Neutrophil to Lymphocyte Ratio as Biomarkers in Head and Neck Squamous Cell Carcinoma

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common neoplasm worldwide. Despite advances in treatment for HNSCC, the patient's survival remains poor. Therefore, in order to improve HNSCC patient's outcome, it is essential to explore novel biomarkers for predicting response to treatment. Herein, we state that the neutrophil to lymphocyte ratio (NLR) is a biomarker to predict the efficacy of chemoradiotherapy (CRT) in HNSCC patients and to predict the wound healing failure in head and neck reconstruction surgery. Although elevated pretreatment NLR was significantly correlated with poor response to CRT, lower preoperative NLR tended to exhibit a higher occurrence rate of post-operative wound healing failure in HN reconstruction surgery. Thus, in case which HNSCC patient with lower NLR has remnant tumor after CRT, salvage surgery with microsurgical reconstruction might include a higher occurrence rate of postoperative wound complications than the present. Head and neck surgeons should take care of the possibility.

Keywords

Head and neck squamous cell carcinoma; Neutrophil to lymphocyte ratio; Biomarker

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common neoplasm worldwide [1]. Despite advances in treatment, patient survival remains poor, and HNSCC is associated with a high mortality rate. Therefore, in order to improve HNSCC patient's outcome, it is essential to explore novel biomarkers for predicting response to treatment.

Tumor microenvironment is known to participate in tumor progression [2]. Inflammation is one of the microenvironment and inflammatory cells such as neutrophil and lymphocyte play an important role for tumor progression. Neutrophils are a type of inflammatory cell that secrete vascular endothelial growth factor (VEGF), chemokines, and proteases that stimulate angiogenesis, and these inflammatory cytokines may establish a tumor microenvironment and promote tumor development and progression. An increase in the number of neutrophils surrounding cancerous tissue can suppress antitumor immune response. In contrast, the number of lymphocytes reflects the activity of the lymphokine-activated killer cells, and a reduction in the number of lymphocytes results in the decreased release of cytokines which can promote apoptosis of tumor cells. Therefore, the increase of neutrophil-to-lymphocyte ratio (NLR) has been reported to predict the poor prognosis in various solid tumors such as colorectal cancer and breast cancer [3,4]. Herein, we state that the NLR is a biomarker to predict the efficacy of chemoradiotherapy in HNSCC patients and to predict the wound healing failure in head and neck reconstruction.

Pretreatment NLR predict the chemoradiotherapy outcome in HNSCC

Treatment with concomitant chemoradiotherapy (CRT) has emerged as a gold standard in the majority of advanced HNSCC. The presumed advantages of CRT over radical surgery are organ preservation, better functional outcome and a lower rate of acute complications. Compared to radiotherapy (RT) alone, the addition of chemotherapy (CT) delivered concomitantly with RT improves the survival of patients with advanced HNSCC with an overall 4% benefit at 5 years [5]. However, some patients treated for Stage III and IV disease does not reach to complete remission after this nonsurgical primary treatment. Therefore, it is essential to explore the biomarker to predict the efficacy of CRT. Nakashima et al. [6] reported that NLR is a potent biomarker for predicting the

clinical response to 5-fluorouracil (5-FU)-based CRT in 124 advanced oral squamous cell carcinomas. The details of their cases as follows. All patients were treated preoperatively with CRT. RT was administered at a daily dose of 2.0 Gy five times a week for 15 days. An oral FU anti-cancer agent, S-1, was concurrently administered at a dose of 80, 100 or 120 mg/day according to each patient's body surface area for 14 days from the initiation of RT. The frequency of NLR-high (≥ 2.4) patients during surgery was significantly higher among the cases who showed poor pathological response (severe destruction of tumor structure but visibly few viable tumor cells even if it works) to preoperative CRT (P=0.038) [6]. Furthermore, Chandrasekara et al. [7] reported that a high NLR (>4.0) at treatment initiation is a negative predictive marker for HNSCC with cisplatin or cetuximab-based CRT. Thus, the pretreatment NLR provides significant improvement for the selection of CRT for HNSCC.

Preoperative NLR predicts wound healing failure in head and neck reconstruction

Head and neck reconstruction surgery involves a high risk of post-operative wound complication such as surgical site infections and flap necrosis **(Figure 1)**.

Figure 1: Flap necrosis after reconstruction for gingival cancer (NLR=2.1<3.5)

Furthermore, such complications can require daily wound treatment and lead to prolonged hospitalization, greatly compromising the patient's quality of life. Therefore, it is necessary that we explore the predictive marker for such wound healing failure. Previously, risk factors such as a high American Society of Anesthesiologists Performance Status (ASA-PS) score and prolonged surgery time have been reported [8], recently Maruyama et al. [9] reported that the NLR differed significantly between the patients with and without post-operative wound healing failure. Lower preoperative NLR (3.5) tended to exhibit a higher occurrence rate of post-operative wound healing failure. They concluded that neutropenia and a decreased NLR may directly impair wound healing, because neutrophils migrate to the wound to

prevent infection. On the contrary, Song et al. [10] reported that hypopharymgeal SCC patients with high NLR (≥ 2.3) more had significantly higher incidence of wound complications (p=0.026). Thus, the role of NLR as biomarker of wound healing failure seems to differ according to the subsite of HNSCC. Further work about the mechanism is needed.

Conclusion

The pretreatment NLR provides significant advantage for the selection of CRT for HNSCC. In the case by which HNSCC (excluding hypopharyngeal SCC) patient with lower NLR having remnant tumor after CRT, salvage surgery with microsurgical reconstruction might include a higher occurrence rate of postoperative wound complications than the present. Head and neck surgeons should take care of the possibility.

Acknowledgments

Conflicts of Interest

The authors declare there are no conflicts of interest.

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