

Organ sparing and clinical outcome with step-and-shoot IMRT for head and neck cancer: a mono-institutional experience

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Abstract

Purpose Intensity-modulated radiotherapy has been suggested as the technique of choice for locally advanced head and neck cancer patients. In the last decade, most radiotherapy departments have focused their efforts in programs to implement this technique. We report our experience for parotid gland and constrictor muscle sparing with intensity-modulated radiotherapy in head and neck cancer using a step-and-shoot technique.

Methods Thirty-four consecutive patients with squamous cell carcinoma of the nasopharynx, oropharynx and larynx treated between June 2008 and June 2011 were retrospectively evaluated. A simultaneous integrated boost was adopted to treat different volumes in 30 fractions over 6 weeks. Priority as organs at risk was given to the parotid

glands as well as the constrictor muscle of the pharynx in 53 % ($n = 18$). Dysphagia and xerostomia were evaluated according to RTOG/EORTC scale at 6, 12 and 24 months. Outcomes were analysed using Kaplan–Meier curves.

Results The median follow-up was 43 months. The 5-year overall survival was 70 %, and local control was 94 %. Grade 2 dysphagia and xerostomia at 6, 12 and 24 months were as follows: 26 % ($n = 9$), 23 % ($n = 8$), 23 % ($n = 8$) and 21 % ($n = 7$), 12 % ($n = 4$), 12 % ($n = 4$), respectively. No grade 3 or 4 toxicity was found. Ordinal logistic regression analysis demonstrated that hyposalivation was the main predictive factor for late dysphagia.

Conclusion Excellent loco-regional results were achieved with acceptable acute and late toxicities. The low rate of late dysphagia was related to parotid gland sparing; we did not observe a correlation between late dysphagia and dose to pharyngeal constrictors.

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Introduction

Surgery and radiotherapy, with or without chemotherapy, represent the standard treatment approach for most patients with head and neck cancers (HNC). Several studies have shown that conventional 3D conformational radiation therapy (3D-CRT) can significantly affect quality of life of head and neck cancer patients, causing acute and delayed side effects, such as xerostomia and dysphagia [1].

It has been also shown that, due to the possibility of producing concave dose distributions with better avoidance of dose-limiting structures, intensity-modulated radiotherapy (IMRT) reduces acute and late toxicity rates

without compromising clinical outcome [2–10]. In particular, doses to the pharyngeal constrictors and larynx have been associated with dysphagia [11, 12], while doses to the parotid glands are correlated with xerostomia [4, 13–16]. Anatomical changes of parotid glands and target volumes are independent of the immobilisation devices utilised. Nevertheless, due to these structure variations, there is a significant risk to deliver higher or lower doses compared with the planned dose. The ability to “paint” the dose with IMRT introduces the need for more precise contouring of organs at risk (OAR) and planning target volume, due to a greater risk of missing the target compared with traditional radiation therapy techniques [17–22]. To minimise the risk of xerostomia, the parotid glands have been evaluated in terms of volumes and doses changed and several trials have stated that IMRT re-planning is mandatory in selected cases. Nevertheless, few data demonstrating a survival benefit of IMRT compared with conventional radiotherapy for HNC have been reported [23, 24]. In this paper, we report our experience and results of parotid gland and constrictor muscle sparing using step-and-shoot IMRT in patients with early and loco-regionally advanced HNC.

Materials and methods

We reviewed the records of 34 patients with primary HNC, treated between June 2008 and June 2011. Of these, 12 patients (35 %) received IMRT as definitive treatment and 22 (65 %) as post-operative treatment with or without sequential and/or concurrent chemotherapy (platinum based). Patient characteristics are shown in Table 1.

Initial evaluation included clinical and laboratory examination, computed tomography (CT) and/or magnetic resonance imaging (MRI) scans of the head and neck region and endoscopy with histological confirmation. Each patient underwent a CT scan without contrast media and with 2.5 mm slice thickness using an individual head-neck mask for patient positioning.

In the radical setting, gross tumour volume (GTV), high-risk subclinical disease (clinical target volume 1, CTV1) and low-risk subclinical disease (clinical target volume 2, CTV2) were defined on CT scan after simulation procedure. PTV1 and PTV2 were generated with an isotropic expansion of 5 mm from CTV1 and CTV2, respectively. These volumes were irradiated to a total dose of 66–70, 60–63 and 54–57 Gy, respectively, with daily fractions of 2.2, 2/2.1 and 1.8/1.9.

In the post-operative setting, two volumes of interest were identified: CTV1 including the tumour bed (primary and involved nodes) and CTV2 including elective lymphatic areas. PTV1 and PTV2 were generated with an isotropic expansion of 5 mm from CTV1 and CTV2,

Table 1 Patients’ baseline characteristics and demographics ($n = 34$)

Factors	Descriptions		
Gender	Male 65	Female 35	
Age	Median 58 years	Range [23–84]	
Primary site	Nasopharynx 18%	Oropharynx 62 %	Larynx 20 %
Stage	Localised 35 %		
	Definitive IMRT ($n = 7$)		
	Definitive IMRT/Cht* ($n = 5$)		
	Locally advanced 65 %		
	Post-operative IMRT ($n = 4$)		
	Post-operative IMRT/Cht* ($n = 18$)		

* Cht Cisplatin

respectively. These volumes were irradiated to a total dose of 62–66 and 50–54 Gy, respectively, with daily fractions of 2.02/2.2 and 1.66/1.8 Gy.

OAR evaluation included the parotid glands in all patients and the constrictor muscles of the pharynx (PCs) in 18 patients (53 %). PC was outlined as a single structure for which the cranial limit was the caudal tips of the pterygoid plates and the caudal limit was the inferior border of the cricoid cartilage.

Acute and late dysphagia and xerostomia were assessed according to the RTOG/EORTC scale at 6, 12 and 24 months.

IMRT was performed with a 6 MV photon beam and step-and-shoot technique delivered with a Linac integrated MLC collimator (Primus Siemens Healthcare USA). The treatment was delivered with a 7–9 fixed field arrangement. Typical field orientations were 0°, 45°, 105°, 155°, 205°, 255°, 315° (seven field arrangement). A margin of 5–10 mm was added to the areas of interest to define the planning target volume (PTV). Treatment planning was performed on a Plato inverse treatment planning system (TPS). OAR contoured routinely, and relative dose constraints were as follows: spinal cord and brain stem with a maximum dose (D1%) of 45 and 54 Gy, respectively; larynx and parotid glands with a mean dose <50 and <26 Gy, respectively. In 18 patients, the pharyngeal constrictors were contoured, with a mean dose constraint ≤ 55 Gy. Pre-treatment verification was performed comparing measured versus TPS-calculated dose maps, with beam imaging system (Bis-2G) from Scanditronix Wellhofer. The measured distribution was compared with the calculated one by evaluating gamma criteria of 3 %/3 mm using a threshold of 10 %.

To assess side effects, patients were examined weekly during radiotherapy, and after treatment completion, they were seen every 3 months for the first year and every 4–6 months thereafter. Data charts, radiation therapy schedules and dose–volume histograms (DVH) of 34 patients with squamous cell carcinoma of the nasopharynx, oropharynx and larynx were evaluated.

Table 2 Results of acute toxicity

	Acute toxicity			
	Xerostomia		Dysphagia	
	<i>n</i>	%	<i>n</i>	%
G ₀	11	32.35	9	26.47
G ₁	8	23.53	12	35.29
G ₂	15	44.12	11	38.24

Statistical method

Ordinal logistic regression and contingency tables with Fisher's exact test were applied in order to analyse the correlation between acute/late dysphagia and xerostomia. The 5-year loco-regional control and overall survival probabilities were estimated using the Kaplan–Meier method. Time to recurrence and overall survival were calculated from the date of diagnosis.

Results

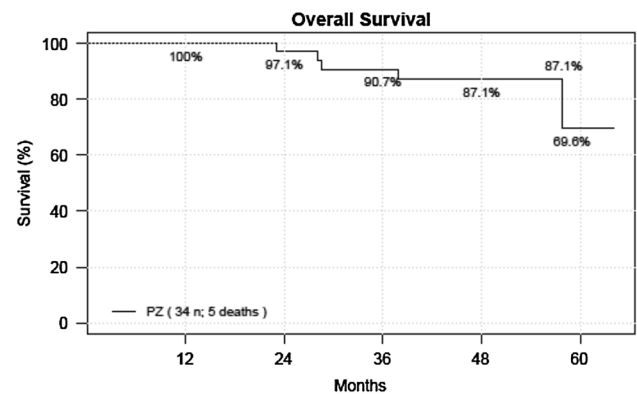
Planning end points were achieved for each study case: in all IMRT plans, the dose constraints reported above were respected according to the dose prescription to the PTVs. The mean dose of definitive and post-operative IMRT was 64.3 Gy (range, 62–66 Gy). A mean contralateral parotid gland dose lower than 26 Gy was achieved in 24 patients (70 %) and a dose ≥ 26 Gy in the remaining ten patients. The average dose to the pharyngeal constrictors was between 51.8 Gy (10 cc) and 52.86 Gy (13 cc).

The median follow-up period of the study was 43 months, with a range of 23–64 months. Acute side effects were mild, with no grade 3–4 effects registered (Table 2). Late toxicity was assessed at 6, 12 and 24 months with an actuarial incidence of G2 xerostomia and dysphagia after 2 years of 12 and 23 %, respectively.

At 24 months, late xerostomia $\geq G1$ was associated with a mean dose to the contralateral parotid glands ≥ 26 Gy ($p < 0.001$) (Table 3). Ordinal logistic regression analysis showed that G2 xerostomia increased the risk of late dysphagia $\geq G1$ at 12 months by 9.5 times (odds ratio 9.319). This effect was virtually unchanged at 24 months. The 5-year overall survival was 70 % (Fig. 1), and the local control rate was 94 %. Five patients developed distant metastasis, and two had local failure, with a median time to recurrence of 17 months. One of the patients with local recurrence was salvaged with surgery and re-irradiation, the other with exclusive irradiation with Cyberknife. Both patients are alive without evidence of disease at the last follow-up visit.

Table 3 Correlation between dose to parotid glands and xerostomia

Xerostomia (24 months)	Parotid gland dose		Total
	<26 Gray	≥ 26 Gray	
None	21	0	21
	100.00	0.00	100.00
G1	2	7	9
	22.22	77.78	100.00
G2	1	3	4
	25.00	75.00	100.00
Total	24	10	34
	70.59	29.41	100.00

**Fig. 1** Overall survival Kaplan–Meier curve

Discussion

Conventional radiation treatment reports show a high incidence of dysphagia [25, 26]. During radiation treatment, acute dysphagia begins and progressively increases: late dysphagia and aspiration are frequently reported months to years later. While acute dysphagia usually recovers rapidly after the end of treatment, late swallowing problems tend to be irreversible. IMRT can achieve an excellent dose distribution, preserving both parotid and swallowing structures with a potential improvement of quality of life. In our IMRT series, we did not observe any grade 3–4 late dysphagia, as in similar studies [4, 17, 27–29] (Table 4). Despite its limitations, our study confirms the importance of hyposalivation in determining dysphagia. Decreased saliva output causes alterations in speech and taste and difficulties with mastication and swallowing, with strong correlation with dysphagia-related quality of life [30]. Limiting mean parotid gland doses to 26–30 Gy can prevent hyposalivation [31, 32]. Several randomised studies showed that parotid sparing with IMRT reduced xerostomia and improved quality of life [4, 33, 34]. In our series, a mean parotid contralateral dose >26 Gy showed

Table 4 Toxicity comparison studies

References	Patients (n)	Fractions (n)	Fraction dose (Gy)	Total dose (Gy)	Treatment time (week)	Acute xerostomia $\geq G_2$ (%)	Late xerostomia $\geq G_2$ (%)	Acute dysphagia $\geq G_2$ (%)	Late dysphagia $\geq G_2$ (%)
Nutting et al. [4] PARSPORT	47	30	2.16	65	6	71	74	85	21
Lee [11] RTOG trial 02-25	68	33	2.12	69.96	6.5	NA	31	NA	18
Eisbruch [17] RTOG 00-22	67	30	2.2	66	6	42	16	52	20
Our study	34	30	2.2	66	6	44	12	38	24

a threefold increase in the risk of xerostomia $\geq G1$ at 24 months.

The pharyngeal constrictors are also involved in late dysphagia. Including only the lateral retropharyngeal nodes in the target and excluding the medial ones, rarely a site of metastasis, it is possible to spare a large part of the muscle [35]. A study showed that for each additional 10 Gy after 55 Gy to the constrictor muscles, the probability of dysphagia increases by 19 % [36]. In particular, the dose to the superior constrictor was reported as the most relevant for late dysphagia [37]. In our patient series treated with IMRT, we did not observe a correlation between late dysphagia and dose to the pharyngeal constrictors. This result could be due to inter-observer variability in the delineation of OAR, as suggested by the wide range of average doses recorded for the pharyngeal constrictors. However, a limit of the present analysis is the fact that the pharyngeal constrictors were defined at planning in only 53 % of patients.

Even though a comparative analysis with another conventional technique was not available at the moment of the present evaluation, the toxicity profile of our IMRT study seems to be acceptable. Nevertheless, due to the retrospective nature of the analysis, another pitfall of our study could be the absence of a baseline systematic evaluation of symptoms. Starting from this background, we are collecting data of pre-treatment symptoms prospectively and we will report a comparative analysis, comparing also toxicity with a historical population subjected to conventional 3D-CRT.

The potential advantage of IMRT in physical dose distribution, with its tight conformality due to steep gradients, could translate into a higher risk of geographical missing. In fact, due to variations in these structures, there is a significant risk of delivering higher or lower doses compared with the planned dose. Volumes and anatomical modification of the parotid glands and target were reported as independent of the type of immobilisation system adopted. Some IMRT series reported a higher incidence of marginal failure and intra-parotid recurrence [4, 38, 39], and one randomised study showed more in-field failures in the IMRT group compared with conventional radiation [36]. In our series, the two local recurrences occurred in field with no correlation with the attempt to spare the parotid glands or pharyngeal constrictors.

Although IMRT has been reported as the best choice to reduce toxicity, especially in terms of xerostomia, the findings of local control and outcome are still inconclusive. Keeping in mind that our study includes different cancer sites and has a short follow-up, our results are in line with other series in terms of overall survival and local control [1, 40].

Different primary tumour sites were found to be associated with different rates of both pre- and post-therapy

swallowing abnormalities. The main criticism of the present report is represented by the heterogeneity of the population of study in terms of site of the primary tumour affecting dose–response relationships.

Conclusions

Acceptable rates of late dysphagia and xerostomia were achieved with optimal disease control. The severity of dysphagia is probably decreased also by reducing xerostomia through parotid gland sparing. IMRT has become the standard of care in our department for delivery of RT in head and neck cancer, reducing acute and late toxicity. Further prospective studies are needed to determine the appropriate dose constraints for other anatomical structures involved in swallowing.

Conflict of interest The authors declare no conflict of interest.

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