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Reirradiation in Head and Neck Cancer: A Curative Intent in Recurrence or Second Tumors

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Abstract

Purpose: To assess the efficacy and safety of reirradiation in head and neck cancer and potential prognostic factors associated.

Material and methods: Cohort study of patients treated with curative reirradiation for recurrence or second primary tumor. The analysis of RR is obtained prospectively from the database available at both centers. Statistical analysis was performed using the R Commander 2.0 software.

Results: Between 2006 and 2013, 40 patients with head and neck carcinoma were reirradiated. The mean dose was 66.39 Gy. 35% of patients showed acute toxicity grade 3 or higher and 20.5% showed chronic toxicity grade 2 or higher. The median follow-up was 11 months. The overall survival at 2 years was 41%; disease free survival and locoregional control at 1 year was 35.9% and 41.1% respectively. The time between treatments and disease-free interval to death and local recurrence were statistically significant ($p < 0.05$); and the first treatment scheme to distant metastases.

Keywords: Reirradiation; Head and neck; Cancer; Retreatment

Introduction

The reirradiation (RR) in head and neck cancer is one of the most controversial points raised in multidisciplinary committees. In the meta-analysis of Blandchard between 46.5% to 60% of patients will have locoregional recurrence. The cause of death is more closely related to the locoregional failure that to the distant metastasis, 50-60% of these patients die due to persistent or recurrent loco-regional disease and 70-90% of those who develop distant metastases also have loco-regional disease. In addition, survivors have a high incidence of second primary tumors with a rate of 14.2%. In these cases, treatment options are limited. The treatment of choice in relapse or second neoplasms in previously irradiated areas is salvage surgery, with survival rates at 5 years of up to 39%. In inoperable tumors and/or unresectable cases, chemotherapy (CT) can be considered as an alternative, although with discrete results, with response rates of approximately 30% and a median survival of 5 to 6 months. It should be noted that the results obtained with cisplatin, 5-FU plus cetuximab, achieve response rates of 36%, an overall survival of 10.1 months and progression-free survival of 5.6 months. The RR in head and neck tumors is not the treatment of choice [1], however, it has gained acceptance for patients with recurrent or unresectable seconds tumors and in cases with poor prognostic factors. In this prospective study, we evaluate the efficacy and safety of reirradiation in head and neck cancer and potential prognostic factors associated with it.

Material and Methods

This is a two-way cohorts study in which patients were treated with curative intent by RR of head and neck carcinoma because of recurrence or second primary tumor. Patients were treated in the Radiation Oncology Department, Virgen del Rocio University Hospital (HUVR), Seville and Radiation Oncology Unit, Rioja Salud Foundation-San Pedro Hospital (FRS-HSP), La Rioja. RR data were obtained prospectively from both centers. First irradiation data was collected retrospectively in some cases. The inclusion and exclusion criteria, as well as the different variables analyzed are shown in Table 1.

Inclusion criteria	Exclusion criteria
Patients with recurrent head and neck cancer or second tumor in the head and neck area, previously irradiated.	Patients with poor performance status
Patient with good performance status, ECOG 0-1	Existence prior chronic toxicity important (>G3)

Time since first irradiation at least 6 months.	Cumulative doses greater than 54 Gy spinal
	Existence of distant metastases
Analyzed Variables	
Location of the primary tumor	Disease-free interval
Staging of the first disease	Variation between initial histological grade and tumor recurrence or second primary
First therapeutic scheme	Second therapeutic scheme
Existence of recurrent disease that required other previous treatments (surgery or CT)	Indication of surgery. Prior to RR
Second disease: local recurrence, nodal recurrence or second primary tumor	Display QT in the second treatment
Interval between radiation treatments, IBT	Get lower or higher doses 60 Gy or 66 Gy

Table 1: Criteria for inclusion and exclusion. Analyzed variables.

Radiation therapy administered in the second course of radiotherapy (RT) was performed using three-dimensional conformal RT (3D) with high-energy photons. Dose per fraction was either 1.8 or 2 Gy. We considered the irradiation of the lower possible volume, to avoiding the radiation of elective nodal chains to minimize side effects and cumulated dose in risk organs.

Toxicities have been defined by CTCAE 3.0 (common terminology criteria for adverse events).

The statistical analysis was performed using the R Commander 2.0 software. Kaplan-Meier method was used for the univariate survival analysis and Cox regression was used for the multivariate survival analysis.

Results

Between September 2006 and September 2013, a total of 40 patients with head and neck carcinoma were re-irradiated; of which 33 were from HUVR and 7 from FRS-HSP. Data from the first and second treatment are summarized in Table 2.

Number (%)		
Sex	Women	7 (17.5)
	Men	33 (82.5)
Mean/median age		59.2/62 (DS 11.83)
Localization		
	Pharynx	7(17.5)
	Larynx	18(45)
	Oral Cavity	9(22.5)
	Unknown primary	4(10)
	Others	2(5)
Histology	Epidermoid	36(90)
	undifferentiated	2(5)
	Adenocarcinoma	1(2.5)
	Others	1(2.5)
T	Tx	5(12.5)
	T1-2	10(30.3)
	T3-4	18(54.54)
N	N0-1	19(54.28)
	N2	13(37.14)
	N3	3(8.57)
Initial Stage	I	4(11.76)
	II	2(5.88)
	III	10(29.41)
	IV	18(52.94)
Radiotherapy	Mean dose	65.94 Gy
Toxicity	Acute (>G3)	9(22.5)
	Chronicle (>G2)	2(5)
Treatment	RT alone	5(12.5)
Scheme		
	Surgery and RT	13(32.5)
	RTQT	13(32.5)
	Surgery and RTQT	9(22.5)
Disease Free Interval		Mean 33.5 /Median 16
Interval between treatments		Mean 44.77/Median 23.5

Table 2: Characteristics of patients during the first and second radiotherapy. Features of second treatment.

Features of the first treatment

The average age of the patients was 59.2 years (median 62 years). Most frequent location was the larynx (45%) the histology squamous

cell carcinoma in 90% of the patients. 82.35% of patients had advanced disease stages (III-IV).

55% had undergone surgery prior to radiotherapy and 60% of patients had undergone CT. Most regimens used CT schemes based on platinum (23 patients) and in 1 patient cetuximab. The therapeutic regimens used in the first treatment was RT exclusively in 5 patients, RT and CT in 13 patients, surgery followed by RT in 13 patients and surgery, RT and CT in 9 patients. Radiotherapy was administered between June 1993 and October 2011. The radiotherapy technique used varied depending on the technology available at the time. 2D technique was performed in a total of 4 patients in HUVR until 2002. The rest of the patients were treated with three dimensional technique (3D).

The average dose administered was 65.94 Gy (standard deviation, SD 66.49) on the primary tumor and affected lymph nodes or surgical bed; and 50 Gy (SD 3.464) on elective lymph node chains. The fractionation employed was 2 Gy (5 times a week, conventional treatment), except in 4 patients treated with fractionation 1.8 Gy. Acute toxicity grade 3 or higher showed in 52.5% of patients. Chronic toxicities G2 or higher after the first treatment were xerostomia and fibrosis, showed in 5% of patients.

Diseases between treatments

After this first RT, 27.5% had disease that was treated with surgery (6 patients), CT (2 patients) and both (3 patients), without RT. This first relapse occurred within was average of 31.09 months and a median of 14 months since the end of the first treatment (SD 33.55).

Features of the second treatment

Second radiation causes were: second primary tumor (27.5%: stage IV 5, stage III 5 and stage II 1 patients), local recurrence or relapse (47.5%) and nodal recurrence (25%). The disease-free interval averaged 33.5 months (median 16 months, DS 46.69) and the mean interval between treatments (IBT) was 44.77 months (median 23.5 months, SD 53.26).

Treatment schemes were: RT alone in 11 patients, RT and CT in 14 patients, surgery followed by RT in 7 patients and surgery followed by CT and RT in 8 patients.

In this way 37.5% (15 patients) of patients were previously operated (microscopic and macroscopic residual disease, 4 and 4 patients) and 72.5% received CT. The CT schemes most commonly used were based on platinum (24 patients) and cetuximab (10 patients).

In terms of the administered radiotherapy, the average dose administered was 66.39 Gy/(SD 6.24) on tumor lesion or surgical bed. In 9 patients the dose was less than or equal to 60 Gy. The fractionation employed was 2 Gy (5 times a week, conventional treatment).

35% of patients presented acute toxicity grade 3 or higher. Chronic toxicity G2 or higher was shown by 20.5% of patients: 5 fibrosis, 4 xerostomia and necrosis, hypothyroidism, trismus or odynophagia 1 respectively.

The median follow-up of patients was 11 months (SD 16.33), being 22 months in survivors (SD 22.13). At the end of the study, 16 patients were alive (11 without disease, 3 with local disease and 2 with metastases); 24 patients had died (14 with local disease, 7 local and distant disease, 1 with distant disease and 2 patients died of non-cancer causes without oncological disease). This relation between the deaths and the existence of local and/or distance disease was statistically significant ($p < 0.001$).

Analytical statistics

Statistically significant variables ($p < 0.05$) for local recurrence and death were the time between treatments and the disease-free interval. The average difference between both groups is indicated in Table 3. The first treatment scheme was associated with distant metastases ($p = 0.01$). The rest of variables were not statistically significant. Univariate survival analysis (Figure 1).

	Local recurrence		Exitus		Metastasis	
	No	Yes	Alive	Deaths	No	Yes
Disease Free Interval	44	24.9	48.37	23.58	39.4	15.7
Interval between treatments	60.16	32.18	69.81	28.08	53.4	18.9

Table 3: Average of months in the variables that were statistically significant.

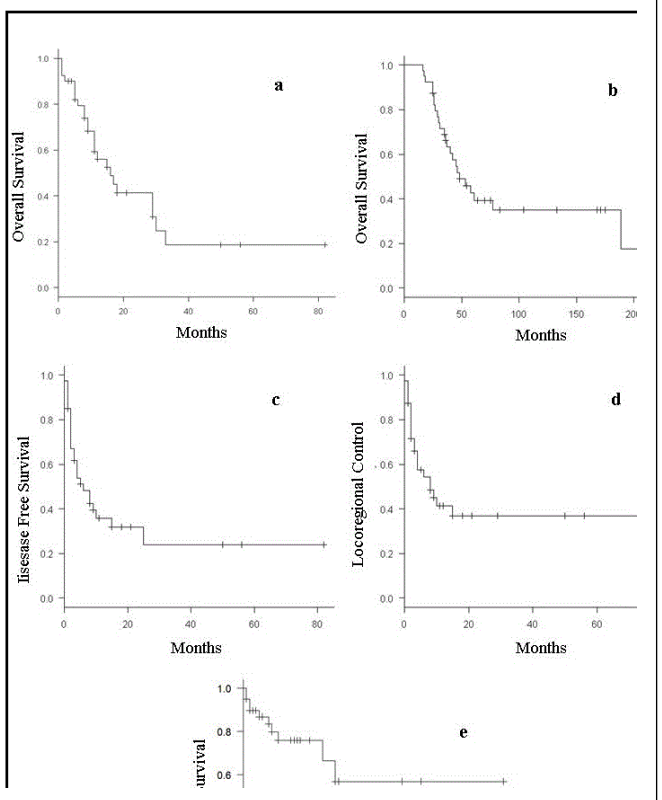

Figure 1: Kaplan Meier Survival. (a) Overall survival (OS) from the end of the second radiotherapy. (b) Overall survival (OS) from the end of the first radiotherapy. (c) Disease-free survival, DFS. (d) Loco-regional control, LRC. (e) Metastases-free survival, MFS.

Overall survival (OS): OS after RR has submitted a median of 16 months (95% CI 11-29). The survival rate at 12 months was 56% (95%

CI 38-70.5), 41% at 24 months (95% CI 24-57) and 18.6% at 36 months (95% CI 5-37).

Disease-free survival (DFS): DFS has submitted a median of 6 months (95% CI 2-15). The DFS at 6 months was 48.2% (95% CI 31.8-62.9), 35.9% at 12 months (95% CI 20.7-51.4) and 31.9% at 15 months (95% CI 17.1-47.8).

Loco-regional control (LRC): LCR is determined by the appearance of tumor disease in the irradiated area after RR. In our study, the median CLR at 6 months was 54.4% (95% CI 37-68), 41.4% at 12 moths (95% CI 24-57) and it remains at 36.8% at 15 months (95% CI 24-57).

Metastasis-free survival (MFS): More than 50% of patients had no distance disease even after more than 25 months (55.7%). The SLM after RR at 6 months was 86.8% (95% CI 71.1-94.3) 75.9% at 12 moths (95% CI 56.8-87.4) and 56.9% at 30 months (95% CI 28.8-77.4).

The univariate survival analysis did not find any statistically significant variable (OS, DFS, LRC or MFS); with the exception of time between treatments, the cut-off point to the 12 months is significant ($p < 0.05$) for the LRC and for the DFS (Figure 2). This was not the case when the cut was established at 24 months.

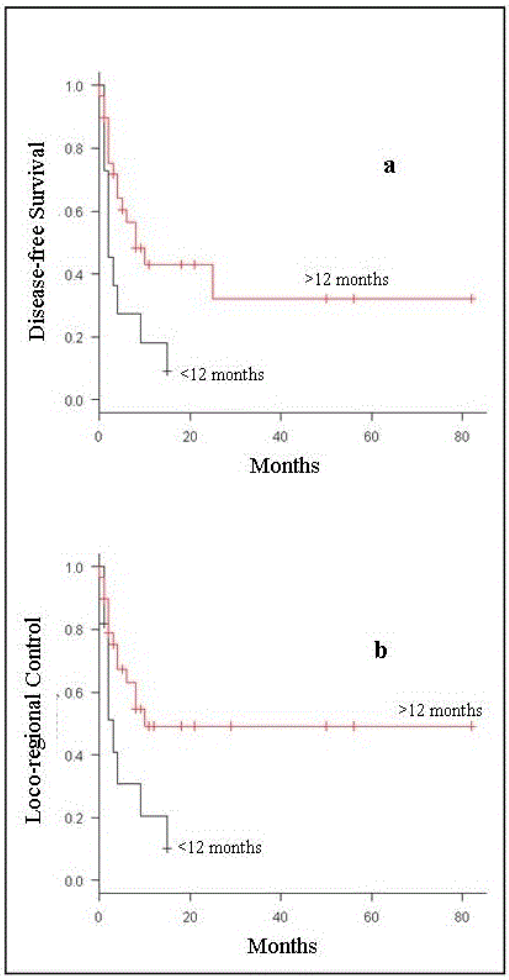

Figure 2: Kapplan Meier Survival, 12 moths cutoff. (a) Disease-free survival, DFS, differences when time passes between minor or major treatments to 12 months ($p = 0.02$), mean 2 vs. 8 months respectly. (b) LRC differences when time passes between minor or major treatments to 12 months ($p = 0.02$), mean 3 months vs. 10 months respectly

Multivariate survival analysis

Due to limited number of statistically significant variables in the univariate analysis, the multivariate analysis was performed for variables that had $p < 0.1$ and $p < 0.2$ (Table 4).

	p <0.1		p <0.2	
	HR	p	HR	p
Overall Survival				
Doses >60 Gy	2.53	0.06	2.2	0.13
Previous surgery to 2nd radiation			1.6	0.3
Disease Free interval	1.02	0.15	1.03	0.1

Interval between treatments	0.9	0.12	0.9	0.09
Disease Free Survival				
First treatment scheme	1.14	0.56	1.05	0.82
Doses >60 Gy	2.9	0.03	2.91	0.03
Previous surgery to 2nd radiation			1.44	0.44
QT in the 2nd treatment			0.94	0.92
Second disease			0.84	0.72
Disease Free interval	0.97	0.11	1.01	0.23
Interval between treatments	1.01	0.35	0.97	0.09
Locoregional Control				
Doses >60 Gy	3.12	0.04	3.2	0.03
Previous surgery to 2nd radiation			2.1	0.1
QT in the 2nd treatment			1.4	0.5
Disease Free interval	1.01	0.41	1.01	0.25
Interval between treatments	0.98	0.14	0.98	0.53
Metastases Free Survival				
Second disease			0.2	0.02
First Disease localization			0.8	0.46
First treatment scheme			3.5	0.007

Table 4: Multivariate analysis, Cox regression, HR: Hazard Ratio.

Where we have used only variables $p < 0.1$, >60 Gy versus <60 Gy was the only statistically significant variable in terms of the MFS and LRC, with a hazard ratio (HR) of 2.9 and 3.12 respectively. If we use the variables with $p < 0.2$, in addition to >60 Gy, the statistically significant variables were second disease and therapeutic scheme received in the first disease in terms of MFS, with a HR of 0.2 and 3.5 respectively.

Discussion

In this study, we have analyzed 40 patients who have been irradiated a second time in the head and neck area. The treatment of choice should be the surgery in case of relapse and the impossibility of this option we will be considered the RR. In addition, the majority of patients who relapse or suffer from a second primary tumor in this area tend to have comorbidities, secondary sequelae of previous treatments (surgery, CT or RT) or of the current disease. All these situations lead to a low "performance status" that contraindicates the possibility of RR. Due to all these situations, the number of patients obtained for the study was low although similar to other studies [2]. The improved outcome by the chemotherapy [3] results a large number of patients who exceed the 6 months interval between irradiation which is the recommended minimum time, thus this could mean an increase in the number of re-irradiations.

The risk of causing irreparable damage is the biggest problem of this treatment and this may influence the quality of life and even survival rate of patients. The use of the most modern techniques of RT (intensity modulated radiation therapy (IMRT) and radiosurgery) have demonstrated reliability and effectiveness in these circumstances and may improve the outcome and quality of life of these patients. In our environment, the technique of treatment available was three-dimensional radiotherapy. In our cohort of patients largely heterogeneous, due to the initial staging, initial location, characteristics of the second disease (local recurrence vs. nodal recurrence vs. second primary), treatment regimens employees (RT, surgery + RT, RTCT or surgery + RTCT), etc., this we consider as a limitation for statistical analysis. Although, this heterogeneity disappears with to the characteristics of radiotherapy employed.

A confounding factor in assessing the results is the treatment carried out between treatments, in what we call the intermediate disease (27.5% of patients). These patients were treated at that time, either with surgery or with CT or both; and its influence was difficult to assess on the second radiation. We can conclude that the means employed were insufficient.

In our study, few patients received elective nodal RT (4 patients) in the second treatment, by protocol these patients only if they had not been previously dealt with it. The rate of severe toxicities >grade 3 in the second treatment, acute (35%) or chronic (20.5%), have not been higher than the reflected in the literature despite the fact that the treatment was performed using three dimensional radiation therapy.

Several studies have suggested prognostic factor, such as tumor size, resectability, the IBT radiotherapy, whether it is second or relapse tumor, anatomic localization or the administered dose as statistically significant factors. In the inferential analysis of our study, the only factors found to be statistically significant were the time between treatments and disease-free interval. These factors have been endorsed by the literature as prognostic factors [4-9]. It is shown that the greater time between treatments the greater DFS and the better LRC, but a greater time doesn´t mean a better DFS. There is another factor that was statistically significant in this analysis: the first therapeutic scheme and its relation with the developing distant metastasis ($p = 0.01$). This situation has not been analyzed in the literature reviewed, so we believe it is the first time that it has been demonstrated. In our analysis, the group treated with surgery, CT and RT was the less favorable. We believe that the explanation is that this group had worse prognostic factors (positive margins, high histologic grade, and capsule overflow). We can consider this a significant variable, due to the possible existence of micrometastases, not clinically demonstrable, prior to the second course of RT. This assertion, however, must be considered with caution and does not mean this group of patients is not candidate for RR. More studies are needed to confirm this result.

22 of the 24 deceased patients had disease at that time, 21 with local disease, 7 of them also with distant disease and only 1 with distant disease exclusively; therefore this deaths you can be related to the progression of their disease ($p < 0.001$). This leads us to think that what compromises the disease-free survival is the locoregional control. Therefore, we believe that improving treatments of local disease we will have higher rates of disease-free survival that would involve higher overall survival rates.

The study shows acceptable rates of survival and loco-regional control, despite the fact that the technique used was the three-dimensional RT. The OS at two years has been 41% and the LRC at 1 year was 41.4%. These rates are within the ranges of survival rate found in the literature [4-11]. The MFS (75.9% at1 year) obtained high rates; this figure is not evaluable because patients die of local complications

before they could develop distant metastases, which reaffirms the importance of local treatment for these patients.

In the survival analysis by subgroups, no significant differences were found, although there are other better prognostic factors endorsed by the literature within the disease is a second primary tumor (Steven and Spencer[12]), there was a possibility of surgery before radiotherapy (Salama) or when RR achieved high dose (Choe).

The only factor has been demonstrated to be statistically significant in relation to DFS and LRC has been the IBT, when stratified the cohort of patients between irradiation (less than or greater than 12 months) our test shown that the greater the time between treatments, the greater the survival rate (Table 3). For the MFS, this variable was not significant. The relation of time between treatments coincides with data published in other studies, where significant differences were observed in survival rate remain favorable for groups in which more time had passed between treatments. This result is supported by numerous studies [4-16]. Therefore, we recommend our series based on the range of 12-month interval such as a favorable prognostic factor to take into account when RR in head and neck carcinoma is indicated.

Multivariate analysis was performed in two circumstances, when the variables were obtained in the univariate $p < 0.1$ and when they were obtained in the univariate $p < 0.2$, due to the low number of patients and the initially few significant variables. Therefore, we must acknowledge that in the multivariate analysis save confounding factors not adequately controlled may be found.

Under this premise, in our series, the only statistically significant variable was reaching higher dose than 60 Gy in the RR analysis to the LRC $p < 0.04$ and $p < 0.03$ for both analysis respectively and DFS $p < 0.03$ in the two analysis. Reaching high doses of radiation has been already been demonstrated by different studies [5-18] to be prognostic factor for the improvement of LRC and OS, so our results are consistent.

The second disease variable ($p < 0.02$) and treatment scheme applied in the first disease variable ($p < 0.007$) were statistically significant a regard MFS, but only in the univariate analysis of these variables had a $p < 0.02$. In the analysis of the second disease, we have to be noted that the number of patients included in each subgroup is low. This more a clearly established prognostic factor in other studies [7-20]. Finally, the treatment scheme received in the first disease continues to demonstrate significant. This reaffirms the possibility of micrometastases prior to the second course of radiation. In the rest variables were not found to have clinical relevance which may be due to the small sample obtained for the study.

Conclusions

The RR in head and neck cancer shows good rates of OS, DFS and LRC with acceptable toxicities. Probably, improving the LRC will results in a improvement of OS. Of the variables studied, the interval between treatments and disease-free interval were the most important prognostic factors.

All these results must be interpreted with caution considering the statistical limitations described above, basically due to the size of the sample and the heterogeneity that this clinical situation presents. We believe there is a need for convenient multi-institutional studies which will increase the statistical power to establish more clearly the role of reirradiation in head and neck carcinoma [14,21-29].

Conflicts of Interest

The authors declare no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required

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