2nd International Congress on Oncological Sciences

Locally advanced head and neck cancer

Radiation Oncology Perspective

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Definition and Management of LAHNC

- Stage III or IV cancers generally include larger primary tumors, which may invade underlying structures and/or spread to regional nodes.
- Treatment is complex for patients with H&N cancers.
- The specific site of disease, stage, and pathologic findings guide treatment
- Combined modality therapy is generally recommended for the approximately 60% of patients with LAHNC.
- The other option for LA-HNC is surgery and RT+/- Chemotherapy

Radiotherapy as Primary Treatment for HNC

- RT plays an important role in the treatment of HNC
- The translation of radiobiological research into clinical practice revelaed altered fractionation regimens
- The concurrent application of chemotherapy (chemo-RT) improved the efficacy of RT

Altered fractionation RT

- *Improve the therapeutic ratio through either dose escalation or shorten the overall treatment time.*

- **676 patients, tonsillar carcinomas retropective study**
- Increase of local tumor control probability by nearly 2% for each 1-Gy increase in total dose for a constant treatment duration.
- Accelerated repopulation begin 30 days following treatment initiation, with a compensatory dose of 0.73 Gy per day required for treatments lasting beyond 30 days.
- The LC probability was decreased by at least 1% for each day that treatment was extended.
- RT duration > 8 wks was an independent prognostic factor for survival in Tax 324**

**Whithers HR, Red Journal, 1995*
** Sher IJROBP 2011

Altered RT fractionation

Regimen	Description	Advantages	Disadvantages
Standard fractionation	70 Gy/2 Gy/35 fx **7 weeks**	-	-
Hyperfractionation	81.6 Gy/1.2 Gy twice daily/68 fx **7 weeks**	Largest improvement in meta-analyses data	Logistically challenging
AF with concomitant boost	72 Gy/42 fx **6 weeks** Initial field: 54 Gy/20 fx/1.8 Gy Boost field: 18 Gy/1.5 Gy/over the final 12 treatments	Fewer total fractions than hyperfractionation	May increase late side effects
DAHANCA	62-68 Gy/2 Gy fx dose 6 fx per week **6 weeks**	Logistically attractive No increase in fx dose	-
Simultaneous Integrated Boost	Differential dosing to different target volumes (1.6 Gy-2.2 Gy) **6-7 weeks**	Single IMRT plan hypofractionation to gros tumor	Lack of supportive data

RTOG 90-03

N=1133 patients, Stage III/IV

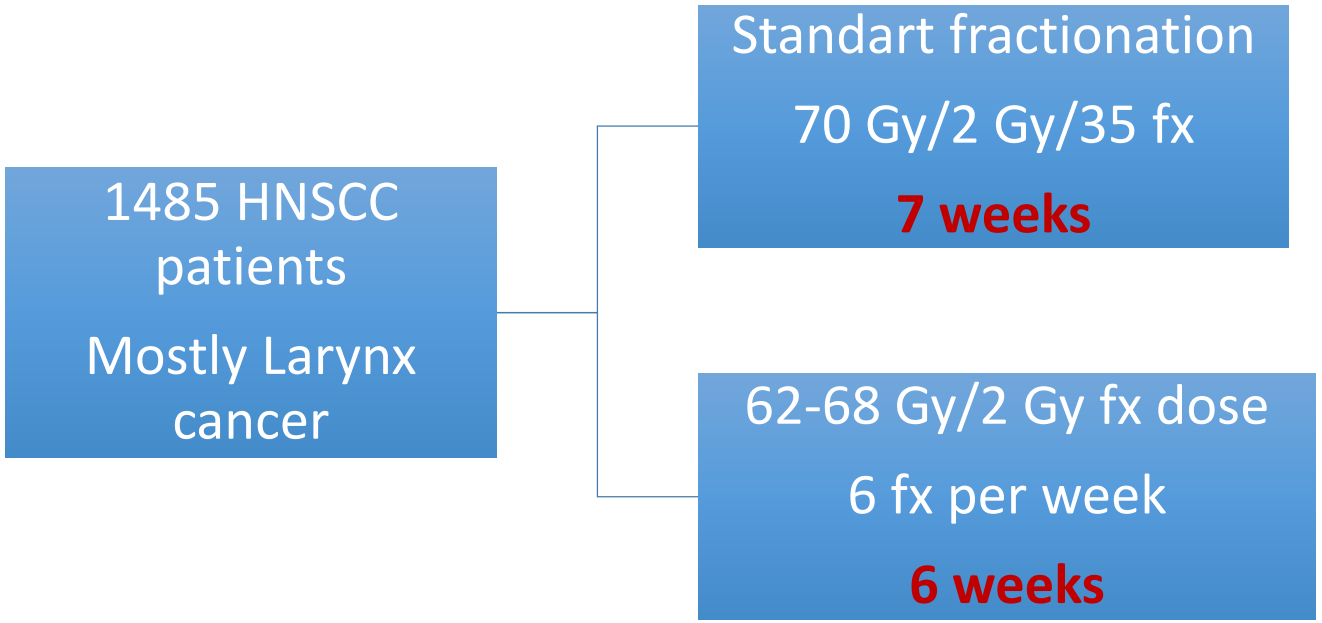
Oral cavity, Oropharynx (60%), Larynx, Hypopharynx

	LRC %	2 year DFS %	2 year OS %	>Grade 3 acute	>Grade 3 late
Standart fx	46	32	46	35	26.8
Hyperfx	**54.4**	37.6 p=0.067	54.5	**54.5**	28
AF with concomitant boost	**54.5**	39.3 p=0.054	51	**58.8**	**37**
Accelerated split course(67.2 Gy/42 fx, 1.6 Gy twice daily, 2 wk break after 38.4 Gy)	47.5	33.2	46	**50.4**	27.6

At 5 years, reduction in LRF Altered fractionation vs. standard was 6.5%, 6.6%, and 1.1%.

Fu *IJROBP* 2000
Beitler *IJROBP* 2014

DAHANCA 6&7



5 year LC improved 60% to 70%

DFS improved 63% to 73%

No difference in 5 year OS (44%)

Acute side effects increased 63% to 73%

No difference in late side effects

For larynx cancer, 6 fractions/week reduced 5-year LF (glottic 27 → 18%, supraglottic 48 → 33%) and improved 5-year voice preservation (68 → 80%, $p = 0.007$)

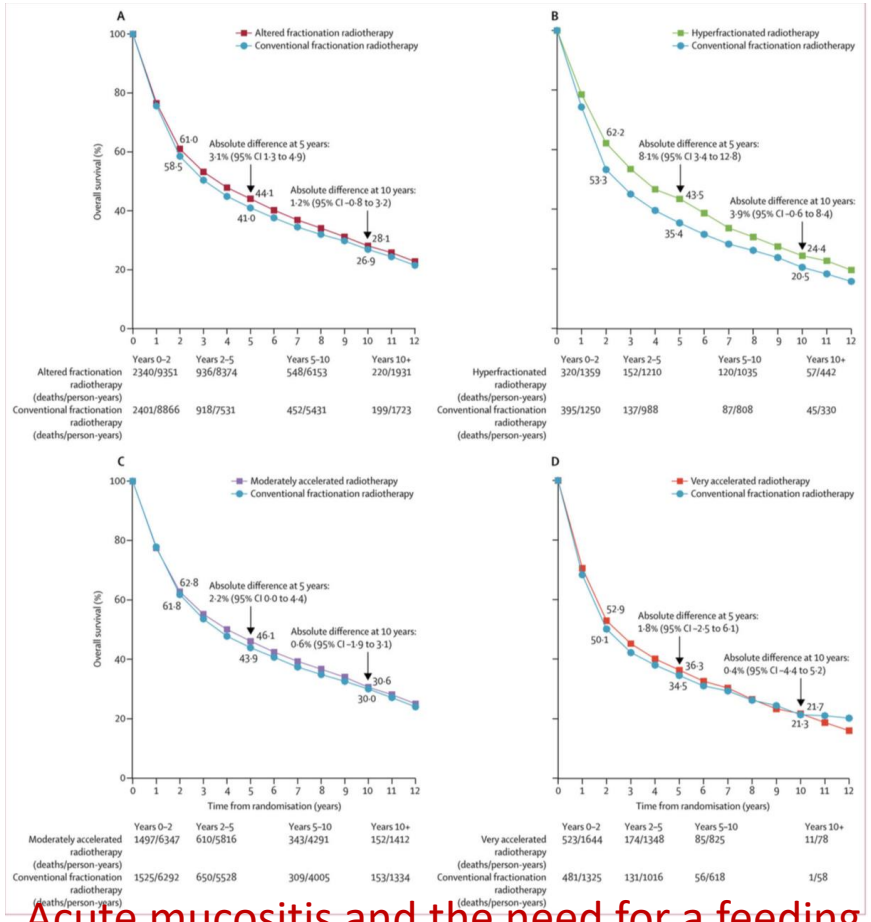
Overgaard Lancet 2003

MARCH Meta-analyses

- 15 phase III trials
- 6515 patients with H&N SCC
- Altered fractionation vs. conventional fractionation
- **5-year OS benefit was 3.4%** for altered fractionation RT
- **5-year OS benefits were 8%** for hyperfractionated and **2%** accelerated RT
- The LRC rate improved by **6.4% at 5 years** with altered fractionation; greater benefit was seen with local compared with nodal control.

Bourhis Lancet 2006

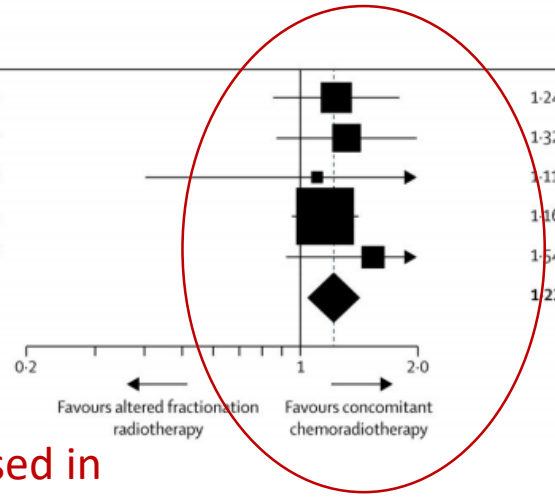
Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis



- Primary or postoperative conventional fractionation RT vs altered fractionation RT (33 trials 11423 patients)
- Conventional fractionation RT plus concomitant chemotherapy vs altered fractionation RT alone (5 trials 986 patients)

	Events (n)/patients (N)		Observed minus expected	Variance	HR (95% CI)
	Altered fractionation radiotherapy	Concomitant chemoradiotherapy			
INRC-HN-9[43]	58/66	55/70	5·9	27·9	1·24 (0·85–1·79)
ORO 9301[55]	50/65	42/64	6·2	22·7	1·32 (0·87–1·98)
EORTC 22962[45]	7/13	9/15	0·4	3·8	1·11 (0·40–3·03)
GORTEC 9902[36]	207/281	196/279	14·7	100·2	1·16 (0·95–1·41)
TMH 1114[37]	34/68	26/65	6·3	14·7	1·54 (0·92–2·56)
Total	**356/493**	**328/493**	**33·6**	**169·4**	**1·22 (1·05–1·42)**

χ^2 test for hetergeneity: p=0·87, I^2=0%
Treatment effect: p=0·0098



Acute mucositis and the need for a feeding tube during treatment were increased in the altered fractionation group but late toxicities were similar between the groups

For lower-risk pts unable to tolerate systemic therapy, primary RT offers good results

Original Article

Radiation Therapy (With or Without Neck Surgery) for Phenotypic Human Papillomavirus–Associated Oropharyngeal Cancer

Adam S. Garden, MD[1]; Clifton D. Fuller, MD, PhD[1]; David I. Rosenthal, MD[1]; William N. William Jr, MD[2]; Gary B. Gunn, MD[1];

- 324 pts with AJCC 7th T1-3N1-2b or T3N0 and <10 pack-years smoking with intact primary treated with RT without systemic therapy.
- 73% received standard fractionation (66 Gy at 2–2.2 Gy/fx), 27% altered fractionation.
- 5-yr PFS T1 90%, T2 83%, T3 70%.
- No significant difference in PFS compared to 439 pts given systemic therapy except trend for T3 pts (5-yr PFS 77%, $p = 0.07$).
- 5-yr LRC 95% with RT without systemic therapy.

Cancer 2016

Definitive RT or concomitant Chemo-RT?

Intergroup Trial

Stage III/IV Larynx Hypopharynx Oral cavity Oropharynx

85% had T4 or N3!

N=295

- SFX RT
  70 Gy/35 fractions/7 wk
- SFX RT+cisplatin (x3)
- Split course RT+Chemo
  (2/30 Gy + 2 cycles cisplatin/5FU → resection if possible → 2/30–40 Gy + 1 cycle cisplatin/5FU)

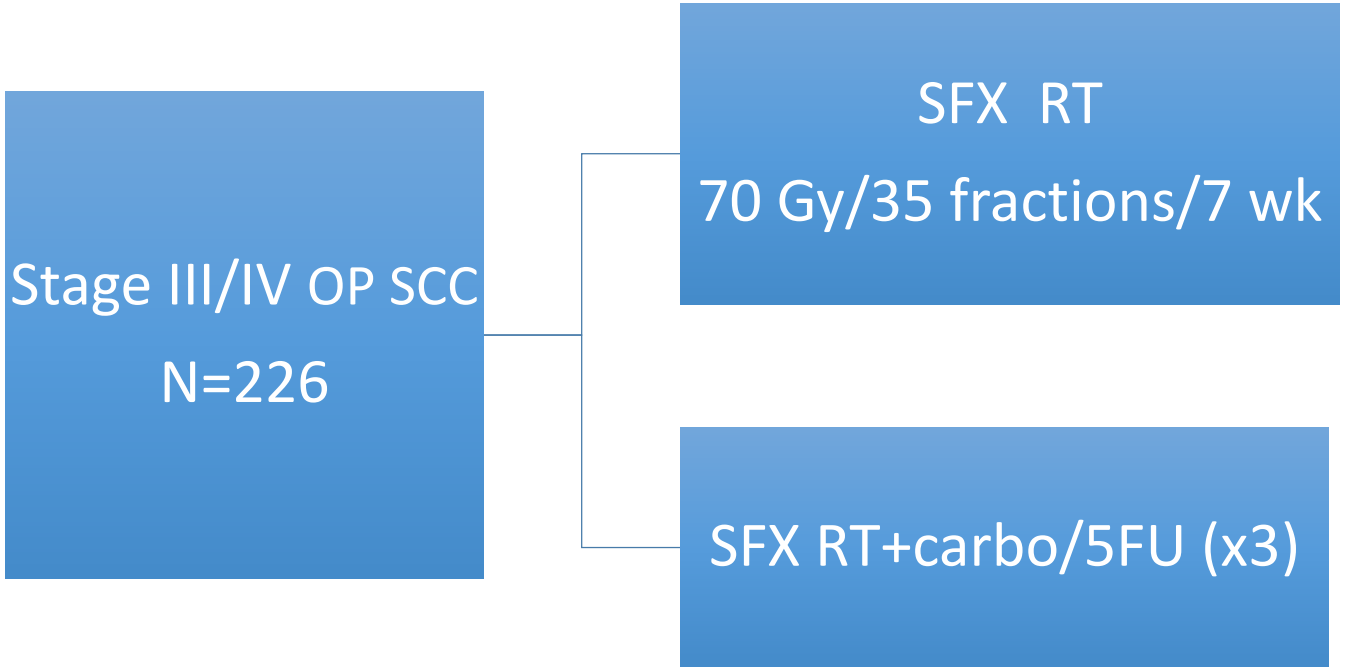
3-year OS (23 → 37%) and DSS (33 → 51%) vs. RT alone.

No difference in distant metastases.

Chemo-RT increased acute toxicity.

Adelstien JCO 2003

GORTEC 94-01



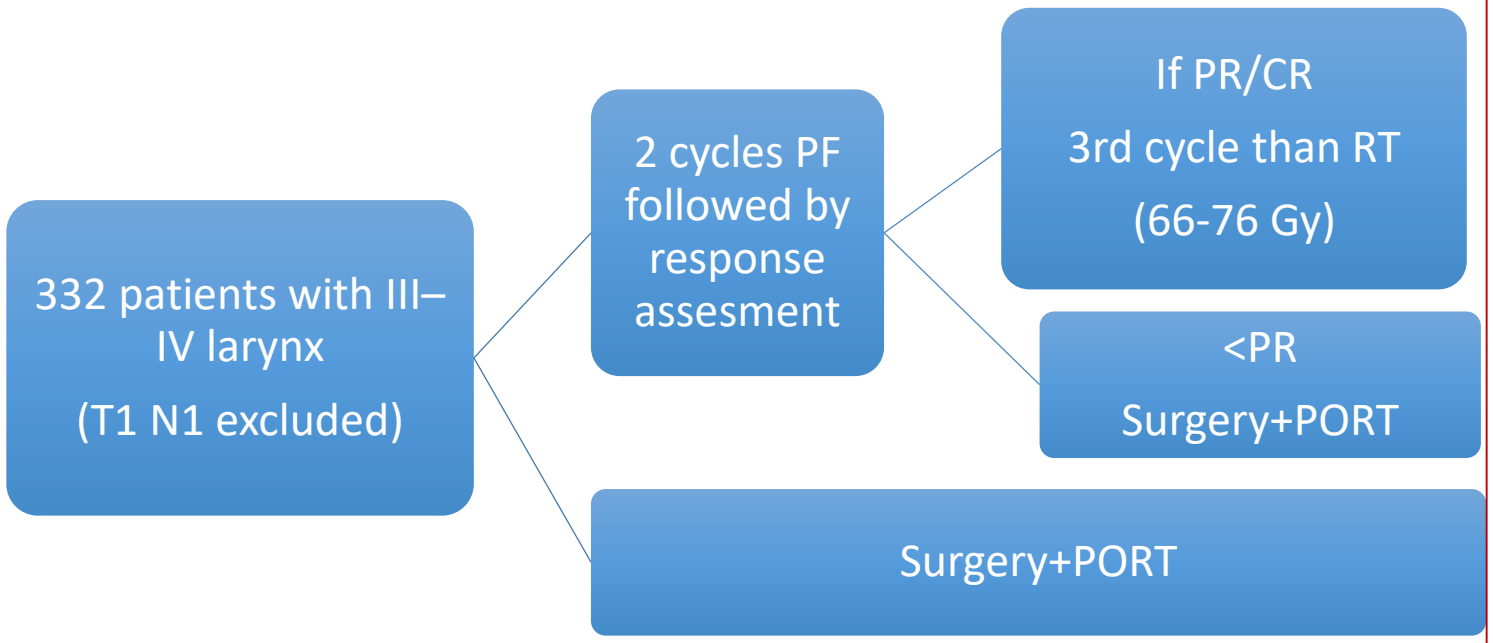
Chemo-RT improved 5-year LC (25 → 48%), DFS (15 → 27%), and OS (16 → 23%)

CRT increased acute toxicity.

Trend for increased late toxicity.

Denis JCO 2004

The Veterans Affairs Study



Larynx preservation at 2 years with induction chemo 64%.

No difference in 2-year OS (68%)

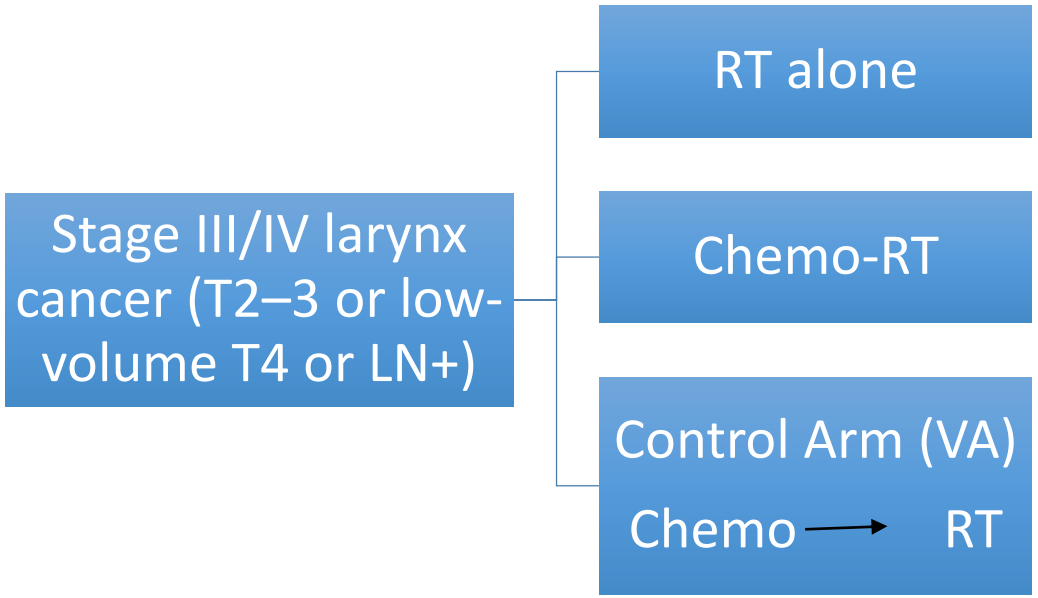
Induction chemo decreased DM, but had higher LF (12 vs. 2%).

Salvage laryngectomy was required for 56% of T4 patients.

Chemo was more beneficial than RT alone?

Wolf, N Eng J Med, 1991

RTOG 91-11

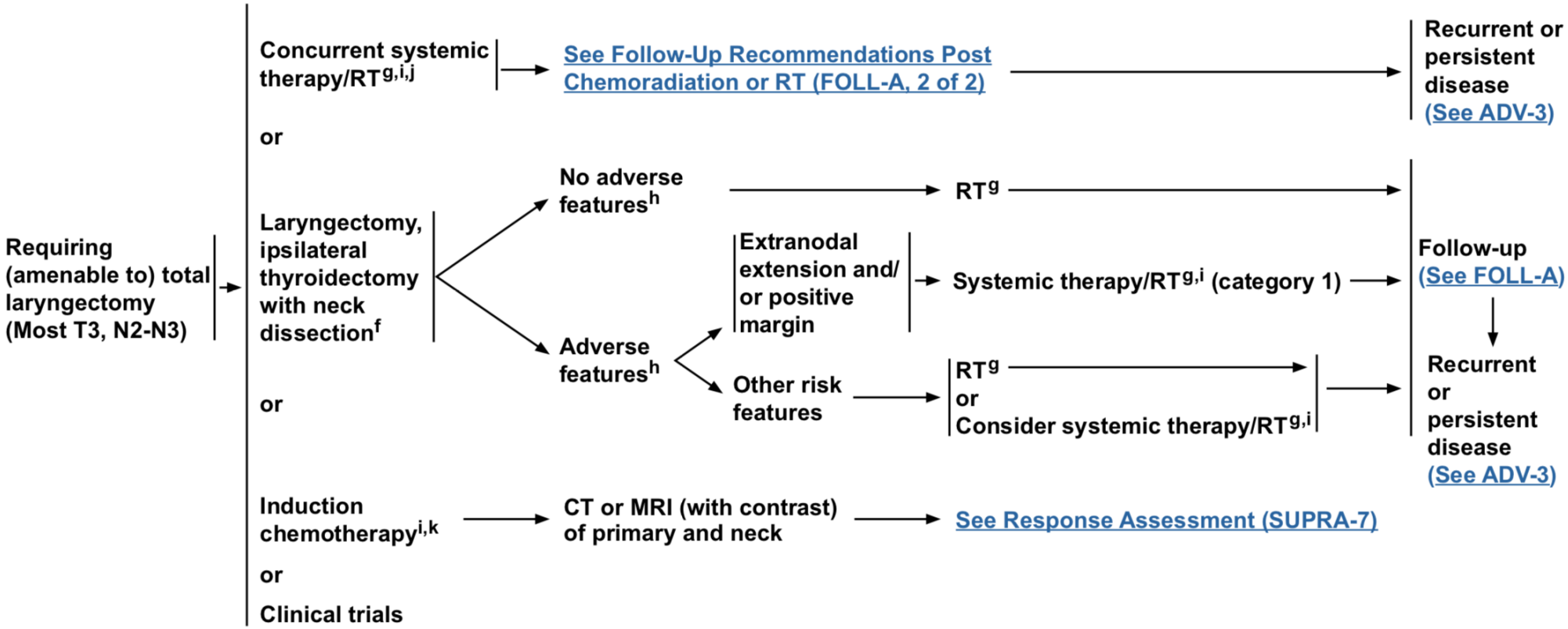


RT: 70 Gy
Induction chemo was cisplatin/5-FU × 2c (with a third cycle if PR/CR, otherwise surgery).
Concurrent chemo was cisplatin × 3c.

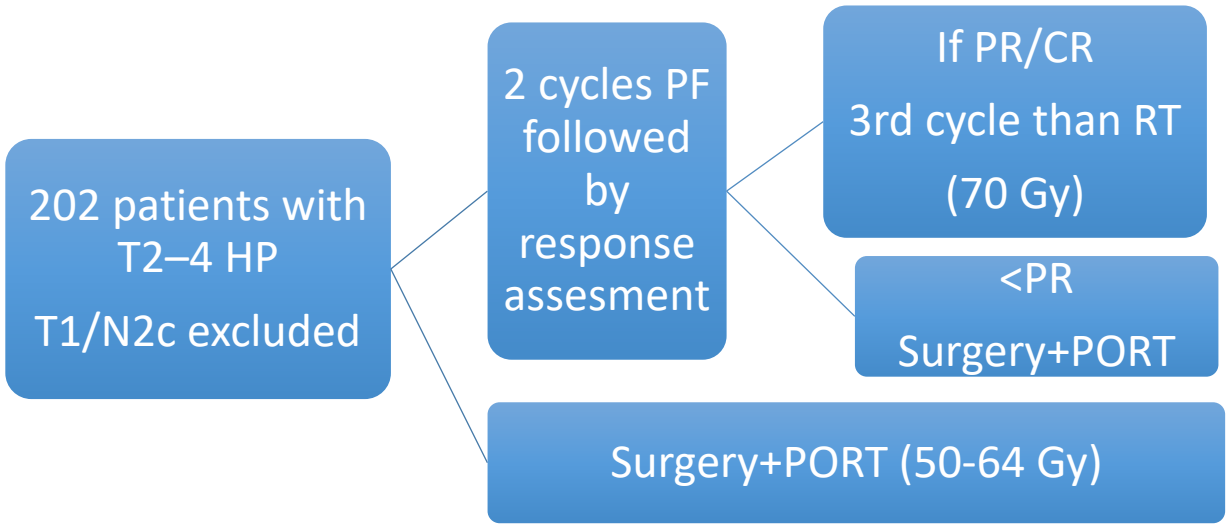
Forastiere NEJM 2003, JCO 2013

- Over RT alone or induction chemo, concurrent chemo-RT improved 10-year larynx preservation (64 → 68 → 82%) and LRC (47 → 49 → 65%).
- Trend toward improved distant control with any chemo (76 → 83 → 84%).
- No significant difference in 10-year OS (32 → 39 → 28%)
- Although more late deaths unrelated to disease with concurrent chemo-RT.

LA- Larynx Cancer



EORTC 24891



54% of patients had a CR after chemo.

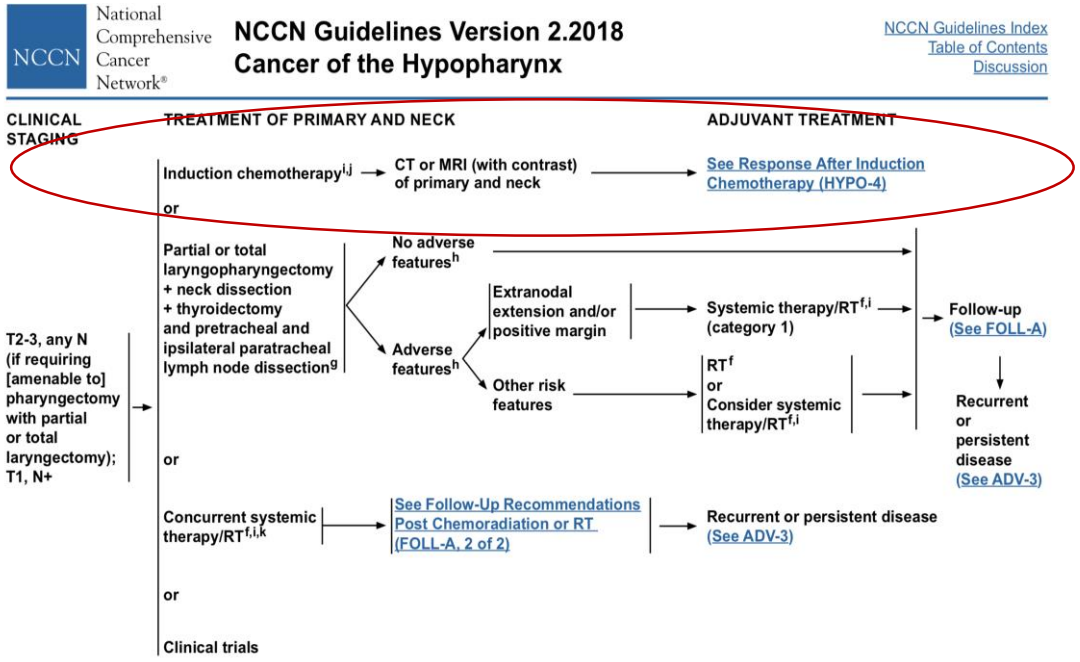
A functioning larynx was preserved in 42% of patients who did not undergo surgery.

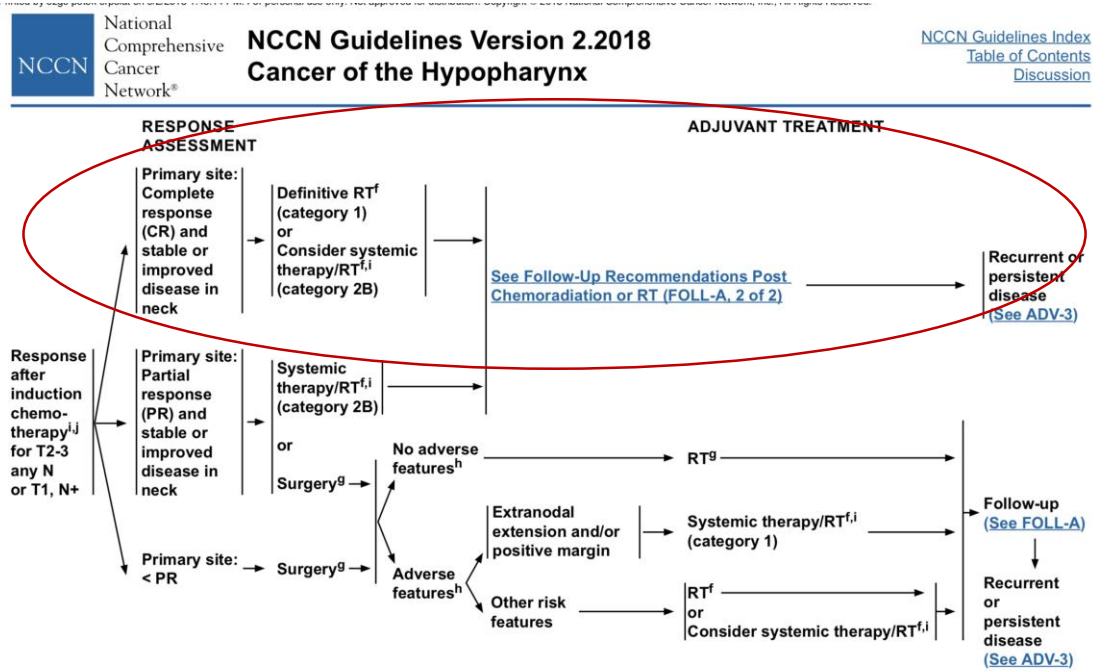
No significant difference in 5-10 year LRF, PFS, or OS.

Although the chemotherapy recipients did show a significant reduction in distant metastases as a site of first failure (*P* = .041).

Lefebvre *J Natl Cancer Inst 1996, Ann Oncol 2012*

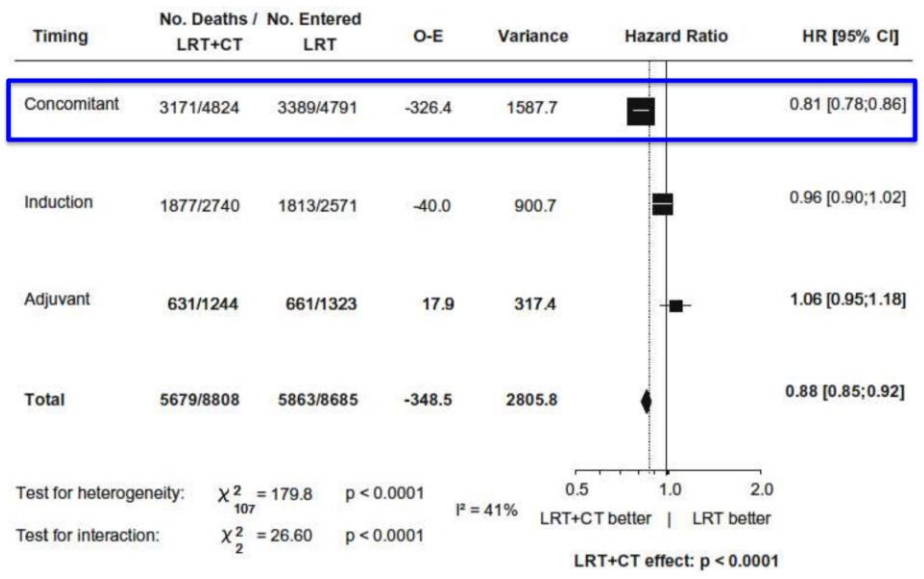
LA-Hypopharynx Cancer





Concomitant Chemo-RT Yielded the Best Survival
MACH-NC Meta-analyses

93 phase III trials and
17.346 patients.



Pignon *Radiother Oncol* 2009

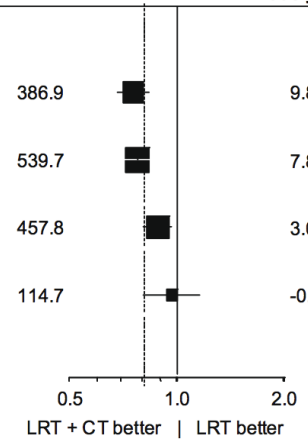
- Any chemotherapy gave 4.5% survival benefit at 5 years
- Greater OS benefit for concurrent (6.5%) vs. induction chemo (2.4%).
- No benefit from adjuvant chemo
- The concomitant schedules markedly improved the LRC. (HR, 0.74; $p < 0.001$)
- Less impressive improvement in distant control (HR, 0.88; $p = 0.04$)

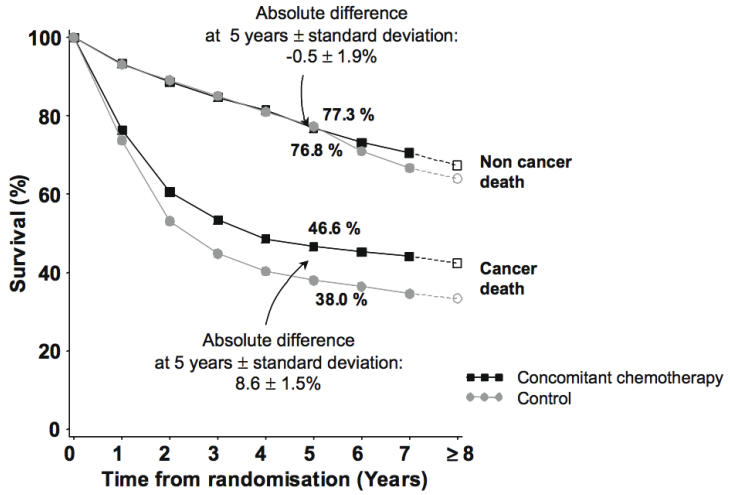
Concomitant Chemo-RT Yielded the Best Survival
MACH-NC Meta-analyses

Category	No. Deaths / No. Entered LRT + CT	LRT	O-E	Variance	Absolute difference at 5 years ± sd
Age					
Less than 50	803/1296	860/1288	-107.6	386.9	9.8 ± 2.1
51-60	1069/1645	1198/1661	-136.4	539.7	7.8 ± 1.8
61-70	972/1368	988/1330	-56.2	457.8	3.0 ± 1.9
71 or over	273/356	260/336	-3.5	114.7	-0.7 ± 3.9

p_inter = 0.02

p_trend = 0.003



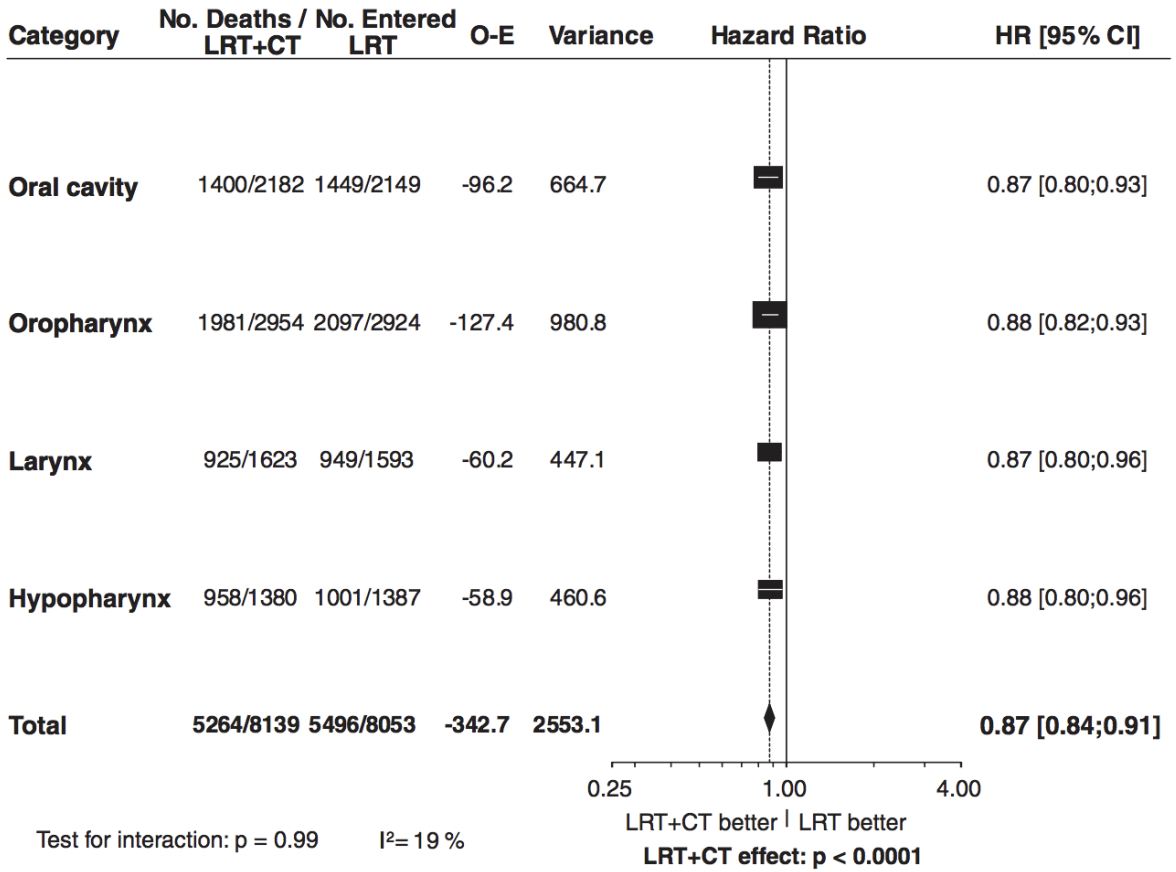


Decreasing chemo-RT benefit with age; none observed if age > 70 years.

Older patients more frequently die from other causes than their head and neck cancer?
Another explanation could be an increase in non-cancer deaths by the chemotherapy in old patients ?

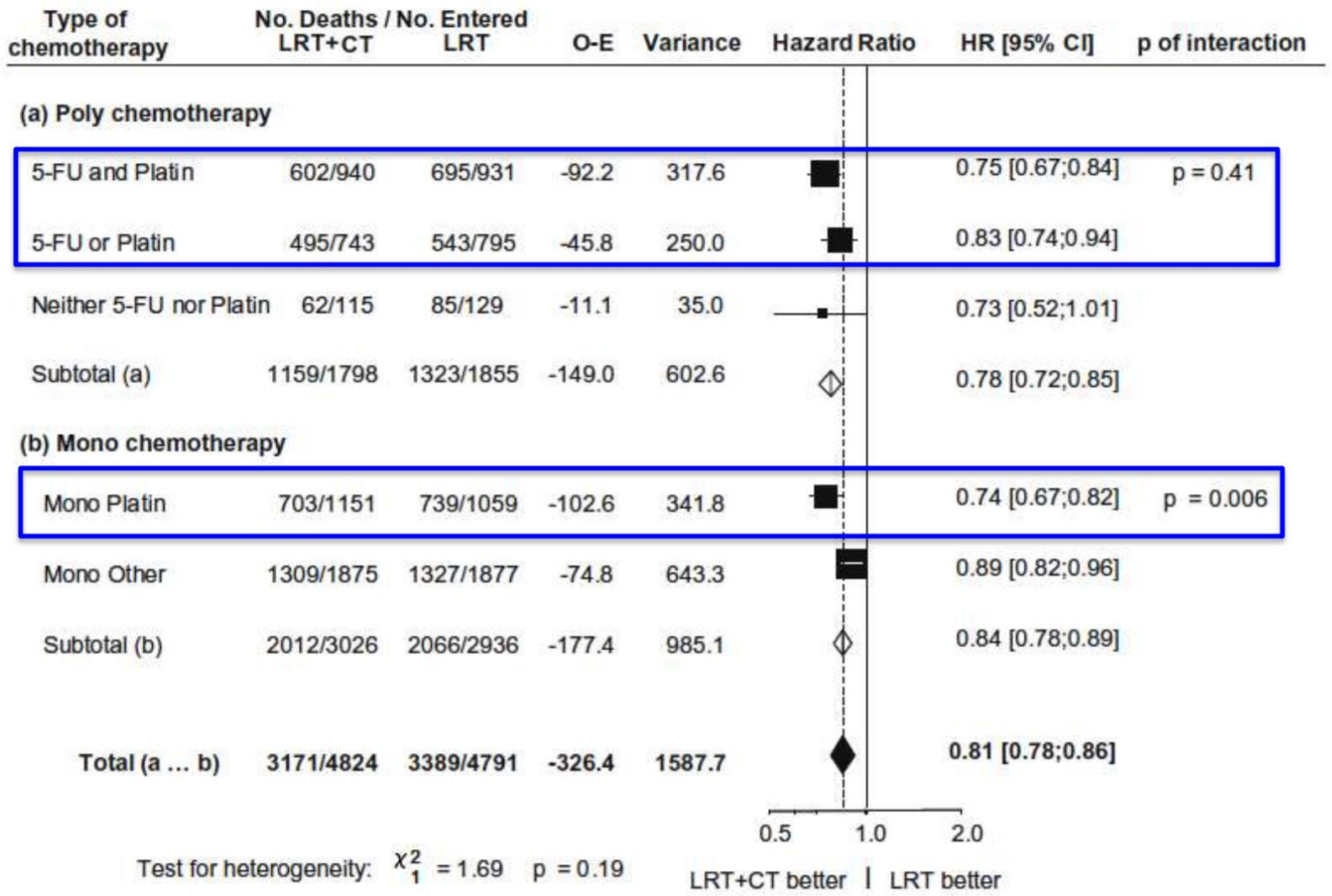
Pignon Radiother Oncol 2009

Concomitant Chemo-RT improved survival for all tumor subsites



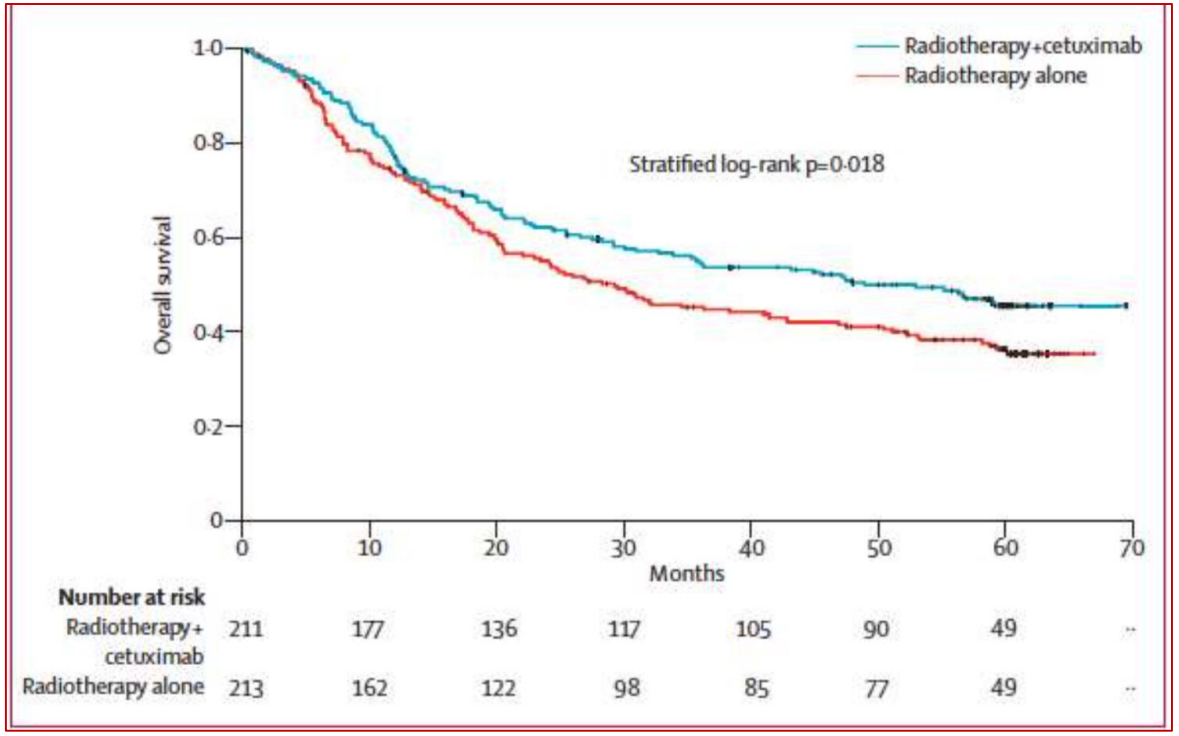
Blanchard P, Radiother Oncol 2011

Overall survival by chemotherapy



Pignon Radiother Oncol 2009

RT+Cetuximab is superior to RT alone



Bonner JA, Lancet Oncol, 2010

- RT not standardized; options included 2/70 Gy, 1.2 BID/72–76.8 Gy, or concomitant boost 72 Gy.
- Cetuximab improved 5-year OS (36 → 46%).
- Improved OS with concomitant boost vs. standard fractionation
- The oropharynx benefited most compared to those with primary tumors in the larynx (HR, 0.87) and in the hypopharynx (HR, 0.94),

What Radiation Fractionation to Use with Concurrent Cisplatin based Chemotherapy

Phase 3 Trials of concomitant chemoradiotherapy+/- Alterted Fractionation

	N	Treatment arms	Primary endpoint	Results	Secondary observations
RTOG 0129	721	1.SFX+cisplatin (x3) 2.AFX+cisplatin (x2)	OS	No difference RT>8 wk HR:2.2	Better outcome for p16+ OP
TROG 02.02	861	1.SFX+cisplatin (x3) 2.SFX+cisplatin (x3)+TPZ	OS	No difference	Better outcomes for p16+ OP Worse outcome if poor quality RT
RTOG 0522	891	1.AFX+cisplatin (x2) 2.AFX+cisplatin(x2)+ Cetuximab	PFS	No difference	Better outcome for p16+ OP More treatment related death and interruption of RT with Cetuximab
GORTEC 9902	840	1.SFX+Carbo+5FU (x3) 2.AFX+Carbo+5FU (x2) 3. Very accelerated RT (64.8 Gy/3.5 weeks)	PFS	1. Arm 1 and 2 Equivalent 2. Arm 3 was inferior	Better outcomes for p16+ OP Worse mucositis and long- term PEG-tube dependence on Arm 2 and 3

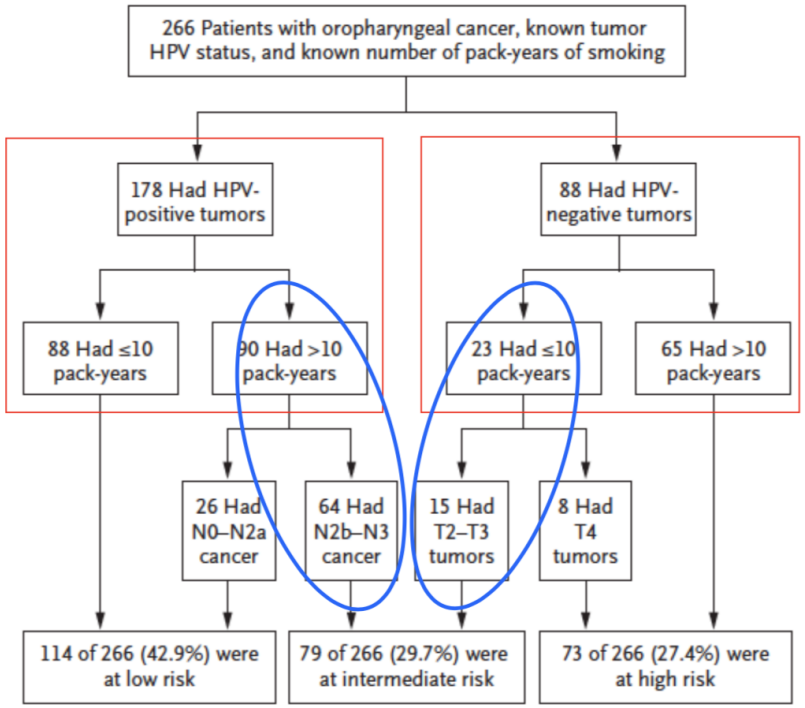
- **Accelerated RT with 2 cycles cisplatin comparable to standard RT with 3 cycles cisplatin.**
- **Concurrent cetuximab superior to RT alone but no advantage when added to cisplatin-RT.**

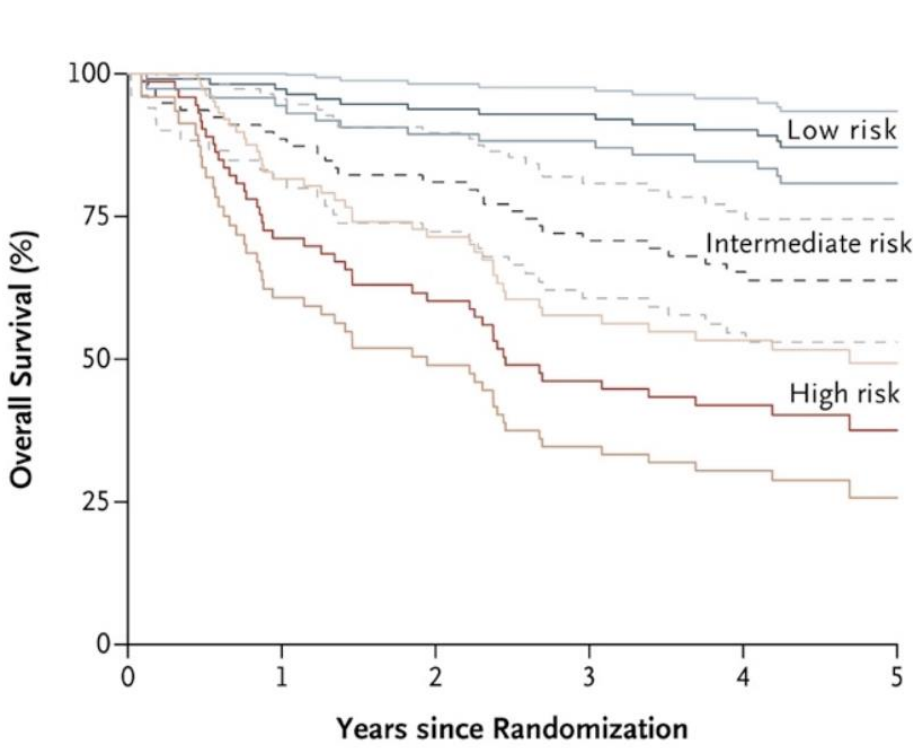
Several important observations from these trials

Trial	Year	*N*	Stage IV	OP	p16+ OP
RTOG 0129[33]	2010	743	78%	60%	50%
TROG 02.02[132,133]	2010	861	87%	55%	57%
RTOG 0522[134]	2011	940	86%	70%	73%
GORTEC 9902[135]	2012	840	NS	66%	NS

- The study populations were dominated by patients with stage IV oropharynx cancer who were largely p16 or HPV positive.
- Separate clinical trials based on tumor HPV status should be designed.
- The TROG trial also identified a strong trend toward an improvement in LRC in the patients with p16-negative treated with the hypoxic sensitizer.
- In the HPV-negative cancers, continued efforts directed at improving outcomes remain the priority

RTOG 0129-RPA analyses





3 year OS 93%

3 year OS 71%

3 year OS 46%

36% of patients with HPV-positive tumors were in the intermediate-risk group

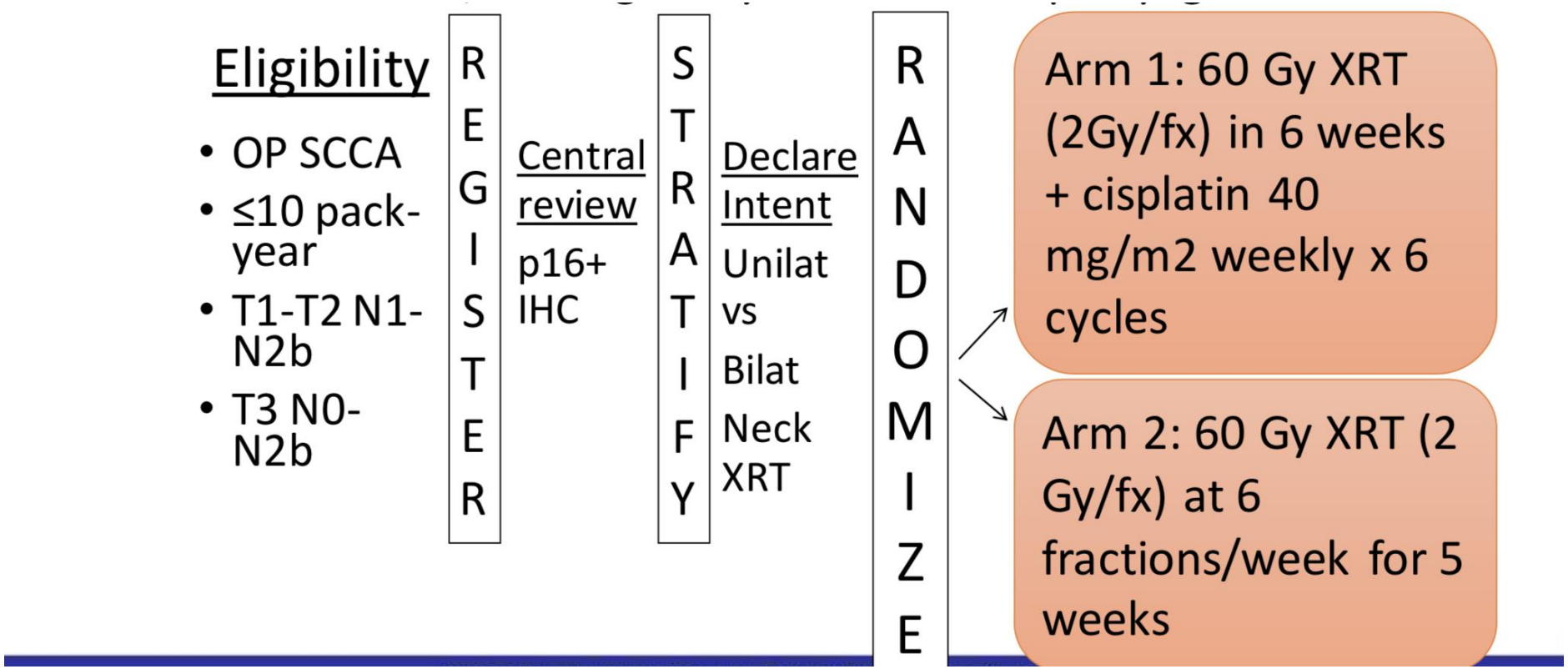
Ang NEJM 2010

Clinical selection of patients for de-intensification schemes

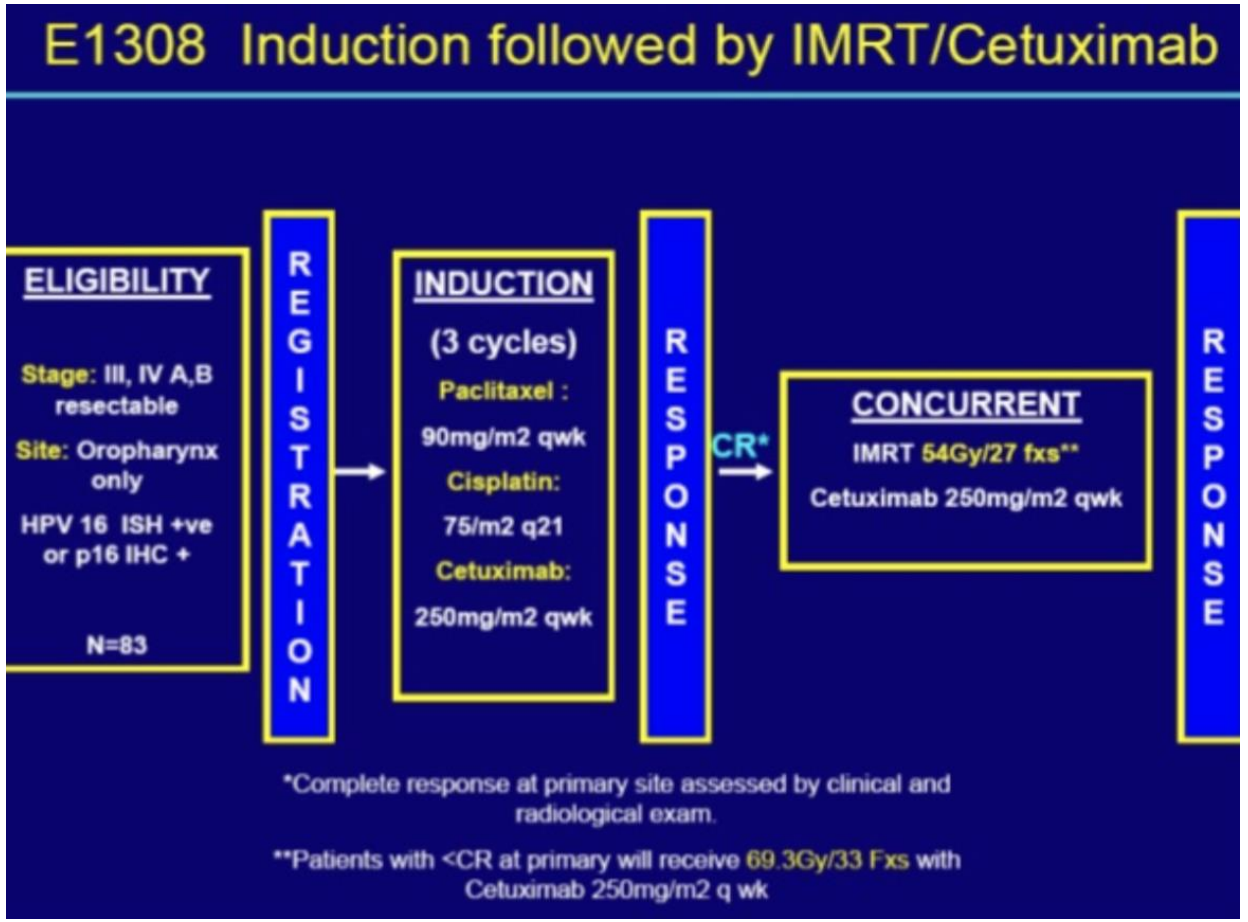
Patients profiles that has achieved excellent outcomes in retrospective and prospective trials:

- P16+
- OP cancer
- Minimum smoking history $\leq$ 10 pack year
- Non bulky primary and non extensive pattern of disease spread

NRG HN002: Phase II RCT for pts with p16 positive non-smoke associated LA- OP



E1308: Reduced dose of RT in patient with HPV +OP achieving a complete response to induction CHT



Postoperative Radiotherapy

Who needs PORT for head and neck cancer?

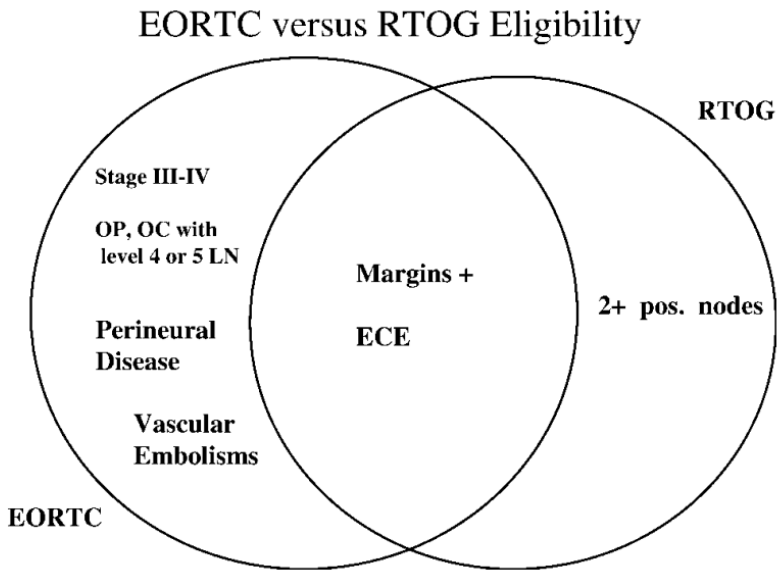
- **Post-op RT alone indications (minor risk factors):**

Close margin, multiple LN+, PNI, LVSI, pT3-4, OP and OC with level 4 or 5 LN

- **Post-op chemo-RT indications (major risk factors):**

Nodal extracapsular extension (ECE) and/or positive margin.

RTOG 95-01 and EORTC 22931
Operable HNC



Patients with high risk pathologic features

- Arm 1: 60-66 Gy
- Arm 2: 60-66 Gy+CisplatinX3

Cooper, NEJM 2004
Bernier, NEJM 2004

EORTC vs RTOG

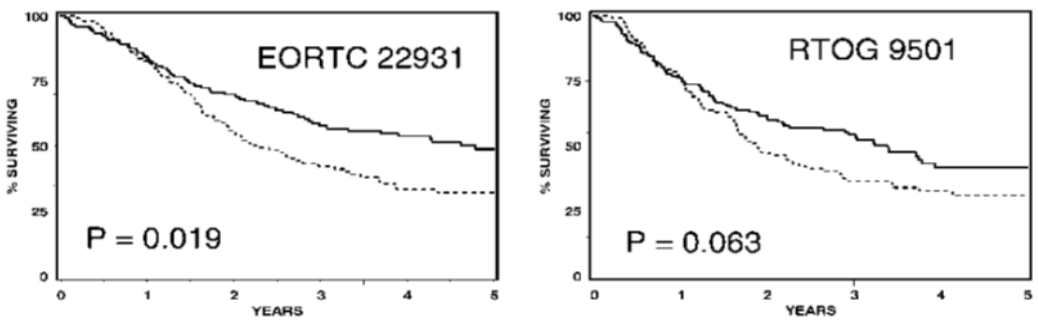
	EORTC N=334	RTOG N=459
N stage (N2-3%)	57%	94%
Positive surgical margin	29%	18%
Oropharynx %	30%	42%
Local-regional control		
RT	69%	67%
CRT	82%	78%
	p=0.007	p=0.01
Overall Survival		
RT	40%	41%
CRT	53%	49%
	(p=0.02)	(p=0.19)

Cooper, NEJM 2004
Bernier, NEJM 2004

DEFINING RISK LEVELS IN LOCALLY ADVANCED HEAD AND NECK CANCERS: A COMPARATIVE ANALYSIS OF CONCURRENT POSTOPERATIVE RADIATION PLUS CHEMOTHERAPY TRIALS OF THE EORTC (#22931) AND RTOG (#9501)

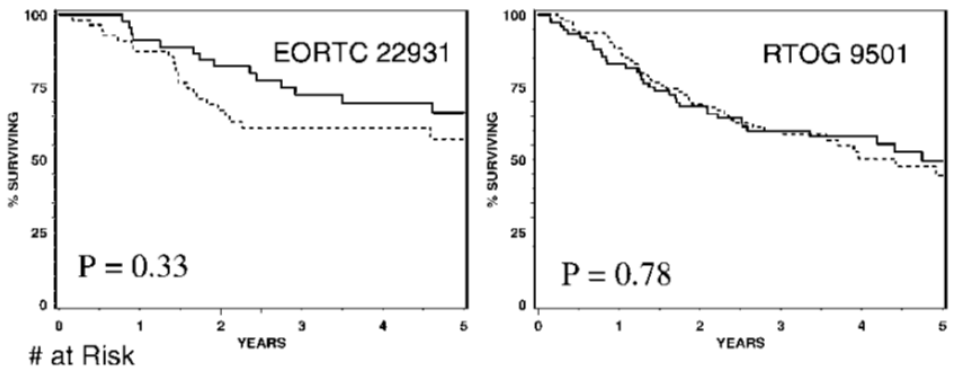
Overall Survival

Patients with positive margin and/or ECE



Overall Survival

Patients without positive margin and/or ECE



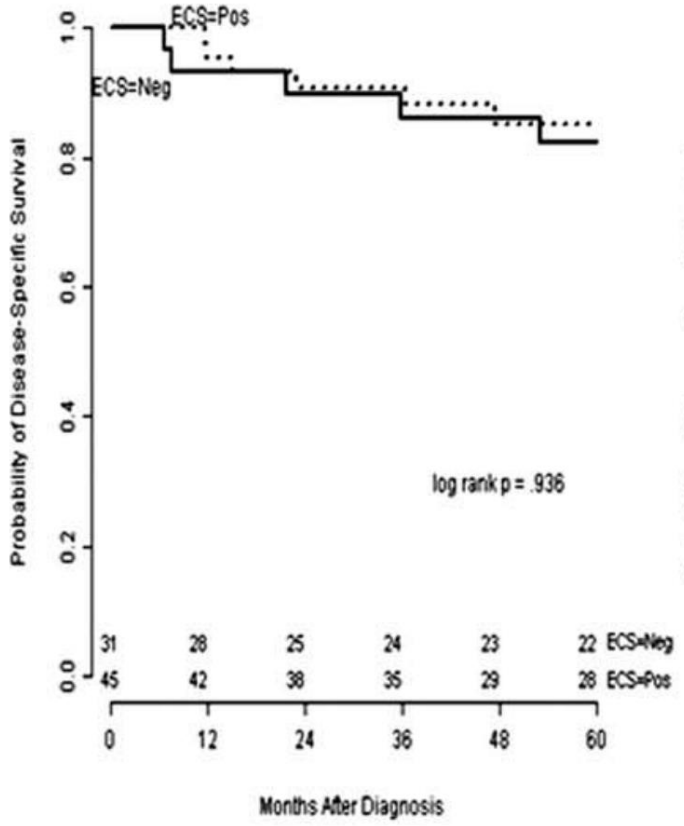
at Risk

Bernier, Head and Neck, 2005

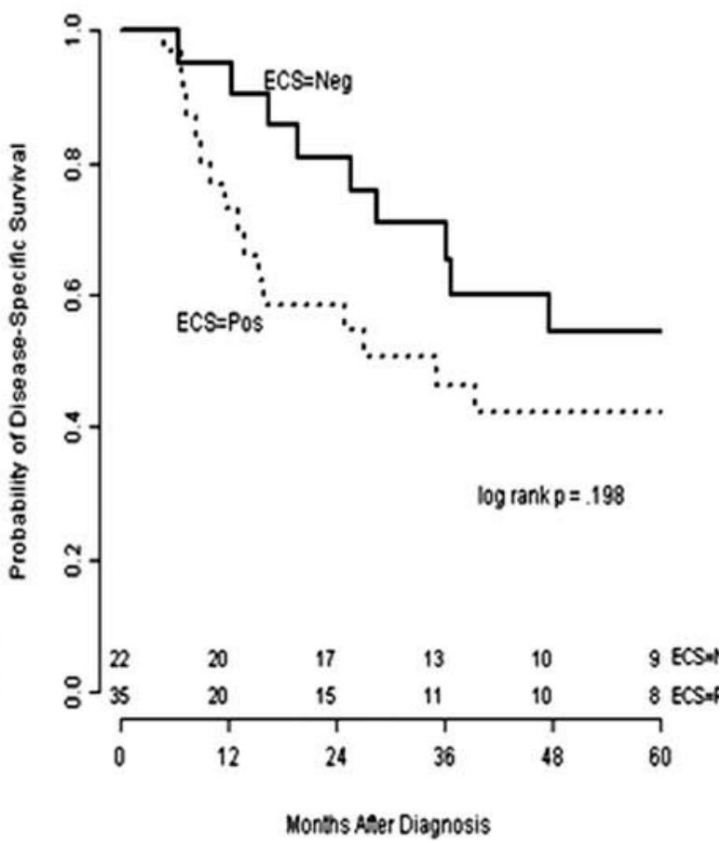
Extracapsular Spread in the HPV+ Patients

ECS was not associated with worse DSS in p16-positive or p16-negative OPC patients.

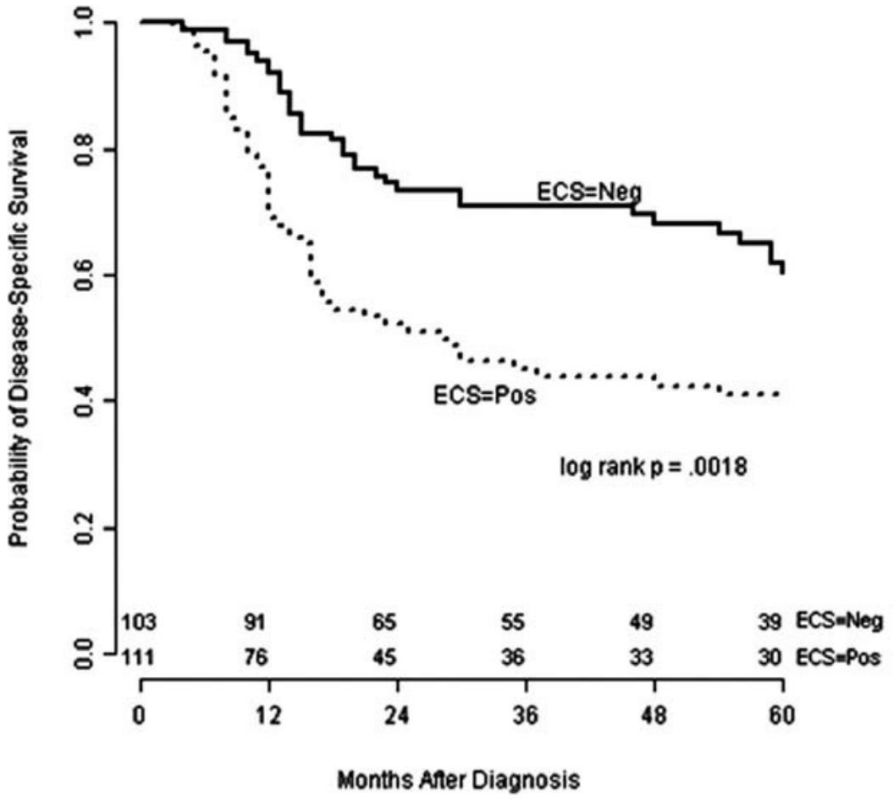
Maxwell JS, Cancer 2013



HPV positive Oropharynx tm

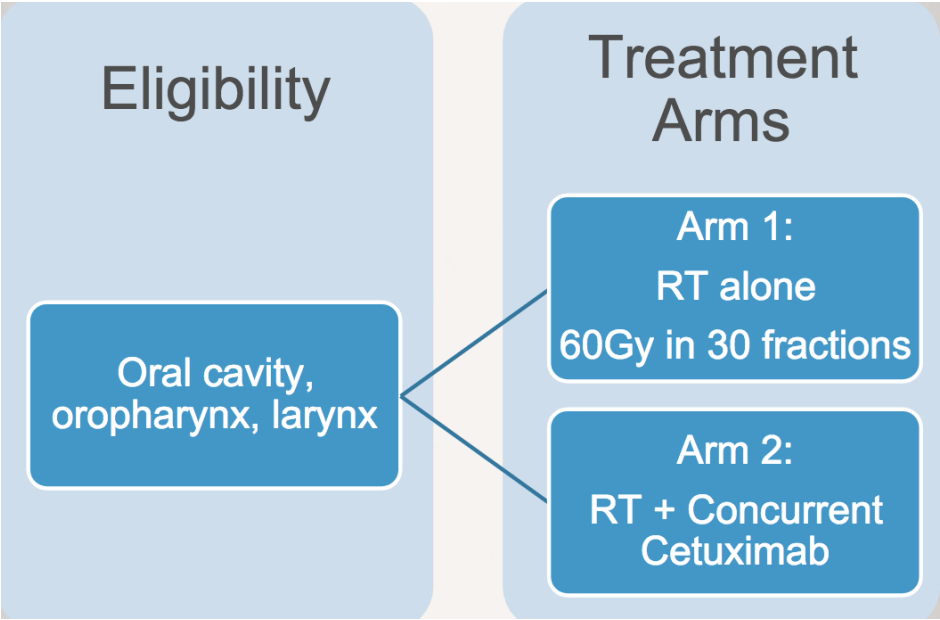


HPV negative Oropharynx tm



Oral cavity tm

LAHNC- Postop RT Ongoing trials
RTOG 09-20



Intermediate risk patients:

PNI, LVI,

Single lymph node greater than 3 cm or two or more lymph nodes (all <6 cm) and no extracapsular extension

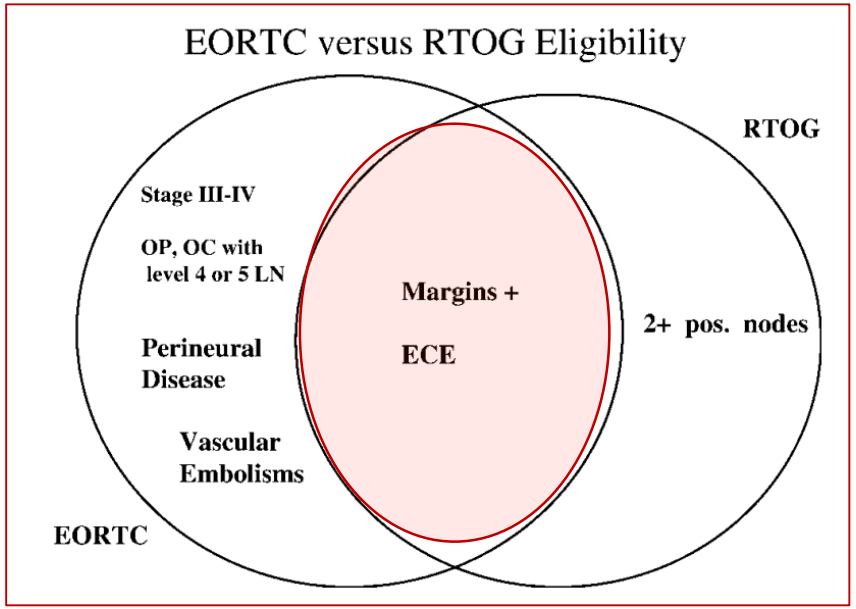
Close surgical resection margins (<5 mm)

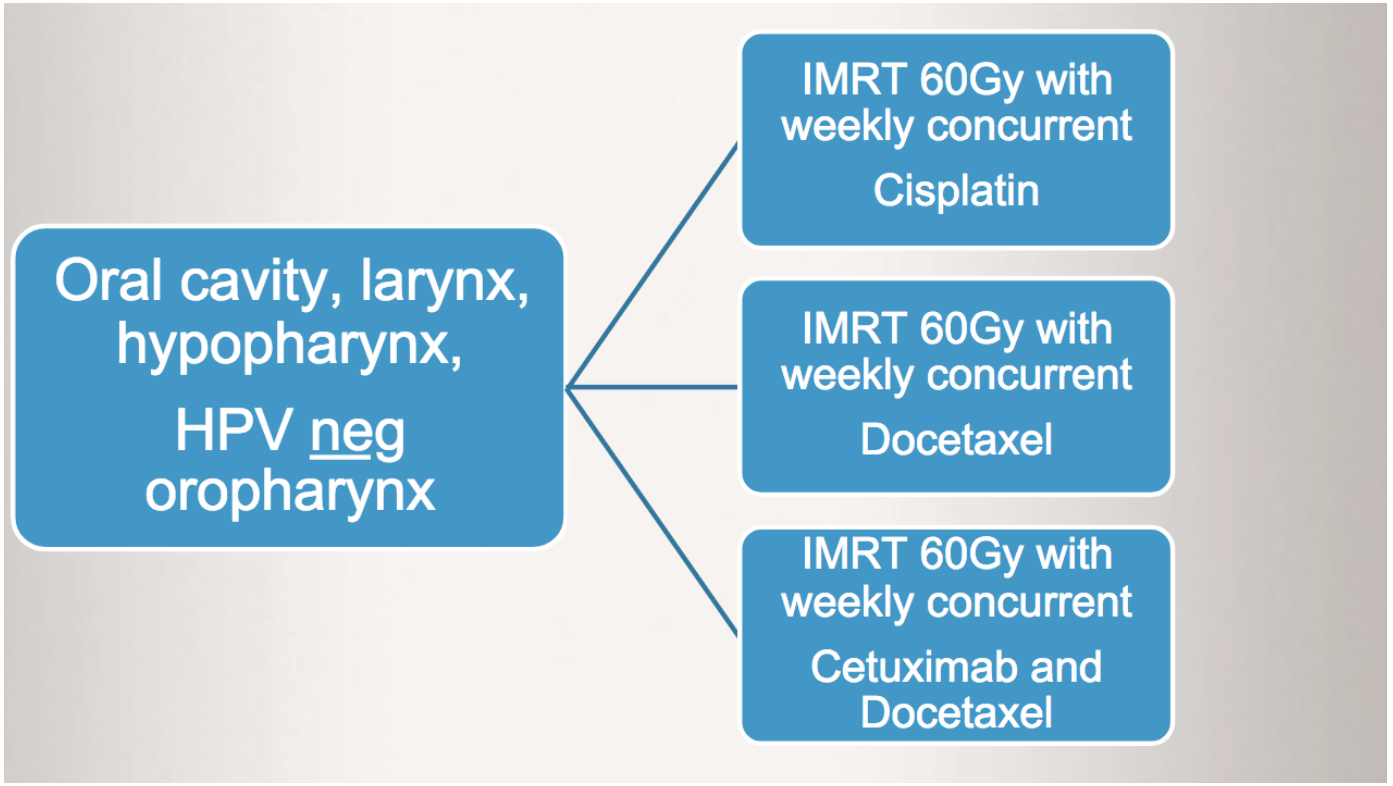
T3 or T4a primary tumor

T2 oral cavity cancer with more than 5 mm depth of invasion

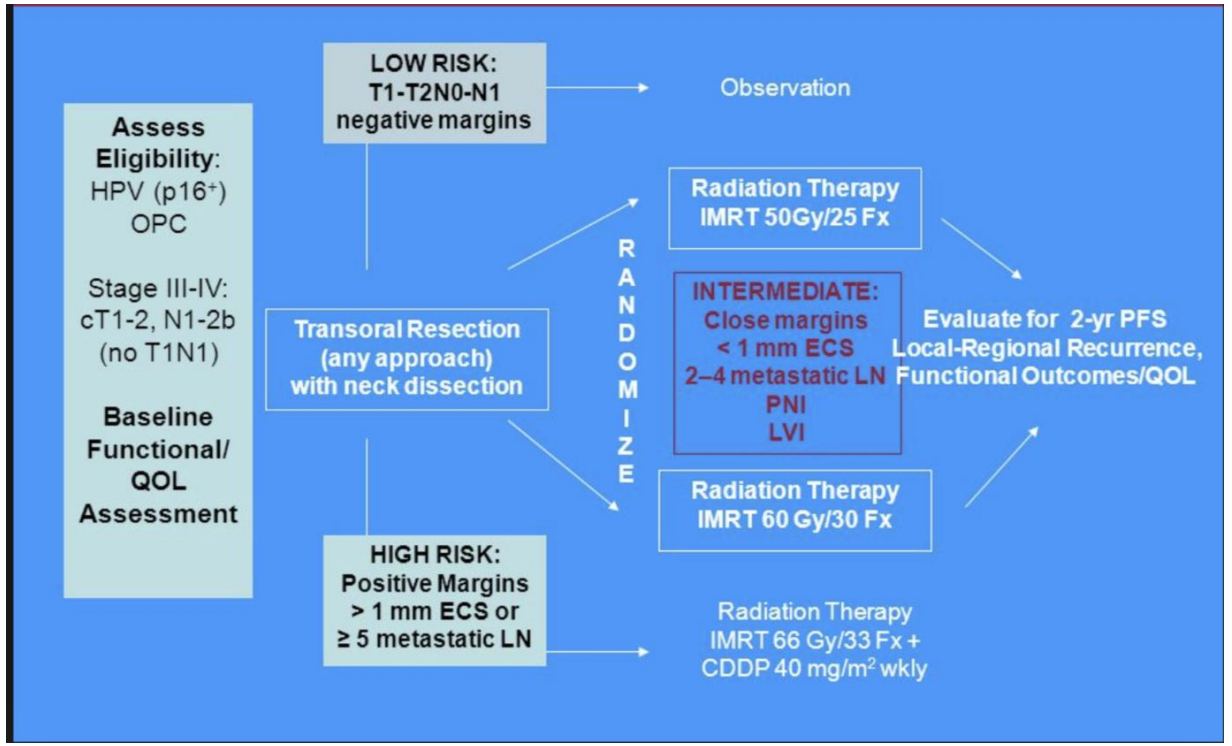
HPV allowed

LAHNC- Postop RT Ongoing trials
RTOG 1216: Phase 2/3 trials





LAHNC- Postop RT Ongoing trials
ECOG 3311



Conclusions

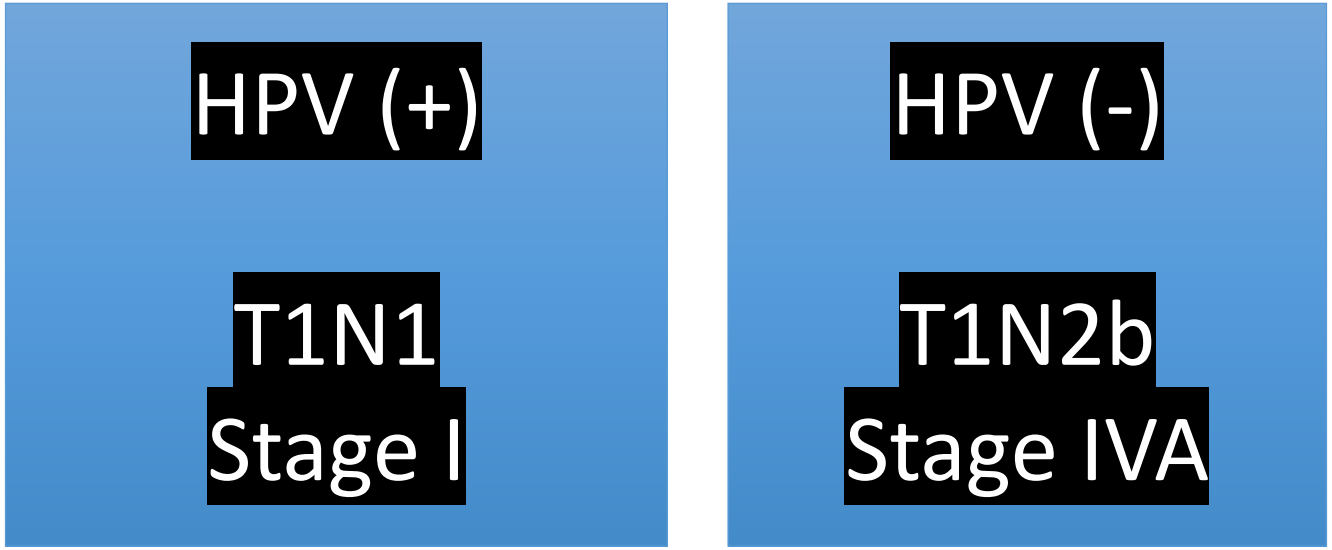
- Altered fractionation improved local control and survival
- RT improved local control and survival with concurrent chemotherapy, especially regimens including a platinum agent.
- Accelerated RT with 2 cycles cisplatin comparable to standard RT with 3 cycles cisplatin.
- Concurrent cetuximab superior to RT alone but no advantage when added to cisplatin-RT.

Conclusions

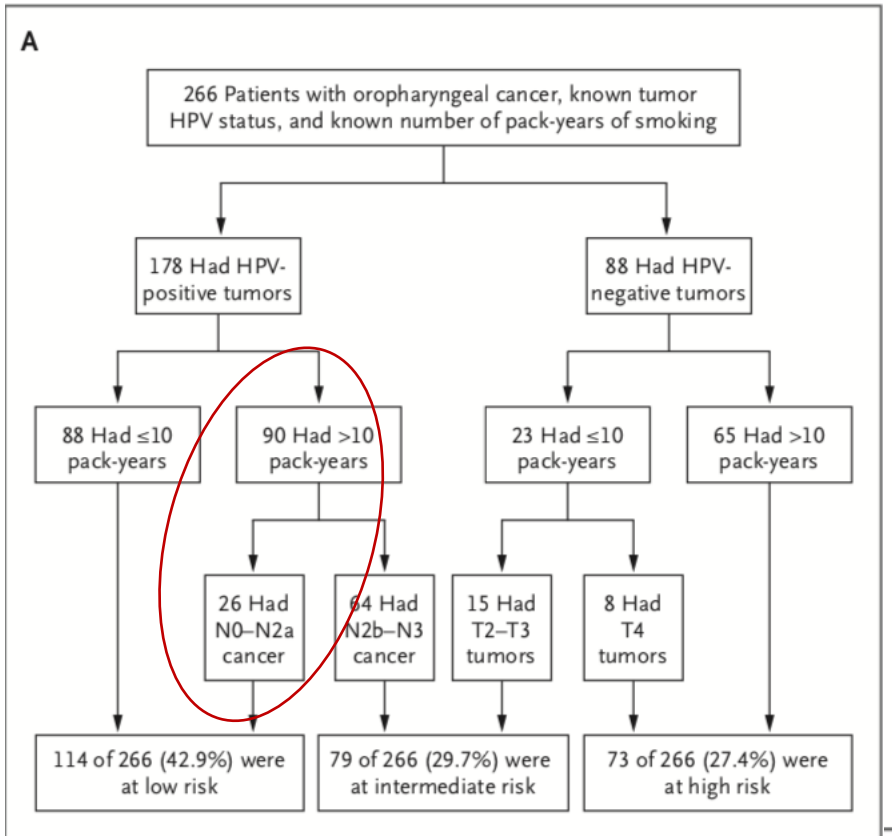
- For patients not candidates for standard cisplatin chemo-RT, consider concurrent cetuximab
- If unable to tolerate concurrent chemo, altered fractionation RT may be used
- If patients have major risk factors such as ECE/+margin, consider postop chemo-RT

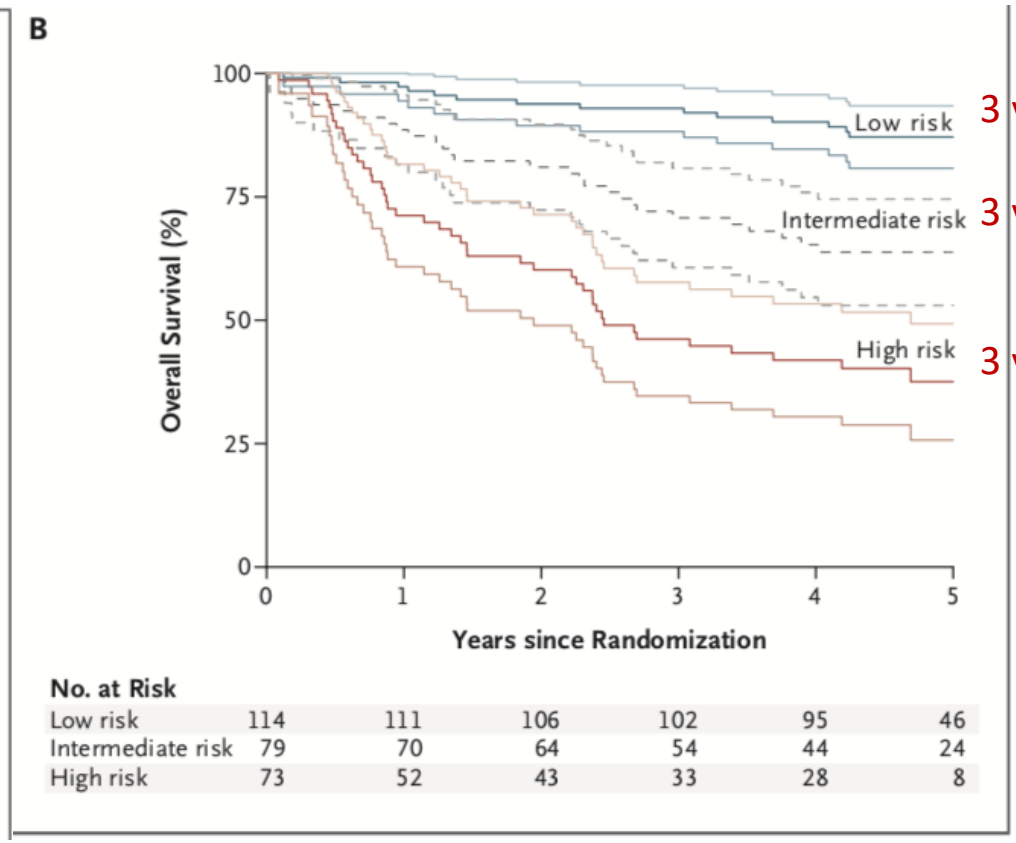
Our case…..

- 60 Y, E, smoker, 40 pack/year
- T1NbM0, tonsillar cancer
- Staged with MRI, PET-CT
- AJCC 2017 staging system
- 2 different scenario



HPV+ OP cancer, cT1-cN1, Stage 1 AJCC 2017



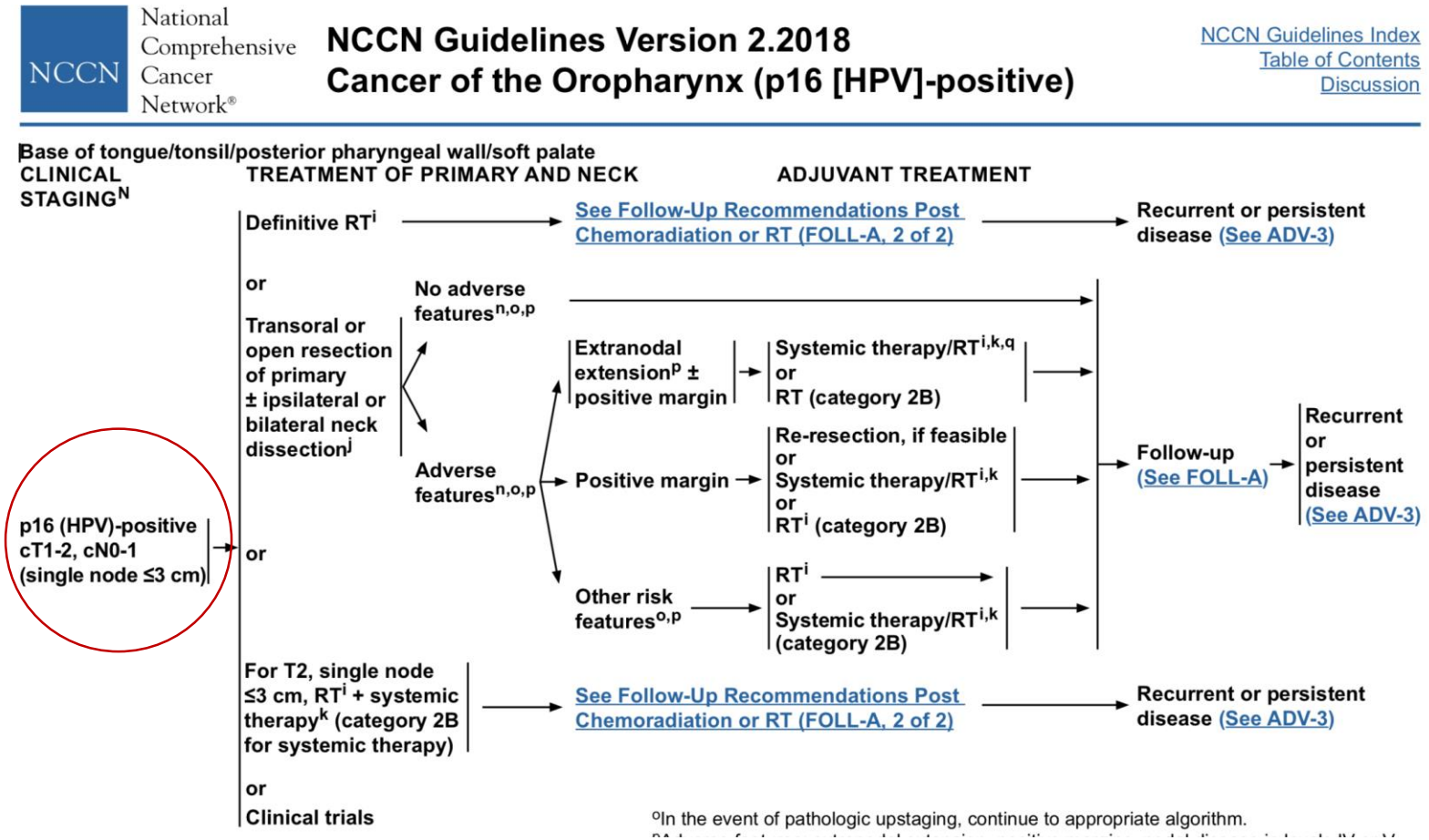


3 year OS 93%

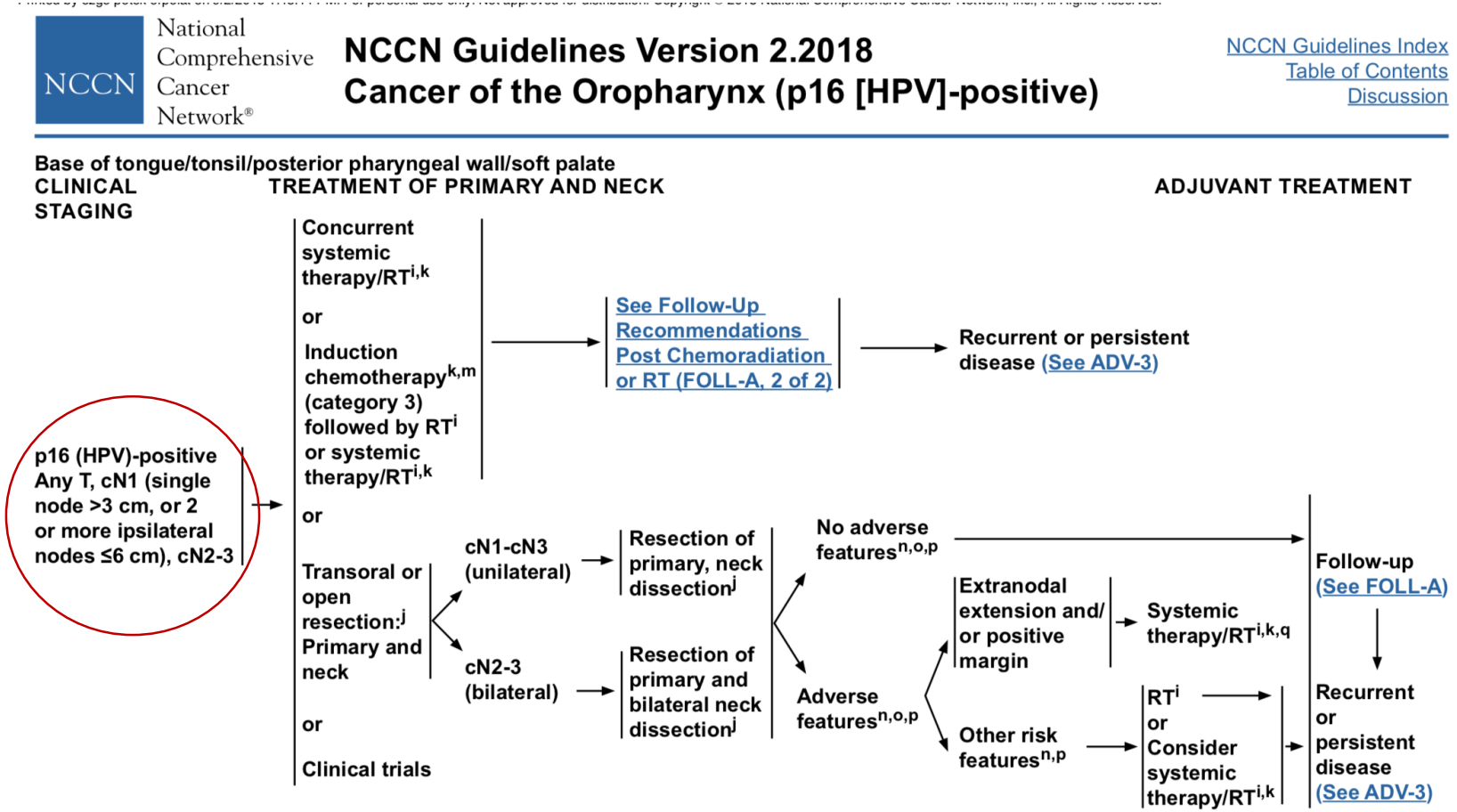
3 year OS 71%

3 year OS 46%

HPV positive, cT1-cN1, Stage 1 AJCC 2017



HPV positive OP, cT1-cN1 (old stage: cN2a-b)



HPV negative OP, cT1-cN2b, Stage IVA AJCC 2017