Integration of clinical variables for the prediction of late distant recurrence in patients with oestrogen receptor positive breast cancer treated with 5 years of endocrine therapy: CTS5

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Running head: A clinical treatment score for risk of late recurrence of ER+ breast cancer

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Abstract

Purpose: Estimating risk of late distant recurrence (DR) is an important goal for managing women with hormone receptor positive breast cancer after 5 years' endocrine treatment without recurrence. We develop and validate a simple clinicopathological tool (Clinical Treatment Score post-5 years (CTS5)) to estimate residual risk of DR after 5 years' endocrine treatment.

Patients and Methods: The ATAC dataset (N=4735) was used to create a prognostic score for post-5-year risk of DR. Validity of CTS5(ATAC) was tested in the BIG1-98 dataset (N=6711). Time to late DR, 5 years after finishing scheduled endocrine therapy, was the primary endpoint. Cox regression models estimated the prognostic performance of CTS5(ATAC).

Results: CTS5(ATAC) was significantly prognostic for late DR in ATAC (HR=2.47 (95% CI, 2.24-2.73), P<0.001), and the BIG1-98 validation cohort (HR=2.07 (1.88-2.28), P<0.001). CTS5(ATAC) risk stratification defined in the training cohort as low (<5% DR risk, years 5-10), intermediate (5-10%), or high (>10%) identified 43% of the validation cohort as low risk, with observed DR rate of 3.6% (95% CI 2.7-4.9) during years 5-10. 63% of node-negative were low risk with 3.9% (2.9-5.3) DR rate between years 5-10, and 24% with1-3 nodes positive were low risk with 1.5% (0.5-3.8) DR rate between years 5-10. A final CTS5 for future use was derived from pooled data from ATAC and BIG1-98.

Conclusion: CTS5 is a simple tool based on information that is readily available to all clinicians. CTS5 was validated as highly prognostic for late DR in the independent BIG 1-98 study. The final CTS5 algorithm identified 42% of women with <1% per year risk of DR who could be advised of the limited potential value of extended endocrine therapy.

Introduction

Women with oestrogen receptor (ER) positive primary breast cancer are generally offered adjuvant endocrine therapy for 5 years. Over 50% of recurrences occur after that time and several studies indicate that extending treatment beyond 5 years can improve disease outcome [1-5]. This improvement is, however, relatively modest and extended therapy carries with it risk of adverse side-effects. Few tools have been developed for selecting patients as candidates for extended therapy or alternatively identifying those that might be spared it. One approach is to identify patients whose risk after 5 years is so low that any benefit would be outweighed by potential side effects.

Clinicopathological parameters such as tumor size, nodal status, and histopathologic grade are routinely used to estimate risk of breast cancer recurrence at diagnosis: we have previously reported a Clinical Treatment Score that integrates these factors to estimate prognosis [6]. Some of these factors have also been reported to be associated with risk after 5 years; for example, we found that nodal status was a powerful prognostic marker for late recurrence [7, 8] whereas tumor size and particularly grade were less prognostic after 5 years. Recently an overview analysis of >60,000 women with ER+ disease who were scheduled to receive 5 years' endocrine therapy and remained disease-free at 5 years, reported the subsequent risk of distant recurrence associated with standard clinicopathologic [9]. Even in patients with T1N0 disease the estimated risk of distant recurrence between years 5 and 20 was 10% for low, 13% for intermediate, and 17% for high histologic grade, respectively. While these data unequivocally demonstrate the importance of these

clinicopathologic factors they include studies from 40 years ago possibly limiting their relevance for contemporary breast cancer patients. The data are also presented largely as categories (e.g. T1, T2) which limits their precise estimates of risk for individual patients to be made. Lastly, the large majority of the population was limited to 5 years' treatment with tamoxifen, and did not allow for possible differences between tamoxifen and aromatase inhibitors (AIs) on long-term risk.

We aimed to develop and test the validity of a simple prognostic tool to estimate risk of late distant recurrence (Clinical Treatment Score post-5-years (CTS5)) based on clinicopathological parameters measured in virtually all breast cancer patients at diagnosis. We used data from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [10] as the training set and from the (Breast International Group) BIG 1-98 trial as the testing set [11].

Methods

Study populations

The CTS5(ATAC) was trained using data from the ATAC trial (International Standard Randomised Controlled Trial, number ISRCTN18233230) in which postmenopausal women with ER-positive or ER-unknown early stage breast cancer were randomly assigned to receive 1mg/day anastrozole, 20mg/day tamoxifen, or the combination for five years [10]. The combination arm was discontinued after the first report of the trial results [12]. We included data from women with ER-positive breast cancer randomized to anastrozole alone or tamoxifen alone, who were distant recurrence-free after 5 years' follow-up, and for whom all clinicopathological data were available (N=4735) (Supplemental Figure 1). Median follow-up was 9.8 years. Data from BIG

1-98 (ClinicalTrials.gov, number NCT00004205) was used to validate the CTS5(ATAC). BIG 1-98 initially (1998-2000) randomly assigned postmenopausal women with hormone receptor-positive early stage breast cancer to receive 5 years' 2.5mg/day letrozole or 20mg/day tamoxifen. Later (1999-2003), sequential therapy was also randomly assigned (2 years' letrozole followed by 3 years' tamoxifen or opposite sequence) [11, 13]. Median follow-up was 8.1 years. For this analysis, all women were included who were distant recurrence-free at 5 years and for whom all clinicopathological data were available (N=6711) (Supplemental Figure 1). For both trials, women were included in the analysis whether or not they received chemotherapy.

The prognostic value of the following variables for post-5-year (late) distant recurrence was determined by univariate Cox regression analyses: nodes, tumor size (mm), grade (1, 2, 3), age at start of endocrine therapy (years), and type of assigned endocrine treatment. Type of endocrine treatment was not significant for late distant recurrence in univariate analyses and therefore not included in the final model. The log-hazard was almost linear for five nodal status groups (nodes: negative, 1 positive, 2-3 positives, 4-9 positives, and >9 positives) but not for continuous tumor size alone. A negative quadratic term was therefore introduced and tumor size was capped at 30mm where the risk plateaued. The final CTS5(ATAC) model included age as a continuous term, tumor size as a continuous term, quadratic tumor size, nodal status (five groups: 0=Negative; 1=1 positive; 2=2-3 positive; 3=4-9 positive; 4= >9 positive) and grade (three groups: 1=low, 2=intermediate, 3=high) and is given by:

$$CTS5(ATAC) = 0.471*nodes+0.980*(0.164*size-0.003*size^2+0.312*grade+0.03*age)$$

A shrinkage factor of 0.980 for the non-nodal part of the score was calculated using a nested Cox model [14] and applied to allow for the small amount of overfitting.

Separate models developed for patients receiving chemotherapy or not did not perform significantly better for either group than a single model including all patients (data not shown).

Statistical analysis

Analyses were performed according to a pre-specified analysis plan, approved by both trial groups, and are summarised below. Full details are given in the supplementary file. The primary endpoint was time to distant recurrence. Distant recurrence was defined as metastatic disease, excluding contralateral disease, and loco-regional and ipsilateral recurrences. The endpoint was censored at last follow-up visit or death before distant recurrence such that risk is a pure risk calculation ignoring deaths.

Cox proportional hazard models were used to create the model in ATAC and the CTS5(ATAC) score was tested in BIG 1-98. Likelihood ratio statistics (LR-χ^2) and Kaplan-Meier survival estimates with corresponding 95% confidence intervals were used to determine the prognostic performance of the CTS5(ATAC) in BIG 1-98. The 5-10 year distant recurrence risk groups were determined in ATAC and defined as: low risk group <5%, intermediate risk group 5-10%, and high risk group >10%. To compare the prognostic performance of CTS5(ATAC) between ATAC and BIG 1-98

trials, CTS5(ATAC) was normalised to have unit variance and the hazard ratios (HRs) and associated 95% confidence interval (CI) were estimated from Cox models. All statistical analyses were two-sided, and $p<0.05$ was regarded as statistically significant. We also compared the newly developed CTS5(ATAC) to the published CTS (termed CTS0 below) that had been developed for estimating prognosis from the time of disease presentation [6]. All analyses were performed with STATA version 13.1 (College Station, Texas, USA).

Results

The ATAC training set and the BIG 1-98 test set consisted of 4735 and 6711 postmenopausal patients, respectively all of whom were assigned to receive a total of 5 years' endocrine therapy (Table1). Women in the ATAC cohort were significantly older by an average of about 3 years, had more node-negative disease (68 vs 61%), more grade 3 tumors (25% vs 20%), and fewer women received adjuvant chemotherapy compared with women in the BIG 1-98 set (19.5% vs 24.2%). Tumor size was similar between the two trials. 330 (7.0%) late distant recurrences were recorded in the training set, with an annual hazard rate of 0.79% (95% CI 0.71-0.88). In BIG 1-98, a total of 370 (5.5%) late distant recurrences occurred with an annual hazard rate of 0.66% (95% CI 0.60-0.73) which was significantly lower than in ATAC (P=0.014) (Table 1).

Training set (ATAC)

Supplemental Table 1 shows the comparisons of the published CTS0 [6] with the CTS5(ATAC) for the prediction of late distant recurrence between years 5 and 10. The CTS5(ATAC) provided significantly more prognostic information compared to the CTS0 (CTS5(ATAC): LR-χ^2=308.6 (5df); CTS0: LR-χ^2=285.0 (9df)) and larger effect sizes were observed (HR=2.47 vs. HR=2.04, respectively). CTS5(ATAC) was slightly more prognostic in chemotherapy-free women compared to those who received chemotherapy (HR=2.50 (2.22-2.81) vs. HR=2.39 (1.94-2.95)) but the interaction with chemotherapy use was not significant (P=0.76).

The prognostic value of CTS5(ATAC) for risk of distant recurrence (±95% CI) between years 5 and 10 is shown in Figure 1a for the whole population and in Figure

1b for the node-positive and node-negative populations separately. Cut-offs in the ATAC population to separate low, intermediate and high-risk populations were 4.35 and 5.02, respectively (Figure 1a). As expected, the majority but not all of the low-risk patients were node negative and conversely the majority of the high-risk were node-positive (Figure 1b).

Overall, 42.0% were categorised as low risk, 31.3% as intermediate, and 26.7% as high risk of developing a late distant recurrence (Table 2). Those categorised into the low risk group had a mean 5-10 year distant recurrence risk of 2.5% (1.8-3.4) compared to 7.7% (6.3-9.5) for intermediate and 20.8% (18.2-23.6) for high-risk groups (Figure 3). Those being intermediate or high risk had a 3.42-fold (CI=2.37-4.95) and 9.43-fold (CI=6.71-13.25), respectively, higher risk of late distant recurrence than the low-risk group. Notably only 2/133 patients with 1-3 nodes positive and categorised as low risk had a recurrence between years 5 and 10 (Table 2). Virtually all patients with 4 or more nodes positive were categorised as high risk. About one-fifth of patients with 2 or 3 nodes positive had risk categorised as low or intermediate risk while 42.9% with 1 node positive were categorise as high risk. Only 57.7% of node-negative patients were categorised as low risk.

Validation set (BIG 1-98)

CTS5(ATAC) performed substantially better in the validation BIG 1-98 cohort than CTS0 (CTS5(ATAC): LR-χ^2=212.1 (1df) vs. CTS0: LR-χ^2=184.5 (1df)). CTS5(ATAC) was significantly prognostic in women who did not receive chemotherapy (HR=2.20 (1.96-2.47), P<0.001; LR-χ^2=168.7 (1df)), and more so compared to those who did

(HR=1.76 (1.46-2.13), P<0.001; LR-χ^2=34.7 (1df)) (Supplemental Table 1) but the interaction with chemotherapy was not statistically significant (p=0.06).

The number of observed distant recurrences was compared with those expected by CTS5(ATAC) in deciles of risk for node-negative and node-positive separately (Figure 2a and b). In each case there were no significant differences between the observed and expected for any of the deciles. The correlation (r) between the observed versus expected across the deciles was 0.89 for node-negative and 0.95 for node-positive. Using the CTS0 a number of deciles showed significant χ^2-values (Supplementary Figure 2) and the r-values were also lower being 0.78 and 0.87, respectively. Concordance between the estimated and actual distant recurrence rates was also shown to be better with CTS5 using Harell's C-index: CTS5(ATAC), 0.712; CTS0 0.641.

We used pre-defined cut-off points of 4.35 and 5.02 from ATAC to determine risk groups for late distant recurrence in BIG 1-98 (Figure 1). These cut-points intersected the risk curves for BIG1-98 at 5.4% and 9.9% for node negative patients and 5.5% and 9.5% for node-positive patients, respectively and therefore were strongly validated by this test set. The distribution of patients into low, intermediate and high risk groups was also very similar in the BIG 1-98 dataset to that observed in the training set (Table 2). The mean 5-10 year distant recurrence risk of patients in BIG 1-98 in those 3 categories was 3.6% (2.7-4.9), 6.9% (5.9-8.5), and 17.3% (14.8-20.1), respectively (Table 2, Figure 3). Thus for each category the actual mean risk for each category fitted well with that of the predicted risk. The curves for node-

negative and node positive women were almost identical in the CTS5(ATAC) regions of overlap in BIG 1-98.

Significant separation between low versus intermediate risk groups (HR=2.19 (1.61-2.98)) and low versus high risk groups (HR=5.33 (4.02-7.07)) were observed (Figure 3). Notably only 4/304 patients with 1-3 nodes positive and categorised as low risk had a recurrence between years 5 and 10. As with the ATAC dataset, in BIG 1-98 virtually all patients with 4 or more nodes positive were categorised as high risk (Table 2). The distribution of patients in the risk categories across histological grades and across the nodal categories was similar between ATAC and BIG 1-98. Again, about one-fifth of patients with 2 or 3 nodes positive had risk categorised as low or intermediate risk but a somewhat smaller proportion of patients with 1 node positive were categorise as high risk (29.7% vs 42.9%). In BIG 1-98 62.5% of node-negative patients was categorised as low risk compared with 57.7% in ATAC.

Combined ATAC and BIG 1-98 sets

To increase the precision of the risk estimates we combined the ATAC and BIG 1-98 datasets such that new coefficients were fitted using the same variables as in the training or validation cohorts. The final CTS5 is represented by the following model:

$$CTS5=0.438*nodes+0.988*(0.093*size-0.001*size^2+0.375*grade+0.017*age).$$

The relationship between the final CTS5 and risk of distant recurrence is shown in Figure 4 with a table of CTS5 values that relate to one-unit intervals of distant recurrence risk. New cut-off points for low (CTS5<3.13), intermediate (3.13 to 3.86), and high risk (>3.86) groups were derived from this final model. An example of the calculation of CTS5 and the associated risk estimate is given in Figure 4.

Discussion

Over the last 3 decades there have been major increases in invasive breast cancer incidence in western countries; in the US it is estimated that over 250,000 women will be diagnosed with invasive breast cancer in 2017 [15], the large majority being cases localised to the breast. About 80% of cases are now diagnosed as ER-positive and almost all of these are prescribed 5-years' adjuvant endocrine therapy. While such treatment markedly reduces mortality (e.g. by about 30% with 5 years' tamoxifen and about 40% with an AI in postmenopausal women) recurrences continue to occur after the 5 years' treatment has ceased. The observations that these events can be decreased by continued treatment [1, 2, 16] means that decisions about whether to continue with therapy or not at 5 years are at the forefront of patient management at that time. We expect that the CTS5 tool reported and validated here will prove helpful to oncologists and patients in making a decision about continued treatment. The integration of clinical pathologic features that are measured in all patients at diagnosis should mean that risk is calculable at little expense globally: the Table in Figure 4 will allow a direct readout and an on-line tool will be provided to facilitate estimates of continuous risk.

Strengths of the study include its use of two large sets of registration standard randomized clinical trial data with detailed clinical follow-up for 10 years. The ATAC training set included the AI, anastrozole, as well as tamoxifen as adjuvant treatment, and although the specific endocrine adjuvant therapy did not feature in the algorithm, this allowed us to infer that the score is valid for both tamoxifen and AI treated patients. This is consistent with the overview analysis of AIs versus tamoxifen [17]. Median five-year follow-up for the two trial combined occurred about 12 years ago. It

is therefore possible that our risk estimates may not accurately reflect those of current patients reaching 5 years. However, the only major changes to the management of primary ER-positive breast cancer since the completion of recruitment to ATAC and BIG1-98 has been the introduction of trastuzumab for patients with HER2+ disease. The CTS5 should be applied with caution in such patients until validated specifically for that population. All patients in the two cohorts were postmenopausal at diagnosis. Although risk of distant recurrence post-5 years has been reported to be similar across age groups other than for the small group of patients diagnosed <35 years of age [9] the present algorithm cannot be extended to premenopausal patients without further validation.

Neither trial collected complete information on the use of extended adjuvant endocrine therapy. However, the first significant data supporting the use of an AI after tamoxifen [1] emerged close to the end of the treatment period for the trials and we estimate that <1% of tamoxifen treated patients in ATAC and <5% in BIG 1-98 received such extended therapy. This would be expected to have minimal impact on our estimates of risk when extended therapy is not used.

Also similar to the EBCTCG paper we found that whether or not patients had received chemotherapy at presentation had no significant impact on residual risk of recurrence when taking the other factors into account. This may relate in part to the observation that the bulk of the benefit from adjuvant chemotherapy is shown over the first 5 years follow-up [18].

The categories of low, intermediate and high risk were chosen to be closely parallel to those defined by several molecular profiling tools for managing ER-positive breast cancer patients [19-21]. However, those tools are applied immediately after surgery largely for the decision to give adjuvant chemotherapy: what is considered low or high risk for that may not be the same as when considering the appropriateness of extended adjuvant therapy. For discussion with individual patients whose preferences for continuing or ceasing endocrine therapy at 5 years is likely to vary markedly, the use of a continuous risk estimate from the CTS5 is likely to be more informative than the categorical estimates (low, intermediate and high) used here for illustrative and comparative purposes.

The agreement between the ATAC and BIG1-98 data was almost complete within the low and intermediate risk categories but somewhat less beyond the intermediate/high cut-off. Thus the instrument may be used with greatest confidence for defining 5-10 years distant recurrence risk when less than 10% and will be of greatest use in assessing the potential value of extended therapy on the basis of risk estimates below that level.

The current report deals only with clinicopathologic profiles. Multigene expression profiles have significantly increased the ability to predict distant recurrence over 10 years after diagnosis in ER-positive breast cancer [22]. Several of these signatures such as the Oncotype *Dx* Recurrence Score [23], PAM50-based Prosigna Risk of Recurrence Score [19, 24], Breast Cancer Index [25, 26], EndoPredict [20, 27, 28], and the NKI 70-gene signature [29] are commercially available and endorsed by several guidelines [30-33]. Although a number of them estimate risk of late as well as

early recurrence, these tests were developed to manage breast cancer patients at diagnosis and have not been calibrated for application 5 years after diagnosis. Over the first 10 years of follow-up clinicopathologic and molecular factors have nearly completely independent prognostic value and their optimal use for prognosis requires their integration [34]. It is near certain that the same is true for the 5-10 year period. The CTS5 provides a straightforward starting point for combining with molecular scores.

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Legends to Figures:

Figure 1: a). Predicted distant recurrence risk (%) in years 5-10 since randomization (start of adjuvant endocrine therapy) for ATAC trial overall population. **b).** Predicted distant recurrence risk (%) in years 5-10 since randomization (start of adjuvant endocrine therapy) for ATAC node-negative and node-positive patients. Solid red lines indicate cut-off points for risk groups. ATAC=Arimidex Tamoxifen Alone or Combination, CTS=Clinical Treatment Score, DR=Distant Recurrence.

Figure 2: Observed versus expected number of events and Chi-square values in the BIG1-98 trial according to deciles of CTS5(ATAC) for node-negative and node-positive patients.

Figure 3: Kaplan-Meier curves and 5-10 year DR rates since randomization for the overall population according to trial (solid lines = ATAC, dotted lines = BIG 1-98). ATAC=Arimidex Tamoxifen Alone or Combination, BIG=Breast International Group**,** DR=Distant Recurrence.

Figure 4: Predicted 5-10 year DR risk (%) since randomization and CTS5 values for the combined data set. Solid red lines indicate cut-off points for risk groups. CTS=Clinical Treatment Score, DR=Distant Recurrence. The arrow shows the CTS5 and equivalent 5-10 year risk of a patient with a 12mm, node negative, grade 2 and 54 years of age. Using the formula [CTS5=0.438*nodes+0.988*(0.093*size-0.001*size^2+0.375*grade+0.017*age)] her CTS5 is 2.61 and her 5-10 year risk of distant recurrence is 3%.

Table 1: Patient and tumor characteristics according to trial of patients who are distant-recurrence free at 5 years after randomization (start of adjuvant endocrine therapy). ATAC=Arimidex Tamoxifen Alone or Combination, BIG=Breast International Group, IQR=Interquartile range, mm=millimetre, CI=Confidence Intervals

	ATAC (N=4735)	**BIG 1-98 (N=6711)**	**P-value**
Age (years), median (IQR)	64 (57-71)	61 (56-67)	<0.001
Nodal status (number of positive nodes)			
Negative	3219 (68.0%)	4090 (60.9%)	
1	643 (13.6%)	1164 (17.3%)	
2-3	523 (11.1%)	780 (11.6%)	
4-9	277 (5.9%)	506 (7.5%)	
9+	73 (1.5%)	171 (2.6%)	
			P-trend<0.001
Grade			
Well	1149 (24.3%)	1524 (22.7%)	
Intermediate	2387 (50.4%)	3828 (57.0%)	
Poor	1199 (25.3%)	1359 (20.3%)	
			P-trend=0.007
Tumor size			
<10mm	864 (19.7%)	1172 (17.5%)	
10-20mm	2356 (49.8%)	3206 (47.8%)	
20-30mm	1028 (21.7%)	1571 (23.4%)	
>30mm	487 (10.3%)	762 (11.4%)	
			P-trend=0.44
Chemotherapy	923 (19.5%)	1627 (24.2%)	<0.001
Treatment			
Tamoxifen 5 years	2374 (50.1%)	1989 (29.6%)	
Anastrozole or Letrozole 5 years	2361 (49.9%)	2042 (30.4%)	
2 years Letrozole/3 Years Tamoxifen	-	1335 (19.9%)	
2 years Tamoxifen/3 Years Letrozole	-	1345 (20.0%)	
Distant recurrence (>5 years)	330 (7.0%)	370 (5.5%)	0.014
Annual rate % (95% CI)	0.79% (0.71-0.88)	0.66% (0.60-0.73)	

Table 2: Distribution of the risk categories in the ATAC and BIG 1-98 cohorts according to tumor size, grade and nodal involvement. ATAC=Arimidex Tamoxifen Alone or Combination, BIG=Breast International Group, mm=millimetre.

	ATAC			
	Low risk (N=1989, 42.0%)	**Intermediate risk (N=1484, 31.3%)**	**High risk (N=1262, 20.7%)**	**Total (N=4735)**
Size				
<10mm	808 (40.6%)	41 (2.8%)	15 (1.2%)	864
10-20mm	1082 (54.4%)	872 (58.8%)	402 (31.9%)	2356
>20mm	99 (5.0%)	571 (38.5%)	845 (67.0%)	1515
Grade				
Well	806 (70.1%)	235 (20.58%)	108 (9.4%)	1149
Intermediate	952 (39.9%)	861 (36.1%)	574 (24.0%)	2387
Poor	231 (19.3%)	388 (32.4%)	580 (48.4%)	1199
Nodal involvement				
None	1856 (57.7%)	1138 (35.4%)	225 (7.0%)	3219
1 node	112 (17.4%)	255 39.7%)	276 (42.9%)	643
2-3 nodes	21 (4.0%)	84 (16.1%)	418 (79.9%)	523
4-9 nodes	0	6 (2.2%)	271 (97.8%)	277
>9 nodes	0	1 (1.4%)	72 (98.6%)	73
	BIG 1-98			
	Low risk (N=2861, 42.6%)	**Intermediate risk (N=2136, 31.8%)**	**High risk (N=1714, 25.5%)**	**Total (N=6711)**
Size				
<10mm	1081 (37.8%)	65 (3.0%)	26 (1.5%)	1172
10-20mm	1585 (55.4%)	1103 (51.6%)	518 (30.2%)	3206
>20mm	195 (6.8%)	968 (45.3%)	1170 (68.3%)	2333
Grade				
Well	1077 (70.7%)	308 (20.2%)	139 (9.1%)	1524
Intermediate	1575 (41.1%)	1301 (34.0%)	952 (24.9%)	3828
Poor	209 (15.4%)	527 (38.8%)	623 (45.8%)	1359
Nodal involvement				
None	2555 (62.5%)	1398 (34.2%)	137 (3.3%)	4090
1 node	277 (23.8%)	541 (46.5%)	346 (29.7%)	1164
2-3 nodes	27 (3.5%)	175 (22.4%)	578 (74.1%)	780
4-9 nodes	2 (0.4%)	21 (4.2%)	483 (95.5%)	506
>9 nodes	0	1 (0.6%)	170 (99.4%)	171