



Review

Establishment of prognostic factors in recurrent nasopharyngeal carcinoma patients who received salvage intensity-modulated radiotherapy: A meta-analysis

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ABSTRACT

Local recurrence remains a major cause of therapeutic failure in patients with nasopharyngeal carcinoma (NPC) and the effective treatment of recurrent NPC (r-NPC) is still a challenge. Intensity-modulated radiotherapy (IMRT) is considered as a favorable technique in the management of r-NPC, especially for extensive lesions. However, local r-NPC is a highly heterogeneous disease and the survival outcome following salvage IMRT varies. Furthermore, due to varied samples and therapeutic protocols, no consensus has been reached in the establishment of prognostic values. Hence, we used Medline and Embase electronic databases to conduct a meta-analysis to generate the best estimation of the prognostic factors in local r-NPC following salvage IMRT. Finally, a total of 783 patients in seven studies were enrolled. Overall, the pooled HR for OS of recurrent T stage and recurrent tumor volume was 1.77 (95% CI = 1.15–2.39) and 2.12 (95% CI = 1.42–2.82), without any heterogeneity. In addition, despite a significant association was observed in the pooled HR of significant compliance for OS, however, significant heterogeneity was also observed ($I^2 = 76.6\%$, $p = 0.039$). Furthermore, no significant association was observed among the pooled HRs for OS in terms of age, gender, recurrent time interval, synchronous nodal recurrence, chemotherapy and total re-irradiation dose. Therefore, the present meta-analysis demonstrated that recurrent T stage and tumor volume may serve as the prognostic factors for OS in patients with r-NPC who received salvage IMRT. The other factors such as age, gender, and optimal re-irradiation dose warranted further investigation.

Introduction

Although there have been recent advances in irradiation techniques and the use of concurrent chemo-radiotherapy, local recurrence still remains a major cause of therapeutic failure in patients with nasopharyngeal carcinoma (NPC), with a rate of approximately 8–10% [1,2]. It is still a challenge in clinical practice to implement effective treatment for patients with locally recurrent NPC (r-NPC) who had received a previous full-dose of radiation therapy (RT), especially in patients with advanced T stage and/or a bulky tumor volume [3].

Various therapeutic strategies, including surgery, stereotactic radiosurgery, and brachytherapy have been utilized in an attempt to cure local r-NPC [4–6]. However, their utility is usually limited by the

infiltrative extension of a recurring tumor. High-dose external-beam irradiation remains one of the most effective salvage treatments for r-NPC, especially for extensive or infiltrative lesions [7,8]. Unfortunately, conventional two-dimensional RT techniques with curative intent was generally associated with a poor survival outcome and a high incidence of severe complications, including temporal lobe necrosis, trismus, deafness, or even death [1,9,10].

Intensity-modulated radiotherapy (IMRT) enables a more favorable balance between target conformation and sparing of critical structures which makes it possible to deliver a high dose to the tumor target, thereby potentially enhancing the therapeutic ratio [11]. Hence, IMRT is considered as a favorable technique in the management and treatment of r-NPC because of its more homogeneous dose distribution and

Abbreviations: AJCC, American Joint Committee Cancer Control; CI, confidence interval; CTV, clinical tumor volume; GTV, gross tumor volume; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; NOS, Newcastle-Ottawa Scale; NPC, nasopharyngeal carcinoma; OS, overall survival; r-NPC, recurrent nasopharyngeal carcinoma; RT, radiation therapy; T, tumor; UICC, Union for International Cancer Control

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lower normal tissue doses when compared with conformal radiotherapy [12]. However, locally recurrent NPC is a highly heterogeneous disease, and the survival outcome of patients with the same recurrent stage following IMRT varies, ranging from several months to long-term survival [13,14]. Therefore, establishing of the prognostic values in patients with local r-NPC may facilitate the clinicians in identify the patients who may most benefit from salvage IMRT. To date, although several studies have investigated the prognostic values in patients with recurrent NPC who received palliative IMRT, due to varied sample sizes and therapeutic protocols, no consensus has been reached in the establishment of prognostic values in r-NPC who received IMRT [14–27].

Hence, we conducted a meta-analysis to generate the best estimation of the prognostic factors in local r-NPC following salvage IMRT.

Material and methods

Search strategy

Using Medline and Embase electronic databases, we conducted a search of studies assessing prognostic values in those with recurrent nasopharyngeal carcinoma who received IMRT for salvage treatment. All relevant studies reported up to November 1st, 2017 were included. The predefined search keywords used were as follows: ('nasopharynx carcinoma' [Emtree] or 'nasopharyngeal neoplasms' [Mesh] or 'nasopharyngeal cancer' or 'nasopharyngeal tumor' or 'cancer of nasopharynx' or 'tumor of nasopharynx' or 'neoplasm of nasopharynx' or 'nasopharynx cancer' or 'nasopharyngeal carcinoma') and ('intensity modulated radiation therapy' or 'intensity modulated radiotherapy' or 'IMRT') and ('recurrent' or 'relapsed' or 'refractory'). The search strategy was in accordance with the preferred reporting items for PRISMA statements [28]. The detailed search strategy is shown in Fig. 1.

Inclusion/exclusion criteria

Only studies that met all of the following inclusion criteria were considered eligible: (1) Pathologically confirmed local-regional recurrent nasopharyngeal carcinoma without evidence of metastasis. (2) The prognostic factors of overall survival were reported. (4) Multivariate cox regression models that adjusted for predominant clinical values were included in the statistical analysis. (5) The univariate/multivariate hazard ratios (HRs) and their 95% confidence intervals (CIs) or a P value for overall survival (OS) were provided in the study; when univariate or multivariate HRs were both provided, the multivariate HR was preferred. (6) More than six points of the NOS score were considered eligible for inclusion.

Data extraction

The OS was chosen as the primary survival outcome. Two experienced authors (M.Z. and Q.Y.) independently extracted the relevant data containing the author's first name, publication year, sample size, disease stage, study type (prospective or retrospective), follow-up time, adjusted variable, prognostic factors, cut-off values of prognostic factors, and HRs associated with 95% CIs for OS as applicable. The HRs and 95% CIs were extracted from multivariate analyses that adjusted for major prognostic factors. In case of doubt or controversy between the two authors involved in data extraction and search strategy, this was discussed with a third independent senior oncologist (Y.C.).

Quality assessment

The Newcastle-Ottawa Scale (NOS) was employed for assessing the quality of enrolled studies [29]. The quality assessment was conducted from three aspects of NOS criterion: (1) selection of subject, the scores varied from 0 to 4, (2) comparability of subject, the scores varied from 0 to 2, (3) clinical outcome, the scores varied from 0 to 3. The total

scores of NOS varied from 0 to 9, and the studies with scores more than 6 were graded as high quality.

Statistical analysis

In the current study, all calculations were performed using the software STATA version 12 (StataCorp LP, College Station, TX, USA). The HRs and their 95% CIs were combined to make calculations of overall effects. The Cochran Q and I^2 statistics were employed to measure the heterogeneity. The fixed effects model was employed for statistical analysis when no significant heterogeneity was observed among the included studies ($I^2 \leq 50\%$). Otherwise, the random effects model was employed for statistical analysis when significant heterogeneity was observed among the eligible studies ($I^2 > 50\%$) [30]. When significant heterogeneity was observed, the sensitivity and subgroup analyses and univariate meta-regression were used to explore the origin of heterogeneity. Begg's funnel plot and Egger's test were applied to assess the publication bias [31]. Conventionally, the adverse prognosis for the group was presented with $HR > 1$ and the associated 95% CI did not overlap with 1. A two-sided $P < 0.05$ indicated statistical significance.

Results

Eligible studies

The initial search in Medline and Embase databases retrieved 178 potentially relevant articles. After review of the titles and abstracts, 138 manuscripts were excluded as they were either reviews, case reports, duplicate records or irrelevant for the current analysis. Next, the remaining 40 studies were further evaluated. Of these, 33 studies were excluded for the following reasons: 11 did not provide full-text, 1 was a non-English article, 6 failed to confine the therapeutic protocol in IMRT, 3 only focused on the side effects of IMRT, 3 did not provide sufficient data to calculate the HRs and their 95% CI for overall survival and 9 include the same cohort of patients at Sun-Yet Cancer Center. Finally, a total of 783 patients in seven studies were enrolled in the current analysis [21–27], ranging from 38 to 245 patients per study (median 70). The flow chart of the selection process is illustrated in Fig. 1.

The predominant characteristics of the included seven studies are illustrated in Table 1. All 7 studies were conducted in China using a retrospective design, AJCC/UICC (American Joint Committee/ Union for International Cancer Control) TNM staging system were employed and the median follow-up time was longer than 24 months. The quality of the studies was high, and their NOS scores ranged from 6 to 8.

Prognostic value for overall survival in patients with recurrent NPC

Prognostic value of gender for OS

Four studies containing 420 patients reported the HRs of gender for overall survival (OS). Overall, the pooled HR of gender for OS in four eligible studies was 0.97 (95% CI = 0.60–1.34) and no significant heterogeneity was observed ($I^2 = 0.0\%$, $p = 0.981$); thus, the fixed effects model was applied. Fig. 2A illustrates the Forest plot of all studies.

Prognostic value of synchronous nodal recurrence for OS

Four studies containing 420 patients reported the HRs of synchronous nodal recurrence for OS. The pooled HR (95% CI) of synchronous nodal recurrence for OS was 1.48 (95% CI = 0.85–2.12) with no significant heterogeneity ($I^2 = 0.0\%$, $p = 0.858$). Fig. 2B illustrates the Forest plot of all studies.

Prognostic value of age for OS

Three studies containing 382 patients reported the HRs of age for OS. The pooled HR (95% CI) of age for OS was 1.29 (95%

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