Head and Neck Cancer

12th Annual Comprehensive Hematology and Oncology Review Course

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Disclosures

	Cristina Rodriguez(Presenter)	Stephen Smith (spouse)
Institutional Research Funding	AstraZeneca Ayala Bristol Myers Squibb Cue Biopharma Kura Merck	Acerta Pharma BV Astrazeneca Bayer Beigene 11/2019 De Novo Biopharma Incyte Corporation Merck Sharp and Dohme Corp. Pharmacyclics Portola Pharmaceuticals
AdvisoryBoard/ Consultancy	Cue Biopharma	Astrazeneca Millenium/Takeda Beigene Karyopharm KITE pharma Incyte ADC Therapeutics

I. Mucosal Squamous Cell Carcinomas

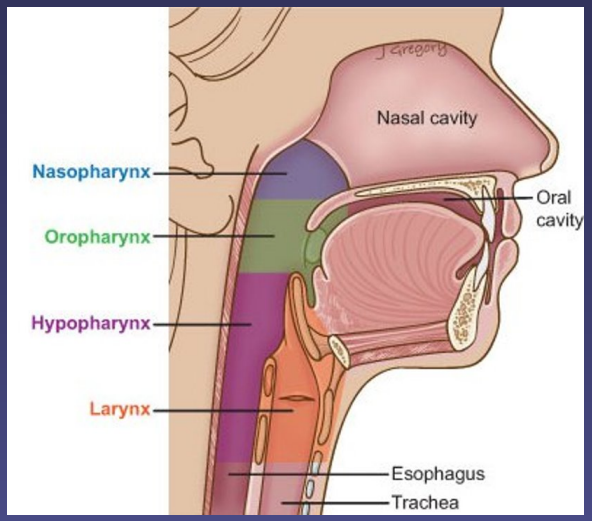
- anatomy epidemiology and pathogenesis
- staging
- treatment by subset
  - locally advanced disease
    - unresectable/organ preservation
    - postoperative therapy
  - metastatic disease

II. Thyroid Cancer

III. Salivary Gland Cancer

Part I

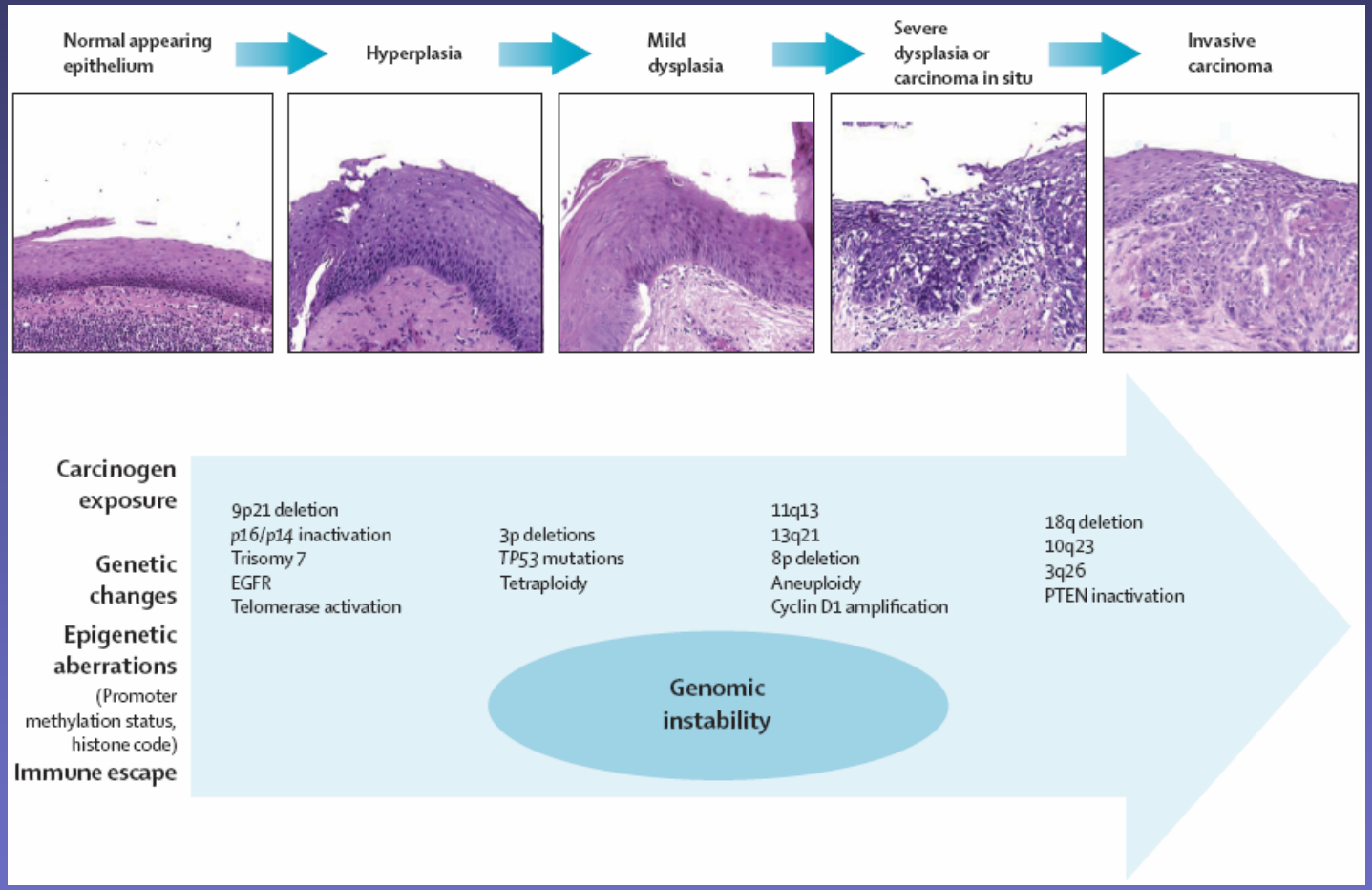
Mucosal squamous cell carcinomas of the head and neck



Pathogenesis

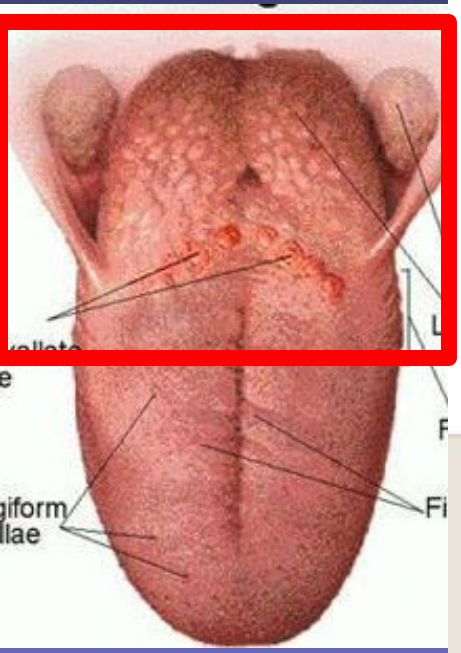
1. Tobacco and alcohol
   - oral cavity, larynx, hypopharynx
   - declining in incidence
   - economic and racial disparity
2. Viral exposure
   - HPV in oropharynx, increasing incidence
   - EBV in nasopharyx

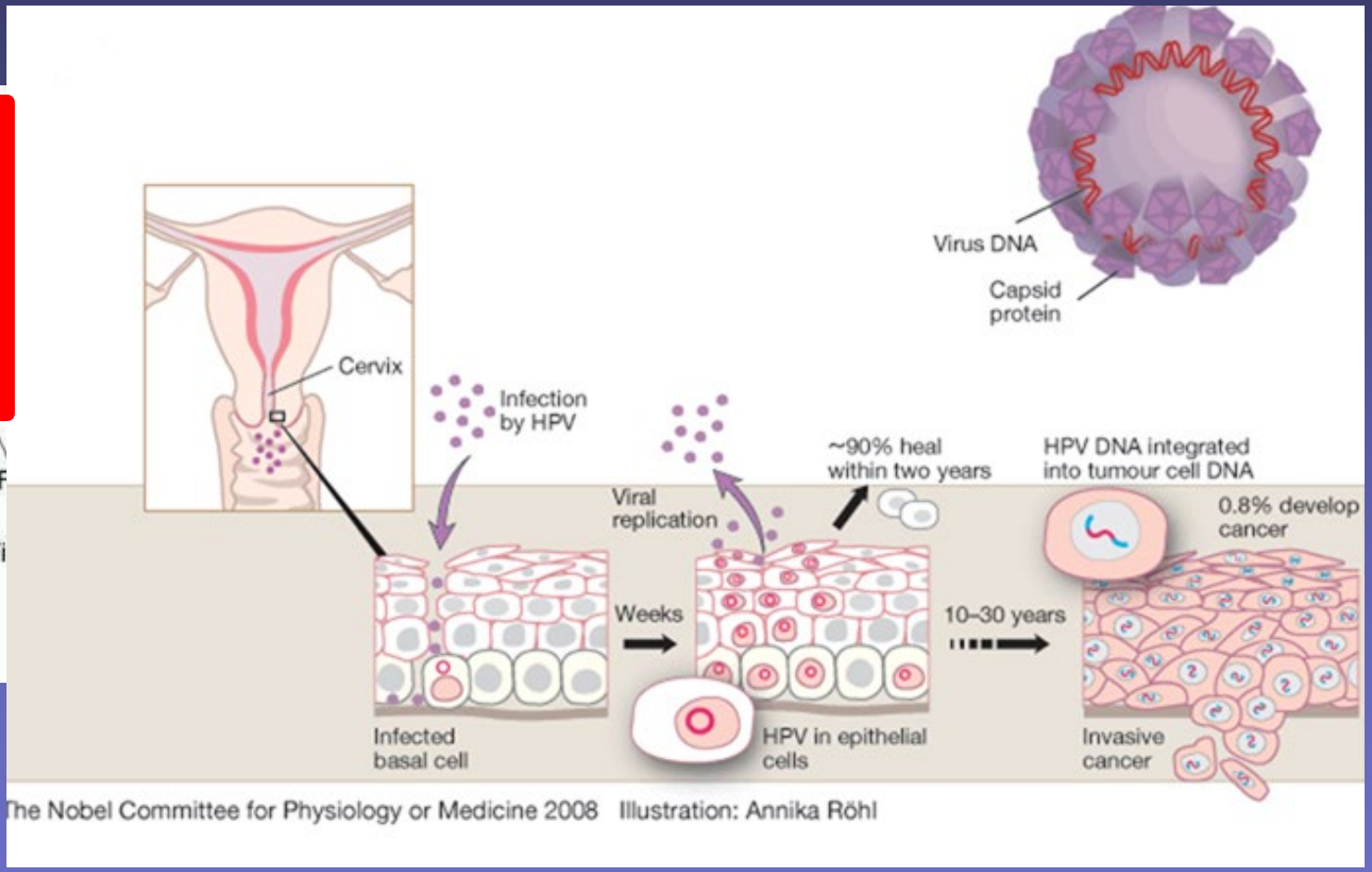
Tobacco and Alcohol



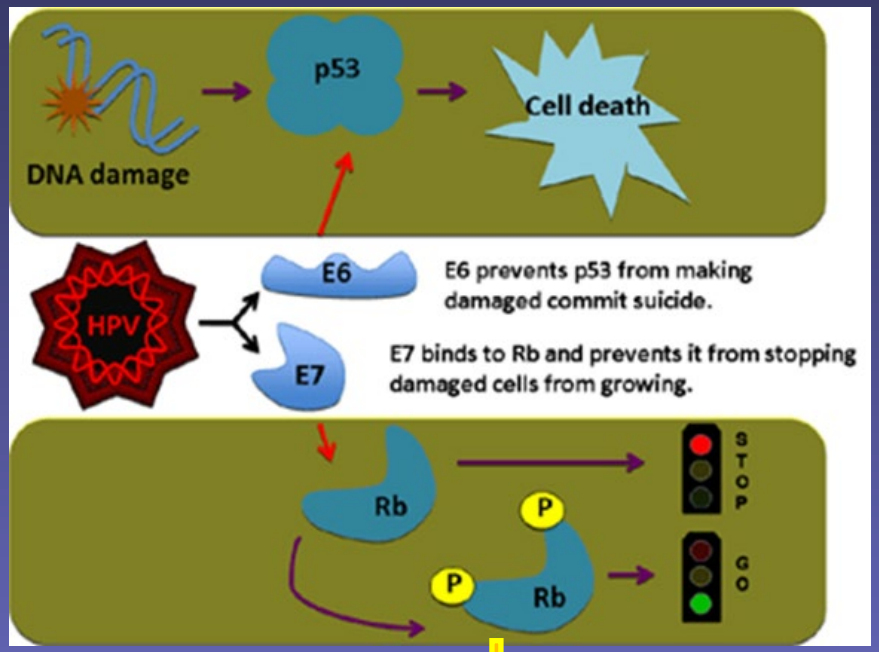
Argiris et al. Lancet. 2008 May 17;371(9625):1695-709.

The oropharynx and HPV16

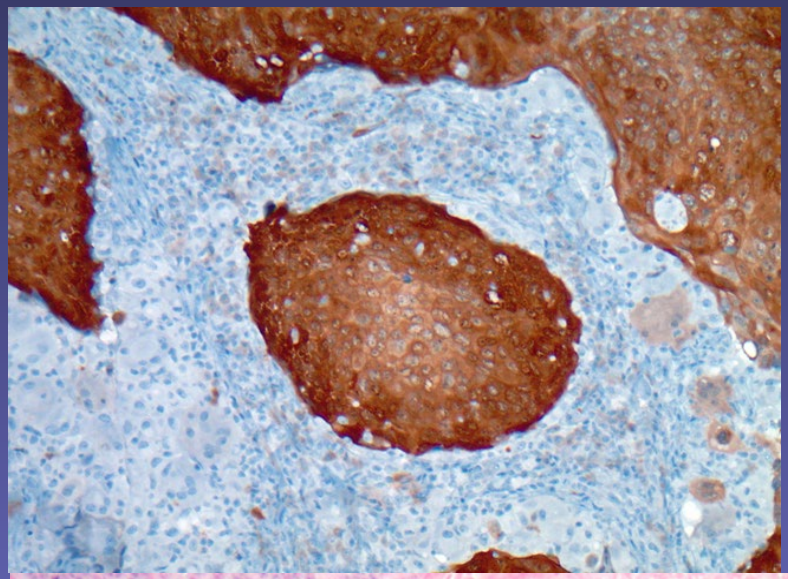


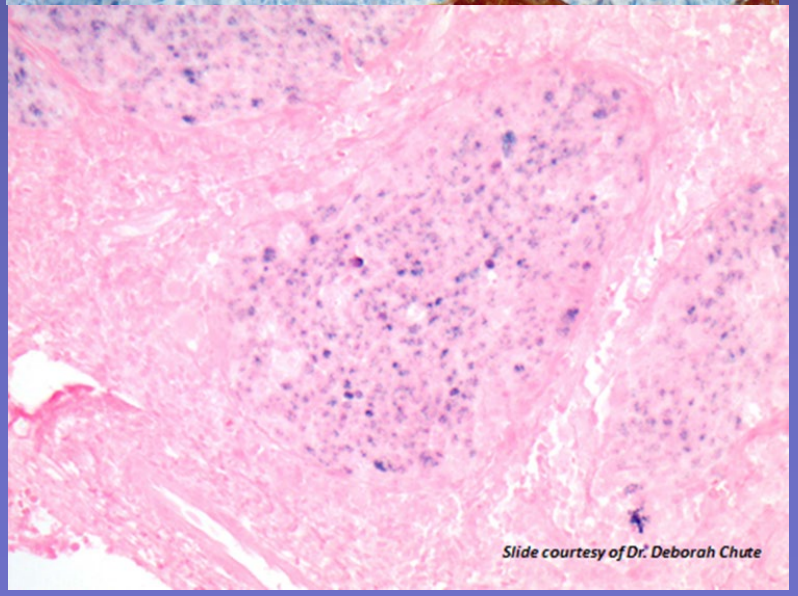


HPV and p16



p16 upregulation





http://genetics.thetech.org/ask/ask359

Patient Characteristics

	HPV related	Non HPV related
Median age	58	68
Race	Caucasian	Higher proportion of African Americans and minorities
Sex	Male	Male
Risk Factors	Sexual activity	Tobacco Alcohol
Performance Status	Minimal comorbidity	Frequent vascular, cardiac, pulmonary comorbidity

Tumor Characteristics

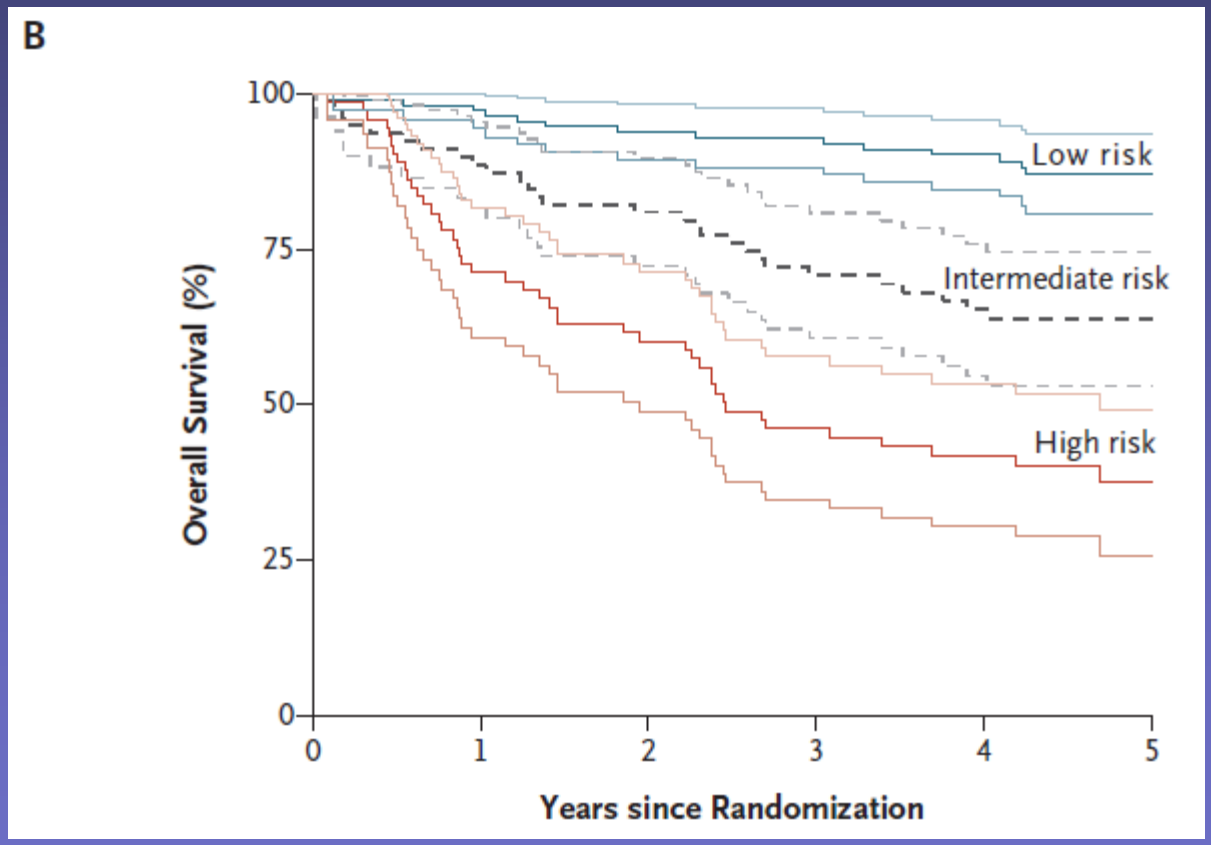
	HPV related	Non HPV related
Subsite	Tonsil Base of tongue	Oral tongue Larynx/Hypopharynx
T/N at presentation	Small T, large N Cystic lymph node appearance	Bulkier primary tumors
Tumor differentiation	Poorly differentiated, nonkeratinizing, basaloid	Well to poorly differentiated
P53, Rb status	Wild type	Mutant

Clinical Behavior

	HPV related	Non HPV related
Chemotherapy responsiveness	High	Lower
Prognosis in curative setting	Excellent 5 year survival	Low rate of long term survivors
Survival expectation in R/M setting	~24 mos	~9mos
Failure patterns	Late recurrences Non pulmonary metastases	Distant, mostly lung Second primary tumors due to condemned mucosa

HPV+ OPC is heterogenous

RTOG 0129



Ang KK et al. N Engl J Med. 2010 Jul 1

Key points on HPV+OPC

- IHC for p16 is highly correlated with HPV-positivity ***in the oropharynx***
- Completion of HPV+ clinical trials have established standards of care
- Treatment deescalation remains a research question in active investigation

Staging

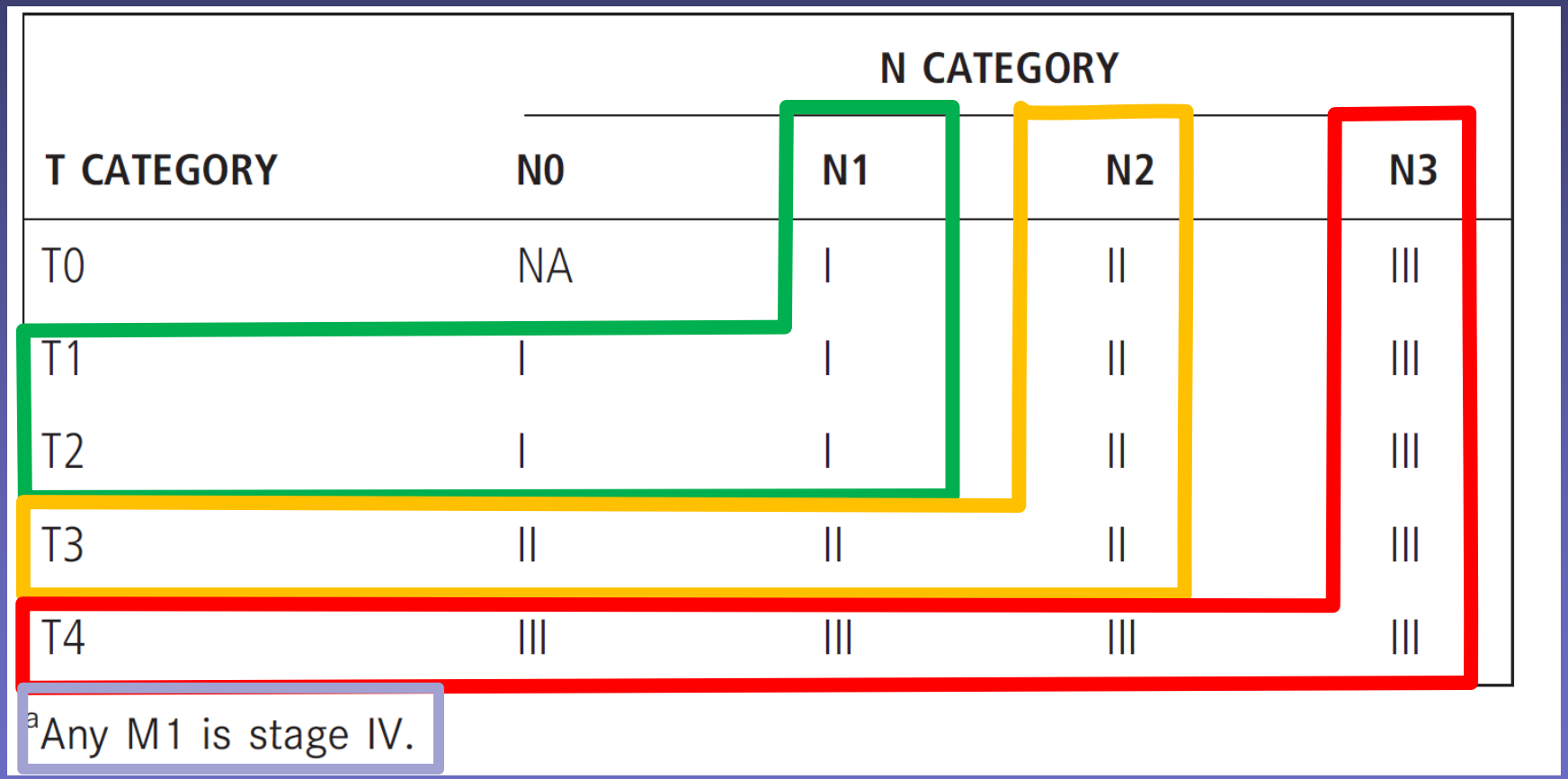
- General Principles:
  - T1-2 lesions small
  - T4 lesions invade into surrounding structures
  - N3 >6cm nodes
- Unknown primaries (Tx)
  - Occur in 10-13% of cases
  - Curable
- **HPV related OPC is now staged separately**

STAGING: AJCC v. 8
NonHPV related

Stage I	T1	N0	M0	15% new diagnoses Surgery or XRT with curative intent 70% or greater 5 year Overall Survival
Stage II	T2	N0	M0	
Stage III	T3 T1-3	N0 N1	M0 M0	75% of new diagnoses Curable with multimodality therapy Usually chemotherapy + XRT 30-50% 5 year over all survival
Stage IVA	T4a T1-4a	N0-1 N2	M0 M0	
Stage IVB	T4b Any T	Any N N3	M0 M0	
Stage IVC	Any T	Any N	M1	10% new diagnoses Incurable, median survival <1 yr

AJCC Cancer Staging Manual, Eighth Edition 2016

STAGING: AJCC v. 8
HPV related OP Cancer



T CATEGORY	N CATEGORY N0	N1	N2	N3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

[a]Any M1 is stage IV.

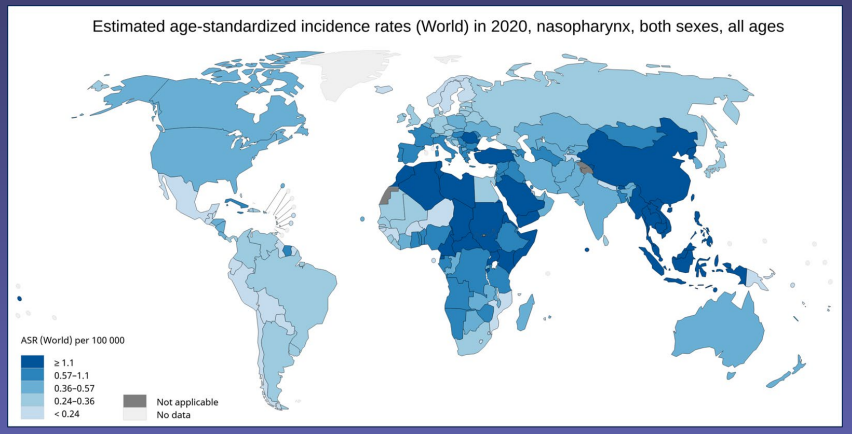
AJCC Cancer Staging Manual, Eighth Edition 2016

Locally Advanced Disease

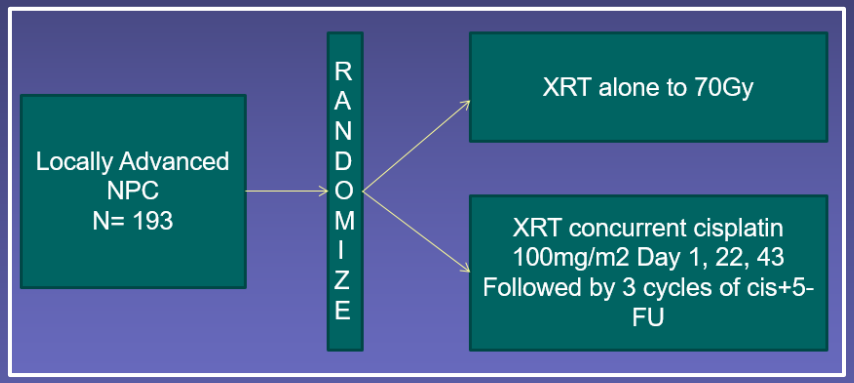
- Curative intent approach is possible
  - Surgery (**preferred for oral cavity**)
  - Radiation
  - Chemotherapy as a single modality: NOT curative
- Multidisciplinary assessment is critical
- Functional outcome/ long term QOL

Organ Preservation: Nasopharyngeal Carcinoma (NPC)

- Epidemiologically distinct
- EBV associated
- Unresectable at diagnosis
- Classic presentation:
  - Middle ear effusions in adults
  - Level V (post triangle) LAD
- Intuitive subset to explore nonsurgical, curative intent therapy



NPC: Intergroup 0099



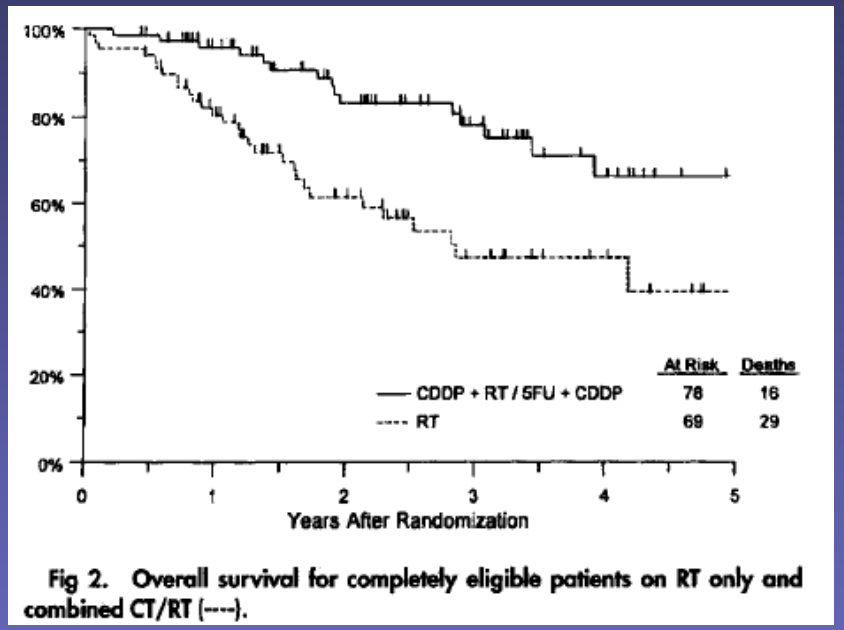


Fig 2. Overall survival for completely eligible patients on RT only and combined CT/RT (----).

- PFS and OS advantage to experimental arm
- Endemic area Phase III studies comparing CRT to CRT + adj cisFU negative

Al- Sarraf. J Clin Oncol 16:1310-1217 1998

Locally Advanced NPC: systemic therapy strategies

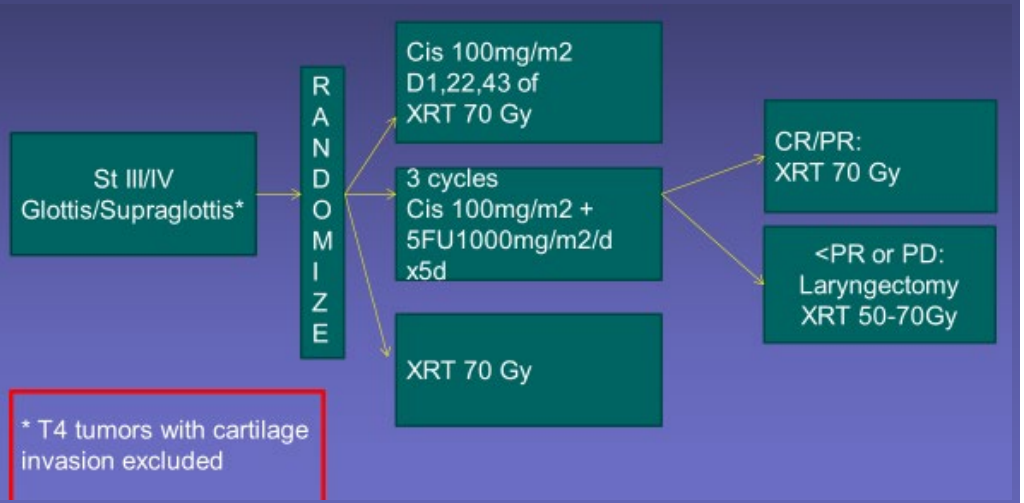
Therapeutic Strategy	Stage	Evidence
Weekly cisplatin + XRT[1]	II-IVB	OR/Toxicity similar
Neoadjuvant gem+cis followed by cisXRT[2]	Stage III-IVB Heavy nodal burden	RFS and distant FFS benefit
Adjuvant capecitabine post cisXRT[3]	III-IVA	FFS and OS Benefit

[1]Lee et al. Ann Oncol 2015 Oct 1
[2]Zhang et al. N Engl J Med. 2019 May 31
[3]Chen et al. Lancet 2021 Jun 4

Organ Preservation: Laryngeal Carcinoma

- Laryngectomy was historical standard of care
- VA Larynx Trial (NEJM 1991)
  - Randomized phase III study
  - surgery vs. chemo followed by XRT for PR/CR
  - 64% in experimental arm had successful organ preservation
  - OS similar, attributed to successful surgical salvage

Landmark Studies in Organ Preservation: Larynx Ca RTOG 91-11



Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.

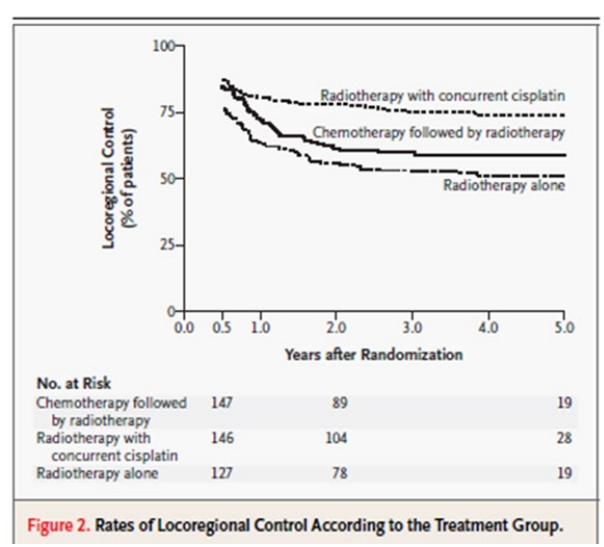


Figure 2. Rates of Locoregional Control According to the Treatment Group.

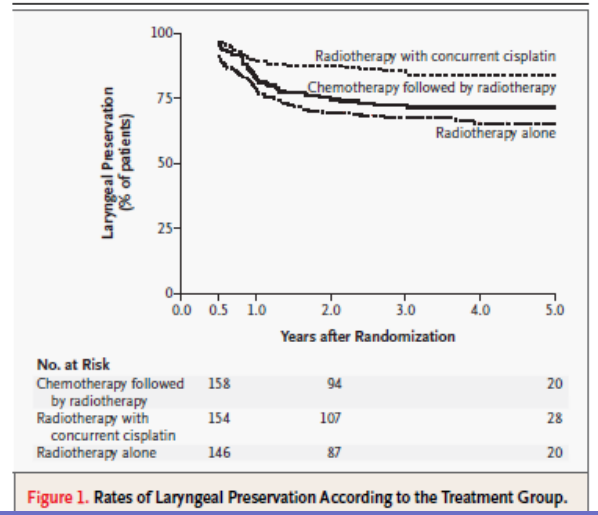


Figure 1. Rates of Laryngeal Preservation According to the Treatment Group.

Organ Preservation: Larynx Cancer RTOG 91-11

Table 2. Grade 3 or 4 Acute Toxic Effects, According to the Treatment Group.*

Toxic Effect	Cisplatin plus Fluorouracil Followed by Radiotherapy						Radiotherapy with Concurrent Cisplatin (N=171)			Radiotherapy Alone (N=171)		
	Chemotherapy Period (N=168)			Radiotherapy Period (N=156)								
	grade 3	grade 4	total	grade 3	grade 4	total	grade 3	grade 4	total	grade 3	grade 4	total
	number of patients (percent)											
Hematologic	43	44	87 (52)	13	10	23 (15)	64	17	81 (47)	3	2	5 (3)
Infection	4	5	9 (5)	2	0	2 (1)	7	0	7 (4)	2	0	2 (1)
Mucosal (stomatitis)	27	7	34 (20)	36	2	38 (24)	64	9	73 (43)	40	1	41 (24)
Pharyngeal or esophageal	—	—	—	30	0	30 (19)	60	0	60 (35)	32	0	32 (19)
Laryngeal	—	—	—	20	1	21 (13)	29	2	31 (18)	23	5	28 (16)
Dermatologic (in radiation field)	—	—	—	16	0	16 (10)	10	2	12 (7)	15	0	15 (9)
Nausea or vomiting	20	3	23 (14)	0	0	0	28	7	35 (20)	0	0	0
Renal or genitourinary	3	0	3 (2)	2	0	2 (1)	6	1	7 (4)	0	0	0
Neurologic	5	1	6 (4)	0	0	0	8	1	9 (5)	0	0	0
Other	20	7	27 (16)	16	2	18 (12)	58	11	69 (40)	9	1	10 (6)
Overall maximal severity	62	49	111 (66)	66	13	79 (51)	99	32	131 (77)	71	9	80 (47)

Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.

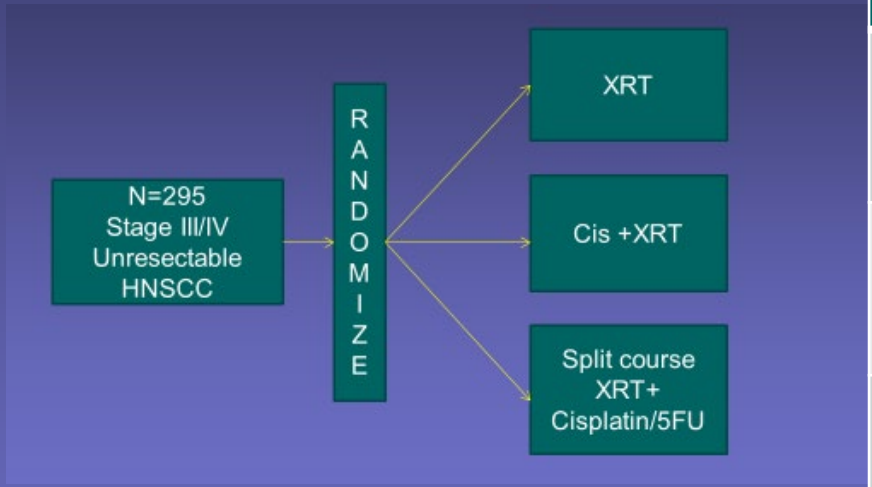
Landmark Studies in Organ Preservation: RTOG 91-11

- Distant metastasis decreased in groups receiving chemotherapy
- Overall survival not significantly different among treatment groups
  - Success of salvage surgery
- Long term results reported in 2013
  - Results hold up with 6.9 years median F/U

Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.

Forastiere A et al. J Clin Oncol. 2013 Mar 1;31(7):845-52.

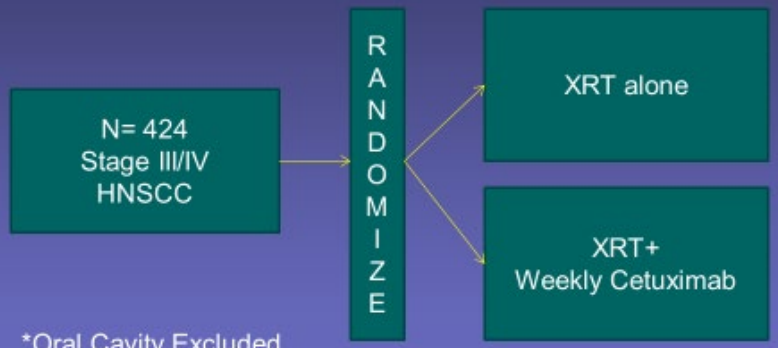
Organ Preservation: Intergroup Study



	Arm A XRT	Arm B cisXRT	Arm C splitXRT
OS (3yr)	23%	**37% A vs B p=0.14**	27%
DSSurvival (3yr)	33%	**51% A vs B p=0.01**	41%
Distant Failure	17.9%	21.8%	19.1%
Toxicity	51%	**85% A vs B p<.0001**	**72% A vs C P<.0001**

Adelstein et al. J Clin Oncol, 2003; 21(1):92-8.

Organ Preservation with cetuximab: Bonner Study



	XRT alone	XRT+ Cetux	p Value
LRCl(3yr)	34%	**47%**	p<.01
PFS(3yr)	31%	**37%**	p=.04
OS(3yr)	45%	**55%**	p=.05
Gr ≥3 toxicity	52%	56%	ND

Bonner JA. NEJM 2006:354:567-78.

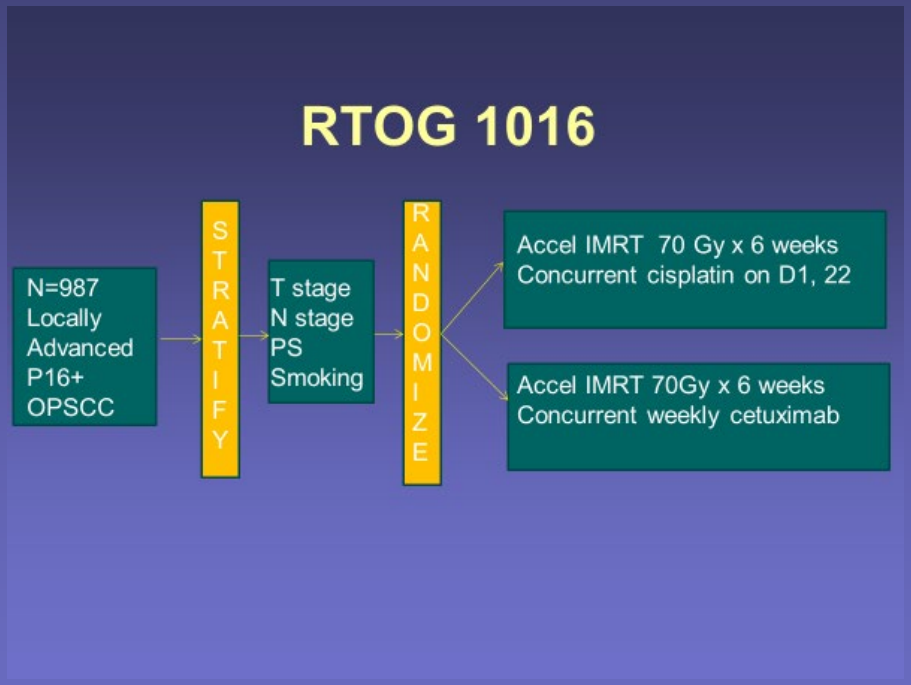
Landmark Studies in Organ Preservation: Bonner Study

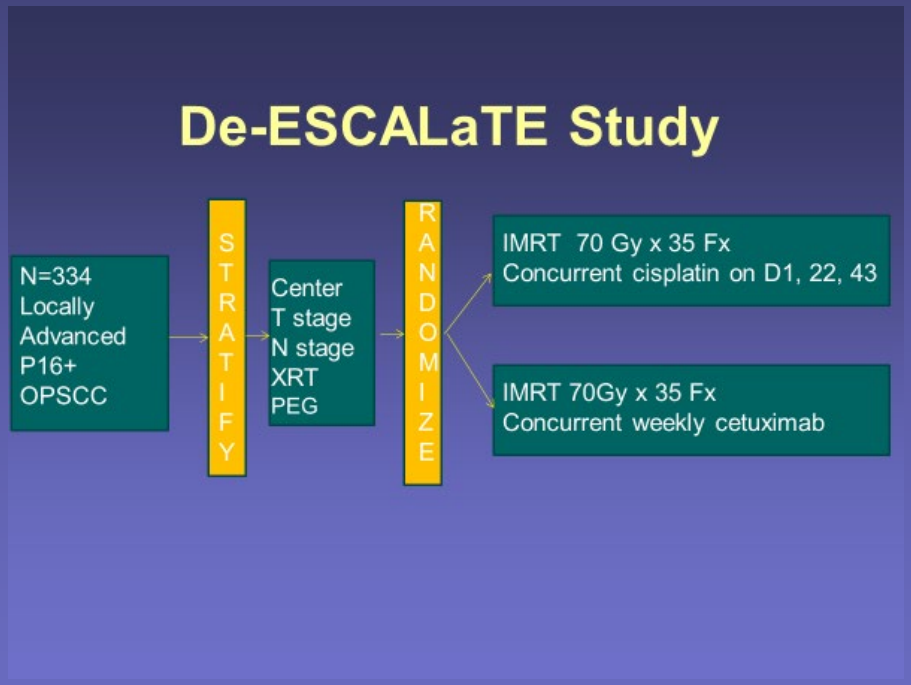
- 60% had oropharynx primaries
  –Subsequent HPV testing shows lower (but present) magnitude of benefit in HPV negative OP pts
- No impact on distant metastatic failure rate
- No identifiable biomarker for response
- Control arm not regarded as standard of care
  – RTOG 1016 with published showing inferiority compared to cis+XRT in HPV+ population

Bonner JA. NEJM 2006:354:567-78.

Rosenthal et al. J Clin Oncol. 2016 Apr 20;34(12):1300-8

Organ Preservation: Oropharyngeal Carcinoma

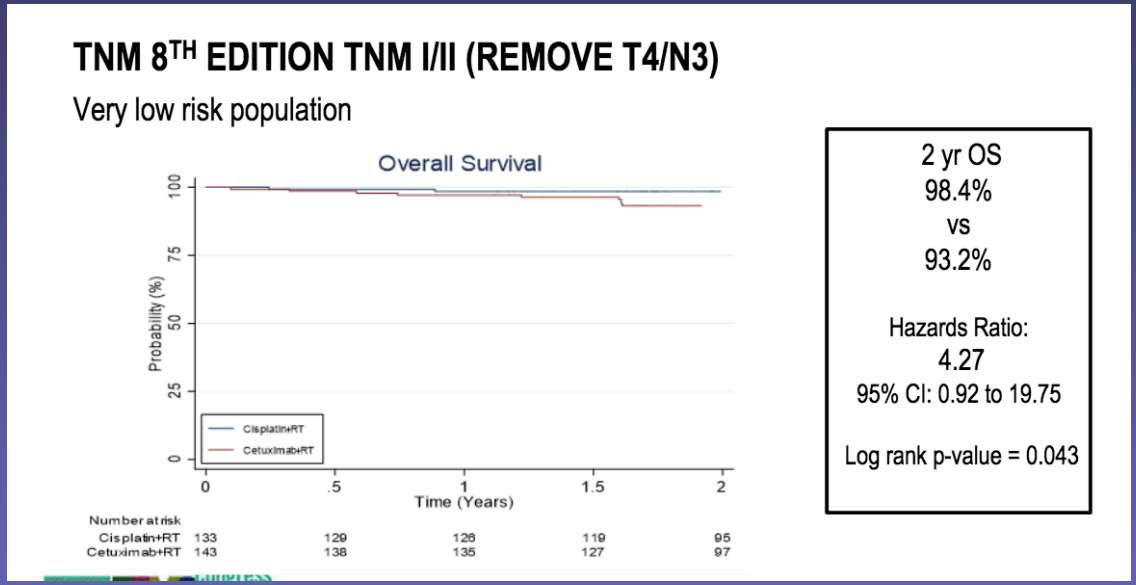




Gillison et al. Lancet.2019 Jan 5;393(10166):40-50
Mehanna et al. Lancet. 2019 Jan 5;393(10166):51-60

Phase III clinical trials in HPV + OPC

- RTOG 1016 and De-ESCALaTE
  - Superiority of cisplatinXRT vs. CetuxXRT in OS, LRC
  - No difference in acute/late tox
  - T score higher in cisXRT in 1016



De-escalation remains a research question in HPV+ OPC

Gillison et al. 2019 Jan 5;393(10166):40-50
Mehanna et al. Lancet. 2019 Jan 5;393(10166):51-60

Functional Imaging after definitive chemoradiation

- Planned neck dissections (ND) post chemoXRT was standard of care for N3 or bulky N2b disease
- PET-NECK randomized 564 pts to ND vs. surveillance with PET-CT at 12 weeks post CRT
- Necks with nonPETavid LNs <1cm observed in exp arm
- Less NDs done in exp arm, no difference in OS

Mehanna et al. N Engl J Med. 2016 Apr 14;374(15):1444-54

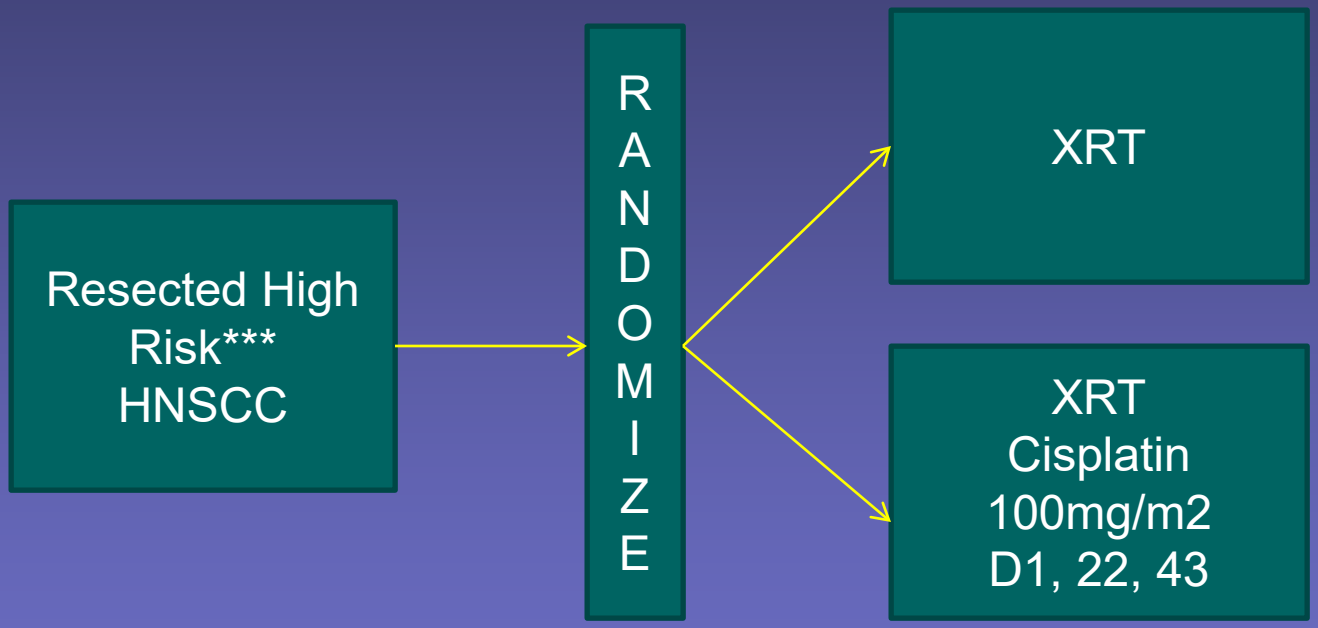
KEY POINTS: Locally advanced disease

- Organ preservation/unresectable disease
  - Concurrent bolus cisplatin based chemoradiation supported by RTOG 91-11, Intergroup, RTOG 1016, DE-ESCALaTE, Intergroup 099
  - CetuximabXRT is inferior to cisXRT in the HPV+OPC
  - Neoadjuvant gem/cis for locally advanced NPC with nodal burden
- PET-CT can be used after chemoXRT to guide need for neck dissection

KEY POINTS: Locally advanced disease

- A multidisciplinary approach is essential
- Patient selection is critical
  - Not everyone is meant for nonsurgical treatment approach
  - Remember exclusion criteria in organ preservation studies
- Deescalation in HPV+ remains a research question

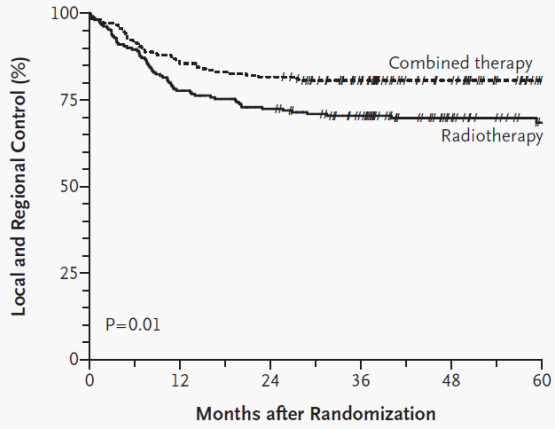
Postoperative therapy RTOG and EORTC studies



*** Eligibility criteria varied in 2 studies

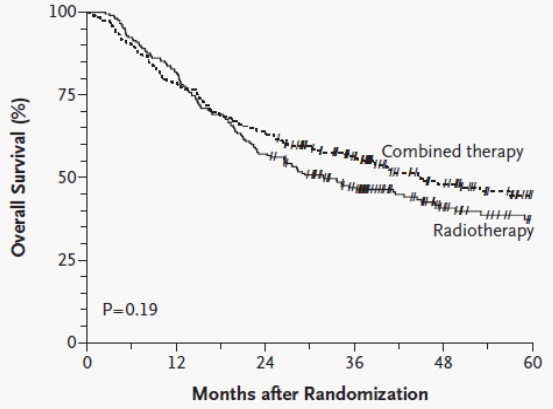
Bernier et al. N Engl J Med. 2004;350(19):1945
Cooper et al. N Engl J Med. 2004;350(19):1937

RTOG 9501



No. at Risk			
Combined therapy	206	123	26
Radiotherapy	210	108	24

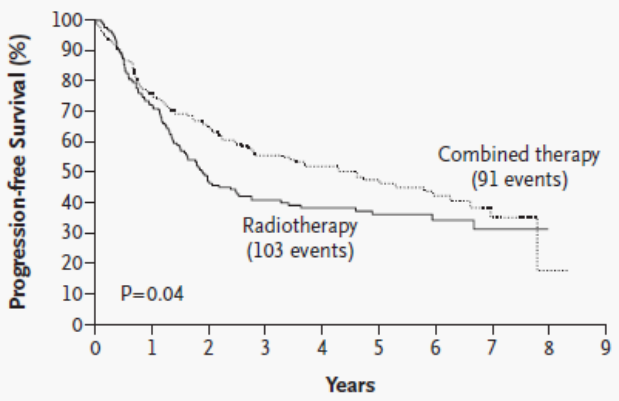
Figure 1. Rates of Local and Regional Control.



No. at Risk			
Combined therapy	206	132	27
Radiotherapy	210	120	26

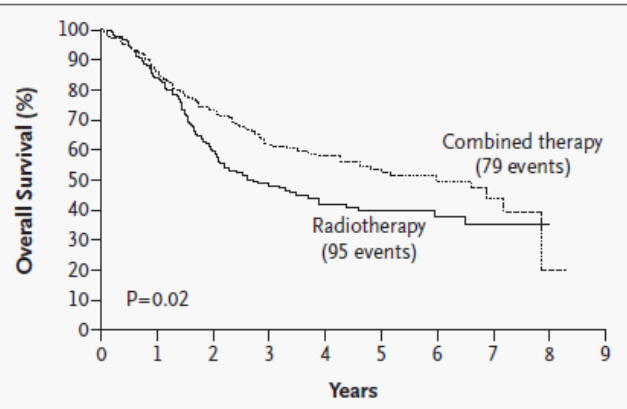
Figure 3. Kaplan–Meier Estimates of Overall Survival.
Overall survival did not differ significantly between groups (P=0.19 by the log-

EORTC 22931



No. at Risk									
Radiotherapy	167	119	73	57	45	30	18	9	0
Combined therapy	167	125	105	85	66	42	29	10	1

Figure 1. Kaplan–Meier Estimates of Progression-free Survival.



No. at Risk									
Radiotherapy	167	139	93	68	49	31	19	9	0
Combined therapy	167	141	118	93	72	47	33	11	1

Figure 2. Kaplan–Meier Estimates of Overall Survival.

Pooled Analysis

Overall survival advantage to Cisplatin + XRT for

- Positive surgical margin
- Extracapsular extension

LRC, PFS benefit confirmed

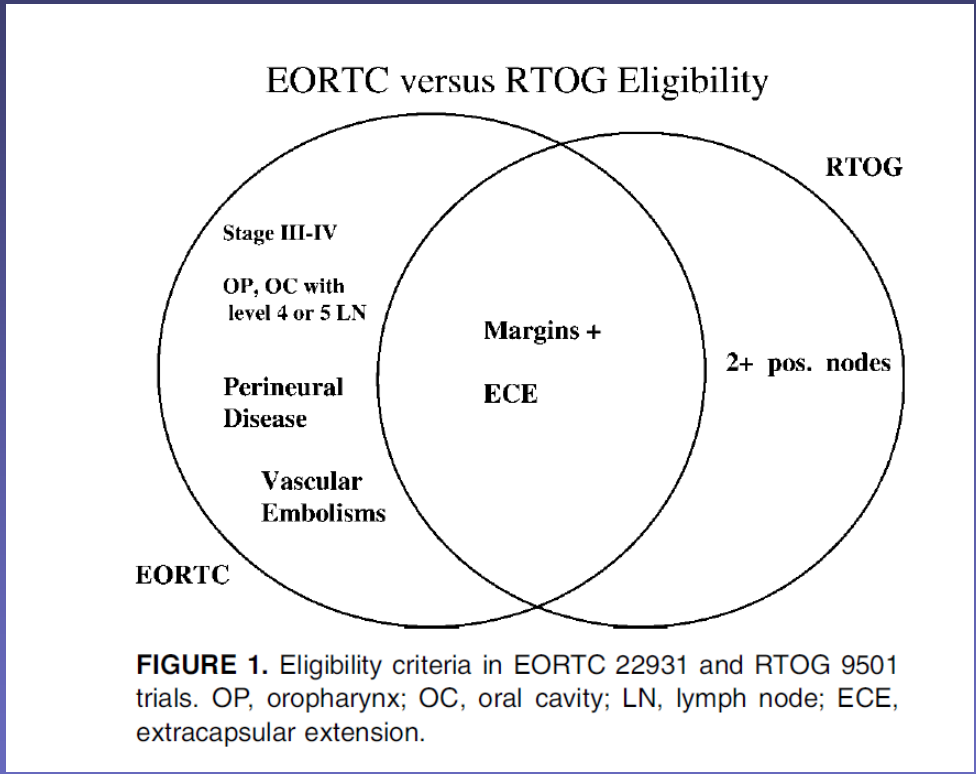


FIGURE 1. Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.

Bernier et al. Head Neck. 2005 Oct;27(10):843-50.

Alternative cisplatin dosing + XRT in postoperative setting

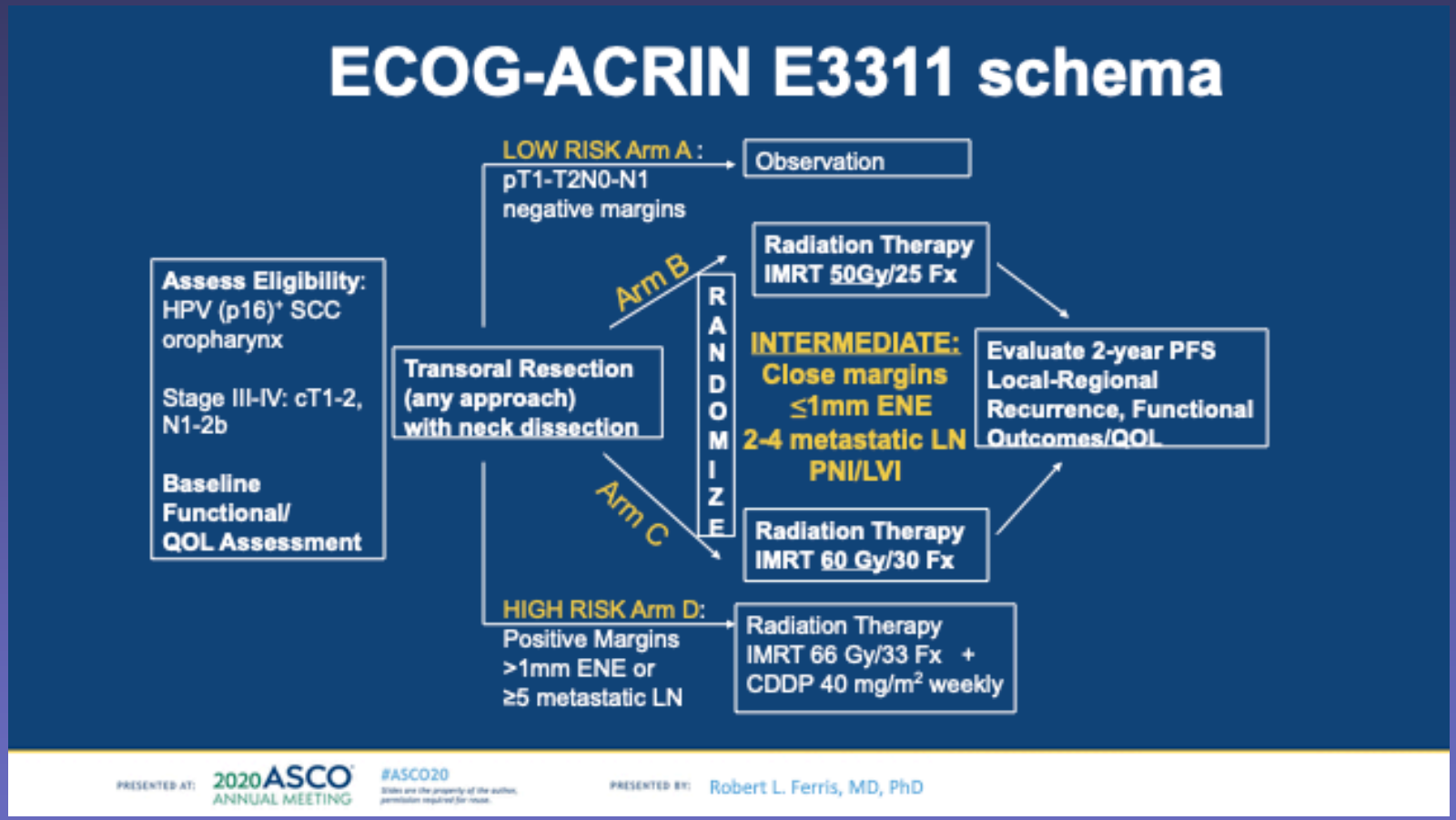
- Randomized phase III study of 30mg/m2 vs 100mg/m2
  - Indian population, mostly adjuvant post resection
  - Inferior LRC with weekly

***Noronha, et al JCO 2018*.**

- Randomized phase III study of 40mg/m2 vs 100mg/m2
  - Japanese study in adjuvant setting for high risk disease
  - Weekly dosing non-inferior

Kiyota et al. ASCO 2020 Abs 6502

Postop treatment in HPV+ OPC



- Arm B met 2 yr PFS threshold, will be compared to nonsurgical therapy

KEY POINTS: postoperative therapy

- High Risk pathologic features that benefit from concurrent cis+XRT:
  - Positive margins
  - Extracapsular nodal extension
- Most data is with 100mg/m2 on days 1,22, 43 of therapy
  - If weekly cisplatin given, use 40mg/m2

The Cisplatin Ineligible Patient

- Limited randomized data specific to population (this is changing)

Trial	Treatment Population	N	Intervention
PembroRad **NCT02707588**	Cisplatin-unfit locally advanced HNSCC	131	Pembro +XRT vs Cetux XRT
REACH **NCT02999087**	Stage III/IVb HNSCC	688	Avel + cis + RT vs cis + RT Avel + cetux + RT vs cis + RT
NRG-HN004 **NCT03258554**	Cisplatin-unfit locally advanced HNSCC	523	Durva + RT vs cetux + RT

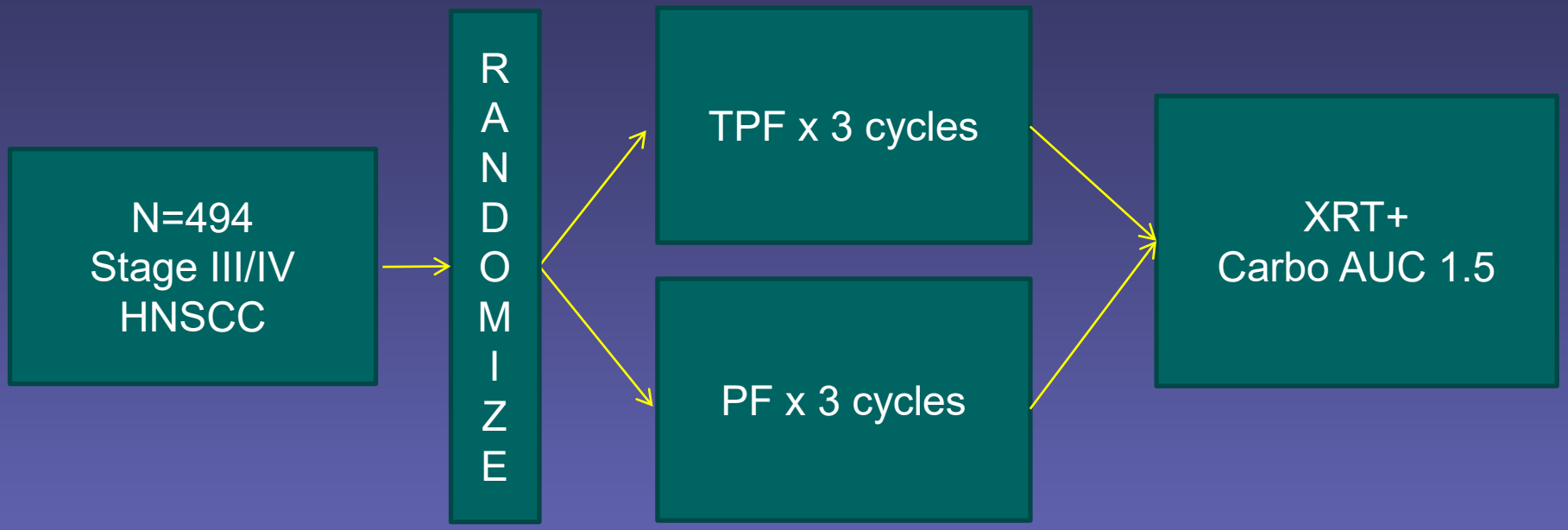
- No data in the postoperative setting

Non bolus cisplatin XRT regimens in Phase III trials

Trial	N	N(%) p16+ OPSCC	Arms	Results
GORTEC 9401[1]	226	Unknown	XRT vs Carbo+5FU XRT	OS DFS superior in carbo+F5u XRT
GORTEC 2007-01[2]	406	41(21%) of 236 OPC	CetuxXRT vs Carbo5FUCetuxXRT	PFS and LRC superior in Carbo5FUCetuxXRT
Bonner IMCL9815[3,4]	253	75(41%) of evaluable pts	XRT vs Cetux XRT	OS and LRC superior in CetuxXRT
TROG 12.01 NCT01855451	189	189 (100%)	Weekly cisplatin +70Gy Cetuximab +70Gy	Pending

[1]Denis et al. J Clin Oncol 2004
[2]Tao et al. J Clin Oncol 2018
[3]Rosenthal et al. J Clin Oncol 2015
[4]Bonner et al. N Eng J Med 2006

Induction Chemotherapy: TAX 324



RESULTS:

- OS, CR rates statistically better in TPF Arm
- Higher rates of hematologic toxicities in TPF arm, with some pts unable to proceed with XRT
- Controversial design due to control arm

Posner M et al. N Engl J Med. 2007 Oct 25;357(17):1705-15.

Induction vs. ChemoXRT trials

Trial	Design	Accrual	OS/PFS	Other findings
PARADIGM[1]	R Phase III TPF chXRT vs Cis XRT	Planned: 330 Actual: 145	No difference in 3 yr PFS and OS	Higher rate of Neutropenic Fever in Induction Arm
DECIDE[2]	R Phase III UofC ChXRT Vs TPF chXRT	Actual: 285	No difference in ORR, OS, PFS	No difference in distant failure

In both studies: control arm performed better than historical controls

[1] ***Haddad R et al. Lancet Oncol. 2013 Mar;14(3):257-64***

[2] ***Cohen et al. J Clin Oncol. 2014 Sep 1;32(25):2735-43.***

Ongoing Clinical Investigation: Themes

- Therapeutic intensification
  - Incorporation of IO agents into standard of care chemoXRT, including neoadjuvant and maintenance PD1
- Therapeutic deintensifcation for HPV+
  - Upfront surgical approaches
  - IO + XRT in NRG HN005
- Cisplatin ineligible pts
  - NRG HN004, Reach study

Clinical Investigation: definitive therapy

Trial	Treatment Population	N	Intervention
KEYNOTE-412[1]	LAHNSCC (HPV+ for select stages/primary sites)	780	Pembro + cis + RT vs. placebo + cis + RT
JAVELIN HN100[2]	LAHNSCC HPV- HNSCC (HPV+ for select stages/primary sites)	640	Avel + chemoRT vs chemoRT alone
IMSTAR-HN[3]	Stage III/IV p16- OPC, L, HP, OC	276	Neoadjuvant nivo, surgery, and adj chemoRT + adj nivo ± ipi vs SOC surgery + chemoRT
KEYNOTE-689[4]	Resectable stage III/IVa L, HP, OC, p16-OPC Stage III p16+ OPC	600	Pembro prior to surgery/with adj chemoRT vs surgery
IMvoke010[5]	LAHNSCC treated with curative-intent therapy	400	Atezo vs placebo after chemoRT
KEYCHAIN[6]	LAHNSCC p16+ OPC, L, OC	114	Cis + RT vs pembro + RT
HN005[7]	Locally advanced good risk p16+ OPC	711	Cis 70GyRT vs Cis 60GyRT vs Nivo 60GyRT

1. NCT03040999. 2. NCT02952586. 3. NCT03700905. 4. NCT03765918. 5. NCT03452137
6. NCT03383094 7. *NCT03952585*

Ongoing clinical investigation: postoperative therapy

Trial (NCT Identifier)	Phase	N	Endpt	Intervention
ECOG 3311 (NCT01898494)	IIR	511	PFS	TORS followed by risk stratification. Low: observation Intermediate: randomized to 50 vs 60 Gy XRT High: 66Gy + weekly cisplatin
PATHOS (NCT02215265)	III	242	QOL/OS	TORS followed by risk stratification. Low: observation Intermediate: randomized to 50 vs 60 Gy High: randomized between 60Gy +/- cisplatin
ORATOR2 (NCT03210103)	IIR	140	OS	Randomize XRT +/- chemotherapy vs TORS
SIRS (NCT02072148)	II	200	DFS LRC	TORS followed by risk stratification Low: observation Intermediate: 50 Gy XRT High: 60 Gy XRT + cisplatin
DELPHII (NCT03396718)	I	384	LRC	TORS followed by risk stratification. Low: observation; Intermediate: 50 Gy XRT High: 60 Gy XRT + cisplatin

Metastatic Disease

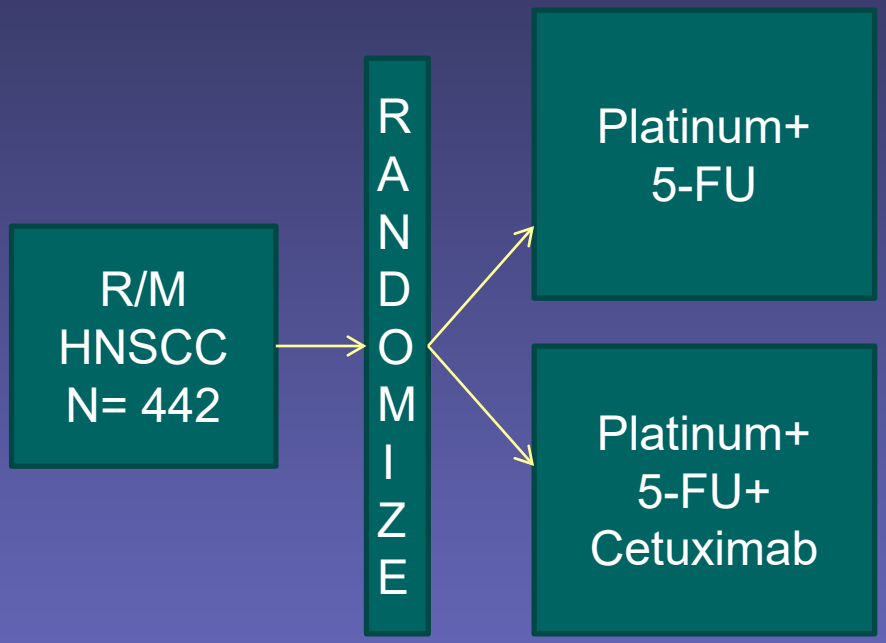
- Poor prognosis, survival measured in months (longer for HPV+ patients)

- Multiple active single agents

- Combination vs. single agent chemotherapy trials reproducibly:

1. Improve response rates
2. Increase toxicity
3. Do not improve in survival

Until 2008: EXTREME trial



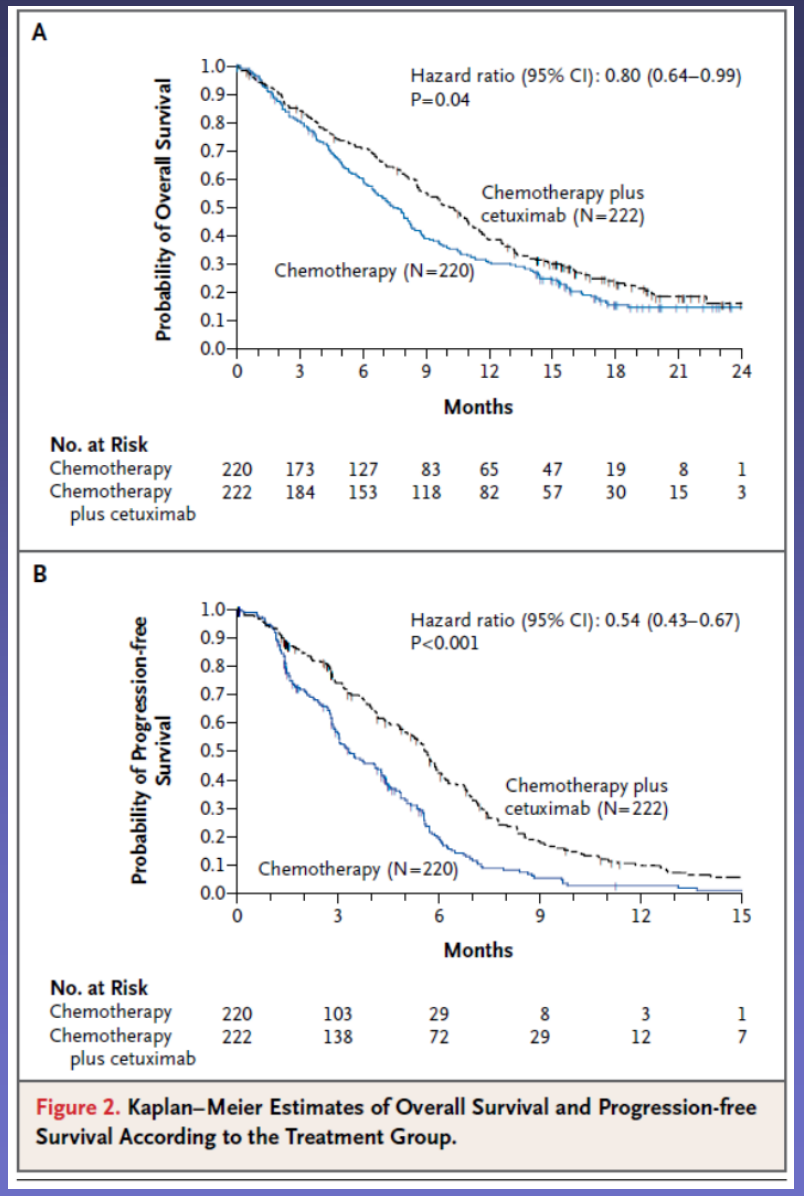
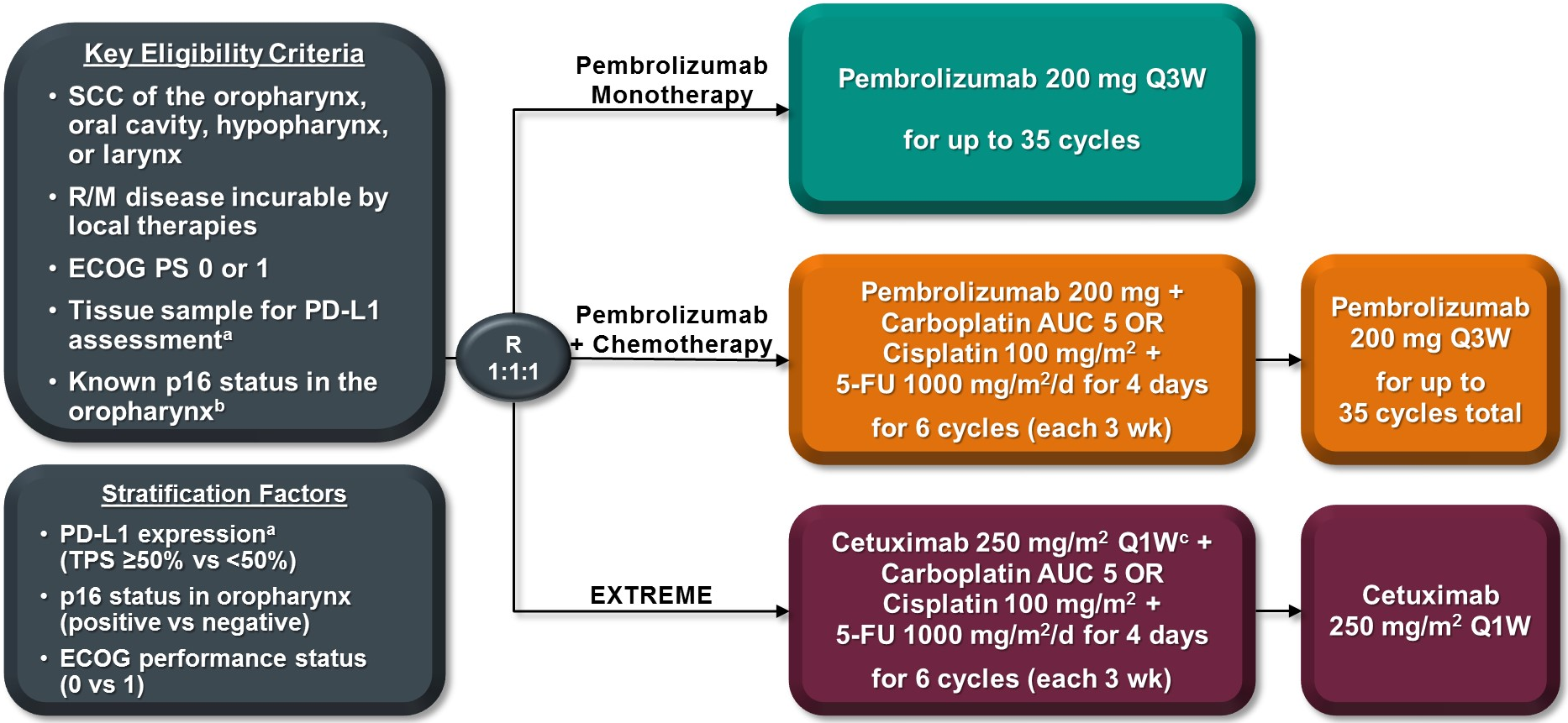


Figure 2. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival According to the Treatment Group.

Vermorken J et al. N Engl J Med 2008;359:1116-1127

PD1 inhibitor in First Line R/M Setting

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/m^2.

Summary of Overall Su

Note:
Results for CPS <1 not reported
Pembro + chemo high rates of Gr 3 AE

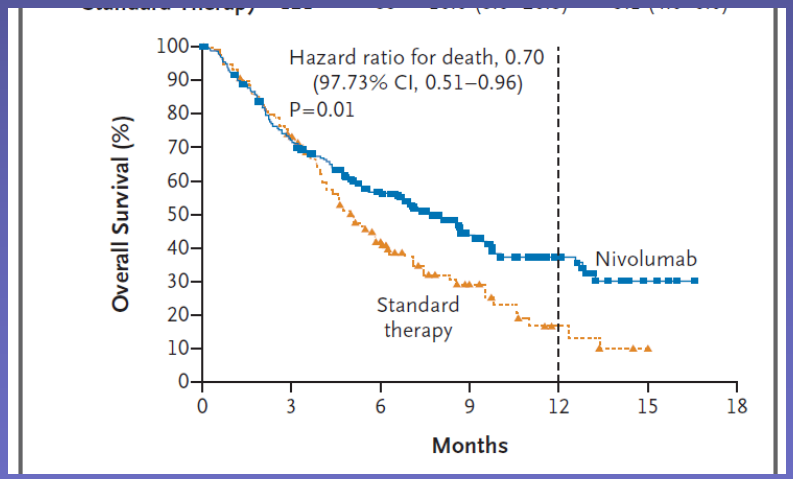
Population	IA2[1] HR (95% CI)	FA HR (95% CI)
Pembrolizumab monotherapy vs EXTREME		
PD-L1 CPS ≥20	0.61 (0.45–0.83); *P* = 0.0007[a]	0.58 (0.44–0.78)[c]
PD-L1 CPS ≥1	0.78 (0.64–0.96); *P* = 0.0086[a]	0.74 (0.61–0.90)[c]
Total	0.85 (0.71–1.03)[b]	0.83 (0.70–0.99); *P* = 0.0199[d]
Pembrolizumab + chemotherapy vs EXTREME		
PD-L1 CPS ≥20	—	0.60 (0.45–0.82); *P* = 0.0004[a]
PD-L1 CPS ≥1	—	0.65 (0.53–0.80); *P* < 0.0001[a]
Total	0.77 (0.63–0.93); *P* = 0.0034[a,b]	0.72 (0.60–0.87)[c]

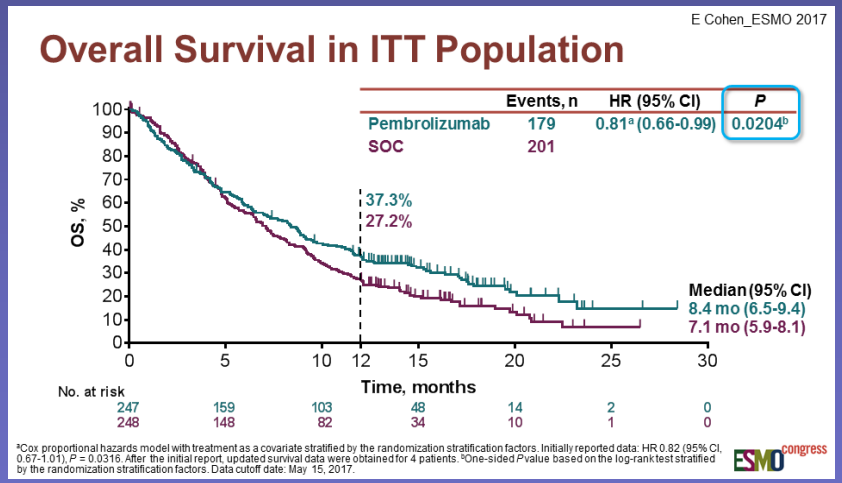
[a]Superiority demonstrated. [b]Noninferiority demonstrated (boundary of 1.2). [c]No statistical testing performed. [d]Superiority not demonstrated.

1. Burtness B et al. *Ann Oncol* 2018;29(suppl 8):LBA8_PR.

PD1 inhibitors: second line (post-cisplatin)

- Two similarly designed trials
  - Checkmate 141 nivo vs clinician choice
  - Keynote-40 pembro vs clinician choice
- PDL1 expression agnostic





Ferris, et al. NEJM 2016 Nov 10
Cohen et al. Lancet 2019 Jan 12

1st Line Metastatic NPC: Gem Cis + PD1 inhibitor

- Two similarly designed trials
  - JUPITER-02 GC+ Toripalimab vs GC+ placebo
  - CAPTAIN-1ST GC+ camrelizumab vs GC+ placebo
- PDL1 expression agnostic
- Both with superior PFS in PD1+GC arms
- OS superior in PD1+ toripalimab

Xu et al ASCO 2021 Abstract LBA2
Zhang et al ASCO 2021 Abstract 6000

KEY POINTS: Metastatic Disease

- Non NPC
  - Pembro/Plat/5-FU prolongs OS compared EXTREME in R/M setting
  - Pembro monotherapy with OS benefit in CPS≥1
  - Nivolumab and Pembrolizumab prolong OS in plat treated R/M disease compared to 2nd line systemic tx (independent of PDL1 or HPV status)
- NPC
  - Gem+Cis+PD1 improves PFS compared to GemCis

Future landscape of head and neck cancer therapy

- Deescalation studies in good risk HPV
  - Upfront surgical resection (robotic) vs lower dose XRT
- Immune checkpoint combinations in R/M
- Cellular therapeutics in R/M
- Integration of immune checkpoint inhibitors into curative intent therapy
- Epidemiologic changes with prophylactic vaccines

Part II
Thyroid Cancer

Thyroid Cancer Review

- **Differentiated Thyroid Cancer**
  - Papillary (85%) and Follicular (5%)
  - Familial in 3-9% (AFP,Cowden's, Werner's)

- **Medullary thyroid Cancer (5%)**
  - Parafollicullar C cells, produce calcitonin
  - Familial (less common, MEN2) or Sporadic (majority)
  - RET

- **Anaplastic thyroid Cancer**
  - Elderly patients, rapid growth, airway compromise
  - Evolved from prior differentiated cancers

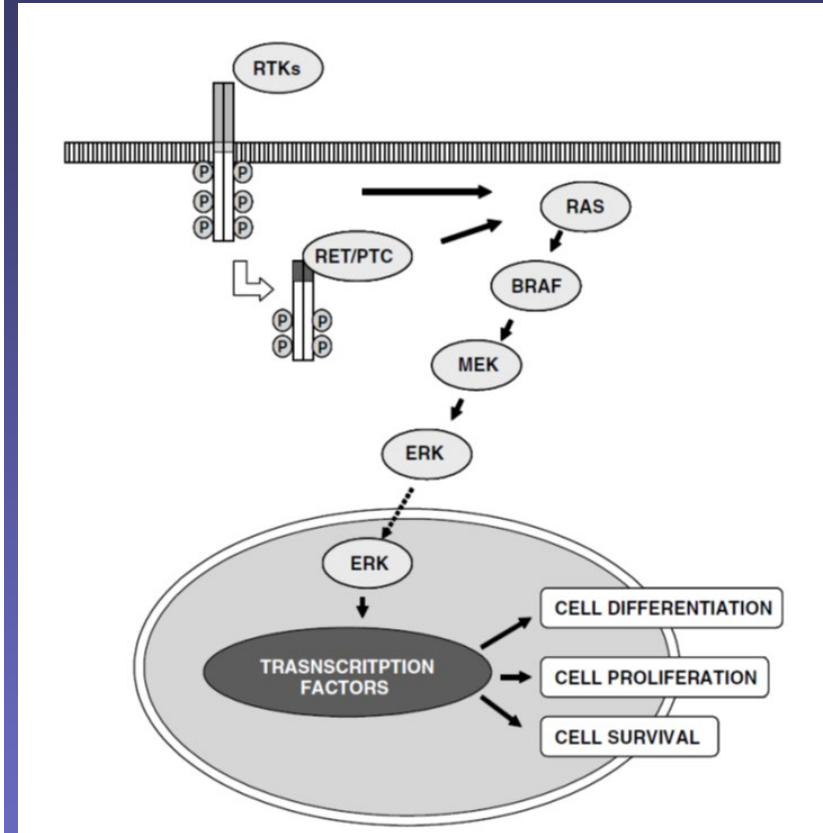
The historical role of the medical oncologist

	Agent	N	Histology	Objective Response Rate	Overall Survival
Gottleib, 1974	doxorubicin	30	All	11 (37%)	Responding patients: 11 months
Shimaoka, 1985	Doxorubicin vs cisplatin & doxorubicin	92	All	7 (17%) vs. 11 (26%)	< 24 months
Williams, 1986	Doxorubicin and cisplatin	22	All	2 (9%)	NR
Ain, 2000	Paclitaxel	20	ATC	10 (53%)	Median OS: 25 weeks

Kondo T et al. Nat Rev Cancer. 2006 Apr;6(4):292-306.

Molecular targets in Thyroid Cancers

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



MAPK signaling pathway

Nikiforov YE. Mod Pathol. 2008 May;21 Suppl 2:S37-43

FDA approved TKIs in RAI refractory DTC

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%
Selpercatinib[3]	RET	Ph1/2 N=27	62%	NR	NR	Mostly Gr1/2

*Cabozantinib with breakthrough FDA designation after positive COSMIC-311 study

** Multikinase inhibitors have activity in DTC, studied in nonrandomized phase II trials: axitinib, pazopanib, sunitinib.

[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]*Wirth et al. ESMO 2019*

FDA approved TKIs in MTC

Agent	Target	Evidence	Obj. Response Rate	PFS	OS	Adverse Events
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=226	56%	NR	NR	Most Gr1/2

[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. ESMO 2019

Anaplastic Thyroid Cancer

- Often unresectable and metastatic at diagnosis, very poor prognosis
- Controlling local disease and improving QOL are priorities of therapy
- Radiation often concurrent with chemotherapy often used to achieve treatment goals
- Paclitaxel has a response rate of ~50%
- Emerging data with BRAF/MEK inh.

BRAF and MEK inhibition

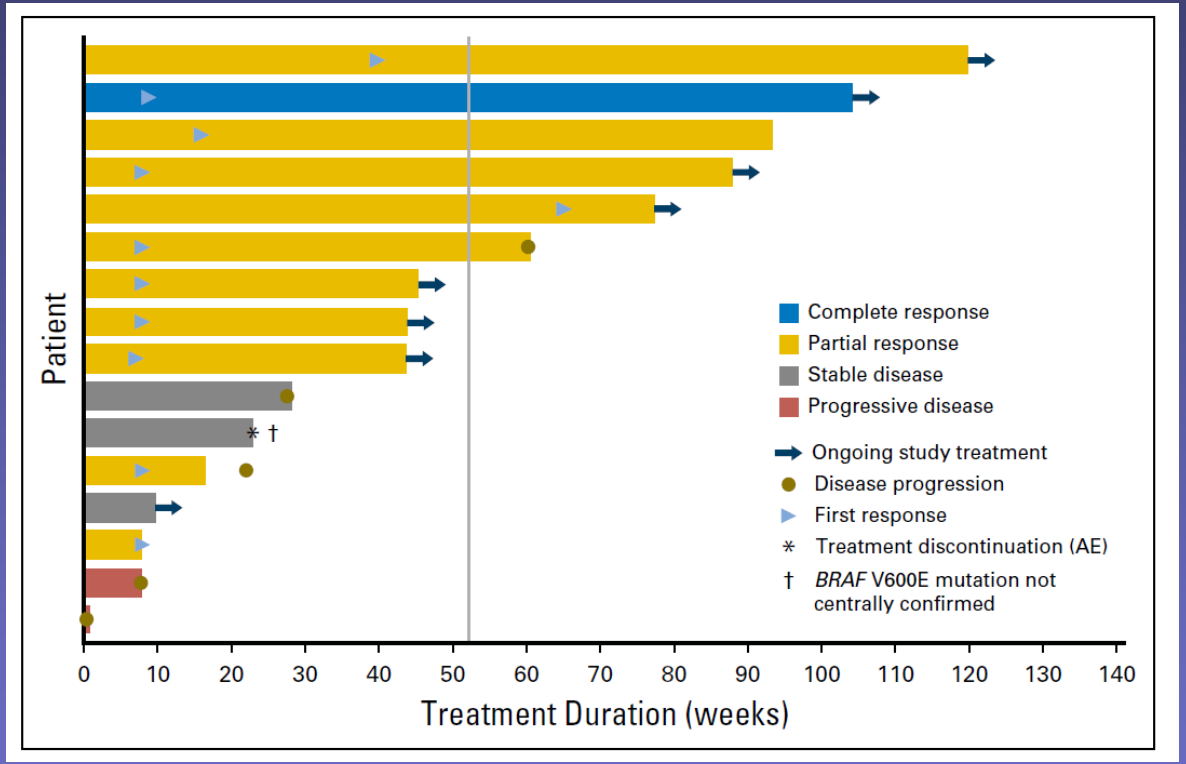
Phase I clinical experience with dabrafenib and trametinib

N= 16 pts with BRAF v600e mutations

Responses in 11 (69%)

80% previously treated with XRT

FDA approved



Subbiah et al. J Clin Oncol. 2018 Jan 1;36(1):7-13

Key Points: Thyroid Cancer

- Multikinase inhibitors are for thyroid cancer independent of mutational status
  - RAI refractory differentiated thyroid cancer
    - Lenvatinib and sorafenib
  - Medullary Thyroid Cancer
    - Vandetanib and cabozantinib
- Anaplastic thyroid cancer
  - Recognize and attempt local control
  - Test for BRAF V600E

Part III
Salivary Gland Cancer

Salivary Gland Cancers

- Uncommon (5% of head and neck CA)
- Diverse histology (2017 WHO)
  - Most common: adenoid cystic (ACC), mucoepidermoid carcinoma, adenocarcinoma
- Variable clinical behavior
  - Indolent subtypes such as ACC
- Molecular profiling
  - Secretory Carcinoma (*ETV6-NTRK3* fusion)

Salivary Gland Cancer: Local or Locally advanced

- Surgical resection of localized disease
- Postoperative radiation therapy in high risk disease
  - Data to support Neutron Radiation
  - Photon radiation also extensively studied and reported in postoperative setting
  - Concurrent chemoradiation being studied in RTOG 1008

Salivary Gland Cancer: Metastatic

- No current standard of care
  - Small trials with heterogeneous population
    - Low response rates, stable disease
    - Contemporary experience with single agent paclitaxel and gemcitabine-cisplatin
  - Recent reports/publications
    - Lenvatinib in adenoid cystic (15%ORR)
    - Entrectinib in NTRK mutant sal gland cancer
    - Trastuzumab+chemo in Her2+ sal gland cancer
    - Androgen deprivation in AR+ sal gland cancer
    - Pembro in PDL1>1% (10% ORR)
- Clinical trials preferred


Thank you!
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SUMMARY TABLE 1
Definitive XRT in Locally Advanced HNSCC

Disease	Standard/s of Care	Evidence
Locally advanced p16+ oropharynx cancer	cisplatin 100mg/m2 bolus + XRT	**RTOG 1016** **DE-ESCALaTE** OS, LRC benefit vs. cetuxXRT
Unresectable HNSCC of OC, OP, L, HP	cisplatin 100mg/m2 day 1, 22, 43 of XRT	**Intergroup Study** OS, DSS and LRC advantage vs XRT or splitXRT
Unresectable HNSCC of OC, OP, L, HP	cetuximab weekly concurrent with XRT	**Bonner Study** OS, LRC and PFS advantage vs XRT
St III-IVB Larynx CA (supraglottis or subglottis)	cisplatin 100mg/m2 day 1, 22, 43 of XRT	**RTOG 91-11** Larynx Preservation and LRC benefit vs XRT or ind.+ XRT

SUMMARY TABLE 2 Noncisplatin regimens Locally Advanced HNSCC

Disease	Standard/s of Care	Evidence
Unresectable HNSCC of OC, OP, L, HP	cetuximab weekly concurrent with XRT	**Bonner Study** OS, LRC and PFS advantage vs XRT
Locally advanced Oropharynx cancer	Carbo + inf 5FU days 1, 22 and 43 of XRT	**GORTEC 94-01** OS and LRC advantage vs. XRT alone

SUMMARY TABLE 3 Checkpoint inhibitors in Metastatic HNSCC

Line of therapy (biomarker)	Drug or Regimen	Evidence
1st line (CPS >1)	Pembrolizumab monotherapy	[1]Keynote-48 Phase III trial
1st line (any CPS)	Pembrolizumab + carboplatin + 5FU	[1]Keynote-48 Phase III trial
2nd line post cisplatin	Nivolumab	[2]Checkmate 141 Phase III trial
2nd line post cisplatin	Pembrolizumab	[3]Keynote-40 Phase III trial

[1]Rischin et al. ASCO 2019 abstract 6000
[2]Ferris, et al. NEJM 2016 Nov 10;375(19):1856-1867
[3]Cohen et al. Lancet 2019 Jan 12;393(10167):156-167

SUMMARY TABLE 4
Nasopharyngeal Cancer

Disease	Standard/s of Care	Evidence	Emerging Evidence
Locally Advanced NPC	Cisplatin + XRT (consider adjuvant cis+5FU)	Intergroup 0099 OS and PFS vs XRT alone	No adjuvant therapy after CRT noninferior in endemic studies
Node+ Locally advanced NPC	Gemcitabine cisplatin followed by cisXRT Adjuvant capecitabine	Zhang et al NEJM Phase III study OS advantage vs. CisXRT Ma et al. Lancet Oncology	
1st line R/M NPC	Cisplatin + gemcitabine + antiPD1 inhibitor 6	**JUPITER-02** **CAPTAIN 1ST**	

SUMMARY TABLE 5
Thyroid Cancer

Disease	Standard/s of Care	Evidence
RAI refractory differentiated thyroid cancer	Sorafenib	Ph III DECISION trial PFS adv. vs placebo
	Lenvatinib	Ph III SELECT trial ORR, PFS adv. vs placebo ORR 64%, allowed prior TKI
Medullary Thyroid Cancer	Vandetanib	Ph III ZETA study PFS adv. vs. placebo
	Cabozantinib	Ph III EXAM study PFS adv. vs. placebo
Anaplastic Thyroid	Paclitaxel	Ph II data, 53% ORR
	Dabrafenib + Trametinib	Ph I data in BRAF V600E mutated pts

SUMMARY TABLE 6
Salivary Gland Cancer

Disease	Standard/s of Care	Evidence/Emerging Data
Local or locally advanced sal. gland cancer	Resection followed by postop XRT for high risk disease	Historical improvement with postop Adjuvant Concurrent chemoXRT under study
Metastatic sal. gland cancer	No treatment standard Clinical trial preferred	Consider molecular profiling: NTRK, Her2 inhibitors have activity Trials for specific molecular abberations available