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**Review Article**

# High dose rate brachytherapy in nasopharyngeal carcinoma: a neglected practice

**Laishram Natasha[1], Rahul Mahawar[2]*, Ningthoujam D. Devi[2], Laishram J. Singh[2]**

[1]Department of Radiation Oncology, Ruby Hall Clinic, Pune, Maharashtra, India
[2]Department of Radiation Oncology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, India

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***Correspondence:**
Dr. Rahul Mahawar,
E-mail: rahulmahawar93@gmail.com



## ABSTRACT

Nasopharyngeal carcinomas (NPCs) are one of the most chemo- and radio- sensitive cancers of the head and neck region. It differs from other head and neck cancers in terms of signs and symptoms, treatment response and overall survival. Surgery is not the preferred treatment option, with chemoradiation being the treatment of choice, with an excellent local control rate, prognosis and overall survival. But the management of recurrent NPC is quite challenging and the treatment options available includes re-irradiation, chemotherapy, brachytherapy or surgery in rare cases. Re-irradiation in case of recurrent NPC is very difficult due to the already irradiated tissue in the radiation path, but re-irradiation with brachytherapy is an excellent treatment option for giving further doses of radiation to the nasopharynx in cases of recurrence or residual disease, by taking in consideration the already irradiated area and the radiation dose given before, and achieving a good local control rate and overall survival.

**Keywords:** Brachytherapy, Chemoradiation, Recurrence, Re-irradiation

## INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a common malignancy in certain parts of the world like South East China, North Africa, and The Arctic. Its incidence is increased in certain ethnic groups like the Bidayuh of Borneo, the Naga tribe in North East India, and Inuits in the Arctic.[1,2] It usually arises from the mucosa of the Fossa of Rosenmuller (FOR) situated on the lateral wall of nasopharynx and spreads to the neighboring structures and distant organs.

It differs significantly from other head and neck cancers in terms of epidemiology, clinical features, treatment response and prognosis. The endemic form of NPC is usually associated with the Ebstein Barr Virus (EBV), and histopathologically are of undifferentiated type, having a better prognosis as compared to HPV associated and other non-viral associated NPCs.[2]

NPCs are usually chemo- and radio- sensitive and they are often used together in various forms in the management of NPC. Chemoradiation (CRT) gives a local control rate of 85%. However, loco-regional recurrence is seen in about 10-15% of the patients.[3] Surgery is not the preferred treatment for recurrent NPC, although surgical resection is a choice for limited disease, but it is associated with a high risk of complications.[4] Given the poor outcome and complications associated with retreatment; more aggressive primary treatment is required to have a higher level of local control with least toxicity.

External beam radiation therapy (EBRT) is the treatment of choice, with a total tumoricidal dose of 70Gy in 35 fractions to the primary target area and lesser dose to the high or low risk areas by various form of EBRT like 2DRT (2-Dimensional radiation therapy), 3DCRT (3-

Dimensional conformal radiation therapy), IMRT (Intensity modulated radiation therapy), etc.

Use of chemotherapy (CT) is associated with a reduction in loco-regional and distant relapses. Use of CRT along with Cisplatin as adjuvant or neoadjuvant chemotherapy have shown an improvement in survival of 78% with chemotherapy versus 47% without chemotherapy at 3 years.[5] Although NPC responds well to CT and RT, some of the patients show poor response, leading to a high chance of local or distant relapse. So, locally persistent NPC usually requires some form of additional treatment after the completion of EBRT.

Some of the NPC patients after treatment takes time to disappear. So, waiting for the local assessment after a period of 8-12 weeks post RT may be required in some cases, so as to diagnose locally persistent disease in these group of slow responders.[6] The treatment options available for recurrent NPC includes re-irradiation with or without chemotherapy, brachytherapy, immunotherapy, targeted therapy or surgery.

Early detection of the recurrence is crucial as the loco-regionally recurrent disease is still potentially curable. Re-irradiation with or without chemotherapy is the treatment of choice for recurrent NPC. Techniques for retreatment by radiation includes IMRT, stereotactic radiosurgery, stereotactic body ablative radiotherapy, proton beam therapy, carbon ion radiation therapy, and/or brachytherapy. Brachytherapy (BT) techniques are the best option for giving further doses of radiation to the nasopharynx due to its physical advantages.

Even though there has been much improvement in the imaging techniques and radiotherapeutic techniques, 20-30% of patients do have local failure if 2D radiotherapy techniques have been used.[7] In the developing and under developed countries, in many of the cancer centers the EBRT is usually given by 2D techniques, so they need to use all the resources available for treating NPC. They need to optimize the different RT techniques available to them.

In centers where IMRT facility is available, IMRT is the standard option for treating NPC. The treatment result has changed over a period of time depending upon the development in the radiation techniques. The disease specific survival with 2D techniques is 78%, 81% with 3DCRT and 85% with IMRT. The overall survival over the same time period is 71% with 2D technique, 73% with 3DCRT and 80 % with IMRT.[2]

## BRACHYTHERAPY

Brachytherapy can be used as a boost after completion of EBRT in selected cases or as a salvage treatment for recurrent cases in the nasopharynx. Interstitial brachytherapy (ISBT) and intracavitary brachytherapy (ICBT) are the main options available for these situations.

### *ISBT*

ISBT is used specially for tumors located in the lateral wall of the nasopharynx (FOR). It can be done only in selected cases, where the radiation sources can be placed directly within the tumor. Good result is seen if the procedure is carried out within 20 days of EBRT.[6] A 5-year local control of 59% have been achieved with this technique. Permanent radioactive seed implant using $^{198}$Au, $^{125}$I have also been used in recurrent NPC with a 2- and 3-years local control rate of 26-41% and 5-23% respectively.[8] However, the technique and expertise are not easily available in many of the low-income countries. Severe late toxicity in the form of nasopharyngeal necrosis, epistaxis, and headache have been reported in 26% of the patients.[4]

This technique can also be used in those situations where the lesion is deep seated or of a larger volume for successful ICBT. Huzheng et al from China studied $^{125I}$ implant in recurrent NPC and compared it with re-irradiation by IMRT technique and found a superior result of local control in comparison to IMRT. At 3 and 8 month follow up, the local control with $^{125}$I implant was 92.3% and 23.1% respectively, while with IMRT it was 85.7% and 16.7% respectively. The local tumor progression free survival was 21 months in $^{125}$I arm and 17 months with IMRT arm. However, the overall survival was not much different, 25 months in $^{125}$I arm and 24 months in IMRT arm. The complication rates were higher in the IMRT group.[9]

This technique is also used to boost the nasopharynx by using removable $^{192}$Ir source. It is not very commonly practiced. It requires patient selection, expertise and is done under general anaesthesia, but may also be carried out under local anaesthesia. Only a few centers in China and Japan do it, where they presented good results in limited disease in nasopharynx.[10]

### *ICBT*

Lack of complete local control usually leads to recurrence at the primary site with increased chance of distant metastasis. So, the aim is to achieve a good local control which can be achieved by EBRT with a local boost by BT or IMRT technique. Though the aim is to not exceed the total cumulative dose beyond 81Gy to the nasopharynx, beyond which unacceptable side effect may start appearing.[11]

With the use of ICBT as a boost after EBRT a definite advantage have been observed in T1 and T2a NPC but the result in T2b is uncertain.[7] There seems to be no definite advantage in T3 and T4 diseases. However, the Massachusetts general hospital report showed a definite advantage in T1-3 NPC treated with 60-66Gy by EBRT

followed by a boost of 10-15Gy to the mucosal surface of nasopharynx by ICBT. The 5-year actuarial local control with and without BT was found to be 93% and 54% respectively for T1 lesion. They found a higher response rate for T3 lesions, possibly due to a higher mucosal dose. For T1-2 lesions the local control rate was 90% and 59% with and without BT respectively.[12]

Guinot et al reported a local relapse rate (LRR) at 5 years of only 5% in T0-2 tumors by using ICBT boost.[13] Levendag et al showed that with ICBT in T1-2 N+ tumors the LRR was 0% with BT boost and 14% when no BT boost was used.[14]

The BT boost was of little advantage in large recurrences where effective dose cannot be delivered effectively to the deeper tumor cells. However, there is a definite improvement in the result by using 3D HDR BT as compared to 2D HDR BT. The dose to the mucosal surface depends upon the depth of the prescription point. Greater depth gives a higher dose to the surface. The doses used for NPC for both EBRT and BT varies from center to center. It ranges from 70Gy EBRT followed by 11Gy BT boost to 60Gy by EBRT followed by 8-20Gy BT boost.[14-17] The best result is seen only in cases where the tumor thickness is less than 5 mm, if it is more than 5 mm then ISBT is a better option, as ICBT cannot be used efficiently because of its rapid dose fall off.

Recurrent NPC is a difficult situation for retreatment by radiation considering the already irradiated tissues in the radiation path. The time elapsed since radiation and the radiation doses given are important prognostic factors.[1,4] A longer local recurrence free period is associated with a better survival result. However, in a second local recurrence the result of retreatment with radiation is worse with a 5-year local control rate of 23% only.[18]

Early recurrences should be considered for ICBT with or without EBRT. HDR BT have a physical advantage over EBRT in limiting the radiation dose to the tumor area and avoiding the vital structures located nearby. A median overall recurrence free survival of 26 months has been reported with a 50% and 25% 3- and 5-year disease free survival respectively.[9] For a better local control, a higher dose is always essential but the tolerance of the neighboring structures should be respected, thus the radiation doses and radiation techniques need to be tailored accordingly.

Importance of HDR BT in the management of locally recurrent NPC have been highlighted by Leung et al[19] also where they have shown a 5-year DFS of 39% and 33% with and without ICBT respectively. A better local control was observed with a total dose more than 60Gy, but dose more than that was associated with greater late complications. Use of IMRT with or without ICBT have shown a better local control (LC) and overall survival (OS) of 60% and 52% respectively but the grade 3 complications were found to be lesser in ICBT group.

The re-irradiation dose is an important prognostic factor for LC and OS. But this dose should be well balanced between EBRT and ICBT doses to achieve a better result. EBRT dose above 60Gy are associated with significant neurological complications. IMRT techniques giving a dose of 50-60Gy have given a result of 100% local control in T1-3 lesions.[20] So, it is projected that for reirradiation, it is the EBRT dose which gives an impact in the OS rate.

Advantages of ICBT in NPC have been published in many publications specially in 2D RT technique. 66Gy of 2DRT followed by 10Gy ICBT boost in 2 fractions usually show good local control in T1-2 disease as shown by Yeo et al.[21] Wu et al also showed a good outcome in T1-2 NPC where they have compared 72Gy by 2DRT with 58Gy by 2DRT followed by 20Gy ICBT.[22] Improved result with ICBT in T1-2 disease have also been shown by Leung et al and Levendag et al in 2D RT, but not in T3-4 disease.[14,16] The controlled trial by IAEA (International atomic energy agency) showed no definite advantage of ICBT in management of recurrent NPC.[23] But the study included advanced T3-4 stages also. IMRT can be effectively used wherever technique is available.

Treatment of recurrent NPC poses a challenge in selecting the proper therapeutic approach for the patient considering the radiation damage already done to the surrounding structures. There is a considerable risk of further deterioration of the function of the neighboring structures leading to a reduction in quality of life (QOL) and other morbidities. To avoid all these treatment related complications, the selection of the therapeutic approach needs to be judicious keeping the patient in mind, so that a better long-term survival with a good quality of life could be achieved.

## ICBT TECHNIQUES AVAILABLE

There are different sets of applicators available-through the oral route or through the nasal route. Both the techniques have been used with good result. The choice of the type of applicator depends upon the center and also the choice of the users. Of all the applicators used for NPC, the Rotterdam applicator which is applied through the oral route is most commonly used. Because of its advantage in conforming to the conformity of the nasopharynx, it is preferred. The procedure is usually carried out with local anaesthesia to the oropharyngeal and nasal region. ICBT can be done in recurrent NPC patients irrespective of the T stage and time lapsed from the last treatment, if the lesion is suitable. By using Rotterdam applicator radiation dose at 10 mm from the axis, results in doses of more than 200% to the surface, without any late complications.[24]

## PROCEDURE FOR ICBT[13]

With the patient sitting comfortably in the chair, 10% Lidocaine solution was sprayed into the oral cavity and

the oropharynx; along with 2% lignocaine jelly which was instilled in both the nostrils and the patient was asked to take deep breath through the nostril (this was done to anaesthetize and lubricate the nasopharynx and both nostrils) (Figure 1).[23] After 5 minutes, two 6Fr infant feeding tube were inserted through the nostrils (one in each nostril) and were taken out through mouth, with help of tongue depressor and surgical forceps (Figure 2).[13]

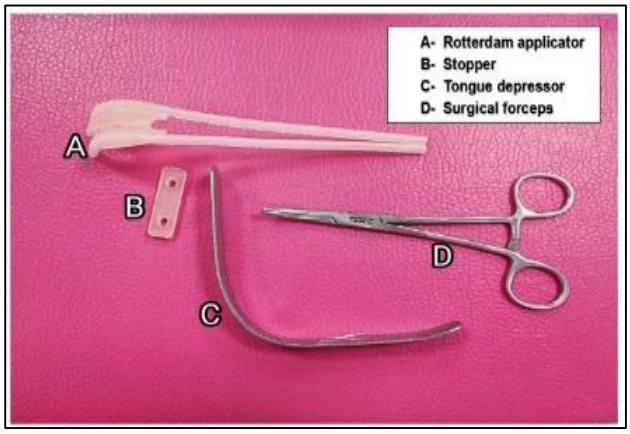


**Figure 1: Instruments used for ICBT.[23]**

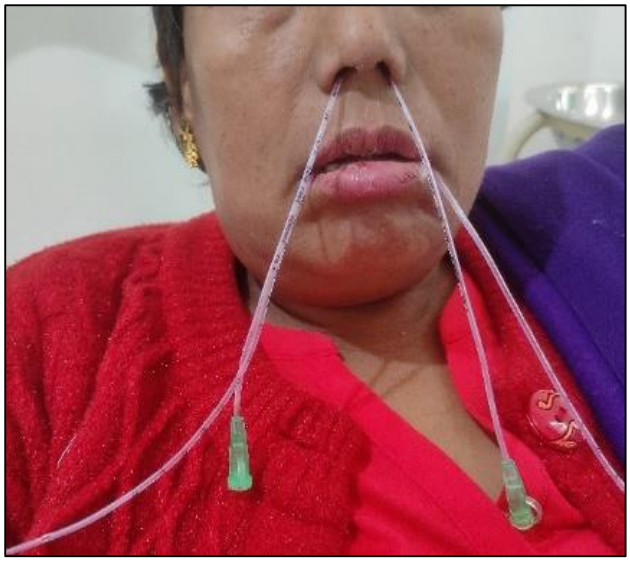

**Figure 2: Two infant feeding tube passing from nostrils to oral cavity.[13]**

The two silicone tubes of the Rotterdam applicator were catheterized through the two ends of the feeding tubes, and with the help of middle and index fingers the applicator was guided into the oral cavity to the nasopharynx through the oropharynx, by pulling the two ends of the feeding tube from the nostril until the silicone tubes come out of the nostrils. After that the feeding tubes are completely pulled out and discarded. The two silicone tubes are pulled out to the maximum extent, so that the curved part fits into the nasopharynx, and with the help of middle and index fingers the ends are palpated inside the oropharynx (we should be able to palpate only the tip of the Rotterdam applicator inside the oropharynx). The applicator is fixed into position (to prevent any dislodgement) by the help of stopper (Figure 3).[13] A suction catheter is used to suck out any oral secretion (to prevent aspiration).

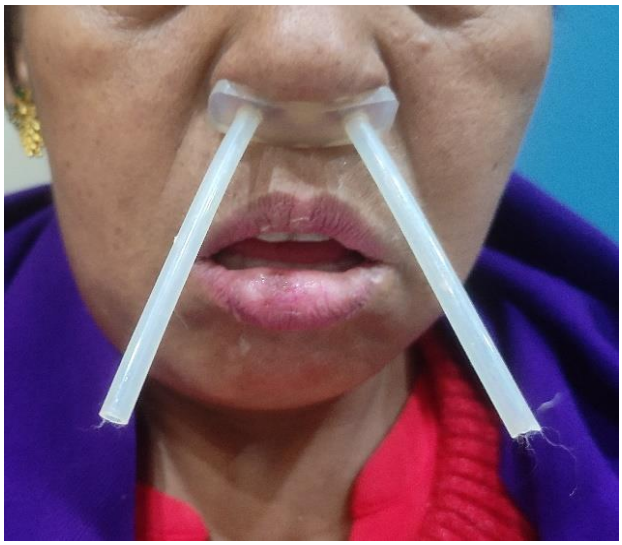

**Figure 3: Rotterdam applicator *in-situ*.[13]**

The patient was then simulated in supine position with dummy sources put inside the applicator. Treatment planning was done with the treatment planning system (TPS) and HDR doses were prescribed depending on the location of the recurrence (Figure 4).[13] If the recurrence was in the FOR or roof of NPC, then the HDR dose was prescribed at 0.5 cm and 1.0 cm from the centre of source respectively. Median treatment length is generally 3 cm.

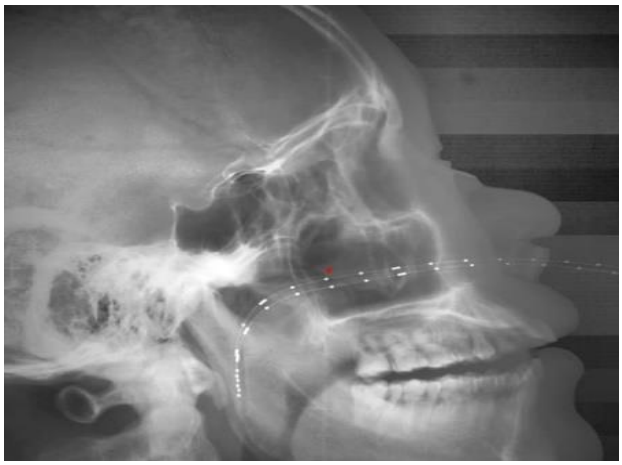

**Figure 4: Orthogonal X-ray of the patient in supine position with dummy source position (Lateral view).[13]**

After the treatment planning is approved, the patient is shifted to the HDR room for treatment with $^{192}$Ir HDR BT. After the completion of radiation treatment, the Rotterdam applicator can be removed and the patient is discharged on the same day. A total dose of 10Gy in 2 fractions (5 Gy/#) was given by HDR BT, one week apart

with or without EBRT for locally recurrent NPC, keeping in mind the previous EBRT dose given by Tele Cobalt-60 machine.

## CONCLUSION

Brachytherapy in any form can be applied for the early cases of NPC as a boost or definitive in cases of recurrent cases. Recurrent NPC management is a therapeutic challenge. Given the vulnerability of the already pre-treated structures surrounding the nasopharynx, any potential salvage retreatment poses a significant risk of severe complication that result in high treatment related morbidity, deterioration of QoL, and even mortality. Though with careful patient selection, long term survival may be achieved after local retreatment in a subgroup of patients with local or regional relapse of NPC.

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