International Scholarly Research Network
ISRN Pathology
Volume 2012, Article ID 519351, 8 pages
doi:10.5402/2012/519351

Clinical Study

Assessment of Histopathological Response in Gastric and Gastro-Oesophageal Junction Adenocarcinoma following Neoadjuvant Chemotherapy: Which Scoring System to Use?

A. Mirza,[1] A. Naveed,[1] S. Hayes,[2] L. Formela,[2] I. Welch,[1] C. M. West,[3] and S. Pritchard[1]

[1] *Departments of Gastrointestinal Surgery and Histopathology, University Hospital of South Manchester, Manchester M23 9LT, UK*
[2] *Salford Royal NHS Foundation Trust, Manchester M6 8HD, UK*
[3] *Translational Radiobiology Group, School of Cancer and Enabling Sciences, The University of Manchester, Manchester Academic Health Science Centre, Christie Hospital NHS Trust, Manchester M20 4BX, UK*

Correspondence should be addressed to C. M. West, catharine.west@manchester.ac.uk

Received 26 June 2012; Accepted 19 July 2012

Academic Editors: A. Navarro, A. Stringer, and T. Yazawa

Background. The standard of care for patients with operable gastric and gastro-oesophageal junction (GOJ) tumours involves neoadjuvant chemotherapy. This improves survival and reduces risk of tumour recurrence following surgery. The various grading criteria published to assess histological response to neoadjuvant treatments have never been compared in terms of their reproducibility and ability to predict survival. *Methods*. A study was carried out of 66 patients with gastric and GOJ (types II and III) adenocarcinoma treated with neoadjuvant chemotherapy according to the MAGIC protocol. Histology slides were reviewed independently by two histopathologists using three published grading systems (Mandard, Japanese, and Becker). Histological, demographic, and survival data were collected. The kappa statistic was used to assess interobserver reproducibility. *Results*. Three (5%) patients had a complete pathological response. There was reasonable interobserver agreement for the grading systems: κ-scores = 0.44 (Mandard), 0.28 (Japanese), and 0.51 (Becker). Only Mandard and Becker scores provided prognostic information: 5-year overall survival rates of 100% for complete or near complete responders versus 35% for nonresponders ($P < 0.05$) for both. Positive lymph nodes ($P = 0.004$) and resection margins ($P = 0.004$) were associated with poor survival. *Conclusion*. Becker's score is most reproducible for the evaluation of histological response. Furthermore, lymph node and resection margins status provides prognostic information.

1. Introduction

Gastric cancer is the fourth most common cancer in the world with an annual incidence of approximately one million [1]. In the UK, there are an estimated 7,700 new diagnoses and 5,200 deaths from the disease each year [2]. Over the past two decades there has been a change in the anatomical subsite distribution of gastric cancer, with a trend for tumours to develop more in the proximal stomach, especially around the gastric cardiac area rather than the distal part of the stomach [3]. It is thought that the lower oesophageal tumours may also be associated with an increasing incidence of gastro-oesophageal reflux disease [4]. These anatomical changes and risk factors have contributed to the increased incidence of gastro-oesophageal junction (GOJ) tumours, which are now classified as a separate group [5].

The TNM staging classification dictates the subsequent management of a gastric tumour. Primary resection of the malignant tumour is the standard treatment for operable disease. The landmark MAGIC trial conducted by the Medical Research Council (MRC) of the UK showed use of neoadjuvant combination chemotherapy involving epirubicin, cisplatin, and 5-FU improved five-year disease-free survival in comparison with patients not receiving chemotherapy prior to surgery [6]. In many countries neoadjuvant chemoradiotherapy is the standard of care for operable disease. The neoadjuvant therapy is used to decrease the tumour bulk and improve the rate of complete surgical

clearance following resection, with the aim of improving survival and reducing risk of tumour recurrence. The evaluation of histological changes in the tumour resection specimen is a method of assessing response to neoadjuvant therapy, and there is evidence that histological response correlates with survival [7].

Table 1 describes three main scoring systems in the evaluation of histological response in gastric (Becker, Ninomiya) and oesophageal (Mandard) cancer. The findings from published studies using these grading systems to assess histological response to either neoadjuvant chemotherapy or chemoradiotherapy are summarised in Table 2. Both microscopic and macroscopic features of a tumour are used to assess response and the absence of cancer cells in the resected specimen represents a complete response [8]. Less than 30% of patients receiving neoadjuvant therapy achieve a complete pathologic response [9].

Comparisons between studies and use of response criteria in routine practice are hampered by the lack of a universally accepted grading system. To date, no study has compared the different scoring systems in terms of their reproducibility and ability to indicate prognosis. Therefore this study aimed to compare published scoring systems in terms of their reproducibility between observers and relationships with prognosis.

2. Methods

2.1. Patient's Characteristics. A study was carried out of 66 patients with locally advanced gastric and GOJ (types II and III) tumours treated with surgery at the University Hospital of South Manchester and Salford Royal NHS Foundation Trust. Inclusion criteria were as follows: diagnosis of histologically proven adenocarcinoma, locally advanced disease, patients fit for surgery, and neoadjuvant chemotherapy. Patients underwent a standard staging protocol of CT scanning, EUS, and staging laparoscopy. The patients were treated with perioperative chemotherapy according to the MAGIC protocol [6]. The chemotherapy was administered for three cycles pre- and postoperatively. A cycle consisted of epirubicin (50 mg/m^2) by intravenous bolus and cisplatin (60 mg/m^2) intravenously with hydration on day one and 5-FU (200 mg/m^2) daily for 21 days by continuous intravenous infusion. After completion of neoadjuvant chemotherapy patients were restaged with a CT scan of the abdomen and chest. The radiological assessment of response was evaluated. In the absence of metastatic disease patients underwent partial or total gastrectomy depending upon the site of the tumour along with D2 lymphadenectomy. Patients with GOJ tumour underwent Ivor-Lewis oesophagectomy. Five consultant surgeons were responsible for the surgical management of the patients. A feeding jejunostomy was inserted in all cases for postoperative nutritional support. Following surgery patients were treated with adjuvant chemotherapy for further three cycles. Patients were subsequently followed up in outpatient clinics. The demographic details of patients which included age, gender, survival status, and follow-up data were collected. The date of tumour recurrence and subsequent management were also recorded. The patient's disease-free survival was calculated from the time of surgery to the time of diagnosis of recurrence or death without recurrence. Overall survival was analysed from the date of surgery to the date of last followup or death. The cancer-specific survival was analysed for all patients from the date of diagnosis to the date of death from cancer or the last followup.

2.2. Histological Review and Scoring Method. The histology slides were obtained from the resection specimen and each case was reviewed independently by two histopathologists. A proforma was developed to collect data for each patient, which included the tumour site, ypTNM stage, tumour differentiation, and status of resection margins. The histological response was scored using all three grading systems described in Table 1. When discrepancy arose, a consensus was reached between the two histopathologists.

2.3. Statistical Analysis. The Kappa score (κ-score) was used to assess interobserver agreement in evaluation of histological response. The κ-score is a statistical measure to assess the reliability of agreement between observers when assessing categorical ratings to a number of items. Landis and Koch provided information for interpreting κ-scores [15]. Histological characteristics including ypTNM, histological grade, and resection margin status were compared against survival. Survival curves were plotted using the method of Kaplan-Meier. Univariate analyses were performed using the log-rank test. A P value < 0.05 was considered statistically significant. SPSS version 16 (SPSS, Chicago, IL, USA) was used for statistical analyses.

3. Results

Data were collected for 66 patients who received neoadjuvant chemotherapy prior to surgery. The average number of preoperative cycles received was 2 (range, 1–3). Thirty-one (47%) patients underwent postoperative chemotherapy with an average of 2 cycles (range, 1–3). Table 3 summarises the characteristics of the study population. The mean age of the patients was 62 years (95% confidence interval (95% CI), 59–64 years). The total number of blocks studied per case was variable with a mean of 6 blocks (range 4–16). For patients with complete response, an average of 12 blocks (range 9–16) was examined histologically. The mean time from diagnosis to surgery was 4 months (range 2–7). Tumour recurrence was documented in 20 (30%) patients who underwent a palliative course of chemoradiotherapy. The mean time for tumour recurrence was 16 months (95% CI, 8–24 months). Twenty-five (38%) patients died during the course of the study and 6 (9%) patients had documented progressive disease and were undergoing further treatment. The mean survival time recorded following surgery was 21 months (95% CI, 15–28 months).

κ-scores were calculated to assess the inter-observer agreement in recording histological response (Table 4). All of the calculated scores were >0.20 showing an acceptable

Table 1: Histological response criteria following neoadjuvant chemotherapy in gastric cancers.

Reference	Scores	Criteria
Mandard et al. [7]	TRG 1	Absence of residual cancer and fibrosis extending through the layers of oesophageal wall
	TRG 2	Presence of rare residual cancer cells
	TRG 3	Increase in number of residual cancer cells, but fibrosis still predominant
	TRG 4	Showing residual cancer out-growing fibrosis
	TRG 5	Absence of regressive changes
Ninomiya et al. [10]	Grade 0	No change ± neither necrosis nor cellular or structural change can be seen throughout the lesion
	Grade 1	1(a) Necrosis or disappearance of the tumour is present in less than 1/3 of the whole lesion 1(b) Necrosis or disappearance of the tumour is present in no more than 2/3 of the whole lesion
	Grade 2	Moderate change ± necrosis or disappearance of the tumour is present in more than 2/3 of the whole lesion, but viable tumour cells remain.
	Grade 3	Marked change ± the whole lesion falls into necrosis and/or is replaced by fibrosis, with or without granulomatous changes. No viable tumour cells.
Becker et al. [11]	1A	No residual tumour/tumour bed
	1B	<10% tumour cells
	2	10–50% residual tumour/tumour bed
	3	>50% no signs of neoplastic regression

Table 2: Scoring grades and published studies with type of chemoradiotherapy used and level of completed response achieved.

Study	Chemotherapy	Radiotherapy	Patients	CR	Survival
Mandard et al. [7]	Cisplatin	37 Gy in 10 fractions of 3.7 Gy	93	18 (19%)	2-year OS 60%
Ninomiya et al. [10]	5-FU, leucovorin, etoposide, cisplatin	—	18	0	2-year survival 28%
Becker et al. [11]	Etoposide, doxorubicin, cisplatin	—	36	0	5-year survival 27%
Lowy et al. [12]	5-FU	45 Gy in 25 fractions	19	2 (11%)	—
Ajani et al. [13]	5-FU, cisplatin, paclitaxel	45 Gy in 25 fractions of 1.8 Gy	41	8 (20%)	5-year survival in CR 100%
Fareed et al. [14]	5-FU, cisplatin, epirubicin	—	45	2 (4%)	—

OS: overall survival; 5-FU: 5-fluorouracil; CR: complete response.

degree of agreement for all of the three grading systems. The highest κ-score was achieved for the grading system described by Becker while the Ninomiya classification had the lowest score. Complete response was documented in only 3 (5%) patients using all grading systems (Figure 1). Table 5 outlines the patient's response categorisation against the three histological criteria used.

Figure 2 show the associations of grades of response with overall survival. 5-year overall survival rates were 100% for complete and near complete responders ($n = 8$) versus 35% (95% CI, 9–18%) for the remaining 58 patients assessed using the Mandard system ($P = 0.035$). 5-year overall survival rates were 100% for grade 1A and 1B responders ($n = 7$) versus 34% (95% CI 9–18%) for the remaining 59 patients assessed using the Becker system ($P = 0.043$). In TRG 3 group only two patients received adjuvant chemotherapy and had poor 5-year survival as compared to TRG 4 ($n = 21$) and TRG 5 ($n = 4$) groups. Pathological ypT stage ($P = 0.29$) and tumour differentiation ($P = 0.43$) had no prognostic significance. Lymph node (N) involvement and the longitudinal resection (R) margin tumour-free status were the two most significant prognostic factors (Figures 3 and 4). The multivariate analysis showed lymph node status ($P = 0.03$) as an independent prognostic factor. Patients who completed both neoadjuvant and adjuvant chemotherapy courses had significantly improved survival ($P = 0.04$) (Figure 5).

4. Discussion

Since the publication of the results of the MAGIC trial, neoadjuvant chemotherapy has become a standard of care in the UK for the management of gastric and GOJ (types II and III) tumours [6]. The MAGIC trial established the efficacy of chemotherapy in the management of gastric and GOJ tumours. In our cohort of patients, complete response was documented in only 3 (5%) patients, which is similar to the results published by other studies involving other neoadjuvant chemotherapy (Table 2). Fareed reported a complete response rate of 4% but histological response was not compared with survival [14]. The complete response rates following neoadjuvant chemoradiotherapy are higher (Table 2). For example, Lowy et al. reported a complete and partial response rate of 73% [12]. No significant difficulty

Table 3: Patient characteristics.

Characteristic	No. (%) of patients
Gender	
Male	49 (74%)
Female	17 (26%)
Tumour differentiation	
Well	3 (5%)
Moderate	26 (39%)
Poor	37 (56%)
Tumour site	
Gatsric	24 (36%)
GOJ	42 (64%)
T stage	
0	2 (3%)
1	6 (9%)
2	21 (32%)
3	34 (51%)
4	3 (5%)
N stage	
Node negative	19 (29%)
Node positive	47 (71%)
Resection margins	
R0	53 (81%)
R1	13 (19%)
Tumour recurrence	
Yes	20 (30%)
No	46 (70%)

GOJ: gastro-oesophageal junction.

Table 4: κ-score results.

Grading Systems	κ-score
Mandard et al. [7]	0.44
Ninomiya et al. [10]	0.28
Becker et al. [11]	0.52

in resection was reported despite radiotherapy causing tissue damage and fibrosis making surgery difficult. Furthermore, the results published by Ajani et al. for a series of gastric cancer patients treated with neoadjuvant chemoradiotherapy showed a complete response rate of 20% with a 100% five-year survival rate [13]. The combination therapy appears to be superior to chemotherapy alone in achieving complete response. No large-scale randomised clinical trial has compared neoadjuvant chemotherapy and chemoradiotherapy and this might be an area that warrants further study in the UK.

Using Becker's scoring criteria patients who had <10% of tumour cells found on the histological review had a 100% five-year survival rate as compared to patients who had >10% tumour cells who had a two-year survival rate of 50% ($P < 0.05$). As Becker's system was the most reproducible, it should be used in future studies. The Japanese Gastric Society (Ninomiya) classification was poor in terms of both reproducibility and prognostic ability. The Becker system

Table 5: Summary of patient's response categorisation against criteria.

References	Scores	No. (%) of patients ($n = 66$)
Mandard et al. [7]	TRG 1	3 (5)
	TRG 2	5 (7)
	TRG 3	13 (20)
	TRG 4	34 (52)
	TRG 5	11 (16)
Ninomiya et al. [10]	Grade 0	11 (16)
	Grade 1	42 (64)
	Grade 2	10 (15)
	Grade 3	3 (5)
Becker et al. [11]	1A	3 (5)
	1B	4 (6)
	2	48 (73)
	3	11 (16)

TRG: tumour response grade.

uses the percentage of viable tumour cells as a measure of response, which appears to be more easily and reproducibly identifiable than the use of the degree of fibrosis and tumour necrosis employed by the other two scoring systems. Furthermore TRG grades 1 and 2 have shown significant association with 100% five-year survival ($P < 0.05$). The histological responses categorised with TRG grades 3, 4, and 5 had poor five-year survival and were also associated with recurrent disease. The RG system proposed by Rullier et al. has also been employed in assessing response at other tumour sites and been used to show that histological response is an important prognostic factor [16].

The histological ypT stage had no prognostic significance. This finding should be reviewed further and it would be important to establish and compare pre- and post-neoadjuvant T stage with survival. Figure 3 shows that the involvement of locoregional lymph nodes was the most important factor determining prognosis following neoadjuvant chemotherapy and surgical resection in gastric and GOJ adenocarcinoma. In patients with node-positive disease overall 5-year overallsurvival was only 25%. Not only the positive lymph node count but also the ratio between positive and the total number of nodes removed which forms lymph node ratio is identified to be an important independent prognostic factor. The involvement of >20% of the lymph nodes with tumour is marked with poor prognosis [17].

The involvement of longitudinal resection margins was also an important prognostic factor which determined postoperative survival (Figure 4). The 5-year survival in patients with tumour infiltration at the resection margin was 0%. The positive resection margins are associated with tumour recurrence, anastomotic leakage, and decreased survival following resection. It is recommended to perform resection of 5 cm of normal tissue distal to the tumour site to avoid positive margins [18]. Although the surgical approach

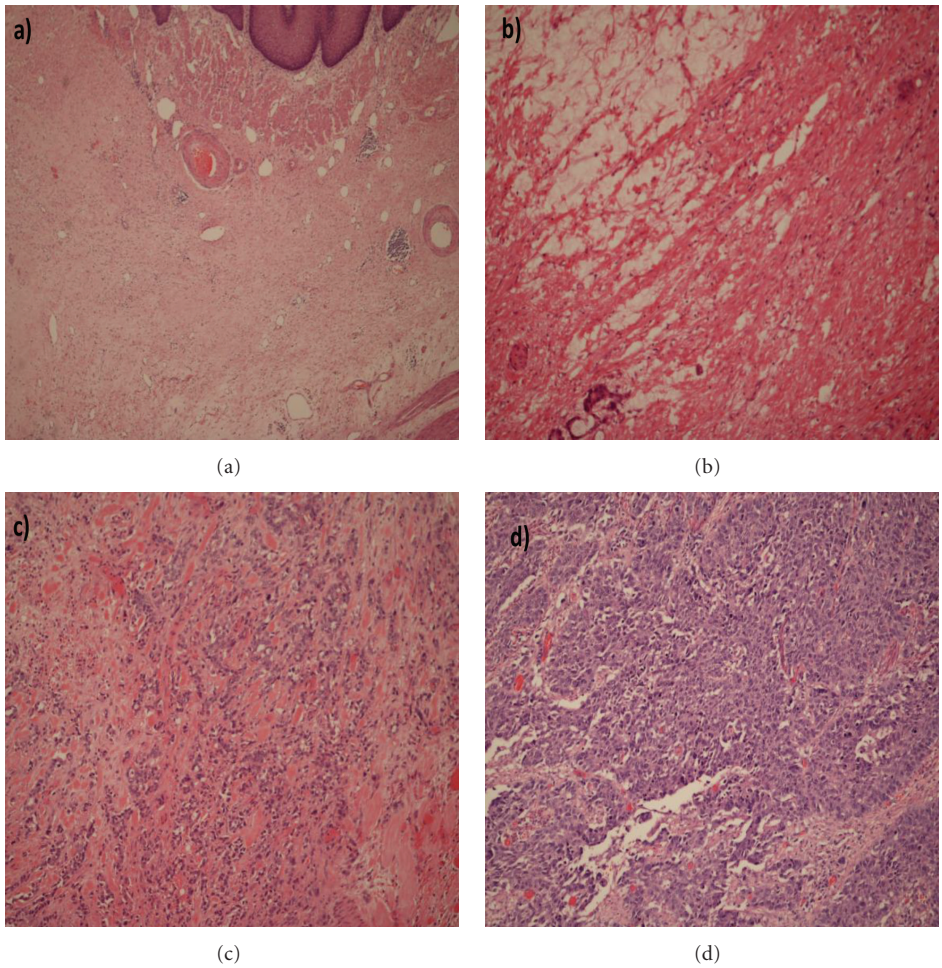

Figure 1: Histological response grading according to Becker's criteria. (a) Grade 1A: no residual tumour/tumour bed (×40), (b) grade 1B: <10% tumour cells (×100), (c) grade 2: 10–50% residual tumour/tumour bed (×100) and (d) grade 3: >50% no signs of neoplastic regression (×100).

to the management of gastric and GOJ tumour is different, the underlying basis of achieving negative resection margins is the same.

The presence of nodal disease, positive resection margins, and incomplete pathological response are directly associated with tumour recurrence. In our cohort of patients, those who had complete or near complete histological response had no recurrent disease and had prolonged disease-free survival. This finding emphasises the importance of achieving complete pathologic response as the most important prognostic factor following administration of neoadjuvant chemotherapy. Today, oncologists and oncology surgeons are faced with the major challenge of identifying patients, who would best respond to neoadjuvant chemotherapy. Various studies have looked at establishing a relationship between demographic details and tumour characteristics, but no single strategy has helped to predict the responders. The answer may come from assessing the core genomic signatures within the tumour which are directly involved in biodegradation and enzymatic activity of administered chemotherapeutic agents. There has been increasing evidence to investigate biomarkers for evaluation of histological response to neoadjuvant chemotherapy [19]. The use of expression profiling identified three genes PERP, S100A2, and SPR3 to be directly associated with complete pathologic response in 15 patients with oesophageal carcinoma who had received neoadjuvant chemotherapy [20]. Another study analysing endoscopic biopsy material identified PDCD6 as an important prognostic marker in gastric cancer [21]. The tumour levels of thymidylate synthase (TS) are directly associated with increasing level of resistance to chemotherapy. The recent investigation of non-small-lung carcinoma identified increased intratumoural expression of TS associated with tumour proliferation and poor prognosis [22].

5. Conclusion

The results of this study show that there is a low degree of histological response following administration of neoadjuvant chemotherapy in gastric and GOJ adenocarcinoma. Given the higher response rates reported for chemoradiotherapy, a comparison of neoadjuvant chemotherapy and chemoradiotherapy should be considered. Both the Becker and Mandard

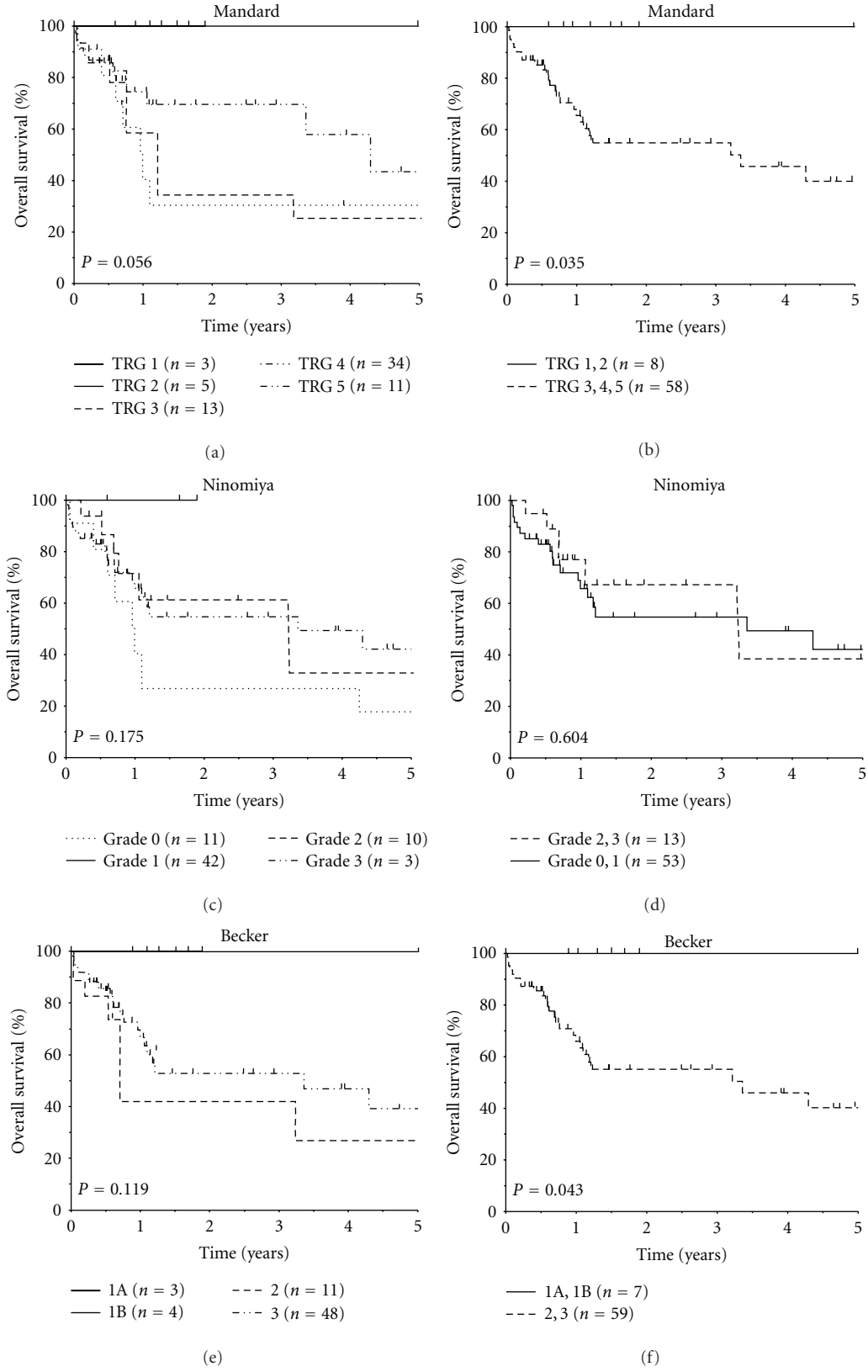

Figure 2: Overall survival plotted against individual grading scores.

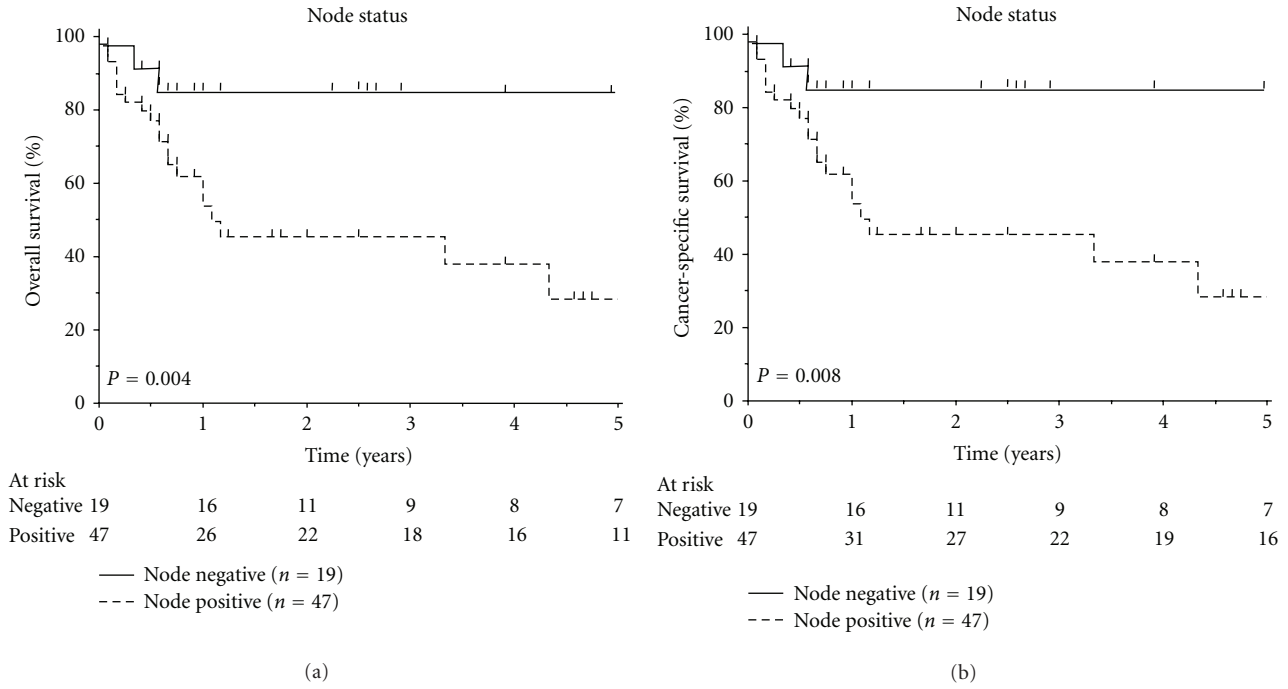

Figure 3: Overall and cancer-specific survival as a function of lymph node status in gastric and GOJ tumours.

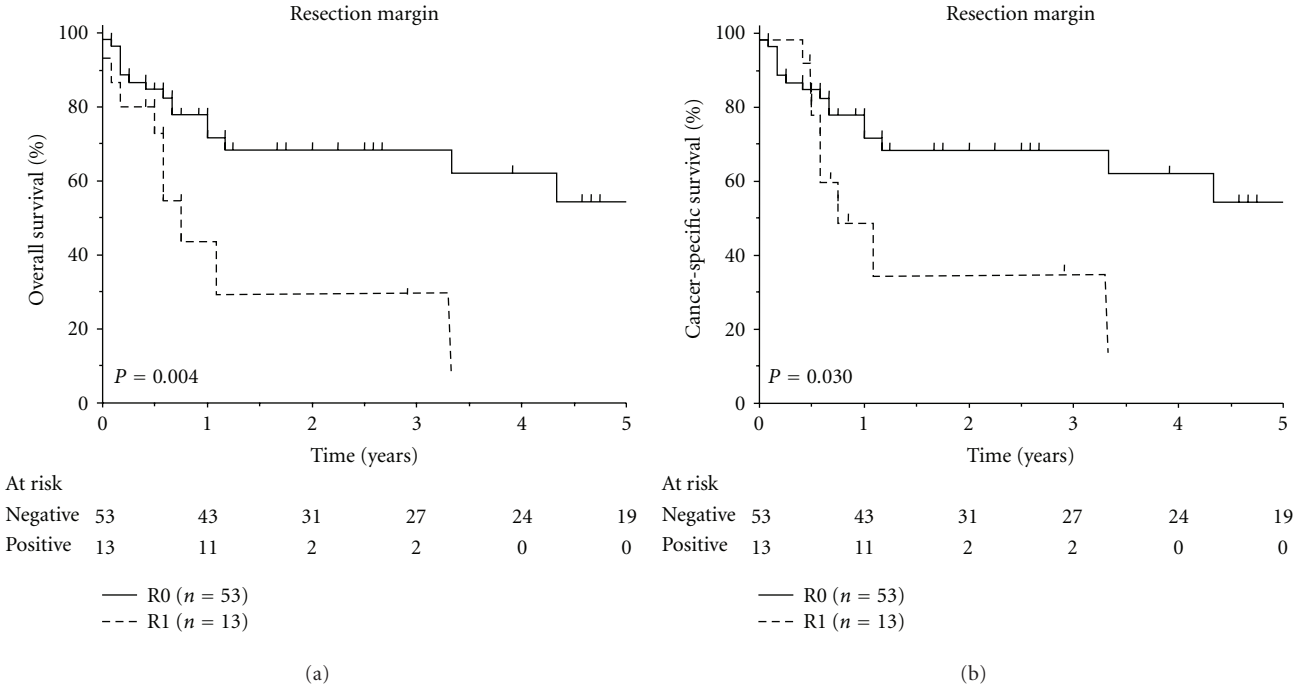

Figure 4: Overall and cancer-specific survival as a function of resection margins in gastric and GOJ tumours.

systems yielded prognostic information. As the Becker system was slightly more reproducible it should be explored further as a possible standard approach for reporting histological response in gastric and gastro-oesophageal junction tumours. In this study the number of patient population was 66 which was the limiting factor in the evaluation of results. The involvement of lymph nodes and the status of resection margins are two important prognostic factors associated with cancer-specific and overall survival. Neoadjuvant chemotherapy delays potentially curative surgery by up to 12 weeks and increases the morbidity associated with cancer treatment. The low response rate associated with

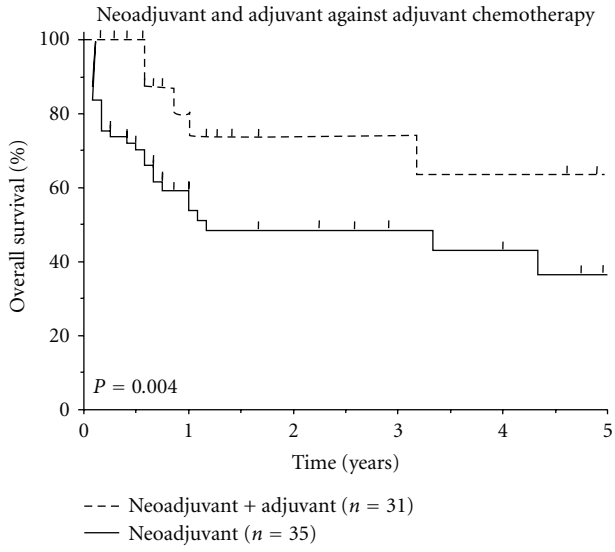

Figure 5: The overall survival comparing patients who completed both neoadjuvant and adjuvant chemotherapy courses versus patient who received only neoadjuvant chemotherapy.

neoadjuvant chemotherapy, therefore, highlights the need to explore molecular markers in diagnostic tumour samples that might identify patients with a high probability of response in order to avoid unnecessary ineffective treatment in those unlikely to respond.

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