Fractionation:
needs learned for modern treatments

Back to the future:
head and neck cancer

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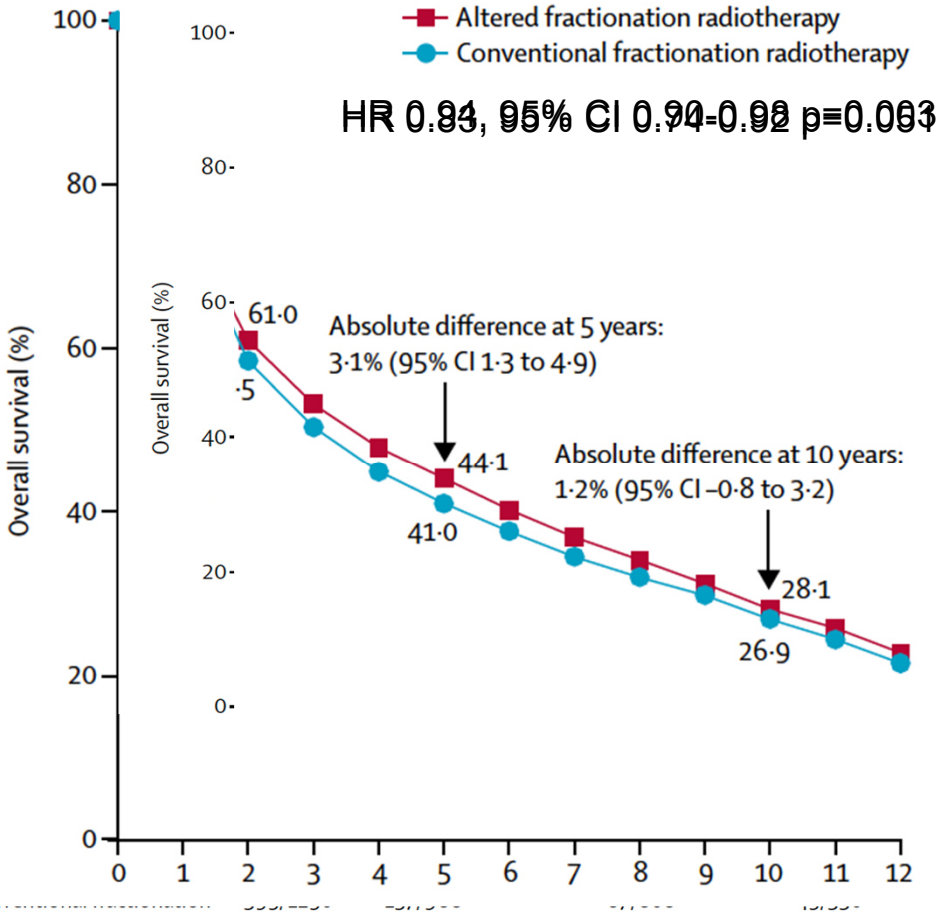
Locally advanced HNSCC: where do we stand?

- Cisplatin-based concurrent CRT is the established standard of care
- Overall survival is still around ≈ 50% at 5 years
- HPV positivity is a strong, independent prognostic factor, yet not predictive
- Progress in care is indisputable (TORS, particle therapy, immunotherapy)
- Expertise remains key for success in both therapeutic & supportive scenarios
- The number of older and frail patients is projected to increase
- There's an unmet need to find alternative treatment paradigms
- Is it still worth to deal with fractionation to improve the therapeutic index?

Back to the future: hyperfractionated radiotherapy



- 33 trials, 11423 patients (>2.5 Gy/fx not included)

	Overall survival
Randomised controlled trials	115
Comparisons	154
Patients	28 978
Events	19 253
Gobal p value	0·074
p value for heterogeneity	0·013
p value for inconsistency	0·91
Hazard ratio (95% CI); P score (%)	
Locoregional therapy	1 (ref); 21%
HFCRT	0·63 (0·51–0·77)
IC_{TaxPF}-LRT	0·69 (0·56–0·85)
ACRT	0·75 (0·66–0·85)

- Hyperfractionated RT + concomitant CT (HFCRT): ranked as best treatment

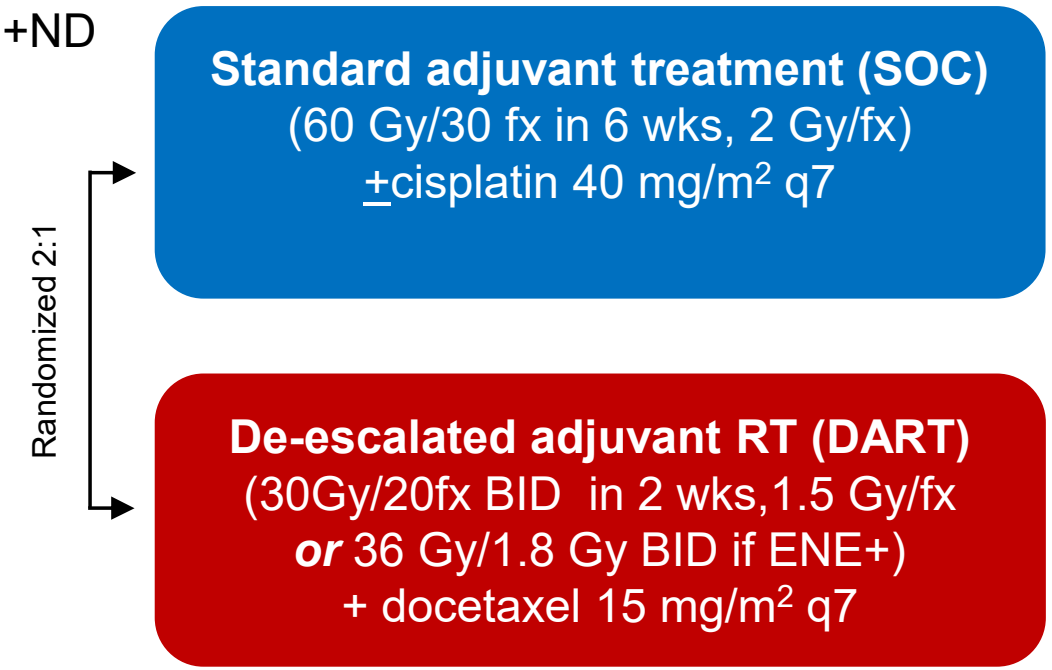
Bourhis J, Lancet Oncol 2006
Lacas B, Lancet Oncol 2017

De-Escalated adjuvant RT vs standard adjuvant treatment for HPV+ oropharyngeal SCC: rdm phase 3 trial (**MC1675**)

- n= 194 (accrual: 10/16-08/20)
- HPV+ OPSCC deemed amenable to TORS+ND
  - pT4 excluded
  - 72% were never smokers

- Stratified by
  - risk group (intermediate vs ENE+)
  - smoking status (≤10 vs ≥10 pk/y)

- Primary endpoint:
  - ≥ G3 AE rate ≥3 months after RT
    (two-sided, a 0.05, beta 0.90; powered to detect a reduction from 25% to 7%)



Ma DJ, J Clinical Oncol 2019
Ma DJ, ASTRO 2021

De-Escalated adjuvant RT vs standard adjuvant treatment for HPV+ oropharyngeal SCC: rdm phase 3 trial (**MC1675**)

- ≥ G3 AE rate @ 3 months post RT: 1.6% with DART vs 7.1% with SOC (p=0.058)
- A feeding tube was required by 1.6% of patients with DART vs 27.4% with SOC (p<0.0001)

2 Year Statistics (95% CI)

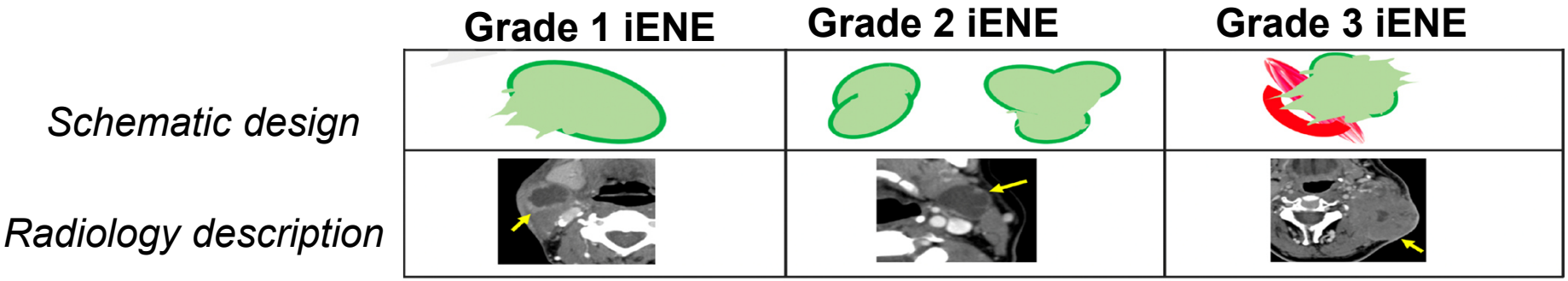
	Entire study		ENE-		ENE+	
	DART	SOC	DART	SOC	DART	SOC
OS	**96.1%** (92.3-100.0)	**97.0%** (91.3-100.0)	**100.0%** (100.0-100.0)	**90.9%** (75.4-100.0)	**93.4%** (87.3-100.0)	**100.0%** (100.0-100.0)
LRC	**95.5%** (91.6-99.5)	**97.9%** (93.8-100)	**100.0%** (100.0-100.0)	**93.3%** (81.5-100.0)	**92.2%** (85.7-99.1)	**100.0%** (100.0-100.0)
PFS	**86.5%** (80.2-93.3)	**95.1%** (88.8-100.0)	**97.6%** (93.0-100.0)	**93.3%** (81.5-100.0)	**78.9%** (69.5-89.6)	**96.2%** (89.0-100.0)

- ENE+ & pN2 patients: 2-year PFS was 42.9% with DART vs 100% with SOC (p not reported)

Ma DJ, ASTRO 2021

De-escalation: much ado about nothing?

- Not part of clinical routine yet, practice-changing data long awaited[1]
- Reduction of radiation total dose seems the most promising strategy
  - pilot ROC trial: 30 Gy + cisplatin in normoxic tumors[2]
  - MSKCC cohort (n=276) with 30 Gy to elective volumes[3]
- Can patient selection be improved by predicting ENE with imaging?[4,5]

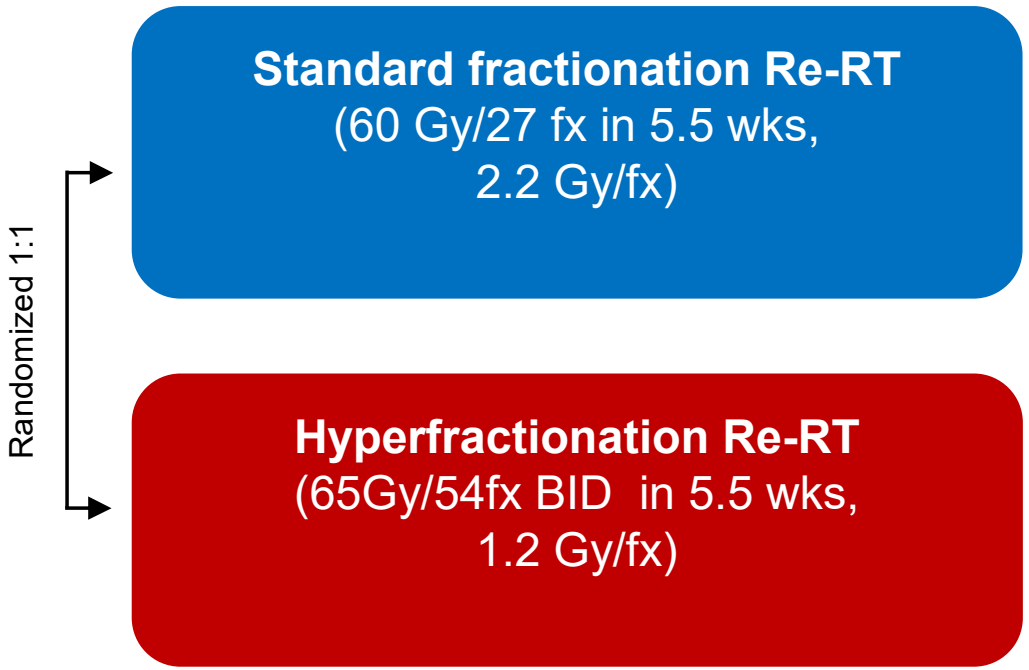


[1] Mensour EA, Front Oncol 2022; [2]Riaz N, J Natl Cancer Inst 2020;
[3]Tsai CJ, Jama Oncol 2022; [4]Kann BH, J Clin Oncol 2020; [5]Henson C – HNCIG initiative, Front Oncol 2023

Hyperfractionation vs standard fractionation in locally advanced recurrent NPC: rdm open-label phase 3 trial

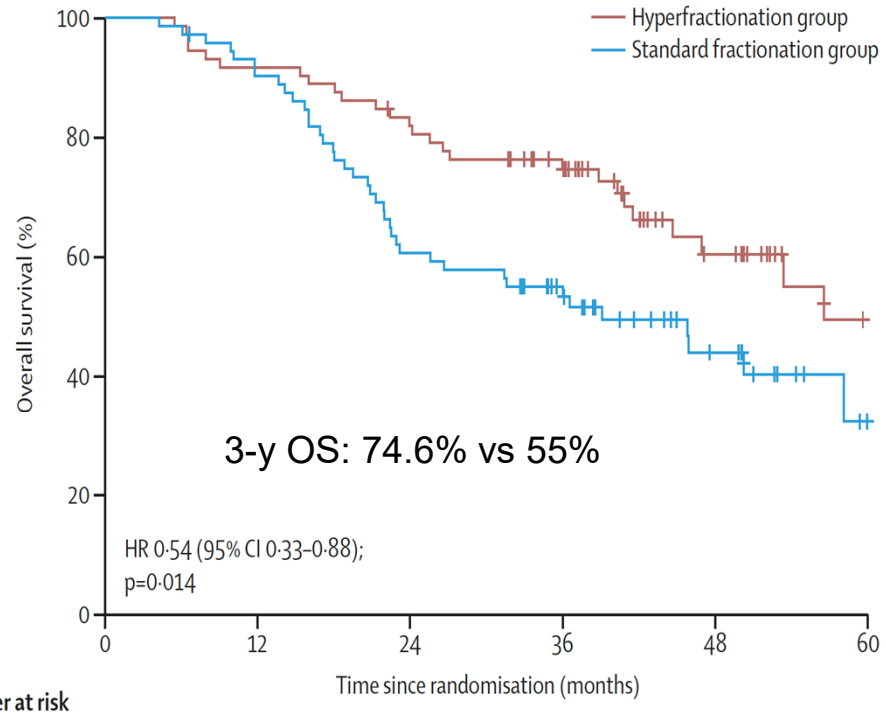
- n= 144 (accrual: 07/15-12/19)
- Unresectable locally advanced, non-keratinizing recurrent NPC
- ≥ 12-month disease-free interval
- Stratified by
  - center
  - recurrent T stage (T2-T3 vs T4)
  - recurrent N stage (N0 vs N1-N2)

•Co-primary endpoints:
  - ≥ G3 late toxicity (two-sided, a 0.05, beta 0.80)
  - OS (two-sided, a 0.05, beta 0.80)



You R, Lancet 2023

OS



Number at risk (number censored)						
Hyperfractionation	72 (0)	66 (0)	58 (1)	47 (8)	20 (28)	7 (39)
Standard fractionation	72 (0)	64 (1)	43 (1)	32 (8)	15 (20)	3 (30)

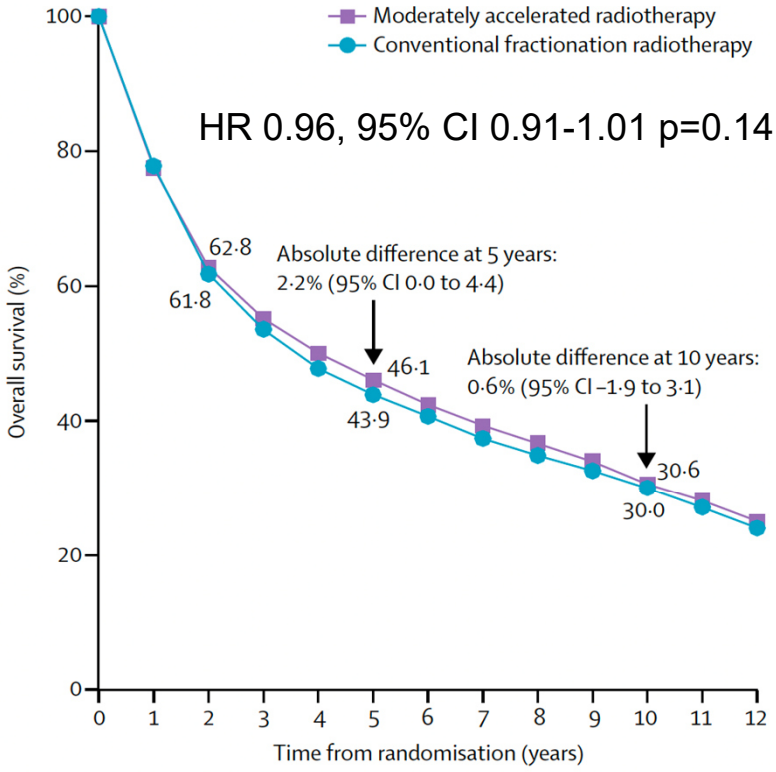
Late toxicity

	Hyperfractionation group (n=68)				Standard fractionation group (n=68)			
	Grade ≥3	Grade 1–2	Grade 3–4	Grade 5	Grade ≥3	Grade 1–2	Grade 3–4	Grade 5
Any late adverse events	23 (34%)	45 (66%)	18 (26%)	5 (7%)	39 (57%)	29 (43%)	23 (34%)	16 (24%)
Nasopharyngeal mucosal necrosis	13 (19%)	10 (15%)	13 (19%)	0	22 (32%)	13 (19%)	20 (29%)	2 (3%)
Nasal haemorrhage	5 (7%)	12 (18%)	0	5 (7%)	14 (21%)	14 (21%)	3 (4%)	11 (16%)
Eye disorders	4 (6%)	15 (22%)	4 (6%)	0	5 (7%)	23 (34%)	5 (7%)	0
Hearing impairment	15 (22%)	23 (34%)	15 (22%)	0	17 (25%)	30 (44%)	17 (25%)	0
Trismus	7 (10%)	27 (40%)	7 (10%)	0	10 (15%)	32 (47%)	10 (15%)	0
Dry mouth	1 (1%)	34 (50%)	1 (1%)	0	2 (3%)	28 (41%)	2 (3%)	0
Dysphagia	5 (7%)	23 (34%)	5 (7%)	0	8 (12%)	15 (22%)	8 (12%)	0
Skin reaction	0	18 (26%)	0	0	0	15 (22%)	0	0
Neck tissue damage	8 (12%)	11(16%)	8 (12%)	0	9 (13%)	10 (15%)	9 (13%)	0
Temporal lobe necrosis	7 (10%)	21 (31%)	7 (10%)	0	18 (26%)	21 (31%)	15 (22%)	3 (4%)

- 3-year LRFS: 53.7% vs 46.8% (p=0.96) 3-year DMFS: 96.5% vs 91.1% (p=0.55)
- ≥ G3 late toxicity: 34% vs 57% (-23% difference; 95% CI: -39% to -7%, p=0.023)

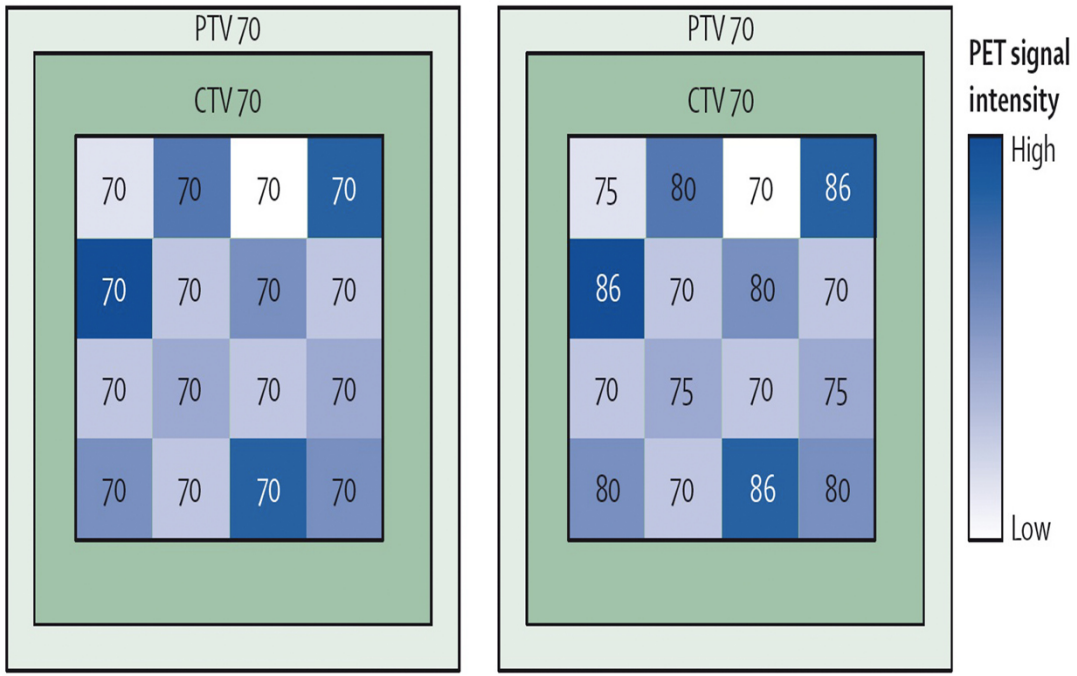
You R, Lancet 2023

Back to the future: (moderately) accelerated radiotherapy



	Years 0–2	Years 2–5	Years 5–10	Years 10+
Moderately accelerated radiotherapy (deaths/person-years)	1497/6347	610/5816	343/4291	152/1412
Conventional fractionation radiotherapy (deaths/person-years)	1525/6292	650/5528	309/4005	153/1334

Dose-painting/subvolume boosting

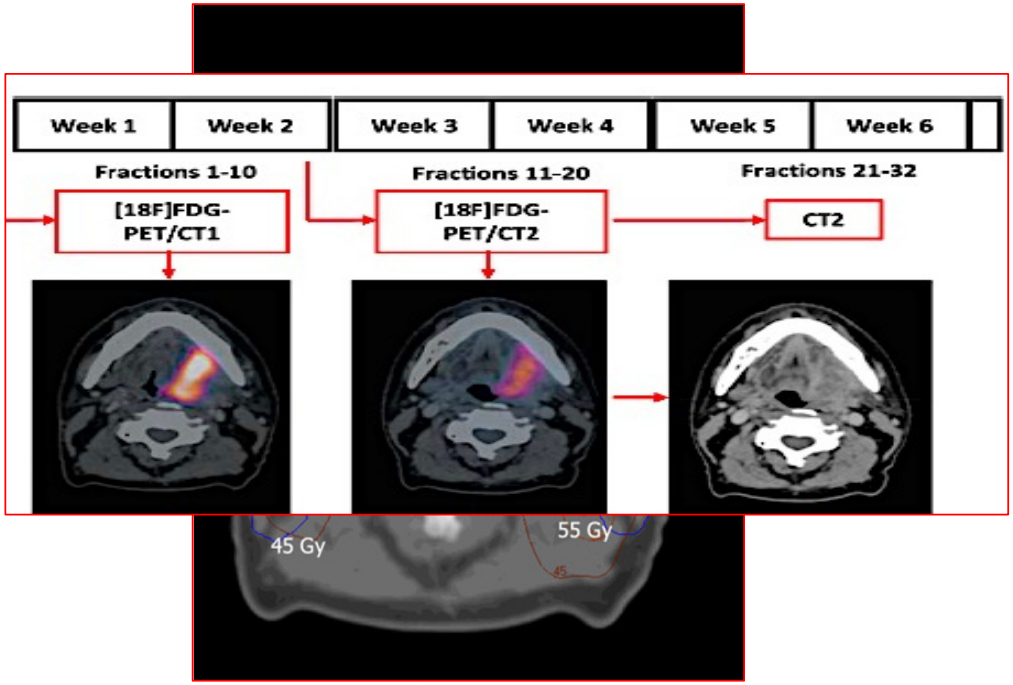


Bentzen SM, Lancet Oncol 2006
Grégoire B, Lancet Oncol 2012

^{18}F-FDG-PET guided dose-painting (DP) compared with conventional IMRT: matched case-control study

- n= 72 (09/03-10/11) treated with
  - FDG-PET guided dose-painting by contour *or*
  - voxel intensity-based dose-painting by number
  - median total dose to the dose-painted target: between 70.2 Gy-85.5 Gy in 30-32 fractions
  - median follow-up: 87.7 months

- n=72 matched on tumor site and T stage
  - treated with conventional IMRT
  - median follow-up: 64.8 months
  - total dose: 69.12 Gy in 32 fractions



- 5-year LC: 82.3% with DP vs 73.6% with standard IMRT (p=.36)
- ≥G3 late dysphagia: 26% vs 15% (p=.005)

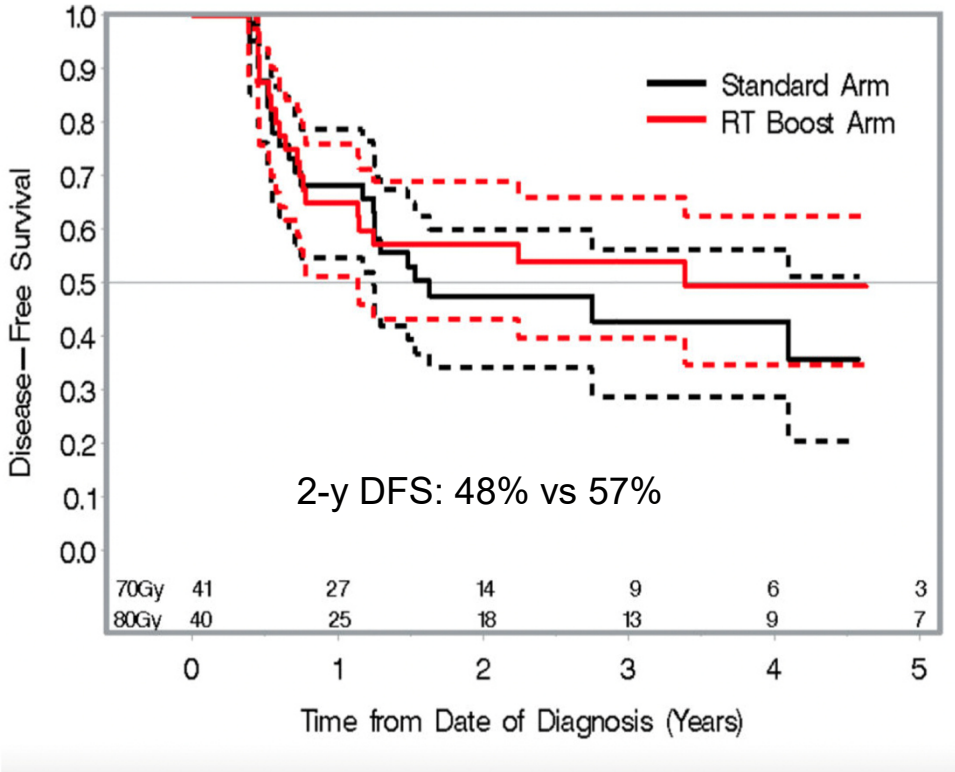
Duprez F, Int J Radiat Oncol Biol Phys 2011; Madani I, Radiother Oncol 2011; Berwouts D, Radiother Oncol 2013; Olteanu LAM, Radiother Oncol 2014; Berwouts D, Head Neck 2017; Olteanu LAM, Acta Oncol 2018

DCE- and DW-MRI directed adaptive boost in unfavorable LAHNSCC: rdm phase II study

- n= 93 (recruitment: 03/14-12/19)
- 81 patients were 1:1 randomized to
  - standard RT arm (70 Gy) *or*
  - RT boost arm (80 Gy)
    (2.5 Gy/fx for last 20 fractions)

- Boost defined as
  - sum of persisting low BV (<7.64 ml/100 g) and persisting low ADC (<1.2 um^2/ms) subvolumes @ fMR (9^{th}-11^{th} fraction)

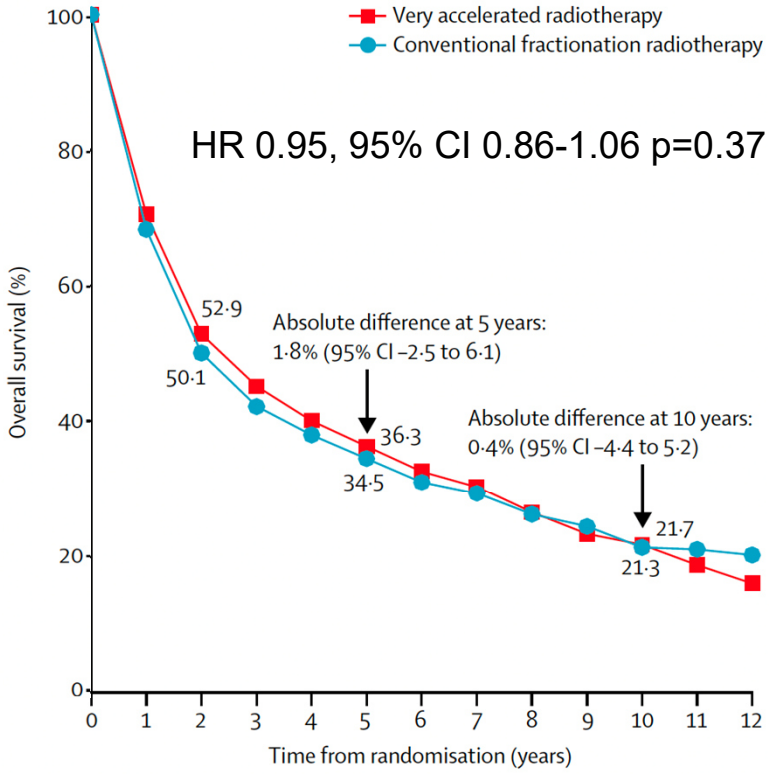
•Primary endpoint:
  - 3-year DFS
    (one-sided, a 0.1, beta 0.83; powered to detect a 20% absolute increase in experimental arm)



- DFS not improved (HR 0.84; 80% CI: 0.55-1.82, p=0.81)

Mierzwa ML, Clin Cancer Res 2022

Back to the future: (very) accelerated radiotherapy

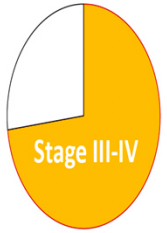


	Years 0–2	Years 2–5	Years 5–10	Years 10+
Very accelerated radiotherapy (deaths/person-years)	523/1644	174/1348	85/825	11/78
Conventional fractionation radiotherapy (deaths/person-years)	481/1325	131/1016	56/618	1/58

The HYPNO trial – sponsor IAEA

International Atomic Energy Agency

- **792 patients** with locally advanced head and neck cancer randomized
- 12 centers, 10 low- and middle-income countries, 4 continents



Bourhis J, Lancet Oncol 2006
Bentzen SM, ASTRO 2023
Lacas B, Lancet Oncol 2017

Hypofractionated vs normo-fractionated accelerated RT ± cisplatin for LAHNSCC: rdm phase 3 trial (**HYPNO**)

STRATIFY:
Performance status
Tumor sub-site
Institution
Chemotherapy

RANDOMIZE

66 Gy in 33F, 6F/week over 5.5 weeks
±weekly cisplatin

55 Gy in 20F, 5F/week over 4.0 weeks
±weekly cisplatin

3-year outcome

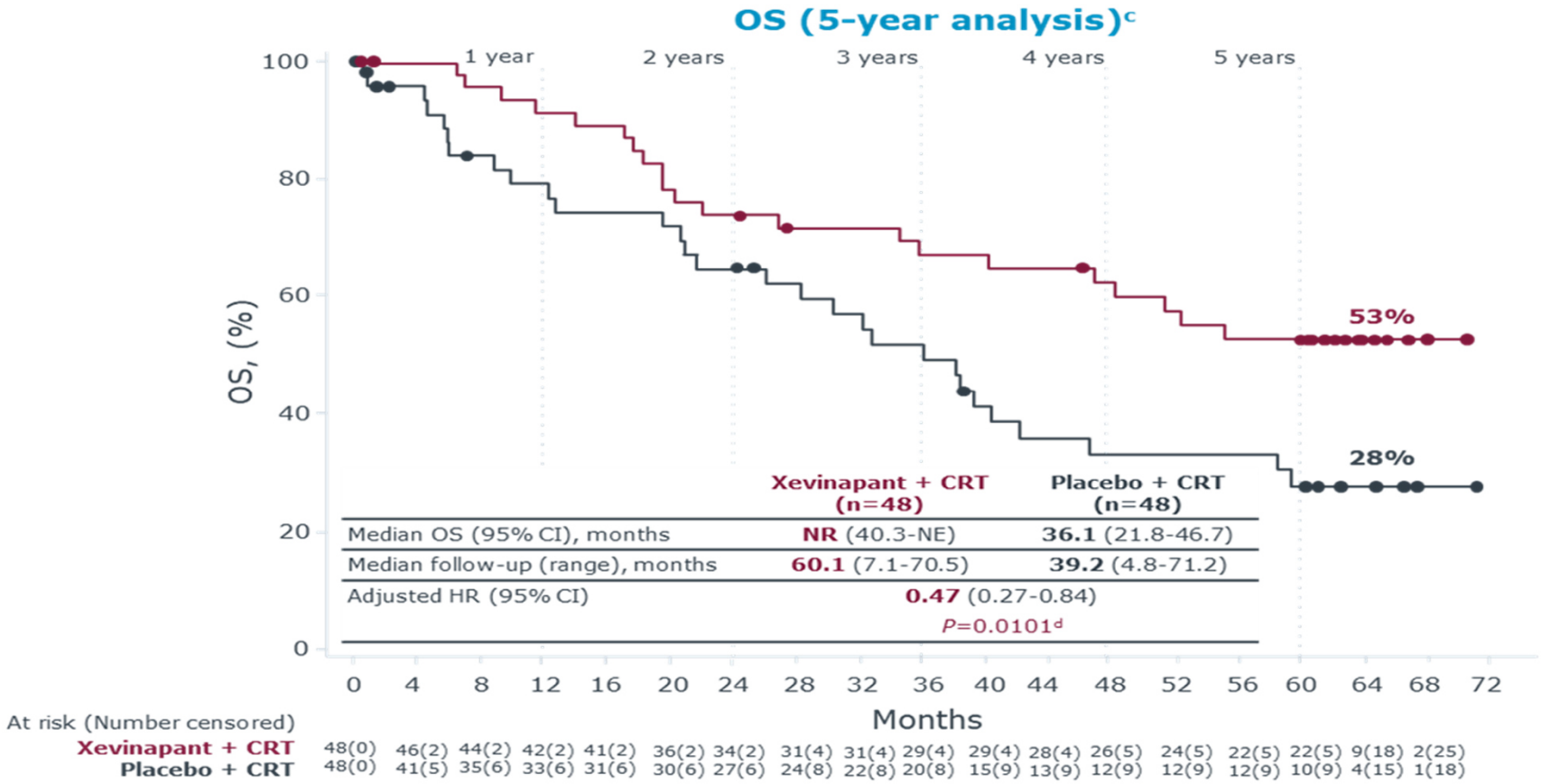
	LRC
Hypo-Fx	50.7±2.7%
Normo-Fx	51.2±2.7%
P-value	0.36

	Late Grade 3+ AEs
Hypo-Fx	18.8±2.4%
Normo-Fx	20.2±2.4%
P-value	0.68

Co-primary endpoints: loco-regional tumor control
Grade 3+ late adverse events

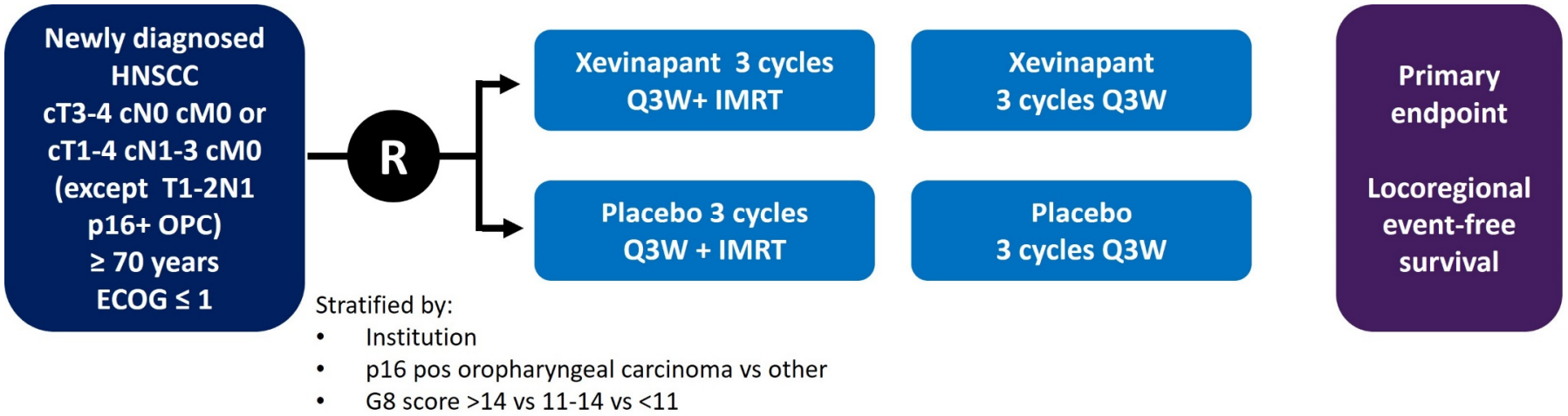
H0: Hypo-Fx non-inferior for BOTH primary endpoints, with non-inferiority margin: Δ=10%

Back to the future: radiosensitization as key solution?



Sun X-S, Lancet Oncol 2020
Tao Y, Eur J Cancer 2023

RT + xevinapant or placebo in older patients with LAHNSCC: rdm phase 2 trial (**EORTC 2120**)



Dose: 70Gy/35fr or 69.96Gy/33fr (high risk volume) + 56Gy/35fr or 52.8Gy/33fr (low risk volume)

Cycles (a cycle is 3 weeks)	C1			C2			C3		
Study Week	W1	W2	W3	W4	W5	W6	W7	W8	
Study Visit Day									
Investigational treatments:									
Debio 1143 or matched placebo									
Background treatment:									
IMRT									

Fractionation: needs learned for modern treatments

- Fractionation is unlikely to be the game changer in de-escalation
- Hyperfractionation is an effective solution that shouldn't be neglected
- Subvolume boosting failed to yield a meaningful benefit in local control
- Intra-treatment, quantitative image-guided dose adaptation is under scrutiny
- Hypofractionation may become popular for head and neck cancer, at last
- **Out-of-the box solutions exploring RT fundamentals should be tested in pragmatic trials to challenge the one-size-fits-all approach**

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