Dose escalation via brachytherapy boost for nasopharyngeal carcinoma in the era of intensity-modulated radiation therapy and combined chemotherapy

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ABSTRACT
To investigate if dose escalation using intracavitary brachytherapy (ICBT) improves local control for nasopharyngeal carcinoma (NPC) in the era of intensity-modulated radiation therapy (IMRT) and concurrent chemoradiation treatment (CCRT). We retrospectively analyzed 232 patients with Stage T1–3 N0–3 M0 NPC who underwent definitive IMRT with or without additional ICBT boost between 2002 and 2013. For most of the 124 patients who had ICBT boost, the additional brachytherapy was given as 6 Gy in 2 fractions completed within 1 week after IMRT of 70 Gy. CCRT with or without adjuvant chemotherapy was used for 176 patients, including 88 with and 88 without ICBT boost, respectively. The mean follow-up time was 63.1 months. The 5-year overall survival and local control rates were 81.5% and 91.5%, respectively. ICBT was not associated with local control prediction (P = 0.228). However, in a subgroup analysis, 75 T1 patients with ICBT boost had significantly better local control than the other 71 T1 patients without ICBT boost (98.1% vs 85.9%, P = 0.020), despite having fewer patients who had undergone chemotherapy (60.0% vs 76.1%, P = 0.038). Multivariate analysis showed that both ICBT (P = 0.029) and chemotherapy (P = 0.047) influenced local control for T1 patients. Our study demonstrated that dose escalation with ICBT can improve local control of the primary tumor for NPC patients with T1 disease treated with IMRT, even without chemotherapy.

KEYWORDS: brachytherapy, intracavitary brachytherapy, intensity-modulated radiation therapy, nasopharyngeal carcinoma, combined chemoradiotherapy

INTRODUCTION
Nasopharyngeal carcinoma (NPC) is an endemic disease in southern China, Hong Kong and Taiwan [1]. The cancer registry report from the Taiwan Health Promotion Administration of the Ministry of Health and Welfare states that 1578 NPC cases were diagnosed in 2012, making it the second most common head-and-neck cancer in Taiwan.
NPC also has a high predilection for local-regional tumor extension as well as distant metastasis. The primary treatment for NPC has been radiation therapy. As part of combined modality treatment, concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy has been recommended for Stage II–IV disease. The typical radiation dose is 70 Gy to the gross tumors, 60 Gy to the high-risk nodal region, and 46–54 Gy to the low-risk subclinical area, using a standard daily fractionation dose of 1.8–2.0 Gy. Two-dimensional radiation therapy (2DRT) was used before the era of 3D conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT). While brachytherapy has been the most common procedure for dose boosting to the primary tumor site during the 2DRT and 3DCRT era, the modern IMRT technique may use the simultaneous integrated boost (SIB) technique to serve a similar purpose. Intranasal insertion, i.e. intracavitary brachytherapy (ICBT), is the main brachytherapy approach because it is relatively easy to use [2–5]. Unfortunately, ICBT is not as effective for treatment of deeply infiltrating tumors such as those of T4 disease with intracranial extension because of the rapid dose fall-off as distance from the radioactive source increases [6–9]. Since IMRT has become the standard treatment for NPC [10, 11], and can achieve excellent local control of the primary tumor, ICBT as a boost treatment following external-beam irradiation has dramatically declined [4].

However, the physical advantage of ICBT in limiting the ‘integral dose’—the unintentional dose to the surrounding normal tissues brought about by external-beam irradiation—is difficult to emulate for IMRT if dose escalation to the primary tumor site is attempted. No published report is available regarding the role of ICBT for primary tumor dose boosting in the IMRT era [12]. In our institute, the use of ICBT, even without residual tumor after IMRT, has been dependent upon the attending physician’s preference. The aim of this study was thus to investigate the possible benefit of an ICBT boost when patients have no gross residual nasopharyngeal tumor after IMRT for the treatment of NPC.

**MATERIALS AND METHODS**

Patients diagnosed with NPC at our hospital from August 2002 to December 2013 were retrospectively reviewed. Patients with distant metastasis at presentation, previous history of cancers, or definitive treatment outside our hospital were excluded. Patients with a pathologic diagnosis of adenoid cystic carcinoma, mucoepidermoid carcinoma, plasmacytoma or clear cell carcinoma were excluded. In our institute, we routinely checked the response of the primary tumor by nasopharyngoscopy every week during the course of IMRT, and all patients with gross residual primary tumor immediately after IMRT had to undergo ICBT boost. Thus, patients who did not complete the course of IMRT or who had gross residual primary tumor immediately after IMRT were also excluded. Because ICBT was not indicated for T4 lesion, we further excluded T4 disease. This study was reviewed and approved by the institutional review board of the Tri-Service General Hospital.

A total of 232 patients with T1–3 N0–3 M0 NPC underwent radiation treatment with curative intent during this period. According to our exclusion criteria, none of the included 232 patients had gross residual primary tumors at the completion of IMRT. There were 168 males and 64 females, with age ranging from 13 to 83 years (median: 49). All diseases were restaged based on the staging criteria of the 2010 version of American Joint Committee on Cancer (AJCC) Cancer Staging Manual [13]. According to the cancer staging work-up of our institute, all NPC patients underwent contrast-enhanced MRI from base of skull, nasopharynx, and neck to the clavicles to identify the T and N classifications. FDG-PET scan was performed when the boundary of locoregional invasion was vague or when distant metastasis was suspected by physical examination or basic imaging studies (chest X-ray, abdominal ultrasound, whole-body bone scan, etc.). There were 49 patients (21%) with Stage I disease, 75 (33%) with Stage II, 84 (36%) with Stage III and 24 (10%) with Stage IV disease (Table 1). Sixty-six patients had N0 disease while the other 166 were N+ at presentation. According to the World Health Organization (WHO) histopathologic classification, only one case (0.4%) was Type 1 (keratinizing squamous cell carcinoma), 25 (10.8%) were Type 2a (non-keratinizing differentiated carcinoma), and 206 (88.8%) were Type 2b (undifferentiated carcinoma) [14].

All patients underwent IMRT in the supine position, with head and neck immobilized using a thermoplastic mask. A whole-field SIB technique was used, with once-daily fractions given five days per week [15]. The gross tumor volume (GTV) encompassed the primary tumor and gross nodes, and the median prescribed dose was 70 Gy (range: 68–72) at 2 Gy per day. The high-risk clinical target volume (CTV2) included the GTV, the entire nasopharyngeal area, the parapharyngeal space, the nasopharyngeal carotid sheath, the retropharyngeal space, the styloid process and its surrounding area, Levels II and III of the neck, and the adjacent level neighboring the gross nodal disease. Level Ib was also included if significantly enlarged nodes at Level II were noted. Level IV and the supraclavicular area were included in the low-risk clinical target volume (CTV3). A 3 mm margin was added to the CTV to form the planning target volume (PTV). The median dose prescribed to the PTV2 and PTV3 was 60 Gy (range: 56–60 Gy) and 50 Gy (range: 50–54 Gy), respectively. The doses were prescribed to include a minimum of 95% of the PTV. The median volume of the primary tumor, excluding the gross nodes, was 18.6 ml (range: 8.6–35.0).

ICBT was used as a boost treatment for 124 patients (53%) within 2 weeks after completion of IMRT (Table 2). The ICBT boost was carried out as previously described [3, 7]. Briefly, we used the microSelectron® stepping source, remote afterloading. One high-dose-rate technique with 192IrIdium as the radiation source. A pair of Nucleotron® nasopharyngeal balloon applicators with dummy

| Stage | N0 | N1 | N2 | N3 |
|-------|----|----|----|----|
| Stage I | T1 | 49 | 41 | 40 | 16 |
| Stage II | T2 | 9 | 25 | 12 | 7 |
| Stage III | T3 | 8 | 10 | 14 | 1 |
| Stage IV | T4 |   |    |    |   |
seeds was inserted into bilateral nasal cavities \cite{9,16}. Before 2012, we used 2D treatment planning for ICBT, and the dose was prescribed at 3–5 mm beneath the balloon surface; after 2012, 3D planning was used, with the radiation dose prescribed at 90% of the isodose curve covering mainly the submucosal area of the nasopharynx. There was no consensus about which kinds of T1–3 patients should receive ICBT in the IMRT era, although T4 disease was a contraindication in our institute \cite{4}. ICBT was carried out as a local boost, depending on the physician’s practice. Because the fraction size and number were inconclusive in the literature, the ICBT protocol was determined by the preference of the attending doctors \cite{3,7,9,16}. Most patients received 6 Gy in 2 fractions within 1 week (range: 3–11 Gy in 1–4 fractions, within a maximum of 2 weeks after IMRT). The radiation dose of IMRT to patients with an ICBT boost was 70 Gy (range: 68–72 Gy), and to patients without an ICBT boost was also 70 Gy (range: 68–72 Gy).

 Concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy was used for 176 patients (Table 3), including 88 with and 88 without an ICRT boost, respectively. The most commonly used chemotherapeutic regimen was cisplatin of 40 mg/m² weekly during the course of IMRT for 8 cycles. For Stages III and IV or other high-risk patients, standard adjuvant chemotherapy was given every 3 weeks for 3 cycles, with cisplatin 80 mg/m²/day on Day 1 and fluorouracil 1000 mg/m² on Days 1 to 4. The SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. We used Pearson’s chi-squared test to measure the correlative significance between various factors and major end points between groups. The follow-up and survival times were calculated from the completion of radiotherapy to the date of last follow-up or death. Local failure date was defined as the date of documented local recurrence in the nasopharyngeal space. The ICBT boost did not involve any additional radiation dose to the regional nodes; thus, we did not include nodal recurrence in the local control analysis. The actuarial cumulative survival probability was computed using the Kaplan–Meier analysis, and the comparison between groups was evaluated with the log-rank test. The following factors were examined for overall survival, using univariate analysis: AJCC stage, sex, age, WHO pathology type, and the use of ICBT and chemotherapy. Cox regression multivariate analysis was used to test for significant prognostic factors. All statistical tests were two-sided, and a $P$-value of <0.05 was considered statistically significant.

### RESULTS

The mean follow-up time was 63.1 months (range: 6–138 months). During follow-up, 13 patients (5.6%) had local recurrences alone, 12 (5.2%) had regional nodal recurrences alone, and 4 (1.7%) had both local and regional recurrences. Distant metastases were noted

| Table 2. Demographic and histologic characteristics of the 232 nasopharyngeal carcinoma patients |
| --- |
| Factor (n, %) | With ICBT boost (n) | Without ICBT boost (n) | $P$-value |
| Sex |
| Male (168, 72%) | 89 | 79 | $P = 0.851$ |
| Female (64, 28%) | 35 | 29 |  |
| Age |
| $<50$ y (119, 51%) | 66 | 53 | $p = 0.528$ |
| $\geq 50$ y (113, 49%) | 58 | 55 |  |
| T classification |
| T1 | 75 | 71 | $P = 0.170$ |
| T2 | 34 | 19 |  |
| T3 | 15 | 18 |  |
| N classification |
| N0 (66, 28%) | 38 | 28 | $P = 0.268$ |
| N1 (76, 33%) | 43 | 33 |  |
| N2 (66, 28%) | 35 | 31 |  |
| N3 (24, 11%) | 8 | 16 |  |
| WHO type |
| Type 1 (1, 0.4%) | 1 | 0 | $P = 0.499$ |
| Type 2a (25, 10.8%) | 15 | 10 |  |
| Type 2b (206, 88.8%) | 108 | 98 |  |
| Chemotherapy |
| No | 36 | 20 | $P = 0.062$ |
| Yes | 88 | 88 |  |

**ICBT** = intracavitary brachytherapy.

| Table 3. The correlation between ICBT and chemotherapy in T1–3 disease |
| --- |
| Factor | With ICBT boost (n) | Without ICBT boost (n) | $P$-value |
| T1 |
| With chemotherapy | 45 | 54 | $P = 0.038$ |
| Without chemotherapy | 30 | 17 |  |
| T2 |
| With chemotherapy | 29 | 18 | $P = 0.298$ |
| Without chemotherapy | 5 | 1 |  |
| T3 |
| With chemotherapy | 14 | 16 | $P = 0.658$ |
| Without chemotherapy | 1 | 2 |  |

**ICBT** = intracavitary brachytherapy.
in 31 patients (13.4%), with or without local or regional recurrences. The 5-year overall survival rate was 81.5%. The 5-year overall survival rates were 90.4%, 84.8%, 82.4% and 51.6% for patients with Stage I, II, III and IV, respectively (P < 0.001, Fig. 1). The univariate analysis of correlations between overall survival and various clinicopathological factors were tested as the following: stage grouping (P < 0.001), T stage (P = 0.549), N stage (P < 0.001), WHO type (P < 0.001), sex (P = 0.193), age (P = 0.008), ICBT (P = 0.096) and chemotherapy (P = 0.728).

The 5-year local control rate was 91.5%. The 5-year local control was 91.8%, 94.3% and 86.0% for patients with T1, T2 and T3 disease, respectively (P < 0.001, Fig. 2). Sex (P = 0.699), age (P = 0.085), WHO type (P = 0.951), chemotherapy (P = 0.195) and ICBT (P = 0.228, Fig. 3A) were not associated with local control. ICBT was done for 75 (51.4%) of 146 patients with T1 disease, 34 (64.2%) of 53 with T2 disease, and 15 (45.5%) of 33 patients with T3 disease. The 5-year local control rate was 98.1% for patients with T1 disease with ICBT, and 85.9% for T1 disease without ICBT (P = 0.020, Fig. 3B); 100% for patients with T2 disease with ICBT, and 91.0% for patients with T2 disease without ICBT (P = 0.184, Fig. 3C); 84.6% for patients with T3 disease with ICBT, and 87.1% for patients with T3 disease without ICBT (P = 0.957, Fig. 3D).

In T1 patients, univariate analysis showed that the 5-year local control rate was not associated with sex (P = 0.578), age (P = 0.649), WHO type (P = 0.990) or use of chemotherapy (P = 0.111). In T1 disease, although the ICBT subgroup had fewer patients undergoing chemotherapy compared with those without ICBT (60.0% vs 76.1%, P = 0.038, Table 3), the local control in the ICBT subgroup was better (98.1% vs 85.9%, P = 0.020). Multivariate Cox regression analysis showed that both ICBT (P = 0.029) and chemotherapy (P = 0.047) influenced local control independently.

A total of 13 (5.6%) patients had radiotherapy-related cranial nerve palsy, and 17 (7.3%) exhibited Lhermitte’s sign. Nine (7.3%) patients in the ICBT boost group had cranial nerve palsy, compared with 4 (3.7%) patients in the group without an ICBT boost (P = 0.240). Ten (8.1%) patients in the ICBT boost group had Lhermitte’s sign, versus 7 (6.5%) in the group without an ICBT boost (P = 0.644). Osteoradionecrosis was not recorded in any of the patients.

**DISCUSSION**

ICBT is used for a local residual tumor or recurrence [3, 4]. ICBT is also used as a boost after 2DRT, even without a residual tumor [2, 4–8]. In our current study, we examined the benefit of ICBT (even with no residual tumor) after IMRT. To our knowledge, this is the first study to analyze the role of ICBT as a way of local tumor dose boosting in the treatment of NPC in the IMRT era. Our results suggest that local boost with ICBT after IMRT of definitive dose can improve local control in NPC patients with T1 disease, independent of whether concurrent or adjuvant chemotherapy is given.

Several reports have demonstrated the benefit of local boost with ICBT for T1–3 NPC in the era of 2DRT [6, 7]. Yeo et al. retrospectively reviewed 178 NPC patients with T1–2 disease [7]. All patients underwent 66 Gy of 2DRT, followed by an ICBT boost of 10 Gy in 2 fractions over 8 days. Their result showed that an ICBT boost supplementing 2DRT is an excellent method of enhancing local control with T1–2 disease. Wu et al. compared the outcomes for patients with T1–2 NPC treated with 2DRT in combination with ICBT versus the outcomes for a historical cohort treated with 2DRT alone [6]. They enrolled 348 patients treated with 2DRT, of whom 175 were treated with 2DRT and ICBT boost. The median dose was 72 Gy in the 2DRT-only group, and 58 Gy of 2DRT plus 20 Gy of ICBT in the ICBT boost group. The investigators reported that both cancer stage and the use of ICBT.
were significant predictive factors for overall survival and local control. They concluded that ICBT following 2DRT improves the therapeutic ratio for T1–2 NPC.

Leung et al. retrospectively investigated the therapeutic gain of ICBT after 2DRT [8]. Their inclusion criterion was T1–2 N0–3 NPC (similar to that of ours). The control group underwent 2DRT, with a total dose of 66 Gy. The ICBT group had a boost dose of 10–12 Gy in 2 fractions separated by a week. Their results supported the fact that ICBT improves local control and overall survival in NPC patients with T1–2 disease. Levendag et al. analyzed three study series in which ICBT was used for locally advanced stage NPC [9]. They pooled 411 advanced NPC patients who underwent 70 Gy of 2DRT with or without ICBT boost. Their results showed that ICBT improves local control for T1–2 disease, but not for T3–4 disease, regardless of N classification or cancer stage. It seems that the radiation dose of the ICBT used in our study was lower than that reported in the literature. However, IMRT tends to provide better conformality than 2DRT; thus, the combined dose of IMRT with ICBT boost was comparable with or higher than that reported in the above literature.

Levendag et al. investigated the optimal radiation dose with supplemental ICBT for NPC treatment [2]. They studied 91 Stage I–IV NPC patients who underwent 2DRT, with or without ICBT. They ended up recommending 77–81 Gy for 2DRT in combination with ICBT for Stage I–II B disease, without chemotherapy. In contrast, our current treatment policy is IMRT without chemotherapy for Stage I disease, and the radiation dose is 70 Gy (using 2 Gy per fraction). This external beam treatment dose is lower than what Levendag et al. have recommended, but the ICBT could boost the radiation dose after IMRT up to a total of 77–81 Gy.

Fig. 3. (A) The 5-year local control rates were 94.3% and 88.7% for patients with and without ICBT boost, respectively \( (P = 0.228) \). (B) In T1 patients, the 5-year local control was 98.1% for 75 patients with ICBT boost, and 85.9% for 71 without ICBT boost \( (P = 0.020) \). (C) In T2 patients, the 5-year local control was 100% for 34 patients with ICBT boost, and 91.0% for 19 without ICBT boost \( (P = 0.184) \). (D) In T3 patients, the 5-year local control was 84.6% for 15 patients with ICBT boost, and 87.1% for 18 without ICBT boost \( (P = 0.957) \).
Recently, a randomized controlled trial from the International Atomic Energy Agency analyzed the effect of ICBT boost in locoregional advanced nasopharyngeal carcinoma [16]. In the study, patients with T3–4 N0–3 and T1–2 N2–3 disease (Stage III–IV) were enrolled, and only 2DRT was used. The study protocol was neoadjuvant chemotheraphy followed by CCRT with/without ICBT boost. The authors concluded that addition of ICBT to external beam radiotherapy and chemotheraphy did not improve the outcome in locoregionally advanced NPC. In this trial, the 3-year overall survival rate was ~63% for all patients, and the 3-year local recurrence-free survival rate was 54.4% and 60.6% ($P = 0.647$) for patients with and without ICBT, respectively. The inclusion criteria, treatment protocol and the technique used for the external beam radiotherapy were different from ours, and it is difficult to compare the results. However, it seems that the results of this trial were dismal and it was difficult to explore the benefits of ICBT. There were problems covering the entire primary tumor in the 2DRT treatment planning. It is possible that under precise IMRT treatment planning, the combined use of ICBT is effective at improving the local control rate.

The literature has shown that ICBT can be used in T1–3 disease as a boost treatment following external beam irradiation, and improves local control [4–8]. However, only limited reports suggested T1–2 disease benefits from an ICBT boost after 2DRT [9]. Our present study provided a hint that there was no benefit for adding ICBT for T2–3 disease after IMRT, and the reason may be that it is difficult to cover the deep nasopharyngeal region using ICBT. An IMRT boost should be considered for high risk T2–3 disease.

The reported incidence of radiotherapy-related cranial nerve palsy is variable, from 1 to 18.4% [17]. In our group of patients, 5.6% had cranial nerve palsy that was comparable with that reported in the literature. The incidence of Lhermitte’s sign in our study was 7.3%, which is lower than that in the literature reports, which ranged from 10 to 21% [18, 19]. Osteoradionecrosis of the nasopharynx has not been documented in our study, but this may still occur after a longer follow-up.

However, there are inherent limitations in this retrospective study. First, more patients in the ICBT arm did not receive chemotherapy ($P = 0.062$), and this maybe a confounding factor. Second, there was no consensus about which kind of patients should receive ICBT in the IMRT era, although T4 disease is the contraindication in our institute. ICBT was carried out as a local boost depending on the physician’s practice instead of randomization, and thus bias might exist in the selection of patients for this therapy. Third, only one patient had WHO Type I disease in our study. Due to racial and geographic differences, the distribution of the pathological classifications varies from region to region [4, 7, 8, 20, 21]. Thus, our results cannot be extrapolated to WHO Type I disease. Fourth, because of the nature of retrospective analysis, some late toxicity may not have been recorded and may thus be underestimated.

In conclusion, our study showed that adding an ICBT boost after 70 Gy IMRT improved local control for NPC patients with T1 disease. A local boost using ICBT after 70 Gy IMRT for early-stage NPC patients could be beneficial, with an enhanced probability of local control and no apparent increase in toxicity. We have changed our treatment policy in response to the results of this research, and ICBT is routinely used as a local boost for T1 disease after IMRT. Because of the retrospective nature of our study, a randomized trial is required for confirmation of the results.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest. They certify that they have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript (e.g. employment, consultancies, stock ownership, honoraria).

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