Session III | Oropharyngeal cancer update in relation with HPV

Genomic features for precision medicine	은영규 (경희대)
Immune landscape & immunotherapy outcomes	정유석 (국립암센터)
De-escalation strategy update	안용찬 (성균관대 방사선종양학과)
Epidemiology & vaccination: Worldwide vs. Korean	이세영 (중앙대)
What's new in surgical approach?	고윤우 (연세대)

Genomic features for precision medicine

은영규

경희대학교 의과대학 이비인후과학교실

The tumors originate in the epithelial cells of the mucosal linings of the upper airway and food passages (the oral cavity, oropharynx, larynx or hypopharynx), which suggests that head and neck squamous cell carcinoma (HNSCC) is a relatively homogeneous disease, as it develops from one cell type in one tissue. Rather unexpectedly, HNSCC is remarkably heterogeneous. This is in part brought about by the complex anatomical structures in which it develops but also relates to the different aetiologies and the large variety of molecular changes that drive carcinogenesis.

The far more favorable outcome of HPV+ compared with HPV- oropharyngeal sqouamous cell cancer (OPSCC) is so substantial that the tumor-node-metastasis (TNM) staging for HNSCC was adapted in the eighth edition to include p16INK4A immunostaining as a surrogate for HPV status. Moreover, several treatment de-escalation trials of HPV+ OPSCC have been initiated, and the results of these are now being awaited, which may lead to personalized treatment based on HPV status.

The lack of rapidly improving patient survival and personalized treatment approaches has propelled research into the molecular landscape of HNSCC. Using expression arrays and, over the past few years, RNA sequencing, subgroups of head and neck tumors characterized by gene expression patterns have been identified. However, the performance of different expression profiling platforms and analysis pipelines as well as differences in immune infiltrate and other stromal components may impact the subgroup definitions. In addition, the prognostic associations of the subgroups are variable, hampering clinical utility. Hence, in contrast to, for instance, breast cancer, classification based on gene expression profiles is not yet common practice for HNSCC, but these profiles are highly informative from a biological perspective. In 2015, The Cancer Genome Atlas (TCGA) con- sortium published the comprehensive genomic data of 279 HNSCCs, including both HPV+ and HPV- tumors. The HPV- tumors are typically characterized by many mutations and numerous chromosomal gains and losses. Intriguingly, in this and earlier studies, a distinct subgroup of HPV- tumors with ‘copy number alteration (CNA)-silent’ profiles emerged, which also displayed specific mutational profiles, suggesting that these tumors form a separate genetic subgroup. The number of candidate cancer driver genes in HNSCC is exploding at present and requires careful biological interpretation.

Genomic profiling

Recent data indicate that HPV+ OPSCCs are more heterogeneous with respect to their expression patterns. Keck MK et al. identified five subtypes of HNSCC, including two biologically distinct HPV subtypes. The authors named the three supergroups in-

flamed/mesenchymal (IMS), basal (BA), and classical (CL), respectively. In all the datasets, HPV+ tumors were not gathered into one group, but fall into two distinct groups: (i) the inflamed/mesenchymal (IMS) supergroup and (ii) the classical (CL) supergroup. It is evident that HPV+ HNSCCs are composed of two distinct gene expression subtypes, namely, IMS-HPV and CL-HPV.

The most distinctive feature of the classical supergroup is the significant enrichment for putrescine (polyamine) degradation pathway, which is relevant for detoxification, related to tobacco use. the classical supergroup has a higher proliferation rate compared with the other groups. Although the CL-HPV and CL-nonHPV subtypes share similarities, they are still two distinct disease entities, reflected in many biologic pathways. Cell-cycle genes, such as mini-chro- mosome maintenance proteins (MCM2 and MCM10), cell division cycle protein kinase (CDC7), and -related genes (CDKN2A, E2F2, and RPA2) are overexpressed in the CL-HPV subtype. The two subtypes also show significant difference in tobacco use with 74% heavy smokers in CL-nonHPV compared with 42% heavy smokers in CL-HPV. The distinguishing features of the IMS group is expression of immune response genes like CD8, ICOS, LAG3, and HLA-DRA related to the infiltration of CD8+ T lymphocytes in tumors. Mesenchymal genes such as vimentin (VIM), matrix metallo-proteinases (MMP9), and S100A4 also show increased expression in the IMS group, which typically associates with increased metastatic risk. Epithelial markers such as P- cadherin (CDH3) and cytokeratins (KRT1, KRT9) are downregulated, suggesting EMT. The two subtypes in the IMS group show a significant difference in cell-cycle pathways and smoking-associated pathways. Similar to the CL-HPV subtype, the IMS-HPV subtype has significantly higher cell-cycle pathway activities, in which HPV is known to play a critical role. between the two HPV subtypes, the IMS-HPV subtype shows a trend toward higher 5-year survival than CL-HPV.

Zhang Y. reported transcriptomic analysis via RNA-deep sequencing on 36 tumor samples (18 HPV+ and 18 HPV-) to define gene expression levels. Supervised differential expression analysis using HPV status as the group variable identified 1,887 and 1,644 genes significantly upregulated and downregulated in HPV+ samples, respectively. TP53, CDKN2A, BRCA2, CYP2E1, KIT, and EZH2 were significantly upregulated in HPV+ tumors, and CCND1, GSTM1, HIF1A, MMP2, CD44, and MET were downregulated. According to Gene Ontology enrichment analysis with LRpath and found that “immune response”, “cell cycle”, and “DNA replication” were upregulated in HPV+ samples compared with HPV-, whereas “extracellular matrix” and “epithelium development” were upregulated in HPV- samples.

Unsupervised clustering using the 6,922 most variably expressed genes among all samples revealed two HPV+ subgroups. Differential expression analysis between the two HPV+ clusters found 3,515 genes significantly differentially expressed. Upregulated genes in one cluster were enriched for “immune response,” “mesenchymal cell differentiation,” and various differentiation and development-related terms; upregulated genes in the other cluster were most significantly enriched for “keratinocyte differentiation” and “oxidative reduction process”. Therefore, the authors named the clusters HPV-IMU and HPV-KRT, respectively. Enrichment testing results showed remarkably elevated immune response in HPV-IMU, consisting of increased T-cell activation, B-cell activation, and lymphocyte activation, and repression of both mesenchymal differentiation and extracellular matrix–related expression in HPV-KRT; it also showed increased keratinization/epidermal differentiation and oxidative–reduction process gene expression in HPV-KRT relative to HPV-IMU. Although we did not find a significant difference in overall survival between HPV-KRT and HPV-IMU with the same TCGA data, HPV-KRT tended to have worse overall survival than HPV-IMU

Seiwert TY et al. reported that the overall mutational burden in HPV- and HPV+ HNSCC was similar with an average of 15.2 vs. 14.4 somatic exonic mutations in the targeted cancer-associated genes. HPV- tumors showed a mutational spectrum concordant

with published lung squamous cell carcinoma analyses with enrichment for mutations in TP53, CDKN2A, MLL2, CUL3, NSD1, PIK3CA, and NOTCH genes. HPV+ tumors showed unique mutations in DDX3X, FGFR2/3 and aberrations in PIK3CA, KRAS, MLL2/3, and NOTCH1 were enriched in HPV- positive tumors. Currently targetable genomic alterations were identified in FGFR1, DDR2, EGFR, FGFR2/3, EPHA2, and PIK3CA. EGFR, CCND1, and FGFR1 amplifications occurred in HPV- tumors, whereas 17.6% of HPV+ tumors harbored mutations in fibroblast growth factor receptor genes (FGFR2/3), including six recurrent FGFR3 S249C mutations. HPV+ tumors showed a 5.8% incidence of KRAS mutations, and DNA- repair gene aberrations, including 7.8% BRCA1/2 mutations, were identified.

Koenigs MB et al. reported the association of estrogen receptor alpha expression with survival in oropharyngeal cancer following chemoradiation therapy. The authors sought to investigate estrogen receptor-alpha (ERa), one of the most commonly used biomarkers in oncology, as a biomarker in HNSC and OPSC. In breast cancer, ERa is used as both a prognostic biomarker and a therapeutic target.

ERa expression was highest in HPV+ tumors and HPV status was the major factor associated with ERa expression. ERa mRNA expression was statistically significantly related to longer overall survival among TCGA HNSC patients who received chemoradiation as primary therapy or adjuvant to surgery; the hazard ratio (HR) per doubling of ERa mRNA was 0.75 (95% CI=0.64 to 0.87, Wald test, $P<0.001$). Patients with ERa-positive tumors had improved OS (log-rank, $P<0.001$), DSS (log-rank, $P<0.001$), PFS (log-rank, $P=0.002$), and RFS (log-rank, $P=0.003$) compared with those with ERa-negative tumors. This relationship between ERa and survival in the OPSC-CR cohort went beyond its association with HPV positivity. Notably, the relationship between ERa expression and survival following chemoradiation was maintained within the subset of patients whose tumors were HPV+.

Conclusions

Over the past decade, the role of HPV in HNSCC has changed the research field, and the impact for staging and prognosis became manifest in the new eighth edition of the TNM staging system. Personalized treatment and the de-intensification of current treatment protocols on the basis of HPV status is on the horizon. Together, this will make a consensus on HPV testing important. The lack of precursor lesions in the upper aerodigestive tract caused by HPV remains puzzling, and it is likely that there is an anatomical separation of productive infection and transforming infection.

Immune landscape & immunotherapy outcomes

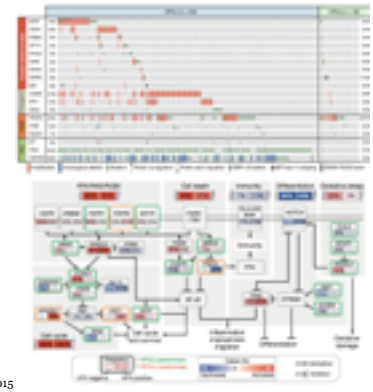
정 유 석

국립암센터 이비인후과

Features of Head & Neck Cancer

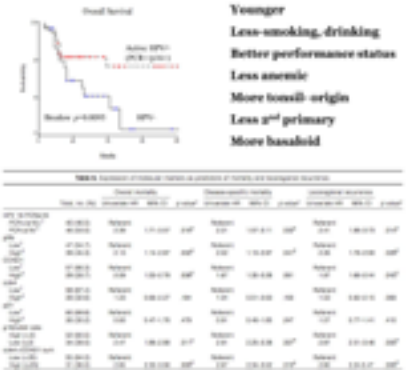
- Lack of therapeutic targets, more 'potent' than classical 'cytotoxic' agents
- Human papillomavirus as an distinct prognostic & 'therapeutic(?)' biomarker
  → De-escalation
- Immunogenic 'hot' feature, especially in HPV(+) cancers
  → Immunotherapy!!

Mutations in HPV(+) and (-) HNSCC



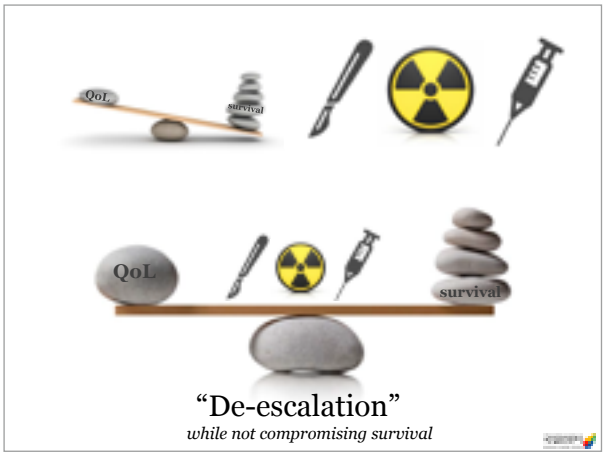
TCGA, *Nature*, 2015

HPV 16 (+) OSCCs HR for overall mortality 0.42 (0.28-0.58)



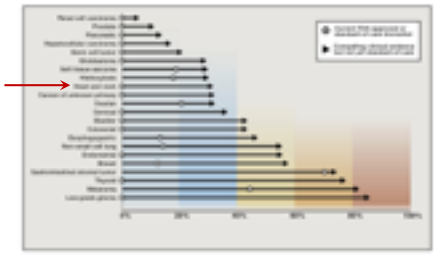
Younger
Less-smoking, drinking
Better performance status
Less anemic
More tonsil-origin
Less 2nd primary
More basaloid

Park et al., *Head Neck*, 2012



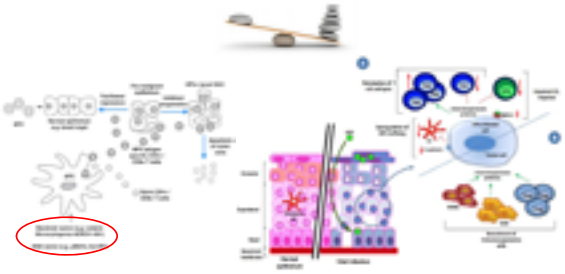
Lack of therapeutic targets, more 'potent' than classical 'cytotoxic' agents

Druggable Alterations in Oncology Today and in the Near Future



Hyman DM, *Cell*, 2017

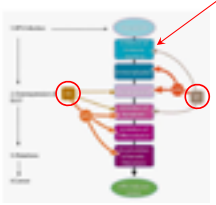
HPV versus Host Immune Response



Masterson L, et al. *Eur J Cancer*. 2014

Grabowska et al. *Open Virol J*. 2012

HPV versus Host Immune Response

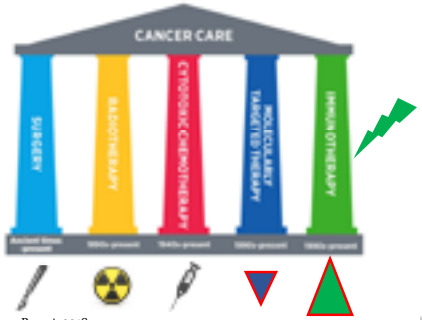


E6 and E7 Antigens as Potential Targets for Immunotherapy

1) Foreign viral proteins
2) Uniquely expressed by cancer cells
3) Constitutively expressed
4) Unlikely lose antigen expression

Mirghani H et al. *Int J Cancer*. *2014*

Pillars for Head & Neck Cancer Treat

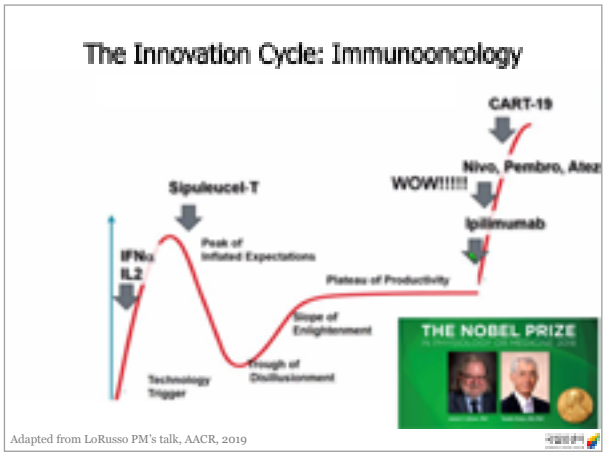


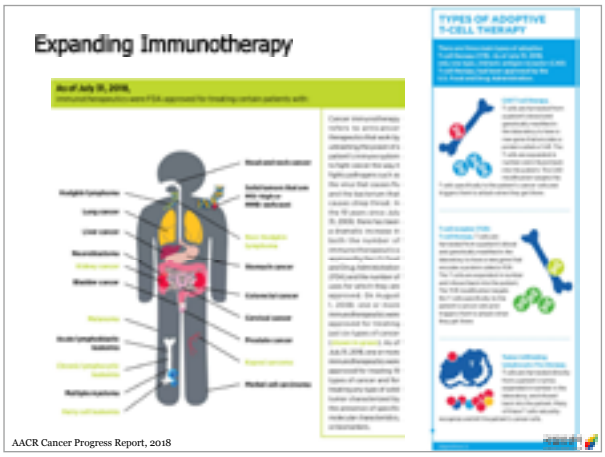
AACR Cancer Progress Report, 2018

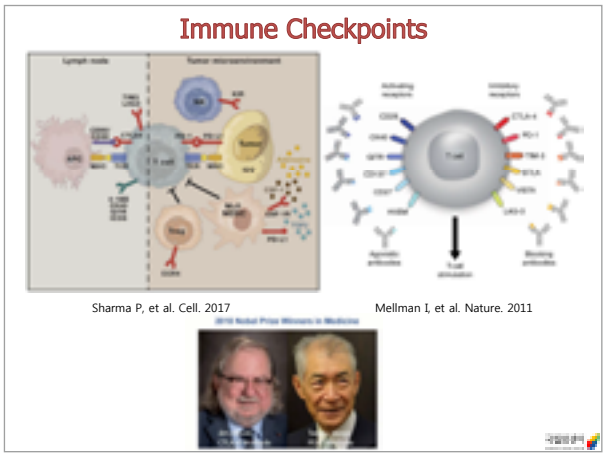
Immunooncology: Old History

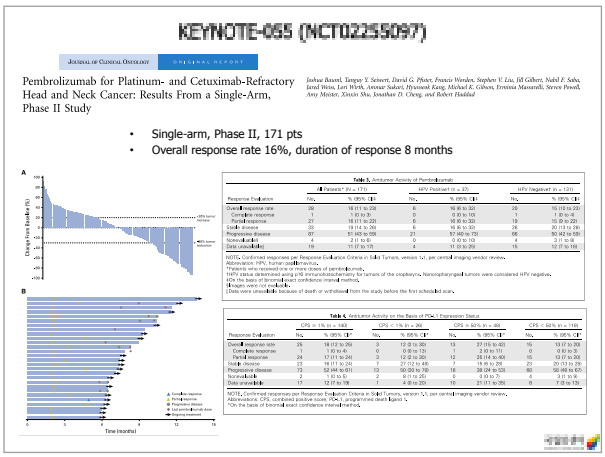
Kirkwood JM et al., *CA Cancer J Clin*, **2012**

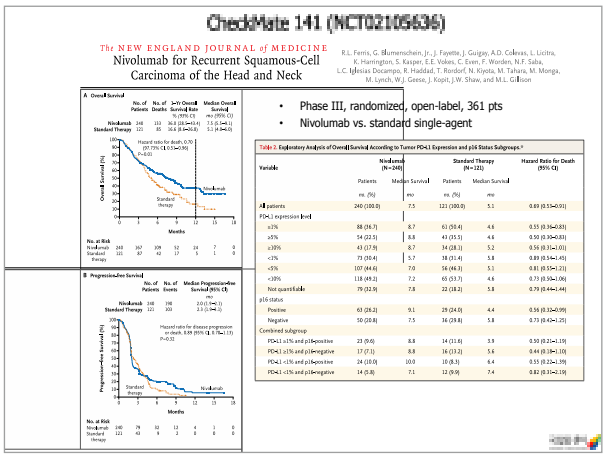

Immunooncology Revolution
Science
Science
CANCER
nature
Cancer Cell
CANCER
CTLA-4 antibody
CAR-T cells
PD-1/ PD-L1 antibodies


The Innovation Cycle: Immunooncology
CART-19
Nivo, Pembro, Atez
WOW!!!!!
Sipuleucel-T
Ipilimumab
IFNα
IL2
Peak of Inflated Expectations
Plateau of Productivity
Slope of Enlightenment
Trough of Disillusionment
Technology Trigger
THE NOBEL PRIZE
Adapted from LoRusso PM's talk, AACR, 2019

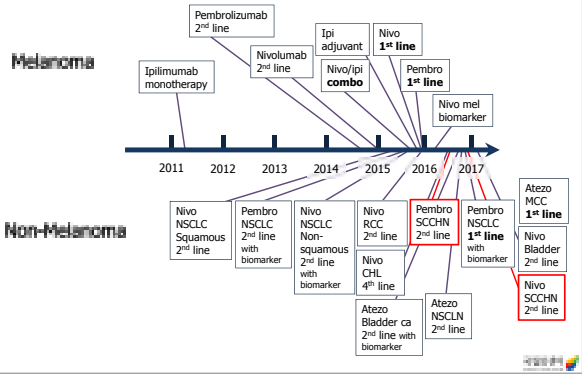

Expanding Immunotherapy
TYPES OF ADOPTIVE T-CELL THERAPY
AACR Cancer Progress Report, 2018


Immune Checkpoints
Sharma P, et al. Cell. 2017
Mellman I, et al. Nature. 2011


KEYNOTE-055 (NCT02255097)
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT
Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study
Single-arm, Phase II, 171 pts
Overall response rate 16%, duration of response 8 months


CheckMate 141 (NCT02105636)
The NEW ENGLAND JOURNAL of MEDICINE
Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck
Phase III, randomized, open-label, 361 pts
Nivolumab vs. standard single-agent

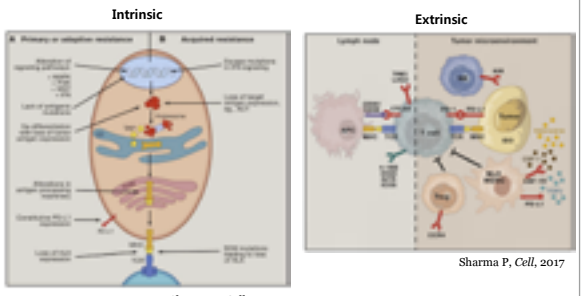
FDA approvals for checkpoint inhibitors



Approved Checkpoint Inhibitors

AACR Cancer Progress Report, 2018

Resistance to ICT: "Reverse Translation"



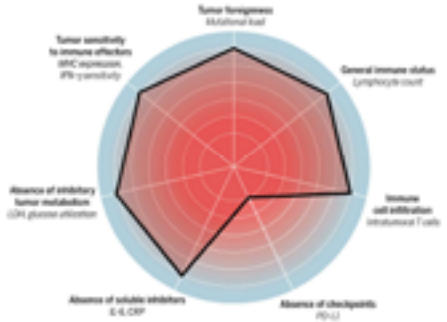
Sharma P, *Cell*, 2017

Sharma P, *Cell*, 2017

Cancer-Immune Phenotypes

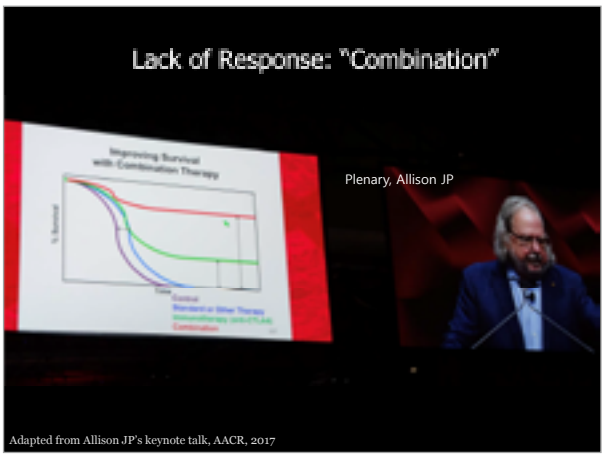
Chen DS, *Nature*, 2017

Predictive markers: "the Cancer Immunogram"



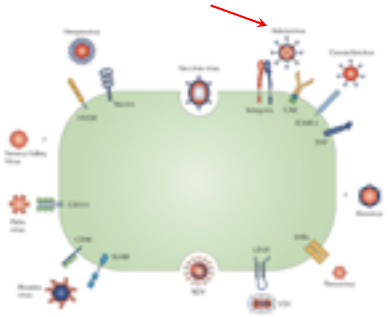
Blank CU, *Science*, 2016

Lack of Response: "Combination"



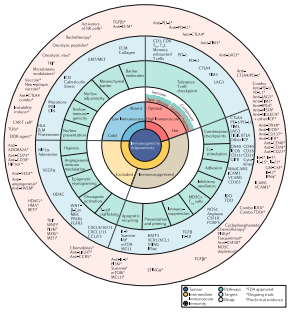
Adapted from Allison JP's keynote talk, AACR, 2017

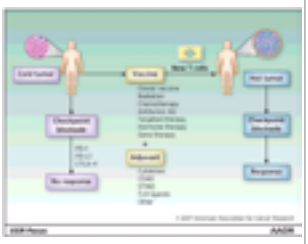
Viruses: Use Devil to Cure Devil (Cancer)



Kaufman HL et al., *Nat Rev Drug Discov*, 2016

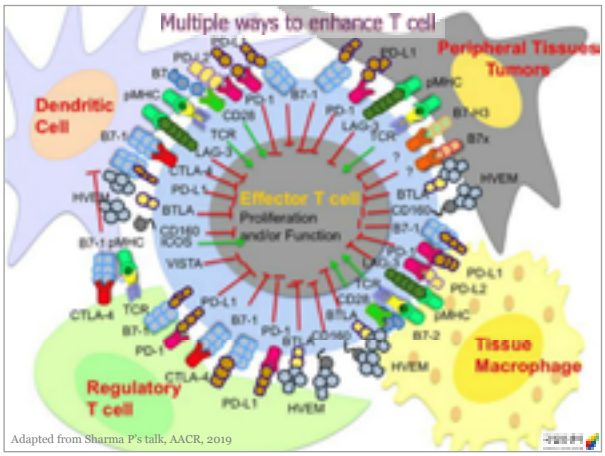
Tumor-Immune Interface: Guide for Therapy





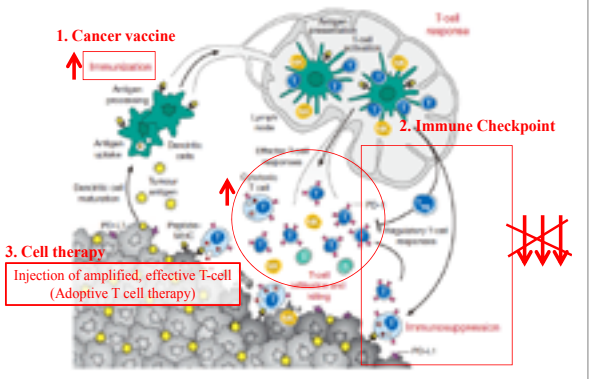
Galon J, *Nature Rev Drug Discov*, 2019

Vonderheide RH, *Clin Cancer Res*, 2019



Adapted from Sharma P's talk, AACR, 2019

Our Optimistic Agenda for Immunotherapy



Nature, 2011. 480(22):480-489

Summary

- De-escalation for HPV+ OPSCC has been part success and part failure
- HNSCC, especially HPV+, is generally immunogenic
- Pembrolizumab and Nivolumab were approved by FDA as second-line, with improved but still limited response
- Combinations, vaccines, or even cell therapies…
- But surgery will still be the 'mainstay' in many respects

De-escalation strategy update

안 용 찬

성균관대학교 의과대학 방사선종양학과교실

De-intensification therapy for HPV(+) oropharynx cancer:
Where are we? And where should we go?

Yong Chan Ahn, MD/PhD
Dept. of Radiation Oncology
Samsung Medical Center
Sungkyunkwan Univ. School of Medicine


Int J Clin Oncol, 2016

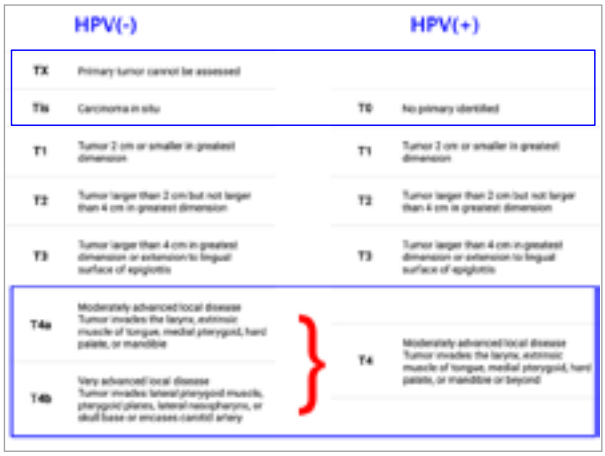
INVITED REVIEW ARTICLE

Clinical features and treatment strategy for HPV-related oropharyngeal cancer

Table 1 Clinical features of human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) and HPV-unrelated OPSCC [10, 43, 46]

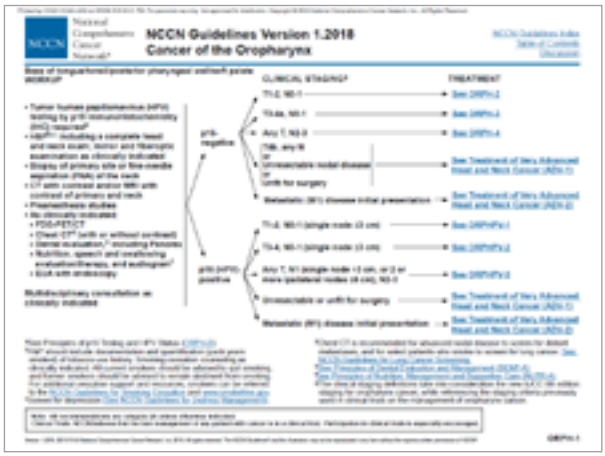
	HPV-related OPSCC	HPV-unrelated OPSCC
Anatomic site	Tonsil and base of tongue	All sites
Age	Younger cohorts	Older cohorts
Sex ratio	3:1 men	3:1 men
Socioeconomic status	Higher	Lower
Histology	Non-keratinized, basaloid	Keratinized
p53	Wild type	Mutated
Stage	Early T, advanced N (cystic)	Variable
Risk factors	Sexual behavior	Alcohol and tobacco
Incidence	Increasing	Decreasing
Survival	Improved	Unchanging
Second primary tumors	Less common	Common

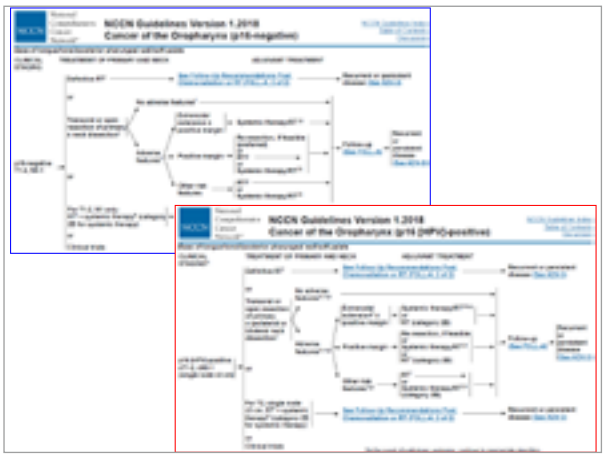
Stage Issue

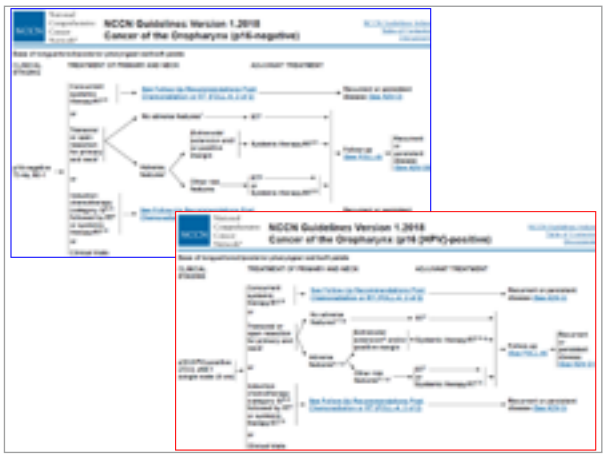


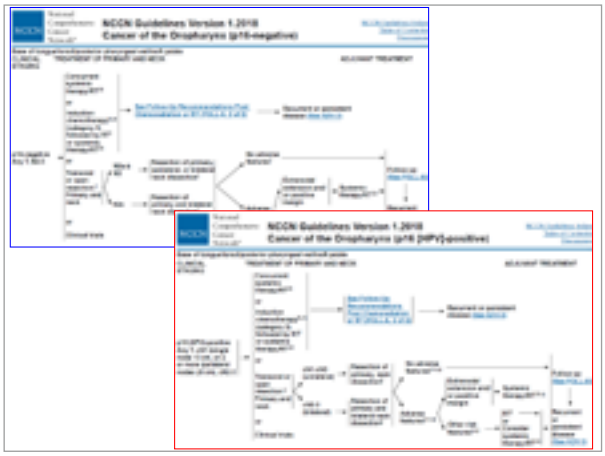
HPV(-)	HPV(+)	HPV(-)	HPV(+)	HPV(-)	HPV(+)	HPV(-)	HPV(+)	HPV(-)	HPV(+)
		N0		N1		N2a,b,c	N2	N3a,b	N3
--	T0				I		II		III
T1		I	I	III	I	IVa	II	IVb	III
T2		II	I	III	I	IVa	II	IVb	III
T3		III	II	III	II	IVa	II	IVb	III
T4a	T4	IVa	III	IVa	III	IVa	III	IVb	III
T4b		IVb		IVb		IVb		IVb	

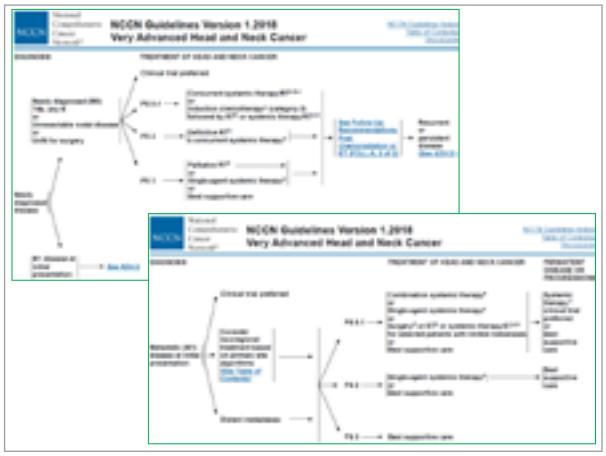
NCCN Guideline
Ver 1.2018











Seminars Rad Oncol, 2018

RADIATION ONCOLOGY

Current Status and Future Directions of Treatment Deintensification in Human Papilloma Virus-associated Oropharyngeal Squamous Cell Carcinoma

- **Transoral Surgery Paradigm**
  - Omission of RT
  - Lowering RT dose
  - Omission of CTx
  - Morbidity of ND
- **Neoadj CTx Paradigm**
- **Targeted Therapy Paradigm**
- **Proton Therapy Paradigm**
- **Reduction Elective Nodal Radiation Volume Paradigm**
- **RT alone Paradigm**

Transoral Surgery Paradigm?

– Omission of RT	• Transection under magnification → Reduction in surgical morbidity without compromising oncologic outcomes. • Omission of RT may be applicable to only minority (subclinical disease). • There is no "close margin" concept in TOS.
– Lowering RT dose	• Sparing primary site with IMRT may not result in less dysphagia (significant dose delivered). • Is TLM/TORS is less intensive than 10 Gy? -- doses ≥50 Gy to pharyngeal constrictors correlate with late dysphagia.
– Omission of CTx	• Adj CTx may not be needed because of enhanced radiocurability of HPV+ OPSCC.
– Morbidity of ND	• Side effects of ND are not discussed and considered by proponents of TOS paradigm.

Systemic Therapy Paradigm?

– Neoadj CTx Paradigm	• 9 weeks of intensive CTx vs. 1 week of RT (10 Gy)? • Increased overall Tx time → prolonging duration, frequency, and severity of toxicities. • RT is being minimally decreased, while CTx is maximally intensified.
– Targeted Therapy Paradigm	• EGFR expression is lower in HPV+ OPSCC, and emerging data suggest that cetuximab may be less efficacious than cytotoxic CTx when combined with def RT.

Potential pathologic outcomes following induction CTx

To irradiate or not? Where to/How to irradiate?

Confusion often leads to improper target delineation, Tx failure, and side effects.

RT Paradigm?

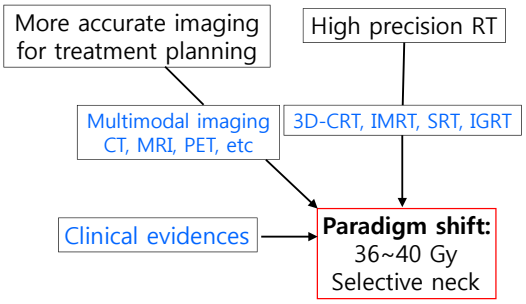
– **PBT Paradigm**	• **Dosimetric advantages in reducing low-radiation dose beam path (anterior oral cavity and posterior neck/brainstem/brain). → Lower Sx burden and better QoL?**
– **ENI Volume Paradigm**	• **Ipsilat RT can be safe with improved QoL in well-lateralized tonsil primary.**
– **RT Alone Paradigm**	• **Very high cure rates with RT alone in stage T1-2, N0-1 OPC with and without consideration of HPV or smoking status.**

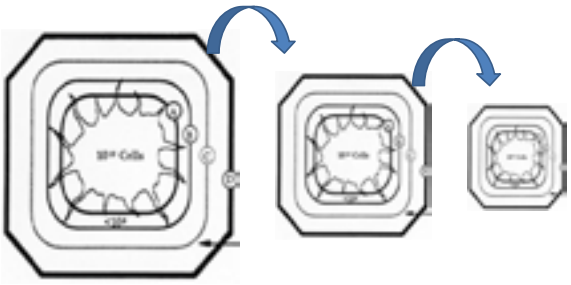
Future Directions

- Several questions remain to be answered.
- HPV status, smoking status, and T and N stage
  - – Very useful as prognosticator, but not perfect...
- Other biomarkers:
  - – Circulating tumor DNA
  - – Hypoxia
- 3 major "preferred" Tx paradigms:
  - – Surgery first.
  - – Radiation first.
  - – Induction first.

How I Do?

Give-up Old Concept!





Strategies for shrinking tumor:
- Shrinking field by 3D-CRT
- Dose painting by IMRT
- Both

Comparison of Dose Schedules at SMC

	3D RT	TomoTherapy	
Main concept	Serial shrinking field	Dose painting	
Subclinical disease	36 Gy/18 Fx's	36 Gy/18 Fx's	36 Gy/18 Fx's
Equivocal lesion	54 Gy/27 Fx's	60~63.6 Gy/Fx's (2*30 or 2.2*18 + 2*12)	
Definite lesion	70 Gy/35 Fx's	66 Gy/30 Fx's (2.2*30)	69.4 Gy/30 Fx's (2.2*18 + 2.4*12)
Number plans	3 times	2 times	
Duration	7 weeks	6 weeks	

Has It Worked Well @ SMC?

CCRT is comparable to S+RT

- 237 patients with stage III/IV oropharynx ca were treated at SMC (Jan '98~Dec '07)
- Matched-pair analysis

	CCRT (N=65)	S+RT (N=65)	P value
3Y OS	80.9%	67.9%	0.096
1Y PFS	85.1%	88.5%	0.469

Abstract at ACOS 2012

ORIGINAL ARTICLE

Tumor volume reduction rate measured during adaptive definitive radiation therapy as a potential prognosticator of locoregional control in patients with oropharyngeal cancer

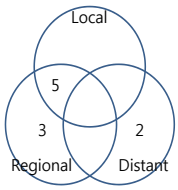
2013, Head Neck

Radiation Therapy

- 3D-CRT (7 weeks):
  - 70 Gy/35 Fx's in 35 patients
- Helical Tomotherapy (6 weeks):
  - 66 Gy/30 Fx's (2.2 Gy*30 Fx's) in 14 patients
  - 68.4 Gy/30 Fx's (2.2 Gy*18 Fx's + 2.4 Gy*12 Fx's) in 10 patients
- Routine adaptive re-plan during RT:
  - 2nd CT simulation after median 15 (12–17) Fx's

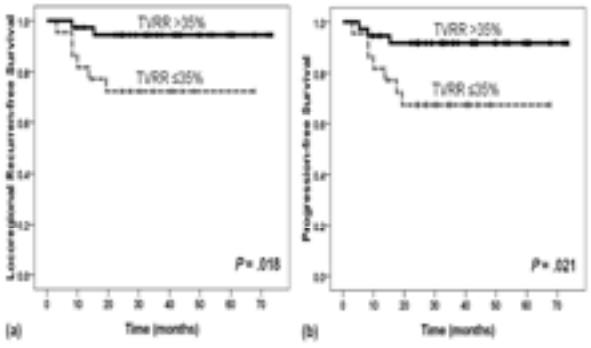
Treatment Outcomes

- Median F/U = 41.3 (9.3–73.5) months
- Response rate = 96.6%:
  - CR 32 (54.2%)/PR in 25 (42.4%)/SD in 1 (1.7%)/PD in 1 (1.7%)
- 6 deaths (including 1 intercurrent death)
- 10 treatment failures



	At 1 year	At 3 years
PFS	89.8%	82.7%
LC	91.5%	86.2%
OS		92.7%

LRRFS PFS vs TVRR



Session III

Clinical Implications

- TVRR during adaptive RT has prognostic value!
- It may serve as predictor that enable individualized therapeutic modification during RT:
  - Escalation of total radiation dose
  - Intensification of chemotherapy during and/or after planned RT
  - Early implementation of surgical salvage

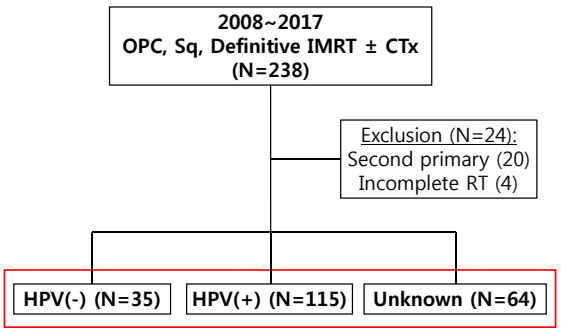
Manuscript in preparation

SNI for oropharyngeal cancer in relation with HPV status

Patients

- Inclusions:
  - From Jan 2008 to Dec 2017
  - Histologically confirmed oropharynx cancer
  - **Curative RT (with IMRT (Tomotherapy))** with/without concurrent systemic therapy
- Exclusions:
  - Non-squamous histologic type
  - Unable to complete the planned RT course
  - RT for postoperative or salvage aim
  - Induction or adjuvant chemotherapy

SMC data (in preparation)



Treatment Scheme

- Policy: Selective neck irradiation + Shrinking field + SIB + Adaptive re-plan
- Dose schedule for 3 levels of target volumes:
  - GTV: 66~68.4 Gy (2.2 Gy x 18 Fxs + 2.2~2.4 Gy x 12 Fxs)
  - High-risk CTV: 60 Gy (2 Gy x 30 Fxs)
  - Low-risk CTV: 36 Gy (2 Gy x 18 Fxs)

		HPV(-) (N=35)	HPV(+) (N=115)	p
CCRT	Yes	31 (88.6%)	107 (93%)	0.476
	No	4 (11.4%)	8 (7%)	
Neck RT	Ipilat	2 (5.7%)	28 (24.3%)	0.054
	Bi → Ipsilat	17 (48.6%)	45 (39.1%)	
	Bilat	16 (45.7%)	42 (36.5%)	
GTV (mean)		36.4 ± 33.4 cc	39.7 ± 34.3 cc	0.618
TVRR* (mean)		40.2% ± 23.3%	41.5% ± 20.2%	0.742

* Tumor volume reduction rate (%) = (pre-RT GTV – mid-RT GTV)/pre-RT GTV * 100

Characteristics

		HPV(-) (N=35)	HPV(+) (N=115)	HPV unknown (N=64)	P-value
Age (mean ± SD)		62.3 ± 11.1 Yrs	59.7 ± 9.2 Yrs	59.3 ± 10.1 Yrs	0.294
Gender	Male	30 (85.7%)	100 (87%)	53 (82.8%)	0.748
	Female	5 (14.3%)	15 (13%)	11 (17.2%)	
ECOG	0	1 (2.9%)	4 (3.5%)	--	0.662
	1	32 (91.4%)	106 (92.2%)	61 (95.3%)	
	2	2 (5.7%)	5 (4.3%)	3 (4.7%)	
Smoking Hx	Yes	28 (80%)	65 (58.6%)	33 (54.1%)	0.033
	No	7 (20%)	46 (41.4%)	28 (45.9%)	
Subsite	Tonsil	15 (42.9%)	89 (77.4%)	47 (73.4%)	0.001
	BOT	13 (37.1%)	24 (20.9%)	14 (21.9%)	
	Soft palate	3 (8.6%)	2 (1.7%)	2 (3.1%)	
	Etc.	4 (11.5%)	--	1 (1.6%)	
Tumor size (mean)		3.1 ± 1.5 cm	2.9 ± 1.3 cm	2.9 ± 1.1	0.571
LN size (mean)		2.6 ± 1.0 cm	2.8 ± 1.2 cm	2.6 ± 1.2	0.390
Involved LNs	None	5 (14.3%)	7 (6.1%)	6 (9.4%)	0.545
	Single	5 (14.3%)	24 (20.9%)	14 (21.9%)	
	Multiple	25 (71.4%)	84 (73.0%)	44 (68.8%)	

Treatment Scheme

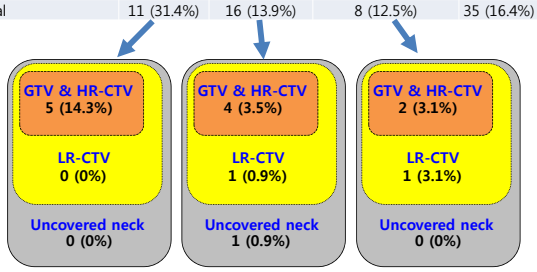
- Shrinking field + SIB
- Routine adaptive re-plan during RT course
- Dose schedule for 3 levels of target volumes:
  - GTV: 66~68.4 Gy (2.2 Gy x 18 Fxs + 2.2~2.4 Gy x 12 Fxs)
  - High-risk CTV: 60 Gy (2 Gy x 30 Fxs)
  - Low-risk CTV: 36 Gy (2 Gy x 18 Fxs)

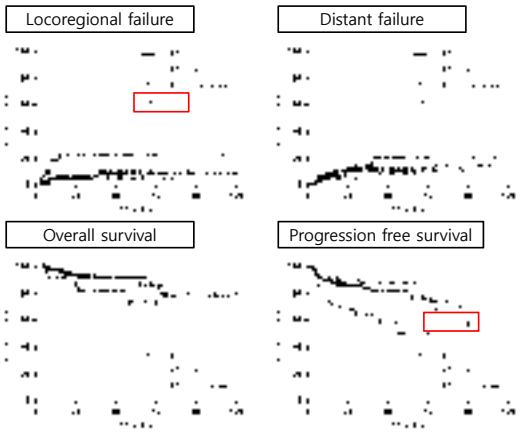
		HPV(-)	HPV(+)	p
CCRT	Yes	21 (91.3%)	64 (92.8%)	0.820
	No	2 (8.7%)	5 (7.2%)	
Neck RT	Ipilat	--	12 (17.4%)	0.056
	Bi → Ipsilat	10 (43.5%)	10 (46.4%)	
	Bilat	13 (56.5%)	25 (36.2%)	
TVRR*		34.5% ± 18.6%	43.0% ± 18.0%	0.062

* Tumor volume reduction rate (%) = (pre-RT GTV – mid-RT GTV)/pre-RT GTV * 100

Sites of 1st Failure (Med FU=35 months)

	HPV(-) (35)	HPV(+) (115)	HPV unknown (64)	Total
Local	2 (5.7%)	1 (0.9%)	--	3 (1.4%)
Local + Regional	**2 (5.7%)**	**2 (1.7%)**	**2 (6.2%)**	**6 (2.8%)**
Regional	**3 (8.6%)**	**3 (2.6%)**	**1 (3.1%)**	**7 (3.3%)**
Regional + Distant	**--**	**1 (0.9%)**	**--**	**1 (0.5%)**
Distant	4 (11.4%)	9 (7.8%)	5 (7.8%)	18 (8.4%)
Total	11 (31.4%)	16 (13.9%)	8 (12.5%)	35 (16.4%)





Conclusions

- Favorable locoregional control
- Infrequent outside the GTV/HR-CTV failure

➢ Current SNI policy seems successful, both in HPV+ and HPV- patients.

➢ Additional effort to improve LRC in HPV- patients may be necessary.

My conclusions

- Stage assignment is important to help clinicians in predicting prognosis, determining Tx modality, and communicating with others (geographically) as well as with selves (temporally).
- AJCC 8th Ed, however, seems based mainly on prognosis with little respect to Tx modality.
- Tx modality had better be determined based on 7th Ed, as applied to current NCCN guidelines.

My conclusions

- De-intensification in mainly surgical or chemotherapeutic options should be considered very cautiously considering added toxicity and cost.
- De-intensification in mainly RT option should include reduction of dose and/or volume and reduction (or omission) of concurrent chemotherapy intensity.
- Further detail needs refinement!

Epidemiology & vaccination of HPV: Worldwide vs. Korean

이 세 영

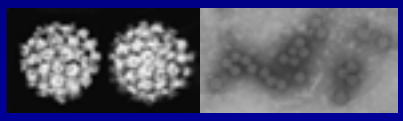
중앙대학교 의과대학 이비인후과학교실

Epidemiology & Vaccination of HPV : Worldwide vs. Korean

Sei Young Lee, M.D.
Dept. of Otolaryngology-Head and Neck Surgery
Chung-Ang University College of Medicine

What is a human papillomavirus(HPV)?

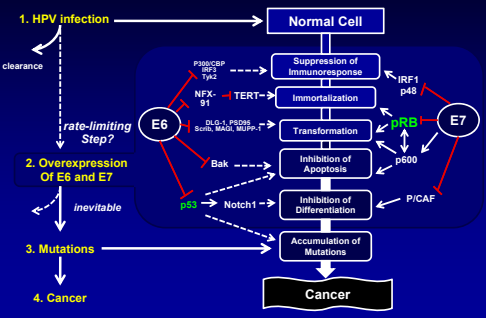
- Papillomaviridae family
- Non-enveloped double-stranded DNA virus
- More than 200 different genotypes
- Specific tropism to epithelial cell



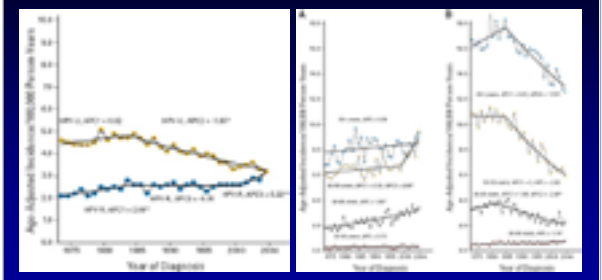
Carcinogenic effect of HPV

- International Agency for Research on Cancer(IARC) classified HPV 16 and 18 as 'oncogenic' in *1995*
- Clinically relevant HPV-mediated diseases include anogenital warts, cervical cancer and/or cervical intraepithelial neoplasia (CIN), and recurrent respiratory papillomatosis (RRP), as well as head and neck and penile cancers

Summary of carcinogenesis



Why HPV comes into spotlight?



Chatuvedi at al. J Clin Oncol 2008

Current HPV detecting methods

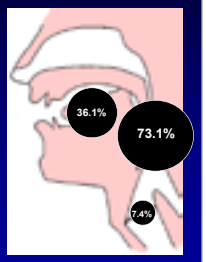
- Detecting HPV viral DNA
  - Target amplification method : PCR
  - Signal amplification method : ISH
- Detecting mRNA : RT-PCR (real time RT-PCR)
- Detecting protein : p16 IHC

HPV in HNSCC

- Detection rate of HPV in OPSCC: 50% or more
  - increased viral access to basal mucosal cell in the tonsillar crypt
  - apparent predilection of OPx to transformation by HPV
- OPSCC is the second most common HPV-associated cancer in the USA, and it is anticipated that, by the year 2020, OPSCC will surpass the cervical cancers

HPV Prevalence in Head and Neck Cancer (Korean data)

	PTC	GC	TC	Total
Number	52	94	36	182
HPV prevalence	38 (73.1%)	7 (7.4%)	13 (36.1%)	58 (31.9%)
HPV-16 prevalence	34 (89.5%)	3 (42.9%)	11 (84.6%)	48 (82.8%)
HPV-16 Integration state	32 (94.1%)	1 (33.3%)	6 (54.5%)	39 (81.3%)
HPV prevalence in control	8/61 [1] (11.6%)	0/15 [2] (0)	1/25 [3] (4%)	9/101 (8.91%)
Significance of HPV association with cancer	*P*<0.0001	*P*>0.05	*P*>0.05	*P*<0.001

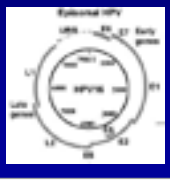


Prevention of HPV-associated HNSCC

- Primary prevention (Vaccination)
  - to prevent initial infection
- Secondary prevention
  - to detect and treat subclinical disease
- Tertiary prevention
  - to prevent cancer recurrence

Primary Prevention – HPV Vaccination

- HPV vaccine was introduced as a preventive method for HPV related disease
- HPV vaccine contains HPV type specific virus-like particle(VLP) and VPLs induce immune responses as a antigen



Effects of HPV Vaccination

- Phase III clinical trials have demonstrated a significant reduction in the incidence of HPV 16/18 anogenital infections, genital warts and cervical and anal precancerous lesion
- The Advisory Committee on Immunization Practices recommendation: female patients aged 9 to 26 years and male patients aged 13 to 21 years

Current Status of HPV Vaccination

- 74 countries have implemented the HPV vaccination in the national immunization schedule - *2017*
- Quadrivalent vaccine : HPV 6/11/16/18, *2006*
- Bivalent vaccine : HPV 16/18, 2007
- Second-generation nonavalent vaccine : HPV 6/11/16/18/31/33/45/52/58, *2014*

4 Issues of HPV Vaccination for HNSCC

(1) Insufficient evidence for clinical efficacy

- There is a time lag between HPV vaccine and the occurrence of cancers
- Vaccinated individuals should be protected against HPV oral infection, however the effect of the vaccine on oral HPV infection is still poorly documented.

4 Issues of HPV Vaccination for HNSCC

(2) Low vaccination rate

- HPV vaccination rate of most countries is less than 50% in the targeted age groups (< 30% in USA)
- These rates are too weak to induce herd immunity
- Safety issues : complex regional pain syndrome(CRPS) and postural orthostatic tachycardia syndrome(POTS) were reported in 2013 with Japan, Denmark and Holland

4 Issues of HPV Vaccination for HNSCC

(3) Short duration of HPV vaccine efficacy

- Genital infection occurs 2~5 years after the onset of sexual activity, whereas oral HPV testing peaks about a decade later
- Vaccine-induced immunity has to be maintained for at least 2~3 decades
- However, vaccine efficacy over such a long period is unknown

4 Issues of HPV Vaccination for HNSCC

(4) Pre-vaccination population

- The vast majority of the population has not been vaccinated because they were already outside of the recommended age range
- Need for the development of secondary prevention measures

Secondary Prevention

- To detect a disease in its earliest stages of development before symptoms
- To stop progression of disease with more lighter and less invasive treatment methods
- The effect of secondary prevention has been well known in the uterine cervical cancer

Who Should Be Screened?

- Incidence of HPV-driven OPSCC: <10 per 100,000
- Identification of higher risk group is needed
  - Men age 55 to 65 with certain behavioral features
  - Partners of patients with an HPV-driven malignancy

Tertiary Prevention

- To prevent HPV-driven OPSCC recurrence
- Traditional post-Tx follow-up

Treatment-related aftereffect → Delayed detection of recurrence → Poor outcome of recurred patients

- Biomarkers can detect recurrence before the development of any clinical or radiological evidence of recurrence

Tertiary Prevention - Biomarkers

Unique oncogenesis of HPV(+) cancer

- HPV(+) cancers express the viral DNA continuously
- Adaptive immune response against viral antigen
- HPV DNA in body fluid and Ab against the viral oncoprotein E6/E7 might be used as tumor biomarkers

What's new in surgical approach?

고 윤 우

연세대학교 의과대학 이비인후과학교실

구인두암의 수술 기법은 병기, 해부학적 위치, 환자 특성 (나이, 직업, 일반적인 건강, 병적 상태의 존재), HPV 상태, 환자 및 임상의사의 선호도 등 다양한 요인에 따라 달라진다.

각 기관마다의 경험있는 술자와 이용가능한 수술 장비 또한 중요한 고려 사항이다.

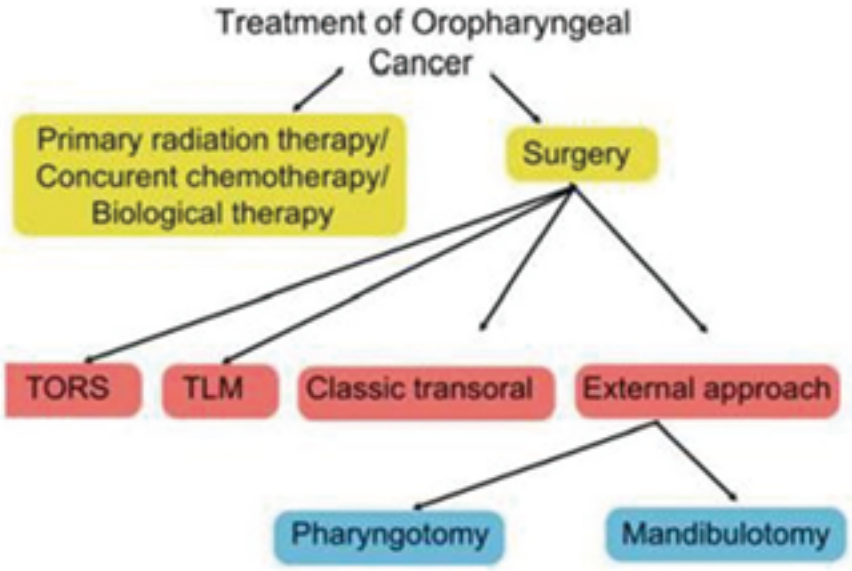


Fig. 1. Scheme of treatment of oropharyngeal cancer.

구인두암의 수술은 Open 또는 Transoral Approach로 크게 나눌 수 있다. Open approach는 일반적으로 mandibulotomy 혹은 pharyngotomy를 이용하며, Transoral approach에는 classic transoral surgery with monopolar cautery, TLM (Transoral Laryngeal Microsurgery), TORS (Transoral Robotic Surgery) 등 다양한 술식이 이용되고 있다. Open approach는 주로 진행성 구안두암(Satge III 또는 IV) 혹은 Salvage surgery로 사용되지만 일부 초기 병기 구인두암의 경우에는 Transoral approach를 통한 수술적 절제가 가능하다.

Selection of the Surgical Technique

구인두의 복잡한 해부학적 구조와 기능적 중요성을 고려할 때 구인두암의 치료를 위해서 다양한 수술적 접근법이 사용되고 있다.

최근에는 방사선 치료 또는 항암-방사선 치료 실패 후 진행된 구인두암의 Salvage therapy를 위해 mandibulotomy, mandibulectomy, 혹은 pharyngotomy 등의 수술접근법 등이 사용된다.

그러나 장기간의 입원, 미용 변형, 위장관 및 기관 절개술의 의존성 등 수술관련 이환율을 낮추기위하여 최근에는 Transoral approach (경구강 접근법)을 이용한 수술적 기법의 사용빈도가 늘고 있다.

Transoral approach (경구강 접근법)을 이용한 수술적 기법(vs. open approaches)의 장점에는 빠른 회복과 짧은 입원 기간 뿐만 아니라 근육 조직과 주요 신경 혈관 구조물 및 정상 조직에 대한 손상 감소 등이 있다.

실제로 TLM (Transoral Laryngeal Microsurgery)의 등장과 최근 TORS (Transoral Robotic Surgery)는 구인두암의 초치료(initial therapy)로서 Open approaches 수술의 역할과 빈도를 감소시키고 있다.

이러한 TLM/TORS 등의 최소 침습 수술 방법(minimally-invasive surgical approaches)은 현재 구인두 내에 국한된 초기병변에 국한되지만, 일부 술자/저자들은 일부 selected advanced stage 구인두암에서도 이러한 술식의 사용이 가능함을 보고하고있다.

최근에 본 교실에서 시행하고 있는 림프절전이를 동반한 구인두암 환자에서의 로봇 경부청소술(Robotic Neck Dissection)을 포함한 TORS 등의 수술적 접근법의 술식과 최근까지의 치료성적을 소개하고자 한다.