XXI CONGRESSO NAZIONALE AIRO

Lezioni di Aggiornamento: Grandangolo in Radioterapia Oncologica

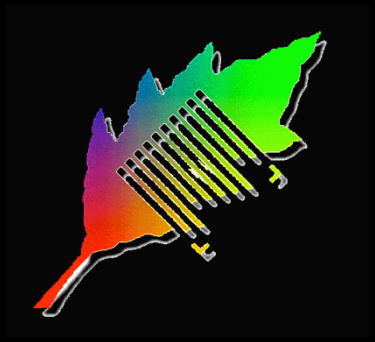
Marco Trovò

CRO –Aviano

Genova, 19-22 Novembre 2011

Lung

- Locally Advanced NSCLC
- Stereotactic Body Radiation Therapy (SBRT)



High-Dose RT/RTOG 0617 bases

Table 3. Phase I and II Trials Establishing the Safety and Potential Efficacy of 74 Gy of Radiation Delivered Using Three-Dimensional Conformal Thoracic Radiation

Study	Radiation MTD (Gy)	Chemotherapy	Median Survival Time (months)
RTOG 0117[34]	74	Carboplatin/paclitaxel	22
NCCTG 0028[35]	74	Carboplatin/paclitaxel	37
UNC[36]	74	Carboplatin/paclitaxel	24
Wake Forest[37]	74	Gemcitabine	18
CALGB 30105[38]	74	Carboplatin/paclitaxel	24

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–10, 2010

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.09.004

CLINICAL INVESTIGATION

HIGHER BIOLOGICALLY EFFECTIVE DOSE OF RADIOTHERAPY IS ASSOCIATED WITH IMPROVED OUTCOMES FOR LOCALLY ADVANCED NON–SMALL CELL LUNG CARCINOMA TREATED WITH CHEMORADIATION: AN ANALYSIS OF THE RADIATION THERAPY ONCOLOGY GROUP

MITCHELL MACHTAY, M.D.,* KYOUNGHWA BAE, PH.D.,† BENJAMIN MOVSAS, M.D.,‡ REBECCA PAULUS, B.S.,† ELIZABETH M. GORE, M.D.,§ RITSUKO KOMAKI, M.D.,¶ KATHY ALBAIN, M.D.,‖ WILLIAM T. SAUSE, M.D.,** AND WALTER J. CURRAN, M.D.††

HIGHER BIOLOGICALLY EFFECTIVE DOSE OF RADIOTHERAPY IS ASSOCIATED WITH IMPROVED OUTCOMES FOR LOCALLY ADVANCED NON–SMALL CELL LUNG CARCINOMA TREATED WITH CHEMORADIATION: AN ANALYSIS OF THE RADIATION THERAPY ONCOLOGY GROUP

Arm	Description	(Prescribed) RT dose/fractionation	Prescribed BED	Chemotherapy
1	88-08 Arm A	60 Gy (2 Gy qd)	72	Induction Cisplatin/vinblastine
2	90-15	69.6 Gy (1.2 Gy bid)	77.95	Concurrent cisplatin/vinblastine
3	91-06	69.6 Gy (1.2 Gy bid)	77.95	Concurrent cisplatin/etoposide
4	92-04 Arm A	69.6 Gy (1.2 Gy bid)	77.95	Concurrent cisplatin/etoposide
5	92-04 Arm B	63 Gy (1.8/2 Gy qd)	74.9	Induction and concurrent cisplatin/vinblastine
6	93-09 Arm B	61 Gy (1.8/2 Gy qd)	72.3	Concurrent cisplatin/etoposide
7	94-10 Arm A	63 Gy (1.8/2 Gy qd)	74.9	Induction cisplatin/vinblastine
8	94-10 Arm B	63 Gy (1.8/2 Gy qd)	74.9	Concurrent cisplatin/vinblastine
9	94-10 Arm C	69.6 Gy (1.2 Gy bid)	77.95	Concurrent cisplatin/etoposide
10	98-01 Arm A	69.6 Gy (1.2 Gy bid)	77.95	Induction and concurrent carboplatin/paclitaxel
11	98-01 Arm B	69.6 Gy (1.2 Gy bid)	77.95	Induction and concurrent carboplatin/paclitaxel

HIGHER BIOLOGICALLY EFFECTIVE DOSE OF RADIOTHERAPY IS ASSOCIATED WITH IMPROVED OUTCOMES FOR LOCALLY ADVANCED NON–SMALL CELL LUNG CARCINOMA TREATED WITH CHEMORADIATION: AN ANALYSIS OF THE RADIATION THERAPY ONCOLOGY GROUP

Parameter	Comparison	Hazard ratio (95% CI)	*p* value
Local-regional failure			
BED	Continuous	0.98 (0.97–0.99)	<0.0001
Age	Continuous	0.77 (0.61–0.99)	0.04
Sex	Female vs. male	RL 1.32 (1.12–1.55)	0.0008
KPS	90–100 vs. 70–80	RL 1.06 (0.89–1.27)	0.52
Histology	Nonsquamous vs. squamous	RL 1.04 (0.89–1.21)	0.61
Stage group	II/IIIA vs. IIIB	RL 1.17 (1.00–1.36)	0.04
RT delivery method	HFX vs. SFX	RL 1.08 (0.93–1.25)	0.33
Chemotherapy	Sequential vs. Induction	RL 1.28 (1.09–1.51)	0.003

HIGHER BIOLOGICALLY EFFECTIVE DOSE OF RADIOTHERAPY IS ASSOCIATED WITH IMPROVED OUTCOMES FOR LOCALLY ADVANCED NON–SMALL CELL LUNG CARCINOMA TREATED WITH CHEMORADIATION: AN ANALYSIS OF THE RADIATION THERAPY ONCOLOGY GROUP

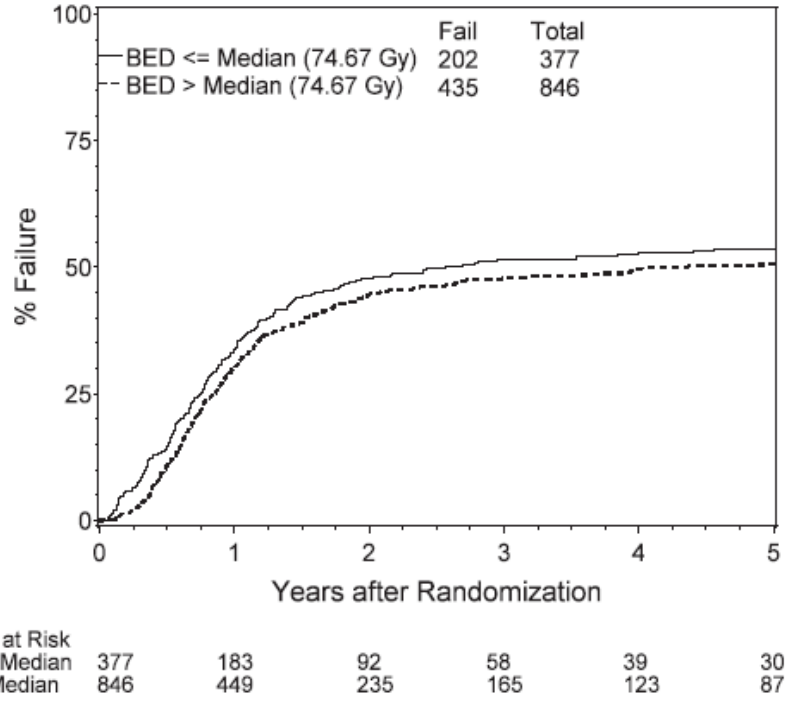


Fig. 2. Actuarial Local failure. BED = biologically effective dose; tBED = time-adjusted BED.

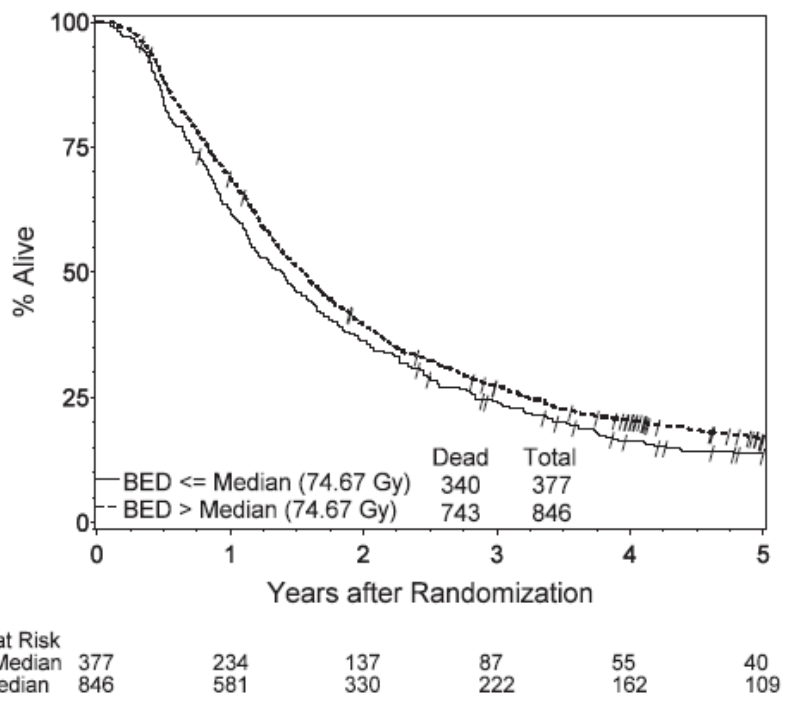


Fig. 3. Actuarial Survival. BED = biologically effective dose; tBED = time-adjusted BED.

HIGHER BIOLOGICALLY EFFECTIVE DOSE OF RADIOTHERAPY IS ASSOCIATED WITH IMPROVED OUTCOMES FOR LOCALLY ADVANCED NON–SMALL CELL LUNG CARCINOMA TREATED WITH CHEMORADIATION: AN ANALYSIS OF THE RADIATION THERAPY ONCOLOGY GROUP

1. RT dose intensity remains important despite the establishment of chemotherapy in Stage III NSCLC
2. 1 Gy BED increase in RT dose intensity is associated with 4% relative improvement in survival, and 3% relative improvement in local-regional control.

ELSEVIER

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0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2011.01.056

CLINICAL INVESTIGATION

PULMONARY TOXICITY IN STAGE III NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH HIGH-DOSE (74 GY) 3-DIMENSIONAL CONFORMAL THORACIC RADIOTHERAPY AND CONCURRENT CHEMOTHERAPY FOLLOWING INDUCTION CHEMOTHERAPY: A SECONDARY ANALYSIS OF CANCER AND LEUKEMIA GROUP B (CALGB) TRIAL 30105

Carboplatin AUC=6 and Paclitaxel 225mg/m2 x 2 → Weekly
Carboplatin AUC=2 and Paclitaxel 45mg/m2 + 74Gy 3D-CRT

R

Carboplatin AUC=5 and Gemcitabine 1000mg/m2 →
Twice weekly Gemcitabine 35mg/m2 + 74Gy 3D-CRT

PULMONARY TOXICITY IN STAGE III NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH HIGH-DOSE (74 GY) 3-DIMENSIONAL CONFORMAL THORACIC RADIOTHERAPY AND CONCURRENT CHEMOTHERAPY FOLLOWING INDUCTION CHEMOTHERAPY: A SECONDARY ANALYSIS OF CANCER AND LEUKEMIA GROUP B (CALGB) TRIAL 30105

Median Survival of 24 months!

Table 2. Number of patients reported treatment related pulmonary toxicity

	Arm	Grade 3	Grade 4	Grade 5	Total
ARDS	A	0	0	0	0
	B	0	1	0	1
Dyspnea	A	3	1	0	4
	B	4	2	0	6
Pneumonitis	A	1	1	0	2
	B	2	0	1	3
Other	A	0	0	0	0
	B	0	0	1	1
Maximum AE	**A**	**4**	**1**	**0**	**5**
	B	**4**	**1**	**2**	**7**

PULMONARY TOXICITY IN STAGE III NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH HIGH-DOSE (74 GY) 3-DIMENSIONAL CONFORMAL THORACIC RADIOTHERAPY AND CONCURRENT CHEMOTHERAPY FOLLOWING INDUCTION CHEMOTHERAPY: A SECONDARY ANALYSIS OF CANCER AND LEUKEMIA GROUP B (CALGB) TRIAL 30105

Table 5. Fisher's exact test of pulmonary toxicity and therisk factor

Risk factor	Grades 0–2	Grade 3–5	*p* value
N 0-2 and V20 <38 (low risk)	26	2	0.0313
N3 or V20 ≥38 (high risk)	16	8	

PULMONARY TOXICITY IN STAGE III NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH HIGH-DOSE (74 GY) 3-DIMENSIONAL CONFORMAL THORACIC RADIOTHERAPY AND CONCURRENT CHEMOTHERAPY FOLLOWING INDUCTION CHEMOTHERAPY: A SECONDARY ANALYSIS OF CANCER AND LEUKEMIA GROUP B (CALGB) TRIAL 30105

1. Previously described predictors of treatment-related pulmonary toxicity in patients treated to 60 Gy were also predictive for toxicity in patients treated with high-dose (74Gy) !!!

2. V5 and V10 were not significant factors.

3. N3 patients are at higher risk of pulmonary toxicity; likely increasing RT volume correlate with increasing toxicity (NB: ENI was allowed)

4. Gemcitabine concurrent with RT is associated with increased lung toxicity

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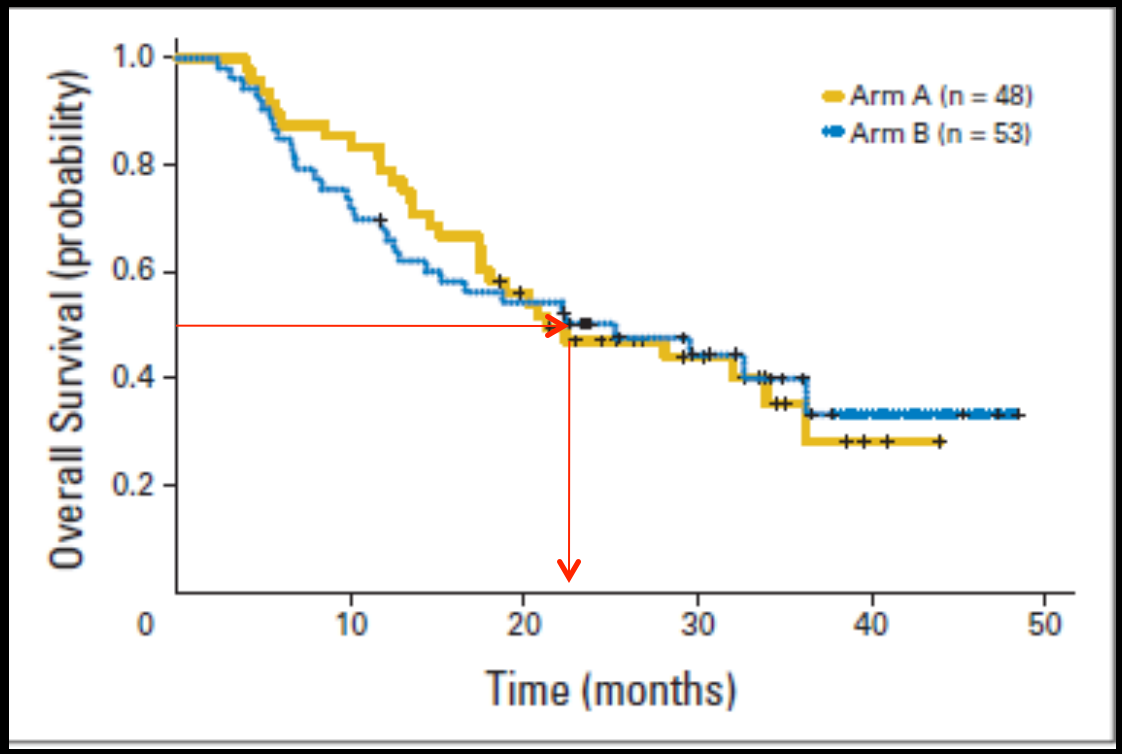
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase II Study of Pemetrexed, Carboplatin, and Thoracic Radiation With or Without Cetuximab in Patients With Locally Advanced Unresectable Non–Small-Cell Lung Cancer: Cancer and Leukemia Group B Trial 30407

Ramaswamy Govindan, Jeffrey Bogart, Thomas Stinchcombe, Xiaofei Wang, Lydia Hodgson, Robert Kratzke, Jennifer Garst, Timothy Brotherton, and Everett E. Vokes



Bepler G. J Thorac Oncol 2011 Mar;6(3):553-8.

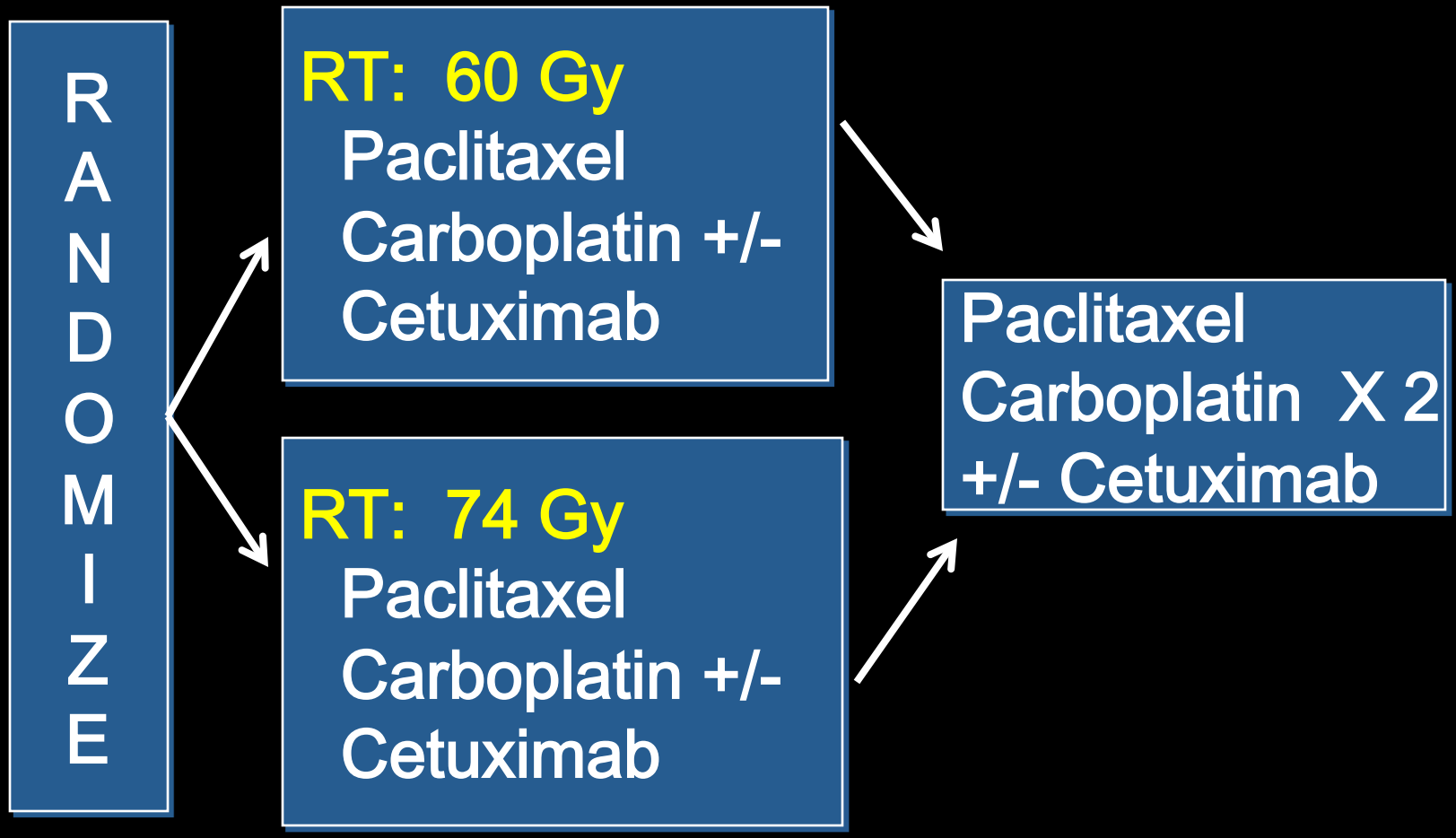
Phase II trial of induction gemcitabine and carboplatin followed by conformal thoracic radiation to 74 Gy with weekly paclitaxel and carboplatin in unresectable stage III non-small cell lung cancer.

A phase II single-institution trial:
Gemcitabine + Carboplatin x 2 → 74Gy-3D-CRT + Paclitaxel+Carboplatin

Median overall survival: 22.7 months

→ induction gemcitabine/carboplatin followed by concurrent paclitaxel/carboplatin with conformal radiation to **74 Gy is safe and tolerable with promising efficacy.**

RTOG 0617, NCCTG N0628,CALGB 30609 Conventional vs. High Dose RT



Courtesy of J.D. Bradley

Eligibility Criteria

- Newly diagnosed, unresectable Stage IIIA/B NSCLC; patients who present with N2/N3 disease and an undetectable NSCLC primary tumor are also eligible
- No supraclavicular or contralateral hilar adenopathy
- Zubrod 0/1
- Age ≥ 18
- FEV1 ≥ 1.2 liters/second or ≥ 50% predicted
- ANC ≥ 1,000, platelets ≥ 100,000, Hgb ≥ 10.0 g/dl
- Serum creatinine within normal institutional limits, or creatinine clearance ≥ 60 ml/min, bilirubin within normal institutional limits; AST and ALT < 2.5 X IULN
- Signed informed consent

Courtesy of J.D. Bradley

Statistical Considerations

- Primary Endpoint: Overall Survival (OS) defined as time of enrollment until death due to any cause
- Hypothesis: Median survival time will increase from 17.1 months to 24 months (for each factor)
- Three interim analyses at 85, 170, and 255 events

Courtesy of J.D. Bradley

Pretreatment Characteristics

	60 Gy (n=216)	74 Gy (n=208)
Age (median)	64	64
Gender		
Male	127 (58.8%)	119 (57.2%)
Female	89 (41.2%)	89 (42.8%)
Race		
Other	27 (12.5%)	30 (14.4%)
White	189 (87.5%)	178 (85.6%)
RT Technique		
3DCRT	**116 (57.3%)**	**113 (54.3%)**
IMRT	**100 (46.3%)**	**95 (45.7%)**
PET Staging	**91.2%**	**88.9%**
Histology		
Adenocarcinoma	86 (39.8%)	73 (35.1%)
Squamous	86 (39.8%)	96 (46.2%)
NSCLC NOS	39 (18.1%)	33 (15.9%)
AJCC Stage		
Stage IIIA	138 (65.7%)	131 (63.6%)
Stage IIIB	72 (34.3%)	75 (36.4%)

Courtesy of J.D. Bradley

RTOG 0617: Dosimetric Data Distribution

	60 Gy (n=216) Mean (Median)	74 Gy (n=208) Mean (Median)
GTV Volume (cc)	134.9 (106.1)	122.7 (85.6)
Lung Volume (cc)	512.5 (463.4)	514.3 (440.0)
Lung V20 (%)	30.2 (30.3)	29.8 (31.5)
Esophagus Dose (Gy)	28.1 (28.1)	27.5 (27.3)
Esophagus V60 (%)	22.1 (22.1)	20.4 (20.1)
Esophagus V20 (%)	48.4 (48.7)	47.6 (46.8)
Mean Margin CTV to PTV (mm)	8.0 (7.0)	7.9 (6.6)

Courtesy of J.D. Bradley

RTOG 0617
Definitely, Probably, or Possibly Related to Treatment (Using CTCAE Version 3.0)

September 2011	Standard Dose: 60 Gy (n=192) Grade			High Dose: 74 Gy (n=183) Grade		
	3	4	5	3	4	5
Worst non-hematologic	79 (41.1%)	14 (7.3%)	4 (2.1%)	85 (46.4%)	17 (9.3%)	8 (4.4%)
Worst overall	84 (43.8%)	45 (23.4%)	4 (2.1%)	78 (42.6%)	52 (28.4%)	8 (4.4%)
Grade 5 Events	(n=4)			(n=8)		
-As scored by institution -No significant difference	2 Pulmonary 1 Thrombosis 1 Death NOS			2 Pulmonary 1 Thrombosis 1 Upper GI Hemorrhage 1 Pulmonary Hemorrhage 1 Pneumonia NOS 1 Esophageal 1 Death NOS		

Courtesy of J.D. Bradley

Follow Up Time

	Standard Dose: 60 Gy	High Dose: 74 Gy	Total
FU Time (Months)	(n = 213)	(n = 204)	(n = 417)
Median	**11.7**	**10.3**	**11.3**
Min - Max	1.1 – 38.1	0.2 – 36.4	0.2 – 38.1
Q1 – Q 3	5.3 – 17.5	4.5 – 16.0	4.7 – 38.1

Courtesy of J.D. Bradley

Overall Survival – RT Comparison

	Standard Dose: 60 Gy		High Dose: 74 Gy	
Months	% Alive	# at Risk	% Alive	# at Risk
0	100.%	213	100.0	204
3	98.5%	190	95.4%	175
6	91.2%	149	87.7%	137
9	84.7%	124	78.4%	116
12	**81.0%**	**104**	**70.4%**	**93**
Dead/Total	58/213		70/204	
Median Sv	**21.7 mos**		**20.7 mos**	

p = 0.02 (one-sided p-value, left tail)

(RTOG 9410 CON-QD one-year survival = 62.1%, MST = 17.0 months)

Courtesy of J.D. Bradley

Multivariate Cox Model Backwards Selection

Covariate	Comparison	HR (95% CI)	p-value
Radiation dose	**60 Gy v 74 Gy**	**1.48 (1.00, 2.22)**	**0.038**
Histology	**Non-squam v Squam**	**1.52 (0.90, 1.99)**	**0.025**
Age	Continuous	1.02 (1.03, 2.77)	0.061
GTV (ITV if GTV unavailable)	**Continuous**	**1.002 (1.000, 1.004)**	**0.011**

Exit criteria = p>0.10; radiation dose and histology forced to remain
Covariates dropped from the model were: gender, lung volume, and esophagus V20.

Courtesy of J.D. Bradley

Conclusions

- The high dose (74 Gy) arms were closed for futility (cannot show a survival benefit with further follow up)
- The trial remains open to accrual to 60 Gy +/- Cetuximab
- Toxicity was similar between arms
- Factors associated with improved overall survival are radiation dose (60 Gy), non-squamous histology, and smaller gross tumor volume
- At this point, we've detected no apparent reason that the 74 Gy arm crossed the futility boundary

Courtesy of J.D. Bradley

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC)

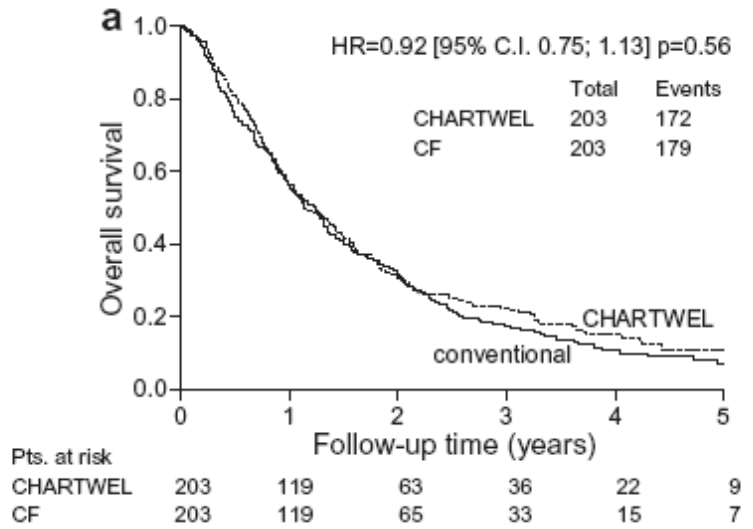
M. Baumann [a,*], T. Herrmann [a], R. Koch [b], W. Matthiessen [c], S. Appold [a], B. Wahlers [d], L. Kepka [e], G. Marschke [f], D. Feltl [g], R. Fietkau [h], V. Budach [i], J. Dunst [j], R. Dziadziuszko [k], M. Krause [a], D. Zips [a], on behalf of the CHARTWEL-Bronchus studygroup [1]

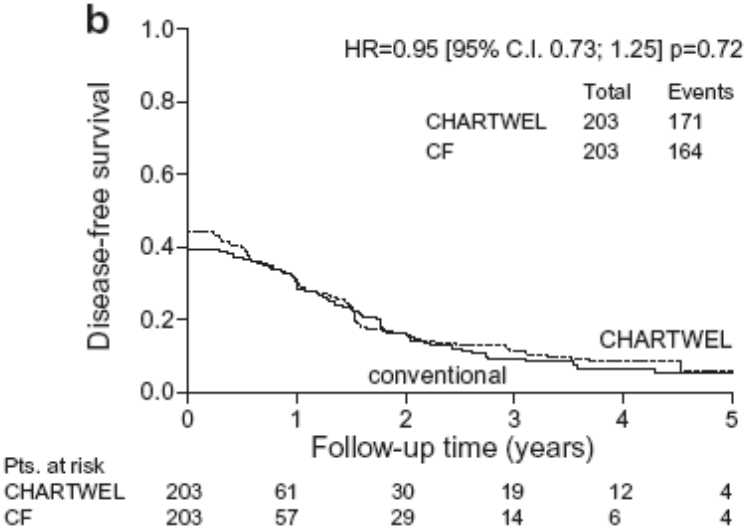
+/-CT → R

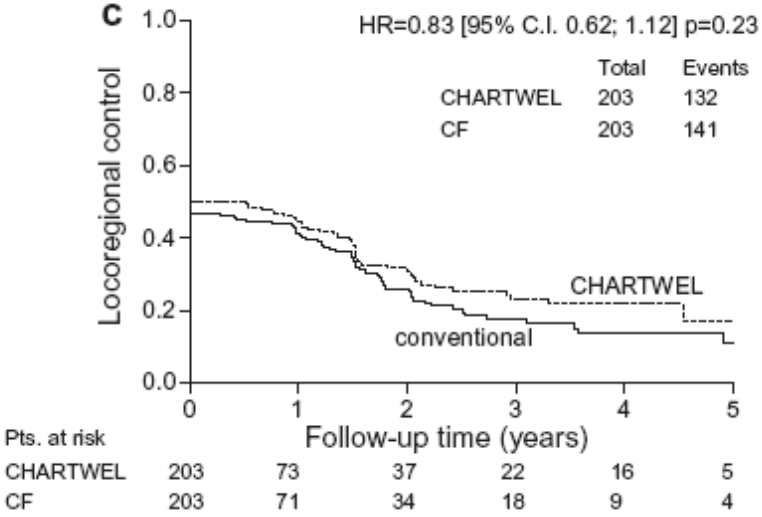
60Gy/40fr/2.5week (Chartwel)

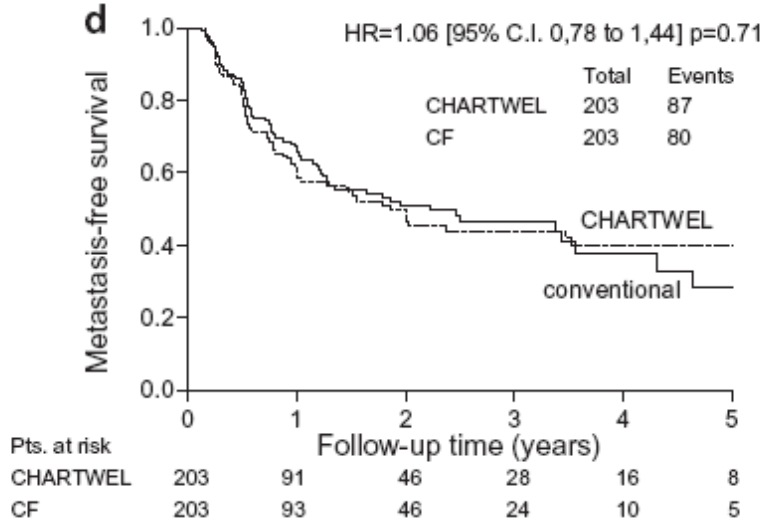
66Gy/33fr/6.5week

Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy



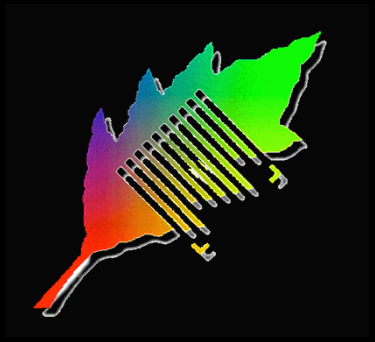






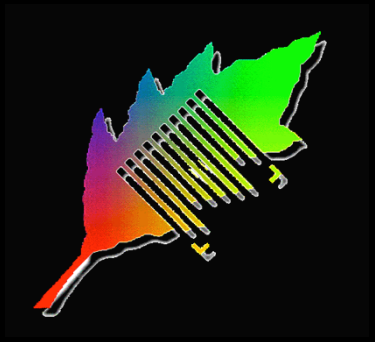
Lung

- Locally Advanced NSCLC
- Stereotactic Body Radiation Therapy (SBRT)



SBRT for Centrally Located Tumors

It is not a therapeutic standard !

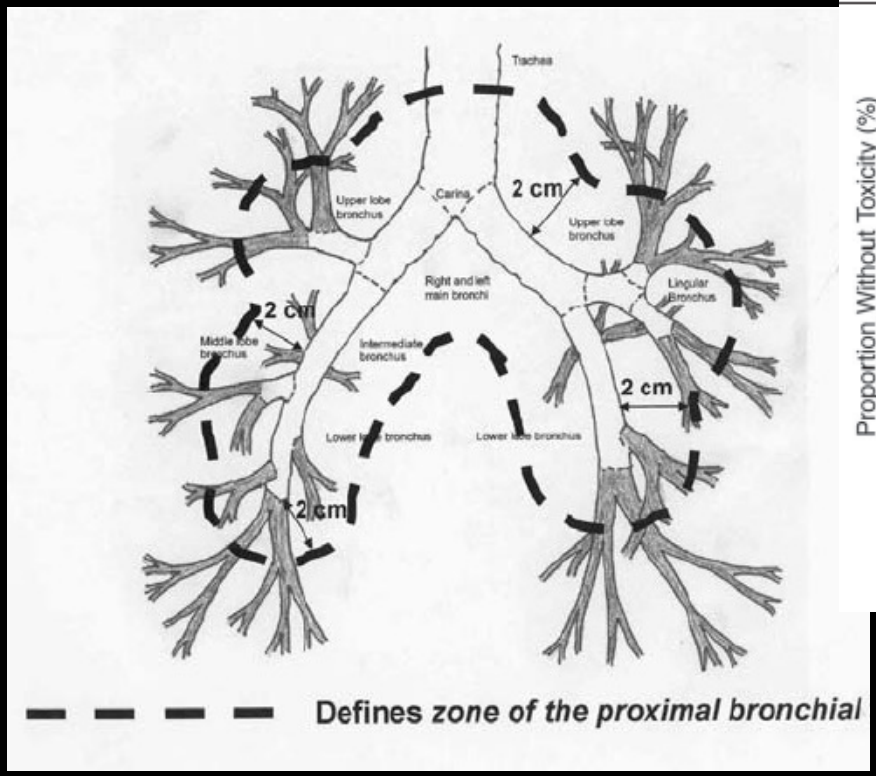


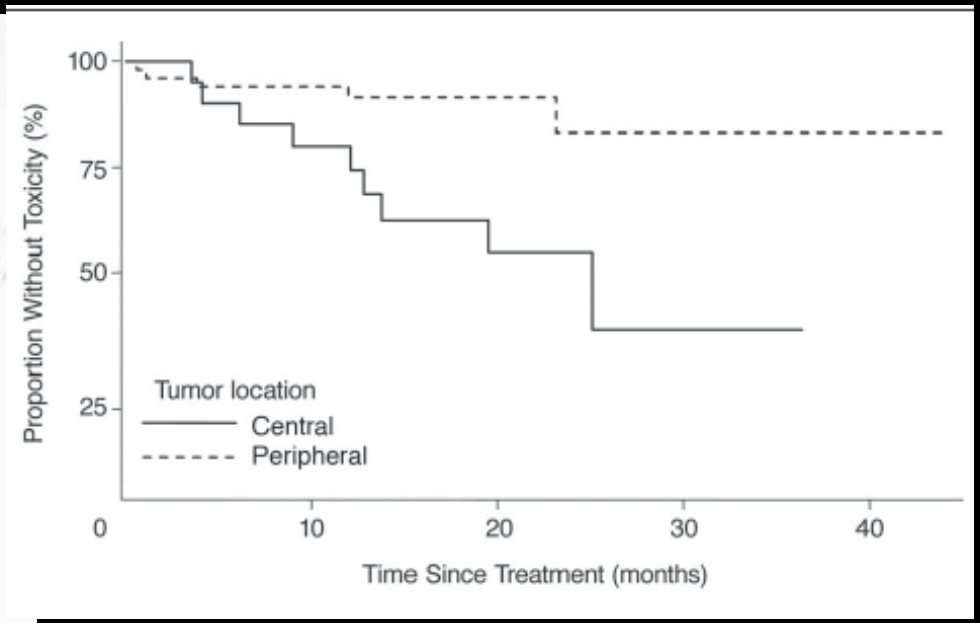
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher





JCO 2007

Prospective Phase I Dose Escalation Results of SBRT for Centrally-located Stage I NSCLC.

Bradley JD. Washington University.

To determine the maximum tolerated dose of SBRT to the proximal bronchial tree.

21 patients:

Dose levels	A	B	C	D
Fractionation	9 Gy x 5	10 Gy x 5	11 Gy x 5	12 Gy x5
BED	85.5 Gy	100 Gy	115.5 Gy	132 Gy

Prospective Phase I Dose Escalation Results of SBRT for Centrally-located Stage I NSCLC.

Bradley JD. Washington University.

OAR	DVH Constraints
Spinal cord	< 20 Gy
Esophagus	< 30 Gy
Brachial plexus	< 25 Gy
Heart	< 30 Gy

Prospective Phase I Dose Escalation Results of SBRT for Centrally-located Stage I NSCLC.

Bradley JD. Washington University.

- No G≥2 protocol related toxicity
- The overall primary tumor control is 95%
- One primary tumor failure in arm A (9Gy x 5)
- This trial will proceed to Phase II to measure efficacy at a dose level of 11 Gy x 5

SBRT for Central Lung Lesions: Treating Beyond RTOG 0813 Parameters.

Stephans K. Cleveland Clinic

RTOG 0813

Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

SCHEMA

Escalating dose levels; at all levels, patients will receive q 2 day fractionation X 5 fractions over 1.5-2 weeks

Dose Level	Level 1	Level 2	Level 3	Level 4	**†Level 5**	Level 6	Level 7	Level 8	Level 9
Dose per Fraction	8 Gy	8.5 Gy	9 Gy	9.5 Gy	**10 Gy**	10.5 Gy	11 Gy	11.5 Gy	12 Gy
Total Dose	40 Gy	42.5 Gy	45 Gy	47.5 Gy	**50 Gy**	52.5 Gy	55 Gy	57.5 Gy	60 Gy

SBRT for central Lung Lesions: Treating Beyond RTOG 0813 Parameters.

Stephans K. Cleveland Clinic

Serial Tissue*	Volume	Volume Max (Gy)	Max Point Dose (Gy)
Esophagus, non-adjacent wall	<5 cc	27.5 Gy (5.5 Gy/fx)	105% of PTV prescription
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	105% of PTV prescription
Great vessels, non-adjacent wall	<10 cc	47 Gy (9.4 Gy/fx)	105% of PTV prescription
Trachea and ipsilateral bronchus, non-adjacent wall	<4 cc	18 Gy (3.6 Gy/fx)	105% of PTV prescription

SBRT for central Lung Lesions: Treating Beyond RTOG 0813 Parameters.

Stephans K. Cleveland Clinic

101 lesions
Median follow-up 9 months
SBRT Schedule:

SBRT schedule	50Gy/5fx	48Gy/4fx	50Gy/10fx	60Gy/8fx	55Gy/5fx
N of patients	62	9	19	7	1

SBRT for central Lung Lesions: Treating Beyond RTOG 0813 Parameters.

Stephans K. Cleveland Clinic

- Local Control 96%

- RTOG 0813 D-V constraints exceeded in 47% of the cases:
Esophagus n=1, heart n=9, trachea n=5, proximal tree n=29

- Grade ≥3 in 3%

SABR in Potentially Operable Patients with Stage I NSCLC.

Lagerwaard FJ, VUUniversity, Netherlands

177 potentially operable patients,
Median age 76 y
SBRT dose: 60 Gy in 3-8 fractions

Median follow-up 32 months:

3-y LC	Median OS	1-y OS	3-y OS	5-y OS
97%	61 months	94.7%	84.7%	51.3%

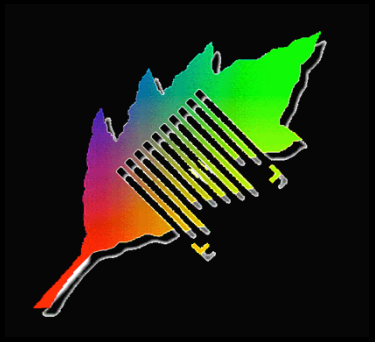
Grade 3 pneumonitis in 2%

Conclusions:

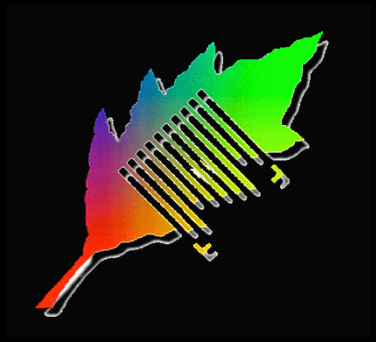
I am very disappointed and saddened by the RTOG 0617 results!

We started to irradiate with SBRT also central lesions

Randomized trial SBRT vs. Surgery are strongly recommended.

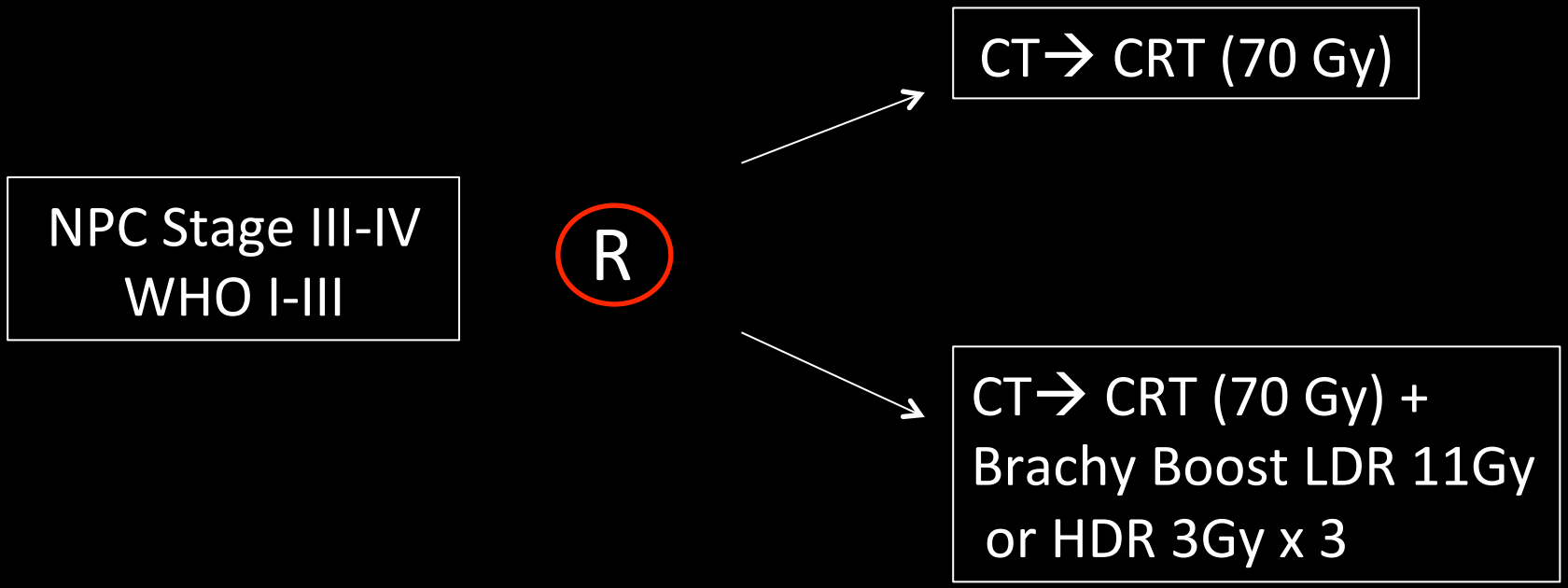


Head & Neck



Brachytherapy Boost in Loco-Regionally Advanced Nasopharyngeal Carcinoma: A Prospective Randomized Trial of the International Atomic Energy Agency

Rosenblatt E.



Brachytherapy Boost in Loco-Regionally Advanced Nasopharyngeal Carcinoma: A Prospective Randomized Trial of the International Atomic Energy Agency

- Median follow-up 29 months (range, 0-67)

275 patients

- **3-year LRFS 60% vs 54% in arms A and B, respectively (p=0.6)**

Brachytherapy Boost in Loco-Regionally Advanced Nasopharyngeal Carcinoma: A Prospective Randomized Trial of the International Atomic Energy Agency

	Variables	3-y LRFS	P	3-y DFS	p	3-y OS	P
Treatment	Standard Boost	60% 54%	0.64	60% 53%	0.49	63% 63%	0.74
Age	<40 >40	67% 51%	**0.05**	64% 51%	0.12	72% 58%	**0.01**
WHO	1-2 3	55% 56%	0.48	54% 57%	0.46	61% 64%	0.95
Stage	T3-4, N2-3 Other	59% 55%	0.37	45% 59%	**0.02**	51% 67%	**0.02**

Epidemiological Changes of Oropharyngeal Cancer and other Head and Neck Squamous Cell Carcinomas Treated from 2003-2010.

Chu K. Princess Margaret Hospital, Toronto

- The incidence of Oropharyngeal cancer (OPC) rose from 2003 to 2010 compared to NO-OPC ($p=0.01$).

- Larger proportion of never-smokers (27% vs 15%, $p<0.001$) and lower proportion of current smokers (50% vs 62%, $p<0.001$) in the OPC vs. NO-OPC.

Epidemiological Changes of Oropharyngeal Cancer and other Head and Neck Squamous Cell Carcinomas Treated from 2003-2010.

Princess Margaret Hospital, Toronto

- The overall average proportion of p16+ OPC was 72%.

- There was a non-statistically significant decline in p16+ in the recent years: 2008 = 79% vs 2010 = 67% (p=0.12).

IMRT for Oropharyngeal Carcinoma: Patient Outcome and Pattern of Failure.

Garden AS MD Anderson Cancer Center

- These are the mature results of a large cohort of OPC patients treated with definitive IMRT.

- 777 patients, stage I-IVB, treated between 2000-2007. Median follow-up of 54 months

- Conventional fractionation in 82%
Accelerated fractionation in 18%
Chemotherapy in 55%

IMRT for Oropharyngeal Carcinoma: Patient Outcome and Pattern of Failure.

MD Anderson Cancer Center

5-year OS: 84%
5-year recurrence-free survival: 82%
5-year local regional control: 90%

Primary site recurrence: 7%
Neck recurrence: 3%
Distant mets in patients with tumor control: 9%

IMRT for Oropharyngeal Carcinoma: Patient Outcome and Pattern of Failure.

MD Anderson Cancer Center

	5-y DFS
Never-smokers & T1-2	90%
Smoker & T3-4	56%

Long-term Regional Control in the Observed Neck following Definitive Chemoradiation for Node-positive Oropharyngeal Squamous Cell Cancer.

Morris L. Memorial Sloan-Kettering Cancer Center

To determine the rate of regional failure in the observed neck in patients with a clinical Complete Response (CR) and a negative PET/CT following definitive chemoradiation

310 Node-positive patients (N1 and N2)
70Gy-IMRT and concurrent CDDP or Cetuximab
Median follow-up 32 months.

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Long-term Regional Control in the Observed Neck following Definitive Chemoradiation for Node-positive Oropharyngeal Squamous Cell Cancer.

Memorial Sloan-Kettering Cancer Center

267 patients (87%): CR → Observation

5-year regional control: 97.8% ←→ 2.2% regional failure
5-year OS: 80%

4 neck recurrences; initial stage N1 (n=2), N2 (n=2).
No association between N-stage and neck recurrence.

Long-term Regional Control in the Observed Neck following Definitive Chemoradiation for Node-positive Oropharyngeal Squamous Cell Cancer.

Memorial Sloan-Kettering Cancer Center

39 patients (13%): Neck Dissection

- n=23 PET/CT positive
  viable tumor in 12/23 (52%)

- n=16 PET/CT negative, clinically positive
  viable tumor in 4/16 (25%)

Defining the Risk of Involvement for each Neck Nodal Level in Patients with early T-Stage Node-Positive HPC-related Oropharyngeal Carcinoma

Sanguineti G. Johns Hopkins University

To assess the risk of ipsilateral subclinical neck nodal involvement for early T-stage Node-positive HPV-related OPC

The prevalence rate of involvement of levels I-V was reported in 94 patients.

For each nodal level the NPV was computed based on literature data of sensitivity/specificity.

Defining the Risk of Involvement for each Neck Nodal Level in Patients with early T-Stage Node-Positive HPC-related Oropharyngeal Carcinoma

Johns Hopkins University

Neck Level	Involvement at pathology	Risk of involvement when negative on CT
IB	8.4%	2.8%
II	89.4%	72.1%
III	38.3%	16.0%
IV	20.0%	7.1%
V	2.6%	0.8%

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IMRT for Oral Cavity Squamous Cell Carcinoma: Pattern of Failures and Predictor of Local Control

Daly MA. Stanford

Study	Treatment	*N*	Median FU (mo)	Systemic therapy (%)	Stage IV (%)	LRC (%)	OS (%)
Gomez *et al.*, 2009 (11	Postoperative	35	28	29	54	77 (3 y)	74 (3 y)
Chen *et al.*, 2009 (13)	Postoperative	22	44	9	73	NA	67 (3 y)
Studer *et al.*, 2007 (12)	Postoperative	28	19	86	54	92/91 (local/regional; 2 y)	83 (2 y)
	Definitive	30	12	70	70	43 (2 y)	30 (2 y)
Yao *et al.*, 2007 (13)	Postoperative	49	24	11	69	82 (2 y)	68 (2 y)
	Definitive	5					
Present study	Postoperative	30	38	60	53	53 (3 y)	59 (3 y)
	Definitive	7		100%	71%	60% (3 y)	38% (3 y)

Int. J. Radiat. Oncol. Biol. Phys 2011;80:1412-1422

IMRT for Oral Cavity Squamous Cell Carcinoma: Pattern of Failures and Predictor of Local Control

Stanford

	N of patients	3-y LC	3-y LRC	3-y DMFS	3-y OS
Post-op IMRT	30	67%	53%	81%	60%
Definitive CT-IMRT	7	60%	60%	71%	57%

Int. J. Radiat. Oncol. Biol. Phys 2011;80:1412-1422

IMRT for Oral Cavity Squamous Cell Carcinoma: Pattern of Failures and Predictor of Local Control

Stanford

Pattern of Failure:

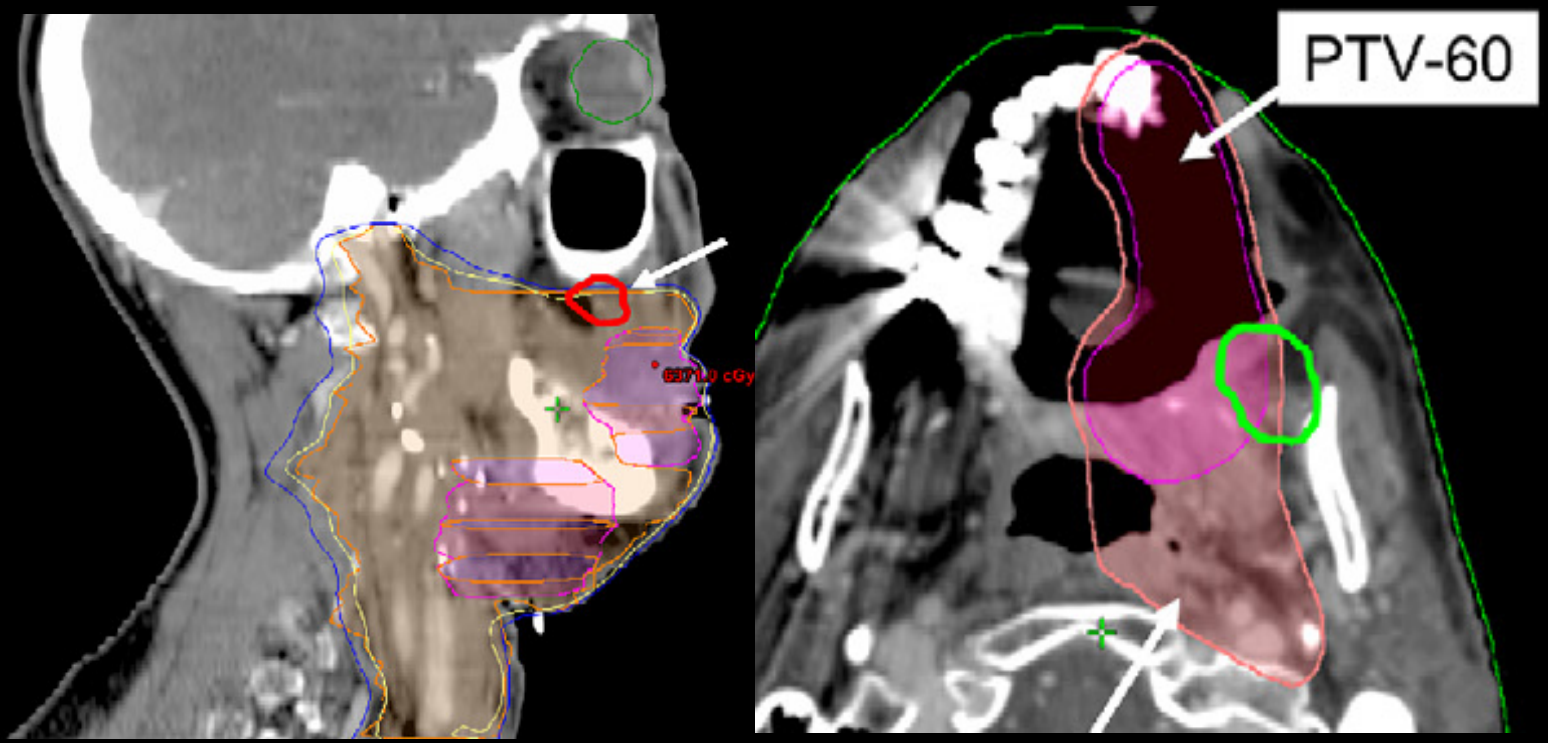
7 in-field local failures
2 marginal local failures

2 in-field regional failures
2 marginal regional failures

Int. J. Radiat. Oncol. Biol. Phys 2011;80:1412-1422

IMRT for Oral Cavity Squamous Cell Carcinoma: Pattern of Failures and Predictor of Local Control

Stanford



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IMRT for Oral Cavity Squamous Cell Carcinoma: Pattern of Failures and Predictor of Local Control

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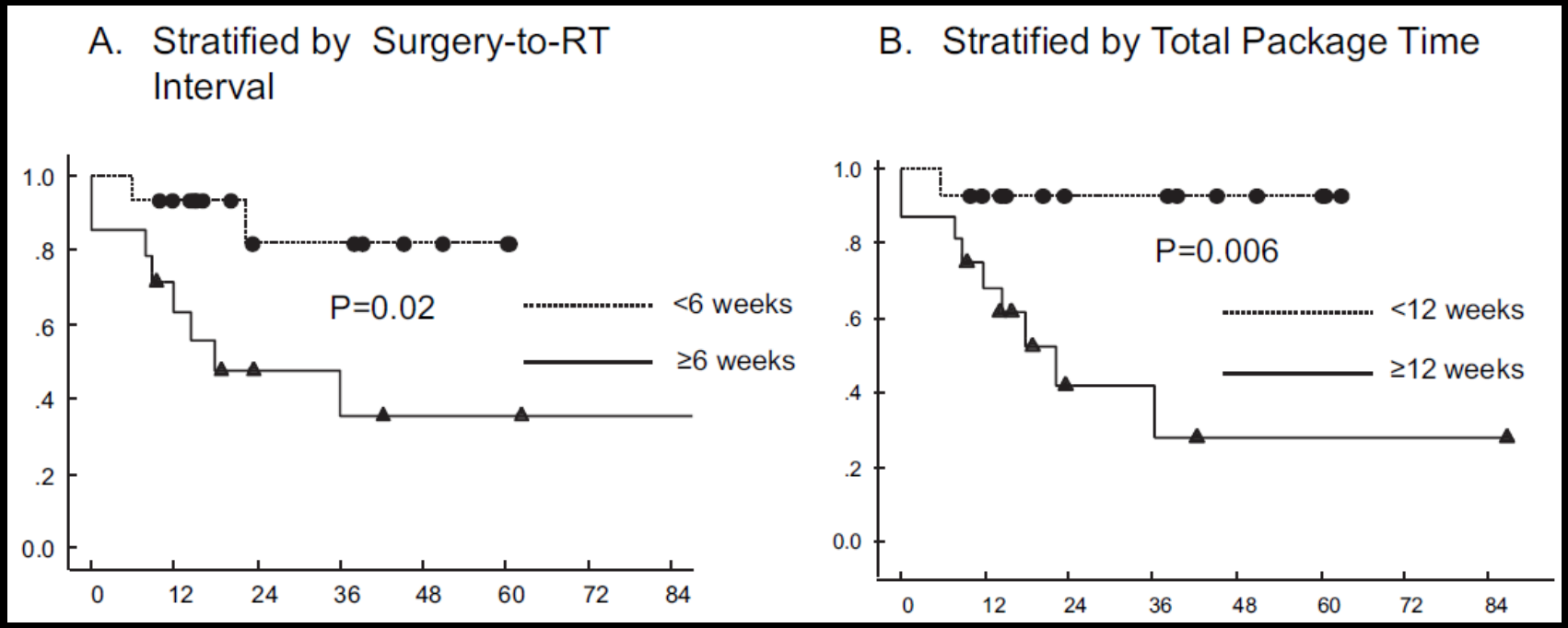


Int. J. Radiat. Oncol. Biol. Phys 2011;80:1412-1422

Marginal Misses after Postoperative IMRT for Head and Neck Cancer.

Chen AM. University of California Davis

90 patients
Median IMRT dose 63 Gy
Concurrent CT in 56%

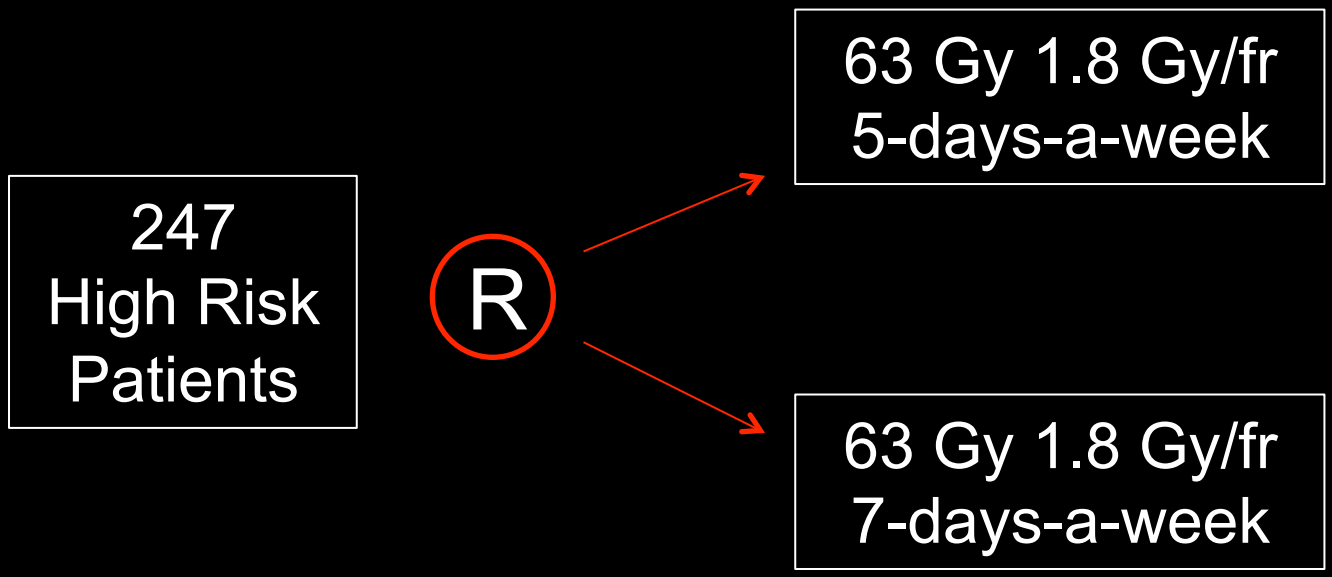
2-year Loco-Regional Control: 80%

- -11/17 (64%): in-field recurrences
- -6/17 (37%): marginal recurrences
  - vicinity of the spared parotid gland n=3
  - dermal/subcutaneous n=2
  - retropharyngeal n=1

Int. J. Radiat. Oncol. Biol. Phys 2011;80:1423-1429

Postoperative Continuous 7-days-a-week Radiotherapy for High-risk Squamous Cell Cancer of the Head and Neck: Long term Results of a Randomized Clinical Trial

Suwinski R Center of Oncology, Gliwice



Postoperative Continuous 7-days-a-week Radiotherapy for High-risk Squamous Cell Cancer of the Head and Neck: Long term Results of a Randomized Clinical Trial

Center of Oncology, Gliwice

	7-y LR Control	7-y Mets Free Survival	7-y OS	Bone necrosis	Xerostomia
5-days-a-week	61%	88%	30%	2%	28%
7-days-a-week	65%	85%	35%	9%	43%

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Parotid-Sparing Intensity Modulated vs. Conventional Radiotherapy in Head and Neck Cancer (PARSPORT): a Phase 3 Multicentre Randomized Controlled Trial.

Nutting CM

Primary end point: Grade ≥ 2 xerostomia at 12 months

94 patients*
Oro/Hypopharynx
Definitive or Post-op RT

R

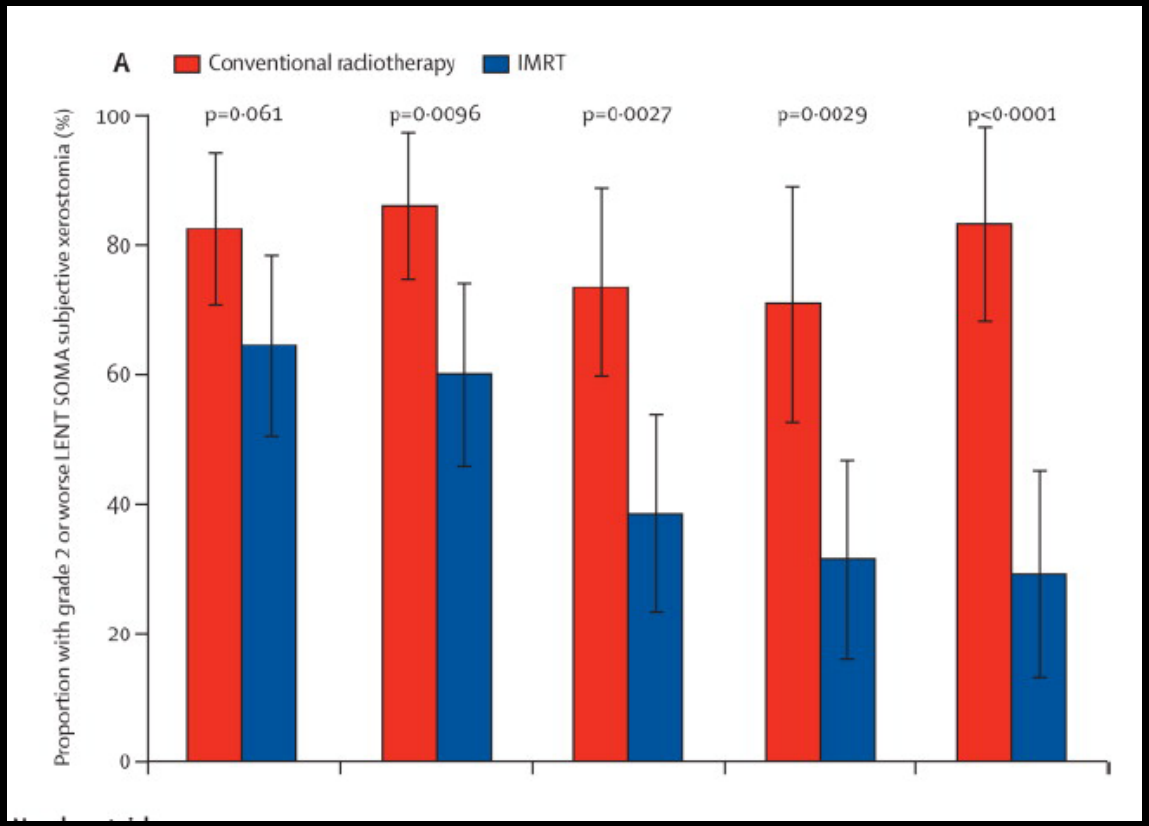
3D-CRT 60-65 Gy

IMRT 60-65 Gy

* To detect a 30% absolute difference of grade ≥ xerostomia

Lancet Oncol. 2011;12:127-136

Parotid-Sparing Intensity Modulated vs. Conventional Radiotherapy in Head and Neck Cancer (PARSPORT): a Phase 3 Multicentre Randomized Controlled Trial.



Lancet Oncol. 2011;12:127-136

Parotid-Sparing Intensity Modulated vs. Conventional Radiotherapy in Head and Neck Cancer (PARSPORT): a Phase 3 Multicentre Randomized Controlled Trial.

	3D-CRT	IMRT
Median dose to primary tumor	65 Gy	65 Gy
Median dose to elective nodes	50 Gy	54 Gy
Mean controlateral parotid dose	61 Gy	25 Gy

Lancet Oncol. 2011;12:127-136

PHASE III STUDY OF RADIATION THERAPY WITH OR WITHOUT CIS-PLATINUM IN PATIENTS WITH UNRESECTABLE SQUAMOUS OR UNDIFFERENTIATED CARCINOMA OF THE HEAD AND NECK: AN INTERGROUP TRIAL OF THE EASTERN COOPERATIVE ONCOLOGY GROUP (E2382)

HARRY QUON, M.D.,* TRACI LEONG, PH.D.,† ROBERT HASELOW, M.D.,‡ BRUCE LEIPZIG, M.D.,§ JAY COOPER, M.D.,¶ AND ARLENE FORASTIERE, M.D.‖

Unresectable stage III-IV H&N SCC

R

RT alone -70 Gy

RT -70 Gy
Weekly CDDP 20mg/m2

Primary site		
Nasopharynx	25 (16%)	16 (11%)
Oral cavity	43 (27%)	51 (34%)
Oropharynx	48 (30%)	37 (25%)
Larynx	7 (4%)	14 (9%)
Hypopharynx	30 (19%)	27 (18%)
Other	6 (4%)	4 (3%)

Int. J. Radiat. Oncol. Biol. Phys 2011;81:719-725

PHASE III STUDY OF RADIATION THERAPY WITH OR WITHOUT CIS-PLATINUM IN PATIENTS WITH UNRESECTABLE SQUAMOUS OR UNDIFFERENTIATED CARCINOMA OF THE HEAD AND NECK: AN INTERGROUP TRIAL OF THE EASTERN COOPERATIVE ONCOLOGY GROUP (E2382)

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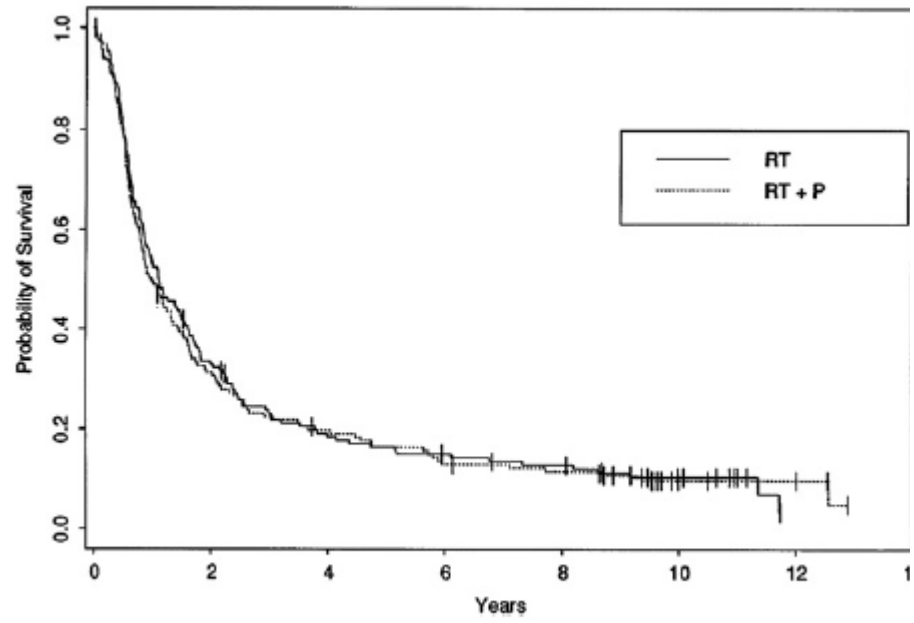

Fig. 3. Overall survival by treatment.

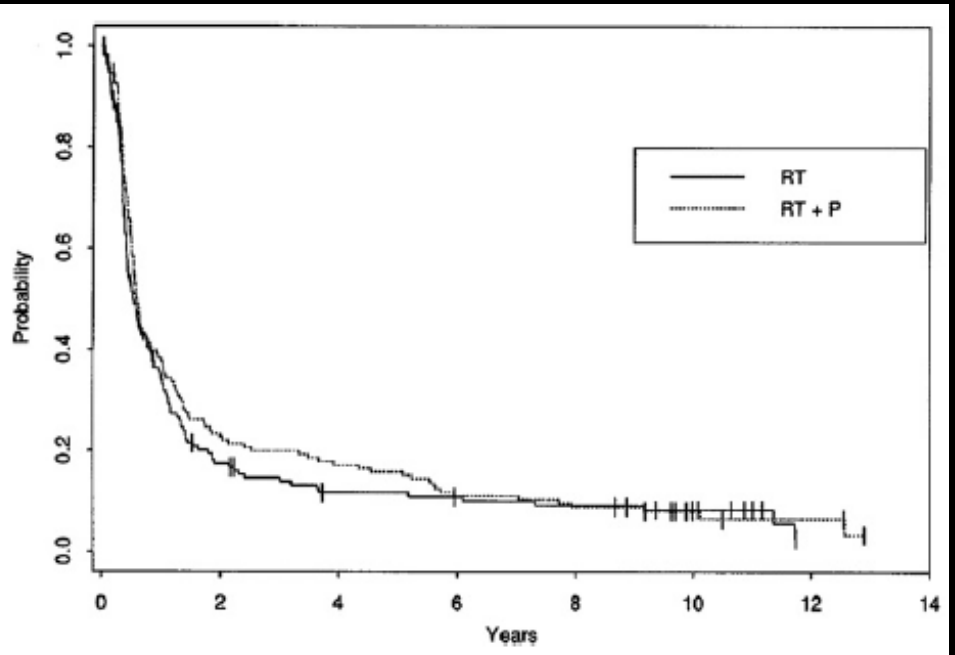

Fig. 2. Failure-free survival by treatment.

Int. J. Radiat. Oncol. Biol. Phys 2011;81:719-725

Conclusions:

I found of interest many abstracts presented at ASTRO-2011 and papers published this year!

4 randomized trials have been published

3 negatives: - Brachy-boost nasopharynx
- PORT 7-weeks vs 5-weeks
- RT vs weekly CDDP+RT in unresectable scc

1 positive : IMRT vs 3D-CRT in “parotid-sapring”

The role of IG-IMRT, as definitive or post-operative treatment, is growing in the management of SCC of the H&N and in particular of the Oropharyngeal Cancer.

Still, technical issues (target delineation) and clinical issues (dose and volume de-intensification, chemo-sensibilization) remains to be solved.

Grazie per l'attenzione!

marco.trovo@cro.it