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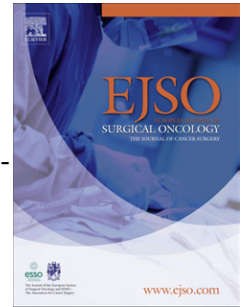
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Impact on survival of the number of lymph nodes removed in patients with node-negative gastric cancer submitted to extended lymph node dissection.

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ABSTRACT

Purpose: This study was designed to establish whether the number of lymph nodes removed has an effect on prognosis in patients with node-negative gastric cancer.

Patients and Methods: We retrospectively analyzed data of 114 consecutive patients who underwent gastrectomy and extended lymph node dissection for node-negative adenocarcinoma of the stomach between 2000 and 2005 . Standard survival methods and restricted cubic spline multivariable Cox regression models were applied.

Results: Median age was 63 years and 67 patients out of 114 (59%) were males. Median number of dissected LNs was 22 (range 2-73). Median follow-up was 76 months. Patients who had ≤ 15 nodes removed had significantly worse distant disease free survival, disease free survival and overall survival at multivariable analysis than other patients. The results did not change when pT1 and pT2-3 cancer patients were analyzed separately. The risk of distant metastases decreased as the number of dissected lymph nodes increased (>15).

Conclusions: More extended lymph node resection offered survival benefit even in the subgroup of patients with early stage disease. Lymphadenectomy involving more than 15 lymph nodes should be performed for the treatment of node-negative gastric cancer.

Synopsis: The impact on survival of the number of lymph nodes removed in patients with node-negative gastric cancer has not been established . This study suggests that more extended lymph node resection offers protection, as patients who had ≤ 15 nodes removed had significantly worse disease free survival and overall survival at multivariate analysis than patients in whom >15 nodes were removed.

Key words: gastric cancer, gastrectomy, extended lymph node dissection, TNM classification, preoperative chemotherapy.

INTRODUCTION

Background

Despite a declining incidence in the Western world, gastric cancer still is a major malignant disease and the second leading cause of cancer mortality worldwide (1). The prognosis of a locally advanced tumour is generally poor in Western surgical and population-based series, with a 5-year overall survival of 25% or less (2), in spite of apparently radical excision of the gastric and nodal components of the disease.

The extent of lymphadenectomy in the treatment of gastric cancer still is a matter of worldwide debate, since the introduction of extended lymphadenectomy (D2) by Japanese surgeons in the 1960s. While Japanese surgeons routinely perform a D2 dissection, the rationale being that the orderly centrifugal pattern of lymphatic tumour dissemination allows for the prediction of the risk of metastasis to specific nodal groups (3), many Western surgeons perform more limited (D1) lymph node dissection, not having found advantages with extensive lymphadenectomy in two large European randomized clinical trials (4, 5) and one meta-analysis (6). Current evidence is compatible with no benefit from D2 resection, but also with substantial benefit in a subgroup of patients with advanced N2 disease, or in all patients after a long-term (15-year) follow-up (7). Furthermore, the benefit from D2 resection is evident only when operative mortality is less than 2%, a result that is achievable only by centres of excellence with a high-volume experience in the resection of gastric cancer (8-10). Previous studies have shown that survival of patients with locally advanced gastric adenocarcinoma is related to the number of regional lymph nodes (LNs) with metastases (11). As the probability of identifying node-positive cancers increases with the number of LNs removed and examined, the UICC-TNM Classification of Malignant Tumours recommends the removal and examination of at least 16 LNs for adequate staging.

Purpose of the study

Extent of lymphadenectomy could play an important role also in less advanced disease. While prospective randomized studies have shown that the lymph node yield is much greater with D2 than with D1 resection, the effect of the number of surgically removed nodes on survival in node-negative gastric cancers has not been established.

Specifically, what still is unclear is whether evaluating more than 15 nodes offers any disease-free or overall survival benefit in this clinical setting. This was the aim of the present study, which evaluated the contribution of the number of removed cancer-negative nodes to the long-term outcome of patients with gastric cancer submitted to D2 dissection.

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PATIENTS AND METHODS

Patient population

We analyzed data of 100 consecutive patients admitted to the Department of General Surgery of the European Institute of Oncology (IEO) in Milan for adenocarcinoma of the stomach between 2000 and 2005. They all underwent gastrectomy (total or sub-total) and extended lymph node dissection, resulting in node-negative disease. Fourteen additional patients, who were referred to IEO for a second opinion, were taken into consideration; they had undergone the same surgical procedure elsewhere and a comprehensive assessment of their clinical records showed that the pathologic stage of their tumours was the same. Data for this study were extracted from the IEO Tumour Registry (TR), an Institutional database activated in March 2006, with the objective of collecting data on all individuals consulting the IEO, independently of whether they actually received treatment at the Institute or not (12). The inclusion criteria for the present study population were: no previous diagnosis of other cancers, radical resection (R0), pathologic diagnosis of adenocarcinoma of the stomach, no LN involvement and no synchronous distant metastases (any pT, pN0 and M0, according to the UICC-TNM Classification). No age limits were defined. This study was approved by the Scientific Research Committee of IEO.

Diagnosis and staging procedures

All patients affected by pathologically-proven adenocarcinoma of the stomach were submitted to a preoperative staging work-up in the attempt to perform curative surgery. It included a physical examination, a CT scan of the abdomen and pelvis, a chest X-ray (or Thorax CT scan in selected cases), a liver US scan, a gastric Endoscopic Ultrasound scan (in selected cases), and upper GI endoscopy and confirmatory biopsies, if they had not already been performed at our Institution. Preoperative PET scan was not routinely used in this clinical series, as at that time it was not available for routine use. Patients were considered eligible for gastrectomy and extended lymph node D2 dissection when they had no evidence of metastatic spread according to preoperative investigations.

Surgical technique

First of all, careful intraoperative staging of disease was performed, in order to rule out peritoneal seeding, ovarian involvement, “drop” metastasis in the pelvis, or gross periaortic adenopathy.. The extent of gastrectomy depended on the proximal distance of the tumour from the cardias: total gastrectomy was performed in all patients with cardias involvement and in the presence of antral and/or body tumours, when a 6-cm gross proximal margin could not be obtained.

Lymphadenectomy included excision of all N1 and most N2 stations (stations 7, 8, 9 and station 11), according to the classification of the Japanese Research Society for the Study of Gastric Cancer (JRSGC) (13, 14). Hepatoduodenal ligament nodes (station 12) were also dissected, limiting the lymphadenectomy to station 12a (left side of the hepatic artery), and leaving parts b and p of the station (right side of the ligament and the part immediately posterior to the portal vein, respectively) undissected. LNs of the surgical specimen were routinely dissected by experienced pathologists with standard techniques. Caudal pancreas was always preserved, according to Maruyama’s technique, even when splenectomy was performed, unless direct involvement of the tumour was clinically evident (15).

Statistical methods

Kruskal-Wallis Test, Chi-square test and Mantel-Haenszel Chi-Square for trends were used to test differences in distributions between patients who had >15 LNs dissected and those who had ≤ 15 .

Distant disease-free survival (DDFS) was defined as the time free of both tumour recurrence at distant sites and death from any cause. Other primary tumours were considered as censoring events. Disease-free survival (DFS) was calculated from the date of surgery to any loco-regional or distant recurrence, other primary tumour and death from any cause. Overall survival (OS) was calculated from the date of surgery to death from any cause. In the absence of any of the above-mentioned events, survivals were censored at last follow-up visit. Survival curves were estimated using the Kaplan-Meier method and compared by the Log-rank test. The prognostic impact of the number of extracted LNs on

survival was evaluated using the multivariate Cox proportional hazard regression model and expressed as hazard ratio (HR) with 95% Confidence Intervals (CI).

The functional form of the relationship between DDFS and the number of dissected LNs analysed as a continuous variable was evaluated fitting a restricted cubic spline multivariable Cox regression model (16). Three knots were placed at quartile values (17, 22 and 29 LNs). Other numbers and positions of knots were examined, and the curves were similar. The model was adjusted for pT, neoadjuvant treatment and place of surgery.

All analyses were carried out with the SAS software (SAS Institute, Cary, NC) and the R software (The R Development Core Team 2004; Free Software Foundation, Boston, MA). All tests were two-sided.

RESULTS

Patient characteristics

Sixty-seven patients out of 114 (58.8%) were males. Median age was 63 years (range 31-87). Median number of dissected LNs was 22 (range 2-73). One hundred patients (87.7%) underwent surgery at the IEO, 14 at other Institutes. Table 1 shows patient and tumour characteristics, stratified by number of dissected LN (≤ 15 LNs versus >15 LNs). Twenty-four patients had ≤ 15 LNs removed, 90 patients had >15 LNs harvested (45 of them >25 lymph nodes). The only significant difference between the two groups was the number of patients who received neoadjuvant chemotherapy: it was significantly higher in the limited lymphadenectomy group ($P=0.03$), as expected.

Survival findings

Median follow-up was 76 months (range 5-129). No patients had a local or regional recurrence, 8 had distant metastases and 11 experienced a second primary cancer at a site other than the stomach. Overall, 9 patients died.

At the univariate survival analysis (Table 2), pT and the number of dissected LNs were found to be associated with DDFS, while the latter was the only statistically significant variable associated with OS.

Figure 1 shows DDFS by number of dissected LNs. Patients with extracted LNs ≤ 15 had a worse prognosis than other patients: adjusted HR 8.1 (95% C.I. 2.5-25.7). This result remained statistically significant even after stratifying for pT (data not shown). The number of dissected nodes had a significant impact also on DFS: adjusted HR of LNs ≤ 15 versus LNs > 15 was 3.1 (95% C.I. 1.3-7.6).

Figure 2 shows OS with stratification by number of dissected LN. Once again, patients with a lower number of nodes had a worse prognosis than patients with a number of nodes exceeding 15, even after stratifying for pT. Multivariable analysis was not performed in the analysis of OS due to the low number of deaths. DDFS, DFS and OS were significantly associated with the number of dissected LNs even after the exclusion of patients receiving neoadjuvant chemotherapy and patients not operated at IEO ($N=87$). pT-adjusted HRs of LNs ≤ 15 versus LNs > 15 were 8.4 (95% C.I. 1.8-38.2) and 3.9 (95% C.I. 1.2-12.2) for

DDFS and DFS, respectively. Univariate analysis of OS showed that patients with extracted LNs ≤ 15 had a worse prognosis than other patients (Log-rank $P < 0.001$).

Figure 3 shows the DDFS risk by number of LNs analyzed as a continuous variable. Fifteen LNs were chosen as reference (HR=1). The risk of the event was inversely proportional to the number of dissected LNs, even over 15 LNs, up to about 20 LNs; thereafter it slightly increased as the number of dissected LNs increased..

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DISCUSSION

Our study was primarily aimed at answering the question whether the number of surgically removed cancer-negative nodes has an effect on distant disease-free (DDFS) and overall survival (OS) in patients with any pT, pN0 TNM-staged gastric cancer, who underwent gastrectomy with extended (D2) lymphadenectomy. The results obtained indicate that patients who have > surgically removed 15 LNs have a statistically significant survival advantage, both in terms of DDFS and OS. Moreover, the evaluation of DDFS risk by number of harvested LNs - analyzed as a continuous variable – suggested that the risk of events was inversely proportional to the number of dissected LNs up to about 20 LNs. Interestingly, the results persisted even when pT1 (“early gastric cancer”) and pT2-3 cancers (locally advanced) were considered separately, thus indicating the need to remove at least 15 nodes also in patients with early stage disease.

Extent of lymphadenectomy in the treatment of locally advanced and early gastric cancer. Its role in pN0 disease.

The extent of lymphadenectomy in the treatment of gastric cancer is still a matter of debate. The first large multicentre randomized study that compared D1 and D2 dissection was conducted in the Netherlands by the Dutch Gastric Cancer Group (4). A total of 711 patients underwent a curative resection (380 in the D1 group and 331 in the D2 group). Morbidity (25 vs. 43%) and mortality (4 vs. 10%) were higher following D2 dissection. Five-year survival rates were similar in the two groups: 45% for the D1 group and 47% for the D2 group. Improved survival was seen in patients with N2 cancer who underwent extended lymph node dissection, but unfortunately it remains difficult to correctly identify patients with N2 disease in preoperative or intraoperative settings. Moreover, as the authors identified splenectomy and pancreatectomy as contributing risk factors for increased morbidity and mortality, they concluded that extended lymph node dissections may be beneficial if morbidity and mortality can be avoided (4). In the most recent update, after 15 years of follow-up, D2 lymphadenectomy was associated with lower locoregional recurrence and tumour-related death rates than D1 surgery (7). Because a safer, spleen-preserving D2 resection technique is available in many centres, authors reached the conclusion that D2 lymphadenectomy is the recommended surgical approach for patients

with resectable disease. D2 gastrectomy is a safe treatment for gastric cancer in Western patients, at least when it is performed at experienced centres (9, 10); moreover, gastric cancer resection should probably be added to the growing list of procedures that are safer when they are performed at high-volume institutions (17). A second large randomized multicentre trial comparing D1 with D2 dissection was conducted by the British Medical Research Council (MRC) (5). Four hundred patients were randomly assigned to treatment (200 to D1 and 200 to D2). The results showed that the D2 group had greater postoperative hospital mortality (13 vs. 6.5%; $p = 0.04$) and higher overall postoperative morbidity (46 % vs. 28%; $p < 0.001$). The five-year survival rates were 35% for D1 resection and 33% for D2 resection. The authors concluded that D2 resection offered no survival advantage over D1 surgery. A more recent single-centre randomized study in Taiwan (18, 19), where 110 patients were randomly assigned to D1 surgery and 111 patients to D3 surgery, demonstrated a survival benefit from extended lymphadenectomy. The morbidity rate was higher after D3 than after D1 resection (17.1 vs. 7.3%). The overall five-year survival was significantly higher in patients in the D3 group than in the D1 group (59.5 vs. 53.6%; $p = 0.041$). A recent meta-analysis (6) reviewing 14 randomized clinical trials (3,432 patients overall), published in 2009 before the acquisition of the 15-year results of the Dutch Trial, confirmed that operative mortality and postoperative morbidity were higher in the D2 group than in the D1 group, and the three- and five-year survival rates were not statistically different.

The Japanese Research Society for the Study of Gastric Cancer (JRSGC) strongly recommends extended lymphadenectomy, although it is still unclear, in terms of high level scientific evidence, whether this procedure improves survival or merely refines staging (20, 21). It is well known that overall survival rates after radical surgical treatment for gastric cancer at Western and Japanese institutions differ substantially. When new lymph node metastases are identified as a consequence of more extended lymphadenectomy and/or more accurate pathologic techniques, nodal staging determines a stage migration of the disease (22). This is a possible explanation of the frequent underestimation of tumour stage in Western series, due to incomplete removal of the LNs necessary for accurate staging. This could partly explain also our findings. We were not able to ascertain whether the difference in the number of lymph nodes found is related to differences in surgical technique or in the quality of histopathological dissection; as a matter of fact, 14 patients were operated on elsewhere and strict adherence to surgical rules of D2 dissection could not be verified. However, in our study DDFS (Fig.1) was adjusted also by surgical centre,

together with pT stage and preoperative chemotherapy occurrence. From the U.S. National Cancer Data Base Report of 2000, we know that only 18% of U.S. patients have ≥ 15 LNs analyzed (23). It is unlikely that selective lymphadenectomy, based upon the gross appearance of LNs, is feasible or appropriate, as 30% of LN metastases occur in nodes less than 3 mm in diameter (24) and surgeons are probably able to correctly diagnose metastatic involvement by macroscopic appearance in only 20% of patients (25). Intraoperative assessment of frozen lymph node sections seems practically unfeasible and largely invalidated by the occurrence of the “skip metastasis” phenomena, as 11% of patients with negative perigastric nodes show metastatic deposits in more distant nodes, even in pT1 tumours (26).

This adds further points of discussion related to the issue of lymph node dissection in T1 tumours (adenocarcinoma confined to submucosa, EGC: Early Gastric Cancer). The incidence of early gastric cancer has recently increased as advances in diagnostic techniques have made it possible to detect small lesions at an early stage. It was reported that radical lymph node dissection should be limited in patients with EGC, because extended lymph node dissection in these patients offers modest survival benefits (26, 27, 28). Consequently, new treatment modalities with minimally invasive techniques, such as endoscopic resection, laparoscopic gastrectomy, and robotic surgery, are becoming more frequent in EGC patients. These minimally invasive techniques are focused on enhanced recovery after surgery (ERAS) and improving quality of life, as the survival rates of EGC patients are high (29, 30, 31, 32). A very recent paper (33) assessed the feasibility of radical distal gastrectomy with a mini-laparotomic approach in EGC patients in terms of long-term survival. A mean of approximately 30 LNs were harvested, and no difference in terms of DFS and OS arose from the comparison with a matched series of patients undergoing conventional surgery with a laparotomic approach through a long midline incision. As in our study, no locoregional recurrence to the regional LNs or carcinomatosis peritonei occurred.

Another recent paper (34) assessed oncological outcomes following laparoscopy-assisted versus open gastrectomy in patients with lymph node-positive EGC. Mean number of retrieved LNs did not differ between the two groups. During a median follow-up of 35 months, 14 patients (8.6%) developed recurrence after open surgery, compared with 4 patients (9.5%) after laparoscopy procedure. Overall 5-year disease-free survival was 89.9% and 89.7% respectively. Lymph node metastatic status was the only independent

prognostic factor for disease-free survival. These data reinforce the assumption that an adequate number of LNs must be harvested, independently of the technique adopted.

Findings obtained by another Italian group (Italian Research Group for Gastric Cancer) were somewhat different. This Group collected and analyzed the clinical and pathological characteristics of 301 lymph node-negative advanced gastric carcinoma patients in a multicentre retrospective study on gastrectomy and D2 lymphadenectomy. The factors associated with better disease-free survival at univariate analysis were age <60, T2 tumours, distal location, intestinal histotype, and number of retrieved nodes >25, whereas in our study disease-free and overall survival were similar in patients having 16-25 or >25 nodes removed. In this study depth of infiltration and histotype were the only 2 independent predictors of 5-year recurrence-free survival at multivariate analysis (35).

Future perspectives

Worthy of a final comment is the potential value of sentinel node technique in the identification of the nodes to be removed. A recent study compared lymphatic mapping in early gastric cancer with indocyanin green (IG) and infrared ray electronic endoscopy (IREE) to IG alone (36). The sentinel node identification rate and sensitivity for IREE versus ICG alone were 99.5 and 85.8% versus 97.0 and 48.4%, respectively. The Authors concluded that dissection of the lymphatic basin, based on IREE, is a safe method of nodal dissection in patients with T1 or limited T2 tumours. These interesting findings need confirmation by larger well-designed studies.

Limitations of this study

Our study suffers from some limitations. The main limitation is that it was a retrospective study, notwithstanding the added value provided by the accurate methodology used for the statistical analyses. Moreover, the low number of patients with a very large number of LNs removed (i.e. only 8 patients had more than 40 dissected LNs) may have led to unreliable risk estimates for that group of patients. Sampling error is a likely explanation for the slight increase in the risk of recurrence when many LNs were removed, as shown in Fig.3.

Thirteen patients received neoadjuvant chemotherapy; this is a potential confounding factor that could influence the pathology assessment of lymph node status, as well as patient survival. As shown in Table 1, preoperative neoadjuvant treatment had an impact on the number of harvested lymph nodes, which was significantly lower. Nevertheless, survival curves were adjusted in our study also for this variable, and the protective effect of the number of removed lymph nodes on survival was maintained (Fig. 1).

Finally, we did not stratify the study population in terms of histological type (intestinal vs diffuse/mixed adenocarcinoma, according to Lauren's classification). However, we analyzed tumor grading (1 to 4) and did not find significant differences in its distribution in the groups (Table 1).

Conclusion

In conclusion, more extended lymph node resection resulted in survival benefit, both in terms of DDFS and OS, for patients suffering from node-negative gastric cancer; moreover, evaluation of DDFS risk by number of harvested LNs demonstrated that the risk of events is inversely proportional to the number of dissected LNs, up to 20. Interestingly, the results did not change when pT1 ("early gastric cancer") and pT2-3 cancers (locally advanced) were analyzed separately, suggesting the need to remove at least 15 nodes even in patients with early stage disease.

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Table 1: Patient characteristics, with stratification for number of dissected lymph nodes

		All patients No. 114	Dissected lymph nodes ≤ 15 No. 24	Dissected lymph nodes > 15 No. 90	χ^2 test P-value
Age	Median (Range)	63 (31-87)	62 (39-78)	63 (31-87)	0.88 ^b
Age	<50	17	2	15	0.45
	50-64	50	13	37	
	≥65	47	9	38	
Sex	M	67	18	49	0.10
	F	47	6	41	
Type of Adenocarcinoma	Intestinal	50	10	40	0.80
	Diffuse	64	14	50	
pT	1	52	12	40	0.25 ^c
	2	46	9	37	
	3	13	1	12	
	X	3	2	1	
Grading ^a	1	16	6	10	0.79 ^d
	2	37	5	32	
	3	36	5	31	
	4	6	2	4	
	NA	13	6	7	
Neoadjuvant treatment	Yes	13	6	7	0.03
	No	101	18	83	

NA: Not Applicable. ^aInformation is missing for some patients; ^bKruskal-Wallis Test ^cpTX excluded. P-value from the Mantel-Haenszel Chi-Square for trend; ^dG1/G2 vs. G3/G4

Table 2: Survival by clinico-pathological characteristics

		At risk	DDFS Events (%)	P-value	OS Events (%)	P-value
All patients		114	14 (12)		9 (8)	
Age	<50	17	2 (12)	0.68	0 (0)	0.38
	50-64	50	5 (10)		4 (8)	
	≥65	47	7 (15)		5 (11)	
Sex	M	67	9 (13)	0.59	6 (9)	0.63
	F	47	5 (11)		3 (6)	
Type of Adenocarcinoma	Intestinal	50	7 (14)	0.64	5 (10)	0.52
	Diffuse	64	7 (11)		4 (6)	
pT	1	52	3 (6)	0.08 0.03 ^a	3 (6)	0.64 0.35 ^a
	2	46	8 (17)		5 (11)	
	3	13	3 (23)		1 (8)	
Number of dissected lymph nodes	2-15	24	8 (33)	<0.01	7 (29)	<0.01
	16-25	45	3 (7)		1 (2)	
	>25	45	3 (7)		1 (2)	
Grading	1-2	53	5 (14)	0.51	4 (8)	0.98
	3-4	42	6 (17)		3 (7)	
Neoadjuvant treatment	Yes	13	2 (15)	0.76	2 (15)	0.32
	No	101	12 (12)		7 (7)	

DDFS: Distant Disease Free Survival; OS: Overall Survival; P-value from the Log-rank test. ^apT1 vs pT2/3

Figure 1: Distant disease free survival with stratification for number of dissected lymph nodes

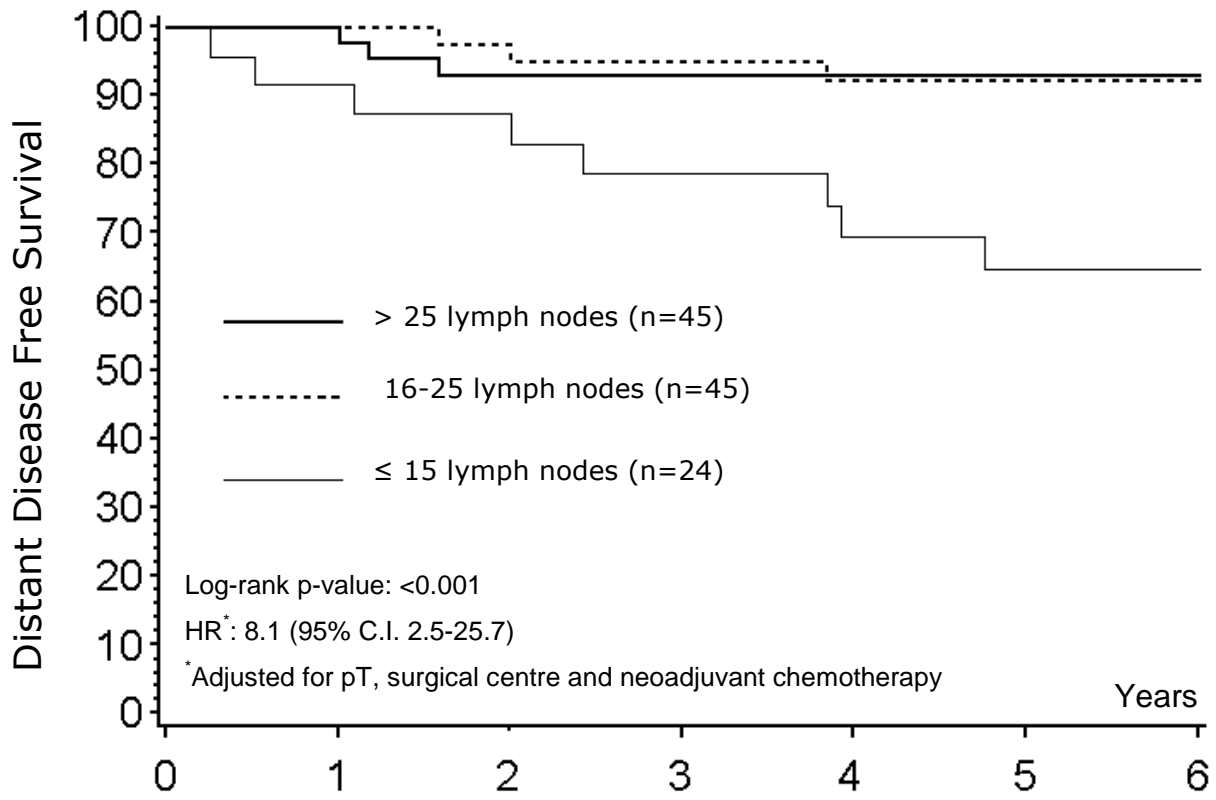


Figure 2: Overall survival with stratification for number of dissected lymph nodes

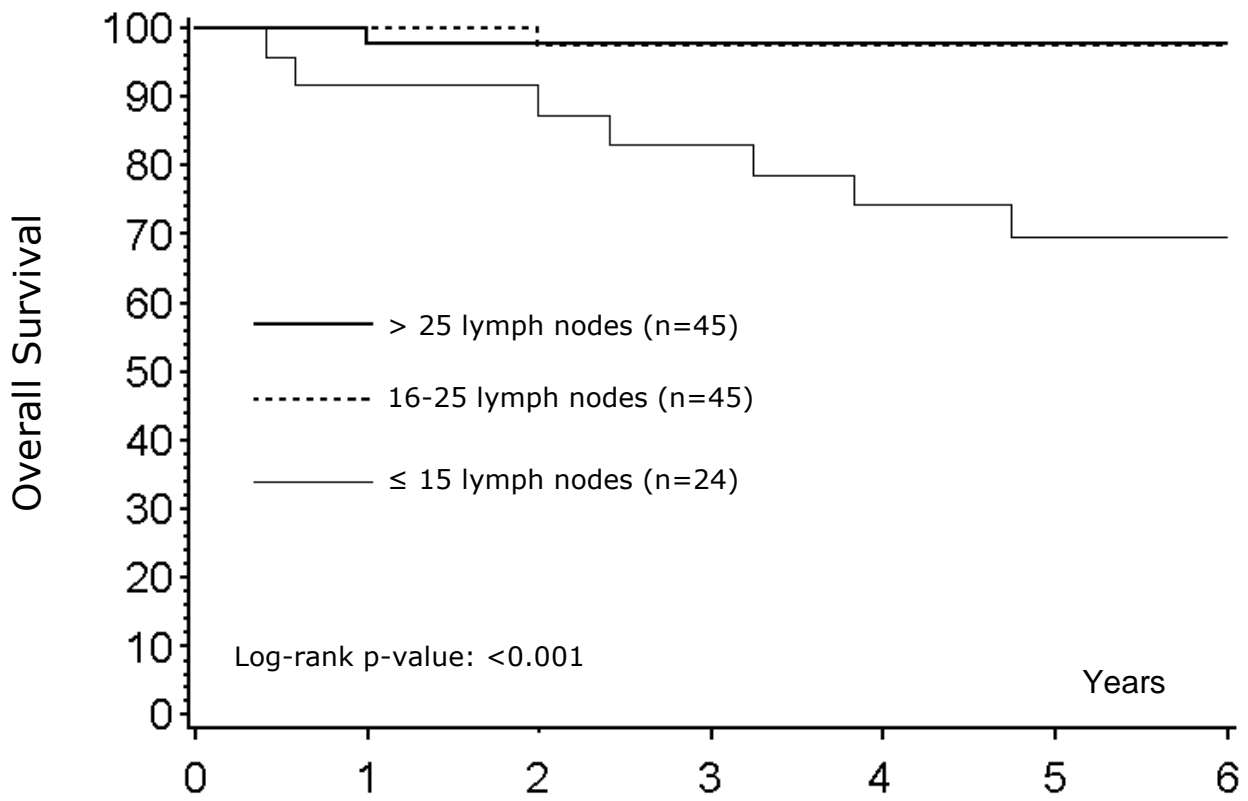
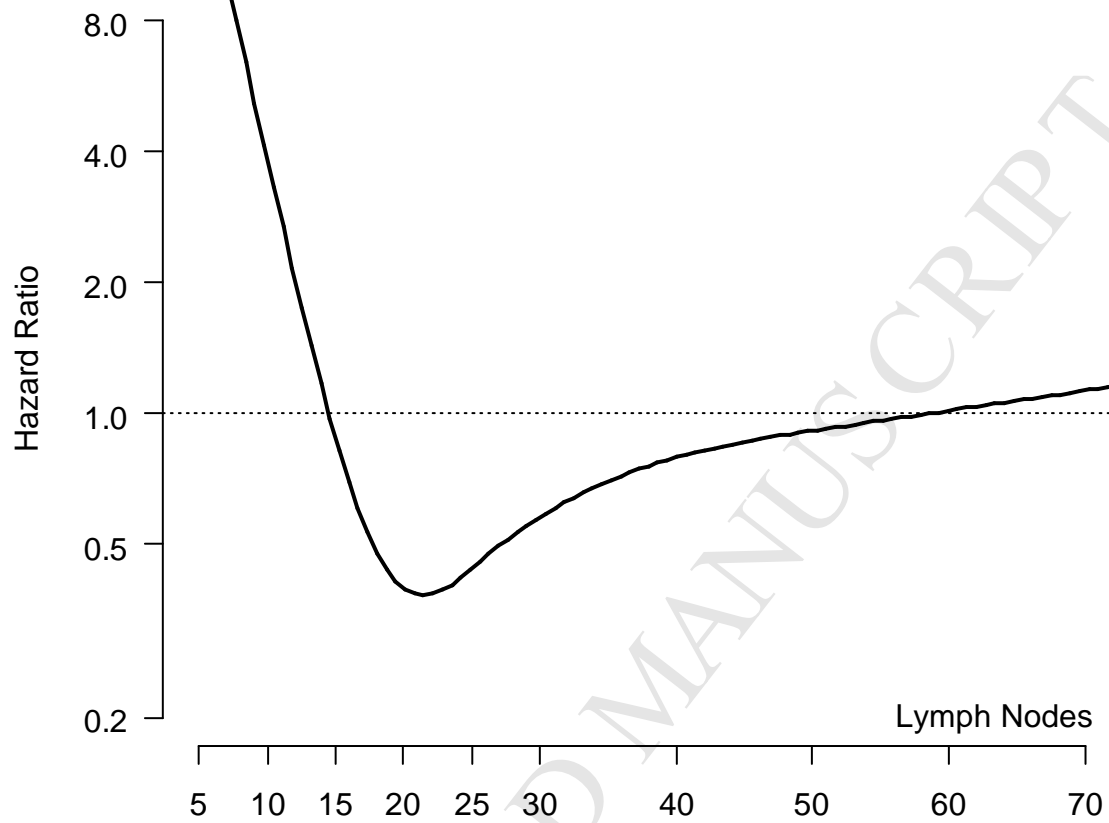


Figure 3: Distant disease free survival according to number of dissected lymph nodes



HR is plotted on a log scale. HR was adjusted for pT, surgical centre and neoadjuvant chemotherapy. 15 lymph nodes is the reference (HR=1).