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CLINICAL INVESTIGATION

Reducing Target Volumes of Intensity Modulated Radiation Therapy After Induction Chemotherapy in Locoregionally Advanced Nasopharyngeal Carcinoma: Long-Term Results of a Prospective, Multicenter, Randomized Trial

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Purpose

The objective of this study was to estimate the long-term survival, late toxicity profile, and quality of life of patients with locoregionally advanced nasopharyngeal carcinoma (NPC) treated with combined induction chemotherapy (IC) and concurrent chemoradiotherapy from a clinical trial focused on reducing the target volume of intensity modulated radiation therapy (IMRT).

Methods and Materials

This prospective, randomized clinical trial was conducted across 6 Chinese hospitals and included 212 patients with stage III-IVB NPC who were randomly allocated to a pre-IC or post-IC group. Eligible patients were treated with 2 cycles of IC+CCRT. All patients underwent radical IMRT. Gross tumor volumes of the nasopharynx were delineated according to pre-IC and post-IC tumor extent in the pre-IC and post-IC groups, respectively.

Results

After a median follow-up of 98.4 months, 32 of 97 (32.9%) and 33 of 115 (28.7%) patients experienced treatment failure or died in the pre-IC and post-IC groups, respectively. None of the patients developed grade 4 late toxicity. Late radiation-induced toxicity predominantly manifested as grade 1 to 2 subcutaneous fibrosis, hearing loss, tinnitus, and xerostomia, whereas grade 3 late toxicity included xerostomia and hearing loss. The 5-year estimated overall, progression-free, locoregional recurrence-free, and distant metastasis-free survival rates in the pre-IC and post-IC groups were 78.2% versus 83.3%, 72.0% versus 78.1%, 90.2% versus 93.5%, and 78.1% versus 82.1%, respectively. The pre-IC group had a significantly higher incidence of xerostomia and hearing damage than the post-IC group. In terms of quality of life, compared with the pre-IC group, the post-IC group showed significant improvement in cognitive function (P=.045) and symptoms including dry mouth (P=.004), sticky saliva (P=.047), and feeling ill (P=.041).

Conclusions

After long-term follow-up, we confirmed that reducing the target volumes of IMRT after IC in locoregionally advanced NPC showed no inferiority in terms of the risk of locoregional relapse and potentially improved quality of life and alleviated late toxicity.

Introduction

Approximately 70% of patients initially diagnosed with nasopharyngeal carcinoma (NPC) exhibit locoregionally advanced disease because of atypical symptoms in the early-stage of the disease and the insidious location of tumorigenesis.[1] Several randomized trials have indicated that induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT) improved failure-free survival and overall survival (OS) compared with CCRT alone in

locoregionally advanced NPC.2, 3, 4, 5 The 5-year OS of patients with locoregionally advanced NPC exceeded 80% after IC+CCRT.[5] For these patients, IC carries the theoretical advantages of pre–radiation therapy (RT) suppression of distant metastases and lesion shrinkage, thereby ensuring safer radiation doses to organs at risk (OARs).[6] After IC, primary tumors have been reported to shrink by 28.5% to 61.4% of their pre-IC volumes.[7,8] Moreover, 70% of patients experienced a >50% reduction in tumor volume.[7]

After IC, when tumors are significantly reduced to the point of being undetectable by imaging methods, they can be considered subclinical lesions and treated with lower doses.[8] Furthermore, as the tumor shrinks, the distance between the tumor and OARs increases, and if delineation of the gross tumor volume of the nasopharynx (GTVnx) is based on post-IC tumor extent, the high-dose irradiation region can be reduced, potentially resulting in a significant decrease in toxicity to the patient. This can also be beneficial for IMRT planning and implementation, allowing for adjustments to facilitate treatment from palliative care to radical RT. This is important because despite achieving satisfactory survival, reducing RT-related toxicity and improving quality of life (QOL) in these patients are growing concerns. However, despite the potential for satisfactory treatment outcomes, there is a lack of robust evidence to support GTVnx delineation according to post-IC tumor extent, and there is currently no consensus on post-IC GTVnx delineation.

In 2012, we initiated a prospective, multicenter, randomized, controlled clinical trial in patients with locoregionally advanced NPC treated with IC+CCRT to address this issue. The primary objective of this study was locoregional recurrence-free survival (LRRFS). The 3-year follow-up results showed that GTVnx delineation based on post-IC tumor extent did not compromise survival. Moreover, the incidence of late toxicity was lower.[9] Verifying the permanence of this survival benefit is crucial for treatment planning. Therefore, in the present study, we aimed to estimate the long-term survival and late adverse effects of delineating GTVnx according to post-IC tumor volume in patients with locoregionally advanced NPC.

Section snippets

Study design and population

This prospective, randomized, controlled clinical trial was performed across 6 Chinese hospitals. The review board at each institution approved the trial protocol (Appendix E1). Written informed consent was obtained from all eligible patients aged 18 to 70 years with previously untreated, histopathologically confirmed, locoregionally advanced NPC (stage III-IVB based on the American Joint Commission on Cancer Staging Manual, seventh edition).[10]

Recruited patients were randomly assigned to a…

Patient characteristics

Between February 2012 and April 2015, 256 patients were screened for eligibility across the 6 sites. Ultimately, 233 patients were enrolled and randomized to the pre-IC or post-IC group (Fig. 1). Baseline demographic and clinical characteristics presented no significant differences between the groups (Table 1; $P > .05$). A total of 212 patients underwent the protocol-defined treatment in the 2 study arms (97 and 115 patients in the pre-IC and post-IC groups, respectively). On February 18, 2022…

Discussion

In this study, survival in the post-IC group was not inferior to that in the pre-IC group, indicating that reduced target volumes did not compromise patient survival. Furthermore, the dose and volume statistics for OARs in patients with stage T3/T4 tumors indicated that the post-IC group was superior to the pre-IC group in terms of OAR protection.

Numerous randomized trials have demonstrated that IC can achieve different degrees of tumor shrinkage for locally advanced NPC.3, 4·[14] However, a…

Conclusion

Post-IC delineation of the target volume based on shrunken GTVnx for locally advanced NPC did not impair locoregional control and long-term survival and resulted in fewer toxicities. This treatment strategy provides a promising approach to guarantee efficacy while reducing toxicity. Although the GTVnx is delineated based on postinduction imaging in this trial, the post-IC CTV1 still covers the entire nasopharynx, and the preinduction volumes are covered in CTV2 to deliver sufficient microscopic …

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The original contributions presented in the study are included in the article and supplementary material. Further inquiries can be directed to the corresponding author.

This clinical trial was registered in the China Clinical Trial Center (ChiCTR-TRC-12002441), which is a World Health Organization International Clinical Trials Registry Platform.

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