European Archives of Oto-Rhino-Laryngology (2019) 276:1487–1492
https://doi.org/10.1007/s00405-019-05381-0

HEAD & NECK

Prognostic value of advanced lung cancer inflammation index in head and neck squamous cell carcinoma

Bernhard J. Jank[1] · Lorenz Kadletz[1] · Julia Schnöll[1] · Edgar Selzer[3] · Christos Perisanidis[2] · Gregor Heiduschka[1]

Received: 23 January 2019 / Accepted: 11 March 2019 / Published online: 16 March 2019

Abstract

Purpose The advanced lung cancer inflammation index (ALI) is a useful tool for prediction of outcome in several malignancies. However, to date, its significance in head and neck cancer patients has not been evaluated.

Methods We retrospectively analyzed data from 93 patients who were diagnosed with head and neck squamous cell carcinoma (HNSCC) and treated with surgical resection and postoperative radiotherapy between 2002 and 2012. The aim of this study was to investigate whether the preoperative ALI is a prognostic indicator for disease-free survival and overall survival in HNSCC patients.

Results A low ALI was significantly associated with a worse 5-year disease-free survival (47.0 vs. 83.5%, $p < 0.001$), and overall survival (44.4 vs. 73.6%, $p = 0.008$). Multivariate analysis showed that low ALI was independently associated with disease-free survival ($p < 0.001$) and overall survival ($p = 0.02$).

Conclusion The ALI could serve as an easily available prognostic indicator for disease-free and overall survival prediction in patients with HNSCC.

Keywords Head and neck squamous cell carcinoma · Advanced lung cancer inflammation index · Disease-free survival · Overall survival · Recurrence risk · Precision medicine

Introduction

Head and neck squamous cell carcinoma (HNSCC) is among the ten most-common cancers worldwide. In Europe, there were approximately 250,000 cases and 63,500 deaths in 2012 [1]. Curative treatment options are either surgical resection with or without postoperative radio-(chemo)therapy or primary radio(-chemo/immuno)-therapy. Neoadjuvant radiotherapy may be applied in selected cases as well. Despite multidisciplinary treatment, the overall survival rate of HNSCC has not improved significantly over the past 2 decades [2].

Virchow's discovery of leukocytes in neoplastic tissue laid the foundation for a connection between inflammation and cancer [3]. Since then, inflammation has been described as a hallmark of cancer by supplying proliferative, anti-apoptotic and pro-angiogenic signals and extracellular matrix-modifying enzymes [4]. Furthermore, inflammation is a common underlying mechanism of action for several risk factors of HNSCC including tobacco smoking, alcohol consumption and chronic inflammatory processes such as chronic trauma to the oral mucosa [5, 6].

Systemic inflammatory biomarkers including C-reactive protein (CRP), blood cell counts and associated ratios including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), or combination of those values in prognostic scores like the Glasgow Prognosis Score (GPS, combining CRP and albumin) or the Advanced Lung Cancer Inflammation Index [ALI, calculated as bodyweight (kg)/height $(m)^2 \times$ serum albumin (g/dl)/NRL] have been investigated in different cancer entities as prognostic tools [7–15].

✉ Lorenz Kadletz
lorenz.kadletz@meduniwien.ac.at

[1] Department of Otorhinolaryngology and Head and Neck Surgery, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria

[2] Department of Oral and Maxillofacial Surgery, University of Athens, Athens, Greece

[3] Department of Radiation Oncology, Medical University of Vienna, Vienna, Austria

The ALI has been reported to be associated with overall survival in non-small cell lung cancer [8], large B-cell lymphoma [16], esophageal squamous carcinoma [17] and colorectal cancer [12]. However, to date, no data exists on the prognostic value of ALI in head and neck cancer patients and its predictive value for disease-free survival and overall survival.

The aim of this study was to investigate the value of ALI as a prognostic indicator for disease-free survival and overall survival in head and neck squamous cell carcinoma patients.

Patients and methods

Study design and patient population

This study is a single-center, observational, retrospective cohort study. The study population was drawn from our in-house retrospective head and neck squamous cell cancer cohort, which includes 130 patients treated with curative surgical therapy followed by postoperative radiotherapy. Exclusion criteria for the cohort were surgery at an external institution, secondary primary carcinoma and prior irradiation. Laboratory data could be extracted for 94 patients. One patient had received organ transplantation and was therefore excluded from the analysis. Ultimately, 93 patients with histologically diagnosed HNSCC, who were treated at the Medical University of Vienna with surgery and postoperative irradiation between 2002 and 2012, were included in this study. Baseline and outcome data were collected retrospectively from electronic patient review charts. The following clinical data were documented: age at diagnosis, sex, tumor site, HPV high-risk status, TNM classification, 8th edition AJCC stage, disease-free survival, overall survival, packs of cigarettes smoked per day, alcohol use, radiation dose received, administered chemotherapy, body weight and height, neutrophil- and lymphocyte count and serum-albumin levels. We calculated the advanced lung cancer inflammation index (ALI), which is defined as body mass index [BMI, bodyweight (kg)/height $(m)^2$) × serum albumin (g/dl)/neutrophil-to-lymphocyte ratio] by Jafri et al. [8]. A low ALI is an indicator of systemic inflammation. We included laboratory data and body measurements that had been collected at most two weeks before surgery. This study was approved by the institutional research board (ECS 1311/2018).

Statistical analysis

The primary outcome of this study was disease-free survival (DFS). The secondary outcome was overall survival (OS). In the absence of a validated cut-off value for ALI, we selected an empirical cut-off at the median value and patients were dichotomized to either high (> median) or low (≤ median) ALI group accordingly. Categorical baseline variables were compared using Fisher's exact test or Chi^2 test and continuous baseline variables were compared using *t* test. Follow-up was defined as the time from the day of surgery until the occurrence of recurrence, death or censoring alive. Rates for DFS were analyzed using the Kaplan–Maier failure function and OS was estimated using the Kaplan–Meier method. Differences between groups were compared using the log-rank test.

Univariate and multivariate analyses were performed using the Cox proportional hazard regression and proportionality was tested for using Cox proportional hazard assumption. Test values with p values < 0.2 in univariate analysis were included in multivariate analysis. Hazard ratio and confidence intervals were calculated. A p value < 0.05 was considered as statistically significant. Statistical analysis was performed using Stata (Macintosh version 14.0, Stata Corp, Houston, TX, USA).

Results

Analysis at baseline

Ninety-three patients diagnosed with head and neck squamous cell carcinoma were included in this retrospective cohort study. The median patient age at diagnosis was 58 years (range 27–72 years). Seventy-two patients (77.4%) were men and 21 (22.6%) were women. Tumor localization was the hypopharynx in 16 (17.2%) patients, larynx in 10 (10.7%) patients, oral cavity in 21 (22.6%) patients and oropharynx in 46 (49.5%) patients. Per the AJCC 8th edition staging, 9 (9.7%) patients were staged as stage I, 11 (11.8%) as stage II, 24 (25.8%) as stage III, 48 (51.6%) as stage IVA and 1 (1.1%) as stage IVB disease. None of the patients had known distant metastases at time of diagnosis. Nineteen patients (21.2%) were HPV high-risk positive. All patients underwent surgery with curative intent, followed by postoperative radiotherapy, with a total dose ranging from 40 to 70 Gy at single doses of 2 Gy per fraction. Eleven (12%) patients received additional postoperative chemotherapy because of extracapsular spread or R1 resection in the final histopathologic workup. The smoker-status was known for all patients, of which 70% were active smoker and 17% were never-smoker. Drinking-status was known for 95% of patients, of which 39% were active drinker and 41% were never-drinker. More detailed information about baseline characteristics is shown in Table 1.

Preoperative ALI in HNSCC patients

Preoperative lymphocyte and neutrophil count, serum albumin and body measures were available in 93 patients. The

Table 1 Basic data and descriptive statistics of patients included in this study

	Total ($n=93$)	Low ALI ($n=46$)	High ALI ($n=47$)	p value
Sex				
Male	72 (77,4%)	37 (80.4%)	35 (74.5%)	0.5 (χ^2)
Female	21 (22.6%)	9 (19.6%)	12 (25.5%)	
Age in years (range)	56 (mean) [27–72]	55.5 (30–70)	57.3 (27–72)	0.34 (t test)
T-classification				
T1	19 (20.4%)	11 (23.9%)	8 (17%)	0.9 (χ^2)
T2	51 (54.8%)	24 (52.2%)	27 (57.5%)	
T3	15 (16.1%)	7 (15.2%)	8 (17%)	
T4	8 (8.6%)	4 (8.7%)	4 (8.5%)	
N-classification				0.1 (χ^2)
N0	18 (19.4%)	7 (15.2%)	11 (23.4%)	
N1	15 (16.1%)	9 (19.6%)	6 (12.8%)	
N2a	5 (5.4%)	–	5 (10.6%)	
N2b	30 (32.3%)	18 (39.1%)	12 (25.5%)	
N2c	8 (8.6%)	5 (10.9%)	3 (6.4%)	
N3	1 (1.1%)	–	1 (2.1%)	
pN0 (HPV+)	–	–	–	0.6 (Fisher's)
pN1 (HPV+)	12 (12.9%)	6 (13.0%)	6 (12.8%)	
pN2 (HPV+)	4 (4.3%)	1 (2.2%)	3 (6.4%)	
HPV HR pos	19 (21.2%)	9 (19.6%)	10 (22.7%)	0.7 (χ^2)
Oropharynx	16 (17.2%)	7 (15.2%)	9 (19.1%)	0.6 (χ^2)
Oral Cavity	3 (3.2%)	1 (2.2%)	2 (4.3%)	
Tumor localization				0.5 (Fisher's)
Hypopharynx	16 (17.2%)	9 (19.6%)	7 (14.9%)	
Larynx	10 (10.7%)	3 (6.5%)	7 (14.9%)	
Oral cavity	21 (22.6%)	12 (26%)	9 (19.2%)	
Oropharynx	46 (49.5%)	22 (47.8%)	24 (51%)	
Postoperative radio-chemotherapy	11 (12%)	6 (6.6%)	5 (5.4%)	0.7 (χ^2)
Staging				0.16 (Fisher's)
I	9 (9.7%)	7 (15.2%)	2 (4.3%)	
II	11 (11.8%)	3 (6.5%)	8 (17%)	
III	24 (25.8%)	11 (23.9%)	13 (27.7%)	
IVA	48 (51.6%)	25 (54.4%)	23 (48.9%)	
IVB	1 (1.1%)	–	1 (2.1%)	
Smoker	65 (69.9%)	35 (76%)	30 (63.8%)	0.27 (χ^2)
Never-smoker	16 (17.2%)	5 (10.9%)	11 (23.4%)	
Ex-smoker	12 (12.9%)	6 (13%)	6 (12.7%)	
Alcohol	($n=88$ patients)			0.2 (χ^2)
Daily drinker	34 (38.6%)	21 (47.7%)	13 (29.6%)	
Never-drinker	36 (40.9%)	15 (34.1%)	21 (47.7%)	
Ex-drinker	18 (20.5%)	8 (18.2%)	10 (22.7%)	
BMI (range)	25 (17.2–34.3)	24 (17.2–33.5)	26 (17.6–34.3)	0.006 (t test)

median pretreatment values to calculate the ALI of our cohort were as following: lymphocyte count was 1.7 G/l (range 0.4–3.6 G/l), neutrophil count was 4.7 G/l (range 2.5–10.8 G/l), albumin was 42.6 g/dl (range 29.7–51 d/dl) and BMI was 24.9 (range 17.2–34.4) The median ALI was calculated as 37.6 (range 10–111). We dichotomized patients into "ALI high" group (ALI > 37.6; low inflammation) and ALI low group (ALI ≤ 37.6, high inflammation), respectively. Baseline characteristics of those groups are listed in Table 1. A significant association could be observed for BMI ($p=0.006$), whereby a high ALI was associated with a higher BMI (Table 1). No differences were observed

for sex, age, N- and T-classification, HPV high-risk status, tumor localization, chemotherapy received, smoker-status or alcohol abuse.

Prognostic value on clinical outcome

Out of 93 patients, 32 (34.4%) suffered from disease recurrence and 45 (48.4%) died during follow-up. Of the 32 recurrences, 20 were local, 5 loco-regional and 7 distant. The median DFS was 13 years (range 0.3–16.2 years) and the median overall survival was 13.2 years (range 0.3–16.2 years). The 5-year DFS and OS was 65.5% and 59%, respectively. Patients with a low ALI had a shorter median DFS (3.8 years) compared to patients with a high ALI (median survival not reached), and a worse 5-year DFS (47% compared to 83.5%, $p=0.0007$, Fig. 1b) Furthermore, patients with a low ALI had a shorter median OS compared to patients with a high ALI (4.3 years vs. 13.7 years, respectively,) and the 5-year overall survival in patients with low ALI was 44.4% compared to 73.6% as shown by Kaplan–Maier analysis (p = 0.008, Fig. 1a).

Parameters included in the univariate Cox-regression analysis included the HPV high-risk status, T- and N-classification, AJCC stage, tumor site, adjuvant chemotherapy, age at surgery, radiation dose, ALI status, number of packs of cigarettes per day and alcohol drinking status.

Univariate Cox-regression analysis for DFS revealed that low ALI ($p=0.002$), number of packs of cigarettes smoked per day ($p=0.017$), tumor site ($p=0.019$) and T-classification ($p=0.007$) were found to be significantly associated with poorer DFS. In multivariate analysis, however, only low ALI (HR 0.2, $p<0.001$) and T-classification (HR 1.93, $p=0.007$) remained significant predictors for worse DFS (Table 2). Univariate Cox-regression analysis revealed that the number of packs of cigarettes smoked per day ($p<0.001$), low ALI ($p=0.01$) and T-classification ($p=0.04$) predicted poor overall survival. In multivariate Cox-regression analysis low ALI (HR 0.44, $p=0.02$) and cigarette-packs smoked per day (HR 1.86, $p=0.006$) remained significant predictors of worse OS.

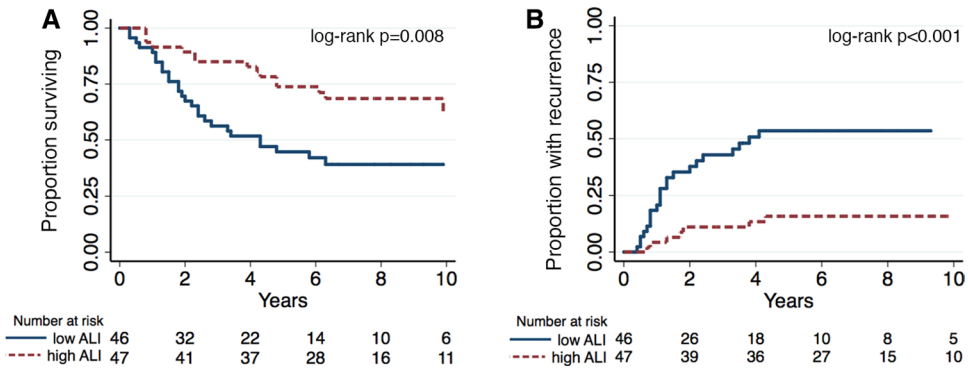

Fig. 1 Kaplan-Maier analysis of OS (**a**) and Kaplan–Maier failure function for disease-free-survival (DFS) (**b**) between patients with low ALI and high ALI

Table 2 Cox-regression analysis

	Univariate			Multivariate		
	HR	*p* value	95% CI	HR	*p* value	95% CI
Disease-free survival						
ALI (high vs. low)	0.28	0.002	0.13–0.62	0.2	0.000	0.08–0.46
Packs/day	1.65	0.017	1.09–2.49	1.35	0.166	0.88–2.04
Tumor site	0.71	0.019	0.53–0.94	0.77	0.1	0.57–1.1
T-classification	1.77	0.007	1.16–2.68	1.93	0.007	1.2–1.6
Chemotherapy (yes/no)	0.24	0.16	0.037-1.7	0.2	0.13	0.027-1.6
Overall survival						
ALI (high vs. low)	0.44	0.01	0.23–0.82	0.45	0.022	0.22–0.89
Packs/day	1.86	0.000	1.32–2.6	1.66	0.006	1.15–2.39
Tumor site	0.8	0.092	0.63–1.03	0.92	0.6	0.68–1.25
T-classification	1.4	0.043	1.01–1.98	1.32	0.12	0.93–1.87
Alc. (drinker vs. non-drinker)	1.65	0.1	0.89–3.02	1.04	0.12	0.54–1.02

Discussion

A readily available biomarker for the prediction of disease recurrence of head and neck squamous cell carcinoma could help identify patients with a high recurrence risk. Early identification of these high-risk patients might enable more aggressive adjuvant therapies and might ultimately help to improve overall survival in this patient population. Systemic inflammation has been linked to carcinogenesis, [5] cancer promotion, and progression [4]. Systemic inflammatory response can easily be measured by standard laboratory tests. Hence, different inflammatory biomarkers have been studied in various cancer entities as potential prognostic indicators for disease outcome [9–11, 18]. In HNSCC patients, elevated NLR has been shown to be an independent prognostic factor for OS in patients with recurrent or metastatic HNSCC [19]. Another recent study investigated the prognostic value of nutritional and hematologic markers in treatment naive HNSCC patients who were treated with definitive chemoradiotherapy. They found that pre-treatment hypoalbuminemia and high NLR were independent marker in multivariate analysis for poor OS and progression-free survival [20]. Furthermore, a low pre-treatment BMI has emerged as a prognosticator for poor overall survival in HNSCC patients receiving primary definitive chemoradiotherapy or radiotherapy but not for patients treated with surgery [21].

Since weight loss and hypoalbuminemia are associated with systemic inflammation in cancer patients, Jafri et al. combined these markers with the NLR and developed a unified index, the Advanced Lung Cancer Inflammatory Index, in 2013 [8, 22]. Subsequently, the ALI has been utilized in different cancer entities and successfully predicted worse overall and disease-free survival [8, 12, 16, 17, 23]. To the best of our knowledge, the ALI has not been investigated for it's prognostic value in HNSCC patients.

In this retrospective observational cohort study, we demonstrated that the ALI has a significant prognostic value in predicting disease-free and overall survival for patients with HNSCC treated with primary resection and postoperative radiotherapy. Therefore, ALI might be a useful marker for personalized recurrence risk assessment in this patient population.

There are several limitations of this study. First, this is a retrospective single-institution study with a small cohort and, therefore, selection bias cannot be fully excluded. We tried to limit this potential bias using a homogenously treated group of HNSCC patients. Second, we did not specifically assess local or systemic infection at the time of data collection. However, since patients were eligible for major surgery, it is highly unlikely that severe infection was present at the time the ALI was calculated. Third, we did not verify our findings on an independent dataset and, therefore, the external validity of these findings is uncertain. Finally, different threshold values for ALI have been utilized in different studies, namely 18 [8, 23], 19.5 [24] and 37.6 [25]. These studies used thresholds determined by ROC curve or by dichotomizing the cohort at the median value, which resulted in two relevant cut-off "sections" described in the relevant literature, particularly at 18–19 and 37 as mentioned above. In our study, the median value was used to stratify patients into "ALI low" and "ALI high", which corresponded to the cut-off value used by Tomita et al. [25]. However, it is not clear why different values emerge in different study populations and which cut-off is most appropriate. The lack of uniformity for this threshold value complicates interpretation of ALI values and, therefore, needs further investigation.

In conclusion, our data provides strong evidence of an association between low ALI and shortened disease-free survival and overall survival in HNSCC patients after surgical resection and postoperative radiotherapy. Given the inexpensive and readily available character of this inflammatory biomarker, it could be easily used in routine clinical practice and, therefore, merits further investigation. External validation of our findings using an independent patient cohort will be needed to assess the robustness of the ALI as a prognostic marker for HNSCC patients.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

Ethical approval The institutional research board approved this study (EK 1311/2018)

Informed consent Informed consent was obtained from all patients to use their clinical data for a scientific purpose.

References

1. Gatta G et al. (2015) Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. Eur J Cancer 51: 2130
2. Pulte D, Brenner H (2010) Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. Oncologist 15:994
3. Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? Lancet 357:539
4. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646
5. Todoric J, Antonucci L, Karin M (2016) Targeting Inflammation in Cancer Prevention and Therapy. Cancer Prev Res 9:895

6. Piemonte ED, Lazos JP, Brunotto M (2010) Relationship between chronic trauma of the oral mucosa, oral potentially malignant disorders and oral cancer. J Oral Pathol 39:513
7. Gomez D et al (2008) Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. World J Surg 32:1757
8. Jafri SH, Shi R, Mills G (2013) Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review. BMC Cancer 13:158
9. Liu G, Ke LC, Sun SR (2018) Prognostic value of pretreatment neutrophil-to-lymphocyte ratio in patients with soft tissue sarcoma: a meta-analysis. Medicine 97:e12176
10. Ma M et al (2018) Prognostic value of inflammatory biomarkers in gastric cancer patients and the construction of a predictive model. Digest Surg. https://doi.org/10.1159/000493432
11. Ohno Y (2018) Role of systemic inflammatory response markers in urological malignancy. Int J Urol 26(1):31–47
12. JM Riedl et al (2017) Inflammatory biomarkers in metastatic colorectal cancer: prognostic and predictive role beyond the first line setting. Oncotarget 8:96048
13. Sun W et al (2016) Pretreatment hematologic markers as prognostic factors in patients with nasopharyngeal carcinoma: neutrophil–lymphocyte ratio and platelet–lymphocyte ratio. Head Neck 38(Suppl 1):E1332
14. Tanaka N et al. (2015) Impact of combined use of blood-based inflammatory markers on patients with upper tract urothelial carcinoma following radical nephroureterectomy: proposal of a cumulative marker score as a novel predictive tool for prognosis. Eur Urol Focus 1:54
15. Selzer E, Grah A, Heiduschka G, Kornek G, Thurnher D, (2015) Primary radiotherapy or postoperative radiotherapy in patients with head and neck cancer: Comparative analysis of inflammation-based prognostic scoring systems. Strahlentherapie Onkologie 191:486
16. Park YH, Yi HG, Lee MH, Kim CS, Lim JH (2017) Prognostic value of the pretreatment advanced lung cancer inflammation index (ALI) in diffuse large B cell lymphoma patients treated with R-CHOP chemotherapy. Acta haematologica 137:76
17. Feng JF, Huang Y, Chen QX (2014) A new inflammation index is useful for patients with esophageal squamous cell carcinoma. OncoTargets Therapy 7:1811
18. Turri-Zanoni M et al (2017) Prognostic value of pretreatment peripheral blood markers in paranasal sinus cancer: Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio. Head Neck 39:730
19. DK Salim et al (2015) Neutrophil to lymphocyte ratio is an independent prognostic factor in patients with recurrent or metastatic head and neck squamous cell cancer. Mol Clin Oncol 3:839
20. Moon H et al (2016) Prognostic value of nutritional and hematologic markers in head and neck squamous cell carcinoma treated by chemoradiotherapy. Radiother Oncol 118:330
21. Takenaka Y et al (2015) Prognostic significance of body mass index before treatment for head and neck cancer. Head neck 37(Oct):1518
22. McMillan DC (2009) Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 12:223
23. Shiroyama T et al (2018) Pretreatment advanced lung cancer inflammation index (ALI) for predicting early progression in nivolumab-treated patients with advanced non-small cell lung cancer. Cancer Med 7:13
24. He X et al (2015) Advanced lung cancer inflammation index, a new prognostic score, predicts outcome in patients with small-cell lung cancer. Clin Lung Cancer 16:e165
25. Tomita M, Ayabe T, Maeda R, Nakamura K (2017) Combination of advanced lung cancer inflammation index and C-reactive protein is a prognostic factor in patients with operable non-small cell lung cancer. World J Oncol 8:175