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# Should high-dose-rate brachytherapy boost be used in early nasopharyngeal carcinomas?

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ABSTRACT

*Background:* Radiation with or without chemotherapy is the main treatment of nasopharyngeal carcinomas (NPC). Local recurrence is difficult to manage. Local control is dose-dependent.
*Aim:* To analyze the effect of an endocavitary brachytherapy boost after external beam radiation (EBRT) to decrease local recurrence.
*Material and methods:* Thirty patients with T0-T2 NPC were treated: 70% T1, 20% T2 and 10% T0; 33.3% N0, 20% N1, 43.3% N2 and 3.3% N3; 90% were undifferentiated carcinoma. All they received a 192-Ir high dose rate brachytherapy (HDR-BT) boost after 60 Gy of EBRT. The Rotterdam applicator was used in most cases, 3-4 fractions of 3.75-3 Gy in two days.
*Results:* With median follow-up (FU) of 63 months, a single parapharyngeal failure resulted in local control of 100% at 3 years and 95% at 5 years. Local control for T0-1 was 100% and for T2 67% at five years ($p = 0.02$). Regional-free recurrence survival was 92% at 5 years. Metastasis-free survival was 84% at 5 years. All cases of metastasis had histopathology of undifferentiated. The overall and cause-specific survival was 96% and 86% at 3 and 5 years. No late complications related to brachytherapy were described.
*Conclusion:* A HDR-BT boost is useful to decrease the incidence of local recurrence of NPC to 5%. With a fractionated schedule of 3-4 fractions in two days, Rotterdam applicator and 3-D planning, no late complications are described. Therefore we recommend to use brachytherapy boost in all early NPC.


## 1. Introduction

Nasopharyngeal carcinoma (NPC) is a common tumour in China but unusual in occidental countries (1/100,000).[1] It is more frequent in males, with two incidence peaks,[2] in the age group 40-60 and 10-25 years old. The NPC is not related to alcohol and tobacco habits, but to carcinogens and Epstein-Barr virus infection.[3] The main location is on the lateral walls and roof of the nasopharynx area, but submucosal spread is not unusual. Unlike other head and neck tumours, the risk of distant spread is high, which is a reason to include chemotherapy even in some early cases. Likewise, the incidence of cervical lymph node involvement at the time of diagnosis is greater than 80%[4] which is the main initial sign of presentation. The histology of most cases are undifferentiated carcinomas, which explains this high risk of lymph node spread.

Surgery in not indicated as the primary treatment of NPC, and radiation with or without chemotherapy is the main therapy.[5–6] Radiation includes in most cases all cervical areas and the primary tumour, and the highest dose for the tumour and positive lymph nodes is 70 Gy. With this approach a good control of disease is obtained, but a percentage of 10-15% of local recurrence is frequent. Several options have been proposed to increase the dose to the nasopharynx by a stereotactic radiosurgery boost (SBRT)[7] or brachytherapy boost.[8] Brachytherapy (BT) can be used with different approaches, but the most common is the endocavitary, after external beam radiation therapy (EBRT).[9] The Rotterdam applicator is an easy to place device and is adapted to the curved anatomy of the nasopharynx. With this system, local failures were observed in 8.2% of T1-2 NPC.[10]

The objective of this work is to make a retrospective study analyzing all the cases treated in a single institution to verify if the

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**Table 1**
Patients' characteristics.

| | | | |
|---|---|---|---|
| Age | 53 (31-72) | | |
| Sex | men | 25 | 83.3% |
| | women | 5 | 16.7% |
| Stage T | T0 | 3 | 10% |
| | T1 | 21 | 70% |
| | T2 | 6 | 20% |
| Stage N | N0 | 10 | 33.3% |
| | N1 | 6 | 20% |
| | N2 | 13 | 43.3% |
| | N3 | 1 | 3.3% |
| Stage TNM | I | 8 | 26.7% |
| | IIA | 2 | 6.7% |
| | IIB | 6 | 20% |
| | III | 13 | 43.3% |
| | IVB | 1 | 3.3% |
| Histology | undifferentiated | 29 | 90% |
| | Non-keratinizing squamous cell | 2 | 6.7% |
| | Keratinizing Squamous cell | 1 | 3.3% |

brachytherapy boost is useful to reduce the risk of local recurrences. Local recurrence-free (LRFS), regional and distant metastasis-free survival (MFS) will be analyzed, and complications will be evaluated. The second objective is to make a bibliographic review of the different factors that can favour the use of BT in early NPC.

## 2. Material and methods

All patients submitted to our department with NPC for definitive radiation were evaluated, and stage cT0- cT2 NPC were proposed to receive a BT boost as part of the radiation treatment. From 2000 to 2017, 30 patients received a nasopharynx boost with high dose rate (HDR) BT, 25 men and 5 women. The median age was 53 years. The initial symptoms were enlarged cervical lymph nodes in half of the cases, and nasal obstruction, epistaxis, medial otitis, impaired hearing, present in most cases. Biopsy of nasopharynx and/or enlarged lymph nodes showed undifferentiated carcinoma in 90%. Regarding the tumour extension, 70% were T1, 20% T2 and 10% T0. In these three T0 cases no tumour was visible in the nasopharynx, but with a proven positive biopsy of undifferentiated carcinoma in the lymph nodes and Epstein-Barr positivity, they were considered primary NPC. There were initial cervical lymph nodes in 66.7 % of the patients. The distribution by stage[11] and the characteristics of the patients are shown in Table 1. A CT scan of the chest and head and neck was performed to exclude distant metastasis. In most cases a MRI of the head and neck was performed.

EBRT with CT planning, was administered in doses of 1.8-2 Gy per day, 5 days a week, for 6-7 weeks. EBRT was 3-D planned in 23% and IMRT in 74%. The total dose for the nasopharynx was always 60 Gy, 70 Gy for positive nodes and 54-60 Gy for elective nodal areas. Twenty patients (67%) received chemotherapy, only in patients with positive lymph nodes, most of them neoadjuvant (19) and concomitant to EBRT (16).

The patients waited for 2 to 3 weeks, time needed to reduce acute mucositis, before starting the boost with 192-Ir HDR-BT with a Microselectron$^{TM}$ (Nucletron, an ELEKTA Company),. During the first years, two patients were treated by means of two Foley catheters introduced by each nostril and the balloon was inflated adapting to the nasopharynx, guided by radioscopy, and received two 5 Gy fractions once a week. Most cases, 28 (94%), were treated with the Rotterdam applicator, then the patient was admitted in hospital for two days. The technique for placing the applicator requires sedation and local anaesthesia of the oropharynx, palate, base of tongue, posterior pharyngeal wall and nostrils. Two thin flexible tubes are placed through both nostrils and come out through the mouth (Fig. 1). The applicator is fixed to the two guide tubes, and moved from the oral cavity to the nasopharynx,

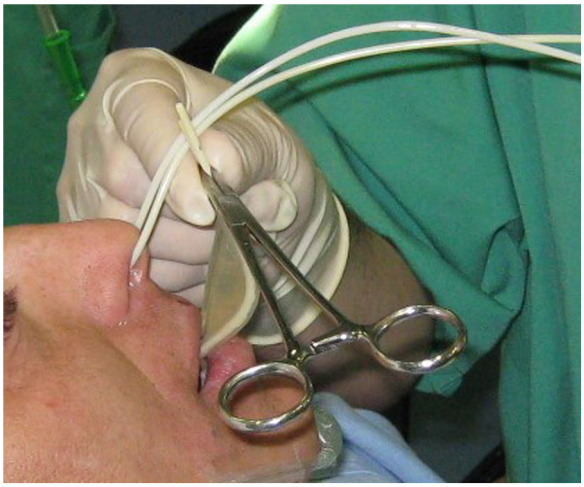

**Fig. 1.** Placement of Rotterdam applicator.

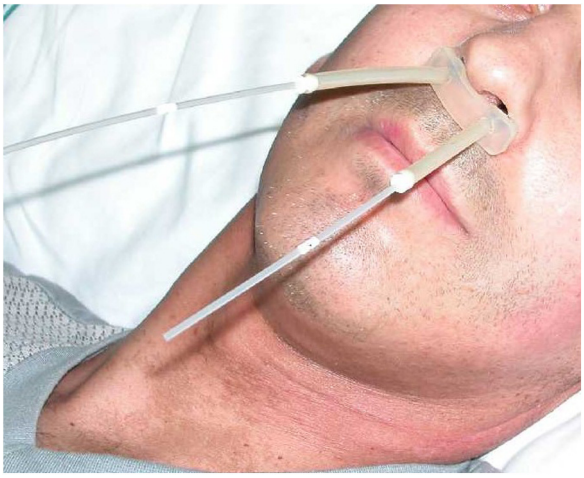

**Fig. 2.** Rotterdam applicator in site.

pulling the two ends of the guides until the tips of the applicator appear through the nostrils and its curved part fits into the nasopharynx (Fig. 2). A planning CT scan is performed every 3 mm, with dummy sources, and the head in hyperextension (Fig. 3). MRI was not used for planning, therefore no clear definition of residual tumour was possible. The Clinical Target Volume (CTV) is drawn one cm lateral to the sources and involves the whole nasopharynx, and, if needed, more margin is added to the previous involved area (Fig. 4). A dose of 3 Gy per four sessions (18 cases) or 3.5-3.75 Gy per three sessions (10 cases) was prescribed to the CTV. The dose to the spinal cord is registered. Sessions are administered twice a day, separated by at least six hours. The patient must stay one night with the applicator. Removal is done the next day with local anaesthesia.

For the statistical analysis of data, SPSS-15 statistical program was used to determine the survival with the Kaplan-Meyer actuarial method. The comparison between series was made with the Log-rank test, considering the significant value for $p < 0.05$. Acute complications will be analyzed following the toxicity scale of the Common Terminology Criteria for Adverse Events (CTCAE 3.0). Chronic complications will be analyzed following the established criteria of the LENT SOMA tables (Late Effects of Normal Tissues scoring system, Subjective, Objective, Management, Analytica).

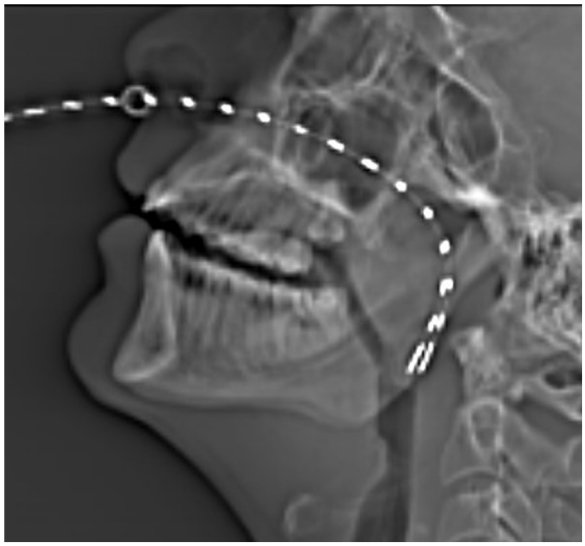

**Fig. 3.** Lateral view with dummy sources.

## 3. Results

The median follow-up (FU) was 63 ± 53 months (range 7-162). A single local failure has been registered, at 44 months of FU, with a 100% LRFS at 3 years and 95% at 5 years. It was an undifferentiated carcinoma, T2 N2 M0, and the relapse was parapharyngeal in an area of underdosing with HDR-BT. The 5-year LRFS for T0-1 was 100% and for T2 67% (p = 0.02), a significant difference. Two cases suffered cervical lymph nodes failure, with 92% free from regional recurrence survival at 3 and 5 years. Both cases were undifferentiated and N2, stage III. Four patients developed distant metastasis, with a MFS of 84% at 3 and 5 years. All were undifferentiated, three T2 and one T0. For cases T2, MFS was 40% at 5 years (p = 0.001). The patient with local recurrence also developed nodal and distant metastasis. All patients with metastasis died, without death from other causes, therefore, the overall survival (OS) and cause-specific survival (CSS) were the same, 96% at 3 years and 86% at 5 years. In undifferentiated cases, the figures decreased to 84% and 76% at 3 and 5 years (p = 0.71), and in the six cases T2, OS and CSS were 80% and 40% respectively (p = 0.008).

The acute toxicity was mucositis 77%, xerostomy 40%, odynophagia 25%, dermatitis G2-3 22%, dysphagia to solids 19%, hypogeusia 16% and hearing loss 16%. The most common late complication was xerostomy in 93% (39% G1, 37% G2, 16% G3); solids dysphagia 57%, hearing loss 57%, hypothyroidism 3%, hypopituitarism 3%, rhinorrhea 3%, temporomandibular joint pain 3% and palate veil stenosis 3%. The total doses and volumes were similar in all cases, and no relationship with toxicity was found.

## 4. Discussion

The NPC develops most frequently with undifferentiated or poorly differentiated cells, which respond well to chemotherapy and radiation, and a combination of both has become the standard treatment,[12] but with primary EBRT with or without chemotherapy, the rate of local relapses are between 10-15%. When tumour cells grow back, there is a greater risk of spreading to the rest of the body.[13] Local recurrences are not easy to manage, with poor results.[14] Carcinomas of most parts of the body are dose-dependent and the higher the dose, the better the local control. However, the total dose in NPC is limited to 70 Gy with EBRT due to the risk of late effects.

BT as a boost in NPC allows to get a high dose in small volumes with a rapid dose fall-off, optimal for the nasopharyngeal cavity. It is logical to use HDR-BT as a final boost to treat a smaller residual tumour volume. This approach was used with low dose rate BT for years, but 2D planning and fixed dose distribution produced suboptimal dosimetry distributions.

Several studies of the Rotterdam group, by Levendag et al, showed that BT boost is useful in early tumours. Three data sets on NPC, from the Vienna, Rotterdam, and Amsterdam series, showed that "in the case of T1-2 N + tumours, the local relapse (LRR) rate was significantly smaller if an endocavitary BT boost was applied,

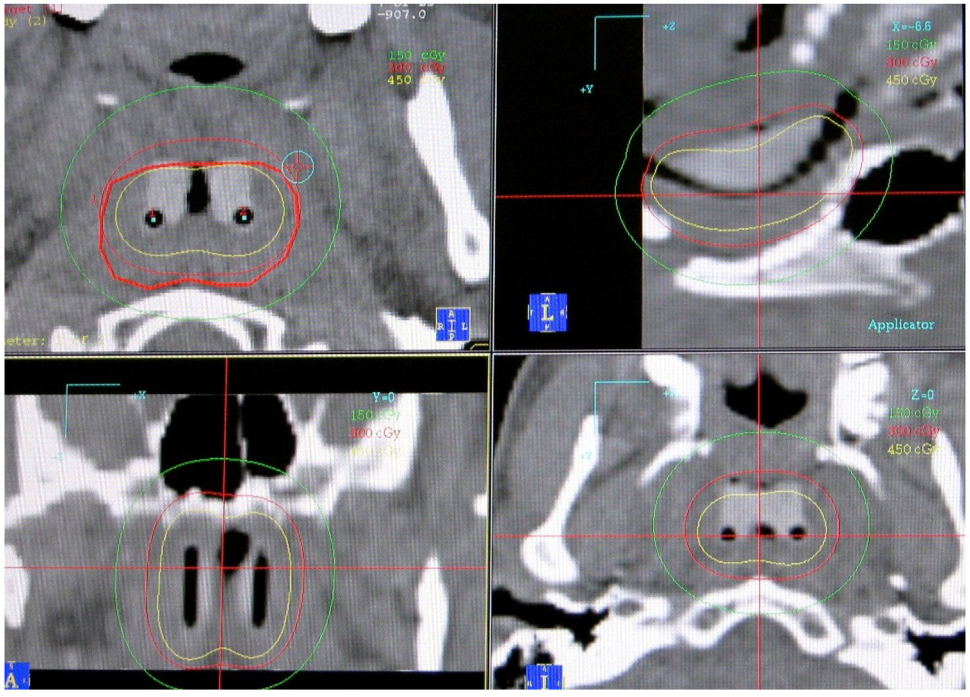


**Fig. 4.** CTV and isodose curves.

0% (0/34, BT boost) vs. 14% (14/102, no BT boost) (p = 0.023). For the T3-4 tumours, an LRR of 10% (4/38, BT or stereotactic radiation boost) was found against 15% (17/111, no boost) (p = 0.463)".[10] It is logical to think that big tumours are not really well boosted with an endocavitary procedure. This is the reason why in our Department HDR-BT boost is only used in T0-2 tumours and the LRR at five years is only 5%.

In order to clarify the actual usefulness of BT, a randomized study was conducted in patients with advanced NPC (T3-T4 N0-3 or T1-T2, N2, N3) treated with standard chemo-radiotherapy.[15] 274 patients with a median FU of 29 months were included, and 3-year local recurrence-free survival (LRFS) was 60.5% with BT boost and 54.4% without it, a non-significant difference. They concluded that BT boost did not improve outcome. These data are worse than expected because 3-year survival in T1-2 tumours was only 60.1% with BT boost in this study. Several aspects must be taken into account, only 80% of patients in the BT group were actually treated with the boost. In the BT boost arm the 3-year overall survival and DFS were 62.9% and 59.8%, and distant metastasis developed in 51% of cases. In our study we obtained 3-year OS and CSS of 96% and metastasis appeared only in 13%. With these data, it is clear that BT boost is not useful in advanced cases. Another retrospective study of Chao et al, with 124 T1-3 N0-3 NPC patients who received BT boost, obtained a 5-year LFRS of 91.5% without difference compared to the group of 108 cases without BT; but in a subgroup analysis comparing only T1, the 5-year LFRS was 98.1% for 75 patients treated with BT boost vs 85.9% for 71 patients without boost (p = 0.02).[16]

If the tumour size is important for local control, there is a difference when using orthogonal X-ray planning compared to 3D-image-guided HDR BT. Ren et al compared 101 patients treated with 2D-HDR-BT after 60 Gy EBRT, and 118 patients treated with 3D-HDR-BT, and showed an improvement in the 5-year actuarial LRFS rates, 100% vs 93.1% (p = 0.024).[17] The prescription point will change the dose to the surface of the mucosa. With the Rotterdam applicator, a standard prescription at 10 mm from the axis results in doses greater than 200% to the surface, without long-term complications, and can be adapted to the shape of the nasopharyngeal anatomy, rather than using 2D points.[18]

Dosage is a major issue, some studies use 70 Gy EBRT plus a boost with 11 Gy LDR or 3 x 3 Gy HDR.[10] Thiagarajan et al used 66 Gy EBRT plus 2 x 5 Gy with 5-year LRFS of 93.8%.[19] Leung et al with the same dose, 66 Gy EBRT plus 10-12 Gy in 2 weekly fractions obtained a 5-year LRFS of 95.8% in 145 patients, that were compared with other 142 NPC treated without boost and 88.3% (p = 0.02)[20]; CSS improved to 94.5% vs 83.4% (p = 0.005). Ren et al used 60 Gy EBRT plus 8-20 Gy HDR-BT boost and achieved 5-year LRFS of 100%.[17] In our department we chose 60 Gy EBRT to give HDR-BT more chance, because the biological effect is greater than with EBRT. Nevertheless, some recent studies from China have shown excellent results with 66 Gy in 30 fractions of IMRT, with 5-year LRFS of 95%, without boost vs 100% with boost but this difference was not significant.[21]

The applicator can be diverse, and balloon devices, ovoids, Rotterdam or other systems can be used. The issue is to cover properly the volume of the CTV. A review of the 45-year experience of a single institution, with several devices obtained 89% of local control at 5 years.[9] In our experience, the Rotterdam applicator is easy to place, comfortable, and well adapted to the anatomy of the nasopharynx, and with 3D-planning and HDR-BT it is one of the best options. We had one local recurrence in the parapharyngeal area, so we must be aware about lateral extension in T2 NPC to ensure that we can cover that volume with HDR-BT.

Late complications occur with local necrosis if the dose is too high. One study compared no boost, one or two fractions of 5 Gy HDR, or three fractions boost, and described perforation of the palate or sphenoid sinus floor, and concluded that the optimal dose of radiotherapy for the nasopharynx area in early stage NPC can be within 72.5 to 75 Gy, and the use of BT had a significant local control (93.9%) and a survival benefit for patients with early stage NPC, but the size of the fractionation should be decreased to reduce complications.[22] In our experience with 60 Gy EBRT plus 4 x 3 Gy or 3 x 3.75 Gy, no necrosis has been described.

The limitations of this study are the low number of cases, the long time of recruitment, an evaluation of response before BT was not performed, and the T0 cases included may not need a BT boost. But the outcome is good and we want to highlight the usefulness of a simple method to increase the dose to avoid local recurrences in the NPC. BT boost is recommended[23] but, in the routine practice, a lot of Radiation Oncology departments use exclusive EBRT even if a HDR-BT facility is available.

## 5. Conclusion

The NPC is well managed with modern EBRT techniques and chemotherapy, but there may be 10-15% of local recurrences that are difficult to manage. A HDR-BT boost is useful to decrease the incidence of local recurrence to 5%. With a fractionated schedule of 3-4 fractions in two days, Rotterdam applicator and 3-D planning, no late complications are described. Therefore we recommend using BT boost as part of the treatment in all early NPC.

## Conflict of interest

None declared.

## Financial disclosure

None declared.

## References

1. Wang Y, Zhang Y, Ma S. Racial differences in nasopharyngeal carcinoma in the United States. *Cancer Epidemiol*. 2013;37(6):793–802.
2. Erkal HS, Serin M, Cakmak A. Nasopharyngeal carcinomas; analysis of patient, tumor and treatment characteristics determining outcome. *Radiother Oncol*. 2001;61:247–256.
3. Chien YC, Chen JY, Liu MY, et al. Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. *New Eng J Medicine*. 2001;345(26):1877–1882.
4. Brennan B. Nasopharyngeal carcinoma. *Orphanet J Rare Dis*. 2006;26:1–23.
5. Lee AW, Poon YF, Foo W, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: overall survival and patterns of failure. *Int J Radiat Oncol Biol Phys*. 1992;23:261–270.
6. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys*. 2006;64(1):47–56.
7. Le QT, Tate D, Koong A, et al. Improved local control with stereotactic radiosurgical boost in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2003;56(4):1046–1054.
8. Levendag PC, Lagerwaard FJ, Noever I, et al. Role of endocavitary brachytherapy with or without chemotherapy in cancer of the nasopharynx. *Int J Radiant Oncol Biol Phys*. 2002;52:755–768.
9. Lee N, Hoffman R, Philips TL, et al. Managing nasopharyngeal carcinoma with intracavitary brachytherapy: one institution's 45-year experience. *Brachytherapy*. 2002;1:74–82.
10. Levendag PC, Keskin-Cambay F, de Pan C, et al. Local control in advanced cancer of the nasopharynx: is a boost dose by endocavitary brachytherapy of prognostic significance? *Brachytherapy*. 2013;12:84–89.
11. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. In: *Pharynx*. 7th ed. New York, NY: Springer; 2010:41–56.
12. Baujat B, Audry H, Bourhis J, et al. Chemotherapy as an adjunct to radiotherapy in locally advanced nasopharyngeal carcinoma. *Cochrane Database Syst Rev*. 2006;18(October (4)):CD004329.
13. Yu KH, Leung SF, Tung SY, et al. Survival outcome of patients with nasopharyngeal carcinoma with first local failure: a study by the Hong Kong Nasopharyngeal Carcinoma Study Group. *Head Neck*. 2005;27(May (5)):397–405.
14. Chua DT1, Sham JS, Kwong DL, Wei WI, Au GK, Choy D. Locally recurrent nasopharyngeal carcinoma: treatment results for patients with computed tomography assessment. *Int J Radiat Oncol Biol Phys*. 1998;41(May (2)):379–386.

15. Rosenblatt E, Abdel-Wahab M, El-Gantiry M, et al. Brachytherapy boost in loco – regionally advanced nasopharyngeal carcinoma: a prospective randomized trial of the International Atomic Energy Agency. *Radiat Oncol*. 2014;9:67.
16. Chao HL, Liu SC, Tsao CC, et al. Dose escalation via brachytherapy boost for nasopharyngeal carcinoma in the era of intensity-modulated radiation therapy and combined chemotherapy. *J Radiat Res*. 2017;58(5):654–660.
17. Ren Y, Zhao Q, Liu H, et al. 3D-image-guided HDR-brachytherapy versus 2D HDR - brachytherapy after external beam radiotherapy for early T-stage nasopharyngeal carcinoma. *BMC Cancer*. 2014;14:894.
18. Levendag PC, Peters R, Meeuwis CA, et al. A new applicator design for endocavitary brachytherapy of cancer in the nasopharynx. *Radiother Oncol*. 1997;45(1):95–98.
19. Thiagarajan A, Lin K, Tiong CE, et al. Sequential external beam radiotherapy and high-dose-rate intracavitary brachytherapy in T1 and T2 nasopharyngeal carcinoma: an evaluation of long-term outcome. *Laryngoscope*. 2006;116(June (6)):938–943.
20. Leung TW, Wong VY, Sze WK, Lui CM, Tung SY. High-dose-rate intracavitary brachytherapy boost for early T stage nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2008;70(Febuary (2)):361–367.
21. Xue F, Ou D, Hu C, He X. Local regression and control of T1-2 nasopharyngeal carcinoma treated with Intensity –Modulated Radiotherapy. *Cancer Med*. 2018;7(12):6010–6019.
22. Chang JT, See LC, Tang SG, Lee SP, Wang CC, Hong JH. The role of brachytherapy in early-stage nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 1996;36(December (5)):1019–1024.
23. Kovacs G, Martinez-Monge R, Budrukkar A, et al. GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update – Improvement by cross sectional imaging based treatment planning and stepping source technology. *Radiother Oncol*. 2017;122:248–254.