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REIRRADIATION USING INTENSITY-MODULATED RADIOTHERAPY FOR RECURRENT NASOPHARYNGEAL CARCINOMA: A REPORT OF 10 CASE SERIES FROM A MOROCCAN CENTER

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ABSTRACT

Aims and Methods: This study aimed to describe clinical outcomes and treatment-related toxicities after re-irradiation using intensity-modulated radiotherapy (IMRT) for patients with local and/or regional recurrent nasopharyngeal carcinoma (NPC) treated at the National Institute of Oncology Sidi Mohamed Ben Abdellah in Rabat- Morocco, between 2016 and 2019. The epidemiological data from the 10 patients were collected and studied. **Results:** Seven patients were female and 3 were male. Mean age at primary diagnosis was 39.3 years. At the time of initial diagnosis, induction chemotherapy was performed in 5 patients, and concurrent chemo-radiotherapy in all patients. The median interval between primary irradiation and recurrence was 5.3 years. Nine patients (90%) had locally advanced recurrent disease. Neoadjuvant chemotherapy was administered to 6 patients (60%) to downsize tumors before radiotherapy, and cisplatin-based concurrent chemo-radiotherapy was administrated to all patients. The mean re-irradiation dose was 61.8 Gy (range, 60-66 Gy). Treatment was delivered at 2 Gy/fraction daily, 5 days a week with a mean duration of 51 ± 5.3 days. Chemotherapy was interrupted in 2 patients (20%) during the concurrent phase to manage severe symptomatic or hematologic toxicities. After a mean follow-up time of 7.8 months, 4 patients died, 4 were alive and disease free and 2 were lost to follow-up. The median overall survival (OS) was 13 months with a 1-year OS rate of 46.9%. Fifty-eight per cent of patients experienced grade 3-4 late toxicities including various degree of hearing impairment, trismus and xerostomia. **Conclusion:** The use of innovative radiotherapy modalities such as IMRT has led to highly conformal radiation treatments, which allow smaller margins and decreased radiation doses to the normal organs at risk (OAR). IMRT should be considered as the preferred option in treating recurrent NPC.

Keywords: Intensity-modulated radiotherapy; Morocco; Recurrent nasopharyngeal carcinoma; Survival; Reirradiation.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a tumor arising from epithelial cells of the nasopharynx [1], and shows a peculiar geographic distribution. The highest incidence rates of NPC are found among the southern China, Southeast Asia, North Africa, and Greenland [2, 3]. It is strongly associated with the Epstein - Barr virus (EBV) [4, 5]. In Morocco, NPC is accounting for 7-12% of all cancers in males, it came in the 8th position among men and 21th position among women, with a sex ratio of 3.1 [6, 7]. With the development of modern radiation technique, excellent loco-regional control rates have been consistently achieved, [8, 9]. However, around 10-20% of patients develop recurrent disease at the

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primary and/or regional site [10- 12]. Salvage treatment for locally recurrent NPC remains a challenge for clinical oncologists. Various modalities including surgery, brachytherapy, stereotactic radiosurgery, nasopharyngectomy, chemotherapy, and a combination of these methods have been used in attempt to cure locally recurrent NPC [13- 15]. However, their utility is usually limited by the extent of disease at recurrence. It is reported that 70-80% of the recurrent NPC were locally advanced [16- 18]. For patients with infiltrative or extensive disease, re- irradiation still remains the most effective modality for controlling local recurrence despite considerable risk of late complications [5, 19, 20]. IMRT is universally the most used modality at present, allowing more homogeneous target coverage and lower doses to normal tissues [17, 21, 22]. High-dose re- irradiation (≥ 60 Gy) has been shown to be more effective than low-dose re- irradiation (< 60 Gy), with greater additional local control and survival rates [23, 24]. However, higher re-irradiation dose is also associated with a greater risk of severe complications including carotid blowout, temporal lobe necrosis, mucosal necrosis, cranial neuropathy [20, 25], especially in series delivering a high total dose (≥ 70 Gy) for the second course of radiotherapy [16-18, 26-29].
The objective of this study was to report oncologic outcomes and treatment-related toxicities after re-irradiation using IMRT for recurrent NPC at our institution.

MATERIEL AND METHODS

This is an institutional retrospective analysis of adult patients with recurrent NPC retreated between 2016 and 2019 in Radiation Oncology Department, National Institute of Oncology Sidi Mohamed Ben Abdellah in Rabat, Morocco. All patients were determined to have recurrent disease after histologic confirmation. The pre-treatment MRI was performed for staging and was employed for contouring through image fusion with the planning CT scan (**Figure.1**). Patients with non-metastatic disease and good PS (The ECOG Scale of Performance Status of 0 to 1) were offered salvage re-irradiation using IMRT. All patients were treated with curative intent. The mean re-irradiation dose was 61.8 Gy, in 2 Gy daily fractions, 5 days a week, with a median duration time of 12.5 days (range 5-16 days). Systemic therapy was given as induction in 6 (60%) patients and concurrently in all patients (100%), platin-based regimens were used.

RESULTS

Treatment at initial diagnosis

Patients and treatment characteristics at initial diagnosis are shown in **Table I.**
Median age was 40.5 years, with a sex ratio of 0.4. Clinical stage was described according to the TNM staging system of the American Joint Committee on Cancer (AJCC). This system was updated to the VIIIth edition 2017 [30]. Three patients had Stage II disease, 5 had Stage III and 2 had Stage IV. Platinum-based chemotherapy was given as induction in 5 patients (50%) and concurrently in all patients. Primary radiotherapy was performed using 3D conformal technique. Tumor in the nasopharynx and positive lymph nodes in the neck received a prescription dose of 70 Gy with daily fractions of 2 Gy, 5 days per week.

Table I. Patients and treatment baseline characteristics

	Characteristics	n (%)
Age (years)	Mean	39.3
	Median	40.5
	Range	[17-61]
Gender	Female	7 (70)
	Male	3 (30)
T stage	T1	1 (10)
	T2	6 (60)
	T3	2 (20)
	T4	1 (20)
N stage	N0	1 (10)
	N1	3 (30)
	N2	5 (50)
	N3	1 (10)
TNM stage	II	3 (30)
	III	5 (50)
	IVA	2 (20)
Treatment protocol	Induction chemotherapy	5 (50)
	Concurrent chemotherapy	10 (100)
Dose (Gy)	Mean	70

Treatment of local recurrence

Patients and treatment characteristics at recurrence are shown in **Table II.**
Median age at recurrence was 44.7 years (range 26-66). 5 patients (50%) had persistent G2-G3 late toxicity from the first radiotherapy. Local recurrence was confirmed histologically in all patients. The sites of recurrence were located in the nasopharynx in one patient (10%), in the nasopharynx and regional nodes in 6 patients (60%), and in the cervical nodes in 3 patients (30%). The mean time to recurrence was 5.3 years from completion of primary treatment. Three patients (30%) had recurrence within 2 years, and 7 (70%) had recurrence 5 years after initial

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treatment. Most of our patients presented with loco-regionally advanced recurrence (90%). Delineation of target volumes and OARs was based on the fused CT-MRI images in all patients. IMRT was performed, using Volumetric Modulation Arc Therapy technique (VMAT). Re-irradiation dose ranged from 60 to 66 Gy to achieve lower normal tissue doses and homogeneous target doses (**Figure2**). Induction chemotherapy was given to 6 patients (60%) based on Adriamycin (50 mg/m^2) + Cisplatin (80 mg/m^2) every 3 weeks, and concurrent chemotherapy was administered to all patients based on weekly cisplatin (40 mg/m^2). Chemotherapy was interrupted during the concurrent phase in 2 patients to manage grade III chemotherapy-induced neutropenia in one patient and deterioration of Karnofsky Performance Status (KPS) in the other patient. The median duration of breaks was 5 days (range 1-18).

Table II. Treatment characteristics of patients with local recurrence

	Characteristics	n (%)
Age (years)	Mean	44.7
	Median	26-66
	Range	42.5
Time to relapse (years)	Median	5.3
	Range	[2-9]
rT stage	rT0	3 (30)
	rT2	1 (10)
	rT3	2 (20)
	rT4	4 (40)
rN stage	rN0	1 (10)
	rN1	3 (30)
	rN2	2 (20)
	rN3	4 (40)
TNM stage	II	1 (10)
	III	1 (10)
	IVA	8 (80)
Treatment protocol	Induction chemotherapy	6 (60)
	Concurrent chemotherapy	10 (100)
Dose (Gy)	Mean	61.8

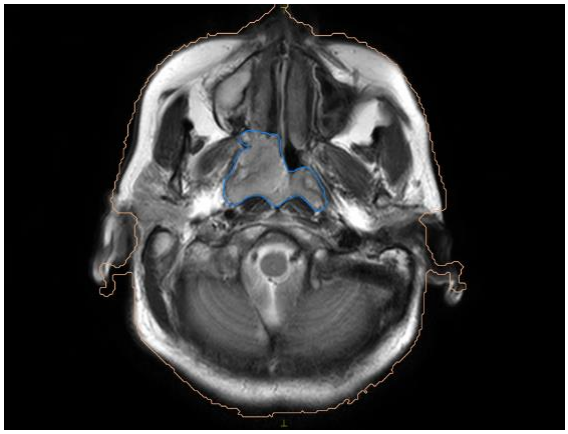

Figure 1: GTV delineation using CT and MRI fusion.

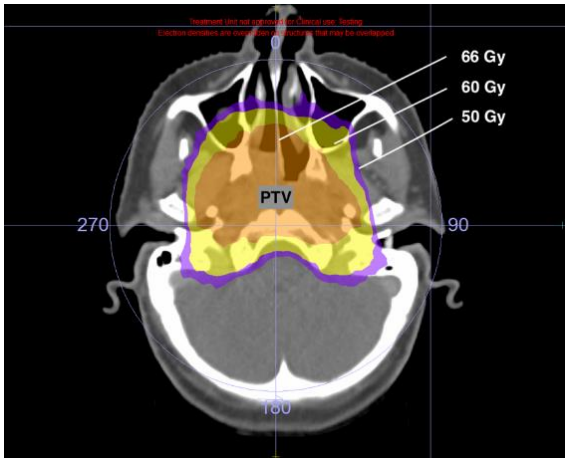

Figure 2: Treatment plan with isodose lines.

Toxicity & outcomes

Grade 1, 2, and 3 acute skin toxicity developed in 4 (44.4%), 2 (22.2%), and 1 (12.5%) patients respectively. Grade 2 and 3 oral mucosa toxicity occurred in 4 (44.4%) and 2 (28.6%) patients, respectively. After completion of chemo- radiation, there was one reported grade 5 treatment-related toxicity with severe pancytopenia, general fatigue and fever, the patient died few days later.

Late toxicities (> 6 months after re-irradiation) were assessable in all patients. Grade 3 or above (G3+) late radiation effects were documented in 4 (58%) patients. The most common late sequels were grade 2-3 xerostomia in 4 patients (57.1%) and hearing impairment in 4 patients (66.7%). Three patients complained of trismus (mild to severe), and one had moderate dysphagia.

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Mean follow-up time was 7.8 months (95% CI, 11-19). After Re-irradiation, 4 patients had died, 4 were alive and without disease, and 2 were lost to follow-up. Median OS was 13 months with a 1-year OS rate of 46.9% **(Figure.3)**

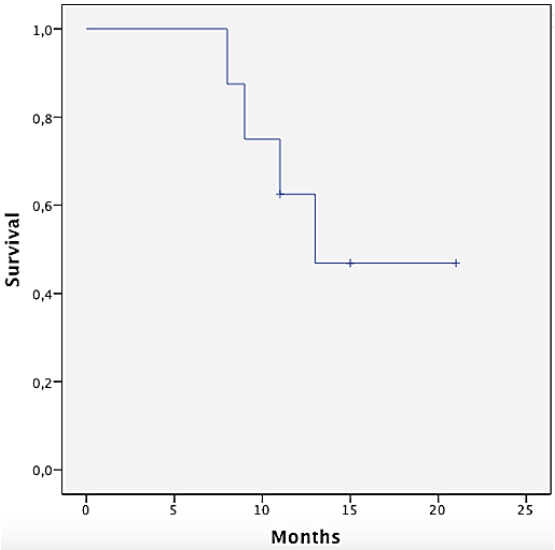

Figure 3. Kaplan–Meier curve for Overall Survival (OS).

DISCUSSION

Using contemporary standard management of NPC, excellent loco-regional control rates have been consistently achieved in the past two decades [8, 9], with series reporting an increase in local control of 7-25% [31, 32]. The improved treatment outcome has been attributed to earlier detection, improved staging accuracy, treatment planning and the use of chemotherapy. However, 10-20% of patients will suffer from local and/or nodal recurrence after primary treatment [11, 12].

The prognosis following recurrent nasopharyngeal carcinoma is very poor without retreatment [33; 34]. A study by Yan et al. [34] reported only one 5-year survivor amongst a group of 276 patients with recurrent disease who received no further treatment. Chang et al. [35] have shown a 1-year overall survival (OS) rate of 54.9 after salvage IMRT for recurrent NPC. In the present study, the 1-year OS was 46.9%, which was comparable with other reports.

Due to the heterogeneity of the recurrent disease and close proximity of previously irradiated organs at risk, it is very difficult to define the optimal treatment strategy. Nevertheless, long-term survival with re-irradiation has been consistently demonstrated for selected patients. Indeed, Leong et al. performed a meta-analysis of 12 retrospective studies including a total of 1768 patients with recurrent NPC treated with re-irradiation using IMRT with or without chemotherapy [25]. They showed that re-irradiation was associated with a 5-year OS rate of 41%, on the other hand, it was also associated with a grade 5 toxicities rate of 33% [25]. Various radiobiological factors including total dose, dose/fraction, dose tolerance of OAR (especially the nasopharyngeal mucosa, carotid vessels and neurological structures) and their prior dose exposure should be carefully considered. Furthermore, the best quality control of radiotherapy technique and precision set-up should be adopted for maximal sparing of the neighboring uninvolved normal tissues.

In the Wang [23] series, patients retreated with doses ≥ 60 Gy had a significantly better survival than those re- irradiated at lower doses. However, more than 50% of the patients in the low-dose group had T3 or T4 disease in this study. Chang et al. [36] noted that a retreatment dose > 50 Gy yielded better survival. Also, in some studies, for T1-T2 lesions, EBRT plus brachytherapy provided the greatest benefit [5, 23, 37]. In contrast, Hwang et al. [37] showed no dose-response relationship for local control and survival. In the study of Teo et al. [20], despite usage of higher re- irradiation dose, the results were poor and the complication rates were high. Our results provide additional evidence that locally recurrent NPC is associated with significant mortality (40%) despite a high re- irradiation dose given with IMRT (60-66 Gy).

One of the most important considerations associated with re- irradiation is the risk and the severity of radiotherapy-related toxicities. According to a recent meta-analysis [25], grade 5 toxicities were observed in 33% of patients, with the most common severe effects being nasal hemorrhage caused by mucosal necrosis, followed by feeding difficulties and radiation encephalopathy [25, 26]. Carotid blowout is one of the major causes of treatment-related deaths. A literature-based systematic review by McDonald et al. on 1554 patients reported an incidence rate of 2.6% following re-irradiation to the head and neck region, and the mortality rate was 76% [38]. Mucosal and adjacent soft tissue/bone necrosis are also frequently observed after re-irradiation, causing foul odor, intense headache, and/or profuse bleeding. Dysphagia is another common toxicity. The cause of dysphagia can be related to trismus, pharyngeal constrictor muscle dysfunction and/or cranial nerve (IX-XII) injury [39]. McNeese et al. [40] and Teo et al. [20] reported that impairment of hearing was one the most frequent late complications, being detected in 56.3%

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after radical re-irradiation. In our study, hearing impairment rate was consistent with published results (66.7%), this high rate might be due to cisplatin-based chemotherapy. Additionally, high-dose external re-irradiation might cause both severe acute and late ototoxicity.

The time interval from primary radiotherapy was described as a prognostic factor, Leong et al. [25] had reported that local control was favorably associated with a time to recurrence of > 36 months. In our study, the average time to re-irradiation was 60 months, which is relatively long and could have impacted the patients' outcomes favorably.

In a prognostic model proposed by Li et al. [41], 5 significant prognostic factors for OS in patients with locally recurrent NPC were identified: age, T-category of the recurrence (rT3–4), size of rGTV, presence of prior radiotherapy-induced grade 3 or above toxicities, and the dose of re-irradiation by IMRT (EQD2 of ≥ 68 Gy). A prognostic index (PI) was constructed based on these 5 factors. A PI score of 252 consistently categorizes patients into good vs poor risk for OS and grade five toxicities. This may serve as a useful model to guide clinicians making decisions about re-irradiation. Lee et al. [39] reported that recurrent T category and tumor size are the most consistent prognostic risk factors, whereas Hwang et al. [27] showed no prognostic significance with respect to T stage and overall stage. In our study, the recurrent stage was not significant for survival (p=0.1).

The efficacy of chemotherapy for recurrent NPC is uncertain. Choo and Tank [42] had reported that more aggressive chemotherapy agents could get tumor response rate to 70% but the median survival was only 7 months. Gebbia et al. [43] reported that the use of cisplatin-based chemotherapy could reach about 65% of tumor response in recurrent and/or metastatic NPC but the mean survival is only about 11 months. These results might suggest that the recurrent NPC be high responsive to chemotherapy but survival with chemotherapy alone is poor.

Despite the lack of high-level evidence, induction and/or concurrent chemotherapy is often given with re-irradiation. Induction chemotherapy is especially considered in patients with rT3–4 diseases because this may down-size the recurrent tumor volume facilitating easier sparing of adjacent organs at risk and eradicate micro-metastases. Concomitant chemotherapy may have a role in enhancing the sensitivity leading to improved local tumor control. However, the potential aggravating effect of chemotherapy related to increased late toxicities should also be addressed [39]. Various chemotherapy agents and their combinations have been investigated in the locally recurrent setting, including cisplatin [44, 45], 5-fluorouracil [45], gemcitabine [46] and taxanes [47]. In the study by Chua et al. [46] evaluating the effects of induction chemotherapy with cisplatin and gemcitabine before IMRT for locally recurrent NPC, 75% of the patients had partial response after induction chemotherapy and complete response was achieved in 61% of the patients after IMRT. In our study, Doxorubicin 50 mg/m^2 and Cisplatin 80 mg/m^2 were given on day 1 every 3 weeks as initial induction. During radiotherapy, Cisplatin 40 mg/m^2 was given weekly because this is a well-tolerated regimen [48].

Sham et al. [49] had reported the value of clinical follow-up and frequent use of fibroscope examination after treatment of NPC. He also suggested the use of imaging techniques and the monitoring tumor markers as supplement. MRI is superior to CT for diagnosing local residual/recurrent nasopharyngeal carcinoma [50, 11] and to differentiate between tumor recurrence and mature post- radiation fibrosis [51].

After radical salvage treatment, follow-up is similar to that recommended by the NCCN [52] and ESMO [53] guidelines as in the setting of primary treatment. This consists of a combination of periodic clinical and radiological assessment. Clinical examination of the nasopharynx and neck, cranial nerve function, fiber optic endoscopy, and evaluation for the presence of systemic symptoms, are performed every 3 months in the first 2 years, half-yearly at 3-5 years after treatment, and annually thereafter. MRI should also be performed every 6-12 months not only for surveillance of the local disease but also the detection of late complications.

In summary, the appropriate treatment for patients with locally recurrent NPC is multidisciplinary with comprehensive consideration of several factors including recurrent tumor factors, prior treatment factors and patient factors. It is important to note that higher radiation dose may not lead to higher chance of survival as fatal complications negate the benefit of tumor control rates [39].

LIMITATIONS OF THE STUDY

This study is limited by its retrospective design, the complication rate is likely underestimated. The mechanism of fatal complications varies with the involved organ(s), and the cause of death due to tumor or fatal complication are not mutually exclusive. The small number of patients also limits the statistical power of the analysis.

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CONCLUSION

IMRT is an effective treatment for patients with locally recurrent NPC, but it is associated with a high rate of major toxicity affecting quality of life. Stratification of patients based on their risk of developing severe toxicity is needed to select patients who will most benefit from re-irradiation. Routine use of MRI to follow post-radiotherapy NPC patients may afford early detection of recurrent disease and may therefore improve salvage rates.

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Conflict of interest:

The authors declare that they have no conflict of interest.

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