

Place of Re-Irradiation in the Management of Local Relapses of Cavum Cancer

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Abstract

➤ Introduction

The rate of local control of nasopharyngeal carcinomas has increased more and more since the systematic use of conformal radiotherapy with intensity modulation. The treatment of local recurrences is essentially based on re-irradiation; but it is limited by the doses previously received by the organs at risk inseries.

➤ Goal of the study

To assess the efficacy and toxicity of re-irradiation of local relapses of nasopharyngeal carcinoma.

➤ Material and method

This is a retrospective study, including 12 patients re-irradiated at the National Institute of Oncology in Rabat for a local or loco regional relapse between 2015 and 2020.

➤ Results

Among 600 irradiated patients, 12 patients presented a local or loco regional recurrence for which they received re-irradiation with intensity modulation. The average age of the patients at the time of the initial diagnosis was 40.8 years (extremes of 22 and 52 years). The tumor was initially classified according to the AJCC 2017 classification as stage II, stage III and stage IV respectively in 2 cases (16%), 4 cases (34%) and 6 cases (50%). The initial treatment was based on neo- adjuvant chemotherapy followed by concomitant radio-chemotherapy in 9 patients (75%) and concomitant radio-chemotherapy alone in 3 patients (30%). Initial irradiation was according to a conventional three-dimensional technique having delivered a total dose of 70 Gy at the rate of 2 Gy per session. All patients were in complete remission. The mean time to local relapse was 7 years (range: 3 to 10 years). The diagnosis was confirmed by anatomo pathological study in all patients. The recurrence was classified as stage II, stage III and stage IV respectively in 3 cases (25%), 5 cases (41%) and 4 cases (33%).

On the therapeutic level, 5 patients (41%) received neoadjuvant chemotherapy followed by concomitant radio-chemotherapy; 6 patients (50%) received concomitant radio-chemotherapy alone and one patient received exclusive radiotherapy. Re-irradiation was intensity-modulated by Arc Therapy,

having delivered a total dose of 60 Gy in all patients at reason of 2Gy per fraction.

After a mean follow-up of 19 months (range: 10 months–34 months), seven patients were in complete remission; two died of the disease after an average follow-up of 10 months and three patients are lost to follow-up.

The late toxicity of re-irradiation was increased auditory toxicity (grade 3 becoming grade 4) in 4 patients, trismus in two patients and cervical fibrosis in two patients.

➤ Conclusion

Re-irradiation is the only salvage treatment for recurrences of nasopharyngeal carcinoma, precisely conformal radiotherapy with intensity modulation which makes it possible to deliver sufficient doses to the level of the tumor volume while sparing the organs at risk which have already been irradiated; however, given the associated toxicity, patients must be carefully selected.

Keywords:- Re-Irradiation; IMRT; Recurrence of Cavum Cancer

I. INTRODUCTION

The undifferentiated carcinoma of the nasopharynx (or the UCNT of the cavum) represents the most frequent histological form of cancers of the cavum in the Maghreb countries, it differs from other squamous cell carcinomas of the head and neck by its characteristic undifferentiated histology, its epidemiology without relationship with alcohol and tobacco and its constant relationship with the Epstein-Barr virus (EBV).

Radiation therapy remains the main treatment for UCNT, and progress recent studies now make it possible to envisage a better probability of tumor control while limiting morbidity (conformal radiotherapy by intensity modulation).

Among patients with locally advanced disease, chemotherapy combined with radiotherapy has increased disease-free survival in several trials.

Local recurrences of cavum cancers have an unfavorable prognosis and pose a management problem. Re-irradiation remains an effective therapeutic option to ensure a good rate of local control, but it is limited by the doses previously received by the organs at risk in series.

Intensity Modulated Conformal Radiation Therapy (IMRT) can be a solution to this problem by delivering sufficient doses to target volumes while sparing these organs at risk.

➤ *Our Study Aims to Goals*

To assess the efficacy and toxicity of re-irradiation of local relapses of nasopharyngeal carcinoma.

II. MATERIALS AND METHODS

This is a retrospective study, including 12 patients re-irradiated at the National Institute of Oncology in Rabat for a local or locoregional relapse between 2015 and 2020.

Diagnosis was based on MRI data (Figure 1) and pathological examination.

All patients were treated with curative intent by conformal radiotherapy with intensity modulation.

➤ *The Data Collected Was:*

- *Patient Age*
- *The Histological Type*
- *The Stage of the Disease*
- *The Therapeutic Protocol*
- *The Average Time to Recurrence*
- *Characteristics of Recurrences.*

➤ *Data analysis :*

The data collected was noted on an operating sheet then entered, stored and processed by SPSS25 and Excel 2013 software.

III. RESULTS

Among 600 irradiated patients, 12 patients having presented a local or locoregional recurrence, the average age of the patients at the time of the initial diagnosis was 40.8 years (extremes of 22 and 52 years). The tumor was initially classified according to the AJCC 2017 classification as stage II, stage III and stage IV respectively in 8%, 66% and 25% of patients. The initial treatment was based on neoadjuvant chemotherapy followed by concomitant radio-chemotherapy in 75% of patients and concomitant radio-chemotherapy alone in 12% of patients. Initial irradiation was according to a conventional technique

three dimensions having delivered a total dose of 70 Gy at a rate of 2Gy per session.

Table 1 Patients and Baseline Treatment Characteristics

	Characteristics	N (%)
Age (years)	Median	40.5 (22et 52)
T stage	T2	2 (16)
	T3	4 (34)
	T4	6 (50)
N stage	N1	2 (16)
	N2	4 (33)
	N3	6 (50)
TNM stage	II	1 (8)
	III	8 (66)
	IVa	3 (25)
Treatment Protocol	Induction chemotherapy	9 (75)
Dose (Gy)	Concurrent chemotherapy	12 (100)
	Mean	70

All patients were in complete remission. The mean time to local relapse was 7 years (range: 3 to 10 years).

Diagnosis was confirmed by MRI (Figure 1) and pathological study in all patients.

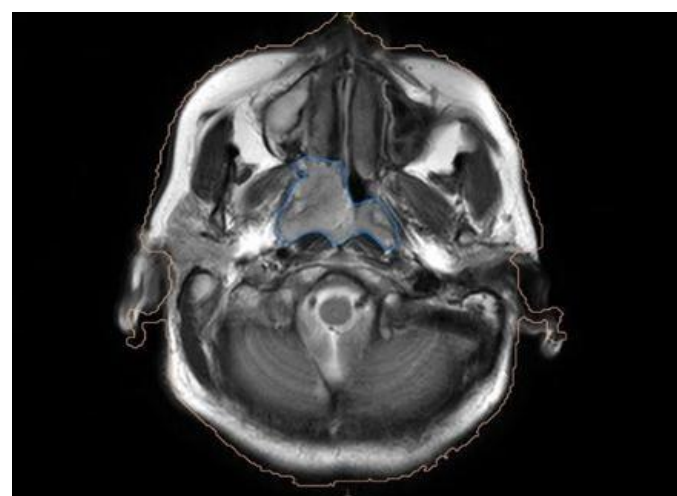


Fig 1 GTV Delineation Using CT and MRI Fusion

Recurrence was classified as stage II, stage III in 16% of cases and stage IV in 66% of cases.

Therapeutically, 5 patients (41%) received neoadjuvant chemotherapy based on gemcitabine (1g/m² IV D1D8) and cisplatin (80mg/m² IV D1) followed by concomitant radio-chemotherapy based on cisplatin (40mg/m² /week) ; 6 patients (90%) received concomitant radio-chemotherapy alone and one patient received exclusive radiotherapy.

Re-irradiation was with intensity modulation by Arc Therapy, having delivered a total dose of 60 Gy in all patients at a rate of 2 Gy per fraction.

Table 2 Characteristic of Recurrence

	Characteristics	N (%)
T stage	T1	
	T2	3 (25)
	T3	5 (41)
	T4	4 (33)
N stage	N1	2 (16)
	N2	4 (33)
	N3	6 (50)
TNM stage	II	2 (16)
	III	2 (16)
	IVa	8 (66)
Treatment Protocol Dose (Gy)	Induction chemotherapy	5 (41)
	Concurrent chemotherapy	12 (100)
	Mean	60

After a mean follow-up of 19 months (range: 10 months–34 months), 58% of patients were in complete remission; 17% of patients died from the disease and 25% of patients are lost to follow-up

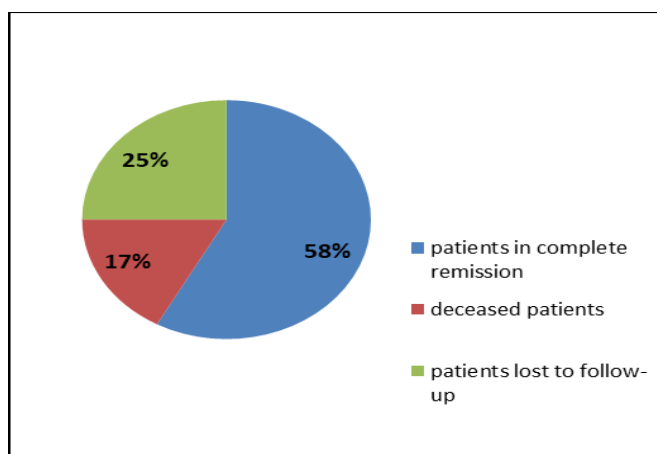


Fig 2 The Evolution of the Patients After A Follow-Up of 19 Months

➤ Grade 1, 2 and 3 Acute Dermal Toxicity Developed in 44%, 34% and 22% Respectively

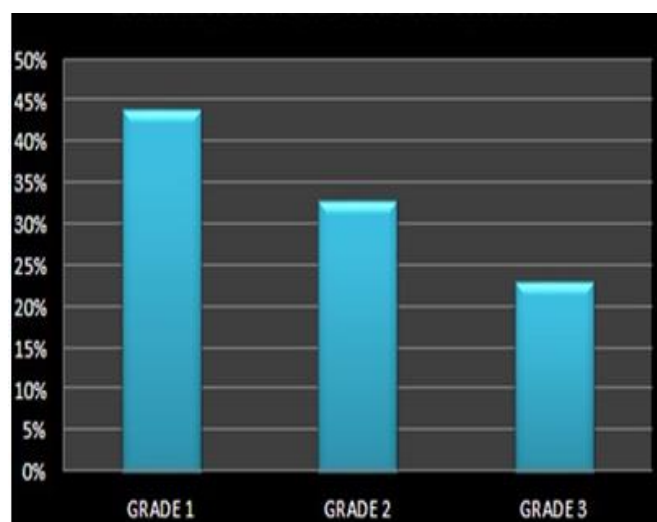


Fig 3 Evaluation of Skin Toxicity

➤ Grade 2 and 3 Oral Mucosal Toxicity Occurred in 33% and 12% Patients, Respectively

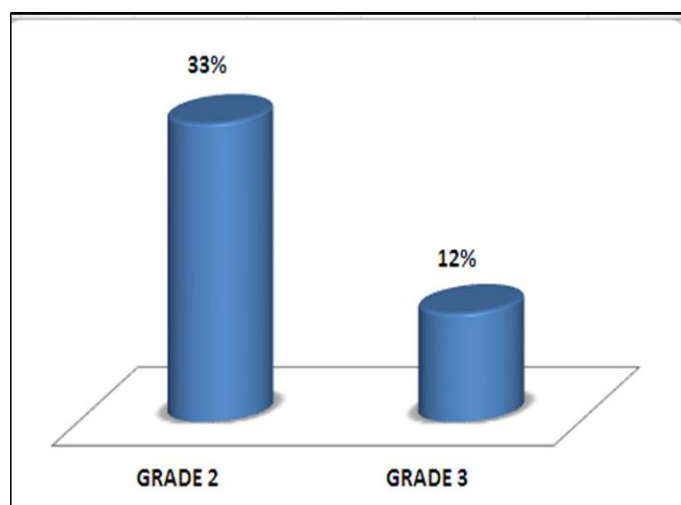


Fig 4 Oral Mucosal Toxicity Assessment

After termination of Concurrent chemotherapy, treatment-related toxicity was reported in a single patient with febrile pancytopenia, the patient died a few days later.

The late toxicity of re-irradiation was: increased auditory toxicity (grade 3 becoming grade 4) in 40% of patients trismus, cervical fibrosis and moderate dysphagia in 20% of patients.

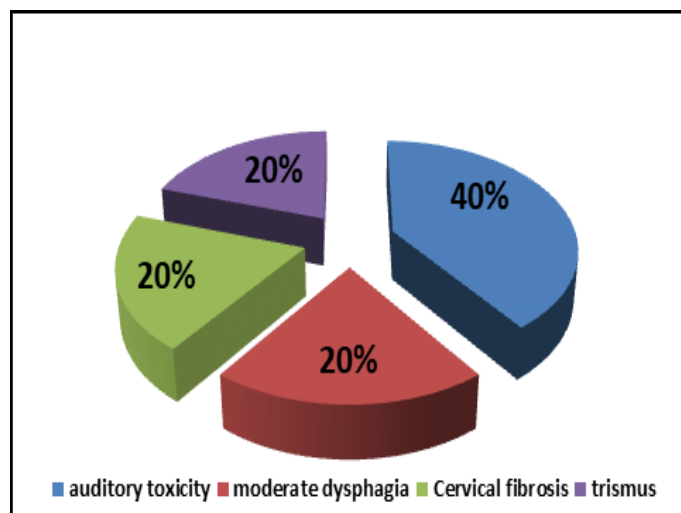


Fig 5 Evaluation of Late Toxicity

IV. DISCUSSION

The prognosis of nasopharyngeal carcinoma has improved dramatically over the past three decades due to advances in disease management, diagnostic imaging, new radiation therapy techniques and the wider application of systemic therapy. Despite the excellent local control of modern radiotherapy, remote failure remains a major challenge.

For patients presenting with a first local failure, the majority of them only have a local recurrence without distant metastases [1]. Recurrent disease is defined as biopsy-proven disease that recurs after a period of remission after completion of initial treatment, most commonly occurring 3 months after treatment [2].

- Re-irradiation, even with IMRT, can lead to significantly lower survival rates.
- Qiu et al. [3] and Chua et al. [4] observed 2-year OS rates of 63%.
- A meta-analysis examining outcomes at 5 years after re-irradiation for nasopharyngeal carcinoma (NPC), pooling 12 studies, also found a trend towards similar results, with a 5-year OS rate of 41% (CI to 95%, 36% to 47%) [5].
- In our study, the SG rate is 58%, which remains identical to the data in the literature.
- Several series confirm that patients treated [17] with doses ≥ 60 Gy had significantly better survival than those re-irradiated at lower doses. This is indeed consistent with our study.
- A number of studies of induction chemotherapy before re-irradiation have generally shown good response rates, particularly with the combination of cisplatin and gemcitabine.

Chua et al. [7] observed a partial response (PR) rate of 75% with 3 cycles of cisplatin and gemcitabine, while Lee et al. [6] observed a PR rate of 70% with cisplatin/gemcitabine and 40% with cisplatin or carboplatin with 5-fluorouracil PCN re-irradiation presents unique challenges regarding risk organ toxicities, both acute and late toxicities can be more severe and require careful anticipation and management. Returning to the literature, we found that re-irradiation was associated with 7.9% to 16.6% of grade 3 and above acute toxicities, most often mucositis, with a lower proportion of patients suffering from xerostomia severe * 8-9, 10]. In addition, the most common acute adverse reactions were grade 1-2 mucositis and xerostomia, and otitis media.

A recent meta-analysis of toxicities [16]. Grade 5 was seen in 33% of patients, with the most common serious effects being nasal bleeding caused by mucosal necrosis, followed by feeding difficulties. In our study, the toxicities were mainly grade I, II, III. No grade V toxicity was observed. Time to recurrence has been described as a prognostic factor, Leong et al. Reported [16] that a delay > 36 months is accompanied by favorable local control. In our study, the average time to re-irradiation was 84 months, which is relatively long and could have had a favorable impact on patient outcomes.

Another new therapeutic approach was based on the use of stereotactic body radiation therapy (SBRT) to target recurrences with high doses of hypofractionated radiation. SBRT is generally only suitable for recurrent small tumors, where high doses can be administered

safely without compromising nearby critical organs. The doses used in the literature range from single fractions of 11 Gy to 14 Gy, 18 Gy in 3 fractions, 30 Gy in 5 fractions, 48 Gy in 6 fractions. In general, most studies had small numbers of patients and short follow-up periods of 1 to 3 years.

Reported 3-year local control rates ranged from 52% to 89%. [11,12,13,14,15]. However, a number of late toxicities were severe, with some patients in the

V. CONCLUSION

Re-irradiation is the only salvage treatment for recurrences of nasopharyngeal carcinoma, precisely conformal radiotherapy with intensity modulation which makes it possible to deliver sufficient doses to the level of the tumor volume while sparing the organs at risk which have already been irradiated; however, given the associated toxicity, patients must be carefully selected.

➤ Limitation of this Study

This study is limited by its retrospective design, the complication rate is probably underestimated. The mechanism of life-threatening complications varies depending on the organ(s) involved, and the cause of death due to tumor or life-threatening complication. The small number of patients also limits the statistical power of the analysis.

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