Radiotherapy dose escalation in the primary treatment of nasopharyngeal carcinoma: a systematic review and meta-analysis

Lester Bryan A. Co, Ryan Anthony F. Agas, JC Kennetth M. Jacinto, Kelvin Ken L. Yu, Michael A. Mejia, Warren R. Bacorro

Department of Radiation Oncology, Benavides Cancer Institute, University of Santo Tomas Hospital, Manila, Philippines

Contributions: (I) Conception and design: LB Co, WR Bacorro, MA Mejia; (II) Administrative support: WR Bacorro, MA Mejia; (III) Provision of study materials or patients: LB Co, WR Bacorro, MA Mejia; (IV) Collection and assembly of data: LB Co, RA Agas, KK Yu, JC Jacinto; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Lester Bryan A. Co. Department of Radiation Oncology, Benavides Cancer Institute, University of Santo Tomas Hospital, España Boulevard, Manila 1015, Philippines. Email: lstrbryan@yahoo.com.ph; lesteraco@gmail.com.

Background: Dose escalation with radiotherapy (RT) in nasopharyngeal carcinoma (NPC) remains underutilized despite significant advances in methods of radiation delivery. RT boost during primary treatment has been shown to improve local control rates, which could have an impact on survival. We summarize the currently available evidence for dose escalation in the primary treatment of NPC.

Methods: Databases were systematically searched for eligible studies from the year 2000. Included studies utilized RT dose escalation (BED >70 Gy) in the form of brachytherapy, external beam RT or stereotactic RT boost after external beam RT for primary treatment of NPC. Local recurrence-free survival (LRFS), overall survival (OS), toxicities and other relevant factors for the chosen studies were then pooled and analyzed.

Results: Two randomized trials and 7 retrospective cohort studies with a total of 2,145 patients were included in the final analysis. Nine hundred and eighty-eight patients received dose escalation, mainly in the form of brachytherapy (90%). Patients were mostly male, from China/Southeast Asia, had T1-T2 disease (80%), underwent RT via conventional techniques (87%). Less than half received concurrent chemotherapy. Three-year LRFS (RR 1.04; 95% CI: 0.85–1.28, P=0.71) and OS were not significantly improved with dose escalation. However, the subset of patients pooled from the retrospective studies who did not receive concurrent chemotherapy showed significant a 5-year locoregional failure-free survival (RR 1.05; 95% CI: 1.02–1.09, P=0.005) benefit. Toxicities were not significantly increased with dose escalation.

Conclusions: RT dose escalation in the primary treatment of NPC does not lead to an increase in LRFS, OS, progression-free-survival and disease free-survival. However, there seems to be a LRFS benefit with dose escalation using brachytherapy in patients with T1-T2 disease and in patients who did not receive concurrent chemotherapy. Dose escalation with brachytherapy is likewise not significantly associated with any increase in the rate of complications. Data for the efficacy and toxicity of EBRT and SRT boost is currently still lacking.

Keywords: Radiotherapy (RT); dose escalation; boost; nasopharyngeal carcinoma (NPC)
Introduction

Nasopharyngeal carcinoma (NPC) is known to be highly radiosensitive, and radiotherapy (RT) remains the mainstay of treatment for non-disseminated disease (1). The treatment of NPC has undergone significant advances in the past two decades, most notably with the emergence of chemoradiation as the standard of care.

In the era of conventional/two-dimensional (2D) external beam radiotherapy (EBRT), and prior to the era of chemoradiation, dose escalation beyond 66 Gy has been shown to enhance local control. This local control benefit was particularly seen in T1/T2 primaries (2,3), with less evidence of benefit for more advanced (T3/T4) primaries (4). While the addition of brachytherapy or EBRT boost was associated with enhanced local control, it was not without additional toxicity (5-8). Whether this improved local control translated to an OS benefit and justified the increased toxicity remained unclear (9,10).

Chemoradiation or the addition of concurrent chemotheraphy (CRT) to RT has led to higher tumor control rates and longer survival (11,12). The adoption of three-dimensional conformal (3DCRT) and intensity-modulated (IMRT) techniques in radiation therapy has allowed for safer delivery of higher EBRT doses up to 70 Gy to the primary tumor site (8,13). Together, these developments have resulted in a shift of the mode of treatment failure after primary therapy to mostly distant failures (12). Nevertheless, persistent local disease and local recurrences are still seen after initial therapy, which can affect patient survival and quality of life.

Local control has been shown to be directly related to the RT dose (2,8,14) and it has been suggested that a local control benefit may be derived from escalating doses beyond 70 Gy and up to 80 Gy. The development of endocavitary brachytherapy techniques that do not require soft palate dissection has allowed for further dose escalation after EBRT without increased toxicity. On the other hand, dose escalation exclusively by EBRT, either by boost or by altered fractionation, has resulted in toxicity despite the use of conformal techniques. While dose escalation beyond 70 Gy has been mostly abandoned, certain centers have continued to employ brachytherapy for this purpose.

The advent of three-dimensional image-guided planning (IGBT) and stepping-source technology in brachytherapy, stereotactic (SRS) and image-guided (IGRT) RT in more recent years warrant a second look at dose escalation. In terms of choice of modality for dose escalation, brachytherapy seems to be preferred in early T-stage NPC (T1/T2), while EBRT has been used mainly in more advanced T-stages. The optimal fractionation scheme and dose still remains to be defined. The aim of this study is to summarize the currently available evidence for RT dose escalation during the primary treatment of NPC in an effort to come up with better guideline to manage this endemic disease.

Methods

A systematic literature review was conducted using the following search engines/databases: PubMed, ASCOpubs, the Cochrane Library, and Google Scholar. The International Clinical Trials Registry Platform, CENTRAL, and clinicaltrials.gov were also searched for ongoing trials. We searched for eligible studies from the year January 01, 2000 to September 30, 2018 using the following keywords: “dose escalation” OR “boost” OR “brachytherapy” AND “nasopharyngeal cancer” OR “nasopharyngeal carcinoma” OR “NPC”. Titles of the studies from the literature search were initially screened and selected for review. Complete texts of the selected abstracts were scrutinized in detail to identify studies for inclusion based on the selection criteria. Finally, purling was done by surveying the reference lists of the identified studies. The date of the last search was on September 30, 2018. Study protocol was registered with the international prospective register of systematic reviews (PROSPERO) with ID number CRD42018096415.

Criteria for selection of studies

Types of participants
Eligible studies investigated outcomes of patients with NPC who were treated with conventionally fractionated primary RT with or without dose escalation/RT boost (boost). NPC belonging to any of the three WHO histologic subtypes were included. Studies investigating recurrent or metastatic NPC, or other histologic types of nasopharyngeal cancer (lymphoma, sarcoma, etc.) were excluded from this analysis.

Types of interventions
The primary intervention investigated was dose escalation/boost with RT during the initial therapy of NPC. RT boost was defined as the intentional addition of a RT dose to the primary tumor after initial EBRT, with cumulative biological equivalent dose (BED) exceeding 70 Gy in patients that were treated with conventional EBRT. The
boost can be in the form of brachytherapy, EBRT or SRT. The boost may be done before, during or after primary RT. The comparator group was no RT boost (no boost). Concurrent chemotherapy was allowed in both groups. Response-adapted addition of RT boost after primary EBRT was also allowed. Studies which utilized non-conventional fractionation schemes for the initial EBRT like altered, accelerated or hyperfractionation were excluded to facilitate cumulative EQD2 comparisons.

**Types of outcomes**

Studies which reported oncologic outcomes and treatment-related toxicity of RT boost and no boost were included in this review. The primary outcomes investigated were local recurrence-free survival (LRFS) and overall survival (OS). LRFS was defined as the proportion of patients alive without a local recurrence at a specified period from the date of randomization or initiation of treatment. OS was defined as the proportion of patients alive after a specified period from the date of randomization or initiation of treatment.

Secondary outcome measures include disease-free survival (DFS), progression-free survival (PFS), and treatment-related toxicity. DFS and PFS were defined as the proportion of patients free from disease and the proportion of patients with disease but are free from any progression, respectively. Treatment-related toxicity was defined as any adverse effect directly attributable to treatment.

**Types of studies**

The review included two randomized controlled trials (RCT). Due to scarcity of evidence regarding the clinical question, retrospective studies were also included in this study. According to the Oxford Center for Evidence-Based Medicine, retrospective cohorts are considered as Level III evidence (15). The following types of studies were excluded in this review: case series with <10 patients per group, single-arm studies, reviews, and full articles not available in English.

**Assessment of methodological quality**

Critical appraisal and assessment for risk of bias was done by 3 reviewers (RA Agas, LB Co and KK Yu) using the McMaster Critical Review Form for Quantitative Studies. There were no disagreements between the reviewers regarding the eligibility of the included studies.

**Data collection, synthesis, and statistical analysis**

Two reviewers (LB Co, RA Agas) did independent data extraction using a tailored spreadsheet (Microsoft Excel). Disagreements with extraction were discussed at length and were ultimately resolved by a third reviewer (JC Jacinto). Data extraction included the title, author, year, study design, study population, sample size, intervention and control arms, outcome measures, and results. When appropriate, pooling of outcomes from published trial results or from data in the survival curve analysis was done. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, only outcomes from studies with similar study designs were pooled (16). Using the Review Manager Software 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), statistical pooling was done following the Mantel-Haenszel model. The chi square statistic was used to investigate heterogeneity. Pooled data that reached an I² of 50% or greater and/or a confidence interval <0.10 was considered to have high heterogeneity and was analyzed using the random effects model. Pooled data not meeting this cutoff were deemed to have low to moderate heterogeneity and was analyzed using the fixed effects model. Other data collected and not pooled were included in the narrative synthesis. An overall summary of evidence recommendation was done using the NHMRC of Australia Body of Evidence Framework that is composed of 5 factors: evidence base, consistency, clinical impact, generalizability, and applicability (17).

**Results**

**Search results**

The initial search yielded a total of 211 abstracts after excluding all duplicates (Figure 1). A total of abstracts were excluded due to the following reasons: prognostic studies (n=7), dosimetric studies (n=29), chemotherapy studies (n=19), applicator studies (n=3), patterns of failure (n=2), toxicity reports (n=12), quality-of-life studies (n=3), gene/genome studies (n=3), EBV/viral studies (n=8), imaging studies (n=6), treatment techniques (n=1), simultaneous integrated boost (n=26), EBRT vs. IMRT (n=1), particle therapy (n=3), recurrent disease (n=5), metastatic disease (n=1), single-arm only studies (n=24), altered fractionation (n=9), review articles (n=20), did not report outcomes (n=4), experimental/feasibility studies (n=3), case report/small series (n=5), other head & neck (n=2), and unrelated...
Three studies were identified after purling (9,18,19). Full texts of 13 studies were assessed for eligibility. Three studies were excluded because the desired outcomes were not reported between comparator arms (20-22). One study had population overlap with another study (23). A total of 9 studies were found to be eligible in the final analysis (Table S1). Two RCTs were included in the review (23,24). Seven were retrospective cohorts with 988 cumulative patients eligible for statistical pooling.

Critical appraisal results

All studies were found to have sound methodological quality, stated objectives clearly, and discussed relevant background on the topic (Table S2). They had well-defined, measurable outcomes with potentially clinically meaningful results. One RCT studied brachytherapy boost in locoregionally advanced NPC (23). Another RCT explored PET-guided dose escalation via EBRT (24). Six retrospective studies utilized brachytherapy for dose escalation (2,9,18,19,25,26). One retrospective cohort studied EBRT boost (15). Patients in four studies (one EBRT, three brachytherapy) underwent dose escalation without concurrent chemotherapy (2,10,19,26).

Main results

I. Randomized studies:
   i. LRFS: two RCTs investigated the use of boost vs. no boost in patients with stage I–IV NPC (23,24). Both studies utilized concurrent chemotherapy with the RT. Pooled 3-year LRFS for both studies...
was not significantly different between the boost and no boost groups with a RR of 1.04 (95% CI, 0.85–1.28, P=0.71). Heterogeneity was moderate ($I^2=58\%$) (Figure 2A);

(ii) OS: after pooling results of OS for both RCTs, there was no significant difference between the two groups with a RR of 1.05 (95% CI, 0.93–1.18, P=0.42). Heterogeneity was low ($I^2=0\%$) (Figure 2B);

(iii) PFS: only outcomes for 3-year PFS were available for statistical pooling. Results showed an RR of 0.97 (95% CI, 0.8–1.19, P=0.78), with high heterogeneity ($I^2=69\%$);

(iv) DFS: pooled analysis for 3-year DFS showed a non-significant RR of 0.94 (95% CI, 0.8–1.11, P=0.48). Heterogeneity was high ($I^2=69\%$);

(v) Treatment-related toxicity: Both studies reported rates of late grade 3 to 4 toxicities. There were no significant differences between the dose escalation and no dose escalation groups (RR =1.00; 95% CI, 0.72–1.40, P=0.99) (Figure 2C).

(II) Retrospective studies:

(i) LRFS: 3- and 5-year LRFS rates of all seven retrospective studies were available for statistical pooling (2,9,13,18,19,25,26). All but two brachytherapy boost studies excluded T3-T4 patients (2,18,19,26). Chao et al. included T3 patients in his cohort, while Ozyar also studied patients with T3 & T4 disease. The lone study utilizing EBRT boost included only patients with primary T3 & T4 disease (15). Pooled analysis showed non-significant improvement in both 3- (Figure 3A) and 5-year LRFS (Figure 3B) between the two groups. (RR =1.04; 95% CI, 1.00–1.08, P=0.07, $I^2=59\%$) and (RR of 1.06 (95% CI, 1.03–1.09, P=0.0003, $I^2=49\%$), respectively.

(ii) OS: all retrospective studies reported OS outcomes, but only reported either 3- or 5-year OS. Three studies had 3-year OS and five studies had 5-year OS data available for statistical pooling (9,19,20). Both 3-year OS (Figure 3C) and 5-year OS (Figure 3D) were not significantly different with the boost vs. no boost groups (RR =1.01; 95% CI, 0.88–1.15, P=0.089, $I^2=84\%$) and (RR

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**Figure 2** Pooled Events from randomized controlled trials. (A) Three-year local recurrence-free survival; (B) 3-year overall survival; (C) grade 3-4 toxicity.
Upon subgroup analysis of four studies that only included patients not receiving concurrent chemotherapy, both 3-year LRFS (Figure 4A) and 5-year LRFS (Figure 4B) were significantly improved with the addition of boost (RR = 1.03; 95% CI, 1.00–1.06, P=0.04, I²=82%) and (RR = 1.05; 95% CI, 1.02–1.09, P=0.005, I²=0%), respectively. Treatment-related toxicity: not all studies reported toxicity outcomes. Of these, cranial nerve neuropathies (grade not specified) were reported in 4 studies (2,19,25,26). There was a significantly higher rate of cranial nerve neuropathies in the group that did not receive any boost (RR = 0.57; 95% CI, 0.39–0.84, P=0.005, I²=42%).

**Figure 3** Pooled events from retrospective studies. (A) Three-year local recurrence-free survival; (B) 5-year local recurrence-free survival; (C) 3-year overall survival; (D) 5-year overall survival.
Rates of ulceration and/or necrosis of the nasopharynx were reported in 3 studies (18,19,26). A trend towards higher rates of ulceration and/or necrosis of the nasopharynx was observed in the boost group (RR = 1.34; 95% CI, 0.66–2.72, P=0.41, $I^2=23\%$).
(III) Subgroup analysis of patients who received concurrent chemotherapy
   (i) For the three retrospective studies with patients that received concurrent chemotherapy, both 3-year LRFS (Figure 4C) and 5-year LRFS (Figure 4D) were not significantly improved with the addition of boost (RR =1.04; 95% CI, 0.90–1.21, P=0.58, \( I^2=86\% \)) and (RR =1.04; 95% CI, 0.90–1.21, P=0.57, \( I^2=84\% \)) (9,18,25).

   (ii) Subgroup analysis of the four studies that included only patients that did not receive concurrent chemotherapy likewise showed a non-significant difference in 5-year OS between the two groups (RR =1.10; 95% CI, 0.97–1.25, P=0.012, \( I^2=83\% \)) (2,10,19,26).

Discussion

This review presents the current available evidence comparing dose escalation (boost) vs. no dose escalation (no boost) in the primary therapy of patients with non-metastatic NPC. Based on the National Health and Medical Research Council’s “additional levels and grades for recommendations for developers of guidelines” (Table S3), the authors recommend that the current evidence for LRFS can be trusted to guide practice in most situations. Evidence in terms of OS and treatment-related toxicity provide some support for the recommendation, but care should be taken in their application. There is limited evidence available for both PFS and DFS, which was deemed insufficient to guide current practice.

Is there an LRFS and OS benefit to dose escalation in NPC?

Overall

Our results show that dose escalation (with either brachytherapy or external beam RT) during the primary treatment of NPC does not result in significant improvement in LRFS, OS, RRFS, DFS or PFS. There was a trend towards improved 5-year LRFS after pooling all retrospective dose escalation studies.

Treated with concurrent chemoradiation? Treated with radiation alone?

Pooled analysis of the subgroup who received concurrent chemotherapy failed to demonstrate either LRFS or OS benefit (9,18,25). In the subset of patients who did not receive any concurrent chemotherapy, there was a significant 3- and 5-year LRFS benefit seen, with a trend towards improved 5-year OS (2,10,19,26). The studies included in the pooled analysis are all retrospective.

With T1/T2 disease? With T3/T4?

Pooled analysis of all patients with T1/T2 disease from retrospective studies showed improved 3- and 5-year LRFS, but no significant OS benefit (2,19,25,26).

Data is more limited for patients with T3/T4 disease treated with boost. Chao found no significant difference in LRFS and OS for patients with T3 disease. Rosenblatt showed that 3-year LRFS and 3-year OS were worse for patients with T3/T4 disease regardless of treatment received. Ozyar did not find any significant differences in LRFS between patients with T1/T2 and T3/T4 disease on univariate and multivariate analysis, which may be due to the limited number of patients in his analysis (9). Yeh’s study included only patients with T3/T4 disease, and failed to show significant differences in both LRFS and OS with dose escalation (10).

Treated with brachytherapy? Treated with EBRT?

Brachytherapy has traditionally been utilized as a boost in the treatment of T1/T2 disease, both in the recurrent or definitive setting. The majority of studies included in this review utilized intracavitary brachytherapy as boost, most commonly in early stage NPC (T1/T2). Rosenblatt et al. and Ozyar et al. included both T3 and T4 patients, while Chao et al. included T3 patients (9,23,25). Both Rosenblatt and Ozyar failed to show any LRFS or OS benefit, while Chao demonstrated LRFS benefit only for patients with T1 disease. The ideal patient selection for ICBT being limited to AJCC 7E T1/T2 disease and select T3 disease with good response after EBRT.

Is there increased toxicity with dose escalation in NPC?

Overall

Pooled data for toxicity from the two randomized trials show no significant differences in Grade 3 to 4 acute & late toxicities (23,24). The most common complication noted was xerostomia. Not all of the studies reported toxicity outcomes in detail, and studies generally did not report the same toxicity outcomes. Of these, cranial nerve neuropathies (grade not specified) were reported in 4 studies (2,19,25,26). There was a significantly higher rate of cranial nerve neuropathies in the group that did not receive any boost. Rates of ulceration/necrosis of the nasopharynx...
were reported in 3 brachytherapy studies (18,19,26). A trend towards higher rates of ulceration/necrosis of the nasopharynx was observed in the boost group compared to the no boost group.

**Treated with brachytherapy? Treated with EBRT?**

Teo reported a non-significant increase in the incidence of chronic radiation nasopharyngeal ulceration/necrosis with brachytherapy. There were no complications that resulted in death or that required hospitalization (2). Ozyar did not note any BRT-related complications aside from nasal synechiae (9). While Chao saw non-significantly increased rates of CN palsy in the boost group (25). Leung had 5-year major-complication-free rates of 89.5% and 85.6% for the brachytherapy boost group and the control group, respectively (P=0.23) (26). Wu et al. noted that the incidence of complications in the EBRT + BRT group appeared to be significantly lower than those seen in the EBRT-alone group (19). The rate of nasopharyngeal ulceration or necrosis was higher in the EBRT + BRT group compared with the EBRT-alone group (2.3% vs. 0%). However, this difference was not significant (P=0.123). Ren had no significant differences in late toxicity, though more patients in EBRT group alone had NP ulceration/necrosis (19).

Wang observed no grade 4 late toxicities and no temporal lobe necrosis, and there was no significant difference in the acute radiation reactions among the three groups in their study (no boost, conventional EBRT boost and PET-guided boost) (24). Yeh had higher 5-year complication-free rates in the group that did not receive dose escalation with EBRT (10). They reported that the 5-year complication-free rates of patients receiving 70.2 and 81 Gy were 14% vs. 2% for xerostomia (P=0.0070), 50% vs. 30% for hearing impairment (P=0.0198), and 91% vs. 82% for temporal radionecrosis (P=0.0400), respectively (10).

Toxicity outcomes from some of the studies suggest that dose escalation with BRT, coupled with a lower EBRT dose, may result in fewer late complications such as trismus, neck fibrosis, cranial neuropathy, and temporal lobe necrosis. Moderate doses of BRT can result in improved local control with relatively low rates of nasopharyngeal ulceration or necrosis. However, a high total radiation dose, or large doses per fraction from EBRT or BT, could lead to perforation or ulceration of structures (i.e., soft palate, sphenoid) in close proximity to the primary site.

Modern RT techniques allow for more conformal dosimetry and employ more precise delivery techniques, while modern brachytherapy regimens use less hypofractionated techniques (3.0–4.0 Gy) and three-dimensional (CT-based) rather than two-dimensional (X-ray based) planning. These recent developments could result in better therapeutic ratio in dose-escalation.

Some of the retrospective studies included in this review are limited by small patient numbers, differing stages and histopathology of disease. None of the studies reported dose escalation specifically to the neck and/or regional disease. In spite of these study limitations, several authors have reported improvement in outcomes with dose-escalation using brachytherapy in conjunction to the standard external beam radiation. Not all studies have demonstrated a clear benefit with the addition of BRT boost. Ozyar et al. did not find a significant difference in local control rates with the addition of BRT (9). However, 32% of his cohort had T3-T4 disease. Dose coverage in such extensive disease would not have been adequately addressed with intracavitary BT. Taken together, the body of evidence would suggest that there is a local control benefit of adding brachytherapy boost after primary EBRT in T1-T2 NPC, particularly in T2 patients.

ICBT was utilized as a means of dose-escalation prior to the emergence of CCRT or IMRT. With the emergence of the latter two, there was a significant improvement of locoregional control. Dose-escalation using ICBT was abandoned by many but not all centers. IMRT was used to dose-escalate via hypofractionation (2.12–2.2 Gy per fraction) with chemotherapy. Initial toxicity limited maximum doses per fraction to 2.12 Gy.

While ICBT is currently mostly reserved for recurrences, some centers use ICBT to escalate RT doses beyond 66–70 Gy. This allows dose escalation for T1-T2 tumors without any undue increase in toxicity such as cranial neuropathy, temporal lobe necrosis or trismus. In T1N0 disease, low EBRT disease followed by boost may lower late toxicities such as CNP and trismus.

With the advent of IGBT (as with the emergence of IMRT techniques for EBRT), the role of brachytherapy in the primary treatment of NPC needs to be given a second look. The Levendag point system used for 2D planning of ICBT three-dimensional planning coupled with the stepping-source delivery now allow us to better sculpt isodose volumes and optimize treatment delivery (27).

Data is more limited for EBRT boost. Both the study by Wang and Yeh failed to show any benefit for LRFS and OS. However, in Wang’s study, there was a significant difference in LRFS and RPFS between the arms that received the lowest and highest BED (conventional chemoradiotherapy group and PET/CT-guided dose.
escalation chemoradiotherapy group, respectively). Both studies included only patients with T3 and T4 disease.

Currently, the use of SRT has been limited to recurrent disease, but experience in this modality seems to be increasing. Institutional single-arm reports are emerging investigating its use in the primary treatment of nasopharyngeal carcinoma (28,29). SRT has probable advantages over conventional and IMRT techniques, in the form of dose conformality and biologically equivalent doses delivered to the primary tumor.

In the current era of IMRT for the primary treatment of NPC, the majority of failures are occurring distantly. Only one study in our analysis included patients who were treated exclusively with IMRT during primary RT. IMRT allows the use of partial hypofractionation schemes during the treatment of the primary tumor, which translates to a higher effective dose received by the tumor. It remains to be seen whether further dose escalation still proffers some benefit in patients who were initially treated with IMRT. Further studies are warranted to define the role of dose escalation for these patients.

Conclusions

Dose escalation in the primary treatment of NPC does not lead to an increase in LRFS, OS, PFS or DFS. However, there seems to be a LRFS benefit with dose escalation using brachytherapy in patients with T1-T2 disease and in patients who did not receive concurrent chemotherapy. Dose escalation with brachytherapy is likewise not significantly associated with any increase in the rate of complications. Data for the efficacy and toxicity of EBRT and SRT boost is currently still lacking. More prospective studies are needed to define other subsets of patients will truly benefit from dose escalation.

Acknowledgments

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

17. National Health and Medical Research Council: NHRMC additional levels of evidence and grades for recommendation for developers of guidelines.
### Table: Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Country (region)</th>
<th>Patient age</th>
<th>Number of patients</th>
<th>Stage grouping</th>
<th>RT characteristics</th>
<th>Other interventions</th>
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<tbody>
<tr>
<td>Wang (2014)</td>
<td>Randomized, controlled trial</td>
<td>Xuzhou, Jiangsu, China</td>
<td>Total: 92; BRT boost: 36; No BRT boost: 56</td>
<td>65-74</td>
<td>Total: 67; EBRT boost: 43; CT-guided boost: 22; PET-guided boost: 21; No EBRT boost: 24</td>
<td>CT-guided EBRT boost: T1: N0, TD 1–2; T2: N1: 4; T3: N0: 4; T4: N0: 4; No EBRT boost: T1: N1: 1; T2: N1: 2; T2: N2: 3; N2: T2: N3: 2; T3: N2: 4; T4: N3: 4</td>
<td>CECT: patients with T3–4 and N2–3 disease received 70 Gy (EMRT) + 10 Gy (BRT) during the course of the EBRT for 8 cycles. For Stages II and IV or other high-risk patients, standard adjuvant chemotherapy was given every 3–4 weeks for 3 cycles, with 80 Gy IMRT/day on day 1 and 1 week of 1.06 Gy/day on days 1 to 4</td>
</tr>
<tr>
<td>Chao (2017)</td>
<td>Retrospective cohort</td>
<td>Taipei, Taiwan</td>
<td>BRT boost: 50 (95%); no BRT boost: 50 (81%)</td>
<td>63.1 (&lt;63-130)</td>
<td>Total: 232; BRT boost: 124; no EBRT boost: 108</td>
<td>EBRT boost: T1: ND; N0: 38; T2: ND; N1: 31; T3: ND; N2: 3; T4: ND; N3: 3</td>
<td>CRT with or without ACT was used for 176 patients, including 86 with BRT and 90 without an EBRT boost, respectively. The most commonly used chemotherapeutic regimen was cisplatin at 40 mg/m² weekly for the course of EMRT. For Stage II and IV or other high-risk patients, standard adjuvant chemotherapy was given every 3–4 weeks for 3 cycles, with 80 Gy IMRT/day on day 1 and 1 week of 1.06 Gy/day on days 1 to 4</td>
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<th>RT characteristics</th>
<th>Other interventions</th>
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<tr>
<td>Wu (2013)</td>
<td>Retrospective cohort</td>
<td>Fujian, China</td>
<td>BRT boost: 44 (22–88); no BRT boost: 86</td>
<td>30–86</td>
<td>Total: 348; BRT boost: 175; no BRT boost: 173</td>
<td>BRT boost: T1: 15%; N0: 30%; T2: 3%; N2: 38%; T3: 3%; N3: 1%; no BRT boost: T1: 27%; N0: 15%; T2: 25%; N1: 24%; N2: 38%; N3: 11%</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Ren (2019)</td>
<td>Retrospective cohort</td>
<td>Sun-Yai Sen, Guangdong, China</td>
<td>BRT boost: 50 (95%); No BRT boost: 50 (45%)</td>
<td>65–83 (64-83)</td>
<td>Total: 141; BRT boost: 40; no BRT boost: 101</td>
<td>Only T2b included: BRT boost NO: 5% N2: 45%; No BRT: NO: 1%; N0: 43%; N3: 15%</td>
<td>EMRT: WHO I–II: 3%; III: 97%; No boost: WHO I–II: 4%; III: 96%</td>
</tr>
<tr>
<td>Leung (2008)</td>
<td>Retrospective cohort</td>
<td>HK, China</td>
<td>BRT boost: 66.5 (22–76); no BRT boost: 66.5 (24–76)</td>
<td>0–78 (60-73)</td>
<td>Total: 297; BRT boost: 145; no EBRT boost: 152</td>
<td>BRT boost: T1: 79%; N0: 60%; T2a: 11%; N1: 29%; T3: 6%; no BRT boost: T1: 66%; N0: 60%; N1: 20%; T2: 21%; N1: 7%; N2: 11%; N3: 3%</td>
<td>BRBT boost: T1: 4%; N0: 38%; T2: 3%; N1: 39%; N2: 4%</td>
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<tr>
<td>Yeh (2007)</td>
<td>Retrospective cohort</td>
<td>Kaohsiung, Taiwan</td>
<td>BRT boost: 50 (94%); no BRT boost: 50 (94%)</td>
<td>68 (61–74)</td>
<td>Total: 118; EBRT boost: 32; no EBRT boost: 86</td>
<td>EMRT: T3: 15; N1: 2; T4: 17; N1: 11; N2: 11; N3: 2; no EBRT boost: T3: 35; N1: 20; T4: 61; N1: 38; N2: 35; N3: 3</td>
<td>Not mentioned</td>
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**Notes:**
- **EBRT:** external beam radiotherapy
- **BRT:** brachytherapy
- **CT:** computed tomography
- **PET:** positron emission tomography
- **MR:** magnetic resonance imaging
- **IMRT:** intensity-modulated radiotherapy
- **HDR:** high-dose-rate brachytherapy
- **LDR:** low-dose-rate brachytherapy
- **NACT:** neoadjuvant chemotherapy
- **CRT:** concurrent chemoradiotherapy
- **ACT:** adjuvant chemotherapy
- **ICBT:** intra-cavitary brachytherapy

**HR, Hong Kong PII, RT:** radiotherapy
**EBRT:** external beam radiotherapy
**BRT:** brachytherapy
**CT:** computed tomography
**PET:** positron emission tomography
**MRT:** intracavitary brachytherapy
**EBRT:** intensity-modulated radiotherapy
**ICBT:** intracavitary brachytherapy
**NACT:** neoadjuvant chemotherapy
**ACT:** adjuvant chemotherapy
**CRT:** concurrent chemoradiotherapy
**AJCC:** American Joint Committee on Cancer
**Table S2**

<table>
<thead>
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<td>Brachytherapy boost</td>
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<td>HDR ICBT</td>
<td>ICBT + BRT</td>
<td>ICBT + BRT</td>
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<td><strong>Bias</strong></td>
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<td>No. Data was missing on two patients</td>
<td>No. Data was missing on two patients</td>
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<td><strong>Results</strong></td>
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<tr>
<td><strong>Conclusions</strong></td>
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**Sample size requirements**

- Wang et al. (2010): Not mentioned
- Yeh et al. (2011): Sample size required not specified
- Leung et al. (2000): Sample size required was not applied in some patients for some reasons
- Olde et al. (1999): Sample size required was not applied in some patients for some reasons
- Leung et al. (2002): Sample size required was not applied in some patients for some reasons
- Teo (2002): Sample size required was not applied in some patients for some reasons

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**What did the study conclude?**

- Wang et al. (2010): Conclusions were appropriate given the study question (e.g., for the intervention)
- Yeh et al. (2011): Conclusions were appropriate given the study question (e.g., for the intervention)
- Leung et al. (2000): Conclusions were appropriate given the study question (e.g., for the intervention)
- Olde et al. (1999): Conclusions were appropriate given the study question (e.g., for the intervention)
- Leung et al. (2002): Conclusions were appropriate given the study question (e.g., for the intervention)
- Teo (2002): Conclusions were appropriate given the study question (e.g., for the intervention)
Two randomized controlled trials and six retrospective studies with low to moderate risk of bias were included in the review. Not all retrospective studies reported outcomes that were eligible for statistical pooling.

Data on EBRT boost is available only from one randomized controlled trial and one retrospective study.

Almost all of the retrospective studies that demonstrated a LRFS benefit involved patients with T1-T2 disease. Studies that included T3-T4 patients failed to show any significant LRFS benefit and showed a trend with worse outcomes.

Not all retrospective studies reported outcomes that were eligible for statistical pooling.

Some of the retrospective studies that demonstrated an OS benefit in involved patients with T1-T2 disease, while the others failed to demonstrate a survival benefit. Studies that included T3-T4 patients failed to show any significant OS benefit and showed a trend with worse outcomes.

The body of evidence provides some support for the recommendations but care should be taken in their application.

All data on the subgroup analysis without concurrent chemotherapy were from four retrospective studies.

Data on EBRT boost is available only from one randomized controlled trial and one retrospective study.

Pooled data from studies including only patients who did not receive concurrent chemotherapy showed LRFS benefit with dose escalation.

Data on EBRT boost is available only from one randomized controlled trial and one retrospective study.

There was no significant increase in toxicity from dose escalation with brachytherapy. Toxicity data for dose escalation using EBRT or SRT is still inadequate.

The absence of a significant benefit in progression free survival may indicate that systemic failure remains a significant problem even in patients with locally controlled disease.

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There was no significant increase in toxicity from dose escalation with brachytherapy. Toxicity data for dose escalation using EBRT or SRT is still inadequate.

The body of evidence can be trusted to guide practice in most situations.

The population studied in the body of evidence is similar to the target population.

The body of evidence provides some support for the recommendations but care should be taken in their application.

The body of evidence can be trusted to guide practice in most situations.