

# **Lymphopenia Association with Planning Target Volume and Lung V5 and its Effect on Survival of Esophageal Cancer receiving Neoadjuvant Chemo-radiation with Dutch CROSS Regime**

## **Intro**

Radiation has a strong lympholytic effect. This effect has been overlooked for decades until recently. As immunotherapy is becoming one of the main systemic treatment of various cancer, it is important to adopt best radiation technique to preserve lymphocyte numbers.

Radiation-induced lymphopenia has been reported to be adversely associated with overall survival and recurrence free survival in various cancers including lung, pancreatic and head and neck cancer. Data of lymphopenia effect on esophageal cancer is lacking. We therefore sought to study the association of lymphopenia and overall survival in esophageal cancer patients who have undergone neoadjuvant chemo-radiation according to Dutch CROSS trial regime.

One of the possible mechanism of severe lymphopenia in radiotherapy is the large volume of low dose bath killing large number of circulating lymphocytes in both systemic and pulmonary circulation. As there is report of relationship of low dose lung dosimetry parameters with lymphopenia in NSCLC, we also aim to study this relationship in esophageal cancer.

## **method**

All esophageal cancer patients from June 2012 to April 2015 in our tertiary university hospital who have received neoadjuvant chemo-radiation according to Dutch CROSS trial regime has been retrospectively reviewed. Total subjects eligible for review is 51. One subject has died before the start of chemo-radiation and thus was excluded from analysis.

Lymphocyte nadir was defined as the minimum lymphocyte value measured between the start of neoadjuvant chemo-radiation and the operation date.

Relationships between lymphocyte nadirs with overall survival (OS) and recurrence free survival (RFS) were evaluated with Cox-regression analysis. Association between Planning Target volume (PTV) and lung dose- volume histogram (DVH) parameters were analysed with multivariable linear regression.

## **Results**

Median OS for this group is 446 days (14.9months). 48 out of 50 subjects have normal baseline lymphocyte counts. Low lymphocyte nadir is found to have negative

effect on patient's overall survival (OS) and recurrence-free survival (RFS) even after adjustment with PTV volume.

PTV volume, in contrast to common belief, has no statistical significant effect on both OS and DFS. Baseline total white cell count, neutrophil and lymphocyte count are not correlated with survival neither.

Analyses of lung DVH parameters revealed significant linear regression coefficient from -0.4 to -0.8 at low dose zone V1-V15 with lymphocyte nadir (P<0.05).

Comparing patients treated with 3D conformal and IMRT technique, there are no statistical significant difference by Mann-Whitney U tests in lung DVH, lymphocyte nadir, RFS and OS (P> 0.3).

### conclusion

Lower lymphocyte nadir is associated with poorer overall survival in this group of patients. Higher low dose lung DVH and larger PTV are associated with lower lymphocyte nadir, in both 3D conformal and IMRT techniques. These findings shall be confirmed with prospective data in future studies. This also suggests immune preserving radiation strategy in radiation by suppressing low dose lung DVH may improve OS in this group of patients

Characteristics	N=51	%
<b>Age at diagnosis</b>		
Under 65	24	47.1
65 and above	27	53.9
<b>Sex</b>		
Male	44	86.3
Female	7	13.7
<b>Histology</b>		
Squamous-cell carcinoma	51	100
Adenocarcinoma	0	0
<b>Finished chemoradiation</b>		
Yes	50	98
No	1	2
<b>Baseline lymphocytes level</b>		
Normal	47	92.2
Low	4	7.8
<b>RT technique</b>		
3D	30	58.8
IMRT	21	41.2
<b>T-classification</b>		
T1-T2	1	2
T3-T4	50	98
<b>N-classification</b>		
N0	0	0