2015 Yearly update of advances in medical oncology

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yearly update of advances in medical oncology

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cetuximab and Radiotherapy Versus Cisplatin and Radiotherapy for Locally Advanced Head and Neck Cancer: A Randomized Phase II Trial

Magrini SM et al, *JCO* 2016

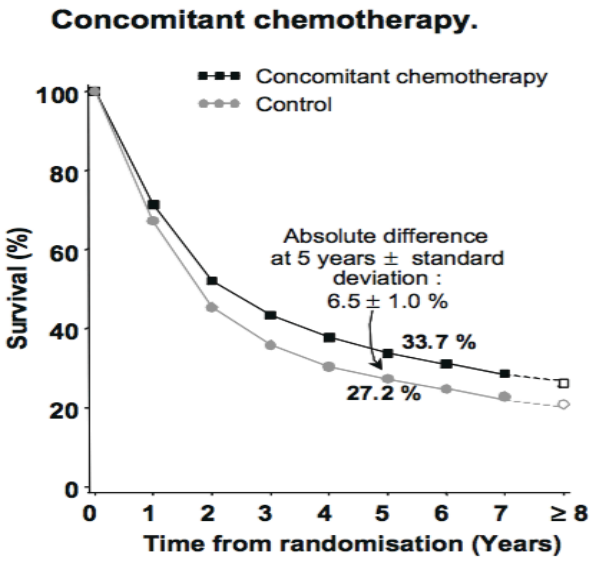
Cetuximab vs. cisPlatin for LAHNC

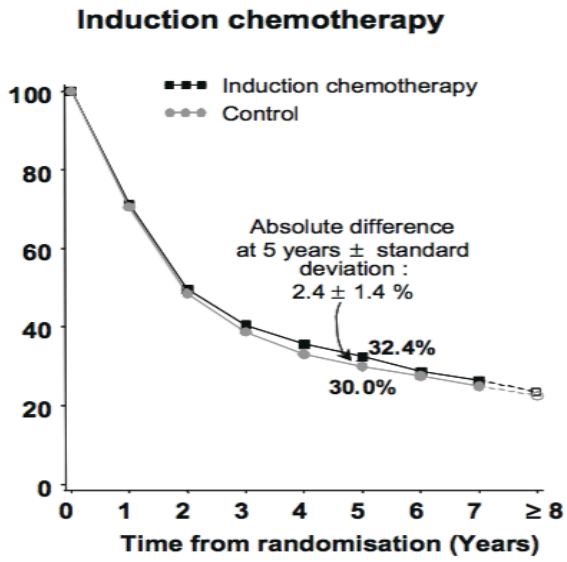
- ✓ well balanced randomized phase II trial
- ✓ few data, one of the very few studies attempting to compare CDDP vs. CTX in the management of locally advanced Head & Neck Cancer

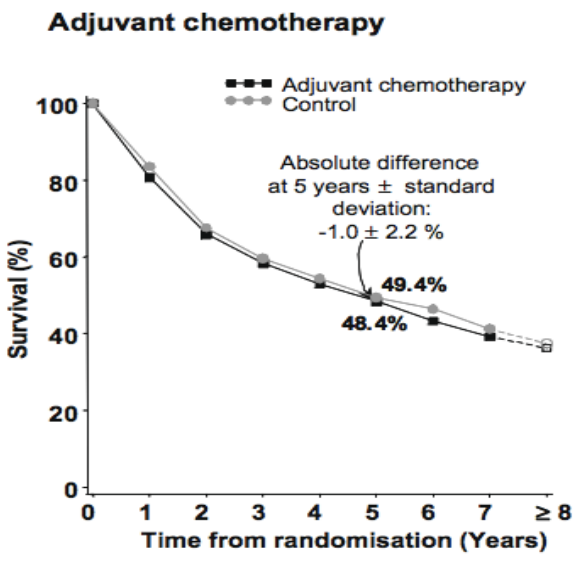
Magrini SM et al, *JCO* 2016

introduction

role of ChT MACH-NC metaanalysis







Pignon JP et al, *Radiother Oncol* 2009

introduction

role of ChT MACH-NC metaanalysis

- ✓ clear advantage in favor of concomitant ChT by terms of: OS, event free survival and loco-regional failure
- ✓ decreasing effect of chemotherapy on survival with increasing age
- ✓ pronounced effect on loco-regional failure for concomitant ChT which was not observed for induction chemotherapy
- ✓ "the role of cetuximab remains to be determined"

Pignon JP et al, *Radiother Oncol* 2009

introduction

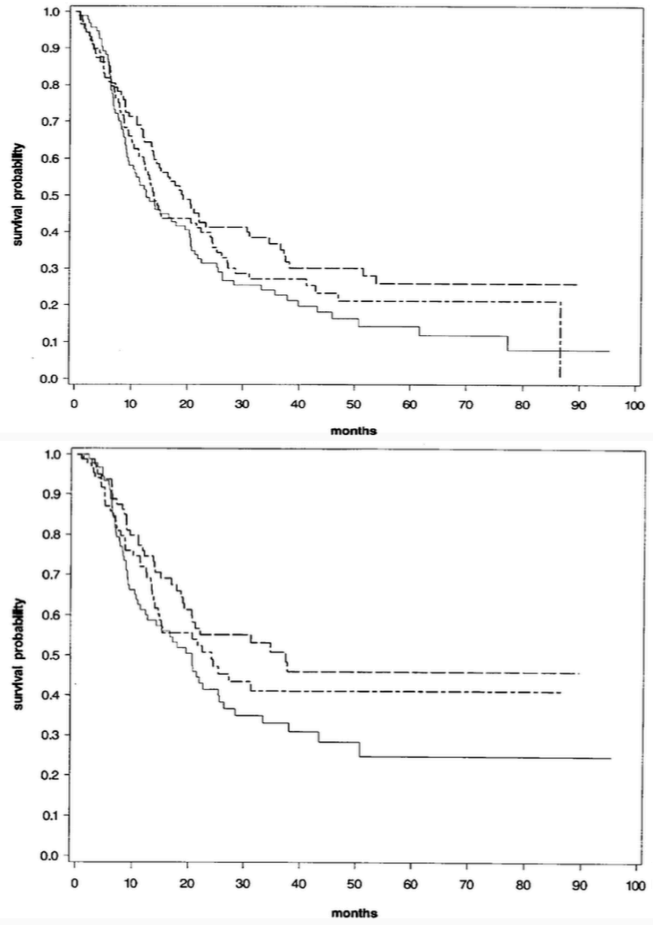
optimal ChT regimen Intergroup Phase III study

RANDOMIZE

Arm A : Radiotherapy Alone

Arm B : Radiotherapy plus Cisplatin

Arm C : Radiotherapy (split course) plus Cisplatin/5FU



Adelstein DJ et al, *JCO* 2003

introduction

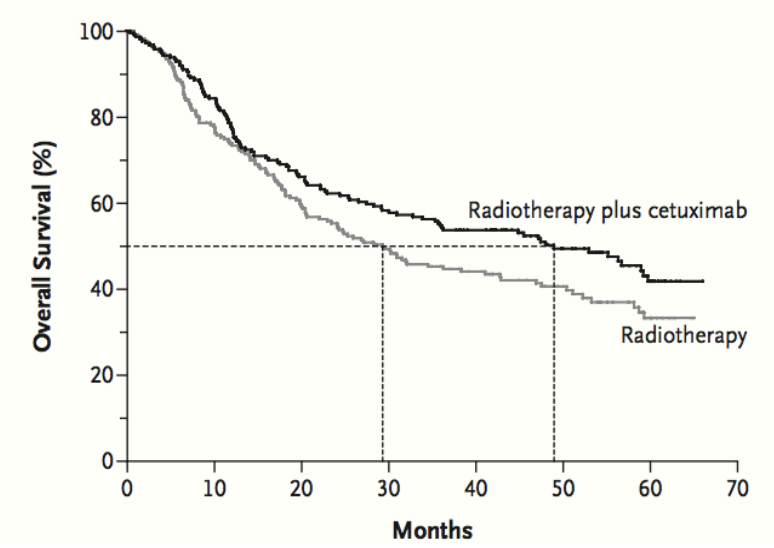
optimal ChT regimen Intergroup Phase III study

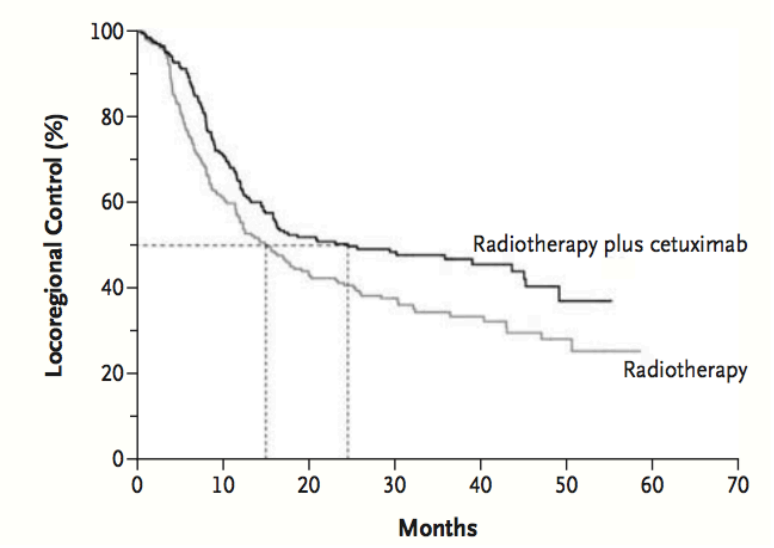
- ✓ addition of concurrent single agent cisPlatin to conventional single daily fraction radiation therapy, significantly improves survival
- ✓ concurrent ChT and radiation can be safely administered with acceptable toxicity

Adelstein DJ et al, *JCO* 2003

introduction

role of Cetuximab Bonner study





Bonner J et al, *N Engl J Med* 2006

introduction

role of Cetuximab Bonner study

✓ LRR: 24.4 months with CTX and 14.9 months with RT alone (hazard ratio 0.68; $p = 0.005$)

✓ OS: 49.0 months vs. 29.3 months (hazard ratio 0.74; $p=0.03$)

✓ grade 3 or greater toxic effects, including mucositis, did not differ significantly between the two groups

✓ treatment with concomitant high dose RT plus CTX improves LCR control and reduces mortality without increasing the common toxic effects associated with RT

Bonner J et al, *N Engl J Med* 2006

introduction

issues about Cetuximab

✓ what if anything does it add to the cisPlatin radiation backbone

- RTOG 0522: did not improve outcome & increased toxicity

✓ how does it compare with cisPlatin head to head?

- RTOG 1016 (U.S.A.)
- TROG (Australasia)
- De ESCALaTE (U.K.)

& - **Italian randomized phase II study**

Bonner J et al, *N Engl J Med* 2006

treatment regimens

✓ RT

max dose 70 Gy with conventional fractionation of 2 Gy per fraction was prescribed to the tumor and the involved sites

✓ ChT

CDDP 40 mg/m2 once per week

✓ CTX

400 mg/m2 as loading dose followed by CTX 250 mg/m2 once per week concomitant to radical RT

toxicity grading

- ✓ graded by using the National Cancer Institute Common Toxicity Criteria scale version 4.0.
- ✓ assessed at: end of treatment, 30 days, 60 days, 3 to 4 months, and 6 months

endpoints

primary endpoint:

- ✓ treatment compliance: defined as number of days of treatment discontinuation and drug dosage reduction

secondary endpoints:

- ✓ local control (LC) at 1 & 2 years
- ✓ metastasis-free survival (MFS)
- ✓ cancer-specific survival (CSS)
- ✓ overall survival (OS)

statistical analysis

- ✓ χ^2 tests to analyze treatment compliance (it was estimated that 65 patients per treatment arm would provide the study with a 80% power to detect a 20% difference in compliance
- ✓ Pearson's χ^2 tests to compare continuous variables
- ✓ Kaplan-Meier to estimate survival end points
- ✓ statistical analysis was performed with the SPSS software (version 17.0; SPSS, Chicago, IL).

inclusion criteria

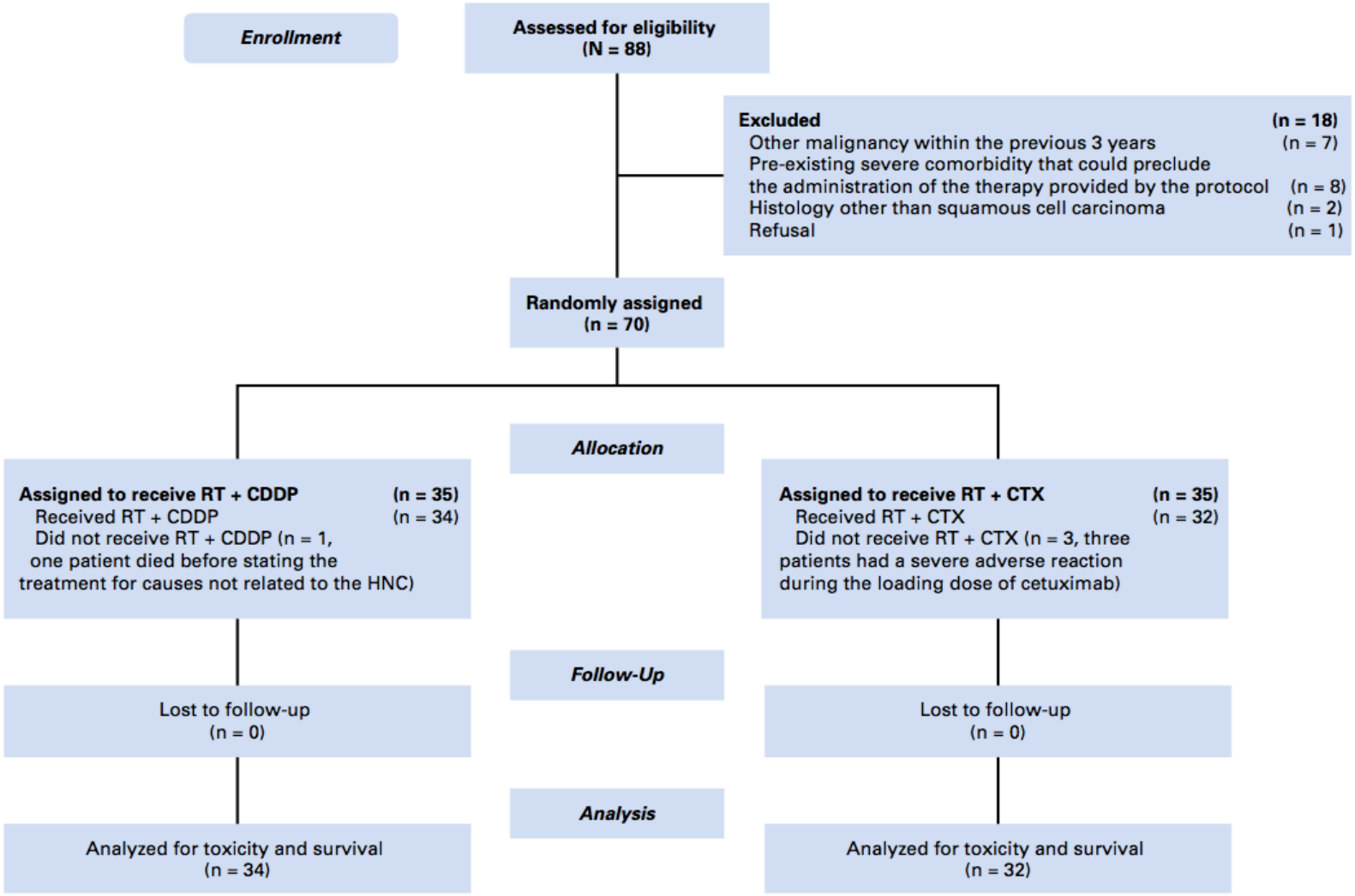
- ✓ histologically confirmed stage III (excluding T1N1), IVA or IVB SCC of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx
- ✓ ECOG PS of 0 or 1
- ✓ adequate hematologic, hepatic, and renal function

Patient and Tumor Characteristics

Characteristic	RT + CT (n = 35)	RT + CDDP (n = 35)	*P*
Age, years*	61 (44-80)	67.5 (36-77)	ns
Sex			ns
Male	26 (74)	24 (69)	
Female	9 (26)	11 (31)	
ECOG performance status			ns
1	21 (60)	22 (63)	
2	14 (40)	13 (37)	
Smoking			ns
Yes, current	18 (52)	18 (51)	
Yes, past	13 (37)	10 (29)	
No	4 (11)	7 (20)	
Alcohol use			.031
Yes, current	22 (63)	11 (31)	
Yes, past	3 (8)	6 (17)	
No	10 (29)	18 (51)	
Cancer location			ns
Oropharynx	17 (49)	16 (46)	
Oral cavity	5 (14)	5 (14)	
Hypopharynx	6 (17)	8 (23)	
Supraglottic larynx	7 (20)	6 (17)	
Stage			ns
III	7 (20)	7 (20)	
IVA	22 (63)	24 (69)	
IVB	6 (17)	4 (11)	
T stage			ns
T1-T2	6 (17)	11 (31)	
T3	14 (40)	9 (26)	
T4a-T4b	15 (43)	15 (43)	
N stage			ns
N0-N1	15 (43)	10 (29)	
N2a-N2b	12 (34)	19 (54)	
N2c-N3	8 (23)	6 (17)	
Grade			ns
GX	9 (26)	14 (40)	
G1	3 (8)	1 (3)	
G2	14 (40)	11 (31)	
G3	9 (26)	9 (26)	

Magrini SM et al, *JCO* 2016

CONSORT flow diagram



Magrini SM et al, *JCO* 2016

results

treatment compliance

- ✓ 4 pts in the CTX arm versus none in the CDDP arm had a break of more than 10 days in RT (P = .05)
- ✓ drug dosage reduction and drug discontinuation were not statistically different between the treatment arms
- ✓ median weight losses was similar
- ✓ pts treated with CTX needed more nutritional support during treatment (P = .032)

Treatment Characteristics and Compliance

Measure	RT + CTX (n = 32)	RT + CDDP (n = 34)	*P*
RT technique			ns
3D	3 (9)	6 (18)	
IMRT	8 (25)	5 (15)	
IMRT-SIB	15 (47)	12 (35)	
Tomotherapy	6 (19)	11 (32)	
RT			
Total dose (T + N)*	70.00 (69.40-70.00)	70.00 (69.90-70.00)	ns
Dose/fraction (T + N)*	2.05 (2.00-2.12)	2.00 (2.00-2.12)	ns
Total prophylactic dose*	56.00 (54.00-56.00)	56.00 (54.00-56.00)	ns
RT dose/fraction (prophylactic)	1.66 (1.60-1.80)	1.60 (1.60-1.80)	ns
Interruption, days			ns
< 5	26 (81)	32 (94)	
5-10	2 (6)	2 (6)	
> 10	4 (13)	0 (0)	
Interruption > 10 days			.05
No	28 (88)	34 (100)	
Yes	4 (12)	0 (0)	
No. of concurrent cycles of CTX or CDDP			ns
≤ 2	1 (3)	1 (3)	
3-4	5 (16)	5 (15)	
5-6	17 (53)	21 (62)	
≥ 7	9 (28)	7 (20)	
CTX or CDDP dosage reduction			ns
No	21 (66)	16 (47)	
Yes, 75%-80%	6 (19)	11 (32)	
Yes, 50%-60%	5 (15)	7 (21)	
AEs possibly related to treatment			ns
No	26 (81)	33 (97)	
Fatal	4 (13)	1 (3)	
Severe	2 (6)	0 (0)	
Severe or fatal AEs possibly related to treatment	6 (19)	1 (3)	.044
Nutritional support			ns
No	9 (28)	17 (50)	
Liquid supplements	11 (35)	6 (18)	
Enteral nutrition	10 (31)	9 (26)	
Parenteral nutrition	2 (6)	2 (6)	
Nutritional support, any	24 (75)	17 (50)	.032
Weight loss, kg†	7 (0-22)	8 (0-16)	ns

Magrini SM et al, *JCO* 2016

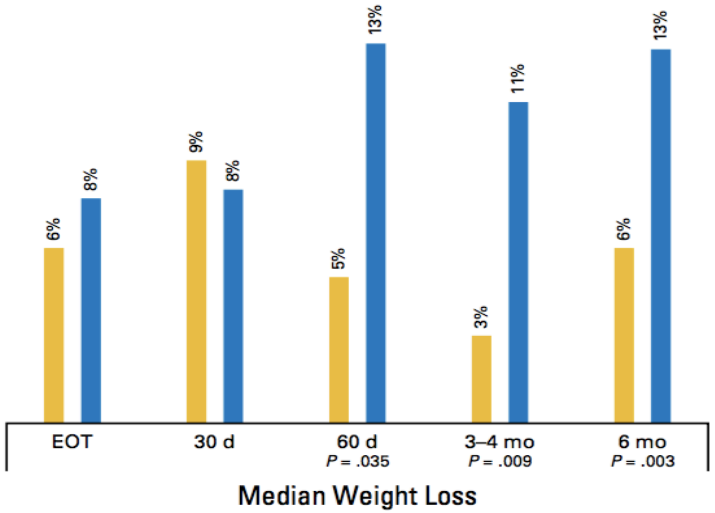
toxicity

- ✓ severe cutaneous toxicity G3 or worse, more common in the CTX arm
- ✓ no differences in mucositis
- ✓ pts in the CDDP arm had hematologic toxicity (G3) more frequently
- ✓ 4 pts in the CTX arm developed septic shock and three died
- ✓ pts in the CTX arm needed more time to recover from cutaneous and mucosal toxicity, with higher rates of persistent toxicity at 1 month after the EOT

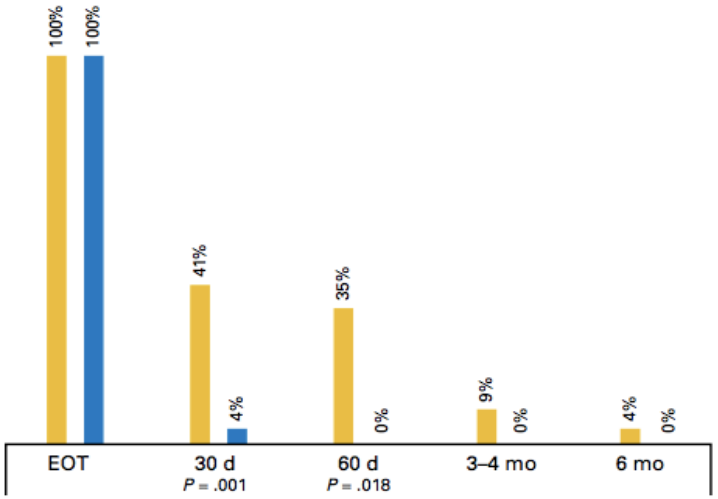
	Acute Toxicity		
	RT + CTX (n = 32)	RT + CDDP (n = 34)	*P*
Cutaneous toxicity at EOT			ns
G0-G1	7 (22)	12 (36)	
G2	11 (34)	15 (44)	
G3	13 (41)	7 (20)	
G4	1 (3)	0 (0)	
Cutaneous toxicity ≥ G3	14 (44)	7 (21)	.039
Mucositis at EOT			ns
G0-G1	4 (13)	1 (3)	
G2	9 (28)	15 (44)	
G3	19 (59)	18 (53)	
Total WBC at EOT			.001
G0	30 (94)	17 (50)	
G1	0 (0)	7 (20)	
G2	0 (0)	6 (18)	
G3	1 (3)	4 (12)	
G4	1 (3)	0 (0)	
Hemoglobin at EOT			< .001
G0	30 (94)	17 (50)	
G1	1 (3)	13 (38)	
G2	0 (0)	4 (12)	
G3	1 (3)	0 (0)	
Platelets at EOT			.003
G0	31 (97)	21 (62)	
G1	0 (0)	9 (26)	
G2	0 (0)	3 (9)	
G3	1 (3)	1 (3)	
Hematologic toxicity ≥ G3	2 (6)	5 (15)	ns
Renal toxicity at EOT			.033
G0	31 (97)	27 (79)	
G1	1 (3)	3 (9)	
G2	0 (0)	3 (9)	
G3	0 (0)	1 (3)	
GI toxicity at EOT			.036
G0	27 (85)	21 (62)	
G1	3 (9)	7 (20)	
G2	2 (6)	5 (15)	
G3	0 (0)	1 (3)	

Magrini SM et al, *JCO* 2016

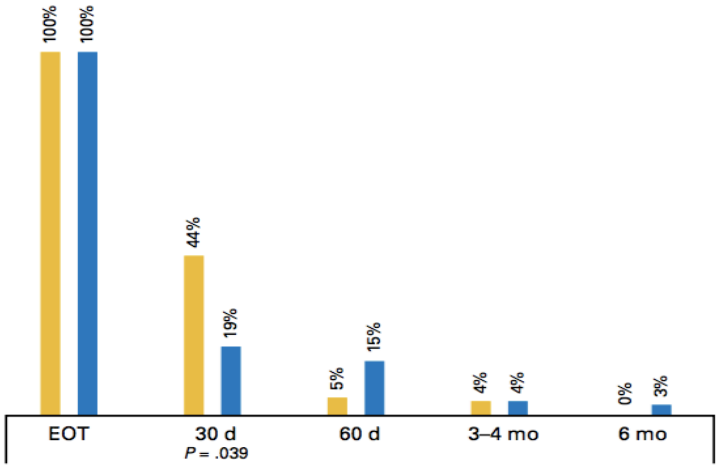
results



Median Weight Loss



Cutaneous Toxicity



Mucositis

Magrini SM et al, *JCO* 2016

therapeutic results

LC
- ✓ CTX: 64% (1y) and 53% (2y)
- ✓ CDDP: 84% (1y) and 80% (2y)

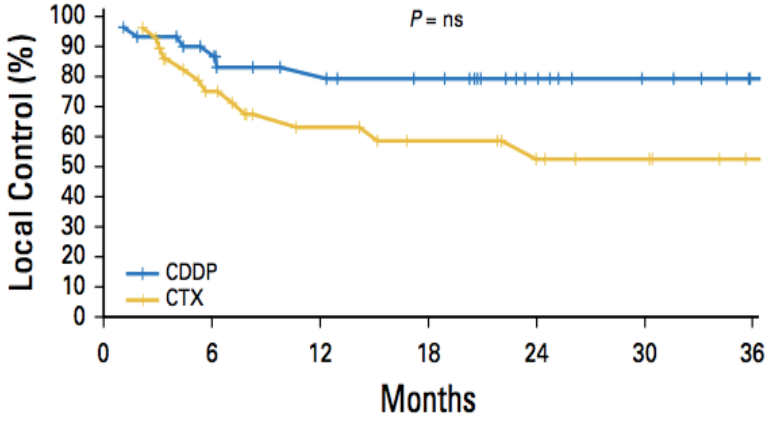
MFS
- ✓ CTX: 97% (2y)
- ✓ CDDP 90% (2y)

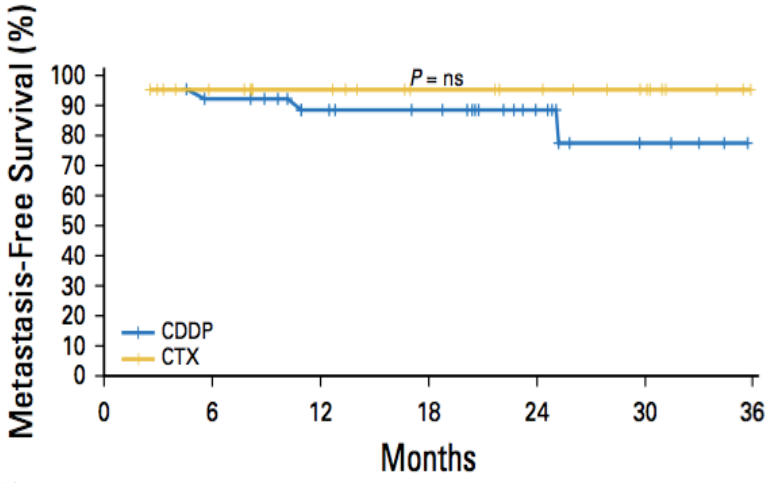
OS
- ✓ CTX: 68% (2y)
- ✓ CDDP: 81% (2y)

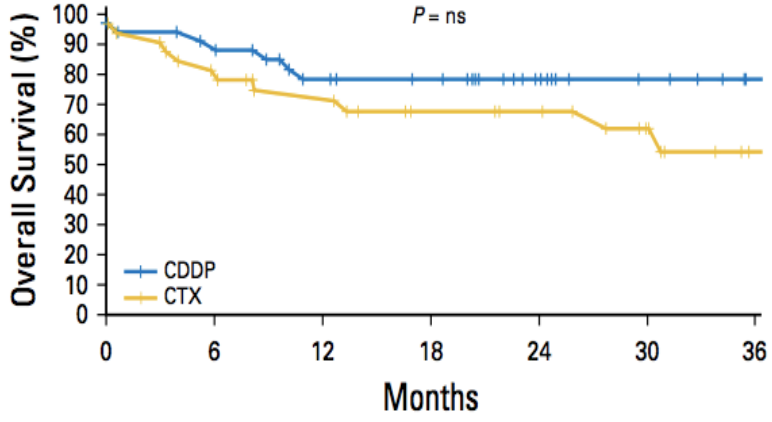
!!! in a subgroup analysis of patients with oropharyngeal and oral cavity tumors, LC, CSS, and OS rates were higher in patients treated with CDDP

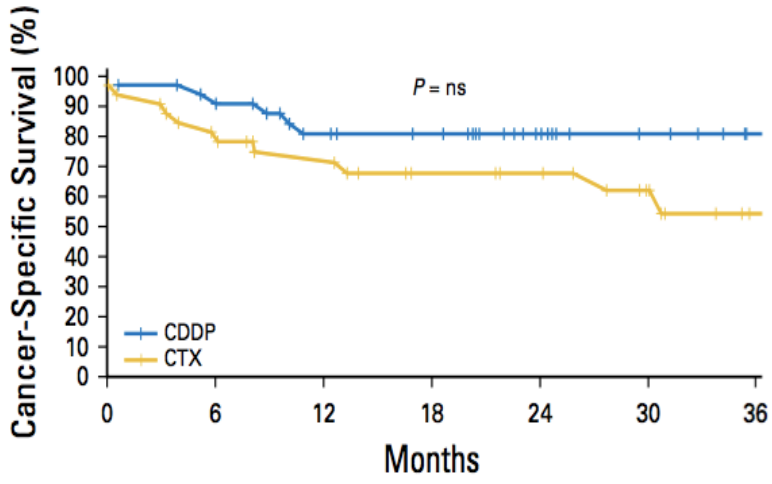
Magrini SM et al, *JCO* 2016

therapeutic results









Magrini SM et al, *JCO* 2016

discussion

therapeutic results

✓ porspective randomized trials

- RTOG 1016 (U.S.A.)
- TROG (Australasia)
- De ESCALaTE (U.K.)

✓ retrospective trials

- MSKCC studies

discussion

MSKCC retrospective studies

- ✓ 174 pts, newly diagnosed LAHNC
- ✓ CDDP/RT (125 pts) vs. CTX/RT (49 pts)
- ✓ exclusion criteria: additional systemic therapy, weekly CDDP
- ✓ median follow up 22.5 mths
- ✓ LRF 5.7% vs. 39.9% ($p<0.0001$), FFS 87.4% vs. 44.5% ($p<0.0001$), OS 92.8% vs. 66% ($p=0.0003$)
- ✓ no statistically significant difference in late Grade 3 or 4 toxicity or feeding tube dependence

→ advantage over CDDP, but results must be interpreted cautiously due to the retrospective nature of the study and significant differences in pt selection

Koutcher L et al, *Int J Rad Oncol Biol Phys* 2011

discussion

MSKCC retrospective studies

- ✓ 360 pts
- ✓ CDDP/RT (259 pts) vs. 5FU/carbo (52) vs. CTX/RT (49 pts)
- ✓ CTX & 5FU/carbo pts older, lower PS, comorbidities, worse renal function
- ✓ median follow up 4 years
- ✓ OS 86.9% vs. 70.2% vs. 40.9%($p<0.0001$)
- ✓ LRF 6.3% vs. 9.7% vs. 40.2% ($p<0.0001$)
- ✓ late toxicity 8% vs. 25% vs. 7.7%

→ CTX inferior & routine use of CTX in the management of LAHNSCC should be considered cautiously

Shapiro LQ et al, *Oral Oncol* 2014

discussion

CTX toxicity

- ✓ 13% of pts in the CTX arm had a treatment break of longer than 10 days (P <.05)
- ✓ 4 pts developed septic shock, three of whom died
- ✓ 1 pt died from aspiration pneumonia

authors' conclusion

✓CTX concomitant to RT lowered compliance and increased acute toxicity rates

✓efficacy outcomes were similar in both arms

✓these results raise the issue of appropriately selecting patients with head and neck cancer who can benefit from CTX in combination with RT.

-

limitations of this study

- ✓ small sample size
- ✓ compliance (primary endpoint), far lower than historical control
  - CTX: 28% of pts received at least 7 Cy vs. 94% (Bonner trial)
  - CDDP: 20% received all planned ChT Cy vs. 90% (RTOG 0522)
- ✓ significant toxicity compared to historical control
- ✓ no p16 or HPV test to further identify pts

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Role of Chemoradiotherapy in Elderly Patients With Limited-Stage Small-Cell Lung Cancer

Corso C et al, *JCO* 2015

ChT/RT in elderly pts with LS SCLC

- ✓ largest so far retrospective analysis, attempting to answer the question: does ChT/RT plays a role in elderly pts with LS SCLC?

introduction

general points

- ✓ lung cancer: leading cause of cancer related mortality
- ✓ SCLC: 15%
  - 45% pts older than 70 years
  - 10% pts older than 80 years
- ✓ standard approach: concurrent ChT/RT

introduction

Warde & Payne meta analysis

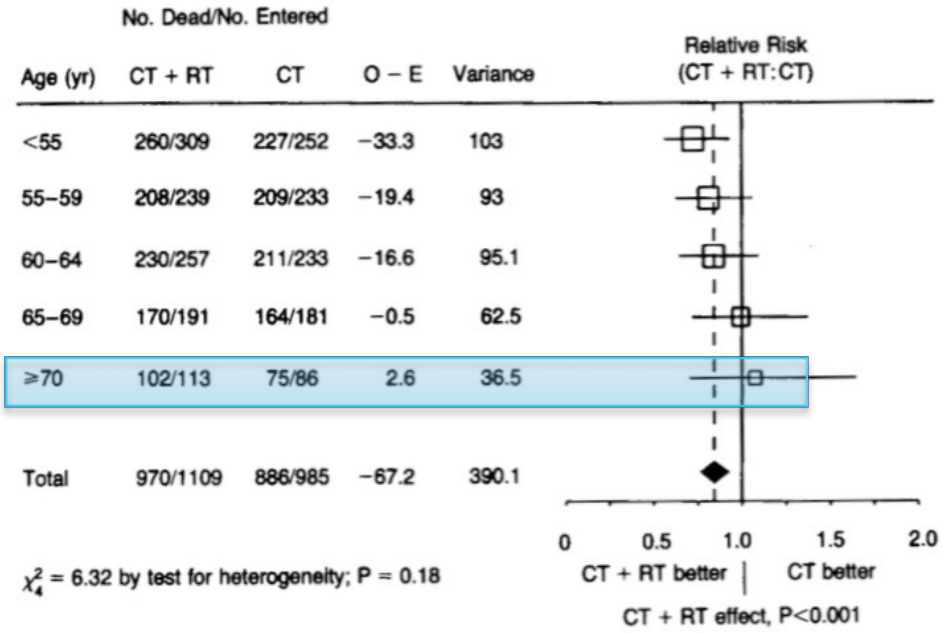
- ✓ radiation therapy improved 2-year survival by 5.4%
- ✓ intrathoracic tumor control was improved by 25.3%

Warde P, Payne D *JCO* 1992

introduction

Pignon et al meta analysis

- ✓ 13 trials, 2140 pts
- ✓ 14% reduction in mortality rate and improved survival
- ✓ trend toward a larger reduction in mortality among younger patients



Pignon LP et al, *N Engl J Med* 1992

issues about ChT/RT in elderly pts

- ✓ role of ChT/RT in eledrly pts
- ✓ survival benefit
- ✓ associated significant toxicity

- no randomized phase III trials to compare ChT/RT vs. ChT

data source & study cohort

- ✓ data from National Cancer Data Base (NCDB)
  - 1500 hospitals in United States
  - patient demographics
  - stage of disease
- ✓ pts ≥ 70 with LS SCLC diagnosed between 2003–2011
  - clinical stage I-III (cT1-T4, cN0-N3)
  - no surgery
  - standard fractionation (1.5 – 2 Gy)
  - survival & follow up greater than 30 days
  - concurrent or sequential ChT/RT

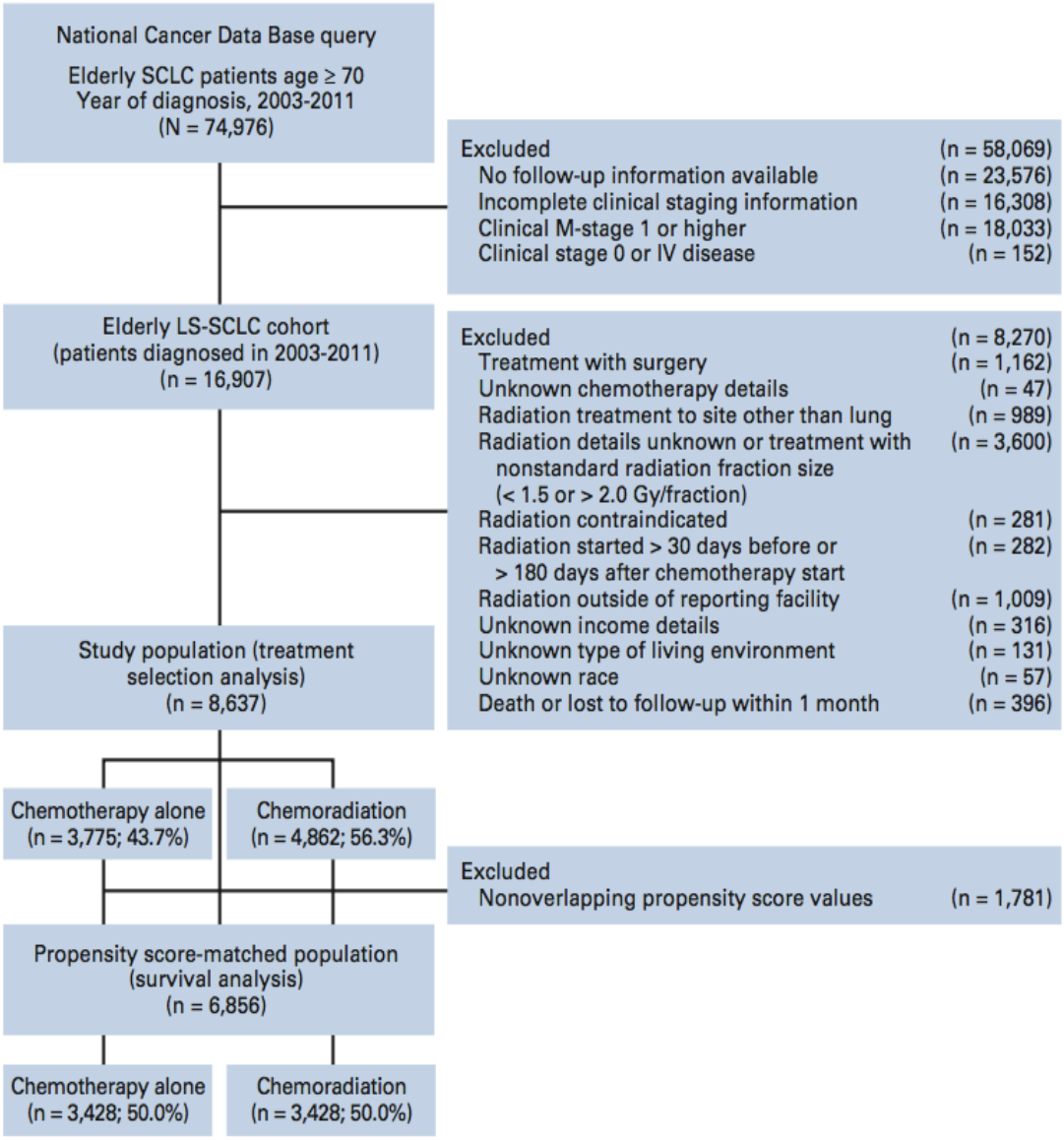
  (concurrent: starting RT 30 days before to 60 days after ChT)

Baseline Demographics and Clinical Characteristics for Patients Treated With CT or CRT

Characteristic	CT (n = 3,775) No.	CT (n = 3,775) %	CRT (n = 4,862) No.	CRT (n = 4,862) %	*P*
Age at diagnosis, years					< .001
Median	76		75		
IQR	73-80		72-78		
≥ 80	1,057	28.0	872	18.0	< .001
Male	1,683	44.6	2,323	47.8	.003
White	3,489	92.4	4,451	91.6	.138
Charlson-Deyo score					< .001
0	1,950	51.7	2,975	61.2	
≥ 1	1,825	48.3	1,887	38.8	
Great circle distance, miles					.03
Median	7.6		7.5		
IQR	3.6-18.8		3.5-18.1		
Clinical stage					< .001
I	471	12.5	773	15.9	
II	359	9.5	550	11.3	
III	2,945	78.0	3,539	72.8	
Clinical T stage					< .001
0-2	1,879	49.8	3,160	65.0	
3-4	1,896	50.2	1,702	35.0	
Clinical N stage					.322
0	802	21.3	1,076	22.1	
1-3	2,973	78.8	3,786	77.9	
Income ≥ $48,000	1,985	52.6	2,442	50.2	.030
Facility type					.294
Academic	800	21.2	1,076	22.1	
Nonacademic	2,975	78.8	3,786	77.9	
Insurance type					.402
Private	360	9.5	490	10.1	
Nonprivate	3,415	90.5	4,372	89.9	
Urban population	2,495	66.1	2,936	60.4	< .001
Chemotherapy type					
Undocumented	333	8.8	296	6.1	< .001
Single agent	179	4.5	130	2.7	
Multiagent	3,263	86.4	4,436	91.2	
Time between CT and RT, days					
Median			21		
IQR			0-56		
Radiation dose, Gy					
Median			59.4		
IQR			50.4-61.2		

Corso C et al, *JCO* 2015

data source & study cohort



Corso C et al, *JCO* 2015

statistical analysis

- ✓ χ^2 tests to compare categorical variables
- ✓ sample ***t*** tests to compare continuous variables
- ✓ Kaplan Meier to determine OS (primary endopoint)
- ✓ Cox hazards to determine significant contributors to differences in OS
- ✓ Charlson-Deyo comorbidity index
- ✓ all analyses were performed by STATA SE 13.1 software

Corso C et al, *JCO* 2015

study cohort characteristics

- ✓ 8637 pts
- ✓ 3775 pts (43.7%) ChT and 4862 pts (56.3%) ChT/RT
- ✓ median follow up: 5.1 y
- ✓ median age: 75 y
- ✓ pts receiving ChT:
  - older
  - higher overall clinical stage
  - medical comorbidities
- ✓ median dose RT 59.4 Gy (50.4 to 61.2 Gy)
- ✓ only 6.8% received the 45 Gy BID regimen

Corso C et al, *JCO* 2015

results

overall survival

- ✓ factors associated with improved OS on univariable analysis
  - ChT/RT
  - age younger than 80 y
  - female sex
  - Charlson – Deyo score 0
  - clinical Stage I
  - non single agent CT
- ✓ strongest association on multivariable analysis:
  - ChT/RT

Corso C et al, *JCO* 2015

results

overall survival

Univariable and Multivariable Analyses of Predictors of OS

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
CRT *v* CT	0.50	0.47 to 0.52	< .001	0.52	0.49 to 0.54	< .001
Age (≥ 80 *v* < 80 years)	1.34	1.27 to 1.41	< .001	1.25	1.18 to 1.33	< .001
Sex (female *v* male)	0.86	0.82 to 0.90	< .001	0.83	0.79 to 0.87	< .001
Race/ethnicity (white *v* nonwhite)	0.93	0.86 to 1.01	.09			
Charlson-Deyo score (≥ 1 *v* 0)	1.26	1.21 to 1.32	< .001	1.23	1.17 to 1.29	< .001
Distance ≥ 7.6 miles	0.99	0.95 to 1.03	.63			
Clinical stage						
II *v* I	1.22	1.11 to 1.34	< .001	1.21	1.11 to 1.32	< .001
III *v* I	1.61	1.50 to 1.72	< .001	1.60	1.50 to 1.71	< .001
Income (≥ $48,000 *v* < $48,000)	0.97	0.93 to 1.02	.22			
Facility type (nonacademic *v* academic)	0.99	0.94 to 1.05	.83			
Insurance type (nonprivate *v* private)	1.01	0.94 to 1.09	.76			
Urban population	1.03	0.99 to 1.08	.18			
CT type						
Single agent *v* undocumented	1.28	1.11 to 1.47	.001	1.25	1.07 to 1.46	.006
Multiagent *v* undocumented	0.96	0.88 to 1.05	.43	0.99	0.90 to 1.09	.89

Corso C et al, *JCO* 2015

results

overall survival

for entire cohort

- ✓ median OS: 15.6 vs. 9.3 mths (p<.001)
- ✓ 3 year OS: 22% vs. 6.3%

for pts older than 80 years (1057 pts ChT and 872 pts ChT/RT)

- ✓ median OS: 13.6 vs. 8.1 (p<.001)
- ✓ 3 year OS: 16.4% vs. 5.2%

for Charleson - Deyo score 2 (medical comorbodities)

- ✓ improvement in both median OS (p<.001) and 3 year OS

Corso C et al, *JCO* 2015

results

concurrent vs. sequential ChT/RT

- ✓ pts ChT/RT
  - 3472 (75.4%) concurrent ChT/RT
  - 1136 (24.7%) sequential ChT/RT
- ✓ modest survival benefit for concurrent treatment over sequential
- ✓ median OS: 17 vs. 15.4 mths (p<.01)
- ✓ 3 year OS: 24.2% vs. 20.3%

Corso C et al, *JCO* 2015

discussion

therapeutic effect – overall survival

- ✓ Pignon et al meta analysis: no survival benefit for pts younger than age 55 years
  - enrollment before 1990 with old fashioned RT techniques
  - small elderly cohort (199 pts of 2103)
  - all studies with multiagent ChT, considered more toxic

- ✓ current study
  - modern RT techniques
  - optimal ChT regimen
  - improvement in supportive care medicine

discussion

therapeutic effect – toxicity

- ✓ Schild SE et al, *Cancer* 2005: no difference in OS but moderate increased toxicity
- ✓ Yen AR et al, C*ancer* 2000 (Intergroup Trial 0096): slightly higher toxicity

- ✓ current study
  - modern RT techniques
  - optimal ChT regimen
  - improvement in supportive care medicine

conclusion

- ✓ elderly pts who are candidates for ChT, should be strongly considered for ChT/RT
- ✓ elderly age should not be a contraindication for combined modality treatment

σας ευχαριστώ!