

# Changing views of gastric cancer in Slovenia

Mirko Omejc, Robert Juvan, Franc Jelenc, Stane Repše  
*Department of Abdominal Surgery, University Medical Centre Ljubljana, Slovenia*

**Key words:** gastric cancer, surgical treatment, survival

**Ključne besede:** rak želodca, kirurško zdravljenje, preživetje

## Abstract

Although declining in incidence in western countries during the last twenty years, gastric cancer remains an important cause of cancer-related death throughout the world. Prognosis of gastric cancer is poor, as it is usually diagnosed late. More attention should be paid to the early detection to improve the effectiveness of treatment and thus survival of patients who develop gastric cancer. Surgery remains the cornerstone of the management. The curative treatment of gastric cancer is now becoming the subject of a multidisciplinary approach. The results of individual surgical centers in Slovenia are comparable to the outcomes in leading centers in Europe.

## Spreminjanje pogledov na raka želodca v Sloveniji

Čeprav njegova incidenca po svetu in pri nas upada, želodčni rak še vedno pomembno prispeva k umrljivosti za rakom. Prognoza je slaba, ker je pogosto odkrit v napredovalem stadiju. Rezultate zdravljenja je mogoče izboljšati le z zgodnejšim odkrivanjem. V zdravljenju je pomemben multidisciplinarni pristop. Glavno vlogo v zdravljenju ima še vedno kirurgija. Rezultati zdravljenja v posameznih centrih v Sloveniji so primerljivi z vodilnimi v Evropi.

---

Prof. Mirko Omejc, M.D., Ph.D.  
Department of Abdominal Surgery  
Hospital of Surgery, University Medical Centre Ljubljana  
Zaloška 7, SI-1525 Ljubljana, Slovenia  
Phone: +386 1 522 31 68  
E-mail: mirko.omejc@mf.uni-lj.si

## INTRODUCTION

Gastric cancer is the second leading cause of cancer-related death throughout the world (1). Incidence and mortality rate of gastric cancer have declined steadily in most countries, especially in the developed countries, such as the United States and Western Europe, while those of adenocarcinoma arising from gastric cardia and oesophagus have been stable or increased, especially among white males (2–4). In the United States, gastric cancer was the leading cause of cancer death in 1930, but it now ranks 14<sup>th</sup> in incidence and 8<sup>th</sup> as a cause of cancer mortality (5). The dramatically decreased incidence in gastric cancer seen in developed countries is mainly due to the marked reduction of well-differentiated ‘intestinal type’ adeno-carcinomas of the fundus and the antrum (6). The incidence of other tumour types affecting the fundus and the antrum (‘diffuse’, ‘infiltrating’ or ‘poorly differentiated’) has declined more slowly. Consequently, in low risk developed countries, the poorly differentiated tumour types tend to occur more frequently than the well differentiated intestinal tumours (6, 7).

Gastric carcinoma generally has a dismal prognosis. In western countries the disease is usually diagnosed late. In the United States, the overall 5-year survival is reported as 37, 18, 11, and 5% for stages II, IIIA, IIIB, and IV, respectively (8). Overall, 5-year survival resulting from a nationwide population-based Swedish study was 19.4% for noncardial stomach cancer and 10.4% for patients with cancer of the gastro-oesophageal junction (9). Similar figures are reported for other European countries (10). In surgical series, the 5-year survival goes from 55% for stage II tumours to 16% for stage IV (T4N1-3M0 or any TN3M0) disease (8, 11). In M1 tumours, a median survival of 7–9 months is observed with no survivors at 5 years (12, 13). In Japan, where detection programs have been established due to the very high incidence of the disease even in young adults, the diagnosis of stage IA and IB disease is more frequent with a 5-year survival of 75% and over (14, 15).

Most cancer statistics in Slovenia, a country of 2 million population, is based on the data of the Cancer Registry of Slovenia, which was founded in 1950. Nowadays in Slovenia, gastric cancer is because of its decreasing incidence the fifth most common cancer in men (after lung, skin, colorectal, and prostate), and the seventh in women (after breast, skin, colorectal, corpus uteri, lung, and cervix uteri). Regarding the mortality, it is on the fourth place in men (after lung, colorectal, and prostate), as well as in women (after breast, colorectal and lung). However, in the 1950s and mid-1960s it was the leading cancer site in incidence as well as in mortality (16–19).

During the observed 40 years, the age distribution of patients has changed. In the period 1993–2001 the percentage of patients aged 80 years and more was much higher than in the period 1963–72 (4, 18, 19).

The exact causes of the decline of gastric cancer are not well understood, but must include improvements in the affluence of diet, food storage (e.g. refrigeration) and, possibly, the decline of *Helicobacter pylori* (HP) infection (20, 21).

## DIAGNOSTICS

Endoscopic examination and biopsy of suspicious changes of the gastric mucosa took on the leading role in the diagnostics of stomach cancer in early 1970s. In preoperative disease staging, standard ultrasonography was introduced in the mid-1980s, whereas endoscopic ultrasonography came into use in the mid-1990s. In the 1980s, pathologists additionally standardized the analyses of resections by Lauren’s histology classification for stomach cancer, malignancy stage (G) and UICC pTNM, and in the 1986, also by R classification. Multiple attempts to develop histological classifications with prognostic significance in gastric carcinoma have been made over the last 40 years. Among them, those developed by Lauren and the WHO’s are the most commonly used (22). Lauren divided all gastric cancers into two main types: intestinal and diffuse (23). The

intestinal type has a glandular structure and is basically well delimited. The diffuse type is composed of small cells, which grow more or less diffusely into the surrounding gastric wall. The intestinal type is more frequent in males and at older ages while the diffuse type shows no difference between sexes and is more frequent in younger ages. Intestinal type is predominant in high-risk areas. It is also argued that the intestinal type is more influenced by environmental factors. However, several studies have failed to find difference in risk factors between diffuse and intestinal types (24, 25).

The WHO classification is based mostly on the morphology of cancer cells and divides gastric cancer histologically into tubular, papillary, mucinous and signet ring cell types (26). The WHO classification is less useful but remains the most widely used system worldwide (27).

In Slovenia, in the period 1993–97, 91% of cases were microscopically confirmed, the percentage of adenocarcinomas, non-differentiated cell carcinomas, non-Hodgkin lymphomas and leiomyosarcomas in these cases was 85%, 7%, 6%, and 0.6%, respectively. In the period 1998–2001, 95% of cases were microscopically confirmed, the percentage of adenocarcinomas, non-differentiated cell carcinomas, non-Hodgkin lymphomas and leiomyosarcomas in these cases was 84%, 7%, 8% and 1.3%, respectively.

The wider use of the Lauren histological classification as well as detailed reporting to the Cancer Registry started in the 1990s. With an increasing percentage of defined cases, a slightly lower percentage of intestinal type, and a slightly higher percentage of the diffuse type has been noticed in the late 1990s (16–18).

## TREATMENT

Surgery has been the cornerstone of the curative management of gastric cancer for over a century. Oncological aspects of gastric surgery became the

main concern in the 1940s. At that time, locoregional relapse was a major issue (28). Analysis of the patterns of local treatment failure revealed many recurrences in the region of the coeliac axis and splenic bed. This was the reason for proposing total gastrectomy with routine splenectomy and node dissection around the coeliac vessels and aorta (29).

In Slovenia until the early 1980s, the principal surgical treatment of stomach cancer involved resection with omentectomy (in principle, distal subtotal resection, total gastrectomy when otherwise not possible). A new strategy was initiated in 1982 that implied surgery planning depending upon the histology type (Lauren), subsite (thirds of the stomach), and depth of infiltration (sT). In 1986, systemic lymphadenectomy of the groups of lymph nodes I- and II-D2 was initiated (30). The proportion of total gastrectomies was gradually increasing from 5–10% to 30–40% (31).

In the first half of the 1990s, a multidisciplinary team of experts elaborated *Recommendations for a Comprehensive Approach to Patients with Digestive Cancer*. These recommendations were adopted by all professional boards and approved by the Health Council at the Ministry of Health of the Republic of Slovenia. They were published as a booklet and thus made available to all Slovenian physicians (32).

In 1995, two workshops and symposia on surgery of gastric cancer with the proceedings *Stomach Surgery* facilitated the implementation of this strategy also in the surgical departments of other hospitals (30). Though radical surgery is the sole treatment modality that offers the possibility of cure, about one third of patients with newly detected stomach cancer have never entered a surgical unit in this time. In 1993, only 72% (374/520) of patients with newly detected stomach cancer were treated at various surgical units, whereas in 2000, only 69% (330/480) (30). The high proportion of patients, not operated upon, definitely contributes to a poor five-year survival of patients with stomach cancer in Slovenia.

Currently, three major surgical strategic controversies are debated. The first deals with the extent of gastrectomy. The second questions the utility of extensive lymph node resection and the third issue has arisen more recently and deals with the best management of early gastric cancer.

### **Extent of gastrectomy**

During the early 1980s, total gastrectomy was considered the standard curative treatment of gastric cancer. It was felt on the basis of some previous retrospective studies that subtotal gastrectomy was inadequate for controlling gastric carcinoma because of the high local recurrence rate (33). However, because of the high overall operative mortality (15% in specialized western centres going up to 29% in the hands of general surgeons), total gastrectomy never gained wide acceptance in western countries (34). Today, due to technical and medical improvements, the overall mortality rate associated with total gastrectomy has dropped considerably, but wide variations persist among countries, and between specialized and general surgical centres.

Quality of life is initially better (overall 6-month recovery) for distal gastric cancer patients who are treated by subtotal gastrectomy in terms of symptoms, daily living activities, anxiety, depression, and body mass index (35). However, this difference tends to vanish later on. Therefore, quality of life considerations should not offset oncologic safety requirements in the planning of curative surgery in gastric cancer.

### **Extent of lymph node resection**

Lymph node metastasis decisively affects prognosis in stomach cancer. Operative clearance of the nodes is of utmost importance and requires a thorough surgical training if it is to be done effectively and safely. Removal of the perigastric lymph nodes only is called D1-resection. In D2-lymphadenectomy, removal of the lymphatic chains along the coeliac axis, the common hepatic and splenic artery, and at the hilum of the spleen is also performed. Earlier, splenectomy was performed in order to remove the

splenic nodes (station 10). The left pancreatectomy was part of the removal technique of the lymph nodes of the splenic artery (station 11). In the meantime, several studies originating from western countries and Japan have demonstrated that systematic splenectomy and caudal pancreatectomy were not necessary and could increase the morbidity of the procedure (36).

The involvement of the splenic nodes (station 10) is most often seen in proximal tumours originating from the big curvature, while splenic artery lymph nodes (station 11) are most frequently involved by tumours situated in the middle of the stomach (37). Therefore, there is now general agreement to perform the resection of station 10 with splenectomy only in the presence of proximal lesions of the big curvature and macroscopic metastases to the splenic hilum (38). Similarly, with the introduction of new surgical techniques, station 11 resection no longer requires caudal pancreatectomy; it is now reserved to direct pancreatic invasion (39).

Nowadays, the D2 procedure is done to achieve accurate staging and regional disease control, and because of potential benefit to a subgroup of patients with occult disease in D2 nodes. D2 lymphadenectomy is safe if done by a skilled surgeon and if splenectomy and pancreatic resection are avoided. Splenectomy should be done only in cases of locally advanced tumour of the upper third of the stomach, tumours of the greater curvature, and those of the gastric cardia. The incidence of lymph node metastases is 10–25%, and if splenectomy is advised, the pancreas should be preserved (40).

In order to avoid unnecessary removal of lymph nodes that are not at risk of tumour, two new approaches emerged recently. The first technique uses a computerised database of information to convert a large amount of information and experience to a treatment decision for an individual patient. Depth of infiltration, tumour size, tumour location, grading, typing, and macroscopic appearance are used to predict the probability of nodal metastases

(41). The second approach uses information derived from dissection of the sentinel node. At present, clinical impact of both approaches is limited due to the low specificity and low positive predictive value (42).

### Early gastric cancer

Early gastric cancer is a well-known entity in Japan, where it represents up to 50% of the gastric neoplasms. The prognosis of early gastric cancer is excellent with 10-year survival rates between 80 and 95% (43). With such good results, the debate is dominated by the desire not to 'overtreat' these patients (44). However, many studies have shown that up to 20% of the early lesions showing submucosal invasion can be associated with lymph node involvement, which bears a poorer prognosis (45). In Japan, surgeons favour endoscopic mucosal resection, which is thought to have high curative potential and to avoid the need for further radical surgery. However, such an approach should only be done if very accurate local staging has been achieved. In Slovenia, the incidence of early gastric cancer has increased,

too. Among patients who underwent surgical procedure at our department, there were 20.5% of patients with early gastric cancer in the period 1998–2002.

### GASTRIC SURGERY IN SLOVENIA

In the last observed period, patients underwent surgery at nine surgical departments of general hospitals in Slovenia. On average, one third of patients were operated on in the University Medical Centre (UMC), Department of Abdominal Surgery, in Ljubljana, the other third in two major regional hospitals, and the last third in the remaining six general hospitals. In the early 1990s, it was often stressed that the treatment of malignant diseases in the centres that can admit a critical number of patients is significantly more effective. In recent years, an increasing proportion of patients have been operated on at larger departments of three major hospitals in Slovenia. In smaller surgical departments, they practically do not operate any

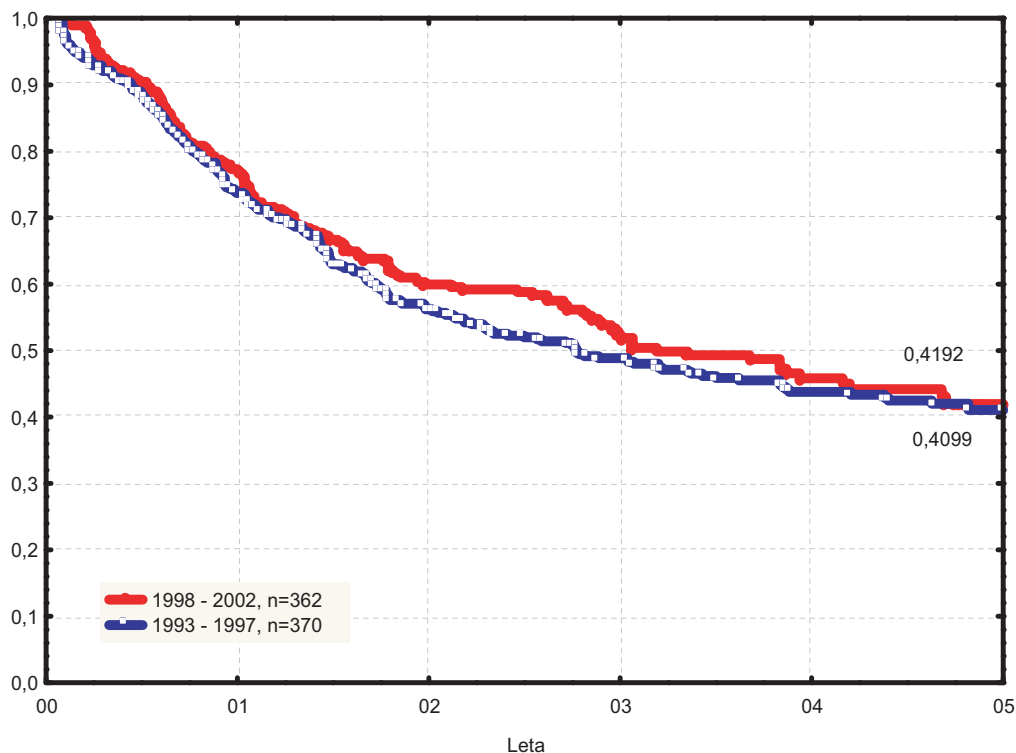


Figure 1. Five year survival of resected patients (R0, R1, R2). Comparison of two 5-year periods (1993–1997 and 1998–2002).

more on the patients with stomach cancer (30–33). In the period from January 1998 to December 2002, 474 patients underwent operation at the Department of Abdominal Surgery, UMC in Ljubljana. At the time of surgery 37.3% of them were older than 70 years, 32.7% were between 61 and 70 years of age, and 30% were younger than 61 years. In 392 cases potentially curative (R0) or palliative (R1, R2) resection was performed (resectability rate 82.7%). In 216 cases (55.1%) this was distal subtotal resection, in 172 (43.9%) total gastrectomy. In 4 cases (1.02%) endoscopic mucosectomy of an early cancer was done successfully. R0 resection was performed in 78.6% (305/392) of patients with post-operative mortality rate of 6.5% (20/305).

Despite all the efforts made in the field so far, the results of treatment on national level are unsatisfying. More attention should be paid to the early detection to improve the effectiveness of treatment and thus survival of patients who develop gastric cancer. Surgery remains the cornerstone of the curative management of gastric cancer. The morbidity and mortality of gastric cancer surgery is associated with the skills of surgeons and with the quality of training programmes. The curative treatment of gastric cancer is now becoming the subject of a multidisciplinary approach including surgery, radiation therapy and systemic therapy, as for colorectal cancer and some other solid tumours.

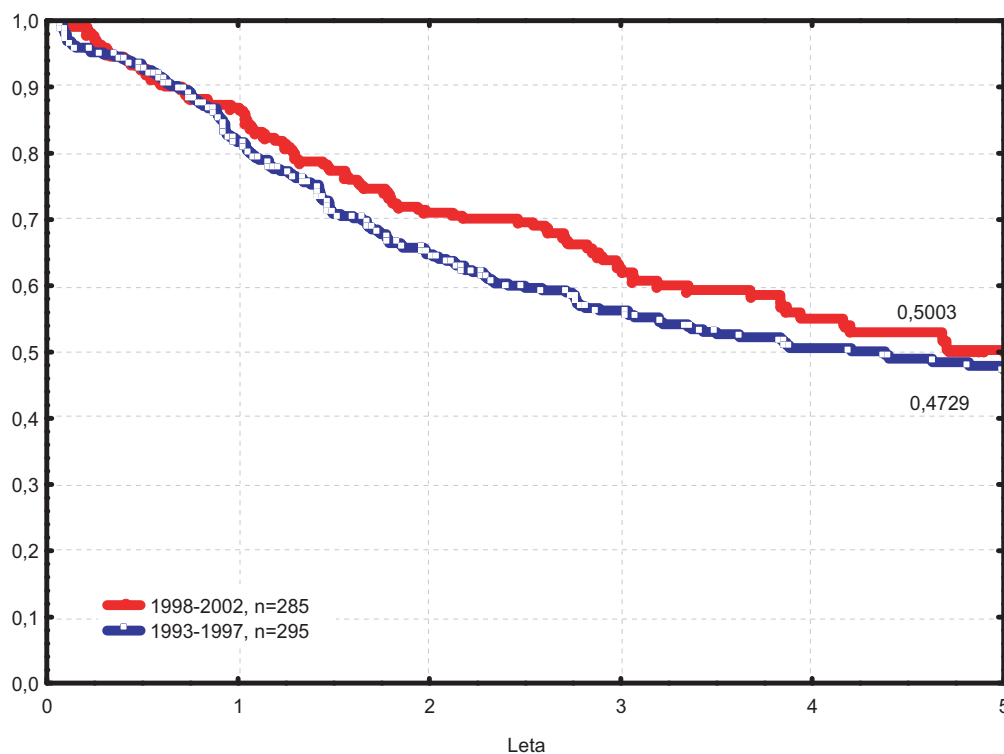


Figure 2. Five year survival of R0 resected patients. Comparison of two 5-year periods. (1993–1997 and 1998–2002).

Five-year survival rate of all resected patients (R0, R1, R2) was 41.92%, while in potentially curatively resected (R0) group it was 50.0%. According to the TNM stage 5-year survival was as follows: pS1 79.66%, pS2 41.09%, pS3 19.43%; in pS4 nobody survived longer than 3.5 years (Figures 1 and 2).

The benefits of our twenty-year endeavours to facilitate the access to endoscopic examinations, follow-up of high-risk patients, multidisciplinary approach to patients, standardized surgical treatment at major surgical units and at specialized cancer treatment departments will probably start to have an impact on the treatment results on the national level only in the next observation period.

## References

1. Coleman M, Esteve J, Damiecki P, Arslan A, Renard H. *Trends in cancer incidence and mortality*. Lyon: IARC, 1993.
2. Verdecchia A, Mariotto A, Gatta G, Teixeira MTB, Ajiki W. Comparison of stomach cancer incidence and survival in four continents. *Eur J Cancer* 2003; 39: 1603–9.
3. Botterweck AA, Schouten LJ, Volovics A, Dorant E, van den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol* 2000; 29: 645–54.
4. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, editors. *Cancer incidence in five continents*. Vol. 7. Lyon: IARC, 1997.
5. Neugut AI, Hayek M, Howe G. Epidemiology of gastric cancer. *Semin Oncol* 1996; 23: 281–91.
6. Correa P. The epidemiology of gastric cancer. *World J Surg* 1991; 15: 228–34.
7. Pinheiro PS, van der Heijden LH, Coebergh JW. Unchanged survival of gastric cancer in the southeastern Netherlands since 1982: Result of differential trends in incidence according to Lauren type and subsite. *Int J Cancer* 1999; 84: 28–32.
8. Hundahl SA, Menck HR, Mansour EG, Winchester DP. The National cancer data base report on gastric carcinoma. *Cancer* 1997; 80: 2333–41.
9. Hansson LE, Sparen P, Nyren O. Survival in stomach cancer is improving: Results of a nationwide population-based Swedish study. *Ann Surg* 1999; 230: 162–9.
10. Faivre J, Forman D, Esteve J, Gatta G (EUROCARE Working Group). Survival of patients with oesophageal and gastric cancers in Europe. *Eur J Cancer* 1998; 34: 2167–75.
11. Roder JD, Bottcher K, Siewert JR, Busch R, Hermanek P, Meyer HJ. Prognostic factors in gastric carcinoma. Results of the German gastric carcinoma study 1992. *Cancer* 1992; 72: 2089–97.
12. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997; 15: 261–7.
13. Vanhoefer U, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Cutsem E, et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European organization for research and treatment of cancer Gastrointestinal tract cancer cooperative group. *J Clin Oncol* 2000; 18: 2648–57.
14. Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, et al. Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer* 1992; 70: 1030–7.
15. Fuchs CS, Mayer RJ. Gastric carcinoma. *New Engl J Med* 1995; 333: 32–41.
16. *Incidenca raka v Sloveniji 2000, 2001 = Cancer Incidence in Slovenia 2000, 2001*. Ljubljana: Onkološki inštitut, Register raka za Slovenijo, 2003, 2004.
17. Pompe-Kirn V, Zakotnik B, Volk N, Benulič T, Škrk J. *Preživetje bolnikov z rakom v Sloveniji = Cancer patients survival in Slovenia*. 1963–1990. Ljubljana: Onkološki inštitut, 1995.
18. Pompe-Kirn V, Zakotnik B, Zadnik V. *Preživetje bolnikov z rakom v Sloveniji = Cancer patients survival in Slovenia*. 1983–1997. Ljubljana: Onkološki inštitut, 1995.
19. Lambert R, Guilloux A, Oshima A, Pompe-Kirn V, Bray F, Parkin M, et al. Incidence and mortality from stomach cancer in Japan, Slovenia and the USA. *Int J Cancer* 2002; 97: 811–8.
20. La Vecchia C, Ferraroni M, D'Avanzo B, Decarli A, Franceschi S. Selected micronutrient intake and the risk of gastric cancer. *Cancer Epidemiol Biomarkers Prev* 1994; 3: 393–8.
21. Correa P. Diet modification and gastric cancer prevention. *J Natl Cancer Inst Monogr* 1992; 12: 75–8.
22. Borchard F. Classification of gastric carcinoma. *Hepatogastroenterology* 1990; 37: 223–32.
23. Lauren P. The two histological main types of gastric carcinoma. *Acta Pathol Microbiol Scand* 1965; 64: 31–49.
24. Correa P, Shiao YH. Phenotypic and genotypic events in gastric carcinogenesis. *Cancer Res* 1994; 54 (Suppl): S1941.
25. Correa P, Chen VW. Gastric cancer. Cancer surveys, 19/20, Trends in cancer incidence and mortality. *Imperial Cancer Research Fund* 1994: 55–76.
26. Oota K, Sobin LH. *Histological typing of gastric and esophageal tumors. International histologic classification of tumors*. 18. Geneva: World Health Organisation, 1990.
27. Cimerman M, Repše S, Jelenc F, Omejc M, et al. Comparison of Lauren's, Ming's and WHO histological classifications of gastric cancer as a prognostic factor for operated patients. *Int Surg* 1994; 79: 27–32.
28. McNeer G, Vandenberg H Jr, Donn FY, Bowden L. A critical evaluation of subtotal gastrectomy for cure of cancer of the stomach. *Ann Chir* 1951; 134: 2–7.
29. Lahey FH. Total gastrectomy for all patients with operable gastric cancer of the stomach. *Surg Gynecol Obstet* 1950; 90: 246–9.
30. Repše S, Juvan R. Kirurgija raka želodca v Sloveniji. In: Repše S, editor. *Kirurgija želodca: kirurška šola*. Ljubljana: Kirurške klinike KC, 1995; 101–12.

31. Repše S, Jelenc F, Žakelj B, Jerman J, Lamovec J, Bitenc M, et al. Rak želodca – spremembe v naši patologiji v dveh desetletjih. *Zdrav Vestn* 1991; 60: 281–5.
32. Repše S. Rak želodca. In: Repše S, editor. *Priporočila za celostno obravnavo bolnikov z rakom prebavil*. Ljubljana: Ministrstvo za zdravstvo R Slovenije, 1997; 13–21.
33. Lortat-Jacob J, Giuli R, Estenne B, Clot P. Value of total gastrectomy for treatment of cancers of the stomach. Study of 482 radical operations. *Chirurgie* 1975; 101: 59–67.
34. Akoh JA, MacIntyre IM. Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1979. *Br J Surg* 1992; 79: 293–9.
35. Davies J, Johnston D, Sue-Ling H, Young S, May J, Griffith J, et al. Total or subtotal gastrectomy for gastric carcinoma? A study of quality of life. *World J Surg* 1998; 22: 1048–55.
36. Maehara Y, Moriguchi S, Yoshida M, Takahashi I, Korenaga D, Sugimachi K. Splenectomy does not correlate with length of survival in patients undergoing curative total gastrectomy for gastric carcinoma. Univariate and multivariate analyses. *Cancer* 1991; 67: 3006–9.
37. Keller E, Stutzer H, Heitmann K, Bauer P, Gebbensleben B, Rohde H (German stomach cancer TNM study group). Lymph node staging in 872 patients with carcinoma of the stomach and the presumed benefit of lymphadenectomy. *J Am Coll Surg* 1994; 178: 38–46.
38. Kasakura Y, Fujii M, Mochizuki F, Kochi M, Kaiga T. Is there a benefit of pancreaticosplenectomy with gastrectomy for advanced gastric cancer. *Am J Surg* 2000; 179: 237–42.
39. Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H, Okajima K. Pancreas-preserving total gastrectomy for proximal gastric cancer. *World J Surg* 1995; 19: 532–6.
40. Kitamura K, Nishida S, Ichikawa D, Taniguchi H, Hagiwara A, Yamaguchi T, et al. No survival benefit from combined pancreaticosplenectomy and total gastrectomy for gastric cancer. *Br J Surg* 1999; 86: 119–22.
41. Omejc M, Mekicar J. Role of computer analysis in gastric cancer surgery: evaluation of the WinEstimate v. 2.5 computer program. *World J Surg*. 2004; 28: 59–62.
42. Gretschel S, Bembenek A, Ulmer Ch, Hunerbein M, Markwardt J, Schneider U, et al. Prediction of gastric cancer lymph node status by sentinel lymph node biopsy and the maruyama computer model. *Eur J Surg Oncol* 2005; 31 (4): 393–400.
43. Jentschura D, Heubner C, Manegold BC, Rumstadt B, Winkler M, Trede M. Surgery for early gastric cancer, a European one-center experience. *World J Surg* 1997; 21: 845–8.
44. Iriyama K, Asakawa T, Koike H, Nishiwaki H, Suzuki H. Is extensive lymphadenectomy necessary for surgical treatment of intramucosal carcinoma of the stomach. *Arch Surg* 1989; 124: 309–11.
45. Hanazaki K, Wakabayashi M, Sodeyama H, Miyazawa M, Yokoyama S, Sode Y, et al. Clinicopathologic features of submucosal carcinoma of the stomach. *J Clin Gastroenterol* 1997; 24: 150–5.