Prevalence of HPV Infection in Head and Neck Cancers by Anatomic Subsite

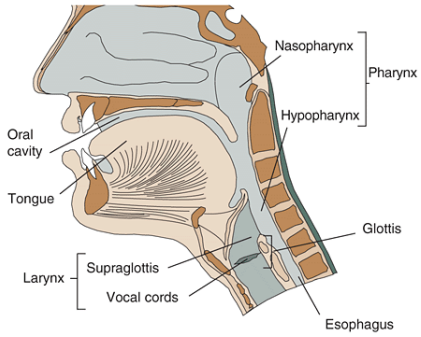
Lihua Liu, PhD

Los Angeles Cancer Surveillance Program

University of Southern California

Head and Neck Cancers

- **A variety of sites in upper aerodigestive tract**
  - Incl. oral cavity, pharynx, and larynx
- **5th most common cancer worldwide**
  - 49,000+ new cases & 11,000+ deaths in U.S. (2010)
- **More than 90% are squamous cell carcinoma**
- **More common in men than in women**
- **Tobacco, alcohol, & other risk factors**



Human Papilloma Virus (HPV)

- **Main etiologic cause for cervical cancer**
- **Types 16 and 18 are most prominent**
  - 100+ types, high risk, low risk
- **Has been linked to HNSCC**
  - Type 16 (in 90+% HPV+ HNSCC), type 18
  - Most common in oropharyngeal site, highest in tonsil
  - Young, non-smoker, non-drinker, more female
  - Sensitive to radiation – better survival
  - Incidence of HPV-related HNSCC is on the rise

Prevalence of HPV in HNSCC

Reportedly varied between 0-100%

- Anatomic subsite
- HPV detection method
- Specimen source and collection methods
- HPV type specific vs. universal primers
- Sample size and composition
- Differentiation of primary, recurrent, and metastatic tumors

Study Objective

- To test the HPV prevalence rates in HNSCC by anatomic subsite, using registry-based tissue samples that are free of reoccurrence and metastasis

Study Design

Use SEER Residual Tissue Repository (RTR) in Los Angeles:

- Convenient, economical
- FFPE tissue blocks of HNSCC cases
- Linked with registry records – primary tumors
- Test by anatomic subsite
- Demographic + tumor characteristics

Study Design

- **200 HNSCC blocks/cases**
  - Chronological preference for more recently diagnosed cases
- **Anatomic subsites**
  - Oral cavity
  - Nasopharynx
  - Oropharynx
  - Hypopharynx
  - Larynx

Hypotheses

HPV prevalence is:

- higher in oropharynx than in other sites
- higher among women than in men

Patients of HPV+, as compared to HPV-

- are younger at diagnosis
- survive longer

Data Collection

- **361 cataloged invasive HNSCC cases reviewed**
  - Excl. unavailable, ineligible, or w insufficient materials (by H&E analysis)
- **198 cases selected (1987-2003)**
- **195 cases remained in the final study sample**
  - Excl. 3 duplicate cases

Sample Repsrentativeness

	CSP (N=13,963)	Study Sample (n=195)
Age		
<40	3%	5%
40-59	33%	39%
60+	64%	56%
Total	100%	100%
Sex		
Male	71%	73%
Female	29%	27%
Total	100%	100%
Race/Ethnicity		
Non-Hispanic White	66%	58%
Black	15%	18%
Hispanic White	12%	17%
Asian/Other	7%	6%
Total	100%	100%
Anatomic site		
Oral Cavity	32%	25%
Nasopharynx	5%	4%
Oropharynx	23%	25%
Hypopharynx	7%	16%
Larynx	33%	30%
Total	100%	100%

Testing Methods

- Test performed by USC Norris Comprehensive Cancer Center Immune Monitoring Core
- Ten 5 micron unstained ribbons cut from FFPE
- DNA isolation from ribbons
- Polymerase chain reaction (PCR)
  - 2 primers amplified the L1 gene of HPV
  - 1 primer amplified a standard housekeeping gene
- HPV genotyping using InnoLIPA (27 HPV types)

Findings

62 out of 195 samples were HPV-genotyped

Overall prevalence rate 31.8%

61 (98%) cases had HPV-16, 1 had HPV-45

2 of the 61 also had presence of HPV-39, 69, and 71

	Study Sample (N=195)	HPV+ (N=62)	HPV Prevalence	*p**
Tumor site				0.01
Hypopharynx	31	7	22.6%	
Larynx	59	19	32.2%	
Nasopharynx	8	2	25.0%	
Oral cavity	49	9	18.4%	
Oropharynx	48	25	52.1%	

Univariate Analysis

	Study Sample (N=195)	HPV+ (N=62)	HPV Prevalence	*p*
Age at diagnosis				0.75
<50	34	11	32.4%	
50-69	107	36	33.6%	
70+	54	15	27.8%	
Sex				0.01*
Male	143	53	37.1%	
Female	52	9	17.3%	
Race/Ethnicity				0.56
Asian	12	3	25.0%	
Black	36	13	36.1%	
Hispanic white	35	8	22.9%	
Non-hispanic white	112	38	33.9%	
SES				0.63
High	34	10	29.4%	
Medium	40	16	40.0%	
Low	97	28	28.9%	
Unknown	24	8	33.3%	

Univariate Analysis (continued)

	Study Sample (N=195)	HPV+ (N=62)	HPV Prevalence	*p**
Tumor size (mm)				0.68
<20	19	7	36.8%	
20-30	48	13	27.1%	
30+	43	12	27.9%	
Unknown	85	30	35.3%	
Tumor grade				0.21
Well differentiated	38	11	28.9%	
Moderately differentiated	86	22	25.6%	
Poorly differentiated	60	25	41.7%	
Unknown	11	4	36.4%	
Tumor stage				0.09
Localized	54	11	20.4%	
Regional	97	32	33.0%	
Distant	30	14	46.7%	
Unknown	14	5	35.7%	

Multivariate Logistic Regression

	Odds Ratio	95% Confidence Limits
Age at diagnosis		
<65 (reference)	1.00	
65+	0.78	0.38 -1.62
Sex		
Male (reference)	1.00	
Female	0.34	0.14 -0.81 *
Race/Ethnicity		
Non-hispanic white (refe	1.00	
Asian	0.88	0.17 -4.61
Black	1.00	0.38 -2.61
Hispanic white	0.55	0.20 -1.53
Socioeconomic status (SES)		
High SES (reference)	1.00	
Medium SES	1.22	0.41 -3.63
Low SES	0.97	0.35 -2.63
Unknown	1.18	0.34 -4.12

Multivariate Logistic Regression (continued)

	Odds Ratio	95% Confidence Limits	
Tumor grade			
Well differentiated (refer	1.00		
Moderately differentiated	0.61	0.22 -1.64	
Poorly differentiated	1.24	0.43 -3.54	
Unknown	1.04	0.21 -5.09	
Tumor size (mm)			
<20 (reference)	1.00		
20-30	0.37	0.10 -1.35	
>30	0.38	0.10 -1.46	
Unknown	0.58	0.17 -1.95	
Tumor stage			
Localized (reference)	1.00		
Distant	3.42	1.07 -10.95	
Regional	2.14	0.80 -5.68	
Unknown	1.43	0.33 -6.16	
Anatomic site			
Oropharynx (reference)	1.00		
Hypopharynx	0.30	0.10 -0.93	*
Larynx	0.51	0.21 -1.25	
Nasopharynx	0.39	0.05 -3.24	
Oral Cavity	0.36	0.12 -1.06	

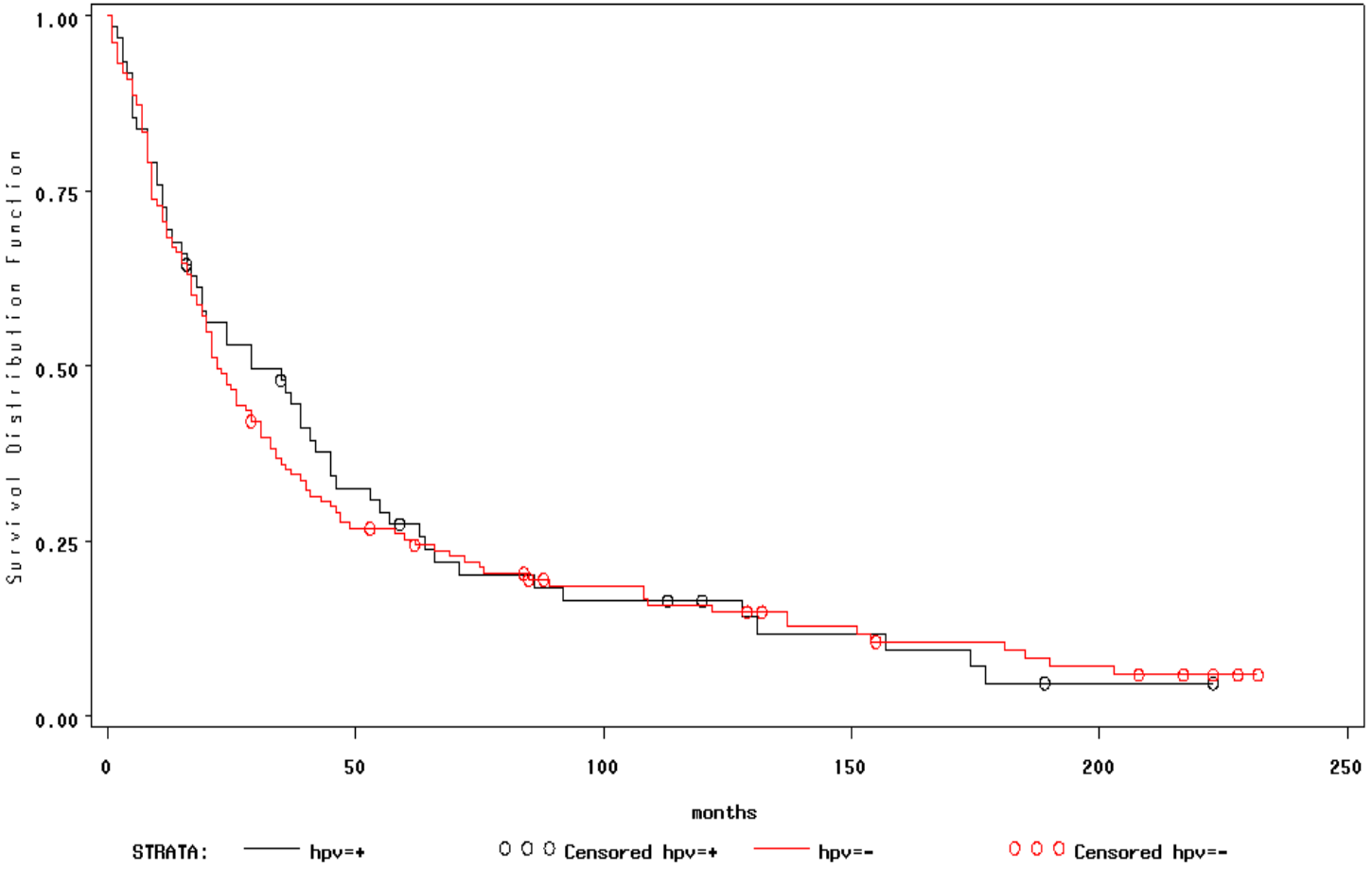
Findings

	HPV+		HPV-		
	#	%	#	%	*p* *
Treatment modality					0.87
No surgery or radiation	7	11.5	17	13.0	
Radiation only	13	21.3	27	20.6	
Surgery only	14	23.0	36	27.5	
Surgery and radiation	27	44.3	51	38.9	
Total	61	100.0	131	100.0	

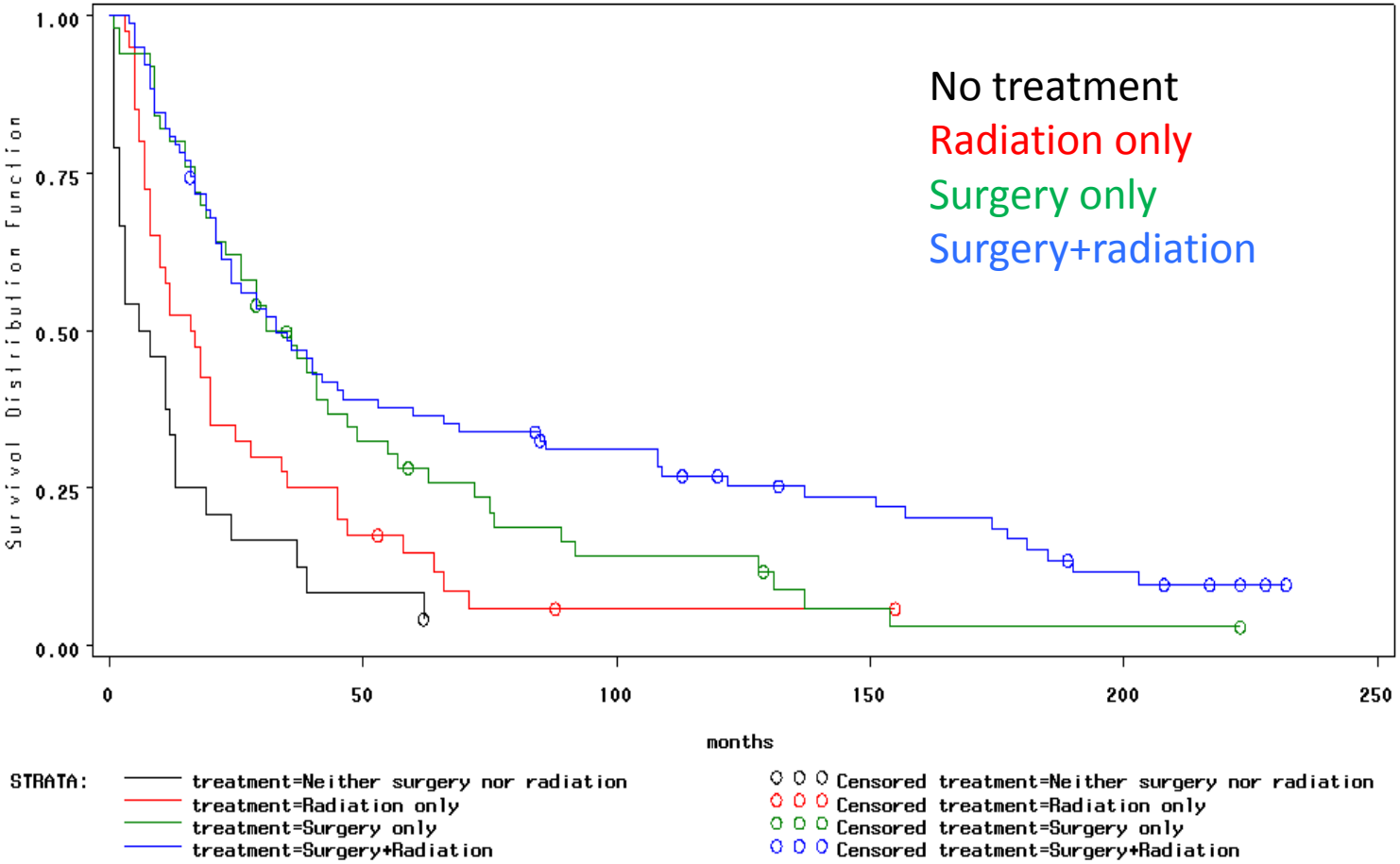
* *P* value was calculated using the Pearson chi-square test.

Kaplan-Meier Survival Probability

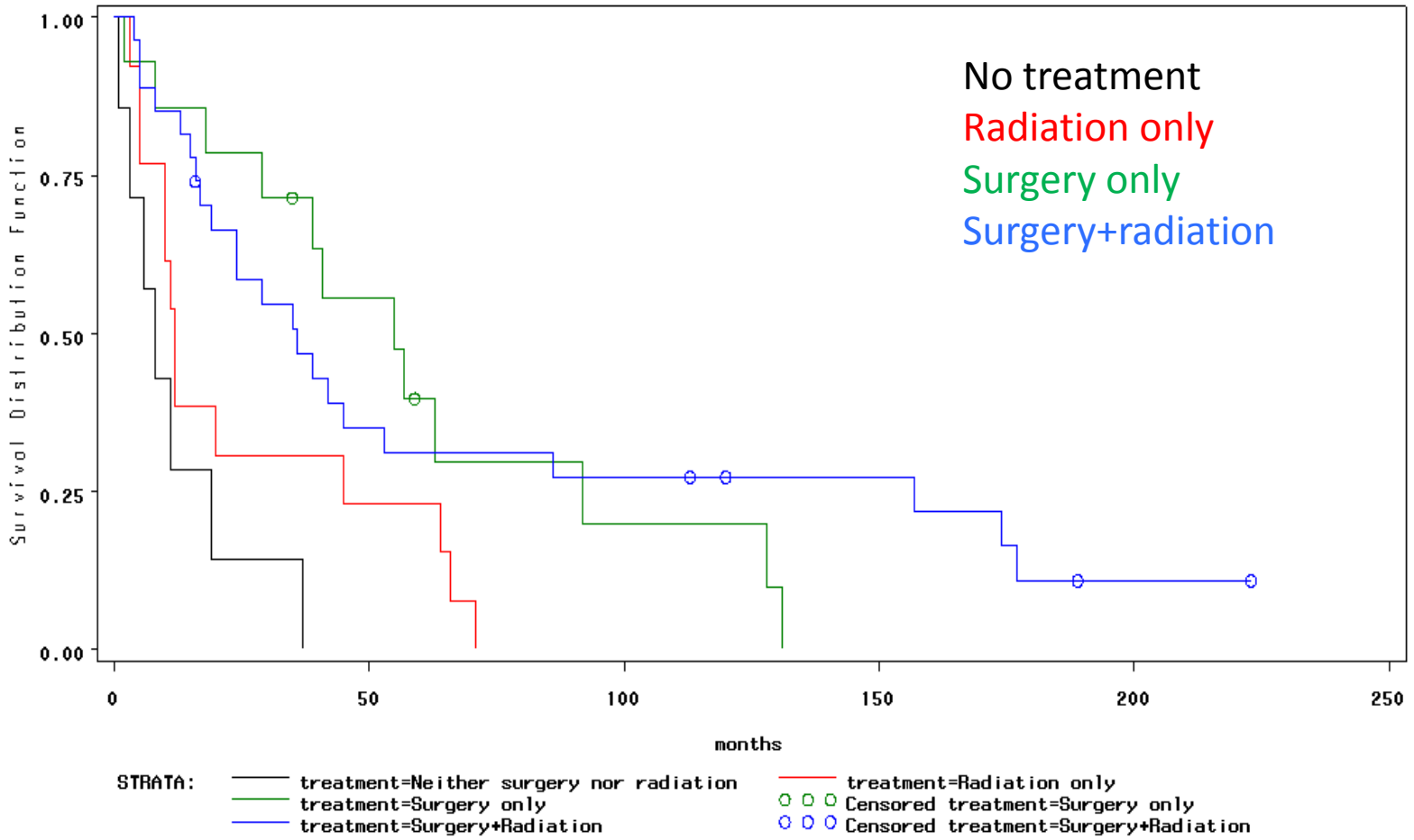
HPV+ vs. HPV-



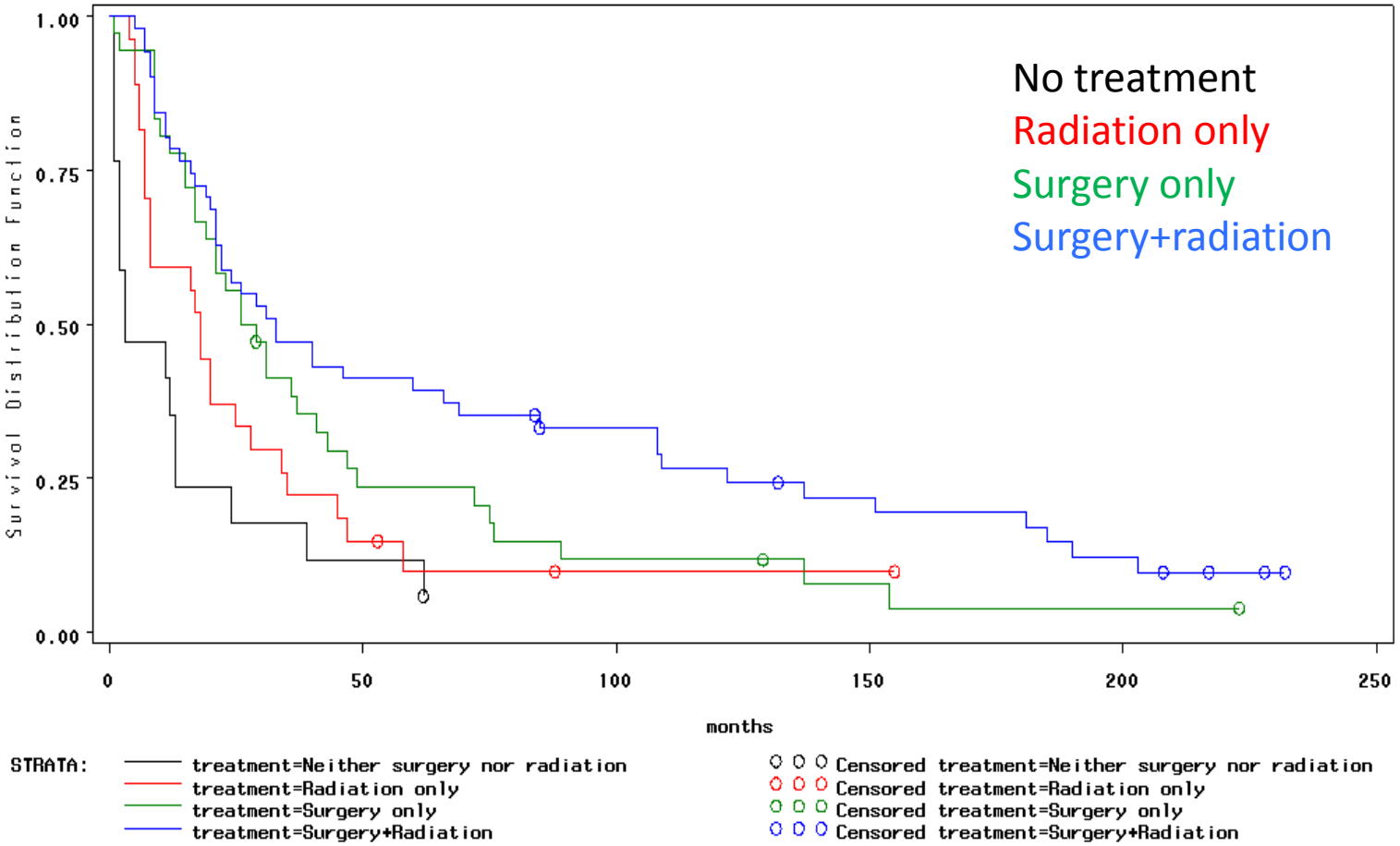
Kaplan-Meier Survival Probability
By treatment modality – all patients



Kaplan-Meier Survival Probability By treatment modality – HPV+



Kaplan-Meier Survival Probability By treatment modality – HPV-



Cox Regression Analyses

Considering:

- Age, sex, race/ethnicity, SES
- Tumor size, grade, stage, site
- Treatment modalities
- HPV status

- HPV status has no effect on survival
- Surgery+Radiation better than others
- Hispanics/Asians better than NH whites
- Low SES, larger tumor, regional stage => poor survival

Summary of findings

- 31.8% Overall HPV prevalence in HNSCC
- HPV present in all H&N subsites
- HPV-16 found in 98% infected cases
- HPV prevalence highest in oropharynx (52.1%)
- HPV prevalence higher in men than in women
- HPV status not affected by demographic/tumor characteristics
- No survival advantage observed for HPV+ patients
- No differences in treatment modality by HPV status

Recommendations

- Testing for HPV should be part of the HNC diagnostic process
- Treatment of HNC should consider the HPV status
- Evaluation of HNC survival by HPV status and treatment modality will help better understand and manage the disease
- The role of HPV in HNC development need to be further studied

Limitations

- Relatively small sample size
- Samples from RTR – many years old
- Over a 7-year diagnostic period
- Convenient sample,
    - not randomly selected
    - not population-based

Acknowledgements

- SEER RRSS N01-PC-35139

- Diane Da Silva, PhD
- Juanjuan Zhang, MS
- Maria Sibug Saber, MD
- Andre Kim, BS
- Myles Cockburn, PhD
- Wendy Cozen, DO
- Uttam Sinha, MD