



## Original Article

# Recovery of Salivary Function: Contralateral Parotid-sparing Intensity-modulated Radiotherapy versus Bilateral Superficial Lobe Parotid-sparing Intensity-modulated Radiotherapy



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## Abstract

**Aims:** To establish whether there is a difference in recovery of salivary function with bilateral superficial lobe parotid-sparing intensity-modulated radiotherapy (BSLPS-IMRT) versus contralateral parotid-sparing IMRT (CLPS-IMRT) in patients with locally advanced head and neck squamous cell cancers.

**Materials and methods:** A dosimetric analysis was carried out on data from two studies in which patients received BSLPS-IMRT (PARSPORT II) or CLPS-IMRT (PARSPORT). Acute (National Cancer Institute, Common Terminology Criteria for adverse events – NCI CTCAEv3.0) and late (Late Effects of Normal Tissue-subjective, objective, management analytical – LENTSOMA and Radiation Therapy Oncology Group) xerostomia scores were dichotomised: recovery (grade 0–1) versus no recovery ( $\geq$  grade 2). Incidence of recovery of salivary function was compared between the two techniques and dose-response relationships were determined by fitting dose-response curves to the data using non-linear logistic regression analysis.

**Results:** Seventy-one patients received BSLPS-IMRT and 35 received CLPS-IMRT. Patients received 65 Gy in 30 fractions to the primary site and involved nodal levels and 54 Gy in 30 fractions to elective nodal levels. There were significant differences in mean doses to contralateral parotid gland (29.4 Gy versus 24.9 Gy,  $P < 0.005$ ) and superficial lobes (26.8 Gy versus 30.5 Gy,  $P = 0.02$ ) for BSLPS and CLPS-IMRT, respectively. Lower risk of long-term  $\geq$  grade 2 subjective xerostomia (LENTSOMA) was reported with BSLPS-IMRT (odds ratio 0.50; 95% confidence interval 0.29–0.86;  $P = 0.012$ ). The percentage of patients who reported recovery of parotid saliva flow at 1 year was higher with BSLPS-IMRT compared with CLPS-IMRT techniques (67.1% versus 52.8%), but the difference was not statistically significant ( $P = 0.12$ ). For the whole parotid gland, the tolerance doses, D50, were 25.6 Gy (95% confidence interval 20.6–30.5),  $k = 2.7$  (0.9–4.5) (CLPS-IMRT) and 28.9 Gy (26.1–31.9),  $k = 2.4$  (1.4–3.4) (BSLPS-IMRT). For the superficial lobe, D50 were similar: BSLPS-IMRT 23.5 Gy (19.3–27.6),  $k = 1.9$  (0.5–3.8); CLPS-IMRT 24.0 Gy (17.7–30.1),  $k = 2.1$  (0.1–4.1).

**Conclusion:** BSLPS-IMRT reduces the risk of developing high-grade subjective xerostomia compared with CLPS-IMRT. The D50 of the superficial lobe may be a more reliable predictor of recovery of parotid function than the whole gland mean dose.

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**Key words:** Head and neck cancer; IMRT; xerostomia

## Introduction

Radiation-induced xerostomia is a common complication in the treatment of locally advanced head and neck squamous cell cancers (LA-HNSCC) that can affect a patient's quality of life [1,2]. Parotid-sparing intensity-

modulated radiotherapy (IMRT) techniques have shown a reduced incidence of high-grade ( $\geq$  grade 2) subjective xerostomia at 1 year when compared with conventional radiotherapy in two phase III randomised clinical trials [3,4]. The PARSPORT trial spared the entire contralateral parotid gland (mean dose 25.4 Gy) in the treatment of oropharyngeal and hypopharyngeal cancers, whereas in the nasopharyngeal cancer study an attempt was made to spare both parotid glands (a mean dose of 32 Gy). Both studies reported a 39% incidence of  $\geq$  grade 2 subjective xerostomia

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described using the subjective component of LENTSOMA and Radiation Therapy Oncology Group (RTOG), respectively, in the IMRT arm.

The contralateral parapharyngeal space is often spared in cases of LA-HNSCC where the disease at the primary site has not crossed the midline and nodal disease is confined to the ipsilateral side. This allows contralateral parotid gland sparing and elective irradiation of the contralateral lymph nodes below the contralateral parapharyngeal space (Figure 1a). However, many clinicians believe that bilateral parapharyngeal space irradiation is essential in the treatment of midline tumours of the head and neck, where bilateral parapharyngeal space lymphatic drainage occurs (base of tongue, soft palate, nasopharynx) and in patients with bilateral nodal disease. In this situation, IMRT can be used to deliver a bilateral superficial lobe parotid-sparing technique (BSLPS) (Figure 1b) [5].

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) committee recommended that additional parotid toxicity studies should be undertaken to determine if spatial/anatomic variations exist in local radiation effects [6]. The aim of this study was to establish whether there is a difference in the incidence of  $\geq$ grade 2 subjective xerostomia and absence of parotid saliva flow at 1 year with BSLPS-IMRT versus contralateral parotid-sparing IMRT (CLPS-IMRT) and whether the dose-response relationship of the parotid gland differs between the two techniques.

## Materials and Methods

### Patients

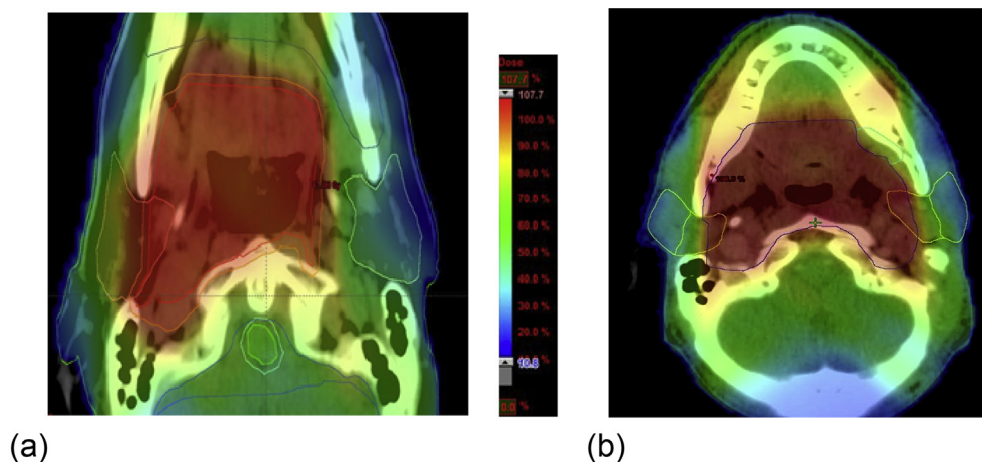
Patients were treated in two prospective trials of parotid-sparing IMRT. The first was a phase III trial of conventional

radiotherapy versus CLPS-IMRT in the treatment of locally advanced oropharyngeal and hypopharyngeal squamous cell cancers (PARSPORT, ISRCTN48243537, CRUK/03/005) [4]. The second was a phase II trial of BSLPS-IMRT technique in the treatment of oropharyngeal and hypopharyngeal cancers (PARSPORT II) [5]. The trials were approved by the local committee of clinical research (CCR2059/MRECC03/6/79 and CCR2588) and the research ethics committee. A dosimetric analysis compared the IMRT-treated group of the cohort of PARSPORT where CLPS-IMRT was used with PARSPORT II where BSLPS-IMRT was delivered.

### Treatment

In both studies, patients were immobilised and contrast-enhanced computed tomography scans were acquired at 2–5 mm intervals through the primary tumour site and the cervical lymph nodes. Gross tumour volumes, clinical target volume for primary site and involved nodal groups (CTV1), nodal groups at risk of harbouring microscopic disease (CTV2), critical structures and parotid glands were delineated according to trial protocol by the treating oncologists [7]. The superficial lobes of both parotid glands were outlined prospectively in the PARSPORT II patients and retrospectively in the PARSPORT IMRT patients by ABM. Radiologically, the parotid gland was divided into the superficial and deep lobes by the retromandibular vein, as this structure runs the same course as the facial nerve.

Radiotherapy was delivered using the five- or seven-beam simultaneous integrated boost IMRT technique. A dose of 65 Gy in 30 daily fractions was prescribed to the median dose-volume point of the planning target volume (PTV1) dose volume histogram (DVH), 54 Gy in 30 daily fractions to PTV2 and the postoperative neck received 60 Gy in 30 daily fractions. A dose constraint (mean dose = 24 Gy)



**Fig 1.** (a) Axial computed tomography image of contralateral parotid-sparing intensity-modulated radiotherapy (CLPS-IMRT) for a right lateral pharyngeal wall tumour. Colour wash: red-orange = high dose (95–100% of prescribed dose), blue = low dose (20–30% of prescribed dose). The IMRT technique used also produces a dose gradient across the ipsilateral parotid gland on the right, thus allowing modest sparing of the right superficial lobe. (b) Axial computed tomography image of bilateral superficial lobe parotid-sparing intensity-modulated radiotherapy (BSLPS-IMRT) for a midline tumour of the base of tongue. Colour wash: red-orange = high dose (95–100% of prescribed dose), blue = low dose (20–30% of prescribed dose). The deep lobes of both parotid glands are included in the high dose region because of their close proximity to the parapharyngeal spaces.

was applied to the contralateral parotid gland in PARSPORT IMRT patients. The superficial lobes of both parotid glands were combined as a single volume in PARSPORT II, with a dose constraint (mean dose = 24 Gy) applied for the planning and optimisation process. In addition, where possible, a dose constraint (mean dose = 24 Gy) with a lower priority was also applied to a whole contralateral parotid gland.

### Chemotherapy

In PARSPORT, when indicated at the investigator's discretion, patients received induction chemotherapy, comprising two 21-day cycles of cisplatin 75 mg/m<sup>2</sup> on day 1 and 5-fluorouracil 1000 mg/m<sup>2</sup> on days 1–4. No concomitant chemotherapy was delivered. In PARSPORT II, patients aged 70 years or under with locally advanced disease received induction chemotherapy as above and concomitant cisplatin (100 mg/m<sup>2</sup>) or carboplatin (AUC = 5) on days 1 and 29 of radiotherapy.

### Data Collection

Mean doses to the ipsilateral and contralateral parotid glands and the superficial lobes were recorded. Acute toxicity scores were recorded prospectively using NCI-CTCAE v3.0 weekly during radiotherapy, weeks 1–4 and at week 14 after radiotherapy [8]. Late toxicity scores (RTOG/EORTC and LENTSOMA) were recorded at follow-up at 3, 6, 12 and 18 months after radiotherapy in both studies [9,10]. The methods used for parotid saliva collections have been described previously [11,12]. Total parotid salivary flow rates were measured before radiotherapy and at 12 months after radiotherapy applying the analytical component of LENTSOMA scores. Where possible, measurements were undertaken at similar times of the day for each patient.

### Data Analysis and Statistical Methodology

The primary objective of this study was to determine the difference in the incidence of ≥grade 2 subjective xerostomia (LENTSOMA) between the two parotid-sparing IMRT techniques at 1 year after IMRT. Secondary objectives described the difference in the incidence of acute ≥grade 2 subjective xerostomia during treatment, the incidence of late ≥grade 2 subjective xerostomia at 3, 6, 12 and 18 months after treatment and recovery of parotid saliva flow rates at 1 year after treatment. Descriptive statistics were used to present the data. Statistical differences in proportions were tested using chi-squared test or Fisher's exact test where appropriate. Student's *t*-test was used to determine differences in continuous variables when normally distributed and by Mann-Whitney if not. For serial dependent datasets, Bonferroni's method of multiple testing was applied to determine statistical significance and set at  $P < 0.01$ . Generalised estimating equations using logistic regression were used to account for differences in incidences at and between specific time points. If recovery was proven to be independent of these two factors, the odds ratio was calculated to determine the risk of ≥grade 2

xerostomia between BSLPS-IMRT and CLPS-IMRT. A statistical analysis was carried out using the Statistical Programme for Social Sciences SPSSv18.0.

It was assumed that the organ of interest was organised as a parallel structure. This provided the probability of a defined toxicity with an increasing mean dose to the organ of interest. Mean doses were converted to equivalent dose at 2 Gy per fraction (EQD2) using the Withers formula [13]. Dose-response curves were generated for ≥grade 2 xerostomia at 1 year (combined superficial lobes mean dose with subjective xerostomia, whole parotid gland or superficial lobe with parotid saliva flow). A logistic dose-response curve with parameters D50 and *k* was fitted using non-linear logistic regression [14].

$$P = \frac{1}{1 + (D_{50}/D)^k}$$

where *P* is the probability of the incidence of toxicity; *D* is the mean dose with D50, the mean dose at which 50% of patients experience toxicity; *k* describes the increase in incidence with increasing dose.

## Results

The PARSPORT trial recruited patients between September 2002 and December 2007 from six UK centres. Acute toxicity on all 47 patients and late toxicity with DVH data on 35 patients who received IMRT in the PARSPORT study were used for this analysis. The PARSPORT II study recruited patients from a single centre between November 2005 and June 2010 [5]. Acute toxicity and DVH data were available on 80 patients and late toxicity and DVH data were available for a subset of 71 patients who had at least 1 year of follow-up. Patient characteristics are listed in Table 1 and highlight the differences between the two groups in terms of the use of induction and concomitant chemotherapy, the proportion of patients who received postoperative radiotherapy and the mean doses delivered to the parotid glands. Human papillomavirus (HPV) status was positive in about 75% of the patients in PARSPORT II, but was unknown in the PARSPORT study. The mean dose to the contralateral parotid gland was significantly lower in the CLPS-IMRT group compared with the BSLPS-IMRT group (24.9 Gy versus 29.4 Gy;  $P < 0.005$ ). The mean dose to the ipsilateral parotid gland was significantly lower in the BSLPS-IMRT group (38.9 Gy versus 45.7 Gy;  $P < 0.005$ ). As expected, with BSLPS-IMRT as used in the PARSPORT II trial, the mean dose to the superficial lobes was significantly lower in this group when compared with the CLPS-IMRT (PARSPORT) trial (26.8 Gy versus 30.5 Gy;  $P = 0.02$ ).

### Prevalence and Incidence of Xerostomia

#### Acute xerostomia

The prevalence of ≥grade 2 dry mouth symptoms was similar in weeks 1–6 in both groups. The peak prevalence was at the end of treatment at week 6 for BSLPS-IMRT patients (59%) and was 70% in the CLPS-IMRT patients at week

**Table 1**

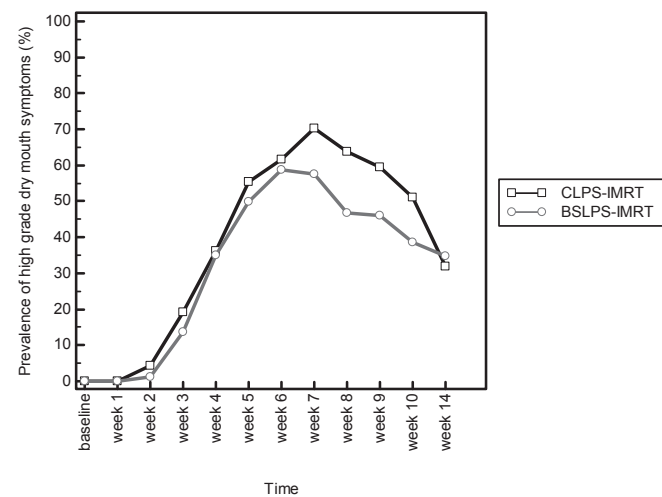
Patient characteristics and mean doses to parotid glands: PARSPORT (contralateral parotid-sparing intensity-modulated radiotherapy; CLPS-IMRT) and PARSPORT II (bilateral superficial lobe parotid-sparing intensity-modulated radiotherapy; BSLPS-IMRT)

Patient characteristics	PARSPORT IMRT (CLPS) (n = 35)	PARSPORT II (BSLPS) (n = 71)
Median age (years)	59.9	56.5
Male gender (%)	25 (71)	56 (79)
Primary site (%)		
Oropharynx	28 (80)	66 (93)
Hypopharynx	7 (20)	5 (7)
AJCC TNM stage (%)		
I–II	13 (36)	3 (4)
III	11 (33)	13 (19)
IVA	10 (28)	55 (77)
IVB	1 (3)	0 (0)
Induction chemotherapy (%)	13 (37)	54 (76)
Primary radiotherapy (%)	26 (74)	60 (84)
Postoperative radiotherapy (%)	9 (26)	11 (16)
Concomitant chemotherapy (%)	0 (0)	57 (80)
Contralateral parotid gland mean dose (Gy) ( $\pm$ 1 standard deviation)	24.9 (14.7–32.2)	29.4 (22.8–36.0)
P value CLPS versus BSLPS		<0.005
Ipsilateral parotid gland mean dose (Gy) ( $\pm$ 1 standard deviation)	45.7 (21.5–60.6)	38.9 (34.3–43.5)
P value CLPS versus BSLPS		<0.005
Combined superficial lobes of parotid glands mean dose (Gy) ( $\pm$ 1 standard deviation)	30.5 (23.1–37.9)	26.8 (23.0–30.6)
P value CLPS versus BSLPS		=0.02

7. Resolution of  $\geq$ grade 2 dry mouth symptoms occurred earlier in the BSLPS-IMRT group with a significant difference in prevalence rates at week 8, 2 weeks after completing radiotherapy (CLPS-IMRT 63.8% versus BSLPS-IMRT 46.7%,  $P = 0.008$ ) (Figure 2).

#### Late Subjective Xerostomia

BSLPS-IMRT patients reported a statistically significant reduction in incidence of high-grade xerostomia (LENTSOMA) at 3 and 6 months, but this was not significant at 12 and 18 months compared with CLPS-IMRT (Figure 3a).



**Fig 2.** The prevalence of acute high-grade dry mouth changes at each time point during and after contralateral parotid-sparing intensity-modulated radiotherapy (CLPS-IMRT) and bilateral superficial lobe parotid-sparing intensity-modulated radiotherapy (BSLPS-IMRT).

Using the RTOG scoring scales, a statistically significant improvement in xerostomia was observed with BSLPS-IMRT at 12 months, but was borderline at 6 months, and was not significant at 18 months (Figure 3b). Generalised estimating equations showed that there was no interaction between the time from IMRT completion and IMRT technique used. Evaluating the risk of developing high-grade xerostomia, the odds ratio showed a lower risk of developing high-grade xerostomia with BSLPS-IMRT when compared with CLPS-IMRT (LENTSOMA odds ratio 0.50, 95% confidence interval 0.29–0.86,  $P = 0.012$ ; RTOG odds ratio 0.49, 95% confidence interval 0.28–0.86,  $P = 0.014$ ).

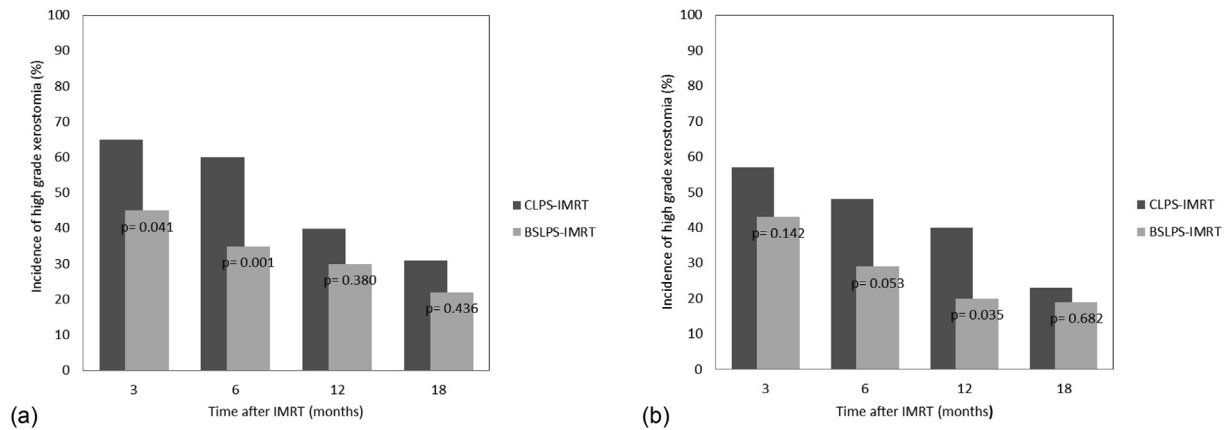
#### Analytical Measure of Late Xerostomia

Parotid saliva flow rates at 1 year were reported on 35 patients in the PARSPORT IMRT cohort and 35 patients in the PARSPORT II study. Apart from absence of parotid saliva production, technical difficulties and/or patient discomfort were the most common reasons for no saliva collection. The incidence of recovery of parotid salivary flow at 1 year after radiotherapy was 67.1% with BSLPS-IMRT versus 52.8% with CLPS-IMRT ( $P = 0.12$ ).

#### Dosimetric Analyses and Calculation of Parotid Gland Tolerance

Dose-response parameters, D50 and  $k$  for  $\geq$ grade 2 subjective xerostomia are summarised in Table 2. D50 and  $k$  for CLPS-IMRT with LENTSOMA analysis (D50 = 34.6 Gy,  $k = 4.6$ ) were similar to BSLPS-IMRT (D50 = 32.6 Gy,  $k = 3.3$ ). The differences between the two scoring systems for both CLPS- and BSLPS-IMRT were evident, with higher D50 values for RTOG scores.





**Fig 3.** The incidence of high-grade subjective xerostomia with (a) LENTSOMA and (b) Radiation Therapy Oncology Group (RTOG) scoring system for the contralateral parotid-sparing intensity-modulated radiotherapy (CLPS-IMRT) and bilateral superficial lobe parotid-sparing intensity-modulated radiotherapy (BSLPS-IMRT) (chi-squared test for proportions,  $P < 0.05$  statistically significant).

The dose-response curves indicating the probability of no recovery of parotid salivary flow at 1 year are presented in Figure 4. The two parotid-sparing techniques are shown together for (a) whole parotid and (b) superficial lobe. Corresponding parameter values are detailed in Table 3.

Figure 4a illustrates a slightly higher D50 value for the BSLPS-IMRT group when compared with the CLPS-IMRT group (28.9 Gy versus 25.6 Gy) but with similar gradients ( $k$ ) (2.7 versus 2.4). The two dose-response curves for the superficial lobe alone (Figure 4b) are in good agreement.

## Discussion

This study has shown that the prevalence of high-grade acute and late subjective xerostomia is significantly lower in patients who received radiotherapy using the BSLPS-IMRT technique, with the overall risk of developing high-grade xerostomia with time lower with BSLPS-IMRT compared with CLPS-IMRT. The PARSPORT trial [4] delivered CLPS-IMRT, whereas the PARSPORT II trial [5] delivered

BSLPS-IMRT. Both studies described the same primary end point: incidence of  $\geq$ grade 2 subjective xerostomia at 1 year and measured recovery at identical time points, thus providing an unique opportunity to compare outcomes between the two techniques. Although CLPS-IMRT has been proven in a phase III study to reduce the incidence of xerostomia without compromising on locoregional control, the technique cannot be applied to treatment of tumours in which both parapharyngeal spaces are at risk of harbouring microscopic disease. The requirement to irradiate the bilateral parapharyngeal spaces in head and neck cancer patients is controversial. This is reflected in variations in clinical practice and also in trial quality assurance guidelines in the UK and internationally. It is up to clinicians to weigh up the risk of involvement of the parapharyngeal space by microscopic tumour metastases for individual patients and to decide whether or not to include this in their CTV. The BSLPS-IMRT technique was designed to test the hypothesis that effective radiotherapy can be delivered to the bilateral parapharyngeal spaces and still avoid xerostomia. BSLPS-IMRT may still increase the risk of local

**Table 2**

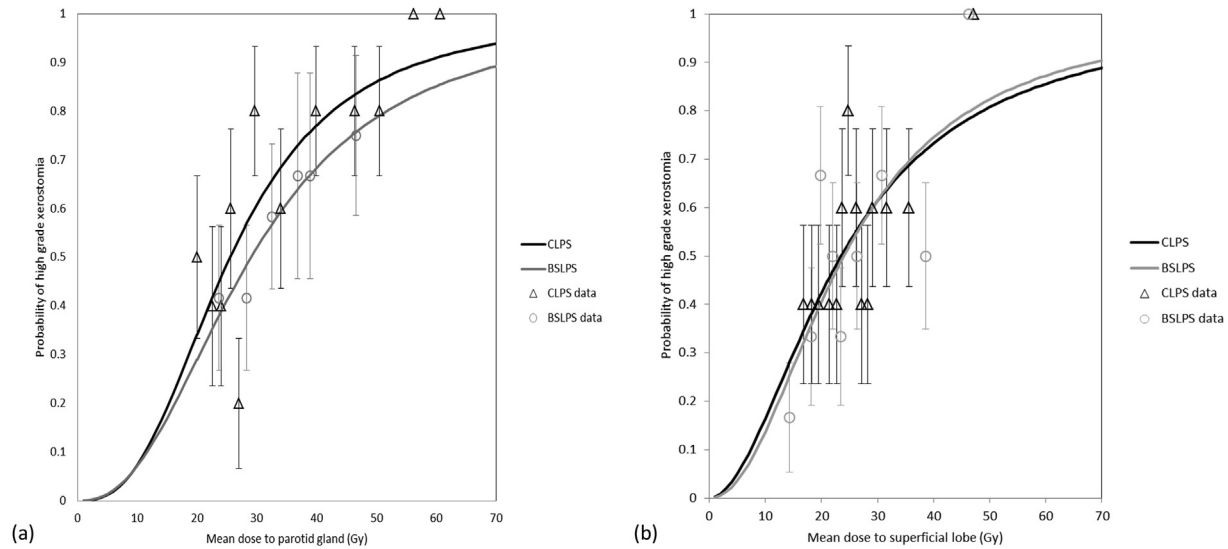
Summary of D50 and  $k$  values and EQD2 values with 95% confidence interval for developing high-grade subjective xerostomia as scored by subjective scoring systems

	Subjective xerostomia LENTSOMA	Subjective xerostomia RTOG
Combined superficial lobes		
CLPS		
D50 (Gy; 95% confidence interval)	34.6 (30.6–38.8)	36.1 (27.0–45.1)
EQD2 D50 (Gy; 95% confidence interval)	35.8 (31.6–40.1)	37.3 (27.9–46.6)
$k$	4.6 (1.5–7.6)	2.9 (–0.2–6.2)
BSLPS		
D50 (Gy; 95% confidence interval)	32.6 (24.3–41.1)	39.0 (29.5–48.5)
EQD2 D50 (Gy; 95% confidence interval)	33.7 (25.1–42.5)	40.3 (30.5–50.1)
$k$	3.3 (0.4–7.6)	3.2 (0.9–5.5)

CLPS, contralateral parotid sparing; BSLPS, bilateral superficial lobe parotid sparing.

LENTSOMA, Late Effects of Normal Tissue- subjective, objective, management analytical.

RTOG, Radiation Therapy Oncology Group.



**Fig 4.** Dose-response curves of (a) whole parotid gland and (b) superficial lobe describing the probability of no recovery of parotid saliva flow at 1 year generated using non-linear logistic regression analysis, error bars representing 1 standard error of mean. The parameters are summarised in Table 2.

relapse in the superficial parotid gland in patients whose tumour lymphatic drainage is directed to the pre-auricular nodes, such as cutaneous squamous cell carcinoma or very advanced nasopharyngeal carcinoma. The superior outcomes observed with BSLPS-IMRT suggest that additional sparing of the ipsilateral superficial lobe with CLPS-IMRT may further reduce grade  $\geq 2$  xerostomia. These outcomes offer additional evidence to the QUANTEC committee to recommend dose volume limits to reduce xerostomia risk. This study has also addressed one of the questions posed by QUANTEC, namely to determine the spatial/anatomic variation of radiation effect [6].

The effect of concomitant chemotherapy on parotid function is uncertain. Eighty per cent of patients received concomitant chemotherapy in the BSLPS-IMRT group. Hey *et al.* [15] reported a lower tolerance dose (TD50) with chemoradiotherapy versus radiotherapy alone when measuring high-grade xerostomia at 6 months. However, multivariate analyses by Eisbruch *et al.* [16] and Chao *et al.* [17] reported that chemotherapy did not have a deleterious effect on parotid function. Data from our group have

suggested that concurrent chemotherapy did not increase the tolerance dose of the parotid gland to radiotherapy [18]. This was confirmed in this study: the incidence of acute  $\geq$ grade 2 subjective xerostomia was lower in the BSLPS-IMRT group compared with the CLPS-IMRT group and late  $\geq$ grade 2 subjective xerostomia at 1 year was similar to CLPS-IMRT.

The incidence of acute  $\geq$ grade 2 dry mouth symptoms during IMRT was similar in both studies. The peak prevalence was higher and later (1 week after IMRT) with CLPS-IMRT. Recovery seemed to be slower with CLPS-IMRT, with a significant difference between the two groups at week 8 (2 weeks after IMRT). Despite the contralateral parotid gland mean dose being significantly lower with CLPS-IMRT when compared with BSLPS-IMRT (24.9 Gy versus 29.4 Gy,  $P < 0.005$ ), the incidence of  $\geq$ grade 2 subjective xerostomia at 1 year was similar in both groups. Although there was some difference between analyses using LENTSOMA versus RTOG, presumably due to the differences in definition of grade 2 xerostomia in these measures, BSLPS-IMRT consistently produced a

**Table 3**

D50 and  $k$  parameters (EQD2) with 95% confidence interval for probability of no recovery of parotid saliva flow at 1 year

	Whole parotid gland	Superficial lobe
CLPS		
D50 (Gy; 95% confidence interval)	25.6 (20.6–30.5)	24.0 (17.7–30.1)
EQD2 D50 (Gy; 95% confidence interval)	26.6 (21.5–31.7)	24.8 (18.3–31.1)
$k$	2.7 (0.9–4.5)	2.1 (0.7–4.1)
BSLPS		
D50 (Gy; 95% confidence interval)	28.9 (26.1–31.9)	23.5 (19.3–27.6)
EQD2 D50 (Gy; 95% confidence interval)	30.0 (27.0–32.9)	24.3 (20.0–28.5)
$k$	2.4 (1.4–3.4)	1.9 (0.5–3.8)

CLPS, contralateral parotid sparing; BSLPS, bilateral superficial lobe parotid sparing.

lower incidence of high-grade xerostomia compared with CLPS-IMRT. This can partly be explained by the mean doses delivered to the ipsilateral parotid gland and superficial lobes. Lower mean doses were delivered to these structures with BSLPS-IMRT, which reduced the probability of damage to the ipsilateral parotid gland. Other studies that have delivered BSLPS-IMRT have reported a similar incidence of high-grade xerostomia at 1 year. Kam *et al.* [3] reported an incidence of high-grade subjective xerostomia (RTOG scores) of 39% at 1 year in patients treated for nasopharyngeal cancers with a mean dose to the parotid glands of 32 Gy, whereas the University of California-San Francisco reported 28% high-grade xerostomia (RTOG scores) at 1 year with 34 Gy to 50% and 24.6 Gy to 80% of each parotid gland [19].

BSLPS-IMRT yielded a higher incidence of recovery of parotid saliva flow than CLPS-IMRT (67.1% versus 52.8%), but this did not achieve statistical significance ( $P = 0.12$ ). Chao *et al.* [17] reported dose-response relationships of the parotid gland in patients who underwent BSLPS-IMRT for the treatment of LA-HNSCC. The mathematical model used implied if both parotid glands received a mean dose of greater than 32 Gy then this predicted a high probability of grade 4 xerostomia (measured by the analytical component of LENTSOMA). However, in that study whole mouth saliva flow rates were used to measure xerostomia without accounting for contributions from other salivary glands. Also, the primary end point was measured at 6 months – a time point that is too early to determine optimal recovery. Pow *et al.* [1] reported recovery of parotid saliva flow rate at 1 year in 83% of patients despite mean parotid gland doses of 42 Gy and 41 Gy. At these mean doses, it was anticipated that there would be no recovery of salivary flow; this provides further evidence that the mean dose to the superficial lobes may play a more influential role in the recovery of parotid saliva flow. Similar conclusions were made by others for advanced nasopharyngeal carcinoma [20,21].

The D50 of the parotid gland after delivering BSLPS-IMRT was reported as 28.9 Gy and in those who received CLPS-IMRT was 25.6 Gy. The discrepancy between the two can be explained by the volume of parotid tissue spared with each technique. BSLPS-IMRT attempted partial sparing of both parotid glands, which allowed a higher dose to each gland to achieve the same effect. By contrast, CLPS-IMRT assumed that the ipsilateral parotid gland was irradiated to a dose above tolerance with no recovery anticipated. Therefore, the contralateral parotid gland required a lower tolerance dose to spare as much of the parotid tissue to achieve the same effect. Further analysis to determine the D50 values of the superficial lobe reported similar doses using either IMRT technique, suggesting that the mean dose to this part of the parotid gland may be a more reliable predictor of recovery of function. However, as our group has concluded previously, subjective reports of xerostomia are probably the most representative measure of patient benefit [22]. Based on the results of other studies, further reductions in xerostomia can be expected up to 2 years after treatment.

Preclinical studies of rat parotid glands have described the glands to have regional differences in radiosensitivity. Konings *et al.* [21] reported that a single dose of 30 Gy to the entire parotid gland resulted in complete loss of parotid flow, whereas there was a 65% reduction in saliva flow when only the cranial part of the gland was irradiated to 30 Gy and a 25% reduction in saliva flow when only the caudal part was irradiated to 30 Gy. Irradiation of the cranial part of the gland involved shielding of the lateral lobe. Irradiation of 50% of the cranial volume led to secondary damage to the lateral lobe. The inverse did not occur. Pringle *et al.* [23] described that the salivary gland stem/progenitor cells resided in the main excretory ducts, of which a large proportion populate the cranial part of the gland. This may explain why radiation to the cranial component may lead to extensive secondary damage of the caudal part of the gland. An analogy between the rat parotid gland and the human parotid gland could be made. The superficial lobe consists of a larger volume of parotid tissue and importantly it is where the main secretory (Stensen's) duct resides. If, like the rat parotid gland, the progenitor cells are in the main duct, then sparing of both superficial lobes, and the parotid gland stem cells within the main ducts, may lead to less stem cell damage and quicker recovery of salivation in humans [23]. This is supported by the low D50 (23.5 Gy) value of the superficial lobe and suggests that the superficial lobe may, in fact, be more radiosensitive and provide evidence that not only volume effects, but also regional variations in radiosensitivity, can affect recovery of salivary function.

The limitations of this study were that this was a non-randomised comparison with relatively small numbers of patients with different tumour stages and subsites and that different chemotherapy schedules were used. The proportion of HPV-positive patients in these in PARSPORT II is known and stated but unknown in PARSPORT; however, we think this probably did not have an effect on the results. Neither of the two techniques used in this comparative study attempted to spare the submandibular salivary glands as the level 1B lymph nodes were included in the CTV. Sparing of these smaller salivary glands may further reduce xerostomia, but may increase the risk of nodal relapse of cancer in level 1B.

In summary, this study has described that BSLPS-IMRT led to reductions in the incidence of high-grade xerostomia compared with CLPS-IMRT. This technique should be considered in appropriate patients.

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