CASE REPORT

INDONESIAN JOURNAL OF CANCER

Re-Irradiation of Recurrent Nasopharyngeal Cancer: A 4-year Follow-up Study of Treatment using 3-Dimensional Conformal Radiotherapy

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ARTICLE INFO

Received : 03 March 2021
Reviewed : 05 April 2021
Accepted : 27 September 2021

Keywords:
3D-CRT, nasopharyngeal cancer, re-irradiation, radiotherapy, radiation-induced toxicity, side effects

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ABSTRACT

Introduction: Nasopharyngeal cancer (NPC) is a prevalent diagnosis of head and neck cancers (HNC) in Asia. In Indonesia, it is estimated that there are 12,000 new cases per year.

Case Presentation: The author reports a 25-year-old male patient with recurrent NPC. This patient was first diagnosed with NPC stage IVB in 2013 and was treated by chemoradiation. In 2016, he found another mass in his neck. The biopsy result showed the recurrence of the NPC with histopathology of Undifferentiated carcinoma (WHO type III). Re-irradiation was planned, and the patient subsequently received 3D-Conformal Radiotherapy (3D-CRT) at our department. Four years after the completion of re-irradiation, the patient was alive and well with no signs of recurrence but still complained about late toxicities like trismus and fibrotic neck.

Conclusions: In this study, we discuss the use of 3D-CRT in the re-irradiation of NPC with its limitation on obtaining optimum dose sculpture compared to more sophisticated and widely spread modalities like intensity-modulated radiotherapy (IMRT). However, with careful planning, we can still obtain optimum tumor dose, minimize organs at-risk (OAR) dose, and subsequently late toxicities that come after. We hope that this study can bring hope to centers with limited facilities, and we suggest further studies on re-irradiation, especially in OAR dose tolerance guidelines.

INTRODUCTION

As the primary malignant neoplasm developed in the head and neck area, with 19,943 new cases reported in 2020, NPC became the eighth most prevalent cancer in Indonesia [1]. Undifferentiated non-keratinizing subtype, which is predominant in Asia, is strongly associated with EBV co-infection. Unlike Asian Countries, NPC is considered scarce in Western Countries, and mostly WHO type-I cases are related to alcohol consumption and smoking [2]. The advancement of modalities of treatment has brought better local control to NPC, but about 10% of patients are reported to develop local recurrences, and re-irradiation is the preferred alternative for these patients [3]. However, re-irradiation brings toxicities of adjacent organs into question, and this case report emphasizes how optimum dose planning especially in organs at risk without compromising tumor control can still be achieved, even with a lack of sophisticated facilities, which is a common case in many centers in Indonesia.

CASE PRESENTATION

In July 2016, a 25-year-old male patient was referred to our department from the Ear, Nose, and Throat (ENT) Department with a diagnosis of recurrent NPC. This patient was first diagnosed with NPC T3N3M0 (Stage IVB) in 2013 and was treated by chemoradiation with a total dose of external radiation (including electron

booster on nodes) of 60 Gy. The procedure was done with 2D conventional technique followed by brachytherapy of 4x5 Gy regimen on another center based in Jakarta. However, no planning data from the previous treatment can be collected. Thus, the organ at risk (OAR) dose of the brain stem, spinal cord, and parotid glands is difficult to be assessed.

For the whole period from 2014 until April 2016, the patient had no symptoms until May 2016 when he found another mass in his neck. No other symptoms were present. The patient then consulted to ENT department Abdoel Wahab Sjahranie General Hospital while doing follow-up for the NPC. The biopsy result on the nasopharynx showed the recurrence of the NPC with an undifferentiated carcinoma (WHO type III). The patient was then referred to the radiotherapy department for re-irradiation. During the examination, we found positive nodes on levels II and III on the right side of the neck with a 6-cm diameter. CT scan was performed, and multiple positive nodes were found on the right neck area with a size of 1.1 x 0.7 cm, 0.7 x 0.6 cm, 0.9 x 0,5 cm, and 0.7 x 0.5 cm as well as one positive node on the left neck of 0.7 x 0.4 cm. A solid nasopharynx mass that obliterated fossa rosenmuller was identified as well (**Figure 1A-B**).

We then decided to do re-irradiation considering that it was a resistive case with more than a minimum of 1 year already passed after the first radiation treatment. The patient subsequently received 3D-Conformal Radiotherapy (3D-CRT) (50 Gy in 25 fractions for nasopharynx and bilateral nodes levels II, III, and IV, followed by 10 Gy for nasopharynx and positive nodes and booster for positive nodes by electrons 18 MeV until 66 Gy. This treatment was done between June 23 and October 18, 2016. These planning therapies are mentioned in the **Figure 2** below.

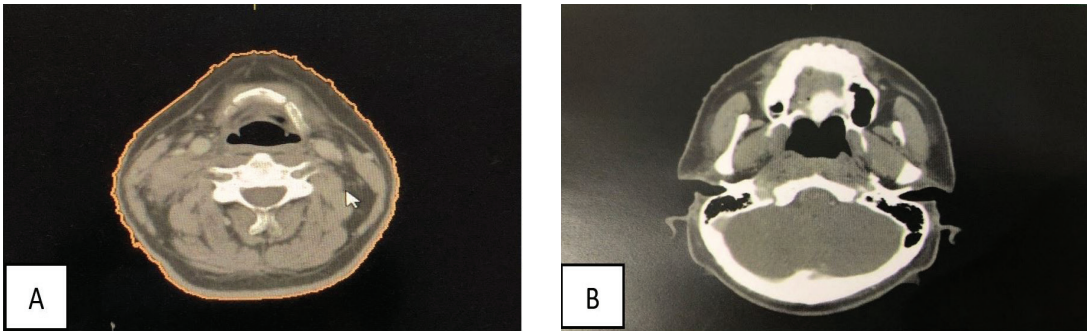

Figure 1. (A) NPC with positive nodes was found on right neck area; (B) Nasopharynx mass obliterated to rosenmuller fossa.

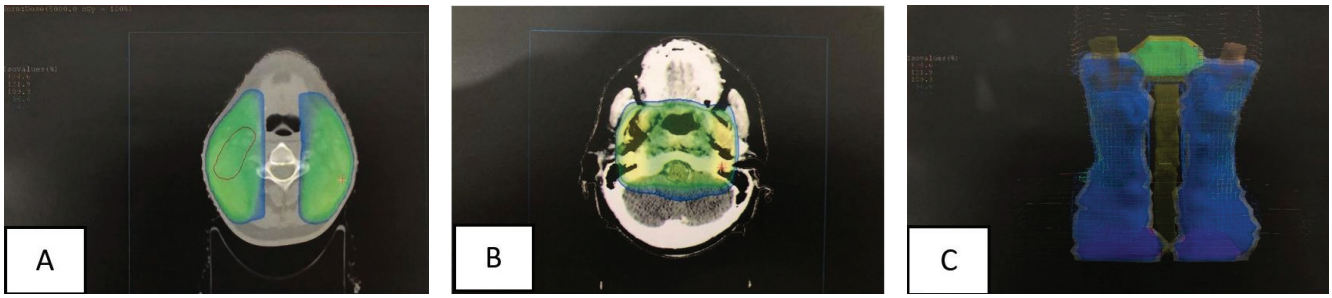

Figure 2. (A) Treatment planning on positive nodes shown in red line delineation; (B) Treatment planning on nasopharynx; (C) Treatment planning showing isodose curve

Table 1. Total dose constraint data for organ at risk at 60 Gy

Organ	Volume (cc)	Constraints	Goal Volume (cc)	Goal Dose (cGy)	Actual Dose (cGy)
Spinal Cord	32,83	Dmax	-	≤ 5000	4841,6 cGy
Brain Stem	35,89	Dmax	10,0	6000 ≤	5154,0 cGy
Right Parotid	24,70	Dmean	-	2600>	**3179,0 cGy**
Left Parotid	22,31	Dmean	-	2600>	**3325,0 cGy**

One month after therapy, the patient returned to our department for a routine post-therapy follow-up. The side effects after therapy were mild to moderate. The side effects on the skin were fibrosis grade 2 and trismus grade 1 according to late effect of normal tissues/subjective, objective, management, analytic (LENT/SOMA) scale [4].

The patient was then evaluated by nasal endoscopy and (99m)Tc MIBI scan; no residual mass was found. Another follow-up test (chest X-ray, abdominal USG, bone scan) revealed no metastasis. In later years after therapy until 2020, the patient was alive & well with no signs of recurrence, but the patient still complained about late toxicities like trismus, porous teeth, and the skin around his neck, which is thick, hard, and tense.

DISCUSSION

In this case report, we discuss a 25-year-old male with a recurrent NPC after previously diagnosed with NPC stage IVB and treated by chemoradiation. This is aligned with a study from Cipto Mangunkusumo Hospital that shows most NPC patients in Indonesia are diagnosed at stage IV with the biggest percentage at stage IVA [5]. According to some literature, in times of conventional radiotherapy, the recurrence rate of NPC patients is almost 58%, and re-treatment is needed regarding this condition [6]. Another research done by Cancer Center in Sun Yat Sen University [7] showed that most recurrence incidents happened less than two years after finishing the treatment, while the Hong Kong study [8] shows 39% of patients will encounter recurrency within 2–5 years. These studies are mostly consistent with our patient who encountered recurrence 3 years after his initial treatment with conventional 2D radiotherapy.

The common possible cause of recurrency is underdosing despite the advancement of radiation techniques, which usually occurred in a portion of T3–4 cases due to their proximity to critical neurological structures [3]. The other possible cause in another study is that these recurrent tumors are the more aggressive and likely to be the more resistant to radiotherapy types [9].

According to National Comprehensive Cancer Network (NCCN), one of the treatments of choice for recurrent NPC is nasopharyngoscopy (if resectable) or re-irradiation ± systemic therapy [10]. The recommended technique for re-irradiation is IMRT compared to 2D or 3D conformal techniques due to better dosimetry and lower rates of late complications [11]. For this patient, the 3D-CRT technique was chosen due to the limitation of the technologies that this center can achieve. The field in field (FIF) technique was used to give better coverage of the tumor and to reduce as much as we can on the organ at risk. We treated this patient with curative intent because of the age and health status of the patient. We hope to give the patient better control of the tumor and a better quality of life.

In most re-irradiation cases, the dose prescribed at gross tumor volume (GTV) in the nasopharynx can be given until 66 Gy and, for elective nodes, until 50 Gy. In these cases, tailored volumes and doses will depend on the OAR dose constraints, the previous dose from sequential treatment, the timespan from initial treatments to re-irradiation, and the clinical manifested toxicity caused by the previous radiotherapy [9]. In our planning, corresponding to the above study, we prescribed a dose until 66 Gy for the GTV which is on the neck nodes levels II, III, and IV. The dose given for elective neck nodes was 60 Gy because it was considered high risk.

Dose constraint data for OAR (**Table 1**) on parotid glands is exceeding quantitative analysis of normal tissue effects in the clinic (QUANTEC) dose constraints due to the limitation of the 3D-CRT technique that we used.

In “Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT)”, a phase 3 multicenter randomized controlled trial to observe the benefit of sparing the parotid by comparing IMRT vs 3D-CRT shows that IMRT gives more benefit in lowering the incidence of xerostomia by reducing the mean dose value of parotid, compared to 3D-CRT (mean dose can achieve less than 40 Gy by IMRT) [13]. However, for the spinal cord and brainstem, our planning could achieve an optimum absorbed dose which is consistent with QUANTEC OAR Dose constraints for the head and neck area [12] but furthermore, no guidelines are present suggesting the maximal cumulative dose (Dmax) organ(s) at risk can tolerate re-irradiation.

Because of a lack of information about the previous tumor and OAR dose received on previous treatment, we could not calculate cumulative Dmax received by OAR in this patient. Nevertheless, with speculation that 50% from dose received by OAR will recover after 12 months of radiotherapy session [9,14] and cumulative Dmax of brainstem could go as high as 79 Gy (when the interval of re-irradiation was more than 12 months) [15], and no symptoms regarding suspected brain and brain stem injury (cranial neuropathy, unsteady gait, limb weakness, memory loss, and limb numbness) [16] were present, our data show no significant liability.

Although the 5-year overall survival in NPC generally has been improved from 50% in the 1980s to 80% today [6], the outcome for patients with recurrent or metastatic NPC in literature is very poor with a median overall survival (OS) of only about 20 months [11]. For comparison, a study from North American experience using IMRT shows that a 3-year OS rate is 49%. Subsequently, the 3-year local, regional, and distant control rates were 46%, 71%, and 79%, respectively. This shows that, when compared to other modalities,

IMRT shows a significantly higher 3-year local control (53% compared to 32%), but late toxicity manifestation is considered almost the same (39% vs. 31%). Patients treated with 3D-CRT with the dose ranging from 58--68 Gy (58, 62, and 68 Gy) have OS, DFS, and LRRFS of 43.2 vs. 64.53 vs. 75%, 29.13 vs. 42.82 vs. 39.7%, and 30.76 vs. 44.19 vs. 45.4% [17,18]. This emphasizes a significant impression that our patient treated with 66 Gy regimen could survive four years after the re-treatment using less sophisticated technology, 3D-CRT, which is considered successful.

Neck fibrosis and trismus are the late toxicities complained by this patient. Our patient in this study experienced radiation fibrosis syndrome (RFS) as one of the late toxicity effects, that can be found in organs inside the radiation area. The injury is caused by the radiation that precipitates the inflammation process and sparks the differentiated myofibroblasts to produce a plethora of collagens and divergent constituents of the extracellular matrix, expedited by the decreased production of remodeling enzymes [19]. Overall, the manifestation of Acute RFS includes skin hyperpigmentation, dermatitis, scarring, mucositis, reduced salivation, ulceration, alopecia, and pain. In HNC, chronic RFS presents some symptoms like xerostomia, trismus, skin sclerosis, dysphagia, osteoradionecrosis, etc [20]. Based on a study from Siala et al. [21] 59.8% of patients have skin fibrosis in the neck area. Nodal involvement increased the frequency of neck fibrosis (66.5% compared to 41.3%). Gender (females) and treatment (certain chemotherapy) had also been associated with neck fibrosis. At the same time, trismus was noted in 43.5% of patients. Age (less than 20 years), gender (females), and more advanced T stage increased the incidence of trismus. These data correlate significantly with our study that our patient is diagnosed with nodal involvement and bony involvement (T3).

Data from the previous treatment is untraceable because, at the time of this case report was written, the writers contacted the previous hospital the patient was radiated, and no previous detail of treatment data like imaging data, delineation data, OAR dose, and treatment planning data was still collectible

CONCLUSIONS

We present a case of recurrent NPC undergoing re-irradiation with the 3D-CRT technique. The survival post-re-irradiation of this patient exceeded the prognosis in the literature. However, this study has a limitation, which is the lack of data regarding previous treatment using 2D conventional technique. Other studies mostly use techniques like IMRT, so we are unable to comprehensively show apple-to-apple comparisons with this case. However, this case brings hope to centers with limited facility when we could not refer the patient to higher facilities. With adequate, careful planning and verification, and knowledge of organ at risk, an optimum treatment could be achieved. Because of the lack of studies in OAR dose tolerance guidelines especially for 3D-CRT re-irradiation, further studies are needed.

DECLARATIONS

Competing of Interest

The authors declare no competing interest in this study.

Acknowledgment

Not applicable

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