WORKSHOP

Trattamenti integrati nella conservazione d'organo: indicazioni e risultati

F. Miccichè

Divisione di Radioterapia

Policlinico A. Gemelli UCSC- Roma

Timing, Drug, Age

Meta analysis

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Evidence 1

Concomitant **RT-CT**

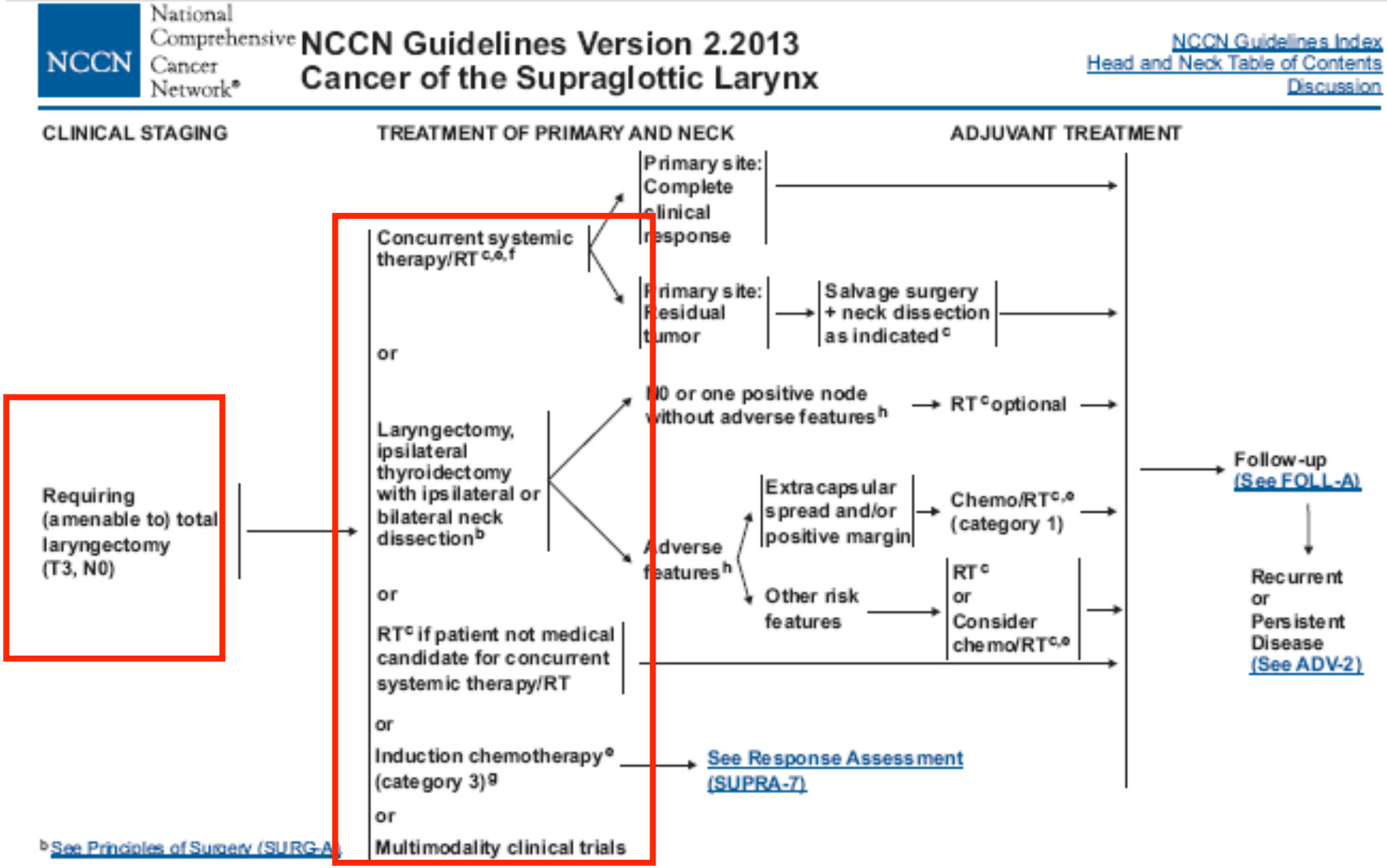
CDDP based **chemotherapy**

Age ***≤ 60 aa***

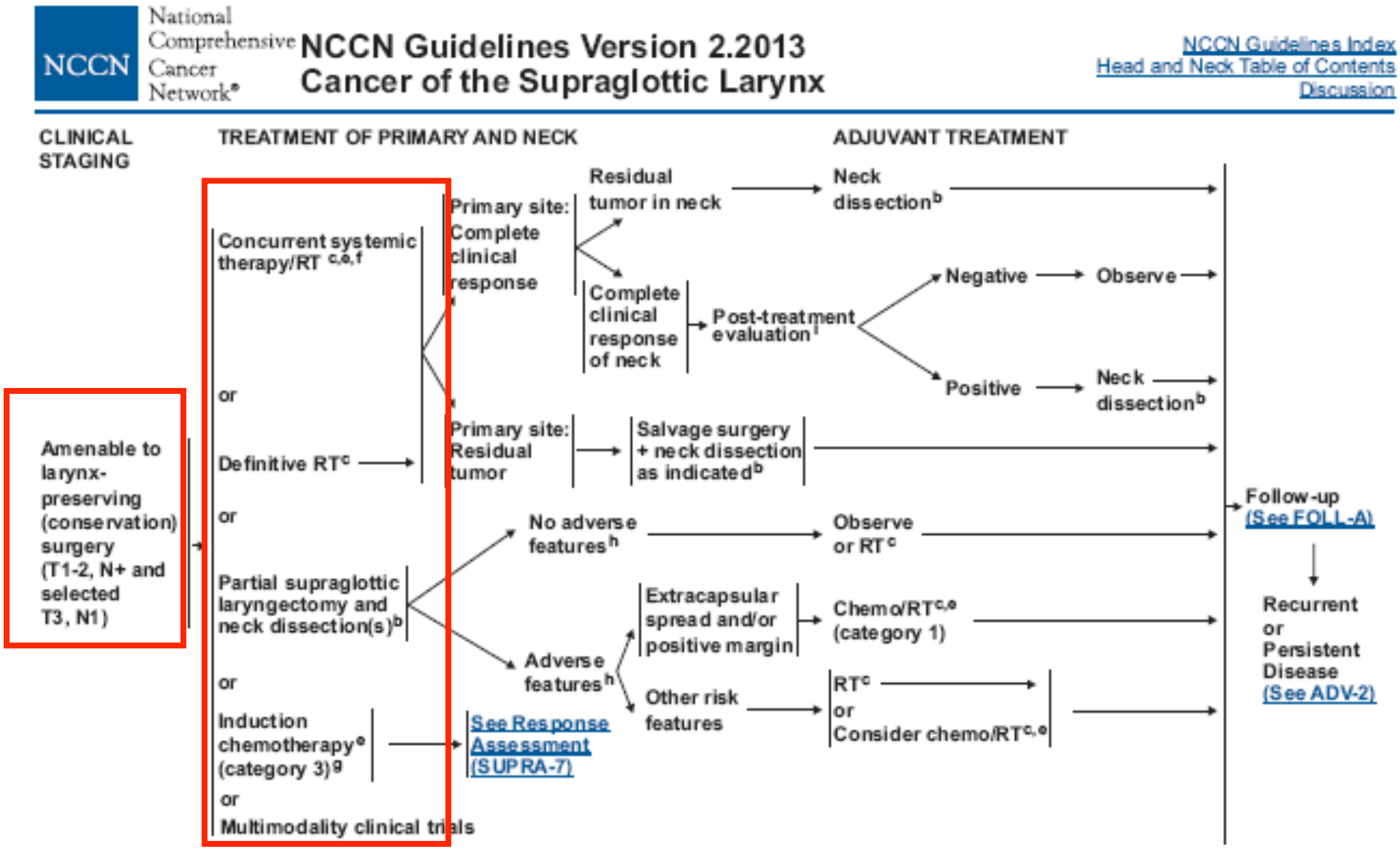
[a] Biostatistics and Epidemiology Department; and [b] Radiotherapy Department, Institut Gustave Roussy, Villejuif, France; [c] Head and Neck Surgery, Hôpital Foch, Suresnes, France

Pignon JP et Al. Radiot Oncol, 2009, Blanchard P. et Al. 2011

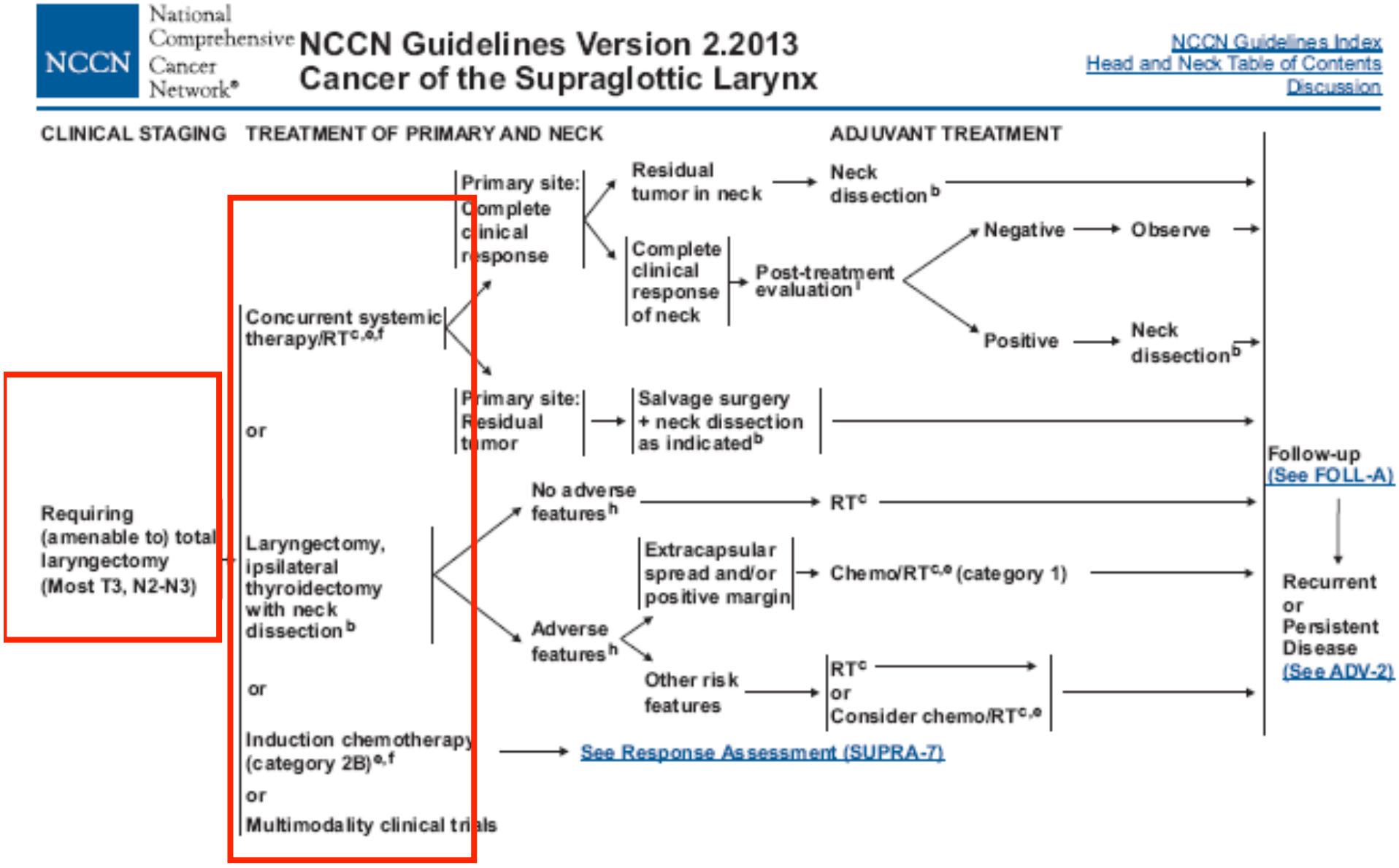
NCCN guidelines (1)



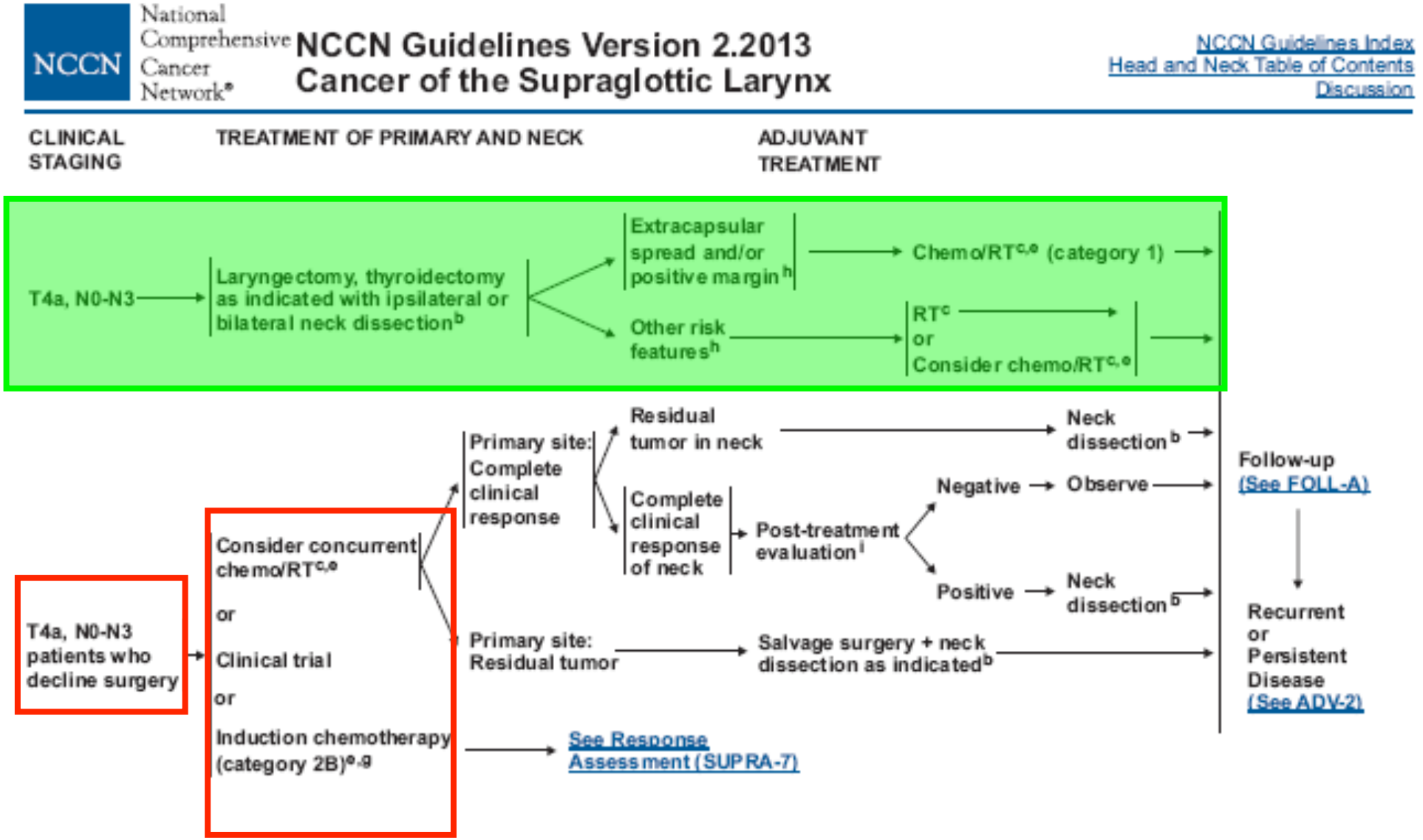
NCCN guidelines (2)



NCCN guidelines (3)



NCCN guidelines (6)



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CRITICAL REVIEWS IN

ARTICLE IN PRESS

Radiotherapy and Oncology xxx (2013) xxx–xxx

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Radiother… …ology

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ELSEVIER

Multidisciplinary rewiew

Review

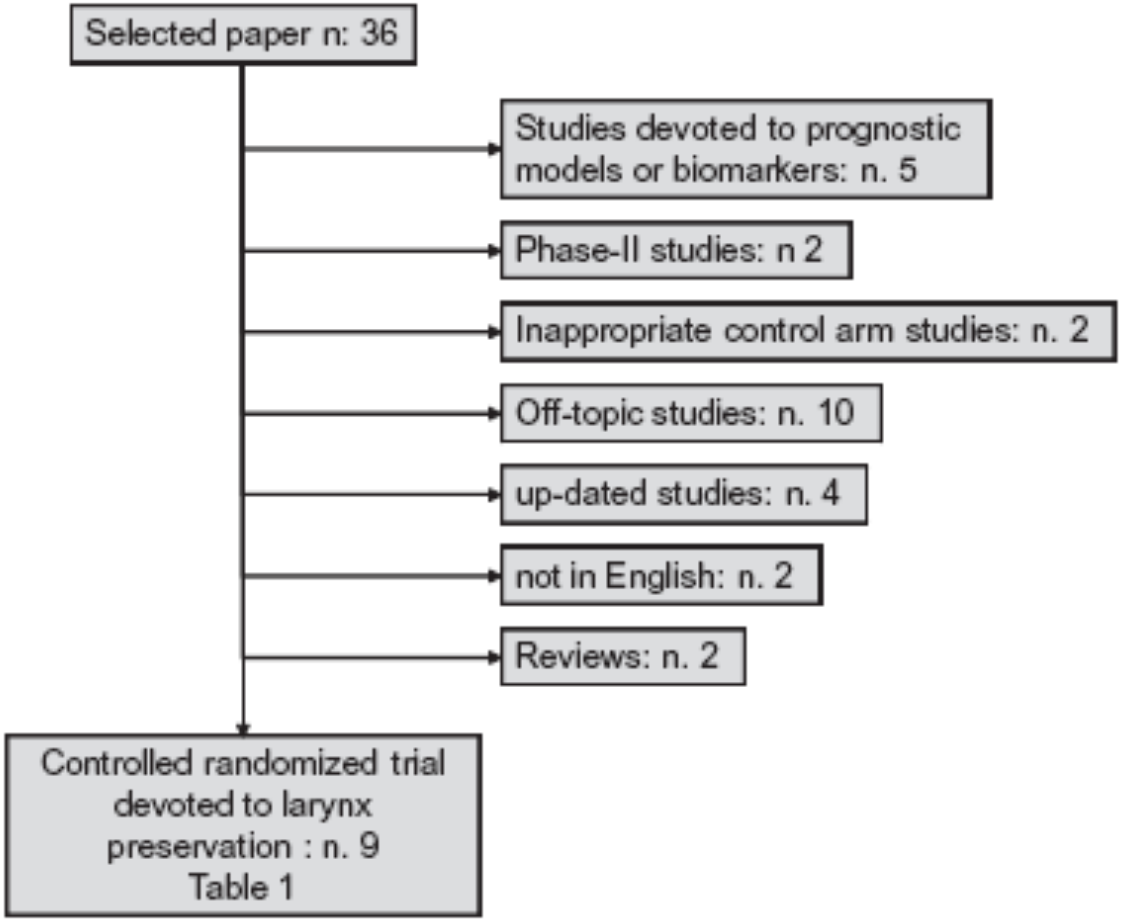
A systematic … …rrent and emerging approaches in the field of larynx prese… …ll

Nerina Denaro [a,*], Elvio Grazioso Russi [b], Jean Louis Lefebvre [c], Marco Carlo Merlano [a]

[a] Oncology Department; [b] Radiation Oncology, ASO Santa Croce e Carle, Italy; [c] Head and Neck Surgery Department, Centre Oscar at the Lambret, France

… …, Emmanuel Babin, Philippe Lang, Francois Janot, Gilles Calais, Pascal Garaud, and Etienne Bardet

Papers selection in Medline



Denaro N. et Al. Radiotherapy and Oncology, August 2013

Papers selection in Medline

Table 1
Phase II–III randomized clinical trials on larynx preservation.

Author (year)	N. pts	Site	Stage	Treatment	LP	*P*	OS
VALCSG [5]	332	Larynx	Stage III–IV	PF → RT vs. S → RT	64%	NA	68% at 2 y 68% at 2 y
EORTC 24891 [7]	202	Hypo pharynx	Stage II–IV	PF → RT vs. S → RT	22% at 5 y	NA	38% at 5 y; 13.1% at 10 y PFS at 10 y = 10.8% 33% at 5 y 13.8% at 10 y PFS at 10 y = 8.5%
GETTEC [14]	68	Larynx	Stage II–IV	PF → RT vs. S →RT	42% (median 8 y)	NA	69% at 2 y 84% at 2 y *P* = 0.006
RTOG 91-11 [8]	547	Larynx	Stage III and IV	PF → RT vs. CRT vs. RT	71% at 5 y; 67.5% at 10 y 84% at 5 y; 82% at 10 y 66% at 5 y 64% at 10 y	0.005 <0.001	59% at 5 y 39% at 10 y 55% at 5 y 27.5% at 10 y 54% at 5 y 31.5% at 10 y
GORTEC 2000-01 [13]	213	Larynx Hypo pharynx	Stage III and IV	PF → RT vs. TPF → RT	57% at 3 y 70% at 3 y	0 .03	60% at 3 y 60% at 3 y
EORTC 24954-22950 [50]	450	Larynx Hypo pharynx	Stage III and IV	PF → RT vs. aPF – RT for 6 weeks	48% at 5 y 52% at 5 y	0.12	53% at 5 y 60% at 5 y
Posner [15]	166	Larynx Hypo pharynx	Stage III/IV (74% resectable)	PF → CRT vs. TPF → CRT	32% LFS a 3 y 52% LFS a 3 y	0.07	40% at 3 y 57% at 3 y
TREMPLIN [17]	153	Larynx Hypo pharynx	Stage III–IV	TPF → CRT vs. TPF → Cet + RT	93% a 3 months 96% in 3 months	NS	85% at 1.5 y 86% at 1.5 y
Prades [51]	71	Pyriform sinus cancer	Stage III–IV	PF•2 q 21 → S or RT vs. P-RT	68% for IC At 2 y 92% for CRT at 2 y	0.016	DFS 36% at 2 y DFS 41% at 2 y

Abbreviations: Y = Year; LP = larynx preservation; OS = overall survival; S = surgery; P = platinum 5FU = fluorouracil; PF = platinum-5FU; T = Taxotere; m = months; LFS = laryngectomy free survival; CRT = chemoradiation; aPF – RT = alternating Platinum-Fluorouracil and RT; Cet = Cetuximab; IC = induction chemotherapy; DFS = disease free survival; NA not applicable; NS = not significative.

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Endpoints selection

Table 2
Endpoints.

Study	Primary End Point	Secondary End Points
VALCSG [5]	LP	OS Tumor response Patterns of relapse
EORTC 24891 [7]	LP	OS Survival with functional larynx cancer related death PFS
GETTEC [14]	OS PFS	LP
RTOG 91-11 [8]	LP	LFS laryngeal function preservation (speech and swallowing)*
GORTEC [12]	LP	OS DFS, laryngoesophageal dysfunction-free survival *
EORTC 24954 [50]	Survival with functional larynx. Larynx in place, without tumor, tracheotomy or feeding tube	PFS
TREMPLIN [17]	LP	Larynx function preservation, OS feasibility of salvage surgery tolerance to treatment

Update at 10 years.
Abbreviations: OS = overall survival; PFS progression free survival; LP = larynx preservation; LFS = Laryngectomy free survival; DFS = Disease free survival.

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Acute and Late toxicities

Acute and late toxicities from analyzed trials.

Study	Treatment Arm	Acute toxicity G3–4%	Late toxicity G3–4%
VALCSG [5]	Surgery arm	TD 5; mucositis 24%	NR
	IC arm	TD 3; mucositis 38%	NR
EORTC 24891 [7]	IC arm	Treatment stop 7 toxic effects; 1TD	NR
	Surgery arm	Treatment stop 1 vascular disease +1 depressive illness	NR
GETTEC [14]	IC arm	Digestive 3%; hematological 1%	NR
	Surgery arm	Digestive 0%; hematological 0%	NR
RTOG 91-11 [8,9]	IC arm	Hematological 52%*; mucositis = 34%*; laryngeal 13%	IC arm → skin toxicity = 5–0%; mucosal = 5–0%; Larynx toxicity = 10–6%; dysphagia = 15–3%; subcutaneous = 11–1%
	CRT arm	Hematological = 47%; mucositis = 43%; laryngeal 18%	CRT arm → skin toxicity = 1–0%; mucosal = 3–0%; Larynx toxicity = 17–6%; dysphagia = 22–3%; subcutaneous = 9–1%
	RT arm	Hematological = 3%; mucositis = 34%; laryngeal 16%	RT arm → skin toxicity = 2–1%; mucosal = 3–1%; Larynx toxicity = 21–3%; dysphagia = 22–2%; subcutaneous = 9–2%
GORTEC[12]	TPF arm	5 TD; neutropenia G4 = 31.5%; infections G3 = 10.9%; stomatitis = 4.6%; thrombocytopenia 1.8%; G4 creatinine elevation 0%	TPF arm → G4 larynx toxicity 6.2%; mucosal 1%; xerostomia = 6.1%; subcutaneous = 4.0%
	PF arm	2TD; neutropenia G4 = 17.6%; infections G3 = 5.8%; stomatitis = 7.8%; thrombocytopenia 7.8%; G4 creatinine elevation 2.0%	PF arm → G4 larynx toxicity 13.6%; mucosal 0%; xerostomia = 2.2%; subcutaneous = 6.6%
EORTC 24954 [50]	Sequential arm	Mucosite 32%; skin reaction 6%; dysphagia 33%	Sequential arm → mucosal 25%; permanent neuropathy = 14%; subcutaneous = 31%
	Alternating arm	Mucosite 21%; skin reaction 0%; dysphagia 20%	Alternating arm → mucosal 28%; permanent neuropathy = 11%; subcutaneous = 28%
TREMPLIN [17]	CDDP arm	Mucositis 43–3% In field toxicity 14–1%	CDDP arm → mucosal 3.5%, xerostomia 10.3%, subcutaneous fibrosis 7.0%, neuropathy 3.4%, laryngoesophageal 8.6%
	Cet arm	Mucositis 43–2% In field toxicity 52–5%	Cet arm → mucosal 1.8%, xerostomia 8.9%, subcutaneous fibrosis 2.0%, neuropathy 0%, laryngoesophageal 9.0%

Abbreviations: TD = toxic deaths; NR = not reported; G = grade; CDDP = cisplatin; IC = induction chemotherapy; Cet = Cetuximab; * = during CT.

Denaro N. et Al. Radiotherapy and Oncology, August 2013

Role of organ preservation surgery

Table 3
Organ preservation surgical techniques.

Technique	Type	Description	Indication	Outcome
Trans oral laser surgery	E	Removal of the small and medium tumors through the mouth from the voice box with no external incisions [52].	- Complete endoscopic visualization of T – <3 mm extension to the cVC - No arytenoid involvement (except vocal process) - Subglottic extension <5 mm - Supraglottic extension no further than lateral extension of ventricle. - Mobile VF without cartilage involvement	Good voice quality and swallowing Low complication rates and costs. Shorter hospitalization, without compromising outcomes (5 year DSS = 95% DFS 63% LP 75%) [41]
SCL	O	Removal of the upper half of the voice box, no VCs: entire thyroid cartilage, bilateral true and false vocal cords, ventricles, paraglottic and preepiglottic spaces, epiglottis, hyoid bone and one arytenoid	More extensive cancers requiring excision of both the upper and mid-portion of the larynx are usually amenable to this procedure	DFS = 84.5% 66.7% of failures were successfully treated with salvage total laryngectomy Complications includes swallowing disorders, hoarse-rough-breathy voice. Up to 17.5%. Aspiration Pneumonia and neo-laryngeal edema. [53]
VPL	O	Removal of one vocal fold - from anterior commissure to vocal process ½ of opposite vocal fold may also be removed if involved; Ipsilateral false vocal cord; Ventricle Paraglottic space (and overlying thyroid cartilage).	Not indicated for large T3 – T4 lesions, or intrarytenoid or cricoarytenoid joint, bilateral arytenoid cartilage and thyroid cartilage involvement or bilaterally diminished VC mobility; supraglottic extension >10 mm at the anterior commissure or 5 mm at the vocal process of the arytenoid; poor pulmonary function	Allows the use of intraoperative frozen sections [54] Achieves near-normal voice and swallowing Postoperative function after removal of the upper 2/3's of the voice box is good while providing excellent cancer control
SHPL	O	Removal of the whole epiglottis, false cords, aryepiglottic folds, pre epiglottic space, and upper half of the thyroid cartilage +/– hyoid bone	Not indicated for involvement of cricoid and thyroid cartilage, VCs fixity, impaired tongue base mobility, cancer within 1 cm of circumvallate papilla	High rates of morbidity and mortality following Rt Long term swallowing failure [55]
TORS	E	Endoscopic robotic resections	Small and intermediate stage larynx. Except for patients with a narrow mandibular arch, anteriorly displaced larynges, or intact dentition	Allow realistic 3D imaging, motion scaling, tremor infiltration High cost [56] TORS has improved visualization and access compared with TLM procedures [56]
Powered microdebrider excision	E	Ablation with microdebrider	Excision of small cancer with a low recurrence rate [57]	No impairment of swallowing or speech. [57]
Coblation excision	E	Removal through ablation	Small intermediate laryngeal and hypopharyngeal cancer	Minimal or no damage to the surroundings tissue, lack of charring in the tissue bed, hemostasis and superior post op pain control [58]
TLM	E	Removal through laser micro surgery	Applied to pharyngeal and laryngeal tumors Not indicated to large T3–4 owing to access issues and the inability to suture tissues closed and to limitation of surgical manipulation of the tissues [40]	Comparable rates of tumor control to open and nonsurgical treatments [32]

Abbreviations: E = endoscopic; O = Open; T = tumor; VCs = vocal cords; cVC = controlateral vocal cord; VF = vocal folds DSS = disease – specific survival; Rt = radiotherapy; DFS = disease free survival; LP = Laryngeal preservation; OS = survival; y = year; SCL = Supracricoid Laryngectomy; SHPL = Supraglottic Horizontal Partial Laryngectomy; VPL = Vertical partial Laryngectomy; TORS = Transoral Robotic Surgery; TLM = Transoral laser microsurgery.

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Conclusion

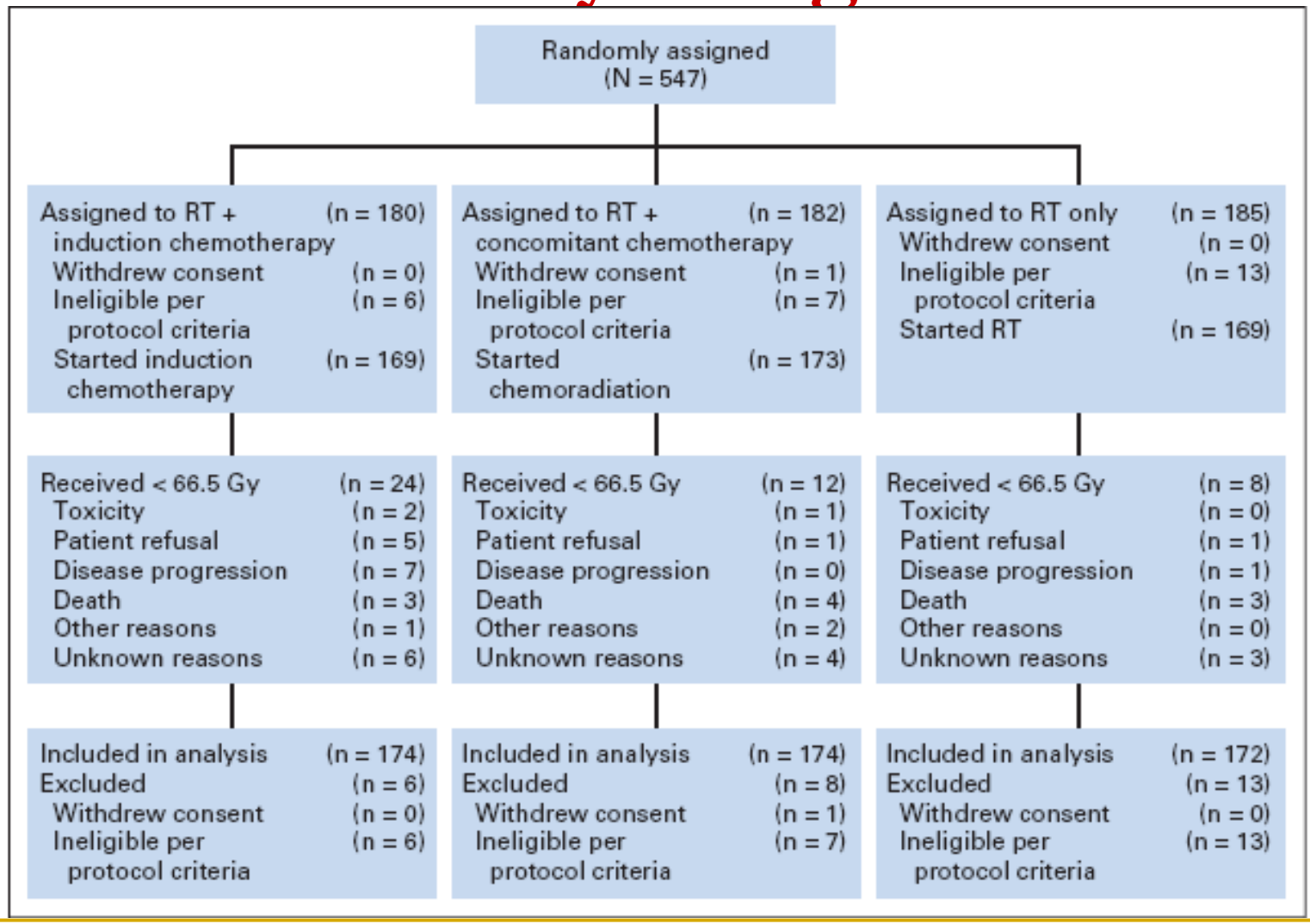
Not one standard larynx preservation treatment accepted worldwide

Heterogeneity for population and endpoint

***Chemotherapy and Radiation Therapy cannot be offered to all patients*, because of acute and possible late toxicities.**

Denaro N. et Al. Radiotherapy and Oncology, August 2013

RTOG 91-11: study design



Forastiere AA et Al. J Clin Oncol 2013

RTOG 91-11: results

Table 1. The 5- and 10-Year Estimates of Efficacy End Points

End Point	RT + Induction Chemotherapy		RT + Concomitant Chemotherapy		RT Alone	
	Estimate (%)	95% CI (%)	Estimate (%)	95% CI (%)	Estimate (%)	95% CI (%)
Laryngectomy-free survival						
5 years	44.1	36.6 to 51.6	47.0	39.5 to 54.5	34.0	26.8 to 41.3
10 years	28.9	21.9 to 36.0	23.5	16.8 to 30.3	17.2	11.2 to 23.3
Larynx preservation						
5 years	70.8	63.9 to 77.6	83.6	78.1 to 89.2	65.8	58.7 to 73.0
10 years	67.5	60.4 to 74.6	81.7	75.9 to 87.6	63.8	56.5 to 71.1
Local control						
5 years	58.2	50.8 to 65.6	71.1	64.3 to 77.9	53.6	46.1 to 61.1
10 years	53.7	46.1 to 61.2	69.2	62.3 to 76.1	50.1	42.5 to 57.7
Locoregional control						
5 years	54.8	47.3 to 62.3	67.7	60.7 to 74.7	51.2	43.7 to 58.8
10 years	48.9	41.3 to 56.5	65.3	58.1 to 72.4	47.2	39.6 to 54.8
Distant control						
5 years	85.3	79.9 to 90.6	86.4	81.2 to 91.6	78.0	71.7 to 84.3
10 years	83.4	77.7 to 89.0	83.9	78.2 to 89.5	76.0	69.4 to 82.5
Disease-free survival						
5 years	37.7	30.4 to 45.0	38.0	30.8 to 45.3	28.0	21.1 to 34.8
10 years	20.4	14.0 to 26.7	21.6	15.2 to 28.0	14.8	9.2 to 20.3
Overall survival						
5 years	58.1	50.6 to 65.5	55.1	47.6 to 62.6	53.8	46.1 to 61.4
10 years	38.8	31.2 to 46.3	27.5	20.4 to 34.5	31.5	24.1 to 39.0

Abbreviation: RT, radiation therapy.

Forastiere AA et Al. J Clin Oncol 2013

RTOG 91-11

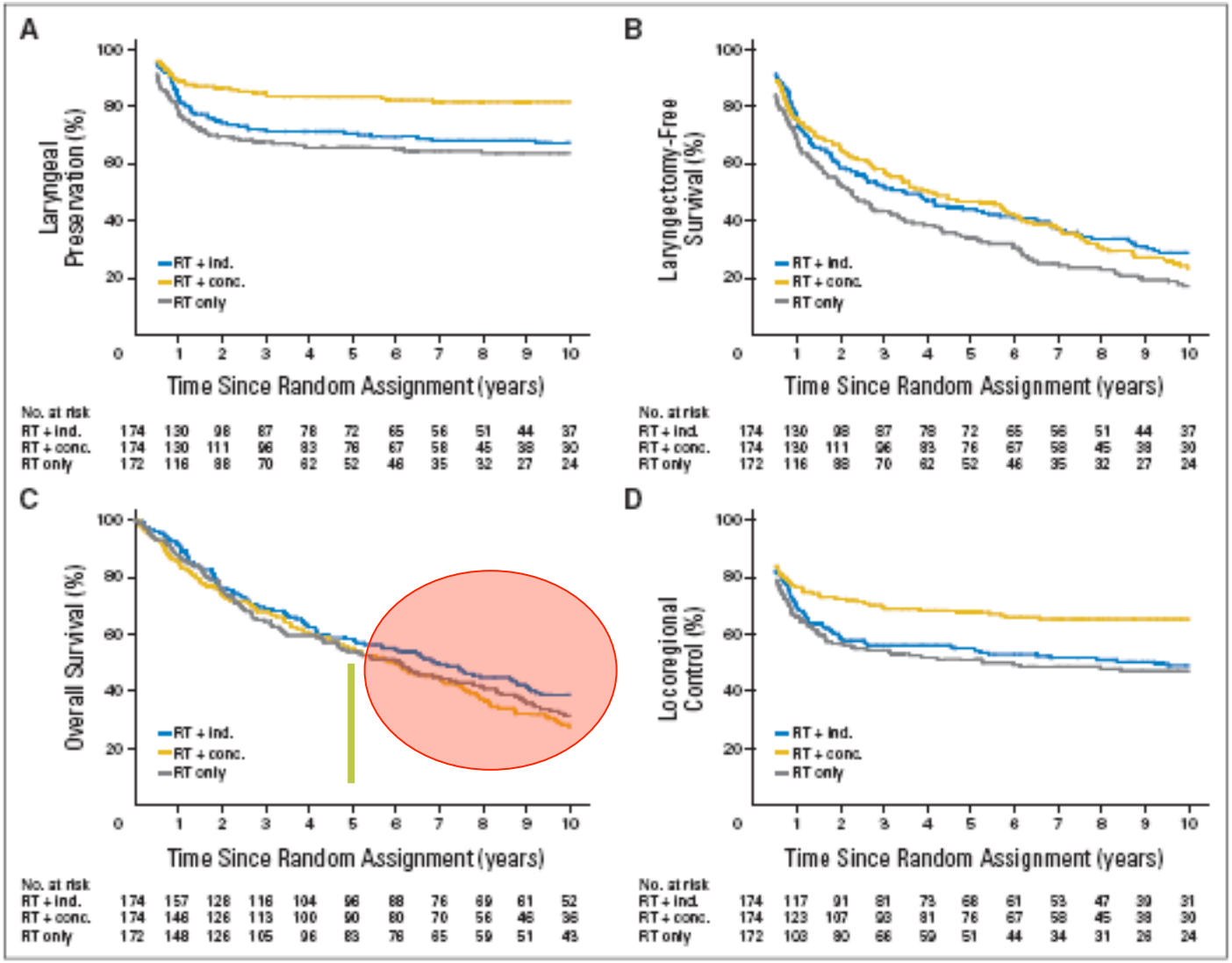
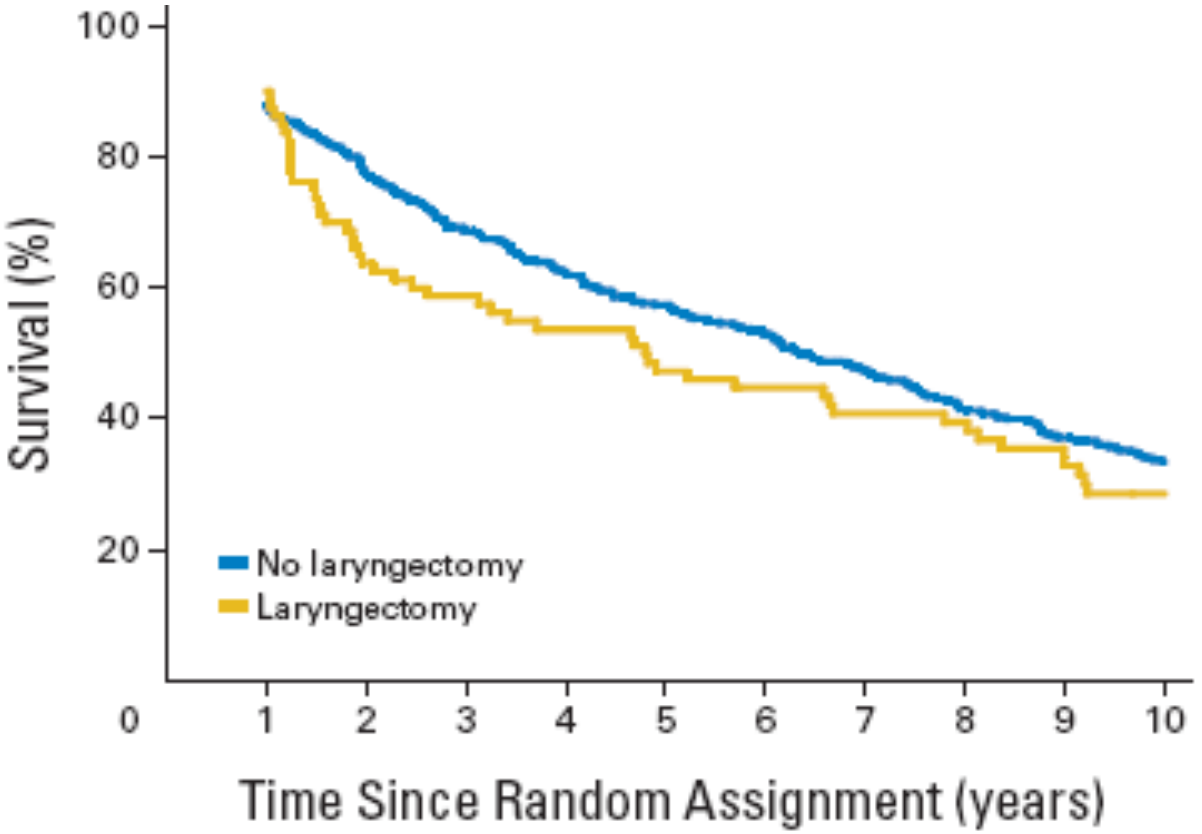


Fig 2. (A) Laryngeal preservation, (B) laryngectomy-free survival, (C) overall survival, and (D) locoregional control according to treatment group. conc., concomitant; ind., induction; RT, radiation therapy.

Forastiere AA et Al. J Clin Oncol 2013

RTOG 91-11



No. at risk											
No laryngectomy	440	379	329	287	258	232	210	180	154	133	112
Laryngectomy	80	72	51	47	42	37	34	31	30	25	19

Survival according to whether or not a laryngectomy was performed in the first year: all treatment arms combined (*P* .21)

Forastiere AA et Al. J Clin Oncol 2013

Taxanes

ORIGINAL ARTICLE

Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer

Marshall R. Posner, M.D., Diane M. Hershock, M.D., Ph.D., Cesar R. Blajman, M.D.,

ORIGINAL ARTICLE

Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Eva Remenar, M.D., Carla van Herpen, M.D., Ph.D.,

N Eng J Med, 2007

European Point of View: GORTEC 2000-01

Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation

Yoann Pointreau, Pascal Garaud, Sophie Chapet, Christian Sire, Claude Tuchais, Jacques Tortochaux, Sandrine Faivre, Stephane Guerrif, Marc Alfonsi, Gilles Calais

Background Chemotherapy with cisplatin (P) and 5-fluorouracil (F) followed by radiotherapy in patients who respond to chemotherapy is an alternative to total laryngectomy for patients with locally advanced larynx and hypopharynx cancer. Data suggest that docetaxel (T) may add to the efficacy of PF. The objective of this trial was to determine whether adding T to PF could increase the larynx preservation rate.

Methods Patients who had larynx and hypopharynx cancer that required total laryngectomy were randomly assigned to receive three cycles of TPF or PF. Patients who responded to chemotherapy received radiotherapy with or without additional chemotherapy. Patients who did not respond to chemotherapy underwent total laryngectomy followed by radiotherapy with or without additional chemotherapy. The primary endpoint was 3-year larynx preservation rate. Secondary endpoints included acute toxicities and overall response. All statistical tests were two-sided.

Results Baseline patient and tumor characteristics were well balanced between the TPF (n = 110) and PF (n = 103) groups. With a median follow-up of 38 months, the 3-year actuarial larynx preservation rate was 70.3% with TPF vs 57.5% with PF (difference = 12.8%; $P = .03$). Patients in the TPF group had more grade 2 alopecia, grade 4 neutropenia, and febrile neutropenia, whereas patients in the PF group had more grade 3 and 4 stomatitis, thrombocytopenia, and grade 4 creatinine elevation. The overall response was 80.0% in the TPF group vs 59.2% in the PF group (difference = 20.8%; $P = .002$).

Conclusions In patients with advanced larynx and hypopharynx carcinomas, TPF induction chemotherapy was superior to the PF regimen in terms of overall response rate. These results suggest that larynx preservation could be achieved for a higher proportion of patients.

J Natl Cancer Inst 2009;101:498–506

Pointreau Y et Al.* J Natl Cancer Inst. *2009

European Point of View

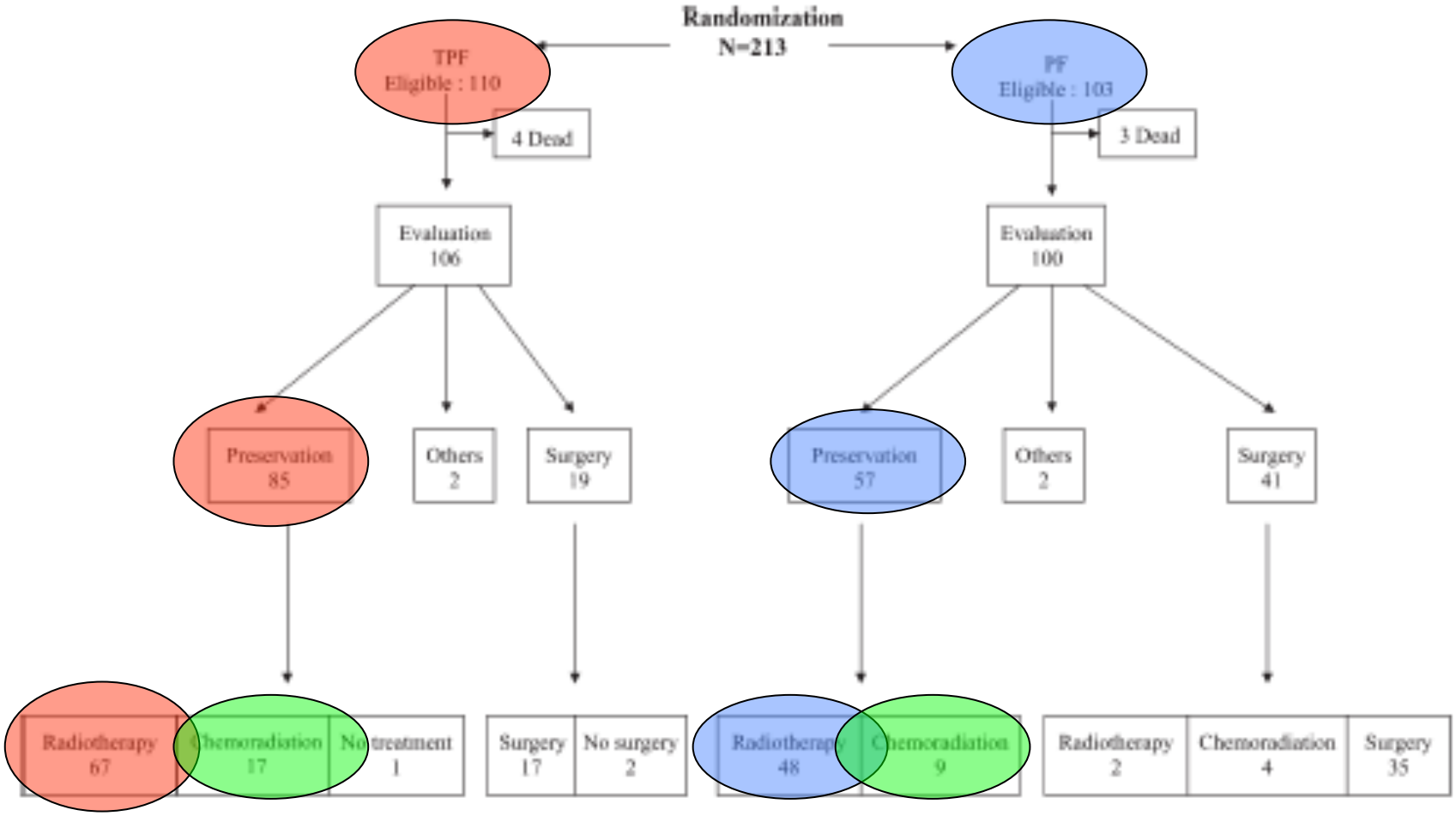
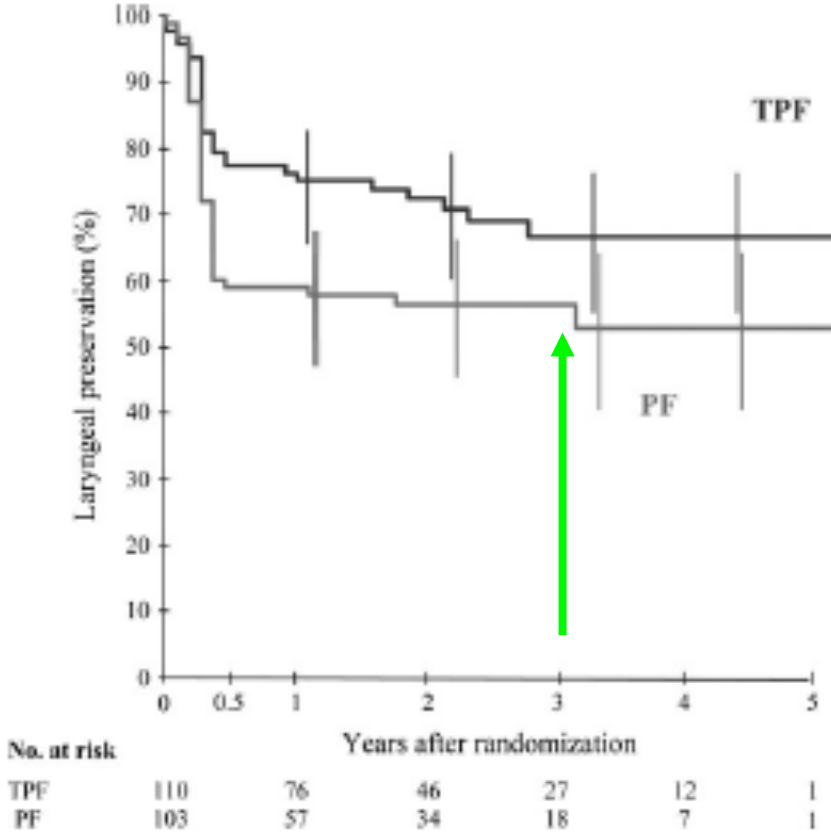


Figure 2. Outcomes among patients who were randomly assigned to docetaxel, cisplatin, plus 5-fluorouracil (TPF) or to cisplatin plus 5-fluorouracil (PF). Of the 213 patients randomly assigned (R), 85 of 106 who received TPF responded sufficiently for larynx preservation via further radiotherapy or chemoradiation, whereas only 57 of 100 who received PF responded sufficiently for larynx preservation via further radiotherapy or chemoradiation. Nonresponding patients received a laryngectomy.

Pointreau Y et Al. ***J Natl Cancer Inst.*** ***2009***

European Point of View



70%

58%

P = 0.03

Pointreau Y et Al. ***J Natl Cancer Inst.*** ***2009***

European Point of View

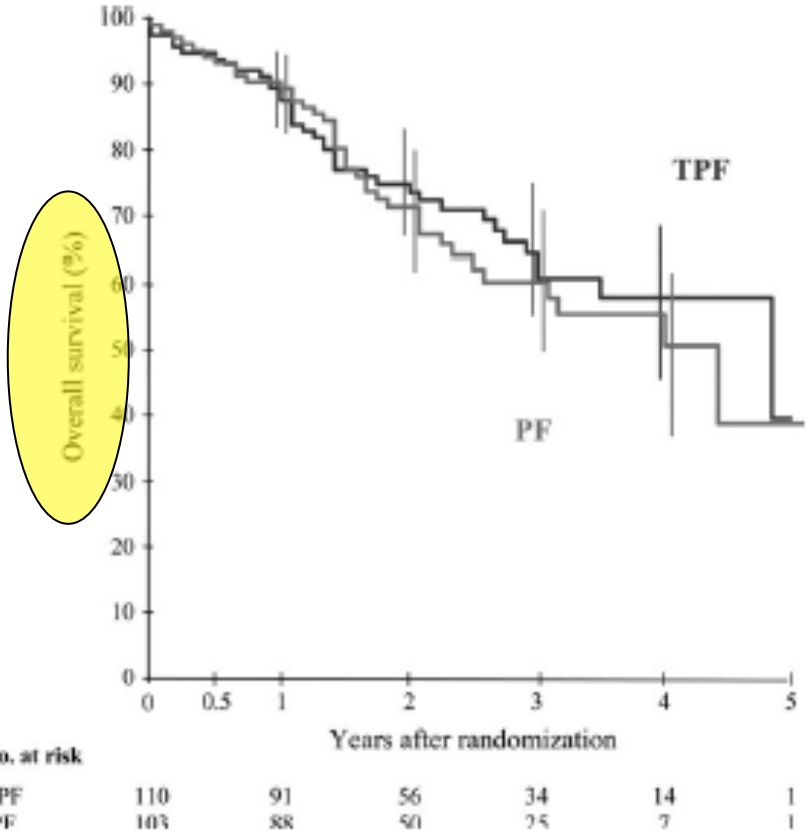


Figure 4. Overall survival among patients who were randomly assigned to docetaxel, cisplatin, plus 5-fluorouracil (TPF) vs cisplatin plus 5-fluorouracil (PF). At 3 years, overall survival rates were not statistically different ($P = .57$, two-sided log-rank test).

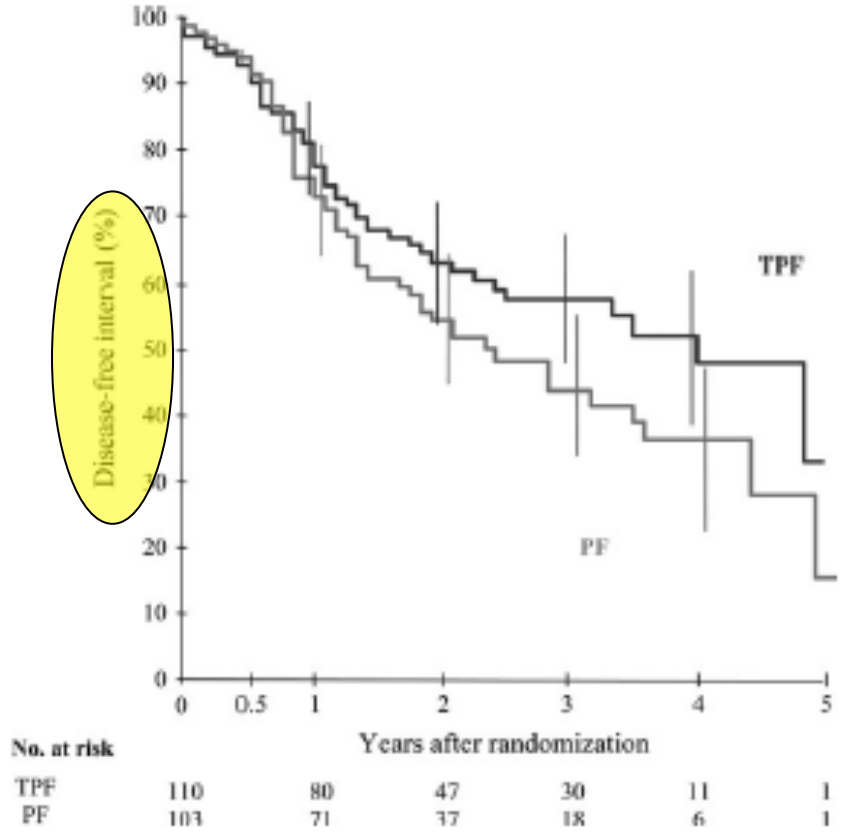


Figure 5. Disease-free interval among patients who were randomly assigned to docetaxel, cisplatin, plus 5-fluorouracil (TPF) vs cisplatin plus 5-fluorouracil (PF). At 3 years, disease-free intervals were not statistically different ($P = .11$, two-sided log-rank test).

Pointreau Y et Al.* J Natl Cancer Inst. *2009

European Point of View

Table 3. Late toxicities in patients with larynx and hypopharynx cancer treated by two different induction chemotherapy regimens and followed by radiotherapy or chemoradiotherapy for larynx preservation in patients with an objective response*

	TPF, %			PF, %		
	Grade			Grade		
Tissue	0	1–2	3–4	0	1–2	3–4
Mucous membrane	54.5	44.5	1	60.0	40.0	0
Salivary glands	18.2	75.7	6.1	32.2	65.6	2.2
Bone	99.0	2.0	0	98.9	1.1	0
Subcutaneous tissue	37.4	58.6	4.0	35.6	57.8	6.6

Grade 4 larynx toxicity occurred in 6.2% of patients in the TPF group (of whom two were treated by concurrent chemoradiotherapy after induction) and in 13.6% of patients in the PF group (of whom three were treated by concurrent chemoradiotherapy after induction) ($P = .1$). Other late toxic effects were comparable

Pointreau Y et Al. J Natl Cancer Inst. ***2009***

Target therapies

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*

N Eng J Med, 2006

IMRT Bio-Intensification

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 539–547, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.09.055

CLINICAL INVESTIGATION **Head and Neck Cancer**

DOSE-ESCALATED INTENSITY-MODULATED RADIOTHERAPY IS FEASIBLE AND MAY IMPROVE LOCOREGIONAL CONTROL AND LARYNGEAL PRESERVATION IN LARYNGO-HYPOPHARYNGEAL CANCERS

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AND CHRISTOPHER M. NUTTING, F.R.C.R.*†

Int. J. Radiation Oncology Biol. Phys., 2011

IMRT Bio-Intensification

Table 1. Patient characteristics ($n = 60$)

Characteristic	Dose Level 1 (63 Gy/28 Fx)	Dose Level 2 (67.2 Gy/28 Fx)
No. of patients	29	31
Follow-up (mo), median (range)	49.0 (35.7–78.3)	35.7 (17.7–62.8)
Age (y), mean (range)	58 (35–80)	63 (43–85)
Sex (male)	23 (79)	24 (77)
Performance status		
0	24 (83)	30 (97)
1	5 (17)	1 (3)
Primary tumor site		
Larynx	17 (59)	16 (52)
Hypopharynx	12 (41)	15 (48)
T stage		
T1–2	9 (31)	7 (23)
T3	14 (48)	17 (54)
T4a	6 (21)	7 (23)
N stage		
N0	10 (35)	13 (42)
N1	7 (24)	7 (23)
N2	10 (35)	11 (35)
N3	2 (6)	0
TNM stage		
I	1 (3)	0
II	1 (3)	0
III	12 (41)	16 (52)
IVA	13 (46)	15 (48)
IVB	2 (7)	0
Neoadjuvant chemotherapy completed according to protocol		
Yes	29 (100)	29 (94)
No	0	2 (6)
Concomitant chemotherapy completed full schedule	29 (100)	30 (97)

60 pts
(55% larynx, 45% hypopharynx)

Dose Level 1: 63 Gy 28 fr
Dose Level 2: 67.2 Gy 28 fr

Dose Level 2 increase in biologically equivalent dose of 9% for the primary tumor (76 Gy)

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Table 2. Type and frequency of acute toxicity (CTCAEv3.0) observed in the Dose Level 1 and Dose Level 2 cohorts ($n = 60$)

	Dose Level 1 ($n = 29$)					Dose Level 2 ($n = 31$)				
Acute toxicity	G0	G1	G2	G3	G4	G0	G1	G2	G3	G4
Dermatitis	0	8 (28)	14 (48)	7 (24)	0	0	9 (29)	15 (48)	7 (23)	0
Dysphagia–pharyngeal	1 (3)	1 (3)	9 (32)	17 (59)	1 (3)	0	0	2 (6)	27 (87)	0
Dysphagia–esophageal	0	3 (10)	8 (28)	17 (59)	1 (3)	0	0	4 (13)	27 (87)	0
Dysphagia– esophageal at 8 wk	11 (42)	6 (23)	5 (19)	3 (12)	1 (4)	4 (14)	7 (23)	12 (40)	7 (23)	0
Fatigue	0	7 (24)	18 (62)	4 (14)	0	0	6 (19)	20 (65)	5 (16)	0
Mucositis	1 (3)	4 (14)	11 (38)	13 (45)	0	0	4 (13)	13 (42)	14 (45)	0
Pain	0	8 (28)	15 (52)	6 (21)	0	0	1 (3)	20 (65)	10 (32)	0
Xerostomia	2 (6)	7 (24)	17 (59)	3 (10)	0	0	7 (23)	16 (52)	8 (26)	0

Abbreviations: CTCAE = common terminology criteria for adverse events; G = grade.
Values are number (percentage).

Table 3. Type and frequency of late radiotherapy adverse effects (LENT-SOMA) at 1 year ($n = 60$)

	Dose Level 1 ($n = 29$)					Dose Level 2 ($n = 31$)				
Site	G0	G1	G2	G3	G4	G0	G1	G2	G3	G4
Skin	16 (76)	4 (19)	1 (5)	0	0	21 (88)	3 (12)	0	0	0
Mucosa	12 (57)	9 (43)	0	0	0	17 (71)	7 (30)	0	0	0
Subcutaneous Tissue	18 (86)	3 (14)	0	0	0	15 (63)	7 (30)	2 (7)	0	0
Larynx	9 (43)	7 (33)	5 (24)	0	0	6 (25)	14 (58)	4 (17)	0	0
Esophagus	15 (71)	5 (25)	0	1 (5)	0	15 (60)	7 (29)	0	1 (4)	1 (4)
Salivary gland	10 (48)	9 (43)	2 (9)	0	0	9 (38)	13 (54)	2 (8)	0	0
Spinal cord	21 (100)	0	0	0	0	24 (100)	0	0	0	0

Abbreviations: LENT-SOMA = late effects in normal tissues–subjective, objective, management, and analytic scale; G = grade.
Values are number (percentage).

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Table 4. Treatment outcomes at 2 years

Outcome	Dose Level 1 ($n = 29$)	Dose Level 2 ($n = 31$)
Follow-up (mo), median (range)	51.2 (12.1–77.3)	36.2 (4.2–63.3)
Local control rate	70.8 (49.7–84.3)	85.9 (66.7–94.5)
Locoregional control rate	67.6 (46.7–81.7)	81.8 (61.6–92.1)
Locoregional progression-free survival	64.2 (43.5–78.9)	78.4 (58.1–89.7)
Disease-free survival	61.5 (58.8–89.9)	78.4 (58.1–89.7)
Larynx preservation rate	88.7 (68.5–96.3)	96.4 (77.2–99.5)
Overall survival	72.4 (52.3–85.1)	74.2 (55.0–86.2)

Values are percentage (95% confidence interval) unless otherwise noted.

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Functional assessment

- A predictive model for tube feeding dependence after curative (chemo-) radiation in head and neck cancer patients

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Functional assessment

Risk variable	Points
T-classification	
Tis – T2	0
T3 – T4	10
N-classification	
N0	0
N+	9
Baseline weight loss	
No	0
Moderate	7
Severe	12

Table 1: Assignment of points for the calculation of the Total Risk Score (TRS) for TUBE$_{M0}$. Each predictive variable was assigned a risk score and summation of these risk scores lead to a total risk score resulting in a corresponding risk of TUBE$_{M0}$.
Tis: carcinoma in situ, N+: positive nodal stage, moderate baseline weight loss: 1-10% weight loss at baseline, severe baseline weight loss: >10% weight loss at baseline.

FORMULA:
TRS = risk points (T-classification) + risk points (N-classification) + risk points (baseline weight loss)

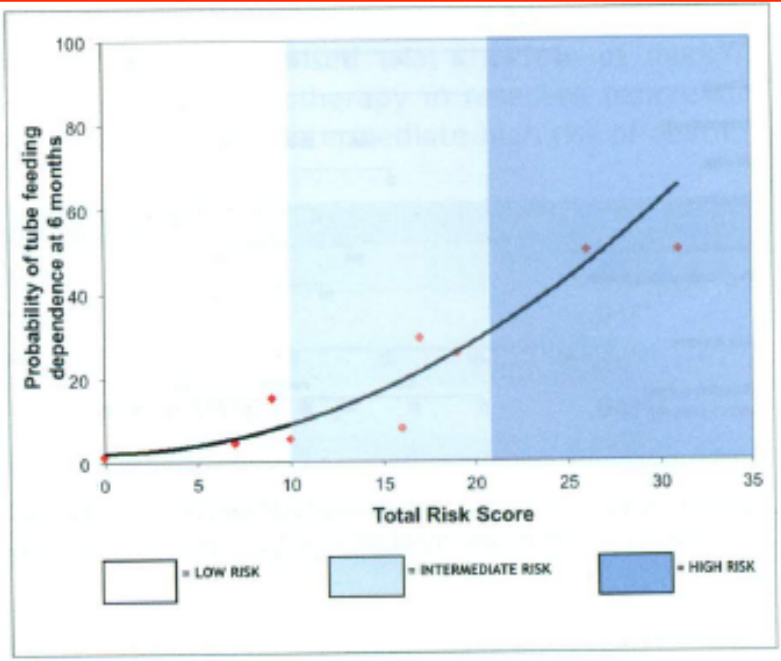

Figure 1: Final NTCP model with the probability of tube feeding dependence at 6 months as a function of the total risk score (TRS). The red squares represent the observed NTCP values. The TRS was divided into low, intermediate and high risk groups. Low-risk, intermediate-risk and high-risk correspond with 0-10%, >10-30% and >30% risk of tube feeding dependence at 6 months (TUBE$_{M0}$), respectively.

Guidelines trial organ preservation

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 5, pp. 1293–1303, 2009

0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2008.10.047

CONSENSUS DOCUMENT

LARYNX PRESERVATION CLINICAL TRIAL DESIGN: KEY ISSUES AND RECOMMENDATIONS—A CONSENSUS PANEL SUMMARY

JEAN-LOUIS LEFEBVRE, M.D.,* AND K. KIAN ANG, M.D.,† ON BEHALF OF THE LARYNX PRESERVATION CONSENSUS PANEL

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Study (Ref)	N	Patients	Stratification	Efficacy endpoints	Treatment arms	Overall survival %	Overall survival Time frame	Larynx preservation rate %	Larynx preservation rate Time frame
VA (1, 10, 11)	332	Stage III/IV Laryngeal SCC No T1N1	KPS Stage N0/1 vs. N2/3 Glottic vs. supraglottic	Response OS DFS	Surgery + RT	68	2 y	–	–
					PF + RT	68	2 y	66	2 y
EORTC 24891 (2, 12)	202	Hypopharyngeal SCC T2-T4 N0-N3 (no N2c)	Institution T2 vs. T3-T4 N0/1 vs. N2/3 Pyriform sinus vs. aryepiglottic fold	OS (primary) DFS FLS*	Surgery + RT	43 33 14	3 y 5 y 10 y	–	–
					PF + local therapy (RT if CR, surgery + RT if no CR)	57 38 13	3 y 5 y 10 y	22* 9*	5 y 10 y
GETTEC (13)	68	Laryngeal SCC T3 N0-N2b	None	OS DFS LP	Surgery + RT	69	2 y		
					PF + local therapy (RT if 80% regression, surgery + RT if <80% regression)	84 $p = 0.006$	2 y	42	Median 8 y
GORTEC 2000-01 14	220	Laryngeal and hypopharyngeal SCC	Not reported	3-year LP rate (primary)	PF	Not reported	–	51	3 y
					TPF (Both arms: If CR, PR and larynx mobility → RT; If NR → surgery + RT)			74	3 y
TAX 324 (6)	501	Stage III/IV SCC of head and neck - unresectable or candidates for organ preservation	Tumor site N0/1 vs. N2/3 Institution	OS (primary) PFS Response	PF → CRT (carboplatin)	48	3 y	Not reported	-
					TPF → CRT (carboplatin)	62 $p = 0.002$	3 y		
RTOG 91-11 (3, 4)	547	Laryngeal SCC Stage III/IV No T1 or large-volume T4	Glottic vs. supraglottic N0/1 vs. N2/3 T2 vs. T3 fixed vs. T3 not fixed vs. T4	LP (primary) OS DFS Local/locoregional control TTDM LFS	RT	75 54	2 y 5 y	66	5 y
					PF → RT	76	2 y	70 $p < 0.001$ vs. CRT	
						59	5 y		5 y
					CRT (cisplatin)	74 55	2 y 5 y	84 $p = 0.003$ vs. CRT	5 y
EORTC 24954-22950 (15)	450	T3-4 laryngeal SCC	Not reported	FLS* (primary)	Sequential PF → RT	48	5 y	53	5 y

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Recommendations **PATIENT SELECTION AND STRATIFICATION**

- Patients eligible should have T2 or T3 laryngeal (glottic or supraglottic) or hypopharyngeal squamous cell carcinoma not considered for partial laryngectomy.
- Exclusion criteria should include laryngeal dysfunction (defined as pretreatment tracheotomy, tumor-related dysphagia requiring feeding tube, or recurring pneumonia within preceding 12 months requiring hospitalization). Age greater than 70 years should also be considered.
- Stratification factors should include the primary tumor subsite (glottis, supraglottis [except epilarynx], or hypopharynx/epilarynx), N stage (N0, N1 vs. N2, N3), and country or region.

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Recommendations (1) *ASSESSMENT*

Baseline assessment for speech and swallowing function

Baseline assessment of vocal cord fixation

TC, RM, performed before endoscopy, PET TC if useful

Partial response is ≥ 50% decrease under baseline in the sum of the products of perpendicular diameters of all measurable lesions with no progression of evaluable disease and no new lesions

Assessment should occur between 2 and 3 months after the last day of radiotherapy

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Recommendations (2)

ASSESSMENT

Assessment by endoscopy/comparative imaging is mandatory

Routine biopsy is not recommended

In case of salvage local surgery total laryngectomy is preferred, but partial laryngectomy can be considered (according to local expertise)

Follow-up: is mandatory assessments related to function and long-term toxicities

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Recommendations

ENDPOINTS

- The primary endpoint should combine assessment of survival and function. The panel created a new endpoint for this purpose: laryngo-esophageal dysfunction-free survival. This endpoint would be measured as the time from randomization, and events would include: death, local relapse, total or partial laryngectomy, tracheotomy at 2 years or later, or feeding tube at 2 years or later.
- Recommended secondary endpoints include overall survival, progression-free survival, locoregional control, time to tracheotomy, time to laryngectomy, time to discontinuation of feeding tube, and quality of life/patient reported outcomes.
- Outcomes (including survival) and characteristics of patients who fail organ preservation and require a salvage laryngectomy should be recorded and reported.

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TISSUE BANKING AND BIOMARKER ASSESSMENT

Recommendations

- Recommended proof-of-principle correlative biomarker studies for near-term trials include EGFR (total, p-EGFR, and EGFRvIII) defined by IHC, excision repair cross-complementary-1gene, E-cadherin and β-catenin, epiregulin and amphiregulin, and TP53 mutation.
- Recommended samples to collect pretreatment include fresh-frozen and formalin-fixed tumor specimens, plasma and serum, and saliva.

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Biomarker

European Journal of Cancer (2012) xxx, xxx–xxx

Available at www.sciencedirect.com

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Circulating Tumour Cells in locally advanced head and neck cancer: Preliminary report about their possible role in predicting response to non-surgical treatment and survival

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New biomarker studies

Circulating Tumour Cells (CTC) positivity before treatment in relation with different clinical features.

	CTC+	CTC −	CTC +/Tot (%)	p (χ2)
Site				
Nasopharynx	0	10	0/10 (−)	0.05
Oropharynx	5	34	5/39 (13%)	
Oral cavity	0	3	0/3 (−)	
Hypofarinx	2	3	2/5 (40%)	
Larynx	1	9	1/10 (10%)	
Paranasal sinuses[a]	3	3	3/6 (50%)	
Grade				
1–2	4	17	4/21 (19%)	NS
3–4	5	28	5/33 (15%)	
Not known	2	17	2/19 (10%)	
T class				
1	0	7	0/7 (0)	NS
2–4	11	55	11/66 (17%)	
N class				
0–1	4	22	4/26 (15%)	NS
2	7	40	7/47 (15%)	
Stage				
I–II–III	1	16	1/17 (6%)	NS
IV	10	46	10/56 (18%)	
T + N categorisation				NS
T1 N0–1-2 T2 N0–1 T3 N0	1/16 (6.3%)			
T2 N2 T3 N1–2 T4 N0–1-2	10/57 (17.5%)			

Conclusion

The most important variable seems to be the *change of CTC number during treatment*: better response and better survival were evident if CTC were always absent or if they disappear during the treatment.

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Conclusions

- Patient selection
- Functional outcomes registration
- Customized therapy
- New predictive and prognostic factors
- Phase 3 ongoing trials results


Mood's Guided Treatment!
By courtesy of G. Mantini