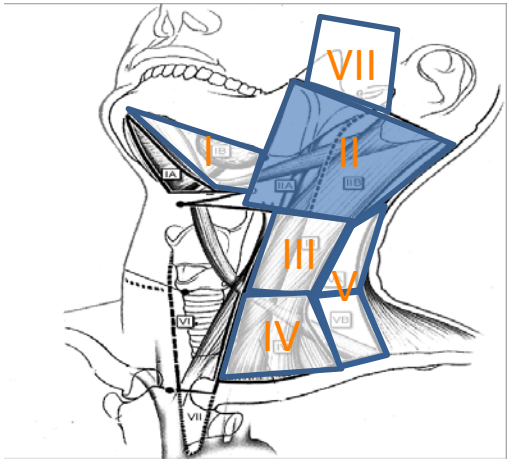


Proposed

Ipsilateral



Contralateral



Lower border ≥2cm below inferior extent of CTVn_7000

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Toxicity, QOL, & Economic Analyses

- CTCAE v5.0
- Swallowing
  - PSS-HN
  - FOIS
- QOL:
  - FACT-H&N
  - MDADI
- Other PROs:
  - PRO-CTCAE
- Economic Analysis:
  - Health Utility Index
  - Resource utilization
  - Lost productivity survey

Correlative Studies

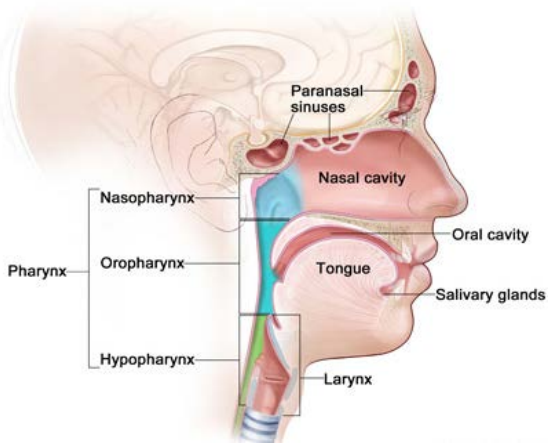
- Radiomic signature:
- Tumour genomic DNA analysis:
  - *TP53* mutations
  - Chromosome 3p loss
  - HPV genotype
- Plasma HPV DNA:
  - HPV ctDNA levels measured using digital PCR

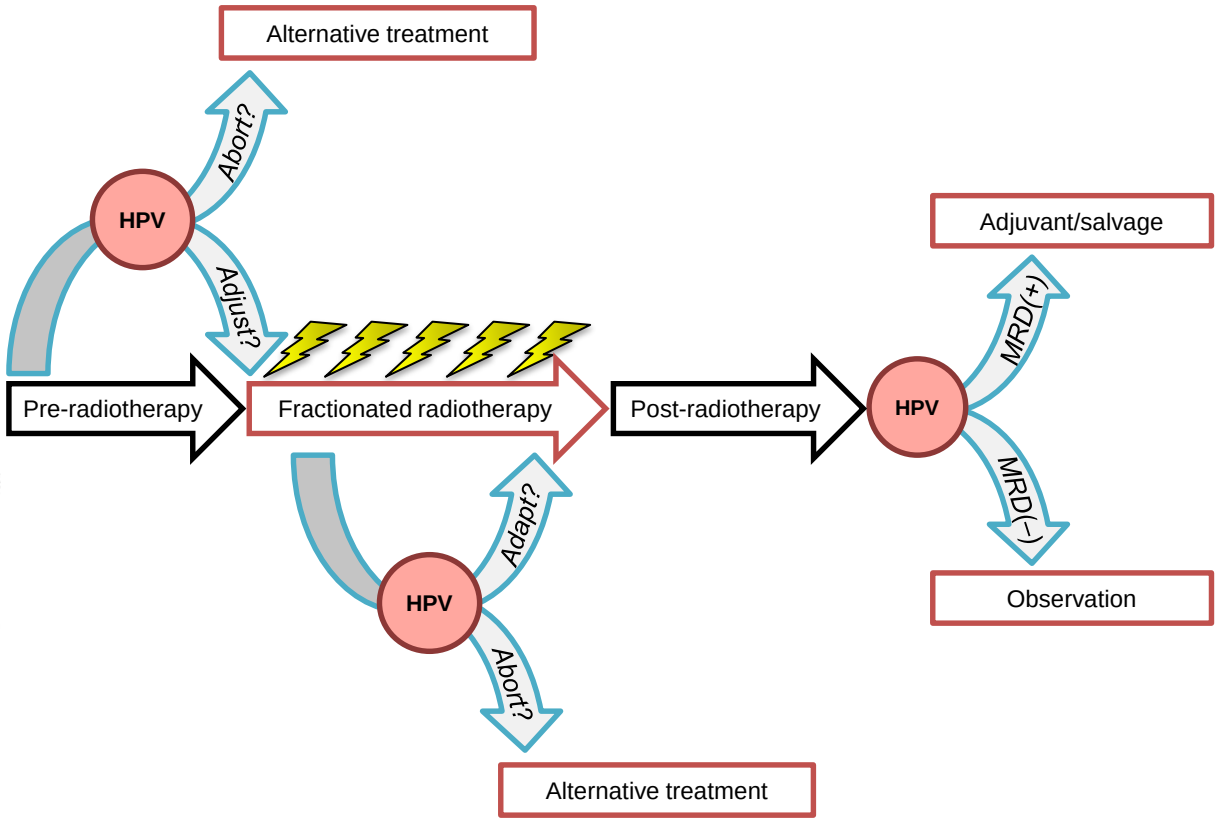
Timeline

- Central activation: February 2019
- 1st patient enrolled at PMH: July 2019

- Risk stratification for clinical trials
- De-escalation for low-risk HPV+ OPSCC
- **Circulating biomarkers for adaptive therapy**

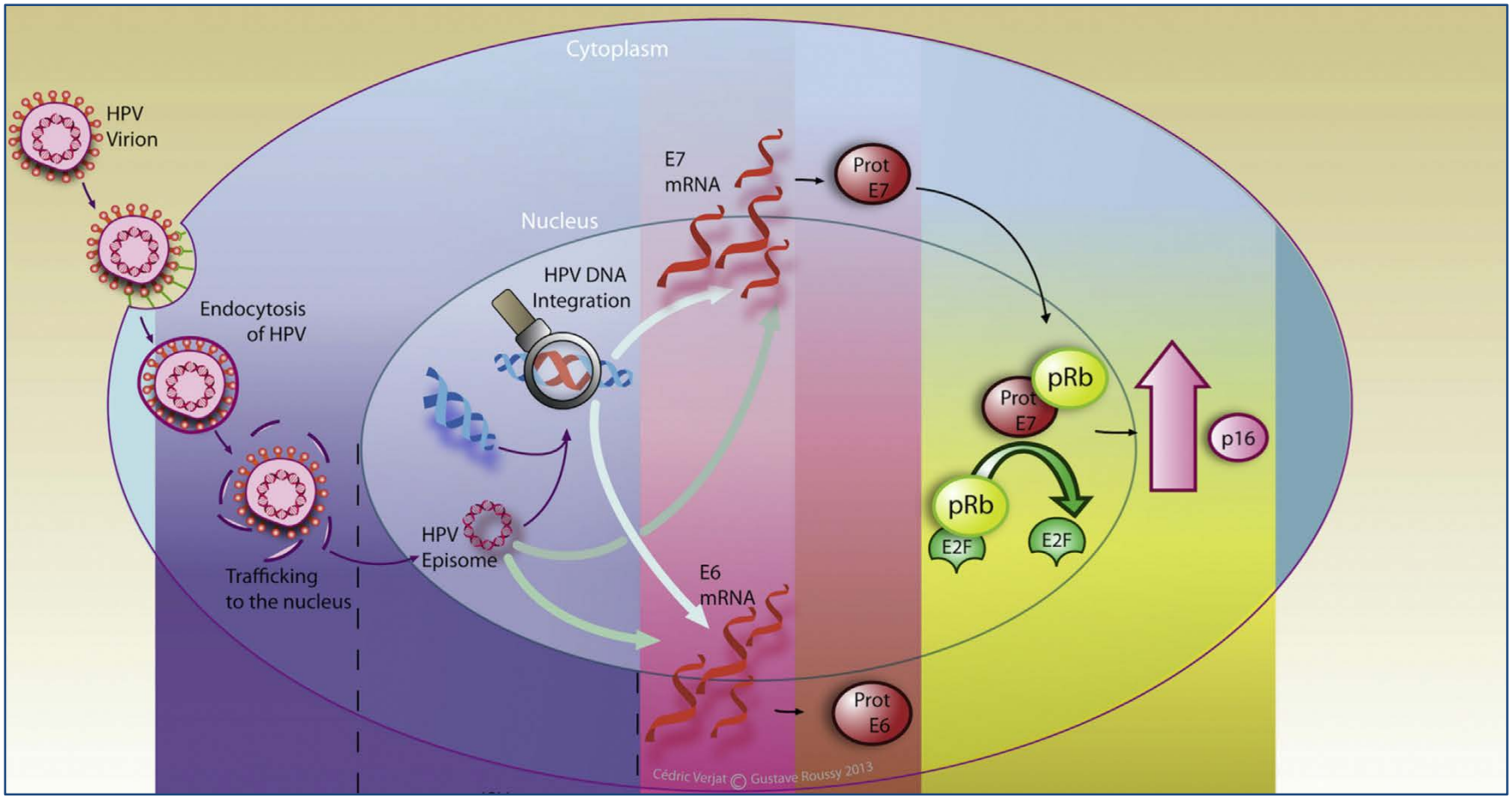
Response Biomarkers in HPV+ Cancers: *Opportunities for Adaptive Therapy*





Rostami & Bratman, Radiother Oncol. 2017

Biological Sources of HPV Biomarkers



- ***HPV antibodies***
- ***HPV DNA***

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Mirghani, Lang Kuhs, and Waterboer, Oral Oncol 2018

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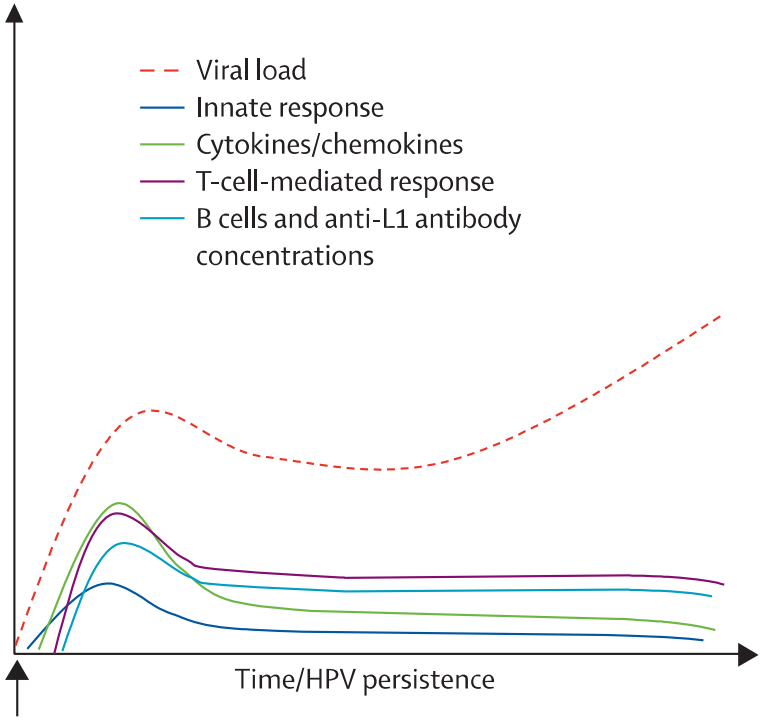
Immune Response to Persistent HPV Infection

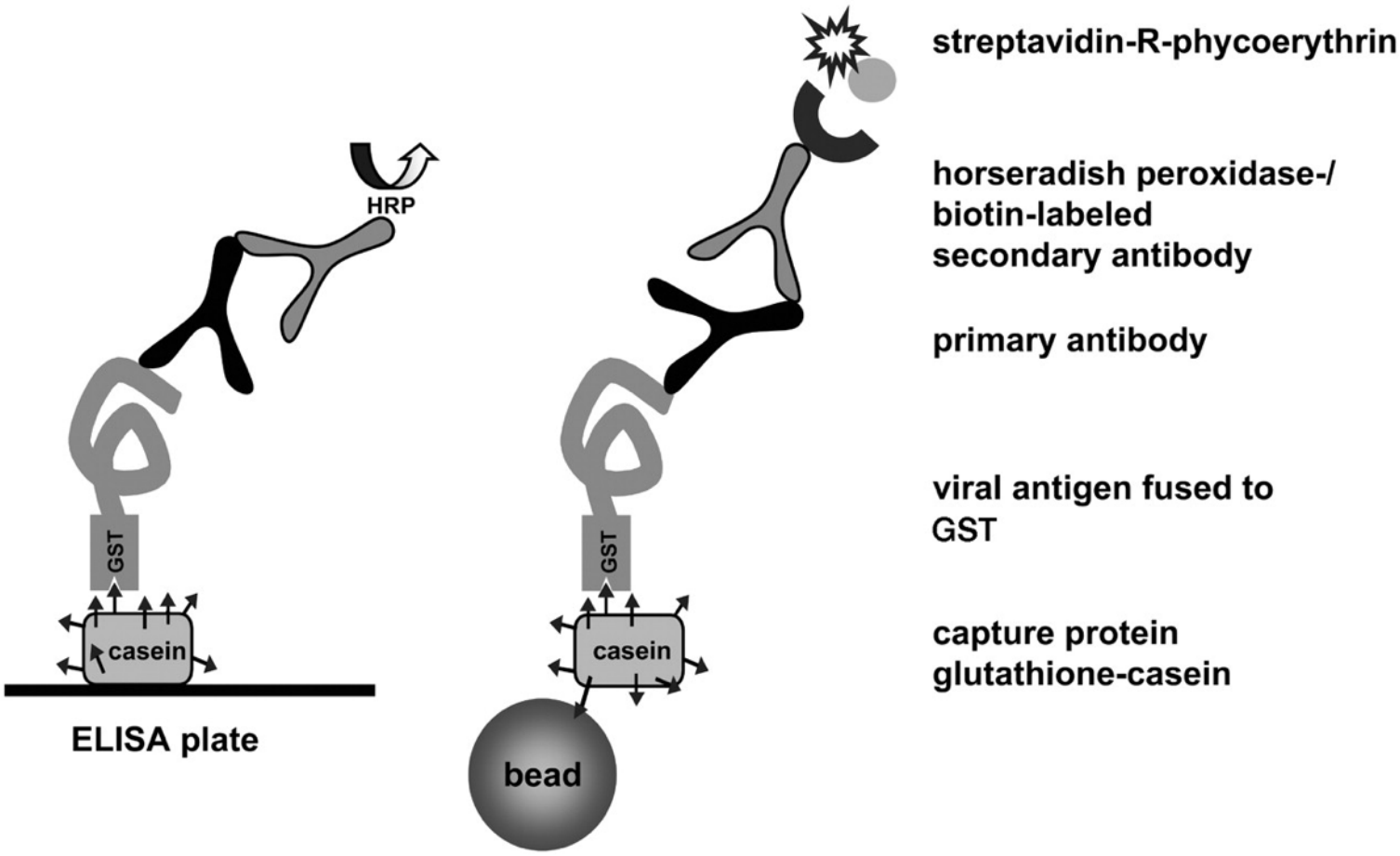


Methods	Antibodies detected
Pseudovirion-based neutralisation assay	Measures most neutralising antibodies and is based on predefined epitopes considered to be important for neutralisation of HPV
Competitive Luminex immunoassay	Measures a limited number of neutralising antibodies and is based on predefined epitopes considered to be important for neutralisation of HPV
ELISA	Measures total antibody concentrations and does not distinguish between neutralising or non-neutralising types

- HPV-specific antibodies detectable in persistent infection

Einstein…Jenkins et al, Lancet Infect Dis 2009

Quantitative HPV Serology



Sehr, Zumbach, and Pawlita, J Immunological Methods 2001
Waterboer…Pawlita et al, Clin Chem 2005

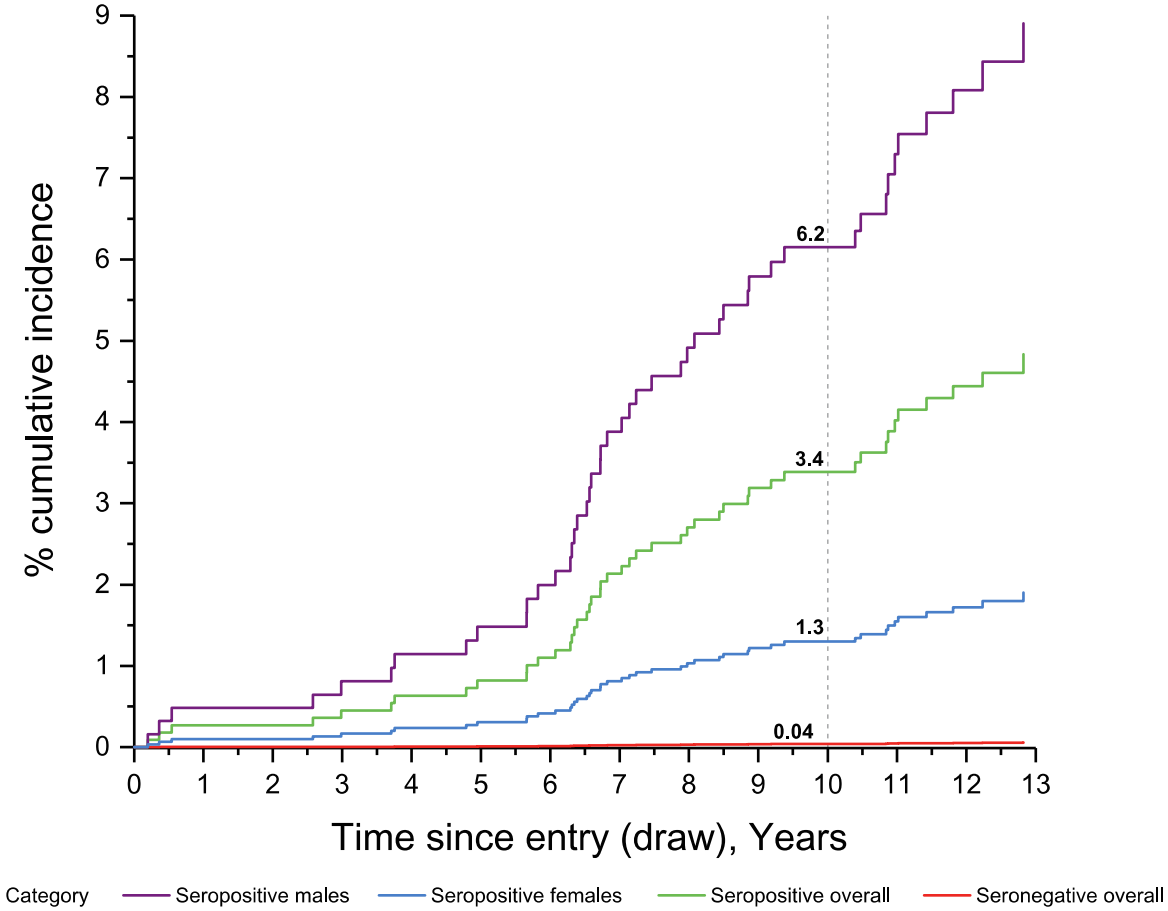
Multiplexed Detection of HPV Antibodies

HPV Serology Marker	Intra-Individual Correlation Estimates
HPV6 E6	1.00
HPV6 E7	0.86
HPV6 L1	0.71
HPV11 E6	0.70
HPV11 E7	N/A
HPV11 L1	0.81
HPV16 E1	0.81
HPV16 E2	0.72
HPV16 E4	0.87
HPV16 E6	1.00
HPV16 E7	0.83
HPV16 L1	0.78
HPV18 E6	1.00
HPV18 E7	1.00
HPV18 L1	0.71
HPV31 E6	0.89
HPV31 E7	N/A
HPV31 L1	0.66
HPV33 E6	0.70
HPV33 E7	0.81
HPV33 L1	0.66
HPV45 E6	0.56
HPV45 E7	1.00
HPV45 L1	0.82
HPV52 E6	1.00
HPV52 E7	0.79
HPV52 L1	0.58

- *Detects antibodies to 27 antigens from 8 HPV types*
- *Analytically validated*
- *Small blood volume requirements*
- *Works on stored frozen samples*

Kreimer…Brennan et al. J Clin Oncol 2013

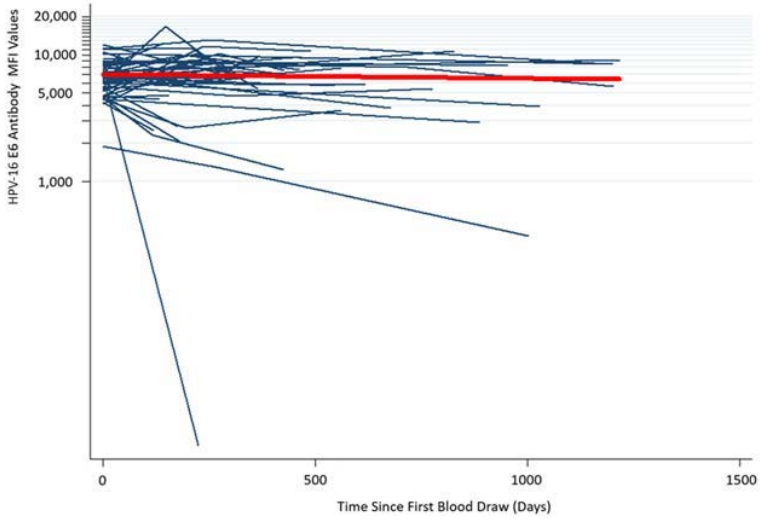
HPV Serology as a Diagnostic Risk Marker

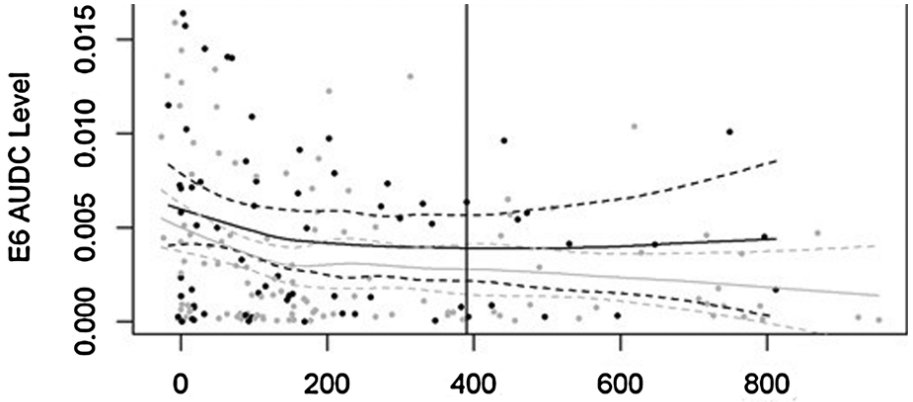


E6 seropositivity → increased risk of OPSCC diagnosis

Kreimer…Waterboer et al. JNCI 2017

HPV Serology as a Response Marker





E6/E7 antibody kinetics post-treatment do not predict relapse

Zhang…D'Souza et al. Oral Oncol 2017
Lang Kuhs…Ferris et al. Cancer 2017
Spector…Worden et al. CCR 2016

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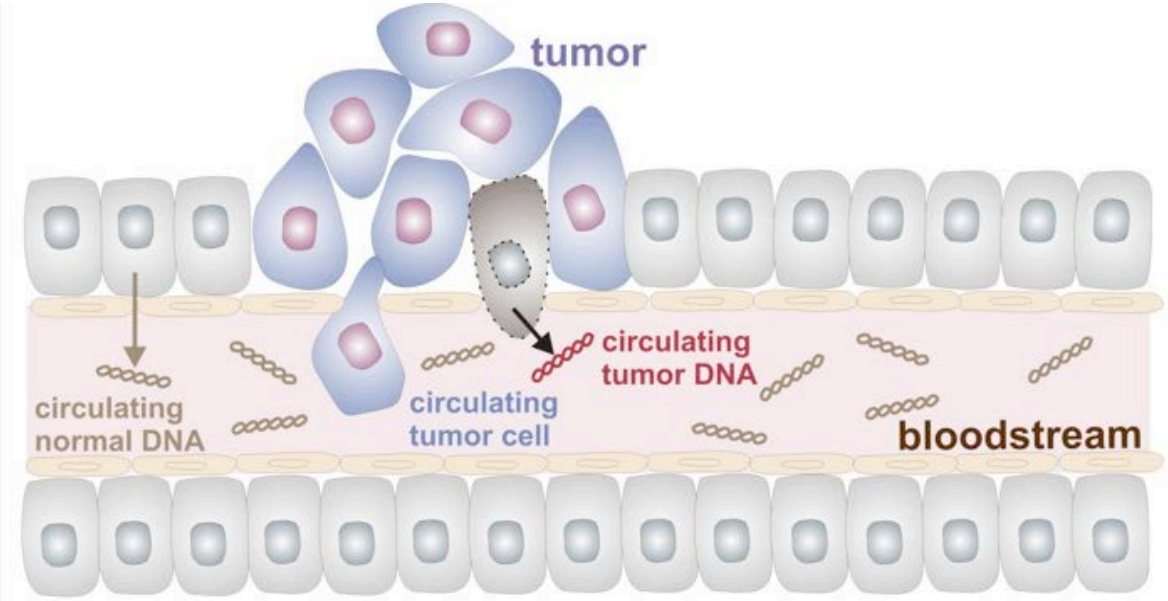
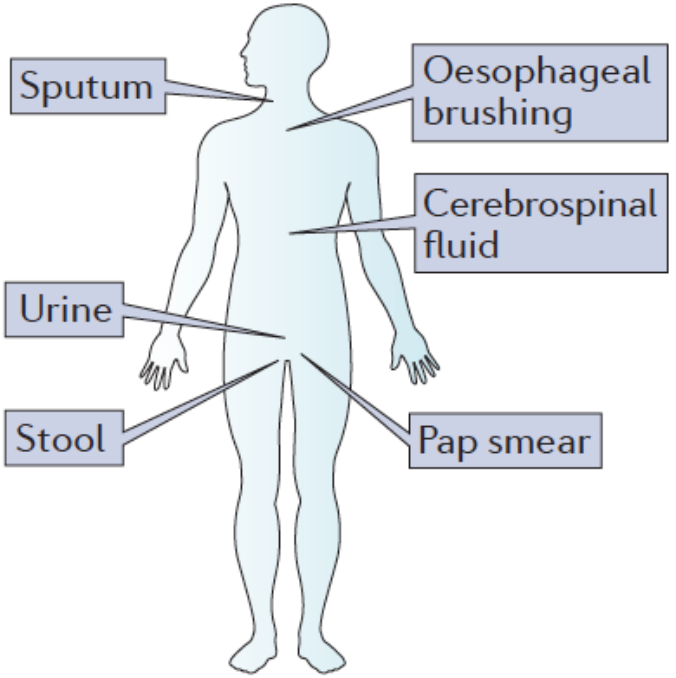
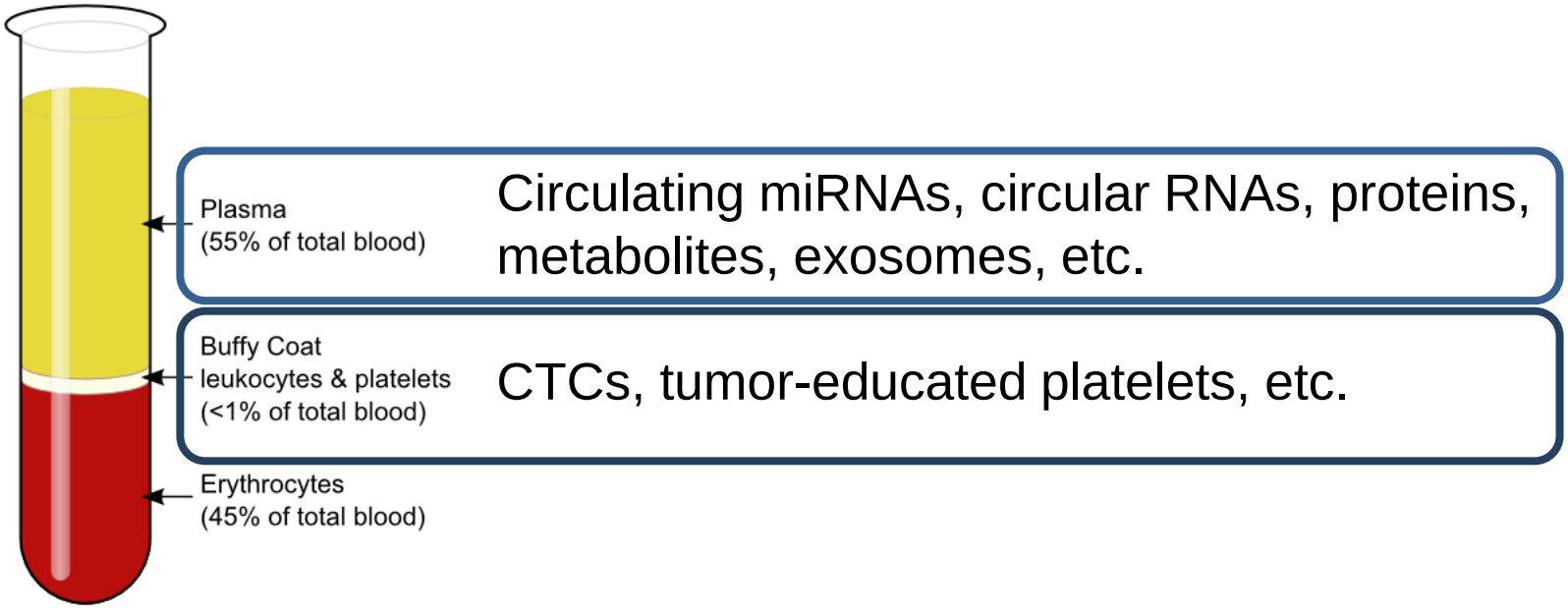
Circulating tumour DNA (ctDNA): Cancer-derived DNA in the Circulation





Other potential sources for ‘Liquid Biopsy’



Advantages of ctDNA:

- Ease of collection/storage
- Linkage to genetic/epigenetic information
- Available analysis platforms

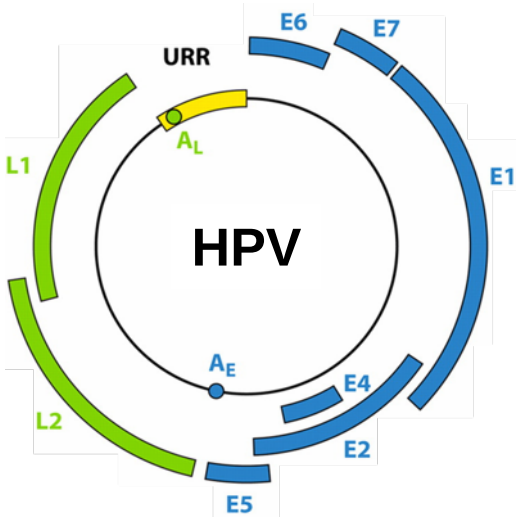
ctDNA:
A needle in a haystack of normal DNA

<1% total cell-free DNA

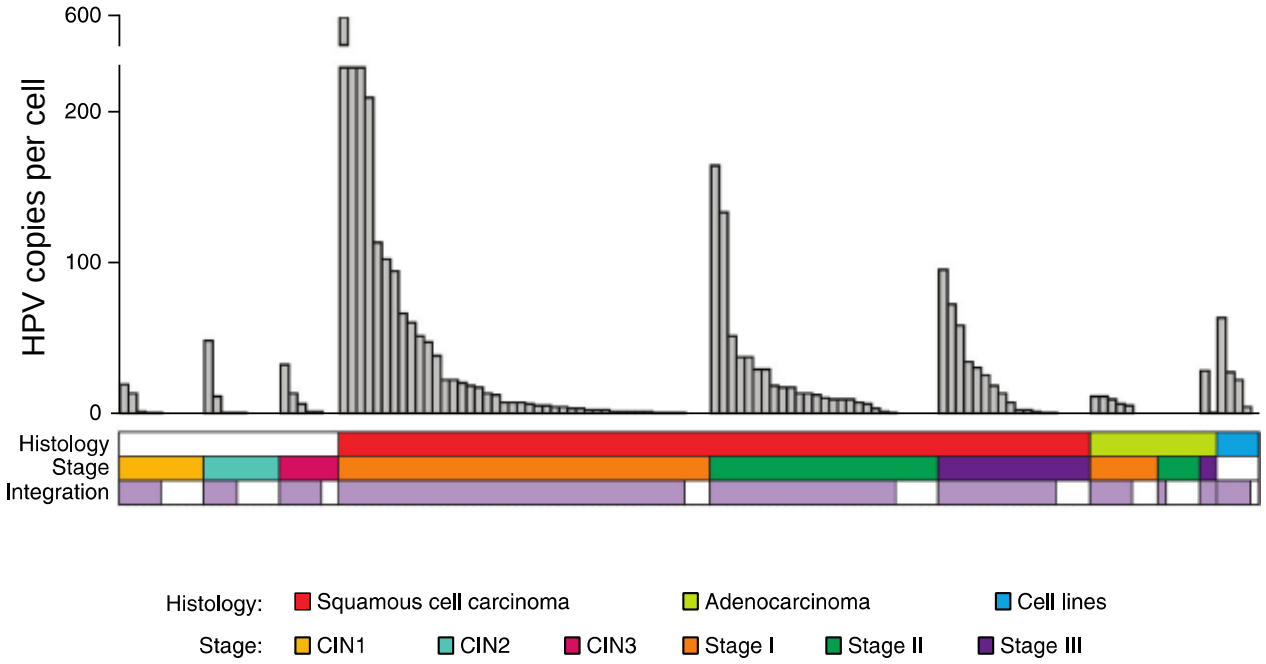
Challenges for detection:

- Low fractional abundance
- Limited amount of blood
- Tumor heterogeneity

HPV DNA Structure in Malignant Cells



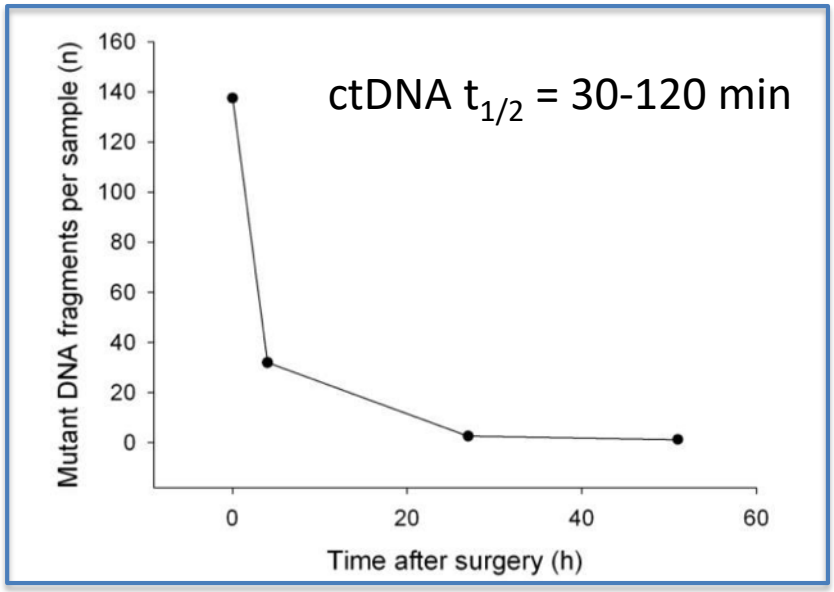
Circular ~8 kb
dsDNA genome



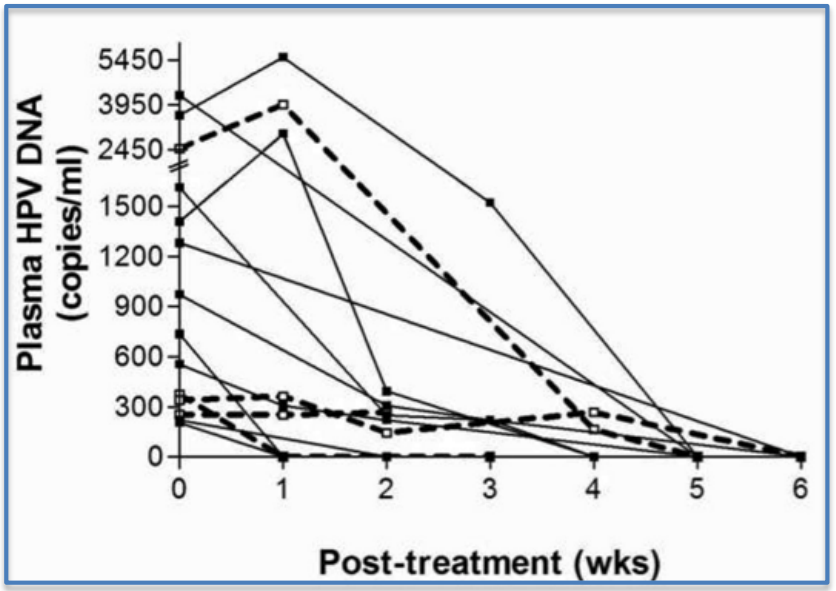
Hu…Ma et al. Nature Genetics 2015

ctDNA Kinetics:
During Locoregional Treatment

Surgery



RT/CRT



Diehl…Diaz et al. Nat Med 2008
To…Lo et al. CCR 2003
Muhanna…Bratman et al. Sci Rep 2017
Cao…Le et al. *IJROBP* 2012

What Factors Affect ctDNA Release Kinetics?

Poorly understood with few clinical studies

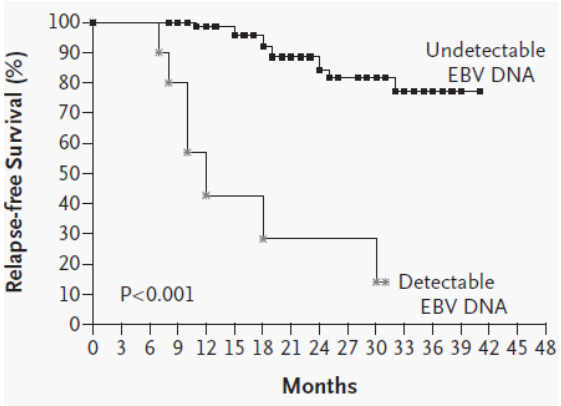
- Number of viable tumour cells
- Mechanism of cell death
- Sensitivity to treatment
- Vascular space invasion
- Microvascular density and permeability
- Clearance of ctDNA from the circulation

ctDNA Kinetics:
Following Locoregional Treatment

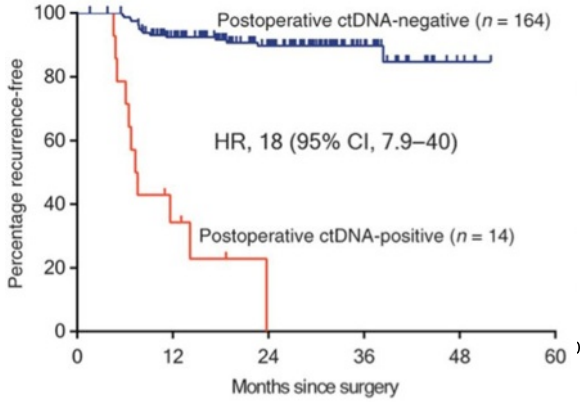
Nasopharygeal Carcinoma

N Engl J Med
2004, 350:2461-2470

HR: 34.5



Colorectal Carcinoma



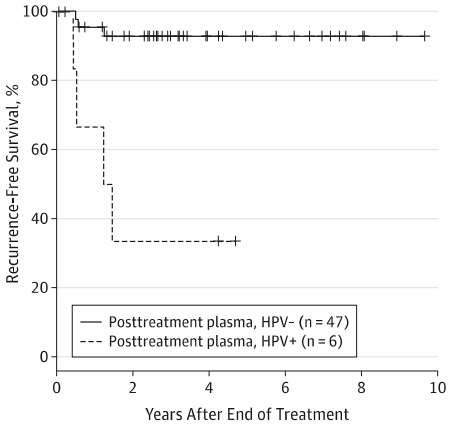
Sci Transl Med
2016, 8:346ra92

HR: 18

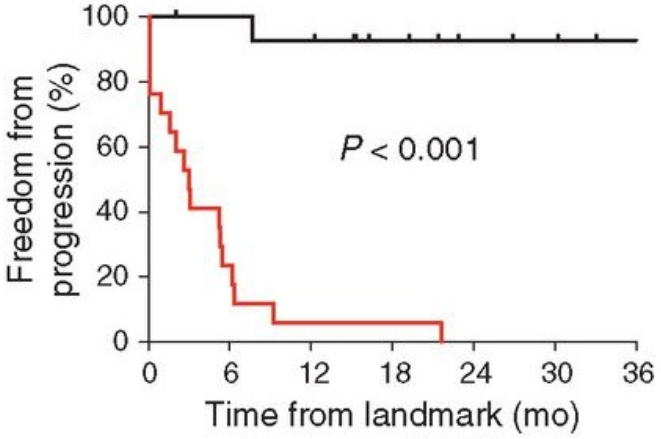
Oropharyngeal Carcinoma

JAMA Otolaryngol
2014, 140:846-854

HR: 12.7



Lung Carcinoma



Cancer Discovery
2017, 7:1394-1403

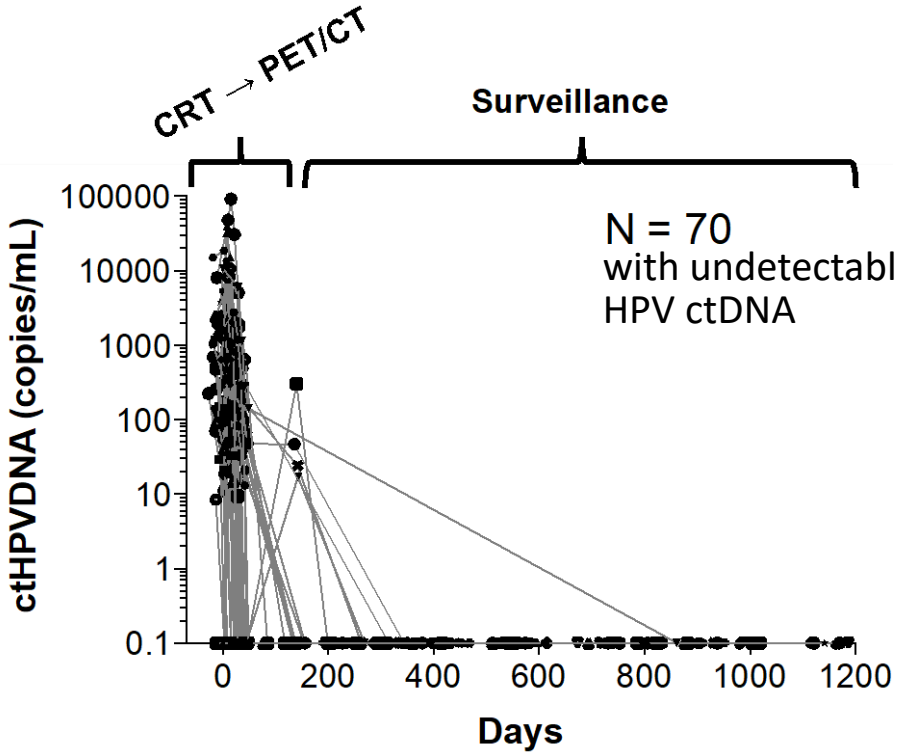
HR: 43.4

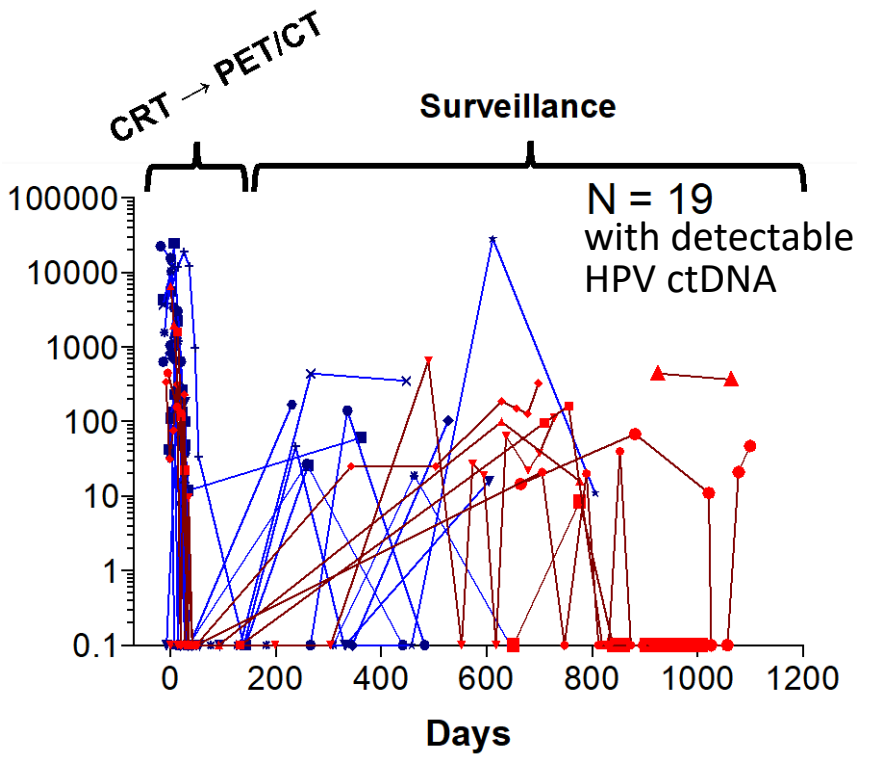
Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

UHN Princess Margaret Cancer Centre

HPV ctDNA Kinetics: *Following Locoregional Treatment*

- Prospective study with serial HPV ctDNA by ddPCR in OPSCC:





100% NPV

42% PPV

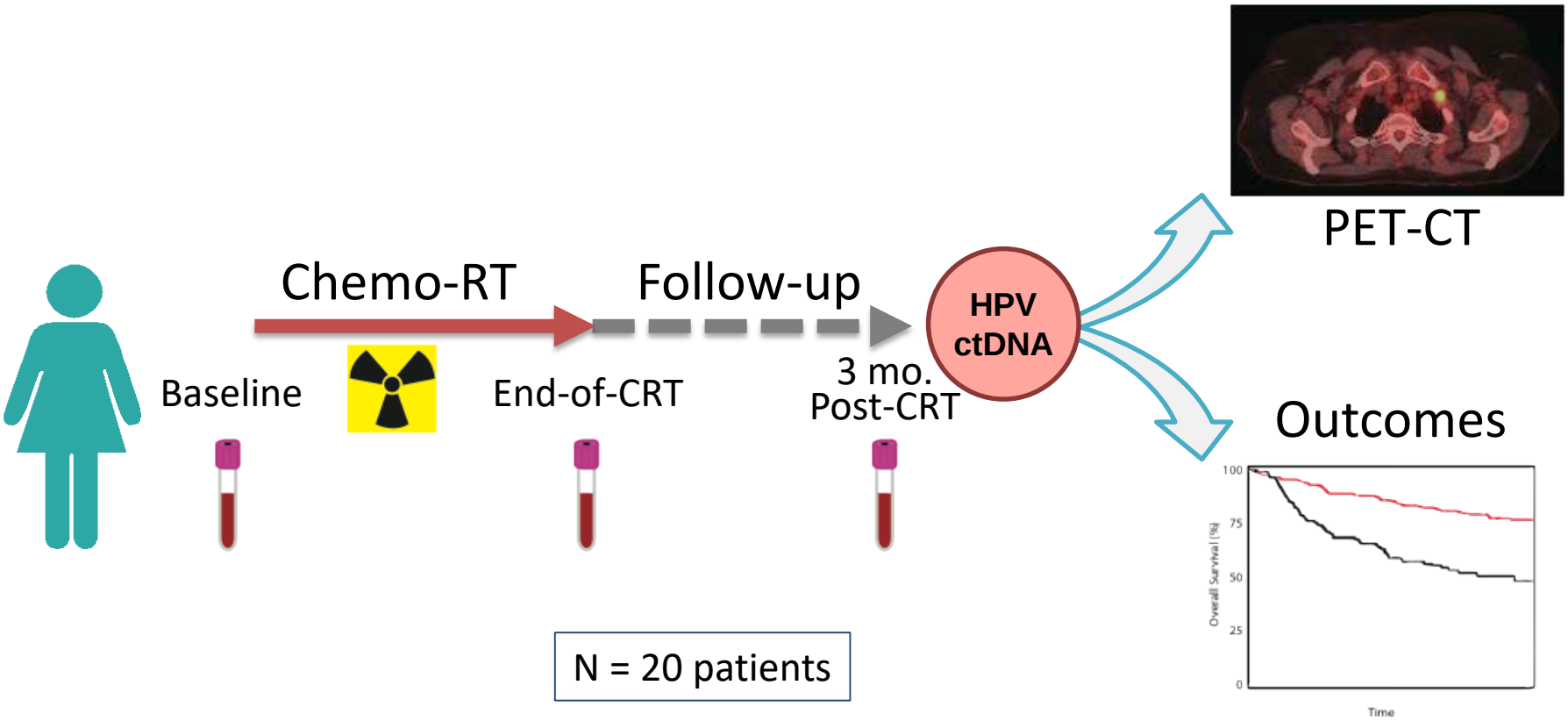
Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

Chera, Kumar, Gupta et al. *ASTRO* 2018, CCR 2019

UHN Princess Margaret Cancer Centre

ctDNA for MRD in Locally-Advanced Cervix Cancer

- Prospective study with serial HPV ctDNA by ddPCR:



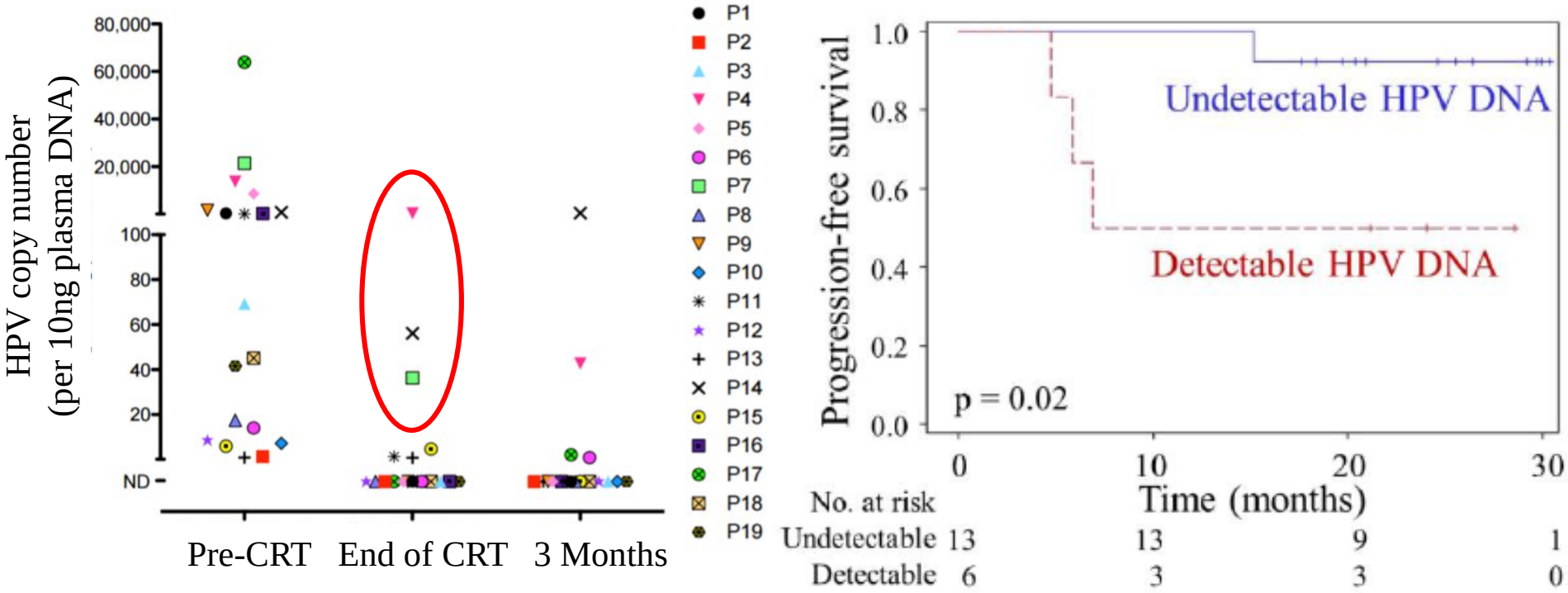
Han, Leung, Bratman, et al. JCO PO 2018

ctDNA for MRD in Locally-Advanced Cervix Cancer

- Objectives:
  - Determine if plasma HPV DNA predates clinical recurrence
  - Determine if plasma HPV DNA improves the accuracy of 3-month FDG PET scan

- Methods:
  - Baseline HPV genotyping performed from cervical swab
  - Multiplexed droplet digital PCR (ddPCR) on 10 ng cfDNA with assays targeting genotype-matched E6 & E7
  - Primary endpoint: PFS

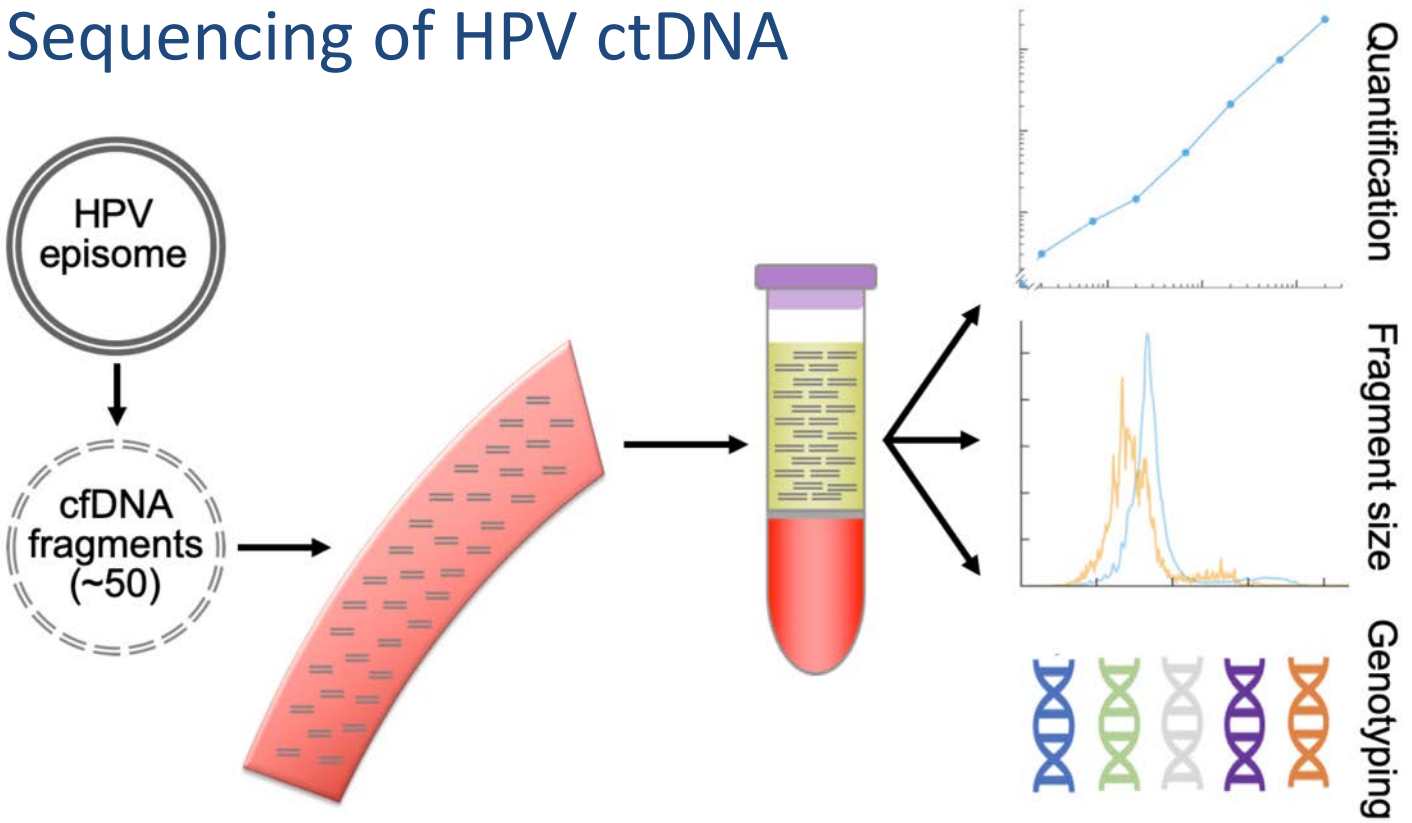
ctDNA for MRD in Locally-Advanced Cervix Cancer



Han, Leung, Bratman, et al. JCO PO 2018

Strategies to Improve ctDNA MRD Detection

- Increase blood volumes
- Repeated ctDNA testing
- Sequencing of HPV ctDNA



Leung, Han, Bratman, et al. Submitted

What is Needed to Implement HPV ctDNA?

Analytical validation of HPV ctDNA

- Limit of detection, sensitivity, specificity, PPV, NPV
- Continued innovation is to be expected

Clinical validation of HPV ctDNA

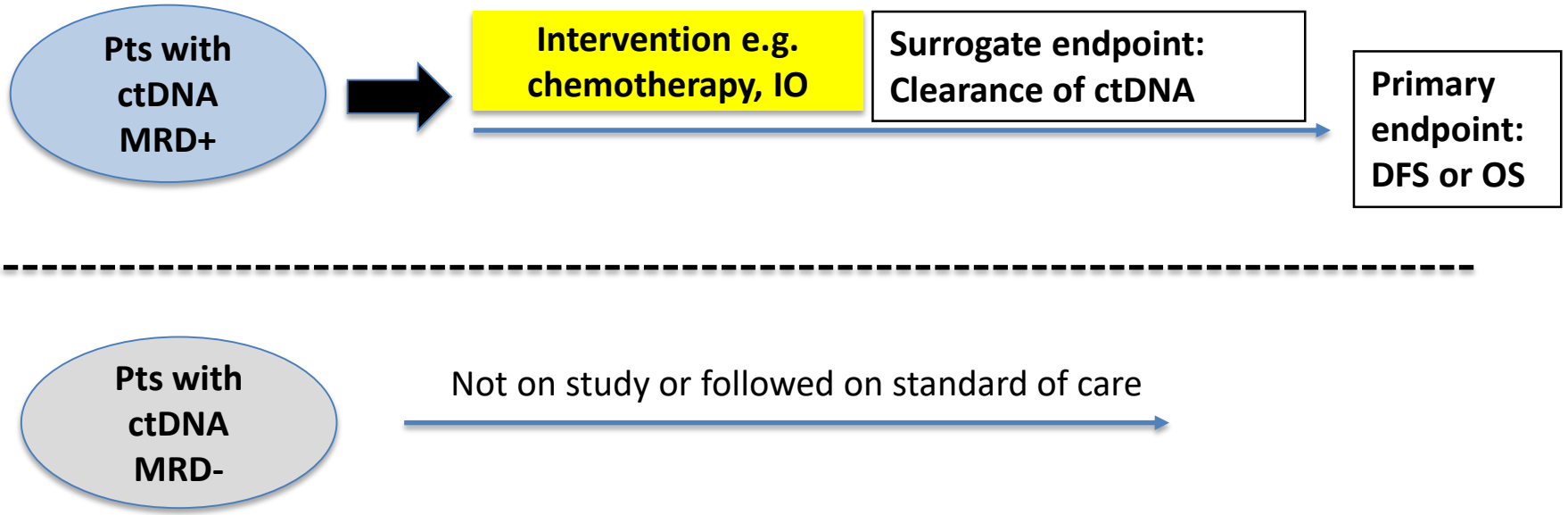
- Does the assay behave similarly when applied to independent cohorts?

Clinical utility of HPV ctDNA

- Does the use of HPV ctDNA testing result in patient or societal benefits?

Target Selection Study Design

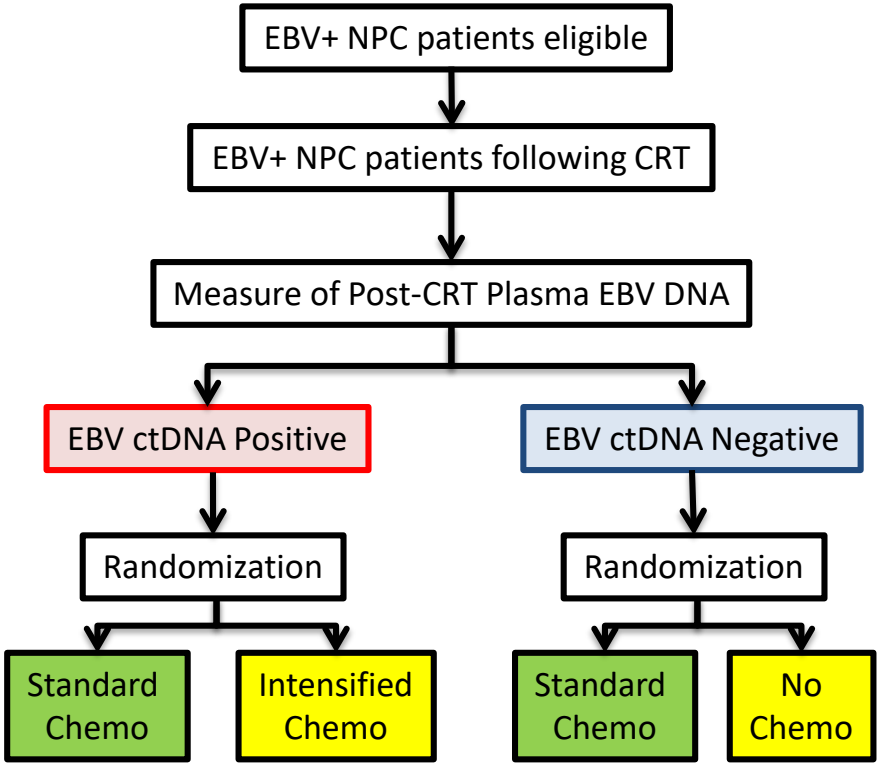
Potential study design to evaluate ctDNA clearance
Using ctDNA to as Surrogate Endpoint



Biomarker-Stratified Study Design

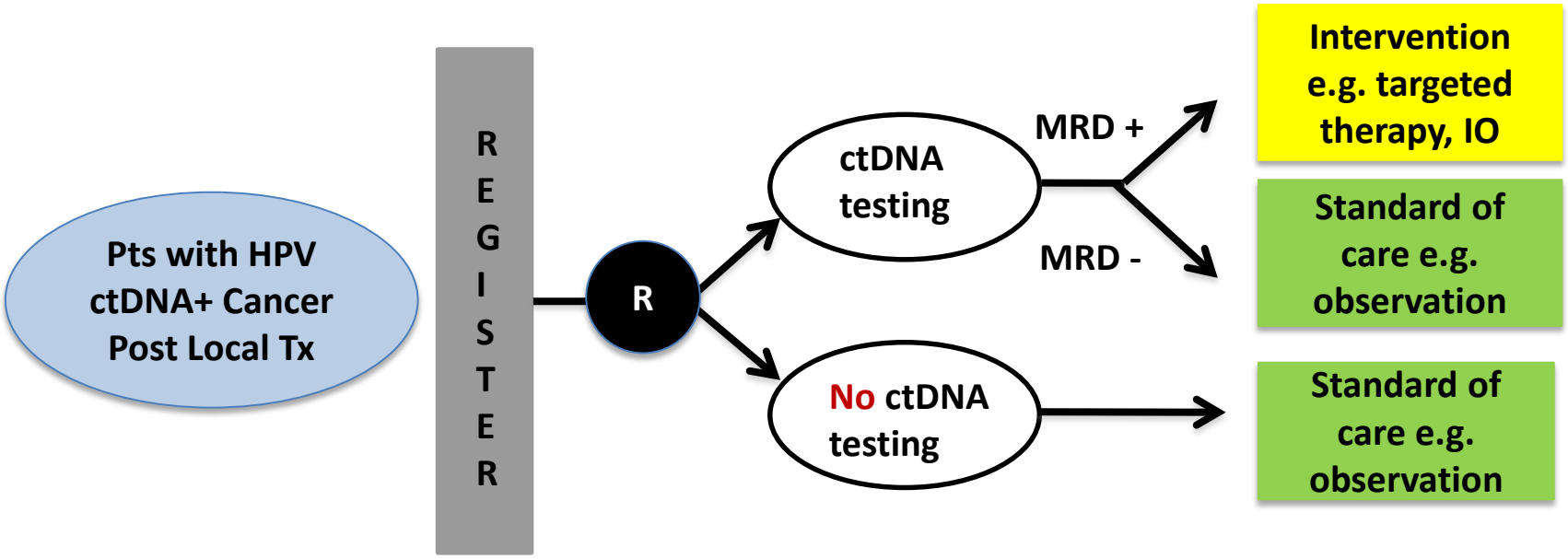
Tests treatment approaches according to ctDNA result
Using ctDNA to Guide Therapy

Plasma EBV ctDNA in Nasopharyngeal Cancer: NRG HN001



Biomarker-Strategy Study Design

Trial designed to validate the predictive value of the biomarker



Sargent, D. J. et al. J Clin Oncol 2005

Acknowledgments

Bratman Lab:
Justin Burgener
Steven De Michino
Marco Di Grappa
Gloria Hu
Meghan Lambie
Ethan Malkin
Ryota Nakashima
Ariana Rostami
Nina Wang
Tracy Zhao
Michael Zheng
Jinfeng Zou

Princess Margaret:
John Waldron
Lillian Siu
Kathy Han
Sophie Huang
Brian O'Sullivan

Odette Cancer Centre:
Eric Leung
Irene Karam

Queen's/CCTG:
Wendy Parulekar
Bingshu Chen
Sarah Hunter & HN10 team!

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

The Cancer Research Society

THE V FOUNDATION for Cancer Research

CONQUER CANCER FOUNDATION of the American Society of Clinical Oncology

Radiation Oncology
UNIVERSITY OF TORONTO

The Princess Margaret Cancer Foundation UHN

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