

# Radiotherapy in Inoperable Mucoepidermoid Parotid Cancer: A Case Report

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## ABSTRACT

**Introduction:** Salivary gland cancer is an uncommon malignancy in the head and neck. The most common histopathologic type in salivary gland malignancies is mucoepidermoid carcinoma (MEC). Radiotherapy has a role in salivary gland malignancy, especially in inoperable cases and postoperative settings. Definitive or postoperative radiotherapy with or without chemotherapy can improve locoregional control (LRC) in patients with parotid mucoepidermoid carcinoma.

**Case Presentation:** We report a case of a 77-year-old male with inoperable MEC of the right parotid, who received definitive radiotherapy. From the three-month evaluation after radiation therapy, we found a significant reduction in the tumor mass.

**Conclusions:** Surgery remains the treatment of choice for patients with salivary gland malignancies. Definitive radiotherapy can be a treatment modality in inoperable cases or patients who refuse surgery. Although the result is not satisfactory, radiotherapy can still give clinical benefits to patients.

## INTRODUCTION

Salivary gland malignancy occurs in 1/100,000 of the population and accounts for < 5% of all head and neck malignancies. It is therefore categorized as an uncommon malignancy [1]. In salivary gland tumors, 85% of tumors originate from the main salivary glands (parotid, submandibular, and sublingual glands), wherein 73% are parotid gland tumors, with 80-85% of benign tumor. Pleomorphic adenomas are the most common histologic findings in benign tumors while mucoepidermoid carcinoma (MEC) is the most common in malignant tumors, accounting for 34% of all parotid gland malignancies [2].

Surgery is the main treatment in non-metastatic and resectable salivary gland malignancies to achieve maximal free margin resection [3]. Regional lymph node dissection is performed in cases with evidence of metastasis either clinically or radiologically or can be considered in the high-risk N0 case [2]. Radiotherapy has a promising role in salivary gland malignancies, especially in non-operable and post-operative settings. Radiotherapy can be a definitive therapy as well as adjuvant radiotherapy in patients with high-risk features

for recurrence, which include positive surgical margin, metastases in lymph nodes, extracapsular extension (ECE), perineural invasion, lymphovascular invasion, large tumor size, and high-grade histopathology [3,4]. On the other hand, for unresectable patients or those who refuse surgery, there is limited information regarding the clinical benefit of definitive radiotherapy. Here, we report our experience in the treatment of inoperable intermediate-grade MEC of the parotid gland and undergo definitive radiotherapy only.

## CASE PRESENTATION

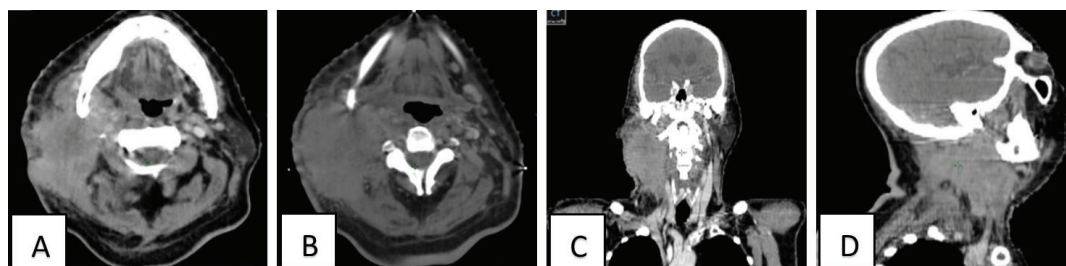
A 77-year-old man with the main complaint of swelling on the right face which had occurred last year. A lump appeared in the area behind the right ear with a size of 3 x 3 cm, which was growing to a size of 11 x 7 cm. The lump was fixed, painless, and reddish. There was no history of malignancy in the family. During radiology examination in January 2018, a contrast-enhanced solid mass was found in the deep lobe and superficial lobes of his right parotid with a size of 7.5 x 5 x 9 cm. Multiple lymph nodes with central necrosis

were found in the submental, bilateral submandibular, and bilateral level II regions, and ipsilateral level III on his neck (**Figure 1**). The left parotid gland and the left submandibular were normal. There was no evidence of distant metastasis from abdominal ultrasonography, thorax x-ray, and bone scan. Therefore, according to AJCC 7.0, it was classified as T4b N3 M0. Excisional biopsy was performed with the conclusion of intermediate grade mucoepidermoid carcinoma without perineural invasion. The patient is advised to get concurrent chemoradiation, but unfortunately, the patient refused to undergo chemotherapy and preferred radiotherapy only. Information regarding the benefits, risks, procedures, effects, and alternatives has been informed to the patient carefully and obtained approval for medical treatment.

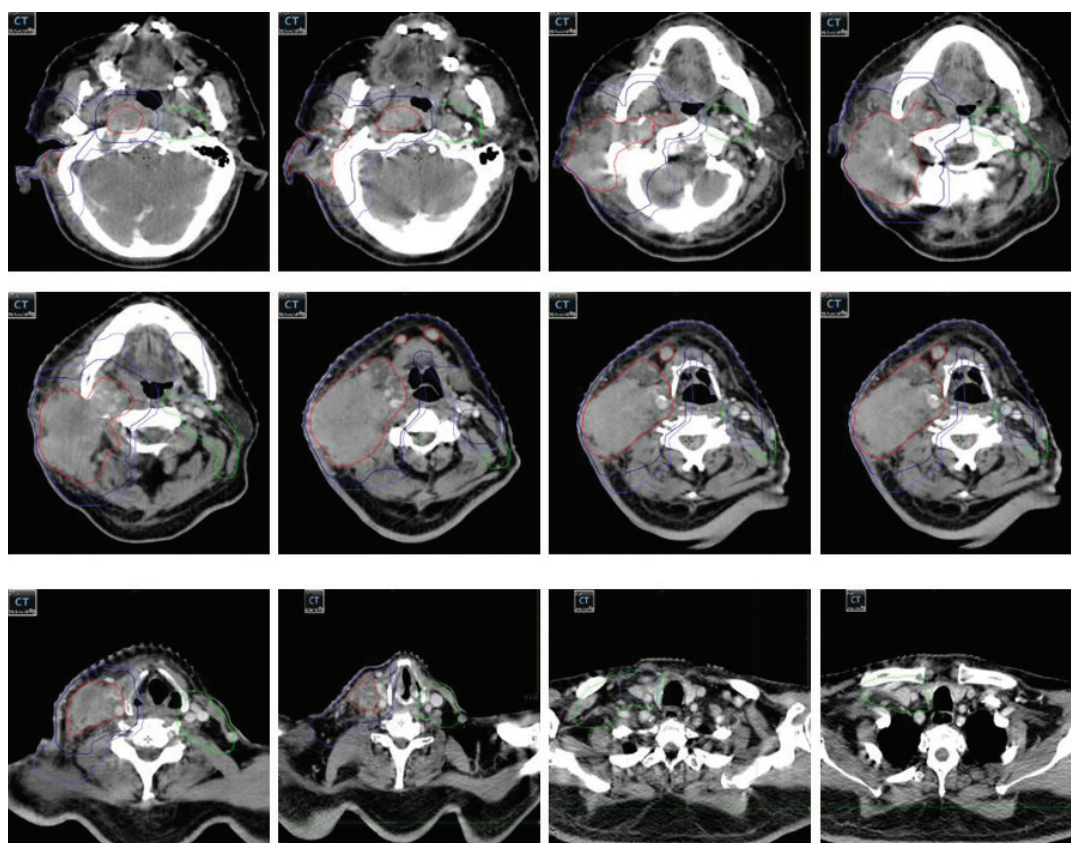
The primary target volume was determined by adding 5 mm margin from gross tumor for high-risk region and 10 mm from gross tumor for low-risk region. The lymph-

node target volume was determined by using the guidelines of delineation by Gregoire et al. [5] at the ipsilateral levels of IA, IB, II, III, IVA, IVB, VA, VB, and VIIA and contralateral levels of IA, IB, II, III, and VIIA (**Figure 2**) [5,6]. Delineation of organ at risk (OAR) followed the delineation guidelines of Brouwer et al. [7], and the dose constraint was adjusted to the QUANTEC criteria [7]. Radiation therapy was delivered in five fractions a week using a TomoTherapy machine (TomoTherapy, Madison, WI). Treatment planning dose distribution can be seen in **Figure 3**. Patients completed the radiation treatment according to the plan with an overall treatment time of seven weeks and two days. During the treatment, the patient had experienced moderate xerostomia, sore throat (first-degree pharyngeal and esophageal RTOG toxicity), radiation field hyperpigmentation (first-degree RTOG skin toxicity), and oral mucosa pseudomembrane (first-degree RTOG mucosa toxicity) which could be well tolerated [8].

**Figure 1.**  
The pre-radiation head and neck CT scan, axial section (A-B), coronal section (C), sagittal section (D).

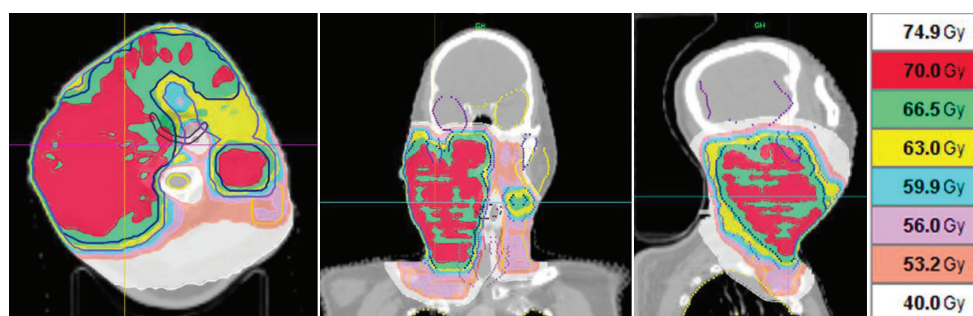


**Figure 2.**  
Head-neck locoregional radiation targets with the Simultaneous Integrated Boost (SIB) Intensity-Modulated Radiation Therapy (IMRT) technique 70/63/56 Gy in 35 fractions; Gross Tumor Volume (GTV) tumor and lymph nodes; Planning Treatment Volume (PTV) 70 Gy = GTV + 5mm (dark blue), PTV 63 Gy = GTV + 10mm (light blue), PTV 56 (green).

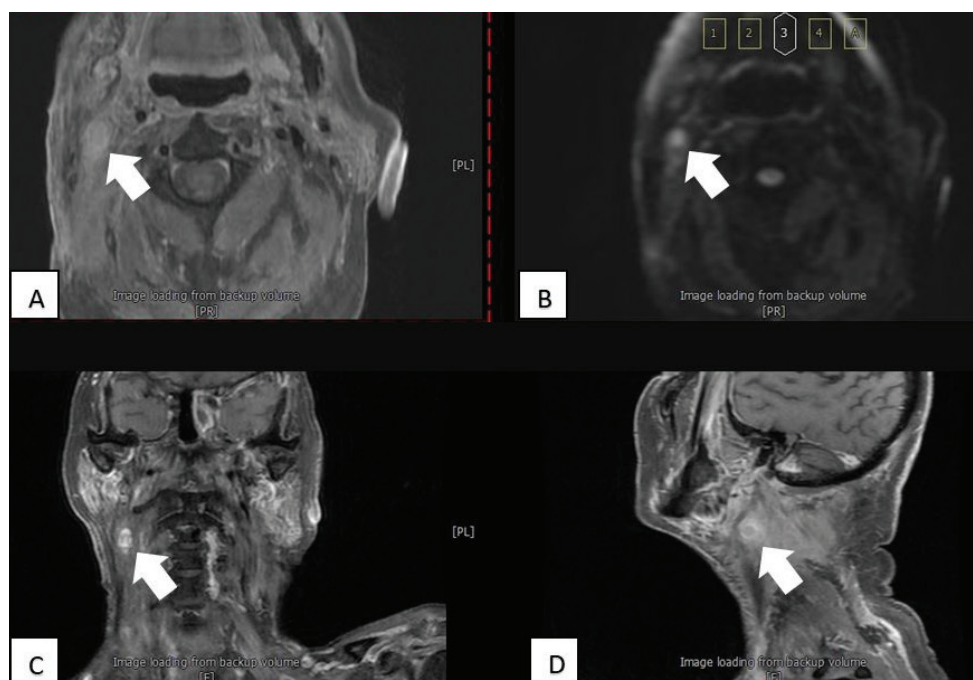


**Figure 3.**

The dose distribution of the SIB IMRT plan with our institutional standards, which is the volume of PTV, gets a minimum of 95% dose or PTV 95 >95%, and the volume of PTV gets a maximum of 107% dose <2%.

**Figure 4.**

T1 MRI evaluation with contrast administration three months after external radiation. Axial section (A), DWI – MRI (B), coronal section (C), sagittal section (D). Examination results showed residual lesions on the right parotid bed with a size of 1.7 x 1.1 x 1.5 cm. No lymph node enlargement was found in the sub-mandible and the neck region.



Three months after radiotherapy MRI evaluation showed a round, unwell-defined, and contrast enhancement lesion located in the right parotid bed with a size of 1.7 x 1.1 x 1.5 cm with a differential diagnosis of residual disease. No lymph node enlargement was seen in the submandibular and the neck region (**Figure 4**). The head and neck CT-scan evaluation six months after radiotherapy showed multiple rounded hypodense lesions that were not well-defined and heterogeneous enhanced after contrast, in the right parotid bed, with various diameter sizes from 0.3 cm to 1.9 cm. Multiple lymph node enlargement regions were at the left level II and IV neck region, with the largest short-axis diameter of 1.4 cm. Patients were considered for salvage surgery and lymph node dissection in the neck region, but this was not possible because of the patient's low-performance status (age-related comorbidity, frailty, and refusing surgery). Chest x-ray follow-up examination one year after radiotherapy showed multiple nodules in both lungs, suggesting pulmonary metastases. It was informed that the patient died one year after the treatment with main complaints of shortness of breath due to pulmonary metastases.

## DISCUSSION

The salivary glands consist of three paired major glands, namely, parotid, submandibular, and sublingual glands, and many small glands located in the upper aerodigestive tract. The parotid gland is the largest salivary gland. Cancer of the salivary glands has a unique and distinctive growth pattern. Malignancies with histopathological Adenoid Cystic Carcinoma (ACC), low-grade MEC, and acinic cell carcinoma are classified as slow-growing tumors. These tumors grow so slowly that they can cause difficulty in determining a benign or non-neoplastic lesion. As for the regional lymphatic spread, salivary gland cancer has a lower incidence than squamous cell carcinoma (SCC). The incidence of regional metastases in salivary gland cancer is estimated to occur in 15% of cases. However, in several histopathology types such as ductal carcinoma, high-grade MEC, carcinoma ex pleomorphic, and adenosquamous carcinoma, the incidence of regional metastases is more common (50% of cases). In contrast, low-grade polymorph adenocarcinoma, low-grade MEC, and ACC have a relatively low incidence of regional metastases.



**Table 1.** Role of definitive radiotherapy in salivary gland malignancies and survival

Study	Year	Sample	Radiation Source	Treatment Modalities	N (%)	Median overall survival (month)
Bhide et.al [23]	2009	80	Photon	Surgery + radiation Radiation	69 (86,2%) 11 (13,8%)	114 (40,8–183,6) 7,2 (3,6–18)
Rosenberg et.al [24]	2011	15	Photon	Definitive chemoradiation Surgery + chemoradiation	7 (46,67%) 8 (53,33%)	2 years LRC 34% 2 years LRC 85%
Spratt et.al [21]	2014	27	Photon	Chemoradiation Radiation	18 (66,7%) 9 (33,3%)	2-year survival 50% (± 19.0%) dan 5-year 29% (± 16.6%)
Rajasekaran et.al [1]	2018	4431	Photon	Surgery Surgery + radiation Surgery + chemoradiation Radiation Chemoradiation Not treated Others	2081 (47%) 1660 (37,5%) 200 (4,5%) 75 (1,7%) 36 (0,8%) 83 (1,9%) 296 (6,6%)	NA NA 52,8 8,6 NA 7,2 NA
Timoshchuk et.al [22]	2018	545	Neutron	Radiation Surgery + radiation	145 (26,3%) 400 (73,7%)	6-year survival rate 59% 6-year survival rate 72%

In addition to the histopathology type, regional metastases are also influenced by tumor size. In a tumor with a size of more than 4 cm, the incidence of regional metastases can reach 20%. Distant metastases most often occur in the lung (80%), bone (15%), liver, and other organs (5%) [9,10].

Patients with an advanced stage of salivary gland malignancy have a poor prognosis. Based on the Epidemiological Surveillance Study in the United States, the 10-year survival rate in locally advanced-stage and advanced-stage salivary gland malignancy is 50–70% in stage III and 30–40% in stage IV [11]. Patients, who are under 54 years old, women, have a low-grade tumor, T1, N0, and free surgical margins will have a better survival prognosis [1].

Generally, it can be concluded that the salivary gland malignancy is not a radiosensitive tumor [12]. Therefore, surgery with free surgical margin resection is the first choice of treatment compared to other therapeutic modalities. This is supported by the National Comprehensive Cancer Network (NCCN) guidelines, which states that surgery is a standard treatment of salivary gland malignancy with adjuvant radiotherapy or chemoradiation in high-risk groups. High-risk groups based on the Dutch Head and Neck Oncology Cooperative Group are advanced stages tumors (T3 and T4), positive lymph nodes, inadequate surgical margins (less than 5mm), perineural invasion, and bone invasion [13,14]. Radiotherapy or chemoradiation can be considered when the patient refuses surgery or in a non-operable advanced tumor [10,13].

During the last two decades, there has been a significant development in the management of non-

operable head and neck malignancies, which is the combination of chemotherapy with radiotherapy. This paradigm significantly enhances local control and survival with the consequence of toxicity escalation. This is under the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) conducted by Pignon et al. [15], which analyzes the administration of external radiation with or without chemotherapy for head and neck squamous cell carcinoma. The administration of concurrent chemoradiation in head and neck malignancies showed an increase in 5-year survival of 4.5% (HR 0.88,  $p < 0.0001$ ). Moreover, the administration of concurrent chemoradiation also shows a reduced risk of distant metastasis. The benefit is proved with the hazard ratio of 0.88 ( $p = 0.04$ ) for the concurrent chemoradiation group, compared to the radiotherapy only [15]. Similar results were also mentioned by Blanchard et al. [16] that chemotherapy causes a 5-year risk of death reduction by 13% in squamous cell carcinoma of the oral cavity, oropharynx, larynx, and hypopharynx. Therefore, based on these results, many clinicians extrapolate these results for other head and neck malignancies, especially in salivary gland malignancy. However, the administration of adjuvant chemoradiation for salivary gland malignancy has not shown an increase in survival especially in high-risk groups [17].

In the case of inoperable salivary gland malignancy, the NCCN recommends definitive radiotherapy or high precision definitive chemoradiation in all histopathological types of salivary gland malignancy except for ACC. Patients are required to receive 70 Gy in the tumor and involve lymph nodes (including subclinical infiltration) with 2 Gy per fraction for seven weeks, and 54–63 Gy

(1.6 and 1.8 Gy/fraction) in the low and moderate risk PTV area. For postoperative patients with a positive margin, radiotherapy with a total dose of 66 Gy in 2 Gy/fraction for high-risk PTV and 54–63 Gy in PTV with low and moderate risk can be considered with a period of radiotherapy started less than 6 weeks after patients underwent surgery [13]. This is consistent with the report of Chen et al. [18] stating that a dose-response relationship might exist for salivary gland carcinomas treated with radiotherapy alone. A dose greater than 70 Gy resulted in better outcomes than less than 70 Gy. A 5-year local control was 70% for patients treated to a dose of 66 Gy or greater but 0% for patients treated to a dose of less than 66 Gy. Moreover, the radiotherapy also gives satisfactory results for distant metastases-free rates up to 85% and 67% at 5 and 10 years, respectively, although in this study, the patient had distant metastases after one year of completing radiotherapy. This study also identified the size of tumor T3–T4 disease ( $p = 0.004$ ) and a radiation dose lower than 66 Gy ( $p = 0.001$ ) as independent predictors of local recurrence [18].

In the operable cases, after physical and radiological examinations showed involvement of neck nodes, neck dissection was the standard of care. Selective neck dissection should include levels I, II, and III for sublingual and submandibular gland cancers and levels IB, II, III, IV, and VA for parotid cancer [9,10]. Elective neck irradiation (ENI) can be given for both postoperative or non-operable patients at the lymph node level without clinical or pathological involvement. The determination of ENI is usually individual and based on disease characteristics including tumor extensiveness, histopathology, and lymphatic drainage from primary tumors [19]. The dose for ENI is 54 Gy, while in positive lymph nodes, the area initially involved and with extracapsular extension is planned to receive 70 Gy at definitive setting and 60–66 Gy on the adjuvant setting. In determining ENI, at least levels Ib, II, and III must be included, while levels IV and V may not be included in cN0. Also, levels IV and V must be targeted when levels II and III are involved [19,20]. Literature studies have shown a low local control of salivary gland malignancy with definitive radiotherapy from photon energy sources. This is caused by low Linear Energy Transfer (LET) produced by photons [21]. Higher LET such as neutron, and heavy-ion result in more unrepairable double-stranded breaks of DNA within the cell directly; whereas, conventional radiotherapy relies on the formation of free radicals and reactive oxygenated species (ROS) that damage DNA indirectly (Table 1) [22].

The table illustrates that definitive radiotherapy can be an option in salivary gland cancer. The study of Spratt et al. [21] evaluated 27 inoperable salivary gland

patients (63%, high-grade tumors) at MSKCC from 1990 to 2009 who received definitive photon-based radiotherapy. The average therapeutic dose of radiotherapy was 70 Gy with 9 patients receiving IMRT and 18 3D-CRT. Chemotherapy was given to 18 patients, mostly platinum-based chemotherapy with a median follow-up of 52.4 months. This therapy showed acceptable results; the 2-year local control result was 69% ( $\pm 21\%$ ), the 2-year LRC was 65% ( $\pm 21.4\%$ ), and the 2-year and 5-year survival rates were 50% ( $\pm 19.0\%$ ) and 29 % ( $\pm 16.6\%$ ), respectively. Univariate analysis was performed and did not show that T-stage, N-stage, histopathology, major or minor salivary gland origin, and chemotherapy administration were the predictors of increased LRC. However, the degree of histology (intermediate vs low,  $p = 0.08$ , HR 4.40; high vs low,  $p = 0.14$ , HR 5.60) tends to result in worse LRC control [21].

Patients treated with definitive radiotherapy only are usually in the advanced stages and have poor prognostic features so the treatment options are not much available. Definitive radiotherapy with the adoption of advanced technology in radiotherapy such as intensity-modulated radiation therapy (IMRT) is likely to escalate the dose to the target while reducing toxicity will lead to increasingly recognizable clinical benefits for the patients. Combined surgery and radiotherapy with or without chemotherapy lead to a significant increase in local and loco-regional controls rather than radiotherapy alone for salivary gland malignancies. For patients with smaller and non-extensive diseases, it appears that radiotherapy alone has potentially been the alternative and feasible option in the future for patients desiring a nonsurgical approach. Moreover, further studies and large randomized clinical trials with specific patient criteria are required to give better perspectives.

## CONCLUSIONS

Surgery remains the treatment of choice for patients with salivary gland malignancy. For patients who are inoperable or refuse surgery, definitive radiotherapy is a reasonable alternative but unfortunately does not give satisfactory results because of the radioresistant characteristic. To improve therapeutic response, radiotherapy with a high LET radiation modality can provide better treatment results with a significant increase in the survival rate.

## DECLARATIONS

### Competing of Interest

The authors declare no competing interest in this study.

### Acknowledgment

None

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