Results from CompARE phase III RCT:

Preliminary Results

Arm 1 vs 3

Arm 1 vs 5

5+5 vs 10 + 0

CI Professor Hisham Mehanna

CompARE trial group

Hisham Mehanna, Martin Forster, Anthony Kong, Mehmet Sen, Andrew Hartley, Dinos Geropantas, Rafael Moleron, Fitsum Ghebretinsea, Isla Humphreys, Claire Gaunt, Zohal Nabi, Satya Garikipati, Joanna Mackenzie, Georgina Casswell, Eleanor Aynsley, Amy Ward, Paul Sanghera, Vinidh Paleri, Paul Nankivell, Piers Gaunt

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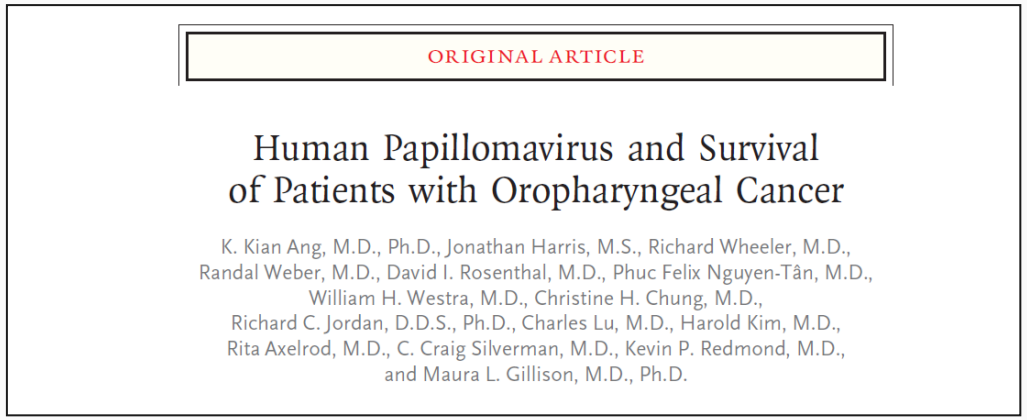
Oropharyngeal cancer (OPC) risk classification

Chemoradiotherapy is a standard of care for locally advanced OPC
Prognosis following can be divided into 3 groups dependent upon association with Human papillomavirus (HPV) and/or smoking and stage:



ORIGINAL ARTICLE

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.

RISK GROUP	3-yr OS	3-yr LRC
Low	93%	90.4%
Intermediate	70.8%	80.9%
High	46%	57.3%

*Based on analysis of RTOG 0129

*Ang KK, et al . Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010 Jul 1;363(1):24-35.

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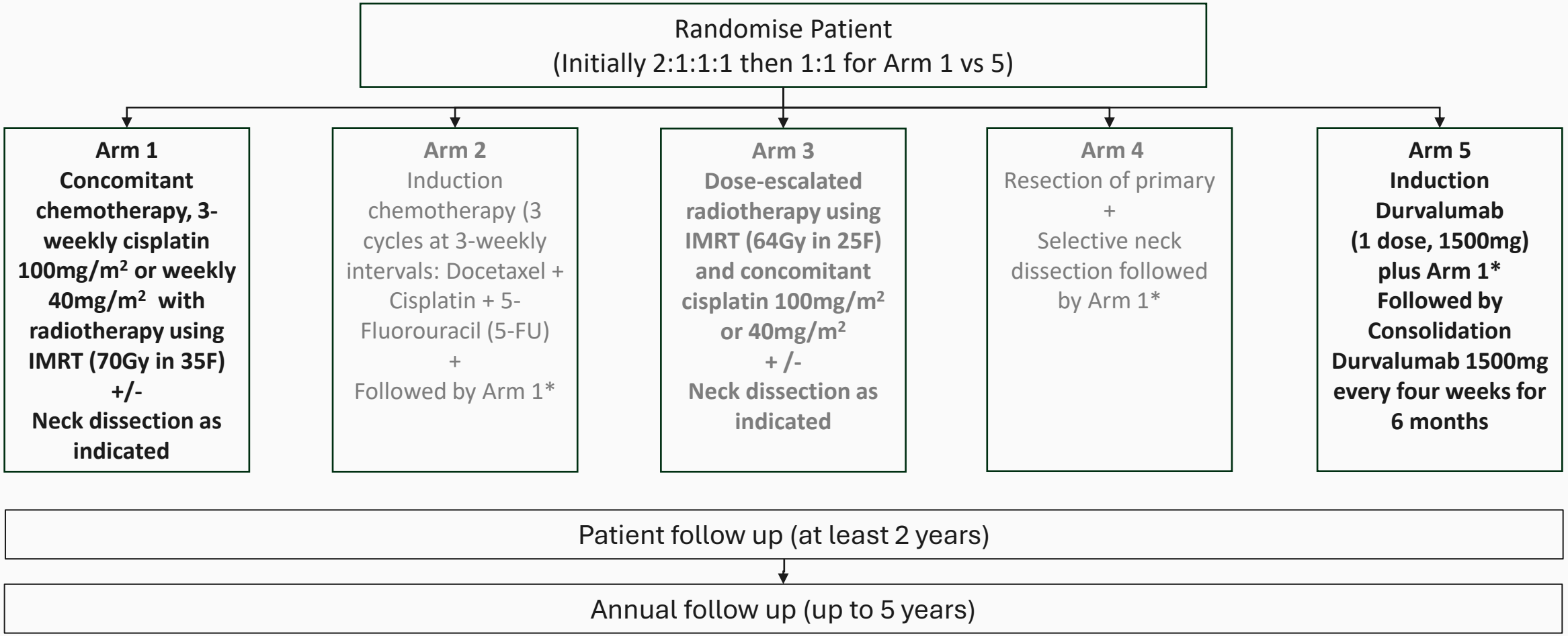
Inclusion Criteria

- Oropharyngeal squamous cell carcinoma
- Multidisciplinary Team (MDT) recommendation: radical CRT
- **Intermediate risk *HPV+***
  - T4 or N3
  - (TNM7) N2b-N3 nodes AND who are smokers ≥10 pack years (current or previous)
- **High risk *HPV negative***
  - T1-T4, N1-N3 or T3-4, N0
- ECOG performance status 0-1
- Fit for CRT and durvalumab
- Aged 18-70

Exclusion Criteria

- ***All T1-T2, N0 HPV-neg OPC***
- Low risk HPV+ patients outside of inclusion criteria
- Unfit for chemoradiotherapy regimens or contraindication or hypersensitivity to any of the IMPs and excipients used in this trial
- Any previous treatment with PD-L or PD-L1 inhibitor, including durvalumab

CompARE: Phase III open label randomised control trial using adaptive multi-arm, multistage (MAMS) design



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Outcome Measures

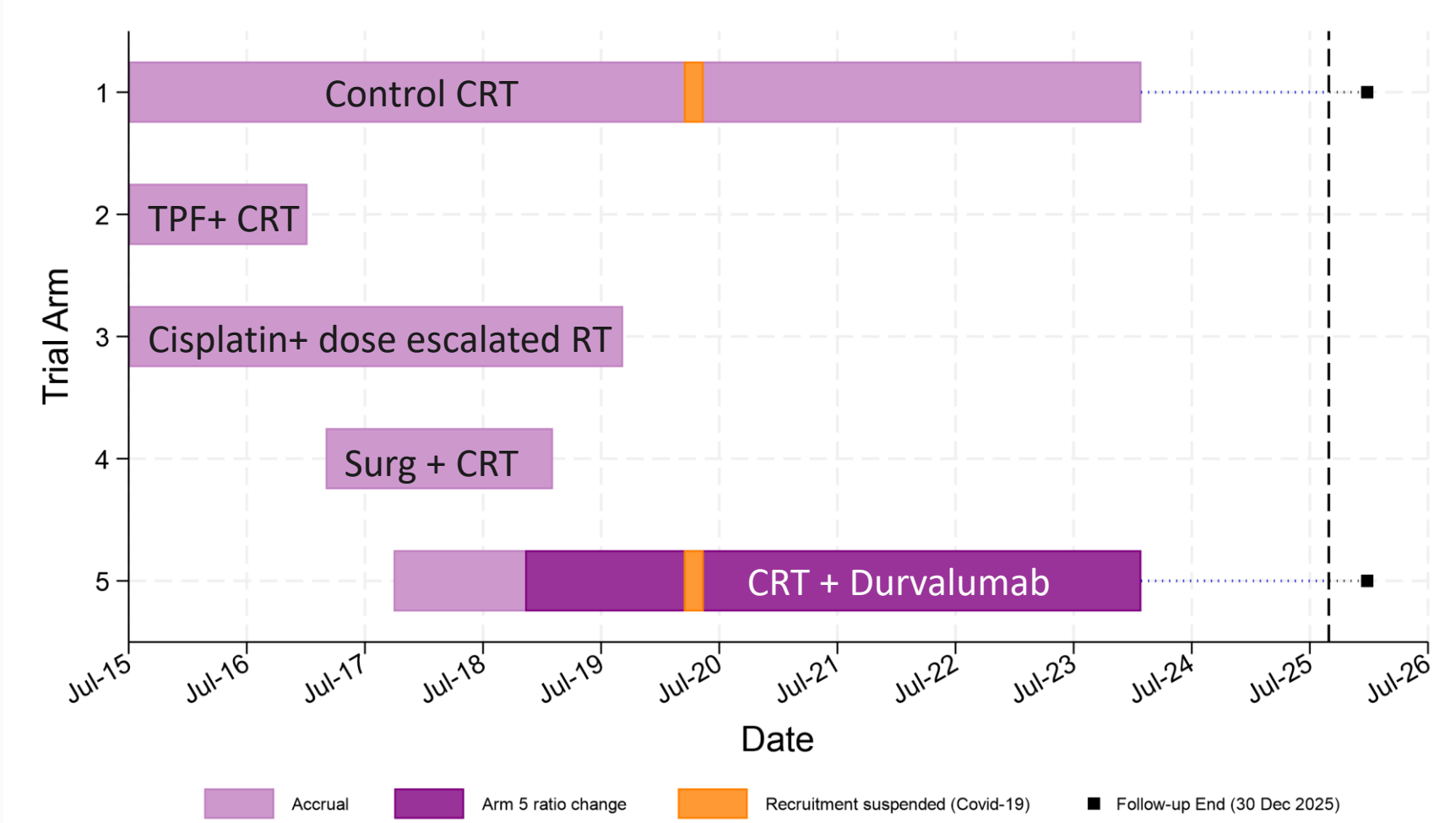
Primary Outcome Measure: Overall Survival (OS) time

Interim Outcome Measure: Event Free Survival (EFS) time

Secondary Outcome Measures

- Toxicity
  - Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
- QoL at 2 years post randomisation
  - EORTC QLQ-C30
  - EORTC H&N35
- Swallowing outcomes at 2 years
  - M.D. Anderson Dysphagia Inventory (MDADI) Questionnaire
- Gastrostomy-dependence: feeding tube utilisation rates at 1 year

Trial Timeline



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Arm 1 versus arm 3 (2:1 randomisation)

Arm 1: 70Gy in 35 fractions with cisplatin over 7 weeks +

Cisplatin 100mg/m2 3 weekly or 40mg/m2 weekly

(Elective dose 56Gy in 35 fractions)

Arm 3: 64Gy in 25 fractions with cisplatin over 5 weeks +

Cisplatin 100mg/m2 week 1 and week 5 or 40mg/m2 weekly

(Elective dose 50Gy in 25 fractions)

Centralised radiotherapy quality assurance programme

Radiotherapy Trials Quality Assurance

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Results : ICHNO 2022

Arm 3 recruitment : 6th July 2015- 12 Sept 2019

Initial suspension due to fatal SUSAR : DMC and independent investigation concluded event not related to radiotherapy.

257 patients eligible for arm 1 versus arm 3 comparison (27 centres).

Overall median follow up :		38.1 months (95% CI. 37.7, 38.4)
	Arm 1: n=172	37.7 months (95% CI. 37.0, 38.2)
	Arm 3: n=85	38.5 months (95% CI. 38.0, 40.2)

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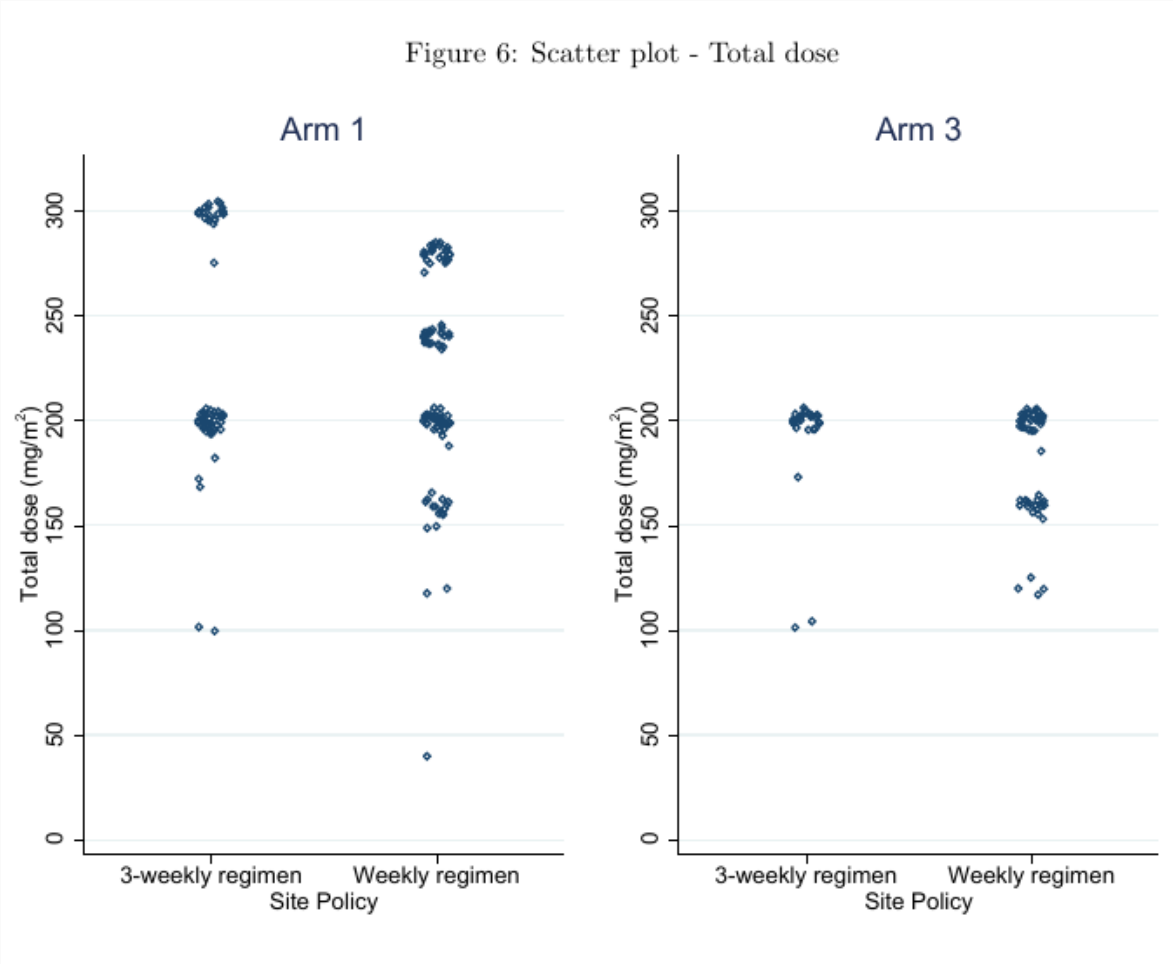
Demographics

Treatment Arm	Arm 1 (172)	Arm 3 (85)	Overall (257)
OPC Risk			
Intermediate	138 (80)	68 (80)	206 (80)
High-risk	34 (20)	17 (20)	51 (20)
ECOG performance status, N (%)			
0	137 (80)	63 (74)	200 (78)
1	35 (20)	22 (26)	57 (22)
Sex, N (%)			
Male	138 (80)	73 (86)	211 (82)
Female	34 (20)	12 (14)	46 (18)
Age at randomisation (years)			
N	172	85	257
Mean (sd)	57 (8)	57 (7)	57 (7)
Range	36, 71	38, 71	36, 71
BMI			
N	172	85	257
Mean (sd)	27 (5)	27 (5)	27 (5)
Range	14, 50	17, 44	14, 50
Smoking Status, N (%)			
Never smoked	24 (14)	9 (11)	33 (13)
Ex-smoker	78 (45)	52 (61)	130 (51)
Current smoker	70 (41)	24 (28)	94 (37)
Alcohol Status, N (%)			
Never drank	10 (6)	4 (5)	14 (5)
Previous drinker	29 (17)	21 (25)	50 (19)
Current	132 (77)	59 (69)	191 (74)
.	1 (1)	1 (1)	2 (1)

	Arm 1	Arm 3
Intermediate risk	138 (80%)	68 (80%)
High risk	34 (20%)	17 (20%)

Balanced

Concomitant Chemotherapy



	Dose reduced	Carboplatin substitution
Arm 1 3-weekly regimen	5 (3.5%)	9 (6.3%)
Arm 3 3-weekly regimen	1 (1.7%)	1 (1.7%)
Arm 1 weekly regimen	12 (2.0%)	10 (1.7%)
Arm 3 weekly regimen	4 (1.6%)	5 (2.0%)

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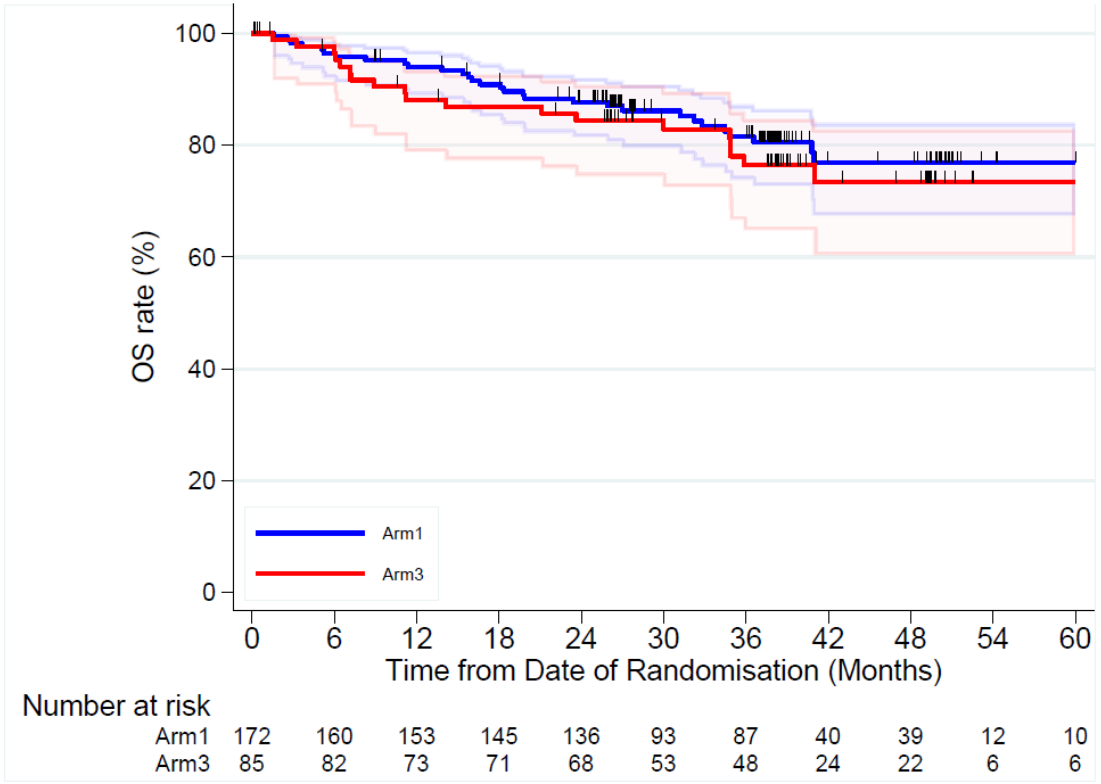
Overall Survival



3-year OS rate:

Arm 1 82% (95% CI 74%, 87%)

Arm 3 76% (95% CI 65%, 85%)

Stratified logrank p = 0.45

Adjusted HR 1.17 (95% CI 0.66, 2.08) adjusting for OPC risk group (high vs intermediate) and regimen (weekly vs 3-Weekly)

50 deaths – Arm 1 : 30
Arm 3 : 20

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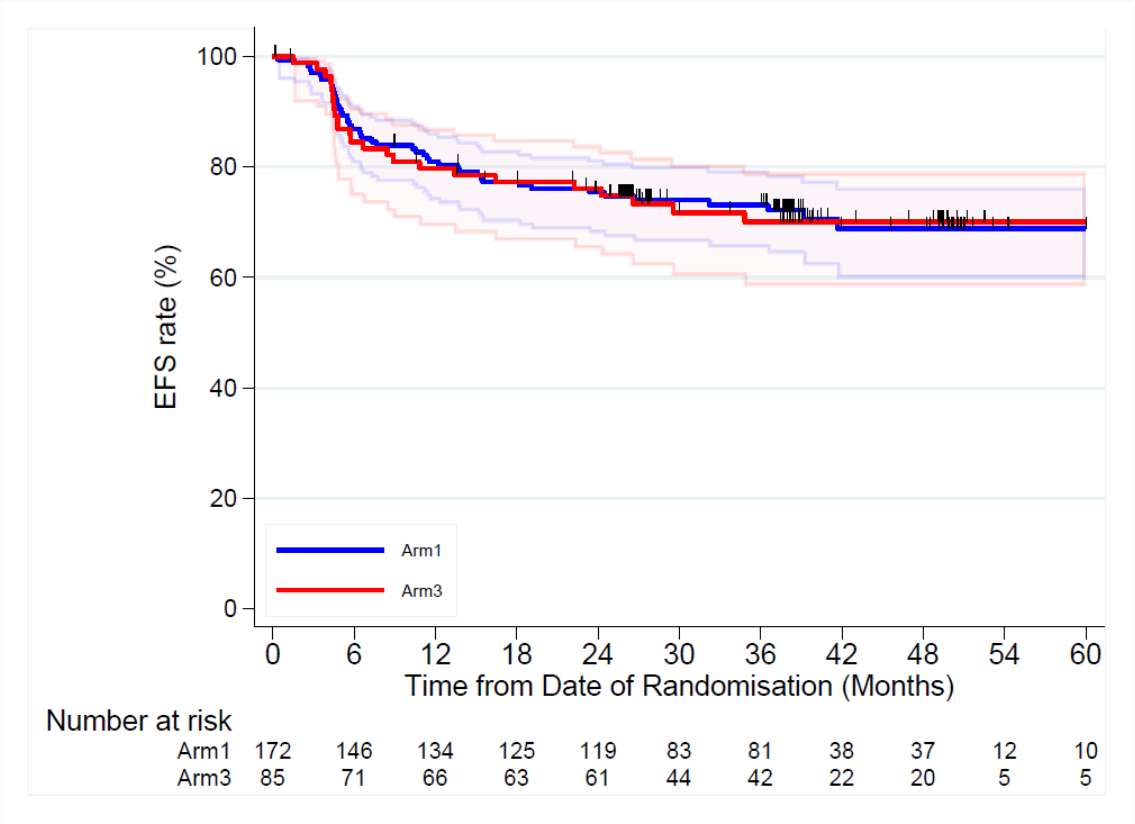
Event Free Survival



3-year EFS rate:

Arm 1 73% (95% CI 66, 79)

Arm 3 70% (95% CI 59, 79)

Stratified logrank p = 0.80

Adjusted HR 1.02 (95% CI 0.63, 1.66) adjusting for OPC risk group (high vs intermediate) and regimen (weekly vs 3-Weekly)

EFS is based on the first event of :

- Primary persistent/residual disease
- Primary recurrence/progression
- Recurrence/relapse/progression of nodal disease
- Distant metastasis
- New second primary
- Death

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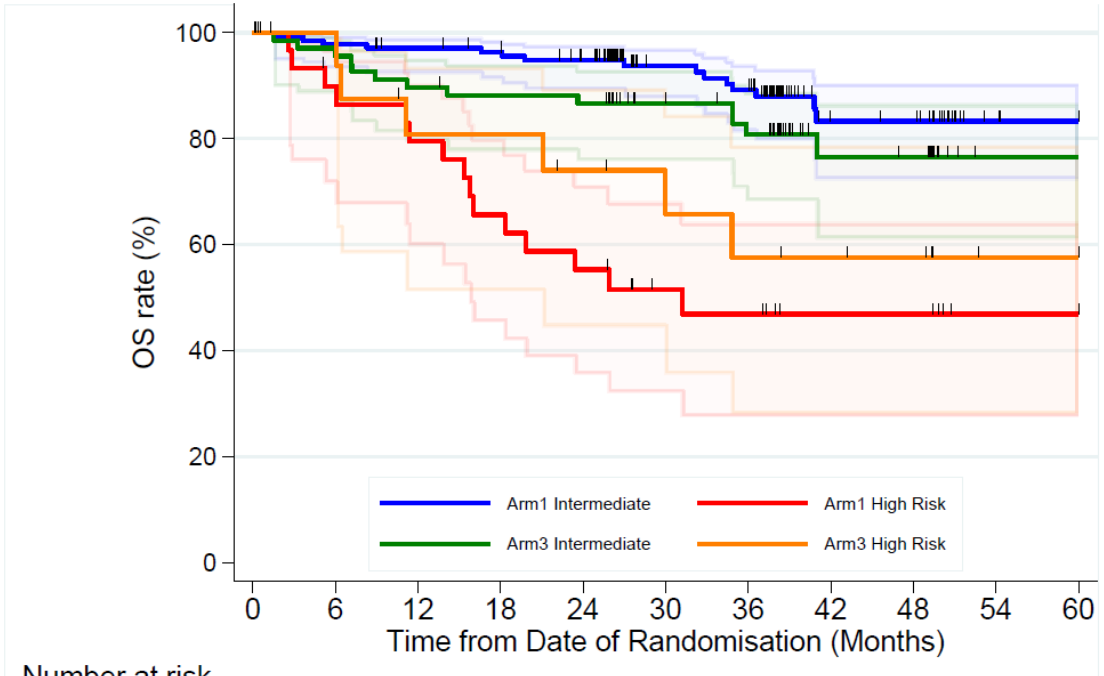
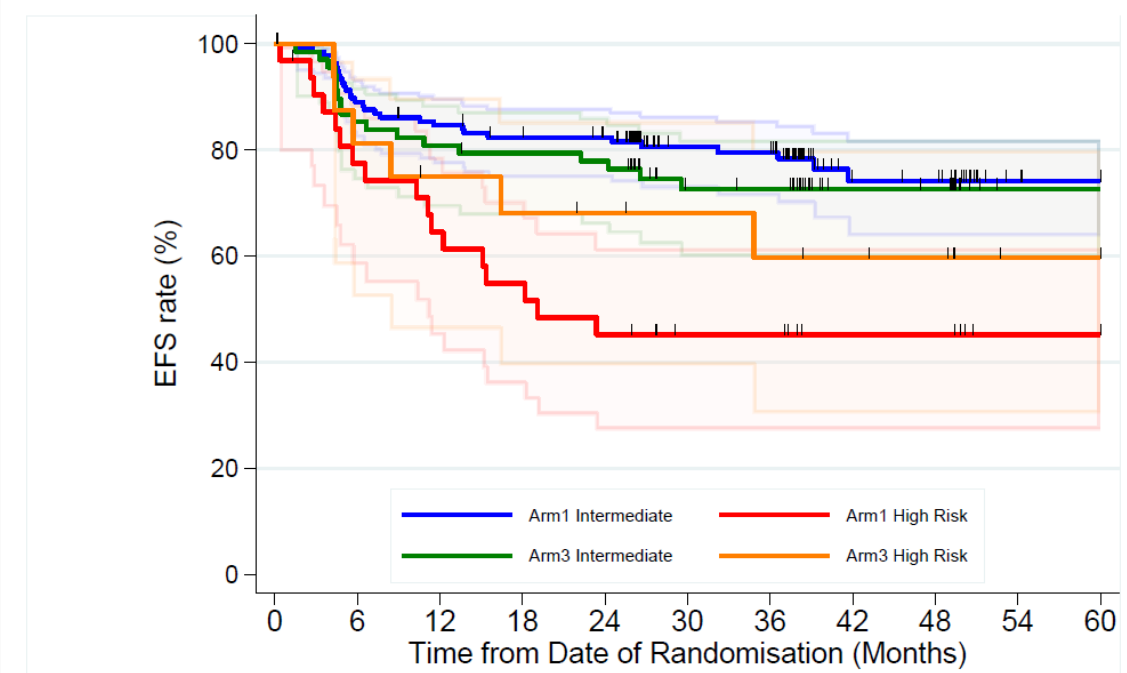
Outcomes: Intermediate vs high risk



Number at risk

Arm1 Intermediate	138	134	130	126	120	82	77	34	33	10	8
Arm1 High Risk	34	26	23	19	16	11	10	6	6	2	2
Arm3 Intermediate	68	66	61	59	58	45	41	18	17	5	5
Arm3 High Risk	17	16	12	12	10	8	7	6	5	1	1



Number at risk

Arm1 Intermediate	138	122	114	108	105	73	71	32	31	10	8
Arm1 High Risk	34	24	20	17	14	10	10	6	6	2	2
Arm3 Intermediate	68	58	55	53	52	36	35	16	15	4	4
Arm3 High Risk	17	13	11	10	9	8	7	6	5	1	1

Acute Toxicity ≥ Grade 3

Toxicity	Arm 1 (172)	Arm 3 (85)	p-value
Mucositis CTCAE v3	44%	59%	**0.021**
Mucositis CTCAE v4	48%	69%	**0.001**
Pharyngeal Mucositis	23%	33%	0.098
Vomiting	5%	13%	**0.017**
Dysphagia	52%	56%	0.474
Dry Mouth	19%	27%	0.120
Pain	22%	32%	0.093

Late Toxicity ≥ Grade 3

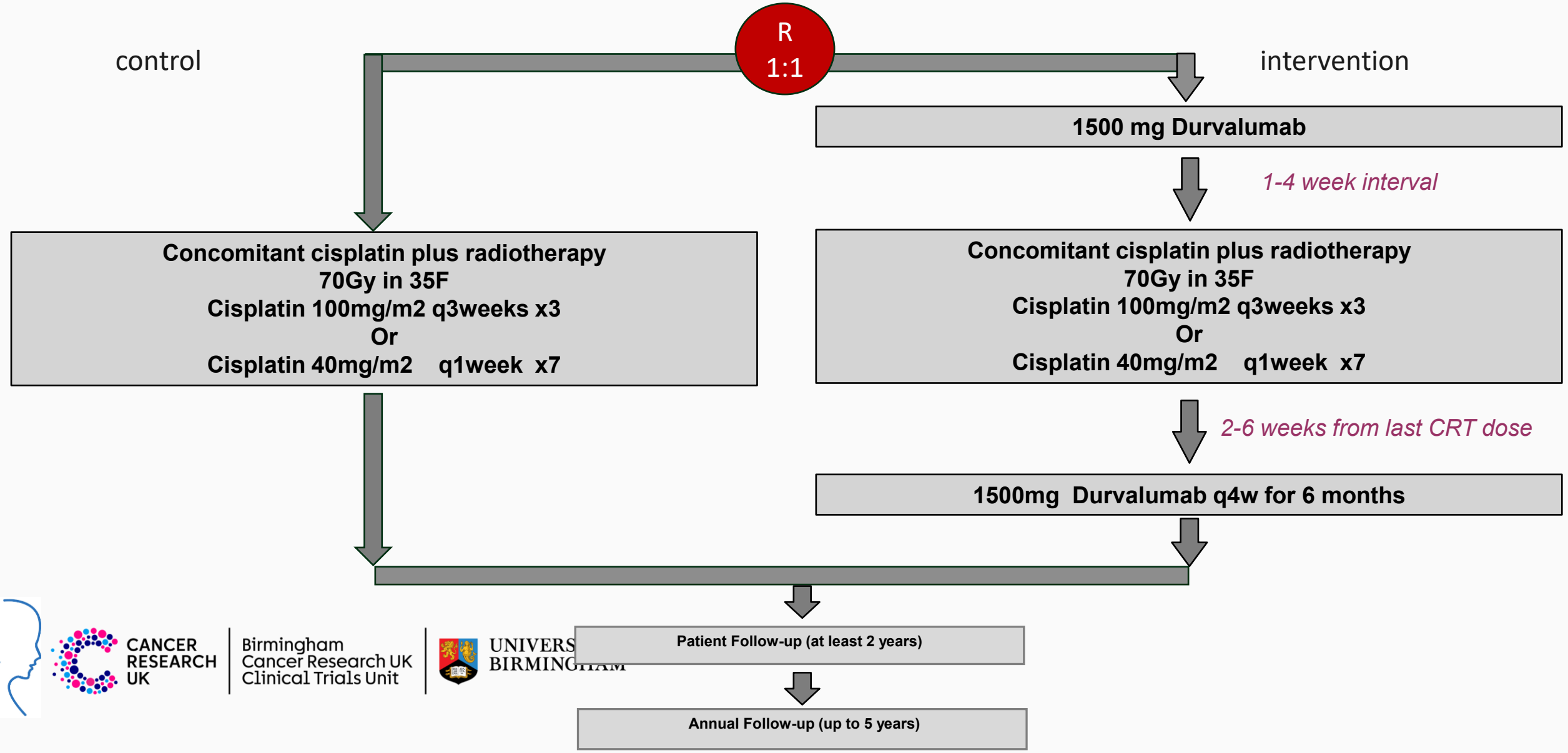
Toxicity	Arm 1 (172)	Arm 3 (85)	p-value
Trismus	1%	5%	**0.042**
Dry Mouth	6%	11%	0.238
Dysphagia	13%	19%	0.252
Mucositis CTCAE v4	3%	4%	0.787

Feeding Tube Use (PEG/NG/RIG)

- Percutaneous endoscopic gastrostomy (PEG) utilisation rates at 1 year:

Arm 1	Arm 3	P value
11%	17%	0.204

ARM 5: ESMO 2025



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Baseline Characteristics

Baseline Characteristic		Standard of Care (SoC) Arm 1 (306) N (%)	SoC + Durvalumab Arm 5 (287) N (%)	Overall (593) N (%)
Sex				
	Male	252 (82)	241 (84)	493 (83)
	Female	54 (18)	46 (16)	100 (17)
ECOG Status				
	0	244 (80)	220 (77)	464 (78)
	1	62 (20)	67 (23)	129 (22)
Primary Sub-site				
	Base of Tongue	111 (36)	104 (36)	215 (35)
	Tonsil	132 (43)	133 (46)	265 (45)
	Palate	8 (3)	4 (1)	12 (2)
	Combination (base of tongue & tonsil)	28 (9)	21 (7)	49 (8)
	Combination (other)	27 (9)	25 (9)	52 (9)
Patient with PEG/RIG/NG at baseline				
	No	266 (87)	255 (89)	521 (88)
	Yes	40 (13)	32 (11)	72 (12)

Baseline Characteristics		Standard of Care (SoC) Arm 1 (306) N (%)	SoC + Durvalumab Arm 5 (288) N (%)	Overall (594) N (%)
OPC Risk Strata				
	Intermediate	260 (85)	243 (84)	503 (85)
	High	46 (15)	45 (16)	91 (15)
T-stage (TNM v7)				
	T1	27 (9)	17 (6)	44 (7)
	T2	59 (19)	65 (23)	124 (21)
	T3	36 (12)	32 (11)	68 (11)
	T4a	168 (55)	158 (55)	326 (55)
	T4b	16 (5)	16 (6)	32 (5)
N-stage				
	N0	17 (6)	20 (7)	37 (6)
	N1	28 (9)	40 (14)	68 (11)
	N2a	8 (3)	11 (4)	19 (3)
	N2b	154 (50)	129 (45)	283 (48)
	N2c	81 (26)	76 (26)	157 (26)
	N3	18 (6)	12 (4)	30 (5)
Smoking Status				
	Never smoked	67 (22)	58 (20)	125 (21)
	Ex-smoker	164 (54)	160 (56)	324 (55)
	Current smoker	75 (25)	70 (24)	145 (24)
Age				
	Median (IQR)	58 (54, 63)	59 (54, 63)	58 (54, 63)
P-16 status				
	Positive	259 (85)	241 (84)	500 (84)
	Negative	47 (15)	47 (16)	94 (16)

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Baseline Characteristics

Balanced

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	T4a	168 (55)	158 (55)	326 (55)
	T4b	16 (5)	16 (6)	32 (5)
N-stage				
	N0	17 (6)	20 (7)	37 (6)
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	Positive	259 (85)	241 (84)	500 (84)
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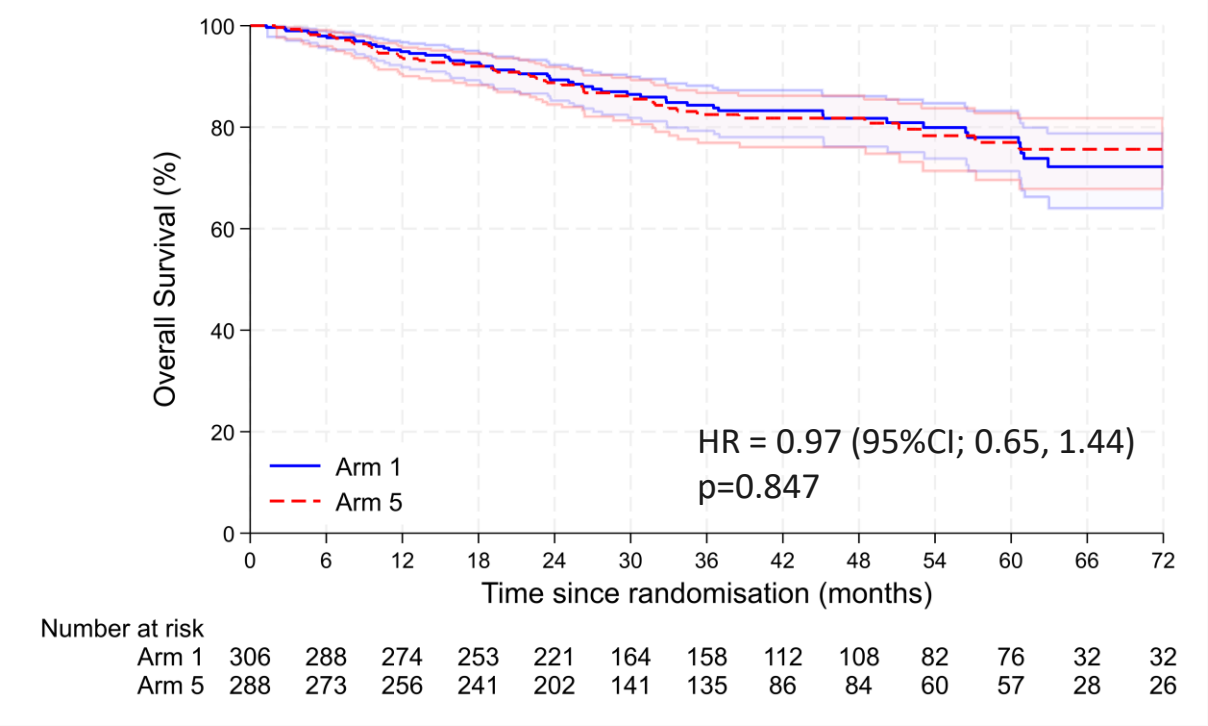
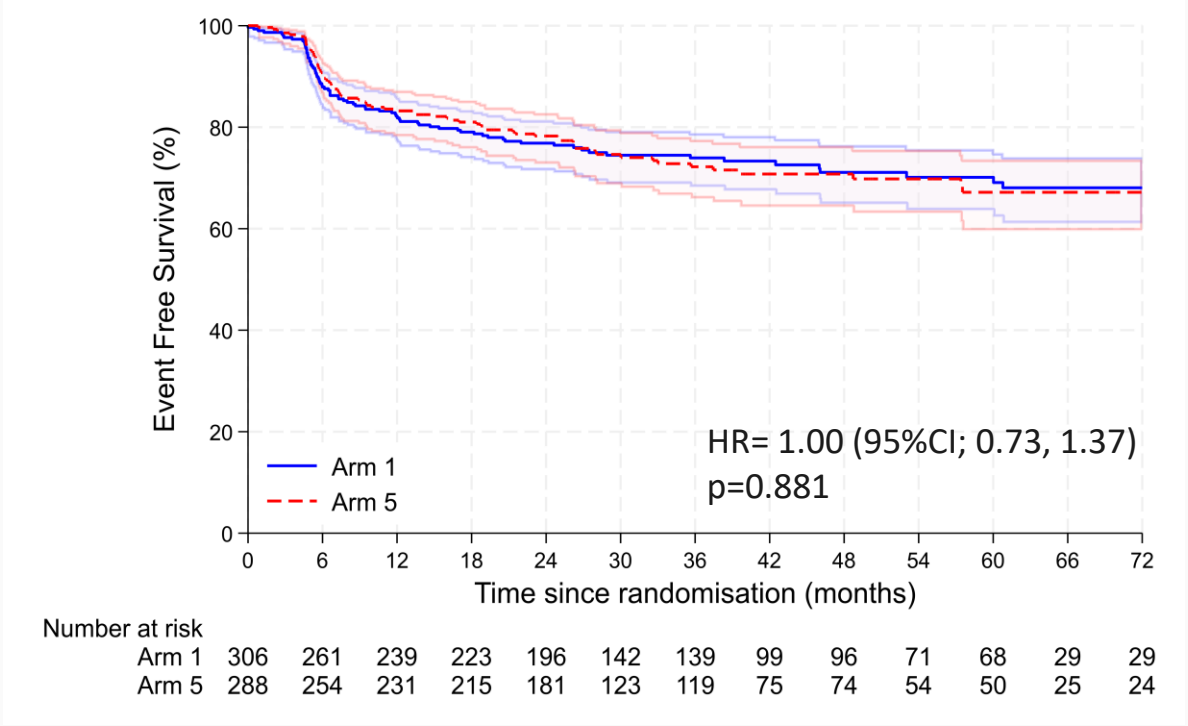
Overall Survival



Event-free Survival



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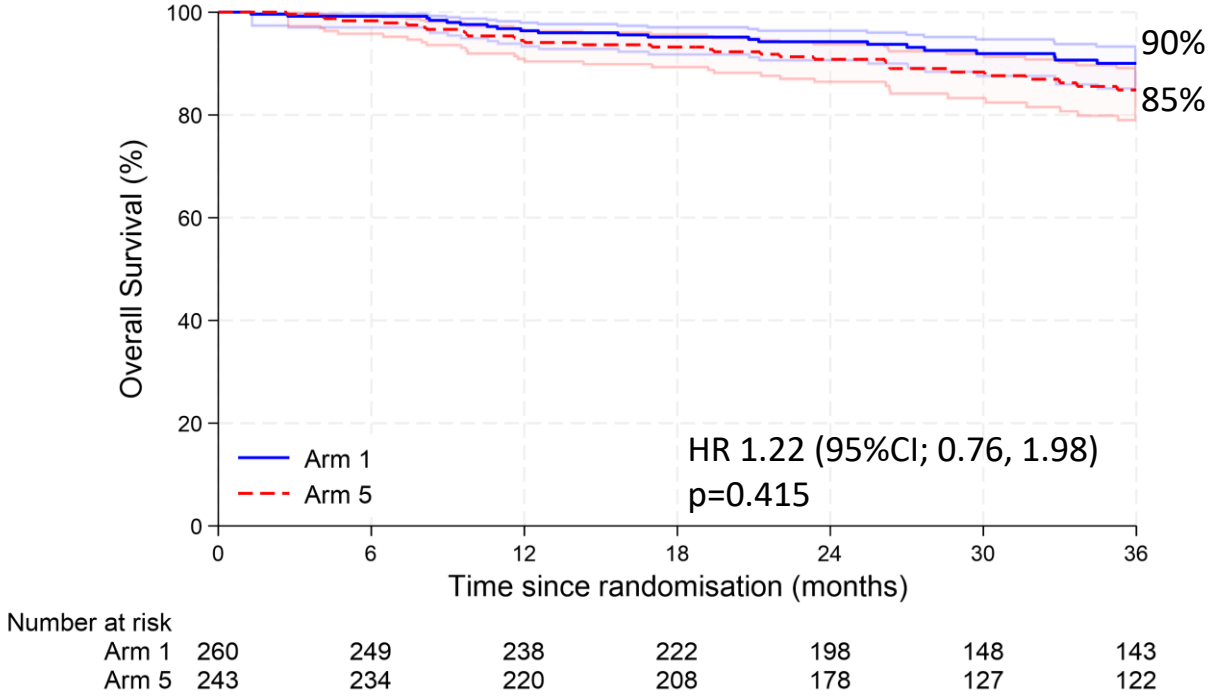
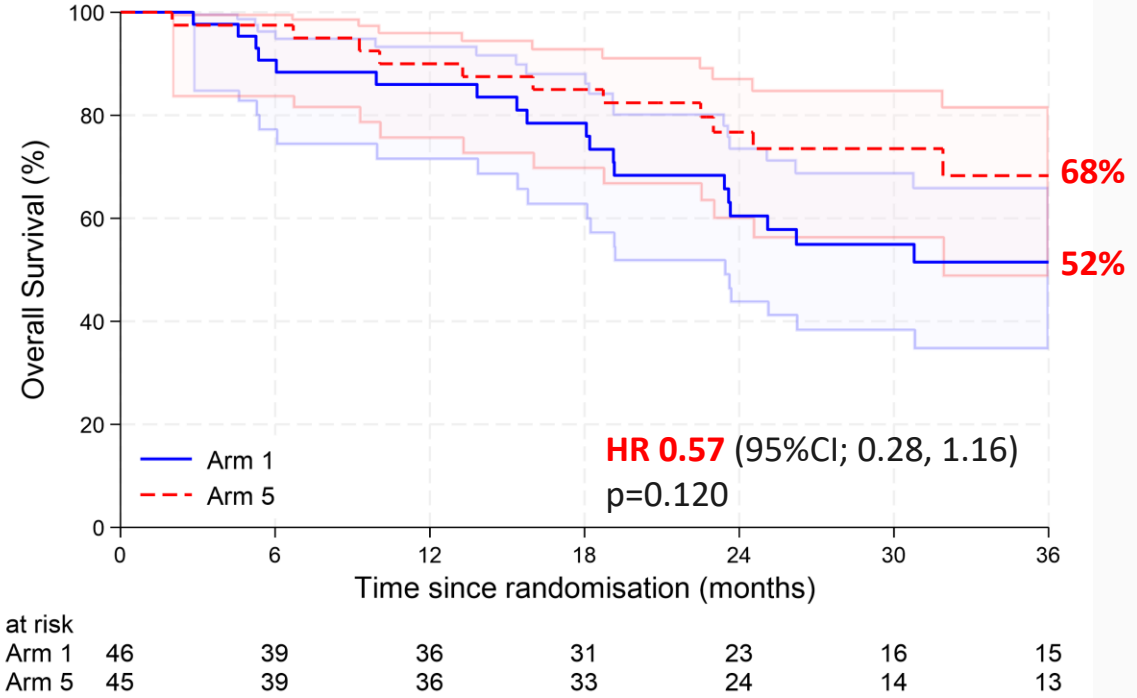
OS by risk group

Intermediate



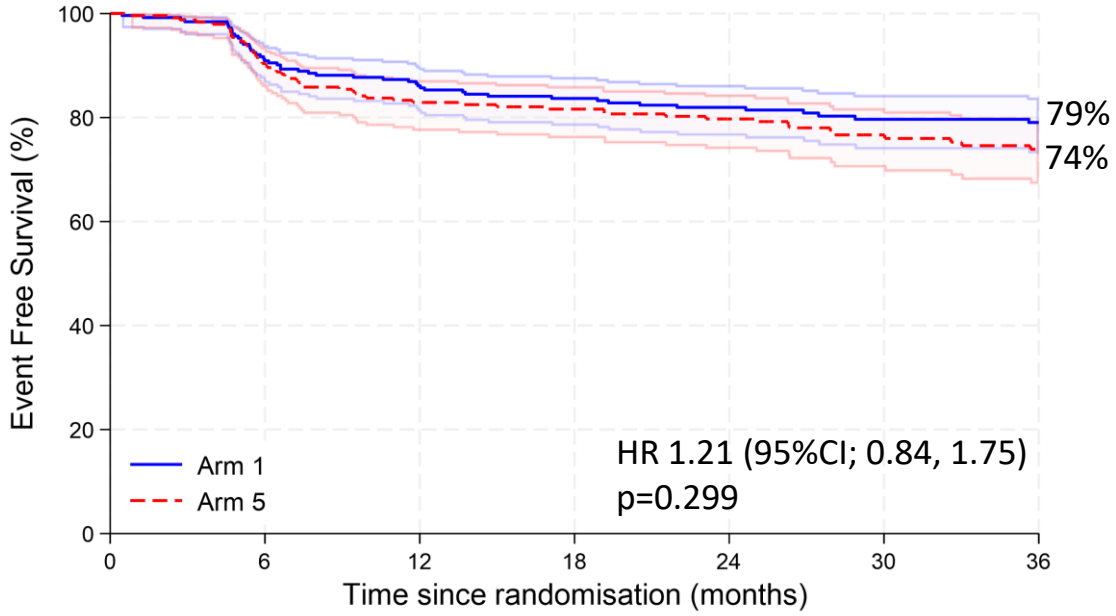
High risk



	3-year outcomes (%)		Survival Analysis	
	Arm 1 (SoC)	**Arm 5 (IO)**	**Cox Regression Hazard Ratio**	**p-value**
Overall Survival	84% (95%CI; 79, 88)	82% (95%CI; 77, 87)	0.97 (95%CI; 0.65, 1.44)	p=0.847
Intermediate-risk High-risk	90% (95%CI; 85, 93) 52% (95%CI; 35, 66)	85% (95%CI; 79, 89) 68% (95%CI; 49, 82)	1.22 (95%CI; 0.76, 1.98) 0.57 (95%CI; 0.28, 1.16)	p=0.415 p=0.120

EFS by risk group

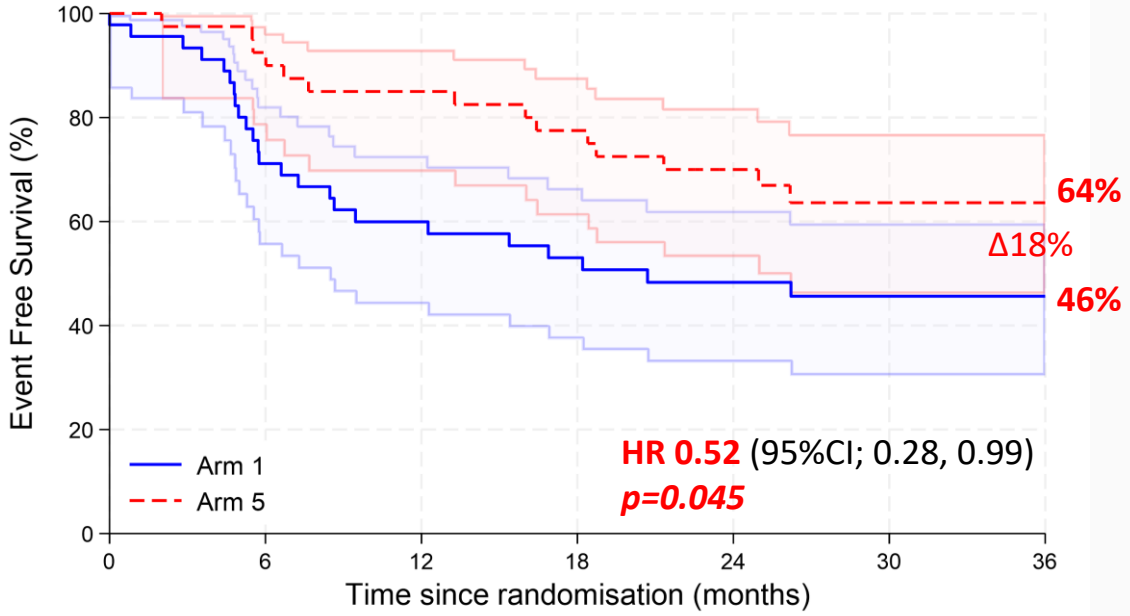
Intermediate (n=503, 85%)



Number at risk

Arm 1	260	229	213	200	176	128	125
Arm 5	243	217	197	184	158	111	107

High risk (n=91,15%)



Number at risk

Arm 1	46	32	26	23	20	14	14
Arm 5	45	37	34	31	23	12	12

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Toxicity

Very similar toxicity rates

Worst reported Grade per patient	Standard of Care (SoC) Arm 1 (298) N (%)	SoC + Durvalumab Arm 5 (283) N (%)	Overall (593) N (%)
2	32 (11)	32 (11)	64 (11)
3	235 (79)	220 (78)	455 (77)
4	31 (10)	27 (10)	58 (10)
5	0	3 (1)	3 (1)

Commonest Severe CTCAE Toxicity (Grade 3+ at least 10%)	Standard of Care (SoC) Arm 1 (298) N (%)	SoC + Durvalumab Arm 5 (282) N (%)
Hearing Impaired	27 (9)	35 (12)
Dry Mouth	59 (20)	53 (19)
Dysphagia	160 (54)	159 (56)
Oral Mucositis (v3.0)	136 (47)	122 (43)
Oral Mucositis (v4.0)	160 (54)	146 (52)
Nausea	45 (15)	53 (19)
Vomiting	33 (11)	37 (13)
Fatigue	40 (13)	40 (14)
Pain	57 (19)	61 (22)
Radiation Dermatitis	41 (14)	30 (11)
Anorexia	92 (31)	105 (37)
Pharyngeal Mucositis	44 (15)	46 (16)

Impact of introduction of ‘5+5’ contouring on efficacy and swallowing outcomes in the phase III randomised CompARE trial

Charles Fong Presented at ESTRO
On behalf of the CompARE trial group

Hisham Mehanna, Andrew Hartley, Charles Fong, Piers Gaunt, Paul Sanghera, Martin Forster, Anthony Kong, Mehmet Sen, Dinos Geropantas, Rafael Moleron, Staya Garikipati, Joanna Mackenzie, Georgina Casswell, Eleanor Aynsley, Amy Ward, Fitsum Ghebretinsea, Isla Humphreys, Claire Gaunt, Elizabeth Miles, Zohal Nabi

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Objective: Evaluate impact of change of contouring technique across trial recruitment period (2015 July – 2024 Jan)

Contouring technique was ‘standard’ ‘10+0’ technique

CTV High-dose [70Gy] = GTV+10mm

CTV Intermediate-dose [No]

CTV Elective Dose [56Gy]

2018 - ‘5+5’ GTVp technique published in Green Journal (Gregoire et al)

2020 July onwards – transfer to ‘5+5’ contouring technique permitted

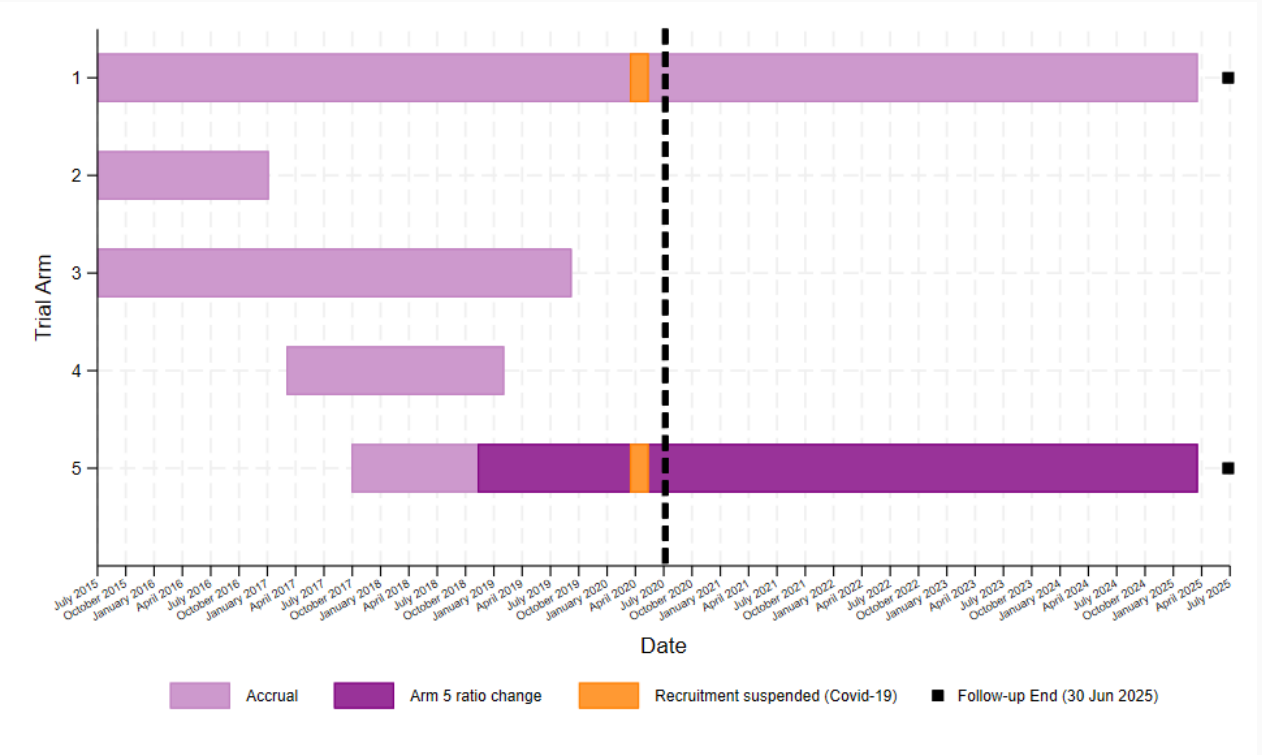
CTV High-dose [70Gy] = GTV+5mm

CTV Intermediate-dose [63Gy] = GTV+10mm (with appropriate editing)

CTV Elective Dose [56Gy]

Quality Assurance – RTQA review of contouring of benchmark case and first ‘live’ case

Case-by-case **‘switching’ of contouring technique not permitted** within each centre



679 cases for contouring effect analysis
(SOC = 397; SOC+Durva = 282)

Baseline Characteristics

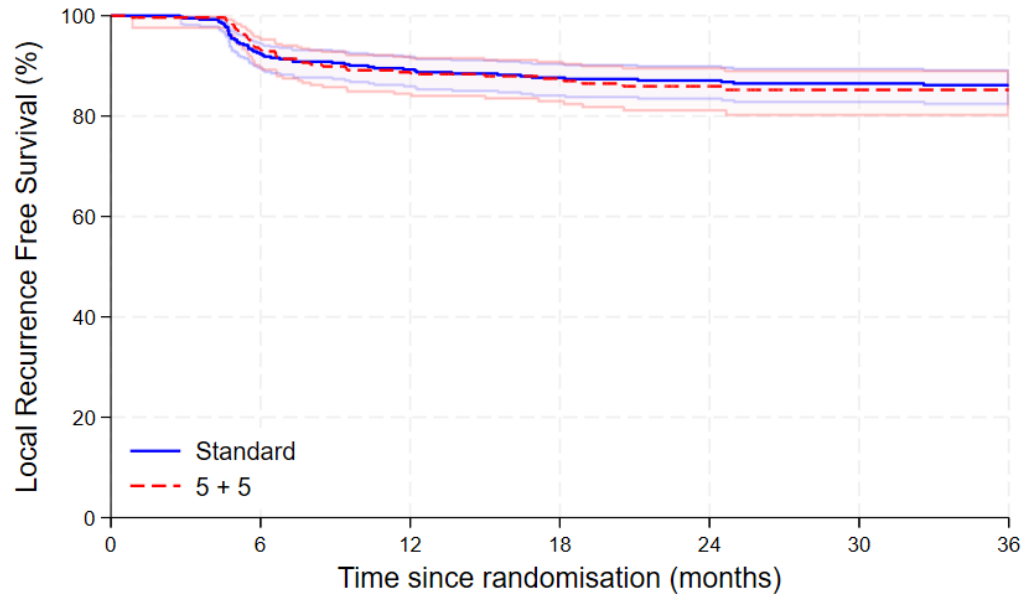
Baseline Characteristic		Standard (403) N (%)	5+5 (276) N (%)	Overall (679) N (%)
Treatment Arm				
	Standard of Care	**261 (65)**	**136 (49)**	**397 (58)**
	Standard of Care + Durvalumab	**142 (35)**	**140 (51)**	**282 (42)**
Primary Sub-site				
	Base of Tongue	143 (35)	98 (36)	241 (35)
	Tonsil	185 (46)	128 (46)	313 (46)
	Palate	7 (2)	5 (2)	12 (2)
	Combination (base of tongue & tonsil)	30 (7)	24 (9)	54 (8)
	Combination (other)	38 (10)	21 (8)	59 (9)
Patient with PEG/RIG/NG at baseline				
	No	333 (83)	261 (95)	594 (87)
	Yes	70 (17)	15 (5)	85 (13)
OPC Risk Strata				
	Intermediate	338 (84)	235 (85)	573 (84)
	High	65 (16)	41 (15)	106 (16)
P-16 status				
	Positive	338 (84)	233 (84)	571 (84)
	Negative	65 (16)	43 (16)	108 (16)
Sex				
	Male	330 (82)	231 (84)	561 (83)
	Female	73 (18)	45 (16)	118 (17)

Baseline Characteristic		Standard (403) N (%)	5+5 (276) N (%)	Overall (679) N (%)
T-stage (TNM v7)				
	T1	40 (10)	16 (6)	56 (8)
	T2	92 (23)	63 (23)	155 (23)
	T3	59 (13)	25 (9)	84 (12)
	T4a	202 (50)	150 (54)	352 (52)
	T4b	10 (2)	22 (8)	32 (5)
N-stage				
	N0	23 (6)	19 (7)	42 (6)
	N1	44 (11)	25 (9)	69 (10)
	N2a	12 (3)	8 (3)	20 (3)
	N2b	201 (50)	135 (49)	336 (49)
	N2c	111 (28)	69 (25)	180 (27)
	N3	12 (3)	20 (7)	32 (5)
Smoking Status				
	Never smoked	80 (20)	51 (18)	131 (19)
	Ex-smoker	205 (51)	164 (59)	369 (54)
	Current smoker	118 (29)	61 (22)	179 (26)
ECOG Status				
	0	308 (76)	225 (82)	533 (78)
	1	95 (24)	51 (18)	146 (22)
Age				
	Median (IQR)	59 (53, 64)	58 (54, 63)	58 (54, 63)

Outcome: Survival ‘5+5’ vs ‘standard 10+0’

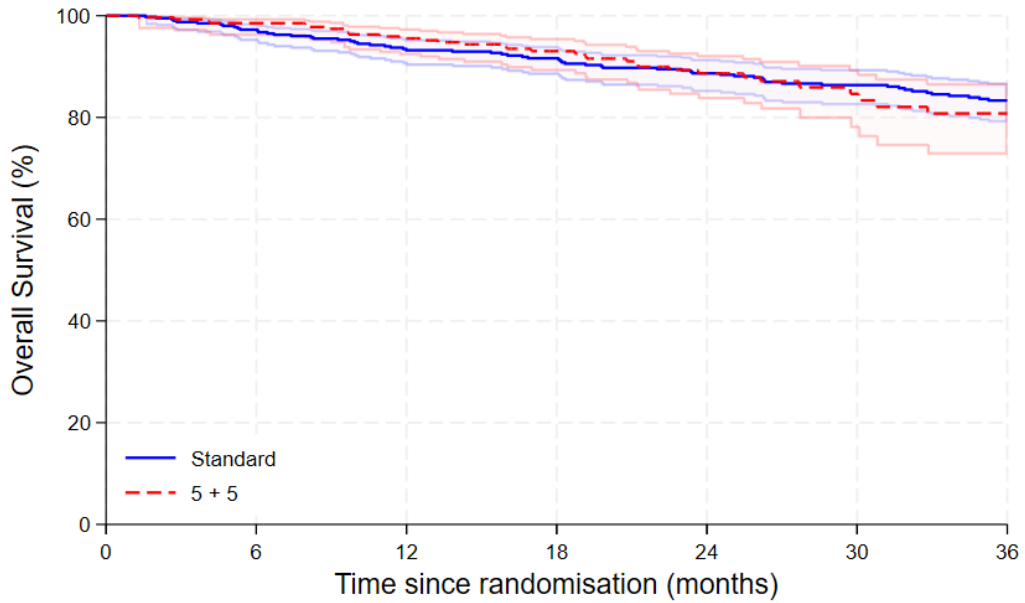
LRFS HR = 1.19 (95% CI; 0.70, 2.02)

OS HR = 0.96 (95% CI; 0.58, 1.61)



Number at risk

Standard	403	362	336	317	298	264	257
5 + 5	276	249	232	181	121	60	59



Number at risk

Standard	403	388	364	345	323	286	275
5 + 5	276	266	254	197	132	66	63

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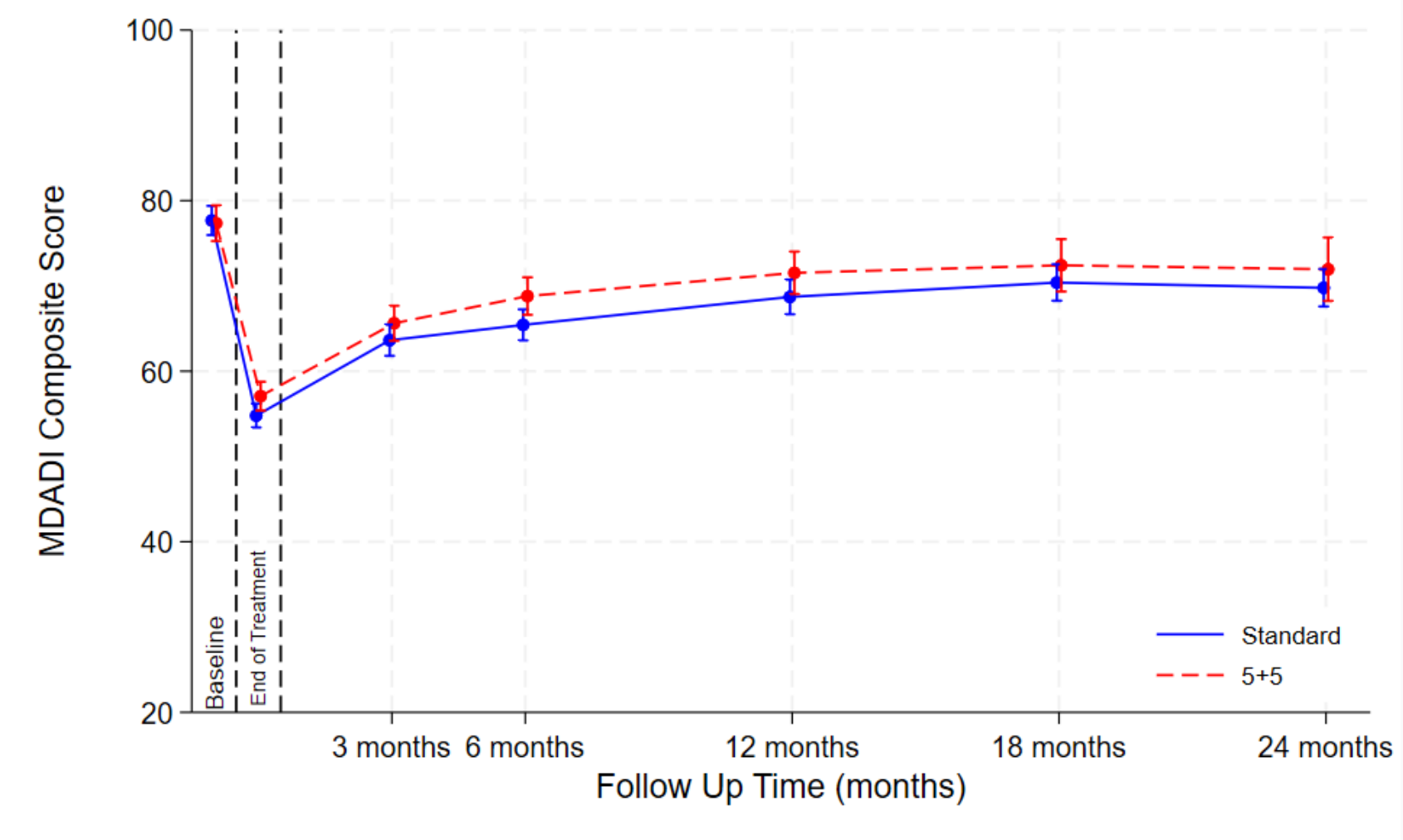
Outcome – MDADI swallow



statistically significant 2 points improvement

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Outcome – other toxicity measures – no signal for significant difference

Acute toxicities (week 1 to 3 months post-RT)

mucositis (CTCAE v3 and v4)

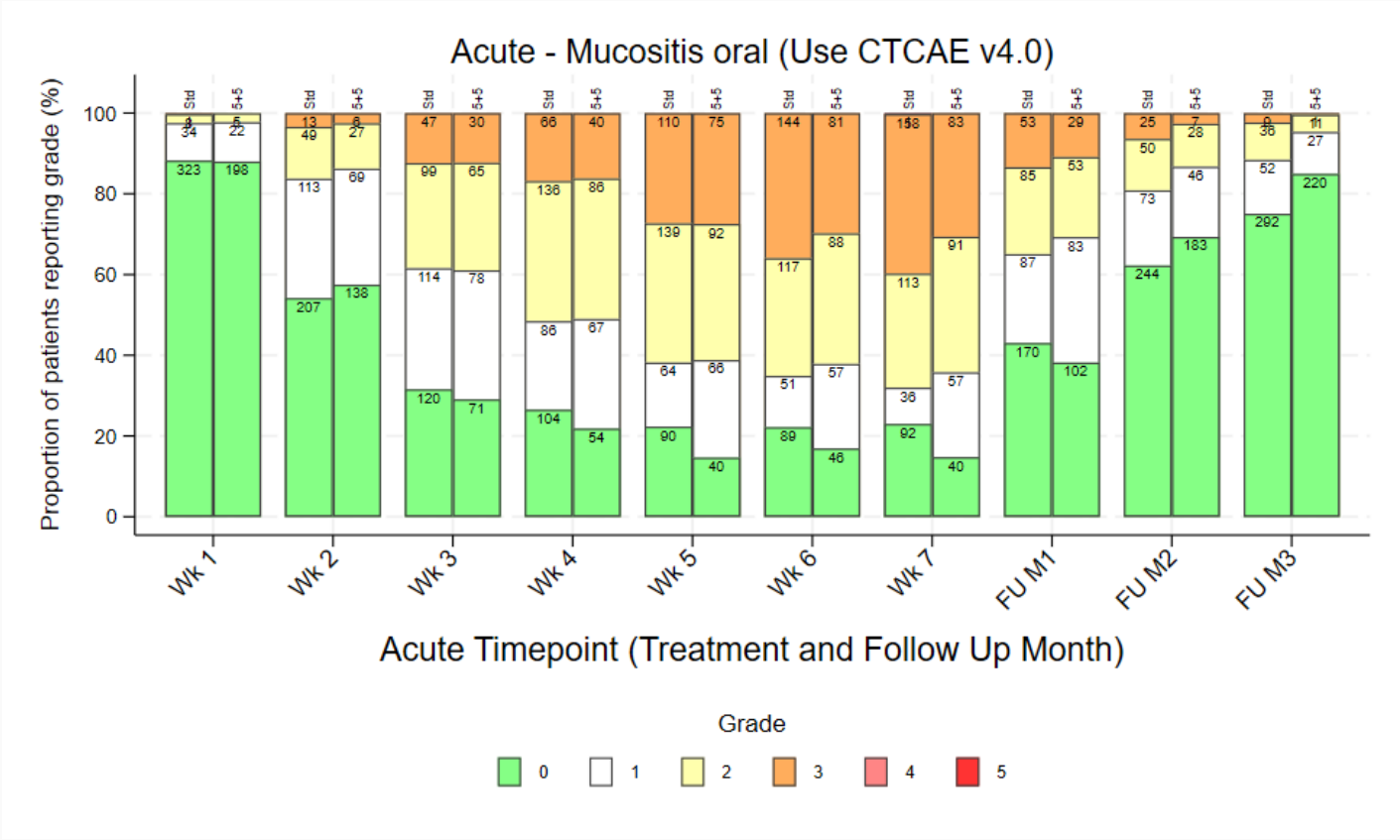
pharyngeal mucositis

radiation dermatitis

dysphagia

RTOG Late

Skin, Subcutaneous tissue, mucous membrane, salivary glands, oesophagus



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Outcome – gastrostomy and feeding tube utilisation rate

At baseline inserted: Standard = 70/403 (18%) vs 5+5 = 15/276 (5%)

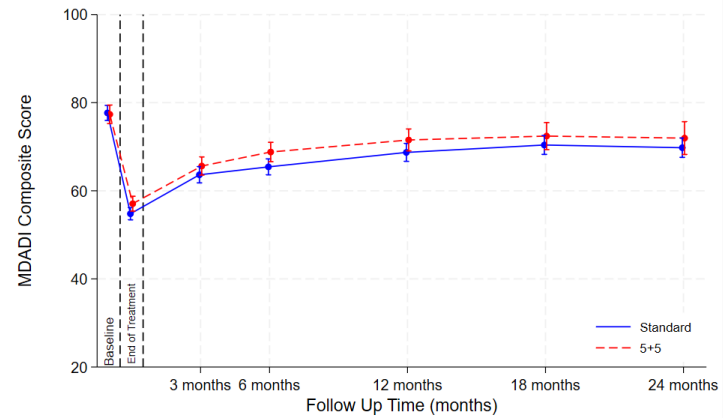
Timepoint	Standard N (%)	5+5 N (%)	Overall N (%)
Week 1	231/361 (64)	131/220 (60)	362/581 (62)
Week 7	334/385 (87)	199/260 (77)	533/645 (83)
Month 1	342/415 (82)	206/296 (70)	548/711 (77)
Month 6	112/381 (29)	64/261 (25)	176/642 (27)
Month 12	45/336 (13)	25/229 (11)	70/565 (12)
Month 24	13/299 (4)	3/115 (3)	16/414 (4)

Discussion

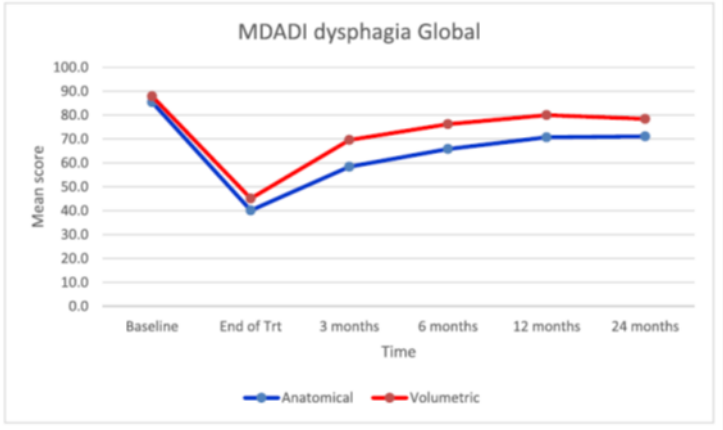
Incremental gains over the years ?

Modest improvement; however no loss of LC

Incremental gains over the years : TORPEDO as the new standard?



CompARE trial (intermediate/high-risk OPC cohort)
'standard 10+0' vs '5+5' outlining
Fong et al, ESTRO 2025



De-Escalate trial (low-risk OPC cohort)
anatomical-based outlining vs volumetric outlining.
Vreugdenhil et al, Clin Onc 2021 https://doi.org/10.1016/j.clon.2021.07.009

TORPEdO Radiotherapy Treatment Planning and Delivery, and QA Guidelines

TORPEdO

A phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer.

RADIOTHERAPY TREATMENT PLANNING AND DELIVERY, AND QA GUIDELINES

Version: 3.0
Dated: 9th Feb 2021

Chief Investigator:	Dr David Thomson (The Christie NHS Foundation Trust)
Sponsor:	The Institute of Cancer Research
Approval:	Cancer Research UK: Clinical Research Committee (CRUK CRC)
Funders: Additional Financial Support:	Cancer Research UK The Taylor Family Foundation
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research

CTV1 : 70Gy(RBE) in 33 fractions
CTV2: 56Gy(RBE) in 33 fractions

Add a 5mm isotropic margin to GTVp to create CTV1p (some discretion permitted)

Add a 10mm isotropic margin to GTVp to create CTV2p

The nodal clinical target volume (CTV1n) is defined by a 10mm isotropic expansion from the nodal GTV(s).

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Table 1: Summarising where, following expansion from GTVp and after editing for air and barriers to spread, CTV2p should be edited off adjacent anatomical structures:

	T1 tumours	T2 tumours	T3 tumours	T4 tumours
Tonsil	Edit CTV2p off parapharyngeal space	Edit CTV2p off medial pterygoid muscle		
Soft palate		Edit CTV2p off medial pterygoid muscle and mobile tongue	Edit CTV2p off mobile tongue	
Posterior pharyngeal wall		Edit CTV2p off pre-vertebral fascia	Edit CTV2p off pre-vertebral fascia	
Vallecular	Edit CTV2p off pre-epiglottic space			
Base of tongue	Edit CTV2p off hyo-glossus muscle			

Organ-at-risk	Dose statistic	Optimal dose constraint
Parotid_R	Mean	Contralateral: <20 Gy(RBE) Ipsilateral: ALARA
Parotid_L	Mean	
Glnd_Submand_R	Mean	Contralateral: <35 Gy(RBE) Ipsilateral: N/A
Glnd_Submand_L	Mean	
Cavity_Oral	Mean	<30 Gy(RBE)
Glottis	Mean	<45 Gy(RBE)
Larynx_SG	Mean	<45 Gy(RBE)
Musc_Constrict_S	Mean	<50 Gy(RBE)
Musc_Constrict_M	Mean	<50 Gy(RBE)
Musc_Constrict_I	Mean	<20 Gy(RBE)
Inlet_Cricophar	Mean	<20 Gy(RBE)
Oesophagus_S	Mean	<20 Gy(RBE)
Bone_Mandible	0.1cc	<73.5 Gy(RBE)
Cochlea_R	Mean	<30 Gy(RBE)
Cochlea_L	Mean	<30 Gy(RBE)
Fossa_Posterior	Mean	As low as possible
BrachialPlex_R*	0.1cc	60 Gy(RBE)
BrachialPlex_L*	0.1cc	60 Gy(RBE)

*IMPT plans only – on side(s) of neck with involved nodes

Dysphagia-optimised intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer (DARS): a phase 3, multicentre, randomised, controlled trial

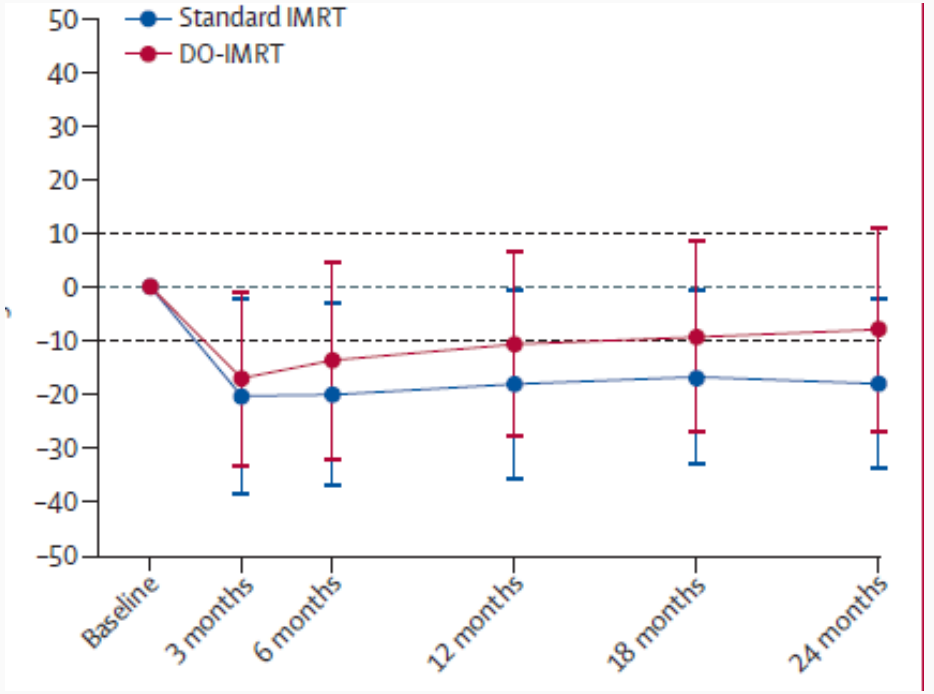
Christopher Nutting, Laura Finneran, Justin Roe, Mark A Sydenham, Matthew Beasley, Shree Bhide, Cheng Boon, Audrey Cook, Emma De Winton, Marie Emson, Bernadette Foran, Robert Frogley, Imran Petkar, Laura Pettit, Keith Rooney, Tom Roques, Devraj Srinivasan, Justine Tyler, Emma Hall, on behalf of the DARS Trialist Group

118 patients were registered, 112 of whom were randomly assigned to DO-IMRT (n=56) or standard IMRT (n=56)

CTV + GTV+10mm

>90% oropharynx

Structure	Constraint	Mandatory Dose constraint	Optimal Dose Constraint
PlanSMPCM	Mean dose	< 50Gy	
PlanIPCM	Mean dose		< 20Gy



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