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Phase I trial

A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer

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Abstract

***Background and purpose*: Intensity modulated radiotherapy (IMRT) allows the delivery of higher and more homogeneous radiation dose to head and neck tumours. This study aims to determine the safety of dose-escalated chemo-IMRT for larynx preservation in locally advanced head and neck cancer.**

***Methods*: Patients with T2—4, N1—3, M0 squamous cell carcinoma of the larynx or hypopharynx were treated with a simultaneous-boost IMRT. Two radiation dose levels (DL) were tested: In DL 1, 63 Gy/28F was delivered to primary tumour and involved nodes and 51.8 Gy/28F to elective nodes. In DL 2, the doses were 67.2 Gy/28F and 56 Gy/28F, respectively, representing a 9% dose escalation for the primary. All patients received 2 cycles of neoadjuvant cisplatin and 5-fluorouracil, and concomitant cisplatin. Acute (NCICTCv.2.0) and late toxicity (RTOG and modified LENTSOM) were collected.**

***Results*: Thirty patients were entered, 15 in each dose level. All patients completed the treatment schedule. In DL 1, the incidences of acute G3 toxicities were 27% (pain), 20% (radiation dermatitis), 0% (xerostomia) and 67% required gastrostomy tubes. For DL 2 the corresponding incidences were 40%, 20%, 7%, and 87%. G3 dysphagia and pain persisted longer in DL 2. With regard to mucositis, a prolonged healing time for DL 2 was found, with prevalence of G2 of 58% in week 10. No acute grade 4 toxicity was observed. At 6 months, 1 patient in DL 2 had G3 late toxicity (dysphagia). No dose limiting toxicity was found. Complete response rates were 80% in DL 1, and 87% in DL 2.**

***Conclusion*: Moderately accelerated chemo-IMRT is safe and feasible with good compliance and acceptable acute toxicity. Dose escalation was possible without a significant difference in acute toxicity. Longer follow-up is required to determine the incidence of late radiation toxicities, and tumour control rates.**

Keywords: Head and neck cancer; IMRT; Toxicity

Most tumours arising in the larynx and hypopharynx are squamous cell carcinomas (SCC) that display a clear radiation dose—response relationship. In locally advanced tumours survival rates are still poor, with most patients dying of loco-regional rather than systemic failure. The addition of concomitant chemotherapy to radical radiotherapy (RT) schedules in locally advanced head and neck cancer (HNC) has been shown to achieve absolute improvements in 5-year survival rates of 8% compared to RT alone [1] and absolute reductions in laryngectomy rates of 43% [2]. Significant improvements in loco-regional control have been shown with altered fractionation schedules [3], but both approaches are, however, associated with significant morbidity [2,4—6]. Attempts to combine both concomitant chemotherapy and altered fractionation schedules using conventional RT techniques have been associated with significant morbidity, with rates of long term dependence on enteral feeding as high as 25—30% [7,8]. In addition, significant acute toxicity can lead to treatment breaks and prolongation of the overall treatment time, which is associated with reduced loco-regional disease-free survival [9] due to accelerated repopulation of tumour clonogens [10]. Although neoadjuvant chemotherapy has not been associated with significant improvements in overall survival [1], it merits further investigation.

Intensity modulated radiotherapy (IMRT) allows improved shaping of dose distributions and hence increased sparing of

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normal tissues. This could potentially abrogate the increased acute and late toxicity associated with concomitant chemoradiotherapy and accelerated RT. In addition, dose inhomogeneities within the tumour that are seen with conventional radiation delivery can also be reduced, which should theoretically be associated with a lower risk of loco-regional recurrence [11].

We present here the results of a phase 1 dose escalation study of neoadjuvant chemotherapy followed by concomitant chemotherapy and moderately accelerated IMRT.

Patients and methods

Patients with histologically proven locally advanced laryngeal and hypopharyngeal SCC (T1–T4, N0–N3, M0) suitable for treatment with primary chemo-radiotherapy with curative intent were eligible. Ethics approval was obtained and all patients gave written informed consent. All patients received neoadjuvant chemotherapy: 2 courses of cisplatin (75 mg/m^2 on day 1) and 5-fluorouracil (5-FU) (1000 mg/m^2 D1–4) on a 3-weekly basis. Concomitant chemotherapy with cisplatin 100 mg/m^2 was given in weeks 1 and 5 of IMRT.

A standard phase 1 dose escalation trial design was used, with 15 patients enrolled in each dose level (DL) (Table 1). DL 1 was chosen based on our centre's experience of a standard dose of 65 Gy in 30 fractions, a wish to keep the treatment time between 5 and 6 weeks to reduce the effects of accelerated repopulation, and a calculated BED equivalent to 70 Gy in 35 fractions. Calculations were performed using the formulae $EQD2 = D(d + \alpha/\beta)/2 + \alpha/\beta$ and EQD2, $T = EQD2,\ t - (T - t) \times D_{prolif}$ [12], where EQD2 represents the equivalent dose in 2 Gy fractions, D and d are the total dose and dose per fraction, T and t take into account changes in the overall treatment time and D_{prolif} is a proliferation factor (0.74 Gy d^{-1}) [13]. Calculations were performed using a tumour α/β of 10 Gy and late effects α/β of 3 Gy. For DL 1, for the primary, $EQD2_{(63Gy,\ \alpha/\beta=10Gy)}$ was calculated as 64.3 Gy and $EQD2_{(63Gy,\ \alpha/\beta=3Gy)}$ as 66.15 Gy, which corrected for the reduction in overall treatment time resulted in EQD_2 of 70 Gy. The nodal $EQD2_{(51.8Gy)}$, taking into account the increase in overall treatment time, was calculated as 47.5 Gy. DL 2 was chosen to represent an increase in BED of 9% for the primary tumour (approximately 76 Gy), for a nodal EQD_2 of about 51 Gy.

DL 1 was designed as a feasibility study of hypofractionated IMRT with the doses prescribed equivalent to 70 Gy in 35 fractions and, therefore, no increase in toxicity rates was expected. Dose escalation was performed once feasibility was demonstrated in DL 1. However, the stopping rules determined that if 0/15 patients had $\geqslant$Grade 3 late complications at 1 year then a $\geqslant$20% risk of Grade 3 late complication rate would be excluded with 95% power. If 1 or 2 patients developed $\geqslant$Grade 3 late complications at the first DL then the number of patients recruited at that level would be increased to 30 to improve statistical power and escalation to the second DL would only be allowed if no further patients developed grade 3 late toxicity (incidence of $\geqslant$Grade 3 late complication rate predicted to be 0–17% and 0–22%, respectively, with 95% power). If more than 2 patients suffered $\geqslant$Grade 3 late complication then recruitment to that level would be stopped (incidence of $\geqslant$Grade 3 complication predicted to be 2–27% with 95% power).

Table 1
Dose schedule for both cohorts

	Initial dose	Dose escalation
Primary tumour site	63.0 Gy in 28# (2.25 Gy per fraction)	67.2 Gy in 28# (2.4 Gy per fraction)
Elective nodal areas	51.8 Gy in 28# (1.85 Gy per fraction)	56 Gy in 28# (2 Gy per fraction)

IMRT technique

All patients were immobilised using a custom-made cabulite head and neck mask. Target volumes and organs at risk (OAR) were delineated on RT planning CT scans following ICRU 50 and 62 guidelines. The entire larynx and hypopharynx complex, including the thyroid cartilage, was included in the primary clinical target volume (CTV1), from 1 cm above the tip of the epiglottis to below the cricoid cartilage or 2 cm above and/or below the superior and inferior extent of the tumour, whichever was larger. Uninvolved barriers to tumour spread, such as bone and fasciae, were excluded. Adjacent structures (i.e. muscle) infiltrated by tumour were included in the CTV1, as well as all involved nodal levels and the retropharyngeal nodes at the level of the hypopharynx. The elective nodal volume (CTV2) included uninvolved levels 2–5 and supraclavicular fossa (SCF) nodes bilaterally and delineation was performed according to the consensus guidelines [14]. A 3 mm margin was added to the CTV1 and CTV2 to obtain the planning target volumes PTV1 and PTV2, respectively [15]. The organs at risk (OAR) delineated were the spinal cord, brain stem, parotid glands, submandibular glands and oral cavity.

The Helios inverse planning module of CadPlan v6.3.5 (Varian Medical Systems, Palo Alto, CA) and Eclipse (Varian Medical Systems, Palo Alto, CA) were used to create IMRT plans, using a simultaneous integrated boost technique (SIB), for dynamic delivery on a Varian 2100CD linear accelerator using 6 MV photons. Inverse planning in Helax-TMS and PINNACLE^3 (Philips Radiation Oncology Systems, Milpitas, CA) was used, using the same SIB technique, for step and shoot delivery on an Elekta linear accelerator (Elekta Oncology Systems, Crawley, UK). Five- and 7-beam arrangements were used. Plans were prescribed to the median of the PTV1 such that 95% of each PTV was encompassed by 95% of the prescription dose with maximum doses to the spinal cord of 48 Gy. Maximum mean dose to the parotid glands was 24 Gy where possible.

Follow up (FU)

All patients were assessed prior to commencement of treatment. Acute toxicity was evaluated for 10 weeks after commencement of chemo-IMRT (i.e. for the 6 weeks of chemo-IMRT and the first 4 weeks of recovery) and at week 14 (8 weeks post treatment). Toxicity scoring was performed according to the NCI CTC v.2.0 criteria. Indications for enteral feeding were weight loss >10% and inability to maintain an adequate calorie intake. Late toxicity was collected at 3, 6, 12, 18 and 24 months and yearly thereafter using the RTOG and LENT SOM scoring systems.

The prevalence of an acute reaction at a specified point in time was defined as the proportion of patients scored as

having that grade of reaction relative to the total number of patients assessed at that specific time point [16]. The incidence of a given reaction was defined as the total number of patients reaching that grade reaction at any time, divided by the total number of evaluable patients [16]. The mean time with a specific grade (G) 3 early reaction was defined as the time in weeks spent with that reaction divided by the number of patients who reached that grade.

Patients were assessed for response at 4–6 weeks following completion of treatment. Complete response (CR) was defined as the complete disappearance of disease as evaluated clinically by nasendoscopy and/or computed tomography. Where residual lesions were present in the larynx or hypopharynx, biopsies were performed to determine the presence of persistent disease. The response rate was defined as the proportion of patients that achieved a specified level of response.

Results

This study commenced in September 2002. A total of 30 patients, 15 in each dose level, were treated. Table 2 shows the patient characteristics. Overall, mean treatment time was 39 ± 3 days in DL 1 and 38 ± 1 days in DL 2, and no patient required treatment breaks. Compliance with both neoadjuvant and concomitant chemotherapy was high (Table 2). Table 3 depicts the acute and late toxicity observed.

Acute toxicity

Overall, during neoadjuvant chemotherapy, 1 patient experienced G4 neutropaenia, one had G3 and 7 had G2. Two patients experienced severe tinnitus, 2 had severe nausea and vomiting and one had renal impairment.

No patient experienced acute grade 4 toxicity. The incidences of G2 and G3 acute toxicity observed in both dose levels are shown in Table 3. During and for the first 8 weeks after chemo-IMRT, the median minimum Karnofsky performance scores (KPS) were 70 (30–90) in DL 1 and 70 (60–90) in DL 2. Median maximum fatigue was grade 2 (1–3) in both dose levels.

Radiation dermatitis

In the DL 1, the peak prevalence of moist desquamation (G3) was 17%, seen in the first week after chemo-IMRT. In DL 2, this figure was 21%, in the last week of treatment. Dry desquamation (G2) started in week 4 in both dose levels and moist desquamation in week 5. At 3 weeks post chemo-IMRT, no patient had moist desquamation and at 8 weeks only 13% of patients in DL 2 had G1 erythema. The average time with G3 dermatitis, in patients who reached that grade, was 1.3 ± 0.6 weeks in the first and 2.0 ± 1.0 weeks in dose level 2.

Radiation-induced dysphagia, pain and mucositis

Fig. 1 shows the prevalence of dysphagia and pain and mucositis as a function of time from the start of chemo-IMRT in both dose levels.

The peak prevalence of grade 3 dysphagia (requirement for enteral feeding) was 64% for DL 1, seen in weeks 7 and 8 (1 and 2 weeks post-IMRT), and 83% in week 9 for DL 2 (Fig. 1). In DL 1, 13% patients still required enteral feeding at week 14 and the same proportion of patients required a soft diet (G2), which had resolved a month later. In DL 2, at week 14, 23% patients had G3 and 38.5% had G2 dysphagia. In this DL, 1 patient re-

Table 2
Patient characteristics

	Cohort 63 Gy	Cohort 67.2 Gy
Median follow up in weeks (range)	87 (55–162)	40 (9–64)
Median age (range)	59 (37–77)	66 (60–85)
Gender		
Male	11	10
Female	4	5
Primary tumour site		
Larynx	7	7
Hypopharynx	8	8
T stage		
T1	0	1
T2	3	3
T3	8	8
T4	4	3
N stage		
N0	4	8
N1	4	2
N2a	1	0
N2b	3	2
N2c	2	3
N3	1	0
Neoadjuvant chemotherapy	15	13
Concomitant chemotherapy	15	14

Table 3
Incidence of acute G2 and G3 toxicity (NCI CTC v. 2.0) expressed in percentage values and maximum RTOG and LENTSOM toxicity at 1 year in DL 1 and 6 months in DL 2 expressed in absolute number of cases (cases with toxicity/cases evaluable)

	63.0 Gy cohort		67.2 Gy cohort	
	G2	G3	G2	G3
Acute toxicity				
Dermatitis	67%	20%	47%	20%
Mucositis	33%	67%	47%	40%
Dysphagia	20%	67%	13%	87%
Pain	47%	27%	53%	40%
Xerostomia	60%	0	73%	7%
	63.0 Gy cohort at 1y		67.2 Gy cohort at 6m	
Maximum RTOG toxicity				
Skin	G1 (2/11)		G1 (3/10)	
Mucosal	G1 (1/11)		G1 (6/10)	
Oesophageal	G2 (1/11)		G3 (1/10)	
Saliva	G2 (1/11)		G1 (7/10)	
Laryngeal	G1 (3/11)		G2 (2/10)	
Maximum LENT SOM toxicity				
Skin (oedema)	G1 (3/11)		G1 (4/10)	
Mucosa	G0 (4/11)		G1 (3/10)	
Oesophageal	G1 (2/11)		G3 (1/10)	
Saliva	G2 (1/11)		G2 (1/10)	
Laryngeal	G1 (3/11)		G2 (2/10)	

quired enteral feeding up to 1 year following completion of treatment and 20% were still on a soft diet at week 18, which had resolved at 6 months post-treatment.

The peak prevalence of grade 3 pain was 27%, seen in week 7 in DL 1 and 45.5% in week 9 in DL 2 (Fig. 1). In DL 1, 47% of patients required opioids for pain control and 80% in DL 2. The time to onset of G3 dysphagia and pain was similar in both dose levels but resolution was delayed in DL 2 (Fig. 2). Overall, average times with dysphagia and pain were longer in DL 2, 5.9 ± 3.4 and 4.1 ± 2.1 weeks, respectively.

The peak prevalence of confluent mucositis (G3) was 58%, seen in week 7 (1 week post-chemo-IMRT) in DL 1 and 33% in week 6 in DL 2. Patchy mucositis (G2) started in week 3 in both dose levels and healing, represented by a reduction in the prevalence of G3 mucositis commenced in week 9 (3 weeks post-chemo-IMRT). Fig. 1 shows a prolonged healing time for DL 2, with prevalence of G2 mucositis of 58% in week 10, i.e. 4 weeks post-chemo-IMRT and 15% in week 14. However, these 2 patients did, in fact, not attend for their week 14 FU and their toxicity was assumed to be the same as on week 10, i.e. grade 2. By week 18 mucositis had healed in both patients.

The peak functional consequences of mucositis, i.e. dysphagia and pain, were correlated with maximum grade mucositis. A highly significant positive correlation was found, in DL 1, between maximum grades of mucositis and pain and between maximum grades of mucositis and dysphagia, with Spearman's rank correlation coefficients 0.7 ($p = 0.002$) and 0.6 ($p = 0.02$), respectively. No significant correlation was found in DL 2.

Xerostomia

The peak prevalence of xerostomia in DL 1 was G2 in 73%, seen in week 7. In DL 2 it was G3 xerostomia in 9% in week 9 (Fig. 3). The prevalence of G3 xerostomia was low and the time course of G2 xerostomia was similar in both dose levels, with a somewhat earlier onset in DL 2, and more rapid resolution in DL 1 (Fig. 3).

Late toxicity

Late RTOG and LENTSOM toxicity scores observed at 1 year in DL 1 and at 6 months in DL 2 are shown in Table 3. Only 1 patient in dose level 2 experienced G3 dysphagia, that was, in fact, a consequential late reaction.

Response

A complete response (CR) was documented in 25 patients (83%), 12 in the first and 13 in DL 2. The overall response rate, CR plus partial responses (PR), was 100%. Of those patients with PR in DL 1, 1 had a differential response (CR in the primary and PR in the nodal disease) and 2 had PR both in the pri-

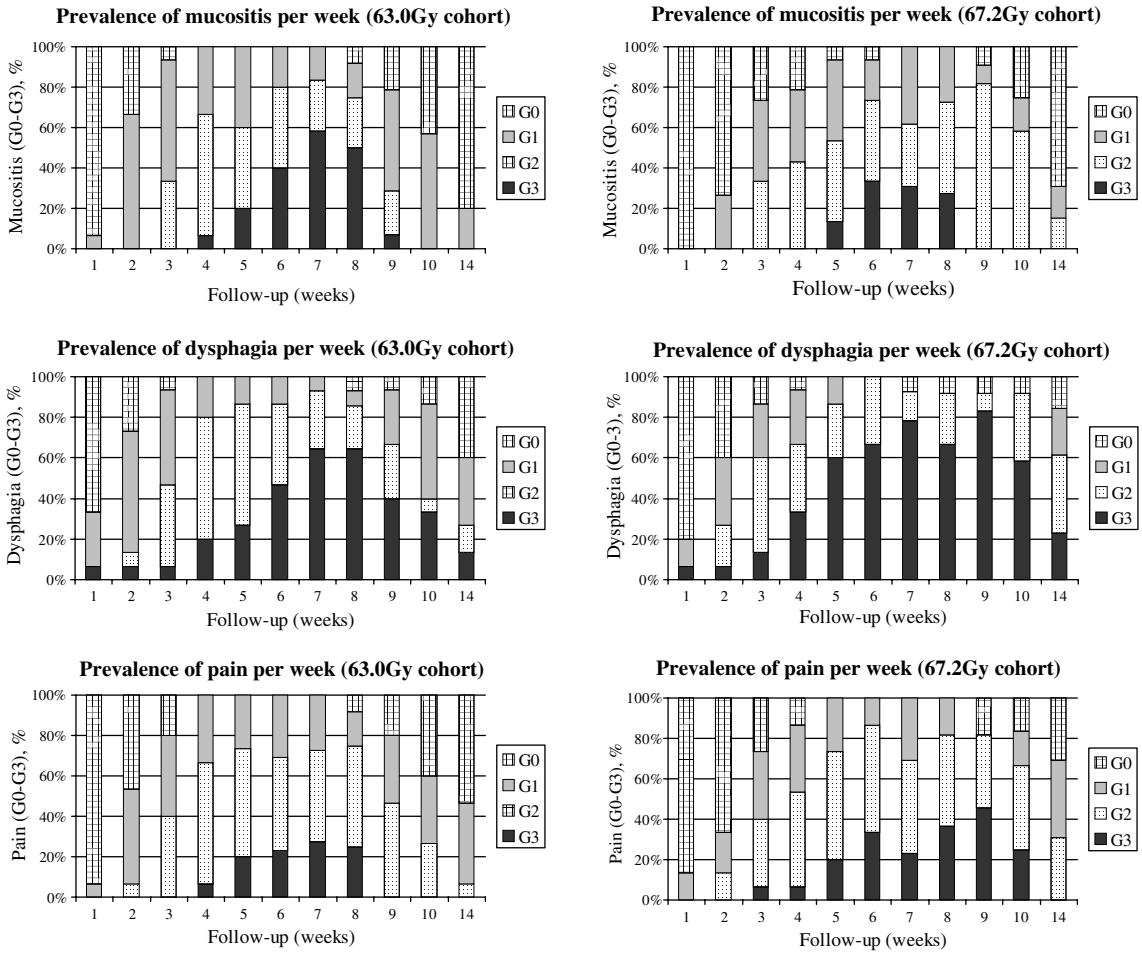

Fig. 1. Prevalence of acute mucositis, dysphagia and pain over time for both cohorts.

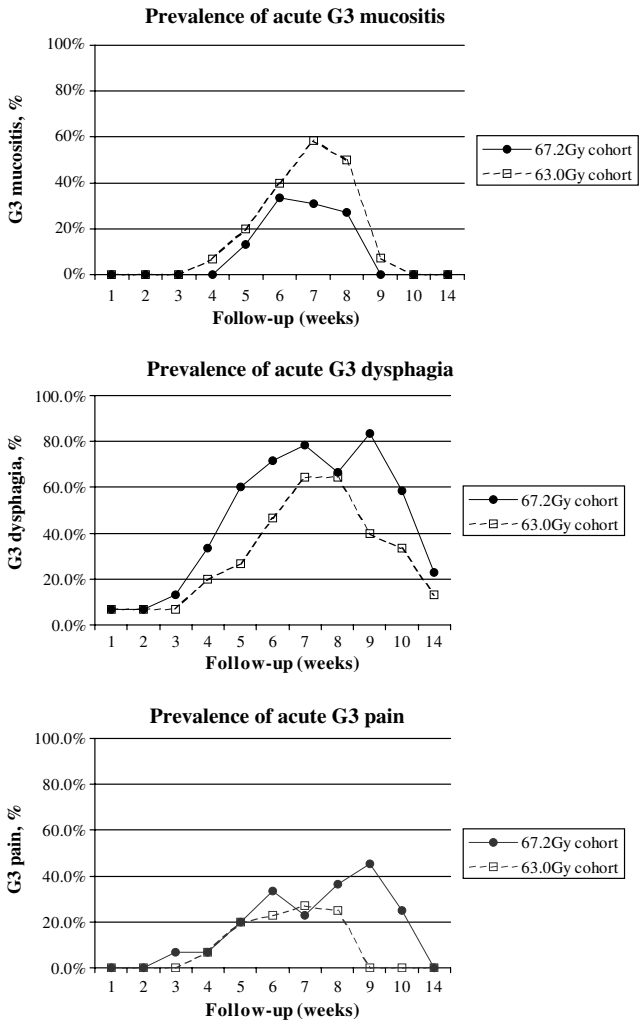

Fig. 2. Prevalence in percentage points of G3 acute mucositis, dysphagia and pain for both cohorts over time.

mary and nodes. In DL 2, 1 patient had a PR in the nodes and the other a PR in the primary. All patients who failed to achieve a CR were managed with salvage surgery, neck dissection alone for the neck failures and plus pharyngo-laryngectomy in patients with PR in the primary. Three of these 5 patients remain alive and disease-free after salvage surgery.

At a median FU of 87 weeks in DL 1 and 40 weeks in the second, median OAS figures were 17 months (12—37) and 8 months (1—14), respectively. Twenty-three (77%) patients are still alive, of whom 22 (73%) are alive and disease-free. There have been 5 (33%) deaths in DL 1, 3 of progressive disease and 2 of second malignancy. One patient died of carcinoma of the bronchus and another of carcinoma of the oesophagus diagnosed 15 and 18 months, respectively, after the original diagnosis. In DL 2, 2 patients died of intercurrent cardiovascular disease. Median time to recurrence was 9 months (6—13). Five recurrences have been reported to date, all in DL 1, three in the high dose volume (HDV), within the PTV1, one in the low dose volume (LDV), within the PTV2 and one in both the LDV and the lung. The overall laryngectomy rate was 10%, 13% in the first and 7% in DL 2.

Discussion

In this phase I dose escalation study we have shown that neoadjuvant chemotherapy followed by radical chemo-IMRT is feasible and that a 9% escalation of the radiation dose to the primary target volume is possible without treatment breaks or dose limiting toxicity. Both radiotherapy and chemotherapy compliance were excellent.

This study was designed to determine the toxicity of combining the delivery of a higher biologically effective radiation dose using IMRT, which can potentially reduce normal tissue damage, with the radio-sensitising properties of concomitant cisplatin. The small number of patients and the design of this study as a dose escalation protocol, as well as the still short follow up period, make it difficult to draw meaningful conclusions from the outcome data. However, some observations can be made. All patients responded to treatment, with an overall CR rate of 83%. It could be argued that these excellent response rates could potentially be related, in part, to the IMRT technique, which can avoid areas of low dose within the target volume. All loco-regional recurrences observed to date appeared in DL 1, a fact that may be a reflection of the short median follow-up in DL 2. However, the effect of an escalated dose of radiation is likely to contribute to improved local control. IMRT is associated with a potential increase of geographical miss. In our study, no recurrences were observed outside the treated volumes. Of the 5 recurrences observed, 3 were in the high dose volume, suggesting the existence of resistant tumour clonogens within this volume. IMRT could potentially be used to further escalate the dose to the GTV in an attempt to overcome resistance factors such as hypoxia. In addition, the fact that 2 patients in our study recurred in the low dose volume suggests dose escalation of the elective neck possibly warrants further evaluation. This is contrary to the generally accepted view that dose escalation of elective tissue is not appropriate.

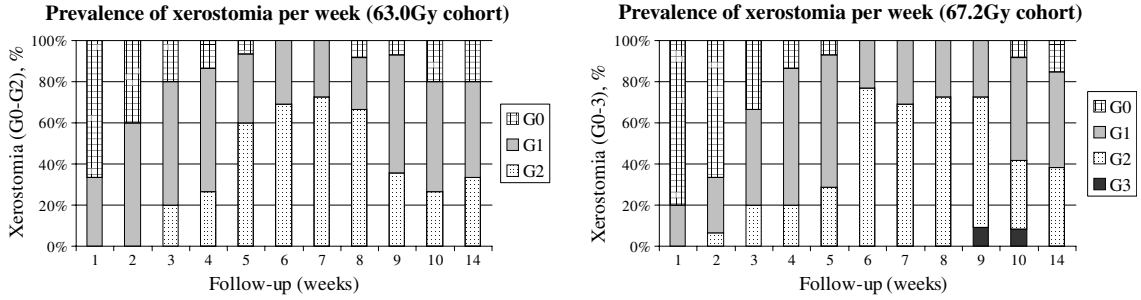

Fig. 3. Prevalence of xerostomia in percentage points for both cohorts over time.

The incidence of moist desquamation was rather low in both dose levels (20%). In our study, the skin was specifically excluded from the target volume and the immobilisation shell was cut out to avoid any build-up effect and to allow skin-sparing. It is interesting to note that the incidence of confluent mucositis (G3) was lower in the dose escalated DL (40% vs. 67%). This most likely represents an underestimation of the true incidence of this grade of mucositis. Most of these patients had high dose target volumes that extended only 1-2 cm above the epiglottis and mucositis in this PTV1 often could only be assessed by flexible nasendoscopy, which is excessively uncomfortable during radical chemoradiotherapy. In agreement with other authors [16,17], we also found a significant positive correlation in the first DL, between maximum grades of mucositis and pain and between maximum grades of mucositis and dysphagia. Overall, patients in the dose escalated DL had higher rates of G3 dysphagia, pain and xerostomia, but these were manageable and did not lead to any unplanned treatment breaks. Although the incidence of G3 mucositis was lower in DL 2, a longer time to resolution was observed. Fig. 2 clearly shows how G3 dysphagia and pain peaked higher, later and lasted longer than in DL 1. This was expected and, reassuringly, recovery was observed in all patients but one, who was still PEG-dependent 1 year following completion of treatment. The time course of acute reactions was similar in both dose levels, with the peak prevalence of acute toxicity occurring towards the end or shortly after completion of treatment. This highlights the importance of close follow-up in the first few weeks post-treatment in this group of patients. One patient in each DL required enteral feeding from the start of treatment due to weight loss secondary to the presence of bulk disease. This was included in the analysis from the beginning to incorporate the radiation toxicity seen as the RT progressed.

Follow up is too short to draw any conclusions on the late toxicity observed. To date, it has been low and, remarkably, the incidence of PEG feeding much lower than that reported in the literature in studies evaluating conventionally-delivered altered fractionation regimens plus concomitant chemotherapy, with reported incidences of long-term PEG feeding as high as 30% [7,8].

Dose escalation caused higher acute toxicity, but there was no dose-limiting toxicity and no treatment breaks. Pending further follow up the late toxicity observed to date was moderate and similar to what would be expected with conventional radiotherapy.

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