Oncology

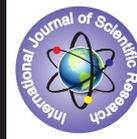**Prognostic Significance Of Involved Lymphnode Ratio in Predicting Recurrence and Survivval in Patients with Head and Neck squamous Cell Carcinoma- An Analytical Study.**

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ABSTRACT Metastatic involvement of cervical Lymph nodes is regarded as an important prognostic factor in head and neck cancer. Our study is aimed at analyzing the significance of involved Lymph node ratio(ILNR),in patients with head and neck squamous cell cancers. An ILNR of 0.16 reached statistical significance in our study, implying that patients with metastatic lymph node ratio more than 0.16 in our study, had reduced time to recurrence(p value 0.002), and DFS(p value 0.01) and distant metastasis free survival(p0.03) and decreased overall survival(0.04). Our analysis revealed that ILNR was an independent prognostic factor predicting recurrence and survival in patients with head and neck squamous cell carcinoma .We also analyzed from our study that ILNR was more significant in patients who were operated upfront than those following chemoradiation .

Introduction:

Squamous cell carcinoma of head and neck is a common malignancy, and is associated with Human papilloma virus(HPV), smoking, tobacco , poor oral hygiene. One of the most commonly used prognostic factors is the tumor-node-metastasis (TNM) staging system. The T status is important in determining the N status and N status in turn plays its role in M status , implying that nodal involvement carries significant prognostic value and determines the disease free survival, recurrence free and possibly the over all survival. Unlike other malignancies like breast, colon where the pathological number of nodes that are dissected or examined are given importance, it is not so in head and neck squamous cell cancers.

Involved Lymph nodes ratio (ILNR), defined as the ratio of the number of positive lymph nodes to the total number of lymph nodes removed. This ratio is more prognostic than the absolute number of nodes which are involved. ILNR is also used as a prognostic factor in patients with bladder cancer , gastric, esophageal cancer .

Materials and methods:

The case records of various head and neck squamous cell carcinoma patients who were treated at our department including radiation and medical oncology between January 2008 till date were analyzed. Total of 197 patients were analyzed. The primary sites included oral cavity{(Tongue-83, buccal mucosa-48,alveolus-23,floor of mouth-21)((175)}, oropharynx (15), and larynx (7). All patients had pathologically confirmed squamous cell carcinoma. Out of these 197 patients, 102 patients were operated upfront, while remaining 95 underwent preoperative chemo radiation followed by surgery. Among the 197 patients, 113 patients had clinical lymph node positivity(cN+) . ILNR was calculated for each patient, defined as ratio of metastatic nodes to total number of lymph nodes retrieved during neck dissection.The endpoints were time to recurrence, disease free survival (DFS)and over all survival.

Statistical analysis:

The endpoints were disease free survival, recurrence free survival, distant recurrence free survival, overall survival (OS). The OS was calculated from the date of surgery to the date of death from any cause or last follow-up. The disease free survival was measured from the date of surgery to the date of any evidence of disease. The DRFS was calculated from the date of surgery to the date of distant metastasis. Survival was estimated using the Kaplan-Meier method and Log-rank test was used for the comparison between the groups. The statistical analyses were performed using SPSS software, with a p value less than 0.05 was considered statistically significant.

Results:

Average lymphnode yield was 6(range 3-23) nodes. An ILNR of 0.16 reached statistical significance in our study. Patients with metastatic lymph node ratio more than 0.16 in our study, had reduced time to recurrence ie recurrence free survival,(p value 0.002), and DFS(p value 0.01),distant recurrence free survival(p-0.03) and decreased overall survival.

113 patients had clinical lymph node positivity(cN+) . Of these 43 patients(37.2%) had 2 or more lymph nodes metastases. The median value of ILNR for lymph node-positive patients was 0.16, (range from 0.07 to0.49). All our patients were categorized as those with ILNR ≧ 0.16(group A) and ILNR < 0.16 (group B)group. Patients with negative lymph nodes were assigned to the LNR < 0.16 group. In c N+, group, of the 113 patients, 54 patients were in group A(47.78%) and among the patients with c N- category,39 patients were in group A with p value 0.07 implying no statistical significance. Hence a clinically N+ disease can have a metastatic node where, ILNR assumes even more significance .

The median follow-up time was 36.2 months. For surviving patients, the follow up time was at least 2 years. Patients with ILNR <0.16 had higher 3 year DFS(74.20 vs 48.23%,p=0.01). Patients with ILNR <0.16 had higher 3-year recurrence free survivval (71.12 % vs. 50.9 %, p = 0.002). Patients with ILNR <0.16 had better 3-year DRFS (81.12 % vs.66.4 %, p = 0.03). Patients with ILNR <0.16(group B) had longer 3-year OS (65.23 % vs.46.43 %, p = 0.04)The subgroup analysis for lymph node-positive patients showed that higher ILNR in our study had poor 3-year OS (p = 0.003, and recurrence free survival (p = 0.011). High ILNR group had poorer DRFS .The over all survival was also poor in group A, compared to group B(p value .036) signifying statistical significance.

Table 1. Description of study:

Total no of patients .	197
cN+(clinically node positive)	113
cN-(clinically node negative)	84
Anatomical Subsites involved	Oral cavity-175 (Tongue-83, Buccal mucosa-48, Alveolus-23, FOM-21)
	Oropharynx-15
	Larynx-7

Table 2. Statistical Interpretation:

Group A(ILNR>.16)		Group B(ILNR<.16)	p value
DFS	74.20	48.23	0.01(significant)
RFS	71.12	50.90	0.002(significant)
DMFS	81.12	66.40	0.03(significant)
OS	65.23	46.43	0.04(significant)

Discussion:

Head and neck squamous cell carcinomas are common malignancies. Most of the cases present in locally advanced stage requiring combined modality treatment. However they show response to treatment and have better survival than other malignancies . One of the most significant prognostic factors is neck lymph nodes metastasis . In the study by Kowalski et al[4]., the number of positive lymph nodes was found to be a predictor of outcome for head and neck cancer patients. Studies have showed a significant correlation between cervical lymph nodes metastasis and increased total number of dissected lymph nodes. The number of positive lymph nodes and the total number of dissected lymph nodes are affected by a lymph nodes dissection procedure and confirmed by pathological examination. The ILNR may have a higher prognostic value in determining lymph nodes status, rather than the mere number of positive nodes. Higher metastatic lymph node ratio is associated with decreased recurrence free, disease free and over all survival.

Pampurik et al[5] analyzed 289 oral cavity cancer patients who received primary surgery with or without adjuvant radiotherapy and showed LNR remained the only independent predictor of OS (HR = 2.0, p = 0.02), disease specific survival (DSS) (HR = 2.3, p = 0.02), and local control (HR = 4.1, p = 0.005). Kim et al.[8] analyzed 211 oral cavity cancer patients who underwent surgery and found that LNR was an independent predictor of DSS (HR = 3.24, 95 % CI = 1.61–6.53; p = 0.001). In our study, we found ILNR was an independent prognostic factor for OS (HR = 5.14; 95 % CI = 2.026–13.07; p = 0.001) and Recurrence free survival (HR = 12.60; 95 % CI = 3.872–37.5; p < 0.001).

The cutoff value for LNR varied across studies. Talole et al. [7] reviewed medical data of 1408 oral cancer patients and found LNR (0.088) was significantly associated with survival outcomes. Hua et al. [6] analyzed 81 hypopharyngeal cancer patients and revealed that those with an LNR $\geqq$ 0.1 had poor OS. In our study, we used a cutoff value of 0.16 to categorize patients into LNR $\geqq$ 0.16 group A and LNR < 0.16 groupB. . All these consistently showed that patients with a higher LNR were shown to have poor survival.

In our study we would like to conclude the following from our analysis:

1. ILNR(involved lymph node ratio) has more prognostic significance than mere number of nodes.
2. Patients with high ILNR(our cut off 0.16) had poor DFS, RFS, DRFS,OS than those with low ILNR
3. A subset analysis revealed that ILNR was more for even c N0 in tongue cancers(p=.003)
4. ILNR was significant even in c N0/cN- patients, there by suggesting that ILNR can be of prognostic value even if nodes are negative clinically.

Although this is a retrospective study, yet the study has shown statistical significance of ILNR in head and neck cancer prognostication. A more detailed analysis in future with more prospective follow up would strengthen the study further.

Conclusion:
ILNR is an important prognostic factor in head and neck squamous cell carcinoma, in determining the disease free survival, recurrence(both local and distant) free survival and over all survival in affected patients. In addition to the AJCC TNM classification system, ILNR may be useful in stratifying risk in patients with head and neck cancer.

Abbreviations:
ILNR-Involved lymph node ratio
DFS-Disease Free survival
DMFS-Distant metastasis free survival/DRFS:Distant recurrence free survival
OS-Over all survival
HR-Hazards ratio

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