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Predictive Factors Related to Salvage External Beam Re-irradiation for Recurrent Head and Neck Squamous Cell Carcinoma after Primary Radical Therapy

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ABSTRACT

Background: Recurrent or second-primary tumor in head and neck cancer (re-HNC) is a challenge. Curative approaches include definitive new course of RT (re-RT) combined to surgery and/or chemotherapy.
Methods: We evaluated the data from 36 patients presenting re-HNC who were treated between 2007 and 2011.
Results: Twenty two (61.1%) patients had surgery and re-RT using IMRT. The median first radiation dose and interval between re-RT and the initial RT course were 60.0 Gy and 28 months. The median follow-up was 24 months. The 2- and 5-year actuarial OS, PFS and LC rates were 58.6%, 83.8%, 75.0%, 24.4%, 25.9% and 13.5%, respectively. On univariate analysis disease free interval > 24 months and free surgical margins, p=0.005 and p=0.012, where related to LC. Free surgical margin and re-RT with concurrent CHT were related to PFS, p=0.029 and p=0.001, respectively. IMRT when compared to other techniques showed LC and PFS advantages, p= 0.047 and p=0.050, respectively. Multimodality treatment (p=0.027) and free surgical margin (p=0.016) were related to improved OS.
Cox regression multivariate analysis confirmed that patients who underwent re-RT with techniques other than IMRT, HR=8.68 (p= 0.003, 95% CI: 0.029 – 0.491) and recurrence free interval < 24 months, HR=6.71 (p= 0.010, 95% CI: 0.039 – 0.637) had an inferior PFS. Gross tumor after or absence of surgery were related to worse LC rates, HR=4.18 (p= 0.041, 95% CI: 0.040 – 0.934).Severe late complications (Grade ≥ 3) occurred in 14 (38.8%) patients.
Conclusion: Re-RT should be offered for patients who are not suitable for surgery or for those with marginal resections, with a clear understanding that severe toxicity is associated and survival is poor.
KEYWORDS: head neck cancer, radiotherapy, re-irradiation, salvage

INTRODUCTION

Loco-regional failures, recurrence or second primary after curative radiotherapy (RT) alone or in combination with surgery and/or chemotherapy (CHT) is a significant problem in head and neck cancer (HNC) and represent a challenge. Re-irradiation (re-RT) is generally not considered the first line approach for managing recurrent or second primary (re-HNC) (1), but the intimate anatomic relation between disease and critical structures often makes surgical re-resection impossible or inadequate, with complications unacceptable to the patient, making the re-HNC a very poor prognosis disease. In this view, salvage therapy in re-HNC is a controversy issue and the best combination approach is still to be defined.

Historically, complete surgical resection, when feasible, was the only curative option and in selected cases, and indeed, surgery alone may constitute an effective salvage treatment, but the initial treatment course substantially reduces the flexibility and intensity of re-treatment. The prognosis of patients with re-HNC is grim if the tumor is left untreated, with a median survival of only 5 months (2-4). CHT alone in this setting is associated with a median survival of 5–6 months, with no chance of long-term control, despite new drugs available (5,6).Potentially curative approaches for re-HNC include definitive surgery with or without adjuvant re-RT. It seems that maximum debulking surgery combined to re-RT can lead to a better local control (LC) when compared to surgery alone (2). Conversely, a new second course of RT for recurrent disease is always a problem and of limited feasibility because of the difficulty to spare adjacent normal tissues, resulting in undesirable late effects especially on the salivary glands, mandible, and muscles of mastication.

Two different modalities of RT can be used in the setting of re-RT: the use of intra-operative interstitial implantation that is suited to deliver a high dose to a limited volume, called brachytherapy or external beam RT, delivered using either tridimensional conformal (3D-CRT) or intensity-modulated RT (IMRT). The last one allows for dose-

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escalation to a wider volume, while minimizing normal tissue toxicity, despite the fact that there is no consensus regarding the treatment targets in re-RT (7, 8). In addition, many reports have also suggested that re-RT concomitantly with CHT is feasible in this setting and may achieve long-term disease control in some patients, at the expense of a substantial rate of late toxicities (8-13).

METHODS

Patients

From 2006 to 2011, 52 patients with a history of prior head and neck RT were referred to the Radiation Oncology Department, Hospital A. C. Camargo, São Paulo, Brazil for a second new course of RT. Of those, 6 were excluded from the analysis because of histological type different of SCC and 10 due the use of high dose rate brachytherapy for re-RT. The data from the charts of the remaining 36 patients, who were treated with curative intent, having re-RT with external beam as part of their salvage treatment, was subject of this analysis. The study was performed under an Institutional Review Board-approved retrospective data analysis. Clinical characteristics of patients and tumor are shown in table 1.

Table 1- Patients charactheristics

variable		N	%
Age	> 60	18	50.0
	< 60	18	50.0
gender	male	24	66.7
	female	12	33.3
Tumor stage*	0	6	16.7
	1	4	11.1
	2	16	44.4
	3	6	16.7
	9	4	11.1
Node stage*	0	12	33.3
	1	2	5.6
	2	16	44.4
	3	6	16.7
RT Technique*	2d	20	55 6
	3d	16	44.4
rTumor stage**	0	16	44.4
	2	12	33.3
	3	4	11.1
	4	4	11.1
rNode satge**	0	18	50.0
	1	6	16.7
	2	10	27.8
	3	2	5.6
Surgery	No	14	38.9
	Yes	22	61.1
Re-RT technique**	IMRT	22	61.1
	2D	2	5.6
	3D	12	33.3
Induction CHT	Yes	25	69.4
	no	11	30.6
Re-RT+ CHT	Yes	24	66.7
	No	12	33.3

Evaluation

All patients were initially evaluated by a multimodality treatment team, comprising an otolaryngologist or head and neck surgeon, medical oncologist, and radiation oncologist. A detailed physical examination, including flexible nasopharyngolaryngoscopy, was performed in all patients. All patients underwent neck computed tomography (CT), magnetic resonance imaging (MR), or both. Positron emission tomography (PET) or PET-CT was performed in 17 (45.9%) patients and histological confirmation of malignancy was required before initiating the re-treatment, for all patients who were not candidates or who refused a surgical resection

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Treatment

All patients were first considered for primary surgical management, if resectable. Eleven (30.5%) patients were not candidates for surgical procedure due to extent of disease, whereas three (8.3%) others chose not to undergo surgery. The use of induction chemotherapy before re-RT was observed in 11 (30.6%) patients. In general, induction therapy was considered for patients with T3-4 tumors or N2-3 lymph node disease. Induction CHT followed by re-RT and concurrent CHT was indicated in 5 (13.9%) patients. Concurrent CHT only was given in 24 (66.7%) patients, typically with a platinum-based regimen. In a first moment patients were strongly urged to undergo prophylactic percutaneous endoscopic gastrostomy (PEG) placement before starting treatment, procedure that was abandoned later.

Re-RT was delivered using IMRT for 22 (61.1%) patients. Twelve (33.3%) patients had 3D-CRT and only 2 (5.6%) patients had conventional technique re-RT. Patients were immobilized using individual devices and were first imaged under fluoroscopy to ensure accurate isocenter placement, then simulated with the mask using tomography and or magnetic resonance imaging. The Eclipse software (*Varian Medical Systems, Palo Alto, Ca, USA*) was used for all patients. The clinical target volume (CTV) included areas of macroscopic disease plus microscopic disease margin in all patients. In general, the CTV margin was 0.5 to 1.0 cm, and the planning target volume (PTV) margin was 0.5 cm. Fourteen (38.9%) patients had elective lymph node irradiation, although 10 (27.8%) patients were treated for neck-only recurrences.

The primary avoidance structures were the spinal cord and brain steam. The goals of inverse planning were to ensure homogenous PTV coverage and limit the additional spinal cord dose or brain steam dose up to 18-20 Gy, despite the dose received in the first RT course.

Statistical methods

The follow-up was measured from the first day of re-RT to the day of death or the last clinic visit before analysis. Actuarial estimates for local and regional progression-free survival (PFS), local control (LC) and overall survival (OS) were calculated using Kaplan-Meier estimates. Breslow's test was used to compare differences is survival estimates because it is more powerful than the log-rank test when the hazard functions are not parallel and it gives more weight to early failures. Cox proportional hazard model was used to examine the effect of the time period between the first and the second radiation courses on survival. All significant tests were two-sided, and statistical significance was accepted for a calculated p value of <0.05.

Toxicity

Acute and late toxicities were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) and determined through retrospective chart review. Adverse events graded up to 2 were considered minor and graded 3 to 5 considered as severe. Minor complications were defined as those managed with conservative, outpatient measures such as wound dressings or medication. Major complications were those that required hospital admission, in-hospital intervention (e.g.: gastrostomy feeding-tube placement, tracheostomy, laser therapeutic interventions) and those that resulted in substantial morbidity.

Acute toxicity was defined as that occurring within 90 days of the completion of treatment. Complications that occurred during treatment and that persisted or were observed after 90 days were considered late toxicity. The acute and late loco-regional toxicities related to the treatment are listed in table 2.

Table 2 – Acute and late toxicity

	Acute		Late	
Grade	(N)	%	(N)	%
0	6	16.7	9	25.0
1	6	16.7	5	13.9
2	14	38.9	8	22.2
3	10	27.8	14	38.9
Total	36	100	36	100

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RESULTS

Twenty two (61.1%) patients had surgery and re-RT, of these 3 (8.3%) had free surgical margins, but with adverse features (extensive lymphovascular, soft tissue or extra capsular tumor invasion), 6 (16.7%) had close margins, defined as tumor with in a distance ranging from 1 to 5 mm form de inked margin and 13 (36.1%) had positive margins (9 microscopic residual tumor less than 1 mm from the inked margin and 4 gross residual disease) resections.

The median first radiation dose and interval between the initial and second treatment course were 60.0 Gy (range, 45-72 Gy) and 28 (range, 9-146) months. All, but 3 patients, who had hiperfractionated re-RT, were treated with conventional fractionated radiation at the time of re-RT. The median cumulative delivered dose in both RT courses and re-RT dose were 115.7 (range,90-140) Gy and 57.5 Gy (range, 30-70.4 Gy) as shown in table 3.Six (16.7%) patients received less than 50 Gy in the re-RT course because of acute toxicity or total radiation dose given in the first treatment. Twenty patients received between 50–59 Gy and 10 (27.8%) received more than 60 Gy in the re-RT. The median overall treatment time was 31 (range, 22-46) days. Twenty four patients (66.7%) had platin-based concurrent CHT.

At a median follow-up of 24 months (range, 9-60) 17 (47.3%) patients are alive, of whom 12 (33.3%) are disease free. Nineteen (52.7%) patients had died, 8 (22.2%) due local disease progression, 7 (19.4%) of distant metastasis and 4 (11.1%) due other causes. The 2- and 5-year actuarial OS rates were 58.6% and 24.4%, respectively (Figure 1). The 2- and 5- year actuarial PFS and LC rates were 83.8%, 75.0%, 25.9% and 13.5%, respectively (Figures 2 and 3). We evaluated the association between LC and re-RT dosage, as well as the presence of associated CHT. The median dose among patients who had local failure was 55 (range, 40-66) Gy, which was not different from the median dose of 58 Gy for patients who were disease free, p=0.518.

On univariate analysis factors related to a better LC were disease free interval > 24 months and free surgical margins, p=0.005 and p=0.012, respectively. Free surgical margin and re-RT with concurrent CHT were related to PFS, p=0.029 and p=0.001, respectively. IMRT when compared to other techniques showed LC and PFS advantages, p= 0.047 and p=0.050, respectively. Table 4.Presence of multimodality treatment (p=0.027) and free surgical margin (p=0.016) were also related to improved OS. When we compared patients with gross residual tumor or who did not have surgery to those patients with free surgical margins, there was also an OS advantage (p=0.002) favoring the last ones. Table 5.Cox regression multivariate analysis confirmed that patients who underwent re-RT with techniques other than IMRT, HR=8.68 (p= 0.003, 95% CI: 0.029 – 0.491) and recurrence free interval < 24 months, HR=6.71 (p= 0.010, 95% CI: 0.039 – 0.637) had an inferior PFS. Figures 4 and 5. Gross tumor after or absence of surgery was related to worse LC, HR=4.18 (p= 0.041, 95% CI: 0.040 – 0.934). Figure 6.

Five (13.8%) patients had distant metastases. Two of them had both local recurrence and distant failure. The sites of distant metastases included lung (2 patients), brain (2 patients) and bone (1 patient). Severe late complications (Grade ≥ 3) occurred in 14 (38.8%) patients. Three (8.3%) had pharyngeal stenosis requiring repeated dilatations, 4 (11.1%) with severe neck fibrosis and 7 (19.4%) patients were tracheotomy-dependent as a result of therapy. We observed no carotid artery blowout.
There were no statistically significant associations between incidence of late complications and the radiation doses or presence of any CHT schedule combined to re-RT.

Table 3 – Irradiation Doses

	Fisrt RT (Gy)	Re-irradiation (Gy)	Total Nominal Dose (Gy)
Mean	58.7	55.2	113.9
Median	60.0	55.5	114.5
Minimum	45.0	30.0	90.0
Maximum	72.0	70.4	142.0

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Table 4 – Univariate analisys for LC and PFS

			LC			PFS		
Variable		N	Censo -red	% LC	p	Censo -red	%	p
Gender	Male Female	24 12	9 4	62.5 66.7	0.486	8 7	66.7 41.7	0.477
Age (years)	≤ 60 > 60	18 18	8 5	55.6 72.2	0.346	8 7	55.6 61.1	0.751
rTumor Stage	0 1 2 3 4	6 4 16 6 4	3 2 4 3 1	50.0 50.0 75.0 50.0 75.0	0.065	2 1 9 1 2	66.7 75.0 43.8 83.3 50.0	0.095
rNode Stage	0 1 2 3	12 2 16 6	4 0 7 2	66.7 100.0 56.3 66.7	0436	7 0 7 1	41.7 100.0 56.0 83.0	0.400
rClinical Stage	1 2 3 4	4 7 20 4	2 1 9 1	50.0 85.7 55.0 80.0	0.491	1 4 9 1	75.0 42.9 55.0 80.0	0.917
Re-RT + Induction CHT	Yes No	25 11	8 5	68.0 54.5	0533	10 5	60.0 54.5	0.693
Re-RT + CHT	Yes No	28 8	8 5	60.7 50.0	0.181	7 6	75.0 25.0	0.001
re-RT + any CHT schedule	Yes No	32 4	10 3	68.8 25.0	0.069	10 3	68.8 25.0	0.069
Re-RT + surgery	Yes No	22 14	8 5	63.6 64.3	0.608	8 5	63.6 64.3	0.608
Re-RT and Surgical Margin	Free < 1 mm Gross No surg.	9 9 4 14	2 3 3 5	77.8 66.7 25.0 64.3	0.352	0 2 3 10	100.0 77.8 25.0 28.6	0.029
Re-RT and Free Surgical Margin	Yes No	18 18	2 13	88.9 27.8	0.005	5 8	72.2 55.6	0.613
r Tumor Clinical Stage	T1-2 T3-4	26 10	9 4	65.4 60.0	0.483	12 3	53.8 70.0	0.719
rNode Clinical Stage	N0-1 N2-3	30 6	11 2	63.3 66.6	0.709	14 1	53.3 83.3	0.361
Re-RT technique	IMRT Other	22 14	4 9	81.8 35.7	0.047	5 10	77.3 28.5	0.050
Cumulati ve dose (Gy)	≤ 160 > 160	22 14	8 5	63.7 64.3	0.608	7 8	68.2 42.9	0.782
Re- RT dose (Gy)	≤ 55 > 55	18 18	6 7	66.7 61.1	0.550	7 8	61.1 55.6	0.733

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Elective node re-RT	No Yes	22 14	8 5	63.6 64.3	0.456	11 4	50.0 71.4	0.651
Neck only Re-RT	No Yes	10 26	3 10	70.0 61.5	0.718	6 9	40.0 65.4	0.322
Multimodality treatment	Yes No	17 19	5 8	70.6 57.9	0.627	5 10	70.6 47.4	0.566
Disease Free Interval (months)	≤ 36 > 36	19 17	7 6	63.2 64.7	0.100	8 7	57.9 58.8	0.131
Disease Free Interval (months)	≤ 24 > 24	22 14	7 6	68.2 57.1	0.012	5 10	64.3 54.5	0.363
Disease Free Interval (months)	≤ 12 > 12	2 34	0 13	100.0 61.8	0.254	0 15	100.0 55.9	0.201

Table 5 - Univariate analisys for OS

Variable		N	Censo-red	% LC	p
Gender	Male Female	24 12	11 8	54.2 33.3	0.626
Age (years)	≤ 60 > 60	18 18	10 9	44.4 50.0	0.567
rTumor Stage	0 1 2 3 4	6 4 16 6 4	4 1 9 3 2	33.3 75.0 43.8 50.0 50.0	0.350
rNode Stage	0 1 2 3	12 2 16 6	7 0 9 3	41.7 100.0 43.8 50.0	0.474
rClinical Stage	1 2 3 4	4 7 20 4	2 4 12 1	50.0 42.9 40.0 80.0	0.856
Re-RT + Induction CHT	Yes No	25 11	13 6	48.0 45.5	0.908
Re-RT + CHT	Yes No	28 8	15 4	46.4 50.0	0.341
re-RT + any CHT schedule	Yes No	32 4	16 3	50.0 25.0	0.081
Re-RT + surgery	Yes No	22 14	11 8	50.0 42.9	0.747
Re-RT and Surgical Margin	Free < 1 mm Gross No surg.	9 9 4 14	0 4 3 12	100.0 55.6 25.0 14.3	0.016

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Re-RT and Free Surgical Margin	Yes No	18 18	4 15	77.8 16.7	0.002
r Tumor Clinical Stage	T1-2 T3-4	26 10	14 5	46.2 50.0	0.702
rNode Clinical Stage	N0-1 N2-3	30 6	16 3	46.7 50.0	0.955
Re-RT technique	IMRT Other	22 14	10 9	54.5 35.7	0.091
Cumulative dose (Gy)	≤ 160 > 160	22 14	11 8	50.0 42.9	0.747
Re- RT dose (Gy)	≤ 55 > 55	18 18	10 9	44.4 50.0	0.738
Elective node re-RT	No Yes	22 14	15 4	31.8 71.4	0.363
Neck only Re-RT	No Yes	10 26	12 7	53.8 30.0	0.148
Multimodality treatment	Yes No	17 19	3 16	82.3 15.7	0.027
Disease Free Interval (months)	≤ 36 > 36	19 17	10 9	47.4 47.1	0.258
Disease Free Interval (months)	≤ 24 > 24	22 14	12 7	45.5 50.0	0.423
Disease Free Interval (months)	≤ 12 > 12	2 34	2 17	0.0 50.0	0.401

Figure 1-

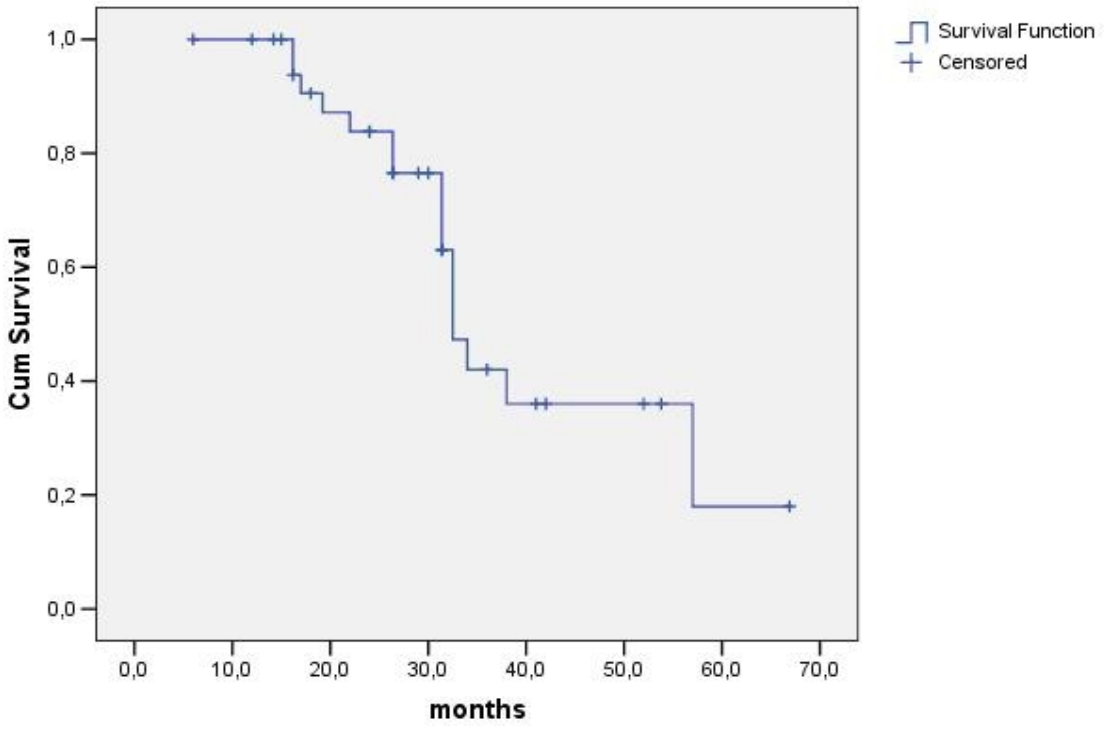

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Figure 2-

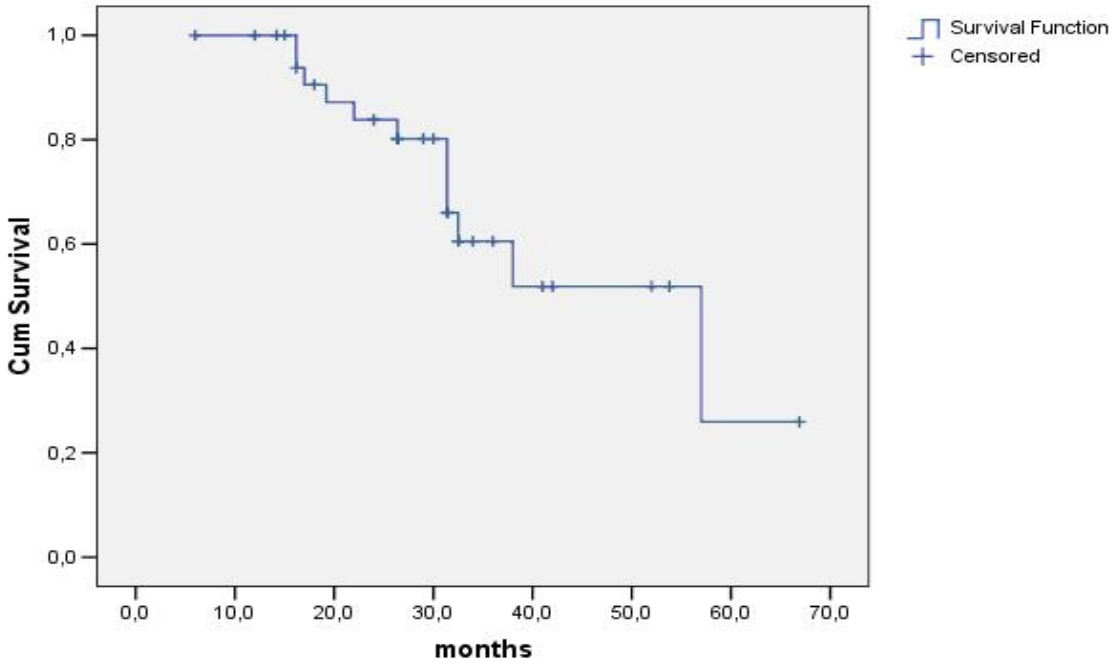

Figure 3-

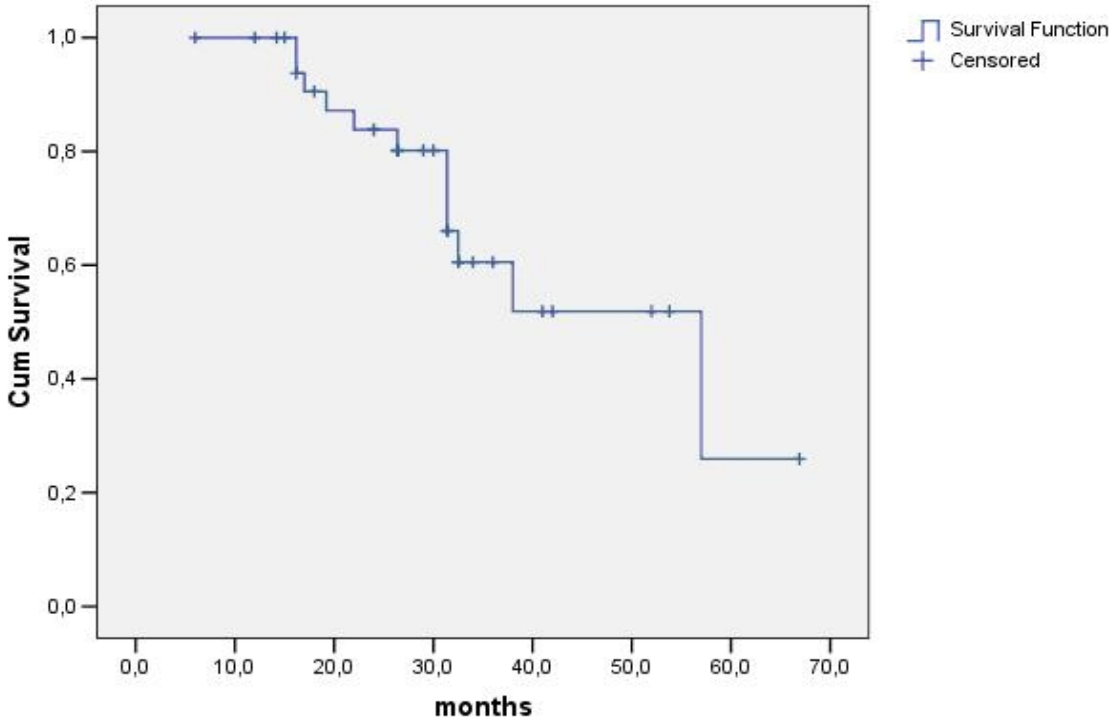

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Figure 4-

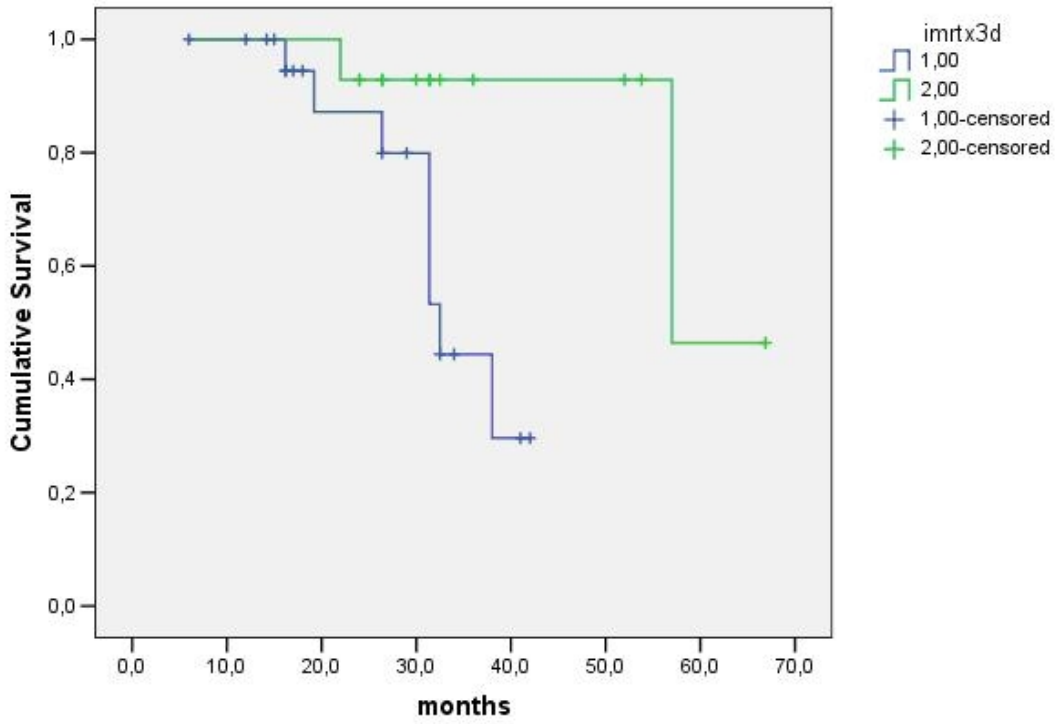

Figure 5-

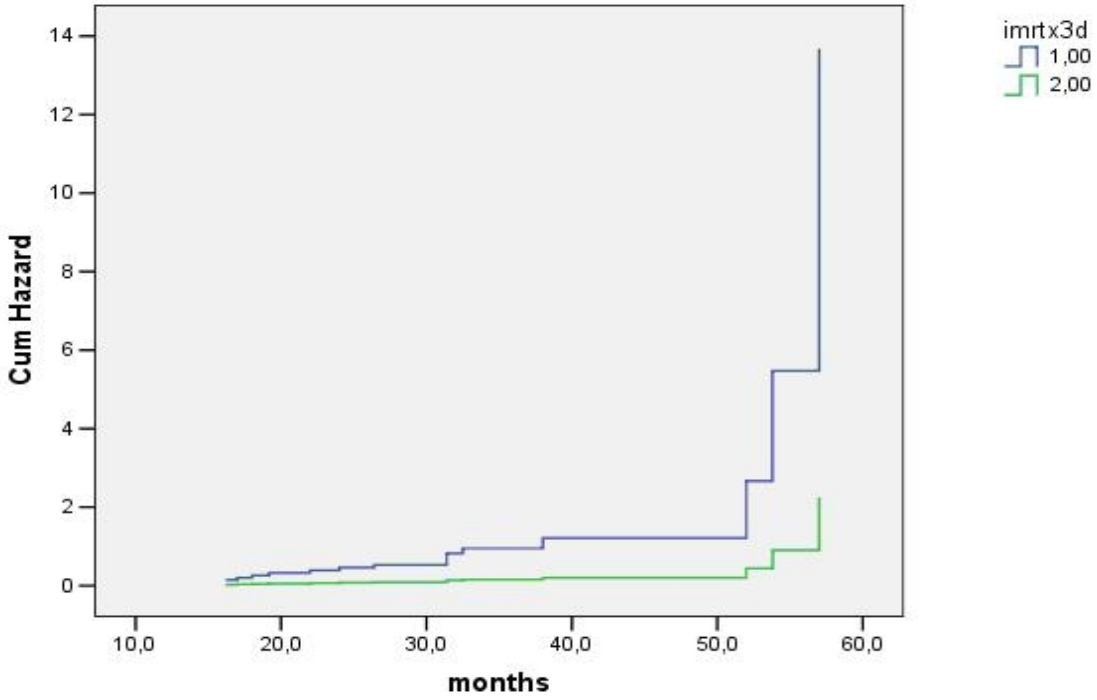

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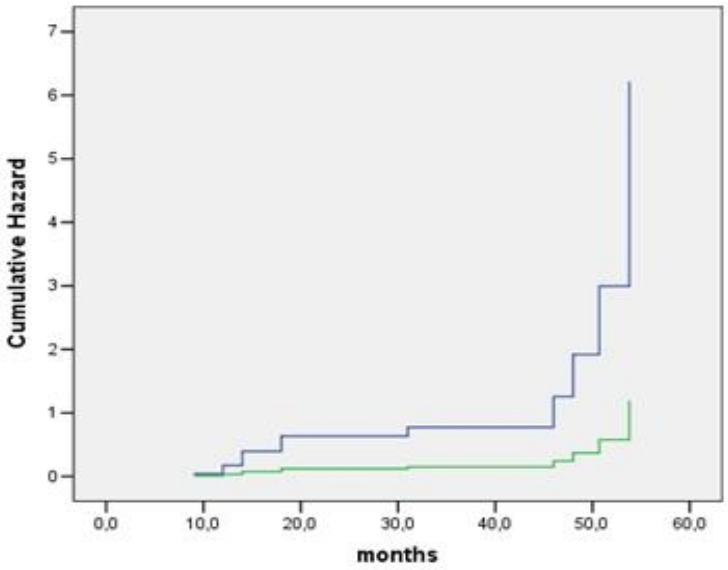
Figure 6-



Number at risk	No	18	17	8	7	5	1	0
	Yes	18	17	8	6	1	0	0

DISCUSSIONS

The management of re-HNC is one of the most challenging procedures in oncology. Surgical re-resection is often impossible or inadequate due the intimate anatomic relation between disease and critical structures, with complications unacceptable to the patient, making the recurrent or second primary HNC a very poor prognosis disease. CHT in the setting of non-resectable local or regional recurrence is associated with a median survival of 5–6 months with no chance of long-term control, despite new drugs available (5,6) and re-RT is generally not considered as the first line approach for managing re-HNC (1).

The literature is scarce in re-RT series. It is very difficult to compare results across different re-RT series because outcomes vary substantially based upon patient selection, treatment technique, and the differentiation between curative or palliative intent of the treatment. We have already published data regarding the use of high dose rate brachytherapy as salvage treatment (14) and in this series we evaluated patients who had only external beam re-RT alone or as part of their salvage treatment. The strength of our series is that it is relatively recent, involves operable and inoperable patients who had re-RT only for non metastatic SCC of HNC, treated with curative intent. The 5-year survival rates in published where re-RT was used with curative intent varies from 13% in unselected series to 93% in highly selected series (15,16). We observed in our series a projected 5-year OS and PFS of 24.4% and 25.9%, respectively.

Results of re-RT based on conventional techniques are scarce in the literature and disappointing. Conversely to our results where the 2- and 5-year actuarial OS were 58.6% and 24.4%, Stevens et al when following 100 patients managed with re-RT without IMRT found 27% and 17% actuarial OS rates. (17).The use of IMRT in recent years resulted in improvements in dose conformability around the targets compared with the 3D-CRT techniques used in the earlier years, allowing re-RT with higher doses and sparing normal surrounding tissues, previously irradiated or not. Due the precise and conformal characteristics of IMRT it has gained acceptance as a potential management alternative in patients with not suitable for surgically complete or partial resection, recurrent disease or with unfavorable pathologic findings following surgery for recurrent disease. In our series, the use of IMRT for re-RT was associate with improved LC and PFS, p= 0.047 and p=0.050, respectively. Cox regression

multivariate analysis confirmed that patients who underwent re-RT with techniques other than IMRT had an inferior PFS, with a relative risk of 8.68 times higher.

We observed a 5-year LC rate of 13.5% in our series, but in a recent review, Kasperts et al (18) reported a 2-year LC for patients who had re-RT ranging from 20% to 61%. Kao et al (19) in a review of selected series observed that 5-year OS rate was 14.6%, related primarily to the re-RT dose, conversely to our results, where the 5-year actuarial OS was 24.4% and the median dose among patients who had local failure was not statistically different from the median dose of 58 Gy given for patients who were disease free, p=0.518, They noted that patients who received more than 58 Gy had a better 5-year OS rate (22%). We observed a quite similar LC rate in 5 years 13.5% when compared to theirs results of 12.5%. Goldstein et al (20) reported the outcomes of 41 patients treated with curative (n=28) or palliative (n=13) re-RT. The majority of patients (78.0%) where treated with IMRT. The median OS for all patients was 10.2 months and the 1-year survival rate was 39.0% (46.3% for curative treatments). Seventy-five percent of curative and 53.8% of palliative had grade 3 or 4 re-RT-related toxicities, while we observed 27.8% of severe acute toxicity.

In our series the median dose of the first RT course was 60 Gy (range, 45-70.4 Gy), quite similar to the median given dose observed in other series. Kramer et al (21) evaluated 38 patients treated with re-RT and concurrent CHT. Their median prior RT dose was 64.2 Gy. For re-treatment patients received cisplatin and paclitaxel along with hyperfractionated re-RT. The observed median survival rate was 12.4 months, with 2- year actuarial OS rate of 35%, inferior to 58.6% observed in our analysis. Sher et al. (22) evaluated data of 35 patients treated between 2004 and 2008. Re-RT median dose was 60 Gy and all patients had concurrent CHT. With a median follow-up of 2.3 years, the 2-year actuarial OS and LC rates were 48% and 33%, respectively. Machtay et al. (23) when analyzing the data of 16 patients treated between 1998 and 2000, observed that 2 patients had gross residual disease after surgery and all other patients underwent complete surgical resection. The 2-year actuarial PFS and OS were 50% and 63%, respectively. Six patients (38%) developed severe late toxicity, including one fatal stroke and two life-threatening major vessel necrosis and/or bleeding events. Biagioli at al (24) analyzed the data of 41 patients treated between 2001 and 2006. All patients had IMRT as re-RT with concurrent CHT. All but 6 patients received 60 Gy. With a median follow-up of 14 months, the 2-year actuarial OS was 48.7%. Conversely to our results, they noted that surgery as a part of the salvage therapy had no survival impact (p = 0.126).

Sulman et al (25) reviewed charts of 74 patients who had re-RT with IMRT treated between 1999 and 2004, observing that 20 (27%) patients underwent salvage surgical resection and 36 (49%) patients received CHT. The observed median interval between initial RT and re-RT was 46 months, higher than 28 months observed in our analysis. They also noted that the median re-RT and cumulative dose were 60 Gy and 116.1 Gy, respectively, doses similar to 60 Gy and 114.5 Gy observed in our series. With a median follow-up of 25 months the 2-year OS and LC rates were 58% and 64%, respectively, very similar to 58.6% and 60.9% observed in our analysis. They noted one treatment-related death and severe toxicity in 15 patients (20%).

In our opinion combination of surgery, CHT and re-RT is the best option for salvage therapy, as the use of multimodality therapy favored OS (p=0.027) in our analysis. Salama et al (10) also confirmed that multimodality therapy was an independent prognostic factor for OS and LC when evaluating a subset of 115 previously irradiated patients.
Popovtzer et al. (26) reviewed the data of 66 patients who underwent re-RT for non-resectable recurrent or second primary HNC. The median re-RT dose was 68 Gy and 71% of the patients had CHT. The PFS in a median follow-up of 42 months was 23%. Fifty patients (77%) had a third recurrence or persistent disease, including 47 (71.2%) loco-regional failures. Severe late complications occurred in 19 patients (29%). Conversely to our results they could not find any statically significant difference in terms the results between both techniques, probably due to the shorter follow-up of the patients who were treated with IMRT.

Spencer et al. (27) published the results of RTOG 96-10 that included patients with recurrent or second primary HNC previously irradiated with a minimum dose of 45 Gy. The cumulative spinal cord dose was limited to 50 Gy, conversely to our series where despite the dose given in the previous RT course, in the re-RT course we aloud no more than 18-20 Gy at the spinal cord.

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The data of 81 patients were assessable and the median first radiation dose was 61.2 Gy. Severe grade 3 and 4 toxicity occurred in 14% and 5% of the patients, respectively, rates inferior to the severe grade 3 acute (27.8%) and late (38.9%) toxicity observed in our analysis, but with the difference that we found no severe grade 4 toxicity. In their analysis 6 (7.4%) patients died of treatment-related toxicity, two of hemorrhage from the tumor site without thrombocytopenia. Conversely to our results, they noted that patients treated more than 3 years after the previous RT had a 1-year OS of 48% compared with 35% for patients treated within 3 years (p = 0.017). In our analysis the interval between the first and second RT favored only the LC of patients who were at least 2 years disease free (p=0.012), with no impact in OS. By Cox regression multivariate analysis we confirmed that patients who were free of recurrence in an interval inferior of 24 months had an inferior PFS, with a relative risk of 6.71.

There is strong evidence that CHT alone does not induce durable complete remission for re-HNC (5,6), but re-RT with concurrent CHT has paralleled its use in the primary setting, with an attempt to increase LC and survival. In our analysis re-RT with concurrent CHT favored PFS (p=0.001).Multimodality treatment (p=0.027) and surgical margin status (p=0.016) were also related to improved OS. When we comparing patients with positive surgical margins or who did not have surgery to those patients with free surgical margins, there was also an OS advantage (p=0.002) favoring the last ones.

In our analysis absence of surgery or gross tumor after that was related to worse LC with a risk of failure 4.18 times higher.Complication rates vary in published studies as a result of the length of survival and type of treatment. In our series, adverse events occurred relatively frequently in patients who had or not associated CHT. One explanation of our relatively high rate of radiation-related toxicities probably is a reflex of the inclusion of all radiation-related toxicities, including both acute and late, in the analysis. We think this is an appropriate approach in a population of patients were survival is likely to be short and for whom any radiation-related toxicity is likely to have a detrimental effect on the quality of life during their remaining life. In our series adverse events occurred relatively frequently, with no statistical significant influence of associated CHT (p=0.929). Acute toxicity was not increased compared to those commonly observed during RT for HNC. Late toxicity was acceptable, although it was clearly increased by comparison with the first RT course.
The multimodality treatment employing re-RT in adjuvant setting, when a salvage complete resection is performed is motive of debate. Athough our results support the routine use of adjuvant re-RT, prospective data are needed to clarify the role of re-RT in circumstances such as free surgical or close margins, where the risk of local new recurrence is relative low and the risk of radiation morbidity is high.

CONCLUSIONS

Complete resection or debulking surgery should be encouraged for all patients presenting with recurrent or second HNC previously irradiated. Re-RT should be offered for patients who are not suitable for surgery or for those with marginal resections, with a clear understanding that survival is poor and many of these patients will suffer severe radiation-related insults to their quality of life, during and after treatment.CHT should be encouraged for all patients as it seems to impact PFS. Phase III studies are still necessary to define which patients are the best candidates for re-RT.

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