Fred Hutch Cancer Center

Head, Neck and Thyroid Cancer

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Disclosures

- Research Funding: Bayer/Fred Hutch Fellowship in Health Economics and Outcomes Research (End 12/2024)

Mucosal Squamous Cell Carcinoma: Anatomy, pathogenesis, staging

Mucosal Squamous Cell Carcinoma: Locally Advanced

Mucosal Squamous Cell Carcinoma: Metastatic Disease

Thyroid Cancer

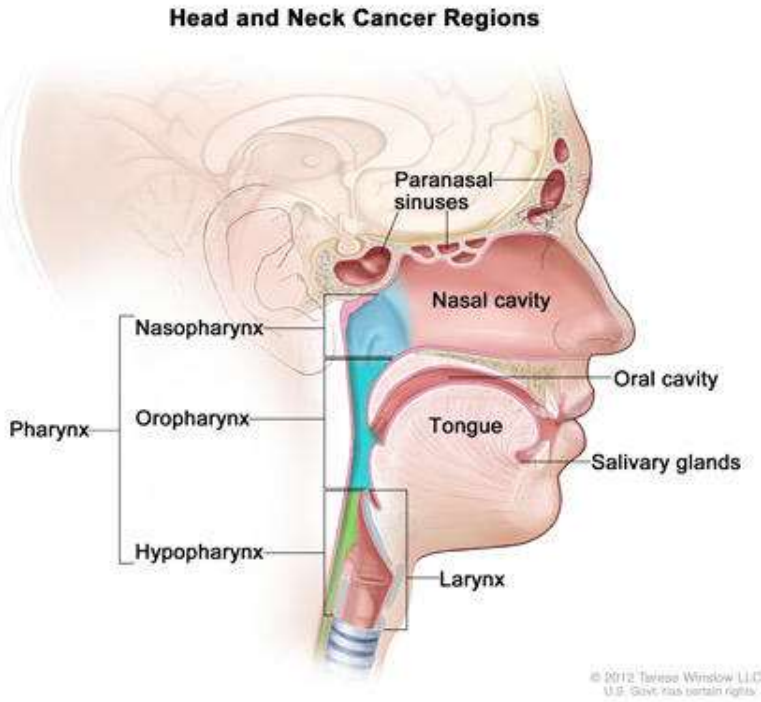
Salivary Gland Cancer

Mucosal Squamous Cell Carcinoma of the Head and Neck (HNSCC)

Anatomy
Pathogenesis
Staging

Primary Site and Anatomy Matter!

- Majority of head and neck cancers are **squamous cell carcinomas** arising from the upper aerodigestive tract (>90%)
  - *Other: glandular tumors (salivary gland), neuroendocrine*
- Primary site is important for staging, treatment, and prognosis!
  - Oral Cavity
  - Oropharynx (Base of Tongue, Tonsils)
  - Hypopharynx
  - Larynx
  - Nasopharynx
  - Nasal Cavity and Paranasal Sinus



https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet

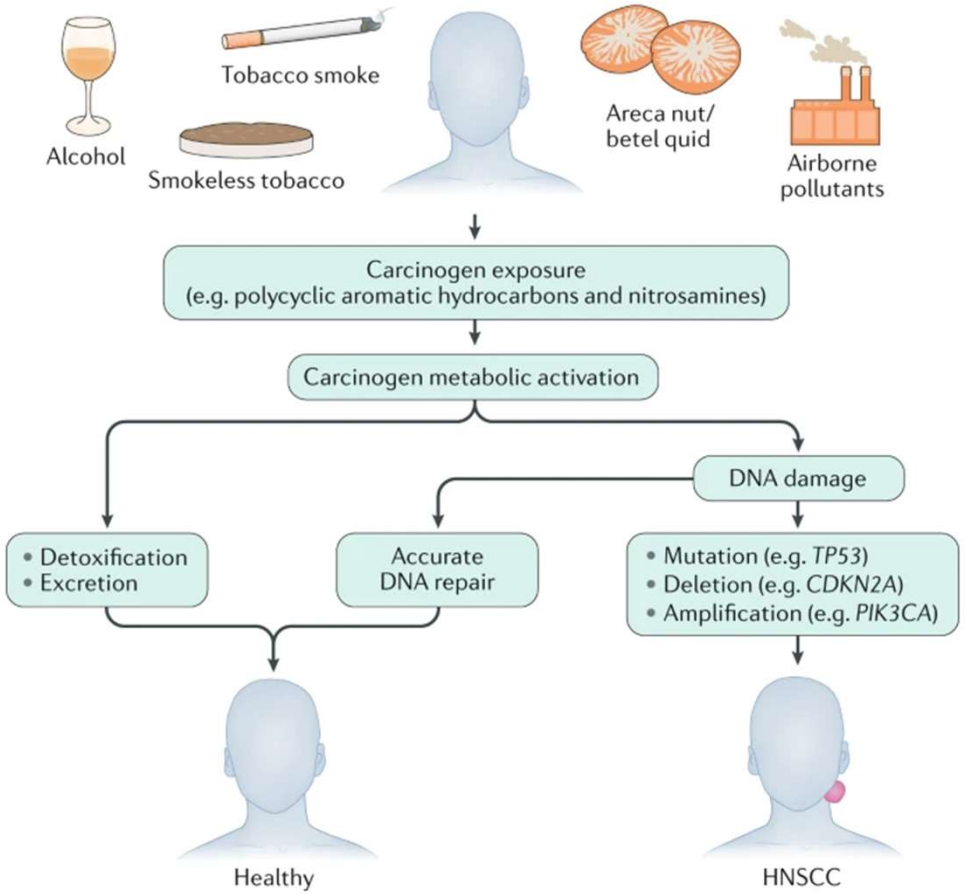
Risk Factors

- Annually 70,000 new cases and 16,000 deaths
  - Males > Females
- Exposure to carcinogens:
  - TOBACCO
  - Alcohol (synergism with tobacco)
  - Other: betel nut chewing, prior radiation, Fanconi anemia, high risk precursor lesions
  - Generally declining in incidence; ongoing racial/economic disparities
- Viral Mediators
  - EBV: Nasopharynx (endemic)
  - HPV: Oropharyngeal cancers; increasing incidence

Siegel, CA: A Cancer Journal for Clinicians, 2024

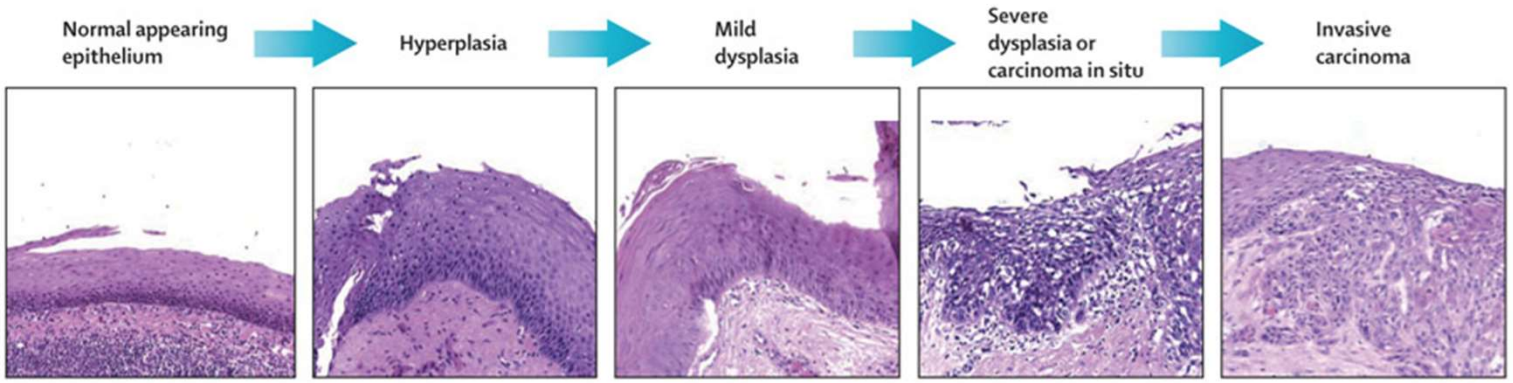
Pathogenesis

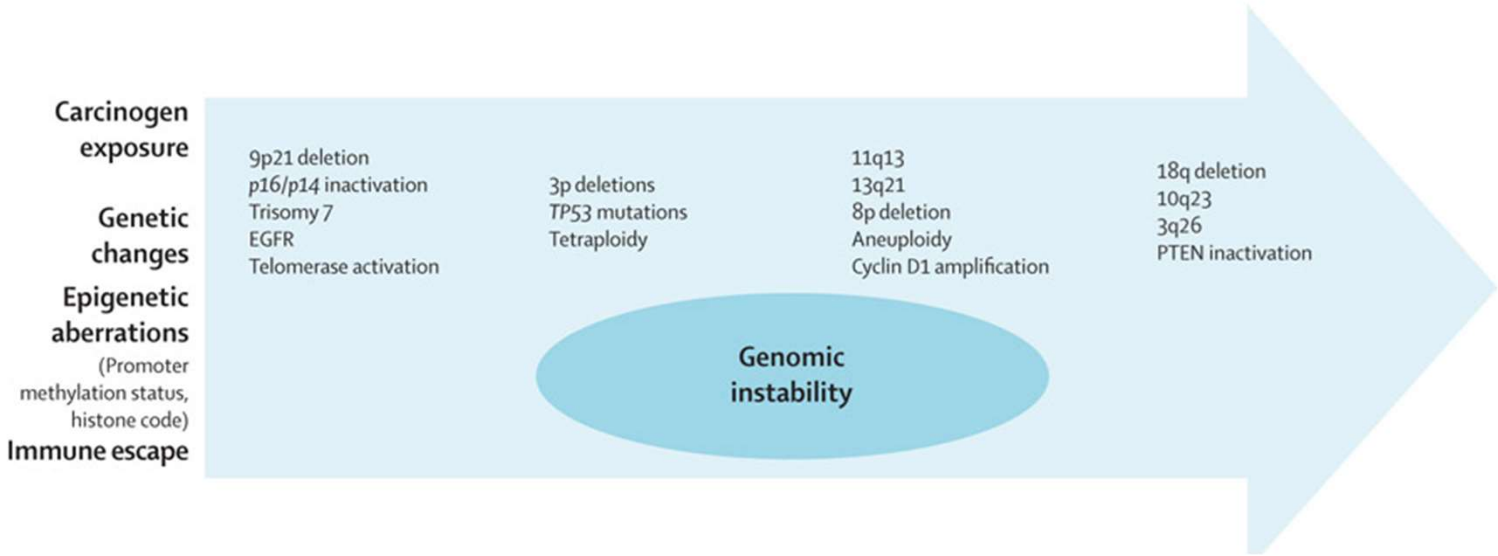
- Carcinogen Exposure
  - **Field Cancerization** effect: risk for second primary malignancy (head and neck, lung, esophagus, bladder)
  - Declining smoking → declining incidence in cancers of the oral cavity, larynx and hypopharynx



Johnson, Nature, 2020

Pathogenesis





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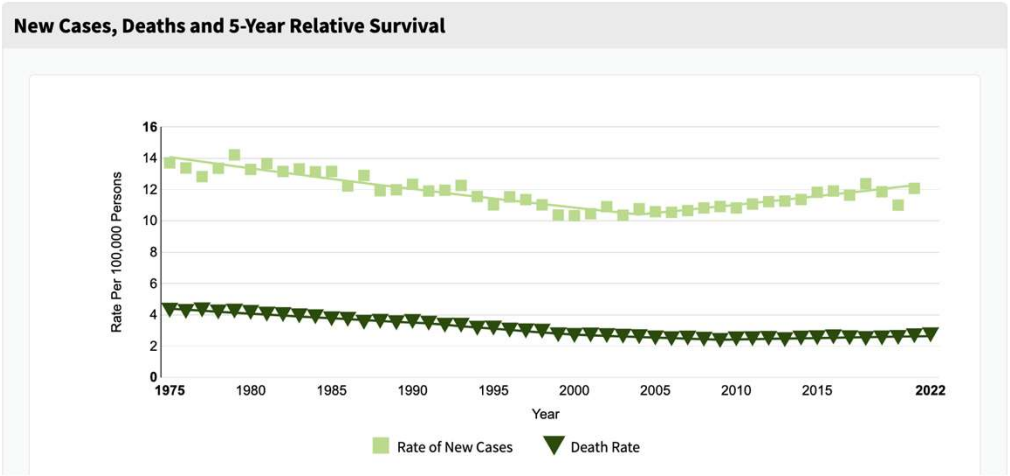
Argiris , Lancet, 2008.

HPV Mediated Cancer of the Oropharynx

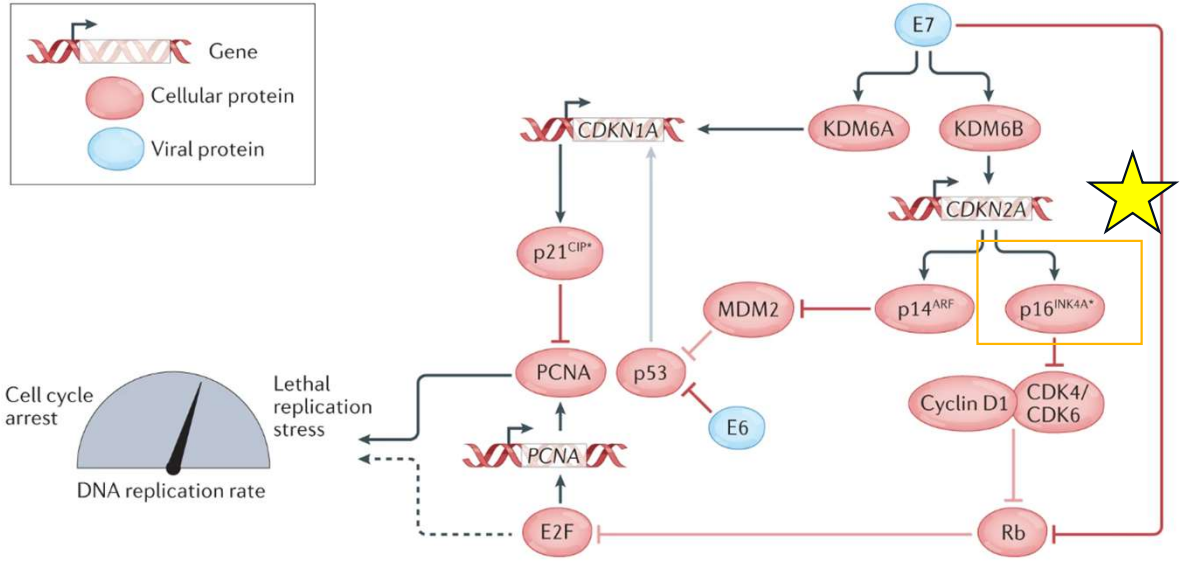
- 70% OP is HPV mediated
  - 90% related to **HPV 16**
  - HPV generally not relevant generally outside the OP
  - Rising in incidence
  - Exposure in early adulthood, cancer decades later for a minority
- Distinct demographics compared to HPV negative HNSCC
- Genetic profiling of HPV positive cancer shows distinct genetic profile from other HNSCC



SEER Cancer Stat Facts: Oral Cavity and Pharynx Cancer. National Cancer Institute. https://seer.cancer.gov/statfacts/html/oralcav.html

HPV has a causal role in OP cancer

- Viral genome integration → viral oncoproteins E6 and E7
  - E6: p53 degradation
  - E7: interacts with Rb
  - → **Upregulation of p16**



Lechner, Nature Reviews Clinical Oncology, 2022

p16 status

- Upregulation of p16 contributes to proliferation
- p16 positivity by immunohistochemistry (IHC) is a reliable surrogate marker of the presence of HPV DNA in tumors of the oropharynx only
  - p16 can be + in other sites, but not reliably correlated to HPV DNA, not prognostic: don't test in non oropharynx primaries
  - Quick turn around time, inexpensive
- p16 positivity is included in staging for the oropharynx

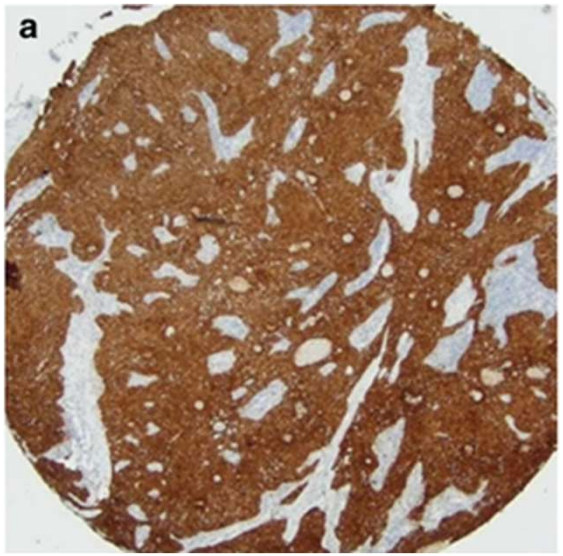
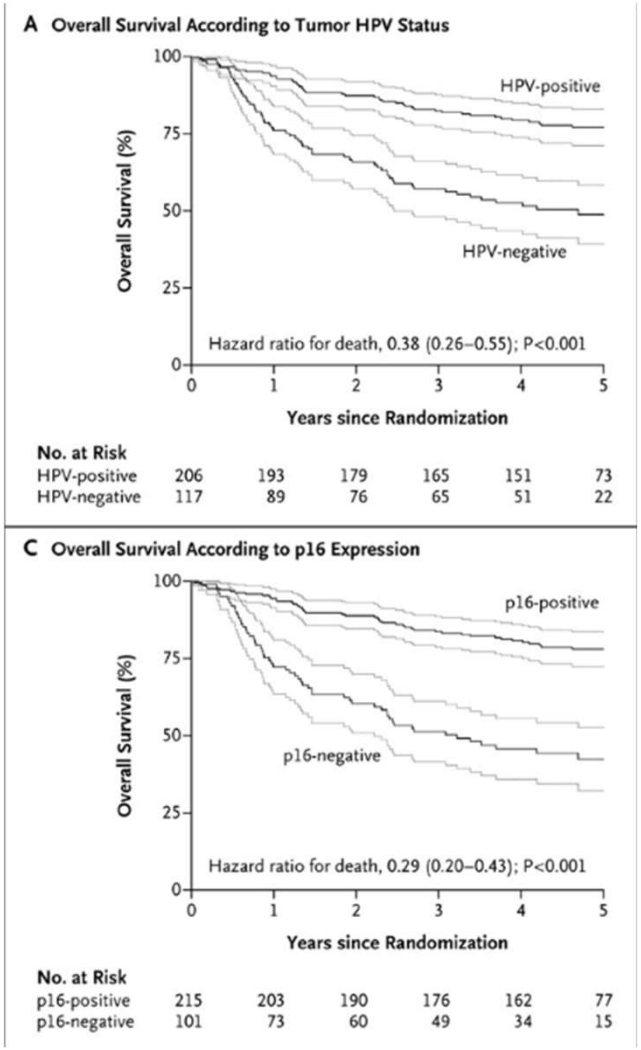


Figure: Shelton, Mod Pathol, 2017

Treatment outcomes with HPV

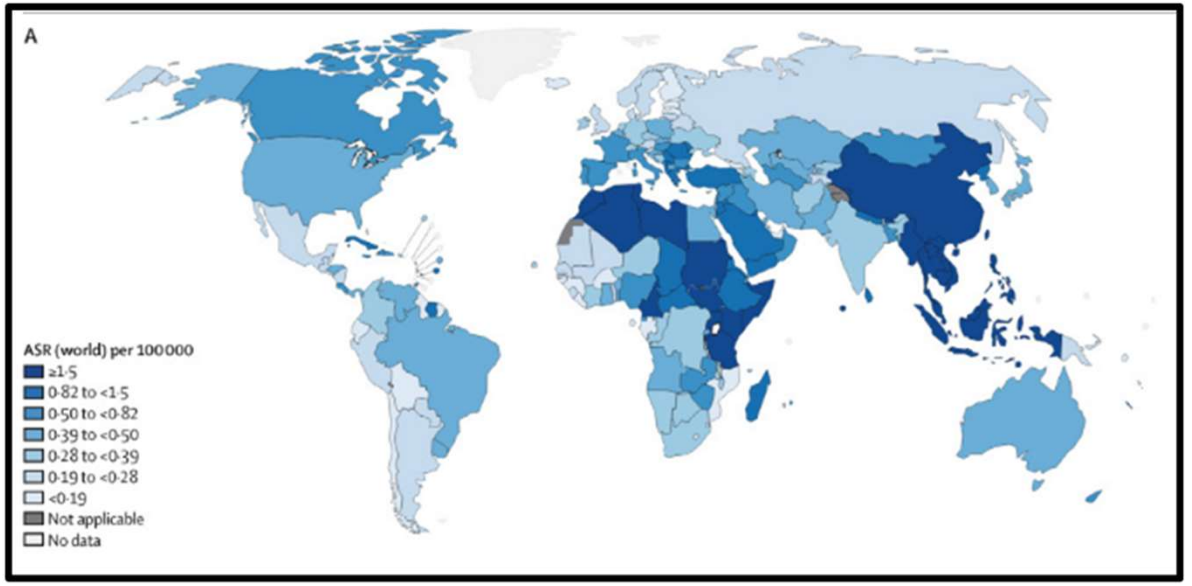
- Clinical features
  - Lower median age
  - Caucasian males
  - Common presentation with small primary, large cystic LAD
- Improved prognosis with HPV mediated HNSCC
  - Improved disease specific and overall survival
  - Improved response to treatment
  - Distinct disease biology
  - Fewer comorbidities; less likely to have second primary malignancies
  - If significant tobacco exposure, favorable prognosis is diminished



Ang, NEJM, 2010

EBV in NPC

- Distinct epidemiology
- Endemic in equatorial regions
- Endemic disease is non-keratinizing, undifferentiated, highly associated with EBV (EBER+ by ISH)
- Very rare in US; see higher proportion of keratinizing, EBER negative disease
  - Uncertain how to treat as majority of evidence is from trials done in endemic regions
- Presentation: middle ear effusions, posterior (level V) cervical adenopathy



Chen et al, Lancet 2019

Staging: General Principles

- Stage HPV+ Oropharynx and NPC separately from other mucosal HNSCC sites
- T1-2 represents a small primary; T4 invading surrounding structures
- N3 is >6 cm or has clinical/pathologic extranodal extension
- Lungs most common site for distant metastases; CT chest required to stage (PET more sensitive; consider if high risk for distant mets with bulky, low cervical adenopathy)

Staging: HPV negative HNSCC

Stage I	T1	N0	M0	20% of new diagnoses; treat with XRT or surgery 5 year OS of 70% +
Stage II	T2	N0	M0	
Stage III	T1,T2	N1	M0	
	T3	N0,N1	M0	70% of new diagnoses Require multimodal therapy (surgery -> (chemo)RT or chemoRT) 5 year OS ranges 30-50% depending on primary site
Stage IVA	T1	N2	M0	
	T2	N2	M0	
	T3	N2	M0	
	T4a	N0,N1,N2	M0	
Stage IVB	Any T	N3	M0	
	T4b	Any N	M0	
Stage IVC	Any T	Any N	M1	10% new diagnoses (metastasis is late event) Treat with palliative intent with systemic therapy Median survival <1 year

Staging: HPV+ OP

Stage I	T0,T1,T2	N0,N1	M0	Surgery or RT
Stage II	T0,T1,T2	N2	M0	chemoRT 5 year OS >80%
	T3	N0,N1,N2	M0	
Stage III	T0,T1,T2,T3	N3	M0	
	T4	N0,N1,N2,N3	M0	
Stage IV	Any T	Any N	M1	Palliative systemic therapy Improved prognosis vs HPV neg

AJCC v8

HNSCC: Locally advanced disease

Organ preservation through definitive chemoRT
Postoperative adjuvant chemoRT

Locally Advanced Disease

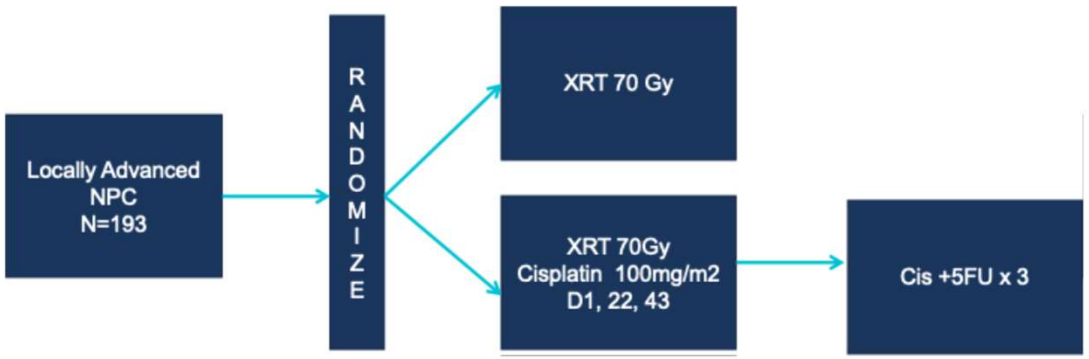
- Majority of patients; required multimodal therapy
  - Surgery and RT both curative modalities; systemic therapy alone is not curative
  - Multidisciplinary approach/evaluation
- Priorities
  - Oncologic outcomes:
    - Locoregional control (drives both long term survival and function)
    - Overall Survival
    - Disease specific survival
  - Functional outcomes
    - Treatment has large impact on physiologic function, senses, cosmesis

Locally Advanced Disease

- Surgery:
  - Preferred for management of oral cavity disease (reconstruction is possible with good functional outcomes)
  - Increasing use of TransOral Robotic Surgery (TORS) for cancers of the oropharynx
- Definitive Radiation
  - Allows for organ preservation in carefully selected patients

Nasopharynx Cancer

- Early use of organ preservation therapy; established curative intent standard for North America



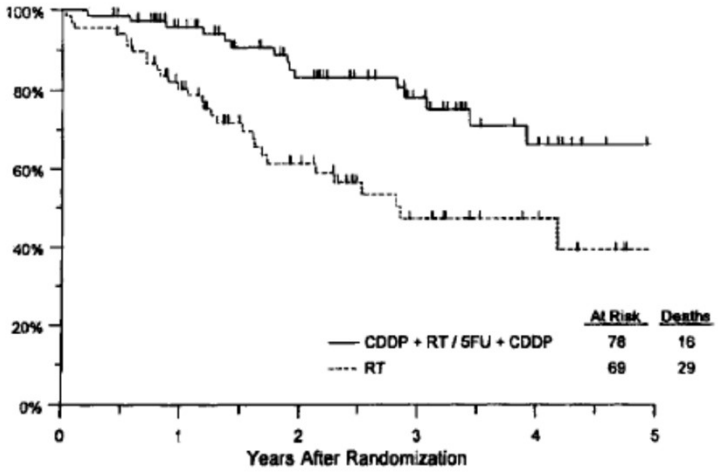
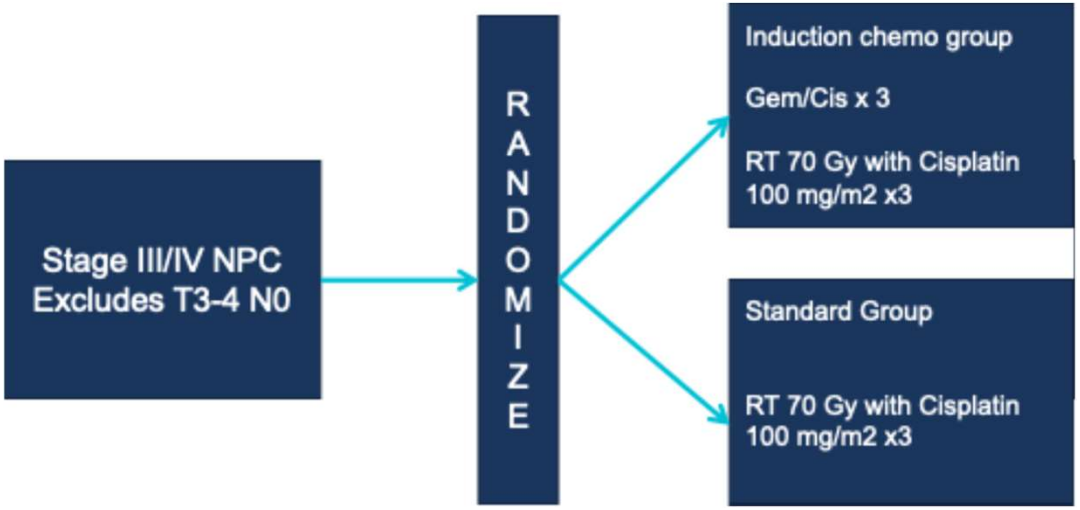


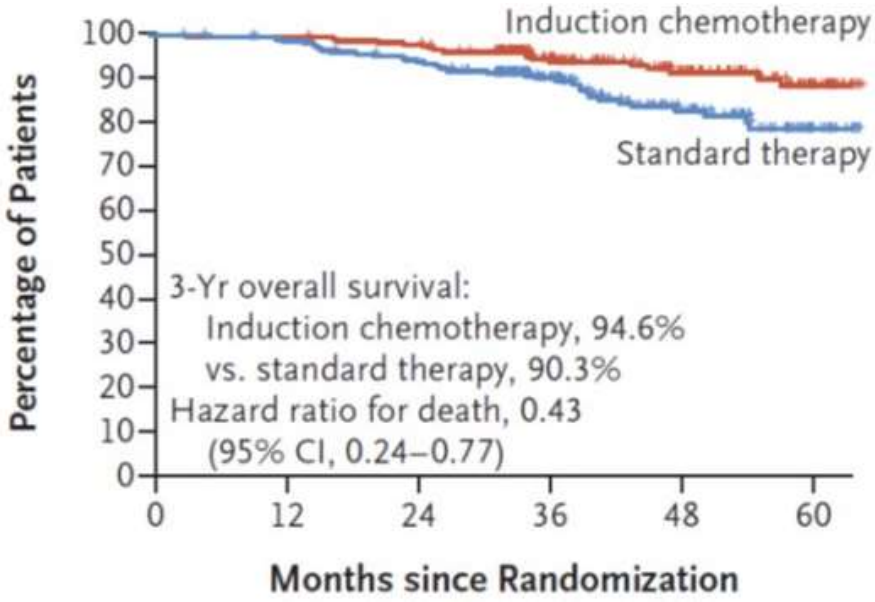
Fig 2. Overall survival for completely eligible patients on RT only and combined CT/RT (----).

- Subsequent studies in endemic area did not find benefit to adjuvant cis/5FU after definitive chemoRT

Al-Sarraf et al, JCO 1998

Induction Chemotherapy for LA NPC





Zhang et al. N Engl J Med. 2019

NPC: Areas of Investigation

- Revisiting adjuvant therapy with non cis/5FU regimens
  - Metronomic capecitabine following definitive therapy improves OS and FFS (Chen 2021)
  - How to apply to patients who received Gem/Cis Induction
- Incorporating immunotherapy into locally advanced setting
  - Decreasing cisplatin exposure

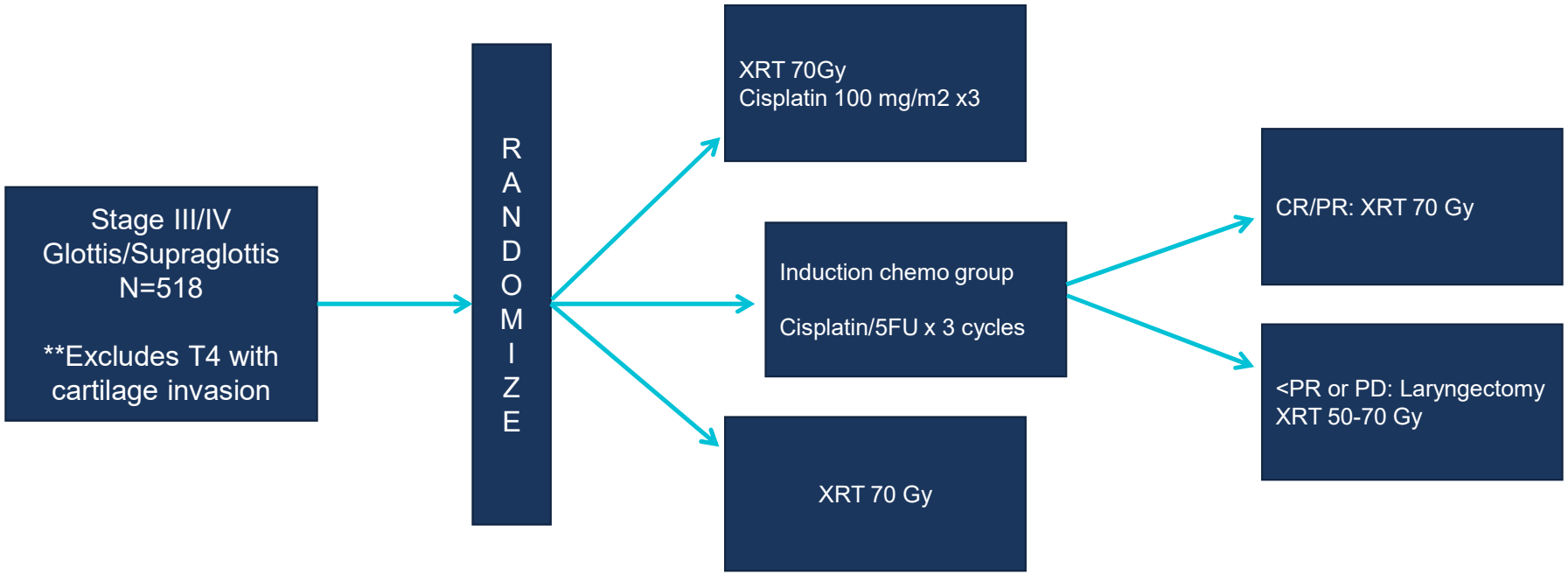
Chen et al, Lancet Oncology 2021

Organ Preservation: Larynx

- Historic standard of care: laryngectomy
- VA Larynx Trial
  - Randomized to surgery and RT vs induction chemotherapy followed by RT (if PR/CR)
  - 64% in experimental arm had organ preservation; OS similar (success of salvage surgery if failure)

VA Larynx Study Group, NEJM 1991

Larynx Preservation: RTOG 91-11



Forastiere, NEJM 2003

RTOG 91-11

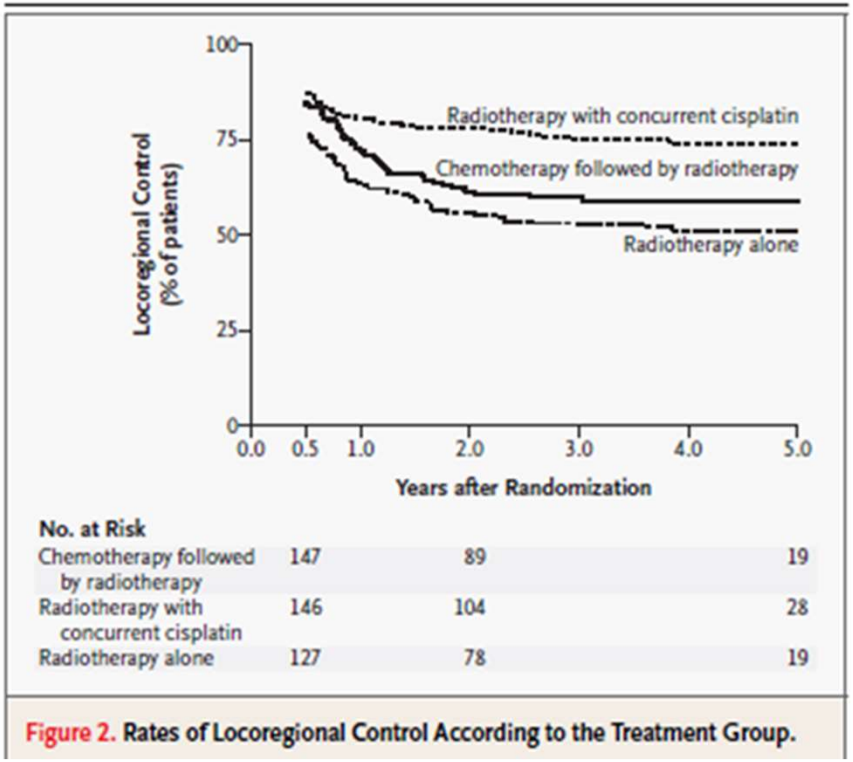


Figure 2. Rates of Locoregional Control According to the Treatment Group.

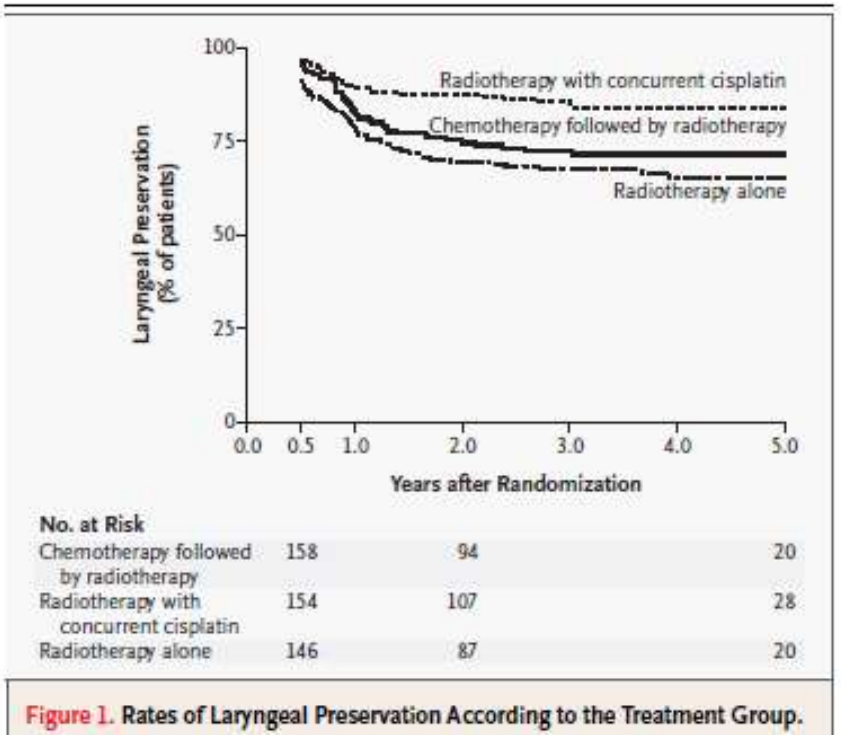
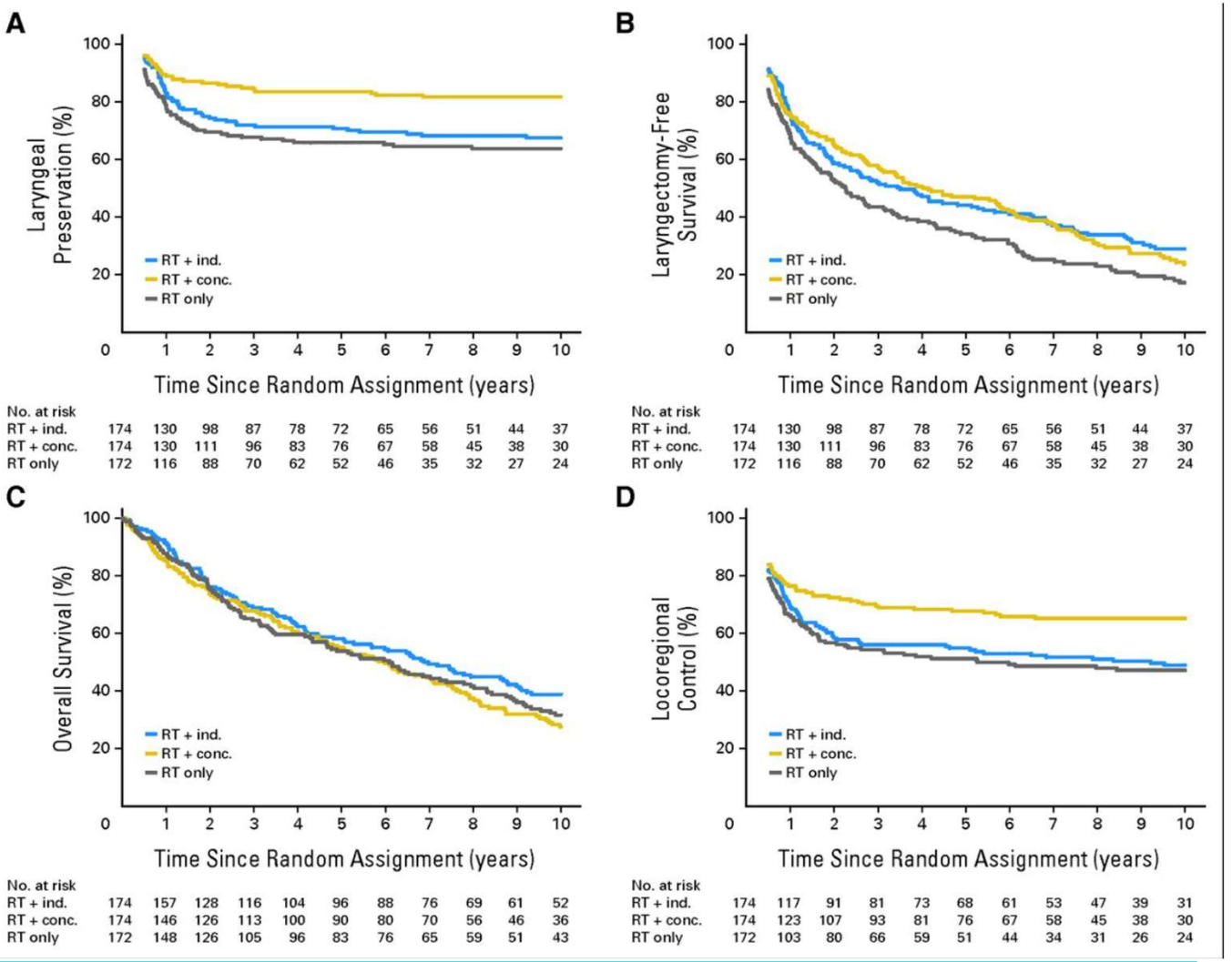


Figure 1. Rates of Laryngeal Preservation According to the Treatment Group.

Forastiere, NEJM 2003

RTOG 91-11

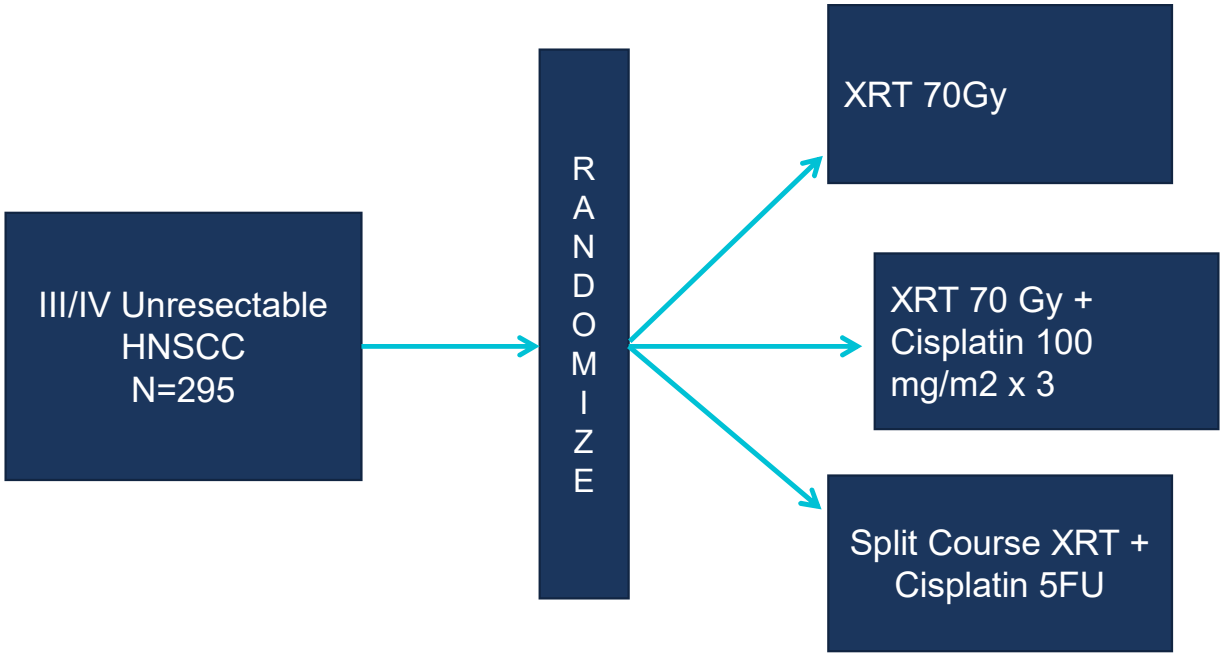
- Long term follow up
- No OS differences
  - Salvage surgery



Forastiere, JCO 2012

Organ Preservation: Intergroup Study

- Can we have organ preservation in other sites?
- Unresectable HNSCC (oral cavity, oropharynx, larynx, hypopharynx)



Adelstein, JCO 2003

Intergroup Study

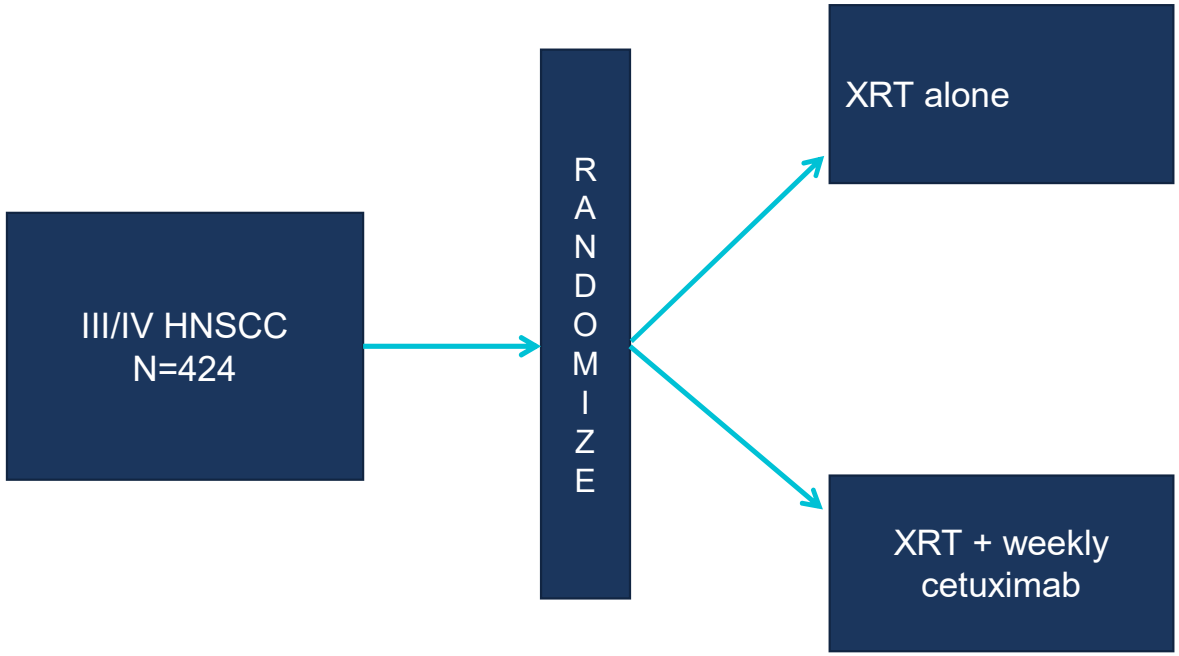
	XRT	Cisplatin + XRT	Split XRT + cis/5FU
3 year OS	23%	**37% (vs XRT, p=0.014)**	27%
3 year DSS	33%	**51% (vs XRT, p=0.01)**	41%
Distant Failure	18%	22%	19%
G3+ Toxicity	51%	**85% (vs XRT p<0.001)**	**72% (vs XRT p<0.001)**

- Addition of cisplatin concurrent with RT improves survival, but increases toxicity significantly

Adelstein, JCO 2003

Organ Preservation: Bonner Study

- Can we avoid cisplatin?



Bonner, NEJM 2006

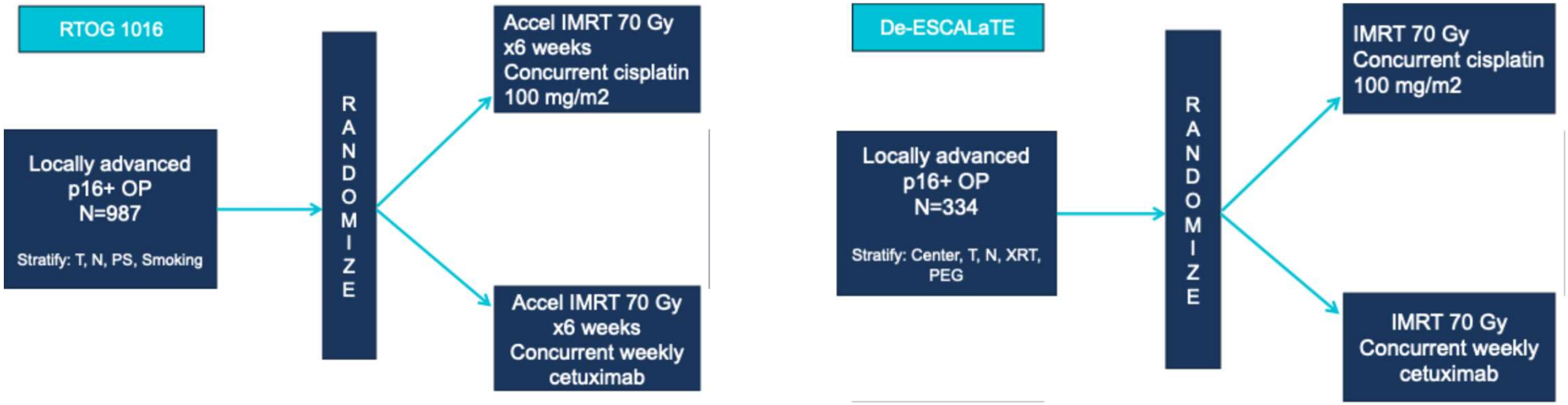
Bonner Trial

- Locoregional control, PFS, and OS improved with XRT + Cetux over RT alone; no change in toxicity compared to XRT alone
- No improvement in distant failures with cetuximab
- BUT, trial was controversial given XRT was known to be inferior to chemoRT
- Subsequent testing:
  - 60% had oropharynx primaries; patients with HPV positive disease seemed to benefit more

Bonner, NEJM 2006
Rosenthal JCO 2016

Organ Preservation: p16+ Oropharyngeal Carcinoma

- Can we de-escalate from cisplatin in p16+ patients who have better prognosis?



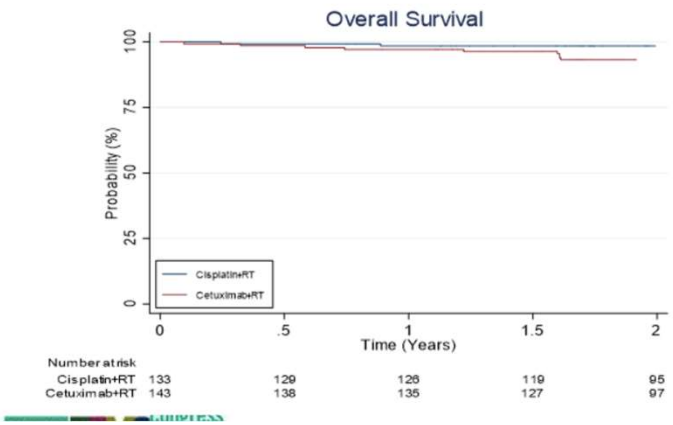
Gillison, Lancet 2019
Mehanna, Lancet 2019

Results

- Both trials show that cisplatin + RT had **superior OS** and locoregional control
- Even in lowest risk patients, improvement with cisplatin
- No difference in acute/late toxicity
- De-escalation remains a research question

TNM 8TH EDITION TNM I/II (REMOVE T4/N3)

Very low risk population



2 yr OS
98.4%
vs
93.2%

Hazards Ratio:
4.27
95% CI: 0.92 to 19.75

Log rank p-value = 0.043

Gillison, Lancet 2019
Mehanna, Lancet 2019

Alternative Cisplatin Dosing?

- CONCERT Study, ASCO 2022
  - Phase III multi-center study in India comparing weekly (40 mg/m2) and bolus cisplatin (100mg/m2 x3) in definitive chemoRT
  - 2 year locoregional control was similar in both arms (60% vs 55%)
  - Median OS similar (25 months vs 30 months)
  - Toxicity favors weekly; decreased hospitalizations in weekly
  - Not reflective of US population/treatment experience
    - Very few p16+ patients, 20% PS 2; 2D RT; treatment interruptions common
- TROG 12.01: Randomized Phase III of low risk p16+ OPC
  - Cisplatin 40 mg/m2 weekly with XRT vs cetuximab weekly with XRT
  - Primary endpoint: symptom severity
  - Improved failure free survival in cisplatin arm, OS similar
  - No difference in toxicity
- Ongoing NRG Trial evaluating cisplatin dosing for both p16+ and HPV neg HNSCC

Functional Imaging After Definitive ChemoRT

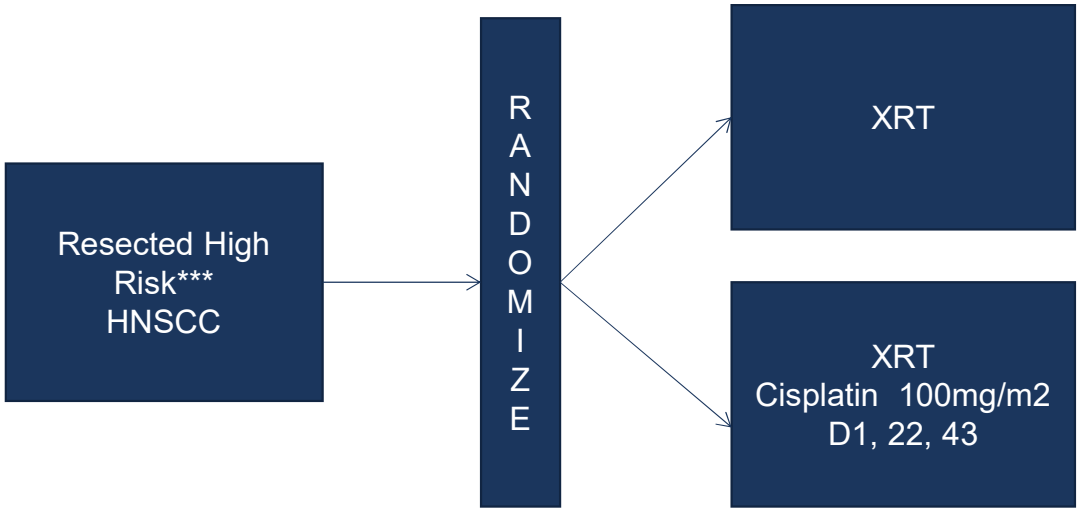
- SOC used to include planned neck dissection for bulky nodal disease after definitive chemoRT
- PET-NECK randomized 564 pts to ND vs. surveillance with PET-CT 12wk post chemoRT
  - If PET showed non avid LN < 1 cm → observation
- Less neck dissections done in exp arm, no difference in OS

Mehanna et al. N Engl J Med 2016

Organ Preservation: Summary

- Definitive chemoRT is a therapeutic approach for patients to allow for organ preservation or in the setting of unresectable disease
  - Cisplatin with concurrent RT is supported by multiple studies
  - Cetuximab with concurrent RT is inferior to cisplatin for HPV+ Oropharynx Cancer
  - Neoadjuvant Gem/Cis for NPC with bulky LAD
  - PET can help guide need for neck dissection post chemoRT
- Patient selection is key!
  - Not all patients are appropriate for organ preservation: significant toxicity; exclusion criteria

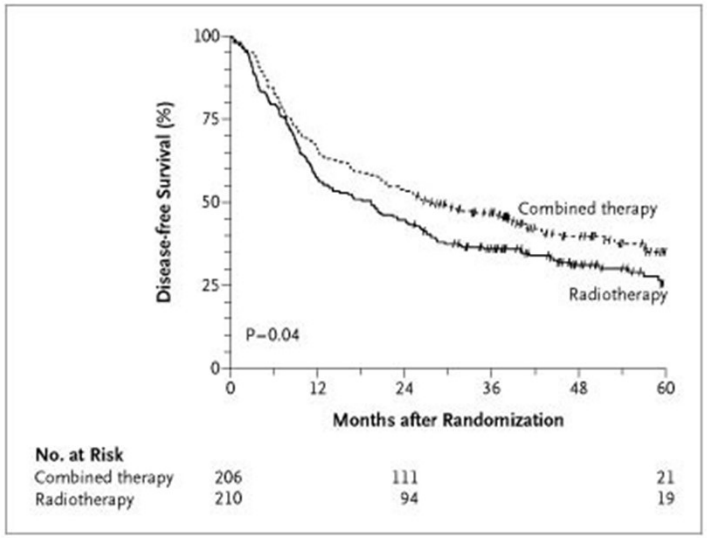
Postoperative Therapy: RTOG and EORTC Studies

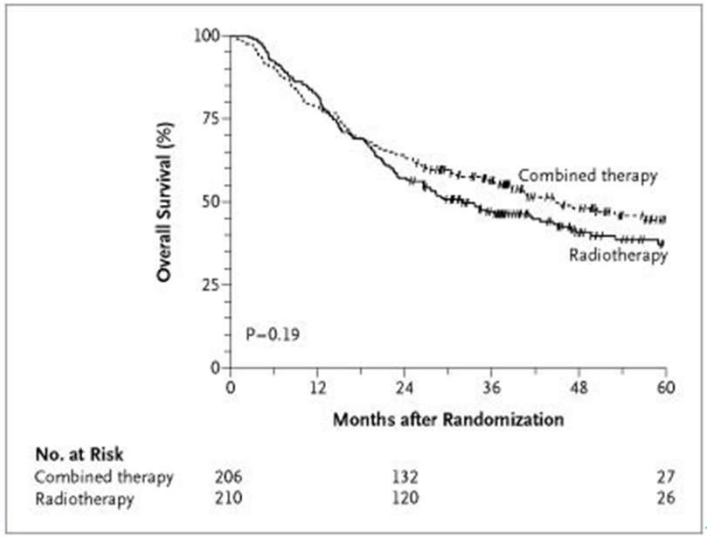


*** Eligibility criteria varied in 2 studies

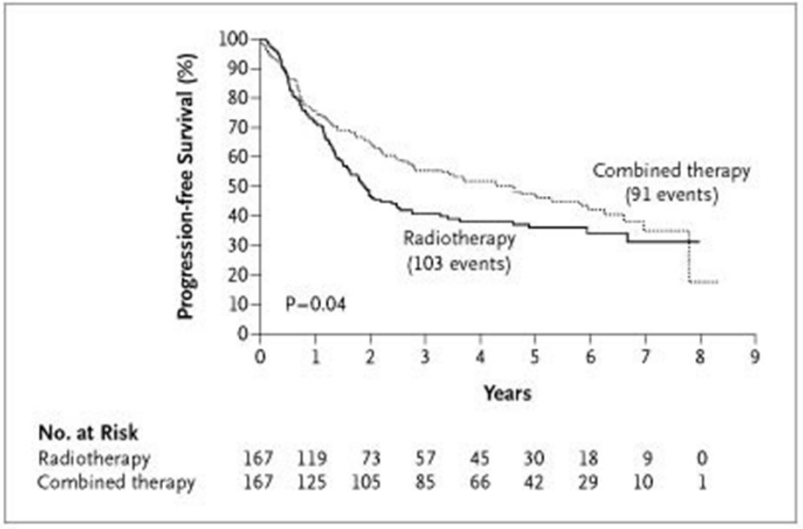
Bernier et al. NEJN 2004
Cooper et al. NEJM 2004

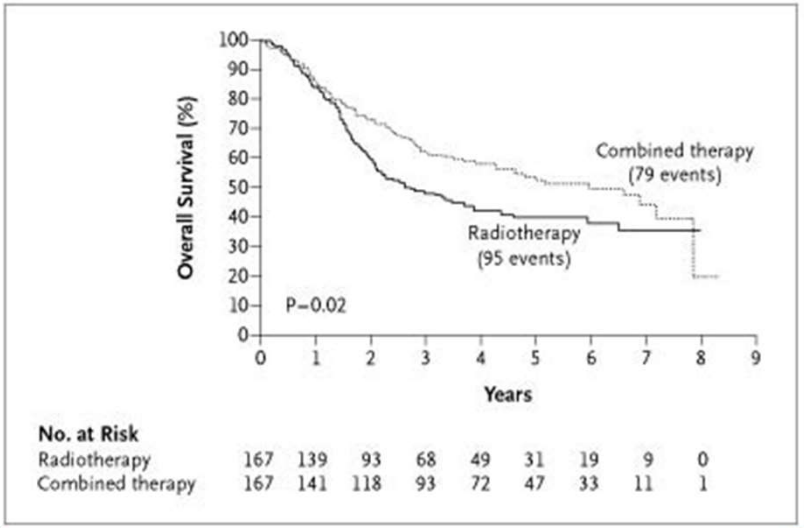
RTOG 9501





EORTC 22931





Bernier, NEJM, 2004
Cooper, NEJM, 2004

Pooled Analysis

- Overall survival advantage to cisplatin + XRT for either **positive surgical margin** or **extranodal extension**

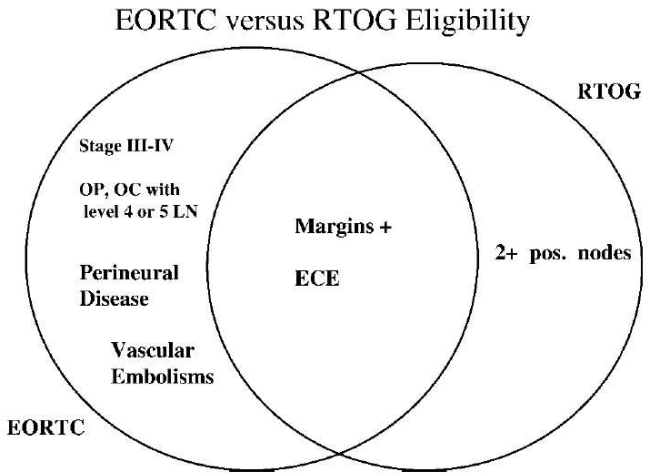


FIGURE 1. Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.

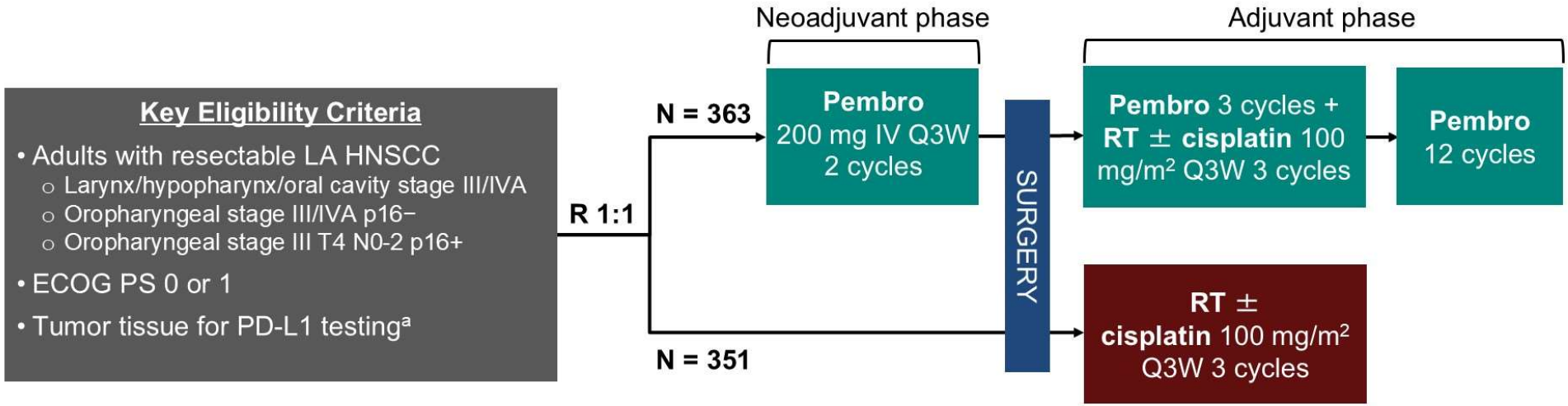
Bernier, Head Neck, 2005

Alternative Cisplatin Dosing in the Adjuvant Setting?

- JCOG 1008
  - Phase II/III multi-center, non-inferiority study in Japan comparing cisplatin dosing in adjuvant chemoRT
  - Weekly 40 mg/m2 vs bolus 100 mg/m2 x3 with RT
  - Similar OS
  - Weekly: less neutropenia/infection/renal/ototoxicity; more thrombocytopenia
- Weekly cisplatin is now used as a therapeutic standard in an ongoing US cooperative group trial in the adjuvant setting

Kiyota, JCO, 2022

KEYNOTE-689 Study (NCT03765918)



Stratification factors

- Primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx)
- Tumor stage (III vs IVA)
- PD-L1 TPS[a] (≥50% vs <50%)

Primary endpoint: EFS per RECIST 1.1 by BICR

Key secondary endpoints: Major pathological response by BIPR (mPR; ≤10% residual invasive SCC in resected primary tumor + all sampled regional lymph nodes), OS

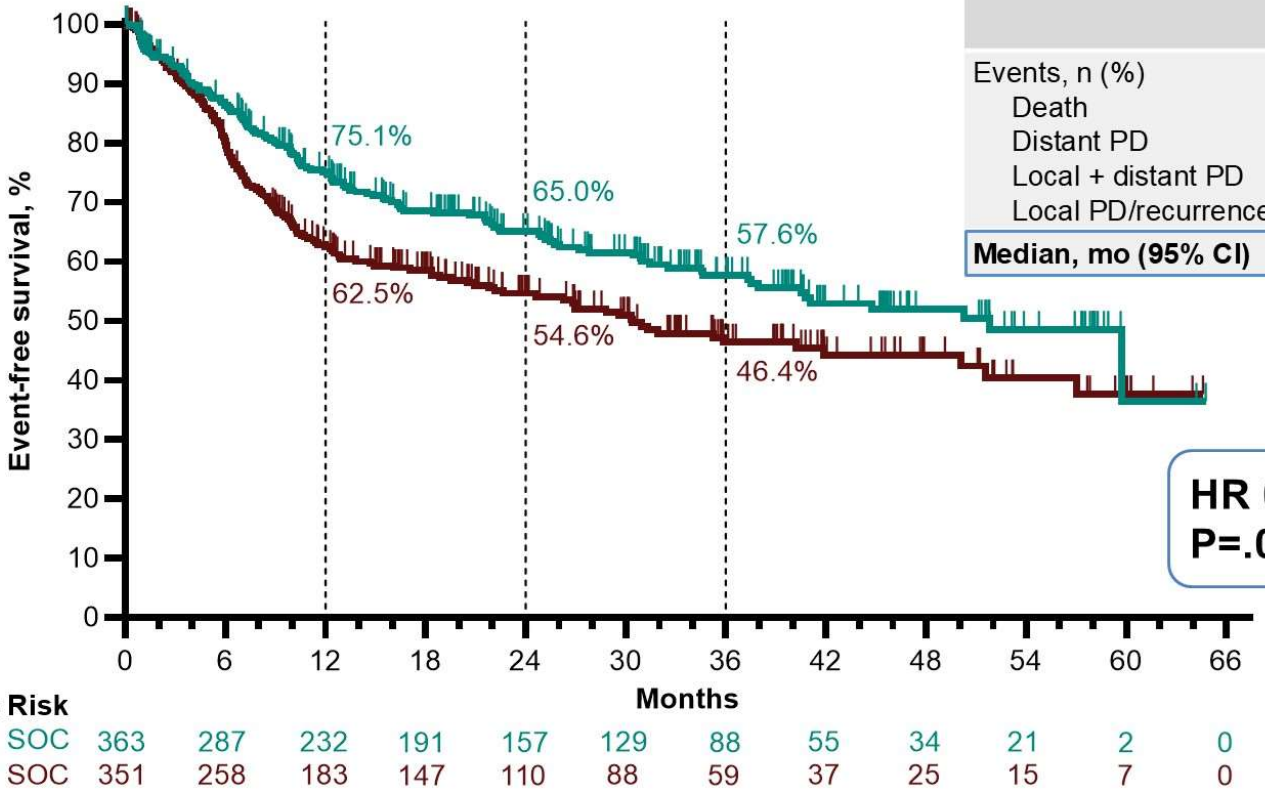
Other secondary endpoints include: Safety

Exploratory endpoints include: Locoregional failure rate, DMFS, second cancers

BICR, blinded independent central review; BIPR, blinded independent pathologist review; DMFS, distant metastasis-free survival; EFS, event-free survival; OS, overall survival; RT, radiation therapy.
[a]Assessed by PD-L1 IHC 22C3 pharmDx; TPS=% tumor cells with membranous PD-L1 staining.

Uppaluri et al, AACR 2025
Adkins et al, ASCO 2025

EFS by BICR,[a] All Participants



	Pembro + SOC (N = 363)	SOC (N = 351)
Events, n (%)	136 (37.5)	159 (45.3)
Death	67 (18.5)	64 (18.2)
Distant PD	26 (7.2)	51 (14.5)
Local + distant PD	4 (1.1)	7 (2.0)
Local PD/recurrence	39 (10.7)	37 (10.5)
Median, mo (95% CI)	**51.8 (37.5–NR)**	**30.4 (21.8–50.1)**

HR 0.73, 95% CI 0.58–0.92, P=.0041*

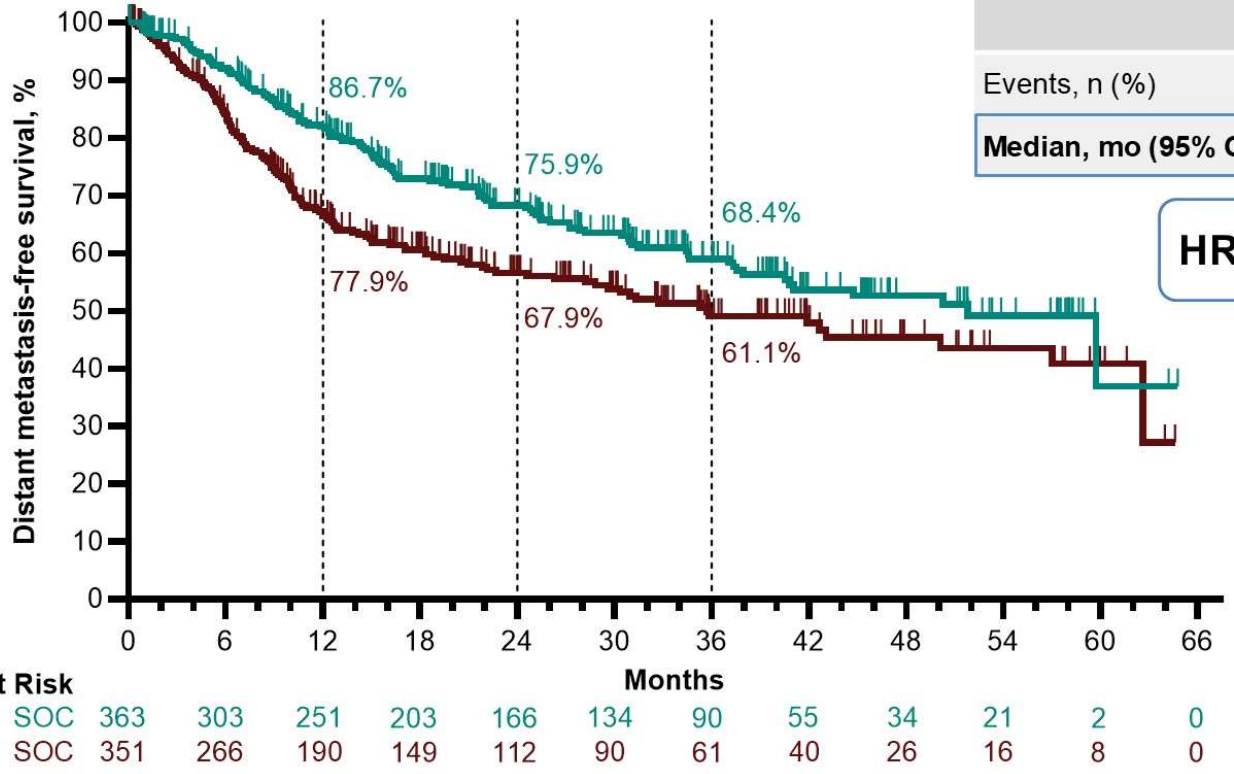
No. at Risk												
Pembro + SOC	363	287	232	191	157	129	88	55	34	21	2	0
SOC	351	258	183	147	110	88	59	37	25	15	7	0

NR, not reached. *Significance boundary was met at IA1.
[a]Defined as time from randomization to first radiographic PD (including during neoadjuvant phase that precludes surgery, local or distant PD/recurrence by imaging/biopsy) or death due to any cause

Data cutoff date: 25 July 2024
Median follow-up (time from randomization to data cutoff date): 38.3 months (9.0–66.5).

Uppaluri et al, AACR 2025
Adkins et al, ASCO 2025

DMFS,[a] All Participants



	Pembro + SOC N = 363	SOC N = 351
Events, n (%)	127 (35.0)	148 (42.2)
Median, mo (95% CI)	**51.8 (37.9–NR)**	**35.7 (26.3–57.0)**

HR 0.71, 95% CI 0.56–0.90

NR, not reached. [a]Defined as time from randomization to date of first record of appearance of distant metastasis or death due to any cause.

Data cutoff date: 25 July 2024
Median follow-up: 38.3 months (9.0–66.5).

Uppaluri et al, AACR 2025
Adkins et al, ASCO 2025

Keynote-689

- Mostly patients with oral cavity disease; hardly any p16+ patients
- EFS is improved with neoadjuvant and adjuvant Pembro
- Surgical completion rates not worse in Pembro group; extent of surgery not changed by Pembro
  - Major pathologic response (<10% residual invasive SCC) seen in ~10%, very low pCR rates
- OS data is not yet mature
- Now FDA approved for neoadjuvant and adjuvant use in **CPS positive patients**

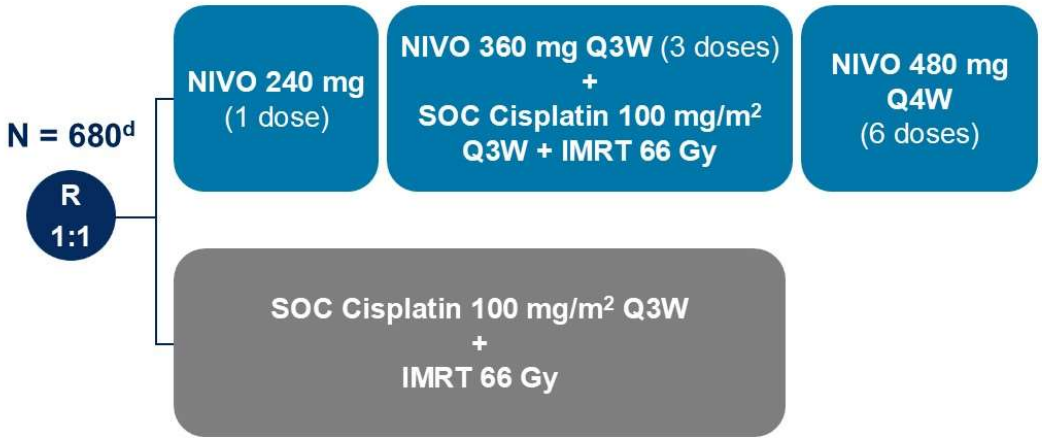
NIVOPOSTOP study design

GORTEC

Key inclusion criteria:

- Adult patients <75 y/o
- ECOG PS 0-1
- SCC of the oral cavity, oropharynx, larynx, or hypopharynx with :
  - Complete macroscopic surgical resection
  - pStage III or IV[b] (AJCC 8th edition)
  - High-risk pathological features of relapse[c]

High Risk:
Positive margin
Extranodal extension
≥4 nodes with multiple PNI



[a]Minimization factors : p16 (OPC p16+ versus OPC p16- and non-OPC) and centers . [b]pStage II p16+ oropharynx if pT3/T4 and tobacco ≥20 packs/year; [c]extra capsular extension (ECE) of lymph node, microscopically positive tumor margins (R1 or close margin ≤ 1 mm), ≥ 4 cervical nodal involvements without ECE, multiple peri-neural invasions; [d]total number of randomized patients between October 2018 and July 2024.

Disease-free survival: (primary endpoint ; ITT)

Analysis based on **252 DFS events**
at the data cutoff of April 30th 2024

Median follow-up: 30.3 months (IQR 16-44.9)

3-years DFS

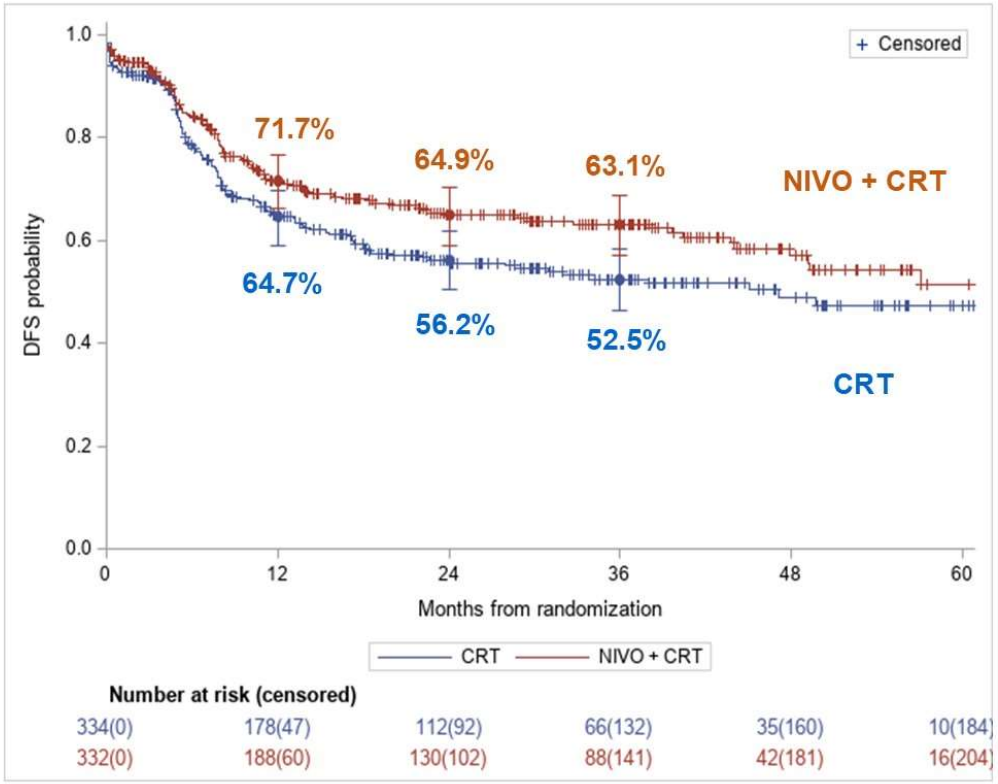
63.1% (95%CI 57.0%; 68.7%)
with NIVO + CRT

versus

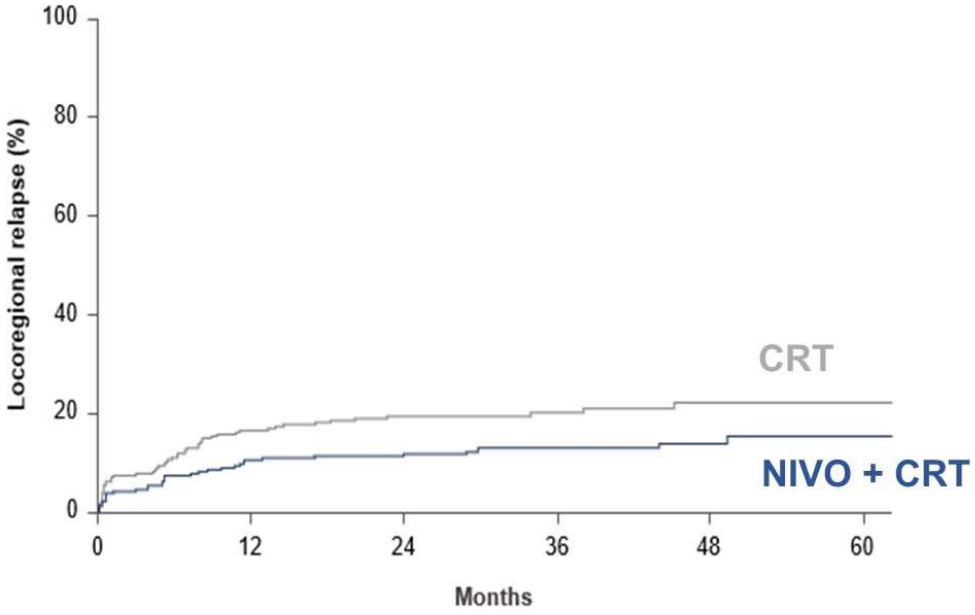
52.5% (95%CI 46.2%; 58.4%)
with CRT

Stratified* HR (95%CI) = 0.76 (0.60; 0.98)
Stratified log-rank p-value=0.034

*HR stratified for p16 status (OPC p16 positive *versus* OPC p16 negative and non-OPC) in Cox model



Cumulative incidence of loco-regional relapses alone



	NIVO + CRT (n = 332)	CRT (n = 334)
Number of events	39	61
Cumulative incidence, %		
1-year	11	16
2-year	12	19
3-year	13	20
Stratified sub-HR (95% CI)	**0.63 (0.42–0.94)**	

Sub-distribution HR stratified for p16 status (OPC p16 positive *versus* OPC p16 negative and non-OPC) in Fine-Gray model

NIVOPOSTOP

- Mostly oral cavity; again very few p16+
- DFS is improved with addition of nivolumab to adjuvant chemoRT
- Benefit is in improved locoregional control
- High risk patient group

	Keynote-689	NIVOPOSTOP
Eligibility criteria	Any Stage III/IVA OC/L/HP/p16 neg OP Stage III p16+ OPC Surgically **resectable** ***Mostly Oral Cavity*** ***Intermediate and high-risk patients***	Path stage III/IV **High risk** resected OC/L/HP/OPC: ECE, 1mm or less margin, 4 LNs with PNI ***Mostly Oral Cavity*** ***Almost all pathologic high-risk***
Treatment	Pembro x 2 Surgery Pembro + (chemo)XRT then Pembro x 12	Nivo x 1 then Nivo+ chemoXRT then Nivo x 6
Results	Improved EFS - ***Mostly Distant Failure Benefit***	Improved DFS - ***LR control Benefit***
Side effects	Not much, consistent with known PD1	Not much, consistent with known PD1
Others	Path responses: 10-13% Lower number of high-risk features on path in Pembro group	

What about Cisplatin Ineligible?

- Historically excluded from studies
- Multiple trials now completed specifically in cisplatin ineligible
  - Immunotherapy trials all negative; positive study with docetaxel in India
- Our institutional approach is to use cetuximab

Trial	N	Intervention	Primary endpoint/Results
NCT02707588 GORTEC 2015-01 PembroRad	133	Pembrolizumab/XRT vs Cetuximab/XRT	2 yr LRC Similar in both arms (60% vs 59%)
NCT02999087 GORTEC REACH	277	Avelumab/cetuximab/XRT vs Cetuximab/XRT	2 yr PFS Similar in both arms (44% vs 31%)
NCT03258554 NRG-HN004	523	Durvalumab/XRT vs Cetuximab/XRT	2 yr PFS Similar in both arms (51% vs 66%)
CTRI/2017/05/008700 Patil JCO 2023	356	XRT vs docetaxel XRT in both definitive and postoperative setting	2 yr DFS and OS superior with weekly docetaxel

Definitive chemoRT using non-cisplatin regimens

- Trials were not done specifically in cisplatin ineligible patients

Trial	N	Intervention	Exp Arm Results	Exp arm Toxicities
GORTEC 9401	226	Carboplatin/5FU/XRT vs. XRT	OS DFS superior	Mucositis/Skin/Nutrition/Heme toxicity worse
GORTEC 2007-01	406	Carboplatin/5FU/Cetuximab/XRT Vs. Cetuximab XRT	PFS and LRC superior OS similar	LFT elevation, leucopenia, PEG, hospitalizations worse
Bonner IMCL9815	253	Cetuximab/XRT vs. XRT	OS and LRC superior	More rash and infusion reactions

Other Considerations

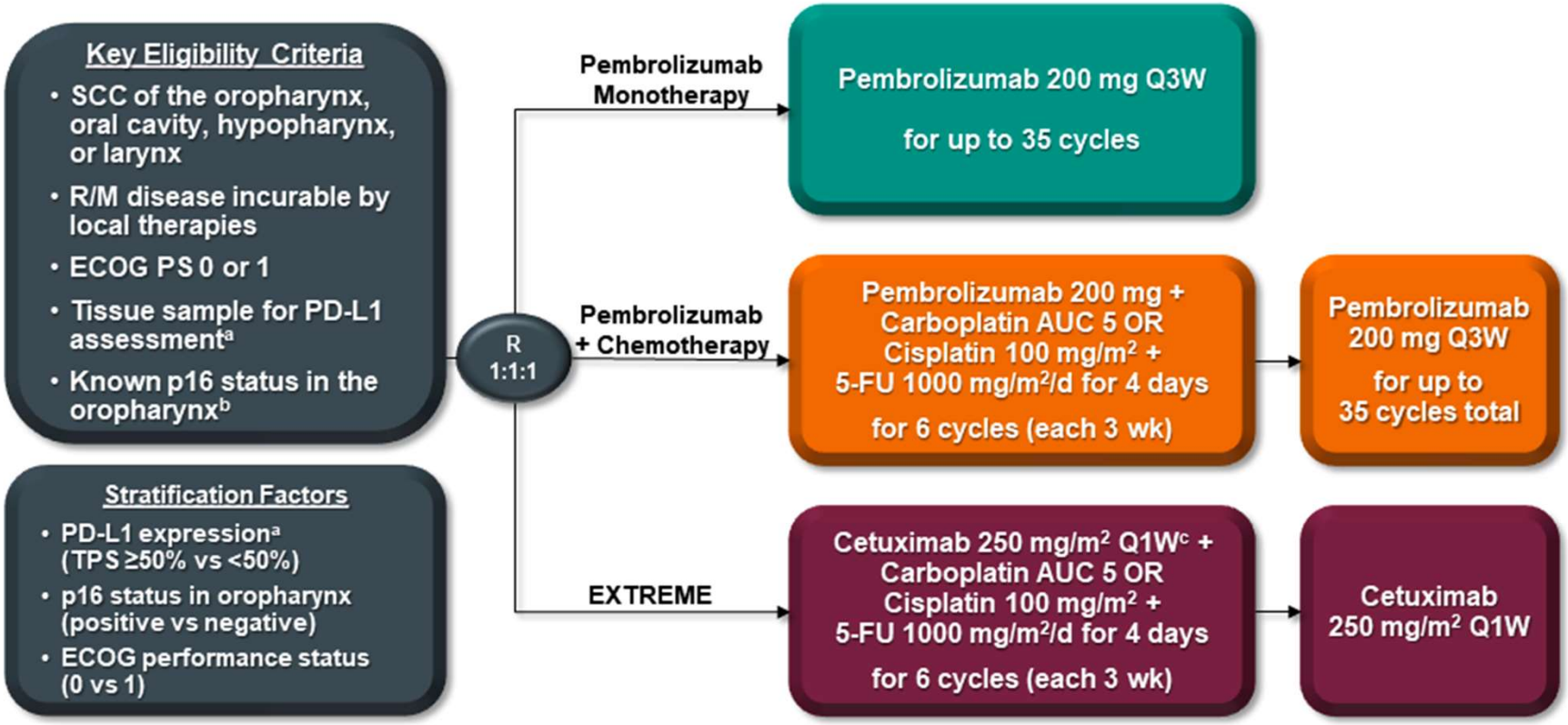
- Supportive care is critical during curative intent therapy
  - High rates of grade 3 toxicity
  - Infusion space for IV fluids; aggressively avoid dehydration
  - Adequate nutrition; PEG
  - Speech and swallow throughout treatment
  - Pain management
  - Management of mucositis
  - SW
  - Tobacco cessation

HNSCC: Metastatic Disease

Metastatic Disease

- Poor prognosis
  - Median OS in months; longer for HPV+
- Multiple active cytotoxic agents
- Many combination trials improved response rates but increased toxicity without OS benefit
- 2008 1L EXTREME Study: Cetuximab + Platinum + 5FU vs Platinum 5FU
  - Improved OS from 10.1 months vs 7.4 months (p=0.04)
  - Very high rates of G3+ toxicity 82%
  - Became the SOC for trial purposes

KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

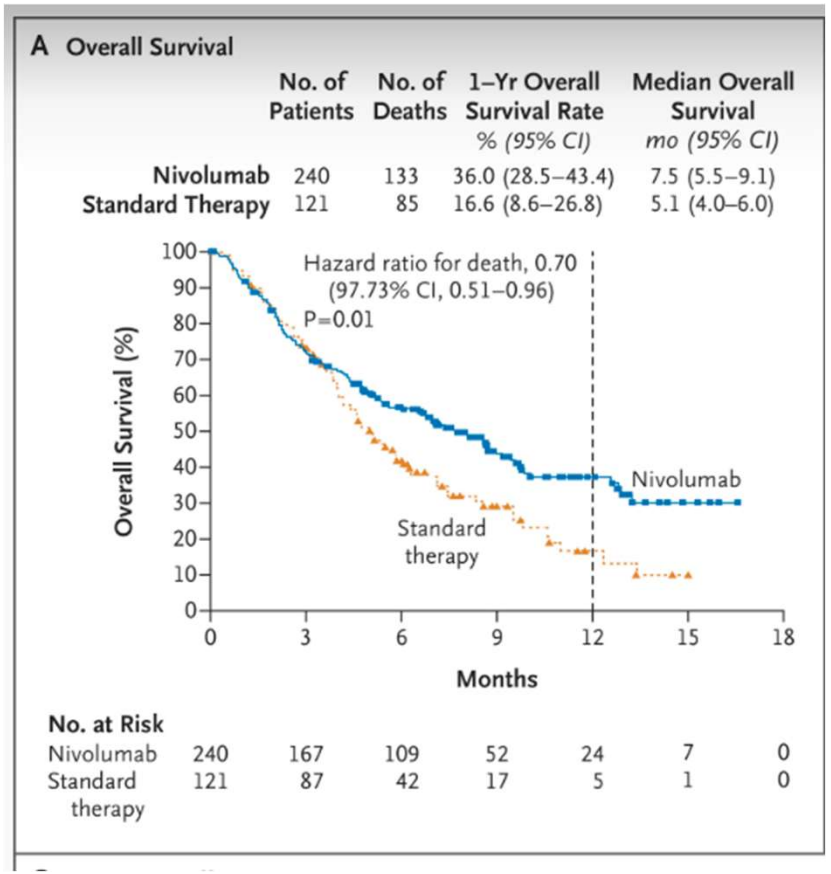
Burtness, Lancet, 2019

Keynote-048: Results

- CPS >/= 1 Pembro Monotherapy vs EXTREME:
  - OS 12.3 vs 10.4 months (p=0.0008)
  - Gr3+ AE 17% vs 70%
  - ORR 19%, DOR 23.4m (vs 4.5 m)
- Magnitude of benefit for Pembro monotherapy higher with higher CPS (>20)
- Any CPS, Pembro + Chemo vs EXTREME
  - OS 13 vs 10.7 m (p=0.003)
  - Gr3+ AE 72% vs 70%
  - ORR 36%, DOR 6.7m (vs 4.3m)
  - CPS negative is rare in HNSCC

Immunotherapy Post Platinum Chemo

- Checkmate 141: Nivolumab vs investigator choice
- Keynote-040: Pembrolizumab vs investigator choice
- Both were PDL1 agnostic
- Both improved OS over investigator choice chemo



Ferris, NEJM 2016
Cohen, Lancet 2019

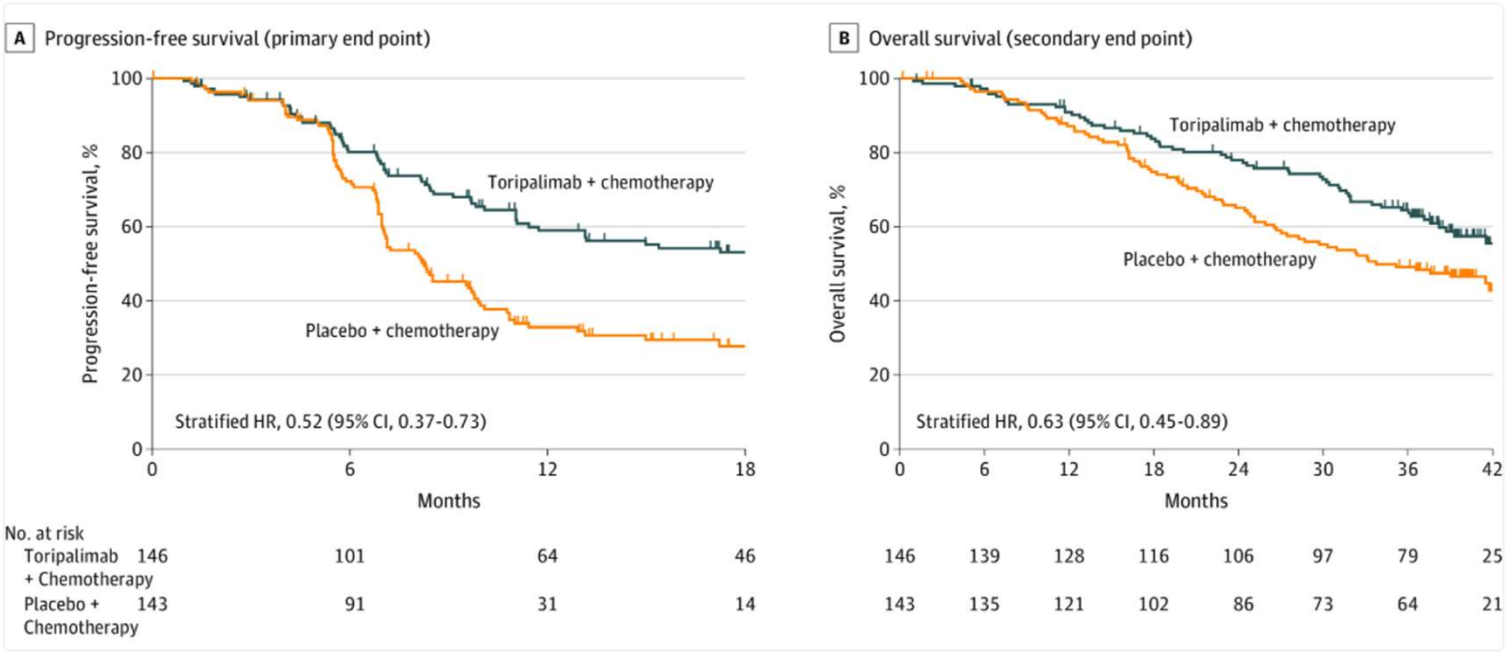
Immunotherapy in R/M HNSCC

Line of therapy (biomarker)	Drug or Regimen	Evidence
1st line (CPS ≥1)	Pembrolizumab monotherapy	Keynote-48 Phase III trial
1st line (any CPS)	Pembrolizumab + platinum + 5FU	Keynote-48 Phase III trial
2nd line post cisplatin	Nivolumab	Checkmate 141 Phase III trial
2nd line post cisplatin	Pembrolizumab	Keynote-40 Phase III trial

NPC

- Multiple studies showing benefit for chemotherapy + PD1 inhibitor
- Toripalimab, Penpulimab now FDA approved in US

Figure 2. Final Progression-Free Survival and Overall Survival Analyses in the Intention-to-Treat Population.



Mai, Nat Med 2021

Thyroid Cancer

Thyroid Cancer

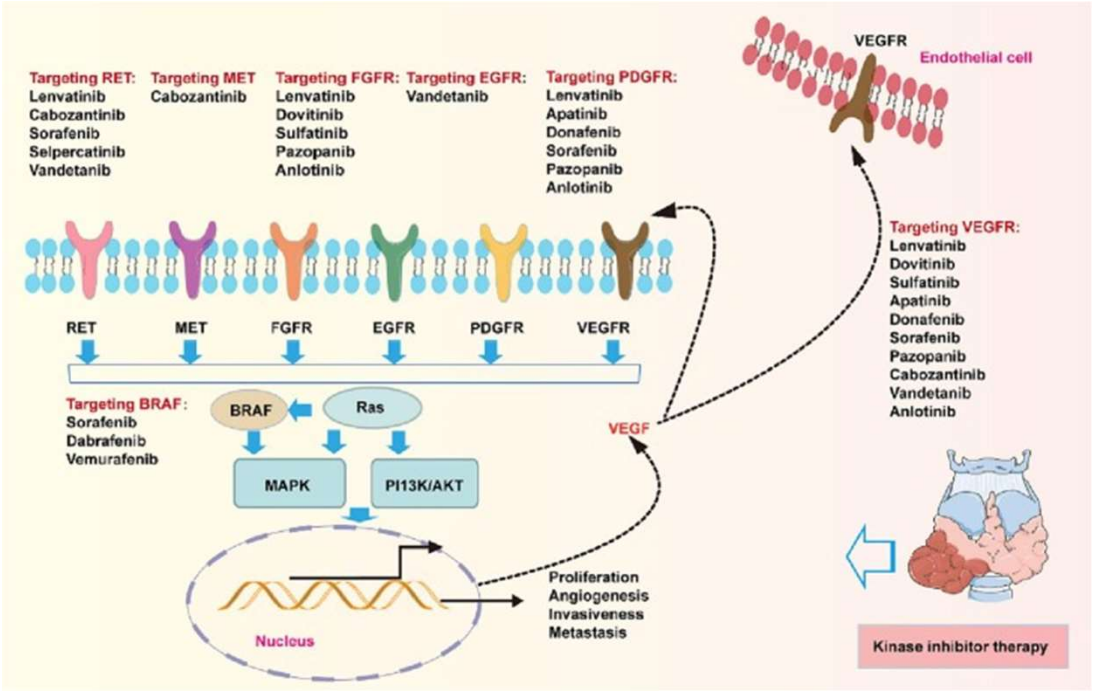
- Differentiated Thyroid Cancer (DTC)
  - Papillary (85%), follicular, oncocytic
  - Can be associated with familial syndromes (Cowden, PTEN Hamartoma Tumor Syndrome)

- Medullary
  - Rare, characterized by RET mutations
  - Derives from parafollicular C cells → produces calcitonin
  - Can be familial (MEN2) or sporadic

- Anaplastic
  - Seen generally in older patients; evolve from prior differentiated thyroid cancers
  - Characterized by very rapid growth with threatened airway

Molecular Targets in Thyroid Cancer

Tumor type	*Prevalence (%)*
Papillary carcinoma	
BRAF	45
RET/PTC	20
RAS	10
TRK	<5
Follicular carcinoma	
RAS	45
PAX8-PPARγ	35
PIK3CA	<10
PTEN	<10
Medulllary carcinoma	
Familial forms of *RET*	>95
Sporadic *RET*	50
Poorly differentiated carcinoma	
RAS	35
β-Catenin (*CTNNB1*)	20
TP53	20
BRAF	15
Anaplastic carcinoma	
TP53	70
β-Catenin (*CTNNB1*)	65
RAS	55
BRAF	20



Nikiforov, Mod Pathology 2008
Zhang, 2023

FDA Approved TKIs in RAI Refractory DTC

- Not all patients need treatment: treatment worsens QOL and some patients have indolent disease

Agent	Target	Evidence	ORR	PFS	OS	AEs
Lenvatinib[1]	VEGF, BRAF, FGFR, RET, KIT	R Ph III vs. Placebo SELECT (N=392)	**64.8%** vs 1.5% (p<0.001)	18.3 vs 3m (p<0.001)	NS	75.9% vs 9.9%
Sorafenib[2]	VEGF, BRAF, RET RAF, PDGFR	R Ph III vs. Placebo DECISION (N=417)	**12.2%** vs 0.5%	10.8 vs. 5.8m (p<0.0001)	NS	37.2 vs 26.3%
Cabozantinib[3] 2L post TKI	VEGFR2, AXL, MET, RET	Phase III COSMIC-311 N=187	**15%** vs 0	Not reached vs. 1.9 mo	NS	64% vs 37%

[1]Schlumberger et al. N Engl J Med. 2015 Feb 12;372(7):621-30.
[2]Brose et al. Lancet. 2014 Jul 26;384(9940):319-28.
[3]Brose at al. Lancet 2021

Mutation specific approved TKIs in DTC

- MUST molecularly profile patients

Agent	Target	Evidence	ORR	PFS	OS	AEs
Selpercatinib[1]	RET	Ph1/2 N=19	79%	1 yr 92%	NR	Mostly Gr1/2
Pralsetinib[2]	RET	Phase I/2 N=20	89%	1 yr 81%	1 yr 91%	Gr1/2
Entrectinib[3]	NTRK	Ph1 N=121(all tumors)	54%	NR	NR	Gr1/2
Larotrectinib[4]	NTRK	Ph1 N=29 (all thyroid)	71%	2 yr 69%	2 yr 76%	Gr1/2
Dabrafenib/ Trametinib	BRAF/MEK	Ph 2 N=53 Dab/Tram vs Dab	30% vs 35%	15.1 m vs 10.7 m		More tox with combo

[1]Wirth et al NEJM 2020
[2]Subbiah et al. Lancet Diab Endo 2021
[3]Doebele AACR 2020
[4]Waguespack EurJ Endo 2022
[5]Busaidy Thyroid 2022

FDA approved TKIs in Medullary Thyroid Cancer

Agent	Target	Evidence	ORR	PFS	OS	AEs
Vandetanib[1]	RET VEGF EGFr	R Ph III vs.Plac ZETA (N=331)	45% vs 13% (p<0.01)	NR vs 19.3 m (p<0.01)	NR	GI: 56 vs 26%
Cabozantinib[2]	RET MET VEGF	R Ph III vs. Plac EXAM (N=330) noXover	28% vs 0%	11.2 vs. 4m (p<0.0001)	NS	Gr3 69% vs 33%
Selpercatinib[3]	RET	Phase I/2 N=143	71%	NR	NR	Most Gr1/2

Pralsetinib FDA indication was withdrawn in 7/2023

[1]Wells, et al. J Clin Oncol. 2012 Jan 10;30(2):134-41.
[2]Elisei et al. J Clin Oncol. 2013 Oct 10;31(29):3639-46.
[3]Wirth et al. N Eng J Med 2020

Anaplastic

- Often unresectable and metastatic at diagnosis
- Very poor prognosis
- Maximizing local control and QOL are critical
  - chemoRT w/ paclitaxel can be used even in advanced disease to maximize local control
- Molecular profiling
  - Phase 1 study with Dabrafenib/Trametinib in BRAF V600E positive, n=16
  - Response Rate 69%
    - 80% treated with prior radiation
  - FDA approved
- New data presented at ASCO: neoadjuvant Dab/Tram + Pembro in BRAF mutated anaplastic

Subbiah, JCO 2018

Salivary Gland

Salivary Gland Cancer

- < 5% of head and neck cancer
- Major (parotid, submandibular, sublingual) or minor glands (throughout aerodigestive tract)
- Characterized by very diverse histology (WHO classification)
  - Adenoid Cystic Carcinoma
  - Mucoepidermoid Carcinoma
  - Adenocarcinoma
- Wide range in behavior
- Molecular profiling
  - Secretory Carcinoma characterized by ETV6-NTRK fusion

Localized or Locally Advanced

- Surgical resection
- Adjuvant radiation in high risk
  - Neutron radiation
  - RTOG 1008 evaluated the role of concurrent chemoRT, awaiting results

R/M Salivary Gland Cancer

- No therapeutic standard of care → clinical trials
- Small trials of heterogeneous histologic types limits conclusions
  - Low response rates, stable disease (inclusion of indolent subtypes)
  - Paclitaxel, RR 26% (no responses in ACC)
  - Gem/Cis, RR 24%
- Targeted agents
  - Lenvatinib: 15% ORR in ACC, off label use
  - NTRK/BRAF/RET inhibitors if positive
  - AR+: ADT used off label
  - HER2+ use various HER2 based therapies; no data on sequencing. NRG HN-010 ongoing
  - Pembro in dMMR or TMB-High

Fred Hutch
Cancer Center

Thank you!

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