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Role of sequential chemoradiotherapy in stage II and low-risk stage III–IV nasopharyngeal carcinoma in the era of intensity-modulated radiotherapy: A propensity score-matched analysis

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ABSTRACT

Objectives: To investigate the role of sequential chemoradiotherapy (SCRT; induction chemotherapy [IC] followed by intensity-modulated radiotherapy [IMRT]) in stage II and low-risk stage III–IV nasopharyngeal carcinoma (NPC).

Materials and methods: Four well-matched groups were individually generated using propensity score matching in patients (n = 689) with stage II (SCRT vs. concurrent chemoradiotherapy [CCRT], SCRT vs. IMRT alone) and low-risk stage III–IV NPC (SCRT vs. CCRT, SCRT vs. IC + CCRT). Five-year overall/disease-free/locoregional relapse-free/distant metastasis-free survival (OS/DFS/LRRFS/DMFS) and acute hematological toxicities were compared between groups. The value of SCRT was further investigated in multivariate analysis and subgroup analysis by adjusting for covariates and limiting IC-to-IMRT time interval, respectively.

Results: SCRT led to equivalent survival outcomes compared to CCRT/IMRT alone and CCRT/IC + CCRT in stage II and low-risk stage III–IV NPC, respectively (all $P > .050$). In multivariate analysis, patients with stage II NPC treated by SCRT obtained higher DMFS (AHR = 0.22, 95% CI = 0.05–1.00, $P = .050$), but not OS, DFS or LRRFS, compared to patients receiving CCRT; non-significant differences were observed between SCRT and other treatments. SCRT with short IC-to-IMRT time interval (≤70 days) achieved higher 5-year survival rates than IMRT alone (DMFS: $P = .046$), CCRT (stage II NPC; OS: $P = .047$; DMFS: $P = .020$) and IC + CCRT (DFS: $P = .041$). Moreover, SCRT was associated with higher, equivalent and lower frequencies of acute hematological toxicities than IMRT alone, CCRT and IC + CCRT, respectively.

Conclusion: SCRT is mainly beneficial in stage II NPC, leading to better DMFS and/or equivalent acute hematological toxicities compared to CCRT/IMRT alone. CCRT is still the best choice for low-risk stage III–IV NPC.

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant head and neck cancer characterized by an unbalanced global distribution; the highest incidences are observed in endemic regions such as Southern China and Southeast Asia [1]. Since NPC is both radiosensitive and chemosensitive, radiotherapy and various chemotherapy schedules are used in clinical practice, including concurrent chemoradiotherapy (CCRT), CCRT + adjuvant chemotherapy (AC), induction chemotherapy (IC) + CCRT, sequential chemoradiotherapy (SCRT; IC followed by radiotherapy).

Owning to technological innovation and progress in the management of NPC, especially the use of intensity-modulated radiotherapy (IMRT), locoregional control has evidently improved; distant metastasis is now the predominant treatment failure [2]. Research has indicated IC can result in early eradication of micrometastases, prevent tumor progression and has fewer toxicities, which makes IC-based strategies a promising approach for locoregionally advanced NPC (LANPC; stage

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III–IV, non-disseminated) [3–6]. Two randomized trials of IC deserve attention. Sun et al. [3] reported three cycles of IC in conjunction with CCRT significantly improved 3-year failure-free survival ($P = .030$) with acceptable toxicities compared to CCRT alone. Lee et al. [4] also provided high-quality evidence to validate the superiority of IC + CCRT over CCRT + AC. These studies indicate IC + CCRT should be a standard of care. However, according to the 2017 National Comprehensive Cancer Network (NCCN) guidelines, CCRT ± AC is the best choice for stage II NPC and LANPC, while IC-based chemoradiotherapy only has a category 3 recommendation that indicates widespread disagreement regarding whether IC is appropriate [7].

As reported in several randomized controlled trials, patients with LANPC showed low compliance to CCRT ± AC (52–63%), with dose reductions and treatment delays and refusals, due mainly to severe adverse reactions [8–10]. By shifting concurrent chemotherapy prior to radiotherapy, SCRT is thought to have the potential to reduce toxicities and prevent distant metastasis compared to CCRT. To date, little is known about the role of SCRT in NPC; only three studies focused on the comparison of SCRT and CCRT in the era of IMRT, and yielded non-significant differences in survival [11–13]. However, these studies did not account for immune-inflammatory predictors, such as the neutrophil-to-lymphocyte ratio (NLR) [14], C-reactive protein (CRP) [15] and serum lactate dehydrogenase (LDH) [16]. Epstein-Barr virus (EBV) DNA, the most valuable molecular biomarker in NPC – which has a significant influence on prognosis – was also omitted [17,18]. Besides, no study performed analysis according to risk stratification (e.g. in stage II NPC), which is essential to design targeted interventions.

Our previous study proved CCRT is better than IC + CCRT in low-risk stage III–IV NPC (i.e., N0-2 + pre-treatment EBV DNA titer < 1000 copies/mL + age ≥18; if age ≥ 54, NLR < 2.70 required) [19]. Although CCRT is the standard strategy for stage II and low-risk stage III–IV NPC, the patient subgroups for whom SCRT is appropriate are still unclear. Therefore, we performed a comparative study with multiple treatment arms to explore the value of SCRT, especially compared to CCRT, in different risk groups.

Materials and methods

Patient selection

We included eligible patients using a prospectively maintained database (cutoff time, December 31, 2016) of Sun Yat-sen University Cancer Center (SYSUCC). A total of 689 patients with newly-diagnosed, pathologically-proven stage II and low-risk stage III–IV NPC based on the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system, undergoing IMRT-based radical treatment (IMRT alone, CCRT, SCRT and IC + CCRT) between November 2009 and May 2012 were included (Supplementary Fig. S1). The definition of low-risk stage III–IV NPC was described in detail in a previous study [19]. This study was approved by the Institutional Review Board and the Ethics Committee of SYSUCC; the need for informed consent was waived. The authenticity of this article has been validated by uploading key raw data to the Research Data Deposit public platform (http://www.researchdata.org.cn), under approval number RDDA2017000297.

Pre-treatment examination

The following examinations were routinely performed two-to-four weeks before treatment began: medical history, physical examination, routine blood test (RBT), biochemistry profiles, nasoendoscopy, neck and nasopharyngeal magnetic resonance imaging (MRI), chest radiography, abdominal ultrasonography and whole-body bone scan; the latter three examinations were replaced by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) in 164/689 (23.8%) patients. Plasma EBV DNA titer, IgA antibodies against viral capsid antigen (VCA-IgA) and early antigen (EA-IgA) were also quantified before treatment. A real-time quantitative polymerase-chain-reaction assay was employed to detect EBV DNA, by targeting the *Bam*HI-W region of the EBV genome using the amplification primers 5′-GCCAGAGGTAAGTGGACTTT-3′ and 5′-TACCACCTCCTCTTCTT GCT-3′; the dual fluorescence-labelled oligomer 5′-(FAM) CACACCCA GGCACACACTACACAT (TAMRA)-3′ served as a probe. The GenBank sequence database was used to obtain all sequence data.

Radiotherapy

The nasopharyngeal and neck tumor volumes were treated using IMRT for the entire course. All patients underwent one fraction daily for 5 days per week. In accordance with the International Commission on Radiation Units and Measurements reports 50 and 62, target volumes were delineated slice-by-slice on treatment planning CT scans using an individualized delineation protocol [20]. Physical examinations, pre-treatment MRI findings and MRI performed after completion of IC were used as reference for delineation of target volumes. The prescribed doses were 66–72 Gy to the planning target volume (PTV) of the primary gross tumor volume (GTVnx; including enlarged retropharyngeal lymph nodes), 64–70 Gy to the PTV of the GTV of the positive lymph nodes (GTVnd), 60–63 Gy to the PTV of the high-risk clinical target volume (CTV1), and 54–56 Gy to the PTV of the low-risk clinical target volume (CTV2) in 28–33 fractions. All targets were treated using the simultaneous integrated boost technique. CTV1 extended 5–10 mm beyond the margin of the GTVnx for potential microscopic spread, including the entire nasopharyngeal mucosa and a 5 mm submucosal region. CTV2 extended 5–10 mm beyond the margin of the CTV1, including potentially involved regions and lymphatic regions, unless the CTV2 was adjacent to critical organs, e.g., brain stem and spinal cord, in which case the extension distance was reduced to 3–5 mm.

Chemotherapy

IC regimens mainly comprised cisplatin–5-fluorouracil (80 mg/m^2 and 4,000 mg/m^2, respectively), docetaxel–cisplatin (75 mg/m^2 and 75 mg/m^2, respectively), docetaxel–cisplatin–5-fluorouracil (60 mg/m^2, 60 mg/m^2 and 3,000 mg/m^2, respectively) every 3 weeks for 2–3 cycles. All chemotherapeutic drugs were administered on day 1 of each cycle, except for 5-fluorouracil which was given via continuous intravenous infusion on days 1–5. The typical IC-to-IMRT time interval was 70 days, which was determined based on three 21-day cycles (63 days) and a previously reported finding (81 days) [21]. Concurrent chemotherapy was cisplatin (30–40 mg/m^2) weekly, or cisplatin (80–100 mg/m^2) 3-weekly for 2–3 cycles concurrently with IMRT.

Patient assessment and follow-up

All patients received weekly RBTs during the whole course of chemotherapy and/or radiotherapy for safety surveillance. Granulocyte colony-stimulating factor was administered to patients who suffered severe/febrile neutropenia; additional RBTs were used to monitor recovery status. Acute hematological toxicities (e.g., anemia, leukopenia, neutropenia and thrombocytopenia) were graded according to the Common Terminology Criteria for Adverse Events ver. 4.0 [22]. Follow-up was measured from the day of diagnosis to day of last visit or death. Each patient attended follow-up appointments at least every 3 months by the first 2 years, then every 6 months thereafter or until death. Biopsy was used to confirm malignancy for patients with recurrent local or suspected residual disease.

Statistical analysis

All statistical methods were applied to the primary (SCRT vs. CCRT) and secondary comparisons (SCRT vs. IMRT, SCRT vs. IC + CCRT).