



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Hypofractionated chemoradiation for head and neck cancer: Data from the PET NECK trial

M. Vreugdenhil^{a,b}, Charles Fong^{a,b}, Paul Sanghera^{a,b}, Andrew Hartley^{a,b,*}, Janet Dunn^c, Hisham Mehanna^a

^a Institute of Head & Neck Studies and Education, University of Birmingham, UK

^b Hall-Edwards Radiotherapy Research Group, Queen Elizabeth Hospital, Birmingham, UK

^c Warwick Clinical Trials Unit, University of Warwick, Coventry, UK

ARTICLE INFO

Keywords:

Hypofractionated chemoradiation
Pandemic
Head and neck cancer
COVID 19
Fractionation

ABSTRACT

There has been increased interest in hypofractionated accelerated chemoradiation for head and neck cancer during the recent first peak of the COVID-19 pandemic. Prospective data regarding this approach from randomised trials is lacking. In the PET NECK study, 564 patients with squamous cell carcinoma of the head and neck receiving definitive chemoradiation were randomised to either planned neck dissection or PET CT scan guided surveillance. In this surgical trial, three radiotherapy fractionation schedules delivered over 7, 6 or 4 weeks were permitted with synchronous chemotherapy. The purpose of this study was to determine efficacy and quality of life outcomes associated with the use of these schedules.

Primary local control and overall survival in addition to quality of life measures at immediately post treatment and 6, 12 and 24 months post-treatment were compared between the three fractionation cohorts.

In the 525 patients where fractionation data was available, 181 (34%), 288 (55%) and 56 (11%) patients received 68–70 Gy in 34–35 fractions (#), 60–66 Gy in 30# and 55 Gy in 20# respectively. At a minimum follow up of two years following treatment there was no significant difference between the three fractionation schemes in local control, overall survival or any quality of life measure.

Despite the obvious limitations of this study, some data is provided to support the use of hypofractionated accelerated chemoradiation to avoid delays in cancer treatment and reduce hospital visits during the peak of a pandemic. Data from on-going randomised trials examining hypofractionated chemoradiation may be useful for selecting fractionation schedules during future pandemics.

Introduction

The morbidity and mortality of patients with both COVID-19 and cancer has been studied in recent months due to the theoretical increased risk of infection and death. A systemic review pooling case mortality data from studies around the world found a higher mortality rate of 25.6% in patients with both cancer and COVID-19 suggesting an increased vulnerability of this population [1]. A UK based cohort study echoes this showing a high mortality (30.6%) in cancer patients linked closely to increasing age and other comorbidities [2]. A small, early cohort study (18 patients, 4 of which received anti-cancer therapy within 4 weeks) indicated a higher mortality rate in patients treated with chemotherapy and immunotherapy [3]. However, more recent, larger studies found recent systemic anti-cancer treatment or

radiotherapy did not influence survival outcome except in the case of patients with haematological malignancy who had received recent chemotherapy [2,4,5]. Early studies suggested a higher infection rate of SARS Co-V-2 in cancer patients likely secondary to their immunocompromised state and possibly associated with hospital transmission of infection [6,7].

During the recent first peak of the COVID-19 pandemic, there has been renewed interest, including in this journal, in hypofractionated chemoradiation and hypofractionated radiation for locally advanced head and neck cancer [8–11]. Hypofractionation may be advantageous in reducing the risk of contracting an infective agent by reducing the number of visits to hospital. In addition, it may permit radical treatment when there is a shortage of radiotherapy capacity due to staff illness or quarantine. Furthermore, shortened radiotherapy schedules may be less

* Corresponding author at: Hall-Edwards Radiotherapy Research Group, Queen Elizabeth Hospital, Birmingham, UK.

E-mail address: andrew.hartley@uhb.nhs.uk (A. Hartley).

<https://doi.org/10.1016/j.oraloncology.2020.105112>

Received 6 November 2020; Received in revised form 18 November 2020; Accepted 19 November 2020

Available online 13 December 2020

1368-8375/© 2020 Elsevier Ltd. All rights reserved.

vulnerable to treatment breaks [12]. In the ASTRO-ESTRO consensus statement for the COVID-19 pandemic, while acknowledging a shortage of evidence, there was strong agreement among panellists on the use of hypofractionated radiation alone in locally advanced disease [9]. There was also agreement to reserve the use of synchronous chemotherapy to standardly fractionated or mildly hypofractionated radiotherapy (2.4 Gy per fraction (#) or less). There was concern among panellists regarding the possible lack of benefit for synchronous chemotherapy with more marked accelerated hypofractionation and the possible worse late toxicity. In contrast in the U.K, the Royal College of Radiologists listed a more profoundly hypofractionated schedule 55 Gy in 20# as a potential option with synchronous chemotherapy although it had been removed from college guidelines for routine use in 2016 [11,13].

In the PET NECK study, 564 patients with squamous cell carcinoma of the head and neck with advanced nodal stage (N2 or N3) receiving definitive chemoradiation were randomised to either planned neck dissection or PET CT scan guided surveillance [14]. The study showed that a similar overall survival was achieved with PET CT scan guided surveillance and that it resulted in fewer operations and was more cost-effective.

Patients were recruited to this study from 2007 to 2012. As this was primarily a pragmatic surgical study, there was no specific radiotherapy contouring protocol or contouring or delivery quality assurance. Three fractionation schemes were permitted to be administered with synchronous chemotherapy, 68–70 Gy in 34–35 fractions (#), 60–66 Gy in 30# and 55 Gy in 20# in keeping with Royal College of Radiologist guidelines contemporaneous with the study recruitment period [13]. In the UK during this time Intensity Modulated Radiotherapy (IMRT) was gradually replacing three dimensional conformal radiotherapy (3DCRT). Initially this change was based on case series reporting lower rates of xerostomia with parotid sparing IMRT and the emerging availability of necessary technology in the UK health system [15]. In 2011, the phase 3 PARSPORT trial reported 2 year results on 94 patients with squamous cell carcinoma of the head and neck who had been randomised to 3DCRT or parotid sparing IMRT. A reduction of grade 2 or worse xerostomia from 83% to 29% was observed with IMRT ($p < 0.0001$) [16]. The presentation of this data prior to publication of the full paper also prompted the gradual adoption of IMRT during the recruitment to the PET NECK study.

The primary purpose of this paper was to investigate whether the use of different radiotherapy fractionation schedules with chemotherapy was correlated with efficacy and quality of life outcomes. The effect of radiotherapy technique, 3DCRT or IMRT was also examined.

Methods

The methods for the conduct and statistical analysis of the PET NECK trial have been published previously [14]. For the purposes of this paper, baseline characteristics including treatment arm, timing of neck dissection, chemotherapy regime, tumour site, age, sex, T stage, N stage, performance status, smoking status, alcohol status and p16 status were compared for the three fractionation cohorts to ensure the characteristics were balanced between groups. Although not the focus of this paper, baseline characteristics of the two technique cohorts (3D CRT and IMRT) were also compared. Differences in baseline factors between groups were tested using the chi-squared test.

With a minimum follow up in surviving patients of two years, local control of the primary tumour and overall survival was compared in the three fractionation cohorts.

To account for imbalance of prognostic factors, p16+ve and p16–ve patients were also considered separately. In the trial, some centres opted to perform the planned neck dissection before definitive chemoradiation. This makes definition and interpretation of regional control complex and thus local control of the primary tumour and overall survival were selected as the efficacy endpoints. A multivariate analysis using Cox regression was performed to identify factors associated with

overall survival.

The administration and analysis of quality of life questionnaires in the PET NECK study has been previously described [14]. Differences in mean scores from baseline to immediately post treatment and at 6, 12, 18 and 24 months between the three fractionation and two technique cohorts were analysed. Finally, a multivariate analysis was performed to assess the effects of radiotherapy technique and fractionation on Global Health status at 2 years measured using the EORTC QLQ-C30 questionnaire.

Results

Data on radiotherapy fractionation was available in 525 (93%) of the PET NECK trial patients. The patient and tumour characteristics in the three fractionation cohorts are given in table 1. There were significantly more patients in the 4 week cohort who were p16 negative (-ve): 23 (48%) compared with 37 (16%) and 41 (30%) in the 6 and 7 week cohorts respectively ($p < 0.0001$). There were also borderline significant differences between the groups in the approved chemotherapy schedule ($p = 0.04$) and the timing of planned neck dissection ($p = 0.03$). The only statistically significant difference between the 3DCRT and IMRT cohorts in the 532 (94.3%) of patients for whom data on radiotherapy technique was available was the imbalance in primary site reflecting the higher proportion of oropharynx patients in the IMRT cohort (293 (88.3%) v 157 (78.5%) receiving 3DCRT ($p = 0.014$)).

There were no statistically significant differences in local control between the 3 fractionation schedules. In p16 positive (+ve) patients receiving 4 week fractionation ($n = 25$) v. 6 week ($n = 193$) v. 7 week ($n = 98$), the 2 year primary local control was 87% (95% CI 74–100%) v. 95% (95% CI 92–98%) v. 92% (95% CI 86–97%). The corresponding figures for p16–ve patients were 85% (69–100%) v. 80% (66–93%) v. 74% (59–88%) ($n = 23$ v. $n = 37$ v. $n = 41$). Similarly there were no statistically significant differences between the 3DCRT and IMRT cohorts.

There were no statistically significant differences in overall survival between the three fractionation cohorts. Survival curves for p16 + ve and p16–ve patients treated within the three fractionation cohorts are given in Figs. 1 and 2. Similarly there were no significant survival differences between the two technique cohorts.

In a multivariate analysis including radiotherapy fractionation and technique, p16 status ($P < 0.0001$), T stage ($p = 0.0002$), N stage ($p = 0.02$) and smoking status ($p = 0.018$) were found to be statically significantly associated with overall survival.

There were no statistically significant differences in mean scores for quality of life at baseline between the 3 fractionation cohorts. Immediately post treatment and at 6,12 and 24 months post treatment, again there were no statistically significant differences in mean scores between the fractionation cohorts for any of the endpoints addressed by the questionnaires. Table 2 illustrates the expected larger drop in mean score experienced by p16 + ve patients between baseline and immediately post treatment in EORTC QLQ C30 overall health status (-33.9 v -18.4 ($p < 0.0001$)), reflecting higher baseline scores in p16+ve patients [17,18]. After correcting for this effect, there remains no significant difference in the mean score for this parameter from baseline to post treatment or 24 months for the 3 fractionation cohorts. With regards to IMRT v. 3DCRT, as might be expected, Table 2 illustrates a trend towards a lower drop in baseline to post-treatment score ($p = 0.06$) and a similar trend from baseline to 24 months ($p = 0.07$) in favour of the IMRT cohort. Table 3 details the number of patients with clinically meaningful change (greater or equal to 10 points) in questionnaire scores (QLQ C30, MDADI, HN35) between baseline and immediately post treatment and at 6, 12, 18 and 24 months post treatment stratified by fractionation cohort. The similar trajectory between the three fractionation cohorts is evident and there were no statistically significant differences.

In addition to the trend in favour of IMRT with correction for p16

Table 1
Baseline characteristics of the three fractionation cohorts.

Baseline characteristic	68–70 Gy in 34–35 fractions	60–66 Gy in 30 fractions	55 Gy in 20 fractions	P-value
Trial treatment arm [n (%)]				0.86
Neck dissection	86 (47.5)	144 (50.0)	28 (50.0)	
PETCT surveillance	95 (52.5)	144 (50.0)	28 (50.0)	
Neck dissection policy before or after CRT (stated at randomisation) [n (%)]				0.03
Neck dissection before CRT	37 (20.4)	87 (30.2)	19 (33.9)	
Neck dissection after CRT	144 (79.6)	201 (69.8)	37 (66.1)	
Approved chemotherapy schedules [n (%)]				0.04
Concomitant platinum	100 (55.3)	181 (62.9)	28 (50.0)	
Concomitant cetuximab	7 (3.9)	14 (4.9)	5 (8.9)	
Neoadjuvant PF and concomitant platinum	2 (1.1)	14 (4.9)	1 (1.8)	
Neoadjuvant TPF with concomitant platinum	69 (38.1)	74 (25.7)	20 (35.7)	
Other agreed schedules	3 (1.7)	5 (1.7)	2 (3.6)	
Tumour site [n (%)]				0.10
Oral	7 (3.9)	3 (1.0)	–	
Oropharyngeal	147 (81.2)	252 (87.5)	45 (80.4)	
Laryngeal	14 (7.7)	14 (4.9)	6 (10.7)	
Hypopharyngeal	10 (5.5)	12 (4.2)	5 (8.9)	
Occult H&N	3 (1.7)	7 (2.4)	–	
Age (years)				
Mean (SD)	57.2 (7.1)	57.8 (7.8)	60.9 (9.2)	
Sex [n (%)]				0.26
Males	153 (84.5)	235 (81.6)	42 (75.0)	
Females	28 (15.5)	53 (18.4)	14 (25.0)	
T-stage [n (%)]				0.51
T1	31 (18.8)	52 (18.1)	9 (16.1)	
T2	65 (35.9)	123 (42.7)	19 (33.9)	
T3	35 (19.3)	53 (18.4)	16 (28.6)	
T4	44 (24.3)	54 (18.8)	12 (21.4)	
Occult	3 (1.7)	6 (2.1)	–	
N-stage [n (%)]				0.18
N2a	33 (18.2)	52 (18.4)	6 (10.7)	
N2b	118 (65.2)	175 (60.8)	32 (57.1)	
N2c	25 (13.8)	52 (18.1)	17 (30.4)	
N3	5 (2.8)	8 (2.8)	1 (1.8)	
ECOG performance status [n (%)]				0.20
0	142 (78.5)	232 (80.8)	38 (67.9)	
1	37 (20.4)	53 (18.5)	18 (32.1)	
2	2 (1.1)	2 (0.7)	–	
Smoking [n (%)]				0.13
Current	60 (33.2)	75 (26.1)	14 (25.0)	
Past	82 (45.3)	125 (43.6)	30 (53.6)	
Never	39 (21.6)	87 (30.3)	12 (21.4)	
Alcohol [n (%)]				0.51
Current	151 (83.4)	233 (82.0)	43 (76.8)	
Past	18 (9.9)	25 (8.8)	5 (8.9)	
Never	12 (6.6)	26 (9.2)	8 (14.3)	
P16 status [n (%)]				<0.0001
p16 +ve	98 (70.5)	193 (83.9)	25 (52.1)	
p16 –ve	41 (29.5)	37 (16.1)	23 (47.9)	

status for global health status noted above, a statistically significant advantage for IMRT over 3DCRT was found for dry mouth immediately post treatment ($p = 0.002$) which persisted at 24 months ($p = 0.01$). Multivariate modelling of global health status (EORTC QLQ C30) at 2 years indicated baseline quality of life as a highly significant factor ($p <$

0.0001). Neither fractionation nor radiotherapy technique were significant factors.

Discussion

During the recent first peak of the COVID -19 pandemic, many radiotherapy departments needed to review protocols for chemoradiation and to make adjustments according to local virus risk and healthcare capacity. This analysis aimed to provide some additional data for clinicians undertaking a risk mitigation approach during a pandemic. The lack of difference in efficacy and quality of life endpoints at baseline (acute effects) and at 2 years (late effects) at least between the 6 and 7 week arm lends some support to mild hypofractionation as recommended by the ASTRO-ESTRO consensus statement and Royal College of Radiologists [9,11]. The authors are not aware of any randomised data comparing the regime 65 Gy/30# over 39 days with the international standard fractionation 70 Gy in 35# with synchronous cisplatin. The former regimen has been used with synchronous cisplatin chemotherapy as a control arm in the ARTDECO study where it was compared in locally advanced laryngeal cancer to a slightly more accelerated and more hypofractionated regime (67.2 Gy in 28# over 37 days) [19]. It has also been employed with synchronous chemotherapy in the DARS study examining the effect on swallowing outcomes of dose reduction to swallowing structures [20]. The long term results of both these studies are yet to be published. However, the use of this regime in two randomised trials, together with data from single centre series and the data from this study would appear to justify the use of this moderate hypofractionated acceleration in the absence of direct phase 3 comparisons [13,21–23].

Use of a 6 week schedule only results in a slight decrease in the number of visits for patients. Based on single centre data the hypofractionated radiotherapy alone regime 60 Gy/25# over 32 days has been suggested for T1-T3 N0-N2c HPV positive and T1-T2 N0 HPV negative tumours [10]. This regime may be more advantageous in terms of reduced patient visits and lower consumption of capacity. However, a detriment in overall survival in the absence of synchronous cisplatin in HPV positive patients has been illustrated in two recent randomised trials [24–25]. In addition in the NRG HN002 trial which randomised good prognosis oropharyngeal patients to 60 Gy in 30# with weekly cisplatin v. 60 Gy radiotherapy alone accelerated over 5 weeks failed to show non inferiority for the progression free survival of the radiotherapy alone arm despite similar overall survival at 2 years [26].

Addition of synchronous cisplatin to a 5 week dose escalated hypofractionated accelerated radiation schedule (64 Gy in 25# over 32 days) has been tested and is currently being further evaluated in a randomised clinical trial [27]. This regime employs a fraction size of 2.56 Gy per fraction. In the ASTRO-ESTRO consensus document there was only agreement for the addition of synchronous chemotherapy up to a 2.4 Gy per fraction threshold. The authors are unaware of data on the combination of 60 Gy in 25# with synchronous chemotherapy but this may be of future interest in lower risk oropharyngeal cancer patients.

The 4 week regime 55 Gy in 20# over 25 days has historically been used with several single agents including methotrexate, cetuximab, carboplatin and capecitabine for locally advanced disease [28–33]. More recent IMRT series have used 55 Gy in 20 fractions with synchronous single agent cisplatin, carboplatin and cetuximab [13,34,35]. The number of patients treated with the 4 week regime and synchronous cisplatin or carboplatin in the PET NECK study is too small to draw conclusions and there remains the possibility of a type II error. The International Atomic Energy Agency is currently examining 4 week accelerated hypofractionated chemoradiation or radiation versus conventional fractionated chemoradiation or radiation in a large international randomised trial [35].

This paper illustrates the difficulties inherent in unplanned analysis of a study which was set up to answer a surgical question in an era before routine radiotherapy quality assurance within clinical trials. In addition

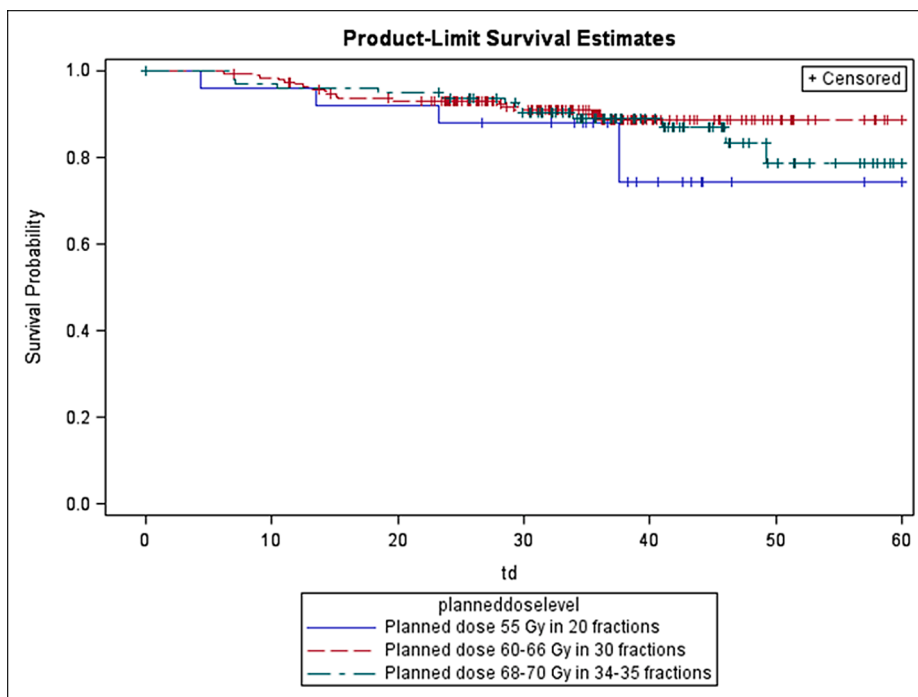


Fig. 1. Overall Survival for p16+ve patients by fractionation cohort (p = 0.43).

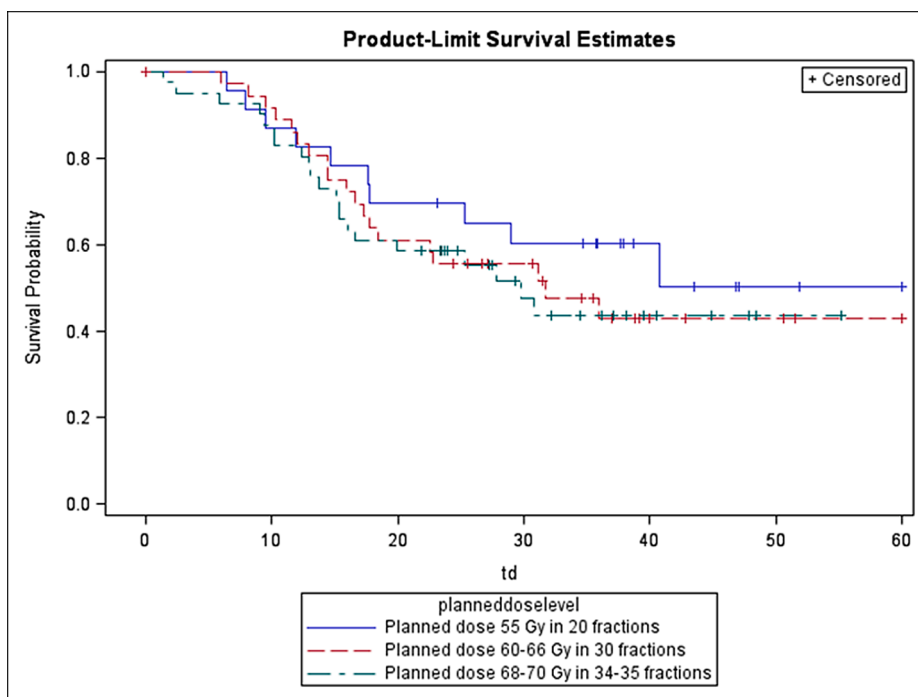


Fig. 2. Overall survival for p16-ve patients by fractionation cohort (p = 0.61).

although we have presented quality of life data, detailed outcomes on physician scored acute and late mucosal toxicity, as might be expected from a radiotherapy study examining a new fractionation or comparing different fractionations are not available from this surgical trial [36]. Furthermore, the lack of data on doses and precise regimens of chemotherapy, the lack of a radiotherapy protocol and contour review, the imbalances in the fractionation groups in terms of p16 status, timing of planned neck dissection and the small numbers in the 4 week fractionation cohort make it impossible to draw firm conclusions on the

basis of the study. However, this study adds to the available data on the use of six and to a lesser extent four week hypofractionated chemoradiation. The results of the ongoing randomised studies discussed above are awaited.

Conclusion

This paper offers some support for the routine use out with the COVID-19 pandemic of 6 week accelerated mildly hypofractionated

Table 2
Changes in mean global quality of life score (EORTC QLQ C30 overall health status) by radiotherapy technique, fractionation cohort and p16 status.

	Change from baseline to post treatment	Change from baseline to 24 months
RT technique		
Conformal [Mean (SD)]	-33.0 (26.8)	-3.5 (21.0)
IMRT [Mean (SD)]	-29.6 (25.2)	0.5 (19.6)
P-value (Wilcoxon)	0.32	0.22
P-value (Mean score stratified by P16)	0.06	0.07
RT fractionation		
68–70 Gy in 34–35 fractions [Mean (SD)]	-33.3 (26.7)	-3.1 (20.4)
60–66 Gy in 30 fractions [Mean (SD)]	-29.8 (25.7)	-0.5 (20.6)
55 Gy in 20 fractions [Mean (SD)]	-28.8 (23.9)	-0.6 (19.5)
P-value (Mantel-Haenszel trend)	0.22	0.34
P-value (Mean score stratified by P16)	0.35	0.73
P16 status		
Positive [Mean (SD)]	-33.9 (25.2)	-1.1 (20.3)
Negative [Mean (SD)]	-18.4 (27.7)	-1.6 (21.9)
P-value (Wilcoxon)	<0.0001	0.78

Table 3
Number of patients with a greater or equal to 10 point change in questionnaire scores (QLQ C30, MDADI, HN35) between baseline and immediately post treatment and at 6, 12, 18 and 24 months post treatment stratified by fractionation cohort.

Time point and group	Decrease by >=10%	Similar	Increase by >=10% (improvement)	Total
Post CRT, n (%)				
68–70 Gy in 34–35	95 (79.2)	20 (16.7)	5 (4.2)	120
60–66 Gy in 30	162 (77.9)	36 (17.3)	10 (4.8)	208
55 Gy in 20	32 (76.2)	9 (21.4)	1 (2.4)	42
p-value (Wilcoxon)				0.82
6 months, n (%)				
68–70 Gy in 34–35	54 (46.6)	48 (41.4)	14 (12.1)	116
60–66 Gy in 30	95 (47.0)	86 (42.6)	21 (10.4)	202
55 Gy in 20	19 (57.6)	10 (30.3)	4 (12.1)	33
p-value (Wilcoxon)				0.47
12 months, n (%)				
68–70 Gy in 34–35	49 (41.2)	43 (36.1)	27 (22.7)	119
60–66 Gy in 30	60 (31.8)	87 (46.0)	42 (22.2)	189
55 Gy in 20	15 (44.1)	14 (41.2)	5 (14.7)	34
p-value (Wilcoxon)				0.96
24 months, n (%)				
68–70 Gy in 34–35	33 (28.2)	62 (53.0)	22 (18.8)	117
60–66 Gy in 30	46 (24.6)	93 (49.7)	48 (25.7)	187
55 Gy in 20	7 (25.0)	14 (50.0)	7 (25.0)	28
p-value (Wilcoxon)				0.27

chemoradiation. To a lesser extent it offers some evidence for the use of 4 week accelerated hypofractionated chemoradiation in the extreme circumstances and risk associated with the peak weeks of a pandemic.

The results of prospective clinical trials examining 4 and 5 week schedules may offer much clearer guidance for future pandemic peaks.

Declaration of Competing Interest

PS reports personal fees from advisory board work for AbbVie, non-financial support from Accuray, non-financial support from Phillips, outside the submitted work.

HM reports personal fees from Warwickshire Head Neck Clinic Ltd, personal fees from AstraZeneca, personal fees from MSD, Sanofi Pasteur, Merck, grants from GSK Biologicals, MSD, Sanofi Pasteur, Silence Therapeutics, GSK PLC, AstraZeneca, other from Sanofi Pasteur, MSD, Merck, outside the submitted work.

MV, CF, JD, AH report no conflict of interest.

Acknowledgements

The original PET neck study was supported by academic grants from the National Institute for Health Research Health Technology Assessment Programme (06/302/129) and Cancer Research UK (C19677/A9674),

References

- [1] Saini KS, Tagliamento M, Lambertini M, McNally R, Romano M, Leone M, et al. Mortality in patients with cancer and coronavirus disease 2019: A systematic review and pooled analysis of 52 studies. *Eur J Cancer* 2020;139:43–50. <https://doi.org/10.1016/j.ejca.2020.08.011>.
- [2] Lee L, Cazier J, Starkey T, Briggs S, Arnold R, Bisht V, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. *Lancet Oncol* 2020;21(10):1309–16. [https://doi.org/10.1016/S1470-2045\(20\)30442-3](https://doi.org/10.1016/S1470-2045(20)30442-3).
- [3] Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21(3):335–7. [https://doi.org/10.1016/S1470-2045\(20\)30096-6](https://doi.org/10.1016/S1470-2045(20)30096-6).
- [4] Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov* 2020;10(6):783–91. <https://doi.org/10.1158/2159-8290.CD-20-0422>.
- [5] de Melo A, Thuler L, da Silva J, de Albuquerque L, Pecego A, Rodrigues L, et al. Cancer inpatients with COVID-19: A report from the Brazilian National Cancer Institute. *PLoS One* 2020;15(10):e0241261. <https://doi.org/10.1371/journal.pone.0241261>.
- [6] Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol* 2020;6(7):1108–10. <https://doi.org/10.1001/jamaoncol.2020.0980>.
- [7] Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020;31(7):894–901.
- [8] Gupta T, Ghosh-Laskar S, Agarwal J. Resource-sparing curative-intent hypofractionated-accelerated radiotherapy in head and neck cancer: More relevant than ever before in the COVID era. *Oral Oncol* 2020;19(111):105045. <https://doi.org/10.1016/j.oraloncology.2020.105045>.
- [9] Thomson DJ, Palma D, Guckenberger M, Balermppas P, Beitler J, Blanchard P, et al. Practice recommendations for risk-adapted head and neck cancer radiation therapy during the COVID-19 pandemic: an ASTRO-ESTRO consensus statement. *Int J Radiat Oncol Biol Phys* 2020;S0360–3016(20):31034–8. <https://doi.org/10.1016/j.ijrobp.2020.04.016> [published online ahead of print, 2020 Apr 14].
- [10] Huang SH, O'Sullivan B, Su J, Ringash J, Bratman S, Kim J, et al. Hypofractionated radiotherapy alone with 2.4 Gy per fraction for head and neck cancer during the COVID-19 pandemic: The Princess Margaret experience and proposal. *Cancer* 2020. <https://doi.org/10.1002/ncr.32968> [published online ahead of print, 2020 Jun 1].
- [11] Roques T, Prestwich R. Head and Neck Cancer and COVID 19 <https://www.rcr.ac.uk/college/coronavirus-covid-19-wh-at-rcr-doing/clinical-information/coronavirus-covid-19-cancer/5/5/2020>.
- [12] Sanghera P, Arnfield J, McConkey C, Hartley A. Gap compensation during accelerated hypofractionated radiotherapy in head and neck cancer. *J Radiother Pract* 2008;7(1):33–8.
- [13] Fong C, Boon I, Boon C, Benghiat H, Hickman M, Nightingale P, et al. Hypofractionated accelerated chemoradiation for oropharyngeal cancer and the 2016 Royal College of Radiologists' Fractionation guidelines. *Clin Oncol (R Coll Radiol)* 2017;29(7):e138. <https://doi.org/10.1016/j.clon.2017.02.003>.
- [14] Mehanna H, Wong WL, McConkey CC, Rahman JK, Robinson M, Hartley AG, et al. PET-NECK trial management group. PET-CT Surveillance versus neck dissection in advanced head and neck cancer. *N Engl J Med* 2016;374(15):1444–54. <https://doi.org/10.1056/NEJMoa1514493>.

- [15] Eisbruch A, Ship JA, Martel MK. Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. *Int J Radiat Oncol Biol Phys* 1996;36:469–80.
- [16] Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. PARSPOrt trial management group. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;12(2):127–36. [https://doi.org/10.1016/S1470-2045\(10\)70290-4](https://doi.org/10.1016/S1470-2045(10)70290-4). Epub 2011 Jan 12.
- [17] Ringash J, Fisher R, Peters L, Trotti A, O'Sullivan B, Corry J, et al. Effect of p16 status on the quality-of-life experience during chemoradiation for locally advanced oropharyngeal cancer: a substudy of randomized trial trans-Tasman radiation oncology group (TROG) 02.02 (HeadSTART). *Int J Radiat Oncol Biol Phys* 2017;97(4):678–86. <https://doi.org/10.1016/j.ijrobp.2016.03.017> [published correction appears in *Int J Radiat Oncol Biol Phys*. 2017 Sep 1;99(1):244].
- [18] Xiao C, Zhang Q, Nguyen-Tân PF, List M, Weber R, Ang K, et al. Quality of life and performance status from a substudy conducted within a prospective phase 3 randomized trial of concurrent standard radiation versus accelerated radiation plus cisplatin for locally advanced head and neck carcinoma: NRG oncology RTOG 0129. *Int J Radiat Oncol Biol Phys* 2017;97(4):667–77. <https://doi.org/10.1016/j.ijrobp.2016.07.020>.
- [19] Gujral DM, Miah AB, Bodla S, Richards T, Welsh L, Schick U, et al. Final long-term results of a phase I/II study of dose-escalated intensity-modulated radiotherapy for locally advanced laryngo-hypopharyngeal cancers. *Oral Oncol* 2014;50(11):1089–97. <https://doi.org/10.1016/j.oraloncology.2014.07.018>.
- [20] Petkar I, Rooney K, Roe JW, Patterson J, Bernstein D, Tyler J, et al. DARS: a phase III randomised multicentre study of dysphagia- optimised intensity- modulated radiotherapy (Do-IMRT) versus standard intensity- modulated radiotherapy (S-IMRT) in head and neck cancer. *BMC Cancer* 2016;16(1):770. <https://doi.org/10.1186/s12885-016-2813-0>. Published 2016 Oct 6.
- [21] Bhide SA, Ahmed M, Barbachano Y, Newbold K, Harrington KJ, Nutting CM. Sequential induction chemotherapy followed by radical chemo-radiation in the treatment of locoregionally advanced head-and-neck cancer. *Br J Cancer* 2008;99(1):57–62. <https://doi.org/10.1038/sj.bjc.6604444>.
- [22] Loo SW, Geropantzas K, Wilson P, Martin WM, Roques TW. Target volume definition for intensity-modulated radiotherapy after induction chemotherapy and patterns of treatment failure after sequential chemoradiotherapy in locoregionally advanced oropharyngeal squamous cell carcinoma. *Clin Oncol (R Coll Radiol)* 2013;25(3):162–70. <https://doi.org/10.1016/j.clon.2012.07.015>.
- [23] Miah A, Schick U, Bhide S, Guerrero-Urbano M, Clark C, Bidmead A, et al. A phase II trial of induction chemotherapy and chemo-IMRT for head and neck squamous cell cancers at risk of bilateral nodal spread: the application of a bilateral superficial lobe parotid-sparing IMRT technique and treatment outcomes. *Br J Cancer* 2015;112(1):32–8. <https://doi.org/10.1038/bjc.2014.553>.
- [24] Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari P, Adelstein D, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet* 2019;393(10166):40–50. [https://doi.org/10.1016/S0140-6736\(18\)32779-X](https://doi.org/10.1016/S0140-6736(18)32779-X) [published correction appears in *Lancet*. 2020 Mar 7;395(10226):784].
- [25] Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTe HPV): an open-label randomised controlled phase 3 trial. *Lancet* 2019;393(10166):51–60. [https://doi.org/10.1016/S0140-6736\(18\)32752-1](https://doi.org/10.1016/S0140-6736(18)32752-1).
- [26] Yom S, Torres-Saavedra PC, Waldron J, Gillison M, Truong M, et al. NRG-HN002: a randomized phase II trial for patients with p16-positive, non-smoking-associated, locoregionally advanced oropharyngeal cancer. *Int J Radiat Oncol Biol Phys* 2019;105(3):684–5.
- [27] Meade S, Gaunt P, Hartley A, Robinson M, Harrop V, Cashmore J, et al. Feasibility of dose-escalated hypofractionated chemoradiation in human papilloma virus-negative or smoking-associated oropharyngeal cancer. *Clin Oncol (R Coll Radiol)* 2018;30(6):366–74. <https://doi.org/10.1016/j.clon.2018.01.015>.
- [28] Chan A, Teoh D, Sanghera P, Hartley A. Radiotherapy compliance is maintained with hypofractionation and concurrent cetuximab in locally advanced head and neck cancer. *Radiother Oncol* 2009;93(3):654. <https://doi.org/10.1016/j.radonc.2009.05.005>.
- [29] Chan AK, Sanghera P, Choo BA, McConkey C, Mehanna H, Parmar S, et al. Hypofractionated accelerated radiotherapy with concurrent carboplatin for locally advanced squamous cell carcinoma of the head and neck. *Clin Oncol (R Coll Radiol)* 2011;23(1):34–9. <https://doi.org/10.1016/j.clon.2010.07.015>.
- [30] Sanghera P, McConkey C, Ho KF, Glaholm J, Hartley A. Hypofractionated accelerated radiotherapy with concurrent chemotherapy for locally advanced squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2007;67(5):1342–51. Epub 2007 Jan 22.
- [31] Teoh DC, Rodger S, Say J, Hartley A. Hypofractionated radiotherapy plus cetuximab in locally advanced head and neck cancer. *Clin Oncol (R Coll Radiol)* 2008;20(9):717. <https://doi.org/10.1016/j.clon.2008.07.003>.
- [32] Tobias JS, Monson K, Gupta N, Macdougall H, Glaholm J, Hutchison I, et al. Chemoradiotherapy for locally advanced head and neck cancer: 10-year follow-up of the UK Head and Neck (UKHAN1) trial. *Lancet Oncol* 2010;11(1):66–74. [https://doi.org/10.1016/S1470-2045\(09\)70306-7](https://doi.org/10.1016/S1470-2045(09)70306-7).
- [33] Jegannathan A, Mais K, Sykes A, Lee L, Yap B, Birzgalis A, et al. Synchronous chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck using capecitabine: a single-centre, open-label, single-group phase II study. *Clin Oncol (R Coll Radiol)* 2011;23(2):149–58. <https://doi.org/10.1016/j.clon.2010.09.010>.
- [34] Benghiat H, Sanghera P, Cashmore J, Hodson J, Mehanna H, Simmons R, et al. Four week hypofractionated accelerated intensity modulated radiotherapy and synchronous carboplatin or cetuximab in biologically staged oropharyngeal carcinoma. *Cancer and Clin Onc* 2014;3(2).
- [35] Jacinto A, Batalha Filho E, Viana L, Marchi P, Capuzzo R, Gama R, et al. Feasibility of concomitant cisplatin with hypofractionated radiotherapy for locally advanced head and neck squamous cell carcinoma. *BMC Cancer* 2018;18(1):1026. <https://doi.org/10.1186/s12885-018-4893-5>. Published 2018 Oct 23.
- [36] Eisbruch A, Harris J, Garden S, Chao C, Straube W, Harari P, et al. Multi-institutional trial of accelerated hypofractionated intensity modulated radiation therapy for early stage oropharyngeal cancer (RTOG 00-22). *Int J Radiat Oncol Biol Phys* 2010;76(5):1333–8. <https://doi.org/10.1016/j.ijrobp.2009.04.011>.