



Adjuvant radiotherapy in malignant tumors of parotid. Experience of the Navarra Hospital Complex

Maitane Rodriguez Mendizábal¹, Sonia Flamarique Andueza¹, Isabel Quílez Sarda², Maider Campo¹, Gemma Asin Felipe¹, Lombardo Rosas Gutierrez¹, Andrea Barco Gomez¹, Fernando Arias de la Vega²

¹Radiation Oncology, Navarra Hospital Complex, Pamplona, Spain

²Maxillofacial Surgery Services, Navarra Hospital Complex, Pamplona, Spain

ABSTRACT

Background: The objective of the study was to review the outcome of patients with parotid cancer treated with postoperative radiotherapy at Complejo Hospitalario de Navarra in the last ten years.

Materials and methods: We retrospectively reviewed patients treated with adjuvant radiotherapy between January 2008 and December 2018. We analyzed demographic data, histopathologic findings, local control (LC) and overall survival (OS).

Results: A total of 40 patients received postoperative radiotherapy during the period mentioned. There were 22 men (55%) and 18 women (45%). Median age was 58 years (19-90). By tumor histology, the most common was squamous cell carcinoma (22.5%) followed by ex-pleomorphic adenoma (15%) and adenoid cystic carcinoma (10%). According to Surgery, 19 patients (47.5%) underwent a total parotidectomy, 20 (50%) partial parotidectomy, and 1 (2.5%) a radical parotidectomy. Twenty-one patients (51.2%) underwent cervical dissection, most of them being supraomohyoid (31.7%). Reasons for adjuvant RT were: R1 resection (35% of the patients), high grade tumors (27.5%) and 17.5% because R1 surgery and R1. Radiation was administered using IMRT in most patients to a total dose of 60 Gy in 30 fractions. The 5-year overall survival (OS) (Kaplan-Meier) was 81% (95% CI: 68.5-96.2%), and 10-years — 64%. The 5-year local control (LC) (Kaplan-Meier) was 82.4% (95% CI: 91.46-73.33%) and the 10-year LC — 72.2% (95% CI: 54.9-96%). To date, only 4 patients (10%) have died due to their parotid tumor.

Conclusion: The adjuvant radiotherapy added to surgery, significantly reduces the risk of recurrence in high-risk patients with a very acceptable survival rate.

Key words: parotid cancer; adjuvant radiotherapy; external beam radiation therapy

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Introduction

Malignant tumors of the salivary glands have a low annual incidence, similar in both men and women. They represent 3 to 5% of malignant head and neck tumors. Although the incidence of head and neck tumors is decreasing, the rate of parotid cancer has increased since 1973 [1]. We need more research to understand the etiology, risk factors,

and pathophysiology of parotid cancer in order to decrease the incidence.

The salivary glands are divided into major (parotid, submandibular, sublingual) and minor (located in the oral cavity, pharynx, and paranasal sinuses). However, 90% of malignant salivary gland tumors are diagnosed in the parotid.

Although the histological classification of salivary gland tumors includes numerous entities [2], the most

Address for correspondence: Fernando Arias de la Vega, Maxillofacial Surgery Services, Navarra Hospital Complex, Pamplona, Spain; e-mail: farias.delavega@outlook.es

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common malignant tumors are mucoepidermoid carcinomas, adenoid cystic carcinomas, and adenocarcinomas. Among the benign tumours, pleomorphic adenomas (5–10% undergo malignant transformation) and Warthin's tumors are the most frequent.

Cytological diagnosis is usually established by FNA with ultrasound control, and its study includes CT and MRI to establish local extension. However, the definitive pathological diagnosis cannot be established until the final study of the surgical piece. PET will rule out metastatic disease and confirm lymph node involvement, if any.

The main treatment is surgery, ideally, by total resection with free margins and preservation of the facial nerve when possible. In high-grade tumors or positive neck nodes, an ipsilateral cervical lymph node dissection will be indicated [3].

Postoperative radiotherapy is indicated in cases with incomplete resections (R1 and R2), in high-grade tumors, such as cystic adenoid carcinomas, and in stages T3 and T4 [3, 4].

In this article, we focus on the role of postoperative radiotherapy in parotid carcinoma, its impact on locoregional control, and its possible prognostic factors. We report the experience of the Radiation Oncology Service (RO) of the Navarra Hospital Complex (CHN) in a postoperative treatment of parotid tumors operated in the Maxillofacial Surgery Service (MFS) during the last decade.

Materials and methods

Characteristics of the patients

Between 2008 and 2018, 40 patients with parotid carcinoma were treated with surgery and radiotherapy at the CHN. The mean follow-up was 84 months (range 6–139) for living patients.

Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Variable	Category	n (%)
Age		Mean 58.3 (19–90 y)
PS (ECOG)		
	0–1	39 (97.5%)
	2	1 (2.5%)
Sex		
	Male	22 (55.0%)
	Female	18 (45.0%)

Table 1. Patient characteristics

Variable	Category	n (%)
T		
	1	12 (30.0%)
	2	23 (57.5%)
	> 2	5 (12.5%)
Localization		
	Superficial	32 (80.0%)
	Deep	4 (10.0%)
	Superficial + deep	4 (10.0%)
Histology		
	Epidermoid	9 (22.5%)
	Ex pleomorphic adenoma	6 (15.0%)
	Adenoid cystic carcinoma	4 (10.0%)
	Secretory	4 (10.0%)
	Mucoepidermoid	3 (7.5%)
	Ductal	3 (7.5%)
	Pleomorphic adenoma	3 (7.5%)
	Sarcomatoid	2 (5.0%)
	Others	6 (15%)
Type of surgery		
	Superficial parotidectomy	20 (50.0%)
	Total parotidectomy	19 (47.5%)
	Radical parotidectomy	1 (2.5%)
Indication RT		
	G3	11 (27.5%)
	R1	14 (35.0%)
	G3 + R1	7 (17.5%)
	Relaps	5 (12.5%)
	Unresectable	1 (2.5%)
	PNI, N+	1 (2.5%)
	Unknown	1 (2.5%)
Dose RT		
	Median (IQR)	60.0 (6)
	≤ 65	28 (70.0%)
	> 65	12 (30.0%)
Time from surgery to RT		
	Median (IQR)	55 (38)
	≤ 60	24 (60%)
	> 60	16 (40%)
Local relaps		
	No	33 (82.5%)
	Yes	7 (17.5%)
Exitus		
	No	31 (77.5%)
	Yes	9 (22.5%)

RT — radiotherapy

The mean age was 58 years (range 19–90). All tumors were located in the parotid gland (20% deep lobe).

Surgery was performed by superficial (50%), total (47.5%) or radical (2.5%) parotidectomy. Surgery included some type of cervical lymph node dissection (ND) in 20 patients (51.2%). This dissection consisted of an ipsilateral SOHD in 13 patients (65%), level IIa excision in 2 patients (10%), radical ND in 2 patients (10%), and radical modified ND in 2 patients (10%). One patient underwent bilateral cervical neck dissection (5%).

The pathological anatomy showed a wide variability of histological subtypes, the most frequent being squamous cell carcinomas (22.5%), followed by ex-adenoma pleomorphic carcinoma (15%), adenoid cystic carcinoma (10%) and secretory carcinoma (10%).

After doing neck dissection, the nodal positivity rate was 40%.

All patients received radiotherapy and the main reasons were the degree of tumor differentiation G3 (27.5%), R1 resection (margin-free < 2 mm) in 35% or a combination of both (17.5%). The dose of RT was 60 Grays (Gy) in most cases and the median gap (time from surgery to application of RT) was 55 days.

Radiotherapy plan

RT was local (parotid bed) in 18 patients (44%) and loco-regional (bed and cervical lymph nodes) in 23 patients (56%).

Patients were treated daily with a dose of 2 Gy up to a median dose of 60 Gy (81–50 Gys). In the case of R1 surgery, the affected margin has been boosted up to 66 Gy. In the 23 patients treated with loco-regional RT, the RT doses on cervical neck nodes ranged between 63 Gy and 50 Gy. Until 2013, 19 patients received radiotherapy with a 3D technique with a combination of photons and electrons. Since 2013, 22 patients have been treated with IMRT. An example of IMRT treatment is shown in Figure 1.

In relation to chemotherapy (CT), most of the patients did not receive concomitant CRT due to poor evidence published on parotid cancer and, more specifically, in the postoperative setting. In this sense, only three patients were treated with weekly cisplatin (two pN1 and R1 resection, and one unresectable squamous cell carcinoma).

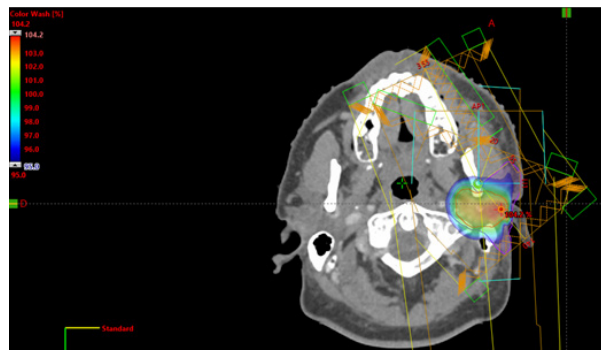


Figure 1. Example of radiotherapeutic treatment by intensity modulated radiotherapy (IMRT)

Statistical analysis

The characteristics of the sample are described by descriptive statistics; frequencies and percentages were used for categorical variables, and for quantitative variables, means and standard deviations (SD) or median and interquartile range (IQR), as appropriate.

Recurrence-free survival (RFS) and overall survival (OS) were measured from the date of diagnosis and the date of recurrence or death, respectively. The Kaplan-Meier method and the log-rank test were used to analyze the differences in survival time between the various factors. Cox proportional hazards regression models were used to assess the relationship between the covariates and both outcomes, which also provided an estimate of the hazard ratios (HR) and 95% confidence intervals (CI). The multivariate regression model was adjusted with those variables with HR less than 0.5 or greater than 2 and adjusted for age and sex.

Results

Local control and toxicity

Seven (17.5%) of the 40 patients included in the study, presented a local recurrence during follow-up. It should be noted that 86% were diagnosed in the first 2 years of follow-up.

Local control at 5 years (Kaplan-Meier) was 82.4% (95% CI: 91.46–73.33%). Local control at 10 years was 72.2% (95% CI: 54.9–96%) (Fig. 2A).

Acute side effects consisted only of epithelitis grade 1–2 in 80% of the patients and grade 3 in the rest. There are no grade > 2 late effects.

Overall survival

During the follow-up period, nine patients (22.5%) have died.

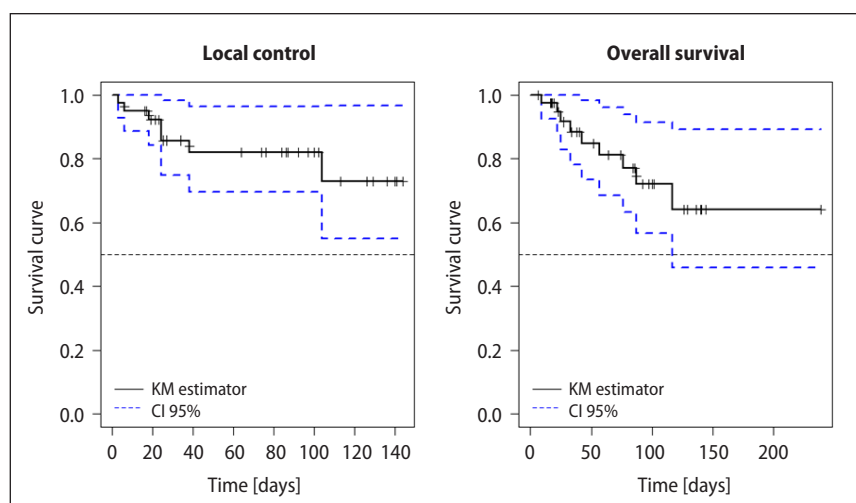


Figure 2. A. Local control (LC); **B.** Overall survival (OS) of the series

Overall survival at 5 years (Kaplan-Meier) was 81% (95% CI: 68.5–96.2%), and at 10 years 64% (Fig. 2B). It should be noted that of the 9 patients deceased in the series, in only 4 (44%) was the cause parotid tumor.

Prognostic factors for local control (LC)

Taking into account the size sample and a very small number of events for both LC and OS, it is unlikely to find significant associated factors. In this sense, the bivariate study (Tab. 2) shows some factors that present HR greater than 2 (grade 3, RT dose > 65 Gy and time until RT > 60 days) that could indicate a certain trend.

Since there are no factors that are significantly associated with LC in the bivariate analysis, those variables that have a HR ≥ 2 or ≤ 0.5 were selected to be entered in the multivariate model together with the age and sex variables (Tab. 3). Indeed, no variable is independently associated with local control in the multivariate model, although it is very possible that it is due to the insufficient power of the analyzes due to few events

Discussion

The role of postoperative radiotherapy as an independent factor in locoregional control of tumors of the salivary glands and, especially, of the parotid glands, is based on retrospective studies [3–11]. The low incidence of these tumors makes it difficult to conduct prospective randomized trials. However, all studies with a significant number of patients, such

as those by Mahmood with 2,170 patients from the SEER base [3] or Terhaard [4] from the DHNOC with 498 patients, have shown a positive impact of postoperative radiotherapy on parotid tumors.

The local control of our series at 5 years was 82.4% comparable with the reported series [5, 6, 11]. In the analysis performed by Kim YH [12] in parotid carcinomas, he concluded that the degree of differentiation, histological grade, pathological T stage, and lymphovascular invasion were independent prognostic factors for local control and survival. In our series, there is no significant factor, although high-grade tumors, especially in those over 65 years of age, have shown a certain tendency to have worse LC.

The high percentage of squamous cell carcinomas (22.5% of the total) is remarkable in our series, with primary parotid tumors being histologically indistinguishable from intraparotid metastases of squamous cell carcinomas. In the latter case, it is usually associated with a history of squamous cell carcinoma in the area close to the gland [13].

On the other hand, long-term follow-up is recommended because recurrence can appear later [14]. In this sense, our data would not support this conclusion given that 86% of local recurrences have occurred in the first 2 years of follow-up.

The time factor plays an important role in the combined treatment of head and neck cancer. Peters et al. [15] postulated that after surgery, residual tumor cells would repopulate to their maximum potential. Because salivary gland tumors generally grow slowly, a lesser adverse effect would be expect-

Table 2. Bivariate COX regression

Bivariate		LC	
Variable	Category	HR (95% CI)	p-value
Age		1.03 (0.98, 1.07)	0.216
Sex			
	Male	Reference	
	Female	0.95 (0.21, 4.27)	0.952
T			
	1	Reference	
	2	1.42 (0.24, 8.31)	0.700
	> 2	1.37 (0.12, 15.51)	0.800
Localization			
	Superficial	Reference	
	Superficial + deep	0.61 (0.07, 5.07)	0.647
Histology			
	Epidermoid	Reference	
	Others	0.36 (0.08, 1.62)	0.185
Dose RT			
		1.04 (0.92, 1.17)	0.505
	≤ 65	Reference	
	> 65	2.45 (0.54, 11.20)	0.248
Indication RT			
	G3	Reference	0.468
	R1	0.73 (0.12, 4.52)	0.738
	G3 + R1	2.59 (0.36, 18.77)	0.348
Indication RT			
	Not G3	Reference	
	G3	3.19 (0.61, 16.6)	0.168
Type of surgery			
	Superficial parotidectomy	Reference	
	Total parotidectomy	2.20 (0.40, 12.1)	0.362
Time from surgery to RT			
		1.00 (0.999, 1.001)	0.788
	≤ 60	Reference	
	> 60	2.17 (0.48, 9.71)	0.311

LC — local control; HR — hazard ratio; CI — confidence interval; RT — radiotherapy. *There is no variable significantly associated with time to relapse-free. There are some factors with a HR greater than 2 (highlighted in red) that could indicate a certain trend

ed from the delay between surgery and postoperative RT, although our data suggest a lower LC when the delay exceeds 60 days.

Regarding irradiation doses, a dose of at least 60 Gy is recommended. The decision to electively

Table 3. Multivariate COX regression

Multivariate*		LC	
Variable	Category	HR (95% CI)	p-value
Age		1.06 (0.98, 1.14)	0.131
Sex			
	Male	Reference	
	Female	2.54 (0.29, 21.9)	0.397
Dose RT			
	≤ 65	Reference	
	> 65	4.21 (0.51, 35.0)	0.183
Indication RT			
	Not G3	Reference	
	G3	4.84 (0.25, 91.3)	0.292
Type of surgery			
	Superficial parotidectomy	Reference	
	Total parotidectomy	2.83 (0.22, 36.1)	0.422
Time from surgery to RT			
	≤ 60	Reference	
	> 60	5.67 (0.53, 61.0)	0.152

LC — local control; HR — hazard ratio; CI — confidence interval; RT — radiotherapy. No variable is independently associated with relapse-free time in the multivariate model, although it could be because of a lack of power due to the few events

treat neck nodes should be based on the T stage and histological type of the tumor. Postoperative cervical radiotherapy is indicated in cases of lymph node infiltration, with doses between 50–66 Gy depending on the degree of involvement. In our study, no statistically significant relationship was found between the RT dose and local control, probably because the radiotherapy treatment was quite homogeneous and with similar irradiation doses. Effectively, the mean dose was 62 Gy, and the total dose was adjusted to the state of the resection margin.

Due to the fact that the time interval of the series was long, various technical improvements have been adopted that have optimized the treatment and made it possible to administer lower doses of radiation to healthy tissues [from RT3D, intensity modulated RT (IMRT) [16] or volumetric RT (VMAT) [17], adaptive radiotherapy [18].

Conclusion

Based on our results and the review of published studies, we recommend postoperative ra-

diotherapy for T3–4 parotid tumors, incomplete resection (R1 or R2), perineural invasion, or high-grade tumors.

Conflicts of interest

None declared.

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