INDUCTION CHEMOTHERAPY FOLLOWED BY CHEMO-INTENSITY MODULATED RADIOTHERAPY (IMRT) FOR LOCALLY ADVANCED NASOPHARYNGEAL CANCER

Aisha B Miah[1], Shreerang A Bhide[1,2], Lyra Del Rosario[1], Jennifer Matthews[1], Robyn Nicol[1], Mary A Tanay[1], Swaranali Gupta[1], Shane H Zaidi[1], Kate L Newbold[1], Kevin J Harrington[1,2*], Christopher M Nutting[1*]

[1]Head and Neck Unit, The Royal Marsden NHS Foundation Trust, London and Surrey.

[2]The Institute of Cancer Research, London, UK

*KJH and CMN are joint senior authors

Corresponding author

Professor CM Nutting
Consultant Clinical Oncologist
The Royal Marsden NHS Foundation Trust
Fulham Road
London SW3 6JJ

Tel: 0207 808 2586
Fax: 0207808 2235
Email : chris.nutting@rmh.nhs.uk

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Abstract

Purpose:

To determine the toxicity and tumour control rates following chemo-IMRT for locally advanced nasopharyngeal cancers (LA-NPC)

Methods:

Patients with LA-NPC were enrolled in a trial to receive induction chemotherapy followed by with parotid-sparing chemo-IMRT. The primary site and involved nodal levels received 65 Gy in 30 fractions (f) and at risk nodal levels, 54 Gy/30f. Incidence of ≥G2 subjective xerostomia was the primary endpoint. Secondary endpoints included incidences of acute and late toxicities and survival outcomes.

Results:

Forty-two patients with AJCC Stages II (12%), III (26%), and IV (62%) (WHO subtype: I (5%); II (40%); III (55%)) completed treatment between January 2006 and April 2010 with median follow-up of 32 months. Incidences of ≥G2 acute toxicities were: dysphagia 83%; xerostomia 76%; mucositis 97%; pain 76%; fatigue 99% and ototoxicity 12%. At 12 months, ≥G2 subjective xerostomia was observed in 31%, ototoxicitiy in 13% and dysphagia in 4%. Two-year loco-regional control was 86.2% (95%CI: 70.0-94.0) with 2-year progression-free survival at 78.4% (61.4-88.6) and 2-year overall survival at 85.9% (69.3-93.9).

Conclusions:

Chemo-IMRT for LA-NPC is feasible with good survival outcomes. At 1 year, 31% experience ≥G2 subjective xerostomia.

Introduction

In Europe, the incidence of nasopharyngeal cancers (NPC) is 1.1 per 100,000 [1] and in the United Kingdom, 0.39 per 100,000 [2]. Treatment with radiotherapy is technically challenging. Clinical target volumes lie in close proximity to the optic apparatus and brainstem which make optimal dose delivery difficult. Additionally, the parotid glands have commonly been irradiated to a high dose - resulting in long-term xerostomia. Two phase III studies have reported on parotid gland-sparing IMRT versus conventional radiotherapy. Pow et al randomised 50 patients between the two radiotherapy techniques [3]. Recovery of parotid function at one year was superior with IMRT compared to conventional radiotherapy (83% versus 9.5%). Global quality of life (QOL) was significantly superior with IMRT when compared to the conventional group. Kam et al randomised 60 patients between IMRT and conventional RT [4]. The primary endpoint of RTOG xerostomia score was significantly better with IMRT (39.3% versus 82.1%, p= 0.001), as were the secondary endpoints of parotid and floor of mouth salivary flow rates. However, both these studies reported patients with early stage nasopharyngeal cancers who received radiotherapy alone.

It is reasonable to expect a higher degree of xerostomia in more advanced cases of NPC. Treatment includes irradiation of the bilateral parapharyngeal spaces which can result in a high dose to the deep lobe of the parotid glands. In the United Kingdom nasopharyngeal cancer is very rare and no clinical experience with outcomes of modern treatment with IMRT has been published. The purpose of this study was to determine the toxicity and tumour control rates following chemo-IMRT for locally advanced nasopharyngeal cancers

(LA-NPC).and in particular to determine the incidence of high grade (≥G2) subjective xerostomia at 1 year.

Methods

Study Objectives / Patient Eligibility

Patients diagnosed with histologically confirmed nasopharyngeal cancer were eligible for the study. Patients <16 years old or with a previous malignancy other than non-melanomatous skin cancer were excluded. Pre-treatment evaluations comprised history and examination, examination under anesthesia, biopsy, dental assessment, hematological and biochemical parameters, computed tomography (CT) scan of the head, neck and chest and magnetic resonance imaging (MRI) of the head and neck was performed. Disease was staged according to the 1997 American Joint Committee on Cancer criteria [5]. Patients were eligible for the trial if they had started induction chemotherapy at another institution. All patients signed written informed consent and the study was approved by the institutional research and ethics committee (Royal Marsden Hospital CCR 2608, clinical trials registration number: NCT02149641)

The primary objective was to determine the incidence of $\geq$G2 xerostomia at 1 year using the subjective component of LENTSOMA[6]. Secondary objectives included: acute and other late radiation toxicities, loco-regional disease-free survival (LRDFS), progression-free survival (PFS) and overall survival (OS).

Trial design

This trial was a prospective longitudinal cohort study to determine the incidence of $\geq$G2 subjective xerostomia (LENTSOMA) in patients treated with chemo-IMRT for locally

advanced nasopharyngeal cancer. A sample size of 42 patients was selected so as to compare the incidence of $\geq$G2 subjective xerostomia to an equivalent number of patients with oropharyngeal and hypopharyngeal squamous cell cancers who received IMRT in the PARSPORT trial [7].

Treatment

Chemotherapy schedule

Patients treated at the Royal Marsden Hospital received induction chemotherapy with two cycles of cisplatin (75mg/m^2) day 1 and 5-fluorouracil (5-FU) (1000mg/m^2) days 1-4 on a 21-day cycle. Patients received concomitant cisplatin 100mg/m^2 on days 1 and 29 of IMRT. Where cisplatin was contraindicated, carboplatin (AUC5) or cetuximab (initial dose 400mg/m^2 then 250mg/m^2 weekly during radiotherapy) was administered. Patients could be recruited to the study if they had received other induction chemotherapy schedules in other institutions

Radiotherapy technique

Patients were recruited to the study during their induction chemotherapy schedule. Patients were immobilised and contrast-enhanced CT scans were taken at 2 mm intervals through the head and neck region. Target volumes and organs at risk (optic apparatus, brainstem, and spinal cord) were delineated following ICRU-50 and -62 guidelines. Ipsilateral and contralateral parotid glands (reference to the location of the primary site) were outlined. In addition, combined superficial lobes of both parotid glands were outlined as a separate volume. Both cochleas were outlined retrospectively. Gross Tumour Volume (GTV)

comprised of residual disease in the nasopharynx and lymph nodes following induction chemotherapy. Clinical Target Volume for primary site and involved nodal groups (CTV1) comprised the GTV with a 1 cm margin, including the entire nasopharynx, bilateral parapharyngeal spaces, the posterior half of the nasal cavity, inferior half of sphenoid sinus (or entire sphenoid if involved), retropharyngeal nodes and lymph node groups with macroscopic disease. Pre-treatment diagnostic imaging was reviewed to confirm sites of macroscopic disease reported at presentation were encompassed within CTV1. CTV2 comprised the superior half of the sphenoid sinus (if uninvolved at presentation) and lymph node groups at risk of harbouring microscopic disease. Planning Target Volumes (PTV) were constructed from CTVs with a 3 mm margin.

Radiotherapy was delivered using five- or seven-beam simultaneous integrated boost IMRT technique. Doses were prescribed to the median dose-volume point of the PTV1 dose volume histogram (DVH) at 65 Gy in 30 daily fractions; 54 Gy in 30 daily fractions were prescribed to PTV2. Maximum dose constraints applied to the spinal cord and brainstem were 46 Gy and 54Gy, respectively; the optic chiasm, 54 Gy, optic nerves and eyes 55 Gy. A dose constraint was applied to the contralateral parotid gland and the optimisation was weighted to particularly spare the superficial lobes of both parotid glands, to a mean dose of less than 26 Gy. No dose constraint was applied to the cochleas.

Outcome assessment

Complete response (CR) was defined as complete disappearance of disease as evaluated clinically including nasendoscopy and CT and MRI at up to 3 months after completing

treatment. RECIST criteria were used to record radiological response. Where residual lesions were present in the nasopharynx or neck, biopsies or fine needle aspirations were performed to determine the presence of persistent disease. Neck dissection was undertaken if patients demonstrated a clinical or radiological partial response (PR), stable disease (SD) or progressive disease (PD) after radiotherapy. Recurrence was defined as clinical, radiological and/or histopathological evidence of disease presenting three months after completing radiotherapy. Where possible, patients proceeded to salvage surgery for persistent or recurrent disease.

Acute toxicity scores were recorded using NCI-CTCAE v3.0[8] weekly during chemotherapy-IMRT, for 4 weeks of recovery and at week 14. Indications for enteral feeding were: weight loss >10%, risk of aspiration defined clinically or at videofluoroscopy and inability to maintain adequate calorific intake. Late toxicity scores (LENT SOMA and RTOG/EORTC [9]) were recorded at follow-up at 3, 6, 12, 18 and 24 months after radiotherapy.

Statistical analysis

The incidence of an acute or late high grade toxicity was defined as the total number of patients reaching grade 2-4 and at any time, divided by the total number of assessable patients [10]. Outcome measures following chemo-IMRT were described by local (at primary site) and regional (neck) control. Loco-regional control rate was defined as the proportion of patients with no evidence of recurrent local and/or neck disease. Loco-regional disease-free survival (LDFS) was calculated as time from start of treatment to recurrent local or

nodal disease. Patients with persistent disease at primary site or neck were included as loco-regional events. Progression-free survival (PFS) was defined as time from diagnosis to development of loco-regional and/or distant disease. Patients who underwent salvage surgery for loco-regional control were classified as disease-free. Overall survival (OS) was measured from diagnosis to death from any cause. Survival analyses were estimated using the Kaplan-Meier method.

Results

Patient characteristics and treatment compliance

Between February 2006 to May 2010, 42 patients were enrolled into the study. However, one patient was subsequently excluded because the pathological diagnosis of undifferentiated carcinoma of nasopharyngeal type was changed to melanoma on further histological review. Patient demographics and disease characteristics are summarised in Table 1. The majority of patients presented with Stage IV disease (64%). Histological classification was WHO Type I - 5%, Type II - 40% and Type III - 55%.

Ninety-eight percent received induction chemotherapy and all patients received concomitant chemo-IMRT. All patients received IMRT in concordance with the trial protocol with median duration of radiotherapy of 42 days. Radiotherapy details are summarised in Table 2. Mean dose to the contralateral parotid gland was 31.6 Gy ± 6.2 (one standard deviation) and to the ipsilateral parotid gland 40.6 Gy ± 6.8. The combined superficial lobes received 26.9 Gy ± 4.9.

Induction chemotherapy

Induction chemotherapy was delivered to 40 patients; one patient declined induction chemotherapy but received concomitant chemo-IMRT. The majority received 2 cycles of PF (86%) at our institution. Three patients (7%) received three cycles of PF chemotherapy and 2 patients (5%) received 3 cycles of TPF at other institutions before being referred for IMRT.

One changed from PF to carboplatin and 5FU for their 2nd cycle of induction chemotherapy due to tinnitus. There were no cases of neutropenic sepsis. Neutropenia was reported in one case which delayed delivery of the 2nd cycle of induction chemotherapy.

Concomitant chemotherapy

All but one patient received concomitant platinum chemo-IMRT, 26 patients (63%) received 2 cycles of cisplatin, 6 patients (14%) received 2 cycles of carboplatin, 4 patients (10%) received 1 cycle of cisplatin and 1 cycle of carboplatin and 4 (10%) completed only 1 cycle of cisplatin during radiotherapy. One patient (2%) with Type II NPC received weekly cetuximab following deterioration of renal function after 2 cycles of induction PF chemotherapy. No cases of neutropenic sepsis were reported. However, neutropenia did delay delivery of concomitant chemotherapy in 3 patients (1 following 2 cycles of PF, 1 following 3 cycles of TPF and 1 following 3 cycles of PF).

Acute toxicity

The incidence of high grade acute toxicities at the end of radiotherapy and 2 months after completing radiotherapy is summarised in Figure 1. No grade 4 toxicities were reported during radiotherapy. Grade 2 xerostomia was reported in 76% of patients at the end of treatment, with 21% persistent xerostomia at 2 months after IMRT. Feeding tube-dependent dysphagia was reported in 24% of patients at the end of IMRT with 6% still reporting G3 dysphagia at 2 months after IMRT. Forty-four percent of patients reported G3 fatigue on completion of IMRT.

Late toxicity

The incidence of ≥G2 subjective xerostomia (LENTSOMA and RTOG) at 12 months was 31% and 28% respectively whereas it was 39% and 41% in the PARSPORT Trial. Recovery with time is illustrated in Figure 2. At eighteen months and two years after completion of chemo-IMRT the subjective xerostomia rate was 21% and 15% respectively. Other high grade (≥G2) late sequelae reported were: ototoxicity (tinnitus and patient reported hearing impairment) (13%) and dysphagia (4%). No cases of neuropathy or visual disturbance were reported.

Patterns of failure

Thirty-eight patients (93%) achieved a complete clinical response at the primary site and 36 patients (88%) at the lymph node sites. One patient proceeded to lymph node dissection with final pathology confirming 4 of 26 lymph nodes with residual disease. Survival outcomes are illustrated in Figures 3-5. With a median follow-up of 37 months (1.0-52.2), five patients have died following disease recurrence 7, 16, 16, 18 and 23 months following treatment. Estimated 2-year loco-regional control was 86.5% (70.5-94.1) with 2-year PFS at 79.0% (62.4-88.9) and 2-year OS at 86.7% (70.9-94.2) (Table 3). The local control rate was 88% and nodal control rate was 88% (Table 3). The sites of distant relapse were mediastinum, lung, liver and bone.

Discussion

In this trial, the local control rate and overall survival is similar to that described by other authors and is similar to conventional radiotherapy outcomes (Table 3). The stage at presentation and histological subtype varies between different studies published in the literature (Table 3). Our study shows better outcomes than the previously published local control rates from the largest UK series [11], although this series were treated with conventional radiotherapy between 1992 and 2005. The majority of cases of NPC diagnosed in North America are keratinising squamous cell carcinoma (Type II) and most of those diagnosed in South East Asia are undifferentiated or poorly differentiated carcinoma (Type III). The former carries a worse prognosis, whilst the latter has a substantially higher incidence of neck lymphadenopathy [12]. In our study, both poorer prognosis Type II (40%) and Type III (55%) disease dominate. The South-East Asian population present with earlier disease stage and Type III NPC, conferring a better prognosis. Poor prognostic indicators in non-endemic NPC include nodal disease and WHO Type II histological subtype [13]. In addition, Wu et al have reported primary gross tumour volume (>25cm^3) to be significant in estimating the probability of local control, distant metastasis and overall survival [14]. Tumour stage was not an independent prognostic indicator. In our study, the majority presented with advanced stage (64%) and presented with post induction chemotherapy primary GTV greater than 25 cm^3. Despite this, we have achieved comparable locoregional control rates and survival to the North American and South-East Asian groups. The EHNS-ESMO-ESTRO clinical practice guidelines [1] described by Chan et al, discuss induction chemotherapy that can be considered in locally advanced cases but is not seen as standard treatment. In our study, patients have received induction chemotherapy safely without a

significant impact on the administration of concomitant chemotherapy. Chan et al describe an overall survival of 76% at 1 year; our study reports an estimated overall survival rate of 87% at 2 years.

High-grade xerostomia is a common problem in patients who have undergone radiotherapy for NPC. Patients may present with direct parapharyngeal tumour extension, bilateral retropharyngeal nodal spread, and bilateral level II nodal spread. Even with IMRT, sparing an entire parotid gland is extremely challenging and, consequently, this can result in a high dose to the deep lobe of the parotid glands. In this study, attempts were made to spare an entire parotid gland and particularly to spare the superficial lobes of both parotid glands. In our study, we report 31% incidence of $\geq$G2 xerostomia (LENTSOMA) and 28% when classified by RTOG scores. These are lower than that reported by Kam using RTOG scoring system (39%) [4] for nasopharyngeal cancers. The sample size for our study was selected to compare the incidence of $\geq$G2 xerostomia reported in patients with oropharyngeal and hypopharyngeal cancers who received IMRT in the PARSPORT trial. Nutting et al reported an incidence of 39% using the LENTSOMA scale and 41% using the RTOG scale.[7]. The differences may be related to uncertainties in observer rated xerostomia but could alternatively be explained by sparing the superficial lobes of both parotid glands in our study. Similar incidences were reported by the UCSF group, 30% [12]. However, Pow et al reported a lower incidence of high grade xerostomia (20%) at 12 months. The low incidence described by Pow may be explained by the early stage of nasopharyngeal cancers treated in this study but again we accept the uncertainties in drawing comparisons across different studies. The findings in our study demonstrate that excellent levels of recovery of salivary

function can still be achieved in the treatment of locally advanced nasopharyngeal cancers, despite only partial sparing of the parotid glands.

Nearly all patients reported ≥G2 fatigue with 66% still reporting high-grade fatigue at 2 months after RT. Fatigue was unexpectedly increased in the IMRT cohort in the PARSPORT trial, 74% reported ≥G2 fatigue during treatment. Dosimetric analysis has suggested that radiation dose to the central nervous system structures may relate to the development of acute fatigue [15]. The radiation doses received by CNS structures are much higher in the treatment of nasopharyngeal cancers and this, in part, may explain the higher incidence of acute fatigue. The relationship between fatigue and radiation dose to central nervous system structures has been evaluated. Higher mean dose to the pituitary gland, brainstem and cerebellum were associated with a higher incidence of ≥ grade 2 fatigue [16].

Ototoxicity, described subjectively as tinnitus and patient reported hearing loss was more evident in this study when compared IMRT studies treating oropharyngeal cancers. However, similar incidences were reported in IMRT studies treating nasopharyngeal cancers with radiotherapy alone [17]. This is explained by the dose delivered to the cochlea. No dose constraints were applied in the planning process, primarily because of the close proximity of the auditory structures to the target volume or in certain instances, the possibility of disease extension into the middle ear. In an attempt to reduce the incidence of long term ototoxicity, dose constraints to the contralateral cochlea could be applied [18]. The use of the ototoxic chemotherapy agent, cisplatin, has not increased the incidence of high grade ototoxicity. This may be partly explained by the low threshold applied to change to carboplatin at the earliest signs of tinnitus. The limitations of the study are small numbers of

patients, due to the rarity of this disease in the UK, heterogeneous chemotherapy treatment, and limited follow up. Due to the rarity of nasopharyngeal cancer in the UK, it will not be feasible to conduct phase III trials in this disease and we will rely on the excellent trials being carried our in China and Hong Kong, together with the meta-analyses which will determine the answer to these important clinical questions.

In this prospective study of sequential induction chemotherapy followed by concomitant chemo-IMRT, administration of cytotoxic drugs did not affect IMRT delivery, with all patients completing radiotherapy in a median of 42 days. Combined superficial lobe parotid sparing IMRT offers good recovery of salivary function in locally advanced cases. The majority of patients completed the planned treatment, only one patient failed to receive the second cycle of concomitant chemotherapy. Overall, induction PF or carboplatin/5-FU and concomitant platinum is well tolerated and demonstrates good disease outcomes with a low incidence of late toxicities, particularly with good recovery of salivary function.

Acknowledgements

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Conflicts of interest:

The authors declare no conflict of interest

References

1. Chan AT, Gregoire V, Lefebvre JL et al. Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5: v187-189.
2. National Cancer Intelligence Network N. Incidence and mortality from head and neck cancers in England 2002-2006. In. 2008.
3. Pow EH, Kwong DL, McMillan AS et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 2006; 66: 981-991.
4. Kam MK, Leung SF, Zee B et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 2007; 25: 4873-4879.
5. Cancer AJCo. Manual for staging of cancer. 1997; 5th ed.
6. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995; 31: 1341-1346.
7. Nutting CM, Morden JP, Harrington KJ et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 2011; 12: 127-136.
8. DCTD N, NIH, DHHS Cancer Therapy Evaluation Program. Common terminology criteria for adverse events v3.0. 2003.
9. Rubin P, Constine LS, 3rd, Fajardo LF et al. EORTC Late Effects Working Group. Overview of late effects normal tissues (LENT) scoring system. Radiother Oncol 1995; 35: 9-10.
10. Bentzen SM. Radiobiological considerations in the design of clinical trials. Radiother Oncol 1994; 32: 1-11.
11. Colaco RJ, Betts G, Donne A et al. Nasopharyngeal carcinoma: a retrospective review of demographics, treatment and patient outcome in a single centre. Clin Oncol (R Coll Radiol) 2013; 25: 171-177.
12. Lee N, Xia P, Quivey JM et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 2002; 53: 12-22.
13. Zhao LN, Zhou B, Shi M et al. Clinical outcome for nasopharyngeal carcinoma with predominantly WHO II histology treated with intensity-modulated radiation therapy in non-endemic region of China. Oral Oncol 2012.
14. Wu Z, Zeng RF, Su Y et al. Prognostic significance of tumor volume in patients with nasopharyngeal carcinoma undergoing intensity-modulated radiation therapy. Head Neck 2012.
15. Gulliford SL, Miah AB, Brennan S et al. Dosimetric explanations of fatigue in head and neck radiotherapy: An analysis from the PARSPORT Phase III trial. Radiother Oncol 2012; 104: 205-212.
16. Powell C, Schick U, Morden JP et al. Fatigue during chemoradiotherapy for nasopharyngeal cancer and its relationship to radiation dose distribution in the brain. Radiother Oncol 2014; 110: 416-421.
17. Lee AW. Nasopharyngeal cancer: advances in radiotherapy. Int J Radiat Oncol Biol Phys 2007; 69: S115-117.
18. Bhide SA, Harrington KJ, Nutting CM. Otological toxicity after postoperative radiotherapy for parotid tumours. Clin Oncol (R Coll Radiol) 2007; 19: 77-82.

Table 1: Patient demographics and disease characteristics. *includes 4 patients who received carboplatin as the second cycle of concomitant chemotherapy during IMRT.

	N=41 (100%)
Median Follow Up (range)	32.2 months (1.0-52.2)
Median Age (range)	53.0 years (17.2-78.0)
Sex	
Female	13 (32)
Male	28 (68)
Performance Status	
0-1	41 (100)
2-4	0
WHO Histological subtype	
I	2 (5)
II	17 (40)
III	22 (55)
T Stage	
T1	5 (12)
T2	13 (32)
T3	9 (22)
T4	14 (34)
N Stage	
N0	12 (29)
N1	11 (27)
N2	16 (39)
N3	2 (5)
AJCC Stage	
I	0
II	5 (12)
III	10 (24)
IVA	24 (59)
IVB	2 (5)
Induction chemotherapy	
Cisplatin + 5-fluorouracil	35 (85)
Carboplatin + 5-fluorouracil	3 (7)
Docetaxel + Cisplatin + 5-fluorouracil	2 (5)
No induction chemotherapy	1 (3)
Concomitant chemotherapy	
Cisplatin	34* (73)
Carboplatin	6 (15)
Cisplatin (1 cycle only)	4 (10)
Cetuximab	1 (2)

Table 2: Radiotherapy treatment details

Structure	Dose (Gy)
PTV1	65 Gy/30F
PTV2	54 Gy/ 30F
Parotid glands (mean dose ± 1sd)	
Contralateral	31.6 Gy ± 6.2
Ipsilateral	40.6 ± 6.8
Combined superficial lobes of parotid glands	26.9 ± 4.9
	Maximum dose Gy (range)
Brain stem	50.7 (34.8- 54.2)
Spinal cord	44.3 (39.2- 47.9)
Optic Chiasm	50.6 (13.4- 54.8)
Left Optic Nerve	50.5 (7.7- 53.8)
Right Optic Nerve	49.5 (12.9- 53.9)
Left Eye	27.8 (2.2- 54.7)
Right Eye	29.4 (3.7-54.1)
Ipsilateral cochlea	59.5 (46.7-69.3)
Contralateral cochlea	55.4 (33.9- 67.8)

Table 3: Comparison to published series

Series (Number of patients)	WHO Histological Classification	AJCC TNM Stage (%)		Outcomes
UCSF experience[11] (N= 67)	I II 51% III 49%	Stage I Stage II Stage III Stage IV	12 18 33 37	(estimated at 4 years) Local control 96% Nodal control 98% Distant control 72% Overall survival-74%
MSK experience[17] (N= 74)	I 5% II 30% III 65%	Stage I Stage II Stage III Stage IV	6 16 30 47	(estimated at 3 years) Local control 91% Nodal control 93% Distant control 78% Overall survival 83%
China[18] (N=63) *presumed	I II III 100%*	Stage I Stage II Stage III Stage IV	14 29 35 22	At 3 years Local control 92% Nodal control 98% Distant control 79% Overall survival 90%
Hong Kong[19] (N= 50)	I II III 100%	Stage III Stage IV	28 72	(estimated at 2 years) Local control-96% Nodal control-n/a Distant control-94% Overall survival-92%
China[20] (N=370)	I 1% II 1% III 98%	Stage I Stage II Stage III Stage IV	 17 53 30	At 3 years Local control-95% Nodal control-97% Distant control-86% Overall survival-89%
Christie[11] (N= 128)	I 13% II 70% III 7% Other 10%	Stage I Stage II Stage III Stage IV	5 23 34 38	At 5 years Local control 52% Overall survival 60%
RMH Phase II trial (N= 41)	I 5% II 40% III 55%	Stage I Stage II Stage III Stage IV	0 12 26 62	(estimated at 2 years) Local control-88% Nodal control-88% Distant control-79% Overall survival-87%

Figures

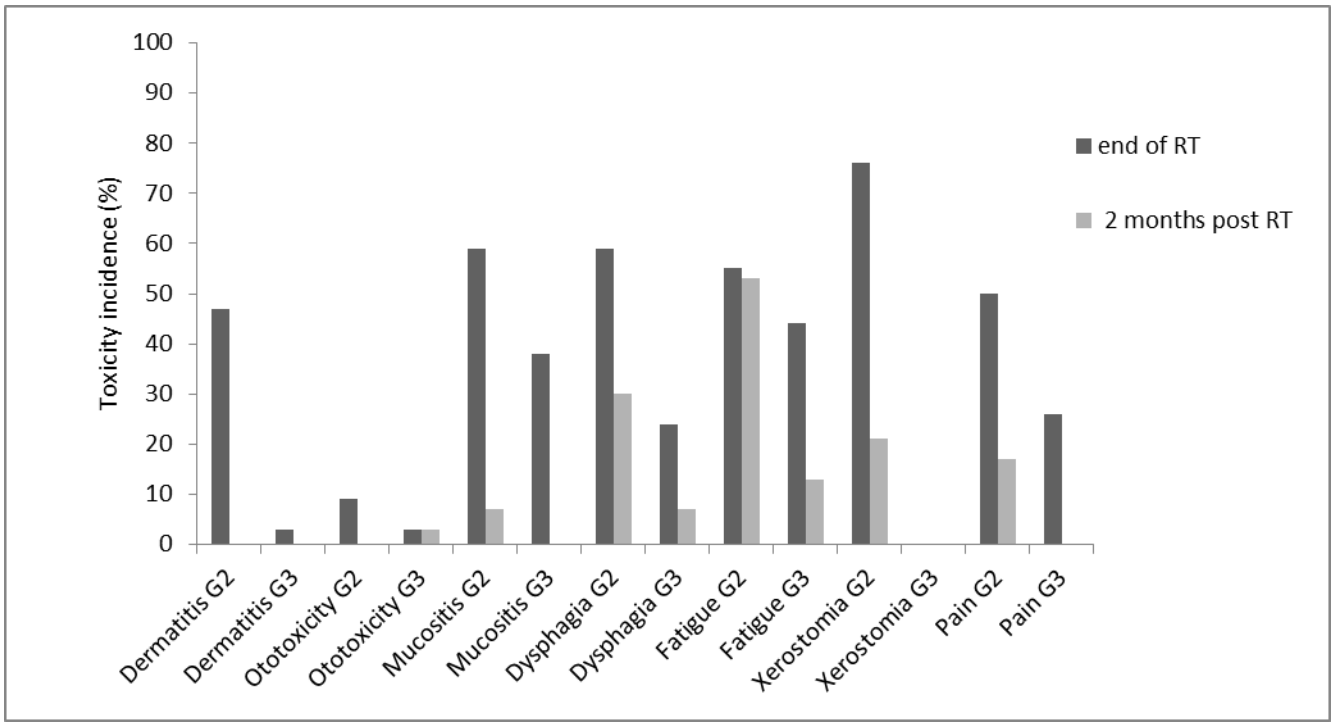


Figure 1: Incidence of acute toxicities at the end of IMRT and 2 months post IMRT, n=41.

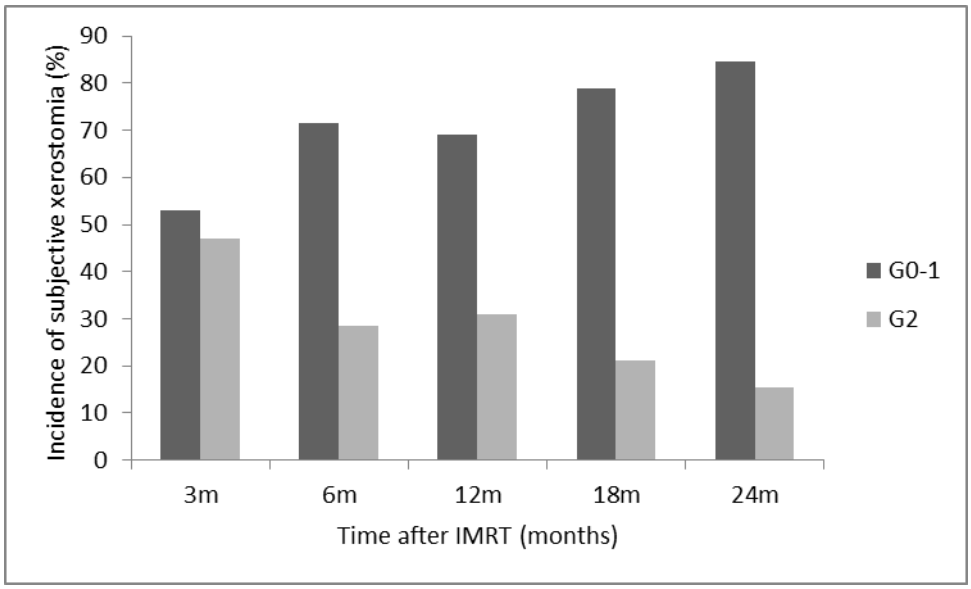
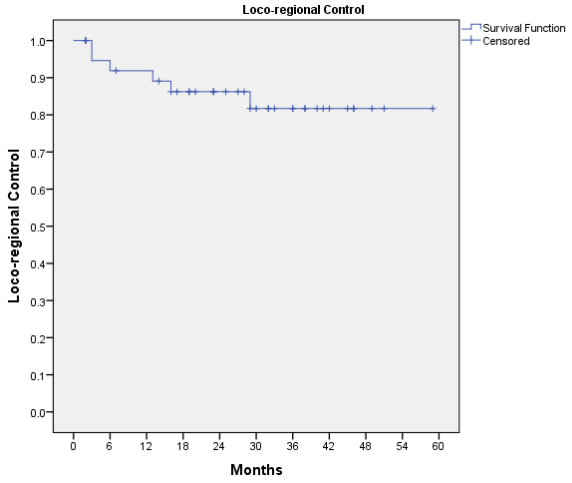
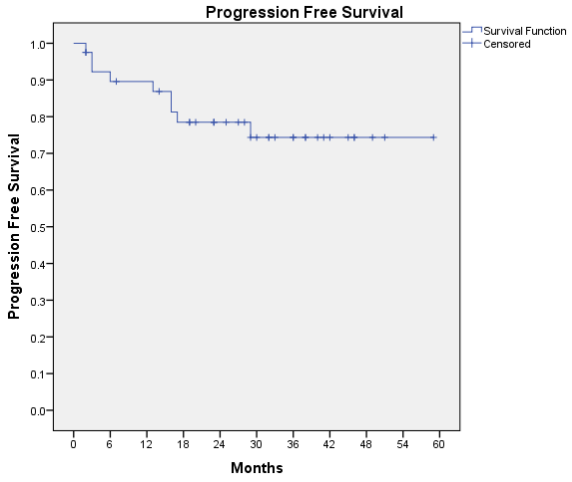


Figure 2: Incidence of subjective xerostomia (LENTSOMA) over time, low grade (G0-1) and high grade (G2).





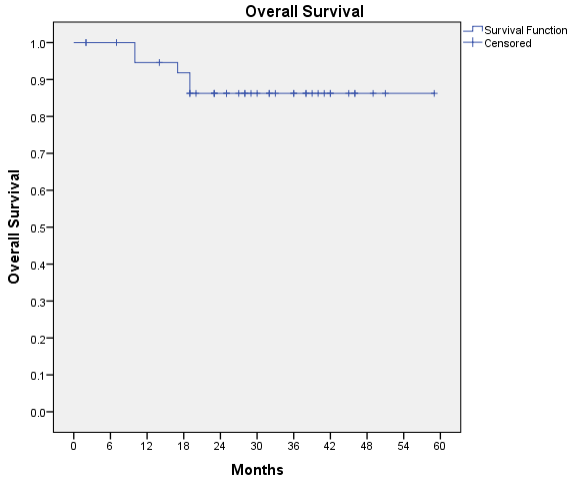


Figure 3a-c: (a) Kaplan-Meier graph of locoregional disease free survival, estimated 2 year LRDFS 86.5% (70.5-94.1), (b) Kaplan-Meier graph of progression free survival, estimated 2 year PFS 79.0% (62.4-88.9), (c)Kaplan-Meier graph of overall survival, estimated 2 year OS 86.7% (70.9-94.2)