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TOxicity Reduction using Proton bEam therapy for Oropharyngeal Cancer

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

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Making the discoveries that defeat cancer

Background - locally advanced oropharyngeal cancer

- Intensity modulated radiotherapy (IMRT) + cisplatin is the standard of care
- Potential for severe late toxicities:
    - Large deteriorations in long-term HRQoL for multiple physical symptoms [1]
    - 1-year gastrostomy dependence for 9% of patients [2]
- Observational data suggested a clinical advantage for proton beam therapy over IMRT

e.g., G3 weight loss or gastrostomy dependence at 12 months for IMPT vs IMRT: OR=0.23 (p=0.01) [3]

- RCT evidence needed to justify inconvenience to patients and increased treatment costs

1. Eur. J Cancer. 2017; 78:91-102 2. Cancer. 2015;121(2):294-301 3. Radiother. Oncol. 2016;120(1):48-55

Phase 3 RCT - Study Design and Aims

Oropharyngeal SCC requiring concurrent chemo-radiotherapy including bilateral neck treatment

T1/2 vs T3/4
N-stage
p16 status
Smoking history

2:1
randomisation

Intensity modulated proton therapy (IMPT)

Intensity modulated radiotherapy (IMRT)

70 Gy / 56 Gy
in 33 fractions
over 6.5 weeks

Cisplatin
100mg/m^2
D1 + D22

Primary objective: to assess whether IMPT compared with IMRT reduces late toxicities in OPSCC

Clinician reported co-primary endpoint: CTCAE grade 3 weight loss (≥ 20% decrease from baseline) or gastrostomy dependence at 12 months post radiotherapy

Patient reported co-primary endpoint: University of Washington quality of life (UW-QoL) physical composite score at 12 months post radiotherapy (saliva, taste, chewing, swallowing, appearance, speech)

Ensuring a valid comparison of IMPT vs IMRT

Radiotherapy: IMPT and IMRT

- Same OAR dose targets and constraints
- Same plan optimisation prioritisation parameters
- Fully optimised function-sparing radiotherapy
- Protocolised reasons for re-planning
- National Radiotherapy Trials Quality Assurance
  - baseline credentialing of contouring and planning
  - prospective quality assurance of all cases

Supportive Care

- Feeding tubes
  - minimum thresholds for use
  - removed if not used for more than two weeks

Patient Reported Outcome Measures

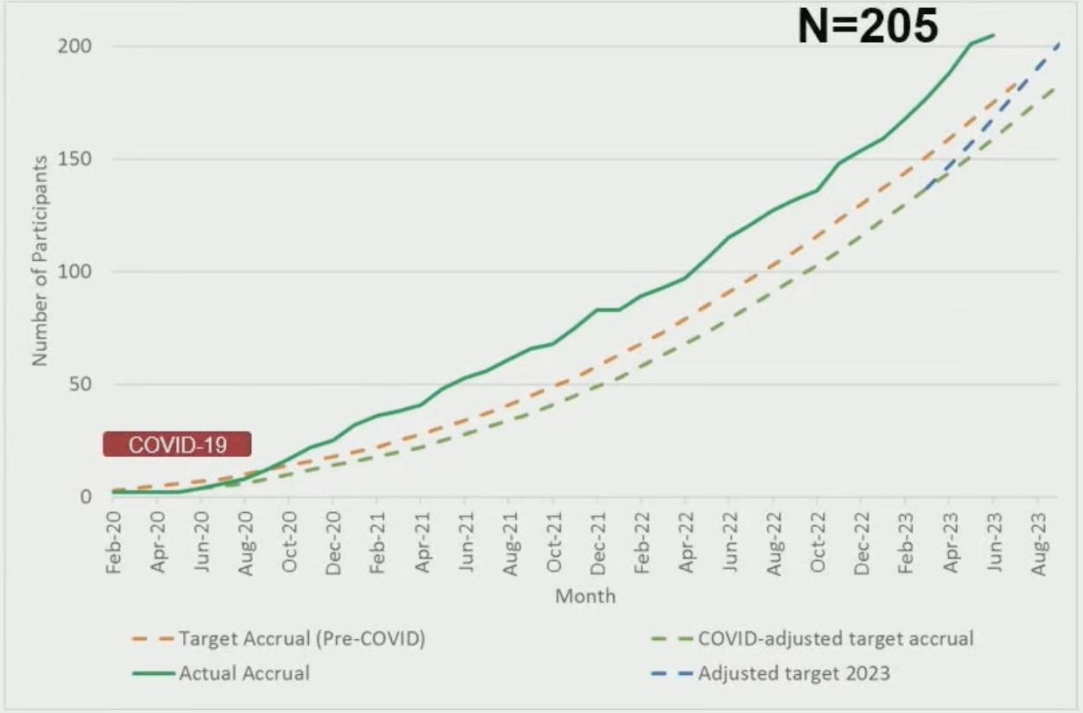
- Questionnaires administered centrally
  - posted to patients for completion
  - independent of the treating clinician

Co-variates for analysis of the primary endpoints

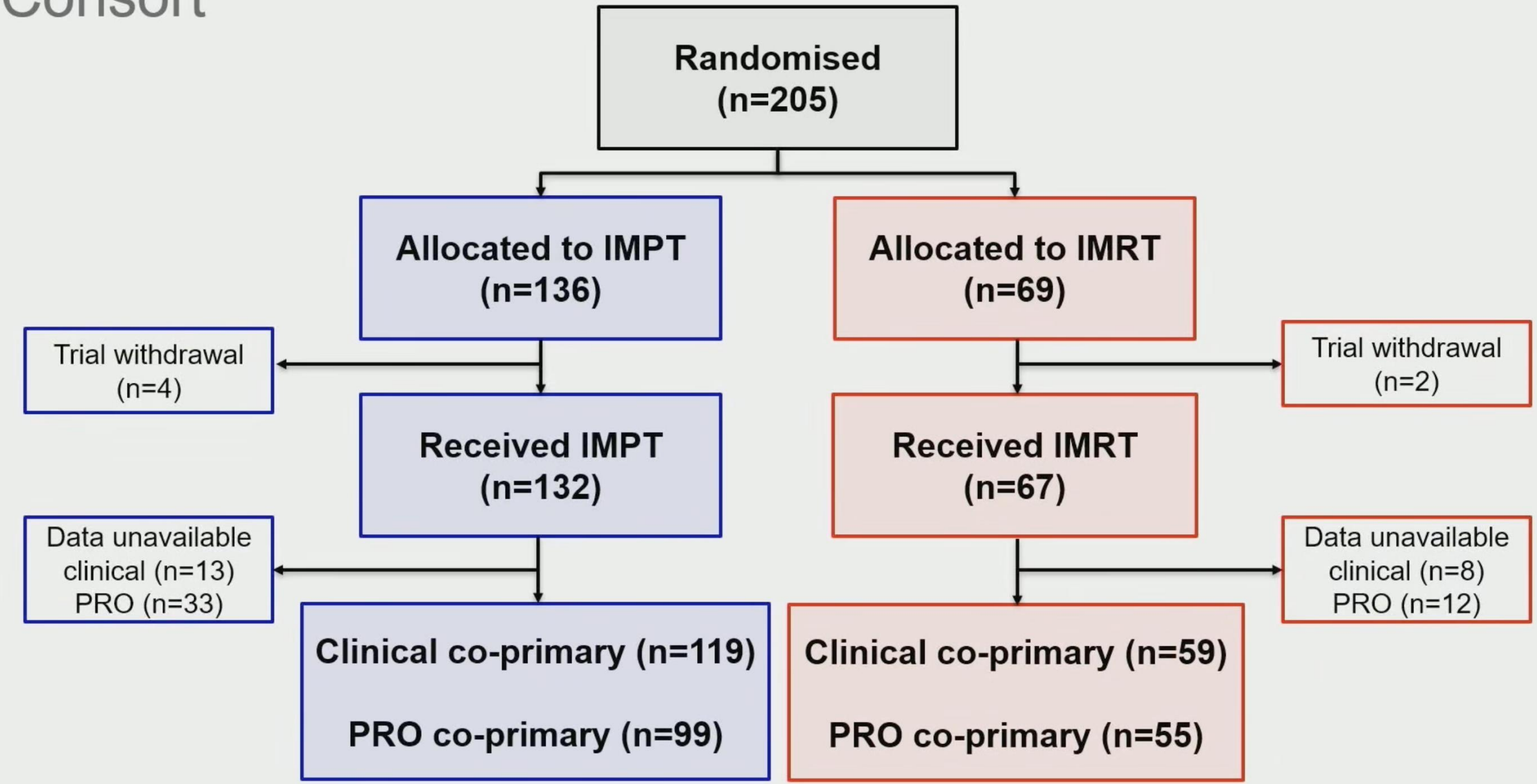
- T-stage, N-stage, smoking history
- Baseline nutritional status (BMI)
- Baseline UW-QoL physical composite score

Recruitment over 3 years, completed ahead of schedule

- For gastrostomy dependence or G3 weight loss,165 participants were required for an odds ratio of 0.23 (2-sided 2.5% significance level, 80% power)
- For UW-QoL, 156 participants were required to demonstrate an 8-point improvement in the mean score (2-sided 2.5% significance level, 86% power)
- **Target sample size 201 to allow for non-evaluability**



Consort


Randomised
(n=205)
Allocated to IMPT
(n=136)
Allocated to IMRT
(n=69)
Trial withdrawal
(n=4)
Trial withdrawal
(n=2)
Received IMPT
(n=132)
Received IMRT
(n=67)
Data unavailable
clinical (n=13)
PRO (n=33)
Data unavailable
clinical (n=8)
PRO (n=12)
Clinical co-primary (n=119)
PRO co-primary (n=99)
Clinical co-primary (n=59)
PRO co-primary (n=55)

Baseline characteristics and treatment compliance

	IMPT	IMRT
Median age	56.9 years	57.7 years
Male, Female	78.7%, 21.3%	81.2%, 18.8%
White Black, Asian or Ethnic minority	99.1% 0.9%	98.3% 1.7%
Employed Unemployed Retired	75.2% 9.4% 15.4%	70.0% 10.0% 20.0%
T1/T2 T3/T4	70 (51.5%) 66 (48.5%)	36 (52.2%) 33 (47.8%)
Bilateral Neck Nodes Involved	30 (22.1%)	14 (20.3%)
Smoking: current or >10PYH	43 (31.6%)	23 (33.3%)
Duration of radiotherapy (median, IQR, days)	44 (44, 44)	44 (44, 44)
Radiation fractions missed and compensated	65/4356 (1.5%)	3/2211 (0.1%)
2 cycles concurrent chemotherapy	127/132 (96.2%)	64/67 (95.5%)

Clinical co-primary: low feeding tube dependence in both arms

Of the 205 randomised patients, 178 (119 IMPT; 59 IMRT) were evaluable at 12 months post radiotherapy

At 12 months after treatment	IMPT	IMRT
Feeding Tube Use	2/119 (1.7%)	1/59 (1.7%)
CTCAE G3 weight loss (≥ 20%)	20/110 (18.2%)	3/53 (5.7%)
Feeding tube use OR G3 weight loss	21/119 (17.6%)	4/59 (6.8%)

- **IMPT odds ratio of 2.8 for feeding tube use or G3 weight loss (97.5% CI: 0.8, 10.4, p=0.08)**
- **IMPT did not decrease gastrostomy dependence or weight loss at 12 months**

PRO co-primary: IMPT did not improve physical HRQoL

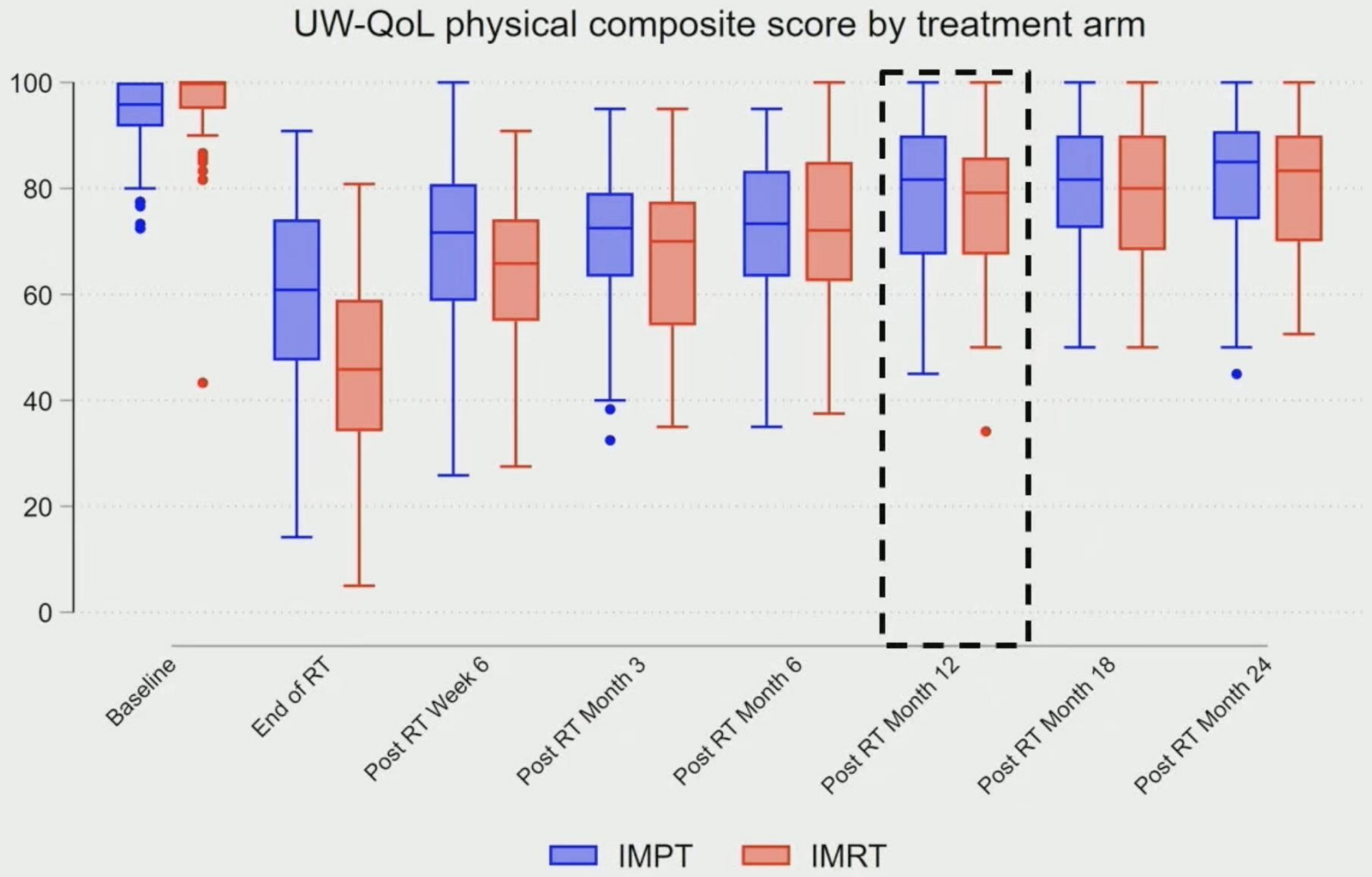
Of the 205 randomised patients, 154 (99 IMPT; 55 IMRT) were evaluable at 12 months post radiotherapy

UW-QoL physical composite score for saliva, taste, chewing, swallowing, appearance, speech

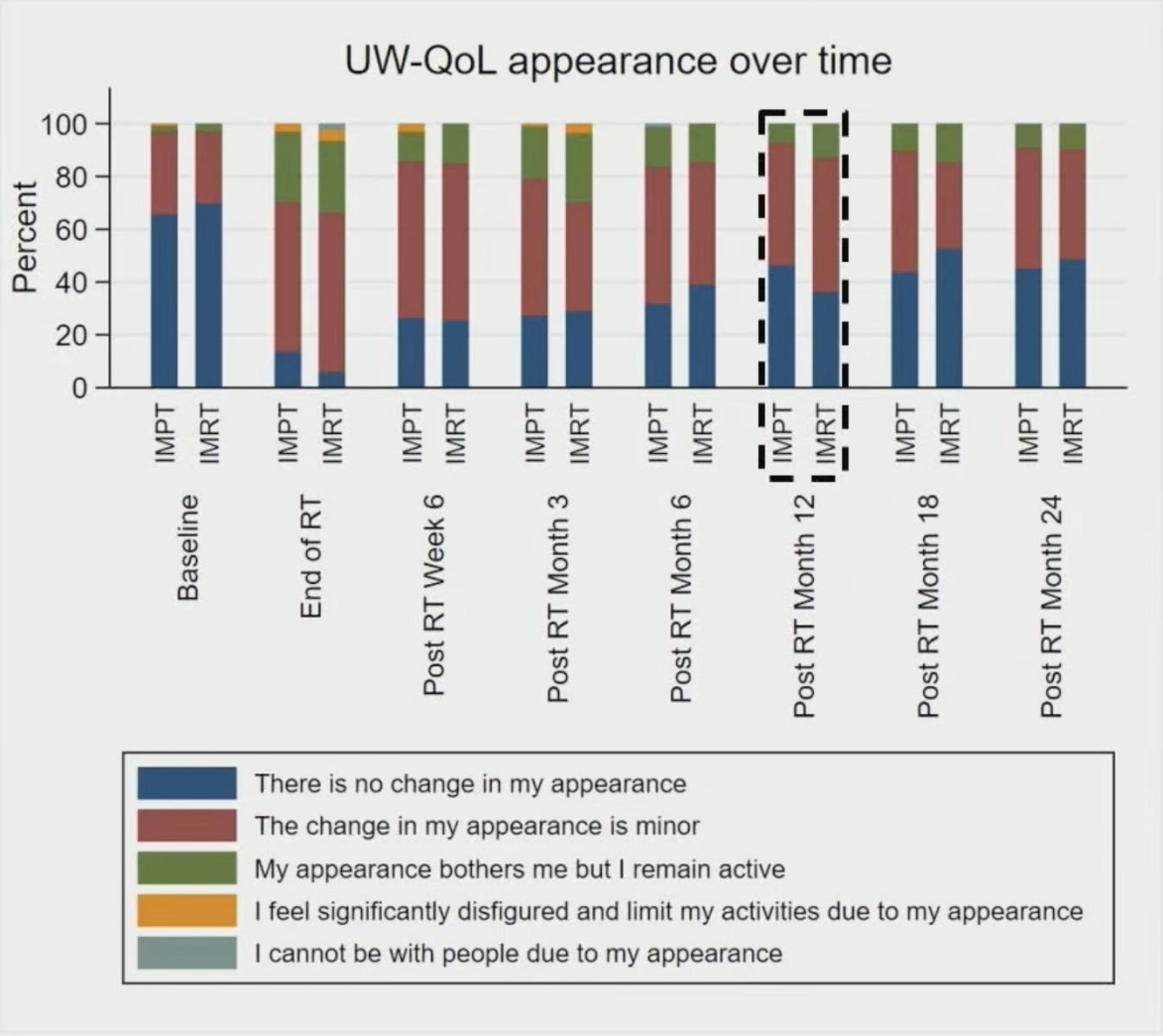
At 12 months after treatment	IMPT	IMRT
Adjusted mean (97.5% CI) UW-QoL physical composite score	78.3 (75.4, 81.3)	77.1 (73.1, 81.0)
Difference between arms = 1.3 (97.5% CI:-3.7, 6.2, p=0.56)		

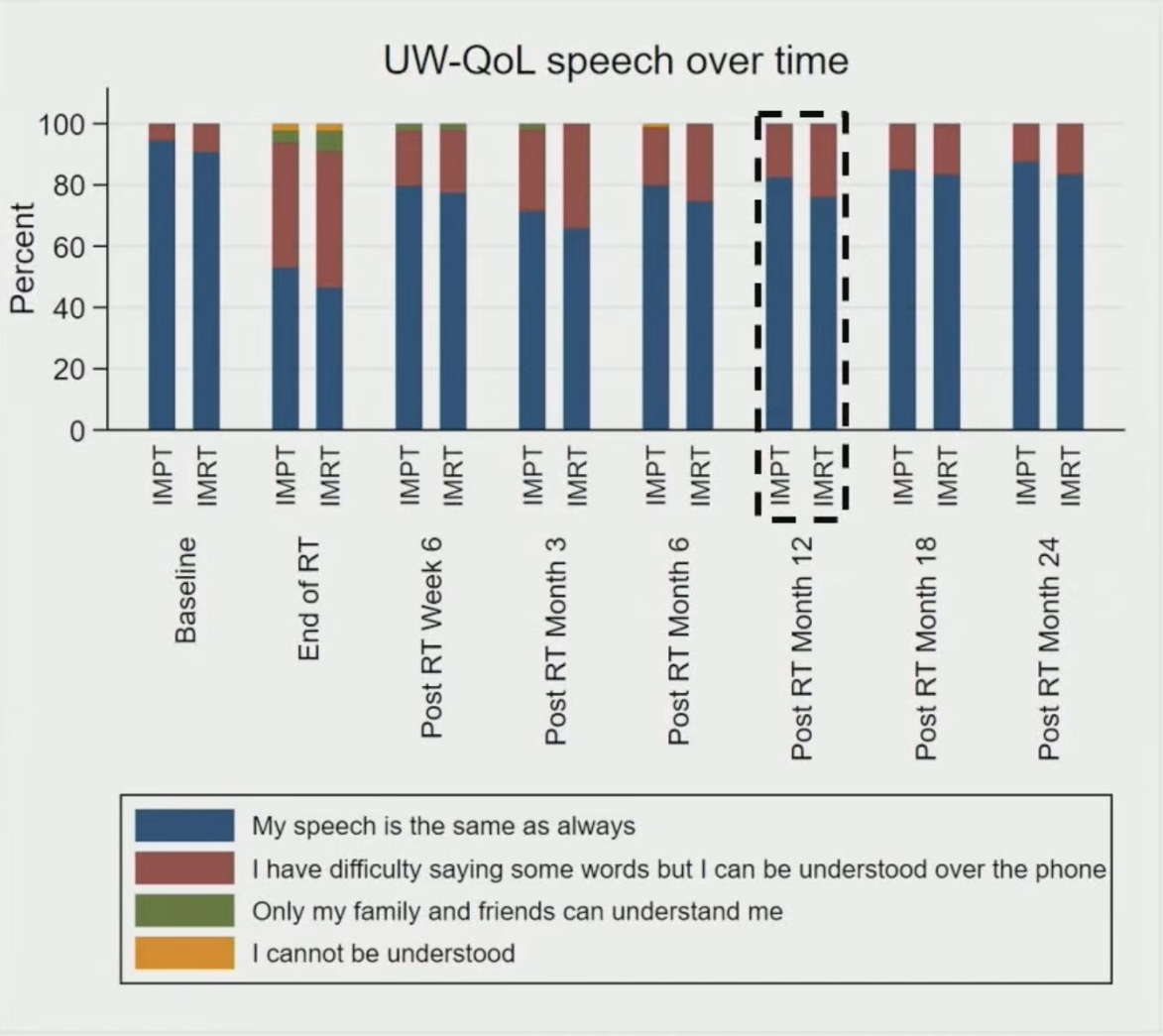
- **No difference in UW-QoL scores at 12 months post radiotherapy for IMPT vs IMRT**
- **MDADI mean scores at 12 months also similar for IMPT vs IMRT: 79.5 vs 79.7**

UW-QoL physical composite score greater for IMPT on completion, but by week 6 scores are similar to IMRT

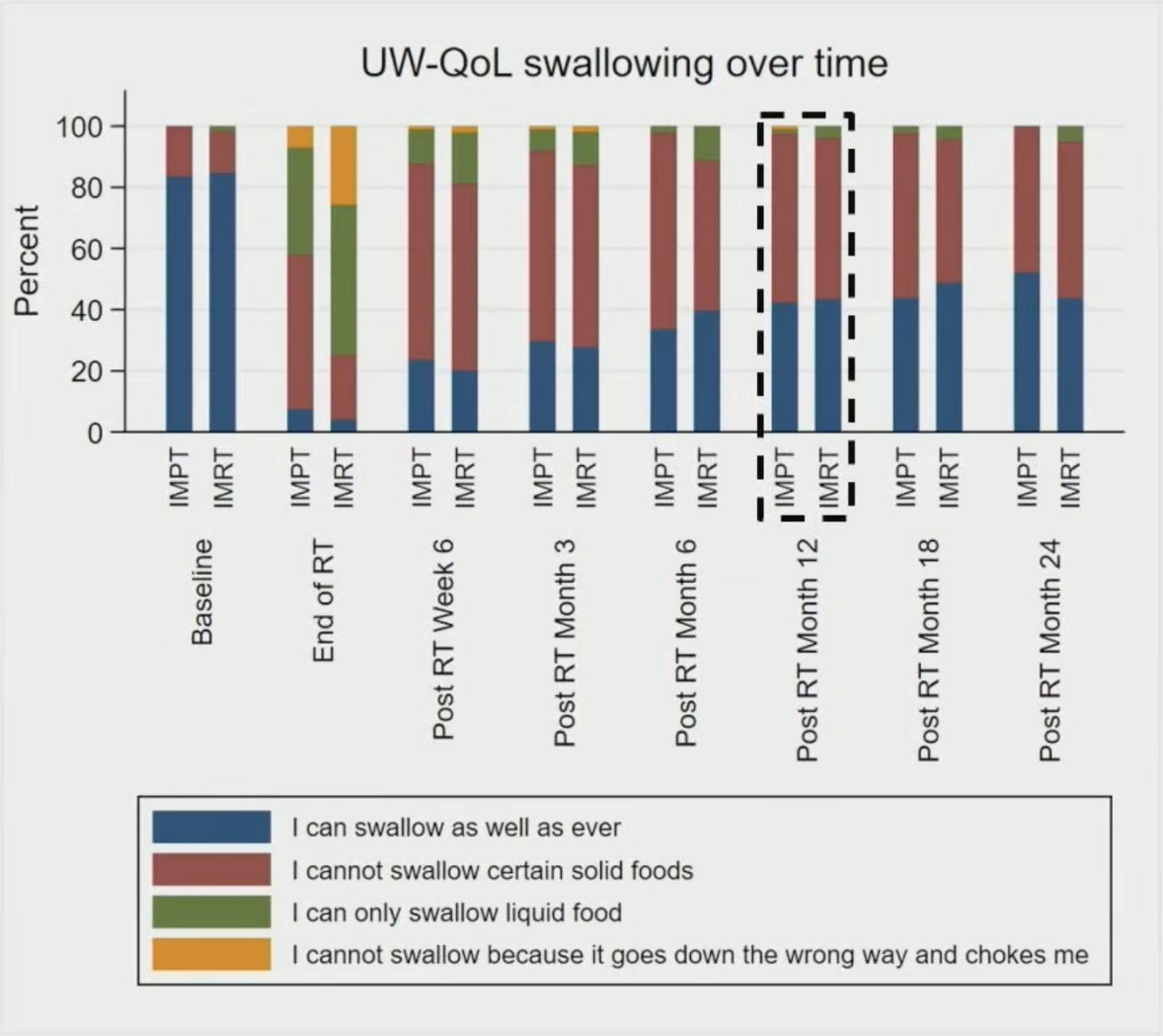


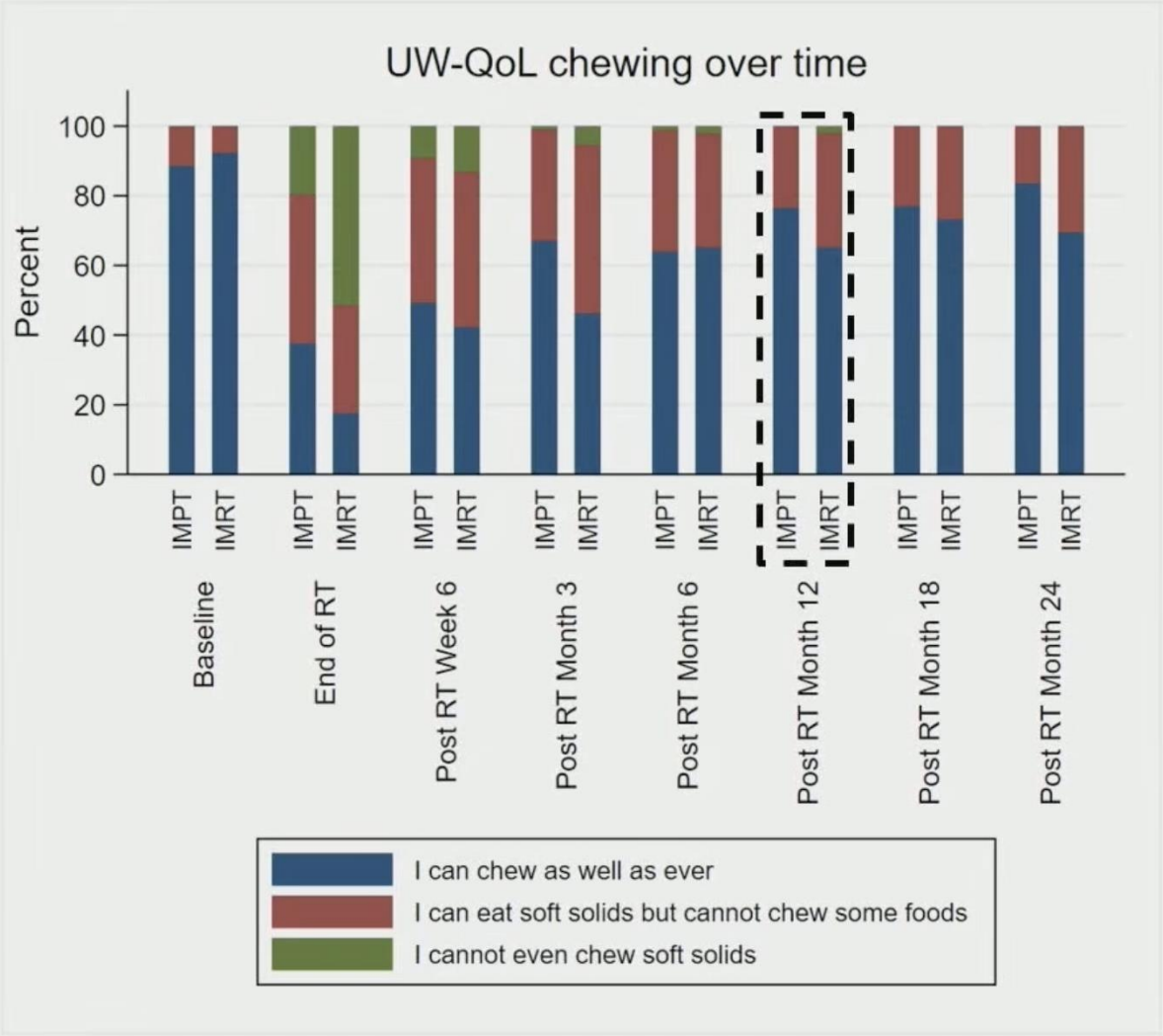
UW-QoL appearance and speech similar for IMPT and IMRT over time



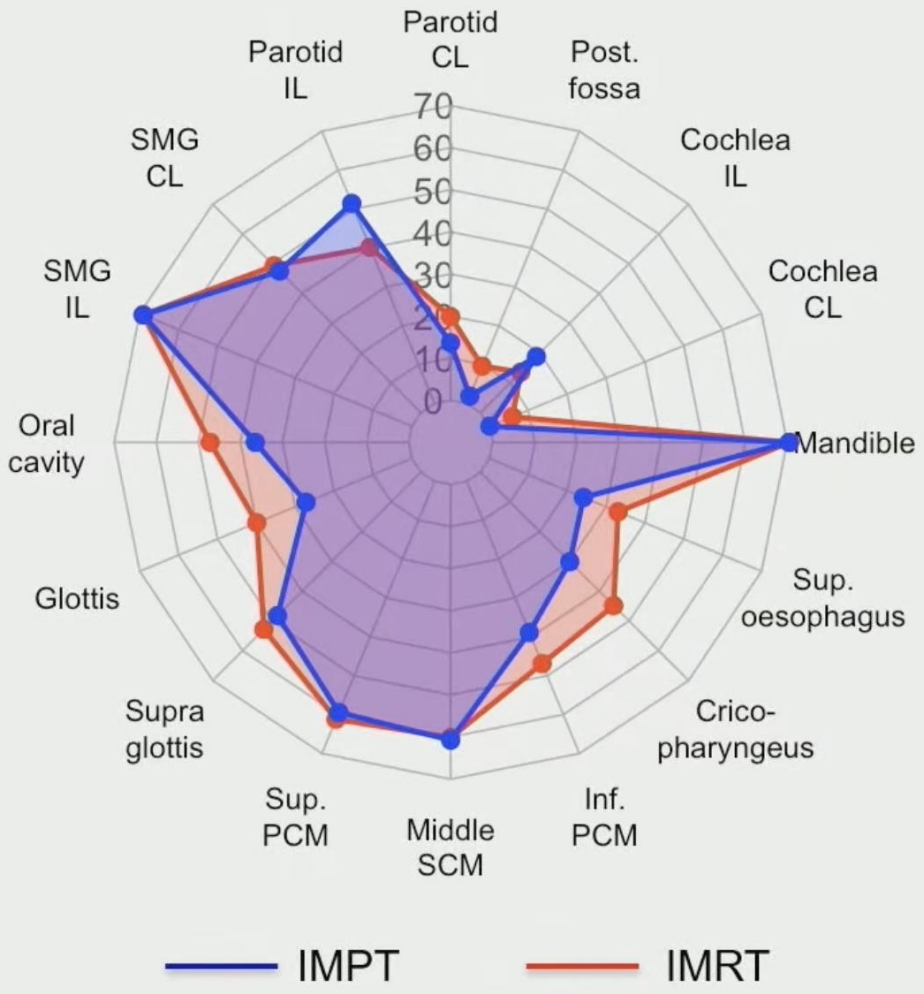


UW-QoL swallowing and chewing scores higher for IMPT on completion, but by week 6 scores are similar to IMRT





IMPT reduced doses to OARs



Organ at Risk	IMPT (median, Gy)	IMPT – IMRT (median, Gy)
Contralateral Parotid	13.6	**- 6.2***
Oral Cavity	36.5	**- 10.8***
Glottic Larynx	27.2	**- 12.7***
Inferior Constrictor	38.9	**- 8.0***
Cricopharyngeal Inlet	30.1	**- 14.7***
Cervical Oesophagus	24.2	**- 8.9***
Contralateral Cochlea	0.1	**- 5.8***
Posterior Fossa	1.9	**- 7.7***

***p<0.001**

Model-based enrichment did not affect UW-QoL scores

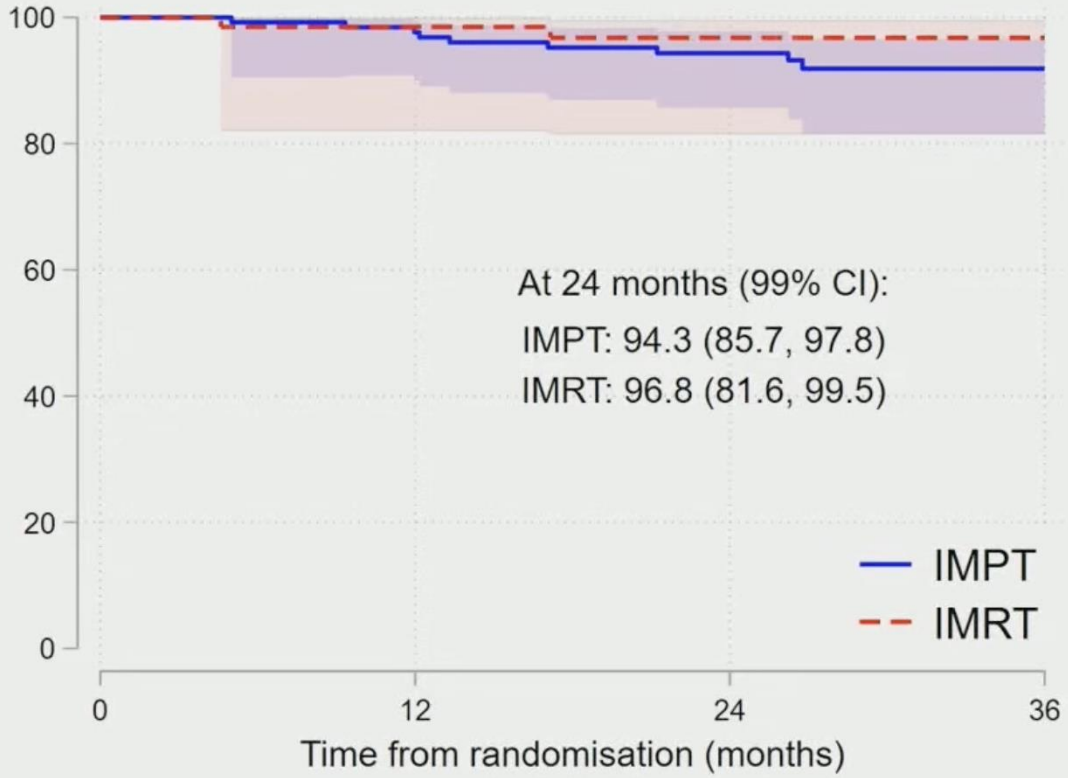
- Anticipated 50% of patients would meet the NTCP criteria for routine use of IMPT in the Netherlands
- 78/153 (51.0%) of evaluable patients met the criteria for treatment with IMPT

Mean (95% CI) UW-QoL physical composite score at 12 months		
	Enriched (met NTCP criteria)	Unenriched
IMPT	78.2 (74.7, 81.6)	78.5 (74.2, 82.9)
IMRT	75.8 (69.3, 82.3)	77.5 (73.1, 82.0)
Difference between arms	2.4 (-4.8, 9.6)	1.0 (-5.0, 7.0)

- **No difference in UW-QoL mean scores at 12 months post radiotherapy for IMPT vs IMRT**

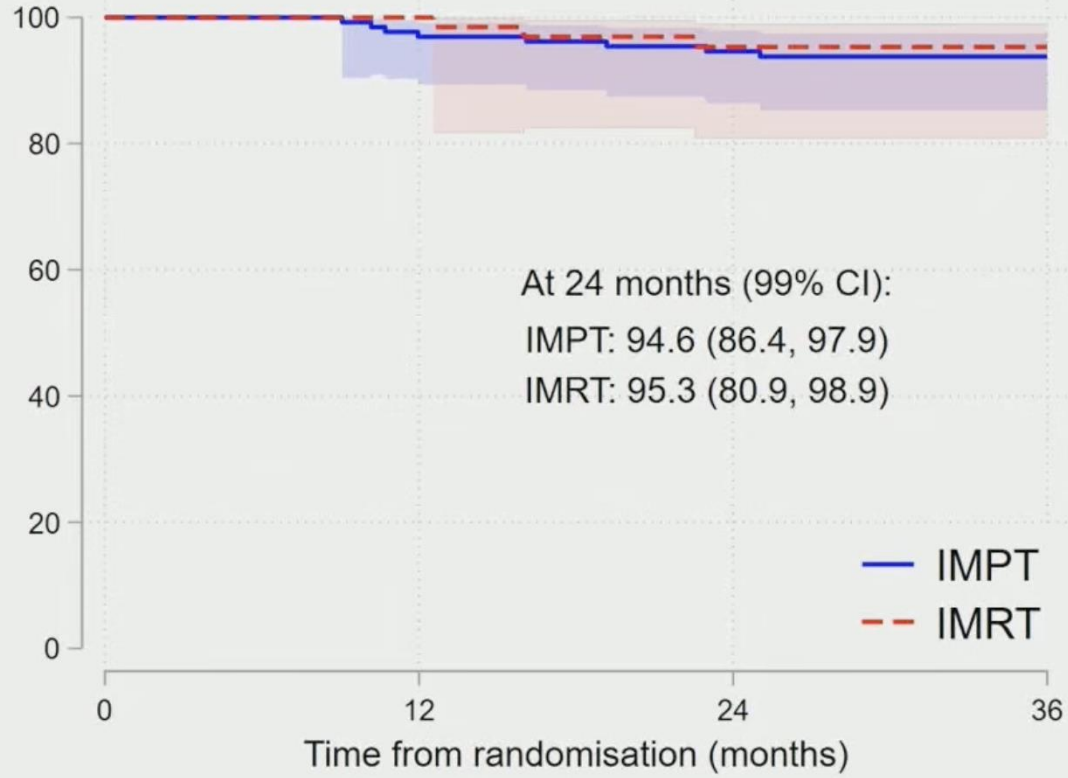
No differences in loco-regional control or overall survival

% Free From Local Recurrence



N at risk (events)							
IMPT	136	(3)	122	(4)	100	(2)	43
IMRT	69	(1)	59	(1)	51	(0)	22

% Alive



N at risk (events)							
IMPT	136	(4)	127	(3)	117	(1)	60
IMRT	69	(0)	66	(3)	59	(0)	28

Conclusions

For locally advanced oropharyngeal cancer:

- No benefit of IMPT compared with IMRT
- Fully optimized IMRT outperforms prior late toxicity and QoL data
- Physicians and patients assured of no requirement to access IMPT