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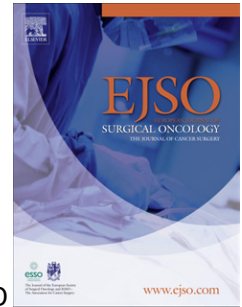
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Original article

Validation of the new AJCC TNM staging system for gastric cancer in a large cohort of patients (n=2,155): focus on the T category

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ABSTRACT

Background. The prognostic value of T subclassification in patients with gastric carcinoma has been just implemented in the new AJCC TNM staging system, which has reclassified T2a and T2b into T2 and T3 tumors, respectively. The aim of the present study was to validate the prognostic significance of the new T categorization within the frame of the latest TNM staging system.

Methods. We retrospectively reviewed the records of 686 T2/T3 patients among 2,155 subjects who underwent radical resection for gastric carcinoma at six Italian centers from 1988 through 2006.

Results. Upon multivariate analysis, the new T categories, extent of lymph node dissection (D) and patient's age were retained by the survival model as independent prognostic factors. In particular, the death risk for patients with T3 tumors was higher than that of patients with T2 tumors (HR: 1.42, P=0.005).

Among the 686 patients previously classified as having T2 tumors, patients with T2 and T3 disease were 270 (39.4%) and 416 (60.6%), respectively. After a median follow-up of 55 months, the 5-year overall survival rates were 67.3% and 52.3% for patients with T2 and T3 tumors, respectively (P<0.001). The survival advantage for the T2 as compared to T3 category was maintained even when N0 and N+ patients were separately considered (P=0.0154 and P<0.001, respectively).

Conclusions. Our data confirm the prognostic difference between the newly proposed T2 and T3 categories, which should be implemented in the routine clinical practice to improve risk stratification of patients with gastric cancer.

Keywords: gastric cancer, TNM staging system, prognostic factors, survival analysis.

INTRODUCTION

The prognosis of resectable gastric cancer is mainly related to the depth of invasion (T category) and lymph node involvement (N category) (1-4). Following the International Union Against Cancer–American Joint Committee on Cancer (UICC-AJCC) TNM classification released in 2002 (5), the T2 category - which is defined as a tumor involving the muscularis propria or subserosa (5,6) - is considered advanced disease but represents a stage with an intermediate prognosis between early gastric cancer (EGC, T1) and serosal involvement gastric carcinoma (T3). Whereas the survival rates of EGC are high (independently of the lymph node status) (7-9) and those of T3 are low (1,2,10), the survival rate of T2 gastric cancer varies significantly in relation to other prognostic parameters (i.e. nodal metastasis) (11-16). Since 1998, the College of American Pathologists suggested that a subclassification of T2 into T2a (tumor with invasion of muscularis propria) and T2b (tumor with invasion of subserosa) should be recommended because “postsurgical survival after resection for cure is significantly different for patients with T2a and T2b lesions” (17).

The prognostic role of T2 subclassification is supported by several lines of evidence. In particular, this T category has been associated with variable nodal involvement rates, N-ratio values as well recurrence and mortality rates. It is unclear whether these findings depend upon the extent of lymphadenectomy (11,12,18,19). In a recently published study performed on 189 patients curatively resected with extended lymphadenectomy, we confirmed that patients with T2a tumors have a significantly better 5-year overall survival as compared to those with T2b neoplasms, with T2 subcategorization being an independent prognostic value at multivariate analysis (20).

Although the 2002 UICC–AJCC classification split the T2 category into T2a and T2b, these subcategories were not maintained in the TNM stage grouping (5). In the light of the above mentioned evidence regarding the prognostic value of T2 subcategorization, this gap of the

2002 TNM version will be filled by the 2010 TNM release. In particular, the new version redefines the T category as follows: T1a = mucosa, T1b = submucosa, T2 = muscularis propria, T3 = subserosa (formerly known as T2b), T4a = perforates the serosa (formerly known as T3), T4b = infiltration of adjacent structures (formerly known as T4) (21).

In the present multicentric study we confirm that the subdivision of the T2 category (T2 and T3 in the new TNM classification) has a significant prognostic value independently of lymph node status in patients with gastric cancer.

PATIENTS AND METHODS

Patients selection and data collection

In this retrospective multicentric study, data were collected from the medical records of 2,155 patients who underwent radical resection (R0) for histologically confirmed T1-T4a gastric carcinoma from January 1988 through December 2006. Patients were operated at six Italian centers experienced in gastric cancer treatment: Clinica Chirurgica Generale 2, University of Padova (n = 352); First Division of General Surgery, University of Verona (n = 387), Institute of Surgical Sciences, University of Siena (n = 391), “Morgagni” Hospital of Forlì (n = 648); Institute of Clinica Chirurgica, University of Brescia (n = 230); Institute of Clinica Chirurgica, Cattolica University of Rome (n = 147).

Eligibility criteria included histologically confirmed R0 gastric resection and pathological evaluation of the total number of resected lymph nodes as well as the number of metastatic lymph nodes. Patients with inadequate number of lymph nodes resected (less than 16 lymph nodes, as required by the AJCC TNM classification for the definition of the N3b category, see below) were excluded from the analysis. Patients with distant metastases (as assessed by thoracic and abdominal CT-scan), tumors of the gastric stump after gastric resection for

benign disease and T4b tumors were also excluded from the analysis. Patients dead in the post-operative period were also excluded.

Depth of primary tumor invasion (pT1a/b, pT2 [muscularis propria], pT3 [subserosa], and pT4a [serosa]) and lymph node involvement (N0 = no metastasis, N1 = 1 to 2 metastatic lymph nodes, N2 = 3 to 6 metastatic lymph nodes, N3a = 7 to 15 metastatic lymph nodes, N3b = 16 or more metastatic lymph nodes) were classified according to the 2010 UICC/AJCC TNM classification (21).

Following the Japanese Classification of Gastric Carcinoma (JCGC) guidelines (6), lymphadenectomy was classified as D1, D2 or D3. In each center the nodal status was assessed by the same pathologist, who also reviewed the slides of all primary tumors. A central pathologic review was employed in the doubtful cases to avoid the single institutional bias.

For all patients, regular 6-month follow-up consisted of physical examination, serum tumor biomarkers, radiological imaging (thoraco-abdominal CT-scan), endoscopic control and chart review or telephone interview.

The final date of follow-up was December 2009 and the median follow-up after surgery was 55 months (range: 3-240 months).

Statistical analysis

Statistical analysis and graphics were performed in the “R” environment version 2.9 (www.R-project.org) and with the SPSS statistical package (SPSS Inc., Chicago, IL). Overall survival (OS) rates and 95% confidence intervals (CI) were determined using the Kaplan-Meier method (22), the event being defined as death for any cause. The log-rank test was used to identify differences between the survival estimates of different patients’ groups (23).

The following independent variables were analyzed for the 686 patients classified as T2 and T3 categories: 1) age (< 65 years vs ≥ 65 years); 2) sex (male vs female); 3) tumor site (cardia

vs upper third vs middle third vs lower third vs multicentric); 4) type of surgical resection (subtotal gastric resection vs total gastrectomy vs extended total gastrectomy); 5) extension of lymphadenectomy (D1 vs D2 vs D3); 6) grading (G1 vs G2 vs G3 vs G4 vs unknown); 7) Lauren type (intestinal vs diffuse vs mixed); 8) T-stage (T1a [mucosa] vs T1b [submucosa] vs T2 [muscularis propria] vs T3 [subserosa] vs T4a [serosa]); 9) number of metastatic lymph nodes (N0 vs N1 vs N2 vs N3a vs N3b).

Spline functions were fitted to evaluate the relationship between the number of metastatic lymph nodes and the number of examined nodes in the different T categories.

At multivariate analysis, all the above mentioned variables were considered. The Cox's proportional hazards model was selected by means of a stepwise procedure (23). For all analyses, only P-values <0.05 were considered significant.

RESULTS

Patients and tumor characteristics

Clinical and pathological data of 686 patients classified T2/T3 are shown in *Table 1*.

The male-to-female ratio was approximately 3:2, with a median (range) age of 69 (27-94) years. In 39% of patients the tumor was limited to the muscularis propria (T2), while in the remaining 61% of cases the tumor involved the subserosa (T3). A D2 or more extended lymphadenectomy was performed in 86% of patients, while a D1 lymphadenectomy was performed in 14% of patients.

The distribution of T2 and T3 was similar for age and sex (P=0.104 and P=0.610) (*Table 1*). By contrast, grade, site and Lauren type of primary tumor, surgical procedure and extent of lymphadenectomy had a statistically different distribution between T2 and T3 patients (all P-

values < 0.05). Adjuvant chemotherapy was performed only for node-positive patients with similar percentages in T2 and T3 patients (35% vs 38%, $P=0.57$).

The median number of lymph nodes removed and examined was 28 (range 16–121).

Non-parametric analysis by means of spline functions showed that in patients with T2 tumors the number of metastatic lymph nodes was not influenced by the number of nodes examined (*Figure 1*). However, for T3 and T4a tumors the number of metastatic lymph nodes increased as a function of the number of examined nodes (*Figure 1*).

Nodal involvement according to depth of invasion of the primary tumor is shown in *Table 1* and *Table 2*. Out of 270 patients with T2 disease, 46% had lymph node involvement (N+), compared with 69% of cases among 416 patients with T3 disease ($P<0.001$). In particular, the incidence of N1 disease was similar for T2 and T3 categories (19 vs 18%, respectively; $P=0.686$); in contrast the incidence of N2, N3a and N3b was significantly different between T2 and T3 categories (18 vs 25%, $P=0.031$; 7 vs 16%, $P=0.003$; 1 vs 10%, $P<0.001$, respectively) (24).

Survival analysis

At univariate analysis, factors significantly associated with overall survival of 686 T2/T3 patients were age, extent of lymphadenectomy and T2/T3 stage (*Table 1*).

Table 3 illustrates the 5-year OS of 686 patients according to T-stage and N-stage.

The 5-year OS rate was 58.3% (CI: 54.5-62.4) for the 686 patients. For patients with T2 lesions the 5-year OS rate was 67.3% (CI 61.1-72.8), compared with 52.3% (CI 47.0-57.4) for T3 cases ($P<0.001$) (*Table 1*).

When patients were stratified according to N stage, the 5-year OS rate was 65.7% (CI: 60.1-71.8) for patients with N0 disease *versus* 53.1% (CI: 48.2-58.6) for those with lymph node metastasis (N+). For patients classified N+, the 5-year overall survival rate was 68.3% (CI

60.3-77.4), 53.4% (CI 45.5-62.6), 45.7% (CI 35.6-56.8), and 13.9% (CI 4.8-40.3) for patients with N1, N2, N3a and N3b disease, respectively (*Table 1*).

Table 3 reported the 5-year OS rate according to T2/T3 category and N category. The 5-year OS rate for N1, N2 and N3a categories was not statistically different ($P=0.271$) for T2 patients (only 2 patients in the T2 subgroup was classified N3b and therefore the survival rate of this subcategories could not be evaluated); by contrast for the T3 subset, 5-year OS rates were statistically significant different between N1, N2, N3a and N3b disease ($P<0.0001$).

Upon stratification of T2 and T3 groups according to the N stage (N0 vs N+), 5-year OS rate was greater for T2N0 vs T3N0 (68.0% vs 63.1%, $P=0.015$) (*Figure 2, upper panel*). Similarly, this difference was statistically significant in favor of T2N+ with respect of T3N+ (66.5% vs 47.2%; $P<0.001$) (*Figure 2, lower panel*). The 5-year OS difference observed between patients with T2N1 tumors and those with T3N1 disease was of borderline significance (71.1% vs 66.4%; $P=0.076$). The 5-year OS rate of patients with T2N2 was not different from that of patients with T3N2 disease (61% vs 49.9%, $P=0.264$). Finally the 5-year OS rates of T2N3a vs T3N3a patients were 76.0% and 39.1%, respectively ($P=0.0328$).

At multivariate analysis age, extent of lymphadenectomy and T stage were retained as independent prognostic factors for the 686 patients (*Table 4*). The mortality risk for T3 patients was significantly higher than that of patients with T2 tumors (HR: 1.420; $P=0.005$).

DISCUSSION

In this retrospective study, which involved six Italian centers experienced in gastric cancer surgery, we investigated the prognostic impact of the new T categories recently implemented in the latest version of the AJCC TNM classification (21), with special attention to the T2 and T3 (formerly T2a and T2b) subcategories, in patients who underwent radical resection for gastric carcinoma. Univariate analysis demonstrated that the 5-years OS rate of patients with

T2 tumors was significantly higher than that of patients with T3 tumors; moreover, at multivariate analysis, the risk of death associated with T2 tumors was significantly lower than that of T3 tumors.

T category distribution

In our experience, the occurrence of T2/T3 tumors was 32% among 2,155 R0 patients. In the study published by Fotia et al., among 624 radically resected gastric cancer patients the incidence of T2/T3 neoplasms was 29% (14); similarly, Sarela et al. reported a 30% incidence of T2/T3 tumors (11). In some Japanese series, the incidence of T2/T3 neoplasms ranges from 10% to 38% (12,13,18,19). Moreover, in our study the tumors were classified as T2 in 12% and T3 in 19% of cases. The different proportions of T2 versus T3 tumors and T3 versus T4a tumors reported in the literature (2,25) may reflect the accuracy of pathological evaluation and the pathologist's attitude to differentiate a real involvement of the serosa (T4a) from the cases in which the infiltration is limited to the subserosa (T3).

Relationship between T and the N category

Using the UICC/AJCC classification, some investigators observed a different correlation between the T2 and T3 gastric wall involvement and the N category (11-14). In our experience the number of metastatic nodes appears to be influenced by the number of examined nodes only for T3 and T4a tumors; however, we did not observe such a correlation for T2 tumors, which supports the different behavior of T2 as compared to T3 neoplasms.

On the other side, we observed a statistically different association between T and N category: in particular, lymph node involvement rate was significantly lower (45%) in T2 cases as compared to T3 cases (69%). The incidence of N1 cases was similar for T2 and T3 patients whereas the N2 and N3a categories resulted significantly more frequent among T3 patients.

Survival findings

Considering the data reported in the international literature, there is no agreement regarding the survival of T2/T3 patients. In the study by Sarela et al., a significantly better 5-year survival was reported for T2 patients with respect of T3 cases (64% vs 46%, $P=0.005$) (11). However, in a subgroup analysis considering only patients with "adequately staged" disease (more than 15 lymph node examined), the same Author reported different results: the 5-year survival rates of patients with N0 disease were similar among T2 and T3 patients (90% vs 86%, $P=0.8$) and the 5-year survival rates of patients with N1 disease were not statistically different between T2 and T3 cases (56% vs 44%, $P=0.3$) (11). Finally, at multivariate analysis, Sarela et al. found that N category and site of primary tumor (but not depth of mural invasion) were independent factors predictive of disease specific death (11).

Similar conclusions were drawn by Fotia et al.: in a study on 182 T2/T3 radically resected gastric cancer patients, they found no statistically different survival between T2 and T3 patients (74% vs 67% 5-year survival, respectively; $P=0.2$) and these categories were not retained as independent prognostic factors at multivariate analysis (14).

In a recent study on 192 radically resected T2/T3 patients, we found that the prognosis of patients classified T2 is significantly better as compared to those classified T3, the 5-year OS rate being 73% vs 31% ($P<0.001$) (20). At multivariate analysis, T-stage (including the T2/T3 subcategories) was retained as an independent prognostic factor and, compared with T1a, the risk of death associated with T3 tumors was statistically greater than that associated with T2 tumors (HR: 1.89 vs 0.97) (20). These results were in line with those reported by Park and coworkers: in a large study (1,118 patients), which included patients with more than 15 lymph nodes removed and examined, they found a statistically significant 5-year survival advantage for T2 with respect to T3 tumors (85% vs 56%, $P<0.001$) (12). In addition, a significant

difference in the survival rates between T2 and T3 patients was observed when cases were stratified according to the N-stage (82% vs 60% in patients with N1, $P<0.001$; 65% vs 35% in N2 cancers, $P=0.0002$; and 52% vs 15%, $P=0.02$ in N3 cases) (12). The same investigators found that the TNM classification including the T2/T3 subcategories was significantly associated with prognosis at multivariate analysis (12).

In the present large multicentric study we confirmed the prognostic value of T2/T3 categories: the 5-year OS of T2 patients was 67%, compared with 52% for T3 cases ($P<0.001$). A statistically significant survival advantage was maintained when T and N subcategories were considered: 5-year OS was greater for T2 N0 vs T3 N0 (68% vs 63%, $P=0.015$) and for T2 N+ with respect of T3 N+ (66% vs 47%; $P<0.001$). This difference was not maintained for all N subcategories, but this could well be due to the relatively small sample size of subgroups. Moreover, the risk of death associated with T2 tumors was significantly lower than that associated with T3 tumors.

In conclusion, the new T category of UICC/AJCC classification can effectively stratify subgroups of patients with gastric cancer. These homogeneous classes of risk are independent of lymph nodes involvement: this finding could be particularly useful considering the different extent of lymph node dissection performed by surgeons.

According to our results, the new classification of the T category should be implemented in the routine clinical setting as it improves the selection of high risk patients, which can ultimately lead to identify subgroups of patients who most benefit from adjuvant treatment.

CONFLICT OF INTEREST

None of the authors has any conflict of interest regarding the manuscript: "Validation of the new AJCC TNM staging system for gastric cancer in a large cohort of patients (n=2,155): focus on the T category".

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All Authors had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends

FIGURE 1. Relationship between number of metastatic lymph nodes and number of examined lymph nodes in T2 (blue line), T3 (red line) and T4a tumors (gray line).

FIGURE 2. Kaplan-Meier survival curves for T2 and T3 tumor stage without (upper panel) and with (lower panel) nodal involvement.

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TABLE 1. Univariate analysis of Overall Survival (OS) in 686 patients with T2/T3 gastric cancer categories

Factor	No. Patients	T2 No. (%)	T3 No. (%)	5-year OS Rate (%)	95% CI	P-value
Sex						0.439
F	280	107 (39.6)	173 (41.6)	59.7	54.0-66.0	
M	406	163 (60.4)	243 (58.4)	53.7	52.4-62.7	
Age						0.00237
<65	249	88 (32.6)	161 (38.7)	64.4	58.4-71.1	
≥65	437	182 (67.4)	255 (61.3)	54.8	50.1-60.0	
Site						0.319
Lower	342	146 (54.1)	196 (47.1)	59.1	53.9-64.7	
Middle	195	85 (31.5)	110 (26.4)	64.3	57.4-71.9	
Upper	93	28 (10.4)	65 (15.6)	37.1	37.1-59.6	
Cardias	37	6 (2.2)	31 (7.5)	46.6	31.0-70.1	
Multicentric	19	5 (1.9)	14 (3.4)	56.8	38.1-84.9	
Surgery						0.492
Gastric resection	427	186 (68.9)	241 (57.9)	59.9	55.3-65.0	
Total gastrectomy	244	84 (31.1)	161 (38.7)	56.0	49.5-63.3	
Extended total gastrectomy	15	0 (0)	15 (3.4)	46.2	15.3-78.2	
D						0.02
D1	96	48 (17.8)	48 (11.5)	49.0	39.3-61.0	
D2	487	188 (69.6)	299 (71.9)	59.3	54.9-64.0	
D3	103	34 (12.6)	69 (16.6)	60.9	50.4-73.5	
Grading						0.977
G1	52	32 (11.9)	20 (4.8)	59.3	46.2-76.1	
G2	258	109 (40.4)	149 (35.8)	58.9	52.8-65.5	
G3	294	92 (34.1)	202 (48.6)	58.4	52.8-64.7	
G4	23	4 (1.5)	19 (4.6)	59.6	41.7-84.1	
G.x	59	33 (12.2)	26 (6.3)	53.8	41.9-69.1	
Lauren						0.438
Intestinal	517	198 (73.3)	319 (76.7)	61.8	57.3-66.6	
Diffuse	140	52 (19.4)	88 (21.2)	52.2	47.0-57.1	
Mixed	29	20 (7.3)	9 (2.1)	53.8	37.0-78.4	
T-stage						<0.0001
T2	270	-	-	67.3	61.1-72.8	
T3	416	-	-	52.3	47.0-57.4	
N-stage						<0.0001
N0	279	149 (55.2)	130 (31.3)	65.7	60.1-71.8	
N+	407	121 (44.8)	286 (68.7)	53.1%	48.2-58.6	
N1	126	52 (19.3)	74 (17.8)	68.3	60.3-77.4	
N2	154	49 (18.1)	105 (25.2)	53.4	45.5-62.6	
N3a	84	18 (6.7)	66 (15.9)	45.7	35.6-58.6	
N3b	43	2 (0.7)	41 (9.9)	13.9	4.8-40.3	

TABLE 2. Pattern of lymph node involvement according to T category in 686 gastric cancer patients

T Stage	N Stage											
	N0		N1		N2		N3a		N3b		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
T2	149	55.2	52	19.3	49	18.1	18	6.7	2	0.7	270	39.4
T3	130	31.3	74	17.8	105	25.2	66	15.9	41	9.9	416	60.6
Total	279	40.7	126	18.4	154	22.4	84	12.2	43	6.3	686	100

TABLE 3. 5-years Overall Survival (OS) according to T2/T3 category and N category

N stage	T2		T3		P
	5-yr OS Rate (%)	95% CI	5-yr OS Rate (%)	95% CI	
N0	68.0	60.6-76.2	63.1	54.9-72.6	0.015
N+	66.5	58.1-75.9	47.2	41.3-54.0	<0.001
N1	71.1	59.4-85.1	66.4	56.0-78.8	0.076
N2	61.2	48.2-77.6	49.9	40.4-61.5	0.264
N3a	69.1	49.7-96.2	39.1	28.3-54.0	0.032
N3b	-	-	12.5	4.0-38.4	NA

TABLE 4. Multivariate survival analysis of 686 gastric cancer patients with T2/T3 categories

Factor	P-value	HR	95% CI
T	0.005		
T3	0.005	1.420	1.110-1.817
D	<0.0001		
D2	0.000722	0.597	0.443-0.805
D3	0.808	0.952	0.641-1.413
Age	<0.0001		
≥ 65	<0.0001	1.677	1.323-2.126

HR=Hazard Ratio; CI = confidence interval

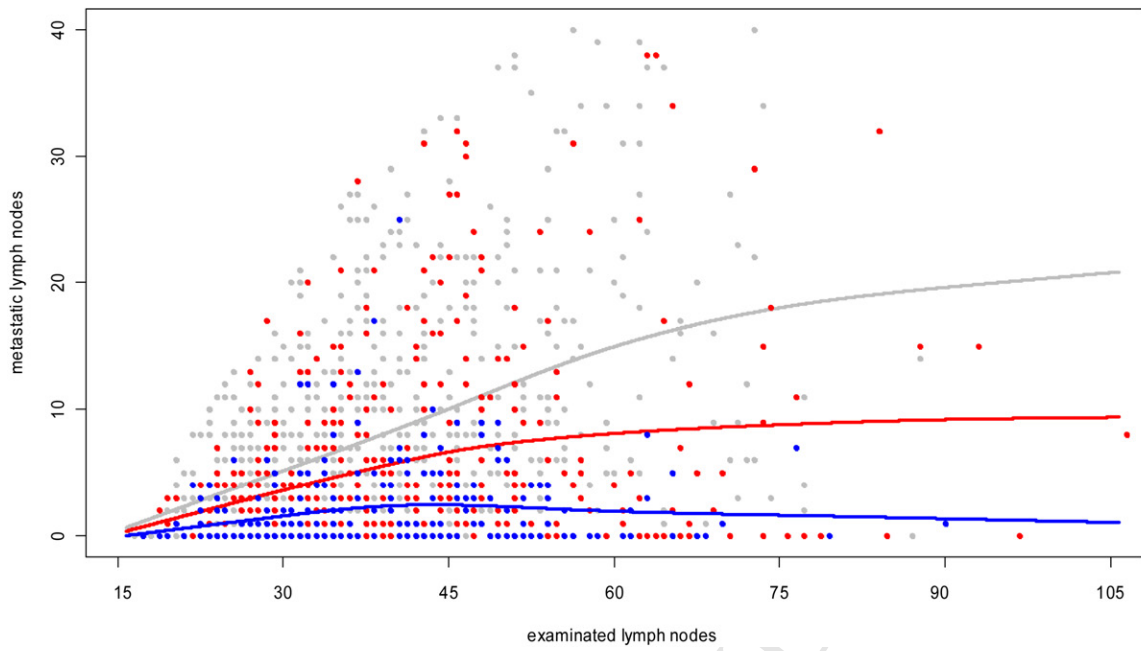


Figure 2 - upper panel

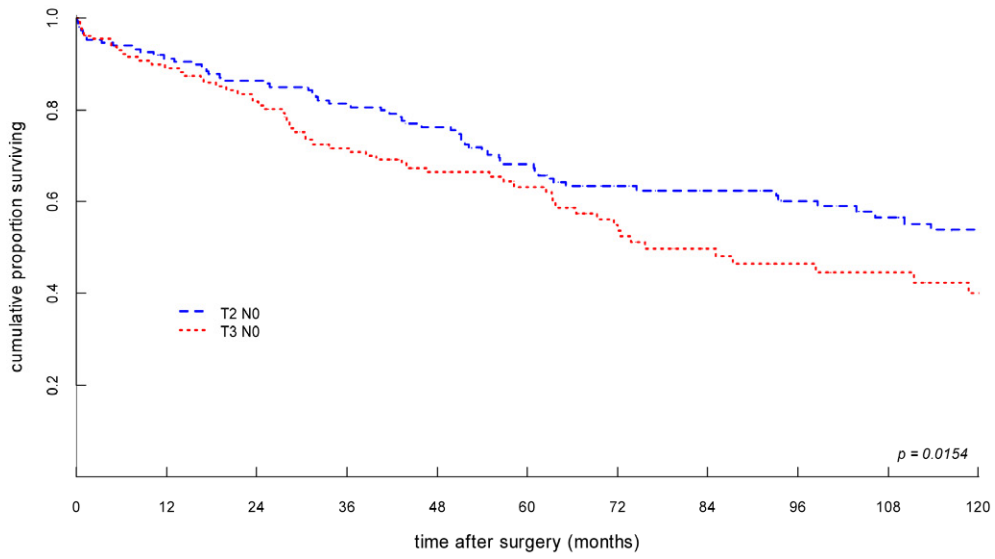


Figure 2 - lower panel

