Correlation of Lymph Node Density and Recurrence in Carcinoma Penis: A Perspective on Optimal Management and Unmet Needs from a Tertiary Care Centre

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Received: 13 December 2017 Accepted: 1 January 2018 Published: 15 January 2018

Abstract

Introduction: Penile carcinoma is a devastating urological neoplasm in which the most assertive prognostic variable is the presence of lymph node involvement. Multiple studies in the current literature have shown that the number of positive lymph nodes predict recurrence free survival (RFS) and overall survival (OS). The objective of this present retrospective analysis is to authenticate the use of LND as a predictor of RFS and OS after ILND. Methods: Our institutional penile cancer database was analyzed for patients who underwent ILND from January 2000 to May 2008. Survival analysis was performed using the Kaplan-Meier method to determine RFS and OS. Two-sided p values <0.05 were considered significant. Results: Patients with complete follow up (n=33) were analyzed for clinico-pathological characteristics. LND?40

Index terms— inguinal lymph node dissection, lymph node density, squamous cell carcinoma penis, overall survival, recurrence free survival, penectomy.

1 I. Introduction

quamous cell penile carcinoma is a belligerent urological neoplasm in which the most assertive prognostic variable is the presence and expanse of lymph node involvement. Therefore, inguinal lymph node dissection (ILND) as a marker of pathological staging is an undeniable fact in the present scenario of uncompromising oncological efficacy. ILND guides adjuvant therapy and offers therapeutic benefit . [1,2,3] Currently prognostication of patients with inguinal and pelvic lymph node involvement is based on TNM staging which distributes the patients into 3 different categories based on: 1) the number of positive lymph nodes; 2) the location of positive lymph nodes; and 3) the presence of extranodal extension. [4,5] When defined initially, the staging criterion was remarkably inconspicuous for providing details about the span and plenum of lymphadenectomy. [6] Multiple studies in the current literature have shown that the number positive lymph nodes predicts RFS and OS. [7,8] These studies on the other hand did not account for the span of ILND done, blurring the real extent of lymph node involvement. The lymph node ratio has been defined as the ratio of positive lymph nodes to the total number of lymph nodes isolated, incorporating both a marker of extend of lymph node dissection and the nodal disease load in a single quantitative variable. Role of LND has been proven beyond any doubt in the management of MIBC [9,10] but the extrapolation of same in patients with squamous cell penile cancer has not been extensively researched upon; to our knowledge currently there is paucity of literature and lack of RCT's with sufficient evidence strength in this part of the world (NE part of India). Additionally there has been a significant disagreement in accurate LND cut off for differentiating poor versus favorable survivability ranging from 6.7-33 %. [11][12][13][14] The incoherence may be explained by a significant variation in the total number of LN removed in past series, as well as different statistical models used to achieve the cutoff value. The wide array of LN removed from pelvic lymph node stations in addition to the inguinal lymph nodes and simultaneous S addition of these positive lymph

nodes in calculating LND skewed the LND calculation. The objective of this present retrospective analysis was to authenticate the use of LND as a predictor of RFS and OS after ILND. We equate our results and analysis with the recent studies in different parts of the world in an effort to validate the variation in cutoff LND and identify how different histopathological and biochemical parameters and statistical rationales affected the results.

2 II. Methods

Our institutional penile cancer database was analyzed for patients who underwent ILND (n=33) in a period between January 2005 to May 2013. Clinical and pathologic characteristics including LND and total number of positive lymph nodes (LNs) were analyzed to determine impact on recurrence free survival (RFS) and overall survival (OS). LND or the percent of positive LN out of total LN's, was calculated as both a continuous and categorical variable at varying thresholds. Demographic and pathologic variables were examined to determine impact on RFS and OS. LND categories were defined using the minimum p value approach according to Mazumdar and Glassman analysis [15] to determine the most significant threshold. Patients underwent bilateral modified templates ILND in all cases. In patients with non-palpable nodes, a superficial dissection above the fascia lata was performed. In cases with palpable lymphadenopathy a deep dissection (below fascia lata) was performed. All lymph nodes were completely embedded prior to pathologist analysis. All specimens were reviewed by senior urological pathologist for issues relating to grade, stage and margins. Descriptive statistics were used to summarize patient characteristics and pathologic features. Continuous variables were compared with the Fisher's exact tests and categorical variables with the chi-square test. Survival analysis was performed using the Kaplan-Meier method to determine RFS. The log rank test was used to compare survival curves. Overall survivals (OS) was calculated from the date of surgery to death from any cause or last follow up. RFS was calculated from the date of surgery to local or distant recurrence or death from cancer. All patients were prescribed a follow-up regimen based on the National Comprehensive Cancer Network guidelines with physical exam every 3-6 months, depending on nodal stage. All statistical analysis was performed with SPSS version 21.Two-sided p values <0.05 were considered significant.

3 III. Results

Thirty three patents (median age 43±12.28 yrs) with complete follow up (median follow up of 64±22.02 months) were analyzed for clinicopathological characteristics. Maximum number of cases were seen in the age group of 41 to 50 yrs (n=13, 39.4%) followed by 31 to 40 yrs age group (n=8, 24.2%).The median age was 44±10.26 yrs in the Group A (LND<40%) as compared to 42±14.56 yrs in the group B (LND?40%) and was found to be significant in the final analysis (t=2.34, p=.007). History of multiple sexual partners was maximally present in LND sub group of .31 to .40 (n=5, chi square coefficient=6.46, p=.263). This result was not significantly associated with the same (Pearson's R=.269, p=.129). Phimosis was mostly seen in the LND subgroup of .31 to .40 (n=7, chi square coefficient=10.05, p=.034, Pearson's R=.363, p=.038). Pathological stage was pT2 in 17 cases (51.5%), high grade T1 in 9 cases (27.3%) and pT3 in 7 cases (21.21%). Tumor grade was 5 (15.15%) in G1, 15 (45.45%) in G2 and 13 (39.39%) in G3. Complete blood analysis was analyzed in both the groups with a NLR ratio of 1.8 vis a vis 3.3 in the 2 groups and the higher values being associated with lower RFS (p.009). This result echoed the analysis of a recent study completed in 2016 which showed a high NLR (?2.82) to be associated with significantly poor CSS (p=.023) than those with a low NLR (Increased neutrophil-tolymphocyte ratio is associated with disease-specific mortality in patients with penile cancer. [16] None of the patients undergoing ILND had fixed LN's on physical examination and also none of the patients in the study underwent neo adjuvant chemotherapy. Overall 13 (39.39%) patients underwent partial penectomy and 20 (60.61%) patients underwent total penectomy. Primary tumor area (measured in CECT W/A & pelvis) in the group A and B were comparable but not found to be significant in the final analysis (p=.335). LND threshold was calculated and patients were further analyzed into two groups of LND<40% and LND?40%. Lymph node area (measured in CECT abdomen pelvis) was calculated (Table 1) in the group A and B but was not found to be significant in the final analysis (p=.597). Phimosis, T stage, recurrence and LVI were the significantly associated (Table 2) categorical variables along with significant correlation coefficients. On the other end of the spectrum were age, N/C ratio, total and positive no. of LN's (Table 1) extracted which were again significantly associated with the LND groups. LND threshold was calculated and further analyzed into two groups of LND<40% and LND?40%. Maximum number of cases with recurrence was seen in LND?40% (n=6) and was seen in only 2 cases with LND<40%. LVI was significantly associated and correlated with LND ? 40% and was one of the factors determining recurrence. The median (IQR) LN yield in the Group A was 16.5 (12.5-21.75) and 22 (13.5-23.50) respectively and was found to be significant in final analysis (p=.032). Similarly the median positive (IQR) LN yield in the Group A was 2.5 (1-3.75) and 8 (5-10) respectively which was significant at the same time (p=.021). Detailed pathological examination of positive LN's showed the presence of ENE (extra nodal extension) in 16 (48.48%) patients. This interpretation vehemently changed pathological staging, leading to a migration from lower pN1 categories to higher pN3 category. pN1, pN2 and pN3 disease was observed in 26 (21.21%), 10 (30.30%), and 16 (48.48%) patients, respectively according to the AJCC 8th edition. After stratification according to LND, 5 year CSS rate was 79.1% in patients with LNR<40% vs 31.9 in patients with LNR?40% (log-rank test: $p<0.001$). In univariable Cox regression models, continuously coded (95% CI: 1.03-1.07; p=0.003) but categorically coded LND (95% CI:

2.80-7.48; p<0.51) was significant predictors of CSS (Figure **??**). Furthermore, in multivariable Cox regression analysis, categorically coded LNR was found to be an independent predictor of CSS (p?0.001). Patients with a LND?40% had from a 2.51-to a 4.08-fold higher probability of dying from their disease compared with patients with a LNR<40%. The inclusion of categorically coded LND in multivariable analysis led to the highest predictive accuracy. Leaving aside the strict prognostic paradigm, we also investigated the most useful LND mark that may help the urologist to patients at various degree of recurrence, in order to contemplate adjuvant management after ILND; nonetheless, the limited number of cases prevented us from achieving a threshold that could efficiently distinguish between cases with low probability of recurrence and that at higher risk of disease related events. For instance, a LNR threshold of 15% allowed us to divide patients into two groups, where 5-year RFS rates of 86% and 44% were associated with a LND <15% and ?15%, respectively. Nonetheless, this effort did not reach significance (p=0.073). LND?40% was significantly predictive of recurrence free survival (Log Rank via Mantle Cox) value: 13.609, p=.0005). RFS was significantly lower for patients with LND?40% (mean survival: 46.22 month vs. 85.79 months, p=.0001, Figure 1). Likewise, overall survival was lower in patients with LND?40% but it did not reach significant level (mean survival: 72.48 month vs. 85.30 months, p=.246, Figure **??**). Actuarial 5 year RFS for the entire group was 75.75% while the actuarial 5 year overall survival for the same group was 84.85%. 5-year DSS in patients with LND of 6.7% or less was 91.7%, while only 23.3% in those with LNR greater than 6.7%. LND stratified 5 Yr RFS 33.3% (LND?40%) Vs 91.7% (LND<40%).

4 IV. Discussion

Loco-regional spread in the inguinal lymph nodes is the most prognostic factor for survival in penile cancer. [17,18,19] In this contemporary study, we showed that the LND could muster a role of prognostic criterion in the present population of surgically managed patients with carcinoma penis and LNM. Recently, LND emanated as the only independent predictor of CSS, with a favorable prognostic ability as compared to the 6th and 7th TNM staging systems. This signifies the fact that LND encompasses tumor burden (number of positive lymph nodes) and the extent of ILND (number of lymph nodes removed) into a single variable. Thus, besides tumor volume, LND can be considered as a marker of surgical efficacy. The LND may be a significant marker of survival both as a categorically and a continuously coded variable. In the current retrospective study, we corroborate the observation that LND is a predictor of worse outcome. Previous studies have proved that LND levels varied widely in the cutoff used to stratify worse prognosis. Present study identified that a LND ? 40% was associated with worse outcome. The analysis further validated the role of LND use as a prognostic tool for predicting recurrence free survival thus validating LND role for clinical purpose. More significantly, we found that continuously coded LND, age, total number of positive LN removed and total number of LN removed outperformed categorically coded LND, phimosis and MSP in multivariate Cox proportional hazard model for RFS. Lymph node burden, representing the total number of positive LN has shown to be associated with worse prognosis in multiple previous studies. Pandey et al. identified a 75.6%, 8.4%, and 0%, 5-year survival with patients who had 1-3, 4-5, and >5 nodes, respectively. [20] Nevertheless, in this study we did find an association between total positive nodes and total number of LN's removed with RFS but not with OS. Likewise in other solid tumors, LND has been proved to be a superior prognostic tool than LN number for carcinoma penis. [21][22][23] Literature investigating LND has identified a survival cutoff, which has ranged widely from 6.7%-33% to classify favorable versus poor prognosis. Our values slightly exceed the previous cutoff values and show RFS was significantly worse with LND ?40%. Our results echoed the work of Li et al. and Lughezzani et al. that identified LND cutoffs of 16% and 22%, respectively, to differentiate poor versus favorable prognosis. Li and his analysis on 71 node positive cases projected that the 16% LND mark separated a 5-year disease-specific survival (DSS) of 81.2% and 24.4% which in multivariate analysis was also independently associated with worse DSS with a HR of 4.31. These outcomes are similar to our 5-year RFS outcomes of 91.7% for patients with LND <40 % vs 33.7% for patients with LND ?40%. Likewise, Lughezzani and team singled out on multivariate analysis that patients with LND ?22% had a 4.55-fold worse CSS. These studies matched our HR of 5.5 for RFS in our multivariate analysis when using a LND ?40%. Interestingly, a higher LN threshold of ? 40% was not associated with significant OS in our study, but this was likely due to the small number of patients with LND ?40% (n=9). A recent survey investigated the role of LND as a marker of survival, suggesting that its prognostic competence may be superior then the TNM staging system. [24] Nevertheless their analysis stem from a small patient population (n=45) with lymph nodepositive carcinoma penis. The authors applied the median LND to stratify survival results but it is not the most correct method to determine a bench mark for clinical analysis. Recently a study validated the prognostic role of the LND in a medium sized population of 60 patients with carcinoma penis treated between 1990 and 2008, using RFS as their primary endpoint. [25] The authors predicted that 7th TNM staging system and LND were the most accurate models and that it significantly differed from TNM criteria alone when compared with the previous models. To our misfortune, the limited number of patients included in the present analysis bars us from determining an additional threshold to significantly distinguish between patients with very low 5-year overall survival rates and individuals at higher risk of disease-related events. Another recent study, using patients from the SEER database, calculated a LND intersect of 33%, but a significant proportion of their cases had insufficient ILND. While their median lymph nodes removed (16 LN) was slightly greater than ours (22 LN, including both groups), the IQR of 13.5 to 23.50 LN highlighted the adequacy of ILND which would validate LND calculations as well as supplement survival statistics. In patients with bulky disease, nodes can be conjoined and an accurate estimation cannot be

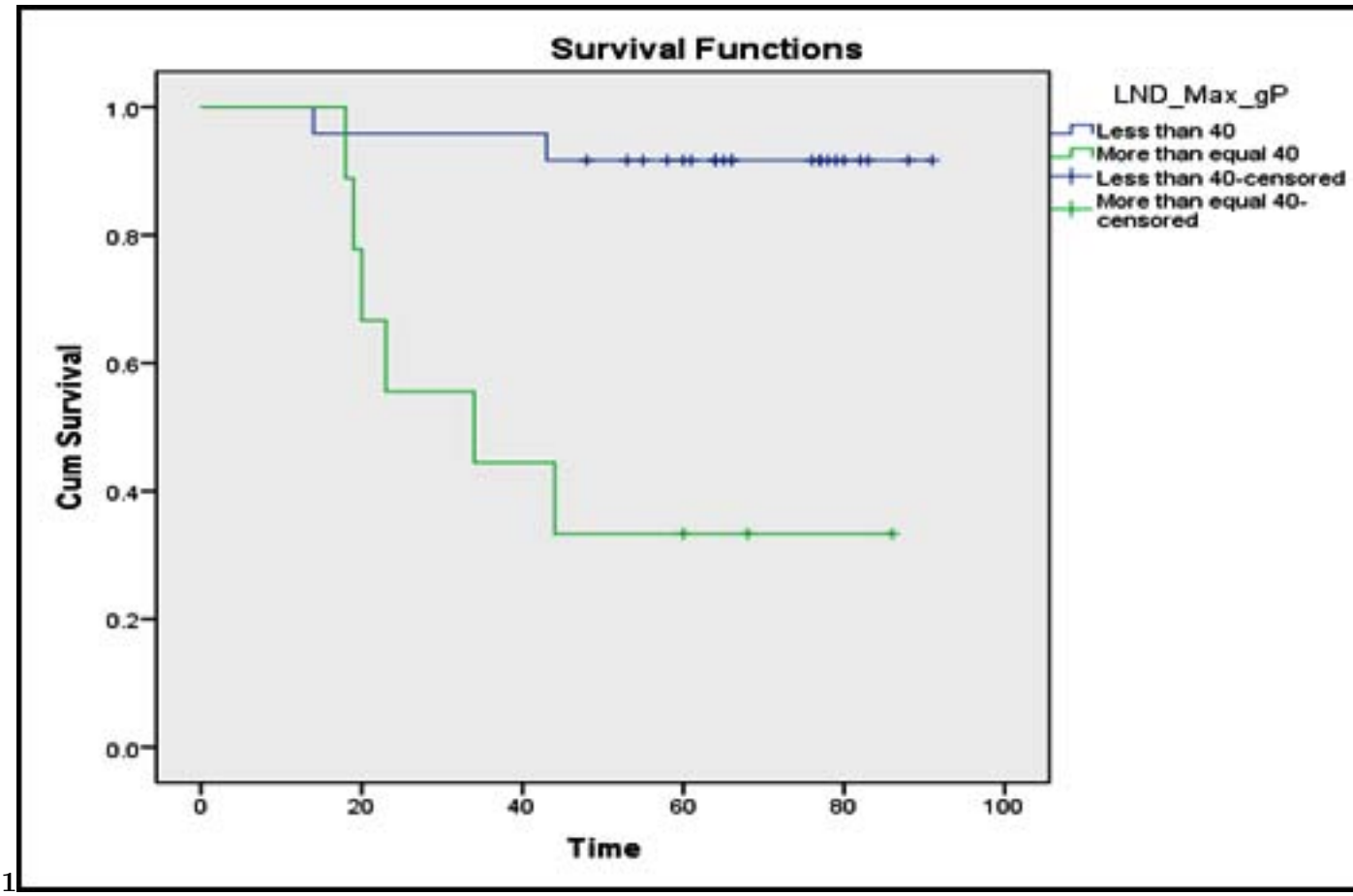
made out so our study group did not include any case with matted nodes that could affect our analysis. As per our results, a LND threshold of 40% provided the most precise discrimination of the aftereffect of patients with lymph node positive carcinoma penis. Specifically, the 5-year CSS rates was 77.3% in LND <40 % vs 33.9 % in patients with LNR ?40% (p<0.01). In the aftermath of recent analysis we discovered some limitations that may have affected the present study. Although our series (n=33) effectively compares with the two previous studies on carcinoma penis, we must recognize that our numbers remain relatively small, which may limit the prognostic significance of our findings.

A few non RCT's have reported on the efficacy of multidrug chemotherapy in advanced carcinoma penis. [26,27] Recently, a 10% complete pathological remission rate has been reported in a study with carcinoma penis undergoing neoadjuvant treatment. [28] These observations support the use of chemotherapy in patients with high disease burden. However, the potential curative intent of chemotherapy has not been validated and RCT's are required to ascertain the effect of chemotherapy in delaying disease advancement. Our study was constrained by the retrospective model as well as the small size of our patient pool and may limit the prognostic implication of our analysis. The extent of patients undergoing ILND represents another catch in the management of carcinoma penis. A more extended ILND increases the number of lymph node yield and a wide spectrum ILND may affect the LND, although the curative footprint of pelvic lymph node dissection is still debatable. In addition, we relied on a single genitourinary pathologist who examined all lymph node specimens which may be source of bias.

5 V. Conclusion

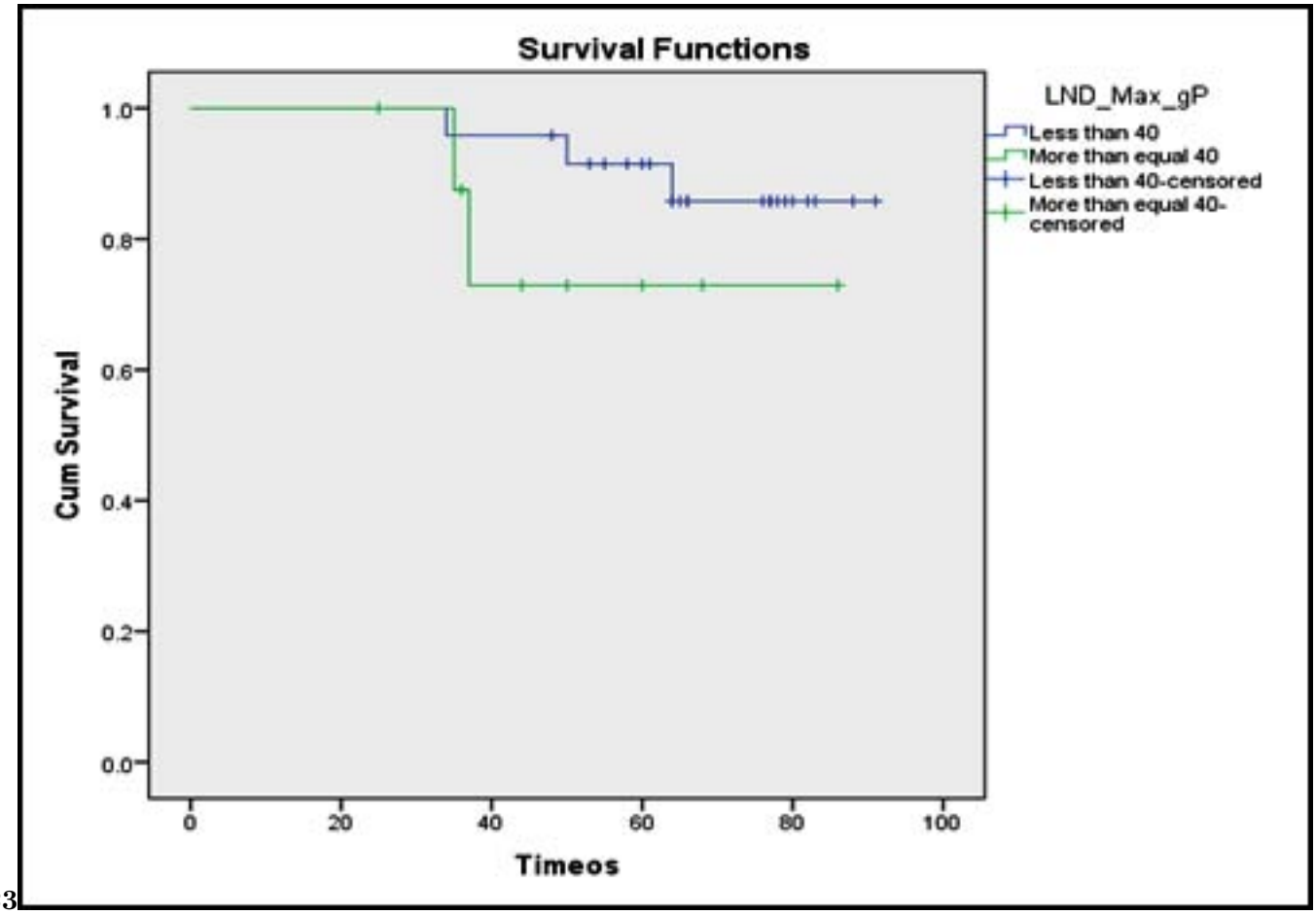
The evolving treatment of carcinoma penis may change the prognostic significance of our LND cutoff, and additional studies are needed to validate this finding in other cohorts. The present retrospective analysis represents the largest single-institutional attempt to validate the prognostic value of the LND in patients with squamous cell carcinoma penis. It's an endeavor to discover optimal mechanisms for the management of patients with LN metastasis with carcinoma penis. Although our analysis awaits independent validation, it supports the use of the LND in clinical practice as an accurate prognostic factor. As the final target should be the individualization of therapy according to risk stratification in patients with LND from penile cancer undergoing radical surgery, we still need to identify and validate further accurate and clinically useful prognostic parameters. We propose that optimal cutoff point for LND and its prognostic significance can be confirmed by multivariate analysis. Furthermore LND and contemporary TNM staging have emerged as a powerful predictive factor for RFS but there is still an unmet need to identify further accurate and clinically useful prognostic parameters. [1]

[1]Correlation of Lymph Node Density and Recurrence in Carcinoma Penis: A Perspective on Optimal Management and Unmet Needs from a Tertiary Care Centre



1

Figure 1: Fig. 1 :



23

Figure 2: Fig. 2 :Fig. 3 :

1

Figure 3: Table 1 :

2

Variable	Chi square Coefficient	P value	Pearson R	P value	<40%/?40% + Cases / Total
Phimosis	4.416	.042	.354	.043	12 / 24 ; 8 / 9
MSP	.733	.392	.149	.408	Non Sig.
CECT (N)	3.417	.065	.322	.068	Non Sig.
CECT (E)	2.068	.150	.250	.160	Non Sig.
Recurrence	12.128	.001	.606	.001	2/24 ; 6/9
T Stage	6.563	.038	.446	.009	9 / 12 / 13; 0 / 5 / 4
Grade	.416	.519	.112	.534	Non Sig.
LVI	6.694	.018	.686	.017	6 / 24 ; 7 / 9
PNI	1.354	.245	.203	.258	Non Sig.

Figure 4: Table 2 :

3

In multivariate Cox regression
model continuously coded variable age (omnibus
coefficient value: 1.108, 95% CI: 1.004-1.223; p=.041,
Figure 3), no. of positive lymph nodes removed
(omnibus coefficient value: 3.681, 95% CI: 1.198-11.311;
p=.023), total no. of lymph nodes removed (omnibus
coefficient value: 0.438, 95% CI: 0.226-0.849); p=.014)
were significant predictors of RFS.

Figure 5: Table 3 :

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