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Re-Irradiation in Squamous Cell Carcinoma of the Head and Neck

Research Article

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Abstract: Background: Re-irradiation as a therapeutic option for locoregional recurrence in patients with recurrent, persistent tumour or second primary malignant neoplasm has great advantages for locally advanced unresectable tumours.
Methods: We intended to characterise the patient pool that underwent re-irradiation and to perform a comparative analysis between previously known data related to prognostic factors with an impact on 2 years OS of these patients, and evaluate the therapeutic impact of re-irradiation in patients with recurrent, persistent tumour or second primary malignant neoplasm in the head and neck region, treated at the Radiotherapy Department in Portuguese Institute of Oncology in Coimbra (IPOC), from the year 2016 to 2020.
Results: A total of 39 patients were included in this study. All patients were submitted to both primary radiotherapy and re-irradiation with a median time interval between treatment of 20 months (minimum: 8 – maximum: 190). Only the time between irradiations was associated with a decrease in the risk of mortality (HR=0.828; CI 95% 0.731-0.939; p=.03). There were no significant differences in terms of toxicity severity between irradiations.
Conclusion: Re-irradiation is an important therapeutic alternative in the treatment of patients with malignant tumours in the head and neck region.

Keywords: *Radiotherapy • Head and Neck • Re-irradiation*

1. Introduction

Squamous cell carcinoma located in the head and neck region is the sixth most common carcinoma in the world[1].

The main cause of death in patients with malignant tumours in the head and neck region is locoregional recurrence, which appears at rates of about 30% to 50% after intensive treatment. Secondary primary tumours can occur in up to 40% of patients treated with curative intent[2].

For patients with metastatic disease at initial presentation, palliative adjunctive measures include RT, surgery, analgesics, and other therapies to control manifestations of disease spread. Historically, single-agent and combination systemic therapy have both been used[3]. A phase III randomised trial of 442 patients found that cetuximab plus cisplatin/5-FU or carboplatin/5-FU improved response rate (36% vs. 20%; p<.001) and median survival compared to the standard chemotherapy doublet of platinum/5-FU in a patient population predominantly linked to tobacco and alcohol use (10.1 vs. 7.4 months; p=.04)[4].

Re-irradiation may be offered to patients with locally and/or regionally recurrent or persistent head and neck cancer[3]. Locoregional progression can be associated with concerning symptoms such as pain, bleeding, dysphagia, dysphonia or airway compromise, dermal ulceration, and foul odours; it can reduce patients' participation with their societies and families. Securing locoregional control with re-irradiation may confer an improved quality of life compared with uncontrolled locoregional cancer progression[5].

A randomised phase III multicentre trial in France (N=130) showed that re-irradiation combined with systemic therapy in patients following a resected recurrence improved disease-free survival, compared to patients receiving only surgery (HR, 1.68; 95% CI, 1.13–2.50; p=.01)[6].

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Re-irradiation as a therapeutic option for locoregional recurrence in patients with recurrent, persistent tumour or second primary malignant neoplasm has great advantages for locally advanced unresectable tumours. The development of surgical techniques and techniques of administration of radiotherapy (RT) has contributed to better therapeutic results with less morbidity in these patients[1].

However, determining the appropriate selection of patients and the dose of re-irradiation to be administered can be a challenge for radiation oncology[7].

The use of intensity-modulated radiotherapy (IMRT) allows the use of higher doses, minimizing the incidence and severity of acute and/or late toxicities, related to the irradiation of surrounding (dose limiting) structures[8].

In the re-irradiation of malignant tumours in the head and neck region, the concern with serious late toxicities remains. Within these toxicities, we chose to highlight osteoradionecrosis and carotid blowout syndrome, among others[9].

Takiar et al. described rates of late complications (osteoradionecrosis and oesophageal stenosis requiring endoscopic dilation) related to re-irradiation, classified as grade 3 or higher, according to the scale of the EORTC/RTOG (European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group) (6) in the order of 50%, for re-irradiation doses above 66 Gy[2].

Ward et al. performed a multivariate analysis of 412 patients, in which it was possible to establish 3 groups and stratify them in relation to 2 years overall survival (OS), depending on the time elapsed between RT treatments, the fact that they had undergone previous surgery, and the presence of organ dysfunction[7].

The RPA identified 3 cohorts. The most favourable (class I) were patients who were more than 2 years from their initial diagnosis and were able to undergo surgical resection. The least favourable (class III) were 2 years or less from initial radiation therapy and were experiencing organ dysfunction at the time of their new diagnosis, regardless of surgical resection status. Patients in class I experienced a 2-year overall survival of 62% with a 4-year survival exceeding 40%. However, despite aggressive re-irradiation, none of the class III patients survived 4 years. Hence, the class III patients may be better served by less morbid interventions[5].

2. Methods

We intended to characterise the patient pool that underwent re-irradiation and to perform a comparative analysis between previously known data, obtained from the literature, related to prognostic factors with an impact on 2 years OS of these patients.

This work intended to evaluate the therapeutic impact (response to treatment, survival analysis, and side effects) of re-irradiation in patients with recurrent, persistent tumour or second primary malignant neoplasm in the head and neck region, treated at the Radiotherapy Department in Portuguese Institute of Oncology in Coimbra (IPOC), from the year 2016 to the end of 2020.

2.1. Inclusion criteria

- Patients with recurrent, persistent tumour or second primary malignant tumour, located in the head and neck region, which had been first treated with a minimum dose of 40 Gy, and which have been re-irradiated with a minimum dose of 40 Gy
- Squamous cell carcinoma histology
- A minimum interval to be considered between RT treatments of 6 months
- Doses per fraction of 1 - 3 Gy
- Radical, palliative, adjuvant treatments

2.2. Exclusion Criteria

- Patients treated with stereotactic radiotherapy techniques and/or with different doses per fraction of treatment from those mentioned above
- Distinct histological entities of squamous cell carcinoma

2.3. Methodology

- Evaluation of response to treatment by analysing the record of clinical and imaging tests performed at follow-up
- Recording the acute radiotoxicity measured by the EORTC/RTOG (6) scale of radiodermatitis, mucositis, xerostomia and dysphagia, incidence of osteoradionecrosis, radiation myelitis, aspiration pneumonia, carotid blowout syndrome, permanent need for enteric feeding and/or respiratory stoma
- Assessment of the need to interrupt and/or suspend treatment for acute toxicity
- Correlation between the prescribed dose and the occurrence of acute or late toxicities
- Relationship between the time elapsed between treatments and acute or delayed toxicity

- Calculation of OS and locoregional failure-free survival
- Comparative analysis with data collected from the literature

2.4. Statistical Analyses

Statistical analysis was performed using the *IBM® SPSS®* version 25. Descriptive statistics included median and interquartile range for continuous variables, and absolute and relative frequency for categorical variables. Distribution normality was assessed using the Kolmogorov-Smirnov test. Chi-square, Wilcoxon signed rank, Mann-Whitney, and Kruskal-Wallis tests were used to establish associations and differences between variables, respectively. The Kaplan-Meier curves were used to analyse the median overall survival. Multivariable Cox regression analysis was performed using the clinical response to each irradiation, time between irradiations and toxicity grading. Univariate logistic regression was used to determine risk factors for severe toxicity after radiotherapy, defined as a Radiation Therapy Oncology Group (RTOG) toxicity grade ≥ 3 (6). A *p*-value inferior to .05 was considered as statistically significant.

3. Results

A total of 39 patients (35 male and 4 female) were included in this study. All patients were submitted to both primary radiotherapy and re-irradiation with a median time interval between treatment of 20 months (min. 8 – max. 190). The median observation period after re-irradiation was 8 months (min. 1 – max. 39) with an interquartile range of 14 months. The head and neck tumours were most commonly located in the oropharynx and larynx (30.8%; n=12). The proportion of patients that underwent concurrent chemotherapy (cCT) during the first treatment and during re-irradiation were 56.4% (n=22) and 23.1% (n=9), respectively. The standard chemotherapy regimen was 3 weekly (100 mg/m^2, 3 cycles) cisplatin with concurrent RT.

Of the 39 patients submitted to re-irradiation, 95% (n=37) presented as recurrent or persistent disease and 5% (n=2) had locoregional and metastatic (M1) disease. It was possible to perform surgical resection of the recurrence in about 26% (n=10) of the patients. Of the 2 patients with M1 disease at the time of re-irradiation one, was submitted to the EXTREME regimen with maintenance cetuximab until progression[4], and the other had no conditions to systemic therapy. They both were submitted to palliative re-irradiation (50 Gy/20 fr/4 weeks). Of the remaining 37 patients, 26% (n=10) were submitted to adjuvant treatment, 31% (n=12) to radical treatment, and 38% (n=15) to palliative RT treatment.

In the first RT treatment course, 46% (n=18) of patients were treated with the helical IMRT technique in *Accuray TomoTherapy TomoHD®*, and 54% (n=21) with the IMRT step-and-shoot technique in the *Siemens ONCOR Avant-Garde®* linear accelerator. In the second RT treatment course, 79% (n=31) of patients were treated with the helical IMRT technique in *Accuray TomoTherapy TomoHD®* and 21% (n=8) patients were treated with the IMRT step-and-shoot technique in the *Siemens ONCOR Avant-Garde®* linear accelerator.

The treatment volumes of the RT treatment were contoured based on international guidelines according to the primary tumour location, radiologic examinations, clinical and pathological staging, the patient performance status, and intent of treatment, and were peer reviewed by radiation oncologists with several years of experience treating this pathology.

The re-irradiation treatment volumes were contoured in accordance with the published recommendations of the *National Comprehensive Cancer Network* (NCCN), including known disease only to minimise the volume of tissue receiving very high doses in regions of overlap. Prophylactic treatment of subclinical disease (elective nodal irradiation) is therefore not routinely indicated in this scenario[3].

The median dose of RT in the first treatment course was 69.96 Gy (minimum: 53 Gy – maximum: 70 Gy) with an interquartile range of 4 Gy and 94.8% of patients were treated with a dose ≥ 60 Gy. The median dose of RT at re-irradiation was 60 Gy (minimum: 40 Gy – maximum: 70 Gy) with an interquartile range of 16 Gy, and 97.4% of patients were treated with a dose ≥ 50 Gy. At the time of re-irradiation, 46% (n=18) of the patients were treated with moderate hypofractionation (from 2.12 to 2.5Gy per fraction, 5 fractions per week) and the remaining 54% (n=21) with conventional fractionation (from 1.8 to 2Gy per fraction, 5 fractions per week).

Disease-related characteristics at the time of initial radiotherapy and re-irradiation are shown in Table 2.

Toxicity grade regarding dermatitis, mucositis, xerostomia, and dysphagia are summarised in Table 3. There were no significant differences in terms of toxicity severity between irradiations, nor the time between irradiations among the different toxicity degrees.

Table 4 compares the toxicity severity during both irradiations in patients undergoing cCT. There were 40.9% (n=9) patients under cCT during the first treatment of radiotherapy that had grade 3 dysphagia, while only 17.6% (n=3) patients not undergoing cCT suffered from

Table 1: Stratification of overall survival (OS) groups at 2 years resulting from multivariate analysis (3).

Class I	Treatment interval > 2 years, in patients submitted to surgery	2 years OS of 62%
Class II	Treatment interval > 2 years, in patients not submitted to surgery or interval < 2 years, without organ dysfunction	2 years OS of 40%
Class III	Interval between treatments < 2 years, with organ dysfunction	2 years OS of 17%

Table 2: Disease features at first and second radiotherapy irradiation.

Variable	Timing, % (n)	
	At first irradiation	At re-irradiation
Location		
Oropharynx	30.8 (12)	
Oral cavity	12.8 (5)	
Nasopharynx	10.3 (4)	
Larynx	30.8 (12)	
Hypopharynx	12.8 (5)	
Others	2.6 (1)	
ECOG Performance status		
0	89.7 (35)	56.4 (22)
1	10.3 (4)	33.3 (13)
2	0.0 (0)	10.3 (4)
T-stage		
T0	5.1 (2)	20.5. (8)
T1	33.3 (13)	5.1 (2)
T2	15.4 (6)	23.1 (9)
T3	17.9 (7)	12.8 (5)
T4	28.2 (11)	38.5 (15)
N-stage		
N0	41.0 (16)	53.8 (21)
N1	23.1 (9)	15.4 (6)
N2	28.2 (11)	20.5 (8)
N3	7.7 (3)	10.3 (4)
M-stage		
M0	100.0 (39)	94.9 (37)
M1	0.0 (0)	5.1 (2)
Clinical stage		
I	20.5 (8)	5.1 (2)
II	12.8 (5)	15.4 (6)
III	15.4 (6)	15.4 (6)
IV	51.3 (20)	64.1 (25)
CT cycles, median (IQR)	2.0 (2)	0.0 (0)
Dose of RT (Gy), median (IQR)	70.0 (4.0)	60.0 (16)
Concurrent chemotherapy	56.4 (22)	23.1 (9)

CT: Chemotherapy, ECOG: Eastern Cooperative Oncology Group, IQR: Interquartile Range, RT: Radiotherapy.

Table 3: Toxicity grading differences between first and second irradiation.

Toxicity grade	Timing, % (n)		Time between irradiations (months), median (IQR)
	After first irradiation	After re-irradiation	
Dermatitis			
1	59.0 (23)	59.0 (23)	21.0 (47)
2	33.3 (13)	30.8 (12)	31.0 (41)
3	7.7 (3)	10.3 (4)	24.5 (19)
Mucositis			
0	35.9 (14)	33.3 (13)	20.0 (14)
1	17.9 (7)	35.9 (14)	26.0 (47)
2	33.3 (13)	12.8 (5)	39.0 (109)
3	12.8 (5)	17.9 (7)	24.0 (89)
Xerostomia			
0	23.1 (9)	5.1 (2)	34.0
1	46.2 (18)	76.9 (30)	21.0 (36)
2	30.8 (12)	17.9 (7)	27.0 (92)
Dysphagia			
0	33.3 (13)	20.5 (8)	26.0 (117)
1	17.9 (7)	35.9 (14)	23.0 (46)
2	17.9 (7)	15.4 (6)	21.0 (25)
3	30.8 (12)	28.2 (11)	16.0 (35)

ECOG: Eastern Cooperative Oncology Group, IQR: Interquartile Range, RT: Radiotherapy.

the same level of dysphagia. The dysphagia toxicity grade was significantly higher in patients undergoing cCT during the first irradiation, but not during the re-irradiation (p=.23). We did not detect any other significant differences in terms of toxicity severity between patients submitted to cCT during both irradiations.

It was found that from a total of 39 patients, approximately 5% (n=2, due to aspiration pneumonitis) had interruption of the first RT treatment. Approximately 13% (n=5) had interruption of the second treatment: 3 due to maintenances related to the treatment machine and 2 due to clinical intercourses (2 respiratory infections).

Severe complications such as osteoradionecrosis, carotid blowout syndrome, or radiation myelitis were not found in any of the patients for a median follow-up time

Table 4: Concurrent chemotherapy (cCT) and toxicity grading following first and second irradiation.

Toxicity grade	After first irradiation		After re-irradiation	
	cCT	Without cCT	cCT	Without cCT
Dermatitis				
1	50.0 (11)	70.6 (12)	44.4 (4)	63.3 (19)
2	40.9 (9)	23.5 (4)	44.4 (4)	26.7 (8)
3	9.1 (2)	5.9 (1)	11.1 (1)	10.0 (3)
Mucositis				
0	27.3 (6)	47.1 (8)	22.2 (2)	36.7 (11)
1	18.2 (4)	17.6 (3)	33.3 (3)	36.7 (11)
2	36.4 (8)	29.4 (5)	22.2 (2)	10.0 (3)
3	18.2 (4)	5.9 (1)	22.2 (2)	16.7 (5)
Xerostomia				
0	13.6 (3)	35.3 (6)	0.0 (0)	6.7 (2)
1	50.0 (11)	41.2 (7)	77.8 (7)	76.7 (23)
2	36.4 (8)	23.5 (4)	22.2 (2)	16.7 (5)
Dysphagia				
0	**22.7 (5)[a]**	**47.1 (8)[a]**	22.2 (2)	20.0 (6)
1	**9.1 (2)[a]**	**29.4 (5)[a]**	33.3 (3)	36.7 (11)
2	**27.3 (6)[a]**	**5.9 (1)[a]**	22.2 (2)	13.3 (4)
3	**40.9 (9)[a]**	**17.6 (3)[a]**	22.2 (2)	30.0 (9)

ECOG: Eastern Cooperative Oncology Group, RT: Radiotherapy.
[a]p=.023

of 41 months. There was a need to use enteral feeding tubes in 26% (n=10) of patients during the first RT treatment and in 28% (n=11) during re-irradiation. The same number of patients with aspiration pneumonitis was found in both RT treatment courses, of about 5% (n=2), and the need for respiratory stoma was 13% (n=5) in the first RT treatment and 26% (n=10) in the second course.

Table 5 summarises the univariate logistic regression models of predictors for severe toxicity (≥ grade 3) during RT and re-RT. The primary tumour location, ECOG status, number of CT cycles, dose of RT, and cCT were included as covariates. There were no significant risk factors for toxicity severity in both irradiations.

In terms of treatment response to re-irradiation, 51% (n=20) of the patients had complete response, 41% (n=16) had local persistence of disease, and almost 8% (n=3) had distant progression of the disease.

The median overall survival and locoregional recurrence-free survival time (calculated from the diagnosis time) were 38.0 months (CI 95% 29.1–46.9) and 32.0 months (CI 95% 24.2-39.8), as shown in Figures 1 and 2, respectively. The median survival time after re-irradiation was 9 months (CI 95% 1.0-46.0). Multivariable cox regression showed that only the time between irradiations was associated with a decrease in the risk of mortality (HR=0.828; CI 95% 0.731-0.939; p=.03).

4. Discussion

Re-irradiation for locoregional failure of head and neck cancer or second primary tumours in previously irradiated areas after a full course of (chemo-)radiation poses a challenging problem for radiation oncologists. Salvage surgery remains the standard of care; however, it is the scenario in only 20% of cases. Chemotherapy alone is not considered a curative treatment option[10].

Patient factors to consider include tolerance to the first course of radiation therapy, persistent late effects, swallowing function, pain, general performance status, social support, and smoking status. Organ dysfunction is an important prognostic factor and is defined in the literature as a composite of feeding-tube dependence, tracheostomy dependence, and soft-tissue damage[5].

For cancers determined to be technically unresectable, or resectable only with unacceptable

Table 5: Univariate logistic regression of predictors for severe toxicity after first and second irradiations.

Variables	After first irradiation		After re-irradiation	
	RR (CI 95%)	P-value	RR (CI 95%)	P-value
Location (reference: oropharynx)				
Oral cavity	0.93 (0.11-7.82)	.949	-	-
Nasopharynx	4.20 (0.33-53.1)	.268	0.24 (0.02-3.01)	.268
Larynx	0.70 (0.13-3.68)	.268	0.51 (0.10-2.59)	.416
Hypopharynx	0.93 (0.11-7.82)	.949	0.48 (0.06-4.00)	.494
ECOG status (reference: 0)				
1	5,08 (0,48-54,03)	.178	1.40 (0.35-5.54)	.632
2	-	-	3.60 (0.32-40.23)	.298
CT cycles (per each cycle)	1.27 (0.74-2.17)	.383	0.97 (0.51-1.84)	.933
Dose of RT (per each Gy)	0.98 (0.84-1.14)	.780	1.06 (0.98-1.13)	.134
Concurrent chemotherapy	3.90 (0.96-15.82)	.057	1.25 (0.28-5.59)	.770

CT: Chemotherapy, ECOG: Eastern Cooperative Oncology Group, RR: Relative Risk, RT: Radiotherapy, 95% CI, Confidence Interval at 95%.

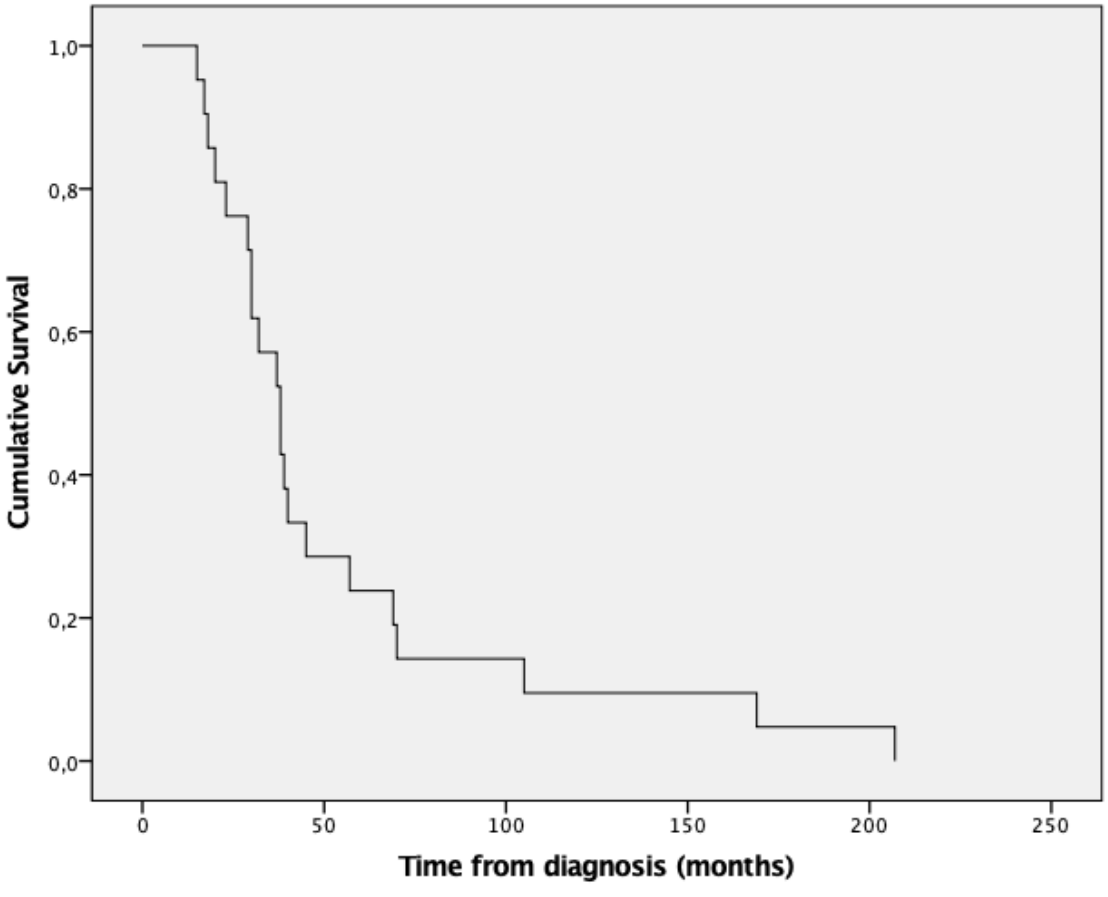


Figure 1: Survival function using Kaplan-Meier estimates following re-irradiation for patients with recurrent/second primary head and neck cancer.

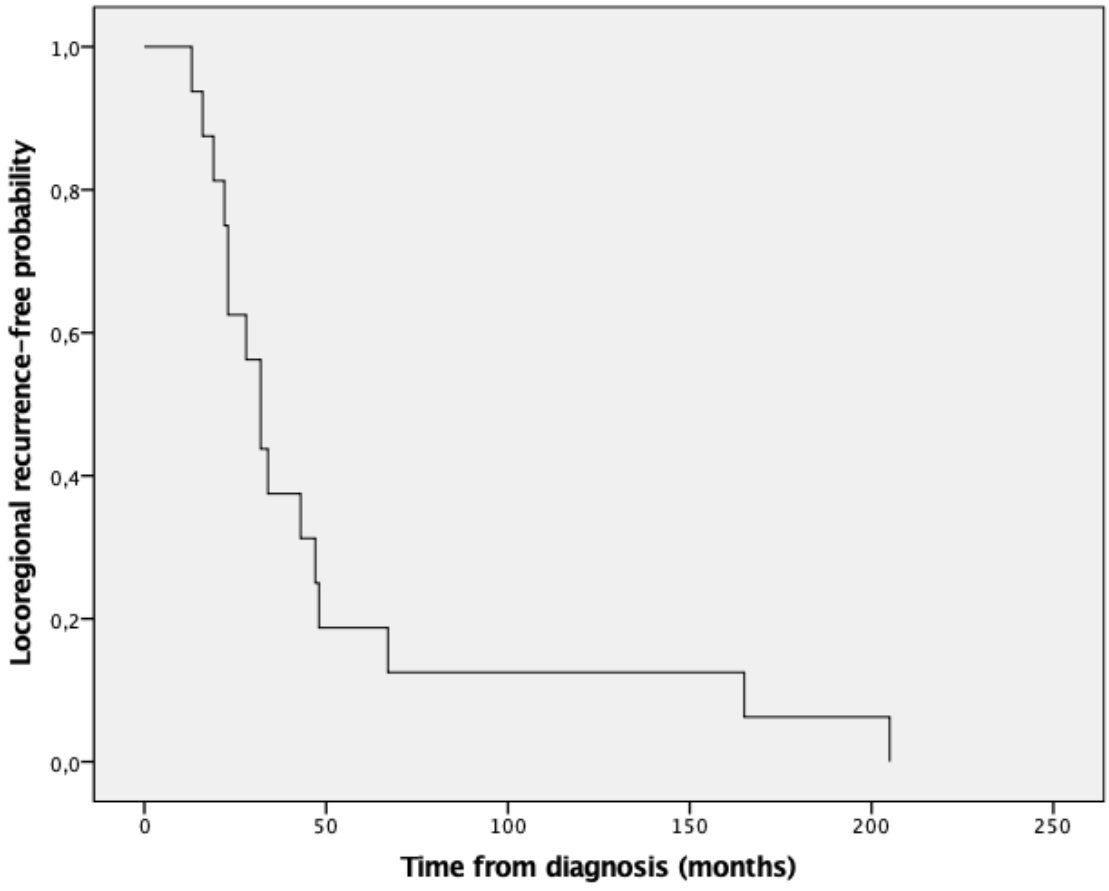


Figure 2: Locoregional recurrence using Kaplan-Meier estimates following re-irradiation for patients with recurrent/second primary head and neck cancer.

morbidity, nonoperative radical re-irradiation may be appropriate with curative intent. This is supported by prospective data, such as the 2 single-arm phase II trials from the RTOG which demonstrated the feasibility of definitive re-irradiation[11, 12].

Re-irradiation is a potentially curative treatment option for some patients with unresectable disease; however, concerns for increased risk of severe or life-threatening treatment-related toxicity and tumour radioresistance pose a challenge[2].

We report our re-irradiation experience using IMRT for patients with recurrent or second primary head and neck cancer.

Several studies have shown that re-irradiation dose strongly correlates with survival[13-15], and in first-line setting, concurrent systemic therapy and radiation are more efficacious than radiation alone[16,17].

From a total of 39 patients analysed, it was found that re-irradiation seems to have been well tolerated by the studied population with severe toxicity rates (≥ grade 3) below 30%. There was no presence of grade 4 or 5 toxicities in the population studied. It was possible to perform surgical resection of the tumour lesion in about 26% (n=10) of patients, which is in accordance with what is described in the literature that the resectability of these patients is about 20%[10].

The median time between RT treatments was 20 months and this was not found to have a negative impact on acute or late toxicity in our patient group, but it did impact patient mortality (HR=0.828; 95% CI 0.731-0.939; p=.03).

We sought to investigate whether the use of concomitant systemic therapy had an impact on the toxicity of these patients. We found that there was only statistical significance in the degree of dysphagia during the first RT treatment, with a greater severity in the group of patients who underwent concomitant chemotherapy. It should be noted that about 56% of the patients analysed underwent concomitant chemotherapy during the first RT treatment, and only 23% did during re-irradiation.

We tried to understand whether these patients were able to complete the initially prescribed RT treatments and found that 5% (n=2, due to aspiration pneumonitis) and 13% (n=5, 3 due to maintenances related to the treatment machine and 2 due to respiratory infections) did not complete the entire dose initially prescribed in the first and second RT treatments, respectively.

With univariate logistic regression, we tried to find some predictor of severe toxicity in these patients, but it was not possible to find statistical significance in the analysed variables.

There was a need to use enteral feeding tubes in about 26% (n=10) of patients during the first RT treatment and 28% (n=11) during re-irradiation, which is in agreement with previously published results of about 20%[10].

The same percentage of patients with aspiration pneumonitis was found in both courses of RT treatment: about 5% (n=2), which is also in accordance with the literature[18].

The need for respiratory stoma was 13% (n=5) in the first RT treatment and 26% (n=10) in the second treatment; there is an estimated prevalence in the literature of about 20%[19].

For a secondary malignancy to be considered possibly attributable to radiation, it must fall within the primary or secondary radiation beam, have a different histology than the primary cancer, have a latency period of several years, not have been present at the time of initial cancer diagnosis, and not be in a patient with a cancer-prone syndrome[20].

In our studied population, 100% (n=39) were submitted to biopsy before re-irradiation, and in all cases we observed the same histology (squamous cell carcinoma). We could suppose that the follow-up time wasn't long enough in order to detect the presence of a secondary primary tumour, since for solid tumours it is estimated that the time for emergence of these neoplasms is greater than 10 years[21].

Multivariable cox regression showed that only the time between irradiations was associated with a decrease in the risk of mortality (HR=0.828; CI 95% 0.731-0.939; p=.03), which is in accordance with the published results from the multivariable analysis described in table 1. Retrospective data suggest that survival decreases dramatically as the time between the 2 courses decreases, and enthusiasm for retreatment should be tempered at shorter timepoints[5].

In our sample of patients, we obtained a median overall survival of 38 months for patients undergoing re-RT. Overall survival at 2 years in our patient population was 76.2%, which is slightly higher than expected. When compared to previously published results, Takiar et al. reported a 2-year OS of about 60% for class I patients in the risk stratification[2].

It should be noted that the study has some limitations insofar as it is a unicentric and retrospective study with a small sample of patients.

5. Conclusion

Re-irradiation is an increasingly important therapeutic alternative in the treatment of patients with malignant tumours in the Head and Neck region.

Technological development has made it possible to increase the precision of radiotherapy treatments. Multidisciplinary discussion throughout the disease process and careful monitoring of toxicities are essential for the correct approach to treating patients with tumours in the head and neck region.

Conflict of interest statement

All authors have participated in the conception and design or analysis and interpretation of the data, drafting the article, or revising it critically for important intellectual content, and the approval of the final version.

This manuscript has not been submitted to, nor is it under review at, another journal or other publishing venue.

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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