Is lymph node ratio prognostic factor for survival in elderly patients with node positive breast cancer?

The Anatolian Society of Medical Oncology

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Is lymph Node Ratio Prognostic factor for survival in elderly patients with positive breast cancer?
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Several studies have now demonstrated that the lymph node ratio (LNR), as a superior indicator of axillary tumor burden to the number of excised nodes. While, about the prognostic value of LNR on the the survival of elderly patients is limited. The aim of this retrospective multicenter study is to evaluate the prognostic value of lymph node ratio in elderly patients with node positive breast cancer.
METHODS: *Onehundredeightyfour patient with operable breast cancer, recruited from 17 institutions, were enrolled into the retrospectively study. Eleven potential prognostic variables were chosen for analysis in this study. Univariate and multivariate analyses were conducted to identify prognostic factors associated with survival.*
RESULT: *Among the eleven variables of univariate analysis, four variables were identified to have prognostic significance for Overall survival (OS): pathologic tumor size (T), No. of positive nodes (N), LNR and estrogen receptor-positive (ER). Among the eleven variables of univariate analysis, two variables were identified to have prognostic significance for Disease-free survival (DFS): N and LNR. Multivariate analysis by Cox proportional hazard model showed that T, LNR and ER were considered independent prognostic factors for OS. Furthermore, LNR was considered independent prognostic factors for DFS.*
CONCLUSION: *In conclusion, the LNR was associated with the prognostic importance for DFS and OS in elderly patients who were administered adjuvant treatments.*

KEY WORDS: Breast cancer, Elderly patients, Lymph Node Ratio

Introduction

Breast cancer is the most common cancer in women and the second leading cause of female cancer death among womenin the world [1]. Due to the fact that the aging one of the major risk factors for breast cancer, almost half of all breast cancer occurs in women ≥65 years of age and more than 30% of breast cancer occurs in women >70 years of age [2]. Despite the high incidence, elderly patients with over 70 years of age have generally been excluded from randomized clinical trials of breast cancer treatments [3].

The presence of axillary lymph node metastasis and the number of involved axillary lymph nodes are the most important prognostic factor in breast cancer [4,5]. Among lymph node positive patients, the overall 5-year survival rate is decreased by nearly 40% compared with node-negative patients with breast cancer [6]. According to the current 7th edition of the American Joint Committee on Cancer (AJCC) staging system, N stage in breast cancer is merely defined by the number of involved lymph nodes [7]. Because of the fact that the number of involved lymph nodes identified depends on the surgical and pathologic procedure, in patients with inappropriately dissected axillary nodes may be insufficient. Thus, these patients receive inadequate treatment. AJCC requires that at least six axillary lymph nodes be removed, while other authorities recommend a minimum 10 lymph nodes be removed [7-9]. There is increasing evidence establishing the prognostic value of the LNR in a number of solid malignancies, including cancers of esophagus [10], gastric [11], pancreas [12], colon [13], vulva [14] and bladder [15]. Eventhough several authors used a value between 0,20 and 0,25 as a minimal cut-off, there is no clear consensus on which value is the most reliable in breast cancer. Recent studies have shown the prognostic value of the LNR as an alternative to N staging in node-positive breast cancer [16-26]. Although there are many studies about the importance of LNR, patients older than 70 years were not evaluated according to age strata in a majority of these studies. Therefore, about the prognostic value of LNR on the survival of elderly patients is limited.

The aim of this study was to investigate the prognostic significance of the clinical, pathological and biological characteristics of 184 breast cancer patients age 70 years or older with node positive breast cancer. Specifically, we investigated that the impact of LNR for DFS and OS in elderly patients receiving adjuvant treatments.

Patients and Methods

PATIENT POPULATION

Between June1991 and May 2012, 184 patient with operable breast cancer, recruited from 17 institutions, were enrolled into the retrospectively study.

They met the following inclusion criteria; 1) they were 70 years or older in age; 2) they had histologically confirmed invasive breast cancer; 3) they were treated with definitive surgical therapy (radical mastectomy or lumpectomy plus axillary dissection); 4) they had axillary lymph node involvement (at least five axillary lymph nodes resected).

Patients treated with neoadjuvant chemotherapy were not included. Patients who had a previous or concurrent second malignancy were excluded.

Factors analysed

Eleven potential prognostic variables were chosen on the basis of previously published clinical trials. The variables were divided into categories: LNR (<0,2, 0,2-0,65 and >0,65), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-1, 2-3), age (<80 or ≥80), grade (well, poor or moderate), ER (positive or negative), progesterone receptor (PR) (positive or negative), c-erbB2 (positive or negative), presence of diabetes mellitus (DM) at diagnosis (present or absent), presence of hypertension (HT) at diagnosis (present or absent), N(1-3 or ≥4) and T (<50 mm or ≥50mm).

The LNR was calculated as the number of involved lymph nodes divided by the number of lymph nodes removed. The cohort was then divided into 3 groups on the basis of previously established LNR cutoffs (<0,2, 0,2-0,65 and >0,65) (24,26).

STATISTICAL ANALYSIS

All of the analyses were performed using the SPSS statistical software program package (SPSS version 11. 0 for windows). The differences of the clinical characteristics in both treatment arms were analyzed by a Fisher's exact test. DFS was calculated from surgery to first evidence of recurrence or second primary breast cancer. OS was calculated from surgery to death. OS and DFS were calculated with the log-rank test. The Kaplan–Meier method was used to draw survival curves. The Cox proportional hazards regression model was used to determine statistically significant variables related to survival. Differences were assumed to be significant when p value of less than 0.05.

Results

PATIENT CHARACTERISTICS

Between June1991 and May 2012, 184 patients with breast cancer were enrolled in this study. Overall, 184 patients [age range, 70-88 years]; median age, 74.0 years were included in the this multicenter retrospective study, of which 95 were aged 70 to 74 years at diagnosis (51. 6%; median age, 72.0 years), 55 were aged 75 to 79

years (29.9%; median age, 76 years), and 34 were aged 80 years or older (18.5 %; median age, 82 years). The median time of follow-up in 184 patients was 29,5 (1-252) months. Patients had smaller tumors at diagnosis, only 16.9% of patients had tumors larger than 5 cm. The number of patients who had DM at diagnosis was 71 (38.6%). Fifty-four patients (29.3%) had HT at diagnosis. The tumors of the elderly patients were more frequently ER positive (92.9%), PR positive (79.9%), and c-erbB2 negative (65.8%). Rate of patients with 1-3 positive nodes was more common (60.9%). The patients' baseline characteristics are listed in Table I.

PROGNOSTIC FACTOR ANALYSIS

The results of univariate analysis for OS are summarized in Table II. Among the eleven variables of univariate analysis, four variables were identified to have prognostic significance: T (p=0.02), N (p=0.03), LNR (p=0.001) and ER (p=0.002).

The results of univariate analysis for DFS are summarized in Table III. Among the eleven variables of univariate analysis, two variables were identified to have prognostic significance: N (p =0.05) and LNR (p=0.02). Multivariate analysis included the prognostic significance factors in univariate analysis. The results of multivariate analysis are shown in Table IV. Multivariate analysis by Cox proportional hazard model showed that T, LNR (Fig. 1) and ER were considered independent prognostic factors for OS (p 0,03, p=0.002 and p=0.02, respectively). Furthermore, LNR was considered independent prognostic factors for DFS (p 0.01) (Fig. 2).

TABLE I - *Characteristics of patients*

Characteristic	No	(%)
Enrolled patients	620	
Sex		
Male	8	4.3
Female	176	95.7
Median age, years	74.0	(70-88)
Age		
70-74	95	51.6
75-79	55	29.9
≥80	34	18.5
PS (%)		
0-1	137	74.5
2-3	17	9.2
Unknown	30	16.3
Pathologic tumor size, mm		
<50	150	81.5
≥50	72	16.9
Unknown	3	1.6
No. of positive nodes		
1-3	112	60.9
≥4	72	39.1
Estrogen receptors		
Positive	171	92.9
Negative	9	4.9
Unknown	4	2.2
Progesterone receptors		
Positive	147	79.9
Negative	31	16.8
Unknown	6	3.3
c-erbB2		
Positive	47	25.5
Negative	121	65.8
Unknown	5	7.6
Grade		
Well	21	11.4
Moderate	90	48.9
Poor	54	29.4
Unknown	19	10.3
DM		
Yes	71	38. 6
No	108	58. 7
Unknown	5	2. 7
HT		
Yes	54	29.3
No	125	67.9
Unknown	5	2.7

TABLE II - *Univariate analysis of OS by categorical variable*

Variables	Log-rank	Degrees of freedom	p-value
Age	1.57	1	0.20
Performance status	0.11	1	0.73
DM	0.11	1	0.73
HT	0.004	1	0.94
Grade	2.79	1	0.09
T	5.02	1	0.02
N	4.68	1	0.03
LNR	20.48	2	0.001
ER	9.40	1	0.002
PR	0.96	1	0.32
c-erbB2	2.16	1	0.33

TABLE III - *Univariate analysis of DFS*

Prognostic factors	OR	95% CI	p-value
Age	0.03	1	0.85
Performance status	2.72	1	0.09
DM	0.44	1	0.50
HT	0.15	1	0.69
Grade	2.79	1	0.09
T	0.01	1	0.90
N	3.55	1	0.05
LNR	7.27	2	0.02
ER	3.36	1	0.06
PR	3.49	1	0.06
c-erbB2	4.84	1	0.08

TABLE IV - *Multivariate Analysis of Prognostic Factors*

Factors	OR	%95 CI	p value
PFS			
N	1.02	0.27-3.72	0.97
LNR	3.58	1.13-9.84	0.01
OS			
N	0.66	0.11-3.91	0.65
T	3.33	1.11-9.97	0.03
LNR	5.86	1.94-17.73	0.002
ER	5.42	1.30-22.63	0.02

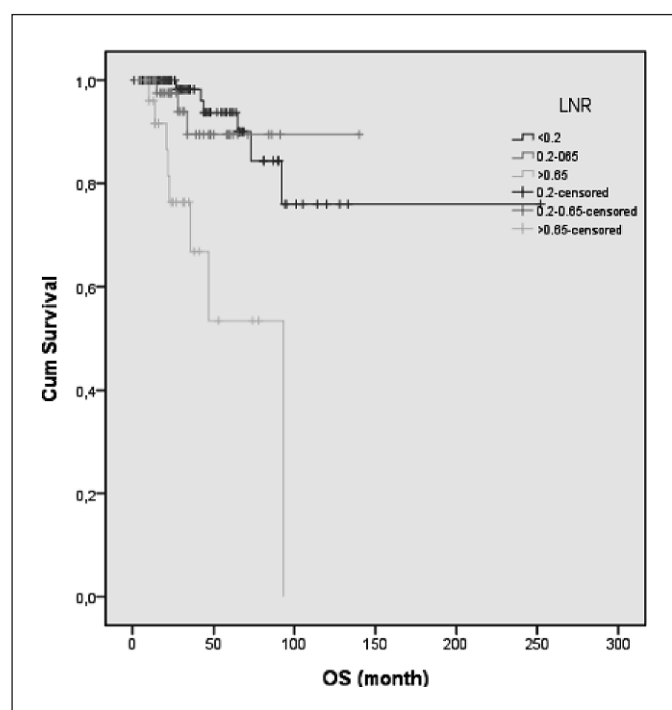Fig. 2: DFS of patients according to LNR.

Fig. 1: OS of patients according to LNR.

Discussion

Due to the fact that the aging one of the major risk factors for breast cancer, more than 30% of breast cancer occurs in women >70 years of age. Besides, aging causes physiologic changes in organ function and drug pharmacokinetics, which can result in reduced therapeutic benefit of chemotherapy. Thus, in older individuals breast cancer is commonly undertreated.

Furthermore elderly patients with over 70 years of age have generally been excluded from randomized clinical trials of breast cancer treatments [1-3]. For this reason, breast cancer in elderly patients is a progressively widespread problem faced by the oncologist.

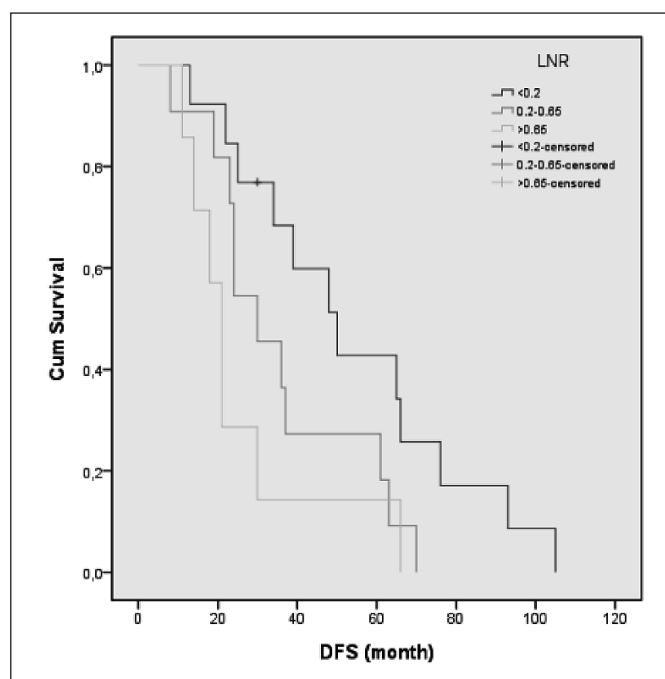Previously many authors showed that the presence of axillary lymph node metastasis and the number of involved axillary lymph nodes were the most important prognostic factors in breast cancer [4,5]. According to the current 7th edition of AJCC staging system, N stage in breast cancer is merely defined by the number of positive nodes; pN1 defined as 1 to 3 positive axillary nodes, pN2 as four to nine positive axillary lymph nodes, and pN3 as ten or more positive axillary lymph nodes [7]. Owing to the fact that the number of involved lymph nodes identified depends on the surgical and pathologic procedure, in patients with inappropriately dissected axillary nodes may be received inadequate treatment. Several studies have now demonstrated that the LNR, defined as the number of involved lymph nodes divided by the number of lymph nodes removed, as a superior indicator of axillary tumor burden to the number of excised nodes [16-26]. In addition to the prognostic value of NR for DFS and OS are supported by several studies [17,22,24]. Although there are many studies about the importance of LNR, patients older than 70 years were not evaluated according to age strata in a majority of these previus studies. Therefore, about the prognostic value of LNR on the survival of elderly patients is limited. The current study demonstrated that suggest that LNR is a stronger prognostic factor for DFS and OS than the involved axillary lymph nodes in elderly patients receiving adjuvant treatments.

The most common presentation of breast cancer in postmenopausal elderly women is an ER+ that are predictive factors of response to hormonal treatments. The association between patient survival and the positivity and level of ER expression was reported by previous

authors [27,28]. Contrary to this, the study of Liu et al.[29] no observed this relationship between ER status and survival. The ER status was found to be an independent prognostic factor of OS, while had no significant effect for DFS in our study.

Several studies in recent years found that breast cancer with elderly patients are more to present with larger tumors. In addition to T was an established prognostic factor on survival in elderly patients receiving adjuvant treatments [24,29,30]. Similarly, T was found as independent prognostic factor for survival.

The present study has some limitations. Firstly, it was retrospective in nature; secondly; the median time of follow-up in 184 patients was shorter than other studies; thirdly, molecular characteristics of the tumor were not evaluated; and fourthly, the number of the patients included was rather small.

In conclusion, the LNR was associated with the prognostic importance for DFS and OS in elderly patients who were administered adjuvant treatments. It may be concluded that these findings may also facilitate pretreatment prediction of survival and can be used for selecting patients for the correct choice of treatment.

Riassunto

Molti studi hanno finora dimostrato che il rapporto linfonodale (LNR) è migliore indicatore del carico neoplastico ascellare rispetto al numero dei linfonodi asportati. Lo scopo di questo studio retrospettivo multicentrico è quello di valutare il valore prognostico del LNR nelle pazienti anziane affette da nodulo neoplastico della mammella.

Nello studio retrospettivo sono state inserite 184 pazienti con cancro operabile della mammella, reclutate presso 17 istituzioni, e sono state scelte per l'analisi 18 potenziali variabili prognostiche. Sono state condotte analisi univariate e multivariate per identificare i fattori prognostici associati con la sopravvivenza.

Tra le undici vatiabili dell'analisi univariata sono state identificate quattro variabili di significato prognostico per la sopravvivenza globale (OS): dimensioni del tumore (T), numero di linfonodi positivi (N), rapporto linfonodale (LNR) e positività dei recettore per gli estrogeni (ER). Tra le undici variabili dell'analisi univariata sono state identificate due variabili di significato prognostico riguardo alla sopravvivenza priva di malattia (DFS): N e LNR.

L'analisi multivariata secondo il modello proporzionale di rischio secondo Cox ha dimostrato che T, LNR e ER sono fattori prognostici indipendenti per la OS. Inoltre la LNR è stata considerata fattore prognostico indipendente del DFS.

In conclusione la LNR è risultata associata con l'importanza diagnsotica per la DFS e la OS nelle pazienti anziane cui erano stati somministrati trattamenti adiuvanti.

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