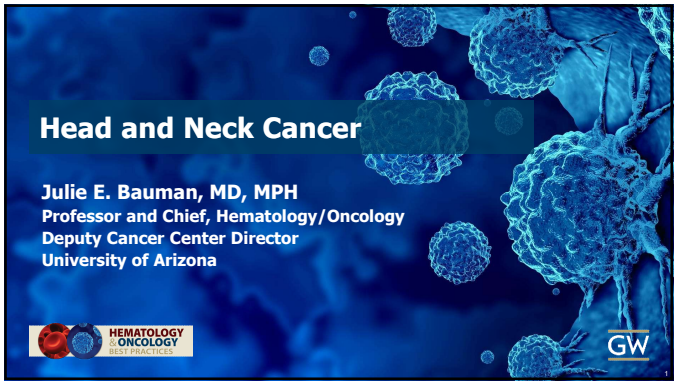


Disclosures

- Personal
  - None
- Clinical Research Grants (to Institution)
  - Aveo
  - BMS
  - Celgene
  - Celldex
  - Eli Lilly
  - Moderna
  - Novartis

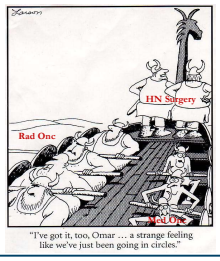
GW 2

Outline

- Epidemiology
  - Clinically Important Anatomy
  - Histology
  - Classic Risk Factors
  - The Emerging Epidemic
- Staging
- Treatment Standards for Definitive Management
- Treatment Standards for Recurrent/Metastatic HNC
- Nasopharyngeal Carcinoma

GW 3

Medical Oncologists and HNC circa 2010
Lumpers not Splitters

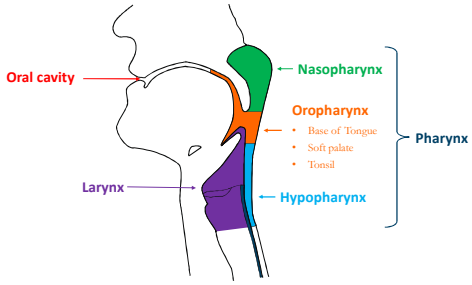


"I've got it, too, Omar … a strange feeling like we've just been going in circles."

- Anatomic distinctions less important
- Common risk factors
- Common pathology
- Common natural history
- Common staging
- Common response to chemotherapy
- Common response to radiation therapy

GW ONCOLOGY UPDATE 4

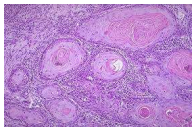
Anatomy



GW 5

Head and Neck Cancer: Pathologic Subtypes

- Squamous cell carcinoma (HNSCC)
  - Predominant pathology
  - >90%
- Nasopharyngeal Carcinoma
- Salivary Gland Tumors
- Other
  - Sinonasal undifferentiated cancer (SNUC)
  - Esthesioneuroblastoma
  - Neuroendocrine carcinoma
  - Sarcomas
  - Mucosal melanoma


Moderately differentiated squamous cell carcinoma with keratin pearl

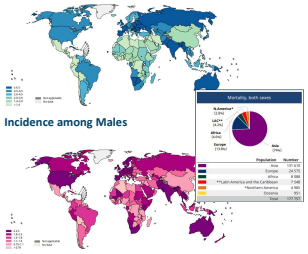
GW

Head and Neck Cancer: Classic Risk Factors

Alcohol

- Tobacco
  - Smoking
  - Chewing
  - Sucking
- Alcohol
  - At least additive with tobacco
  - Independent risk
- Areca nut/betel quid
  - Southeast Asia
- Poor oral hygiene
- Diets low in fruits and vegetables

Global Oral Cancer Disparities



Incidence among Males

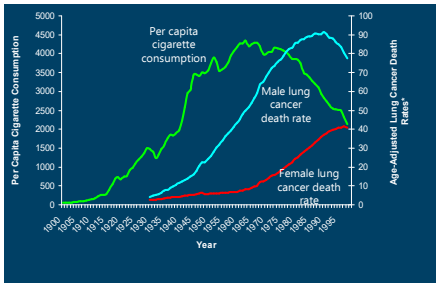
Incidence among Females

- Strong association with SES, education
- Proximal behavioral risk factors (AR 50%)
  - Tobacco
  - Alcohol
  - Betel quid/areca nut
- Distal socioeconomic factors (AR 50%)
  - Pollution
  - Food security
  - Affordable, healthy diet
  - Hygiene
  - War

GLOBOCAN 2020: gco.iarc.fr/today/data/factsheets/cancers/1-Lip-oral-cavity-fact-sheet.pdf

Boing AF et al. J Epidemiol Community Healthy 2011;65:709-14.
Johnson NW et al. Adv Dent Res 2011;23(2):237-46

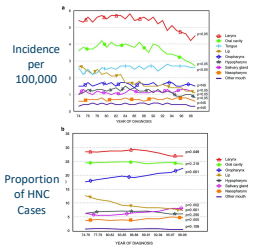
Tobacco Use in the USA: 1900-1999*



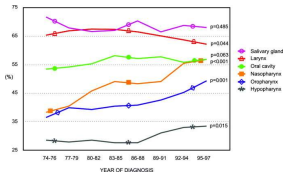
*Age-adjusted to 2000 US standard population.

Source: Death rates: US Mortality Public Use Tapes, 1960-1999, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2001. Cigarette consumption: Us Department of Agriculture, 1900-1999.

U.S. Trends in Incidence and Prognosis for HNC



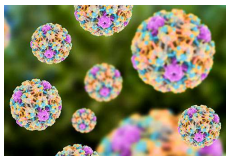
Cases by Anatomic Site



5-Year Survival by Anatomic Site

Carvalho et al. Int J Cancer 2005;114:806-16.
https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.20740

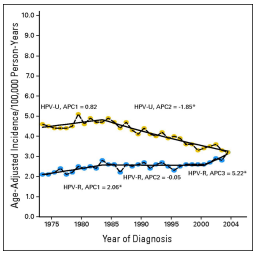
Human Papillomavirus 16: The Emerging Epidemic



HPV 16 L1 Capsid

- **HPV 16**
  - dsDNA virus
  - Causes half of cervical cancer
  - Causes two-thirds of oropharynx cancer
- Behavioral risk factors
  - Younger age at sexual debut
  - Number of lifetime sexual partners
  - Age at first oral sex
  - Infrequent use of condoms
  - Nonuse of barriers
- Vaccines
  - Induce antibodies against L1 capsid protein

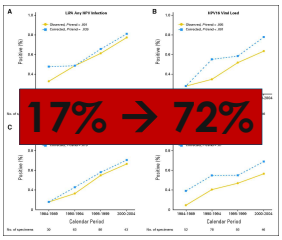
Age-adjusted HNC Incidence (U.S. SEER): HPV-related and HPV-unrelated Anatomic Sites



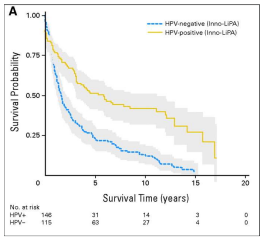
Chaturvedi, A. K. et al. J Clin Oncol 2008; 26:612-9.

20 Year Data: SEER Registry, 1984-2004

Proportion of Oropharynx Cancers with HPV



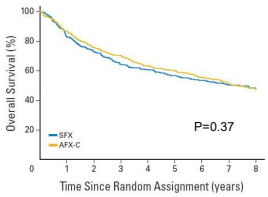
Survival after Diagnosis by HPV Status



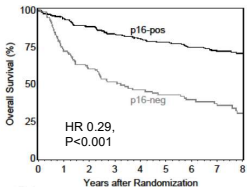
Chaturvedi A K et al. J Clin Oncol 2011;29:4294-4301.

RTOG 0129: Overall Survival

All patients

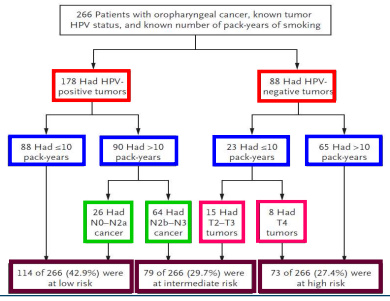


Oropharynx patients



Nguyen-Tan et al. J Clin Oncol 2014;32: 3858-67.
Ang K et al. NEJM 2010;363:24-35.

RTOG 0129: Overall Survival RPA



Ang K et al. NEJM 2010;363:24-35.

Key Points for the Medical Oncologist:
Becoming Splitters not Lumpers

HPV(-) HNSCC
- Environmental
- Tobacco, alcohol, betel quid
- Oral cavity, pharynx, larynx
- Lower SES
- Asia, Eastern Europe
- Worse prognosis
- Multimodality treatment paradigms developed for HPV-

HPV(+) HNSCC
- Viral
- Sexually transmitted
- Oropharynx
- Higher SES
- North America, Western Europe
- Better prognosis
- Multimodality treatment paradigms: over-treatment?

GW ONCOLOGY UPDATE 16

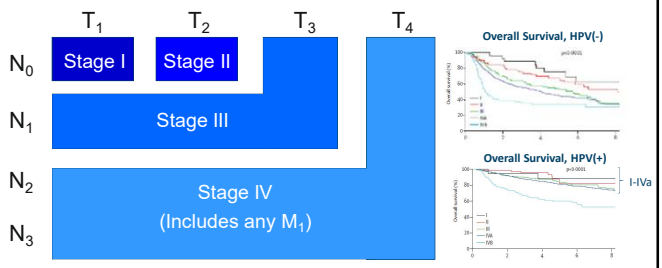
New Diagnosis of HNSCC: Staging Evaluation

- Complete head and neck examination
- Examination under anesthesia as indicated
  - Panendoscopy for HPV(-) HNSCC
  - Utility less evident with modern imaging
- Head and neck cross-sectional imaging (locoregional TN staging)
  - Contrasted CT or MRI
- Chest imaging (distant M staging)
  - Chest CT
  - PET/CT (best value T3-4, N+)
  - < 10% present with distant metastases

Bauman JE. Head and Neck Cancer. In Cecil's Internal Medicine, 26th edition. Amsterdam: El Sevier, 2020.

GW 17

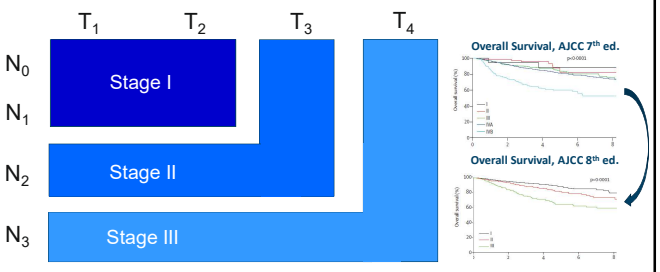
HNC Staging, AJCC 1st -7th Editions (1977-2018)



O'Sullivan et al. Lancet Oncol 2016; 17:440-51

GW 18

HPV+ Oropharynx, AJCC 8th Edition (2018-)



O'Sullivan et al. Lancet Oncol 2016; 17:440-51

19

Previously Treated Locally Advanced (PULA) HNSCC: General Principles

- Curative-intent
- Definitive modalities: surgery or radiation therapy
- Definitive modality depends on functional expectations, anatomic site
  - Oral cavity: surgery
  - Oropharynx: minimally invasive surgery or RT
  - Hypopharynx: RT
  - Larynx: RT if **functional** larynx is feasible
- In T1-T2 disease, single modality preferred
- Systemic therapy: adjunct to RT

Bauman JE. Head and Neck Cancer. In Cecil's Internal Medicine, 26th edition. Amsterdam: El Sevier, 2020.

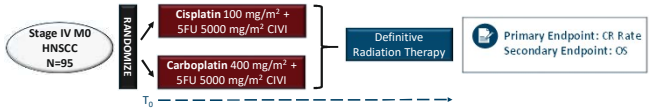
20

PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
- Definitive RT: Induction vs. concurrent chemotherapy
- What about cetuximab?
- Adjuvant RT: Indications, dose, and schedule
- Larynx preservation

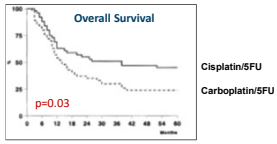
21

Definitive Setting: CDDP Induction Superior to Carboplatin



N = 95 (Stopped early for efficacy)

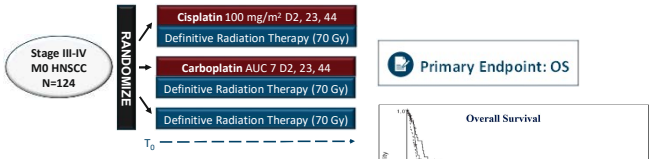
	ORR	CR
Cisplatin	92%	27%
Carboplatin	76%	20%

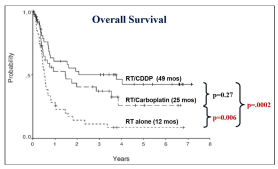


De Andres et al. *J Clin Oncol* 1995;13:1493.

GW 22

Definitive Setting: HeCOG Concurrent Study





Fountzilas et al. *Med Oncol* 2004; 21:95.

GW 23

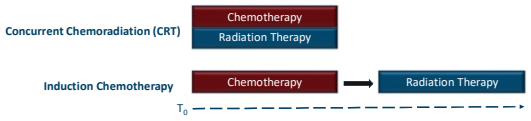
PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
  - **Standard:** Use cisplatin in the curative-intent setting
- Definitive RT: Induction vs. concurrent chemotherapy
- What about cetuximab?
- Adjuvant CRT: Indications, dose, and schedule
- Larynx preservation

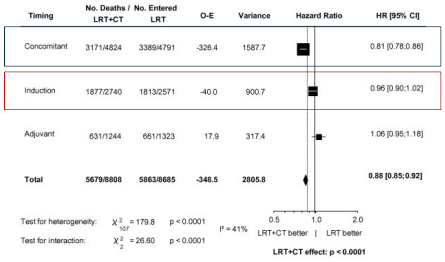
GW 24

PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
- Definitive RT: Induction vs. concurrent chemotherapy
- What about cetuximab?
- Adjuvant RT: Indications, dose, and schedule
- Larynx preservation

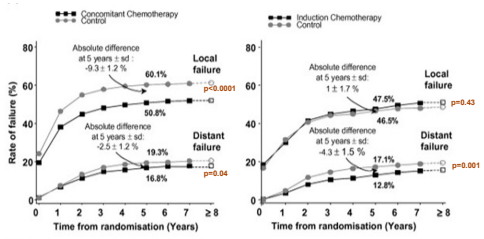


Concurrent vs. Induction Chemotherapy
MACH-NC Meta-Analysis (n=17,346) HR for Death



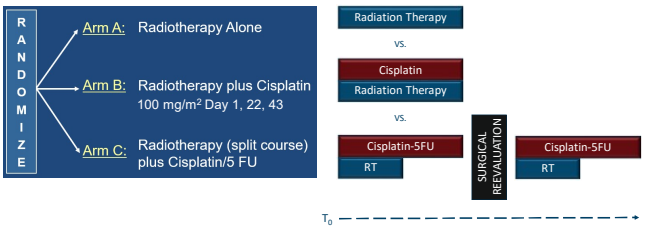
Pignon et al. Radiotherapy and Oncol 2009;92:4-14.

Failure Patterns after Concurrent or Induction Chemotherapy



Pignon et al. Radiotherapy and Oncol 2009;92:4-14.

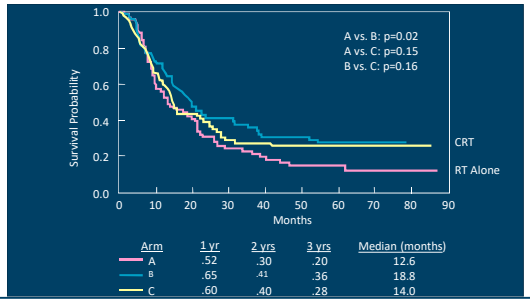
Intergroup 0126



Adelstein D et al. J Clin Oncol 2003;21:92-8.

GW ONCOLOGY UPDATE 28

INT 0126: Overall Survival

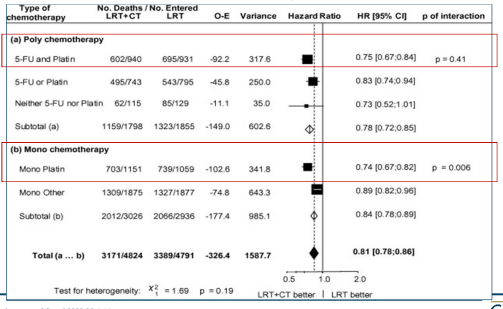


Arm	1 yr	2 yrs	3 yrs	Median (months)
A	.52	.30	.20	12.6
B	.65	.41	.36	18.8
C	.60	.40	.28	14.0

Adelstein D et al. *J Clin Oncol* 2003;21:92-8.

GW

Concurrent CRT: Phase III Experience



Type of chemotherapy	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]	p of interaction
(a) Poly chemotherapy							
5-FU and Platin	602/940	695/931	-92.2	317.6		0.75 [0.67;0.84]	p = 0.41
5-FU or Platin	495/743	543/795	-45.8	250.0		0.83 [0.74;0.94]	
Neither 5-FU nor Platin	62/115	85/129	-11.1	35.0		0.73 [0.52;1.01]	
Subtotal (a)	1159/1798	1323/1855	-149.0	602.6		0.78 [0.72;0.85]	
(b) Mono chemotherapy							
Mono Platin	703/1151	739/1059	-102.6	341.8		0.74 [0.67;0.82]	p = 0.006
Mono Other	1309/1875	1327/1877	-74.8	643.3		0.89 [0.82;0.96]	
Subtotal (b)	2012/3026	2066/2936	-177.4	985.1		0.84 [0.78;0.89]	
Total (a ... b)	**3171/4824**	**3389/4791**	**-326.4**	**1587.7**		**0.81 [0.78;0.86]**	

Test for heterogeneity: χ^2_1 = 1.69 p = 0.19

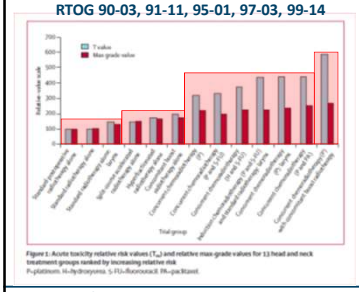
0.5 1.0 2.0
LRT+CT better | LRT better

Pignon et al. Radiotherapy and Oncol 2009;92:4-14.

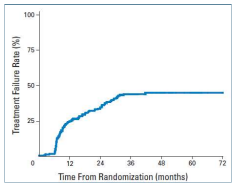
GW

Increasing Toxicity Burden of Multimodality Treatments

RTOG 90-03, 91-11, 95-01, 97-03, 99-14



RTOG 91-11, 97-03, 99-14

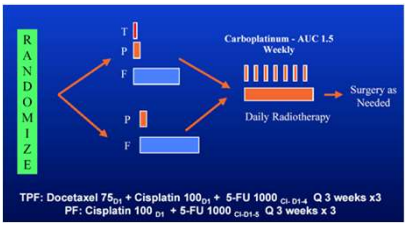


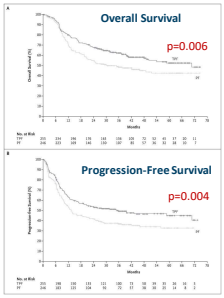
Severe Late Toxicity in 43%:

- ≥ Gr. 3 toxicity 6 mos. after treatment
- Feeding tube ≥ 2 yrs. after treatment
- Non-cancer death ≤ 3 yrs. after treatment

Trotti et al. *Lancet Oncol* 2007; 8: 613-24.
Machtay et al. *J Clin Oncol* 2008; 26: 3582-89.

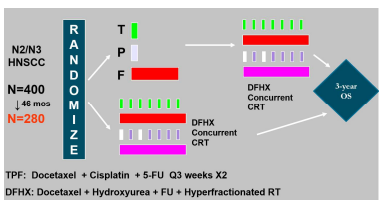
TAX 324: Triplet vs. Doublet Induction Chemotherapy

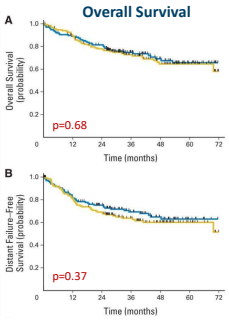




Posner et al. *NEJM* 2007;357:1705-15.

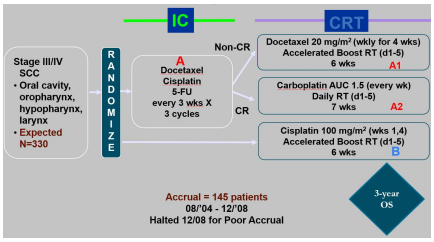
DeCIDE: Docetaxel-Based CRT +/- Induction Chemotherapy to Decrease Events in HNC

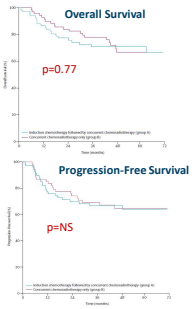




Cohen E. et al. J Clin Oncol 2014;34:2735-43.

PARADIGM: Induction followed by CRT vs. CRT

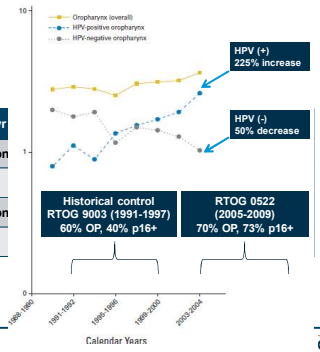




Haddad R. et al. Lancet Oncol 2013;14:257-64.

The Problem of Time Trends

	OS at 3-yr
DeCIDE	Estimation
(N=400→280)	Actual
PARADIGM	Estimation
(N=300→145)	Actual



Chaturvedi A K et al. J Clin Oncol 2011;29:4294-4301.

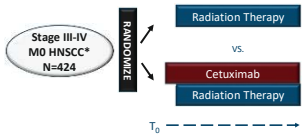
PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
- Definitive RT: Induction vs. concurrent chemotherapy
  - **Standard**: Concurrent cisplatin + conventional fractionation RT (INT 0126)
- What about cetuximab?
- Adjuvant CRT: Indications, dose, and schedule
- Larynx preservation

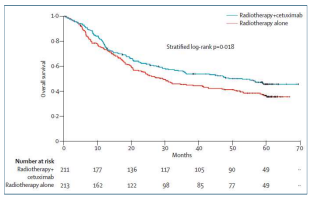
PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
- Definitive RT: Induction vs. concurrent chemotherapy
- What about cetuximab?
- Adjuvant CRT: Indications, dose, and schedule
- Larynx preservation

Definitive RT with or without Cetuximab



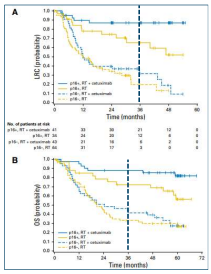
Overall Survival



*AJCC v.7

Bonner J et al. *NEJM* 2006;354:567-78.
Bonner J et al. *Lancet Oncol* 2010;11:21-8.

Cetuximab and p16 Status



3-Year Locoregional Control

	HR	95% CI
p16+	0.31	0.11-0.78
p16-	0.78	0.49-1.25

$P_{interaction} = 0.087$

Overall Survival

	HR	95% CI
p16+	0.38	0.15-0.94
p16-	0.93	0.59-1.48

$P_{interaction} = 0.085$

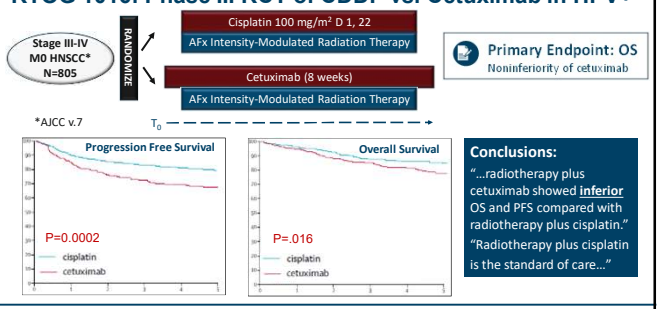
Conclusions:

"…regardless of p16 status, patient outcomes were improved by the addition of cetuximab to RT compared with RT alone."

"…p16 status – although a strong prognostic biomarker – does not predict and is not a biomarker of the effect of cetuximab…":

Bonner J et al. *NEJM* 2006;354:567-78.

RTOG 1016: Phase III RCT of CDDP vs. Cetuximab in HPV+



Conclusions:

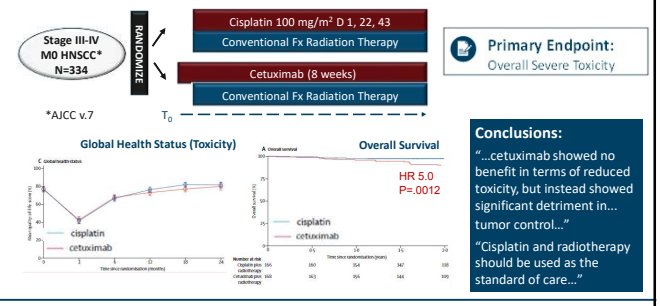
"…radiotherapy plus cetuximab showed **inferior** OS and PFS compared with radiotherapy plus cisplatin."

"Radiotherapy plus cisplatin is the standard of care…"

Gillison et al. *Lancet* 2019; 393:40-50.

GW 40

De-ESCALaTE HPV: Phase III RCT of CDDP vs. Cetuximab



Conclusions:

"…cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in… tumor control…"

"Cisplatin and radiotherapy should be used as the standard of care…"

Mehanna H et al. *Lancet* 2019; 393:51-0.

GW 41

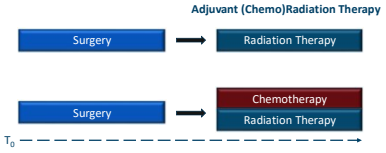
PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
- Definitive RT: Induction vs. concurrent chemotherapy
- What about cetuximab?
  - Cetuximab-RT is superior to RT alone regardless of p16 status
  - **Standard**: concurrent cisplatin-RT in cisplatin-eligible patients
  - **Standard:** cetuximab-RT only in cisplatin-ineligible
- Adjuvant CRT: Indications, dose, and schedule
- Larynx preservation

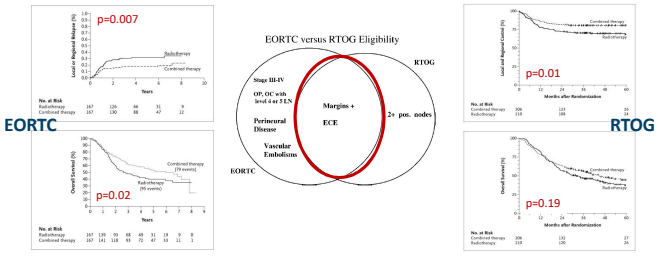
GW 42

PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
- Definitive RT: Induction vs. concurrent chemotherapy
- What about cetuximab?
- Adjuvant CRT: Indications, dose, and schedule
- Larynx preservation



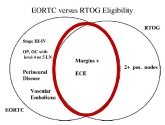
EORTC 22931 and RTOG 9501
Adjuvant RT +/- Cisplatin 100 mg/m² D1, 22, 43



Bernier J et al. N Engl J Med 2004;350:1945-52.
Cooper J et al. N Engl J Med 2004;350:1937-44.

Bernier et al. Head Neck 2005; 27:843-850

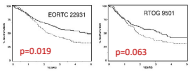
The Evolution of Pathologic Risk Criteria



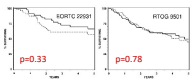
Pooled post-hoc analysis:
EORTC 22931 and RTOG 9501

Overall Survival

Patients with positive margin &/or ECE



Patients without positive margin &/or ECE

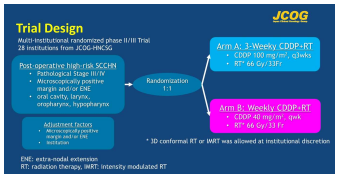


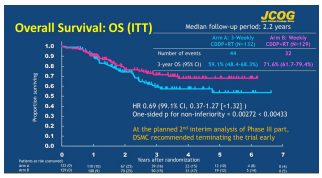
High Risk
- Positive Margin
- Extracapsular Nodal Extension

Intermediate Risk
- Perineural invasion
- Lymphovascular invasion
- Multiple positive LN
- Level IV or V LN

Bernier et al. Head Neck 2005; 27:843-850

JCOG 1008: Phase II/III Trial of Adjuvant CRT with 3-Weekly vs. Weekly Cisplatin in Pathologic High Risk HNSCC





Cisplatin Dosing:
100 mg/m² every 3 weeks
vs. 40 mg/m² weekly

Kiyota N et al. J Clin Oncol 38: 2020 (suppl; abstr 6502).

JCOG 1008: Toxicities

Acute Hematological Toxicities

Hematological	Arm A: 3-Weekly CDDP+RT (N=120)		Arm B: Weekly CDDP+RT (N=122)	
	Any grade	Grade 3-4 (%)	Any grade	Grade 3-4
Total	129 (100%)	79 (61.2%)	122 (100%)	79 (64.8%)
Leukopenia	123 (95.3%)	71 (55.0%)	114 (93.4%)	75 (61.5%)
Neutropenia	118 (91.5%)	63 (48.8%)	106 (86.9%)	43 (35.3%)
Anemia	129 (100%)	18 (14.0%)	122 (100%)	16 (13.1%)
Thrombocytopenia	85 (65.9%)	3 (2.3%)	102 (83.6%)	4 (3.3%)
Febrile neutropenia	7 (5.4%)	7 (5.4%)	5 (4.1%)	5 (4.1%)

Acute Non-hematological Toxicities*

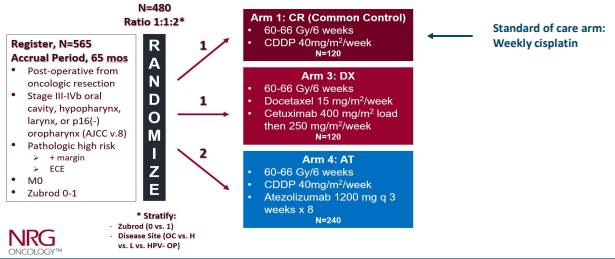
Non-hematological	Arm A: 3-Weekly CDDP+RT (N=129)		Arm B: Weekly CDDP+RT (N=122)	
	Any grade	Grade3-4(%)	Any grade	Grade3-4
Mucositis	118 (91.5%)	30 (23.3%)	113 (92.6%)	34 (27.9%)
Dysphagia	75 (58.1%)	24 (18.6%)	59 (48.4%)	14 (11.5%)
Dermatitis	118 (91.4%)	19 (14.7%)	112 (91.8%)	14 (11.5%)
Nausea	87 (67.4%)	17 (13.2%)	57 (46.7%)	6 (4.9%)
Infection	25 (19.4%)	15 (11.6%)	18 (14.8%)	8 (6.6%)
Hyponatremia	119 (92.2%)	13 (10.1%)	100 (82.0%)	13 (10.7%)
Renal impairment	51 (39.5%)	0 (0%)	36 (29.5%)	0 (0.0%)
Hearing impairment	22 (17.1%)	5 (3.9%)	9 (7.4%)	2 (1.6%)
Peripheral neuropathy	7 (5.4%)	0 (0.0%)	2 (1.6%)	0 (0.0%)

3-Weekly: Less thrombocytopenia
Weekly: Less neutropenia

3-Weekly: No advantage
Weekly: Less dysphagia, nausea, infection, renal injury, ototoxicity

Kiyota N et al. J Clin Oncol 38: 2020 (suppl; abstr 6502).

NRG/RTOG 1216: Ongoing Phase II/III RCT in Pathologic High Risk HNSCC



Study Chair: JE Bauman

PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
- Definitive RT: Induction vs. concurrent chemotherapy
- What about cetuximab?
- Adjuvant CRT: Indications, dose, and schedule
  - Pathologic high risk: adjuvant, concurrent cisplatin-RT
  - Intermediate risk: shared decision-making
- Larynx preservation

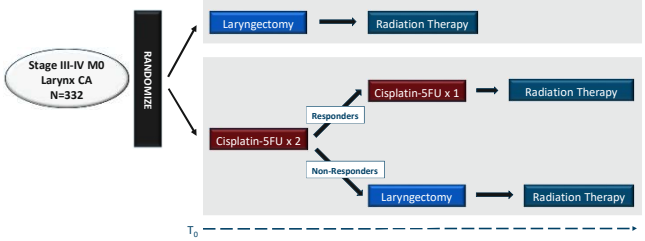
GW 49

PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
- Definitive RT: Induction vs. concurrent chemotherapy
- What about cetuximab?
- Adjuvant CRT: Indications, dose, and schedule
- Larynx preservation

GW 50

VALCSG: Induction Chemotherapy + RT vs. Surgery + RT Phase III RCT



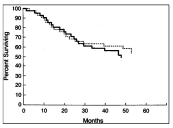
The Department of Veterans Affairs Laryngeal Cancer Study Group (VALCSG). N Engl J Med 1991;324:1685-90.

GW 51

VALCSG Laryngeal Preservation Trial: Outcomes

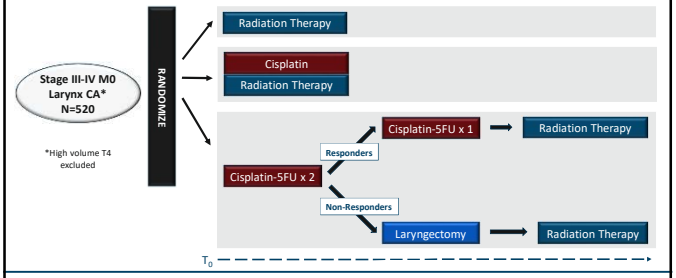
	Surgery → RT N=166	Chemotherapy → RT N=166
Response Rate (CR)	NA	85% (31%)
3-year Overall Survival	56%	53%
Laryngectomy	166 (100%)	59 (36%)
Early vs. Late Salvage Before or ≤ 3 mos of RT > 3 mos after RT	NA	48 (29%) 11 (7%)
T4 Tumors	42 (100%)	24 (56%)

Overall Survival



The Department of Veterans Affairs Laryngeal Cancer Study Group (VALCSG). N Engl J Med 1991;324:1685-90.

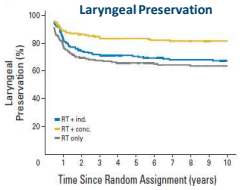
RTOG 91-11: Randomized Trial of 3 Nonsurgical Strategies for Larynx Preservation



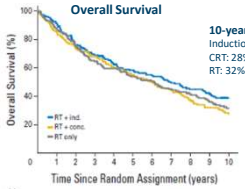
Forastiere AA. *J Clin Oncol* 2013;31:845-52.

RTOG 91-11: Outcomes (Median F/U 10.8 Years)

Laryngeal Preservation



Overall Survival



10-year OS:
Induction: 39%
CRT: 28%
RT: 32%

	RT vs. Induction HR (p value)	CRT vs. RT HR (p value)	CRT vs. Induction HR (p value)
Larynx Preservation	1.26 (p=0.35)	0.46 (p<0.001)	0.58 (p=0.005)
10-year OS	1.15 (p=0.29)	1.08 (0.53)	1.25 (p=0.08)

Forastiere AA. *J Clin Oncol* 2013;31:845-52.

PULA HNSCC: Controversies and Standards

- Cisplatin vs. carboplatin
- Definitive RT: Induction vs. concurrent chemotherapy
- What about cetuximab?
- Adjuvant CRT: Indications, dose, and schedule
- Larynx preservation
  - **Standard:** CRT
    - Concern for late mortality
  - **Alternative Standard:** Induction → RT (in responders)
    - Salvage laryngectomy more likely
    - Consider TPF (European standard)

GW 55

PULA HNSCC: Key Take-Aways

- Use **cisplatin** in the definitive setting
- When RT is the definitive modality, deliver **concurrent** chemotherapy
- Cetuximab-RT is only standard for **cisplatin-ineligible** patients
- Adjuvant CRT:
  - Adjuvant CRT in **pathologic high risk** (+margin, ECE)
  - Shared decision-making for intermediate risk
- Larynx preservation:
  - **Surgery up front for dysfunctional larynx** (T4)
  - **CRT is standard**; induction is an alternative

Bauman JE. Head and Neck Cancer. In Cecil's Internal Medicine, 26th edition. Amsterdam: El Sevier, 2020.

GW 56

Recurrent and Metastatic (R/M) HNSCC: General Principles

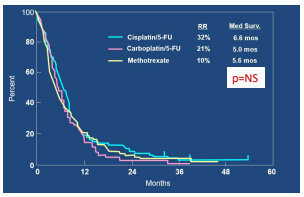
- Locoregionally confined: consider salvage surgery or (re)irradiation
  - 20% long-term DFS
- Systemic therapy: palliative-intent
- Multi-agent therapy when symptom burden is high
- Anti-PD1 immunotherapy has replaced EXTREME as 1st line standard

Bauman JE. Head and Neck Cancer. In Cecil's Internal Medicine, 26th edition. Amsterdam: El Sevier, 2020.

GW 57

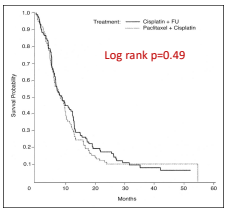
R/M HNSCC: Classic Palliative Studies

SWOG 8514



Doublet is not superior to singlet except for RR

E1395

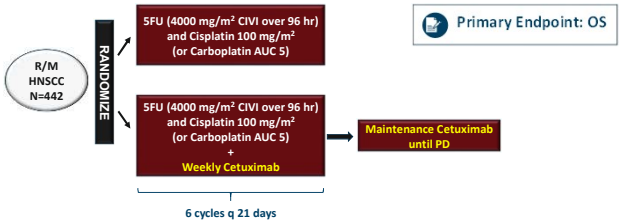


Platinum partner is not significant for RR or OS

Forastiere A et al. *J Clin Oncol* 1992;10:1245-51.
Gibson MK et al. *J Clin Oncol* 2005;23:3562-3567.

GW ONCOLOGY UPDATE 58

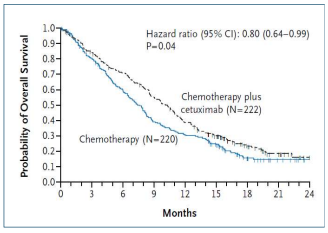
EXTREME Study: Platinum-5FU +/- anti-EGFR mAb Cetuximab in R/M HNSCC



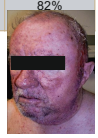
Vermorken J et al. *NEJM* 2008;359:1116-27.

GW 59

EXTREME Study: Outcomes



	Chemotherapy	Chemotherapy + Cetuximab
Response Rate	20%	36%
Median Survival	7.4 months	10.1 months
Grade 3-4 Toxicity	76%	82%



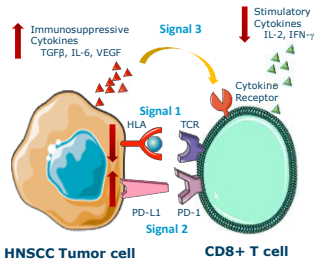
Acneiform Rash

Vermorken J et al. *NEJM* 2008;359:1116-27.
Bauman JE et al. *Arch Dermatol* 2007;143(7):889-892.

GW 60

HNSCC suppresses adaptive immunity

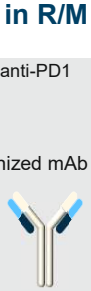
- **Signal 1:** Reduced antigen processing and presentation
- **Signal 2:** Anergic T cells
  - ↑ Co-inhibitory receptors: CTLA-4, PD-1
  - ↓ Co-stimulatory receptors: CD137, OX40
- **Signal 3:** Tumor-permissive cytokine profile

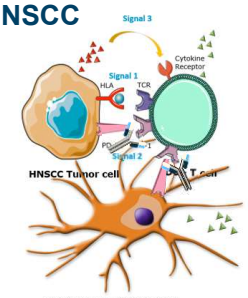


Adapted from Robert Ferris, MD, PhD

Targeting Signal 2 in R/M HNSCC

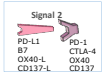
- **2016:** FDA Approval of two anti-PD1 mAb in R/M HNSCC
  - Nivolumab
  - Pembrolizumab
- High-Affinity, IgG4, humanized mAb against PD1





Bauman JE, Immunotherapy in Head and Neck Cancer: *e pluribus unum*. Multidisciplinary HNC Symposium, Scottsdale AZ, Feb 15, 2018.

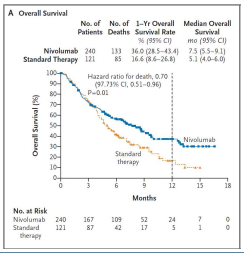
CheckMate 141: Nivolumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy: *Targeting Signal 2*



Randomized Phase III
N=361
2014-2015
Eligibility:
- R/M HNSCC
- Platinum-refractory
- ECOG 0-1

2:1

- Nivolumab 3 mg/kg q 2 weeks
- Investigator's Choice: Methotrexate, Docetaxel, or Cetuximab



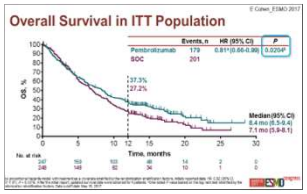
Ferris et al. *NEJM* 2016; 375:1856-67.

KEYNOTE-040: Pembrolizumab vs. Investigator's Choice in R/M HNSCC after Platinum Therapy: *Targeting Signal 2*

Randomized Phase III
N=495
Eligibility:
- R/M HNSCC
- Platinum-refractory
- ECOG 0-1

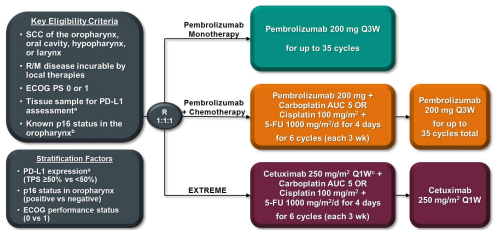
1:1

- Pembrolizumab 200 mg IV q3 weeks
- Investigator's Choice: Methotrexate, Docetaxel, or Cetuximab



Cohen EEW et al. *Lancet* 2019;393:156-67.

KEYNOTE-048 Study Design (NCT02358031)

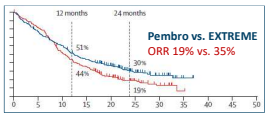


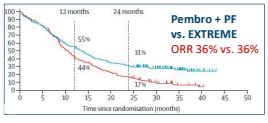
Final analysis data cutoff date: 2/25/19
N=882

Burtness B et al. *Lancet* 2019; 394: 1915-28.

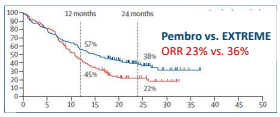
KEYNOTE-048 Outcomes

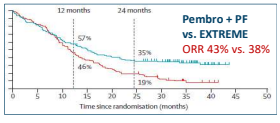
Overall Survival, CPS ≥ 1%





Overall Survival, CPS ≥ 20%





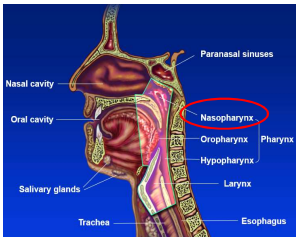
Burtness B et al. *Lancet* 2019; 394: 1915-28.

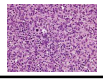
R/M HNSCC: Key Take-Aways

- First-line palliative systemic therapy, platinum-sensitive:
  - **Standard**: Pembrolizumab, with or without platinum-5FU
  - **CPS 0%:** Pembro-PF
  - **CPS ≥ 1%:**
    - High symptom burden: Pembro-PF
    - Low symptom burden: Pembro
- First-line systemic therapy, IO-ineligible: EXTREME
- First or second-line systemic therapy, platinum-resistant:
  - **Standard**: Pembrolizumab or Nivolumab
- Second-line systemic therapy
  - Chemotherapy (singlet or doublet), +/- cetuximab

Johnson DE et al. *Nat Rev Dis Primers* 2020;6(1):92 .

Nasopharyngeal Carcinoma: General Principles

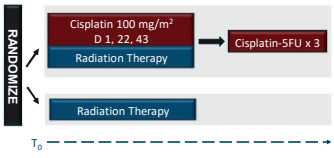


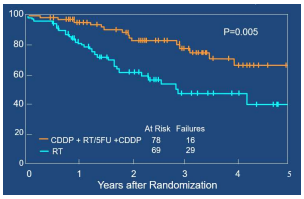


Endemic EBV+
"lymphoepithelioma"

- Etiology
  - Epstein-Barr Virus (EBV): SE Asia
- Histopathology
  - WHO Type I: Keratinizing
  - WHO Type II: Differentiated Non-keratinizing
  - WHO Type III: Undifferentiated Non-keratinizing
- Rarely operable
- Definitive modality: RT
- Systemic failure more common
- Chemotherapy sensitive

PULA Nasopharyngeal Carcinoma: INT 0099





Al-Sarraf et al. *J Clin Oncol* 1998; 16:1310

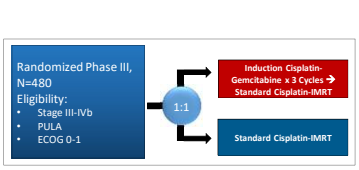
CRT in PULA Nasopharyngeal Carcinoma: MAC-NPC Meta-Analysis

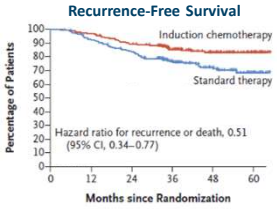
	# Trials	N	HR (95% CI)	P-value
Overall	**19**	**4806**	**0.79 (0.73-0.86)**	**<0.0001**
Induction	6	1039	0.96 (0.80-1.16)	
Adjuvant	4	888	0.87 (0.68-1.12)	
Concurrent	7	1834	0.80 (0.70-0.93)	
Concurrent + Adj.	6	1267	0.65 (0.56-0.76)	

"The additional benefit of adjuvant chemotherapy could not be determined, perhaps because it is so difficult to administer."

Blanchard et al. *Lancet Oncol* 2015; 16:645-55

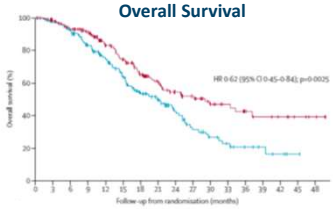
Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma





Zhang Y et al. *N Engl J Med* 2019;381:1124-35.

R/M Nasopharyngeal Carcinoma: Gemcitabine-Cisplatin vs. 5FU-Cisplatin

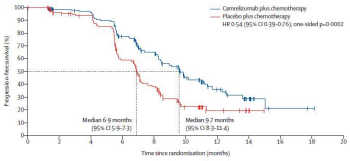


	Gem/Cis	5FU/Cis	P value
ORR	64%	42%	<0.0001
Median OS	29.1 mos	20.9 mos	0.0025

Zhang et al. *Lancet* 2016; 388:1883-92.

R/M Nasopharyngeal Carcinoma:
Gemcitabine-Cisplatin +/- Camrelizumab (anti-PD-1 mAb)

Progression-Free Survival (IRC)



	GCC	GC	P value
ORR	87%	81%	NS
Median PFS	9.7 mos	6.9 mos	0.0002

Yang et al. *Lancet Oncol* 2021; 22:1162-74.

73

Nasopharyngeal Carcinoma: Key Take-Aways

- Endemic cause: EBV
- Definitive modality: RT
- PULA **standard**: Induction cisplatin-gemcitabine → CRT
- R/M **standard**: Cisplatin-gemcitabine + camrelizumab (anti-PD1)

74