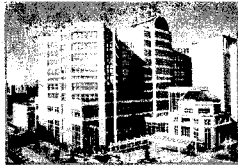
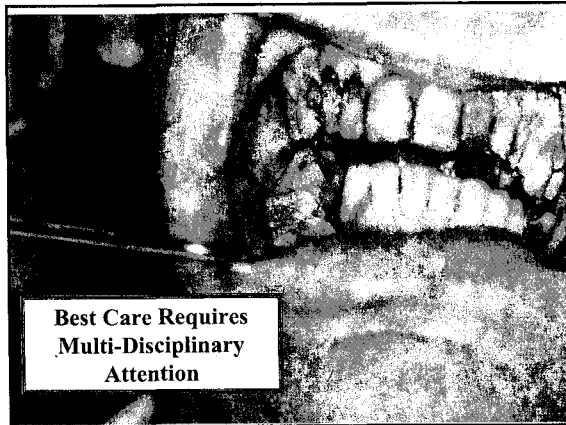


### Combined Therapy for Locally Advanced SCCHN

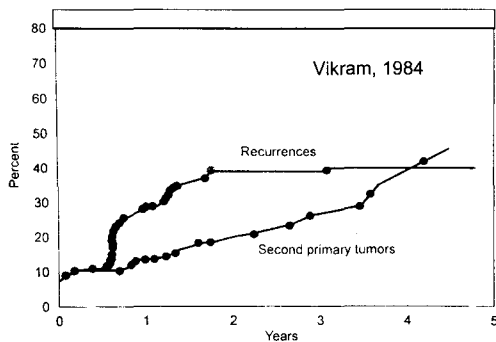


Merrill S. Kies  
Seoul, Korea  
11/23/02

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Best Care Requires  
Multi-Disciplinary  
Attention



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### Outcomes In SCC

- Stages I & II: 1/3 of patients; curative results 60 - 80%; SPTs current focus
- Stages III & IV: 2/3 of patients; multimodal tmt; 40 - 80% local recurrence, 10 - 30% distant
- 20 - 30% of deaths not cancer-related
- Treatment goals are to cure cancer, preserve or improve function, and maintain cosmesis. Must consider the disability potential in tmt planning

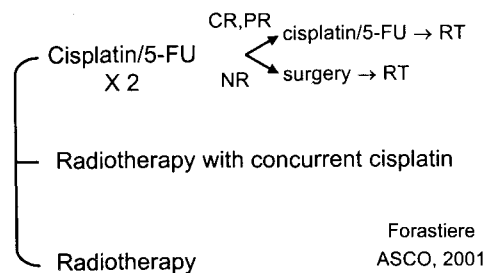
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### Selected Randomized CT-RT Trials in Squamous H/N Cancer

Study	Patient Group	Experimental Arm	Outcome
Brizel (1998)	"Advanced"	HFRT + CF →CF x 2 (N=56)	Improved local control 70 v 44%; trend to better OS 55 v 34% (p=.07) @ 3 yrs
Wendt (1998)	Unresectable	RT + PFL (N=130)	Survival improved – 48 v 24% @ 3 yrs
Calais (1999)	Unresectable – oropharynx	RT + cbdca/5-fu (N=109)	Survival improved – 51 v 31% @ 3 yrs

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### R91-11 Phase III Trial to Preserve the Larynx



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### Eligibility Criteria

- Squamous cell carcinoma of glottic or supraglottic larynx
- Stage III or IV  
T1 excluded  
T4 excluded if tumor penetrated through cartilage or invaded > 1 cm into base of tongue
- No distant metastases

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### Patient Characteristics

	Induction (N=171)	Concurrent (N=169)	RT (N=170)	Total (N=510)
SG	68%	67%	72%	69%
Glottic	32%	33%	28%	31%
Stage III	64%	67%	64%	65%
Stage IV	36%	33%	36%	35%

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### Response After Two Courses of Induction Cisplatin/5-FU

	No. of Pts (%)	
	Primary	Neck
CR	35 (21)	19 (23)
PR	105 (63)	34 (40)
Stable	11 (7)	14 (17)
PD	4 (2)	3 (3)
Unknown	11 (17)	14 (17)
Total*	166	84

\* 5 patients did not receive chemotherapy

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### Treatment Received

	No. of Courses			
	0	1	2	3
Chemotherapy				
Induction	3%	4%	13%	81%
Cisplatin/FU				
Concurrent	5%	7%	24%	65%
cisplatin				

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### Treatment Received

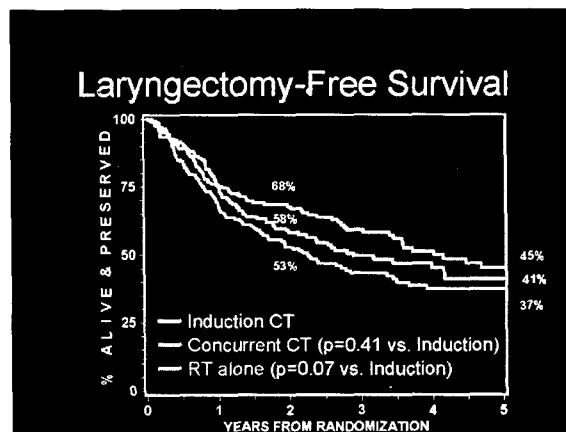
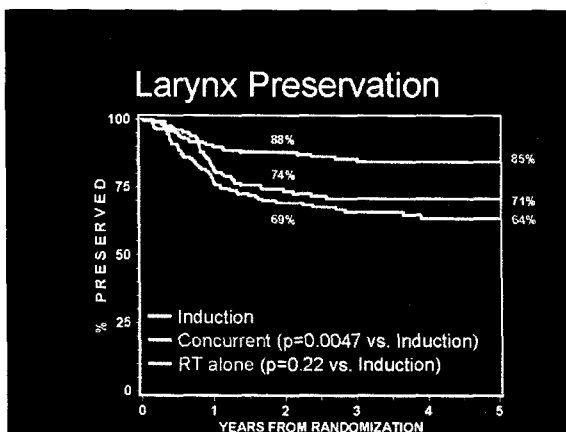
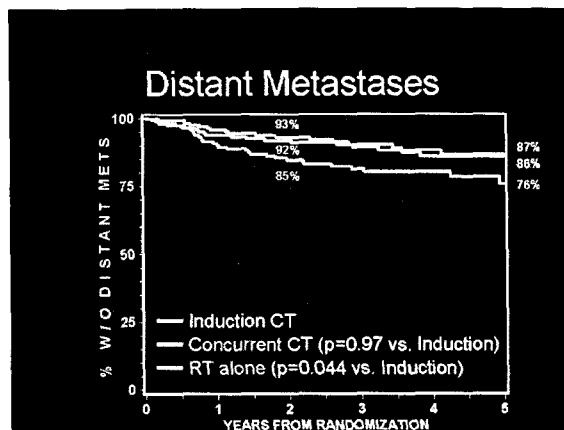
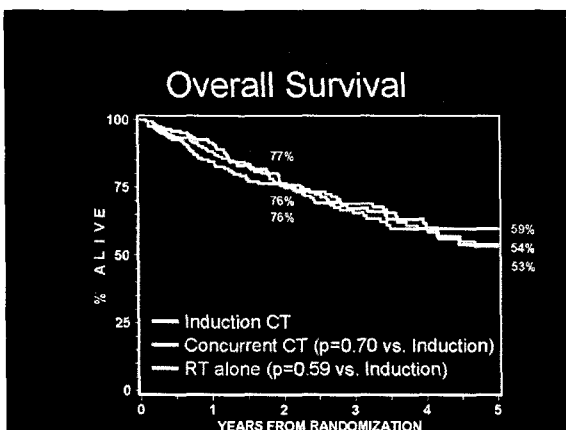
	Radiotherapy
	95% planned dose (>67.2 Gy)
Induction	84%
Concurrent	91%
RT	95%

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### Overall Toxicity

Treatment	Grade			Total
	3	4	5	
Induction	38%	28%	2%	68%
RT	42%	8%	0	50%
Concurrent	59%	19%	2%	80%
RT alone	43%	5%	0	48%

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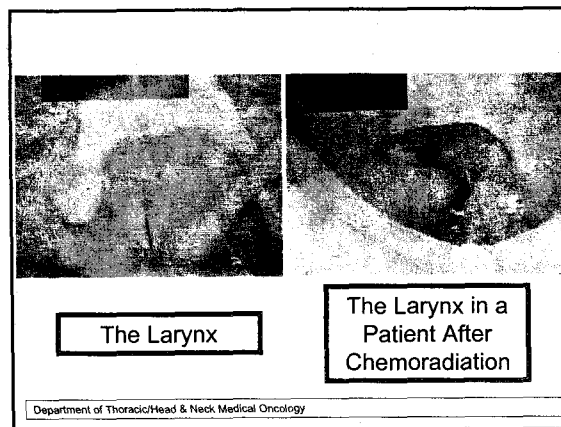
Conclusions

? THE WINNER

Chemoradiation

or is it?

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### Conclusions

Concomitant CF-RT results in a 15% greater chance of larynx preservation at 2 yrs.

No survival advantage

? Function. No data regarding voice quality, quality of life, and swallowing functions

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### Active Investigations

- **Phase II chemoradiation projects**
  - Docetaxel/Cisplatin-RT
  - T-FH2X
- **Induction chemotherapy**
- **Introduction of novel compounds**
  - Antiangiogenesis strategies (endostatin, angiostatin, TNP 470)
  - EGFR Blockers (TK inhibitors, c225, antisense oligonucleotides, ligand conjugates)
  - p53 modulation
  - Targeting ras (e.g. SCH66336)

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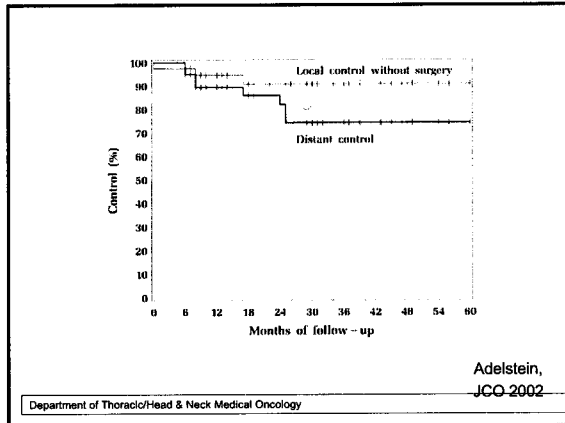
### Phase II – Cleveland Clinic CT – RT

WEEK	1	2	3	4	5	6
SFU	■				■	
DDP	■				■	
RT	■					

SFU : 1000 mg/m<sup>2</sup>/d IV C1 x 4 days  
 DDP : 20 mg/m<sup>2</sup>/d IV C1 x 4 days  
 RT : 72 Gy @ 120 cGy bid

Adelstein,  
JCO-2002

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### T-FH2X Recurrence Pattern

Kies,  
JCO-2001

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### Current Phase II Protocols

Boston: docetaxel/cisplatin/5-FU → cbdca-RT  
 Chicago: paclitaxel / cbdca → T-FH2X

**Interpretation:**

- Induction chemotherapy will reduce DM
- Locoregional control is the core objective of therapy, but how best to get there? ... and with preservation of function
- Should improved chemotherapy affect locoregional management?

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### Protocol 9502: Treatment Plan

Induction Chemotherapy → T-FHX  
 Regimen: Weekly Carboplatin (AUC 2)  
 Paclitaxel 135 mg/m<sup>2</sup> (3h) x 6  
 Goal: Systemic Control  
 ↓  
 T-FHX (week 8)  
 Goals: Locoregional Control  
 Organ Preservation  
 Salvage surgery for residual disease at primary site, neck  
 dissection for N<sub>2</sub>/N<sub>3</sub> (recommended) or residual disease.

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### TN Stage

	N <sub>0</sub>	N <sub>1</sub>	N <sub>2a</sub>	N <sub>2b</sub>	N <sub>2c</sub>	N <sub>3</sub>	Total
T <sub>x</sub>	-	-	-	4	-	2	6
T <sub>1</sub>	-	-	2	2	-	1	5
T <sub>2</sub>	-	2	3	4	1	1	11
T <sub>3</sub>	-	1	1	6	6	4	18
T <sub>4</sub>	6	6	2	5	7	3	29
Total	6	9	8	21	14	11	69

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Vokes, 2002

RFS MOS

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Recurrence  
 ↙ distant  
 ↘ locoregional

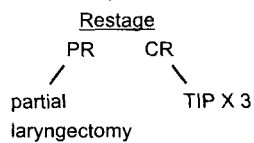
Locoregional & Distant progression

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### TIP → Larynx

Intermediate stage scc of the supraglottic and glottic larynx

Paclitaxel 175 mg/m<sup>2</sup> d1  
 Ifosfamide 1000 mg/m<sup>2</sup> d1-3  
 Cisplatin 60 mg/m<sup>2</sup> d1 } q 21 d x 3



Khuri

Department of Thoracic/Head & Neck Medical Oncology

### TIP → Larynx // Results (N=24)

M/F            17/7  
 Age            Median 58 yrs  
                   (range 20-79)  
 Staging        T2N0-T4N1  
 Responses  
   pCR        8 (33%)  
   PR         14 (59%)

Khuri,  
 ASCO 2002

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**TIP → Larynx // Results (N=24)**

**Outcome**

- Median f/u time 28 mos
- 6/8 pCR patients ned
- 6/24 recurrences, 1 SPT, 4 salvage laryngectomies and overall 21/24 patients disease free

Khuri, ASCO 2002

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**TIP → Larynx**

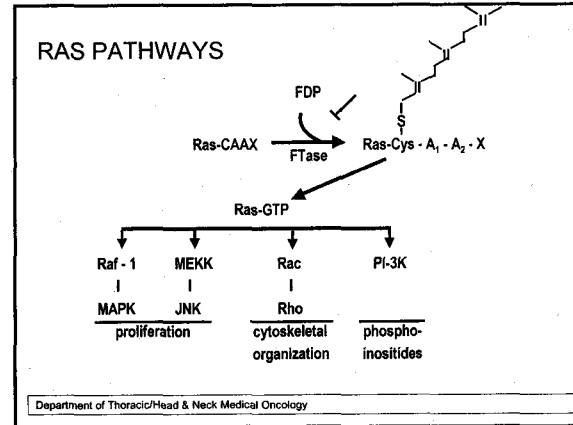
Pre-Treatment 5/18/01      Post Chemotherapy 8/29/01

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**TIP → Larynx**

9/12/02

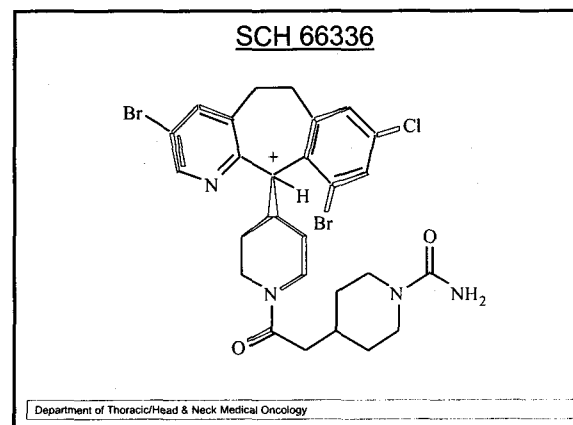
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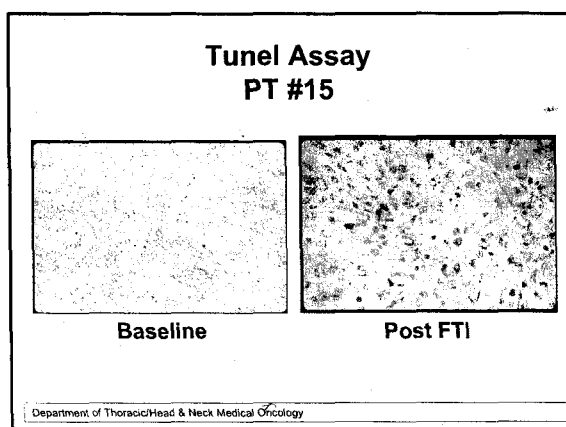
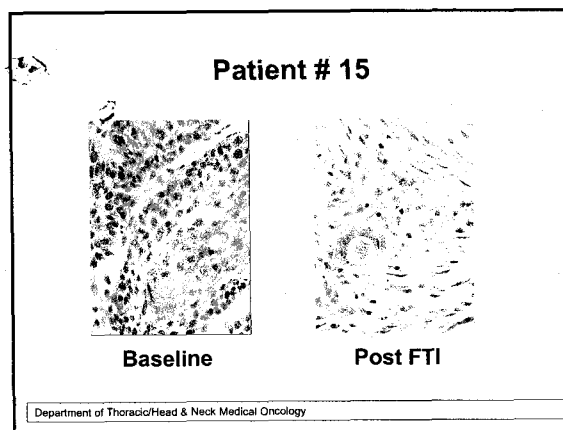
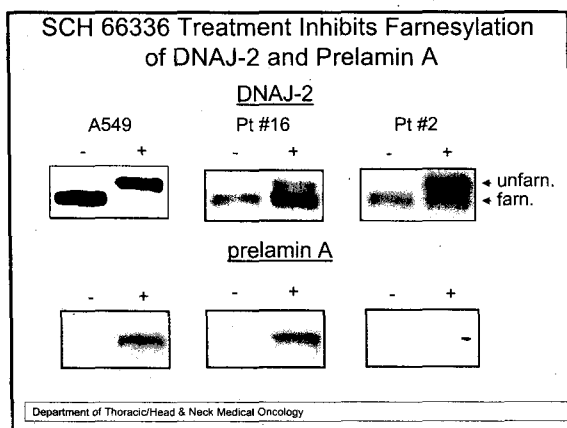
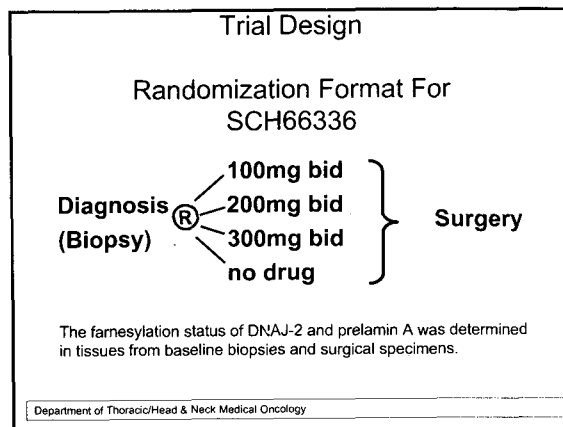
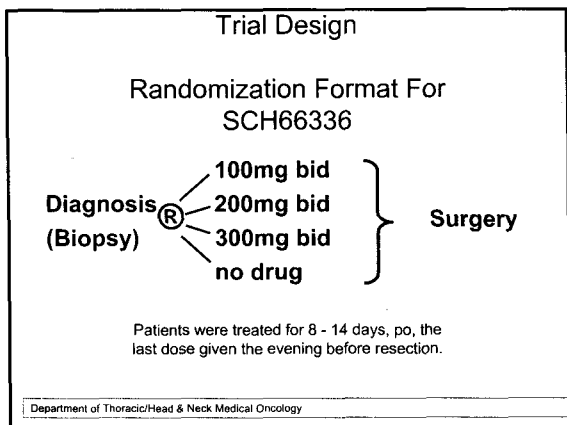


**Targeting Farnesyltransferase**

- Ftase inhibitors block farnesylation of Ras
- Preclinical studies have demonstrated activity for FTI in head and neck scc cell lines, with or without Ras mutations
- Phase IB induction trial of SCH 66336

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- ### In Summary...My Take:
- Surgical resection remains the mainstay of treatment for OC and T4 larynx primary tumors
  - Chemoradiation is superior to radiotherapy alone for advanced cancers of the oropharynx, hypopharynx, and nasopharynx
  - Ongoing phase II trials sequence induction chemotherapy and concomitant RT
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**Summary ...**

- What to do with T1/2 N1/2 OP, HP?
  - Radiotherapy
  - ⊗ Radiotherapy + C225
- Post op/high risk?
  - Radiotherapy
  - ⊗ Radiotherapy + CT

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**Summary ...**

- The induction chemotherapy format is a useful instrument to test a novel regimen and to validate the achievement of biochemical endpoints.
- Current focus is on continuing phase I/II clinical trials, the integration of novel cmpds with chemotherapy and radiation, and the more precise identification of critical molecular targets.
  - CT-RT (FHX / CDDP-XRT)
  - ⊗ CT-RT + "targeted" cmpd
  - Induction → CT-RT
- Clinical trial objectives will continue to focus on tumor control/dfs but also longitudinal PS and speech/swallowing functional data should be obtained

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