

Adjuvant Therapy in Locally Advanced Head and Neck Cancer



Ezra EW Cohen
University of Chicago



Financial Support

This program is made possible by an educational grant from Eli Lilly Oncology, who had no input in its content.

Conflicts of Interest

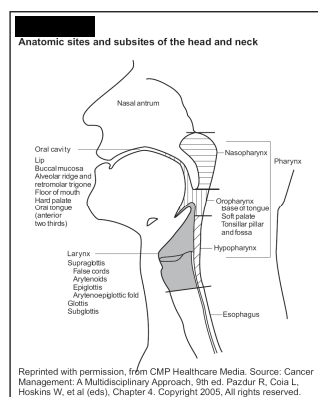
Dr. Cohen has received honoraria from Bristol-Myers Squibb and Sanofi-Aventis.

He has consulted for Amgen.

Heterogeneity

- Primary sites
 - Lip
 - Oral cavity
 - Oropharynx
 - Hypopharynx
 - Larynx
 - Paranasal sinuses
 - Nasopharynx
 - Salivary glands
- 95% are squamous cell carcinomas

Anatomic Sites and Subsides of the Head and Neck

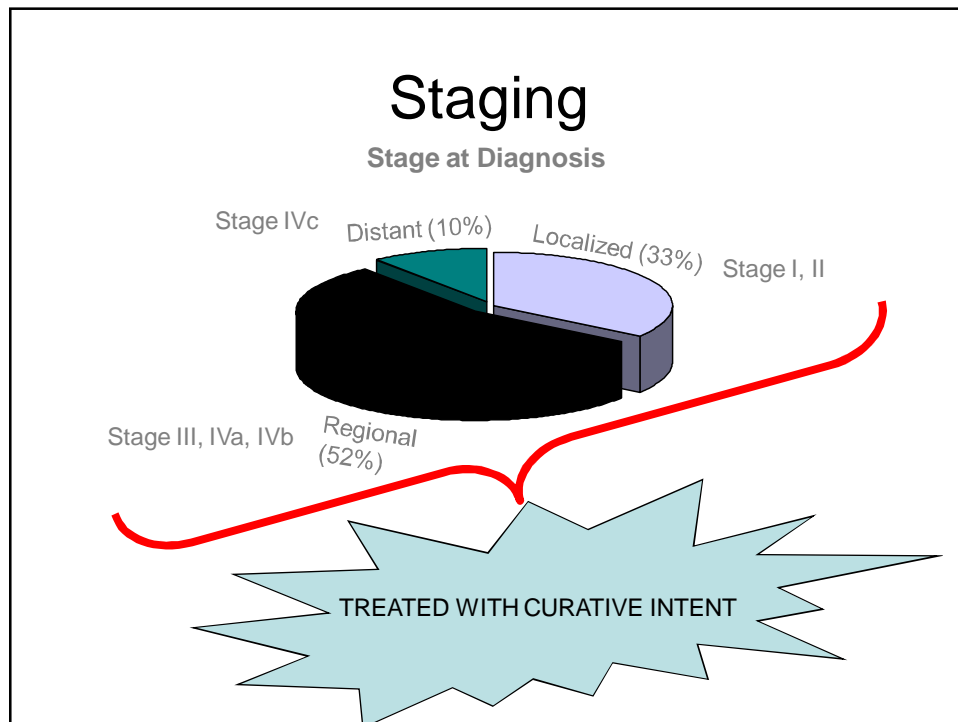


Incidence

- 2008, US:
 - 40000 new cases
 - 7600 deaths
- Worldwide:
 - 500000 new cases
 - 6th leading cause of death
- M:F = 2:1

Survival

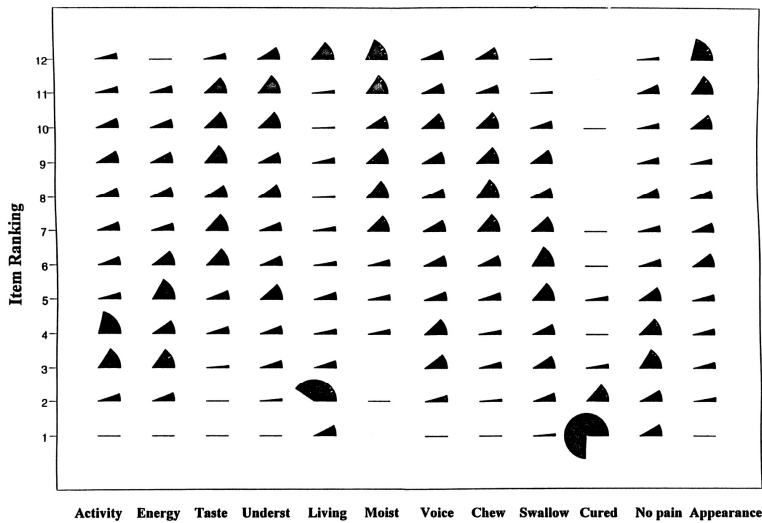
- Overall 50% long-term survival
 - Recurrence
 - Second malignancies
 - Co-morbidities



Risk Factors

- Age (majority of patients >50 years old)
- Tobacco
- Alcohol
- Viral
 - Epstein-Barr virus (NPC)
 - HPV (oropharynx)
- Hereditary (rare):
 - Family history increases risk (3.5X)
 - Rare genetic syndromes, e.g. Fanconi's Anemia

Cure is Paramount, QoL is Important



Activity Energy Taste Underst Living Moist Voice Chew Swallow Cured No pain Appearance

Priority Item*

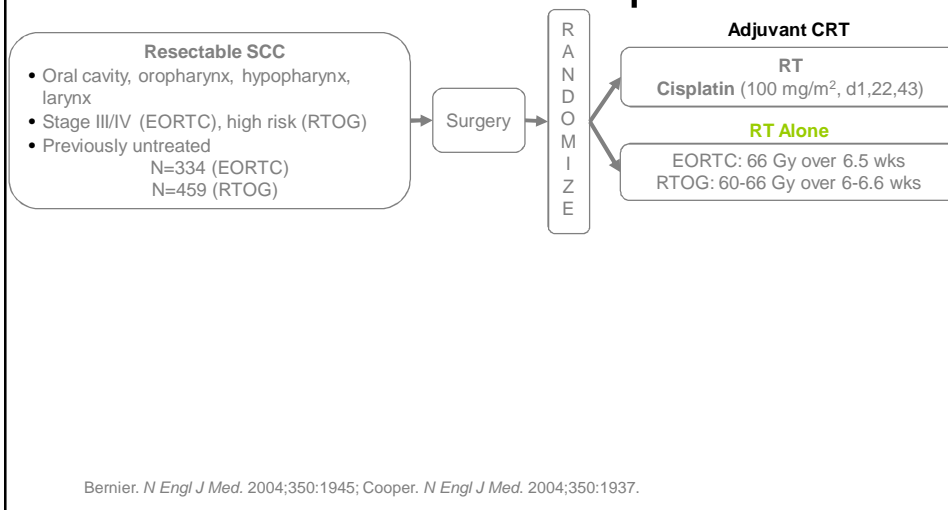
* Reader is referred to Methods section for complete listing of scale items

List, M. A. et al. J Clin Oncol; 18:877 2000

JOURNAL OF CLINICAL ONCOLOGY

Post-Op CRT

EORTC 22931 and RTOG 9501 Phase III Trials: Adjuvant RT \pm Concomitant Cisplatin



Post-Op CRT

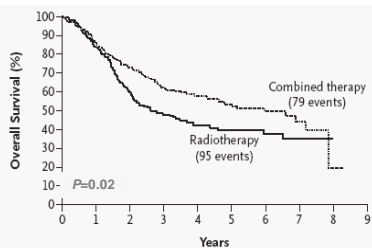
- | | |
|-------------------------|--------------------------|
| • EORTC 22931 | • RTOG 9501 |
| – 334 patients | – 459 patients |
| – Primary endpoint: PFS | – Primary endpoint: LRC |
| – Positive margins 28% | – Positive margins 18% |
| – ≥ 2 LN 54% | – ≥ 2 LN or ECS 82% |
| – ECS 57% | |

Post-Op CRT Phase 3 Studies

* p<0.05	EORTC (Bernier, 2004)		RTOG (Cooper, 2004)	
	CRT	RT	CRT	RT
Incidence of Locoregional Failure	18%	31%*	16%	29%*
Incidence of Metastases	21%	25%	20%	23%
Grade >3 Adverse Effects	41%	21%*	77%	34%*
5-Year Estimated PFS	47%	36%*	NR	
5-Year Estimated OS	53%	40%*	HR=0.84 (0.65-1.09), P=0.19	
2-Year Locoregional Control Rate	NR		82%	72%*
DFS			HR=0.78 (0.61-0.99)*	

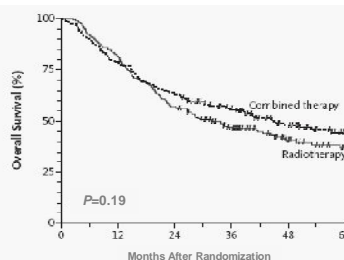
EORTC 22931 and RTOG 9501

OS (EORTC)



No. at Risk	0	1	2	3	4	5	6	7	8	9
Radiotherapy	167	139	93	68	49	31	19	9	0	
Combined therapy	167	141	118	93	72	47	33	11	1	

OS (RTOG)



No. at Risk	0	12	24	36	48	60
Combined therapy	206	132				27
Radiotherapy	210	120				26

•Pooled Analysis:

- The most significant prognostic factors for poor outcome were ECS and positive margins
- Subjects with 2 or more lymph nodes without ECS, did not seem to benefit

Targeting EGFR in SCCHN

- EGFR is almost universally expressed in SCCHN
- Expression has been linked to poor prognosis
- Inhibition of EGFR by monoclonal antibodies or small molecules:
 - effective preclinically
 - demonstrate reproducible clinical activity

Phase II Randomized Trial of Postoperative Chemoradiotherapy Plus Cetuximab for High-Risk Squamous Cell Carcinoma of the Head and Neck (RTOG 0234)

M. S. Kies¹, J. Harris², M. Z. Rotman³, J. N. Myers¹, R. L. Foote⁴, M. Machtay⁵, D. Khuntia⁶, W. L. Straube⁷, K. K. Ang¹, and P. M. Harari⁸

¹UT MD Anderson Cancer Center, Houston, TX, ²American College of Radiology-Radiation Therapy Oncology Group, Philadelphia, PA, ³SUNY Downstate Medical Center, Brooklyn, NY, ⁴Mayo Clinic, Rochester, MN, ⁵Jefferson Medical College, Philadelphia, PA, ⁶University of Wisconsin, Madison, WI, ⁷Washington University, St. Louis, MO, ⁸University of Wisconsin School of Medicine, Madison, WI

Supported by RTOG U10 CA21661, CCOP U10 CA37422 and ATC U24 CA 81647 grants from NCI. Additional support was provided by Sanofi-Aventis and Bristol-Myers Squibb.

Objectives

Primary:

A randomized phase II study of chemoradiotherapy with cetuximab, in high-risk postoperative head and neck patients, to evaluate disease-free survival relative to chemoradiation of RTOG 9501.

Treatment Schema

S T R A T I F Y	<u>Zubrod Score</u>	R A N D O M I Z E	<u>Arm 1</u>
	1. 0		<u>Week 1:</u> Cetuximab 400mg/m ²
	2. 1		<u>Weeks 2-7:</u> 60 Gy (2 Gy/day) - CDDP 30mg/m ² + cetuximab 250 mg/m ²
	<u>Risk Category^a</u>		<u>Arm 2</u>
1. Positive margins	2. High risk (≥ 2 positive nodes or extranodal capsular spread)	<u>Week 1:</u> Cetuximab 400 mg/m ²	
		<u>Weeks 2-7:</u> 60 Gy (2 Gy/day) - Docetaxel 15 mg/m ² + cetuximab 250 mg/m ²	

Gross total resection must be completed within 7 weeks of randomization.

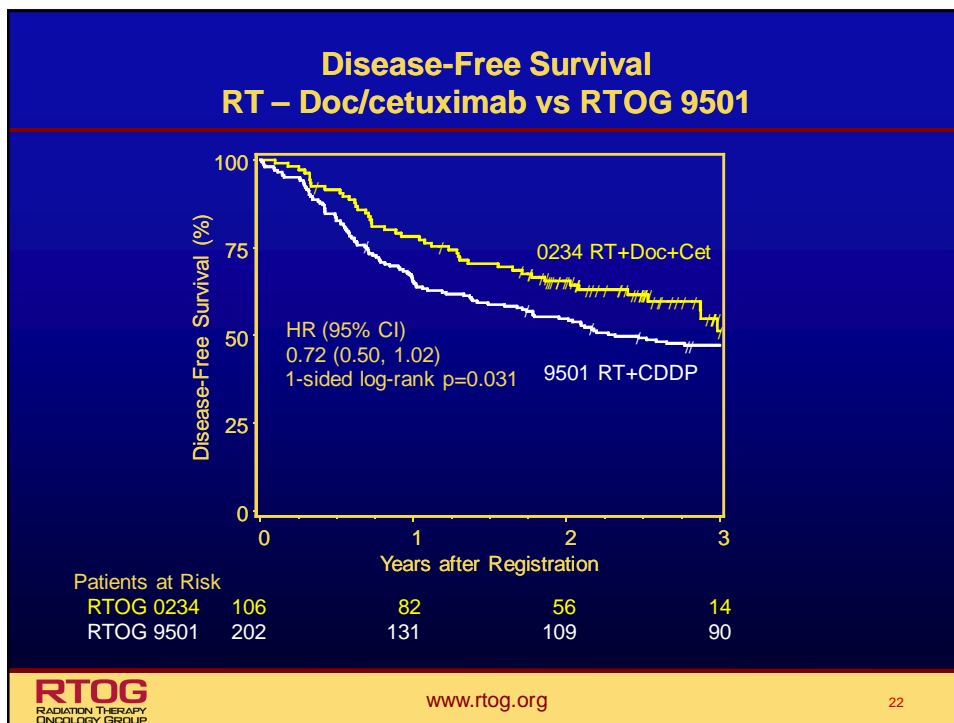
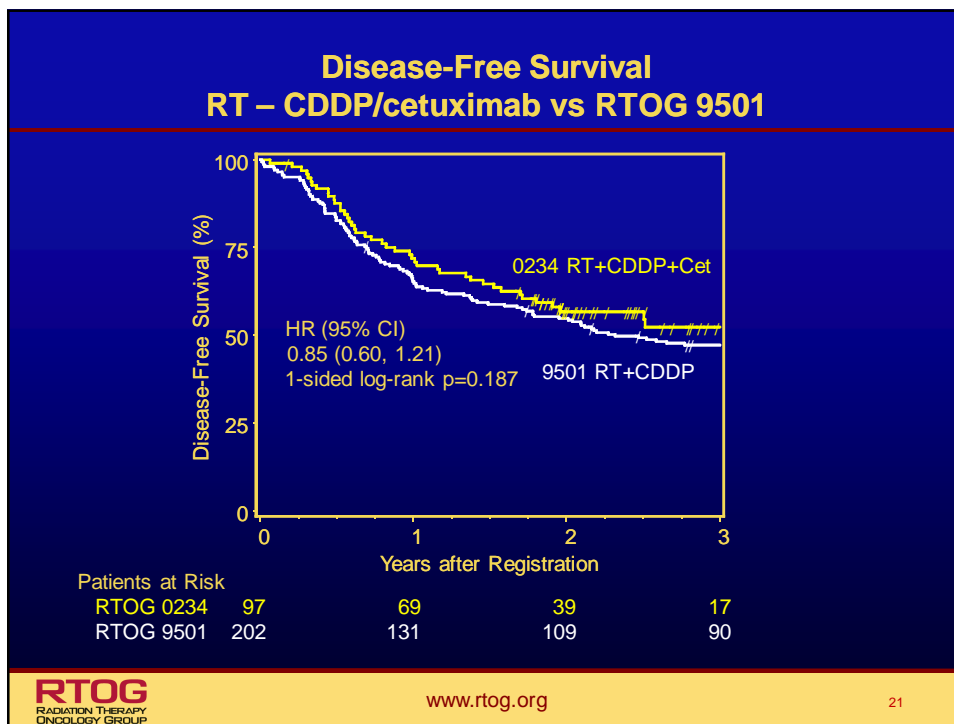
^aIf both risk factors are present, patient will be stratified as "positive margins"

RTOG 0234 / Eligibility

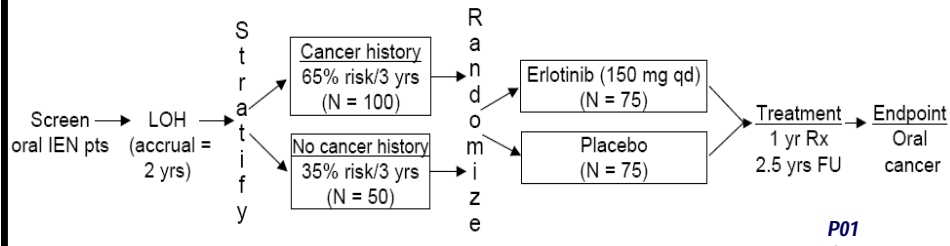
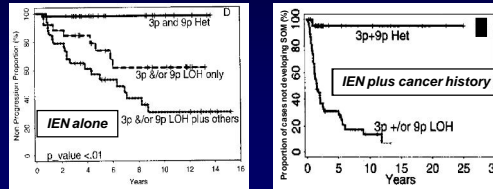
- Stage III / IV SCCHN s/p gross total surgical resection
- Must have positive resection margins and / or ≥ 2 nodal metastases and / or ECS
- Performance Status 0 / 1

Adverse Events/ Grades 3 – 5 (%)

	RT – CDDP / cetuximab (n = 97)			RT – Doc / cetuximab (n = 106)		
	<u>3</u>	<u>4</u>	<u>5</u>	<u>3</u>	<u>4</u>	<u>5</u>
Hypersensitivity	3	0	0	2	1	0
Bone Marrow	22	6	0	9	5	0
Infection	9	6	0	10	1	1
Metabolic	14	0	0	11	3	0
Mucositis	34	3	0	28	5	0
Rash	34	5	0	37	2	0
Respiratory	5	0	1	7	2	0
<u>Overall (%)</u>	73	13	1	75	13	1



Erlotinib Prevention of Oral Cancer (EPOC)

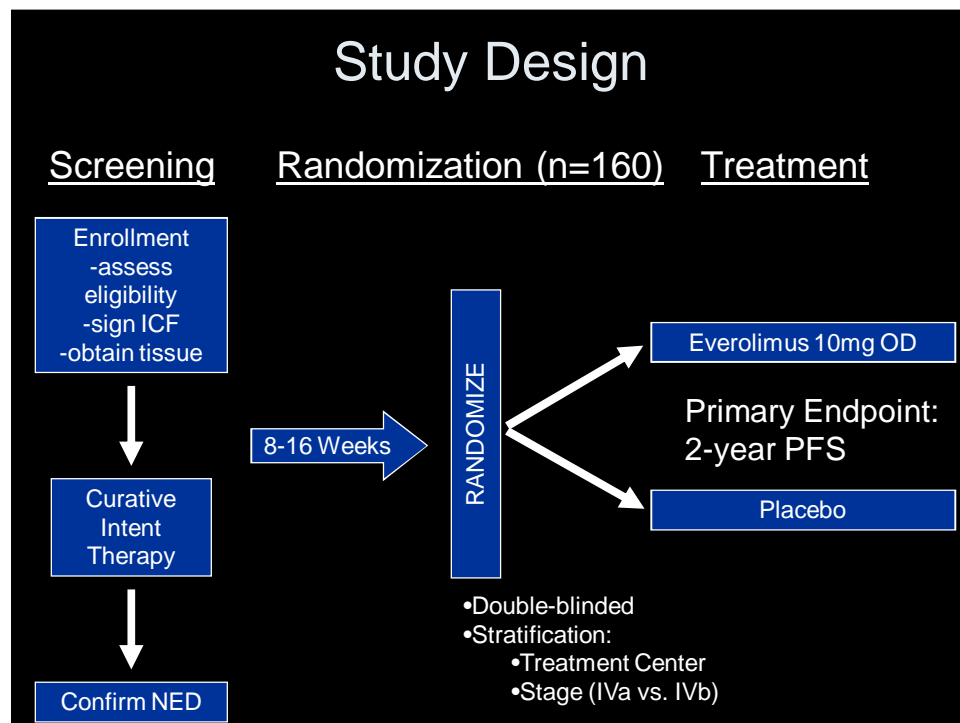


P01

MDACC (Papadimitrakopoulou, Lippman, Mao et al)
 U Chicago (Cohen et al)
 MSKCC (Boyle et al)
 Emory (Shin et al)

Mammalian Target of Rapamycin Inhibitors as Possible Adjuvant Therapy for Microscopic Residual Disease in Head and Neck Squamous Cell Cancer
 Cherie-Ann O. Nathan,^{1,7} Nazanin Amirghahari,^{1,7} Xiaohua Rong,^{1,7} Tony Giordano,^{2,7} Don Sibley,^{3,7}
 Mary Nordberg,^{4,7} Jonathan Glass,^{5,7} Anshul Agarwal,^{1,7} and Gloria Calditone
 Departments of ¹Otolaryngology-Head and Neck Surgery, ²Biochemistry, ³Anatomy and Cellular Biology, ⁴Pathology, ⁵Medicine, and ⁶Biometry and ⁷Fesli-Weller Cancer Center, Louisiana State University Health Sciences Center, Shreveport, Louisiana

Randomized Phase II Trial of Everolimus Versus Placebo as Adjuvant Therapy in Patients with Locally Advanced Squamous Cell Cancer of the Head and Neck (SCCHN)



Conclusions

- High risk post-operative patients benefit from the addition of chemotherapy to radiotherapy
- The decision to undergo surgery first should be undertaken with care and does not represent the standard of care for most head and neck cancer patients.
- New therapies are being introduced in an effort to improve outcomes further.

We thank Eli Lilly for their support of this program.

