



Regional chemotherapy

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Introduction

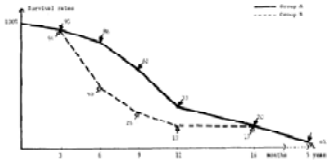
- Head and Neck Squamous Cell Carcinoma (HNSCC):
 - 5th most common malignancy
 - over 600,000 new cases worldwide
 - over 300,000 deaths
 - 50-70% locally advanced, (functionally) inoperable disease
- ➔ (Concomitant) chemoradiation (CCRT)

Introduction

- Contents:
 - Is regional chemotherapy new?
 - Phase II results
 - Randomised trial
 - Subgroup analysis
 - Does completeness of treatment make a difference?
 - Conclusion

Introduction

- Richard et al 1974
 - Randomised weekly Intra-arterial MTX + RT vs RT alone
 - Median surv 9 vs 6 months



Introduction

- Molinary et al 1982
 - MTX or Bleomycine pre-operative
 - 85 patients
 - More toxicity with MTX
 - Despite impressive remissions microscopic tumor was spread around the original tumor bed

Introduction

- Baker et al 1984 (review):
 - Despite almost 3 decades of experience, the use of intraarterial (IA) chemotherapy for the treatment of head and neck cancer is not universally accepted. The overall reported response rates are not substantially different from the therapeutic results obtained with systemic therapy.

Introduction

- Richard et al 1991
 - EORTC randomised
 - 222 patients vincristine and bleomycine pre-op
 - Overall no difference
 - Floor of mouth tumors did better with pre-op chemo

Introduction

- Robbins 1997
 - 60 patients, 57 evaluable patients
 - Stage III/IV head and neck carcinoma
 - Overall CR: 74%
 - Only 4% loco-regional recurrence

Introduction

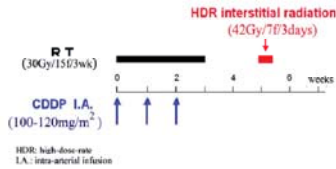
- Homma et al 2005
 - Stage III/IV refused surgery or inoperable (n=24)
 - 43 patients
 - 3 yr PFS: 69% (56% inoperable cases)
 - 2 pts neurological deficits (grade III)

Introduction

- Robbins et al RTOG 9615
 - 67 pts, 11 centers
 - T4 Oral Cavity, Oropharynx, Larynx, Hypopharynx
 - Overall CR 80%
 - 2 y DFS 46%

Introduction

- Nishioka et al 2006
 - Four patients ¾ CR
 - Intra-arterial 100 mg/m² cisplatin conc. with 30 Gy 15/5 followed by brachy boost



Introduction

- Wu et al 2008
 - Intra-arterial MTX as continuous infusion port a cath 50 mg/day 7.5 days followed by 10 weekly bolus of 25 mg
 - Fifteen patients all CR
 - Median FU 43 months no recurrences

Introduction

- Damascelli et al 2007, phase II trial
- Neoadjuvant paclitaxel* 230-150-(150-150) mg/m²
- Sixty patients stage IV
- 75% CR on imaging

*bound to albumin nano particles

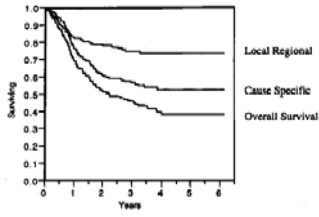
Introduction

- Mitsudo et al ASCO 2008
- 30 patients stage III/IV
- Pre-op Intra-arterial
 - docetaxel 15 mg/m²/week/4
 - Cisplatin 5 mg/m²/day/20
- RT 40 Gy/four weeks
- Path resp rate: 89% CR

Introduction

- Mitsudo (cont.)
- Same regimen as organ preservation with 6 weeks treatment
- LR 20% -> salvage operation
- One local recurrence, on DM

Targeted chemoradiation for advanced head and neck cancer:
Robbins et al 2000



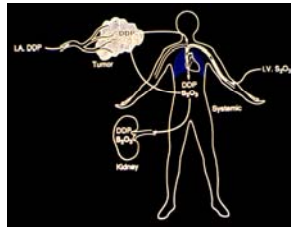
Initial CR:
 Primary: 80%
 Regional: 61%

Number of Patients at Risk

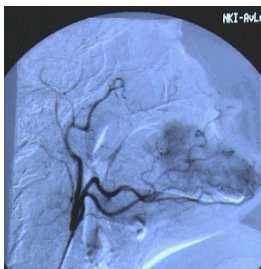
213	139	109	72	40	23	3	Local Regional
213	151	112	76	41	24	3	Cause Specific
213	151	112	76	41	24	3	Overall Survival

Intra-arterial chemoradiation

- Treatment schedule
 - Chemotherapy
 - day 2, 9, 16, 23
 - < one hour after radiotherapy
 - Intra-arterial cis Pt (150 mg/m²)
 - Na-thio sulfate (9 gr/m² in 15 minutes)
 - Na-thio sulfate (12 gr/m² in 6 hours)
 - Radiotherapy
 - 70 Gy 35 fractions 5/week



Intra-arterial chemoradiation



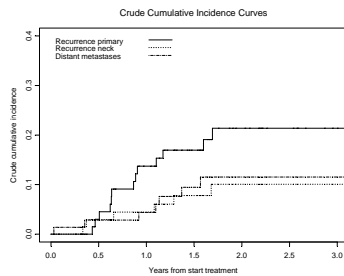
Phase II trial at NKI

Intra-arterial Phase II

- Inoperable head and neck cancer of the Oropharynx, oral cavity, hypopharynx or larynx
- Intra-arterial chemoradiation 70 Gy 35 fractions 4x150 mg/m² cisplatin
- 79 Patients
- FU 3 years

Intra-arterial Phase II


Recurrence pattern



Balm et al Head and Neck 2004


Randomised trial

- So,
- Intra-arterial chemoradiation results seemed reproducible at NKI




Randomised trial

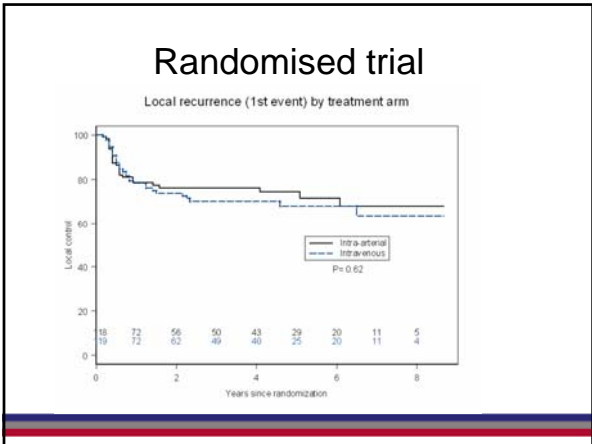
- CKTO 2000-01
- Inclusion criteria:
 - Oropharynx, Oral Cavity, Hypopharynx
 - Inoperable or functional inoperable (i.e. requiring total glossectomy)
 - Stage IV
 - T3/4, any N stage

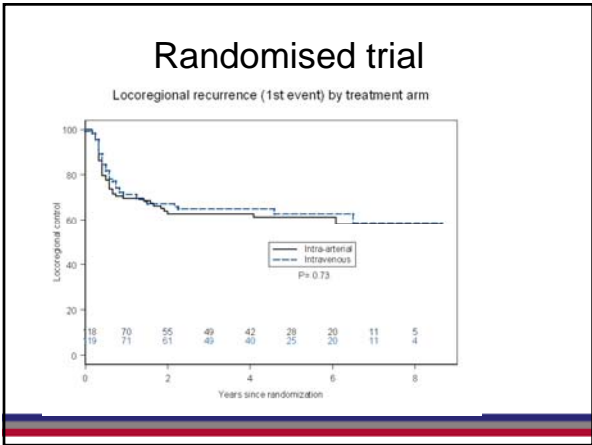


Randomised trial

- 01 01 2000 – 23 11 2004
- 240 / 240 patients included
- Median FU: 33 months
- Mean age: 56 years
- M/F: 2.5/1
- Comparing:
 - Intra-arterial CisPt 4x150 mg/m2, day (2,9,15,22) and systemic rescue Na-Thiosulfate
 - Intra-venous CisPt 3x100 mg/m2 (1, 22, 43)
 - With concomitant RT, 70 Gy 35 fractions, week 7

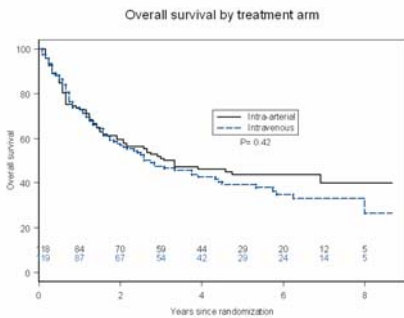








Randomised trial



Randomised trial

- Conclusion:
 - No difference between treatment arms
 - More bilateral infusions than others due to patient selection (inoperability)
 - Will selection make a difference?

Patient selection: TNM stage

- local extension (T)
 - regional extension (N)
 - distant metastases (M)
- } categorization

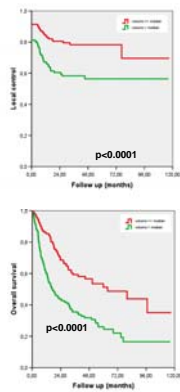
but...

- higher T-stages (T3-4) determined by surgical criteria
- value in nonsurgical treatment unknown

Patient selection: tumor volume

- tumor volume has been found to be a predictor of outcome after RT for several solid tumor types (e.g. cervix, lung)
- tumor volume is a known prognostic factor in RT for early stage HNSCC
- role of tumor volume in combined CCRT only scarcely investigated

**T3-4
Head and neck
carcinoma
371 patients
various regimens
chemoradiation
cut off 30 cc**



Knegjens et al submitted

Subgroup analysis

- With tumors crossing the midline > 1 cm intra-arterial treatment is divided over the two feeding arteries (50% of the cases)
- With lateralized tumors this is not the case:
 - Does a lateral localization of the tumor indicates a difference in response?

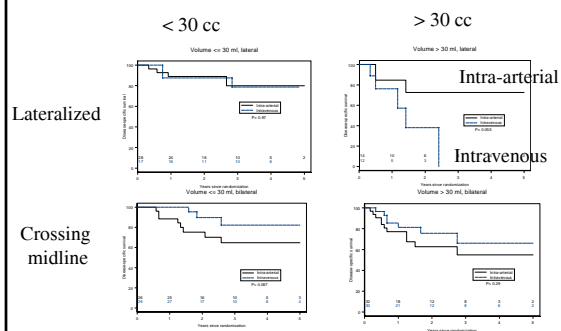
Subgroup analysis

- Tumors for intravenous and intra-arterial treatments were scored as lateralized (>1 cm over midline) or not.
- Tumor volume was measured

Results subgroup analysis

- Local control
 - intra-arterial vs. intravenous
 - tumor not crossing the midline
 - HR=.17, 95% CI: .05-.60, p=.0025
 - Mainly attributable to those patients with > 30 cc tumor volume

Results Subgroup analysis



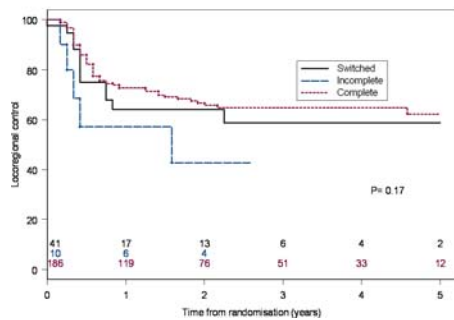
Treatment compliance

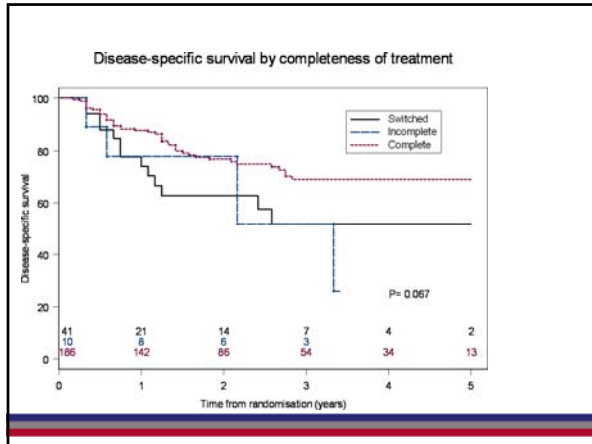
- Does completeness of treatment make a difference?

Radplat Phase III Compliance

- Intra-arterial:
 - 78% complete course
 - Three patients no chemoradiation
 - 10 patients received only intravenous
 - 15 patients <4 courses
- Intravenous:
 - 80% complete course
 - One patient died before treatment
 - 23 patients <3 courses
 - 2 patients no chemoradiation

Locoregional recurrence (1st event) by completeness of treatment





Disease specific survival

Compliance:	>80%	80% or less
intravenous	77%	58%
Intra-arterial	72%	60%

Toxicity differences?

Randomised trial Side Effects

Gastrostomy	IA		IV	
	N	%	N	%
no	7	6	14	12
after start RT	48	44	54	48
started before	54	50	44	39
Missing	11	9	7	6

P=0.16

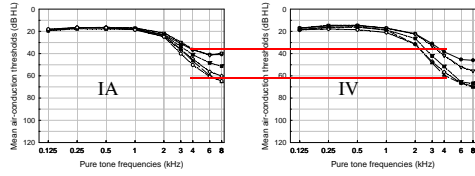
Randomised trial Side Effects

Acute toxicity Grade >2 (CTC 2.0)	Intra-arterial (%)	Intravenous (%)	P value
Renal	1	9	<0.0001
Platelets	12	6	0.19
Hemoglobin	12	7	0.23
Leucocytes	50	36	0.085
Any hematological	52	42	0.22

Randomised trial Side Effects

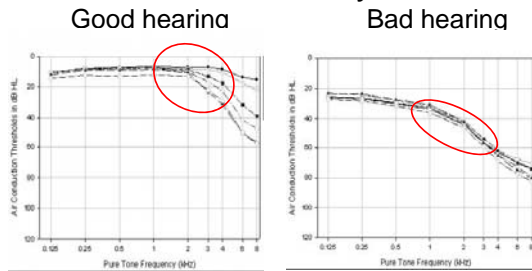
Acute toxicity Grade >2 (CTC 2.0)	Intra-arterial	Intravenous	P value
Skin (%)	10	23	0.051
Mucosa (%)	50	54	0.5
Ototoxicity (%)	53	58	0.4
Cardiac/Pneumonia (n)	5	9	0.02
Neurological (n)	9	1	0.005

Ototoxicity



No difference in ctc >2 (53 vs 58%)
 Less damage with intra-arterial in high freq.
 26 vs 38 qualified for hearing aid (>35 dB)

Ototoxicity



Courtesy: C.L. Zuur

Conclusion

- Intra-arterial chemoradiation is not superior nor inferior to intravenous
- Lack of phase III data on non-RADPLAT approaches
- Tumor volume is an easy assessable outcome predictor for large (T3-4) Head and Neck carcinomas
- For large (>30 cc) lateralized tumors intra-arterial cisplatin chemoradiation can be superior to systemic chemoradiation
- Complete chemotherapy course increases control rate
