Original Research Article

Metastatic Lymph Node Ratio: A Promising Parameter and Its Relation with Patient Related Factors in Cases of Primary Organ Malignancy

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Abstract

Background: Metastatic lymph node ratio (MLR) is defined as the ratio of number of positive lymph nodes (LNs) or LNM to total nodes harvested (LNH). Recent studies have suggested that MLR is more accurate in predicting overall survival and recurrence‑free survival rate compared to the number of positive nodes alone. ***Materials and methods:*** Total 58 cases of primary organ malignancy were evaluated from June 2018 to June 2019 including Head and neck (HN), Breast, Gastrointestinal tract (GIT) and Genitourinary tract (GUT) malignancy. Age, gender, LNH, LNM, MLR, tumor stage and tumor grade were accessed for each of the cases. ***Results:*** Out of total 58, there were 12, 33, 11 and 2 cases each of HN, Breast, GIT and GUT malignancy respectively. M:F ratio was 1:2.2. Maximum cases (39.6%) were seen in the age group of 35-45 years. 186 out of 530 LNs showed metastasis. Mean MLR for lymph node-positive cases were 0.3. Majority of HN malignancy cases (41.6%) were found in T1/T2 stage, breast malignancy cases (42.4%) in T2 stage, GIT malignancy cases (63.6%) in T3 stage, 50% of GUT malignancy cases in T3 and 50% were in T4 stage. Maximum well‑differentiated (10, 83.3%) cases belonged to HN, moderately (15, 45.4%) and poorly differentiated (18, 54.5%) to breast respectively. We found significant association of MLR with tumor stage and tumor grade. (p-value < 0.001) ***Conclusion:*** The routine inclusion of MLR in tumor reporting by pathologists may become a prognostic aid for clinicians along with TNM staging system.
Keywords: Metastatic lymphnode ratio, primary organ malignancy, lymph node metastasis.

INTRODUCTION

The status of regional lymph node metastasis (LNM) has been widely considered as an important prognostic factor to plan subsequent management of patients with primary organ malignancy [1]. Lymph nodes (LNs) draining a tumor may enlarge due to metastasis (LNM) or reactive hyperplasia [2]. One of the most commonly used prognostic factors is the tumor-node-metastasis (TNM) staging system [4]. Although LNM is a simple, convenient, and reliable method for precise staging, the identified number of metastatic LNs depends on the number of dissected LNs. A low number of examined LNs may lead to false understating and subsequent underestimation of cancer spread. This phenomenon is referred to as stage migration.

Metastatic lymph node ratio (MLR) is defined as the ratio of number of positive LNs or LNM to total nodes removed or harvested (LNH) and is used as an important prognostic factor. Recent studies have suggested that MLR is more accurate in predicting overall survival and recurrence-free survival rate compared to the number of positive nodes alone.

There is also disparity regarding the number of LNs to be resected [1]. 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 [4].

Some groups have recently proposed the metastatic lymph node ratio (MLR) as an alternative prognostic factor to supplement the limitations of the

conventional N staging system, particularly when a limited number of LNs is obtained [3].

The routine inclusion of MLR in tumor reporting by pathologists may become a prognostic aid for clinicians alongside tumor stage and tumor grade [2].

AIMS AND OBJECTIVES
- To evaluate the prevalence of various primary organ malignancy and its metastasis.
- To evaluate the distribution of primary organ malignancy as per the age and gender of the patients.
- To evaluate total LNH, LNM, and MLR in resected specimens of primary organ malignancy.
- To evaluate the cases as per their MLR groups.
- To evaluate the relation of MLR with tumor stage and tumor grade.

MATERIALS AND METHODS
We carried out a retrospective observational study. In the current study, we included the cases of primary organ malignancies that came to the hospital over a period from June 2018 to June 2019. Total 58 resection specimens of primary organ malignancy with local LN clearance were included in this study.

Age, gender, LNH, LNM, MLR, tumor stage and tumor grade were accessed for each of the cases. All data were recorded in MS Excel sheet. These data were represented in tabulated as well as graphical formats. We calculated the p – value as and when required and p – value of < 0.001 was considered as significant. The statistical analysis was performed using MS Excel and SPSS software.

RESULTS
Total 58 cases of primary organ malignancies were studied in the present study. There were 12, 33, 11 and 2 cases each of Head and neck (HN), Breast, Gastrointestinal tract (GIT) and genitourinary tract (GUT) malignancy respectively [Table – 1]. HN cases included buccal mucosa (5), tongue (5), and thyroid (2). GIT cases included colon (10) and stomach (1). GUT cases included penis (1) and kidney (1).
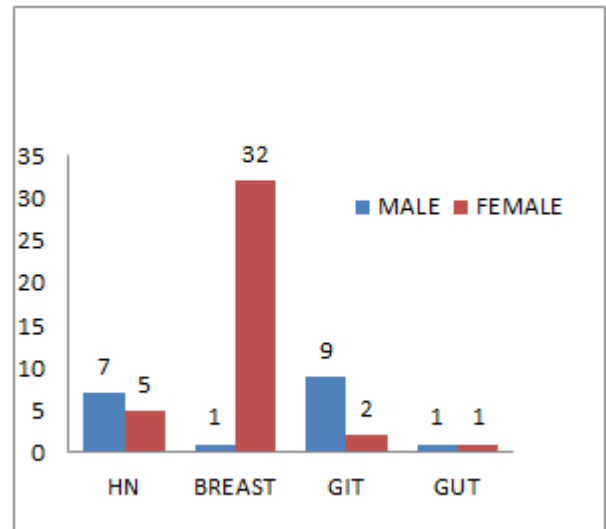
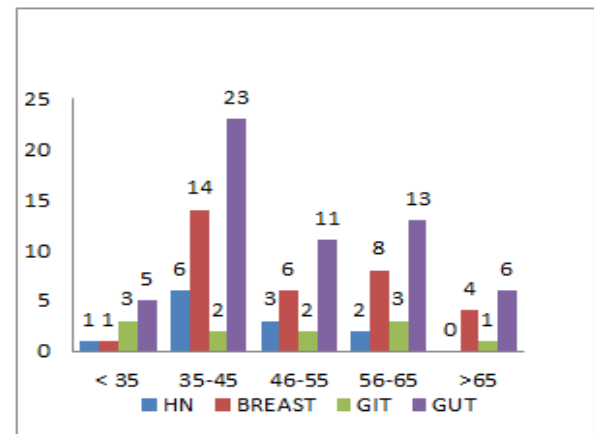

Fig-1: Distribution of cases as per the gender

Fig-2: Distribution of cases as per the age group

There was a marked female preponderance (40) over males (18). [Figure – 1] Male to female ratio was 1:2.2. There was a marked female preponderance especially in cases of breast (96.9%) with male preponderance in HN (58.3%) and GIT (81.8%) cases. Maximum cases (39.6%) of primary organ malignancies were seen in the age group of 35-45 years [Figure – 2].

LNH and LNM were evaluated for all the cases. Total 530 LNs were harvested from 58 cases. LNM were observed in 186 LNs (32 cases) [Table – 1].

Table-1: Distribution of cases as per primary organ malignancy, LNH and LNM

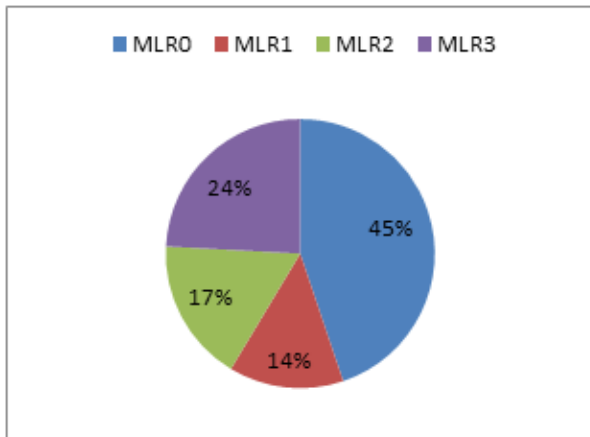| PRIMARY ORGAN	NO. OF CASES	LNH	MEAN LNH	CASES WITH METASTASIS	LNM	MEAN LNM
HN	12	112	9.3	3	5	0.41
BREAST	33	335	10.1	22	164	4.9
GIT	11	76	6.9	4	11	1
GUT	2	7	3.5	2	6	3
TOTAL	58	530	29.8	31	186	9.31

Fig-3: Distribution of cases as per the MLR groups

The ratio of metastatic LN to total number of resected LN was divided into four groups: MLR 0 = 0, MLR 1 = 0-0.3, MLR 2 = 0.3-0.6 and MLR 3 = 0.6-1 [Figure – 3]. The mean value of MLR for lymph node-positive patients was 0.3.

Mean MLR for HN was 0.03 (0.0–0.18), for breast was 0.42(0.0 – 1.0), for GIT was 0.13 (0.0–0.72), and for GUT was 0.83 (0.6–1.0). There were 7, 21, 22, and 8 cases, respectively, in tumor stage T1, T2, T3, and T4. [Table – 2]

Table-2: Distribution of cases as per the tumor stage

PRIMARY ORGAN	T1	T2	T3	T4	TOTAL
HN	5	5	1	1	12
BREAST	1	14	13	5	33
GIT	1	2	7	1	11
GUT	0	0	1	1	2
TOTAL	7	21	22	8	58

Majority of HN malignancy cases (41.6%) were found in T1/T2 stage and 83.3% were well differentiated. Majority of breast malignancy cases (42.4%) were found in T2 stage and 54.5% poorly differentiated. Majority of GIT malignancy cases (63.6%) were found in T3 stage and 54.5% were moderately differentiated. 50% of GUT cases were in T3 and 50% were in T4 stage and 50% was well differentiated and 50% were poorly differentiated. Distribution as per tumor grade showed well differentiated (14), moderately differentiated (22), and poorly differentiated (22) cases [Table – 3]. Maximum well differentiated (10, 83.3%) cases belonged to HN, while maximum moderately differentiated (15, 45.4%) and poorly differentiated (18, 54.5%) to breast respectively. Maximum total cases in MLR3 group were poorly differentiated.

Table-3: Distribution of cases as per the tumor grade

PRIMARY ORGAN	WD	MD	PD	TOTAL
HN	10	1	1	12
BREAST	0	15	18	33
GIT	3	6	2	11
GUT	1	0	1	2
TOTAL	14	22	22	58

We evaluated the relation of MLR with tumor stage and tumor grade [Table – 4, 5]. There was significant association between MLR with tumor stage and tumor grade (p-value < 0.001).

Table-4: Relation between tumor stage and MLR

TUMOR STAGE	MLR1	MLR2	MLR3	TOTAL
T1	1	0	1	2
T2	3	7	4	14
T3	3	3	7	13
T4	1	0	2	3

Table-5: Relation between tumor grade and MLR

TUMOR GRADE	MLR1	MLR2	MLR3	TOTAL
WD	3	0	1	4
MD	3	3	5	11
PD	2	7	8	17

DISCUSSION

The present study evaluated the data regarding age, gender, LNH, LNM, MLR, tumor stage and tumor grade from primary organ malignancy cases resected with local nodal clearance. LNH, LNM and MLR were studied for correlation with tumor stage and tumor grade.

The prevalence of involvement of primary organ in our study was HN (20.6%), Breast (56.9%), GIT (18.9%) and GUT (3.4%), which was comparable to the study done by Shinde V *et al.* [2].

The peak age group of affected patients in our study was 35-45 years. There was marked female preponderance over males in our study. These findings of our study were comparable with the study done by various other studies [2]. Akagi *et al.* and Zeng *et al.* reported male predominance in colorectal and gastric carcinoma, as did Chen *et al.* in or opharyngeal malignancy [4, 6, 7]. The male predominance in GIT and HN malignancies may reflect lifestyle related behavior as alcoholism, processed junk food, smoking, and tobacco chewing.

The recommended LNH values are 10, 12, 12, and 40 in breast, GIT, GUT, and HN respectively. Shinde *et al.* found mean LNH values 23.7, 15.5, 6.6 and 9.9 in HN, Breast, GIT and GUT respectively which were similar to our study. Techniques to further improve the yield of LNH include meticulous dissection

during grossing, intratumoral India ink injection during surgery, ex-vivo intra-arterial injection of methylene blue, and chemical fat clearance using acetone and alcohol. Shinde *et al*. found mean LNM values 0.6, 4.4, 1.4 and 0.9 in HN, Breast, GIT and GUT respectively which were similar to our study [2].

We categorized all cases into four groups as per the MLR grouping. Our results showed 44.8%, 13.7%, 17.2% and 24.13% cases in MLR0, MLR1, MLR2 and MLR3 groups respectively. Mean MLR in our study was 0.3. Both these findings were comparable with the study done by Saedi *et al*. [3]

In our study, Mean MLR for HN was 0.03 (range 0.0–0.18), for breast was 0.42(0.0 – 1.0) for GIT was 0.13 (0.0–0.72), and for GUT was 0.83 (0.6–1.0) and it was comparable to the study done by Shinde V *et al*. They found Mean MLR for HN 0.06 (0.0–0.67), for breast 0.29 (range 0.0–1.0), for GIT 0.26 (0.0–1.0) and for GUT 0.1 (0.0–0.56).D2. They found maximum cases of breast (59.6%), GUT (53.8%), and HFNT (45%) belonged to T2 stage, while GIT (60.0%) belonged to T3. Distribution as per tumor grade showed well-differentiated (22), moderately differentiated (68), and poorly differentiated (10) cases. Maximum well-differentiated cases belonged to HFNT (13, 59.0%), while maximum moderately differentiated and poorly differentiated to breast (38, 55.8%) and (7, 70.0%), respectively as in our study [2].

LNH, LNM and LNR cutoff values show organ wise variation, hence need standardization before their usage in cancer staging systems. [1] Serial recuts, use of immunohistochemistry, one step nucleic acid amplification, and polymerase chain reaction can further aid in detecting minute nodal metastases [2].

In present study, majority of HN malignancy cases (41.6%) were found in T1/T2 stage and 83.3% were well differentiated. Majority of breast malignancy cases (42.4%) were found in T2 stage and 54.5% poorly differentiated. Majority of GIT malignancy cases (63.6%) were found in T3 stage and 54.5% were moderately differentiated. 50% of GUT cases were in T3 and 50% were in T4 stage and 50% was well differentiated and 50% were poorly differentiated. Titipungul *et al*. found majority of breast malignancy cases (55.7%) in T2 stage and 32% moderately differentiated. [8] Khetarpal *et al*. found 76% moderately differentiated, 18% well differentiated, and 6% poorly differentiated breast cases. [9] Dedavid *et al*. found 82% of colorectal cancers in stage T3/T4 and 61% belonging to well/moderately differentiated group. [10] Suchitra *et al*. found 40% oral malignancies in T4 stage [11].

We found significant association between MLR with tumor stage and tumor grade (p-value < 0.001), which was comparable to the study done by Saedi *et al*. [3].

A study done by Chen *et al*. on HN case reported that patient with higher MLR was shown to have poor survival. [4] LNR and number of positive lymph nodes are important prognostic factors with regard to overall survival for patients with node-positive breast cancer, but LNR has a more correlated value in breast cancer subtypes [5]. Lee *et al*. in his published study declared that the MLR was a simple and reproducible prognostic factor that supplemented the limitation of the conventional N staging system and provided more accurate prognostic stratification in advanced gastric cancer [12]. Kwon *et al*. in his study showed that MLR is one of the main factors in predicting 5 years survivals of patients with gastric cancer [13]. Lymph node (LN) metastasis is one of the most important prognostic factors of gastric cancer [3]. Wright *et al*. found that higher MLR was associated with higher risk of death in GUT cases [14].

CONCLUSIONS

Previous studies did not define a specific cutoff value for MLR, but patients with a higher MLR were shown to have poor survival. In addition to the AJCC TNM classification system, LNR may be useful in stratifying risk in patients with primary organ malignancy. MLR is more valuable and reliable prognostic factor than total metastatic LN because it removes the effects of total number of resected LNs in determining patient prognosis. The routine inclusion of MLR in tumor reporting by pathologists may become a prognostic aid for clinicians along with TNM staging system. This can predict relapse and survival of cancer patients more closely.

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