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Subtotal gastrectomy with conventional D2 lymphadenectomy for carcinoma of the distal gastric portion: A retrospective cohort study on clinical outcomes[☆]



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HIGHLIGHTS

- Results in 228 patients with distal gastric carcinoma were delineated.
- Patients underwent surgery in 2005–2007.
- The overall cumulative 1-year survival rate was 83.8%.
- The overall cumulative 5-year survival rate was 54.4%.
- Probability of cumulative 5-year survival decreases five times when N ratio is > 0.25.

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ABSTRACT

Background: The study was aimed to delineate the postoperative morbidity, mortality and long-term follow-up results after R0 subtotal gastrectomy with D2 lymphadenectomy for invasive non-disseminated adenocarcinoma of the distal gastric portion.

Methods: Between January 2005 and December 2007, 228 patients with median age at hospitalisation 66.6 ± 11.4 years underwent the above mentioned surgery for histologically proven distal gastric adenocarcinoma.

Results: Postoperative morbidity was documented in 92 (40.4%) of patients within 30 days. An anastomotic leakage was diagnosed in two (0.9%), peritonitis in two (0.9%), anastomosis in five (2.2%), and prolonged ileus in six (2.6%) patients. Nine patients died (3.9%). The overall 1-year survival rate was 83.8%, and the 5-year survival rate was 54.4%. Gender, age, TNM stage, pN, and N ratio were independent factors predicting a long-term prognosis for patients.

Conclusions: A R0 type distal subtotal gastrectomy with standard D2 lymphadenectomy for a histologically proven invasive adenocarcinoma of the distal gastric portion without distant metastasis offers acceptable postoperative morbidity and mortality, and considerably high overall cumulative 5-year survival rate. The probability of cumulative survival decreases five times when the ratio between metastatic and examined lymph nodes is > 0.25.

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1. Introduction

Trends for gastric cancer incidence and mortality are declining in both sexes in Lithuania since 1978 [1,2]. Nevertheless, incidence and mortality rates from gastric cancer still remain high in the country. In 2010, the crude and age-standardized incidence rates

were 27.7 and 21.5 per 100,000 for both sexes individuals of all ages, and accounted for 911 new gastric cancer patients – 534 men and 377 women [1]. Not surprisingly, 680 deaths from gastric cancer were reported to the Lithuanian cancer registry in 2010.

Currently, a margin-negative surgical resection (R0) which entails wide excision of primary tumour with *en bloc* removal of associated regional lymph node stations is the only potentially curative therapy for invasive non-disseminated gastric cancer. Despite the well known fact that a conventional or modified D2 lymph node dissection is associated with low morbidity and a survival benefit [3,4] in patients with favourable prognostic factors [5–8], the extent of gastric excision and the extent of lymph node dissection remain subject to controversy [4,9–11]. Furthermore, there are many other areas for controversy including application of adjuvant therapy modalities [12], and targeted therapies tailored by gastric adenocarcinoma subtype [13,14].

Results of the studies from not widely known high volume cancer centres could be considered for further discussions regarding the value of subtotal gastrectomy with extended perigastric lymph node surgery for distal gastric cancer. To delineate the postoperative morbidity, mortality, and long-term follow-up results following R0 gastrectomies with D2 lymphadenectomies for an invasive non-disseminated distal gastric cancer, was the primary endpoint of this retrospective study. To define the risk factors predicting early postoperative morbidity and a long-term prognosis for patients, was the secondary endpoint of the study. Study was performed at Lithuanian National Cancer Institute which is the only specialised cancer care institution accredited by Organization of European Cancer Care Institutes.

2. Material and methods

Between January 2005 and December 2007, 228 patients with median age at hospitalisation 66.6 ± 11.4 years (range, 34–98) underwent a R0 type distal subtotal gastrectomy with the conventional D2 lymphadenectomy for histologically proven invasive non-disseminated adenocarcinoma of the distal gastric portion. Patients with a distant metastatic disease and patients with non-invasive early gastric cancer were not considered for this study.

The 7th edition of the International Union Against Cancer TNM classification was applied for TNM staging of the carcinoma [15]. All operations were undertaken according to the second English edition of Japanese Classification of Gastric Carcinoma [16,17]. This resulted in 16.51 (SD \pm 6.785) median of perigastric lymph nodes retrieved (range, 2–45) and 3.387 (SD \pm 2.29) median of metastatic lymph nodes (range, 0–15).

Billroth I (67 patients), Billroth II (8 patients), Balfour (103 patients), and Hoffmeister –Finsterer (50 patients) methods were used for a gastrointestinal continuity restoration following subtotal gastrectomy [18]. Any adverse event from normal treatment course was considered as a complication.

The severity of postoperative complications was stratified according to the Clavien-Dindo model [19]. Procedure-related mortality was defined as a postoperative death from any cause within 30 days. Detailed general and histological characteristics of 228 gastrectomized patients are shown in Table 1.

Statistical analyses were performed using the SPSS 20 software package. Such factors as sex, age group, underlying disease, ASA grade, cancer stage and TNM category, and a gastrointestinal continuity restoration method were used to evaluate dependence of distribution of the postoperative complication rate within groups. Cut off values for the ratio between metastatic and dissected lymph nodes (N ratio or LNR) were grouped as follows: LNR 0, LNR $>0-0.09$, LNR $>0.09-0.25$, and LNR >0.25 [19–23].

Cumulative survival time was the time from the surgical

Table 1

General and histologic characteristics of the group of 228 gastrectomized patients.

Variable	Number	Percentage
Sex		
Male	140	61.4
Female	88	38.6
Age groups		
<60 years	70	30.7
60–74 years	86	37.7
>74 years	72	31.6
Co-morbidities		
Cardiovascular	134	58.8
Pulmonary	36	15.8
Diabetes	13	5.7
Other	118	51.8
Stage		
I	110	48.2
II	61	26.8
III	57	25.0
pT category of TNM		
1	75	32.9
2	109	47.8
3	42	18.4
4	2	0.9
pN category of TNM		
0	121	53.1
1	79	34.6
2	28	12.3
Differentiation		
G1	23	10.1
G2	63	27.6
G3	132	57.9
Missing G value	10	4.4
Invasion		
Perineural	14	6.1
Perivascular	27	11.8
Lymphovascular	6	2.6
Perineural and perivascular	10	4.4
No invasion	171	75.0
Adjuvant chemotherapy		
Applied	61	26.8
Not applied	167	73.2

intervention until the date of death or until March 2013 for surviving patients. Survival curves were produced by means of the Kaplan–Meier model. The log-rank test was used to evaluate the statistical differences between the survival curves. The chi-square test was employed to compare categorical outcomes. Means were compared by using the Student's *t* test. Differences with *P* values less than 0.05 were considered as statistically significant. Factors found to be associated with long-term survival by univariate analysis were assessed using the Cox's proportional hazards multivariate regression model.

3. Results

3.1. Postoperative 30 day morbidity and mortality

92 patients (40.4%) had postoperative morbidity. In terms of Clavien – Dindo classification, complications were stratified as follows: I – 20 patients (8.8%), II – 46 patients (20.2%), IIIA – nine patients (3.9%), IIIB – seven patients (3.1%), IVA – one patient (0.4%), and V – nine patients (3.9%). An anastomotic leakage was diagnosed in two (0.9%), peritonitis – in two (0.9%), anastomosis – in five (2.2%), and prolonged ileus – in six (2.6%) patients. The mean length of stay in hospital was 17.82 days (SD \pm 6.292). Nine patients died (3.9%).

3.2. Prognostic factors for postoperative morbidity

Complications developed in 18.6% of patients in <60 years age group, in 31.4% of patients in 60–74 years age group, and in 41.7% of patients in >74 years age group ($p = 0.012$). The postoperative morbidity rate was 19.6% for ASA I, 30% for ASA II, 32.4% for ASA III, and 53.8% for ASA IV patients. The lowest complication morbidity was observed following the application of the Balfour or Billroth I gastrointestinal continuity restoration method, 27% and 31.3% respectively. There was no statistically significant difference between the four gastrointestinal continuity restoration groups. Neither the ASA grade nor gastrointestinal continuity restoration method, sex, underlying disease, or gastric cancer stage, showed any significant difference on postoperative morbidity.

3.3. Delineation of cumulative 5-year survival

The overall 1-year survival rate was 83.8% (CI 95% 78.3–88.0), and the 5-year survival rate was 54.4% (CI 95% 47.7–60.6) in 228 gastrectomized patients. Fig. 1 delineates a cumulative 5-year survival in patient groups stratified according to gastric cancer stage, pT, pN, and N ratio. The differences in survival curves were statistically significant for each category. However, an application of the

particular gastrointestinal continuity reconstruction method showed no statistically significant difference for cumulative long-term survival rates.

3.4. Factors predicting cumulative long-term survival

Univariate analysis showed that the female gender, age group, pT, pN, TNM stage, N ratio, and uneventful postoperative period were statistically significant factors associated with the better 5-year survival rate. Table 2 shows a cascade dependence of the 1-year and 5-year cumulative survival on the N ratio. The multivariate analysis using Cox's proportional hazards model with the mentioned factors as covariates, revealed that five of seven factors, i.e. gender, age, pN, TNM stage, and N ratio, are statistically

Table 2

Dependence of long-term survival on the ratio between metastatic and dissected lymph nodes.

N ratio	One year survival with CI 95%	Five year survival with CI 95%
0	92.6 (87.5–97.7)	72.1 (63.3–80.9)
0–0,09	88.9 (82.7–95.1)	72.2 (63.4–81.0)
0,1–0,25	84.4 (77.3–91.5)	46.9 (37.1–56.7)
>0,25	61.2 (51.6–70.8)	14.3 (7.4–21.2)

N ratio – the ratio between metastatic and dissected (examined) lymph nodes. Log-rank test $p < 0.001$.

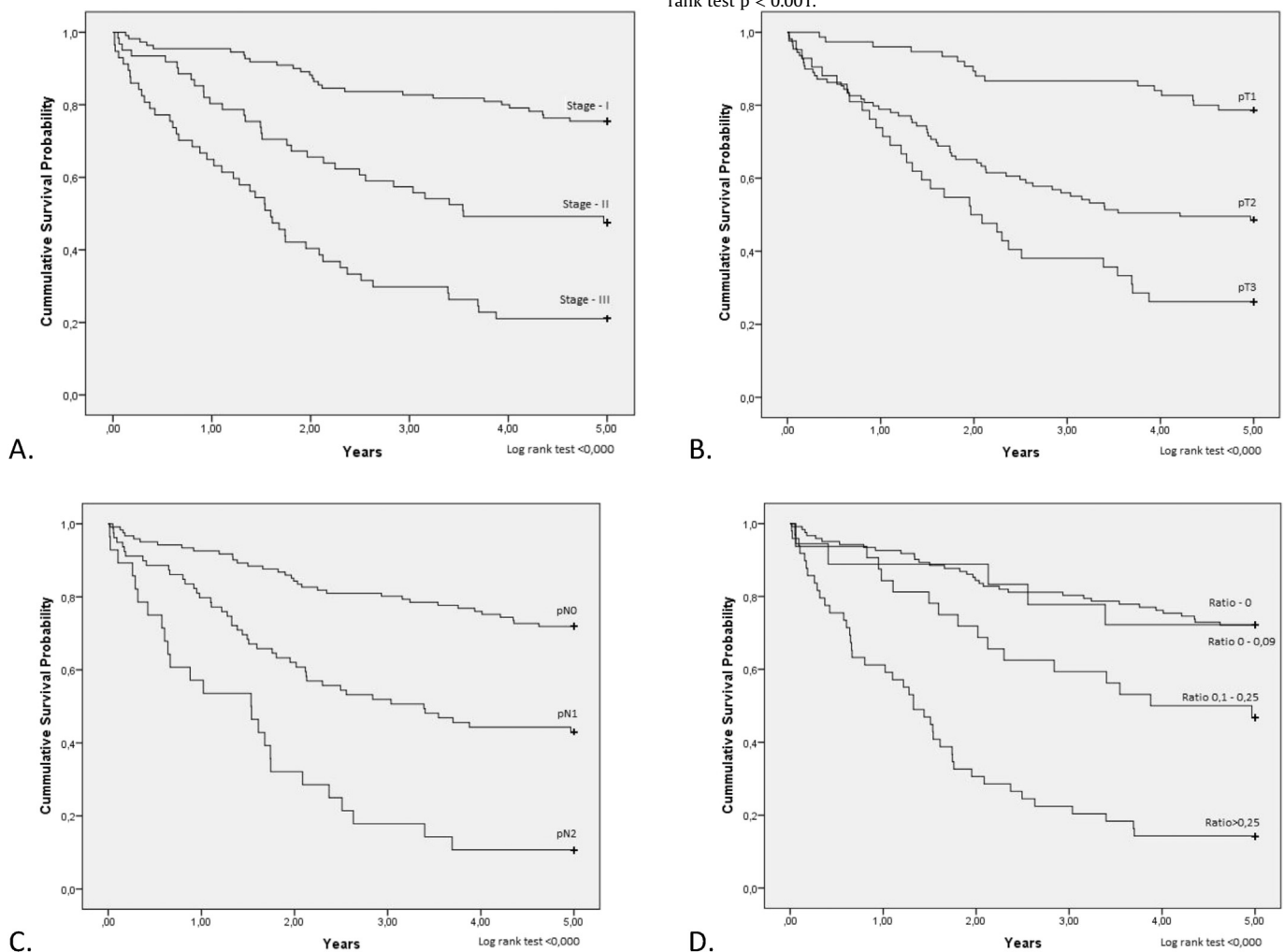


Fig. 1. Cumulative 5-year survival probability in patient groups stratified according to gastric cancer stage (A), pT (B), pN (C), and N ratio (D). pT – classification of the primary gastric cancer described by pathologist, pN – classification of the removed lymph nodes described by pathologist, N ratio – the ratio between metastatic and dissected (and examined) lymph nodes described by pathologist.

significant independent factors predicting a long-term prognosis (Table 3).

4. Discussion

Gastric cancer treatment varies in the extent of surgery, post-operative morbidity and mortality, and long-term outcomes around the world [24]. This Lithuanian study suggests the following items.

First, the role of age as a risk factor for post-operative comorbidity matters. This finding is not surprising as 58.8% of the patients suffered from chronic cardiovascular conditions, and 15.8% of them had chronic pulmonary problems. However, some studies suggest that age can be insignificant postoperative morbidity factor [25]. We could not prove it. Gender was not a significant risk factor for 30 day postoperative morbidity. Other authors, however, identified the female gender as a risk factor for early post-operative complications [26]. The lowest complication rate was after the Balphour gastrointestinal continuity restoration ($p = 0.065$). This can be explained by the fact that this reconstruction type is the most common and the most perfected in the national institution.

Second, the overall postoperative mortality rate of 3.9% compares favorably with data from other countries where the reported mortality rate was within 3.1–8.3%. Table 4 demonstrates that.

Third, the overall survival rate of 54.4% is comparable with leading international centers data, though some studies from Japan have reported significantly higher rates [27]. The variation in published results may have been influenced by differences in the treated patient groups. In our study, 48.2% of patients had stage I gastric cancer.

Fourth, N staging criterion is considered to be the determining factor for poorer patients' survival, and our 10.7% survival rate with metastatic lymph nodes from the second level lymph node stations confirms that – although some studies reported higher 5-year survival rates for this patient subgroup of up to 33.4% [30–32].

Fifth, our study confirms that the most agreeable independent risk factors for cumulative long term survival are the TNM stage, metastatic perigastric lymph nodes, and the N ratio [33–36]. Besides, it specifically highlights the prognostic factors for five years survival after R0 gastrectomies with D2 lymphadenectomies for invasive non-disseminated adenocarcinoma of the distal portion of the stomach.

Higher N ratio values significantly correlated with lower survival in our study, confirming that the N ratio can provide accurate prognostic stratification associated with gastric cancer

[6,20,37–40]. Moreover, it has also been recommended that the N ratio should be used in prognostic assessment, particularly to avoid a problem called stage migration, when a limited number of lymph nodes is obtained [41]. We acknowledge that N ratio values used in this paper are most common mentioned in the literature. Nevertheless, the value of the N ratio should be confirmed in prospective randomized trials, because now many authors use different values in their researches.

This retrospective study has a few limitations. It was not possible to recruit, assess, and follow up more patients due to limited population size, and the absence of an approved centralized referral system towards the leading cancer centre of the country in 2005–2007. However, 228 patients who underwent the subtotal gastrectomy with conventional D2 lymphadenectomy for histologically proven adenocarcinoma of the distal gastric portion is rather sufficient cohort for surveillance. An absence of the group of patients with non-invasive gastric cancer downgraded the cumulative five year survival probability, especially in patient with stage I gastric cancer. We presume that results of this study were biased as there were patients who ignored the potential advantages of adjuvant chemotherapy. It is also important to mention that chemotherapy was not recommended for patients with T2N1 disease in 2005–2006. Nevertheless, this study can be regarded as reflection of a structured surgical philosophy and activity within one of the busiest national cancer centre of the Baltic States. Little is known about them.

5. Conclusion

The outcomes of this study suggest that a R0 type distal subtotal gastrectomy with the conventional D2 lymphadenectomy for a histologically proven invasive non-disseminated adenocarcinoma of the distal gastric portion offers low postoperative morbidity and mortality, and a considerably high overall cumulative 5-year survival rate of 54.4%. Gender, age, pN, TNM stage, and N ratio are independent factors predicting a long-term prognosis for patients. When the ratio between metastatic and examined lymph nodes is > 0.25 , the cumulative five year survival rate is 14%, indicating that the probability of cumulative survival decreases up to five times.

Competing interests

All of the authors declare that there are no conflicts of interest and have accepted no financial sponsorship in producing and presenting this manuscript. Each author listed is in agreement with the content of the manuscript.

Conflicts of interest

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Ethical approval

This study was approved by local ethics committee.

Author contribution

Povilas Kavaliauskas performed literature search, collected data, performed statistical analysis, conducted the study, wrote the draft

Table 3
Multivariate analysis of prognostic factors for 5-year survival after R0 gastrectomies with D2 lymphadenectomies for adenocarcinoma of the distal portion of the stomach.

Variables	Hazard ratio	95% Confidence interval	P Value
Gender			
Female	1	–	0.02
Male	1.7	1.1–2.6	–
Age group			
<60	1	–	0.01
6 0–74	1.7	1–2.9	0.064
>74	2.34	1.3 to 4.1	0.002
TNM stage			
I	1	–	0.02
II	2.7	1.3 to 5.5	0.01
III	3.3	1.3 to 8.2	0.01
pN			
pN0	1	–	0.006
pN1	1.3	0.6 to 2.8	0.49
pN2	3.7	1.3 to 10.2	0.013

Table 4
Series of studies on short and long term results following gastrectomy for gastric cancer.

Series	Year	Country	Cases	30 day Mortality	Five year survival
Randomized trials					
Bonenkamp [9]	1999	Dutch	711	6.6%	33%: D1 34%: D2
Sasako [27]	2008	Japan	523	0.8%	69.2%
Cuschieri [10]	1999	UK	337	NA	34%
Prospective studies					
Degiuli [4]	2004	Italy	191	3.1%	63.5%
Koppert [25]	2012	Netherlands	3177	8.2%	35%
Edwards [11]	2004	UK	118	8.3%: D1; 7.3%: D2	32%: D1 59%: D2
Retrospective studies					
Mocan [28]	2013	Romania	180	5.0%	43%
Zilberstein [29]	2012	Brasil	274	4.4%	70.4%
Our data	2014	Lithuania	228	3.9%	54.4%: D2

D1 – lymphadenectomy D1, D2 – lymphadenectomy D2.

of the paper. Rytis Maziukas performed literature search, collected data, conducted the study, wrote the draft of the paper. Justas Kuliavas performed literature search, wrote the draft of the paper. Narimantas Evaldas Samalavicius conceptualized and designed the study project. Raimundas Lunevicius conceptualized and designed the study, supervised the project, performed literature search, made critical revisions, and made a major contribution writing the final version of the manuscript.

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