European Journal of Cancer 67 (2016) 119–129

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Neutrophil-to-lymphocyte ratio as a prognostic marker in locally advanced nasopharyngeal carcinoma: A pooled analysis of two randomised controlled trials☆

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Received 22 April 2016; received in revised form 17 July 2016; accepted 10 August 2016

KEYWORDS
Neutrophil-to-lymphocyte ratio;
Nasopharyngeal carcinoma;
Locally advanced;
Biomarker;
Prognosis

Abstract ***Purpose:*** To assess the prognostic value of neutrophil-to-lymphocyte ratio (NLR) in patients with International Union Against Cancer (UICC)–staged III/IVA,B nasopharyngeal carcinoma (NPC), who were enrolled into two randomised controlled trials of concurrent/adjuvant chemotherapy when added to radiotherapy (SQNP01), and induction chemotherapy when added to chemoradiotherapy (NCC0901).

Material and methods: A post hoc analysis of pooled cohorts from SQNP01 (N = 221) and NCC0901 (N = 172) was performed. We employed a threshold of pre-treatment NLR = 3.0 (median) to stratify patients. Survival outcomes were compared using log-rank test. Multivariable Cox regression analyses were performed to assess association between NLR and overall survival (OS), disease-free survival (DFS), distant metastasis–free survival (DMFS), and locoregional recurrence–free survival (LRFS).

Results: High NLR (≥3.0) was associated with advanced T-status (p = 0.002), N-status (p = 0.002), overall UICC stage (p = 0.004), and high pre-treatment Epstein–Barr virus DNA titre (p = 0.001). High NLR was not associated with OS (0.94 [0.67–1.32], p = 0.7), DFS (0.98 [0.73–1.33], p = 0.9), DMFS (1.02 [0.66–1.57], p = 0.9), and LRFS (1.37 [0.84–2.22], p = 0.2) on univariable and multivariable analyses, while conventional clinical indices (T-status, N-status, and overall UICC stage) were prognostic of clinical outcomes. High NLR also did not predict for a treatment effect with the experimental arms in both trials.

☆ Presented in part at the European Cancer Congress, Vienna, Austria, 2015.

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http://dx.doi.org/10.1016/j.ejca.2016.08.006

Conclusion: Our pooled analyses that were confined to a homogenous patient population of locally advanced NPC do not suggest that NLR adds prognostic value to conventional clinical indices in identifying patients with unfavourable disease.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a unique cancer with specific patterns of racial and geographical distribution [1]. The endemic form of disease is also invariably associated with the Epstein–Barr virus (EBV). As a result, the genotype and clinical phenotype of NPC are remarkably distinct from other epithelial cancers of the head and neck region, and rightfully, patients who are diagnosed with this disease are stratified using a specific TNM stage classification that differs from other head and neck cancers [2]. Using the current proposed system of stage classification, patients harbouring more advanced stages of disease (American Joint Committee on Cancer [3]/International Union Against Cancer [4] stage III/IVA,B disease) are recommended for combination chemotherapy and radiotherapy (RT), as the primary curative treatment [5]. While such a treatment intensification strategy has led to substantial gains in overall cure rates of patients in this subgroup, there is also wider recognition that locally advanced NPC is clinically heterogeneous, and conventional clinical indices are imprecise in predicting for patients who ought to receive systemic intensification or deintensification with RT. To date, plasma cell-free EBV DNA titre remains the only biomarker with clinical utility in NPC [6–8]. There is, thus, a critical need for additional biomarkers for prognostication and precise treatment stratification in patients with this disease.

In recent times, several studies have reported on the association of elevated pre-treatment neutrophil-lymphocyte ratio (NLR) with adverse prognoses in multiple tumour types [9–14]. While the relative risks seem comparable between studies (hazard ratio [HR] $\approx$ 1.5–2.0), the tested cohorts are highly heterogeneous comprising of patients harbouring localised and metastatic disease. Patients are also mostly retrospectively audited, thus likely having received non-standardised treatments. Finally, there have only been few studies on the prognostic impact of NLR in NPC. Given the limitations of studies to date, we aimed to test the association between NLR and clinical outcomes in a cohort of patients with locally advanced NPC, who have been pooled from two single-institution randomised phase III trials of definitive RT with or without concurrent and adjuvant chemotherapy (SQNP01) [15], and concurrent chemo-RT with or without induction triplet chemotherapy (NCC0901) [16].

2. Methods

2.1. Patient cohorts

We performed a post hoc analysis on two randomised phase III trials that were conducted at National Cancer Centre Singapore [15,16]. SQNP01 was the preceding trial, conducted between September 1997 and May 2003. In this study, 221 patients were assigned to either two-dimensional RT (2DRT, n = 110) alone or concurrent and adjuvant chemotherapy with 2DRT (C-2DRT + AC, n = 111). NCC0901 was the later trial conducted between September 2004 and August 2012 and recruited 172 patients to either concurrent chemotherapy and intensity-modulated RT (C-IMRT, n = 86) or induction chemotherapy in combination with C-IMRT (IC + C-IMRT, n = 86).

All newly-diagnosed biopsy-proven NPC patients with American Joint Committee on Cancer (AJCC) [3]/International Union Against Cancer (UICC) [4] 1997 T3-4NxM0 or TxN2-3M0; WHO type II or III histology [17]; Eastern Cooperative Oncology Group performance status 0 or 1; and adequate bone marrow, renal and hepatic functions; and who were deemed fit to receive chemo-RT were eligible for the trials. Patients with prior treatment for NPC and second malignancy were excluded. In addition, patients with uncontrolled hypercalcaemia; serious active infection; other serious concomitant systemic disorders incompatible for the trial; pregnant, lactating, reproductive females without adequate contraceptive measures; or hepatitis B carriers were also excluded to enter NCC0901.

Ethical approval and waiver of informed consent of patients were obtained from the host institution review board (CIRB Ref. No.: 2015/2571). Patient records/information was anonymised prior to analysis.

2.2. Radiotherapy

RT techniques that were employed in both trials were as described previously [15,16]. Briefly, patients from the SQNP01 study received 70 Gy in 7 weeks (2 Gy per fraction) using 2DRT, a modified Ho's technique. A total dose of 70 Gy in 35 fractions were delivered to the primary tumour and pathologic lymph nodes, while the rest of the uninvolved neck was given 60 Gy in 30 fractions.

In the NCC0901 cohort, RT began 3 weeks following the last dose of chemotherapy in the IC + C-IMRT arm.