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Nomogram Predicting Survival After Resection of Non-Functioning Neuroendocrine Tumors of the Pancreas Based on SEER Data

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1. Abstract

1.1. Background: Although Pancreatic Neuroendocrine Tumors (PNETs) are a rare form of pancreatic tumor, their incidence is on the rise. Overall survival for these patients strongly correlates to the stage at diagnosis. Other prognostic factors that may impact on survival include tumor grade and lymph node metastases. The aim of this study was to construct a prognostic nomogram to estimate individual 5-year survival for patients with resected nonfunctioning PNETs with no distant metastases.

1.2. Methods: A search of the SEER 18 database (November 2017 release) was performed for neuroendocrine tumors of the pancreas in adult patients who were diagnosed between 2004 and 2014. Patients with functional tumors or those who had incomplete data were excluded from the study. The TNM staging was performed according to the Eighth edition of the AJCC. A nomogram was constructed to predict individual patient's survival.

1.3. Results: There were 4613 patients identified as potentially eligible for the study, but complete data was only available for 1046 patients (22.7%). Patients were between 39-93 years old with 70% of patients having T2 or T3 disease at time of diagnosis. Increasing tumor grade and stage, as well as age, were inversely proportional to survival over time. Nodal stage did not seem to influence cumulative survival, and the overall survival over time for males was less than that of females.

1.4. Conclusion: This study shows a simple nomogram for prediction of long term survival of patients with resected nonfunctioning non-metastatic pancreatic neuroendocrine tumors based on age, tumor grade and T stage.

2. Introduction

United states statistics shows that pancreatic neuroendocrine tumors (PNETS) represent 1-5% of all solid pancreatic tumors with reported annual incidence of (PNETs) of 2.2 per 1 000 000; 1.4 times more common in males than females [1]. The incidence of theses neoplasms increases with advancing age, particularly in the last few decades [2,3]; which could be explained by increased use of cross-sectional imaging in medical practice.

Reports of autopsy series shows higher incidence of PNETS that ranges from 0.8% to 10% in some series, these lesions are totally incidental and may have no clinical significance [4-5]. Functional tumors that secret any hormones of clinical importance are symptomatic even in small lesions due to the clinical syndrome associated with them such as hypo-glycaemia with insulin secreting tumors and peptic ulceration with gastrinomas, the biology of these lesions is likely to be different from non-functional tumors [6]. There is increasing evidence to suggest that PNETs arise from pluripotent cells in pancreatic ductal epithelium [7], almost 10% of these tumors are associated with a familial endocrine neoplasia syndrome such as MEN-1, Von Hippel- Lindau diseases and MEN2 [8-9] these tumors tend to be functional. Nonfunctional PNETs are more prevalent type and constitutes 70-90% of PNETS; although they do not produce syndromes of hormonal excess, the biology is variable; while some remain dormant and do not progress; they can grow in size and invade normal tissue and metastasize to other organs commonly liver, lungs and bone [9]. They are often detected incidentally on imaging or when they become symptomatic as a result of continuing growth and invasion commonly leads to pancreatitis.

The primary treatment of PNETs is surgical resection for pancreas localized disease and in a select group with liver metastases when the bulk of the tumor can be extirpated by 90-95% [4, 10-11]. The behavior of these neoplasms can be diverse, ranging from a long indolent course particularly lesions less than 2 cm in maximal dimension or more aggressive course with potential for local invasion and distant metastases [12]. Surgical resection is the only known therapeutic approach to cure PNETs or provide benefit for long term survival the reported median overall survival (OS) for all patients with resected PNETs is 28 months, survival correlates directly to the stage at diagnosis, based on tumor size, grade and distant metastases [1]. Previous studies have shown that certain tumor features such as grade, stage, mitotic count, Ki 67 index and lymph node metastases are significant prognostic factors that affect survival [6]. The current staging system relies on the tumor-node- metastasis (TNM) staging for these tumors, but it is a relatively poor tool for predicting the long-term survival for individual patients. The WHO classification has been widely adopted as a prognostic system for PNETS more recently.

Information regarding survival and prognostic predictors of patients with PNETs are derived from single- center surgical series that may not accurately reflect the real life general population of patients with these tumors [6]. Survival of patients with PNETs seems to have increased over the time that the Surveillance, Epidemiology and End Results (SEER) registry has been collecting data [14]. Nomograms are proved method for individual patient's prognosis and survival estimation (13). Nomograms are being used more often to calculate the likelihood of prognosis for individual patients on known clinic-pathological prognostic parameters [15]. The SEER database currently collects information relating to cancer incidence and survival from population-based cancer registries covering almost 30% of the 23 USA. The registry provides a specific code required to make the distinction between functional and nonfunctional neoplasms [16-17]. The aim of this study was to construct a prognostic nomogram to estimate individual 5-year survival for patients with resected nonfunctioning PNETs with no distant metastases.

3. Materials and Methods

A search of the SEER 18 database (November 2017 release) was performed for neuroendocrine neoplasms of the pancreas in adult patients who were diagnosed between 2004 and 2014. Only patients who had surgery with curative intent with no distant metastases (M0) were included in the analysis. Primary site and histology were coded according to the International Classification of Disease for Oncology, third edition (ICD-O-3). Patients with PNETs were identified by using a combination of ICD-O-3 codes and histopathologic codes (8246, 8240,8000, 8010, 8150-56). Functioning neoplasms and those associated with MEN syndrome were excluded from the final analysis. Data collated included age, ethnicity, surgical treatment choice of the primary lesion, tumor stage/grade/size, lymph node dissection and the number of involved lymph nodes, overall survival and whether the tumor was the final cause of death.

3.1. Statistics

Demographic features and clinical characteristics were analyzed using the two-tailed student t-test for continuous variables and Chi-squared test for categorical variables. Wald type confidence intervals were also calculated. Survival analysis was performed on patients who had complete data available; patients with incomplete data were excluded from the analysis. Descriptive analyses were performed comparing patients according to grade, stage and nodal involvement and the survival impact of those factors on survival was analyzed using the Kaplan Meir curve and log rank test. Multivariate cox proportional hazard model was verified by correlation and test of residual plots; the goodness of fit was analyzed using concordance index and the receiver operating characteristic (ROC) curve. The model was validated using bootstrapping with a 1000 bootstrap sample because of its ability to discriminate among patient outcomes and to avoid biased estimation.

A nomogram was developed based on the Cox multivariate analysis to enable the prediction of survival factors for individual patients. Patients with missing variables were excluded. Patients were randomly divided into two different cohorts (training and test) based on month of birth for testing and validation of the nomogram. 5-year disease specific survival was calculated using the Cox proportional hazard model, and the resultant nomogram was validated using the Harrell concordance index. This index is like the ROC curve but more suitable for censored data.

Disease specific survival was calculated using the Kaplan-Meier curve method. Calibration of the model was assessed by comparing the median predicted survival on the nomogram with the actual disease specific survival for all patients. This was performed by using 200 bootstrap resamples to reduce bias and to ensure model accuracy was not overstated. Survival analysis was performed using the statistical package for the social sciences (SPSS), while the nomogram was constructed using the "hdnom" package.

4. Results

In total there were 4613 patients identified as potentially eligible for the study, but complete data was only available for 1046 patients (22.7%). Patient ages at time of diagnosis ranged between 39 to 93 years old, with a median age of 63 years old. The female patient population comprised 45% of the total cohort. A large proportion of the patients had either T2 or T3 disease at time of diagnosis, with males having a higher proportion of more advanced disease (Table 1). Patients had grade 1 tumor (664,63 %), grade 2 (188), 18%, grade 3 ,194 19%. The type of surgery was 79% underwent a distal pancreatectomy, and lymph node metastases were seen in 35.9% of cases. Specimens in 32% of patients showed positive lymphovascular invasion. The median overall survival was 84 months (std. Error 2); median survival for grades 1,2 and 3 was 99, 75 and 34 months respectively ($p=<0.0001$) figure 2. The median survival for T1,T2,T3,T4

was 107, 88,76 and 50 respectively (p=<0.0001; and by nodal status for N0 and N1 was 99 and 81months (p=0.02) (Figures 1-4) but that was not significant in the multivariate analysis (Table 2). The patients included in the analysis were divided into two groups according to their month of birth. The first group was labelled the trial cohort and the second group was the test cohort; these were compared and used for validation of the nomogram. In the trial cohort, certain factors were deemed to have significant impact on overall survival (Table 2). This was achieved through performing univariate analysis, and these variables can be seen in the nomogram (Figure 6). Increasing tumor grade and stage were inversely proportional to survival over time. Nodal stage did not seem to influence cumulative survival, and the overall survival over time for males was less than that of females (Figure 4).

Survival was estimated for 5 years using the Cox proportional hazard model and the nomogram was based on the variants that were found to be significant predictors. These variables were specifically included in the nomogram. Survival curves were plotted using the Kaplan Meir curve and were compared using the Log-rank test. It was found that N stage had significant effect on survival only in stages T1 and T2 (p=0.015) but not in locally advanced stages (T3 and T4) p=0.62 in the multivariate analysis, (Table 2 and 3). The bootstrap corrected concordance index was found to be 0.74 for the trial group and 0.73 for the test group. Internal validation and calibration is shown in (Figures 6,7). The predicted estimations of survival probabilities of the resulted nomogram are closely aligned with observed survival rates. As an example, a 70 years old patient with a grade 3, T3 tumor will score 160 points on the nomogram with a 5 years survival of 5% (Figure 5).

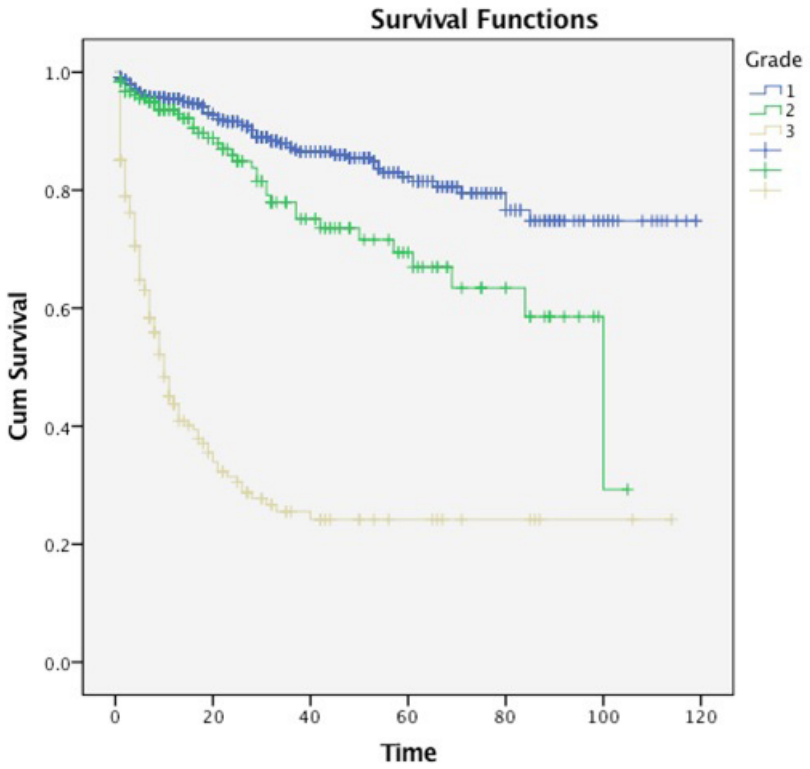

Figure 1: Survival by grade

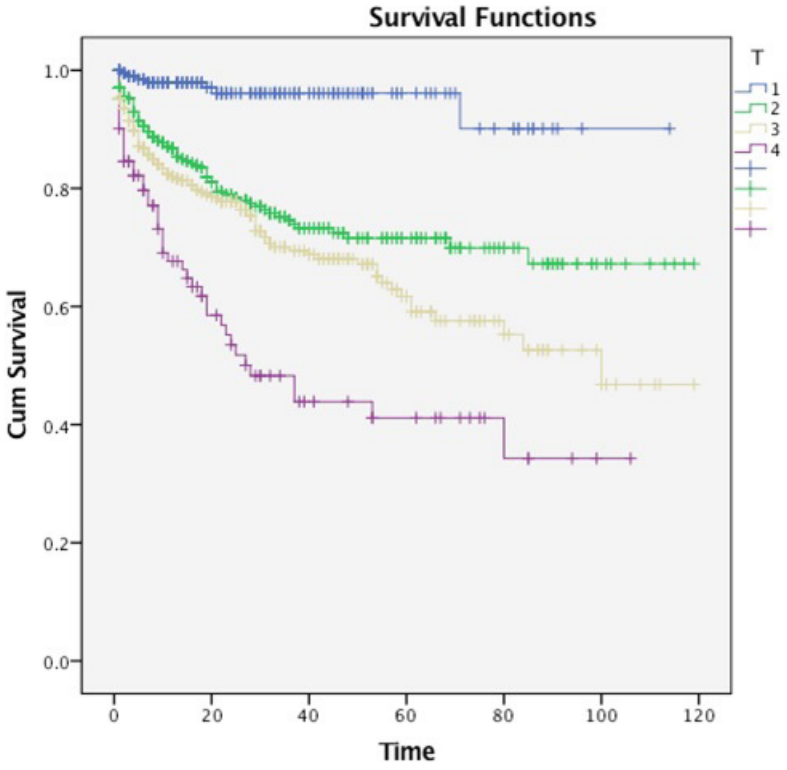

Figure 2: Survival by T stage

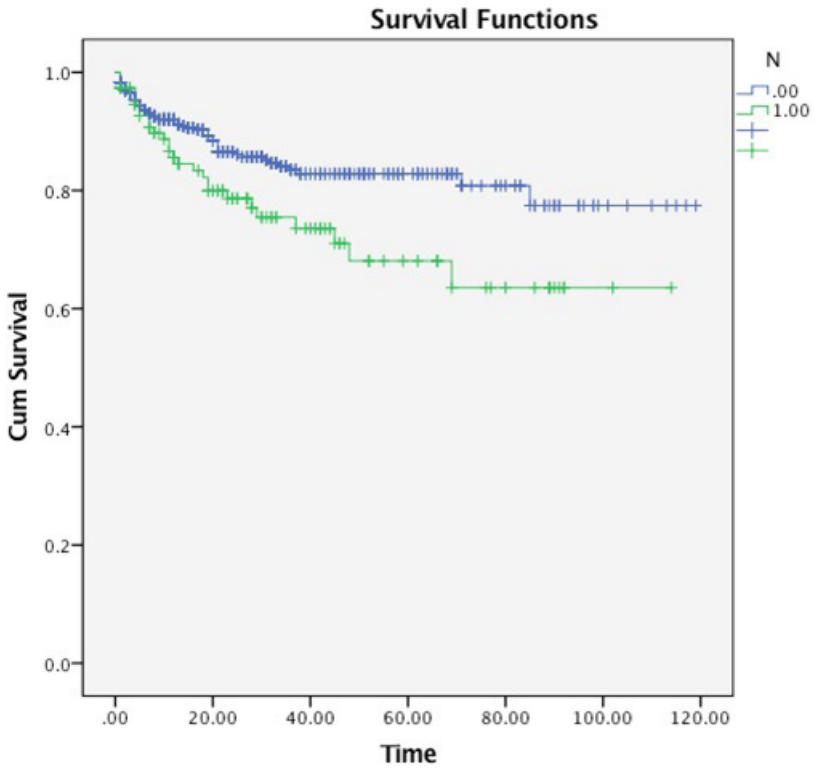

Figure 3: Survival by nodal stage

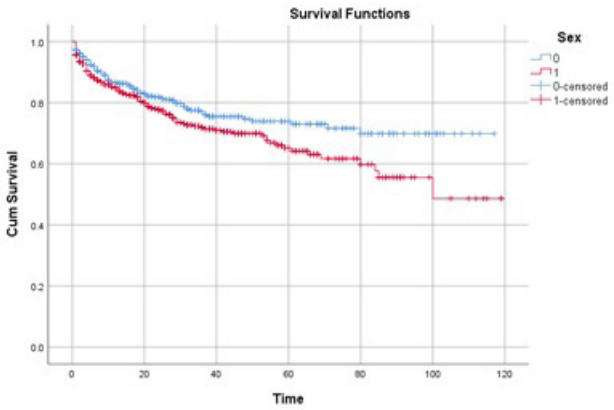

Figure 4: Survival by gender

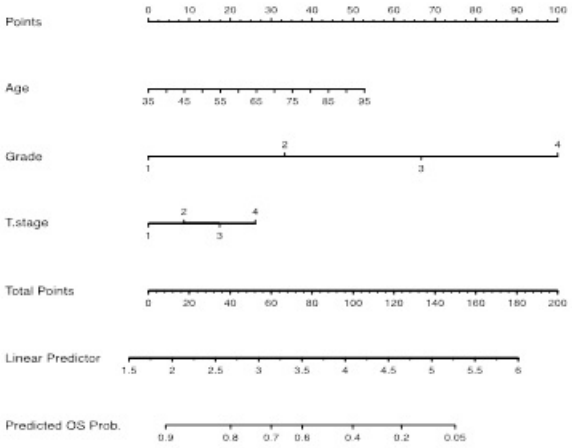

Figure 5: Nomogram including the various prognostic factors deemed to impact survival.

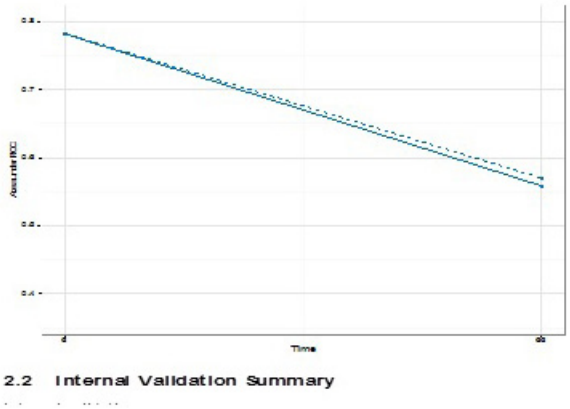

Figure 6: Internal validation of the nomogram

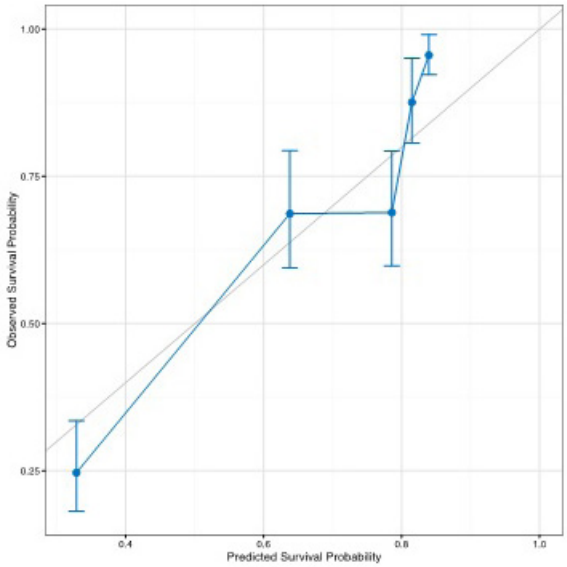

Figure 7: Internal calibration

Table 1: General demographic features, descriptive statistics of the patients included in the final analysis

Characteristics	Number	Total%
Gender		
Female	471	45% 55%
Male	575	
Total	1046	
T Stage (male:female)		
T1	216 (112:104)	
T2	366 (207:159)	20.6% 35% 35.7% 8.7%
T3	373 (207:166)	
T4	91 (49:42)	
Grade		
Grade 1	664	
Grade 2	188	63.5% 18% 14.7% 3.8%
Grade 3	194	
Type of Surgery	826	
Distal pancreatectomy (Code 30)	94	
Enucleation		79% 9% 7% 5%
Pancreaticoduodenectomy	74	
Total pancreatectomy	52	
Age		
Minimum	39	
Median	63	
Maximum	90	
N stage		
N0	670	64.1% 35.9%
N1	376	
Number of removed lymph nodes		
No nodes	251	24% 14% 62%
1-3	147	
>3	648	

Table 2: Multivariate analysis of prognostic factors

	Exp B	SE	Wald	Sig	95% CI Lower-- Upper	
Sex	.685	.137	7.608	.006	.523	.896
Grade			173.172	.000		
Grade(1)	.088	.236	105.716	.000	.056	.140
Grade(2)	.139	.264	56.084	.000	.083	.232
Grade(3)	.563	.221	6.747	.009	.365	.868
T			27.015	.000		
T(1)	.118	.419	26.000	.000	.052	.268
T(2)	.593	.203	6.612	.010	.398	.883
T(3)	.617	.188	6.632	.010	.427	.891
N	.934	.139	.237	.626	.711	1.227
Age	1.043	.007	34.303	.000	1.028	1.058

Table 3: WHO Classification of PNETS

Grade	Mitotic Count	Ki-67 index	Differentiation
Grade 1	<2/10HPF	<= 2%	Well differentiated
Grade 2	2-20/10HPF	3- 20%	Moderately differentiated
Grade 3	>20/10HPF	>20%	Poorly differentiated

5. Discussion

This study shows a simple nomogram for prediction of long term overall disease specific survival of patients with resected nonfunctioning pancreatic neuroendocrine neoplasms based on age, tumor grade and T stage. Nomograms have been shown to be more accurate than other staging systems in predicting long-term outcome for cancer patients [18]. The optimal prognostic classification of PNETs has not been well defined. The World Health Organization (WHO) has classified neuroendocrine tumors into three categories according to size, mitotic counts, and the Ki 67 proliferative index; this seems to correlate well with the risk of disease recurrence [17]. In comparison, tumor grade is assessed on histopathological tissue examination and can be readily documented. Possible limitation of using Ki 67 is the fact that there is no consensus on the optimal cutoff values that could be used for stratification of prognosis [19]. The American Joint Committee on Cancer TNM classification is the most widely used staging system in the clinical setting [20]. Tumor size and hence the T stage remains an important factor to determine the outcome of cancer surgery. DNA microarray analysis is a promising tool to differentiate between benign and malignant pancreatic neuroendocrine tumors [21]. The European Neuroendocrine Tumor Society has combined the TNM staging with mitotic numbers and Ki 67 to formulate a system that is superior to the traditional TNM classification [17]. Additional clinical and pathological variables that have been proven to have an impact on prognosis are age, gender and site of metastatic disease [22]. In this study, we found that age but not gender is a significant factor and thus was incorporated into the nomogram. Overall survival for patients decreased with increasing age, as can be seen in figure 4. Patients with distant metastases have been excluded from the study as they may represent a biologically different subset of pancreatic neuroendocrine tumors.

Previous studies have shown four variables as important prognostic factors which include Ki 67, tumor size, nodal metastases and invasion of adjacent organs. Lymph node metastases in this study was not identified as a statistically significant variable in reducing overall survival. Invasion of adjacent or nearby organs is not specifically reported in the SEER database. Neuroendocrine neoplasms rarely invade adjacent tissues, and this is only seen in locally advanced or high grade tumors. Thus, organ invasion is likely to be a surrogate of other independent prognostic factors with tumor grade being the most important [23].

Lymph nodes metastases have not been proven in this study to be a significant prognostic factor; there was minimal difference in overall survival between patients who had node negative disease compared to node positive disease. This may reflect the fact that in clinical practice the removal of lymph nodes is not consistent during surgical resections. Several previous studies have shown that lymph nodes metastases are not significant factor for long-term survival after resection of PNETS. Liver metastases have been shown to decrease survival of patients with PNETs; this correlates with the number of lymph nodes involved. With enough long-term follow-up, higher proportions of lymph node metastases would be observed to decrease disease-related survival. Adequate evaluation of number and extent of lymph node involvement is necessary in patients who undergo resection of PNETs [24].

This study is limited by the data that is not captured on the SEER database such as tumor markers (eg. Chromogranin A) and the Ki67 index. The latter has been proven to be one of the most reliable indicators of the prognosis of PNETs. In addition, parameters such as tumor grade/stage, and N stage were deficient in some patients, which reduced the number of patients in this study. These parameters if reported in future studies may prove to be useful prognostic indicators. The database also fails to capture those patients who may have developed a recurrence and subsequently received adjuvant treatment. It is not known if Somatostatin analogues (SSAs) alter the natural history and survival of PNETs, but there is evidence that they

induce anti-proliferative effects. Overall, they are unlikely to reduce tumor burden, but the disease often remains stable in patients with nonfunctional tumors. Such treatment may have improved the overall survival of PNETs [25-26]. Everolimus, a drug with immunosuppressant properties that targets the mTOR pathway, has been shown to significantly prolong progression-free survival among patients with progressive advanced pancreatic neuroendocrine tumors [11, 27-28]. The finding that lymph nodes metastases has a prognostic significance only in early stage disease (T1,T2) and has no effect on survival was unexpected but it is supported by the findings in recent report on the SEER Data [29]; Bilimora et al also found on a large cohort of patients that in the absence of distant metastases, grade and age are independent prognostic factors but nodal metastases were not [30]. These results have been reproduced in other studies [31-33].

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