Impact of lymph node ratio in the colorectal cancer staging system


University Hospital of Parma, Italy
**Department of Surgical Science, Unit of General Surgery and Organ Transplantation
**Department of Medicine, Unit of Gastroenterology

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AIM: Some researchers have proposed the Lymph Node Ratio (LNR) as a prognostic index for post-surgical colorectal cancer follow up.

MATERIAL AND METHOD: Two hundred patients with colorectal cancer (ratio F/M of 2:1) were studied. Patients were divided in subgroups according to N-stage and LNR score, subgroups of LNR were made on quartiles. For each subgroup 5 year survival rate was calculated and comparison between groups was carried out.

RESULTS: There were 104 patients on N0, 38 on N1 and 58 on N2 stage. Survival rate at 5 years was 61.30% for the N0 subgroup, 18.70% for the N1 subgroup, and 12.31% for the N2 subgroup (Fig. 1). The most significant p value, was reported between N0 and N1 as well as between N0 and N2 subgroup (p=0.001). Nodes positive were 44 a LNR ranging from 1% to 25% (1% < LNR < 25%); 24 patients from 26% to 50% (26% < LNR < 50%). In 6 patients LNR was ranging from 51% to 75% (51% < LNR < 75%) and in 8 patients from 76% to 100% (76% < LNR 100%); overall survival rate in different quartiles was respectively 27.12%, 9.38%, 16.67% and 1.56%.

CONCLUSION: LNR is a reliable prognostic index in post surgical colorectal cancer staging.

KEY WORDS: Colectomy, Colorectal cancer, Lymphnode Ratio, TNM, Prognostic index.

Introduction

Clinico-pathological significance of the tumor nodes metastasis classification system for CRC(colorectal cancer) (which classifies patients into prognostic groups according to depth of the primary tumor, presence of regional lymph node (LNs) metastases and evidence of metastatic spread) is still an object of debate.

The main concern is about the number of LNs with confirmed metastasis, depending on the number of LNs retrieved. It is related to several factors as patient age, tumor grade and site, surgical extent as well as the pathology report.

Some researchers have proposed the lymph Node Ratio (LNR), defined as the number of metastatic LNs divided by the number of LNs retrieved, as a reliable prognostic index for post-surgical colorectal cancer follow up. This LN index has been already validated in various malignancies. Hence the increasing clinicopathological significance of LNR in CRC might be advantageously used in the current staging of CRC to increase its prognostic impact and to optimize chemio adjuvant therapy.

LNs metastases usually proceed slowly interesting the closest nodes to the lesion first and then extending segmentally to involve peri and paracolic nodes; Some studies reported that the first sentinel node may also occur some distance away from the primary tumor.
It might be due to lymphatic channels obstruction leading
to bypassing of the lymphatic drainage to nonsen-
ti nal lymphnodes.
It has been hypothesised that other factors might also
account for skip metastasis. Some authors suggest the use of sentinel lymph node
biopsy in clinical practice to reduce the extent of surgery.
However skip metastasis and the distribution of lymph
node metastasis over a wide area argue against limited
resection for colon cancer. Previous studies examined the impact of negative lymph-
nodes on long-term survival rate in colon-rectal cancer
patients undergoing surgery. These studies highlighted
that prognostic value of this parameter is independent
from cancer staging, and that it results as a more accu-
rate factor than total number of lymph-nodes retrieved.
An elevate number of negative lymph-nodes led to a
lower mortality rate, especially in early stages.

The link between negative lymph-node and survival rate
is still unknown. Some studies reported that 20% of patients undergoing
surgery, with negative lymph-node, develop a systemic
recurrence of disease in the long term follow up. Hidden
metastasis might explain this date.

The effect on hidden metastasis on prognosis for colon-
rectal cancer is still a subject of debate. The lymph-
nodes metastases represent a relevant prognostic factor
for long-term survival in colon-rectal cancer patients
undergoing surgery. Already Dukes, in 1932, identified the lymph-node key
role, (beyond the neoplasia), in the colon-rectal staging
of neoplasia; this importance was acknowledged in the
TNM classification system, proposed by AJCC and
UICC (Union Internationale Contre Cancer), the most
actually adopted, that encompasses, cancer extension(T)
presences of skip metastasis (M) and lymph-nodes stag-
ing (N);

The intent to modify staging criteria for post-surgery
colorectal cancer follow up originated from the current
absence of a gold standard method to reduce uncertances
in the interpretation of post-surgical follow up data.

An accurate lymph-adenectomy and an attentive evalu-
ation of the number of ablated lymph-nodes are, without doubt, remarkable for appropriate staging and treatments on long-term survival of colorectal cancer patient, after surgery.

The number of lymph-node to ablate in order to achieve
an adequately curative resection in colorectal cancer
surgery is still controversial. There are a large number
of studies debating on this issue and the most recent
guidelines of the American Joint Committee on Cancer
recommend a number of lymph-node to be examined
major-equal to twelve. On the basis of the above men-
tioned issues we aim to confirm that LNR is a reliable
independent prognostic factor in post surgery colorectal
cancer follow up and that it might be an adjuvant tool
to TNM staging.

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<th>TABLE I - Patients Characteristics</th>
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<tr>
<td>Number of cases analyzed</td>
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<td>Mean age (years)</td>
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<td>Male/Female</td>
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<td>Factors tumours related</td>
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<td>Numbers of lymphnode in specimen</td>
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<td>Surgical approach</td>
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Materials and Methods

In this study we have retrospectively reviewed 352 (159 female and 193 male) patients with colorectal neoplasia, who underwent surgical treatment at the Unit of General Surgery and Organ Transplantation of Parma University Hospital, between January 2003 and December 2005. All subjects who turned out with a diagnosis of colorectal adenoma were excluded from the study as well as patients without complete follow-up. Two hundred patients with a definite diagnosis of colorectal cancer (ratio F/M of 2:1) were finally studied (Table I). All subjects underwent pan-colonoscopy and chest-abdomen CT scan. Patient with rectal cancer underwent also ultrasound- endoscopy and/or pelvic MRI.

Pre-surgical protocol encompassed anti-thromboembolic therapy with low-density heparin and IV antibiotics. All
the operations were performed by laparotomic approach and/or videolaparoscopic approach (with a patients’ ratio 5/1). The patients affected by rectal cancer were treated with Total Mesorectal Excision (TME). For all patients age, sex, tumor location, histology, grading, pT-stage, pN-stage, number of lymph-node ablated and number of positive lymph-node were recorded. All metastatic lymph nodes and all surgically ablated lymph nodes were carefully recorded. Staging of neoplasia was made referring to the American Joint Committee for Cancer guidelines on TNM. Patients were divided in subgroups according to N-stage and LNR score, calculation of positive lymph nodes ratio on total ablated was made; subgroups of LNR were made on quartiles. The patients were followed up every six months with abdominal ultrasonography or TC abdomen and measurement of carcinoembryogenic antigen. After the second year a clinical evaluation, colonoscopy, TC abdomen every year for the next 4 years were done. For each subgroup 5 year survival rate was calculated and comparison between groups was carried out. For statistical analysis SPSS/7.0 software for Windows was used. Statistically significance was fixed for p< 0.05.

Results

Adeno-carcinoma was the most frequent histological diagnosis (Table I). Most lesions were localized at the sigma –rectum segments comparing to other localization. Surgery was performed by laparotomic approach and video-laparoscopic approach (5/1 of the patients). Surgery was performed by four colorectal surgery consultants. Overall age of the subjects studied in the sample population was 72.75. There were 104 patients on N0, 38 on N1 and 58 on N2 stage. Survival rate at 5 years was 61.30% for the NO subgroup, 18.70% for the N1 subgroup, and 12.31% for the N2 subgroup (Fig. 1). The most significant p value, on comparing survival outcomes, was reported between N0 and N1 as well as between N0 and N2 subgroup (p=0.001). A statistical-
ly significant difference, was also reported between N1 and N2 subgroups (p=0.05). Furthermore comparing survival rate between N0 and N1/N2 subgroups yielded significant results (p=0.01) with a five years survival rate of 61.30% and of 18.23% respectively (Fig. 2). With regard of nodes positive patients, classified on lymph-node ratio value (LNR= number of metastatic LNs divided by the number of LNs retrieved) 44 reported a LNR ranging from 1% to 25% (1% < LNR 25%); 24 patients from 26% to 50% (26% ≤ LNR 50%). In 6 patients LNR was ranging from 51% to 75% (51% ≤ LNR 75%); and in 8 patients from 76% to 100% (76% ≤ LNR 100%); overall survival rate in different quartiles was respectively 27.12%, 9.38%, 16.67% and 1.56% (Fig. 3).

A statistically significant difference was showed between all the subgroup of patients regarding overall survival rate: between 1% LNR 25% and 26% LNR 50% p value was p=0.025 between 1% LNR 25% and 76% LNR 100% p value was p=0.001; between 1% LNR 25% and patients with 51% LNR 75% p value was p=0.05. A statistically significant difference (p=0.025) was also reported between patients with 1 LNR 50% and those with 51% LNR 100% (Fig. 4).

Moreover an overall 5 years survival rate of 27.12% was reported in patients with 1% LNR 25% and a one of 8% was reported as well in 26% LNR 100% (Fig. 5).

**Discussion**

From a review of the literature, ranging from 2005 to 2011, it has been shown that LNR is assuming increasing relevance as reliable prognostic index with respect of conventional TNM classification in post-surgical colorectal cancer staging. Several studies already showed an high independent prognostic value for LNR in colorectal cancer staging. Our study confirmed previous observations about the relevance of LNR as reliable post-surgical prognostic factor also in different subgroups of colorectal cancer patients as divided according to LNR values. It should however be stated that a correct surgical approach remains critical for colorectal cancer patients on post surgical follow-up. An incorrect lymph-nodes ablation may lead to lower number of positive nodes reported.

In our study we contributed to a further validation of LNR as reliable aid to current standards for post-surgery colorectal cancer staging. On the basis of our study, in accordance with previous authors, we propose to introduce LNR as an adjuvant tool in the current standard for colorectal cancer staging after colorectal surgery.

LNR would be also easily reproducible and able to give information about cancer infiltration, spreading and metastatic potential. It may also play a role in establishing an appropriate chemotherapy plan.

Our proposal yielded from this study is that these patients might be reliably followed up on a new prognostic setting including the TNM system and LNR staging. The LNR would worthily contributes to identify high risk subgroups of patients requesting a highly intensive post-surgical follow up as well as low risk subgroups with low impact post-surgical adjuvant protocols.

**Conclusions**

This study demonstrated that LNR is a reliable prognostic index in post surgical colorectal cancer staging. It performs better than conventional TNM classification only on 5 years overall survival rate with an independent high prognostic value.

**Riassunto**

**AIM:** Alcuni autori hanno proposto la Lymphnode ratio (LNR) come un indice prognostico per il follow up del cancro del colon retto operato.

**Materiali e metodi:** 200 pazienti affetti da carcinoma del colon retto (ratio F/M:2:1) sono stati valutati e divisi in sottogruppi in accordo all’interessamento dei linfonodi ed al LNR score; I sottogruppi LNR sono stati divisi in quartile. Per ogni gruppo è stata valutata la sopravvivenza a 5 anni e paragonata tra I gruppi in esame.

**RISULTATI:** 104 pazienti N0, 38 casi N1, 58 casi N2. La quota di sopravvivenza a 5 anni era 61,3% per gli N0, 18,7% per il gruppo N1,12,31% per il sottogruppo N2. Il valore p statisticamente più significativo è stato calcolato tra N0 ed N1 così come quello tra N0 ed N2 (p=0.001). I casi con linfonodi positivi erano 44 nel sottogruppo LNR 1%-25%,24 nel sottogruppo 26%-50%,6 casi nel sottogruppo 51%-75%, 8 casi nel sottogruppo 76%-100%. La sopravvivenza è stata rispettivamente di 27.12%,9.38%,16,67% e 1,56%.

**CONCLUSIONE** LNR è un indice prognostico possibile da considerare nella stadiazione del paziente operato di resezione colon retto.

**References**


It is very important to remember that the LNR is deeply influenced by the number of positive retrieved lymph nodes as for the not affected ones, and therefore that obviously the LNR results should be deeply influenced from an insufficient number of lymph nodes removed, of either type, and that their removal must be the more complete as possible. The bias of this study resides in the difficulty to consider really standardized the single exeretic operation in regard of the tumour site and of the surgical skills of the single operative equipe. In other words the possibility of consider always truly complete the retrieval of all regional lymph nodes.

Anyways the plan and the accuracy of this study offers the best possible approach to the to be expected prognosis based on lymph nodes evaluation.