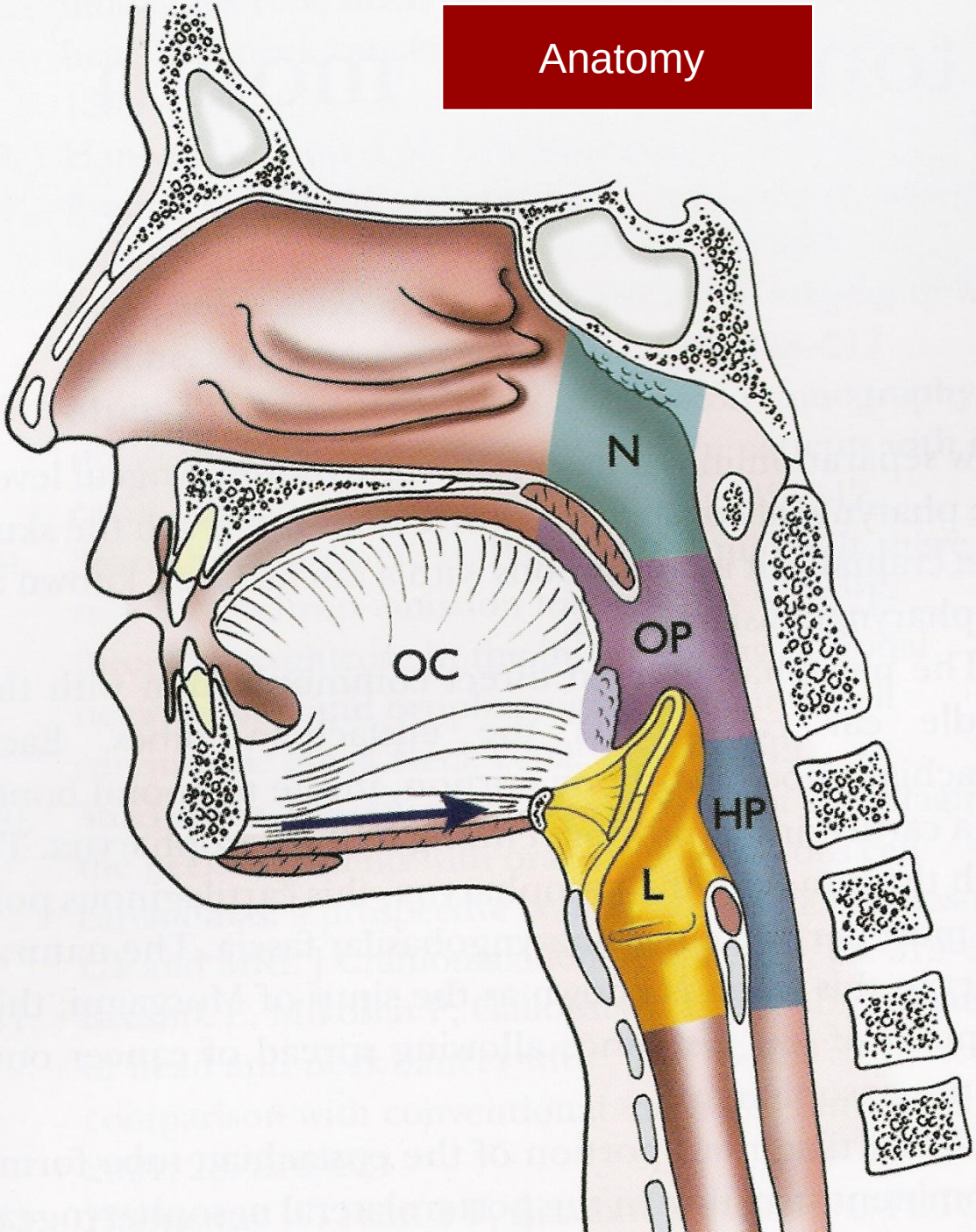
CHEMOTHERAPY AND TARGET THERAPY FOR HEAD AND NECK CANCER

Head and neck cancer

- Heterogeneous disease
  - Oral cavity, oropharynx, larynx, hypopharynx
    - Mostly SCC
      - Common etiology: smoking and drinking (betel nut for oral ca)
      - Similar biological behavior
  - Nasopharynx:
    - WHO class type III: undifferentiate ca (NPC)
  - Nasal and paranasal sinus
  - Salivary gland

NASOPHARYNGEAL CANCER

Anatomy



Pathology – WHO classification

- Nasopharyngeal carcinoma
  - Keratinizing squamous cell ca: type I
    - Similar with that in rest of aerodigestive tract
  - Non-keratinizing ca: type II and III
    - Differentiated non-keratinizing ca (type II)
    - Undifferentiated ca (type III)
- Type I distinct from type II/III
  - Type II/III so called “NPC”

Features of type II/III

- EBV association
  - EBV-encoded RNA in nearly all tumor cells
  - Premalignant lesion also harbor EBV
- Radiation sensitivity
- Tend to distant metastasis

Epidemiology

- Uncommon disease in most countries
  - Incidence 1/100000
- More frequent in
  - Southern China: Hong Kong 15-30/100000
  - Northern Africa
  - Alaska
- Genetic, ethnic, environment factors

Epidemiology

- North America
  - I/II/III: 25/12/63% → some are SCCs
- Southern Chinese
  - I/II/III: 2/3/95% → almost all typical NPC

Symptoms/signs

- Epistaxis and nasal obstruction/discharge
  - Mass in nasopharynx
- Tinnitus and hearing impairment
  - E-tube dysfunction, lateral extension
- Headache, diplopia, facial pain/numbness
  - Skull-base invasion, nerve palsy(5th/6th)
- Neck mass
- Signs of distant metastasis
  - Lung/bone/liver

Diagnosis and staging

- Endoscopic exam: nasopharynx
  - Punch biopsy
- Plain film: CXR
- Abdominal echo
- Bone scan
- CT and MRI
  - Both for local and distant evaluation
  - MRI better for soft tissue resolution
  - Low-risk(stage I) may not need
  - After treatment, MRI better
- PET: role to be defined

Prognostic factor

- TNM
- EBV
- Tumor size, age, gender, nerve palsy ….

NPC

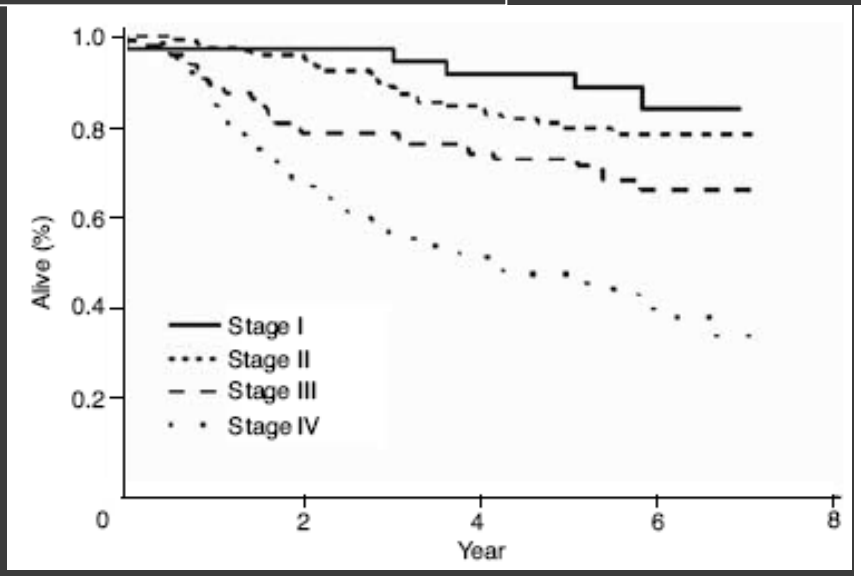
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIa	T2a	N0	M0
Stage IIb	T1	N1	M0
	T2a	N1	M0
	T2b	N0, N1	M0
Stage III	T1	N2	M0
	T2a, T2b	N2	M0
	T3	N0, N1, N2	M0
Stage IVa	T4	N0, N1, N2	M0
Stage IVb	any T	N3	M0
Stage Ivc	any T	any N	M1

T = tumor; N = node; M = metastasis.

Disease status monitored by plasma EBV DNA

Stage I/II over 90% cure rates

EBV and NPC prognosis



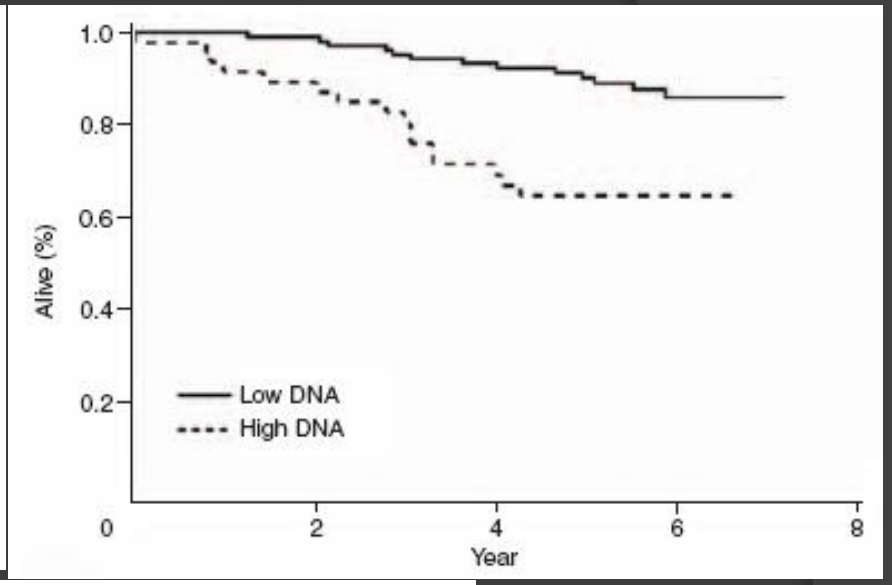


Table 2. Actuarial Survival of Patient Groups With Different UICC Stages and With Different EBV DNA Levels Within UICC Stages

Stage	No. of Patients	5-Year Survival (%)	95% CI (%)
I	36	92	83 to 100
II	119	80	73 to 88
III	95	73	64 to 82
IV	126	47	38 to 56
I + II, low DNA*	108	91	85 to 97
I + II, high DNA*	47	64	53 to 75
III + IV, low DNA	73	66	50 to 81
III + IV, high DNA	148	54	44 to 65

JCO 2006 Dec.1

Pattern of failure

- T1-2 N0-1: good outcome
- T3-4 N0-1: local failure dominant
- T1-2 N2-3: distant failure dominant
- T3-4 N2-3: both

Treatment

- RT as the mainstay
  - Difficult surgical approach
  - Sensitive to radiotherapy
- RT volume (field) and dose
  - Primary tumor: 65-75 Gy
  - Involved neck: 65-70 Gy
  - Uninvolved neck: 50-60 Gy

Morbidity from RT

- Dose-limiting organ
  - Brain stem
  - Spinal cord
  - Pituitary-hypothalamic axis
  - Temporal lobes
  - Eyes
  - Middle/inner ears
  - Parotid glands

Efficacy of RT

- Control rate
  - T1/T2: 75-90%
  - T3/T4: 50-75%
  - N0/N1: 90%
  - N2/N3: 70%
- Incorporate chemotherapy to RT

Incorporate chemotherapy

- Induction (neoadjuvant)
- Concurrent
- Adjuvant

Adjuvant chemotherapy

Two phase III randomized trial

- Italian (Non-cisplatin based)
  - R/T vs R/T + VCA
    - Vincristine/cyclophosphamide/adriamycin
  - No benefit

JCO 6: 1401-10, 1988

- TCOG
  - R/T vs R/T + PFL (cisplatin, 5FU, LV)
  - No benefit
  - 6 tx-related mortality

Int J Radiat oncol Biol phys 2002;52:1238-44

Concurrent chemoradiotherapy

Three phase III randomized trial

- U.S.: Intergroup study 0099 trial

JCO 16: 1310-1317, 1998

- Hong Kong

JCO 20: 2038-2044, 2002

- Taiwan: TVGH

JCO 21: 631-637 ,2003

Intergroup Study 0099

- Phase III trial
  - CCRT + adjuvant CT
  - RT alone
    - RT: 70 Gy
    - Cisplatin 100mg/m^2, D1, q3w x 3 (for CCRT)
    - PF x 3
      - Cisplatin 80mg/m^2, D1 + 5FU 1000mg/m^2, D1-4, q4w
  - Benefit in RFS and OS

JCO 16: 1310-1317, 1998

Hong Kong study

- Ho's N2,or N3 stage or N1 with node size > 4cm, 1994-1999
- CCRT vs RT alone
  - RT: 66Gy
  - Cisplatin 40mg/m^2, weekly x 8
- Primary end point: PFS
  - Positive, in T3 group

JCO 20: 2038-2044, 2002

Taiwan, VGH

- TVGH, Taiwan, 1993-1999
- CCRT vs RT alone
  - RT: 70-74 Gy
  - Cisplatin 20mg/m^2/d + 5FU 400mg/m^2/d by 96 hrs infusion) x 2
- Benefit: PFS and OS

JCO 21: 631-637, 2003

Neoadjuvant C/T + R/T

Three phase III randomized trial

- Asian-Oceanian Clinical Oncology Association study
  - No benefit, in RFS and OS

Cancer 1998; 83: 2270-83

- International Nasopharynx Cancer Study Group
  - Benefit in DFS, not OS

Int J Radiat Oncol Bilo Phys 1996; 35:463-9

- China
  - Benefit in DFS, not OS

JCO 2001; 19:1350-7

Incorporate chemotherapy

- Induction (neoadjuvant)
- Adjuvant

- Concurrent → current standard

- Ongoing: induction C/T → CCRT

Meta-analysis-CCRT vs RT

Meta-analysis of chemoradiotherapy compared to radiotherapy alone for stage III/IV nasopharyngeal cancer

Chemotherapy timing	5-year survival	
	Odds ratio [OR], 95% CI	
	OS	DFS
Neoadjuvant alone	0.65 (0.51-0.84)	0.63 (0.51-0.79)
Concurrent alone	0.72 (0.40-1.30)	0.68 (0.46-0.99)
Concurrent + adjuvant	0.30 (0.16-0.55)	0.30 (0.17-0.53)
Adjuvant alone	0.49 (0.18-1.31)	0.60 (0.34-1.04)
All	0.65 (0.51-0.83)	0.59 (0.51-0.68)

78 randomized controlled trials (9279 patients)

Proc Am Soc Clin Oncol 2004; 23:491a

Recurrent/residual disease

- Site
  - Neck
  - Nasopharynx
  - Distant
    - Bone, lung, liver
- Treatment option
  - Surgery
  - Re-irradiation
  - Systemic chemotherapy: palliation

Palliative Chemotherapy

- Xeloda 1.25 g/m2 bid: PR 17.6%; CR 5.9%; SD 52.9%; PD 23.5%; TTP 4.9 mo, MS 7.6 mo
- Gemzar 1250 mg/m2, d1,8/21d: RR 48%; TTP 5.1 mo; MS 10.5 mo
- CPT-11: RR 14%; MS 11.4 months (28 patients)
- Vinorelbine 20 mg/m2 followed by Gemzar 1000 mg/m2; d1,8/21d: RR 36%;RD 5.1 mo; PFS 5.6 mo; MS 11.9 mo
- Gemzar+Vinorelbine: RR 36% (39 patients); median survival 9 months
- Carboplatin AUC 5.5+Taxol (175 mg/m2, 3hrs/21d): PR 25%, SD 25%; MS 9.5 mo
- Ifosfamide plus leucovorin-modulated 5-FU: RR 56% in a report of 18 patients; although median survival had not been reached, 51% were still alive at one-year
- Erbitux+Carboplatin: RR 12%; MS 8 months (50 patients)

UpToDate

J Formos Med Assoc 2004;**103**:496-510

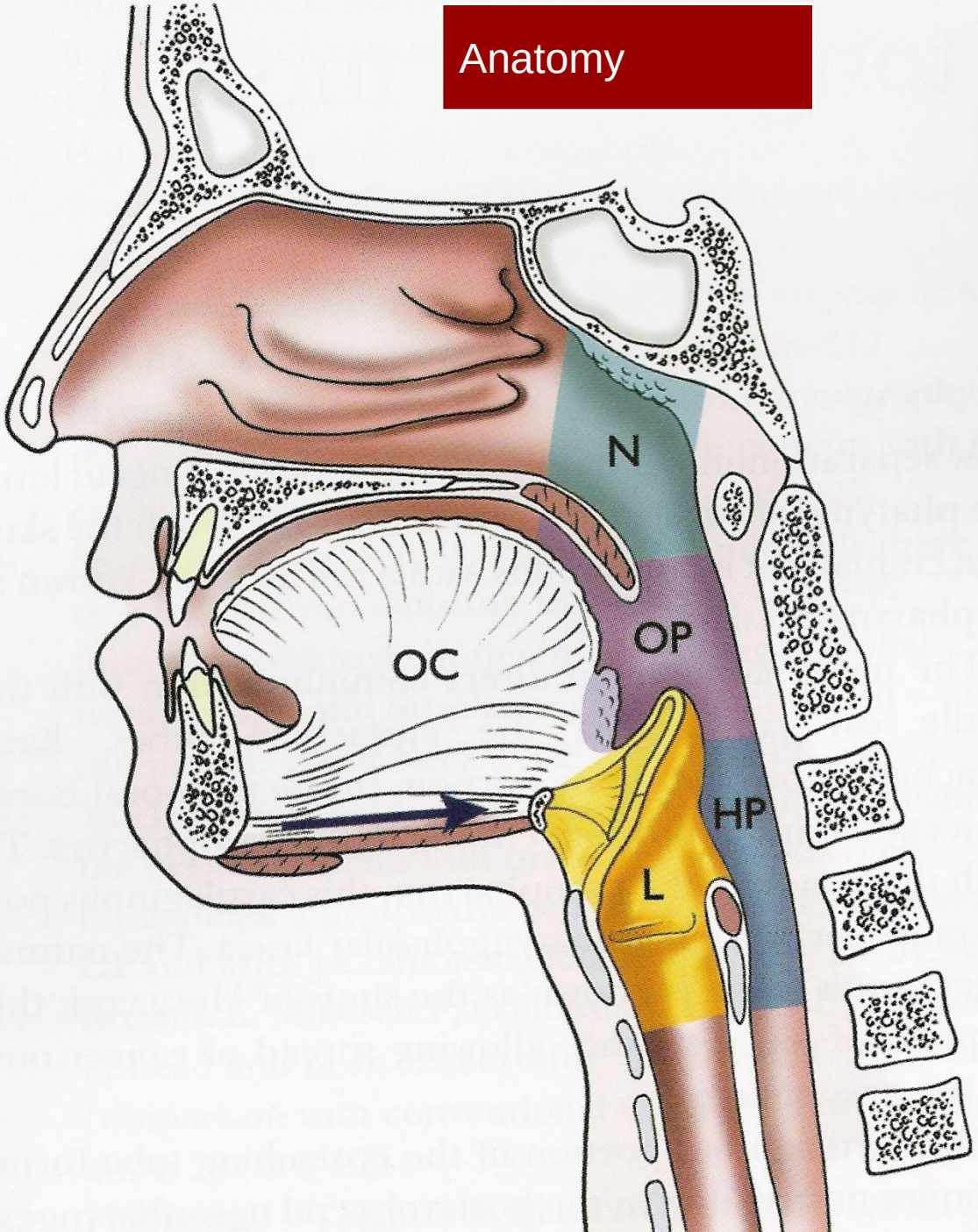
Chemotherapy and Target therapy

HEAD AND NECK SCC

Outline

- Introduction, staging
  - Who needs multimodality treatment
- Incorporate chemotherapy to definitive local tx
  - Adjuvant
  - Induction
  - Concurrent
- Organ preservation
  - Laryngeal cancer as an example

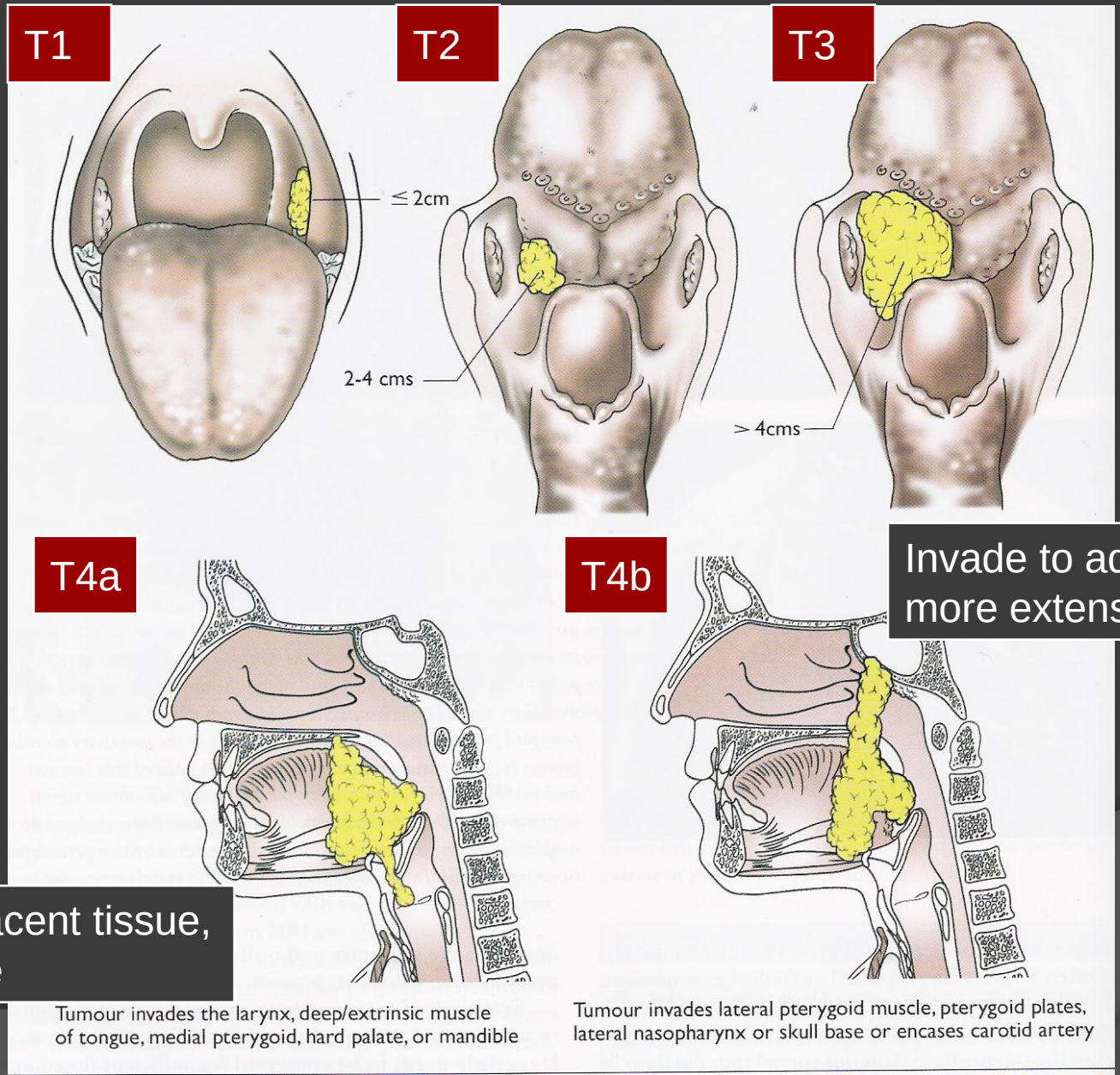
Anatomy



Generally, T stage

- Depends on anatomical location, complicate
- General concept of T stage
  - T1, T2: confined, not invade adjacent tissue
  - T3: larger, may invade adjacent tissue
  - T4: deeply invade adjacent tissue/organ
    - 4a, 4b: depends on extend of invasion
    - Critical structure: skull base, pre-veterbral fascia, internal carotid artery, mediastinum

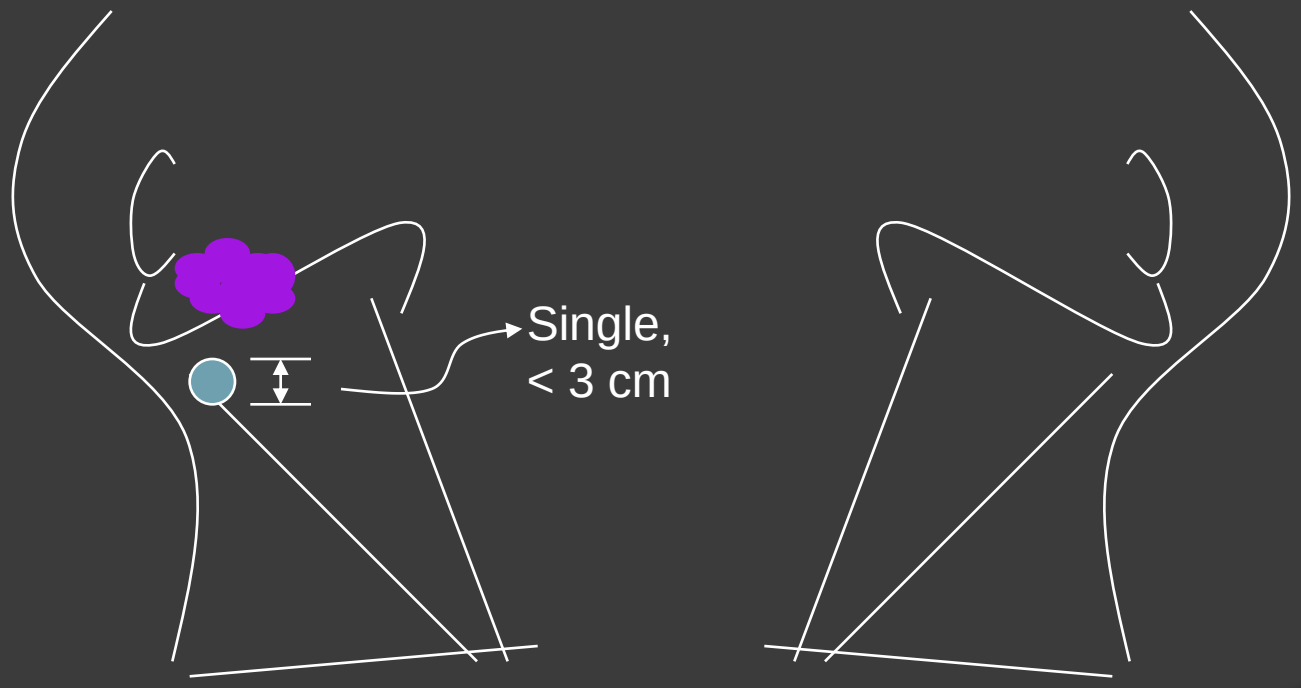
T stage of oropharyngeal cancer



Invade to adjacent tissue, less extensive

Invade to adjacent tissue, more extensive

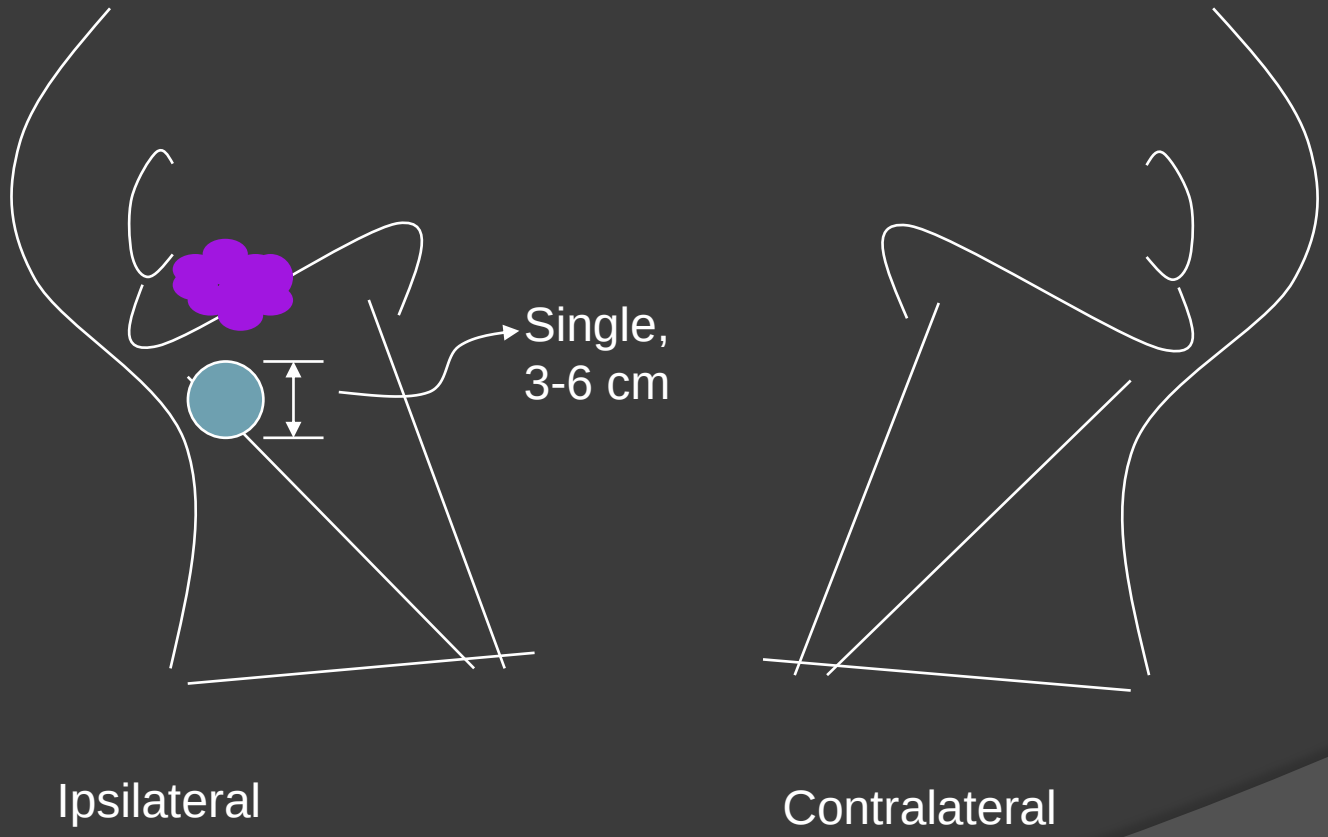
N1 Single ipsilateral, < 3cm



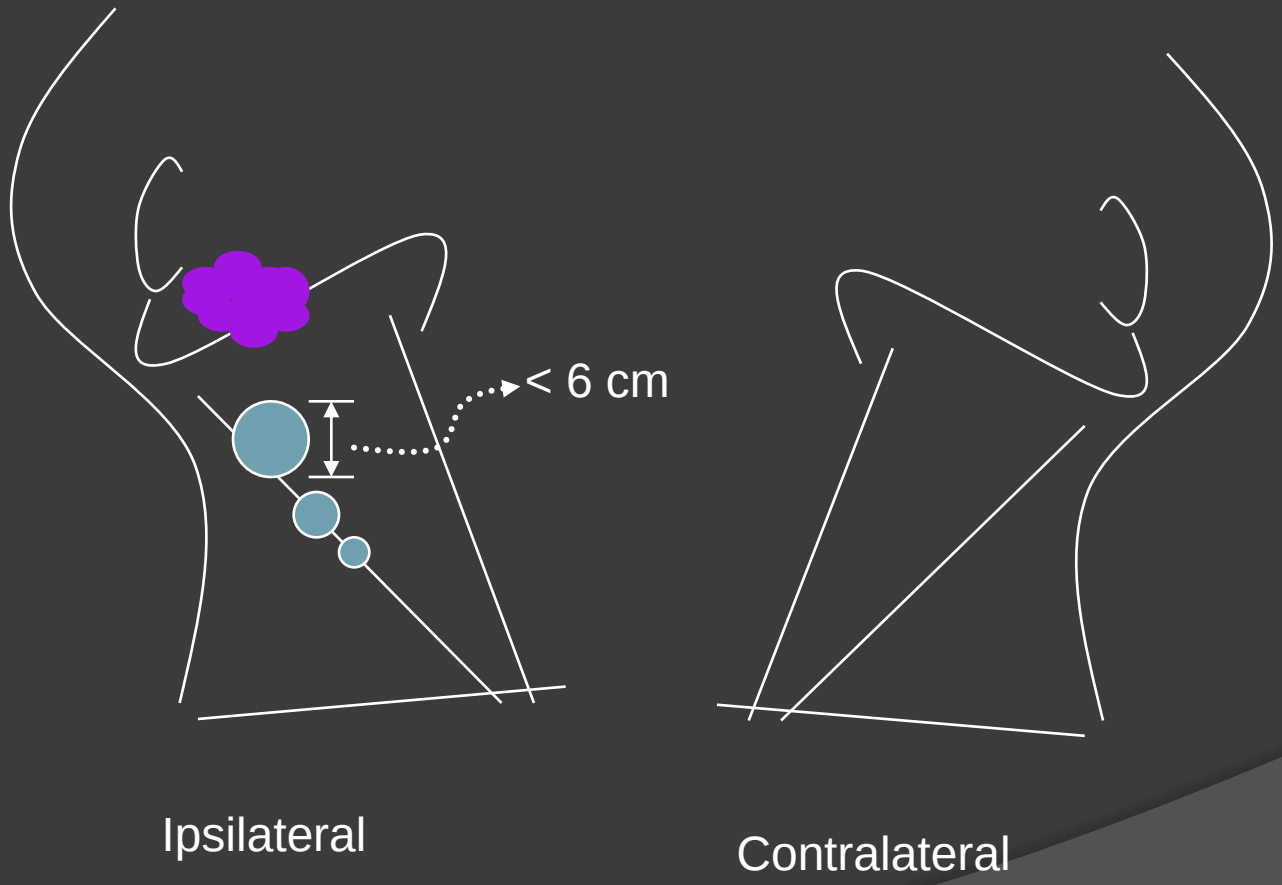
Ipsilateral

Contralateral

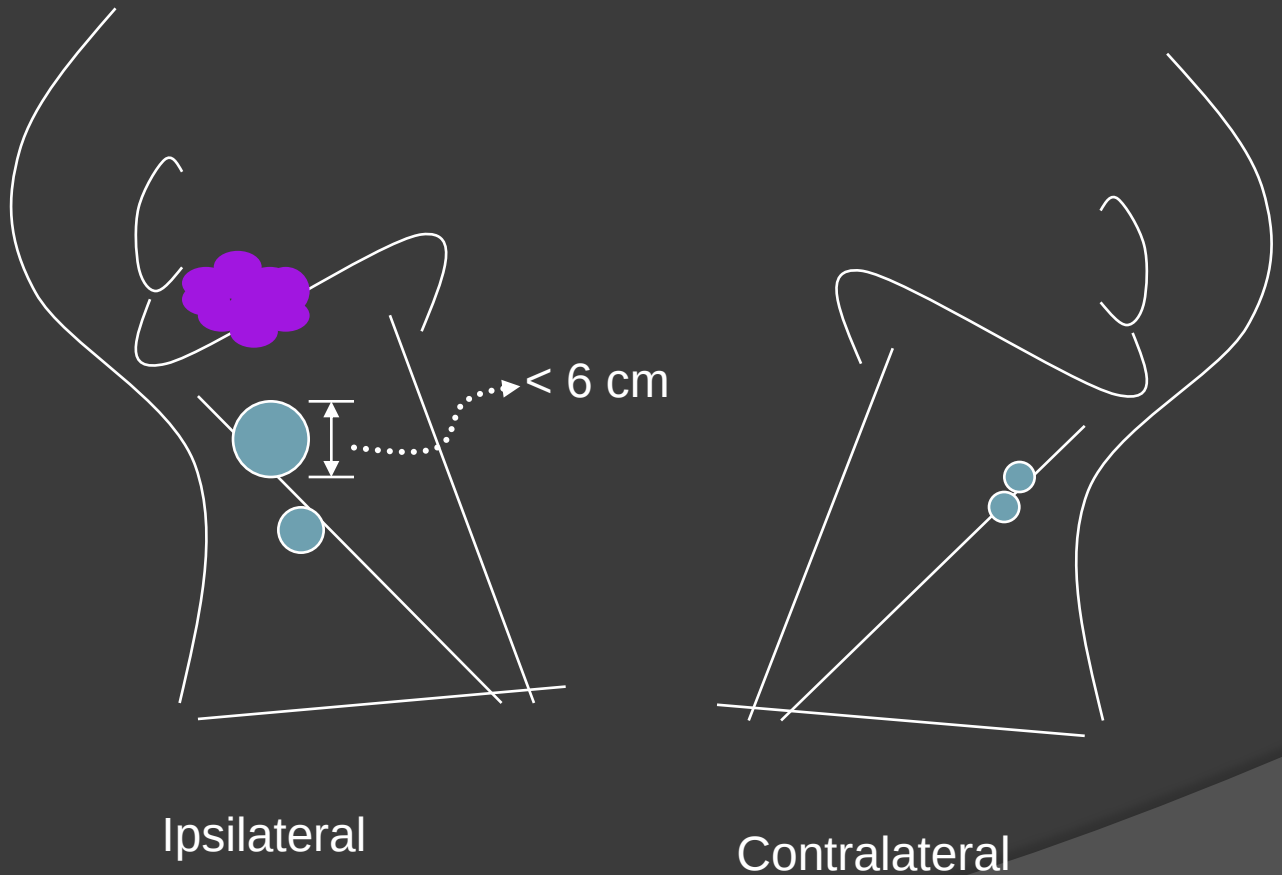
N2a Single ipsilateral, 3-6cm



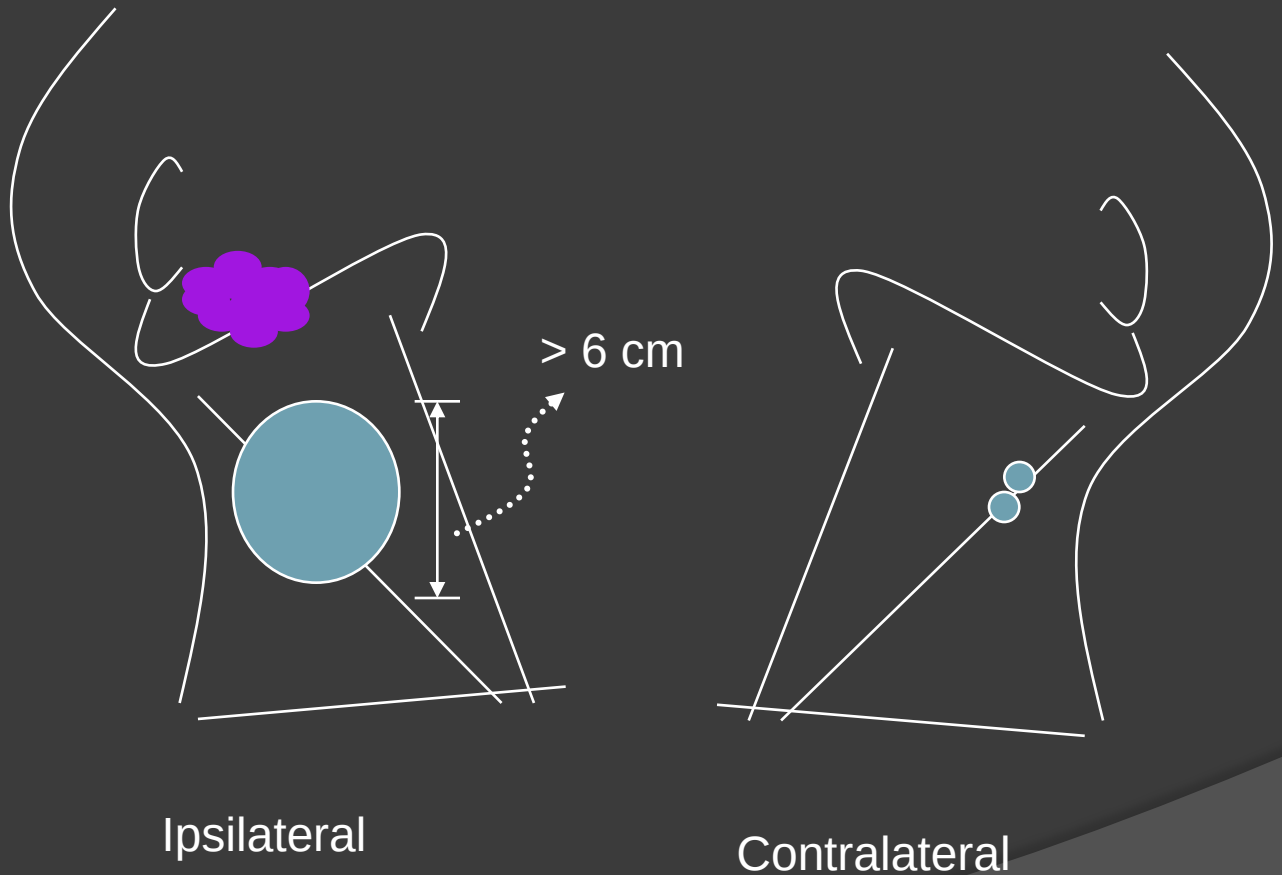
N2b Multiple ipsilateral, < 6cm



N2c Bilateral or contralateral, < 6cm



N3 Any LN > 6cm

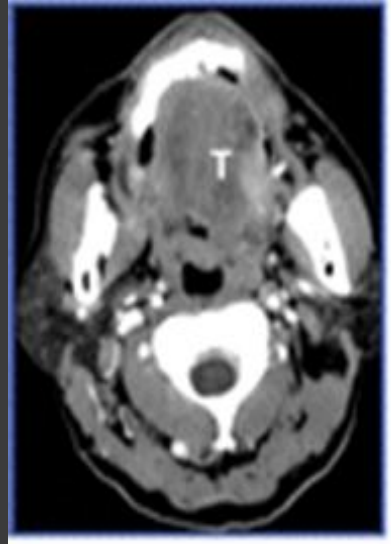


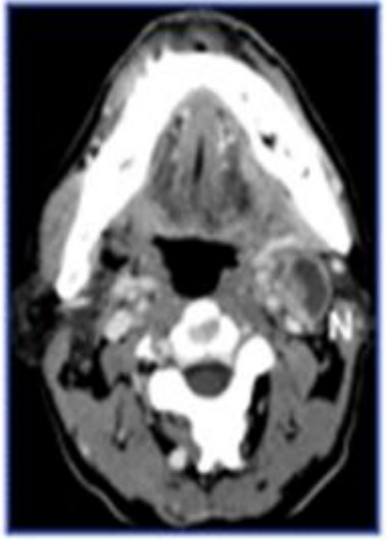
Staging

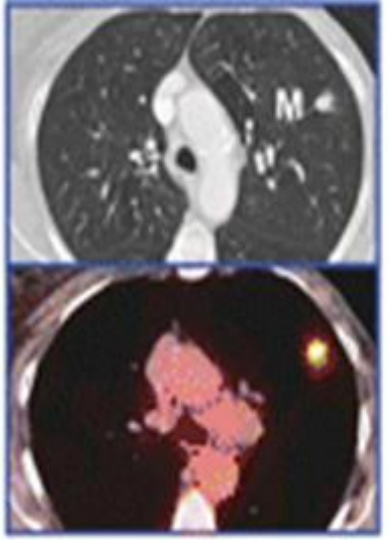
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVa	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVb	T4b	Any N	M0
	Any T	N3	M0
Stage IVc	Any T	Any N	M1

Resectability

- Depends on T stage
  - T1, T2: resectable
  - T3: may be resectable
  - T4: mostly unresectable
- Depends on surgical team
  - Wide excision → reconstruction
  - ENT surgeon → plastic surgeon
- Depends on patients
  - Organ preservation







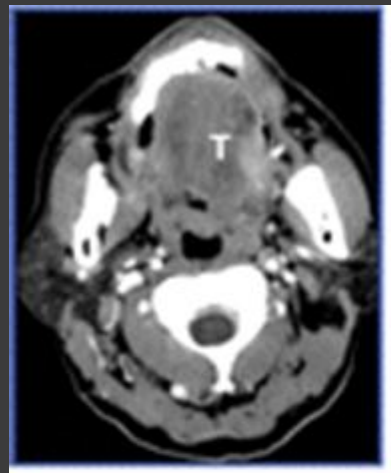
TNM Staging

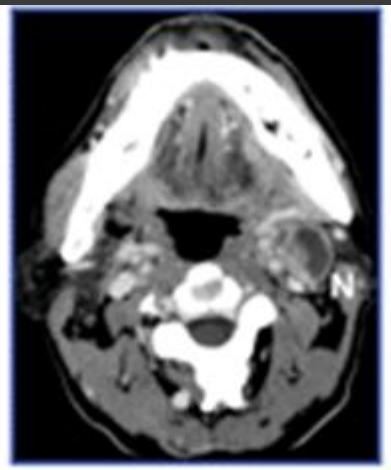
Early stage
(Stage I – II)

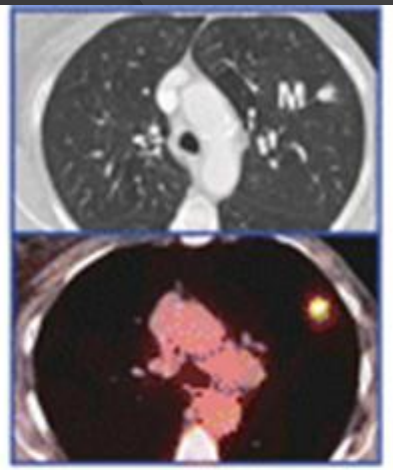
Locoregionally advanced
(Stage III – IVB)

Metastatic
(Stage IVC)

Treatment modality







TNM Staging

Early stage
(Stage I – II)

Locoregionally advanced
(Stage III – IVB)

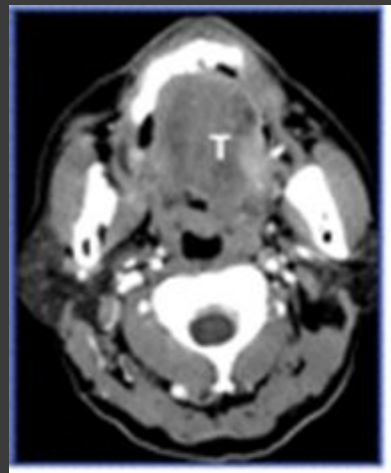
Metastatic
(Stage IVC)

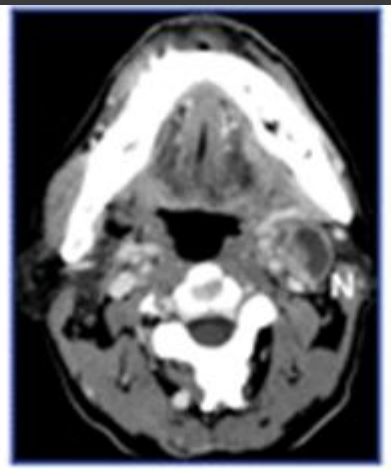
Treatment modality

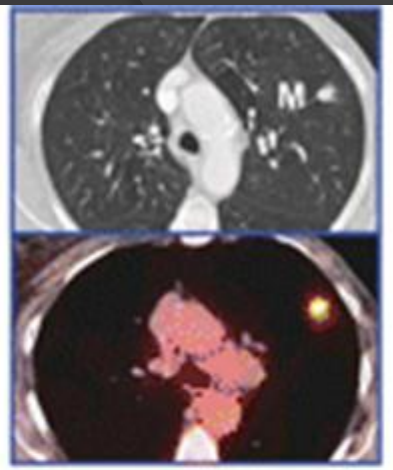
Surgery

Or

Radiotherapy







TNM Staging

Early stage
(Stage I – II)

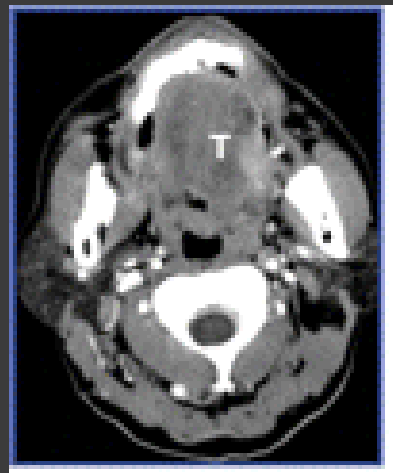
Locoregionally advanced
(Stage III – IVB)

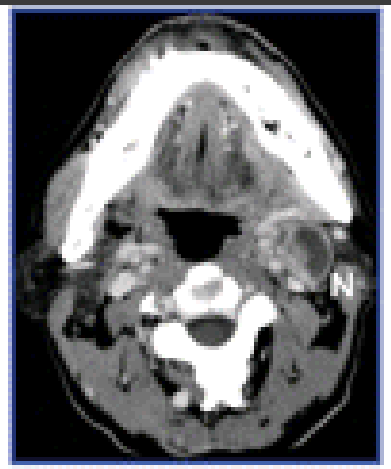
Metastatic
(Stage IVC)

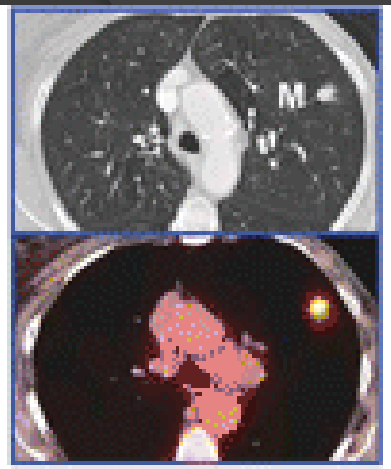
Treatment modality

Surgery
Or
Radiotherapy

Chemotherapy





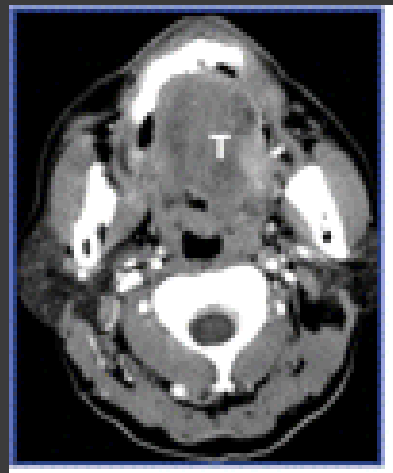


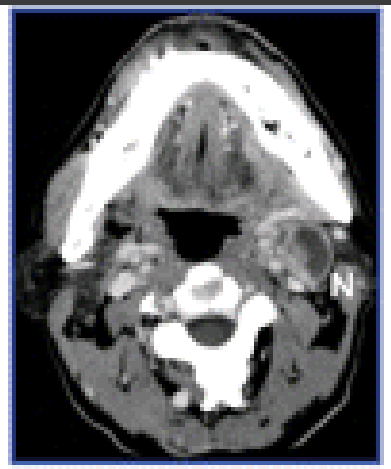
TNM Staging

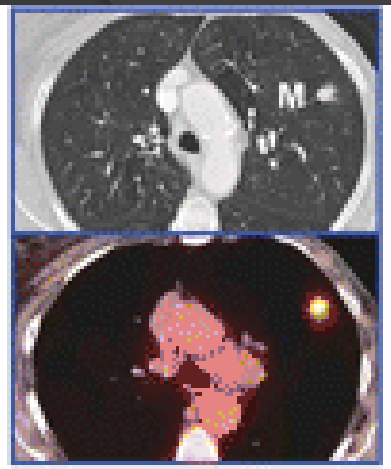
Early stage (Stage I – II)	Locoregionally advanced (Stage III – IVB)	Metastatic (Stage IVC)
Surgery Or Radiotherapy	Surgery Radiotherapy Chemotherapy	Chemotherapy

Treatment modality

CA Cancer J Clin, 58(1):32-53, 2008







TNM Staging

Early stage
(Stage I – II)

Locoregionally advanced
(Stage III – IVB)

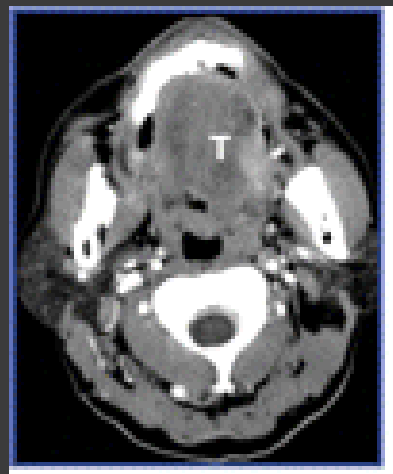
Metastatic
(Stage IVC)

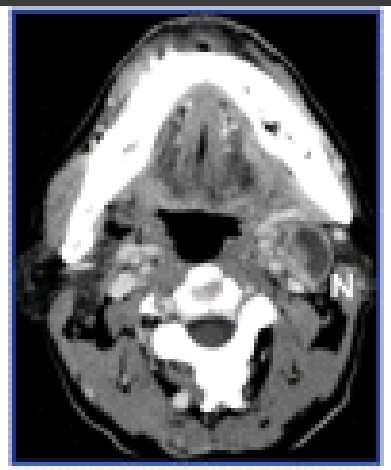
Treatment modality

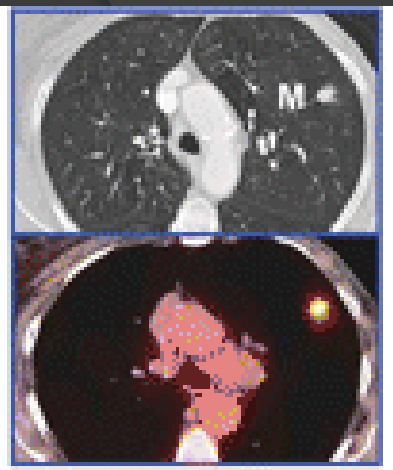
Surgery
Or
Radiotherapy

Surgery
Radiotherapy
Chemotherapy
Target Therapy

Chemotherapy
Target Therapy







TNM Staging

Early stage (Stage I – II)	Locoregionally advanced (Stage III – IVB)	Metastatic (Stage IVC)
15-30%	60-80%	2-17%
Treatment modality		
Surgery Or Radiotherapy	Surgery, Radiotherapy, Chemotherapy	Chemotherapy

Incorporation of chemotherapy

- Before definitive treatment:
  - Induction/neoadjuvant chemotherapy
- After definitive treatment
  - Adjuvant/consolidation chemotherapy
- Concurrent with radiotherapy
  - Concurrent chemoradiotherapy

Intergroup 0034

Cisplatin 100mg/m2, D1
5-FU 1000mg/m2/d IVF 24hrs, D1-D5
} q3w

442 pts, resectable, III/IV, SCC

- Surgery → C/T x 3 → XRT
- Surgery → XRT

Compliance of adjuvant C/T: 63%

Oral	27%
Oropharynx	26%
Hypopharynx	17%
Larynx	30%

4 yrs	DFS	OS	LRR	Dist Mets
CT/RT	46%	46%	19%	15%
RT	38%	44%	24%	23%
p	NS	NS	NS	0.03

Laramore GE et al. Int J Radiat Oncol Biol Phys 1992; 23: 705-713

NCI

443 pts, resectable, III/IV, SCC

A: Surgery → XRT

B: C/T x 1 → Surgery → XRT

C: C/T x 1 → Surgery → XRT → C/T x 6

Cisplatin 100mg/m2, D1
Bleomycin 15mg/m2, D3-D7

Cisplatin 80mg/m2, monthly

Compliance:
9% complete 6 cycles
27% complete > 3 cycles
45% received none

Oral	46%
Hypopharynx	35%
Larynx	19%

5 yrs	DFS	OS	LRR	Dist Mets
A	55%	35%	41%	24%
B	49%	37%	42%	22%
C	64%	45%	30%	13%
p	NS	NS	NS	0.011 (C vs A)

Cancer 1987; 60: 301-311
J Clin Oncol 1990; 8: 838-847

Adjuvant chemotherapy

- Poor drug delivery
- Decrease distant metastasis
- No effect on locoregional control
- No survival impact
  - Owing to insufficient dose density?
  - Disease nature-related?

GETTEC, French

Cisplatin 100mg/m2, D1
5-FU 1000mg/m2, D1-D5
} q3w, 3 cycles

318, HNSCC, oropharynx stage II-IV

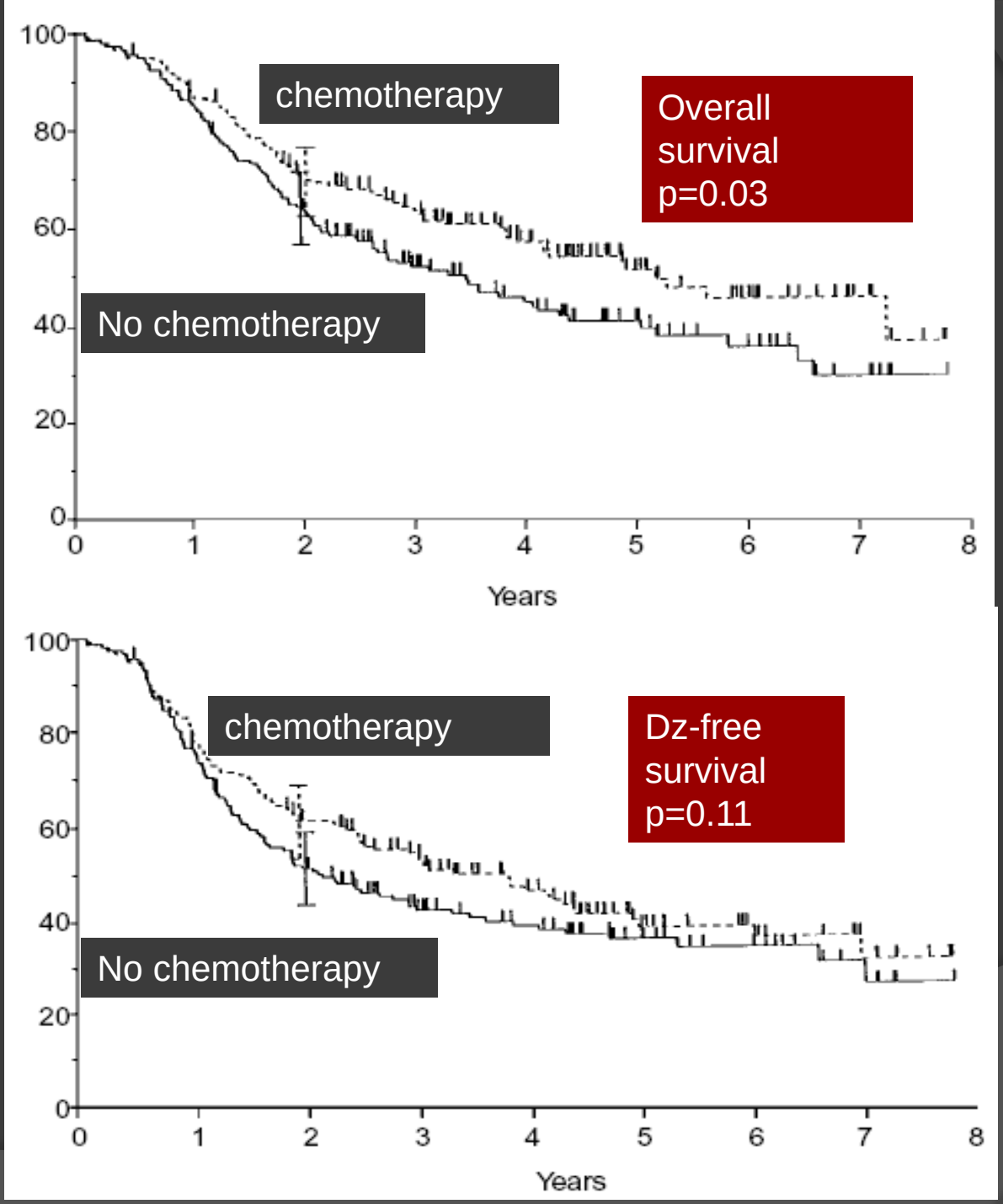
→ Induction C/T → Operable: Surgery → RT
Inoperable: RT

→ Operable: Surgery → RT
Inoperable: RT

Type of event	Number of events	Relative risk	95% CI	*P* value
Loco-regional recurrence or head neck second primary	118	1.15	0.14–1.69	NS
Metastasis	54	1.36	0.79–2.34	NS
Second primary other than head and neck	25	1.23	0.55–2.75	NS
Death	165	1.39	1.03–1.88	0.04

British Journal of Cancer 2000; 83: 1594-1598

GETTEC, French



GSTTC, Italy

Cisplatin 100mg/m2, D1
5-FU 1000mg/m2, D1-D5
} q3w, 4 cycles

237, HNSCC, stage III/IV

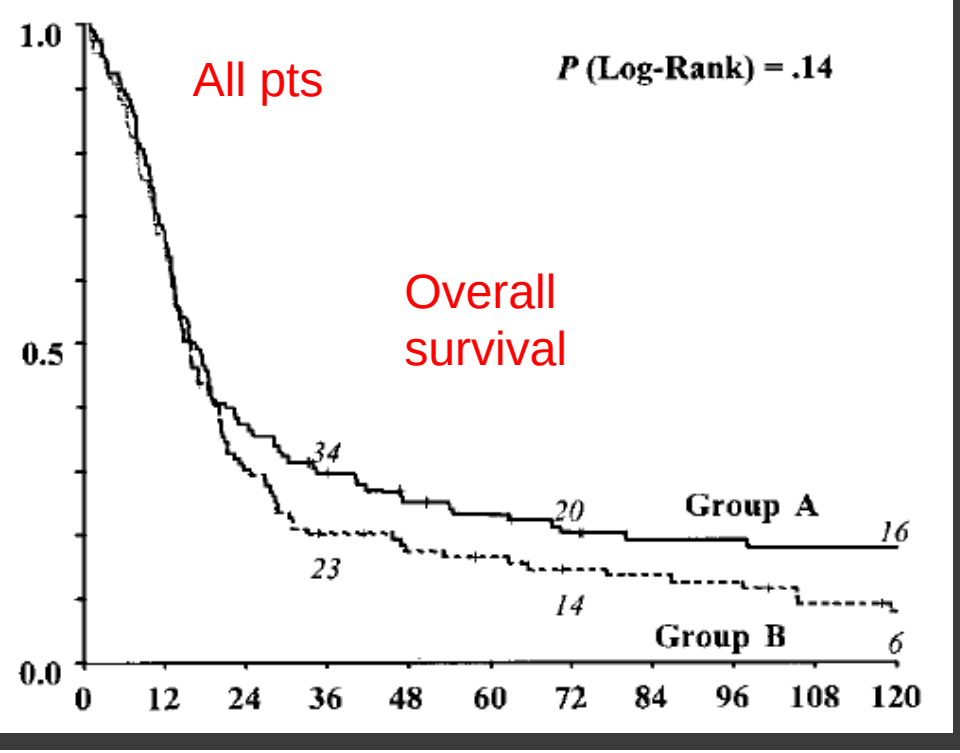
A → Induction C/T → Operable: Surgery → RT; Inoperable: RT

B → Operable: Surgery → RT; Inoperable: RT

Oral cavity
Oropharynx
Hypopharynx
Para-nasal sinus

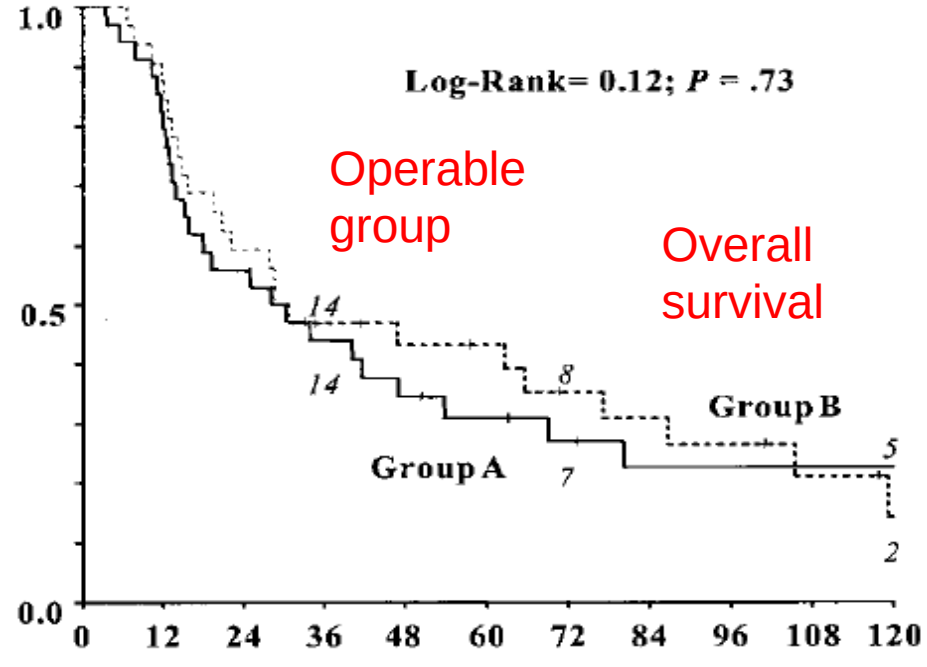
	A	B
Operable	29%	27%
Inoperable	71%	73%

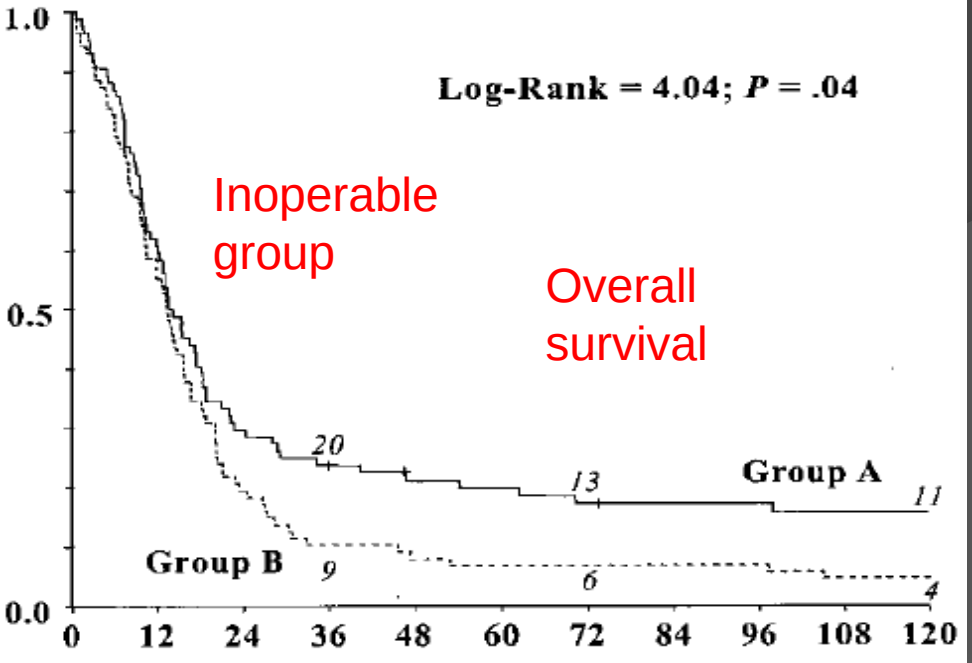
Journal of the National Cancer Institute 1994; 86: 265-272
Journal of the National Cancer Institute 2004; 96: 1714-1717



3-yr distant metastasis rate

	Inoperable	Operable
A	24%	3%
B	42%	31%
p value	0.04	0.01





SWOG

158, Head Neck epidermoid carcinoma, stage III/IV

A → Surgery → RT

B → Induction C/T → Surgery → RT

Cisplatin 50mg/m2, D1
MTX 40mg/m2, D1
Bleomycin 15U/m2, D1, D8
Vincristine 2mg, D1
Q3w, 3 cycles

Oral cavity	35%
Oropharynx	28%
Hypopharynx	16%
Larynx	21%

4yr	OS	DFS	Local recur	Regional recur	Distant mets
A	40%	31%	40%	14%	49%
B	38%	23%	48%	24%	28%
p					0.07

→ No survival benefit

Laryngoscope 1988; 98: 1205

Induction chemotherapy

- Good drug delivery
- Decrease distant metastasis
  - GSTTC, SWOG
- No improvement of locoregional control
- Survival impact??

Concurrent chemoradiotherapy

Sanchiz F et al.

859 pts, HNSCC stage III/IV

- Conventional RT — 60Gy/30fx, 2Gy/d
- HFxRT — 70.4Gy, 1.1Gy bid
- CCRT (conventional RT) — 5FU 250mg/m2, qod

Oral cavity	29%
Nasopharynx	11%
Hypopharynx	14%
Larynx	36%
Other	10%

	RR	10yr OS	10yr DFS
A: RT	67.8%	17%	17%
B: HFxRT	90%	40%	31%
C: CCRT	96.3%	42%	37%
p		<0.01(A v B) <0.01(A v C)	<0.01(A v B) <0.01(A v C)

Int J Radiat Oncol Biol Phys. 1990; 19: 1347-1350

Browman GP et al

175 pts, HNSCC T3/T4

- CCRT
- RT alone

Identical RT in both arms

RT: 60Gy/30fx, conventional

C/T: 5-FU 1200mg/m2/d, infusion D1-D3, D22-D24

Oral cavity	12%
Oropharynx	42%
Hypopharynx	14%
Larynx	27%
Other	5%

	Complete response	3yr PFS	3yr OS
CCRT	68%	40%	58%
RT	56%	30%	42%
p value	0.04	0.057	0.08

More mucositis, weight loss, and skin toxicity in CCRT arm

Journal of Clinical Oncology 1994; 12: 2648-2653

Aldelstein DJ et al

100 pts, HNSCC stage III/IV

- RT alone
- CCRT

RT: 66-72Gy, conventional, 1.8-2Gy/fx

Cisplatin: 20mg/m2/d
5FU: 1000mg/m2/d
Infusion, D1-D4 D22-D25

Residual dz or recurrence

Primary site resection +/- neck dissection

Oral cavity	4%
Oropharynx	44%
Hypopharynx	16%
Larynx	36%

5yr	OS	RFS	Dist. Mets-free survival	OS with primary site preserve	Local control without resection
RT	48%	51%	75%	34%	45%
CCRT	50%	62%	84%	42%	77%
p value	0.55	0.04	0.09	0.004	<0.001

→ Survival benefit from better local control

Cancer 2000; 88: 876-883

GORTEC

226 pts, oropharynx III/IV

- CCRT: Carbo 70mg/m2/d, D1-D4; 5FU 600mg/m2/d, D1-D4 — q3w, 3 cycles
- RT alone: Identical RT in both arms; RT: 7000cGy/35fx, conventional

Dose delivery

	RT dose
RT	6920 cGy
CCRT	6960 cGy

	1st	2nd	3rd
Carbo	98%	86%	66%
5FU	98%	88%	67%

3yr	DFS	OS	Dist. mets	LR control
CCRT	31%	51%	11%	66%
RT	20%	42%	11%	42%
p value	0.04	0.02	NS	0.02

Journal of National Cancer Institute 1999; 91:2081-2086

Jeremic B et al, Japan

130 pts, HNSCC stage III/IV

- CCRT (HFxRT)
- HFxRT alone

Identical RT in both arms

RT: 77Gy/70fx/35d, 1.1Gy bid

C/T: 5FU 6mg/m2/d, 5days/wk

Oral cavity	21%
Oropharynx	37%
Hypopharynx	16%
Larynx	17%
Nasophaynx	9%

5yr	OS	PFS	Local recur.-PFS	Dist. Mets-PFS
CCRT	46%	41%	50%	86%
RT	25%	25%	36%	57%
p value	0.0075	0.0068	0.041	0.0013

Similar stomatitis, esophagitis in both arm,
more leukopenia and thrombocytopenia in CCRT arm

Journal of Clinical Oncology 2000; 18: 1458-1464

ECOG RTOG

295 pts, HNSCC unresectable III/IV

- A: RT alone — RT: 7000cGy/35fx, conventional identical in three arms
- B: CCRT — Cisplatin 100mg/m2, D1, D22, D43
- C: CCRT (RT 3000cGy)
  - CR or unresectable → CCRT (RT 4000cGy)
  - PR → surgery → CCRT (RT 3000cGy)

Cisplatin 75mg/m2, D1
5FU 1000mg/m2/d x 4d
q4w x 3

Oral cavity	13%
Oropharynx	59%
Hypopharynx	19%
Larynx	9%

	3y OS	Dist. Mets as first site	Treatment compliance
A	23%	17.9%	92.6%
B	37%	21.8%	85.1%
C	27%	19.1%	73%
p	0.014 (A vs B)	NS	0.001(A vs C) 0.05(B vs C)

Journal of Clinical Oncology 2003; 21: 92-98

Taylor SG et al

RT 70Gy/35fx

215 pts, HNSCC stage III/IV, unresectable

- C/T → RT (A): Cisplatin 100mg/m2, D1; 5-FU 1000mg/m2, D1-D5 — Q3w x 3
- CCRT (B): Cisplatin 60mg/m2, D1; 5-FU 800mg/m2, D1-D5 — Qw x 7

Sinus	1%
Oral	32%
Oropharynx	23%
Nasopharynx	6%
Hypopharynx	27%
Larynx	11%

	LR recurrence	Dist Mets	3-yr OS	3-yr dz specific survival
A	55%	10%	36%	41%
B	41%	7%	42%	55%
			NS	p=0.011

	A	B
% Cisplatin	97%	88%
% 5-FU	97%	79%
% RT(>65Gy)	78%	81%
% RT delay	No difference	

Journal of Clinical Oncology 1994; 12: 385-395

Concurrent chemoradiotherapy

- Enhance locoregional control
- Minimal effect in distant metastasis
- Improve survival
  - Superior than sequential chemoradiotherapy
  - Disease nature: local recurrence predominant
- Enhance RT toxicity
  - Mucositis, skin toxicity, BW loss
  - Leukopenia depends on C/T type

Brockstein B et al

PFLI
- Cisplatin 100mg/m2, D1
- 5FU 640mg/m2/d, CVI, D1-D5
- Leucovorin 100mg q4h po, D1-D6
- INF-α 2MU/m2/d, D1-D6

q3w

PFLI-FHX

164 pts → Induction C/T x 3 → CCRT

FHX
- 5FU 800mg/m2/d x 5/wk
- Hydroxyurea 1000mg q12h, 11doses/wk
- RT 6000cGy/30fx

(C/T)HF2X

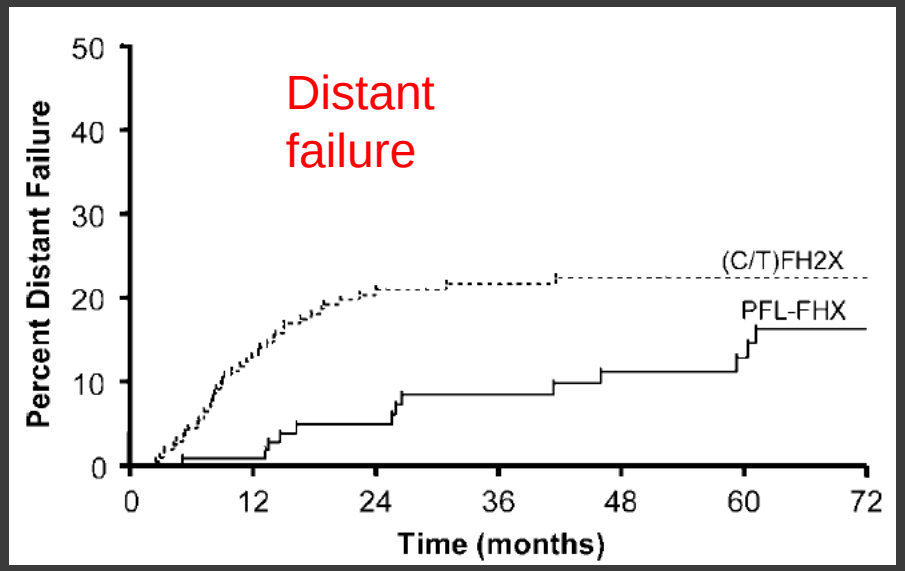
230 pts → Intensified CCRT

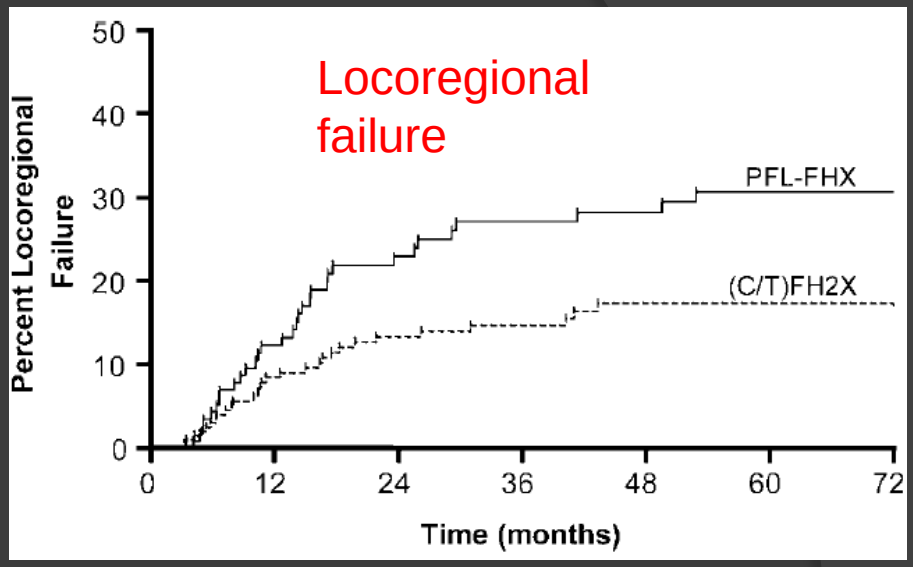
Cisplatin 100mg/m2, D1
or
Paclitaxel 100mg/m2, D1
q3w x 3

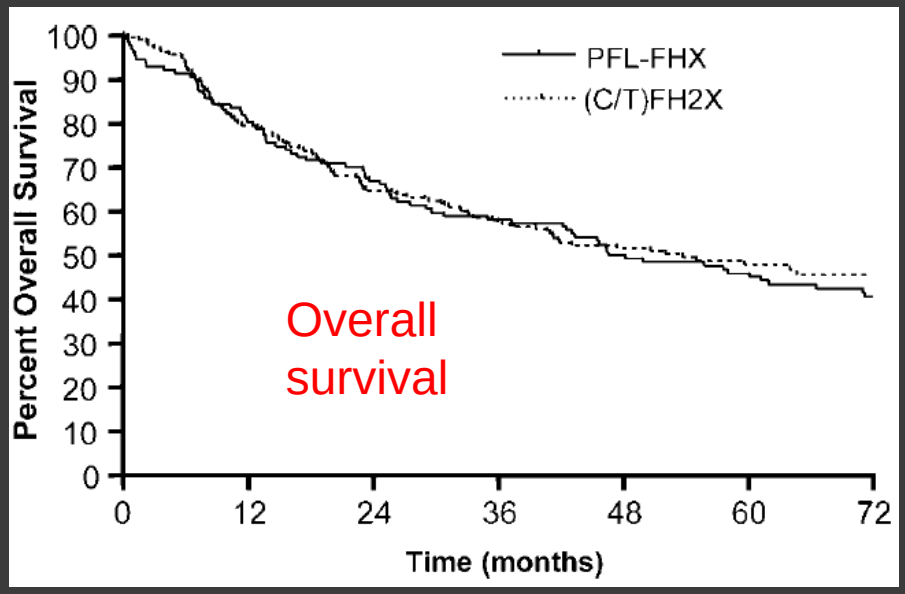
+

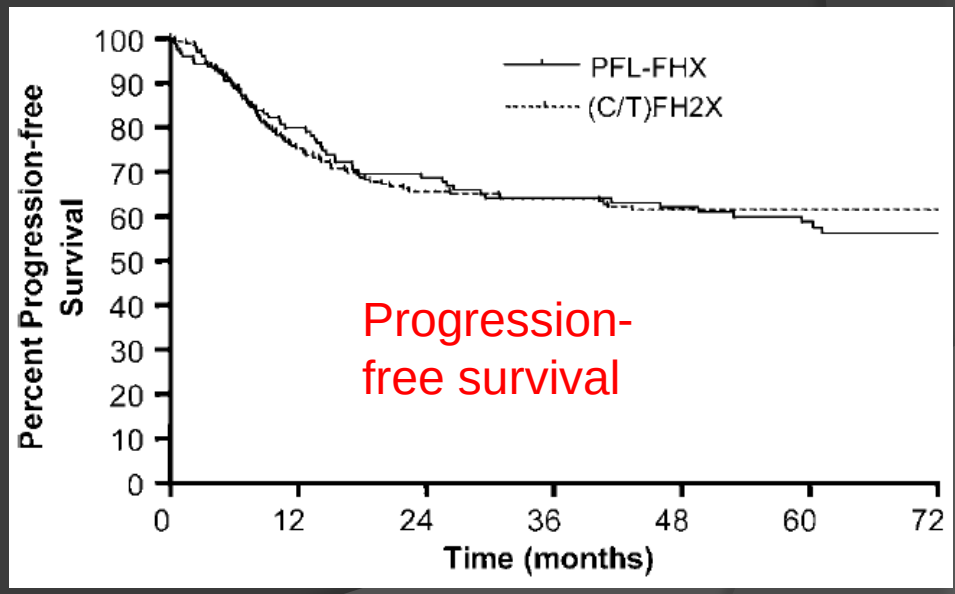
5FU 800mg/m2/d x 5/wk
Hydroxyurea 1000mg q12h, 11doses/wk
RT 6000cGy/30fx

J Clin Oncol. 1995; 13: 876-83
Annals of Oncology 2004; 15: 1179-1186









J Clin Oncol. 1995; 13: 876-83
Annals of Oncology 2004; 15: 1179-1186

C/T impact on failure pattern

- Induction or adjuvant chemotherapy
  - Decrease distant metastasis
    - Related to systemic dose, adequate delivery?
- Chemotherapy concurrent with RT
  - Decrease locoregional recurrence
    - Enhance RT effect
- Add induction chemotherapy to CCRT
  - To reduce distant failure since local control adequate

Yale 6557 protocol

C/T: Cisplatin 20mg/m2/d x 4d
5FU 800mg/m2/d x 4d
LV 500mg/m2/d x 4d
q4w

CCRT:
RT: 70Gy/35fx
Cisplatin 100mg/m2, q3w

42 pts, HN cancer, stage III/IV resectable/unresectable → C/T x 2 → CCRT → Non-responder → operation

Hypopharynx	24%
Larynx	38%
NPC	9.5%
Tongue base	19%
Tonsil	7.5%
Unknown	9%

- Induction C/T: RR 76%
- C/T→CCRT: 67% CR

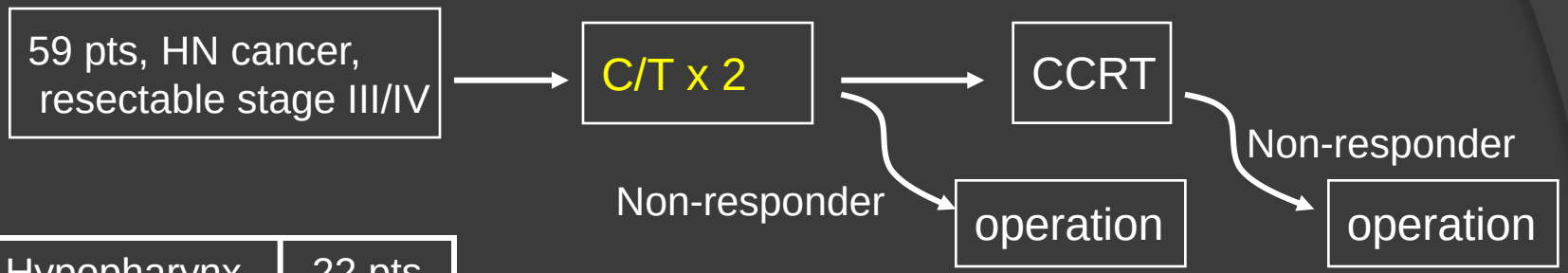
5y PFS	5y OS	2y Local control	2yr Distant control
54%	52.4%	76.3%	79%

Journal of Clinical Oncology 2004; 22: 3061-3069

SWOG

C/T: Cisplatin 100mg/m2
5FU 1000mg/m2/d x 5d
q3w

CCRT:
RT: 72Gy/36fx
Cisplatin 100mg/m2, q3w



Hypopharynx	22 pts
Tongue base	37 pts

- Induction C/T: RR 78%
- C/T→CCRT: 54% CR

3y PFS	3y OS	3y PFS with Organ preservation
57%	64%	52%

Journal of Clinical Oncology 2005; 23: 88-95

Incorporate Taxane

- Improve response rate in metastatic dz
  - 70%→ 90%
- Incorporate to induction regimen
  - Eliminate more micrometastasis

Taxane
Cisplatin
5-FU

Vs.

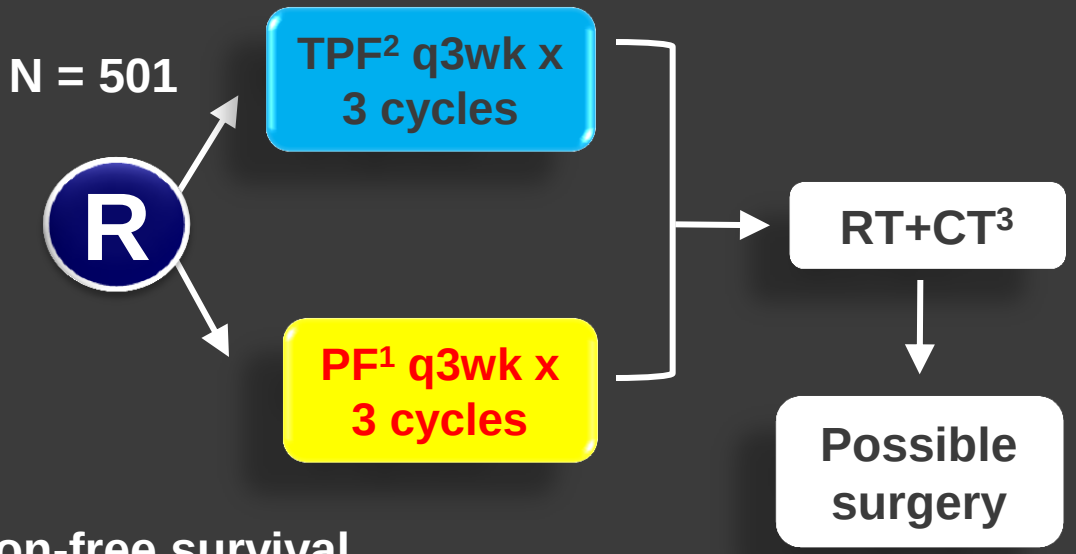
Cisplatin
5-FU

TAX 324 Phase III Trial of Induction Docetaxel-Cisplatin-5FU (TPF) vs PF in Unresectable HNC: Study Design

Patient Population
- Stage III or IV
- Inoperable SCCHN

Stratification
- Center
- N status
- Primary site

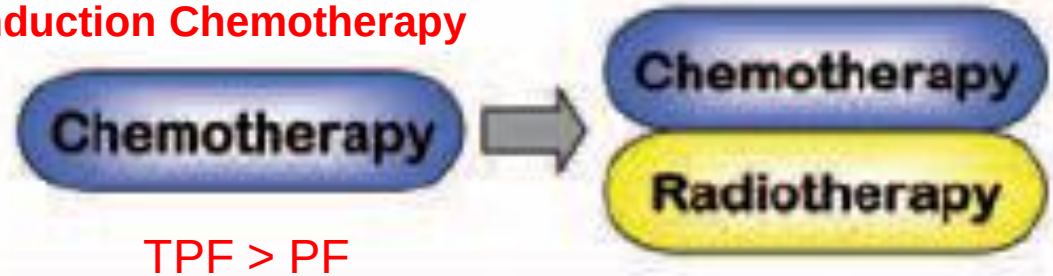
Endpoints
- Primary: OS
- Secondary: progression-free survival, response rates after induction, toxicity



[1] Cisplatin: 100 mg/m² D1 – 5FU: 1000 mg/m² D1 - D5
[2] Docetaxel: 75 mg/m² D1 - CDDP: 100 mg/m² D1 – 5FU: 1000 mg/m² D1 - D4
[3] Weekly Carboplatin (AUC 1.5) x 7 - Conventional radiotherapy = 70 Gy

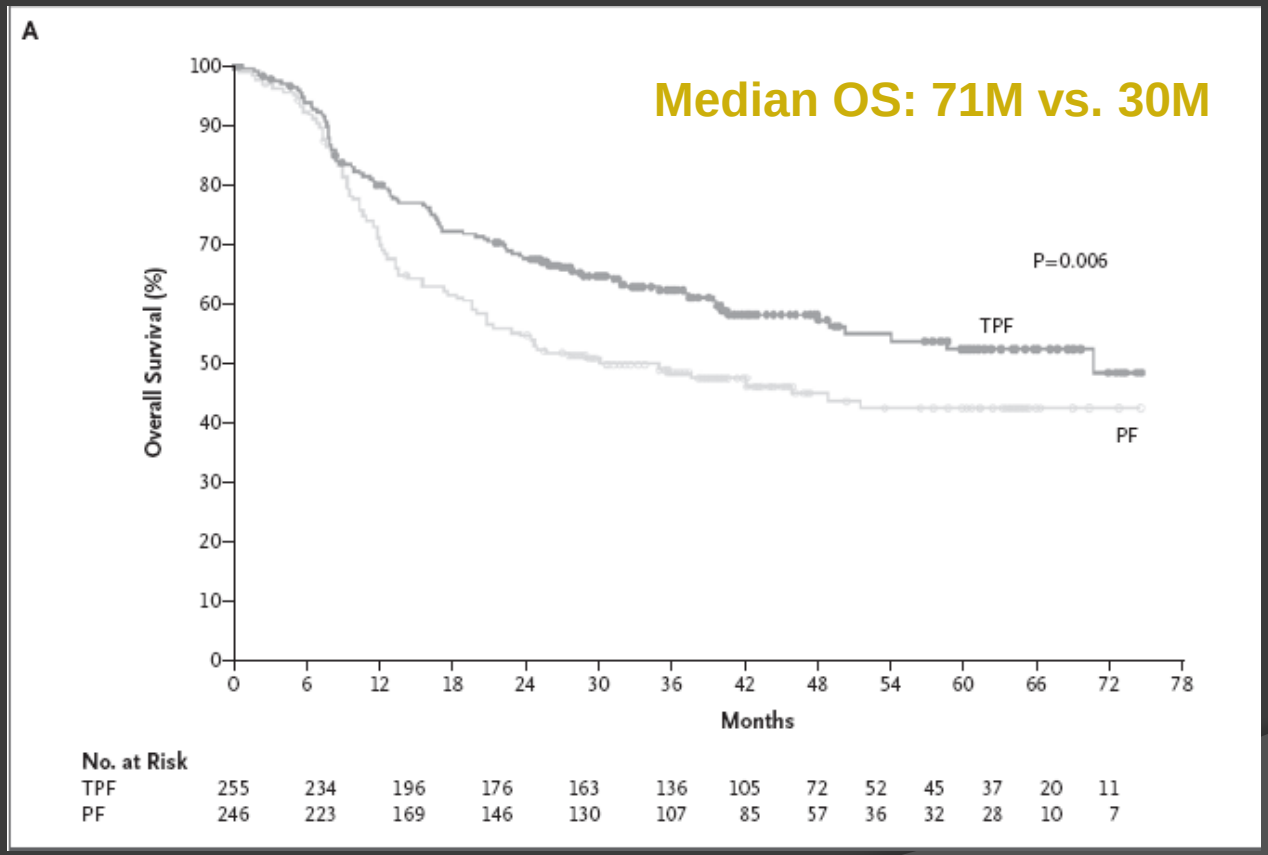
Posner et al. N Engl J Med. 2007;357:1705-17115.

Induction Chemotherapy



TPF > PF

arboplain, Weekly



NEJM 357:17, 2007

TAX 324: Toxicity During Induction Chemotherapy

Number of patients	TPF (n=251)	PF (n=243)
NCIC-CTC Classification	Grade 3/4	Grade 3/4
Anemia	12%	9%
Thrombocytopenia	4%	11%*
Neutropenia	83%	56%*
Febrile neutropenia	12%	7%*
Nausea	14%	14%
Alopecia	4%	1%
Stomatitis	21%	27%
Lethargy	5%	10%*
Vomiting	8%	10%
Diarrhea	7%	3%
Anorexia	12%	**12%**

***Statistically significant (P < .05)**

Posner et al. N Engl J Med. 2007;357:1705-17115.

TAX 324 Phase III Trial of Induction TPF: Key Points

- TPF significantly improves survival versus PF
  - 14% absolute improvement in 3-y survival
  - 10% absolute improvement in 5-y survival
  - 26% reduction in mortality (P = 0.014)
- Sequential therapy with TPF is tolerable and safe
  - Toxicity of TPF arguably less than that of PF
  - No significant difference in long-term toxicities (enteral feeding tube and tracheostomy)
- Sequential therapy with TPF followed by carboplatin-based chemoradiotherapy represents an acceptable standard of care for locally-advanced SCCHN

Ongoing trials

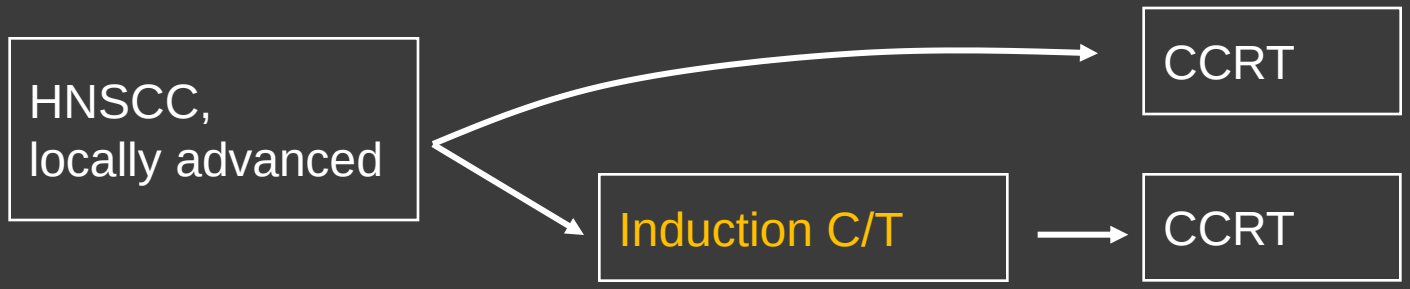


Table 2. Randomized Phase III Trials Comparing Concurrent Chemoradiotherapy With Induction Chemotherapy Followed by Concurrent Chemoradiotherapy

Group	Stages	Sites	Induction Regimen	Concurrent Regimen	Survival End Point	Targeted Improvement (%)	Accrual Goal (No. of patients)
University of Chicago	N 2-3	All	DPF × 2	DFHX	3 years	50-65	400
SWOG/ECOG	III-IV*	Oropharynx	DPF × 3†	P	2 years	60-71	398
Dana-Farber Cancer Institute	III-IV	All	DPF × 3	Various§	3 years	55-70	300

Abbreviations: D, docetaxel; P, cisplatin; F, fluorouracil; H, hydroxyurea; X, hyperfractionated radiation administered on alternate weeks; SWOG, Southwest Oncology Group; ECOG, Eastern Cooperative Oncology Group.
*Resectable patients only, excluding T_{1-2} N_1.
†Nonresponders after first induction course undergo surgery.
§See text.

Journal of Clinical Oncology 2006; 24: 2624-2628

Post OP RT or CCRT

Risk factors of post-op recurrence

- Primary tumor
  - Positive or close margin
- Neck
  - Multiple LN: >2
  - Extracapsular extension
  - Perineural invasion
  - Vascular embolism
- Both locoregional and distant

Annals of Oncology 2004; 15: 1179-1186
Head and Neck 2000; 22: 680-686

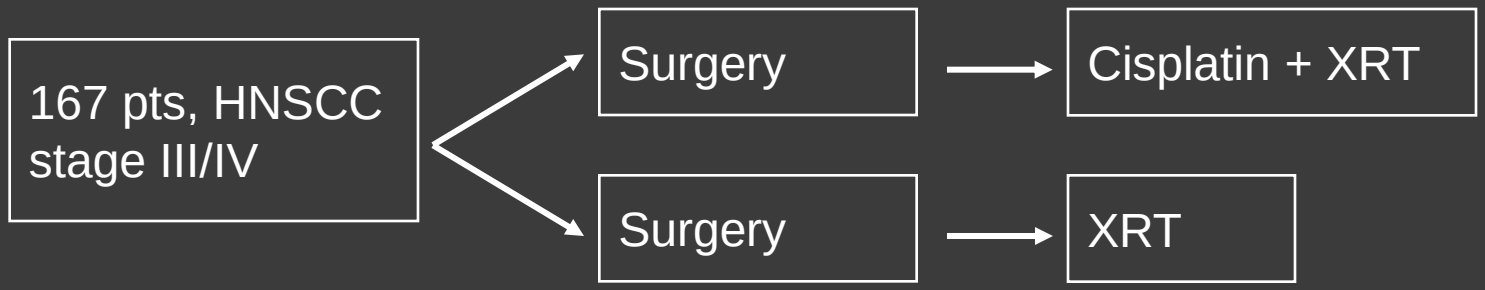
Adjuvant RT

- For possible residual disease
  - Positive margin or close margin
  - Multiple neck LN
- Attempt to decrease local failure
  - Decrease subsequent distant failure
- CCRT better than RT ?

Radiology 1970; 95: 185-188
Clinical Otolaryngology 1982; 7: 185-192
Head and Neck Surgery 1984; 6: 720-723
Head and Neck Surgery 1987; 10: 19-30

EORTC 22931

Cisplatin 100mg/m2, D1, D22, D43
XRT 54Gy/27fx, Boost 12Gy/6fx



pT3/T4 + any N
pT1/T2 + N2/N3
pT1/T2 + N0/N1 + unfavorable patho

	Margin	Perineural invasion	Extracapsular spread	Vascular embolism
Positive	28%	13%	57%	20%
Negative	71%	85%	43%	80%
Unknown	1%	2%		

Oral cavity	26%
Oropharynx	30%
Hypopharynx	20%
Larynx	22%
Unknown	1%

N Eng J Med 2004; 350: 1945-1952

EORTC 22931

	C/T on time without delay
1st	88%
2nd	66%
3rd	49%

	5yr PFS	5yr OS	LRR	Dist Mets
CCRT	47%	53%	18%	21%
RT	36%	40%	31%	25%
p value	0.04	0.02	0.007	0.61

	Acute mucosa reaction	Mucosa fibrosis	Xerostomia	Severe leukopenia
CCRT	41%	10%	14%	16%
RT	21%	5%	20%	-
p value	0.001			

N Eng J Med 2004; 350: 1945-1952

RTOG 9501

Cisplatin 100mg/m2, D1, D22, D43

XRT 60Gy/30fx, Boost 6Gy/3fx

416 pts, HNSCC, high risk of recurrence

- Surgery → Cisplatin + XRT
- Surgery → XRT

Positive margin	17%
LN>2 or extracapsular extension	83%

Oral cavity	27%
Oropharynx	42%
Hypopharynx	10%
Larynx	21%

N Eng J Med 2004; 350: 1937-1944

RTOG 9501

45.9 months follow-up time

	DFS	OS	LRR	Dist Mets as 1st event
CCRT	40%	52.5%	19%	23%
RT	30%	45%	30%	20%
p value	0.01	0.19	0.01	0.46

	Acute adverse effect	Late adverse effect
CCRT	77%	21%
RT	34%	17%
p value	0.001	0.29

hematological,
mucosa,
GI tract

N Eng J Med 2004; 350: 1937-1944

Post-op adjuvant CCRT

- Decrease locoregional recurrence
- Not affect distant metastasis
  - Though systemic side-effect
  - Insufficient dose delivery?
  - Single agent not enough?
- Actually improve survival
  - Locoregional recurrence dominant in HNSCC

Table 1. Effect on survival of adding chemotherapy to locoregional treatment: Results from the MACH-NC 2000 analysis [1, 2]

Design	*n* of studies (*n* of patients)	Hazard ratio (95% CI)	*p*-value	Absolute survival benefit[a]	
				2 yrs	5 yrs
Adjuvant	8 (1,854)	0.98 (0.85–1.19)	.74	1%	1%
Induction	31 (5,269)	0.95 (0.88–1.01)	.10	2%	2%
Induction with platinum and 5-FU [1, 2]	15 (2,487)	0.88 (0.79–0.97)	.01	NA	5%[b]
Concurrent	26 (3,727)	0.81 (0.76–0.88)	<.0001	7%	8%
Total	65 (10,850)[c]	0.90 (0.85–0.94)	<.0001	4%	4%

The Oncologist 2010;15(suppl 3):3–7

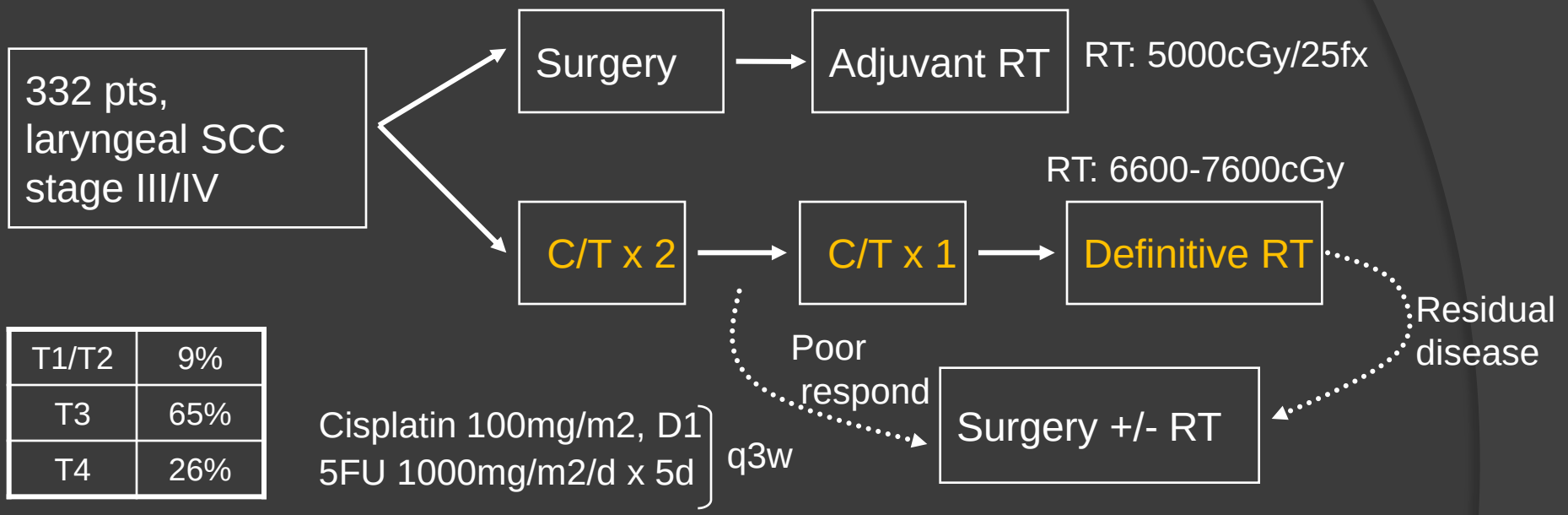
Organ Preservation

- Laryngeal cancer as an example
  - Supraglottic
  - Subglottic
    - T1: limited, not extend to glottis
    - T2: extend to glottis, but normal cord mobility
    - T3/T4: cord fixation, invade adjacent tissue
  - Glottic
    - T1a/b: limited to one/both sides, no cord fixation
    - T2: impair cord motility, to supra- or subglottis
    - T3/T4: cord fixation, invade adjacent tissue/organ

Laryngeal cancer

- Historically
  - Early: T1, T2
    - RT alone, surgical salvage, or
    - Surgical → adjuvant RT
    - Larynx usually preserved
  - Advance: T3, T4
    - RT alone not sufficient
    - Surgical resection, usually total laryngectomy

Veterans Affairs Laryngeal Cancer Study Group



T1/T2	9%
T3	65%
T4	26%

Glottis	37%
Supraglottis	63%

2yr	DFS	OS	Recur at primary	Recur at regional	Distant mets	Laryngectomy-free survival
Surgery	75%	68%	2%	5%	17%	
C/T →RT	65%	68%	12%	8%	11%	39%
p value	0.12	0.98	0.001	NS	0.001	

New England Journal of Medicine 1991; 324: 1685-1690

QOL assessment

- Veterans Affairs Laryngeal Cancer Study Group

- C/T → RT vs. Surgery → RT
  - “pain”, “mental health”, “bother “
- Laryngectomy vs. Laryngeal preserve
  - “pain”, “mental health”, “bother”
  - “role physical”, “social function”, “emotion”, “response”
- No difference in speech and eating

Arch Otolaryngol Head Neck Srug 1998; 124: 964-971

EORTC

194 pts, hypopharynx SCC stage II/III/IV

Surgery → Adjuvant RT

RT: 5000cGy/25fx

C/T x 2 → C/T x 1 → Definitive RT

RT: 7000cGy

Residual disease

Poor respond → Surgery +/- RT

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d
q3w

T2	20%
T3	75%
T4	5%

Pyriform sinus	78%
Aryepiglottic fold	22%

5yr	DFS	OS	Recur at local	Recur at regional	Distant mets	Laryngectomy-free survival
Surgery	32%	35%	17%	23%	36%	
C/T →RT	25%	30%	12%	19%	25%	35%
p value	NS	NS	NS	NS	0.041	

Journal of National Cancer Institute 1996; 8: 890-899

GETTEC, French

68 pts,
laryngeal SCC
all T3

- Surgery → Adjuvant RT — RT: 5000cGy/25fx
- C/T x 3 → Definitive RT — RT: 7000cGy

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d] q3w

Supraglottis	31%
Glottis	41%
Unknown	28%

	2yr DFS	2yr OS	8yr Laryngectomy-free survival
Surgery	78%	84%	
C/T →RT	62%	69%	42%
p value	0.02	0.006	

Inferior outcome !!

Oral Oncology 1998; 34: 224-228

RTOG 91-11

518 pts,
laryngeal SCC
III/IV

- RT alone
- CCRT
- C/T x 2 → C/T x 1 → RT

CCRT:
RT 7000cGy/35fx
Cisplatin 100mg/m2, q3w

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d
q3w

Poor respond → Surgery +/- RT

Residual disease

T2	12%
T3	78%
T4	10%

Supraglottis	69%
Glottis	31%

5yr	DFS	OS	Intact larynx	LR control	Distant mets
A: RT	27%	56%	70%	56%	22%
B: CCRT	36%	54%	88%	78%	12%
C: C/T→RT	38%	55%	75%	61%	15%
p	0.02(C v A) 0.006(B v A)	NS	0.005(B v C) 0.001(B v A)	0.004(B v C) 0.001(B v A)	0.03(B v A)

Speech/swallow : similar

New England Journal of Medicine 2003; 349: 2091-2098

VOLUME 24 · NUMBER 4 · FEBRUARY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Single-Cycle Induction Chemotherapy Selects Patients With Advanced Laryngeal Cancer for Combined Chemoradiation: A New Treatment Paradigm

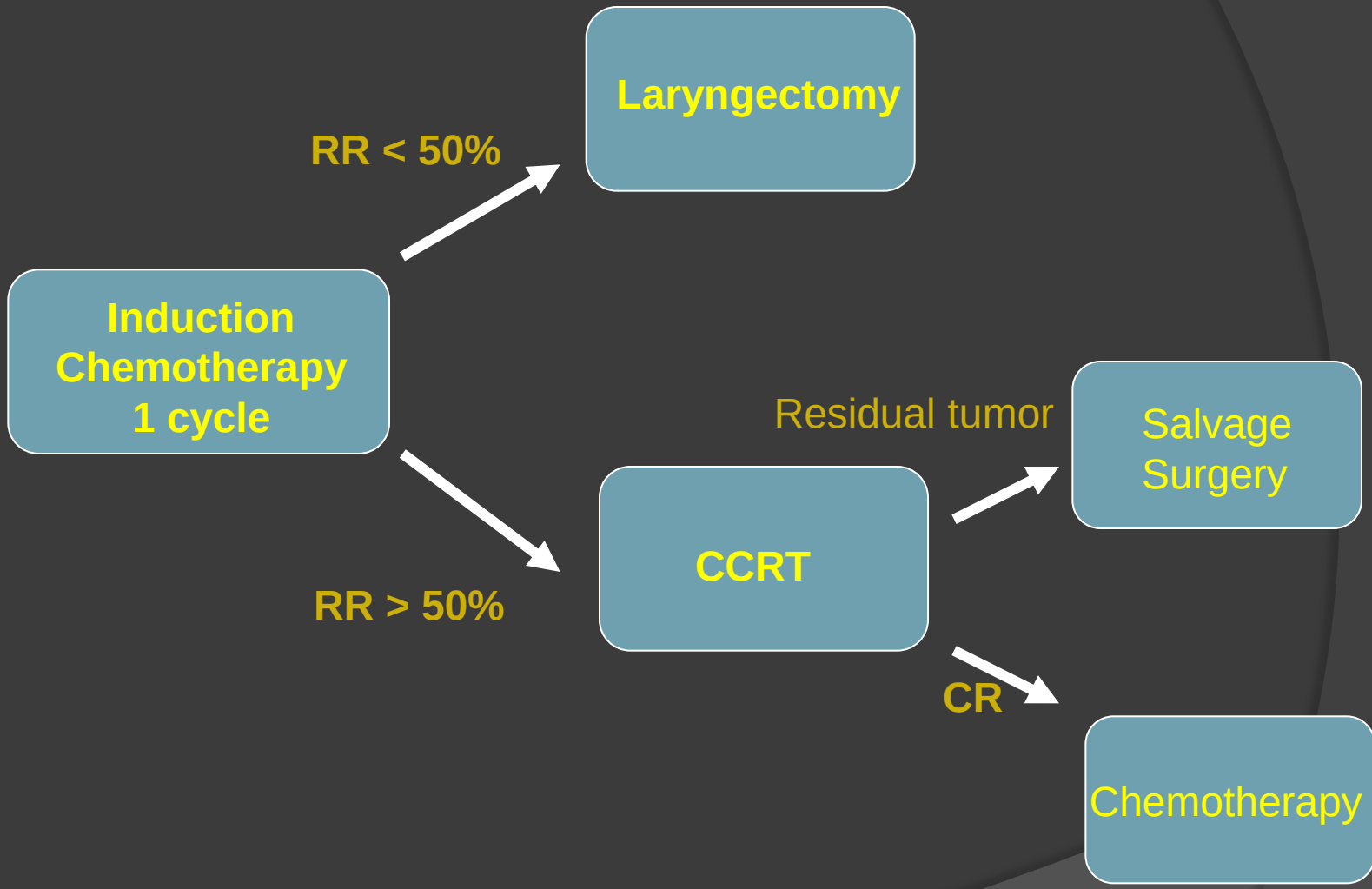
Susan Urba, Gregory Wolf, Avraham Eisbruch, Francis Worden, Julia Lee, Carol Bradford, Theodoros Teknos, Douglas Chepeha, Mark Prince, Norman Hogikyan, and Jeremy Taylor

Individualized Therapy !

Patients and Methods

The chemotherapy was cisplatin 100 mg/m^2 on day 1 and fluorouracil 1,000 mg/m^2/d for 5 days. Patients who achieved less than 50% response had immediate laryngectomy. Patients who achieved more than 50% response went on to concurrent chemoradiotherapy. Histologic complete responders after chemoradiotherapy received two more cycles of chemotherapy. Patients with residual disease after chemoradiotherapy had planned salvage surgery.

J Clin Oncol 2006; 24:593-598



J Clin Oncol 2006; 24:593-598

Laryngeal preservation

- Chemoradiotherapy becomes standard
  - No negative survival impact, at most series
- Organ preserved, but function?
  - Fibrosis, choking, difficult speech
  - Reconstructed organ followed by rehabilitation
    - Function may be better
    - Loss of organ, psychological stress

Treatment in recurrent or metastatic HNSCC

R/M Head & Neck Cancer

- 20%–30% of patients
- Locoregional recurrence can be salvaged by surgery or re-irradiation.
- Most patients with recurrent or metastatic (R/M) disease only qualify for palliative treatment

Treatment option

- Supportive care
- Single-agent chemotherapy
- Combination chemotherapy
- Targeted therapies either alone or in combination with cytotoxic agents

Ann Oncol 2005;16 Suppl 2:ii258-ii264.

Goals of treatments

- Symptom control
- Prevention of new cancer-related symptoms
- Improvement in quality of life (QoL)
- Objective tumor response (OR), disease stabilization (SD) or both combined (disease control; DC)
- Prolongation of overall survival (OS) and progression-free survival (PFS).

Factors influnce QoL and OS

- Medical conditions (cardiovascular and/or pulmonary diseases)
- Malnutrition
- Infections (local, aspiration pneumonia, systemic)
- Hypercalcemia
- local pain
- bleeding (arterial, venous, capillary)

Al-Sarraf M. Head and neck cancer: chemotherapy concepts. Semin Oncol 1988;15:70-85.

Recurrent / Metastatic HNC

- Median survival 4 months in untreated patients
- Median survival of treated patients with is 6 months and the 1-year survival rate is around 20%.
- These statistics have not been affected by the use of chemotherapy.
- Single agent for R/M HNC: ORR range from 15%-35%

- Cisplatin
- Carboplatin
- Paclitaxel
- Docetaxel
- 5-FU
- Methotrexate
- Ifosfamide
- Bleomycin
- Gemcitabine[19] (nasopharyngeal)
- Cetuximab[20]

Single agent RR with advanced SCCHN

Table 2. Phase II Trial Single-Agent Response Rates in Patients With Advanced SCCHN

Agent	No. of Patients Assessable	Response Rate (%)	Median Survival (months)	Year of Publication	Reference
Methotrexate		8-77 (average 31)		1984	9,8
Bleomycin		6-45 (average 21)		1977-84	9,89
Cisplatin		14-41 (average 28)		1983-94	9,34,35,90
Carboplatin		25		1986	91
Oxaliplatin		10		1996	71
Cyclophosphamide		36		1980	92
Doxorubicin		24		1980	92
Hydroxyurea	18	39		1980	10
Vinblastine		29		1980	10
Vinorelbine		6		1994	74
Fluorouracil		15		1984	9
Gemcitabine	61	13		1994	93
Capecitabine	14	8		2003	94
Orzel	42	21		2001	95
Irinotecan		0-14		2005	72
Paclitaxel 24-hour infusion	34	40 (4 CRs)	9.2	1998	39
Paclitaxel 96-hour infusion	Chemotherapy naïve/paclitaxel naïve/paclitaxel exposed	13/0/0	5.5	2004	41
Docetaxel		21-42		1994-2005	36-38,96
Pemetrexed	35	26	6.4	2001	97
Ifosfamide		26		2003	69
Cetuximab	103	13		2005	75
Erlotinib	115	4		2004	73
Gefitinib	47	11	8.1	2003	70
Sorafenib (BAY 43-9006)	10	6 SD (60%); 4 SCCHN + 2 NPC; range, 3-6 cycles		2005	87

A Dimitrios Colevas JCO 2006 June

single-agent chemotherapy

- Methotrexate, Cisplatin, 5-fluorouracil (5-FU) and Bleomyin
- Response of short duration, ~3–5 months, in 15%–30% of cases and only rarely complete response (CR)
- Pemetrexed, vinorelbine, irinotecan, capecitabine, orzel, S-1 and the taxanes paclitaxel and docetaxel
- The taxanes are among the highest scoring agents, with response rates varying between 20% and 43%

Cisplatinum and Bleomycin for advanced or recurrent HNSCC: a randomised factorial phase III controlled trial.

- 31 patients treated with single-agent cisplatin demonstrated prolonged survival compared with 26 patients treated with supportive measures only

- patients who respond do quickly. Of the 16 responders, 75% responded after the first cycle and the remaining 25% after the second cycle .

Cancer Chemother Pharmacol 1985;15:283-289.

Results of a randomised phase II study comparing docetaxel with methotrexate in patients with HNSCC

- in the randomized phase II study of docetaxel versus methotrexate , the response rate was reported as significantly higher in the docetaxel arm with 27% [95% confidence interval (CI) 21.7% to 32.3%] OR compared with 15% (95% CI 11.2% to 18.8%) in the methotrexate arm.

Eur J Cancer 2004;40:2071-2076.

Other single agent for HNSCC

- Neither vinorelbine, ifosfamide, irinotecan, nor pemetrexed has been evaluated in a randomized phase III study for R/M HNSCC.

Recurrent / Metastatic HNC

Combination therapy

1. ➤ **Cisplatin or carboplatin + 5-FU [15,16] ± cetuximab [17]**
2. ➤ **Cisplatin or carboplatin + docetaxel or paclitaxel [15]**
3. ➤ **Cisplatin/cetuximab [18]**

1 &2 are the most active regimens, result in higher response rate of 30-40%

Combination chemotherapy

- **standard platinum-based combinations**
- Cisplatin/infusional 5-FU (PF) regimen:

  a better outcome than what was observed with single-agent treatment, at least with respect to OR rates and CR rates
- Response rates were notably lower for the subsets of patients who had prior surgery and radiation and those who had metastatic disease

Combination chemotherapy

- In a number of randomized phase III trials performed in the 1990s, this PF regimen was shown to be superior to single-agent regimens, in terms of response rates but not meaningful survival advantage

Phase III PF vs single agent in advanced HNSCC

Randomized Trials: Combinations vs Monotherapy			
Intergroup	**n**	**RR, %**	**MS, Mos**
Cisplatin/5-FU	79	32	5.5
Cisplatin	83	17	5.0
5-FU	83	13	6.1

FP > Cisplatin or 5-FU alone!!

Jacobs C, et al. J Clin Oncol. 1992;10:257-263.

Phase III Combinations vs single agent in advanced HNSCC

Randomized Trials: Combinations vs Monotherapy			
Intergroup	**n**	**RR, %**	**MS, Mos**
Cisplatin/5-FU	87	32	6.6
Carboplatin/5-FU	86	21	5.0
Methotrexate	88	10	5.6

J Clin Oncol. 1992;10:1245-1251.

platinum–taxane combinations

- Regimens with carboplatin and paclitaxel did not seem to be much different from regimens with cisplatin and paclitaxel
- Docetaxel 65 mg/m(2) and carboplatin (AUC of 6) were given IV in a 21-day cycle to 68 patients. Response probability was 25 percent
- The major toxicity : neutropenia, with 36 patients (61 percent) experiencing Grade 3 or worse.
- Median PSF was 3.8 months (95%CI, 3.1-4.8) Median OS was 7.4 months (95%CI, 6.2-8.9).

Cancer Invest 2007;25:182-188

Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395)

- The paclitaxel plus cisplatin (PP) combination was directly compared with the PF regimen in the Intergroup trial E1395
- Patients received either paclitaxel 175 mg/m^2 (over 3 h) and cisplatin 75 mg/m^2, both on day 1, or the classical PF regimen.
- The OR rate was 27% with PP and 26% with PF. The overall grade 3/4 toxicity rate was similar between the two groups.
- However, grade 3/4 mucositis (31%) was only observed in the PF arm, while the occurrence of neurotoxicity was similar in the two groups.
- Median OS was 8.7 months in the PF group and 8.1 months in the PP group.

J Clin Oncol 2005;23:3562-3567

two-drug and three-drug platinum–taxane combinations.

- The TPF regimen, consists of docetaxel, cisplatin and infusional 5-FU, TAX323/EORTC24971 (Europe) and TAX324 studies (USA)

- Overall response rate: 44%,
- Median time to progression : 7.5 months
- Median OS : 11 months.
- Febrile neutropenia occurred rather frequently (in 15% of patients).

Am J Clin Oncol 2000;23:128-131

Recurrent and/or metastatic SCCHN: Phase III chemotherapy results in first line

No improvement in overall survival in recent decades

Year	Reference	No. of patients	Regimen	OS	ORR	Grade 3/4 toxicity
1992	Forastiere AA, et al.[1]	277	Cisplatin + 5-FU Carboplatin + 5-FU Methotrexate	**NS**	32% 21% 10%	Neutropenia Mucositis
1992	Jacobs C, et al.[2]	249	Cisplatin + 5-FU 5-FU Cisplatin	**NS**	32% 13% 17%	Vomiting Mucositis
1994	Clavel M, et al.[3]	382	CABO Cisplatin + 5-FU Cisplatin	**NS**	34% 31% 15%	Vomiting
2005	Gibson MK, et al.[4]	218	Cisplatin + 5-FU Cisplatin + paclitaxel	**NS**	27% 26%	Reduced for cisplatin + paclitaxel

CABO = cisplatin, methotrexate, bleomycin, and vincristine; NS = not significant

1. Forastiere AA, et al. J Clin Oncol 1992;10:1245–1251; 2. Jacobs C, et al. J Clin Oncol 1992;10:257–263
3. Clavel M, et al. Ann Oncol 1994;5:521–526; 4. Gibson MK, et al. J Clin Oncol 2005;23:3562–3567

Combined chemotherapy

- None of the combination chemotherapy regimens demonstrated an OS benefit when compared with single-agent methotrexate, cisplatin or 5-FU.

- Combination chemotherapy should preferably be used in younger patients with good PS and with symptomatic disease who require prompt symptom relief.

Combined chemotherapy

- No combination cytotoxic chemotherapy has shown superiority over another in a randomized prospective trial for patients with R/M HNSCC.
- CP and CF doublets have comparable efficacy as palliative regimens for advanced HNSCC based on randomized clinical trial data.
- Triplet cytotoxic regimens have been less extensively studied and should not be used outside of a clinical trial in the treatment of R/M HNSCC.

The 2nd line Chemotherapy choice in HNSCC

(1) New generation of chemotherapy:
Taxotere, gemcitabine, and Navelbine.
Gemcitabine in VGH: prolonged stabilization.

(2) Anthracycline-based regimen: MEPFL
(mitomycin, epirubicin, cisplatin, 5-FU, and LV)

(3) High dose ifosfamide and etoposide(IE).
Good KPS needed.

Annals of Oncology 2010; 21: vii252-vii261.

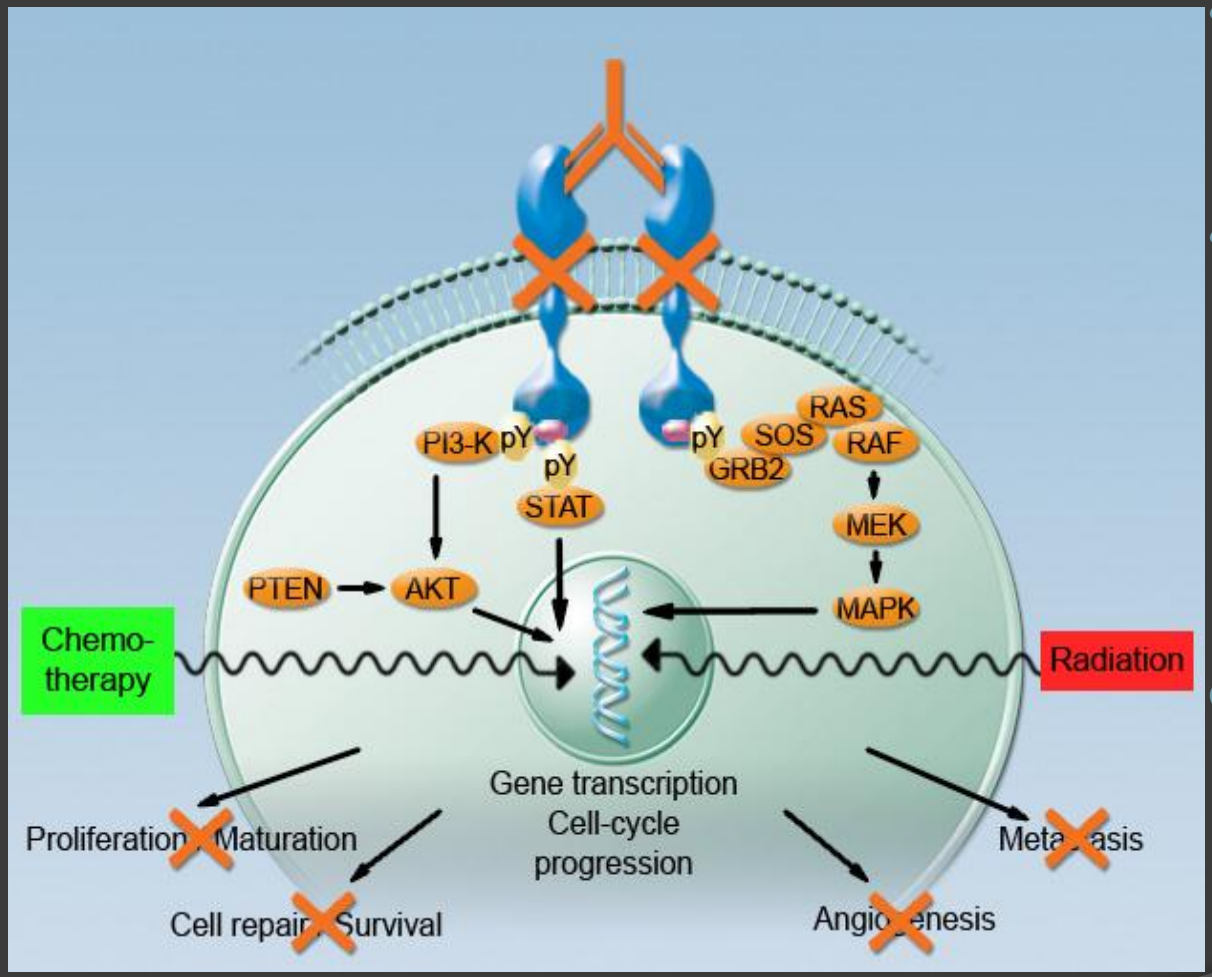
TARGET THERAPY IN HNSCC

ERBITUX + RT IN LOCALLY ADVANCED SCCHN

Mechanisms of action
- Erbitux® (Cetuximab) -

HNSCC

High EGFR expression predicts poor survival.



- **Erbitux is an IgG1 MAb targeting the EGFR**
- **Binding blocks EGFR signaling and inhibits proliferation, angio-genesis and metastasis, and stimulates apoptosis and differentiation**
- **Fc region may induce antibody-dependent cell-mediated cytotoxicity (ADCC) (immune response)**

Courtesy of José Baselga (modified)

Erbitux in locally advanced SCCHN: Bonner Phase III study

Stage III and IV non-metastatic SCCHN

N=424

R

RT (n=213)

Erbitux + RT (n=211)

Erbitux initial dose (400 mg/m^2)
Erbitux (250 mg/m^2) + RT (wks 2–8)

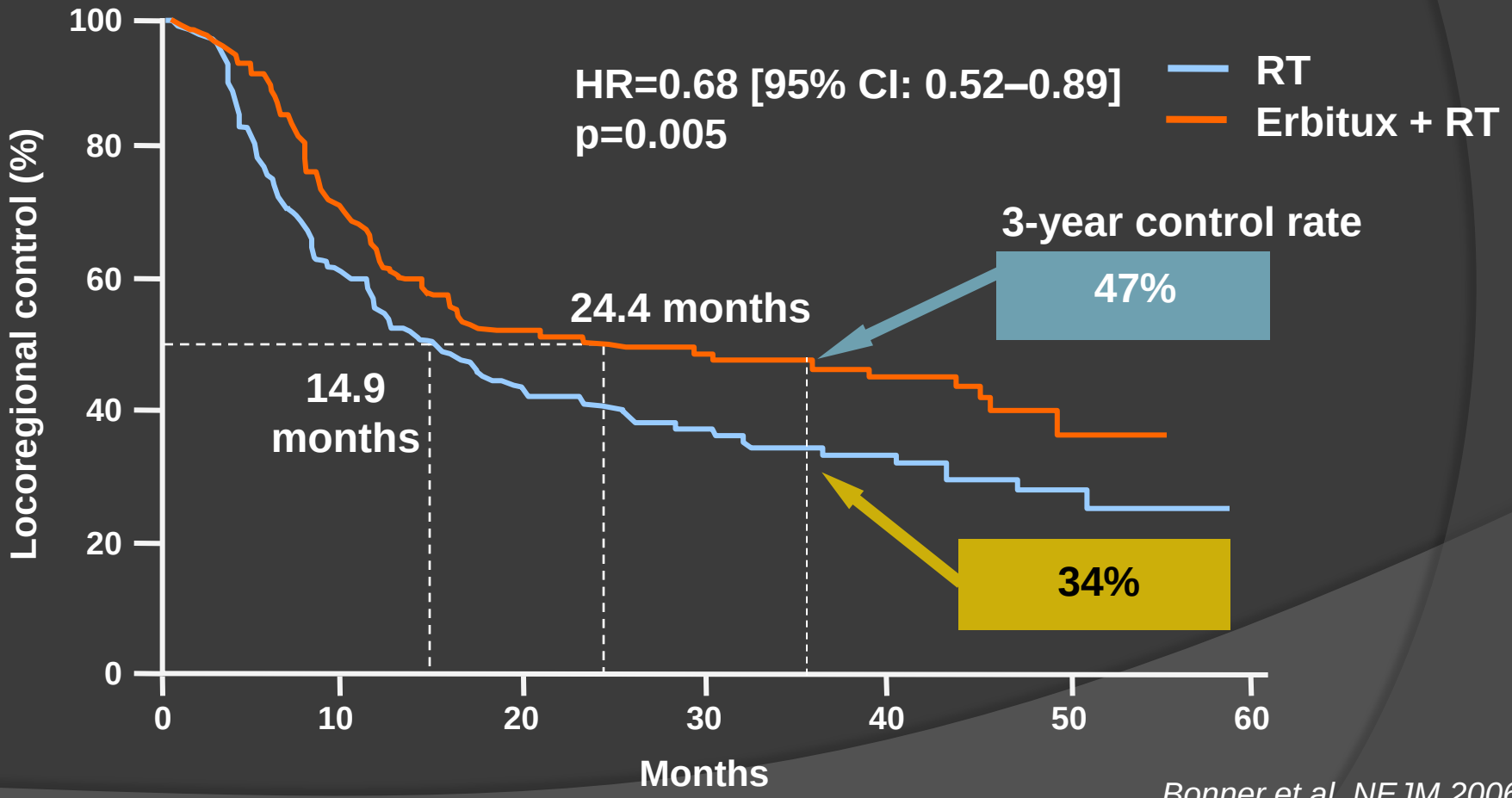
Primary endpoint: duration of locoregional control

Secondary endpoints: OS, PFS, RR, QoL, and safety

Bonner et al. NEJM 2006

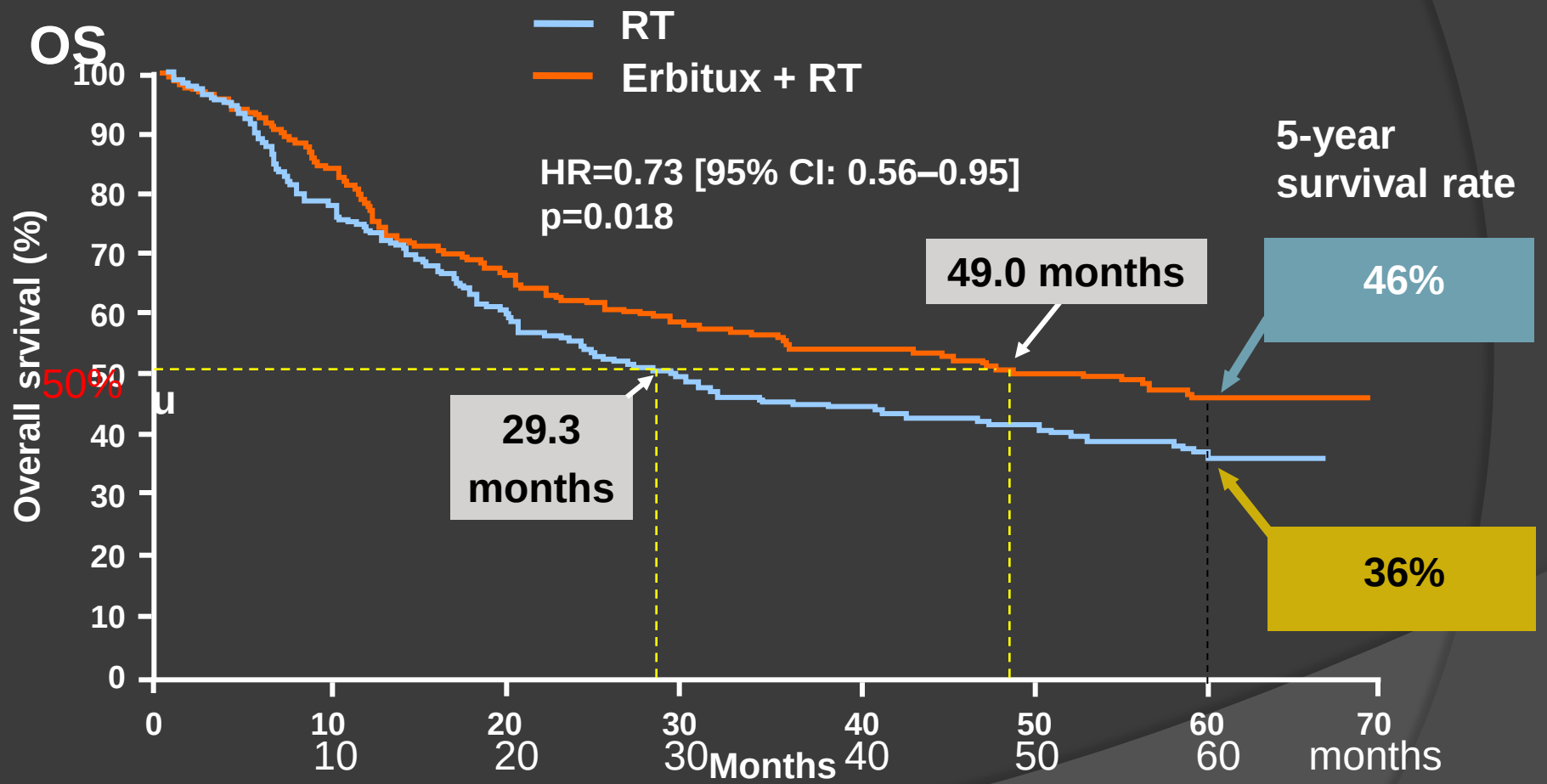
Erbitux in locally advanced SCCHN: Significant benefit in locoregional control

Erbitux + RT significantly increases median duration of locoregional control vs RT alone by 10 months



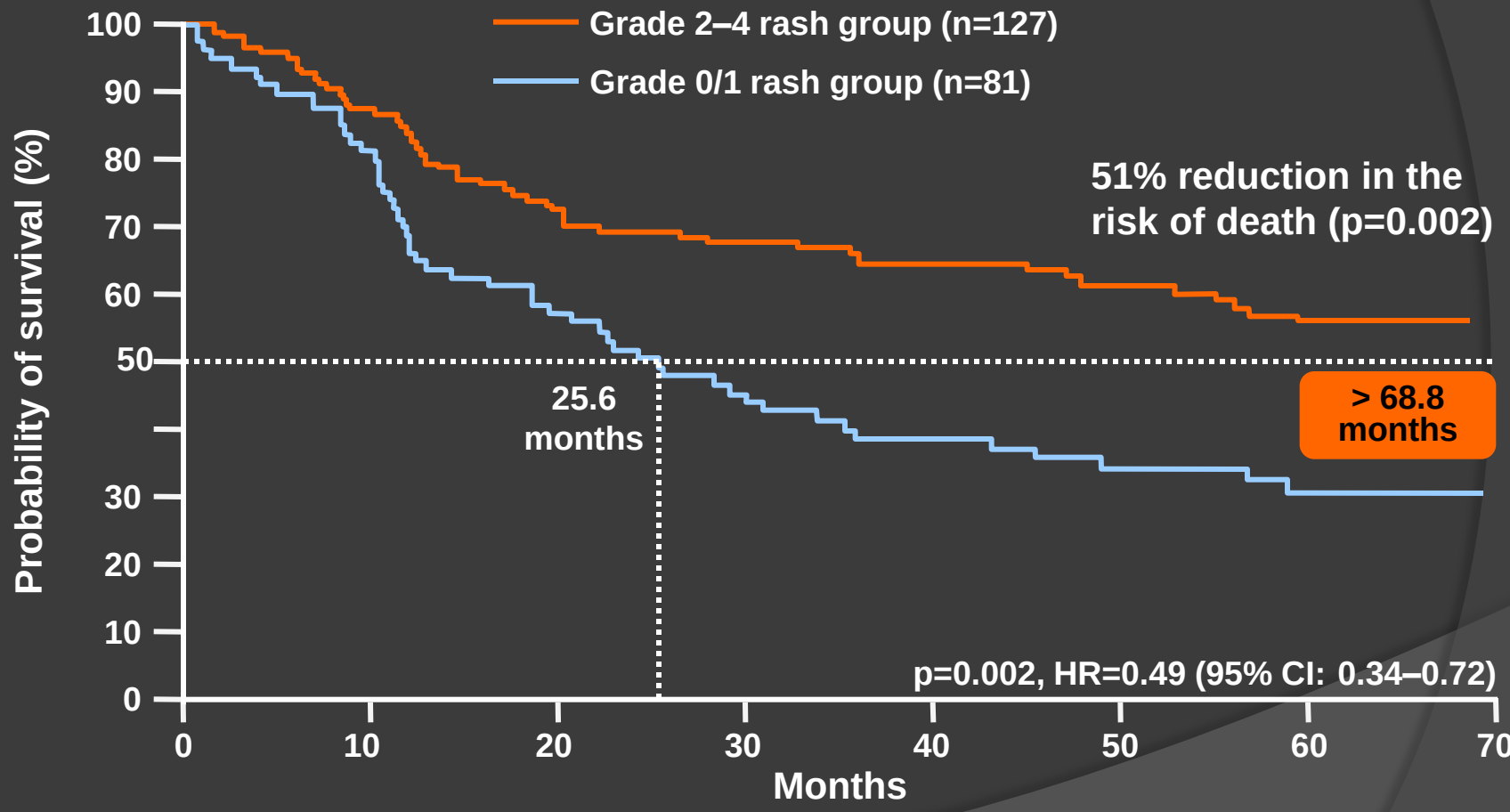
Bonner et al. NEJM 2006

Erbitux in locally advanced SCCHN: 5-year survival update



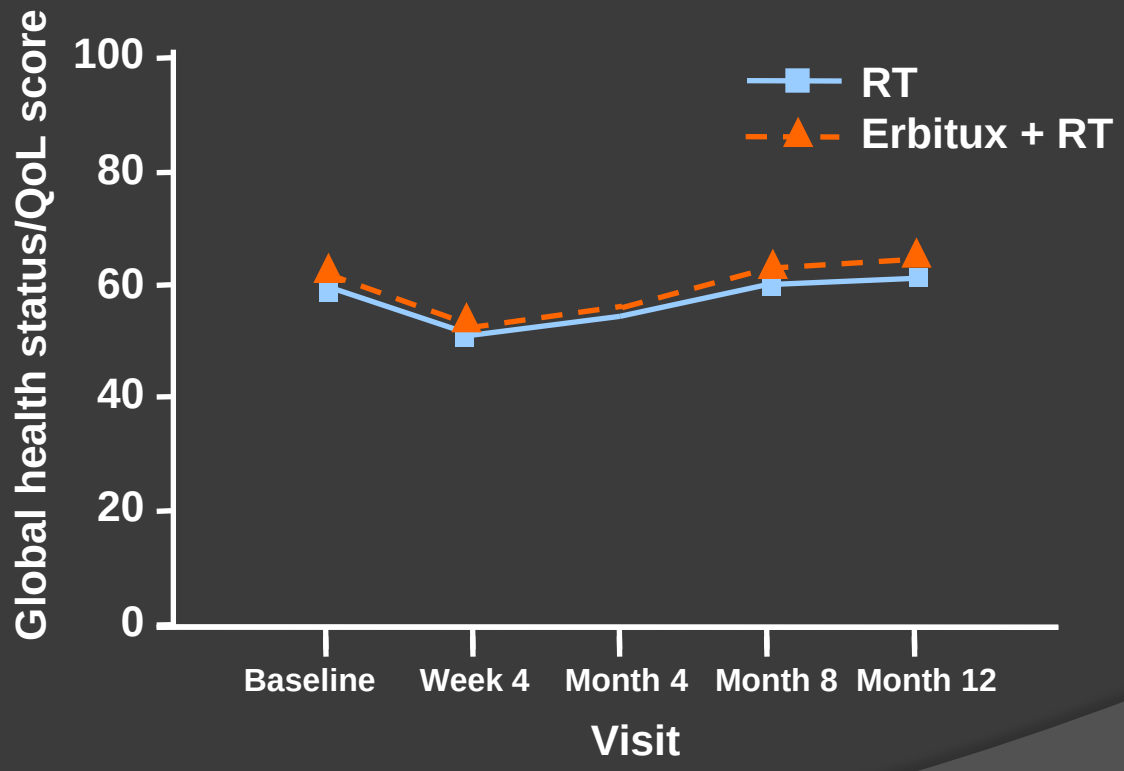
Bonner et al. Lancet Oncol 2010

Erbitux in locally advanced SCCHN: Skin rash correlates with survival



Bonner et al. Lancet Oncol 2010

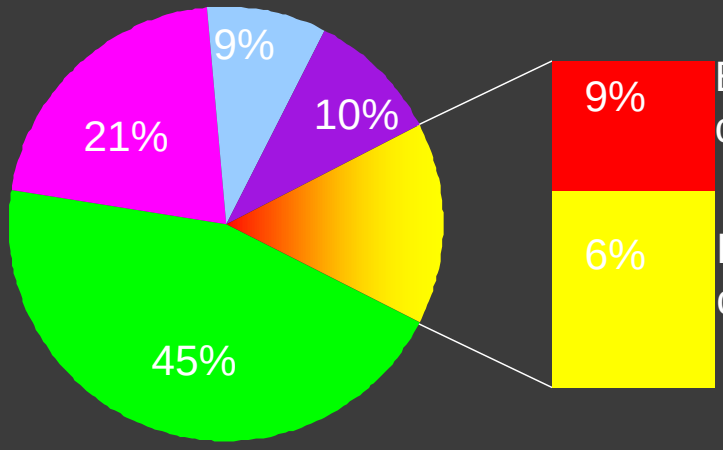
Adding Erbitux to RT increases survival without compromising QoL



QoL: post-baseline scores for the EORTC QLQ-C30

Curran et al. JCO 2007

CRT: percentage of treatment-related deaths after primary treatment



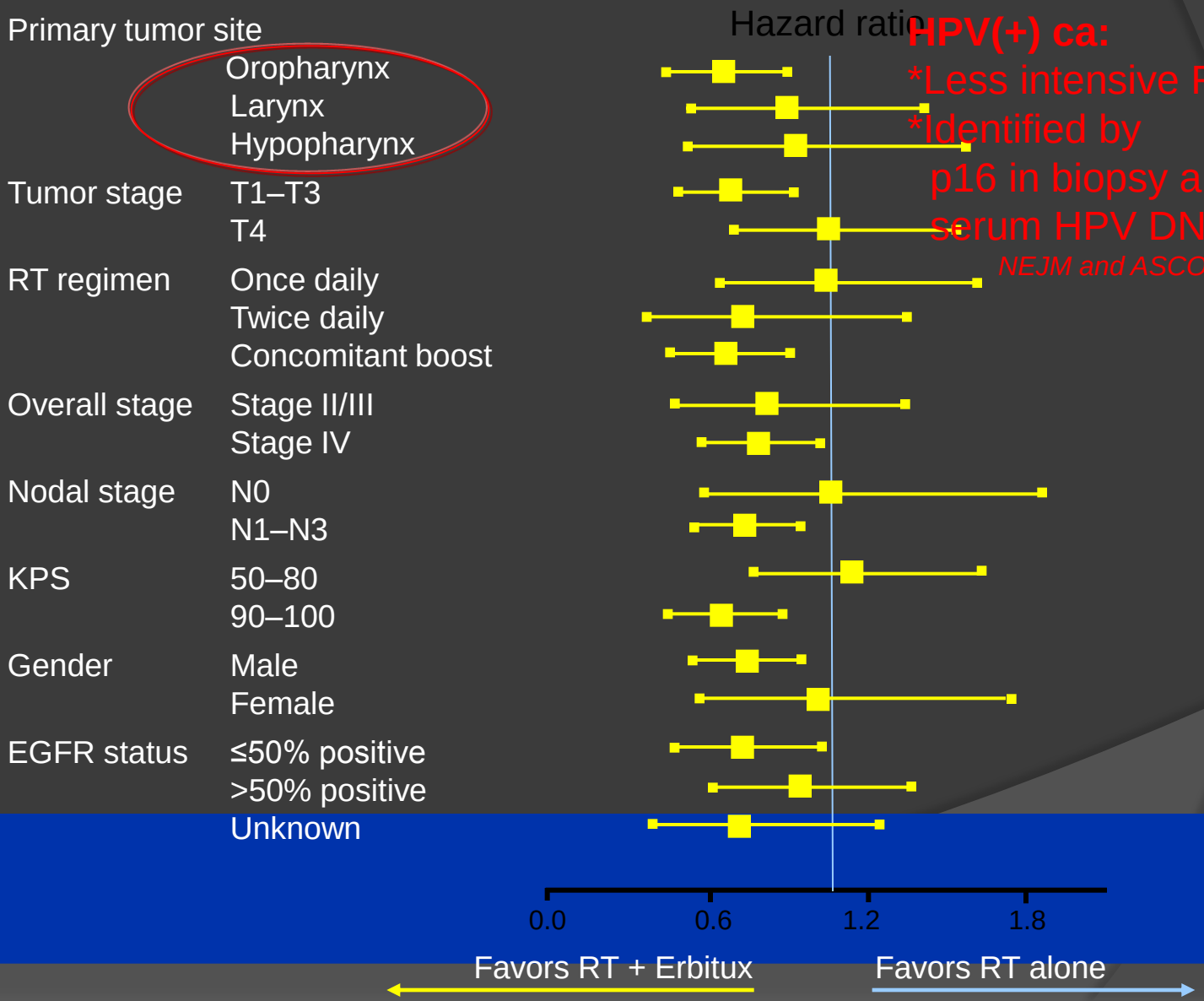
Early deaths due to treatment-related complications

Late deaths due to treatment-related complications

Cause of death	Time of occurrence, years median (range)
Disease progression	1.5 years (0.3–8.6)
Comorbidities	1.9 years (0.07–8.8)
Treatment-related	0.3 years (0.03–3.4)
Second primary tumors	3.5 years (1.5–10.1)
Unknown	5.1 years (1.1–9.5)

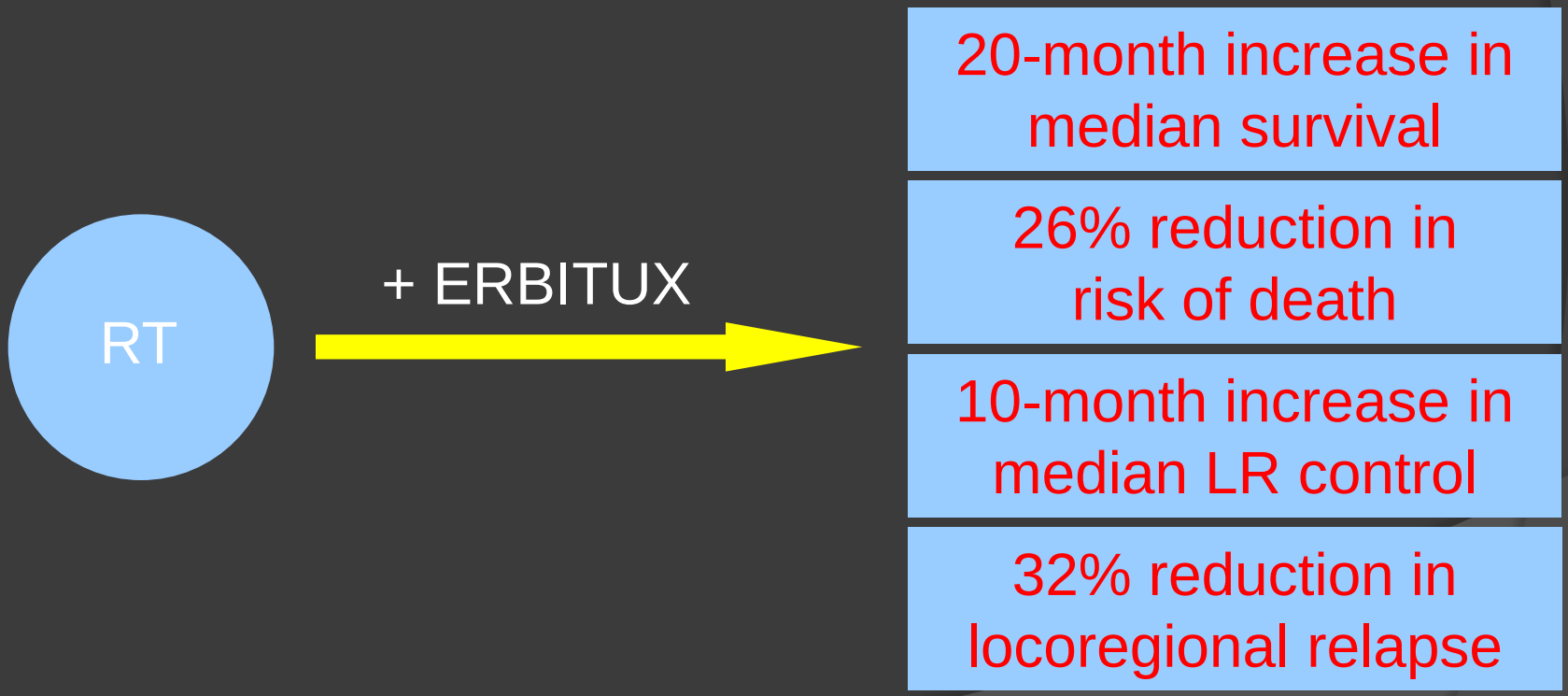
Argiris A, et al. Clin Cancer Res 2004;10:1956–1962

Forest plot: Subgroup analysis of overall survival – 5-year update



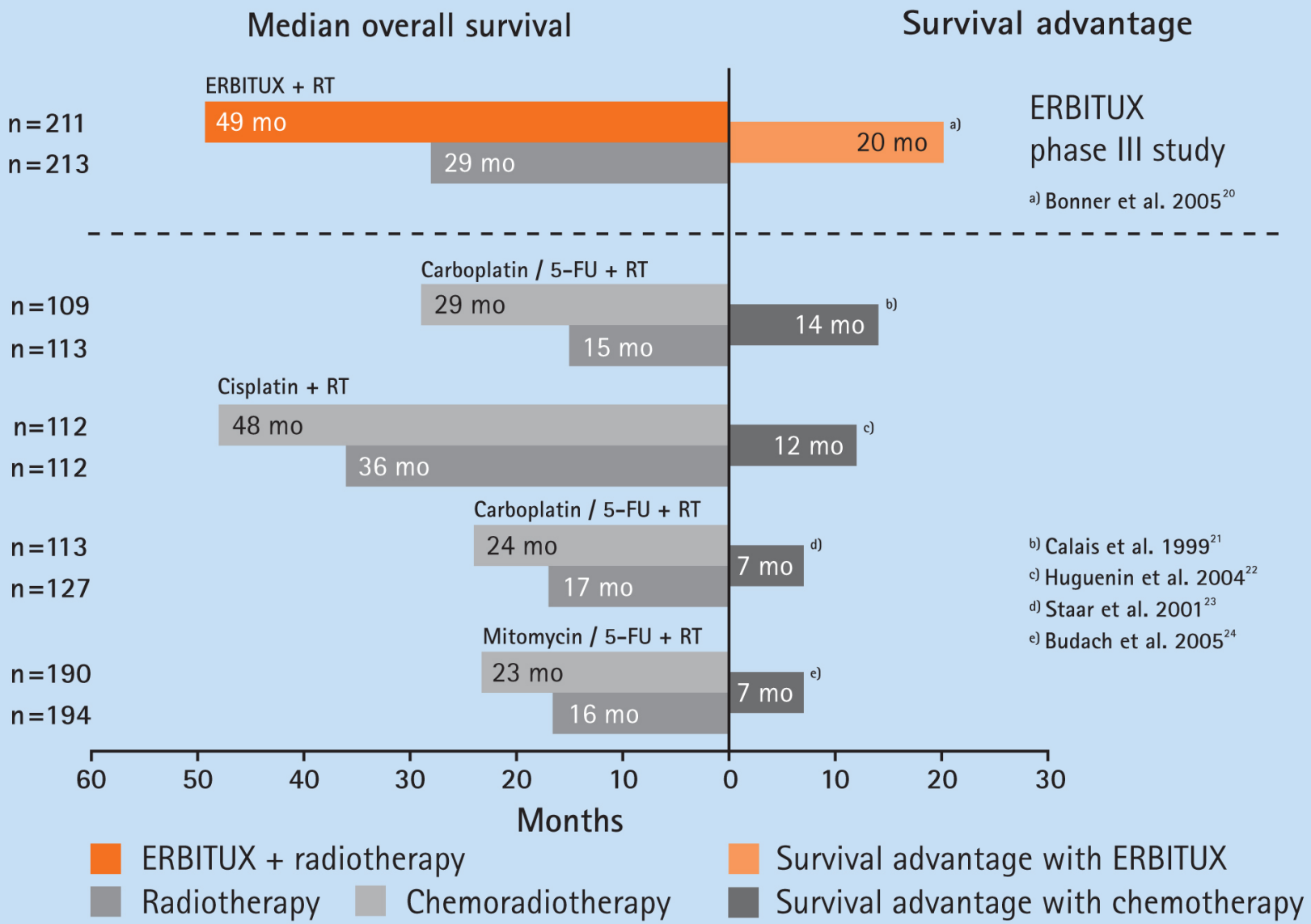
ERBITUX in locoregionally advanced SCCHN: efficacy summary

- ERBITUX + high-dose RT demonstrated significant efficacy benefits over high-dose RT alone



Bonner J, et al. N Engl J Med 2006;354:567–578

Survival of ERBITUX + radiotherapy compared to large randomized trials of chemoradiotherapy vs radiotherapy



Comparison of overall survival advantage of different combinations (MACH-NC meta-analyses, Bonner study)

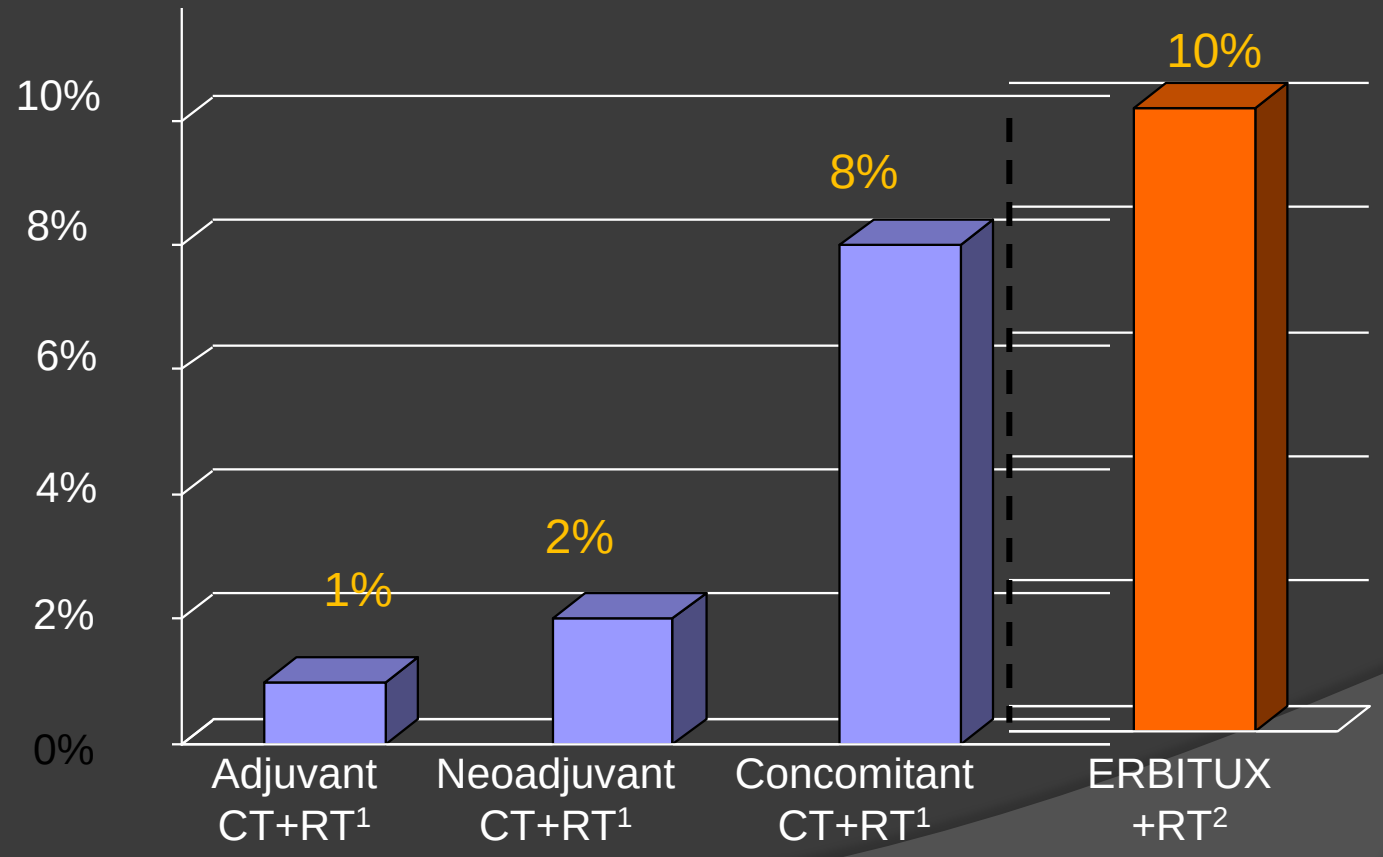
	Hazard ratio (95% CI)	CT or Erbitux effect (p-value)	Absolute benefit	
			At 2 years[a]	At 5 years[a]
Adjuvant CT+RT[1]	0.98 (0.85–1.19)	0.74	1%	1%
Neoadjuvant CT +RT[1]	0.95 (0.88–1.01)	0.10	2%	2%
Concomitant CT + RT[1]	0.81 (0.76–0.88)	<0.0001	7%	8%
ERBITUX + RT[2]	**0.73 (0.56–0.95)**	**0.02**	**7%**	**10%**

[a]Assuming survival rates of 50% at 2 years and 32% at 5 years in control groups

Pignon JP, et al. Lancet 2000;355:949–955
Bonner J.A, et al. as presented ASTRO 2008

Comparison of the 5-year overall survival benefit (MACH-NC meta-analyses, Bonner study)

ERBITUX+RT improves significantly long-term survival advantage at 5 years



1) Pignon JP, et al. Lancet 2000;355:949–955
2) Bonner J.A, et al. ASTRO 2008

Development of chemotherapy in R/M SCCHN

1977: cisplatin shows efficacy in 1st-line SCCHN

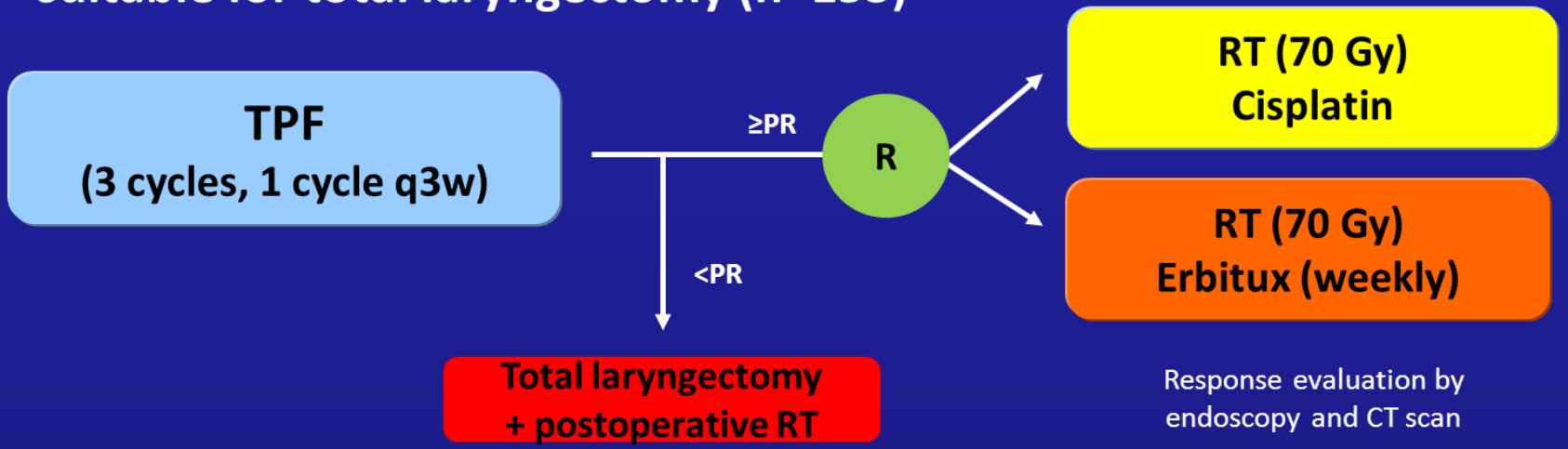
	N	Regimen	ORR (%)	Median OS (months)	Significant OS benefit
Grose et al 1985	100	Methotrexate Cisplatin	16 8	5.0 4.5	No
Forastiere et al 1992	277	Cisplatin + 5-FU Carboplatin + 5-FU Methotrexate	32* 21 10	6.6 5.0 5.6	No
Clavel et al 1994	382	CABO Cisplatin + 5-FU Cisplatin	34* 31* 15	7.3 7.3 7.3	No
Gibson et al 2005	218	Cisplatin + 5-FU Cisplatin + paclitaxel	27 26	8.7 8.1	No
Vermorken et al 2008	442	Platinum + 5-FU Platinum + 5-FU + Erbitux	20 36*	7.4 10.1*	Yes

CABO, cisplatin, methotrexate, bleomycin, vincristine
*significant

Clavel et al. Ann Oncol 1994; Forastiere et al. JCO 1992; Gibson et al. JCO 2005;
Grose et al. Cancer Treat Rep 1985; Vermorken et al. NEJM 2008; Wittes et al. Cancer Treat Rep 1977

GORTEC TREMPLIN study: Erbitux + RT for larynx preservation

Previously untreated SCC larynx/hypopharynx suitable for total laryngectomy (n=153)



Response evaluation by endoscopy and CT scan

Primary endpoint: larynx preservation 3 months after treatment

Secondary endpoints: larynx function preservation and survival 18 months after treatment

Lefebvre JL, et al. J Clin Oncol 2009;27(Suppl.15):abstract 6010

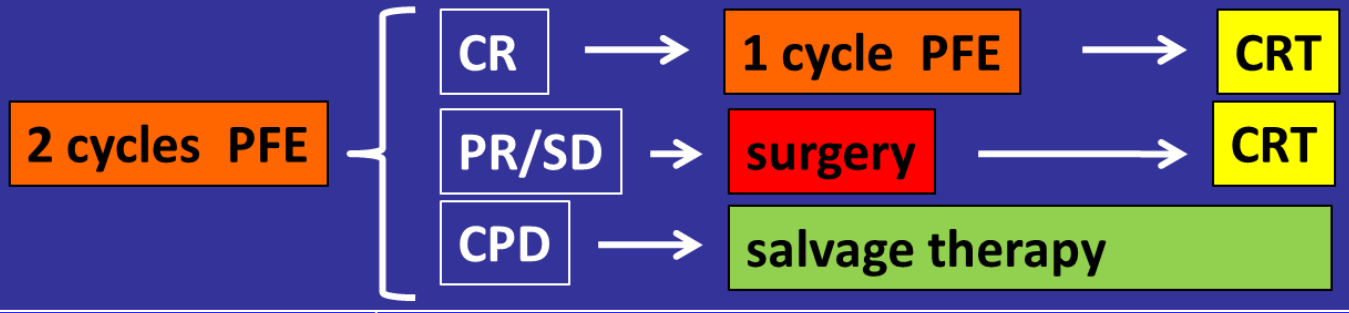
Table 1. TREMPLIN trial: Compliance and larynx preservation [6]

	Post-TPF induction treatment	
	Radiotherapy + cisplatin ($n = 60$)	**Radiotherapy + cetuximab ($n = 56$)**
Patients starting treatment, *n*	58	55
Patients receiving the full treatment protocol, *n* (%)	25 (43)	39 (71)
Larynx preservation rate 3 months after treatment, *n* (%)[a]	55 (92)	54 (96)

[a]As a proportion of all randomized patients.
Abbreviations: TPF, docetaxel, cisplatin, and 5-fluorouracil.

The Oncologist, Vol. 15, No. suppl_3, 30-32, October 2010

Induction PFE (cisplatin and 5-FU + Erbitux) followed by CRT + Erbitux in locally advanced OCSCC, phase II study



PFE:	
cisplatin	100 mg/m^2 day 1 in each induction cycle
5-FU	1000 mg/m^2 days 1–3 in each induction cycle
Erbitux	400 mg/m^2 day 1, then 250 mg/m^2 weekly on weeks 2–6
CRT:	
RT	70Gy
cisplatin	30 mg/m^2 weekly on weeks 1–7
Erbitux	250 mg/m^2 weekly on weeks 1–7

Pei-Jen, Alex, Lou, IFHNOS Seoul 2010

RTOG H-0234 phase II trial: Locally advanced resected

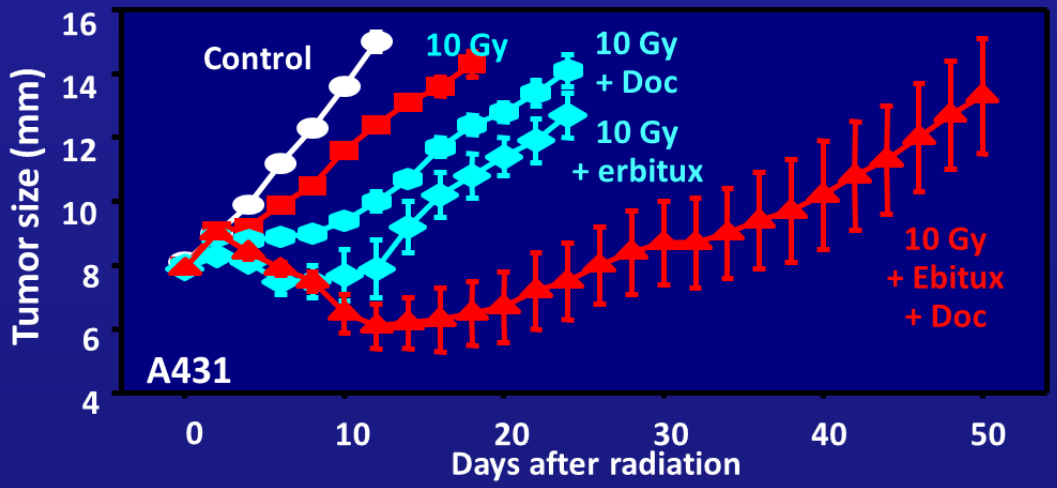
RTOG® Radiation Therapy Oncology Group

N=243
Surgical resection
High risk

RANDOMIZE

RT + ERBITUX (400 → 250 mg/m^2, qW)
+ DDP (30 mg/m^2, qW)

RT + ERBITUX (400 → 250 mg/m^2, qW)
+ Docetaxel (15 mg/m^2, qW)



Erbitux in R/M HNSCC

1st-line SCCHN: EXTREME trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Ricard Mesia, M.D., Fernando Rivera, M.D., Ph.D., Eva Remenar, M.D., Andrzej Kawecki, M.D., Ph.D., Sylvie Rottey, M.D., Ph.D., Jozsef Erfan, M.D., Dmytro Zabolotnyy, M.D., Ph.D., Heinz-Roland Kienzer, M.D., Didier Cupissol, M.D., Frederic Peyrade, M.D., Marco Benasso, M.D., Ihor Vynnychenko, M.D., Ph.D., Dominique De Raucourt, M.D., Carsten Bokemeyer, M.D., Armin Schueler, M.S., Nadia Amellal, M.D., and Ricardo Hitt, M.D., Ph.D.

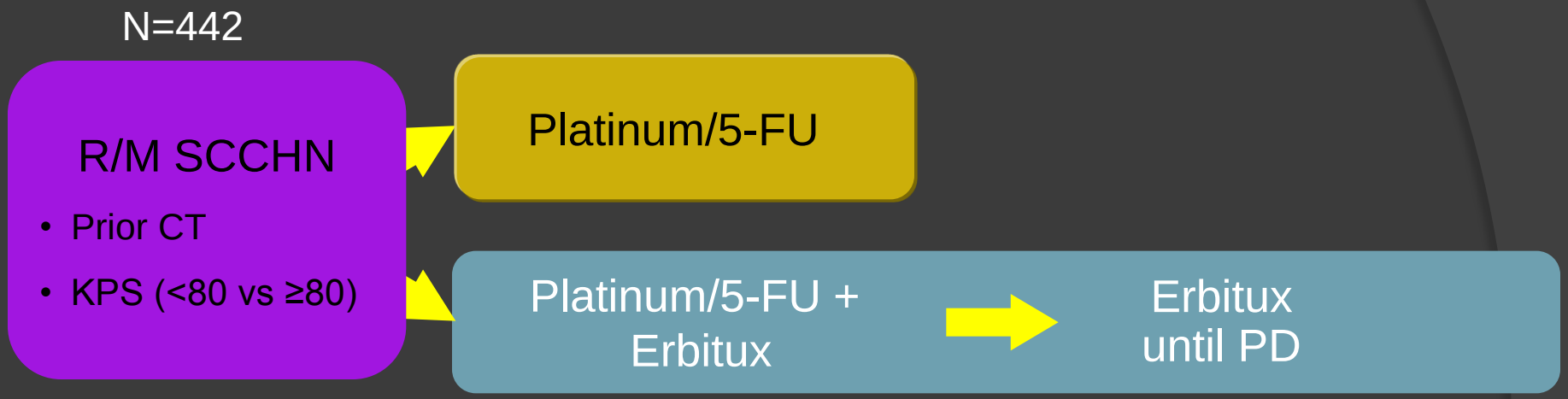
N ENGL J MED 359;11 WWW.NEJM.ORG SEPTEMBER 11, 2008

1st-line SCCHN: EXTREME trial

- Randomized, phase III, multicenter study
- 80 sites in 17 European countries
- No prior EGFR testing was required for study entry
- Previously untreated patients with recurrent or metastatic SCCHN
- Patients were stratified according to:
  - Prior chemotherapy
  - KPS (<80 vs ≥80)
- Treatment: platinum (cisplatin or carboplatin) plus 5-FU, with or without Erbitux

Vermorken et al. NEJM 2008

EXTREME Trial: Design



Platinum/5-FU
Cisplatin (100 mg/m^2 IV, day 1) or
Carboplatin (AUC 5, day 1) +
5-FU (1000 mg/m^2 IV, days 1–4)
Every 3 weeks, up to 6 cycles

Erbitux
Initial dose 400 mg/m^2
then 250 mg/m^2 weekly
until progressive disease (PD)

Primary endpoint: OS
Secondary endpoints: PFS, RR, safety

Vermorken et al. NEJM 2008

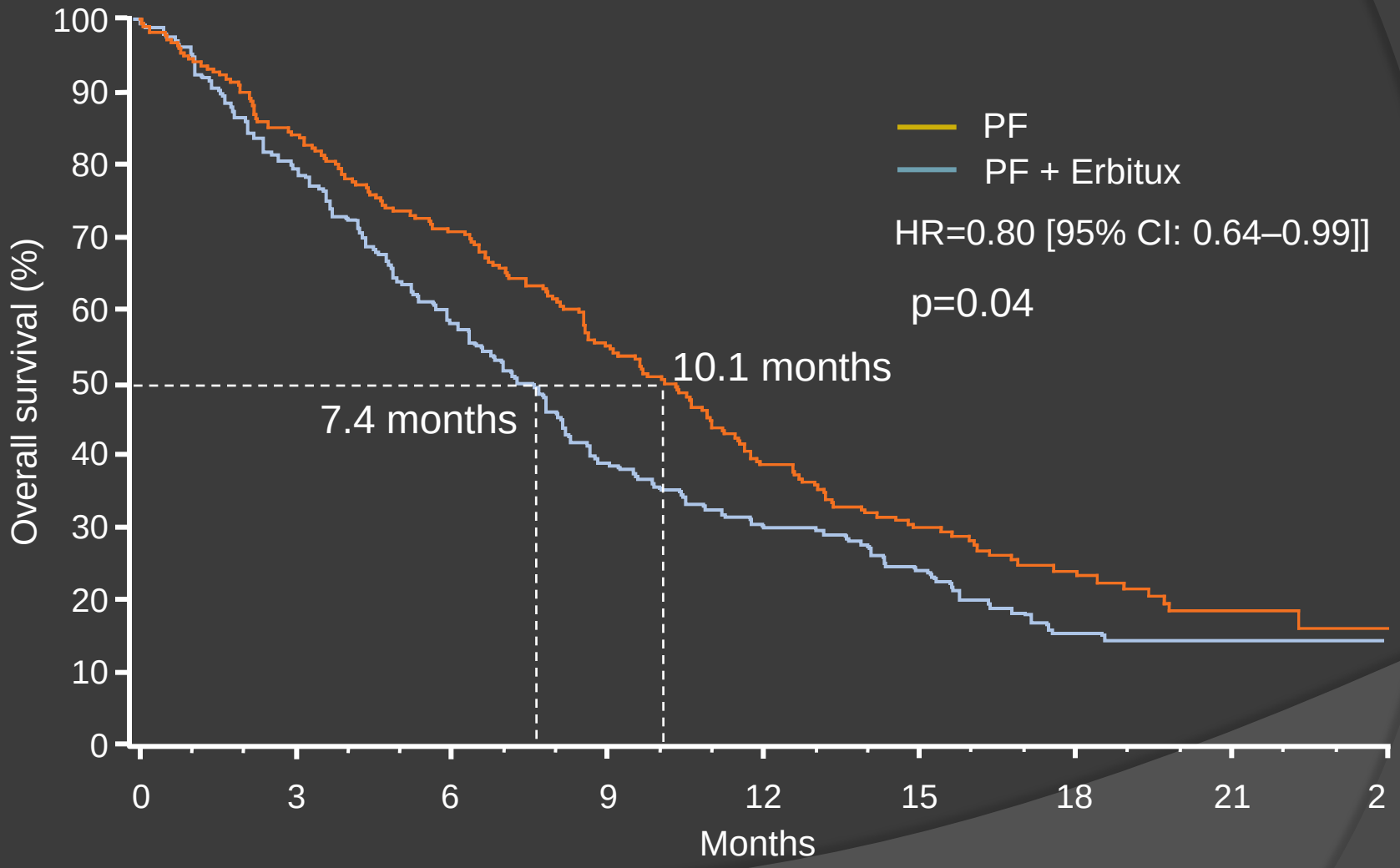
EXTREME Trial: Patient characteristics

Characteristic	PF (n=220)	PF + Erbitux (n=222)
Median age, years	57	56
Male/female, %	92/8	89/11
Extent of disease, %		
Locoregionally recurrent	54	53
Metastasis*	46	47
KPS score, %		
<80	11	12
≥80	89	88

*Metastasis with or without locoregional recurrence

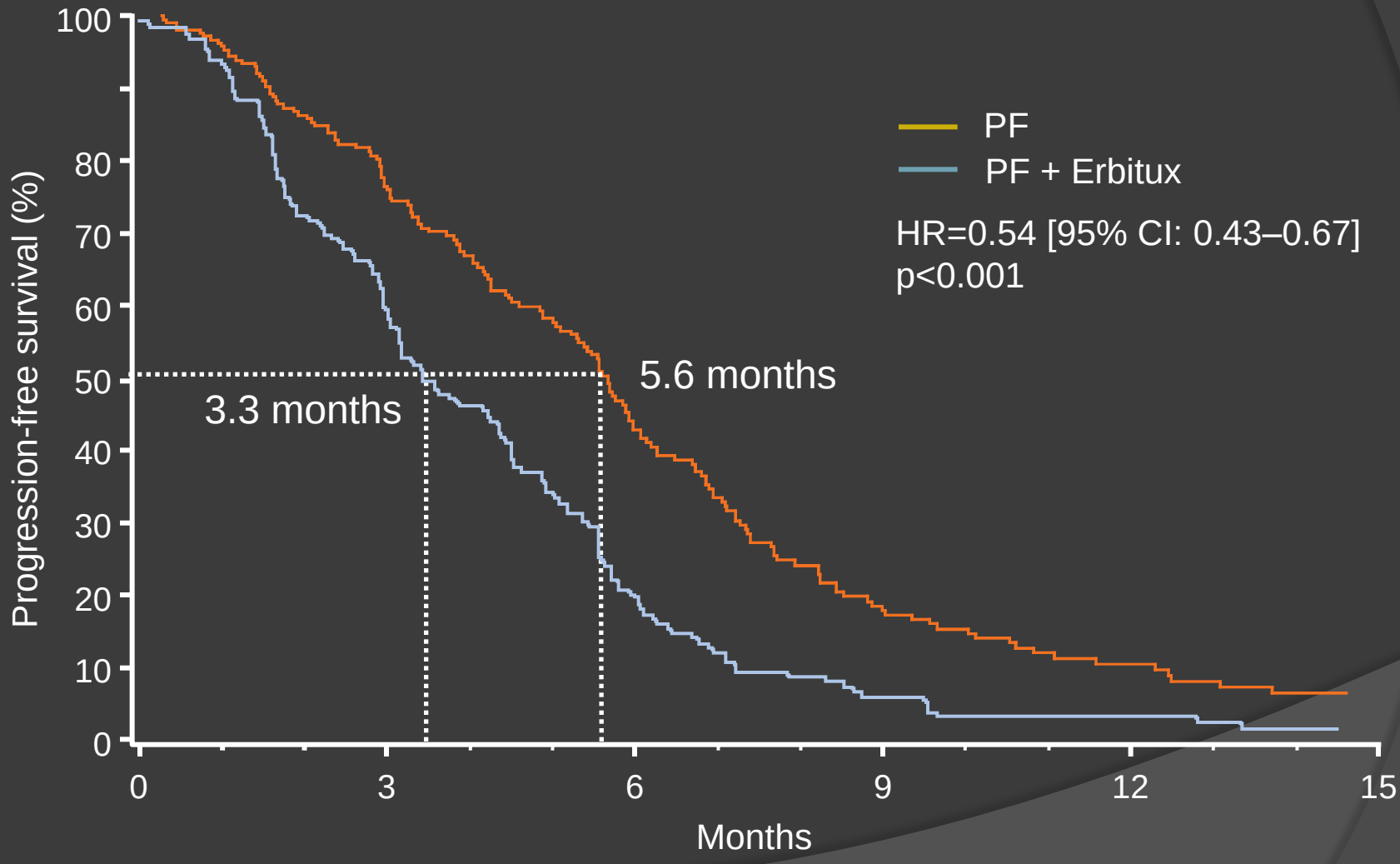
Vermorken et al. NEJM 2008

EXTREME: Overall survival



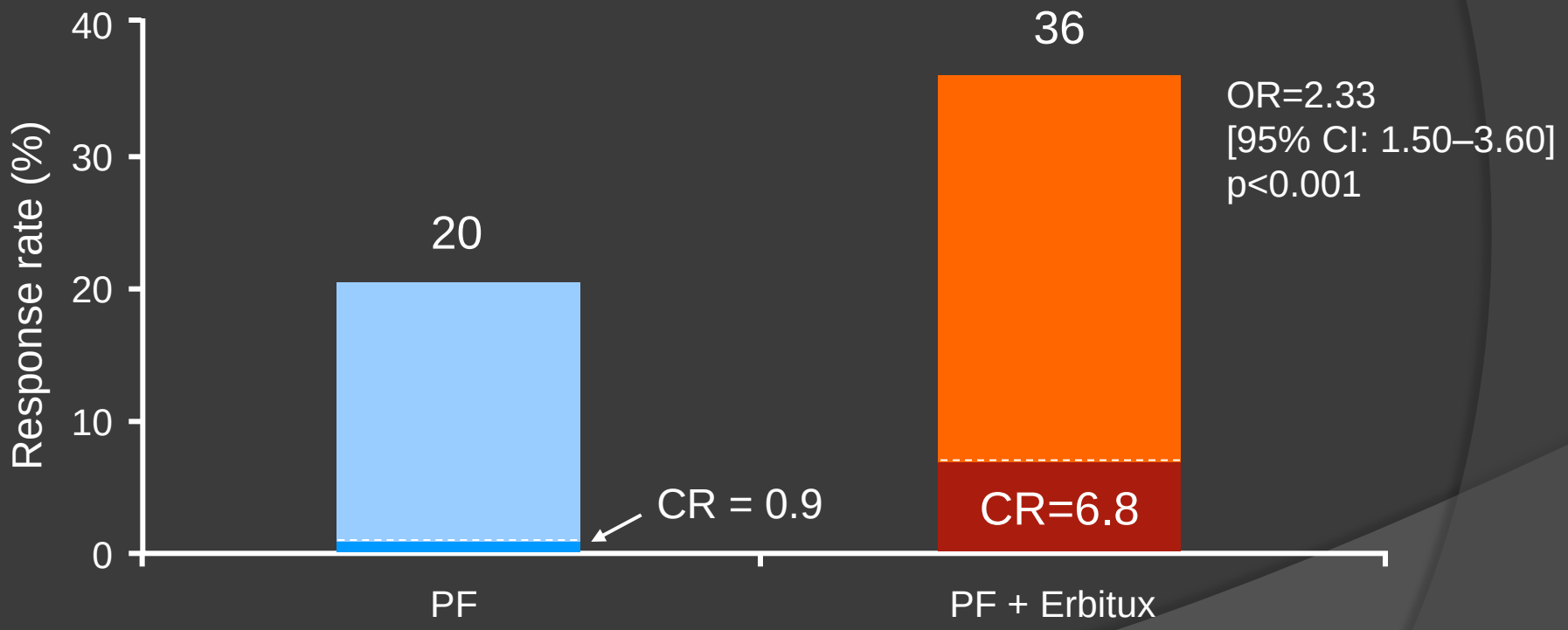
Vermorken et al. NEJM 2008

EXTREME: Progression-free survival



Vermorken et al. NEJM 2008

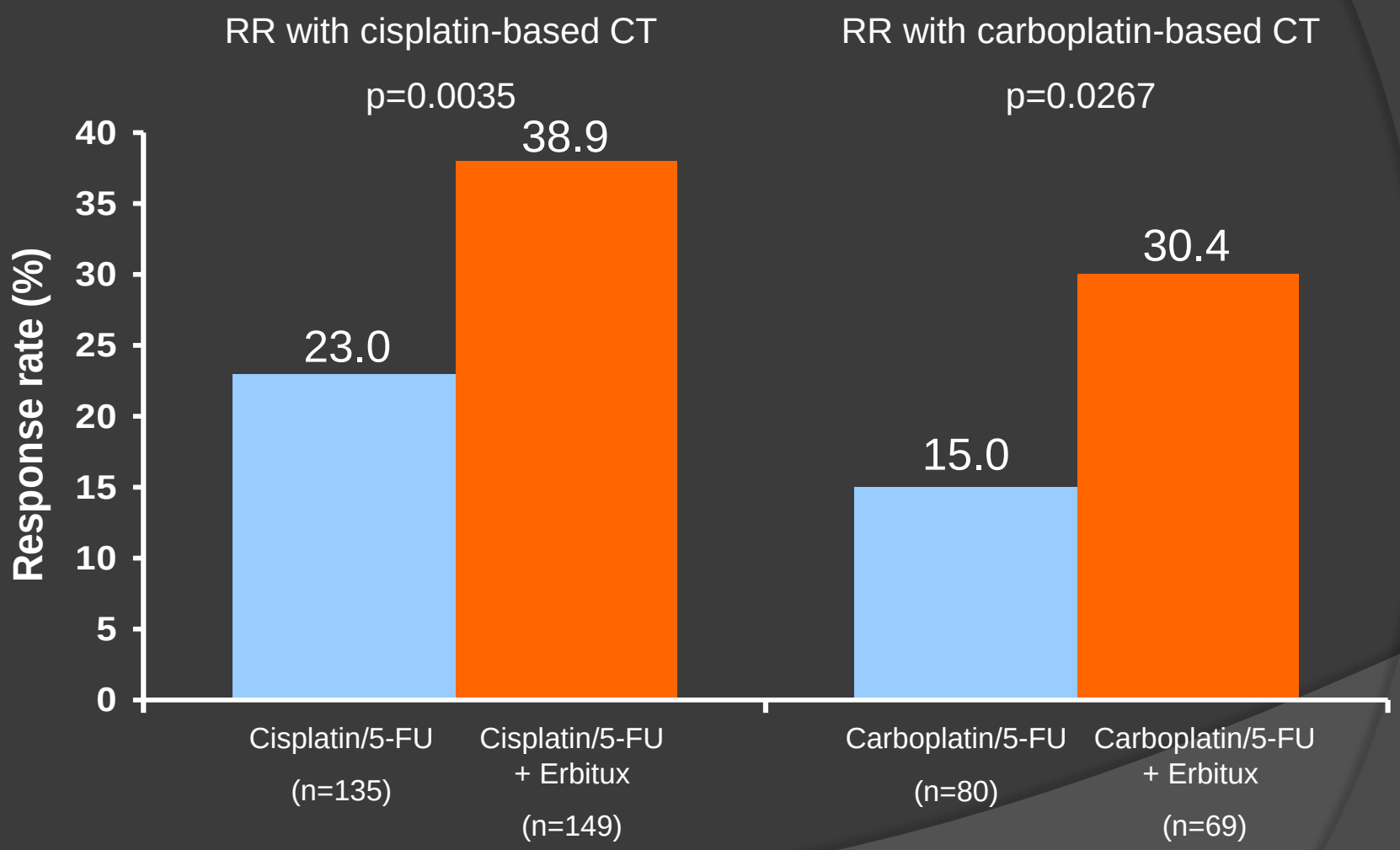
EXTREME: Response



CR; complete response

Vermorken et al. NEJM 2008

RR: Cisplatin vs carboplatin-based CT



Vermorken et al. NEJM 2008

Table 3. Grade 3 or 4 Adverse Events in the Safety Population.*

Event	Cetuximab plus Platinum–Fluorouracil (N=219)		Platinum–Fluorouracil Alone (N=215)		P Value†
	Grade 3 or 4	Grade 4	Grade 3 or 4	Grade 4	
	number of patients (%)				
Any event	179 (82)	67 (31)	164 (76)	66 (31)	0.19
Neutropenia	49 (22)	9 (4)	50 (23)	18 (8)	0.91
Anemia	29 (13)	2 (1)	41 (19)	2 (1)	0.12
Thrombocytopenia	24 (11)	0	24 (11)	3 (1)	1.00
Leukopenia	19 (9)	4 (2)	19 (9)	5 (2)	1.00
Skin reactions‡ *	20 (9)	0	1 (<1)	0	<0.001
Hypokalemia	16 (7)	2 (1)	10 (5)	1 (<1)	0.31
Cardiac events§	16 (7)	11 (5)	9 (4)	7 (3)	0.22
Vomiting	12 (5)	0	6 (3)	0	0.23
Asthenia	11 (5)	1 (<1)	12 (6)	1 (<1)	0.83
Anorexia	11 (5)	2 (1)	3 (1)	1 (<1)	0.05
Hypomagnesemia *	11 (5)	8 (4)	3 (1)	1 (<1)	0.05
Febrile neutropenia	10 (5)	2 (1)	10 (5)	4 (2)	1.00
Dyspnea	9 (4)	2 (1)	17 (8)	5 (2)	0.11
Pneumonia	9 (4)	3 (1)	4 (2)	1 (<1)	0.26
Hypocalcemia	9 (4)	5 (2)	2 (1)	0	0.06
Sepsis (including septic shock)	9 (4)	6 (3)	1 (<1)	1 (<1)	0.02
Tumor hemorrhage	3 (1)	2 (1)	6 (3)	4 (2)	0.33
Decreased performance status	2 (1)	1 (<1)	4 (2)	4 (2)	0.45
Respiratory failure	1 (<1)	0	5 (2)	4 (2)	0.12

EXTREME: Quality of life

original article

Annals of Oncology
doi:10.1093/annonc/mdq077

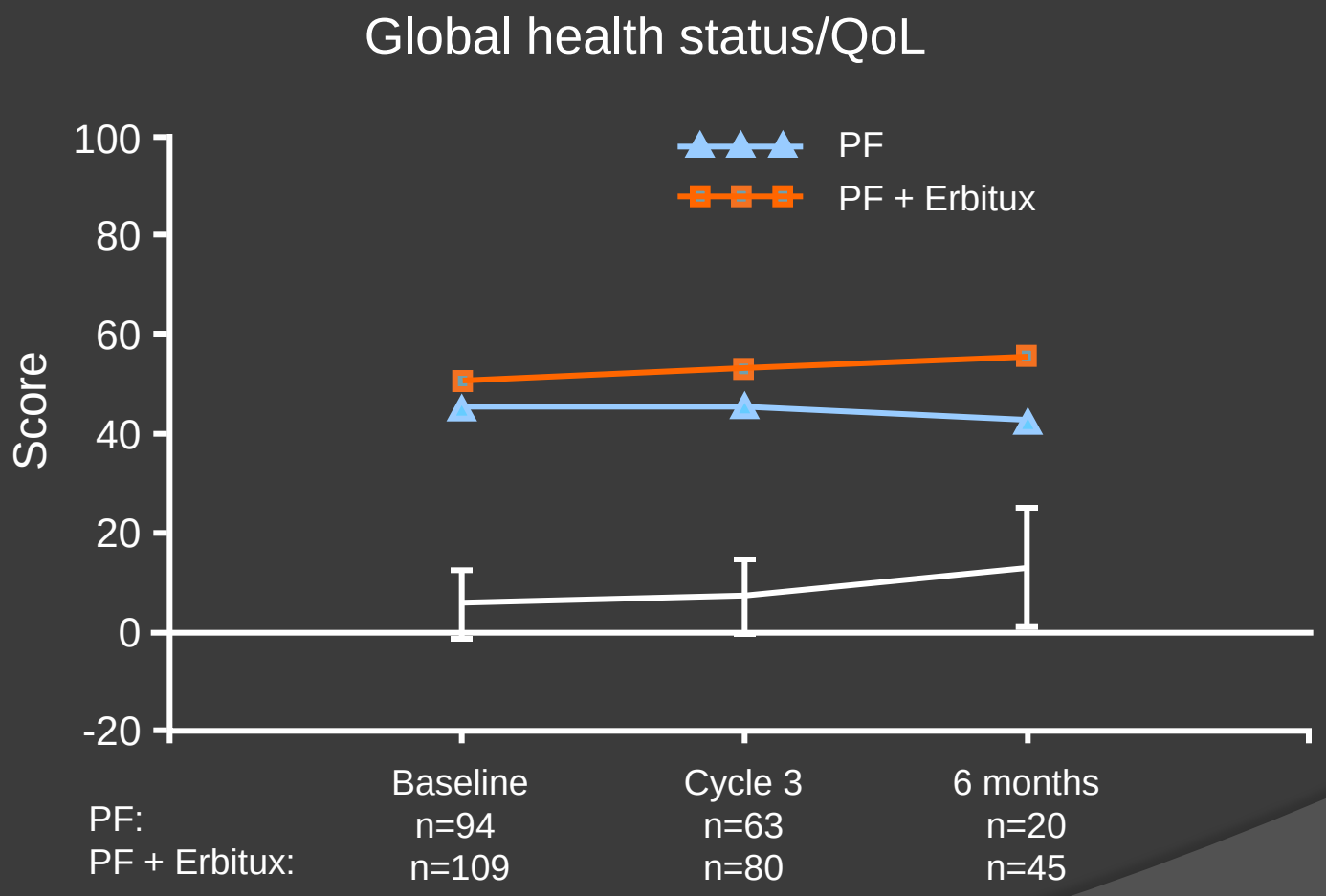
Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck

R. Mesía[1], F. Rivera[2], A. Kawecki[3], S. Rottey[4], R. Hitt[5], H. Kienzer[6], D. Cupissol[7], D. De Raucourt[8], M. Benasso[9], P. Koralewski[10], J.-P. Delord[11], C. Bokemeyer[12], D. Curran[13], A. Gross[14] & J. B. Vermorken[15]*

[1]Department of Medical Oncology, Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain; [2]Medical Oncology Department, Marqués de Valdecilla University Hospital, Santander, Spain; [3]Head and Neck Cancer Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [4]Medical Oncology, Ghent University Hospital, Ghent, Belgium; [5]Medical Oncology Department, University Hospital '12 de Octubre', Madrid, Spain; [6]3rd Medical Department, Kaiser Franz Josef Spital, Ludwig Boltzmann Institute for Applied Cancer Research, Vienna, Austria; [7]Department of Medical Oncology, Val d'Aurelle-Paul Lamarque Regional Cancer Centre, Montpellier, France; [8]Head and Neck Unit, François Baclesse Centre, Caen, France; [9]Oncology Department, San Paolo Hospital, Savona Italy; [10]Oncology, Rydygier Memorial Hospital, Krakow-Nowa Huta, Poland; [11]Department of Medical Oncology, Claudius Regaud Institute, Toulouse, France; [12]Department of Oncology, Hematology, BMT with section Pneumology, Hubertus Wald Tumorzentrum, University Cancer Center Hamburg, University Hospital, Hamburg, Germany; [13]Statistics, OMEGA Research, Santry, Dublin, Ireland; [14]Global Statistics, Merck KGaA, Darmstadt, Germany and [15]Department of Medical Oncology, Antwerp University Hospital, Edegem, Belgium

Mesía et al. Ann Oncol 2010

EXTREME: Quality of life

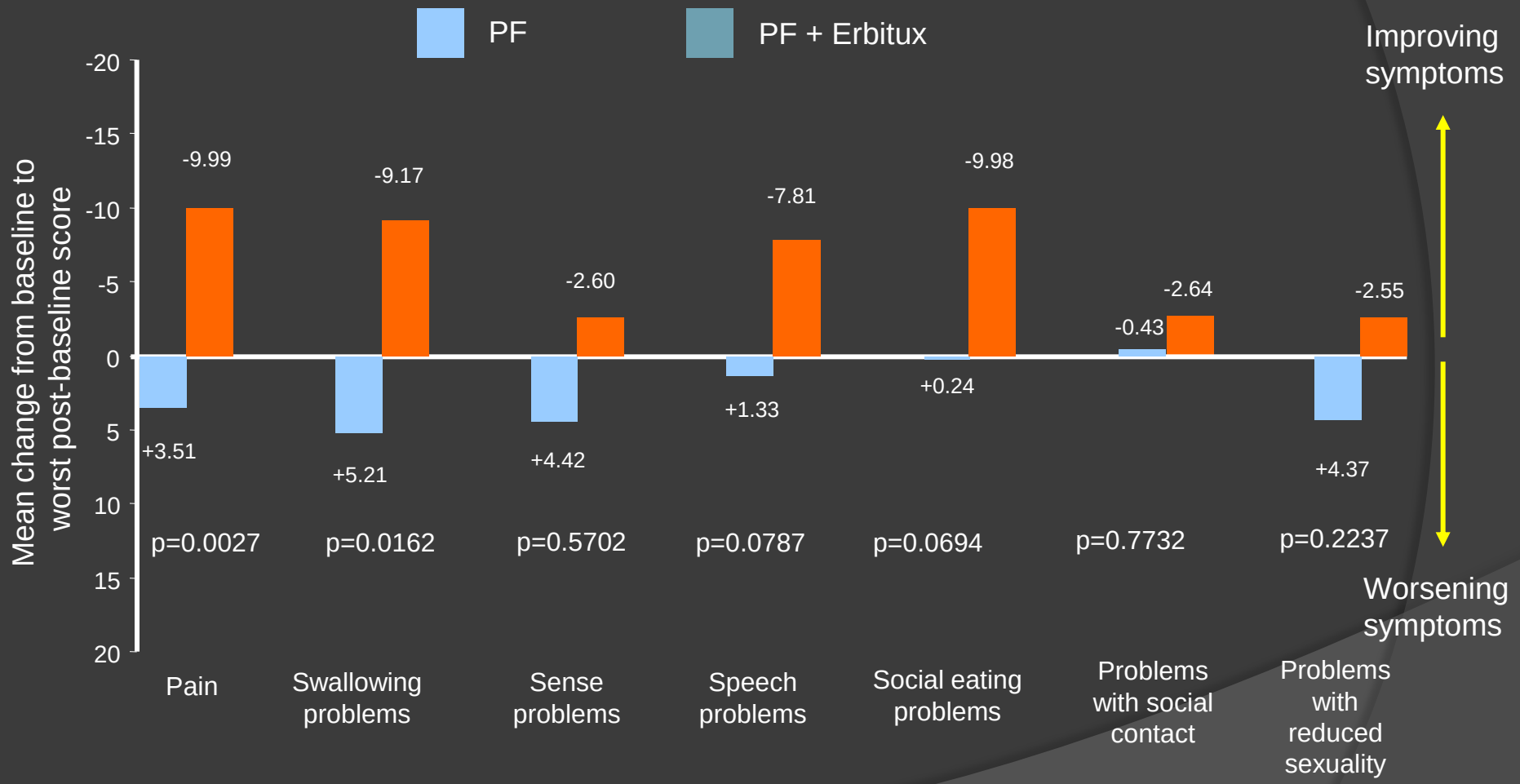


<50% of patients completed a baseline questionnaire; =95% CIs for difference in treatment groups

EORTC QLQ-C30

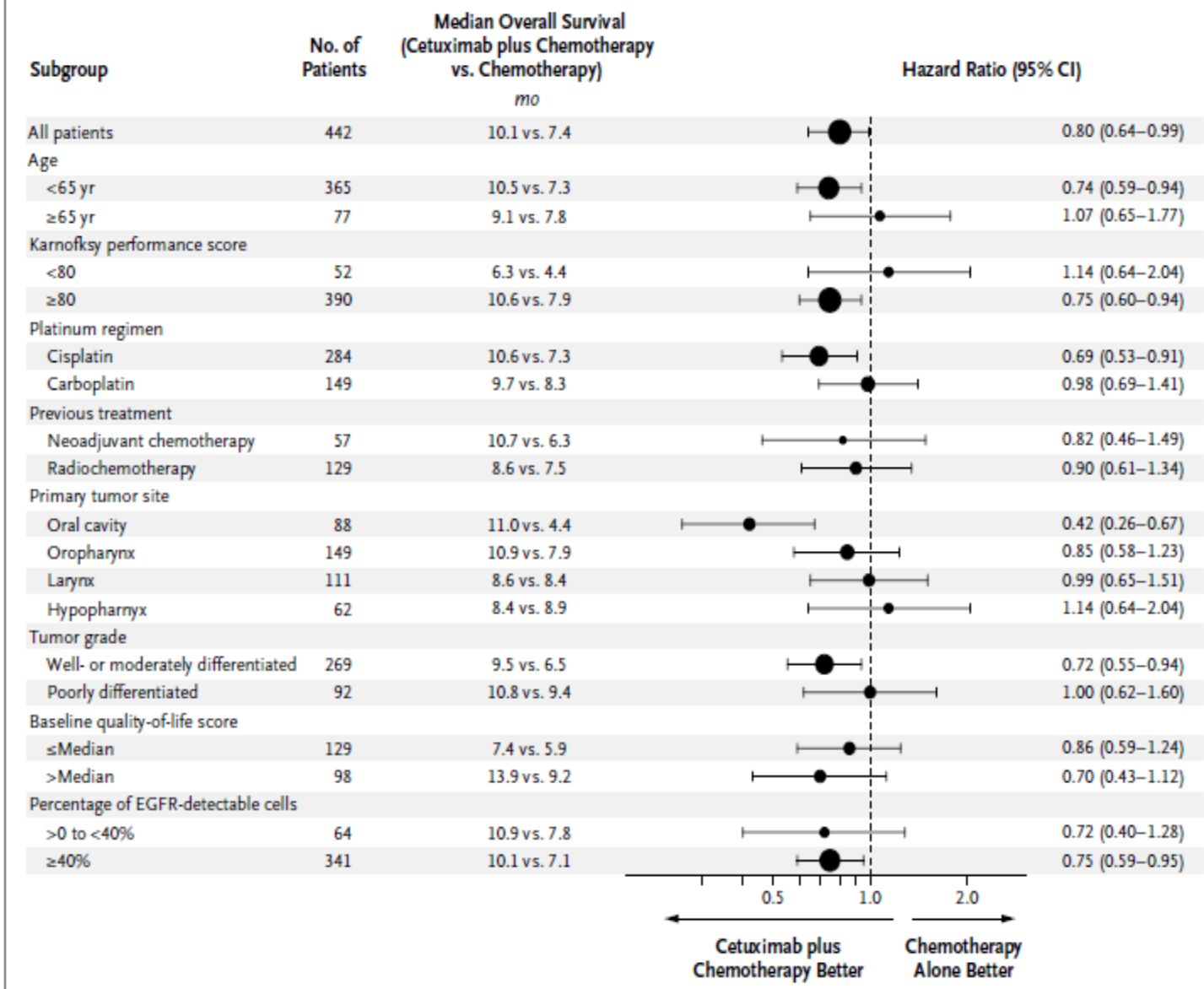
Mesía et al. Ann Oncol 2010

EXTREME: Symptom control

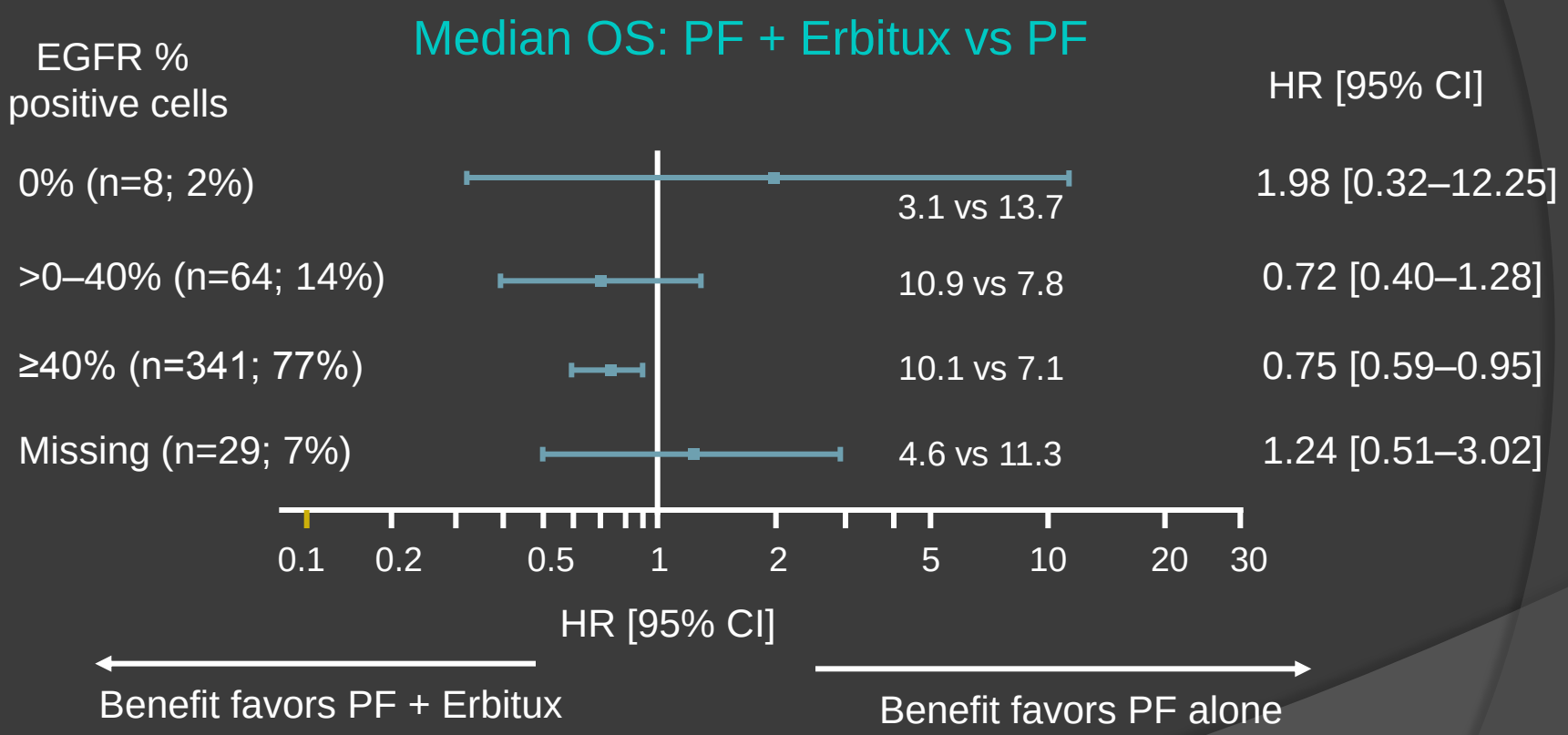


QLQ-H&N35 module

Modified from Mesía et al. Ann Oncol 2010


Subgroup
No. of Patients
Median Overall Survival (Cetuximab plus Chemotherapy vs. Chemotherapy)
mo
Hazard Ratio (95% CI)
All patients 442 10.1 vs. 7.4 0.80 (0.64–0.99)
Age
<65 yr 365 10.5 vs. 7.3 0.74 (0.59–0.94)
≥65 yr 77 9.1 vs. 7.8 1.07 (0.65–1.77)
Karnofksy performance score
<80 52 6.3 vs. 4.4 1.14 (0.64–2.04)
≥80 390 10.6 vs. 7.9 0.75 (0.60–0.94)
Platinum regimen
Cisplatin 284 10.6 vs. 7.3 0.69 (0.53–0.91)
Carboplatin 149 9.7 vs. 8.3 0.98 (0.69–1.41)
Previous treatment
Neoadjuvant chemotherapy 57 10.7 vs. 6.3 0.82 (0.46–1.49)
Radiochemotherapy 129 8.6 vs. 7.5 0.90 (0.61–1.34)
Primary tumor site
Oral cavity 88 11.0 vs. 4.4 0.42 (0.26–0.67)
Oropharynx 149 10.9 vs. 7.9 0.85 (0.58–1.23)
Larynx 111 8.6 vs. 8.4 0.99 (0.65–1.51)
Hypopharnyx 62 8.4 vs. 8.9 1.14 (0.64–2.04)
Tumor grade
Well- or moderately differentiated 269 9.5 vs. 6.5 0.72 (0.55–0.94)
Poorly differentiated 92 10.8 vs. 9.4 1.00 (0.62–1.60)
Baseline quality-of-life score
≤Median 129 7.4 vs. 5.9 0.86 (0.59–1.24)
>Median 98 13.9 vs. 9.2 0.70 (0.43–1.12)
Percentage of EGFR-detectable cells
>0 to <40% 64 10.9 vs. 7.8 0.72 (0.40–1.28)
≥40% 341 10.1 vs. 7.1 0.75 (0.59–0.95)
0.5
1.0
2.0
Cetuximab plus Chemotherapy Better
Chemotherapy Alone Better

EXTREME: EGFR expression and survival



Modified from Vermorken et al. NEJM 2008

EXTREME: Outcome and EGFR FISH data

	OS		PFS		RR	
	PF + Erbitux	**PF**	**PF + Erbitux**	**PF**	**PF + Erbitux**	**PF**
FISH+	10.5 mo	7.2 mo	6.2 mo	3.1 mo	36.0%	11.8%
FISH-	10.6 mo	7.8 mo	5.7 mo	4.1 mo	34.3%	22.3%
FISH+ vs FISH-	HR 1.02	HR 1.04	HR 0.86	HR 1.05	OR 1.08	OR 0.46
95% CI	[0.69–1.51]	[0.71–1.51]	[0.58–1.27]	[0.71–1.54]	[0.54–2.18]	[0.18–1.22]

PF + Erbitux patients: 50 FISH+, 108 FISH-; PF patients: 51 FISH-, 103 FISH-

Licitra et al. JCO 2009 [Abs 6005]

Adding Erbitux to CT in 1st-line SCCHN: Consistency in outcome

Author	Phase	N	Regimen	ORR (%)	Median PFS (months)	Median OS (months)
Burtness et al. 2005	III	117	Cis + placebo Cis + Erbitux	10 26*	2.7 4.2	8.0 9.2
Bourhis et al. 2006	I/II	53	PF + Erbitux	36	5.1**	9.8
Vermorken et al. 2008	III	442	PF PF + Erbitux	20 36*	3.3 5.6*	7.4 10.1*
Hitt et al. 2007	II	42	Pacli + Erbitux	60	5.0	NR***
Buentzel et al. 2007	II	23	Pacli/Carbo + Erbitux	56	5.0**	8.0

*Significant; **TTP: ***Median OS not reached after a median follow-up of 5.6 months

Burtness et al. JCO 2005; Bourhis et al. JCO 2006; Vermorken et al. NEJM 2008; Hitt et al. ASCO 2007; Buentzel et al. ASCO 2007

Erbitux in 1st-line SCCHN
A major clinical advance

Highlighted by ASCO:

"... the results of this trial [EXTREME] are particularly noteworthy and are changing clinical practice."

Petrelli et al. JCO 2009

Platinum/5-FU plus Erbitux in 1st-lin SCCHN Summary

- Adding Erbitux to platinum/5-fluorouracil
  - Significantly improves OS
  - Significantly increases PFS
  - Almost doubles RR
- Platinum-based CT + Erbitux is feasible in SCCHN pts
- Erbitux shows benefit regardless of EGFR expression or EGFR gene copy number
- PF + Erbitux is a new standard in 1st-line SCCHN

ESMO clinical recommendations

- This is the first time in >30 years that superiority (in terms of survival) of a new regimen over standard platinum-based combination chemotherapy has been observed.

- Cetuximab and platinum-based chemotherapy is now considered as a new standard for the treatment of R/M-SCCHN for those who are able to tolerate platinum-based combination chemotherapy regimens

Ann Oncol 2009;20 Suppl 4:121-122

EGFR-targeting therapy in HNSCC

Drug	Phase	Reference	Response (%)
Cetuximab	II	Vermorken 2007 [61]	13
Erlotinib	II	Soulieres 2004 [77]	4.3
Gefitinib	II	Cohen 2003 [78]	10.6
	II	Cohen 2005 [79]	1.8
	II	Kirby 2006 [80]	8.5
	III[a]	Stewart 2009 [81]	7.9
Lapatinib	II	Abidoye 2006 [82]	0
BIBW 2992	II[a]	Seiwert 2010 [83]	21.7

J. B. Vermorken, et al. Annals of Oncology 2010; 21: vii252-vii261.

BIBW 2992

- highly potent inhibitor of EGFR/erbB1 and erbB2. It retains activity for EGFRvIII mutation and provides a sustained blockage of receptor and inhibition of tumor cell proliferation

BIBW 2992 versus cetuximab in patients with metastatic or recurrent HNSCC, a randomized, open-label phase II study

- a randomized, open-label, phase II study of BIBW 2992 versus cetuximab in R/M-SCCHN patients after failure of platinum-containing therapy.
- The primary end point of that study was tumor shrinkage of target lesions before any crossover.
- Diarrhea, dehydration, epistaxis and asthenia occurred more frequently with BIBW 2992, but also tumor shrinkage occurred more frequently with BIBW 2992 than with cetuximab (OR 21.7% versus 13.3%).
- Median PFS with BIBW 2992 was 16 weeks (95% CI 10–19) and 10 weeks (95% CI 8–17) with cetuximab.
- BIBW is the first TKI to demonstrate antitumor activity in SCCHN that appears to be at least comparable to cetuximab.

Seiwert TY, et al. J Clin Oncol 2010;28 15 Suppl. Abstr 5501.

Gefitinib in SCCHN: Response Data

Response	n (%)*
CR	1 (2)
PR	4 (9)
SD	21 (45)
PD	22 (47)

- Gefitinib 500 mg QD PO
- N = 47 eligible patients
- Half received previous palliative treatments
- ORR: 11% (95% CI: 3.5-23.1)
- Disease control (CR + PR + SD): 53%
- Median survival of 8.1 mos
- 13% had disease control ≥ 6 mos
- Skin toxicity strong predictor of survival

Cohen EE, et al. J Clin Oncol. 2003;21:1980-1987.

VEGF-targeting therapy in HNSCC

(1) Avastin-based chemotherapy combination. Vessel normalization, decreased intra-tumoral pressure, enhanced chemotherapy delivery, and suppression of BM-derived EPC.

Tarceva and Avastin (chemo-naïve or 1st line Tx failure)

*4/48 CR; 3/48 PR; DCR near 50%; PFS 4 months; OS 7.1 months (Lancet Oncology 2009)

***Response associated with high ratios of tumor pVEGFR2/total VEGFR2 endothelial pEGFR/total EGFR**

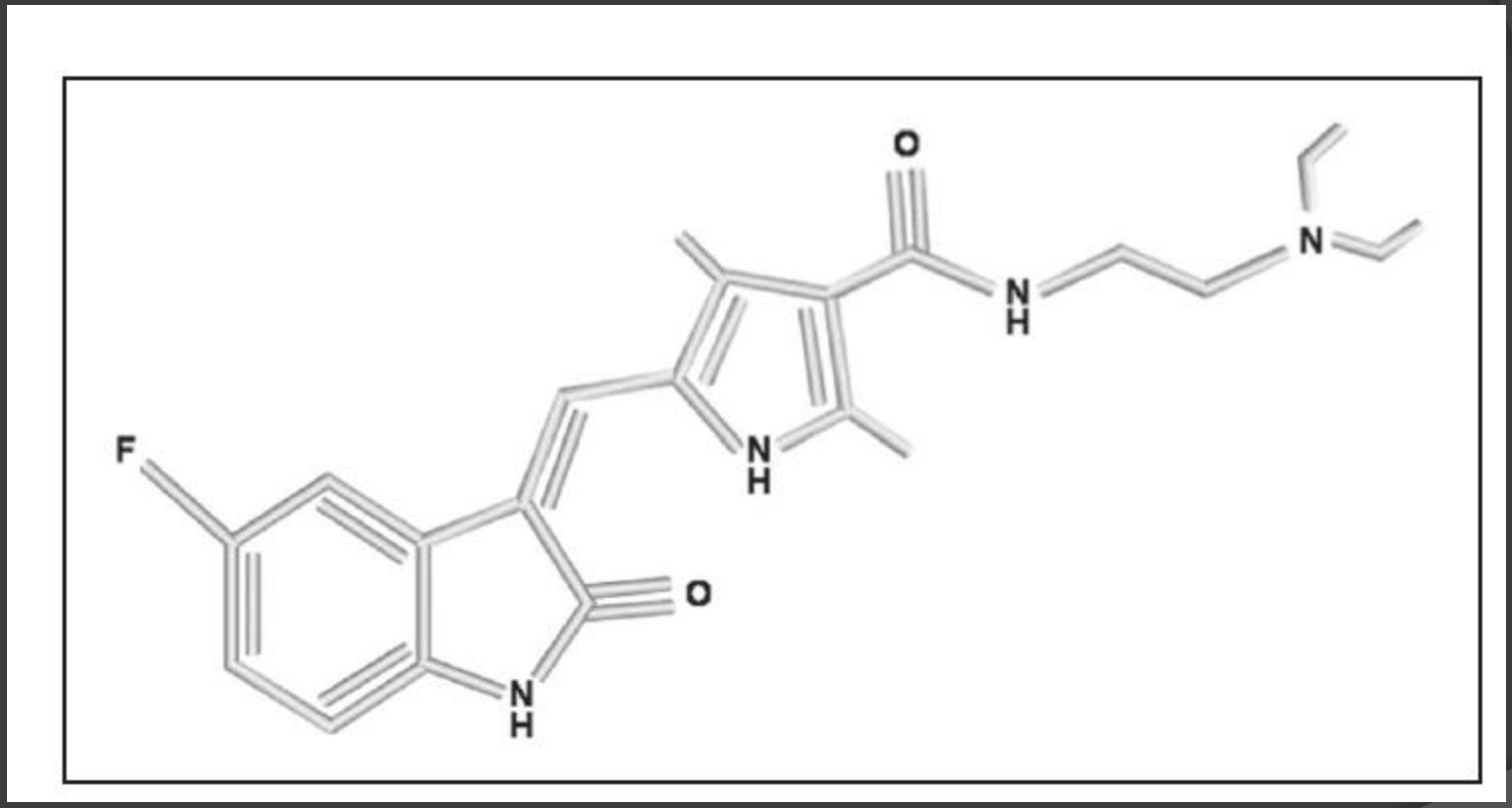
Avastin and Alimta (chemo-naïve; oral cavity 18%)

*30% RR and 86% stabilization.
Time to progression 4.9 months; OS 11.5 months(JCO 2011)

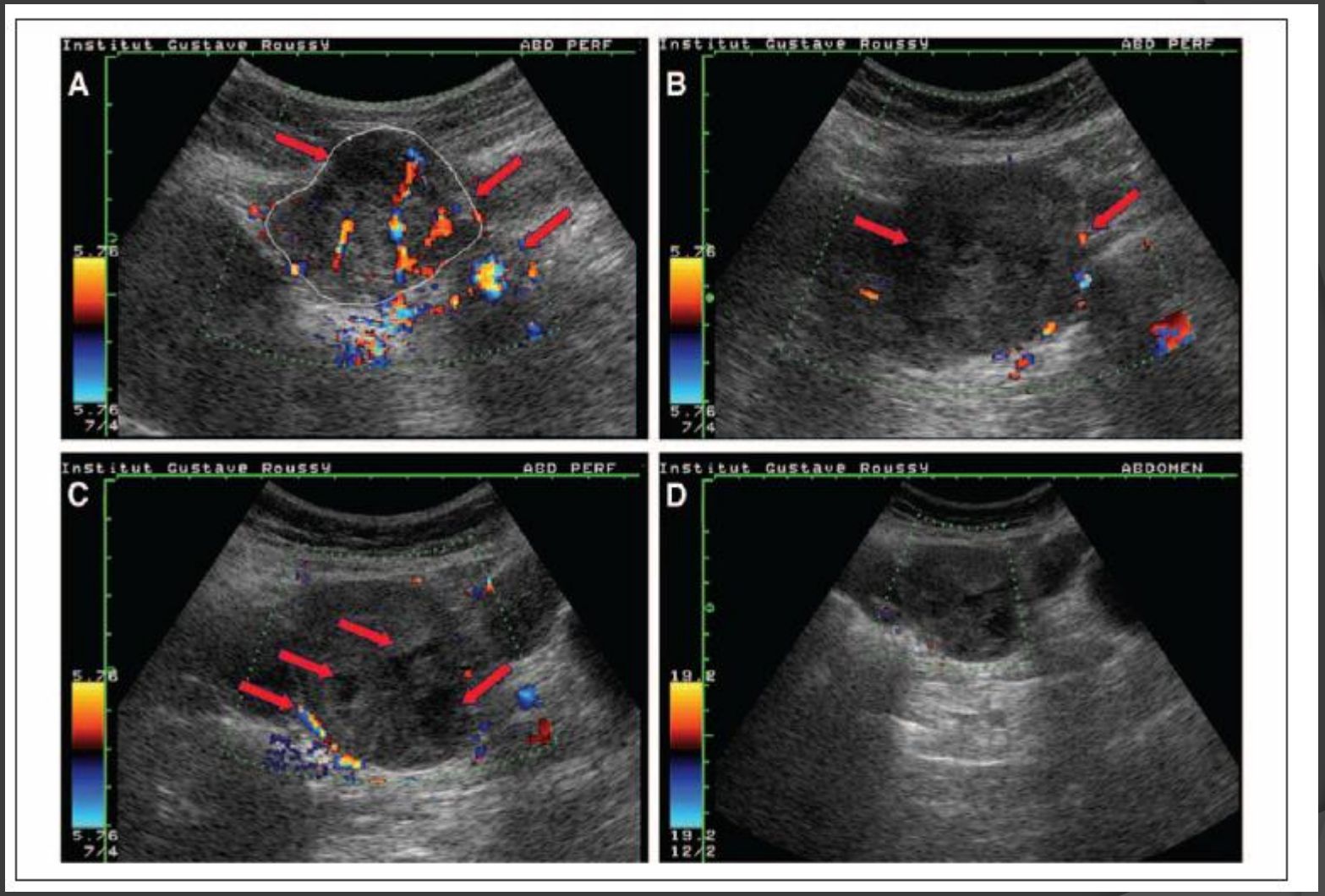
Avastin-PF or -IE in NTUH

(2) Multi-targeted TKI.

Sunitinib

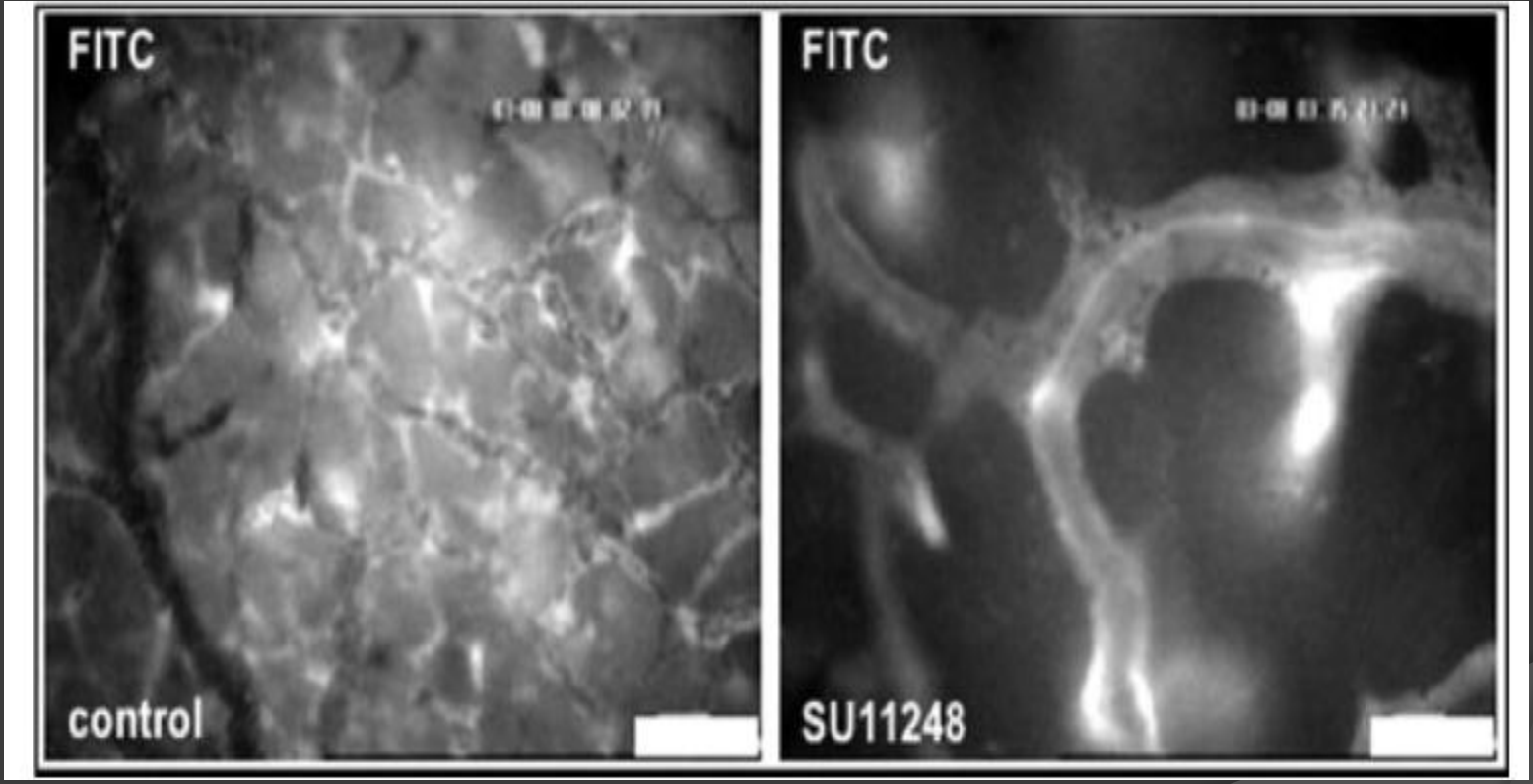


Multi-targeted TKI towards VEGFR1, VEGFR2, PDGFR, c-KIT, and FLT-3.



After sunitinib, tumor necrosis increased and vessel density decreased.

Vessel normalization also seen in sunitinib use.



Marcus Czabanka, et al. IJC 2009; 124: 1293-1300.

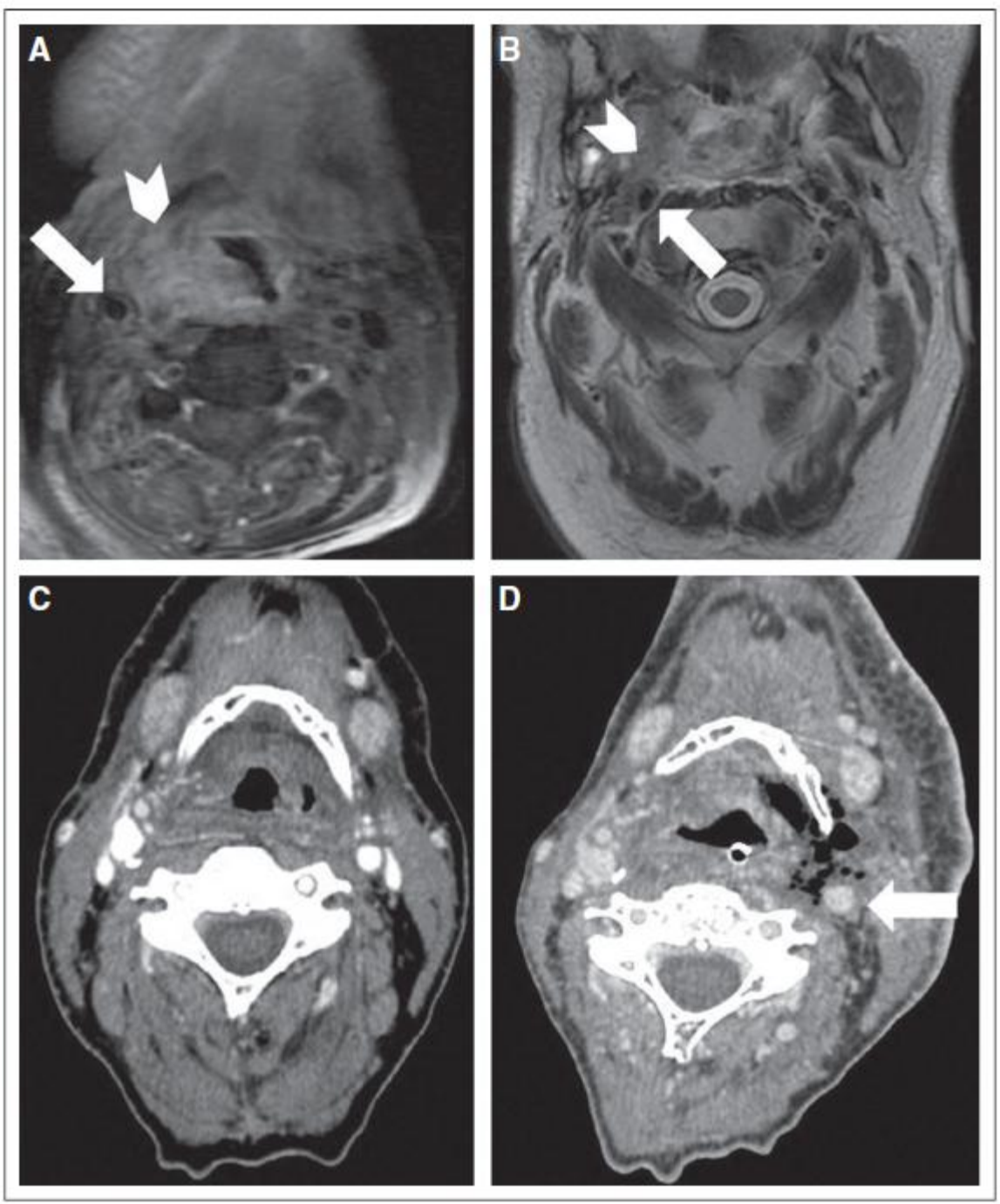
Sunitinib in advanced HNSCC

***Good response but bleeding events to cause early closure.**

Tumor necrosis/fistula in neck, close to major vessels, and maybe too advanced status.** ***Too responsive!!!

PDFGR inhibition to cause pericyte maturation arrest and fragile vessels---** ***rupture.

Carotid artery distance



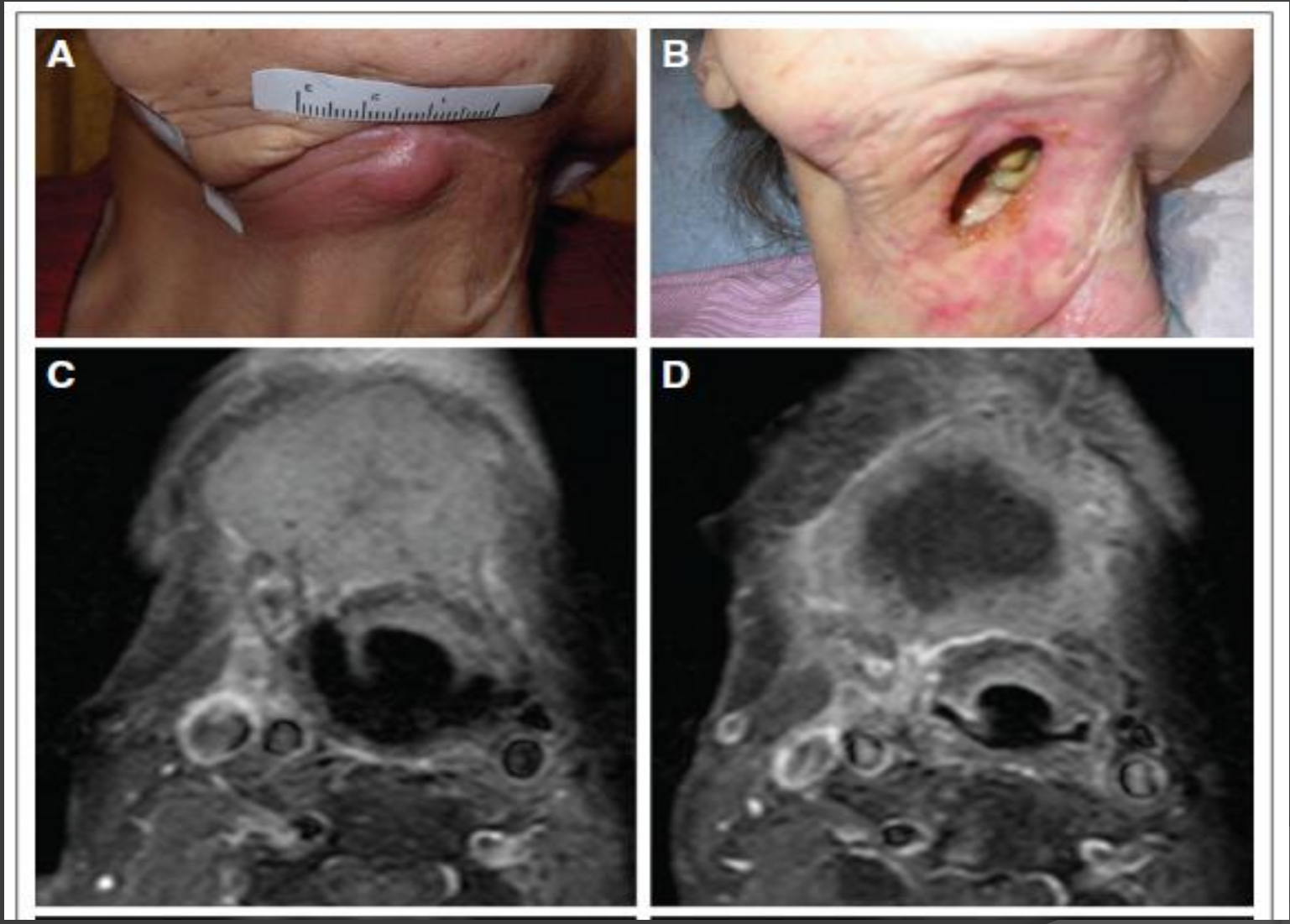
PR in 1
SD in 18
Unconfirmed PR: 5
Minor response: 6

Disease control rate: 19/38(50%)

Grade 5 bleeding: 4

Necrosis

Tumor skin ulcers & fistulas: 15



Very similar to NTUH experiences.

GORTEC value

(1)Show activity of sunitinib in advanced HNSCC, even in 2nd line.

(2)Present tumor death patterns of sunitinib and imply bleeding events.

(3)Possible biomarkers choice.

Good patient selection, avoiding bleeding events, and biomarkers development.

HNSCC

(1) Resectable and operable disease: op

(2) Unresectable/inoperable or organ preservation: CCRT

(3) Multiple modality in locally advanced dz

HNSCC

*Resectable disease: operation

After op, high risk P't(multiple LNs, LVI, PNI, extracapsular invasion, margin +, poor differentiated): adjuvant CCRT

*Locally advanced disease: induction CT (PF, TPF, MEPFL, PF+Erbitux, TPF+Erbitux) followed by op +/- adjuvant CCRT

Unresectable HNSCC or for organ preservation

(1) **CCRT** better than RT or induction CT then RT in organ preservation for larynx/hypopharynx cancers.

(2) CCRT still many pitfalls: choking, poor chest care

(3) **Induction TPF before CCRT: better survival(TAX 324)**

(4) **Erbitux roles in induction and CCRT**

Metastatic HNSCC

(1) PF standard

(2) **PF + Erbitux(survival benefit, 10 months)**

(3) Taxane, CPT-11, oxaliplatin, gemcitabine, Navelbine, Avastin, Sutent: second line choices

(4) **5-year survival only 50% in stage I-IVB**
Still poor outcomes

HNSCC

(1) Prevention most important.

(2) Still poor outcomes.

Multiple modality Tx strategies and new potential powerful agents needed

THANK YOU!