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The Outcomes of Intensity Modulated Radiotherapy versus Conventional 2D Radiotherapy in Patients with Oropharyngeal or Hypopharyngeal Squamous Cell Carcinoma. A Case-Control Study

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Abstract

Introduction: Head and neck cancers' radiotherapy (RT) is challenging due to the irregular target volumes and the proximity of multiple organs at risk. The purpose of this study is to compare the toxicity, loco-regional control and the pattern of tumour recurrence after intensity modulated radiotherapy (IMRT) or conventional 2D radiotherapy (2D CRT) in patients with squamous cell carcinoma (SCC) oropharyngeal or hypopharyngeal cancers.

Material and method: We retrospectively compared the outcomes of SCC oropharyngeal or hypopharyngeal cases treated by IMRT or 2D CRT from 1998 to 2010 in a Canadian Academic Hospital. We matched the patients in the two groups according to primary tumour location and clinical stage. The information on treatment, toxicity and outcomes was retrieved from patients' medical records. For the patients having a recurrence after IMRT, the CT scan at relapse was fused with the planning CT. For the patients recurring after 2D CRT, we matched the CT images with the relative position of the radiotherapy fields. Statistical analysis was made using GraphPad Prism software.

Results: We included a total of 50 patients in the IMRT group and 50 in the 2D CRT group. The median age was 62 and 58 years, respectively, and the median follow-up was 18 and 22.6 months, respectively. Some of the side effects were less frequent on the IMRT group compared to the 2D CRT: xerostomia (16% vs 64%, P=0.0036), mucositis (70% vs 74% P=0.5451), weight loss (18% vs 46% P= 0.0027), radionecrosis/mandibular fracture (0 % vs 2%), fibrosis (0% vs 10%), and telangiectasia (0% vs 4%). However, acute dermatitis and late dysphagia were more frequent in the IMRT group (44% vs 28% P=0.0042; and 14% vs 2% P=0.028; respectively). The overall survival at 2 years was for 74.03% for IMRT and 60% for 2D CRT (P< 0.001) and the 5 years actuarial locoregional control was 89.54 % for IMRT group, and 62.48% for the 2DCRT

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group (P< 0.001). Three patients from the IMRT group had a local recurrence (2 in-field and 1 marginal), while in the 2D-CRT group, there were 10 patients with a local recurrence (6 in-field and 4 marginal).

Conclusion: SCC oropharyngeal and hypopharyngeal patients treated with IMRT and concurrent cisplatin had better outcomes and fewer side effects, when compared to similar cases treated with 2D CRT. The local recurrence had a similar pattern for both techniques.

Keywords: *IMRT, 2D CRT, radiotherapy, oropharyngeal cancer, outcome, recurrence*

1. Background

Intensity Modulated Radiotherapy (IMRT) was first introduced 30 years ago and is already established as the preferred technique for treating head and neck cancers (HNC).

The transition from 2D CRT to 3D CRT and then to more conformal techniques like IMRT/VMAT was made at a different pace in various regions and institutions. Higher spatial accuracy allows a better sparing of the organs at risk (OARs) allowing the decrease of the side effects. However, new technology implementation needs to be made while understanding the necessary challenges in planning, delivery, and quality assurance.

For oropharyngeal cancer patients the IMRT reduced the toxicity without worsening the clinical outcomes when compared with 2D/3DCRT, according to a review of the literature and meta-analysis by *Alterio et al* (1). For hypopharyngeal cancers, a retrospective analysis of technological improvements' clinical impact concluded that overall survival (OS), progression free survival (PFS) and freedom from local recurrence were improved with IMRT over 2D-RT and reduction in acute toxicity was observed (2).

However, there is also conflicting data in the literature. A systematic review and meta-analysis of the outcomes of IMRT vs 2D/3D CRT in HNC patients treated with curative intent was performed by Gupta et al and included 1155 patients from 7 randomized controlled trials. For the nasopharyngeal cancer patients the use of IMRT was translated into a relative reduction in the risk of loco-regional relapse and in the risk of death of 24% and 30%, respectively, compared to 2D/3D CRT. However, this benefit was not found for pharyngeal and laryngeal cancers. The evidence for IMRT use resulting in reducing moderate to severe acute and late xerostomia compared to 2D/3D-RT was considered as consistent but moderate-quality (3).

In the early days of IMRT implementation unusual side effects were seen, caused by a high dose delivered in non-target areas. It was the result of plan optimisation process in the context of delineating only the proximity OAR or a limited number of OAR (4). Additional data regarding the side effects of IMRT RT compared to 2D/3D CRT and the local recurrence patterns may lead to identifying new sensitive structures, avoid common errors and improve the clinical practice.

The primary objective of this study was to compare the early and late side effects (grade 2 or more) for IMRT and 2D CRT, respectively, in patients with oropharyngeal or hypopharyngeal cancer. Loco-regional control and patterns of recurrence analysis were secondary objectives.

2. Methods

2.1. Study design

Using a matched case-control design, we compared a cohort of patients diagnosed with oropharyngeal or hypopharyngeal squamous cell carcinoma (SCC) treated with IMRT (2004-2010) with a similar historical cohort treated in the same institution with 2D CRT(1998-2004). Matching has been done by the tumour site and stage. A review of the medical records up to 2022 has been done to assess the toxicity profile, locoregional control and the pattern of tumour recurrence.

2.2. Patients' selection

The study included patients with oropharyngeal or hypopharyngeal SCC who were treated with curative intent. We excluded the patients with carcinoma of the base of the

tongue (due to wide individual variability in target volume delineation and inaccurate assessment of the extent of recurrence on CT scan) and those with other synchronous primary tumour and/or those receiving biological therapy.

2.3. Staging, response evaluation and toxicity grading

The staging was done according to the AJCC staging manual 2010 (The 6th edition). Evaluation of the response to treatment was done using the WHO criteria. Toxicity grading was performed according to the NCIC common toxicity criteria version 4.03. Weight loss was defined as a non-voluntary decrease of at least 3 kg during radiotherapy.

For patients treated with IMRT the review of the radiotherapy plans was done by reviewing the charts on the planning system, while for patients treated with 2D CRT it was done by reviewing the patients' radiotherapy charts together with the x-ray check films. The tumour recurrence analysis was made together with a Radiologist for the conventional radiotherapy group, using CT scans/MRI.

2.4. Workflow (IMRT)

The simulation was done using a thermoplastic mask and multislice CT simulator with slice thickness from 2 to 5 mm, iv contrast and fusion with diagnostic MR.

Delineation of the target volumes and the organs at risk (OAR) was done according to the ICRU 50, 62 or 83 reports' definitions (The ICRU 83 for IMRT). In definitive radiotherapy, delineation of the gross tumour volume (GTV) was done based on imaging and clinical examination. In most cases a margin of 0.3 cm was added around the spinal cord and the brainstem to obtain planning risk volume (PRV)

The high-risk clinical target volume (CTV) included the GTV primary and nodal plus a margin of 0.7 – 1cm. In N0 lymph nodes, CTV low risk was delineated according to the DAHANCA, EORTC, GORTEC, and RTOG consensus guidelines. The planning target volume (PTV) was delineated by adding a margin of 0.3 - 0.5 cm to the corresponding CTV. The radiotherapy doses were prescribed to the PTVs. Five cases were done by forward planning (treated by step and shoot technique) but the majority of cases were done by inverse planning and treated by sliding window technique. Doses to OARs were kept within the tolerance limits according to the local protocols, based on international recommendations.

IMRT treatment delivery was done using 6MV linear accelerators by (3 – 9) angled beams using the Simultaneous Integrated Boost (SIB) technique in most cases. Concurrent weekly Cisplatin 40 mg/m2 was used in most of the patients.

At recurrence, fusion of the new CT/MRI or PET scan with the planning CT scan has been performed. The recurrence was considered as “in field” if 25-95% of its volume was located in the high dose region, “marginal” for a value of 5-25% and “out-of-field” for less than 5%.

2.5. Workflow (2D CRT)

Conventional radiotherapy had been planned using the conventional simulator and two lateral opposing fields matched with the low anterior neck field.

Treatment delivery had been performed using the cobalt unit and 6 MV linear accelerators. Patients had been treated up to 45 Gy to the lateral opposing fields to the neck then off-cord. Patients with residual lymph nodes in the posterior neck had been boosted by a 9 MeV electron beam.

Localization of the site recurrence either in the high dose region (60 Gy or more) or low dose region (< 60 Gy) or both has been done using the CT data describing the site of recurrence and its maximal 3D diameters then multiplying them to obtain the volume of recurrence and correlating that volume to the conventional 2D radiotherapy fields (on the x-ray check films) in relation to a bony landmark (e.g the hyoid bone). For example, if the majority of recurrent tumour is located above the hyoid bone it is considered in the high dose region and if it is located in the low anterior neck region it is considered in the low dose region.

3. Results

This study included 50 patients treated using 2D CRT (1998-2004) and 50 patients treated using IMRT (2004-2010). Patient details and treatment characteristics are presented in Table 1 and Table 2.

Table 1. Patients' characteristics in the two groups

	IMRT(N=50)		2D CRT (N=50)	
	value	*%*	**value**	*%*
Age (Median)	62 years		58 years	
Smoking	18	*36%*	16	*32%*
Alcohol	21	*42%*	19	*38%*
Sex				
Male	18	*36%*	27	*54%*
Female	32	*64%*	23	*46%*
Primary tumour location				
Tonsil	31	*62%*	30	*60%*
Pharingeal wall	9	*18%*	8	*16%*
Soft palate	5	*10%*	0	*0%*
Pyriform synus	4	*8%*	11	*22%*
Postrcricoid	1	*2%*	1	*2%*
T stage				
T1	12	*24%*	8	*16%*
T2	15	*30%*	13	*26%*
T3	14	*28%*	7	*14%*
T4	19	*38%*	22	*44%*
N stage				
N0	0	*0%*	4	*8%*
N1	7	*14%*	11	*22%*
N2a	6	*12%*	9	*18%*
N2b	6	*12%*	4	*8%*
N2c	5	*10%*	2	*4%*
N3a	7	*14%*	4	*8%*
N3b	19	*38%*	16	*32%*

** IMRT – Intensity Modulated Radiotherapy; 2D CRT – 2D Conformal Radiotherapy; N – Number; RT – Radiotherapy*

Table 2. Treatment details for the SCC oropharynx and hypopharynx patients in the two groups

	IMRT(N=50)		2D CRT (N=50)	
	value	*%*	**value**	*%*
RT dose (Gy)				
Median	67.5		66	
Range	60-70			
Number of fractions				
Median	30		33	
Range	30-33			
Treatment type				
Definitive RT	45	*90*	38	*76*
Adjuvant RT	5	*10*	12	*24*
Concurrent Cisplatin	38	*76*	5	*10*
PEG	40	*80*	0	*0*

** IMRT – Intensity Modulated Radiotherapy; 2D CRT – 2D Conformal Radiotherapy; N – Number; PEG – percutaneous endoscopic gastrostomy.*

3.1. Side effects

In the IMRT group there were significantly less patients developing acute (moderate) grade 2 or more ***xerostomia*** (16% vs 64%, P=0.0036) as identified during weekly clinical exams and reported according the NCIC common toxicity criteria. There was also less frequent ***weight loss*** (18% vs 46%, P=0.0027) compared to the 2DCRT group. The 8 patients who experienced xerostomia in IMRT cases were stage IVa and IVb (Table 3). Dmean for the ipsilateral parotid glands was 23.28 Gy to a volume of 21.26 cc and Dmean for the contralateral parotid gland was 19.79 Gy to a volume of 20.09 cc, respectively. The odds ratio for observed xerostomia grade 2 or more was 0.10.

In the IMRT group there were more patients reporting acute ***dermatititis*** (44% vs 28%, P=0.0042, OR 2.02) and ***dysphagia*** (grade 2 or more) (14% vs 2%, P=0.0284).

Acute ***mucositis (grade 2 or more***) was almost equally reported for IMRT and 2D CRT (70% vs 74%, P=0.5451, OR 0.61). Other acute side effects like laryngitis and otitits media were rare and the difference between the two techniques was not relevant (Figure 1).

Table 3. Anatomical site and clinical stage of patients treated with IMRT and developing acute xerostomia

Primary tumor anatomic site	T	N	Stage
Soft palate	2	2c	IVa
Tonsil	2	2b	IVb
Tonsil	2	2b	IVa
Tonsil	4	2a	IVb
Tonsil	1	2b	IVa
Tonsil	4	2b	IVb
Pyriform sinus	4	1	IVa
Pyriform sinus	4	0	IVa

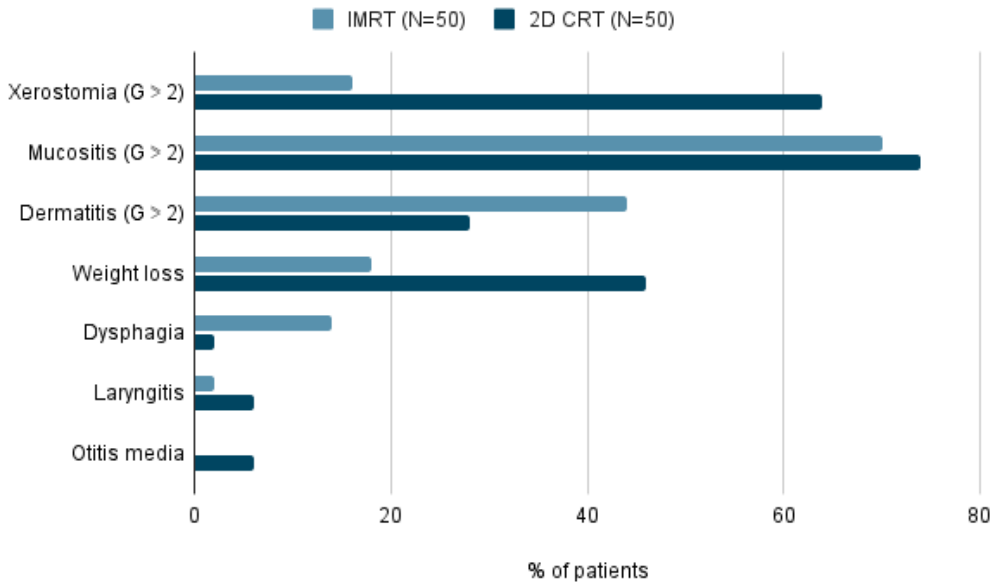

Figure 1. Radiotherapy acute side effects in oropharyngeal and hypopharingeal SCC in two matching case-control groups treated with 2D CRT or IMRT

Late ***skin*** side effects were significantly less frequent in patients treated with IMRT compared with 2D CRT; Radiation-induced ***osteonecrosis*** and ***fracture of the mandible*** were not reported for IMRT but were reported in one patient (2%) in 2D CRT (P = 0.4361).

Two patients of those who had acute dysphagia in the IMRT group subsequently developed ***esophageal stenosis*** and underwent endoscopic dilatations. ***Hypothyroidism*** was reported in 16% of patients receiving 2D CRT but thyroid function tests were not routinely requested for patients receiving IMRT. Late xerostomia was reported in 8 patients (16%) in the IMRT group versus 32 patients (64%) in the 2D CRT group.

3.2. Outcomes

The response rate assessed at 2 months after treatments' end was 93% for IMRT and 89% for 2D CRT. The median follow-up in the IMRT group was 18 months and in the 2D CRT was 22.6 months. The overall survival at 2 years was 74% for IMRT and 60% for 2D CRT (P< 0.001). The 5-year actuarial locoregional control (LRC) was 89.5% for IMRT and 62.48% for 2D CRT (P<0.001). The multivariate analysis identified IMRT as an independent factor for improving the locoregional control (P = 0.0102).

Local recurrence was seen in 3 patients (6%) in the IMRT group versus 10 patients (20%) in the 2D-CRT group (P= 0.0377, OR 0.25). In the IMRT group 2 of them recurred in the high dose PTV (in-field) and the 3rd patient's recurrence was marginal (Table 4). Two out of the 3 patients who recurred were treated by the step-and-shoot technique. In the 2D CRT group 6 patients had in-field recurrences and 4 patients had borderline recurrences**.** Patients experiencing local recurrences did not have any treatment gaps.

Distant metastases were almost equal in the two groups (6 patients treated with IMRT and in 7 patients treated with 2D CRT).

Table 4. Clinical details of the local recurrence of cases in the IMRT group

Primary tumour site	Stage	RT dose	Recurrence site	Recurrence category	Concurrent Cisplatin
soft palate	T3N2M0	70Gy/35 fr 50 Gy/25 fr	level II	in-field	yes
oropharyngeal wall	T4N2M0	70Gy/33 fr 50.4Gy/28 fr	posterior oro-pharingeal wall	in-field	yes
tonsil	T2N1M0	60Gy/25 fr 50 Gy/25 fr	tonsil peri-epiglotic space level II	marginal	no

4. Discussion

We performed a comparative analysis of the treatment outcomes for two matched case-control groups of patients diagnosed with SCC of oropharynx or hypopharynx treated either with IMRT or 2D CRT in an academic Canadian hospital.

As expected, some of the acute side effects, like ***xerostomia***, were significantly less frequent in the IMRT group compared to 2D CRT (16% vs 64%, P=0.0036). The patients

receiving IMRT and developing xerostomia had extensive primary tumour and nodal involvement, which hampered the parotid gland sparing. A mean dose equal or higher to 26 Gy to the parotid gland is correlated to a significant decrease for the stimulated salivary flow (5). The PARSPORT trial compared IMRT to 3D CRT and reported significantly lower rates of xerostomia in the IMRT group than in the conventional radiotherapy group (38% vs 74% at 12 months, P=0.0027) (6). However, except for the difference in the treatment technique, and the time of assessing it, xerostomia evaluation was more accurate in this study, salivary flow measurements being conducted. A recently published cohort study compared radiation-induced xerostomia and quality of life for HNC patients treated with either IMRT or 3D CRT. The measured salivary flow, excretion fraction on scintigraphy and xerostomia-related quality of life were all superior in the IMRT arm (7).

Mucositis had almost the same frequency in both groups (70% vs 74%, P = 0.5451, OR 0.61), despite the higher use of concurrent Cisplatin in the IMRT group. In a study published in 2005 included 450 HNC patients treated by 154 USA radiation oncologists, the rate of moderate and severe acute oral mucositis was 35% and 28%, respectively. A cumulative dose above 50 Gy, concomitant chemotherapy and nasopharyngeal/oropharyngeal location were risk factors for severe oral mucositis. The majority of patients were treated with conventional fractionation but the details on technique were not mentioned (8).

Acute Grade 2 or 3 ***dermatitis*** was significantly more frequent for the IMRT group compared to 2D CRT group (44% vs 28%, P=0.0042, OR 2.02). The explanation might be the lower skin-sparing effect due to the oblique incidence of the photon beams used for IMRT. A scoring system incorporating clinical and dosimetric factors (age, body mass index and concurrent chemotherapy status and V60 Gy delivered on 5 mm within the body contour) proved to be useful in predicting dermatitis occurrence for HNC patients treated with IMRT (9).

Weight loss of at least 3 kg was reported in 18% of patients treated with IMRT vs 46% for 2D CRT (P=0.0012). This may be due to the fact that most patients in the IMRT group had a percutaneous endoscopic gastrostomy (PEG) feeding tube placed, allowing them to have an adequate caloric intake during treatment. Predictive factors for weight loss during HNC RT were analyzed in many studies. In a group of 87 patients treated with 3D CRT 48.7% had severe weight loss (>5% of the body mass), which was more frequent at higher doses and in younger patients. Advanced tumour stage and combined treatment modality (surgery, RT and chemotherapy) were risk factors for weight loss, but body mass index without the assessment of body composition was not a reliable factor (10). Data from a prospective cohort of HNC patients treated with either 3D CRT or IMRT showed that the risk of losing more of 10% of body weight was higher for radical RT compared to adjuvant RT and for 3D CRT compared with IMRT. The maximum weight loss was on the third and fourth week of treatment and 40% of patients had a weight gain during the first week (11).

IMRT has a steep dose gradient which allows dose escalation to target volumes, dose reduction to the organs at risk and therapeutic ratio improvement. A dose of 67.5 Gy/30 fractions in IMRT group is biologically as effective as 70 Gy/35, significantly higher than 66 Gy/33 fractions used in the 2D CRT. Dose per fraction was higher for some volumes in the IMRT group, which increase the risk of late side effects.

Except for dysphagia, caused by oesophageal stricture in two patients, we did not observe an increase of the ***late toxicity*** in the IMRT group. In our study xerostomia was reported in 16% in the IMRT group vs 64% of patients in the 2 DCRT group. The difference in percentages of xerostomia is probably due to the fact that IMRT allowed rapid fall of the dose beyond the target volume/s and hence

it led to parotid sparing. On the other hand, the use 2D radiotherapy included larger volumes of the normal tissues including the parotid gland which led to more early and the late side effects especially xerostomia. Our results are in line with those reported by a systematic review on treatment outcomes and toxicity after RT for HNC, which identified late xerostomia as significantly more frequent in patients treated with 2D or 3D CRT (12).

An interesting evaluation of dose-volume and dose-length parameters in HNC patients treated with 3D CRT or IMRT showed that V54, V60, and lengths receiving circumferential disease higher than 50 Gy and 54 Gy at cervical oesophageal level were significantly higher for patients receiving IMRT compared to 3D CRT. At minimum 4 years post treatment 30% of patients in the IMRT group and 15% of patients in the 3D CRT group had documented symptomatic oesophageal strictures (13). These findings underline the importance of delineating and sparing anatomical structures formed by late-responding normal tissues and follow-up patients on long term.

In our study, the 5-year actuarial ***LRC*** was significantly longer in the IMRT group compared to the 2D CRT group (89.54% vs 62.48%, P<0.0001) but the difference might be due to other factors except for the radiotherapy technique. Concurrent cisplatin was received by most of the patients treated with IMRT and most probably contributed to the better outcomes. However, the IMRT technique was an independent factor for improving the locoregional control. Similarly, the systematic review by *Koulolias et al* reported 83.6% LRC for IMRT and 74.4% for 2D and 3D CRT at 3 years (P = 0.025) (12).

We analyzed the spatial location of the local recurrence in relation with the treatment fields and observed that in the 2D CRT group, 6 patients had in-field local recurrence and 4 had a marginal recurrence. Since the weight loss was reported in almost half of the 2D CRT patients, there is a higher risk of intrafractional motion within the immobilization mask or geometrical target displacement, leading to a suboptimal coverage.

In the IMRT group 3 patients had a local recurrence. The two patients having in-field recurrence had initial extensive stage, and the one having marginal recurrence did not receive concurrent chemotherapy.

IMRT implementation made possible the OARs sparing, which raised concerns about increasing the risk of regional recurrence due to exclusion of some volumes which could harbour subclinical disease. Except for isolated reports, most of the studies did not confirm this hypothesis. Reporting the relapse pattern made possible creating and updating contouring guidelines for the HN cancers. *Dawson et al* reported recurrence patterns after parotid sparing RT in a group of patients treated with 3D CRT or IMRT. There were no failures in the tissue adjacent to the spared parotid gland, but four patients developed in-field recurrences in the jugulodigastric nodes with superior extensions in the ipsilateral neck (14). After that, consensus guidelines have been published suggesting the superior limit of level 2 nodes to be at the caudal edge of the transverse process of C1 (15).

Chao *et al* reported a 2-year actuarial locoregional control rate of 85% and an ultimate locoregional control rate after surgical salvage of 89%. In this study, there was only one marginal recurrence, located in the region adjacent to the spared parotid gland. This was in a patient with a T3N0 piriform fossa tumour treated post-operatively where recurrence was in the level II nodal region adjacent to the spared parotid gland. Of the 11 in-field recurrences, 9 were within the high-dose CTV and 2 within the low-dose CTV *(16).*

The limitations of our study come from the relatively low number of cases, limited follow-up, and the incomplete information inherent in retrospective studies. Despite our efforts to match patients on primary tumour site and staging, there are some differences between the two groups. There were also some differences in the individual percentages of T or N stage, even the patients were matched

on combined TNM staging the percentage of surgical patients was higher in the 2D CRT group, so the treatment response, for example, could not have been evaluated in those patients. Concurrent chemotherapy was given to the majority of IMRT cases, which would be expected to influence both the treatment toxicity and outcomes. The outcomes were indeed better, but the toxicity was not higher in this group, which shows that the relative reduction of the toxicity by IMRT compared to 2D CRT counterbalanced the additional increase of toxicity caused by the use of the chemotherapy.

However, to the best of our knowledge this is the first case-control study comparing 2D-CRT and IMRT for oropharynx and hypopharynx SCC. Our results illustrate the necessity of delineating the skin and cervical oesophagus as organs at risk for the IMRT treatments in order to decrease the risk of acute and late toxicity. Closing the care gap in the low- and middle-income countries may imply an accelerated transition from 2D to IMRT, situation in which our results might be helpful, as transition experience. Information on the site of relapse and the patients developing xerostomia, especially for the IMRT cases, can help clinicians estimate the risk on similar cases.

5. Conclusion

The use of concomitant radiochemotherapy delivered by IMRT decreased the toxicity, except for acute dermatitis and late dysphagia, improved the locoregional control and overall survival in patients with oropharyngeal and hypopharyngeal SCC, when compared with patients treated with 2D CRT. The recurrence pattern was similar for IMRT and 2D RT.

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