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Relationships between primary tumor size, number of involved nodes and survival among 8,044 cases of Merkel cell carcinoma

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Abstract

BACKGROUND—The effects of primary tumor size on nodal involvement and of number of involved nodes on survival have not been examined in a national database of Merkel cell carcinoma.

OBJECTIVE—Analyze a retrospective cohort of MCC patients from the largest US national database to assess the relationships between these clinical parameters and survival.

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METHODS—8,044 MCC cases in the National Cancer Data Base (NCDB) were analyzed.

RESULTS—There was a 14% risk of regional nodal involvement for 0.5 cm tumors which increased to 25% for 1.7cm (median sized) tumors and to >36% for \geq 6 cm tumors. The number of involved nodes was strongly predictive of survival (0 nodes, 76% five-year relative survival; 1 node, 50%; 2 nodes, 47%; 3–5 nodes, 42%; and \geq 6 nodes, 24%; $p < 0.0001$ for trend). Younger and or male patients were more likely to undergo pathological nodal evaluation.

LIMITATIONS—NCDB does not capture disease-specific survival. Hence, relative survival was calculated by comparing overall survival to age- and sex-matched US population data.

CONCLUSION—Pathologic nodal evaluation should be considered even for patients with small primary MCC tumors. The number of involved nodes is strongly predictive of survival and may help improve prognostic accuracy and management.

Keywords

Merkel cell carcinoma; neuroendocrine carcinoma of the skin; National Cancer Data Base; prognosis; sentinel lymph node biopsy; average tumor size; nodal spread; regional node metastasis

Introduction

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer with a five-year disease-associated mortality of 46%¹. MCC is challenging to control due to its propensity for loco-regional recurrence and early microscopic spread to regional nodes and distant sites. Primary tumor size is the most commonly available prognostic factor for MCC; however its relationship with nodal disease has been controversial. One study concluded that sentinel lymph node biopsy (SLNB) is not justified for primary MCC tumors \leq 1cm in size, as they were unlikely to harbor microscopic nodal disease². Two other studies concluded that primary tumor \leq 1cm had a 24–26% risk of nodal disease^{3,4}.

The prognostic significance of number of involved regional nodes has not yet been determined for MCC. Analogous to melanoma⁵ and other cancers^{6,7}, it is plausible that an increasing number of involved nodes may be associated with an increased risk of death from MCC. To address both of these issues, we analyzed data from the National Cancer Data Base (NCDB, established in 1989 as a joint project of the American College of Surgeons and the American Cancer Society)⁸. We sought to determine whether small primary MCC tumors have a significant risk of nodal involvement and whether a larger number of involved nodes is associated with poorer survival.

Methods

All studies were performed in accordance with Helsinki principles and institutionally approved (IRB approval #6585). 10,020 cases diagnosed between January 1, 1985 and December 31, 2004 were identified from the NCDB using MCC-specific histology code 8247. 1,684 cases missing all TNM information, and 292 distant metastatic cases that lacked tumor size information were not included resulting in a cohort of 8,044 cases.

All cases with primary tumor diameter data (n=5,722) were included for tumor size analysis (Figure 1) regardless of extent of disease or presence of follow up information. NCDB recorded the primary tumor size (maximum tumor diameter by pathological or clinical report in millimeters) up to 70 mm. Larger tumors were recorded as 70mm (1% of primary MCCs).

To characterize the relationship between tumor size and nodal information (Figure 2), cases presenting with distant metastases (n=199) and patients without tumor size information (n=2,322) were eliminated from this analysis. 4,027 cases that also had nodal data were included for this analysis.

To assess the relationship between number of involved regional nodes and survival (Figure 3), we studied all patients with no metastatic disease, available follow up and regional nodal data (n=1,305).

To examine factors affecting the likelihood of pathological nodal evaluation (Figure 4), 7,845 cases who had no distant metastatic disease at diagnosis were analyzed. Differences in pathological evaluation between “younger” (<70 years) versus “older” (over 70 years) cases, and between men versus women were determined using chi square test and error bars were calculated using binomial standard error.

STATISTICAL METHODS

NCDB does not record the cause of death for the cases it tracks. Given that the median age of diagnosis for MCC is 76, deaths among this cohort will often be due to age-associated non-MCC causes. To adjust for decreased survival associated with advanced age and sex in this cohort, we used a “proportional excess hazard model⁹” to analyze survival relative to age- and sex-matched population data from the Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/data/statab/lewk3_2003.pdf). This approach assesses the expected survival for the cohort (based on age and sex) and thereby determines the “excess” risk of death that is associated with MCC beyond that attributable to the patient’s age and sex (Lemos et al and Dickman et al^{1,9}). The overall survival used an unadjusted proportional hazards model. SAS software (SAS Institute Inc, Cary, North California) was used.

Results

The demographic characteristics of 8,044 MCC patients diagnosed between 1985–2004 are presented in Table 1. The NCDB had primary tumor size information on 5,722 cases (71.1%) and no tumor size information on 1,976 cases. The NCDB collects follow-up data from the time of initial diagnosis at five-year intervals. Follow-up data was available for 4,542 of the 8,044 cases. Among 1,830 live patients, median follow-up was 64.2 months (range 0.5 – 198 months).

The distribution of MCC primary tumor sizes is shown in Figure 1. The median primary MCC tumor size among 5,722 patients with available tumor size information was 1.7 cm (0.1cm – 7.0 cm) (Figure 1). Note: Fewer than 1% of lesions were over 7 cm in size. These were truncated at 7 cm at the time of accrual. Patients with no distant metastatic disease for whom both tumor size and regional nodal status were available (n=4,027), are depicted in Figure 2. Key findings included: 1) increased risk of nodal involvement with larger primary tumors, 2) For 0.5 cm tumors, the observed risk of nodal involvement is 14%, while the estimated risk per the fitted regression line is 20.7% (95% CI, 16.2–25.1). This difference is likely due to the lack of a linear relationship at the extreme ends of the data. 3) For 1.7 cm (median sized tumors), the observed risk of nodal involvement is 25%, while the estimated risk per the fitted regression line is 24.9% (95% CI, 21.5–28.3). (Figure 2).

The prognostic significance of the number of positive lymph nodes was analyzed among 1,305 patients with no distant metastatic disease at presentation who had nodal information available. The overall survival (Figure 3A) for patients with 0, 1, 2, 3–5 and 6+ nodes were 62%, 38%, 38%, 32% and 19% respectively (0 node: HR=1.0 [reference], 1 node: HR = 1.88, CI: 1.6–2.3, p<0.0001; 2 nodes: HR = 1.89, CI: 1.4–2.5, p<0.0001; 3–5 nodes: HR =

2.51, CI: 2.0–3.2, $p < 0.0001$; 6+ nodes: HR = 3.9, CI=3.1–5.0, $p < 0.0001$). Although the difference between the overall survival curve for 3–5 nodes (38%) and 1 node (32%) is statistically significant ($p = 0.002$), from a clinical standpoint these percentages are similar. The 5-year relative survival (Figure 3B) for patients with 0, 1, 2, 3–5 and 6+ nodes were 76%, 50%, 47%, 42% and 24% (0 node: HR=1.0 [reference], 1 node: HR = 2.16, CI: 1.6–3.0, $p < 0.0001$; 2 nodes: HR = 2.27, CI: 1.5–3.5, $p < 0.0002$; 3–5 nodes: HR = 3.43, CI: 2.4–5.0, $p < 0.0001$; 6+ nodes: HR = 5.66, CI = 4.0–8.0, $p < 0.0001$).

The frequency of pathologic node evaluation decreased with age for both sex (Figure 4), and more men had pathological staging of their lymph nodes than women among any age group. These differences were statistically significant (young versus old male, $p < 0.0001$; young female versus old female, $p < 0.0001$; young male versus young female, $p = 0.008$; old male versus old female $p < 0.0001$).

Discussion

This study examined 8,044 cases from the National Cancer Database to determine the relationship of MCC regional nodal involvement with primary tumor size and the relationship of number of involved nodes with survival. Our findings indicate that patients with small primary MCC tumors have significant risk of nodal disease at the time of presentation and that the number of involved nodes is strongly predictive of survival.

Prior studies of primary tumor size (27 to 153 cases), reported a median size of 1.2 cm or 1.9 cm^{3,10,11}. Among 5,722 cases in the present study, median tumor size was 1.7cm, close to the cut-off (2.0 cm) between stage 1 and stage 2 MCC in the current MCC staging system¹².

Prior studies examining the relationship between primary tumor size and nodal disease have had conflicting conclusions. Stokes et al reported that only two of 54 patients with tumors ≤ 1 cm had grossly apparent clinical nodal disease, and that all others were both clinically and microscopically negative. They concluded that pathological lymph node evaluation was not indicated for patients with MCC tumors ≤ 1 cm. In contrast, Sarnaik et al reported that 42% of clinically occult regional nodal metastases occurred in patients with tumors that were ≤ 1 cm¹³. We previously reported that 32% of MCC patients with clinically uninvolved regional lymph nodes had occult involvement when examined pathologically¹⁴. Similarly, Fields et al³ reported a 26% risk of occult nodal involvement among 66 patients with ≤ 1 cm tumors and Schwartz et al⁴ reported a 24% risk of occult nodal involvement among 42 patients with < 1 cm lesion. The present study, based on national registry data of a far larger number of patients than any prior study, corroborates the conclusions by several other groups^{3,4} that even small MCC tumors have a significant risk of nodal involvement at the time of diagnosis.

The effect of the number of involved nodes on survival has not been previously described for MCC. In this study, similar to results in breast cancer⁷, melanoma^{16,17}, and esophageal cancer⁶, we found that the number of metastatic regional lymph nodes was an important predictor of survival in patients with MCC. While this dataset is the first to demonstrate an association between survival and the number of involved nodes in MCC, unfortunately, it is not feasible to determine whether or not inclusion of this variable would improve prognostication beyond the current AJCC staging system. This is because the NCDB did not (until recently) record the clinical nodal status for patients who underwent pathologic nodal evaluation. It is thus not possible to determine if pathologically node-positive patients had clinically apparent (stage IIIB) or clinically occult (stage IIIA) nodal disease. In the future, it will be possible to carry out multivariate analyses to determine whether the number of

involved nodes improves prognostic accuracy in staging because the NCDB currently captures clinical nodal information for all patients.

Similar to other cancers including breast and prostate^{18,19–21}, we found the likelihood of patients undergoing pathological nodal evaluation decreased with advancing age. Because advancing age and comorbid conditions may limit a patient's ability to undergo pathological nodal staging²² this observation is not surprising. In this study, we also observed that women were less likely in all age groups than men to have pathologic nodal evaluation. Subset analyses indicated that the greater likelihood of men to undergo pathological nodal evaluation cannot be ascribed to factors including primary site (face versus extremity) or lesion size as these factors were similar between men and women. This trend of increased pathologic nodal evaluation among males was previously observed for liver, pancreatic, esophageal, and stomach cancers^{18,23} and ascribed to differences in socioeconomic and insurance coverage (women are more likely to have financial or insurance constraints with advancing age as compared to men). We could not explore such associations for MCC as socioeconomic data were unavailable for this cohort.

The current dataset has several limitations. In the past, NCDB did not frequently capture clinical nodal status if pathological node status was recorded. Hence we were unable to discern whether a patient's nodal involvement was occult or clinically apparent. This limitation will be less significant in future analyses as both clinical and pathological node data are now being collected by the NCDB. Another limitation of the dataset is that it does not have MCC-specific mortality information. Hence, analyses were performed using relative survival of the subjects within this cohort as compared to age- and sex-matched population data¹. However these analyses are not race-matched.

In conclusion, the findings from this national dataset demonstrate that there is no primary tumor size for which the risk of nodal involvement is clinically negligible. Although pathologic nodal evaluation for MCC is not indicated in certain circumstances (eg if the regional nodes will be treated by radiation even if the node biopsy is negative and/or if improved prognostic information is not desired by the patient), this study supports the notion that small primary tumor size should not be used to eliminate a patient from consideration of pathologic nodal evaluation. This study also demonstrates that the number of involved nodes is strongly predictive of survival and thus may be relevant for clinical management and potentially useful in future MCC staging systems.

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Abbreviations

SLNB	Sentinel lymph node biopsy
NCDB	National Cancer Data Base

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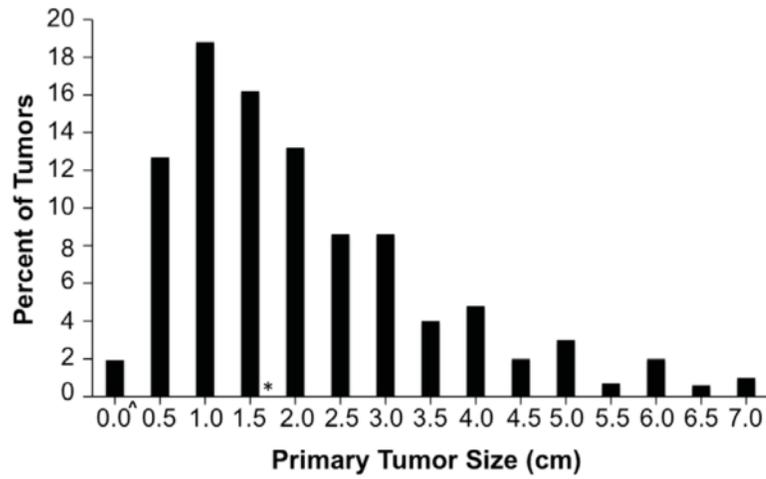


Figure 1. Size Distribution of Primary MCC Tumors among 5,722 cases

Primary tumor sizes from 5,722 cases were rounded to the nearest 0.5 cm (e.g. 0.8 – 1.2 cm tumors are shown as 1.0 cm). The median tumor size was 1.7 cm (shown by asterisk).

^Among 109 cases depicted as “0.0 cm”, 56 cases were 0.2 cm and 53 cases were 0.1 cm.

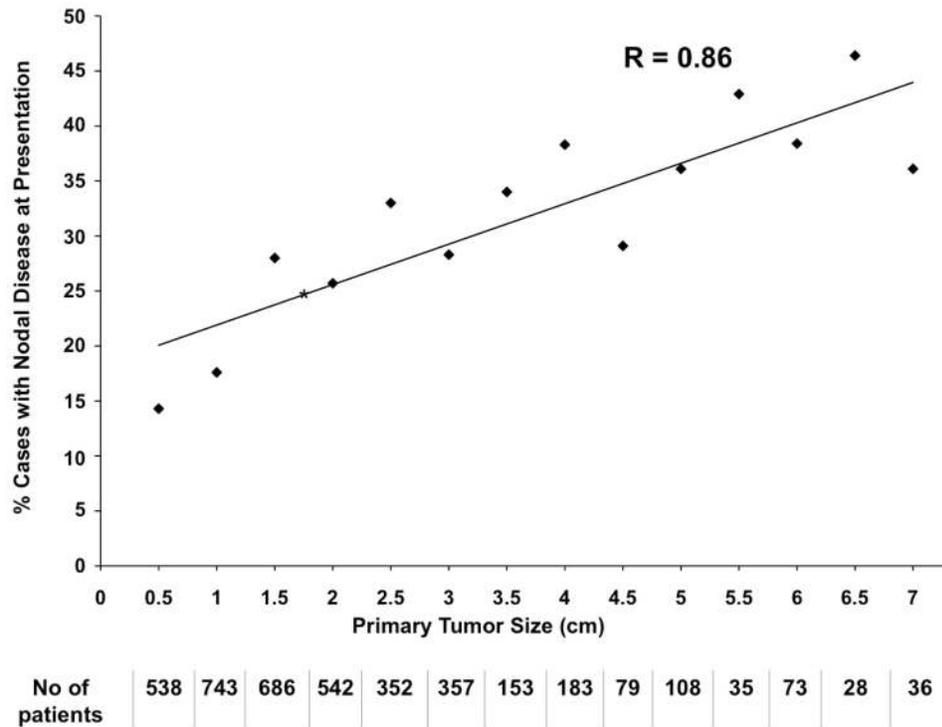


Figure 2. Relationship of Primary Tumor Size to Regional Nodal Disease

Among 4,027 evaluable patients, the percentage with clinically or pathologically involved lymph nodes at presentation is shown relative to primary tumor size (Pearson correlation coefficient (R) = 0.86 with 95% confidence interval of 0.61–0.95), $p < 0.001$). The number of patients presenting with each primary tumor size is shown below the X axis. An asterisk (*) at 1.7 cm indicates the median tumor size at presentation. 114 cases are in the “0 cm” bin (56 cases were 0.2 cm, 53 cases were 0.1 cm, and 5 cases were recorded as 0.0 cm; these may have represented ‘unknown primary’ or in situ tumors). 21% of these 114 cases with “0” cm size in fact had nodal disease at presentation.

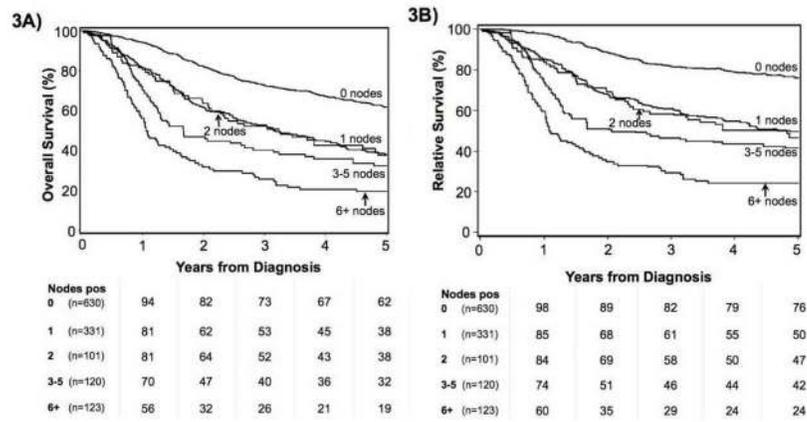


Figure 3. Relationship between number of positive regional nodes at diagnosis and survival Overall survival (3a) and relative survival (3b) is plotted for 1,305 patients who had no distant metastasis at the time of diagnosis and for whom nodal status at presentation was available. Percent surviving is indicated below ‘Years from Diagnosis’ for each number of positive nodes.

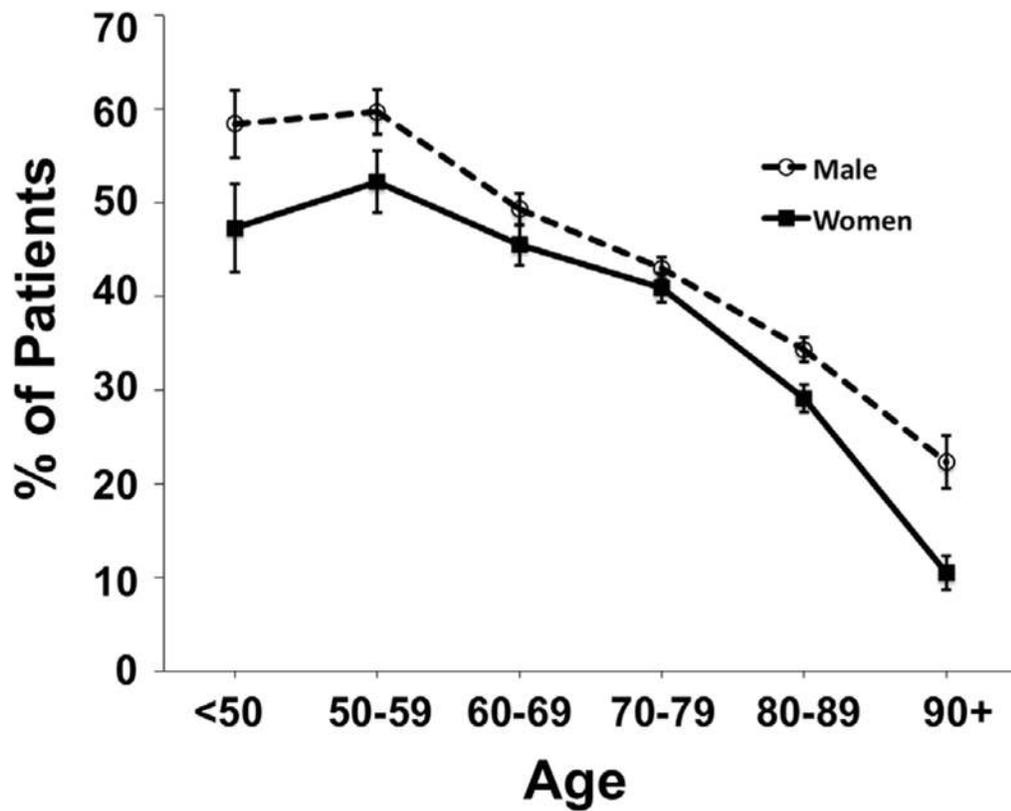


Figure 4. Proportion of patients who underwent pathological regional nodal evaluation
 Among patients with no distant metastatic disease at presentation, more men underwent pathological nodal staging of their lymph nodes than women in each age category. Pathological staging of nodes decreased with advancing age for both sex. Error bars represent binomial standard error. Data from 4,809 males and 3,036 females are shown. The frequency of pathologic node evaluation was significantly different as a function of age and sex (young versus old male, $p < 0.0001$; young female versus old female, $p < 0.0001$; young male versus young female, $p = 0.008$; old male versus old female $p < 0.0001$).

Table 1

Demographics of MCC cases used for each Figure.

	Any figure (n=8044)	Figure 1 (n=5722)	Figure 2 (n=4027)	Figure 3 (n=1305)	Figure 4 (n=7845)
Gender					
Male	4943 (61)	3440 (60)	2463 (61)	866 (66)	4809 (61)
Female	3101 (39)	2282 (40)	1564 (39)	439 (34)	3036 (39)
Age					
<50	306 (4)	209 (4)	154 (4)	72 (6)	302 (4)
50-59	677 (8)	451 (8)	339 (8)	151 (12)	654 (8)
60-69	1424 (18)	1011 (18)	722 (18)	289 (22)	1391 (18)
70-79	2861 (36)	2001 (35)	1401 (35)	508 (39)	2790 (36)
80-89	2272 (28)	1658 (29)	1158 (29)	258 (20)	2211 (28)
90+	504 (6)	392 (7)	253 (6)	27 (2)	497 (6)
Race					
White	7747 (96)	5512 (96)	3894 (97)	1265 (97)	7556 (96)
Black	102 (1)	77 (1)	45 (1)	15 (1)	95 (1)
Native American	12 (<1)	10 (<1)	7 (<1)	1 (<1)	12 (<1)
Asian, Pacific Is.	64 (1)	50 (1)	36 (1)	6 (<1)	64 (1)
Other/Unknown	119 (1)	73 (1)	45 (1)	18 (1)	118 (2)
Stage					
Local	4437 (55)	2994 (52)	2994 (74)	630 (48)	4437 (57)
Regional	1836 (23)	1033 (18)	1033 (26)	675 (52)	1836 (23)
Local/regional	1572 (20)	1496 (26)	--	--	1572 (20)
Metastatic	199 (2)	199 (3)	--	--	--
N. of involved nodes					
0	1592 (20)	1006 (18)	999 (25)	630 (48)	1585 (20)
1	742 (9)	436 (8)	411 (10)	331 (25)	717 (9)
2	218 (3)	139 (2)	131 (3)	101 (8)	210 (3)
3-5	250 (3)	151 (3)	144 (4)	120 (9)	243 (3)
6+	252 (3)	156 (3)	143 (4)	123 (9)	239 (3)

	Any figure (n=8044)	Figure 1 (n=5722)	Figure 2 (n=4027)	Figure 3 (n=1305)	Figure 4 (n=7845)
Unknown	4990 (62)	3834 (67)	2199 (55)	--	4851 (62)
Tumor size					
0-2.0 cm	3579 (44)	3579 (63)	2538 (63)	464 (36)	3488 (44)
2.1-5.0 cm	1862 (23)	1862 (33)	1305 (32)	271 (21)	1774 (23)
>5.0 cm	281 (3)	281 (5)	184 (5)	40 (3)	261 (3)
Unknown	2322 (29)	--	--	530 (41)	2322 (30)

See Methods for details of case selection. Basic criteria were as follows: Figure 1 – all patients with tumor size known, regardless of stage; Figure 2 -- tumor size known, local and regional stage; Figure 3 – number of nodes and vital status known, local and regional stage; Figure 4 – all patients with any non-metastatic stage at presentation. Numbers in parenthesis for each individual parameter represent percent values.