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FACTORS INFLUENCING THE SURVIVAL OF PATIENTS AFTER RADICAL SURGERY FOR GASTRIC CANCER

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the papers listed below, which will be referred to in the following by their Roman numerals:

I Arak A., Kull K. Factors influencing survival of patients after radical operation for gastric cancer. A regional study of 406 patients over a 10-year period. Acta Oncologica 1994; 33:913–920.

II Arak A., Kull K. Correlation of lymph node metastases with other prognostic factors of curative gastric cancer. Proceedings of the XVI International Cancer Congress. Bologna 1994, by Monduzzi Editore S.p.A., pp. 1733–1737.

III Arak A., Lehtola J., Mäkelä J., Tuominen H. Gastric cancer: surgical management and prognosis. Annales Chirurgiae et Gynecologiae (submitted for publication).

IV Arak A., Kull K. Extended lymphadenectomy in gastric cancer surgery. Estonian Physician 1994; 1:45–51 (in Estonian).

V Arak A., Kull K. Gastric carcinogenesis. Estonian Physician 1994; 6:476–483 (in Estonian).

VI Arak A., Kull K., Lehtola J., Mäkelä J., Tuominen H. Radical surgery for gastric cancer. Estonian Physician (in Estonian, in press).

INTRODUCTION

Despite the general tendency of decrease in the incidence of gastric cancer in the world, it still represents one of the leading causes of death from malignant diseases in many countries (Craanen, 1992). In Estonia the incidence of gastric cancer is higher and its decline has been less expressed than it is in most of the neighbouring North-European countries (Cancer Society of Finland, 1990; Cancer Society of Finland, 1992; Holleb, 1991; Lauren, 1993; Lindahl, 1988; Tekkel, 1992; Thomson, 1994). In addition, most cases of gastric cancer are detected in advanced stages and only very rare we can operate for tumors in early stages. The differences in the overall survival curves for gastric cancer patients after curative operations are large, with 5-year survival rates of more than 60% in Japanese and less than 40% in non-Japanese series (Akoh, 1992; Bozzetti, 1990; Breaux, 1990; Ovaska, 1989; Maruyama, 1987b; Murray, 1989; Noguchi, 1989).

The high survival rates obtained in Japan are attributed to a successful screening program for the detection of early gastric cancer, accurate staging and aggressive surgical treatment with combined organ resections and extended lymphadenectomy (Cuschieri, 1989). The improvement in early gastric cancer diagnosis is referred to various advances in diagnostic intervention including fiberoptic gastrointestinal endoscopy, double-contrast radiography, and mass screening in a high risk population. These advances have increased the early gastric cancer prevalence in Japan from approximately 2% in 1950 to over 30% in 1980 and over 50% in 1990 (Maruyama, 1987b; Maruyama, 1989; Nakamura, 1992; Noguchi, 1989; Soga, 1988). Extended lymph node dissection (R2–R3 lymphadenectomy) became standard treatment in Japan for all cases of gastric cancer during the middle of the 1970s and most of the Japanese authors have pointed out the relationship between extensive lymph node dissection and better cure results (deAretxabala, 1988; Maruyama, 1987b; Maruyama, 1989; Soga, 1988). Unfortunately, in the opinion of many authors, other treatment modalities, such as the adjuvant chemotherapy, offered modest benefit in the improvement of the results of curative gastric cancer (Bleiberg, 1992; Korenaga, 1992; Schlag, 1987; Shiu, 1987b)

In the Western world only half of the patients have resectable tumor, and less than a half of these are suitable for curative resection (Bonenkamp, 1992). Besides, radical lymphadenectomy is performed in only 50% of all European patients, and the treatment of gastric carcinoma by general surgeons has shown results considerably poorer than those reported by special referral centres (15%) (Akoh, 1991; Jaehne, 1992; McCulloch, 1994). The generally held perception that gastric cancer is a disease that is diagnosed late, has high operative mortality rate and overall 5-year survival rate of less than 15% has led to

a nihilistic attitude towards treatment of the disease outside Japan (Akoh, 1991; Allum, 1989; Guardagni, 1993; Inoue, 1993; Sano, 1992).

As extensive screening programs are not still feasible in Europe, the therapeutic results can be improved only by using extensive surgical techniques. Because of the good results shown in Japanese studies the practice of extended lymphadenectomy has found increased acceptance in many hospitals outside Japan in recent years (Bonenkamp, 1993; Jatzko, 1992a; Roukos, 1990; Sigal, 1991). In our hospital the principles of extended lymphadenectomy were introduced at the end of the 1970s and now we consider this procedure unavoidable in curative gastric cancer surgery.

The prognosis of cancer patients is determined by a series of patient-, tumor- and treatment-associated factors (Adam, 1989; Maruyama, 1987b; Maruyama, 1989; Moriguchi, 1991a; Noguchi, 1989). In the ideal situation, as many prognostic factors as possible should be known before initiation of therapy to design a therapeutic concept for the individual patient. Therefore, the identification of prognostic factors and determination of their clinical relevance is an important aspect of oncological research.

Because surgery remains the only method of treatment that offers the potential for cure for gastric cancer patients, it is most important to examine the influence of the extent of gastric resection and regional lymphadenectomy on survival. The questions most often asked are as follows: How much of the stomach should be resected? How useful is lymphadenectomy? If gastric resection is to be performed, how wide the resection of neighbouring organs should be?

To seek answers to these questions and to evaluate the influence of different clinicopathological and treatment related factors on the prognosis of primary gastric cancer patients we conducted a retrospective study of 406 patients, whose primary gastric carcinomas had been resected with curative intent in Hospital of Oncology, Tartu from 1978 to 1987.

The previous studies performed in Estonia concerned the precancerous conditions or the relationship between precancerouses and gastric cancer (Rätsep, 1976; Villako, 1992). The surgical treatment of gastric cancer is not studied.

REVIEW OF LITERATURE

1. Incidence

Marked variation in the incidence of gastric cancer as well as a general tendency of decrease is observed around the world. The incidence varies approximately tenfold internationally, the highest rates per 100,000 inhabitants are observed in Japan (males 82; females 36), parts of China (males 58; females 25) and Costa Rica (males 59; females 25). Intermediate rates prevail in Europe, where the incidence is slightly higher in the south (Italy: males 44; females 20) and eastern Europe (Poland: males 44; females 17) compared to the northern and western parts (England: males 19; females 8). The lowest incidence rates are seen in the United States (whites: males 8; females 3), Australia (males 15; females 6) and in Africa (Nigeria: males 7; females 4). A twofold variation in the incidence of gastric cancer has been found within the Nordic region, covering Denmark (men 14, women 8), Iceland (men 31, women 14), Norway (men 18, women 9) and Sweden (men 25, women 13) (Hansson, 1991; Hansson, 1993). In Finland it was the most common malignant neoplasm in both male and female patients up to the 1950s (65 per 100 000 in the male population and 38 per 100 000 in the female population), but in 1980s the incidence was 21 and 11 per 100 000 respectively (Lauren, 1993). In general, the risk of gastric cancer in the Northern hemisphere tends to increase with increasing latitude (Cancer Society of Finland, 1992; Hansson, 1993). A substantial annual decline in stomach cancer incidence is of about 2%–7% in most regions (Hoel, 1992). However, no significant decrease has been found in some of these regions in the recent decade and therefore the decline in the incidence could not be interpreted as evidence that the disease is disappearing (Correa, 1991; Macintyre, 1991).

Up to 1980s stomach was the most common location of cancer in Estonia. Although this place has been conquered by the lung cancer in 1980s the incidence of gastric cancer is still frequent and the percentage of advanced cases is too high for the contentment with the situation. The morbidity rate in our country has changed from 53.1 in male and from 39.4 in female per 100 000 in 1970s to 41.9 in male and to 32.0 in female per 100 000 in 1980s (Cancer Society of Finland, 1990; Tekkel, 1992). It is also one of the main causes of death due to cancer: according to the data of the Estonian Cancer Registry about 450 to 500 patients per year died from this malignance.

2. Survival

Stomach cancer continues to carry a dismal prognosis in most Western countries where the overall 5-year survival ranges from 5 to 20%, in Estonia this rate is 17% (Akoh, 1992; Bollschweiler, 1993; Bozzetti, 1989; Breaux, 1990; Craanen, 1992; Cady, 1989; Cancer Society of Finland, 1990; Hoel, 1992; Inoue, 1991; Ovaska, 1989). The differences in the overall survival curves for patients with carcinoma in the stomach after curative or radical operations are large, with 5-year survival rates of more than 60% in Japanese and less than 40% in non-Japanese series (Akoh, 1992; Bozzetti, 1990; Breaux, 1990; Ovaska, 1989; Maruyama, 1987b; Murray, 1989; Noguchi, 1989).

The analysis of one hundred series published in English has shown an improvement in 5-year survival rates over the past 30 years (Akoh, 1992). The 5-year survival rate after resection has increased significantly from 20.7% before 1970 to 28.4% before 1990, and following curative or radical resection from 37.6% before 1970 to 55.4% before 1990. When the Japanese series were excluded from the analysis the 5-year survival rate after all resections is 23.4%, and after curative or radical resection 39.4% before 1990. Wanebo et al. (1993) compared the results of gastric cancer therapy as recorded by the American College of Surgeons study with the results of a number of selected Japanese hospitals (by Maruyama, 1987b) (Table 1.1):

Table 1.1

Comparison of gastric cancer therapy between the American College of Surgeons and selected Japanese hospitals (by Wanebo, 1993)

	Incidence		Resected patients survival	
	Japan	United States	Japan	United States
No.of patients	15,589	18,365	12,535	10,237
Stage I (%)	33.7	17.1	95.6	50.0
Stage II (%)	14.5	16.9	70.1	29.0
Stage III (%)	28.7	35.5	36.3	13.0
Stage IV (%)	23.1	30.5	23.1	3.0
Survival (%)	45.5	14.0	56.3	19.0

3. Prognostic factors

The prognosis of patients with malignancy depends upon biological aspects of the tumor, tumor–host relationship, and the therapy prescribed (Janssen, 1992; Moriguchi, 1991a). Some authors describe high-risk populations for gastric cancer, such as the Japanese, as having different epidemiological (social, dietary, infectious) factors compared with low-risk populations in North-

America and in Europe (Adam, 1989; Bollschweiler, 1993; Maehara, 1991a; Maehara, 1992d; Parsonnet, 1991; Wanebo, 1993). The inverse socio-economic gradient has been observed in most populations, and the rate in lower socio-economic classes is two to three times that in more affluent classes (Adam, 1989; Correa, 1992; Hansson, 1993; Kato, 1992). Dietary factors and improvements in food storage and handling are thought to be major factors relevant to the decline of gastric cancer in high risk regions. Reduction in toxic methods of food preservation, such as smoking and pickling, declining salt consumption, widespread use of refrigeration, and increasing fruit and vegetable consumption, may account for many of the changes in stomach cancer incidence (Hoel, 1992; Lauren, 1993; *paper V*).

Some authors have found the higher incidence of the intestinal type should be correlated with a high-risk population and a better prognosis of survival (Lauren, 1965; Lauren, 1993; Adam, 1989; Bollschweiler, 1993). Others have described, that the histologic tumor type is not an important independent prognostic factor and postulated differences in the relative frequency of intestinal (differentiated) and diffuse (non-differentiated) cancers in different countries ought not to have a heavy impact on the survival rates (Maruyama, 1989).

The prognosis of patients with gastric carcinoma is determined by a series of prognostic factors. These factors can be grouped into three categories: patient related, tumor related, and treatment related. There may be a multitude of interactions of different strength among the different factors. The identification of these factors, their interactions and determination of their clinical relevance is extremely important.

3.1. Patients related prognostic factors

Age

That gastric cancer is a disease of ageing is demonstrated by the fact that about 50% of the cases in male and 60% of the cases in females occurred in those who are older than 60 years (Wanebo, 1993). Young age is rare among the patients and this disease rarely occurs in children (Bollschweiler, 1993; Maehara, 1991a; McGill, 1993; Tso, 1987).

It has become clear that age in itself is a prognosticator of cancers. Observations of cancers of the lung, colon, breast, prostate gland and kidney have shown that advancing age reduces growth of tumors (Ershler, 1986; Janssen, 1991). In patients with gastric cancer, some authors noted a close relationship between the prognosis and age of the patients (Bollschweiler, 1993; Bozzetti, 1986; Maehara, 1991a; Matley, 1988), while others found no such relationship (Mitsudomi, 1989; Moriguchi, 1991a; Moriguchi, 1993a). Moriguchi, 1993b found an increased mortality in the very young (<30 years) and the very old (≥

80 years) age groups for patients with gastric cancer who had undergone gastrectomy. For young patients, a poor prognosis is attributed to a delay in the diagnosis or to a more aggressive course of the disease (Maehara, 1991a; Matley, 1988). The long-term life expectancy for elderly patients who had undergone gastrectomy is reduced because of the exhausted immunological response or there may be a relatively prolonged life expectancy because of the slow progression of the tumor (Bozzetti, 1986; Tsukuma, 1983).

The shorter survival time in young patients is related to larger tumor size, extended serosal invasion, diffuse macroscopic type, poorer differentiation, peritoneal dissemination and lymph node metastasis, although some authors have found that gastric cancer in elderly may also be significantly large and may have metastases when detected because of relatively mild symptoms (Bandoch, 1991; Esaki, 1990; Janssen, 1991; Lauren, 1965; Maehara, 1991b; Maehara, 1991c; Maruyama, 1987b; Mishima, 1987; Moriguchi, 1993b). In addition, many authors have reported that gastric cancers in the elderly are more frequently located in the distal part of the stomach, compared with those in young patients (Bandoch, 1991; deCalan, 1988; Husemann, 1989; Kawaura, 1988; Moreaux, 1988; Rohde, 1991; Welvaart, 1980).

Some investigators argue that total gastrectomy for the elderly might lead to increased deaths without essentially improving the long-term prognosis (Shiu, 1987a). It is well known that more than 50% of the elderly patients have pulmonary or cardiovascular complications before operation and some operative deaths could be attribute to such complications deteriorating after operation (Bandoch, 1991). Therefore, as total gastrectomy carries a risk of excessive intraoperative blood loss, longer operative time, and pulmonary complications compared with cases of a distal partial gastrectomy, caution is needed when attempting extensive surgical resection in elderly patients (Korenaga, 1991). However, when tumors are located at the cardia or have spread involving the entire stomach beyond the confines of subtotal gastrectomy, total gastrectomy is certainly indicated irrespective of the patient´s age (Maruyama, 1987b; Mishima, 1987; Shiu, 1987a)).

Sex

In general, gastric carcinoma affects men more often than women (Bollschweiler, 1993; Craanen, 1992; Hoel, 1992; Korenaga, 1992). The male: female ratio usually falls between 1.5 and 3.0 and tends to be higher in areas with a high than with a low incidence (Hansson, 1993; Nakamura, 1993). The higher percentage of women may reflect the ageing of most countries with women living longer, thereby allowing for a greater occurrence of gastric cancer (Wanebo, 1993).

In most studies the sex of patients seems not to be a significant factor influencing the prognosis; however, clinicopathological factors of gastric cancer between the sexes do differ (Arveaux, 1992; Haugstvedt, 1993; Jatzko,

1992a; Maehara, 1992b; Msika, 1989; Roder, 1993; Shiu, 1987). The age, tumor size and location, Borrmann type, and especially histology were considered as the sex-related associations. The non-differentiated types, which show a diffusely infiltrative growth pattern and results in a shorter survival time than seen with differentiated type, are prominent in women (Armstrong, 1986; Tso, 1987). In particular, advanced cases were dominant in women and most often a non-curative resection was done (Maehara, 1992b). Some authors found more men with proximal cancers than with distal cancers (deCalan, 1988; Husemann, 1989; Janssen, 1991; Kawaura, 1988; Moreaux, 1988; Rohde, 1991; Welvaart, 1980).

3.2. Tumor related prognostic factors

According to the General Rules for the Gastric Cancer Study in Japan, four pathologic factors — gastric wall invasion, lymph node metastasis, peritoneal dissemination and liver metastasis — have proved to be the significant prognostic factors and are useful as criteria for classification according stage (Kaijtani, 1981). After curative gastrectomy, in patients without peritoneal dissemination or liver metastasis, mainly gastric wall invasion and lymph node metastasis were thought to determine the stage of tumor progression (Kaibara, 1987a; Maehara, 1991c; Maruyama, 1987a; Maruyama, 1987b; Maruyama, 1989; Moriguchi, 1990; Moriguchi, 1992; Msika, 1989). In addition, tumor gross appearance, tumor location, size and histologic type are also reported to be the independent prognostic factors in patients without distant metastasis (Bozzetti, 1986; Jatzko, 1992a; Kaibara, 1987a; Maehara, 1991c; Maruyama, 1987a; Moriguchi, 1990; Noguchi, 1989). All these factors may be closely linked to the others and dispose the prognosis after curative surgery.

Depth of invasion

Most studies agree on the fact that depth of invasion within the gastric wall is one of the most important prognostic factors (Allum, 1989; Arveux, 1992; Bozzetti, 1986; Maruyama, 1987a; Msika, 1989). The prognosis of early gastric cancer is remarkably good, compared with advanced tumors: the 5-year survival after gastrectomy for early gastric cancer is over 90%, as compared with 30–40% for patients with T2–T4 cancer (Boku, 1989; Guadagni, 1993; Inoue, 1991; Lawrence, 1991; Moreaux, 1993; Noguchi, 1989; Sowa, 1989).

In Japan, where the developments in diagnosis and the introduction of mass screening programs have been in use, the proportion of early gastric cancers has risen from 9.4% for the period 1963–1966 to 43.8% during 1979–1987. At the same time in the USA the overall proportion of gastric cancers diagnosed early

is only 3–4% constantly and European series report a value <10% (Bollschweiler, 1992; Guardagni, 1993; Inoue, 1993; Sano, 1992).

Although the overall 5-year survival rate for patients with early gastric cancer has improved, the problem of cancer recurrence remains. As a rule, lymphatic metastases and vascular metastases are rare when cancer cells are limited to the mucosa, but they begin to appear when the cells have penetrated into the submucosal layer. In general, recurrence after gastrectomy because of early gastric cancer is mainly related to the following factors:

1) Depth of invasion — mucosal or submucosal (Inoue, 1993).
2) Histologic type — differentiated or non-differentiated (Adachi, 1993; Lawrence, 1991; Mishima, 1987; Moreaux, 1993).
3) Presence or absence of lymph node metastasis (Endo, 1990; Hioki, 1990; Ichiyoshi, 1990; Inoue, 1991; Itoh, 1989; Lawrence, 1991; Maehara, 1992d; Moreaux, 1993).
4) Vascular invasion and hematogenous metastases — the mucosal hypervascularity is more common for the protruded differentiated carcinomas (Adachi, 1993; Eriguchi, 1991; Sano, 1993).
5) Macroscopic type. Lymph node metastasis are significantly more frequent in the protruded or combined type of early gastric cancer such as IIa+IIc, and from large tumors (>2.0 cm in diameter) which are poorly differentiated and invade the submucosa (Boku, 1989; Habu, 1990; Hioki, 1990).
6) Peritoneal dissemination is extremely rare in patients with early gastric cancer (Endo, 1990; Hioki, 1990; Inoue, 1991; Itoh, 1989; Lawrence, 1991; Maehara, 1992d; Moreaux, 1993).

In contrast to the current experiences in Japan, most of the gastric carcinomas are diagnosed at advanced stages in Western part of the world, so that the survival rates are generally poor. After curative gastrectomy in patients with advanced carcinoma of the stomach, a close relationship was noted between the extent and the area of serosal invasion of carcinoma and the prognosis (Baba, 1989b; Boku, 1990; Haraguchi, 1991; Kaibara, 1987a; Korenaga, 1994; Moriguchi, 1990; Maehara, 1991b; Maehara, 1992c). A factor also relating to intraperitoneal dissemination is the possibility of cancer infiltration from metastatic lymph nodes. Serosal invasion cases have many lymph nodes in which cancer cells invade perinodal fatty tissues, and that these cases have the peritoneal dissemination (Boku, 1990).

Lymph node metastases

The localised forms of malignant disease are clinically most significant since small tumor loads can be treated more effectively than disseminated ones (Debruyne, 1991). If growth of tumor cells at secondary sites — lymph node metastasis — has occurred, the prognosis becomes worse. Nodal involvement has been reported to have the same prognostic significance as the depth of

invasion (Okusa, 1990). One of the important causes of recurrence for gastric cancer patients is found to be the incompletely dissected lymph node micrometastasis and the best survival rates after curative surgery appeared to be in patients with no or limited nodal disease (N0 and N1) (Boku, 1989; Maehara, 1992d; Noguchi, 1989).

A number of studies have paid meticulous attention both to the site and extent of nodal involvement. Histological analysis of all the lymph nodes removed at the operation make nodal staging more accurate and increase the incidence of higher stages when compared to series with less rigorous node dissection. After extended curative resection about half of the patients with gastric carcinoma have been found to have lymph node metastases (Bollschweiler, 1993; Wang, 1993). Independent risk factors for the occurrence of lymph node metastasis are found to be submucosal or deeper invasion, large tumor size, and lymphatic involvement by tumor cells (Maehara, 1992d; Okamura, 1988). The depth of invasion correlates strongly with the incidence of lymph node metastases. The incidence of metastases to lymph nodes in patients with early gastric cancer has been reported as varying from 0% to 7% in cases of intramucosal cancer, and from 2.3% to 50% in cases of submucosal cancer (Hioki, 1990; Iriyama, 1989; Lauren, 1965; Moreaux, 1993). Incidence of lymph node metastases increases markedly if the muscular layer (>40% of cases) or serosa (>80% of cases) is penetrated (Boku, 1990; Roukos, 1990; Wang, 1993). These associations are explained by the findings that lymph capillaries are found only in the deep lamina propria adjacent to and within the muscularis mucosae; the upper and middle levels of the lamina propria of the gastric mucosa contain no lymph capillaries. The entire mucosa show a rich supply of blood capillaries, many of which are adjacent to the basal lamina of gastric glands and the surface epithelium (Lehnert, 1985; Ming, 1992; Sano, 1992).

The expected extent of lymph node metastasis can be predicted approximately by the location of the tumor. Studies show an orderly spread to the nodes clearly related to the position of the tumor, which occurred with decreasing frequency along identifiable lymphatic chains along the arteries, and converged to a wide area around the upper abdominal aorta (Maruyama, 1989; Sigal, 1976; Soga, 1988). If the tumor is located at the upper third of the stomach, cardiac and lesser curvature nodes are the most common sites followed by left gastric, celiac axis and splenic vessels nodes; cardiac carcinoma also may often involve the inferior oesophageal and diaphragmatic lymph nodes. With the tumor at the middle third, lesser and greater curvature nodes and infrapyloric and left gastric nodes are involved frequently; the nodes around the oesophagogastric junction also may be frequently involved. In this group of tumors it is important to point out that nodes along the splenic vessels and in the hilus of the spleen are involved in approximately 10% of instances. With the tumor at the lower third, infrapyloric nodes are the most frequent,

followed by lesser and greater curvature nodes. Involvement of left gastric, common hepatic, and celiac nodes are frequent regardless of tumor location (Boku, 1989; deAretxabala, 1987; Maruyama, 1989; Mishima, 1987; Noguchi, 1989; Roukos, 1990; Wang, 1993). Limited spread to perigastric nodes correlates to better survival rates than deposits around the celiac artery, the poorest prognosis being associated with metastases in the hepatoduodenal ligament, behind the pancreas head, at the root of mesentery, and along the aorta (station numbers 12 to 16) (Maruyama, 1989). In advanced cases the pattern of lymphatic spread is reported to be unpredictable from the location of the tumor (Maruyama, 1989; Ponsioen, 1989).

Analysis of the histologic types of gastric cancer reveals no differences in frequency of node metastases (Maehara, 1992c; Roukos, 1990). In some studies the relationship between tumor size or Borrmann type and incidence of lymph node metastases is also reported (Maehara, 1992c; Maruyama, 1989). Nevertheless, these factors are closely related to the depth of invasion and the lymph node involvement is more significantly caused by it.

It seems likely that, regardless of possible geographic differences in aggressivity of stomach cancer, the lymphogenous metastases follow the same paths of dissemination. Most of patients demonstrated very similar incidence of lymph node metastasis in the various node stations in curatively resected cases (Bollschweiler, 1993; Maruyama, 1989).

Borrmann type

Macroscopic classification of the tumor would be the most useful clinically, because the macroscopic types are closely related to tumor histologic type, pattern of spread, and ultimately, prognosis. For example, polypoid and ulcerating circumscribed tumors mostly evinced a well or moderately differentiated histologic type and a rather fair prognosis, when ulcerating infiltrative and diffusely infiltrative tumors often revealed a poorly differentiated histologic type and poor prognosis (Abe, 1991; Maehara, 1992a; Nakamura, 1992). Gross appearance is also reported to be the independent prognostic factor for curative gastric cancer by soma authors (Arveaux, 1992; Haugstvedt, 1993).

Histologic type

Most of the other pathological features of gastric carcinoma have been shown to be closely related to histologic subtypes. The histologic composition of gastric carcinoma varies from case to case and from area to area. As a result, several histologic classifications have been proposed. Lauren divided gastric carcinomas into two types: intestinal and diffuse, with relative frequency of 53% and 33% respectively; the remaining 14% of carcinomas did not fit into these patterns and were unclassified (Lauren, 1965). Based on the pattern of

tumor growth and invasiveness, the gastric carcinomas are divided into expanding and infiltrative types (Ming, 1992). In the Ming´s classification the microscopic patterns of tumor growth are reflected in the gross appearance of the tumor. Nakamura (Nakamura, 1992) simply divided the gastric cancers into differentiated and non-differentiated types, using gland formation as the indicator for differential diagnosis. In this study histology was classified according to the WHO classification as papillary and well or moderately differentiated tubular adenocarcinoma, interpreted as the differentiated types, and poorly differentiated adenocarcinoma, signet-ring cell, mucinous, or undifferentiated carcinomas, interpreted as the non-differentiated types (Oota, 1977). There are similarities between these classification: carcinomas of the differentiated type are mostly intestinal and expanding carcinomas, and carcinomas of the non-differentiated type are diffuse and infiltrative carcinomas (Ming, 1992). The non-differentiated types are found more often in the advanced stages than in the early stage, and these results may be explained by difficulties in detecting and more rapid growth of this type of cancer (Ikeda, 1994; Janssen, 1991; Lauren, 1965; Moriguchi, 1991b). In addition, the differentiated adenocarcinomas tend to give rise to vascular metastases, and non-differentiated to lymphatic ones or show peritoneal dissemination, also some authors have found out no significant differences in the survival rate based on histopathologic type of gastric cancer (Adachi, 1993; Lawrence, 1991; Mishima, 1987; Moreaux, 1993).

Beside being morphologically different, the two types appear to differ with respect to their epidemiological characteristics (Lauren, 1991; *paper V*). The differentiated (intestinal) types seem to be particularly age dependent whereas the non-differentiated (diffuse) types strike all age groups uniformly (Bandoch, 1991; Lauren, 1991; Lundegardh, 1991; Ming, 1992). Accordingly, the predominance of intestinal types of cancer increases with increasing age. More men are also marked among patients with the intestinal type of gastric carcinoma (Lauren, 1991; Lundegardh, 1991; Ming, 1992). It has been suggested that the remarkable decline in gastric cancer, which has been witnessed during the past few decades, is due mainly to a decrease in the incidence of the intestinal types; but no significant difference between high- and low-risk areas has been found in the age-adjusted rates for the diffuse types of gastric cancer (Amorosi, 1988; Correa, 1988; Correa, 1991; Correa, 1992; Lauren, 1993; *paper V*).

However, despite the differences in the epidemiological and pathologic features, according to most of the authors the histologic type of gastric cancer itself has no significant influence on the prognosis in multivariate analysis (Haugstvedt, 1993; Maruyama, 1987a; Nakamura, 1993; Roder, 1993; Roukos, 1990).

Location

Gastric carcinomas may occur anywhere in the stomach. About one half of them involve the pyloric mucosa; one quarter, the cardial mucosa, and another quarter, middle part of the stomach. In reports from the recent years, the cardia is involved in more than 25% of cases, and there is a decrease of antral carcinomas (Bollschweiler, 1993; Craanen, 1992; Hermann, 1993; Ming, 1992; Meyers, 1987; Wanebo, 1993).

Although a relatively less common neoplasm, adenocarcinoma of the cardia is drawing more attention whereas carcinomas of the proximal third of the stomach have increased in relative frequency, and have significantly worse prognosis and higher hospital mortality than those of other locations (Antonioli, 1982; Cady, 1977; Husemann, 1989; Maruyama, 1987b; Meyers, 1987; Powell, 1990). Carcinoma of the cardia is characterised by younger patients and a high percentage of advanced tumor stages (between 50 and 75%) (deCalan, 1988; Husemann, 1989; Kawaura, 1988; Moreaux, 1988; Rohde, 1991). Carcinomas of the upper third of the stomach have lymph node metastases more often than those of the distal stomach (Bollschweiler, 1993). 5-year survival rates for patients with cardial cancer ranging from 10% to 15% in most series; better 5-year survival rates are reported occasionally, but it is less than 1/3 in all collected series (Adam, 1989; Blomjous, 1992; Bollschweiler, 1993; Stipa, 1992; Rohde, 1991).

Size

The mean diameter of advanced tumors is much larger than that of early carcinomas (6 to 7 cm versus < 4 cm), and directly correlates with a lower survival rate in advanced cases (Nakamura, 1992). In general, the tumors documented in Japan have smaller diameter than those documented in Europe (Bollschweiler, 1993; Haugstvedt, 1993; Maruyama, 1987b; Roder, 1993). Tumor size seems to be closely associated with other pathologic factors of gastric cancer and is not independent prognosticator itself.

3.3. Treatment related prognostic factors

Radical surgery

Despite the new developments in the treatment of gastric cancer, such as neoadjuvant and intraperitoneal chemotherapy, surgical resection is still the therapy of choice. Statistical analyses show that, even though there are predetermined clinicopathologic factors that govern survival, the surgeon's choice and manner of execution of surgery can have a significant effect on prognosis (Akoh, 1992; Maruyama, 1987b; Pacelli, 1993; Shiu, 1987a; Stipa, 1994). Although the first successful resection of a carcinoma of the stomach

was accomplished more than 100 years ago, the optimal surgical management of this disease is still the subject of debate (Adam, 1989; Holleb, 1991). Some surgeons perform only simple gastrectomy, while others advocate extensive gastrectomy with *en bloc* lymphadenectomy.

In general, the basic tenets of oncologic resection for epithelial cancers require wide excision of the primary tumor and *en bloc* removal of the lymphatic drainage network, including the regional lymph nodes and intervening lymphatic vessels (deAretxabala, 1987; Shiu, 1987a; Smith, 1991). Long established and practised, the concept has been undergoing revaluation for carcinomas of the breast, colon, and head and neck region. For these tumors, radiation therapy, chemotherapy and hormonal therapy have shown increasing effectiveness, to the extent that they may indeed permit lesser resectional surgery without jeopardising tumor control. For gastric cancer, however, these modalities have only limited therapeutic value at the present time (Bleiberg, 1992; Korenaga, 1992; Schlag, 1987; Shiu, 1987a; Shiu, 1987b). For successful control of this disease, the absence of distant metastases and the peritoneal dissemination is essential, but sufficient gastrectomy with extended lymph node dissection and combined organ resection is also important (Adachi, 1992; Adam, 1989). Even when surgery is palliative due to the presence of various incurable factors, gastrectomy still seems preferable to gastrojejunostomy, because symptoms are alleviated and the survival time is prolonged (Korenaga, 1988a).

There are two modalities of surgery for gastric cancer: limited and extended. Limited surgery includes endoscopic polypectomy for a mucosal polypoid cancer, endoscopic laser therapy, and local excision of the stomach wall for a small mucosal cancer in experimental studies (Eriguchi, 1991; Guadagni, 1991; Hioki, 1990; Inoue, 1991; Lawrence, 1991; Sue-Ling, 1992; Yasuda, 1993). Extensive surgery is indicated in all cases of advanced gastric cancer and in cases of early gastric cancer with submucosal invasion. The goals of extended radical surgery are to excise direct contiguous invasion from the primary to the surrounding organ, to achieve complete lymph node dissection, and to excise localised peritoneal implantation (Boku, 1989; Korenaga, 1988a; Maruyama, 1987b; Noguchi, 1989). The techniques of radical operation have been well standardised by the Japanese Research Society for Gastric Cancer (Kaijtani, 1981).

Extent of gastrectomy

The resection, either distal or total, is determined by the proximal distance from the cardia. The distal division line is always placed at the duodenal bulb because the pylorus is usually a barrier to the distal extension of gastric cancer (Kakeji, 1991). There is general agreement that a distance of 6 cm from the cranial edge of a gastric cancer, as measured by the pathologist on the fresh specimen, can guarantee a safe margin of proximal transection in the vast

majority of operable cases (Bozzetti, 1988; Bozzetti, 1992a; Maruyama, 1987b). According to some authors this distance can be reduced somewhat when dealing with tumors confirmed to the muscularis propria, in early and non-early well-circumscribed types and the intestinal variety according to the Lauren´s classification (Adam, 1989; Bozzetti, 1992b; Gennari, 1986; Gouzi, 1989; Launois, 1991; Stipa, 1994).

Total gastrectomy *de principle* is open to question in the management of cancer of the antrum and of the cardia. A number of investigators contend that total gastrectomy is the treatment of choice for infiltrative tumors and there is also a tendency to perform total gastrectomy for the diffuse type according to Lauren´s classification (Adam, 1989; Bandoch, 1992; Bozzetti, 1990; Bozzetti, 1992a; Cuschieri, 1986; Gennari, 1986; Gouzi, 1989; Iida, 1993; Sigal, 1991; Stipa, 1994). On the other hand, only a minority of recurrences is confirmed to the gastric stump and would have consequently been prevented by a total gastrectomy — fact that points against the better radicality of total versus subtotal gastrectomy (Bozzetti, 1990; Dent, 1988; Moriguchi, 1992). The second justification is therefore better lymph node dissection, mainly by associated splenectomy and juxtapancreatic node dissection, although in fact splenic system nodes can be dissected without associated pancreatectosplenectomy (Maruyama, 1987b). The other lymph node groups, the dissection of which could be theoretically dependent on the extent of gastric resection are the paragastric nodes, but technically the lymphadenectomy in this region can also be performed with subtotal resection to the same radical degree obtained in total gastrectomy (Bozzetti, 1990; Hüscher, 1992). Nevertheless, because advanced lesions tend to metastasise to all the regional nodes, the only procedure that is theoretically capable of encompassing the primary tumor with its lymphatic drainage is total gastrectomy combined with splenectomy and distal pancreatic resection (Adam, 1989; Launois, 1991). Poorer prognosis is reported in patients who had undergone total gastrectomy, which likely is reflective of the extent of disease, proximal tumor location, and surgical perspective (radical or potentially radical). Nevertheless, gastrectomy does not have to be total to be curative, and many total gastrectomies without extensive lymphadenectomy performed in the West are non-curative procedures (Monson, 1991; Nakamura, 1992).

Because of its technical simplicity and lower postoperative mortality, some surgeons favour high, distal subtotal gastrectomy in the treatment of middle and lower third tumors (Adam, 1989; Gennari, 1986; Gouzi, 1989; Launois, 1991; Stipa, 1994). This procedure should include a high transection of the stomach proximally and at least 1 centimetre of duodenum with excision of at least 80% of the stomach, ligation of the left gastric artery at its origin, resection of both omenta and dissection and removal lymph nodes located in the hepatoduodenal ligament, hepatic, celiac and left gastric arteries, and in the left paracardial region; preservation of the spleen seems to be preferable (Adam, 1989;

Launois, 1991). However, complete R2 or R3 lymph node dissection with subtotal gastrectomy may be dangerous: lymph node dissection along the splenic artery and at the splenic hilus (N groups 10 and 11) requires the interruption of both the posterior gastric artery and the short gastric vessels, with a risk of ischaemia for the gastric remnant (Guadagni, 1993).

The type of surgery for proximal cancer of the stomach remains a subject of controversy. Cardial cancer's site at the border between the thorax and abdomen can make the intraoperative staging and the choice of the optimal surgical procedure (type of incision, type and extent of lymphadenectomy, type of reconstruction of the digestive tract) extremely difficult, the operation dangerous and too often unsuitable for extended surgery (deCalan, 1988; Kaibara, 1987b; Kawaura, 1988; Rohde, 1991; Moreaux, 1988; Welvaart, 1980). Carcinoma of the gastric cardia has been found to have such dismal prognosis by some authors that any surgical treatment is thought to be essentially palliative — hence, the recommendation that the less extensive proximal subtotal resection should be performed (Adam, 1989). Nevertheless, proximal resection of the stomach is not generally recommended by the majority of surgeons because of the high percentage of post-operative complications and reduced radicality associated with it (deCalan, 1988; Kaibara, 1987b; Kawaura, 1988; Maruyama, 1987b; Moreaux, 1988; Rohde, 1991; Santoro, 1991; Stipa, 1992; Welvaart, 1980). In addition, carcinoma of the cardia commonly spreads into the oesophageal wall and thus a wide oesophageal resection is also required to control the disease in this area (Iida, 1993; Stipa, 1992).

Lymphadenectomy

In Japan there is wide consensus on the desirability of a standardised extensive node dissection as proposed by the Japanese Research Society for Gastric Cancer (Kaijtani, 1981). The extensive lymph node dissection is found to give better survival rates compared with limited dissection, and decreases the incidence of local recurrence without added morbidity and mortality (deAretxabala, 1987; Korenaga, 1988a; Maehara, 1993; Maruyama, 1987b; Maruyama, 1989; Noguchi, 1989; Soga, 1988). Although several retrospective Japanese studies have showed the importance of extensive lymph node dissection, a radical lymphadenectomy in Europe is performed in less than 50% of all curatively operated patients (Heberer, 1988; Valen, 1988). In the United States only a small percentage of cases had operations similar to the Japanese R2 dissection; only in 13% of gastrectomies the celiac node are dissected, which is minimal for the R2 lymphadenectomy (Wanebo, 1993). This may, in part, explain the disappointing 5- and 10-year survival rates even after potentially curative resections in the Western hemisphere compared with the Japanese results (Akoh, 1991; Akoh, 1992; Allum, 1989; Bunt, 1994; Dent, 1988; Ovaska, 1989; Wanebo, 1993).

Thus, the extent of lymph node metastasis and whether or not these metastatically involved lymph nodes are dissected are important factors which influence the prognosis of patients with gastric cancer (Maehara, 1991c; Msika, 1989). In general, according to the Japanese surgeons, at least the R2 dissection of the lymph nodes seems to be certainly needed in all these cases where primary gastric cancer reaches an advanced stage (Maehara, 1991b; Maehara, 1992c; Maruyama, 1989; Mishima, 1987; Moriguchi, 1990a). Some non-Japanese authors find no differences in the probability of survival for patients with gastric cancer between R1 and R2–R3 lymph node dissection or report about the increased postoperative mortality after extensive lymphadenectomy (Dent, 1988; Irvin, 1988; Roukos, 1990). However, the reported high morbidity after R2 resection in Western countries seems to result from a lack of properly trained surgeons and quality control (Bonenkamp, 1992). Several Western studies have also shown the survival advantage of extensive over limited lymphadenectomy without increasing the postoperative morbidity and mortality (Bonenkamp, 1992; Gunven, 1991; Jatzko, 1992b; Keller, 1994; Pacelli, 1993; Siewert, 1993).

When focusing on the problems of lymphadenectomy one has to consider, however, that the extent of lymphadenectomy is difficult to quantify by the surgeon alone. Due to this fact, the intraoperative assessment of the TNM stage is unprecise with up to 40% overstaged or understaged cases (Jaehne, 1992). Therefore, an accurate histopathologic examination of the resected specimen, including the dissected lymph nodes, seems to be absolutely necessary for quantifying the extent of lymphadenectomy and for exact staging (Maruyama, 1989; Takahashi, 1994).

Resection of adjacent organs

Adjacent organ resection in gastric cancer surgery was started in Japan in the 1960s with the goal of increasing the rate of survival (Maruyama, 1987b). The spleen, distal pancreas, transverse colon and mesocolon, gallbladder, abdominal oesophagus, left adrenal gland, and the left lobe of the liver can be removed to eradicate direct contiguous invasion from the stomach to these surrounding organs or to enable more complete lymph node dissection without technical difficulty as well as without any trouble occurring postoperatively (Iida, 1993; Iriyama, 1994; Launois, 1991; Maruyama, 1987b; Noguchi, 1989). Resection of invaded organs proved to be worthwhile even in patients with multiple organ involvement. Some authors have employed extremely extensive methods of surgery in the treatment of Borrmann type 4 gastric carcinoma (specially the so-called linitis plastica type) — left upper abdominal evisceration. With this operative technique, the stomach and transverse colon, pancreas body and tail, spleen and left adrenal gland are resected en bloc (Furukawa, 1988). However, patients with tumors extending to adjacent organs frequently have factors apparent at laparotomy (peritoneal dissemination, liver metastasis and wide-

spread nodal involvement) which indicate incurability (Bines, 1993; Korenaga, 1988b; Mishima, 1987; Maruyama, 1989).

Distal pancreaticosplenectomy for lymph node dissection is used because of the intimate relation of nodes to these organs. Sequential section examination of the distal pancreas, with surrounding nodes dissected during surgery, is shown remnant nodes in 75% along splenic artery suggesting that organ resection in the absence of true invasion is necessary to improve the node dissection (Furukawa, 1988; Noguchi, 1989).

Local invasion of surrounding structures and organs is a frequent occurrence in patients with gastric cancer, the reported incidence ranged from 10 to 23 per cent (Bozzetti, 1990). Combined resection is performed in 37–85% of patients undergoing gastrectomies for cancer (Habu, 1990; Korenaga, 1988b). In the opinion of Japanese authors surgeons should be aggressive in performing gastrectomy with *en bloc* removal of invaded organs when cancer appears to be in a potentially curable cases, because more than 20% of the patients undergoing curative resections survived more than five years (Bozzetti, 1990; Habu, 1990; Korenaga, 1988b; Maruyama, 1987b). 5-year survival rates were reported to be 33% to 48% for patients with liver resection; 29% to 31% for those with colon resection, and 24% to 43% for those with pancreas and spleen resections (Noguchi, 1989; Korenaga, 1988b).

Diagnosis of contiguous invasion is not easy. Direct invasion is proven histologically in 45% to 57% of cases with combined organ resection for intraoperative macroscopic diagnosis of direct invasion (Noguchi, 1989). For example, the tumors arising at the greater curvature of the gastric body and antrum invade the mesocolon occasionally, but the direct invasion of the transverse colon is uncommon (Adachi, 1992). Parenchymal invasion is proven histologically in 33% of macroscopically diagnosed direct invasion into liver, another 1/3 have invasion limited to the capsule, and the final 1/3 have fibrous adhesions only (Noguchi, 1989). False-positive cases might, in part, be a factor in the high figures of 5-year survival reported for combined resections.

Splenectomy

There is no consensus of opinion regarding the therapeutic value of splenectomy. A number of investigators reported that patients who have undergone combined gastrectomy and splenectomy had a longer survival time than did those who had been treated by gastrectomy alone (Bozzetti, 1990; Koga, 1981; Maruyama, 1987b; Noguchi, 1989). Others, however, observed that the prognosis after gastrectomy was improved in patients with intact spleen and that a combined splenectomy may adversely affect the prognosis (Clark, 1991; Maehara, 1991b; Noguchi, 1989). There are also some reports that splenectomy has no affect on the prognosis of patients with gastric cancer, but may increase the morbidity after curative gastrectomy and should be avoided unless the spleen is close to or invaded by the tumor (Brady, 1991; Korenaga, 1992).

Fulminating infectious disease is one common and fatal complication after splenectomy, not only in young but also in adults (Maehara, 1991b; Viste, 1990). However, other workers have found that the spleen has negative effect on tumor immunity or that splenectomy did not adversely affect cellular immunity (Clark, 1991; Fuyuhiro, 1984; Kanayama, 1985; Noguchi, 1989).

Splenectomy has commonly been performed simultaneously with total gastrectomy to treat patients with gastric cancer, especially when the primary tumor is located in the upper or middle third of the stomach (Clark, 1991; Korenaga, 1992). Regional lymphatic drainage from this site is to the splenic hilar lymph nodes and radical lymphadenectomy of these first order lymph nodes usually include splenectomy.

Postoperative complications and mortality

Many clinicians continue to view the results of gastric cancer surgery with pessimism. Although radical surgical resection offers the only prospect of cure, the postoperative complication and mortality rates are regarded as unacceptably high by many non-Japanese practitioners (McCulloch, 1994). Complication rates of 20–40% are commonly reported in the Western series (Adam, 1989; Allum, 1989; Bonenkamp, 1993; Gennari, 1986; Launois, 1991; Macintyre, 1991; Pacelli, 1991; Viste, 1988). Review of 49 series over the world with patients operated on approximately at the same period show that 33 had an operative mortality rate of <10%; 14 had an operative mortality rate of between 10% and 20% and two of >20%; the median was 4.6% and the mean was 7.8%, ranged from 0% to 28.0% (Macintyre, 1991). Especially in elderly patients results seem to be controversial: some reports have shown increasing complication and mortality rates with age, whereas others have challenged these findings (Bandoh, 1991; Pacelli, 1991; Viste, 1988). In recent years, preoperative preparation, anaesthesia, surgical technique, and postoperative care have significantly improved, to the extent that postoperative morbidity and mortality have decreased to a much more acceptable level for gastric resections (deAretxabala, 1987; Pacelli, 1991; Smith, 1991).

The difference between the survival rates from Japan and from the rest of the world has been so great that it has led to the suggestion that the biology and natural history of the disease in Japan is somehow different (Maruyama, 1989). Similarly, the lower Japanese operative mortality rates have been variously attributed to a higher proportion of patients with early disease, younger mean age, lower incidence of coexisting pathology, and a body habitus in Japanese patients which makes surgery technically easier (Korenaga, 1988b; Macintyre, 1991; Maruyama, 1987b; Maruyama, 1989). However, some authors have concluded that in Europe extensive lymphadenectomy can be also done safely if carried out by properly trained surgical oncologists (Bonenkamp, 1992).

Other treatment possibilities

Although there has been recent progress in gastric cancer surgery and improvement of treatment results, we had to accept limits of radicality, especially in patients with peritoneal metastasis, liver metastasis, distant lymph node metastasis, and Borrmann type 4 cancer (Aranha, 1989; Maruyama, 1987b). In order to improve the treatment results in such cases, other treatment modalities such as adjuvant and neoadjuvant chemotherapy, intraperitoneal chemotherapy, intra-arterial infusion into hepatic artery for liver metastases, hormonal therapy (tamoxifen), immunotherapy, and hyperthermia have been introduced, but these methods have little effectiveness for advanced gastric cancer at the present time (Ajani, 1993; Bleiberg, 1992; Harrison, 1989; Hermann, 1993; Highley, 1993; Kim, 1992; Shiu, 1987b; Takahashi, 1994).

AIM OF THE STUDY

The general objective of the study was to analyse the results of curative (radical) gastric cancer surgery in Tartu Hospital of Oncology and to define the prognostic factors for patients with curative gastric cancer in Estonia.

The specific aims were:

1) to write up the clinicopathological features and to evaluate the independent patients related, tumor related and treatment related prognostic factors for curative gastric cancer;
2) to determine the indications and the suitable extension of dissection of organs and lymph nodes in radical gastric cancer surgery;
3) to compare the treatment policy and long-term results of gastric cancer surgery in non-specialized and specialized oncological institutions.

MATERIAL AND METHODS

1. Patients

This thesis is based mainly on three studies where the different aspects of gastric cancer surgery were analysed. Among 690 patients with primary gastric cancer (with the exception of stomach stump cancer) treated surgically at the Department of Surgery, Tartu Hospital of Oncology, Estonia during the 10-year period from 1978 to 1987, there were 406 (58.8%) patients who had undergone curative resection of tumors with extended (R2 or R3) lymphadenectomy (Kajitani, 1981). Adjuvant chemotherapy (5-FU alone or FAM-combination) was administered in 122 more advanced cases without significant influence on the survival. The medical reports of all these patients were analysed in the first study (*paper I*). For the second study (*paper II*) we used data on 361 patients who had undergone curative surgery for primary gastric cancer from 1978 through 1986; i.e. all data of the patients analysed in the first study expected the patients operated on in 1987.

From these studies the following cases were excluded:

1. Patients who had undergone bypass procedures or palliative resections because of distant metastases or technical inoperability (n=240);
2. Patients who had undergone total (n=13) or subtotal (n=22) gastrectomies with only group 1 lymph node dissection (R1 lymphadenectomy). We classified these cases as non-curative, because the perigastric lymph nodes as the first barrier for cancer cells are involved at least in 10% of T1 cases, more deeper invasion is frequently associated with N2 metastases (Hioki, 1990; Inoue, 1991; Inoue, 1993; Iriyama, 1989; Lauren, 1965; Lawrence, 1991; Lehnert, 1985; Maehara, 1992d; Moreaux, 1993; Sakita, 1989). Therefore the risk of locoregional recurrence after R1 lymphadenectomy is extremely high. These operations were performed in limited number of elderly patients with concomitant diseases and with high operative risk. Moreover, lymph node metastases and the postoperative prognosis must be evaluated only in the series of curative gastric resections because there is insufficient information regarding lymph node involvement after incomplete lymphadenectomy in patients treated with noncurative resection.
3. Some patients (n=9) with N4 metastases, who had undergone R4 lymphadenectomy (i.e. dissection of N4, mainly the para-aortal lymph nodes) with very high postoperative mortality or early recurrence (Inada, 1994; Kaijtani, 1981). We have desisted from this procedure at the present.

All patients were followed after surgery, and relative 5-year survival rates were calculated. Only patients who had clearly died of gastric cancer were

considered as tumor-related deaths. All the data concerning the death of patients were collected from the database of the Estonian Cancer Registry.

Third study (*paper III*) is based on 203 patients with histologically proved primary gastric cancer treated at the Department of Surgery of Oulu University Hospital, Finland during the 5-year period from 1983 to 1987. For this study the medical reports of the Oulu University Hospital and the database of the Finnish Cancer Registry were used. The co-operation traditions between gastroenterologists of Oulu and Tartu Universities have had about twenty years history. The previous joint-studies concerned the relationship between precancerous conditions and gastric cancer but not the gastric cancer itself (Lehtola, 1989). Although the incidence of gastric cancer has markedly decreased during recent decades in Finland as well as in most industrialised countries, the decline is less marked in some regions where the data are closer to those of in Estonia, for example in North-Finland. In addition, the treatment policy of gastric cancer is quite different in these two countries. There is the network of specialised oncological aid for cancer patients in Estonia and the more extensive surgery has been in use. The gastric cancer patients in Finland are treated by the general surgeons with conventional methods of surgery (see "*Operative methods*"). Because of these differences it is extremely interesting to compare the data of gastric cancer patients in Oulu and Tartu regions. We tried to evaluate the influence of clinicopathological factors and operative procedures on the prognosis of patients with primary gastric cancer treated at the Department of Surgery of Oulu University Hospital, Finland (*paper III*, see "*Results*"). In the "*Discussion*" the comparison of prognostic factors and treatment aspects of gastric cancer between Tartu and Oulu materials (*paper VI*) will be presented.

2. Methods

The medical reports of all patients were analysed to ascertain the characteristics and duration of symptoms, the physical findings and laboratory data on admission. Operative records were investigated with regard to operative findings, adjacent organ invasion, lymph node metastases, and operative procedure including gastrectomy with different extension, lymph node dissection, and combined organ resection. Pathological findings were reviewed with respect to the depth of invasion, size, location, gross appearance, histologic type of tumor, and lymph node involvement. These operative and pathologic findings were principally based on the UICC TNM classification and on the General Rules for Gastric Cancer Study outlined by the Japanese Research Society for Gastric Cancer (Hermanek, 1987; Kajitani, 1981). All specimen removed were examined pathologically.

Table 2.1

The number and the anatomical name of regional lymph nodes and N categories (N1, N2, N3, N4) for each primary gastric cancer locating in the upper (C), middle (M) or lower (A) third, and whole stomach

\Location of the tumor Lymph nodes	Lower	Middle	Upper	Whole
No.1 right cardial	N2	N1	N1	N1
No.2 left cardial	N3	N2	N1	N1
No.3 along the lesser curvature	N1	N1	N1	N1
No.4 along the greater curvature	N1	N1	N1	N1
No.5 suprapyloric	N1	N1	N2	N1
No.6 subpyloric	N1	N1	N2	N1
No.7 along the left gastric artery	N2	N2	N2	N2
No.8 along the comm. hep. artery	N2	N2	N2	N2
No.9 around the celiac artery	N2	N2	N2	N2
No.10 at the splenic hilus	N3	N2	N2	N2
No.11 along the splenic artery	N3	N2	N2	N2
No.12 in the lig. hepatoduodenal	N3	N3	N3	N3
No.13 behind the pancreatic head	N3	N3	N3	N3
No.14 at the mesenteric root	N3	N3	N3	N3
No.15 at the middle colic artery	N4	N4	N4	N4
No.16 para-aortic	N4	N4	N4	N4

Depth of invasion was divided into T1 (tumor confined to mucosa and submucosa), T2 (invasion of proper muscle layer and subserosa), T3 (invasion into serosa) and T4 (invasion of contiguous structures) according to the UICC rules (Hermanek, 1987).

Tumor location was divided into the upper (cardia, cardia+corpus), the middle (corpus, corpus+cardia, corpus+antrum) and the lower (antrum, antrum+corpus) third or the total (more than two thirds) involvement of the stomach.

Histology was classified according to the WHO classification as papillary and well or moderately differentiated tubular adenocarcinoma, interpreted as the differentiated types, and poorly differentiated adenocarcinoma, signet-ring cell, mucinous, or undifferentiated carcinomas, interpreted as the non-differentiated types (Nakamura, 1992; Oota, 1977).

Macroscopic types of tumor were classified according to Borrmann's classification as type 1 — polypoid, type 2 — ulcerated evaluated, type 3 — ulcerated with partially diffuse infiltrating border and type 4 — diffusely invading tumor (Kaijtani, 1981).

Lymph nodes from different anatomical positions (lymph node stations 1 to 16, Table 2.1) were divided into four N-groups (N1, N2, N3 and N4) according to the General Rules for Gastric Cancer Study outlined by the Japanese

Research Society for Gastric Cancer (Kaijtani, 1981). In each case only the most distant lymph node station affected is mentioned.

3. Operative procedures

There are three components in the standard curative gastrectomy performed at the Departmant of Surgery, Tartu Hospital of Oncology: (1) the total or subtotal gastrectomy, (2) the extensive lymphadenectomy (3), and the *en bloc* resection of adjacent organs. All lymph nodes and neighbouring organs are always removed *en bloc* with the stomach and surrounding fatty tissue (Berjozov, 1976; Bozzetti, 1990; Iida, 1993; Maruyama, 1987b; Sigal, 1976).

The required *cancer-free distance* at the proximal margin is at least 5 cm in circumscribed tumors and at least 8 cm in infiltrative tumors. *Total gastrectomy* is defined as the removal of the whole stomach and is indicated when the proximal distance from the cardia is less than required or in Borrmann types 3 and 4 (Maruyama, 1987b). In case of *subtotal gastrectomy* all the lesser curvature up to oesophagus and most of the greater curvature higher than the level of splenic hilus have been dissected. This type of gastrectomy is performed mainly in cases of circumscribed tumors. The lesser omentum and the greater omentum with the anterior leaf of the mesocolon is always removed together with the stomach.

Lymph node dissection, called R2 lymphadenectomy, always includes the perigastric nodes (excluding the left cardial nodes in distal gastrectomy), and nodes located along the left gastric, common hepatic, splenic and coeliac arteries (Table 2.1). In cases of non-antral location the nodes in the splenic hilum and left cardial nodes were also removed. To achieve better lymph node removal in this region the splenectomy is performed in most of these cases.

The nodes of group 3 (R3 lymphadenectomy) from the hepatoduodenal ligament, behind the pancreatic head and body, and the root of mesenterium were also dissected in cases of palpable changes in the perigastric lymph nodes (Table 2.1). The anterior leaf of both the hepatogastric and hepatoduodenal ligaments with lymph nodes and fatty tissue is removed, preserving only the common and hepatic arteries, as well as the portal vein and common bile duct. The removing of the pancreatic capsule and the nodes behind pancreatic head and body is also important (Kajitani, 1981; Inoue, 1991; Maruyama, 1987b; Mishima, 1987).

If needed, frozen sections are examined before making decisions about the extent of lymphadenectomy. In cases of metastases, the aim of the dissection is to have a margin at least of one uninvolved group of lymph nodes distal to the most peripheral involved group of node stations.

The removal of the neighbouring structures or organs (spleen, oesophagus, pancreas, mesocolon, transverse colon, diaphragm, liver, gallbladder) was performed in cases of direct invasion or to achieve better lymphadenectomy.

The reconstruction of the gastrointestinal tract is performed by gastro-jejunostomy with Brown's anastomosis or by the Roux-en-Y method after subtotal gastrectomy, and by end-to-side or end-to-end Roux-en-Y oesophago-jejunostomy after total gastrectomy.

Conventional gastrectomy used in radical gastric cancer surgery at Oulu University Hospital is either the total or distal subtotal removal of the stomach and perigastric regional lymph nodes, i.e. R1-lymphadenectomy according to the Japanese General Rules for the Gastric Cancer Study (Kaijtani, 1981). In this study the gastric resection is classified as radical if the lymph node involvement was restricted to the perigastric (N1) nodes, no tumor was left following the surgery, and no microscopical invasion in the resection margins was found on the postsurgical histological examination. The minimal distance of the upper resection margin in radical cases was 5 cm, however in infiltrative cases total gastrectomy was always performed. No patients with T4 tumors were operated on with curative intention. Roux-en-Y method is applied to reconstruct the alimentary tract.

4. Definitions

Advanced gastric cancer was defined as "invasion or deeper invasion of the tumor into muscularis propria layer by histopathological examination" (Kaijtani, 1981).

Early gastric cancer is defined as a disease in which the depth of invasion is limited to the gastric mucosa or submucosa, regardless of the presence or absence of lymph node metastasis (Sleisenger, 1993, p.765).

Since the UICC TNM classification gives no any definition of *radicality* or *curability*, we decided to use the terms of the General Rules for Gastric Cancer Study outlined by the Japanese Research Society for Gastric Cancer (Cuschieri, 1986; Kajitani, 1981; Rohde, 1989):

1. *Absolute curative resection*. There are no peritoneal and hepatic deposits. All macroscopic cancer i.e., primary tumor with margins histologically free of cancer and all involved lymph nodes are removed. At least one echelon of non-involved lymph nodes must have been removed beyond those containing secondary deposits (resection level R must be higher than level of nodal involvement N);
2. *Relative curative resection* — the only difference between this and "absolute curative" is that R equals N;

3. *Relative non-curative resection* — although there is complete removal of the tumor, the criteria described above are not met.
4. *Absolute non-curative resection* — there is evidence of residual cancer.

Absolute or relative curative resections are defined as the operation with curative (radical) intention, and relative or absolute non-curative resections are defined as palliative operation in this study.

Extensive lymph node dissection (extensive lymphadenectomy) is defined as the removal of more than perigastric lymph nodes, etc. N2, N3 (or N4) nodes.

Postoperative mortality was defined as the number of deaths within the 30 days after surgery. All postoperative deaths were included in the survival analyses as it is recommended by Akoh, 1992.

5. Statistical methods

The statistical data analysis was made in the SPSS-for-Windows 6.0 system, using uni- and multivariate analyses of variance. For the univariate analysis the cross-tabulation and two-sample analysis of variance was used. For the multivariate data analysis the multiple stepwise regression analysis. All factors affected the relative 5-year survival rates were analysed by the Cox regression model of survival analysis in a forward stepwise regression method.

The significance's were calculated by the chi-squared statistics using Likelihood ratio, Pearson's and Mantel-Haenszel's tests for linear association.

RESULTS

The results are divided into two main parts: the results of the radical gastric cancer surgery in Tartu Hospital of Oncology, Estonia, and the results of the gastric cancer surgery in Oulu University Hospital, Finland. The main part of this retrospective study presents a review of prognostic factors influencing the survival of 406 gastric cancer patients radically operated on in the Tartu Hospital of Oncology in 1978–1987 (*paper I and II*). To compare the different policies for gastric cancer surgery the analysis of prognostic factors for 203 patients with gastric cancer treated in the non-specialized, general surgical institution (Department of Surgery of the Oulu University Hospital) during the 5-year period from 1983 to 1987 was also performed (*paper III*).

1. Patient related prognostic factors

Age

To analyse the influence of the age patients were classified into 6 groups by the age at the time of operation. The mean age was 62.4 years and median 63 years (range 31–85 years). 7 (1.7%) of patients were at the age of below 40 years, 49 (12.1%) at the age of 40–49 years, 106 (26.1%) at the age of 50–59 years, 119 (29.3%) at the age of 60–69 years, 115 (28.3%) at the age of 70–79 years and 10 (2.5%) at the age of over 80 years (Figure 1). Although all the operated patients showed the peak of incidence between 60 and 70 years and patients with early gastric cancer between 50 and 60 years, the age distribution of early gastric cancer patients did not differ significantly from the overall distribution of age groups observed in this study.

In general the elderly patients had shorter duration of symptoms (Table 3.2). We observed epigastric pain and anorexia more frequently in younger patients, general symptoms were more typical for the elderly patients (Table 3.4).

Table 3.1

Multiple regression analysis of variables influenced by the age of patients

Variable	Location (p<0.05)		Nodal status (p<0.05)	
Age group	Antrum	Non-antral	N0	N+
Younger group (n=162)	69 (42.6)	93 (57.4)	102 (63.0)	60 (37.0)
Elderly group (n=244)	131 (53.7)	113 (46.3)	123 (50.4)	121 (49.6)

* — in all tables the relative frequences in percentages are presented in parentheses

According to the results of univariate and multiple regression analysis only the antral location of primary tumor and the presence of lymph node metastases was more frequent in patients over 60 years of age (Table 3.1). There were no significant differences in the distribution of tumor size, Borrmann types, T values or morphological types of cancer by the age groups.

In patients over 60 years of age the incidence of general postoperative complication and mortality rates were significantly higher (Table 3.15). In contrast no significant difference was found in the incidence of surgical complication.

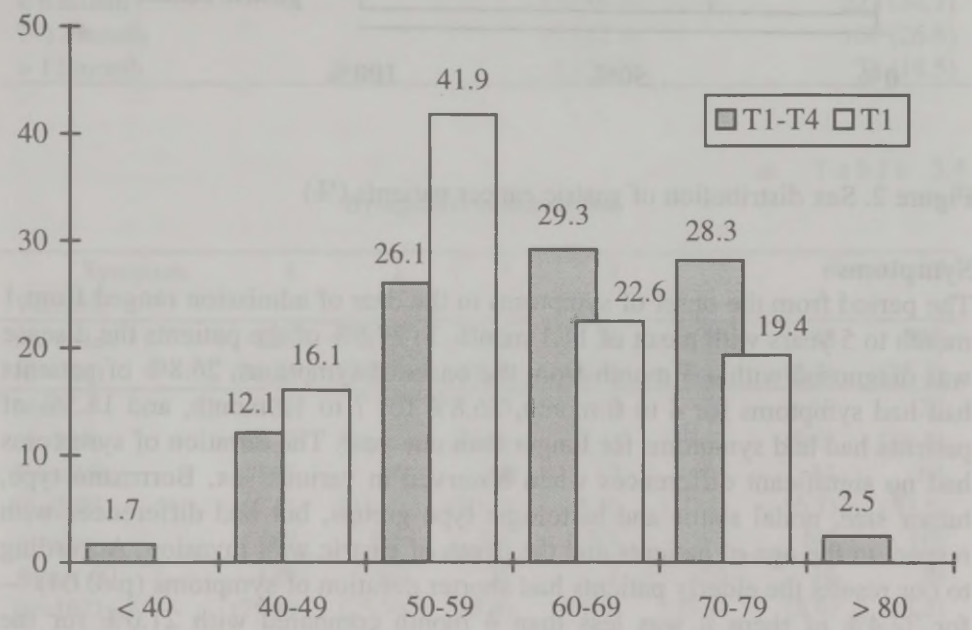

Figure 1. Age distribution of gastric cancer patients

Sex

In the 10-year period from 1978 to 1987 the sex distribution showed a male predominance 1.35:1 for all gastric cancer cases in Estonia but not for curatively operated patients (0.95:1) and moreover not for the patients with early gastric cancer (0.48:1) in the material of Tartu Hospital of Oncology (Figure 2).

No differences was found in the sex-distribution of any prognostic factors or symptoms at the time of admission (Table 3.4). There was also no significant independent factors for male or female patients according to the results of multivariate analysis (p-value for the full regression 0.561).

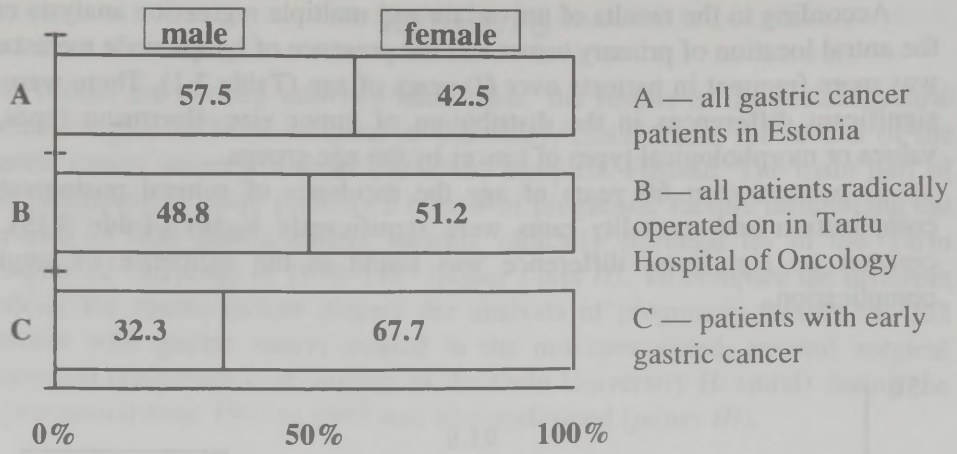

Figure 2. Sex distribution of gastric cancer patients (%)

Symptoms

The period from the onset of symptoms to the date of admission ranged from 1 month to 5 years with mean of 11.1 month. In 27.8% of the patients the disease was diagnosed within 3 month from the onset of symptoms, 26.8% of patients had had symptoms for 4 to 6 month, 26.8% for 7 to 12 month, and 18.5% of patients had had symptoms for longer than one year. The duration of symptoms had no significant differences when observed in various sex, Borrmann type, tumor size, nodal status and histologic type groups, but had differences with respect to the age of patients and the depth of gastric wall invasion. According to our results the elderly patients had shorter duration of symptoms (p=0.04) — for 32.4% of them it was less than 4 month compared with 21.0% for the younger patients; 23.4% for the patients at the age below 60 years and 15.2% at the age over 60 years group had had complaints for more than the 12 month before the admission (Table 3.2).

Table 3.2

Duration of symptoms in different age groups

Duration of symptoms	< 60 year of age	≥ 60 years of age	all cases
< 4 month	34 (21.0)	79 (32.4)	113 (27.8)
4–6 month	45 (27.8)	64 (26.2)	109 (26.8)
7–12 month	45 (27.8)	64 (26.2)	109 (26.8)
> 12 month	38 (23.4)	37 (15.2)	75 (18.5)

The patients with early gastric cancer had relatively longer duration of symptoms when compared with other patients (p=0.008, Table 3.3): the mean duration of symptoms for patients with early gastric cancer was 17.8 month compared with 11.1 month for all patients (12.3 month for T2, 10.8 month for T3 and 9.0 month for T4 tumors).

Table 3.3

Duration of symptoms and depth of gastric wall invasion

Duration of symptoms	T1	all T
< 6 month	12 (38.7)	222 (54.7)
7–12 month	10 (32.3)	109 (26.8)
> 12 month	9 (29.0)	75 (18.5)

Table 3.4

Symptoms at admission

Symptom Variable	1	2	3	4	5	6	7
All cases	**285**	**123**	**91**	**28**	**159**	**33**	**135**
(n=406)	**(70.2)**	**(30.3)**	**(22.4)**	**(6.9)**	**(39.2)**	**(8.1)**	**(33.3)**
Male	139	57	49	16	75	19	72
(n=198)	(72.7)	(28.8)	(24.7)	(8.1)	(37.9)	(9.6)	(36.4)
Female	141	66	42	12	84	14	63
(n=208)	(67.8)	(31.7)	(20.2)	(5.8)	(40.4)	(6.7)	(30.3)
p-value	NS	NS	NS	NS	NS	NS	NS
Age < 60	**129**	42	**25**	7	58	14	**38**
(n=162)	**(79.6)**	(25.9)	**(15.4)**	(4.3)	(35.8)	(8.6)	**(23.5)**
Age ≥ 60	**156**	81	**66**	21	101	19	**97**
(n=244)	**(63.9)**	(33.2)	**(27.0)**	(8.6)	(41.4)	(7.8)	**(39.8)**
p-value	.001	NS	.008	NS	NS	NS	.001
T1	24	**4**	7	1	**6**	**0**	8
(n=31)	(77.4)	**(12.9)**	(22.6)	(3.2)	**(19.4)**	**(0.0)**	(25.8)
T2–T4	261	**119**	84	27	**153**	**124**	127
(n=375)	(69.6)	**(31.7)**	(22.4)	(7.2)	**(40.8)**	**(33.0)**	(33.9)
p-value	NS	0.04	NS	NS	0.04	0.03	NS
N0	**169**	58	53	15	91	12	65
(n=225)	**(75.1)**	(25.8)	(23.6)	(6.7)	(40.4)	(5.3)	(28.9)
N1–N3	**116**	65	38	13	68	21	70
(n=181)	**(64.1)**	(35.9)	(21.0)	(7.2)	(37.6)	(11.6)	(38.7)
p-value	0.04	NS	NS	NS	NS	NS	NS

(continued)

Symptom / Variable	1	2	3	4	5	6	7
Antrum	**127**	**79**	55	14	88	**5**	75
(n=200)	**(63.5)**	**(39.5)**	(27.5)	(7.0)	(44.0)	**(2.5)**	(37.5)
Corpus	**110**	**31**	24	13	50	**4**	41
(n=140)	**(78.6)**	**(22.1)**	(17.1)	(9.3)	(35.7)	**(2.9)**	(29.3)
Cardia	**29**	**8**	7	1	12	**20**	11
(n=42)	**(69.0)**	**(19.0)**	(16.7)	(2.4)	(28.6)	**(47.6)**	(26.2)
Total	**19**	**5**	5	0	9	**4**	8
(n=24)	**(79.2)**	**(20.8)**	(20.8)	(0.0)	(37.5)	**(16.7)**	(33.3)
p-value	0.02	.007	NS	NS	NS	.000	NS
Borrmann	137	60	48	**21**	68	**9**	53
I–II (n=193)	(71.0)	(31.1)	(24.9)	**(10.9)**	(35.2)	**(4.7)**	(27.5)
Borrmann	147	63	43	**7**	91	**24**	82
III–IV(n=213)	(69.0)	(29.6)	(20.2)	**(3.3)**	(42.7)	**(11.3)**	(38.5)
p-value	NS	NS	NS	0.01	NS	0.04	NS
Differentiated	117	53	**49**	14	59	12	61
(n=171)	(68.4)	(31.0)	**(28.7)**	(8.2)	(34.5)	(7.0)	(35.7)
Non-differ.	168	70	**42**	14	100	21	74
(n=235)	(71.5)	(29.8)	**(17.9)**	(6.0)	(42.6)	(8.9)	(31.5)
p-value	NS	NS	0.01	NS	NS	NS	NS
Ø < 4 cm	46	17	14	1	19	**1**	**11**
(n=57)	(80.7)	(29.8)	(24.6)	(1.8)	(33.3)	**(1.8)**	**(19.3)**
Ø 4–7 cm	131	64	41	17	75	**11**	**64**
(n=192)	(68.2)	(33.3)	(21.4)	(8.9)	(39.1)	**(5.7)**	**(33.3)**
Ø > 7 cm	108	42	36	10	65	**21**	**60**
(n=157)	(68.8)	(26.7)	(22.9)	(6.4)	(41.4)	**(13.4)**	**(38.2)**
p-value	NS	NS	NS	NS	NS	0.02	0.04

1 — epigastric pain; 2 — nausea and/or vomiting; 3 — anorexia; 4 — gastrointestinal bleeding; 5 — dyspepsia; 6 — dysphagia; 7 — general complains (fatigue, weakness).

Incidence of complaints and their association with different clinicopathologic variables at the time of the first admission of the patients is presented in Table 3.4. Epigastric pain (77.4% in early and 70.2% in advanced cases), weight loss (45.2% and 61.8%), dyspepsia (19.4% and 39.2%) and general dyscomfort (25.8% and 33.3%) were more frequent symptoms for both the patients with the early as well as with the advanced gastric cancer (Table 3.4). Nausea/ vomiting, dyspeptic complains and dysphagia were associated with deeper (T2–T4) gastric wall invasion. There were significant differences in the frequencies of existing symptoms between the patients with different location of cancer: nausea/vomiting, anorexia, dyspepsia and general dyscomfort were more frequent in cases of antral tumors; epigastric pain in cases of corporal tumors and in patients with total involvement of the stomach. Cardial tumors were more likely to cause dysphagia. In patients with total stomach cancers more frequently the palpable epigastric pain (in 33.3% of all these cases) and

palpable tumor (in 54.1% of all these cases) was found on the objective investigation. Bleeding was observed more frequently in patients with Borrmann type I–II cancers, when the Borrmann type III–IV tumors were more often the cause of dysphagia.

251 (61.8%) patients had weight loss at the time of admission (Table 3.5), which was the evidence of advanced stage of disease in these patients: its incidence and quantity changed significantly with T stages (p=0.005). The weight loss was also more noticeable in patients with infiltrative types of cancer (p=0.016).

Table 3.5

Weight loss at admission

Extent of weight loss (kg)	0–5	6–10	11–15	> 15	All cases
Number of patients	65	119	41	26	251
(%)	(16.0)	(29.3)	(10.1)	(6.4)	(61.8)

Laboratory findings

Main laboratory data are listed in Table 3.6. In general we observed only few patients with abnormal laboratory findings: hypoproteinaemia (serum protein level less than 50.0 g/l) was found in 4 cases, uraemia (serum urea level more than 10.0 mmol/l) in 30 cases and hyperbilirubiaemia (serum bilirubin level more than 21.5 mmol/l) in 39 cases. Although in 6.9% of patients one of the symptoms was gastrointestinal bleeding, anaemia (serum haemoglobin level less than 100 g/l) was found in 21.4% of cases. The abnormal renal or liver function was not significantly associated with higher postoperative complications or mortality.

Table 3.6

Laboratory findings at the admission

Laboratory data	Mean	Range	Abnormality	Abnormal findings
Protein (g/l)	75.11	42.0 to 118.0	<50.0	in 4 (0.9%) cases
Urea (mmol/l)	6.04	1.7 to 15.8	>10.0	in 30 (7.4%) cases
Bilirubin (mmol/l)	13.9	1.7 to 49.2	>21.5	in 39 (9.6%) cases
Hgb (g/l)	122.4	40.0 to 176.0	<100.0	in 87 (21.4%) cases

2. Tumor related prognostic factors

Depth of invasion

Thirty one (7.6%) of our patients had T1, 63 (15.5%) had T2, 218 (53.7%) had T3 and 94 (23.2%) had T4 tumors (Figure 3). The distribution of the other pathologic variable by T stages by the results of univariate analysis are presented in Table 3.7.

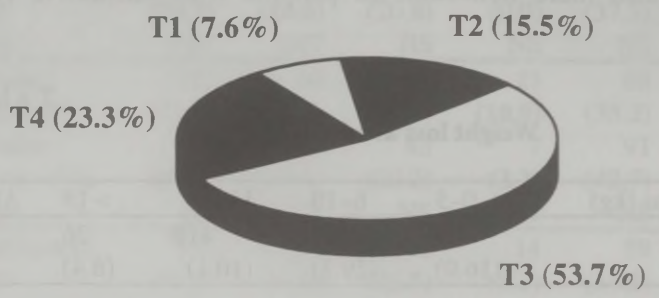

Figure 3. Distribution of T stages.

We found significant differences in the distribution of Borrmann type, nodal involvement, location of tumor, histologic type, and tumor size by the T stages. The deeper the gastric wall invasion the more infiltrative the Borrmann type. The characteristic feature for the early gastric cancer was the absence of nodal involvement (in 90.3% of these cases). Early gastric cancer was more frequently located in the middle part of the stomach when T2–T3 tumors were found in the distal part in most cases; T4 tumor was typical for the total involvement of the stomach more than other T stages. Differentiated histologic types dominated in T1–T2 cases, T3–T4 tumors had more frequently undifferentiated morphological pattern. Tumor size had also strong correlation with tumor invasion: the deeper the invasion extended the larger the tumor size was. According to the results of multivariate analysis the distribution of the Borrmann type (p=0.0008), tumor size (p=0.00001) and histologic pattern of the cancer (p=0.019) were significantly associated with the depth of the gastric wall invasion.

There were only 31 patients (7.6% of all curative cases) with early (T1) cancers operated on with radical intention in Tartu Hospital of Oncology in the observed period. Early tumors were more frequently located in the middle part of the stomach (58.1%), had non-infiltrative forms of growth (93.6%) and well or moderately differentiated histologic features (64.5%); in 35.5% of cases the size of tumor was more than 3 cm (Table 3.7). In early cases the lymph node metastases were recognised in 9.7% of cases, all up to N2 nodes.

Table 3.7

Distribution of pathologic variables by T stages

Variable	T1	T2	T3	T4	all T
Borrmann	(p<0.0001)				
I	7 (**22.6**)	3 (4.8)	6 (2.8)	1 (1.1)	17 (4.2)
II	22 (**70.9**)	36 (**57.1**)	91 (41.7)	27 (28.7)	176 (43.3)
III	2 (6.5)	11 (17.5)	67 (**30.7**)	25 (26.6)	105 (25.9)
IV	0 (0.0)	13 (20.6)	54 (**24.8**)	41 (**43.6**)	108 (26.6)
N stage	(p<0.0001)				
N0	28 (**90.3**)	37 (58.7)	106 (48.6)	54 (57.4)	225 (55.4)
N1	0 (0.0)	7 (11.1)	45 (20.6)	5 (5.3)	57 (14.0)
N2	3 (**9.7**)	10 (15.9)	57 (26.1)	29 (30.9)	99 (24.4)
N3	0 (0.0)	9 (14.3)	10 (4.6)	6 (6.4)	25 (6.2)
Location	(p<0.0001)				
Antrum	12 (38.7)	34 (**54.0**)	120 (**55.0**)	34 (**36.2**)	200 (**49.3**)
Corpus	18 (**58.1**)	23 (36.5)	72 (33.0)	27 (28.7)	140 (34.5)
Cardia	1 (3.2)	6 (9.5)	18 (8.3)	17 (18.1)	42 (10.3)
Total	0 (0.0)	0 (0.0)	8 (3.7)	16 (**17.0**)	24 (5.9)
Histology	(p<0.0001)				
Differ.	20 (**64.5**)	42 (**66.7**)	79 (36.2)	30 (31.9)	171 (42.1)
Non–differ.	11 (35.5)	21 (33.39	139 (**63.8**)	64 (**68.1**)	235 (57.9)
Tumor size	(p<0.0001)				
< 4 cm	20 (**64.5**)	13 (20.6)	19 (8.7)	5 (5.3)	57 (14.0)
4–12 cm	11 (35.5)	40 (**63.5**)	112 (**51.4**)	29 (30.9)	192 (47.3)
>12 cm	0 (0.0)	10 (15.9)	87 (39.9)	60 (**63.8**)	147 (38.7)

Lymph node metastases

One hundred and eighty one (44.6%) patients had the lymph node involvement, in 57 (14.0%) cases it extended to N1-nodes, in 99 (24.4%) cases to N2-nodes and in 25 (6.2%) cases to N3-nodes (Figure 4).

To assess the influence of other clinocopathological variables on the extent of nodal involvement we used data on 361 patients who had undergone curative surgery for primary gastric cancer at the Tartu Hospital of Oncology, Tartu, Estonia from 1978 through 1986 (*paper II*). It is 45 patients less than analysed in other papers (i.e. the patients operated on in 1987). There were 174 men and 187 women in this study. The mean age was 62.3, ranged from 31 to 85. 134 (37.1%) total and 227 (62.9%) subtotal gastrectomies were performed. In all cases the extensive lymph node dissection was used: R2 lymphadenectomy in 239 (66.2%) and R3 lymphadenectomy in 122 (33.8%) cases.

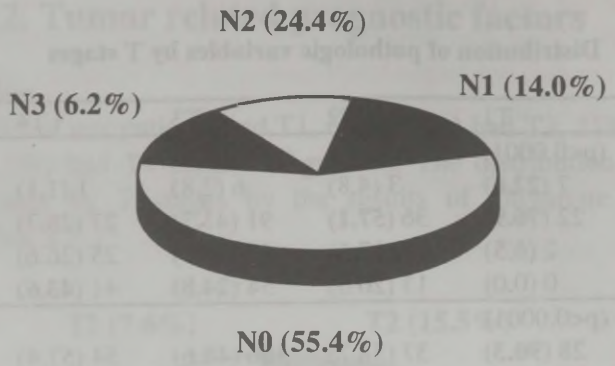

Figure 4. Distribution of N stages.

The nodal involvement was found in 167 (46.3%) patients. Metastases limited with perigastric (N1) nodes presented in 51 (14.1%) patients, the involvement up to N2 nodes was found in 89 (24.7%) and up to N3 nodes in 27 (7.5%) cases. Lymph node involvement was diagnosed in 65.4% of patients who survived less than one year, in 57.8% of patients who survived less than three years and in 26.9% of cases with five year survival time ($p<0.00001$).

Table 3.8 shows the incidence of node negative and node positive cases for other clinical and pathological variables according to the univariate analysis. Lymph node metastases occurred more frequently in cases of muscularis propria or deeper invasion, tumor size more than 4 cm and infiltrative macroscopic type. In this study the node positive cases were found more frequently in elderly people than in younger ones.

Multiple regression analysis indicated that the age of patients ($p=0.034$) and Borrmann type ($p=0.0023$) were statistically the independent prognostic factors for lymph node involvement. Although the Borrmann type is closely related to the degree of gastric wall invasion and tumor size, it was the only independent pathologic prognostic factor associated with lymph node status. In our study the univariate analysis shows the significantly different distribution of node negative and node positive cases only when the early cases (T1) and advanced tumors were compared. The distribution of lymph node negative and positive cases differed significantly in two groups of lymphadenectomy ($p<0.0001$) but not in patients who underwent gastrectomy with different extension.

Table 3.8

The distribution of cases without lymph node metastases and with lymph node for different clinicopathological variables

Variable	No. of cases	Without lymph node metastases	With lymph node metastases
Age (p<0.001)			
<50	50	29 (58.0)	21 (42.0)
50–59	94	60 (63.4)	34 (36.6)
60–69	104	59 (57.0)	45 (43.0)
70–79	103	43 (41.7)	60 (58.3)
>79	10	4 (40.0)	6 (60.0)
Sex (NS)			
Men	174	93 (53.4)	81 (46.6)
Women	187	103 (55.1)	84 (44.9)
T stage (p<0.001)			
T1	29	26 (89.7)	3 (10.3)
T2	54	29 (53.7)	25 (46.3)
T3	190	90 (47.4)	100 (52.6)
T4	88	51 (58.0)	37 (42.0)
Borrmann type (p<0.005)			
I–II	177	108 (61.1)	69 (38.9)
III–IV	184	86 (46.5)	98 (53.5)
Location (NS)			
Antrum	187	101 (54.0)	86 (46.0)
Corpus	116	70 (60.3)	46 (39.7)
Cardia	15	6 (40.5)	9 (59.5)
Total	10	5 (47.6)	5 (52.4)
Histologic type (NS)			
Differentiated	152	88 (57.9)	64 (42.1)
Non-differentiated	209	108 (51.7)	101 (48.3)
Size (p<0.005)			
< 4 cm	54	46 (85.2)	8 (14.8)
≥ 4 cm	307	150 (48.9)	157 (51.1)
Gastrectomy (NS)			
Total	134	66 (49.3)	68 (50.7)
Subtotal	227	130 (57.3)	97 (42.7)
Lymphadenectomy (p<0.00001)			
R2	239	148 (61.9)	91 (38.1)
R3	122	50 (41.3)	72 (58.7)

Histologic types

The most common histologic types were moderately differentiated tubular adenocarcinoma (25.6%) and poorly differentiated adenocarcinoma (25.4%), followed by undifferentiated carcinomas (18.2%), well differentiated carcino-

mas (12.8%) and signet ring cell carcinomas (10.6%) (Table 3.16). Mucinous adenocarcinomas (5.7%) and papillary adenocarcinomas (1.7%) were found only in single cases.

The non-differentiated gastric carcinomas (poorly differentiated adenocarcinoma, signet ring cell, mucinous and undifferentiated carcinomas) tend to spread more extensively in the gastric wall — we found the non-differentiated types of gastric cancer more often in T3–T4 stages than in the early cases (p=0.000001). Most of the non-differentiated cancers had infiltrative macroscopic type of grow (p=0.0007). Our findings also indicate that the ratio of non-differentiated tumors increased strongly with the increasing tumor size (p=0.00002), but the nodal status had no differences associated with histologic type of cancer (p=0.162). We also did not observed differences in the distribution of the histological types by the sex or age of patients in our material.

Location

49.3% (n=200) of our patients had cancer with antral location, 34.5% (n=140) with corporal location and only 10.3% (n=42) with cardial location (Figure 5). In 5.9% (n=24) of cases more than two parts of the stomach were involved and these cases are classified as cancers with total tumors. During the observed 10-year period we did not notice significant changes in the locational distribution of tumors.

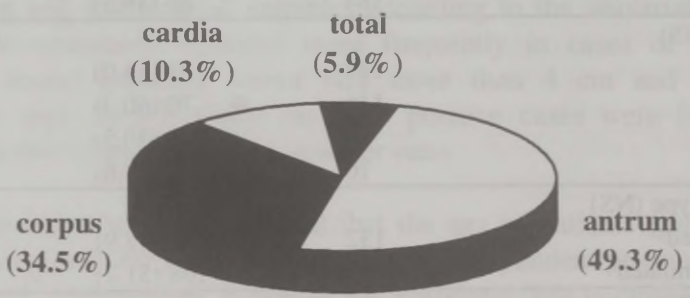

Figure 5. Location of gastric cancer.

Most minute (less than 4 cm in diameter) gastric cancers were found in the antrum or corpus of the stomach (p=0.000001). The cardial and total tumors proceed more silently and are larger at the moment of diagnosing. We also found significantly lower incidence of early tumors and higher incidence of cancers with deeper (T3–T4) invasion in cardia compared with other locations (p=0.000003). The infiltrative Borrmann types were located more often in the upper part or had total involvement of the stomach (p=0.000001). Cardial tumors were also more common in younger patients (p=0.013). There were no significant differences in the distribution of the histologic types (p=0.056), N stages (p=0.081), and sex of patients (p=0.919) by the location of the tumor.

Borrmann type

The ratio of the circumscribed and the infiltrative macroscopic types of tumors according to the Borrmann classification was 0.9:1.0 (193:213). In 17 (4.2%) cases the macroscopic type of tumor was classified as Borrmann I, in 176 (43.3%) cases as Borrmann II, in 105 (25.9%) cases as Borrmann III and in 108 (26.6%) cases as Borrmann IV (Table 3.16). Univariate analysis showed the significantly different distribution of depth of invasion ($p=0.000001$), location ($p=0.000001$), size ($p=0.000001$), morphology ($p=0.00074$), nodal involvement ($p=0.027$) by Borrmann types of the primary tumor. Infiltrative types of gastric cancer were more frequently associated with deeper gastric wall invasion, cardial location or total involvement of the stomach, larger tumor size, non-differentiated histologic types and lymph node involvement.

Size

The mean diameter of the removed tumors was 6.2 cm, ranged from 1 to 23 cm. Fifty seven (14.0%) patients had cancers with diameter less than 4 cm, in 192 (47.3%) cases the tumor size was 4 to 7 cm, in 123 (30.3%) cases it was 8 to 12 cm, and in 34 (8.4%) cases more than 12 cm (Table 3.16). The distribution of tumors by size was greatly different for Borrmann types ($p<0.00001$), T stages ($p<0.00001$), histologic type ($p=0.00002$), and also for tumors with different location ($p<0.00001$) — tumor size was larger in infiltrative types of tumor, in cases with deeper invasion, non-differentiated histological pattern, and cardial or total involvement. The size of tumor was not influenced by the age or sex of patients.

3. Treatment related prognostic factors

Gastrectomy

226 (55.7%) distal subtotal, 170 (41.8%) total and 10 (2.5%) proximal subtotal gastrectomies were performed (Table 3.9). Distal subtotal gastrectomy was the most common operation performed in our study. Total gastrectomy was more often used in cases of deeper invasion, in cases of cardial or total involvement of the stomach and large tumor size. Proximal subtotal gastrectomy was performed only in single cases of cardial tumors (n=10), and was avoided in most cases because of limited radicality and high postoperative complications rate.

Table 3.9

Extent of gastrectomy

Variable	Total	Combined total	Distal subtotal	Combined distal subtotal	Proximal subtotal
All cases	33 (8.1)	137 (33.7)	199 (49.0)	27 (6.7)	10 (2.5)
T stage	p<0.05				
T1	4 (12.9)	4 (12.9)	23 (74.2)		
T2	5 (7.9)	13 (20.6)	37 (58.7)	5 (7.9)	3 (4.3)
T3	17 (7.8)	66 (30.3)	120 (55.0)	9 (4.1)	6 (2.8)
T4	7 (7.4)	54 (57.4)	19 (20.2)	13 (13.8)	1 (1.1)
N stage	NS				
N0	17 (7.6)	70 (31.1)	122 (54.2)	12 (5.3)	4 (1.8)
N1	10 (17.5)	16 (28.1)	26 (45.6)	5 (8.8)	
N2	5 (5.1)	42 (42.4)	43 (43.4)	4 (4.0)	5 (5.1)
N3	1 (4.0)	9 (36.0)	8 (32.0)	6 (24.0)	1 (4.0)
Location	p<0.0001				
antrum	7 (3.5)	19 (9.5)	152 (76.0)	22 (11.0)	
corpus	19 (13.6)	70 (50.0)	47 (33.6)	5 (2.9)	
cardia	3 (7.1)	28 (68.7)			10 (24.2)
total	4 (16.7)	20 (83.3)			
Borrmann	p<0.01				
I–II	19 (9.8)	36 (18.7)	118 (61.1)	15 (7.8)	5 (2.6)
III–IV	14 (6.6)	101 (47.4)	81 (38.0)	12 (5.6)	5 (2.3)
Size	p<0.001				
< 4 cm	4 (7.0)	10 (17.5)	41 (71.9)	1 (1.8)	1 (1.8)
4–7 cm	18 (9.4)	34 (17.7)	119 (62.0)	15 (7.8)	6 (3.1)
8–12 cm	9 (7.3)	67 (54.5)	35 (28.5)	9 (7.3)	3 (2.4)
> 12 cm	2 (5.9)	26 (76.5)	4 (11.8)	2 (5.9)	
Histology	NS				
Differentiated	15 (8.8)	40 (23.4)	101 (59.1)	10 (5.8)	5 (2.9)
Non-differ.	18 (7.7)	97 (41.3)	98 (41.7)	17 (7.2)	5 (2.1)

Univariate analysis of variance showed that the combined gastrectomies were more frequently performed for the treatment of T3–T4 tumors, but also in cases of infiltrative Borrmann types and larger tumor size. According to our treatment policy of gastric cancer the invasion of neighbouring organs by the primary tumor or the lymph node metastases is not hindrance to radical surgery, excluding the invasion of large blood vessels. Neighbouring organs were resected in 176 cases (42.9%), most frequently the spleen (n=141), oesophagus (n=32), the distal part of the pancreas (n=28), transverse colon (n=12), and transverse mesocolon (n=12). Resections of the liver (n=5), diaphragm (n=5) or duodenum with the proximal part of the pancreas (n=3) were also performed. More than one neighbouring organ was resected in 60 cases and more than two

in 21 cases: mostly the splenectomy was combined with resection of the oesophagus (n=32), distal pancreatectomy (n=27) or resection of the transverse colon (n=10).

One hundred forty one (34.7%) patients did undergo splenectomy. In all these cases the splenectomy was performed to obtain the better lymph node dissection and not because of the direct invasion of the primary tumor into the spleen. Nevertheless there was no significant correlation with the extent of the lymph node involvement and splenectomy although we had decided about the need of splenectomy mostly by the accidental biopsies of the lymph nodes before gastrectomy. In patients subjected to splenectomy the non-antral location (85.1%), deeper (T3–T4) invasion (85.8%) and infiltrative type of growth (72.3%) of primary cancer were more frequent.

Table 3.10

Univariate analysis of postoperative complications associated with splenectomy

Type of complications	p-value	With splenectomy (n=141)	Without splenectomy (n=265)
General–all cases	0.003	34 (24.1)	36 (13.6)
cardiovascular		10 (7.1)	5 (1.9)
pulmonal		10 (7.1)	22 (8.3)
other organs		4 (2.8)	7 (2.6)
thrombembolic		8 (5.7)	1 (0.4)
septic*		2 (1.4)	1 (0.4)
Surgical–all cases	0.0001	35 (24.8)	25 (9.4)
infectious		22 (15.6)	18 (6.7)
others		13 (9.2)	7 (2.7)
Mortality	0.0001	16 (11.3)	8 (3.0)

* — all general septic conditions without simultaneous local surgical complications

Unfortunately the patients who underwent gastrectomy combined with splenectomy had higher frequency of both the general and surgical postoperative complications as well the higher mortality rate (Table 3.10). Also splenectomy was mainly associated with total gastrectomy (92.9%) and R3 lymphadenectomy (70.9%) it was the only independent prognostic factor (p=0.0033) associated with higher postoperative complication rate according to the multivariate analysis.

Extensive lymphadenectomy

In 64.0% (n=260) of the cases the patients underwent the dissection of N1 and N2 nodes (R2-resection) and 36.0% (n=146) were the so-called R3-resections. The former was more frequently ($p<0.05$) associated with subtotal gastrectomies and the latter with total or combined total gastrectomy (Table 3.11).

Table 3.11

Distribution of lymphadenectomies with different extension by the gastrectomies

Gastrectomy	R2-lymphadenectomy	R3-lymphadenectomy
All cases	260 (64.0)	146 (36.0)
Total	10 (30.3)	23 (69.7)
Combined total	33 (24.1)	104 (75.9)
Distal subtotal	188 (94.5)	11 (5.5)
Combined distal subtotal	20 (74.1)	7 (25.9)
Combined proximal subtotal	9 (90.0)	1 (10.0)

These differences were caused by the stage of primary tumor. As a rule the more extensive lymph node dissection as well as the more extensive gastrectomies were performed in cases of more advanced primary tumor — T2–T4 stage; Borrmann type III–IV; tumor size more than 8 cm (Table 3.9 and Table 3.12). Moreover, the extent of lymph node metastases which became evident at the postoperative histologic examination had different distribution in R-groups: we found that R2-dissection was more frequently performed in cases of limited nodal (N0–N1) involvement and R3-dissection in cases with more distal (N2–N3) lymph node metastases (Table 3.12). The extent of lymphadenectomy was similar in different age and sex groups, and for cancers with different morphologic pattern.

The Japanese definition of radical resection of gastric cancer is divided into absolute curative and relative curative resection relative to the distance of node dissection from the level of nodal involvement — "R minus N" factor (Cuschieri, 1986; Kajitani, 1981; Rohde, 1989; Shiu, 1987). Using these definitions, all our operations may be classified as follows: 325 (80.1%) were absolute curative, and 81 (19.9%) were relative curative (N2 cases in R2-group and N3 cases in R3-group; Table 3.12). In addition, in 77 (19.0%) cases the "R minus N" was equal to 1, in 193 (47.5%) cases it was equal to 2, and in 55 (13.6%) cases equal to 3.

Postoperative complications and mortality

We documented the postoperative complications as general and surgery-related, as it is also made by others (Gouzi, 1988; Launois, 1991; Mäkelä, 1992). The incidence of the complications and the mortality caused by these complications is presented in Table 3.13.

Postoperative complications and mortality according to operative procedure are given in Table 3.14. The surgical complications rate was highest for combined total gastrectomy followed by combined subtotal gastrectomy; the general complications rate was highest for proximal gastrectomy followed by combined and simple total gastrectomy. Both the surgical and general

complications rate was significantly higher after R3 resections (21.2% and 24.0% respectively) compared with R2 resections (10.8% and 13.8% respectively) (p=0.0064 and p=0.0146).

The incidence of general postoperative complications resulted to be significantly higher in older patients (p=0.002). In contrast no significant difference was found in the incidence of surgical complications (Table 3.15). No significant differences were also found in the incidence of surgical complications in different sex groups.

Table 3.12

Extent of lymphadenectomy by the pathologic variables

Variable		R2-lymphadenectomy	R3-lymphadenectomy
All cases		260 (64.0)	146 (36.0)
T stage	(p<0.001)		
T1		27 (87.1)	4 (12.9)
T2		40 (63.5)	23 (36.5)
T3		149 (68.3)	69 (31.7)
T4		44 (46.8)	50 (53.2)
N stage	(p<0.000001)		
N0		170 (75.6)	55 (24.4)
N1		34 (59.6)	23 (40.4)
N2		56 (56.6)	43 (43.4)
N3		–	25 (100.0)
Borrmann type	(p=0.00001)		
I–II		145 (75.1)	48 (24.9)
III–IV		115 (54.0)	98 (46.0)
Location	(p<0.000001)		
Antrum		167 (83.5)	33 (16.5)
Corpus		72 (51.4)	68 (48.6)
Cardia		17 (40.5)	25 (59.5)
Total		4 (16.7)	20 (83.3)
Histology	(NS)		
Differentiated		117 (68.4)	54 (31.6)
Non-differentiated		143 (60.9)	92 (39.1)
Size	(p<0.000001)		
< 4 cm		47 (82.5)	10 (17.5)
4–7 cm		140 (72.9)	52 (27.1)
8–12 cm		60 (48.8)	63 (51.2)
> 12 cm		13 (38.2)	21 (61.8)

Table 3.13

Postoperative complications and mortality caused by these complications

	Incidence	Mortality
General–all cases	70 (100.0)	
pulmonal	31 (44.3)	6 (19.4)
cardiovascular	15 (21.4)	7 (46.7)
thrombophlebitis	6 (8.6)	0 (0.0)
thrombembolia a. pulmonalis	4 (5.7)	2 (50.0)
renal	4 (5.7)	2 (50.0)
CNS	4 (5.7)	1 (25.0)
liver	3 (4.3)	1 (33.3)
sepsis	3 (4.3)	2 (66.7)
Surgical–all cases	60 (100.0)	
intra-abdominal infection	19 (31.6)	2 (10.5)
acute pancreatitis	18 (30.0)	2 (11.1)
anastomotic leakage	11 (18.3)	4 (36.4)
wound infection	10 (16.7)	0 (0.0)
haemorrhage	1 (1.7)	0 (0.0)
ileus	1 (1.7)	0 (0.0)

Table 3.14

Complications and mortality rates after surgery

Gastrectomy	Surgical complications (p=0.018)	General complications (p=NS)	Postoper. mortality (p=0.008)
Total (n= 33)	3 (9.1)	5 (15.2)	2 (6.1)
Combined total (n=137)	35 (24.8)	32 (24.1)	16 (11.7)
Subtotal (n=199)	18 (9.0)	26 (13.1)	4 (2.0)
Combined subtotal (n= 27)	4 (14.8)	2 (7.4)	1 (3.7)
Proximal (n= 10)	0 (0.0)	5 (50.0)	1 (10.0)
All cases (n=406)	60 (14.5)	70 (17.5)	24 (5.9)

In the uni- and multivariate model extent of surgery (gastrectomy, lymphadenectomy, splenectomy) and preoperative objective findings (haemoglobin, bilirubin, urea, protein, weight loss) were analysed. According to the results of this analyses the splenectomy performed with gastrectomy was independently associated with both the surgical and general complications (p=0.0001). We found the anaemia (p=0.027) for higher general complications rate and weight loss (p=0.029) for higher surgical complications rate in addition to splenectomy to be the independent prognostic factors.

Table 3.15

Distribution of complications by age groups

Age of patients (years)	Surgical (NS)	General (p=0.0157)
30–39 (n=7)	1 (14.3)	0 (0.0)
40–49 (n=49)	3 (6.1)	4 (8.2)
50–59 (n=106)	21 (19.8)	11 (10.4)
60–69 (n=119)	18 (15.1)	25 (21.0)
70–79 (n=115)	16 (13.9)	29 (25.2)
>79 (n=10)	0 (0.0)	2 (20.0)

Mortality

In our study the 30-day postoperative mortality for all radically operated patients was 5.9% (24 of 406). This rate 11.7% following combined total gastrectomy was higher than that following gastrectomy alone (6.1%), but the mortality rate 3.7% following combined subtotal gastrectomy was close to that following subtotal gastrectomy alone (2.0%) (Table 3.14). The mortality rate was also high for proximal subtotal gastrectomy (10.0%), but the number of cases in this group was too small (n=10) for conclusion making. Further, it should be noted that the mortality rate after R3 lymphadenectomy (11.0%) was higher than the mortality rates after R2 lymphadenectomy (3.1%).

In patients over 60 years of age the postoperative mortality rate was also significantly higher (7.3% versus 3.7%) compared with young patients, but it was similar for male and female patients.

Univariate analysis revealed both the general (p=0.000001) and surgical (p=0.044) complications, extent of lymphadenectomy (R3 versus R2) (p=0.00259) and splenectomy (p=0.0015) as the significant prognostic factors for postoperative mortality. Acute cardial insufficiency (n=7), pulmonal complications (n=6), and anastomotic leakage (n=4) were the complications which more frequently led to mortality in postoperative period.

Results of multivariate regression analysis showed that the presence of preoperative weight loss (p=0.043), incidence of general complications (p=0.00001) and more extensive (R3) lymph node dissection (p=0.013) were the independent factors which led to higher postoperative mortality.

4. Univariate analysis of prognostic factors

All the prognostic factors for the patients with curative gastric cancer analysed in this study may be connected to the survival of these patient, but the intensity of influence is various. In the multivariate analysis, where all interactions between variables are considered, some of these factors may not become evident as prognosticators. Table 3.16 shows the distribution of the prognostic factors and the 5-year survival rates for the patients who underwent curative surgery calculated by the univariate analysis. Relative survival rates after surgery for cure for gastric cancer including postoperative mortality were 80.3% at one year, 66.8% at two year, 55.7% at three year, 50.5% at four year and 46.1% at five year.

The total 5-year survival rate after surgery for early gastric cancer was 80.7%, for T2 tumors 54.0%, for T3 tumors 44.0% and for T4 tumors 34.0% compared with 46.1% in all radically operated cases. The 5-year survival rates differed much depending on the presence of metastases in the lymph nodes and were strongly correlated with the extent of the nodal involvement. It was 60.0% for patients without nodal involvement, 42.1% for N1-cases, 25.3% for N2-cases and 12.0% for N3-cases.

Two macroscopic characteristics of gastric cancer — Borrmann type and tumor size — had close relation to the survival rates. Borrmann type I cancer had 5-year survival rate of 76.5%, type II — 57.4%, type III — 38.1%, and type IV — 30.6%. From the patients who had the cancers with diameter less than 4 cm 71.9% were alive after 5 year of surgery, for cancers with size 4 to 7 cm this rate was 44.3%, for cancers with size 8 to 12 cm — 43.1%, and for cancers with diameter more than 12 cm it was 23.5%. The survival rates were nearly two times higher in the cases of the antral (51.5%) or the middle (47.9%) location than in the cardial (28.6%) location or in the total involvement (20.8%) of the stomach.

Non-differentiated types cancer resulted in a shorter survival than was seen in cases of the differentiated types. Survival rates were noticeably higher in cases of papillary (57.1%) and well (63.5%) or moderately (50.9%) differentiated adenocarcinoma. The 5-year survival rate in our study was also relatively high in cases of poorly differentiated adenocarcinomas (47.2%) and signet ring cell carcinomas (36.7%), that might be associated with poor prognosis. The 5-year survival rate was lower for patients with the cancer of mucinous (30.4%) or undifferentiated (32.4%) structure.

Table 3.16

Incidence and 5-year survival rates in relation to different prognostic factors

Prognostic factor		No. of patients	5-year survival rate (%)
Sex:	male	198 (48.8)	46.9
	female	208 (51.2)	45.2
Age:	30–39 years	7 (1.7)	71.4
	40–49 years	49 (12.2)	44.9
	50–59 years	106 (26.1)	55.7
	60–69 years	119 (29.3)	47.9
	70–79 years	115 (28.3)	36.5
	>79 years	10 (2.5)	20.0
T stage:	T1	31 (7.6)	80.7
	T2	63 (15.5)	54.0
	T3	218 (53.7)	44.0
	T4	94 (23.2)	34.0
N stage:	N0	225 (55.4)	60.0
	N1	57 (14.0)	42.1
	N2	99 (24.4)	25.3
	N3	25 (6.2)	12.0
Location:	Antrum	200 (49.3)	51.5
	Corpus	140 (34.5)	47.9
	Cardia	42 (10.3)	28.6
	Total	24 (5.9)	20.8
Borrmann type:	I	17 (4.2)	76.5
	II	176 (43.3)	57.4
	III	105 (25.9)	38.1
	IV	108 (26.6)	30.6
Histologic type:	Papillary adenocarcinoma	7 (1.7)	57.1
	Well differentiated tubular adenoca.	52 (12.8)	63.5
	Moderately different tubular adenoca.	112 (27.6)	50.9
	Poorly differentiated adenocarcinoma	108 (26.6)	47.2
	Mucinous adenocarcinoma	23 (5.7)	30.4
	Signet ring cell carcinoma	30 (7.4)	36.7
	Undifferentiated carcinoma	74 (18.2)	32.4
Tumor diameter:	< 4 cm	57 (14.0)	71.9
	4–7 cm	192 (47.3)	44.3
	8–12 cm	123 (30.3)	43.1
	> 12 cm	34 (8.4)	23.5
Gastrectomy:	Distal subtotal	226 (55.7)	56.2
	Proximal subtotal	10 (2.5)	50.0
	Total	170 (41.8)	32.4

(continued)

Prognostic factor	No. of patients	5-year survival rate (%)
Lymphadenectomy: R2	260 (64.0)	52.7
R3	146 (36.0)	34.3
Extent of lymphadenectomy relative to nodal stage (R minus N):0	81 (20.0)	23.5
1	77 (19.0)	31.2
2	195 (48.0)	59.0
3	53 (13.0)	54.7

In addition to the patient- and tumor-related prognostic factors the extent of surgical intervention also influence the survival rates of gastric cancer patients. The 5-year survival rate after distal subtotal gastrectomy was 57.3%, after combined distal subtotal gastrectomy 48.1%, after proximal gastrectomy 50.0%, after total gastrectomy 42.4%, and after combined total gastrectomy 29.9%.

The overall 5-year survival rate was 52.7% for R2-resections and 34.3% for R3-resections. Comparing the lymphadenectomies with different extension as to the extent of lymph node involvement (R minus N), extensive lymphadenectomy had a favourable effect only provided it encompassed more than one uninvolved group of lymph nodes. The 5-year survival was 27.2%, when R minus N was equal to 0 or 1 and 58.1%, when it was equal to 2 or 3. For the patients who had underwent splenectomy the 5-year survival rate was 30.5% compared with 54.3% in patients without splenectomy.

To find the influence of the subgroups of these factors on the survival the two sample analysis of variance was performed (Table 3.17). This analysis brought forth as favourable factors the age below 70, tumor location in the lower or middle part of the stomach, Borrmann I–II type, tumor size less than 4 cm, differentiated histological type, T 1–2 stage, limited (N0–N1) lymph node involvement, subtotal gastrectomy, R2 versus R3 lymphadenectomy and the extent of lymphadenectomy more than one N-group from the involved lymph nodes. The influence of the age of the patient at the moment of the operation, tumor sites and different histological types was statistically less marked than other factors. The year of the operation and the sex of patients did not have a significant influence on the survival.

Table 3.17

Univariate analysis of prognostic factors influencing the 5-year survival of gastric cancer patients

Variable	P-value	Favourable	5-year survival rate	Un-favourable	5-year survival rate
Sex	NS[1]				
Age	<0.01	< 70 years	51.9	≥ 70 years	35.2
T stage	<0.0001	1–2	67.8	3–4	41.0
N stage	<0.00001	0–1	56.4	2–3	22.6
Histologic type	<0.01	differentiated	55.0	non-differ.	39.6
Borrmann type	<0.0001	I–II	59.1	III–IV	34.3
Size of tumor	<0.0001	< 4 cm	71.9	≥ 4 cm	41.8
Location	<0.0001	antrum/ corpus		cardia/	
			50.0	total	25.8
Gastrectomy	<0.00001	subtotal	55.0	total	32.4
Lymphadenec-tomy	<0.00001	R2	52.7	R3	34.3
R minus N[2]	<0.00001	2–3	58.1	0–1	27.2

[1] — not significant, [2] — extent of lymphadenectomy relative to nodal stage

Table 3.18 and Figure 6 show the relationship between the 5-year survival rate and the presence of lymph node metastases at the different levels of intramural cancer invasion. In general, the 5-year survival rate correlated well with both the extent of lymph node metastases and the depth of tumor penetration. There was a significant difference of the 5-year survival rates between the node-positive and the node-negative groups, 28.7% and 60.0% respectively, and also between the early and the advanced cases of cancer, 80.7% and 43.2% respectively.

Table 3.18

Incidence and the 5-year survival rates in relation to T and N stages

T	T1		T2		T3		T4		all T	
N	n[1]	5-y[2]	n	5-y	n	5-y	n	5-y	n	5-y
N0	28	82.1	37	64.9	106	56.6	54	51.9	225	60.0
N1	0	–	7	71.4	45	42.2	5	0.0	57	42.1
N2	3	66.7	10	30.0	57	28.1	29	13.8	99	25.3
N3	0	–	9	22.2	10	10.0	6	0.0	25	12.0
all N	31	80.7	63	54.0	218	44.0	94	34.0	406	46.1

[1] — number of cases, [2] — 5-year survival rate (%)

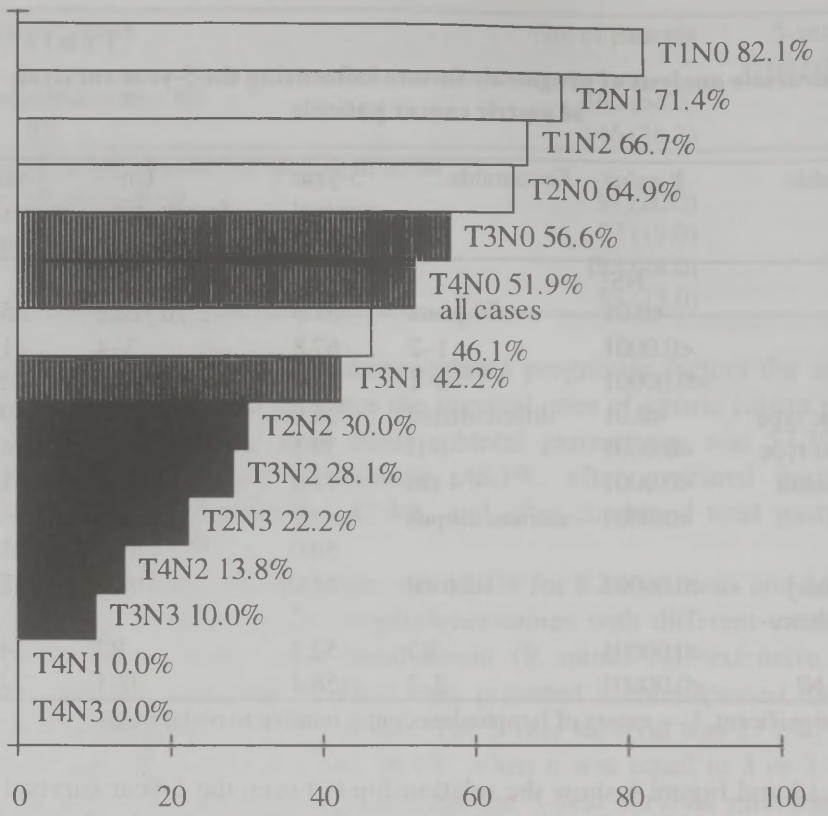

Figure 6. 5-year survival rates in different TN stages after curative gastric cancer surgery in Tartu Hospital of Oncology

The 5-year survival rate for early gastric cancer showed unexpectedly lower survival values (66.7%), when lymph node metastases are present, in comparison with the survival rate of patients without lymph node metastases (82.1%). The lowest 5-year survival rate was for the patients with T3–T4 tumors with N3–positive nodes (6.3%). The extent of lymph node involvement showed the dependence on the T stage.

5. Multivariate analysis of prognostic factors

All the prognostic factors are closely interrelated. For example larger tumor size may be associated with higher degree of gastric wall invasion and presence of lymph node metastases, it may need more extended gastrectomy and so on (Moriguchi, 1992). Therefore the analysis of these factors by multivariate models provides more information pertinent to decision-making processes than simple statistical analysis does.

In the multivariate analysis using the Cox regression model (Table 3.19), all factors tested by the univariate analysis were used. This analysis identified five prognostic variables — nodal involvement, extent of gastrectomy, depth of gastric wall invasion, histologic type of cancer, and age of patients at the time of operation — that significantly influenced the prognosis of our patients.

Table 3.19

Results of the Cox regression multivariate analysis of prognostic factors after curative surgery for gastric cancer

Variable	Relative risk to death (95% CIE[1])	P-value to remove
Nodal involvement		0.0000
N0	1.0	
N1	1.57 (1.04–2.37)	
N2	2.48 (1.81–3.41)	
N3	3.98 (2.45–6.48)	
Extent of gastrectomy		0.0003
Subtotal	1.0	
Total	1.68 (1.27–2.23)	
Depth of invasion		0.0098
T1	1.0	
T2	2.04 (0.84–4.96)	
T3	2.27 (0.99–5.23)	
T4	3.24 (1.38–7.62)	
Histologic type		0.0168
Papillary or tubular	1.0	
Poorly differentiated	1.01 (0.70–1.43)	
Others[2]	1.51 (1.09–2.09)	
Age		0.0172
< 70 years	1.0	
≥ 70 years	1.42 (1.07–1.88)	
Did not significantly improve model:		P-value to enter
Borrmann type		0.1145
Location		0.2414
Size		0.5152
Extent of lymphadenectomy		0.0588
R minus N factor		0.4656
Sex		0.4634

[1] — 95% confidence interval for relative risk of death, [2] — mucinous, signet ring cell and undifferentiated carcinomas

Among these, lymph node involvement was the most important independent prognostic factor followed by the depth of invasion and the histological type of cancer. The risk of death was 1.57 times higher in N1 cases, 2.48 times higher

in N2 cases, and 3.98 times higher in N3 cases compared with patients without lymph node metastases. According to the results of this analysis the extent of gastrectomy was the only independent treatment related prognostic factor. The age of patients also influenced the risk of death in the multivariate model if the patients below and over 70 years of age were compared. Other tumor related factors — Borrmann type, location and size of the tumor, as well as the extent of lymphadenectomy, and sex of patients did not significantly improve the model where all the interactions between variables were taken into account.

6. Results of gastric cancer surgery in Oulu University Hospital

We studied the data of 203 patients with primary gastric cancer treated at the Department of Surgery of Oulu University Hospital, Finland during the 5-year period from 1983 to 1987 (*paper III*). The lower third of the stomach appeared to be the most common location, invaded in 44.3% of the cases, followed by the upper third (22.7%), the middle third (21.1%) and the total involvement (11.8%). The distribution of macroscopic types of tumors showed the prevalence of infiltrative cases (Borrmann type I–II — 45.3%, type III–IV — 54.7%). The pathological examination found Lauren´s intestinal type in 50.2%, diffuse type in 35.0% and mixed type in 14.8%% of the cases. The ratio of the intestinal type to the diffuse type was 1.43. T1 was found in 9.9%, T2 in 16.8%, T3 in 32.5% and T4 in 39.4% of the cases. The lymph nodes were involved in 49.3% of the cases (N1 in 15.8% and N2 in 33.5 according to the TNM classification). In 12.3% of the cases the extent of nodal involvement could not be retrospectively established. Distant metastases were diagnosed in 23.7% of the patients.

Palliative gastric resections in Oulu was performed in 47 (23.2%) and symptomatic bypass-procedures in 27 (13.3%) cases. Although only 3.4% of the patient did not undergo surgery, in more than half of those who did, potentially curative resection was not feasible. Although palliative resection for gastric cancer is mainly indicated to improve the quality of the patients remaining life by reducing the danger of complications (Mäkelä, 1992), it also offers a possibility of longer survival for patients who cannot undergo radical surgery. In Oulu study 6.4% of the patients were alive five years after palliative resection. We agree with authors, who think that if the resection is palliative due to the presence of various incurable factors, it still seems preferable to laparotomy alone or gastrojejunostomy (Korenaga, 1988b; Maehara, 1992a).

Radical gastrectomy was performed in 88 (43.3%) with overall 5-year survival of 45.5%. Conventional gastrectomy used in radical gastric cancer surgery at

Oulu University Hospital was either the total or distal subtotal removal of the stomach and perigastric regional lymph nodes, i.e. R1-lymphadenectomy according to the Japanese General Rules for the Gastric Cancer Study (Kaijtani, 1981). The gastric resection was classified as radical if the lymph node involvement was restricted to the perigastric (N1) nodes, no tumor was left following the surgery, and no microscopical invasion in the resection margins was found on the postsurgical histological examination. No patients with T4 tumors were operated on with curative intention in Oulu.

The cure results in Oulu are easily comparable to those in contemporary Western hospitals where gastrectomy is performed without extended lymphadenectomy, but they are inferior to those in centres where extensive lymph node dissection is routinely practised (Akoh, 1991; Bollschweiler, 1993; Brems-Dalgaard, 1993; Haugstvedt, 1993; Lindahl, 1988; McCulloch, 1994; Noguchi, 1989; Siewert, 1993).

Table 3.20

Results of the Cox regression multivariate analysis for prognostic factors after curative surgery in Oulu University Hospital

Variable	Relative risk to death (95% CIE[1])	P-value to remove
T stage		0.0000
T1	1.00	
T2	4.99 (1.45–17.15)	
T3	9.56 (2.89–31.64)	
Did not significantly improve model		P-value to enter
age		0.1915
sex		0.9166
Borrmann type		0.0698
tumor size		0.0919
location		0.1743
Lauren type		0.5437
type of gastrectomy		0.5730
N stage		0.8080

[1] — 95% confidence interval for relative risk of death

Univariate analysis indicated that tumor size, location, gross appearance, degree of gastric wall invasion, presence of lymph node and distant metastases, and radicality of operative procedures were the significant prognostic factors of survival. No significant relationship was found between the survival rates and the age or sex of patients, Lauren histopathological type or splenectomy performed with gastrectomy. In a Cox multivariate analysis of the eleven clinicopathological and treatment variables, analysed by univariate analysis, the T stage and the presence of distant metastases independently affected survival.

When curative cases were analysed by the Cox regression model, only the gastric wall invasion appeared as an independent prognosticator (Table 3.20).

In addition to the patients curatively operated on, we found 108 (53.2%) patients with tumors T2–4N0–N2(N3) (Table 3.21) in Oulu material who could have been possibly operated on with curative intention, if the combined resections of neighbouring organs and the extensive lymph node dissection had been used. In 19 cases the carcinomas were classified as M1 tumors only because of the metastases in non-perigastric lymph nodes. These cases might have been classified as T3–T4N3 tumors according to the General Rules of Japanese Research Society for Gastric Cancer (Kaijtani, 1981). We believe that in these cases of approach to the nodal staging the more extensive lymphadenectomy ought to be favoured. Moreover, the number of patient with lymph node metastases may be larger if great number of nodes are dissected and more patients with occult metastasis may be detected (Gunven, 1991). There was a considerable number of N2 nodes involved (9.6%) in patients with early gastric cancer operated on in Tartu. No lymph node metastases was found in T1 cases in Oulu, but the N2–N3 nodes were not normally dissected with the standard gastrectomy.

Table 3.21

Patients in the Oulu University Hospital who might have been operated on with curative intention by extensive methods of gastric cancer surgery

Type of operation	T1-2 N0	T2 N2	T3 N0-1	T3 N2	T4 N0-1	T4 N2	T3 M1[1]	T4 M1[1]	all TNM
Palliative	1[2]	2	6[2]	19[2]	5	14			47
Symptomatic				2	4	14	2	5	27
Explorative					6	16	3	9	34
total	1	2	6	21	15	44	5	14	108

[1] — these cases were classified according to the UICC TNM classification as T3–T4M1 cases only because of the lymph node metastases in "non-perigastric" nodes, but could be classified as N3 nodes according to the JRSGC classification;

[2] — in 6 cases the postoperative histologic examination showed the cancer cells at the proximal resection margin

DISCUSSION

The prognosis of patients with malignancy depends upon three groups of factors: biological and epidemiological aspects of the tumor, tumor–host relationship, and the therapy prescribed (Akoh, 1992; Bollschweiler, 1992; Janssen, 1992; Lauren, 1993; Moriguchi, 1991a). In our study we focused on patients with primary gastric cancer who had undergone curative resection and obtained evidence of prognostic significance of different clinical, pathologic and therapeutic factors of curative gastric cancer. Identification of prognostic factors in resected gastric carcinoma is necessary for the prediction of the outcome of patients. The analysis of prognostic factors influences also the choice of therapy. In the ideal situation, as many prognostic factors as possible should be analysed before the initiation of therapy to design a multimodal therapeutic concept for the individual patient.

The differences in the overall survival curves for patients with gastric carcinoma after curative or radical operations are large, with 5-year survival rates of 60% or more in Japanese and 40% or less in non-Japanese series (Akoh, 1992; Breaux, 1990; Bozzetti, 1990; Maruyama, 1987b; Murray, 1989; Noguchi, 1989; Ovaska, 1989). Relative survival rates after surgery for cure for our patient including postoperative mortality were 80.3% at one year, 66.8% at two year, 55.7% at three year, 50.5% at four year and the 5-year survival rate was 46.1%. In this study univariate analysis brought forth as favourable factors the age below 70, tumor location in the lower or middle part of the stomach, Borrmann I–II type, tumor size less than 4 cm, differentiated histological type, T 1–2 stage, limited (N0–N1) lymph node involvement, subtotal gastrectomy, R2 versus R3 lymphadenectomy and the extent of lymphadenectomy more than one N-group from the involved lymph nodes. The year of operation and the sex of patients did not have a significant influence on the survival.

Variables which influence survival time after curative gastrectomy for gastric cancer are inter-related. Multivariate analysis helps to determinate the importance of each variable, and useful prognostic factors can be identified. While independent prognostic factors for survival time have been defined based on multivariate analysis, there is a discrepancy in the data in different reports, probably, because some studies had less statistical power owing to smaller numbers of patients or because patients were stratified differently with respect to certain clinicopathological characteristics (Moriguchi, 1992). We consider our material large enough for this analysis. Multivariate analysis identified five prognostic variables for our patients that significantly influenced the risk of death. Among these, lymph node involvement was the most important independent prognostic factor, followed by the extent of gastrectomy, the depth of invasion, histological type of cancer and the age of patients.

1. Patients related prognostic factors

Age

Gastric cancer is most frequently observed during the seventh decade of life within European series and only the patients in Japan are almost 6–10 years younger. The mean age is reported to be 64–68 years (Bollschweiler, 1993; Jatzko, 1992a; McCulloch, 1994), in our study it was 62.4 years and median 63 years (range 31–85 years). Therefore we consider the age of our patients to be comparable with patients from the other European countries.

We found the age to be a significant prognostic factor. The results show that it is the younger patient that benefit most from extensive surgery. Unfortunately the high 5-year survival rate for patients in the 30–39 year group (71.4%) after extensive radical surgery does not reflect the complete real situation. Because of the more aggressive course of the disease in young people the number of curatively operated patients in this group is relatively low (1.7%) and the overall prognosis is worse than it is in other age groups. By this fact also the similar distribution of histologic types of gastric cancer in different age groups of our radically operated patients could be explained.

30.8% of our patients were over 70 years old. We found a decreased 5-year survival in the old (over 70 — 35.2%) and the very old (over 80 — 20.0%) age groups. Hereby it must be noted that recurrent gastric cancer is the dominating cause of death among elderly patients operated on for gastric cancer. However, too few autopsies are made in this group of patients and the real cause of death may be other than gastric cancer.

In lights of our findings, age is not a contraindication to radical resection for gastric cancer. When considering the indications for total gastrectomy, elderly patients should not be regarded as a contraindication solely because they are aged. Nevertheless aggressive surgery with extensive lymphadenectomy does not always seem to contribute to a favourable prognosis in elderly patients, who usually have concomitant systemic cardiovascular and respiratory disorders and who are therefore at high risk for general postoperative complications and death. In our patients over 60 years of age the incidence of these complications as well as the mortality rate resulted to be significantly higher than in younger patients (Table 3.15). In contrast no significant difference was found in the incidence of surgical complication. Lower survival rates of the elderly patients in our study may be also caused by the more frequent lymph node involvement.

Sex

The male:female rate of gastric cancer patients in Estonia is 1.35:1, while in most reports the incidence of gastric cancer in male is said to be 1.5 times or more higher than it is in female (Bollschweiler, 1993; Holleb, 1991; Jatzko, 1992a; Maruyama, 1987b; Maruyama, 1989; Soga, 1988). The difference can

be attributed to a difference in the mean span of life which is about ten years lower for men in Estonia, in other words there is a high incidence of gastric cancer in the females who have outlived their male counterparts. Sex distribution showed a female predominance for curatively operated patients (male:female ratio 0.95:1) and moreover for the patients with early gastric cancer (male:female ratio 0.48:1) on the material of Tartu Hospital of Oncology. These differences can not be explained by the more aggressive course of the disease in men as the distribution of other pathological variables was statistically similar in the two sex groups. Uni- and multivariate analysis also showed no significant differences in the postoperative mortality and survival rates between male and female patients. That means that there are relatively fewer male patients capable of undergoing radical surgery and have early cancers only in single cases as men tend to care less for their health and turn later to doctors than women.

Symptoms

The exact date of onset of the first symptom is frequently not easy to establish and the subjective symptoms are differently described by the patients. Therefore these data are difficult to compare. The average duration of symptoms is reported to be 4 to 6 month for patients with curative gastric cancer (Akoh, 1991). In some studies the patients with early gastric cancer had symptoms more than one year before diagnosing in 45.5% of cases (Moreaux, 1993). For our patients the mean duration of symptoms was 11.1 month. Patients with early gastric cancer had relatively longer duration of symptoms when compared with total of all patients. The latter fact might be explained by the result that early gastric cancer have differentiated morphologic pattern more frequently than advanced ones, as it is reported in some other studies (Ikeda, 1994; Nakamura, 1992). Differentiated types of gastric cancer are thought to be the result of a long-term process associated with a range of sequential precancerous conditions having their own symptomatology, which is difficult to separate from gastric cancer symptoms (Correa, 1991; Lauren, 1993; Sue-Ling, 1993).

Previously it has been suggested that a history of symptoms of longer than 6 month is associated with more favourable prognosis, when short history (less than 3 month) and the absence of epigastric pain or dyspeptic symptoms are associated with rapid growth of the tumor and poor prognosis (Armstrong, 1986; Msika, 1989; Tso, 1987). In the present study we found no significant differences in survival rates associated with duration of preoperative symptoms.

In our study the elderly patients had shorter duration of symptoms than young patients. It is difficult to explain because there were no significant differences in the distribution of main pathologic variables as well as the subjective symptoms by age groups. It may be possible that the elderly stand at attention for their health more accurately than the younger ones. If we add the low rate of men among the patients with early gastric cancer we may conclude

that the young men with dyspeptic disorders need special attention. The diagnosis is reported to have been made late in young patients also by others (Maehara, 1991a).

The present study is in agreement with other reports about the high predominance of epigastric pain and weight loss among the presenting symptoms (Craanen, 1992; Crean, 1994; Maehara, 1991a; Moreaux, 1993; Sue-Ling, 1992; Wanebo, 1993). Epigastric pain (77.4% in early and 70.2% in advanced cases), weight loss (45.2% and 61.8%), dyspepsia (19.4% and 39.2%) and general dyscomfort (25.8% and 33.3%) were more frequent symptoms for both the patients with the early as well as with the advanced gastric cancer (Table 3.4).

The expressive clinical symptomatology and the long duration of pre-operative symptoms in a high percentage of cases is true in this study. Although the symptoms of gastric cancer are reported to be very similar to the symptoms of benign conditions such as peptic oesophagitis, gastritis and peptic ulcer, such nonspecific symptoms, particularly during the sixth or seventh decade of life, should not be regarded routinely as benign, non-neoplastic disease, and should not be treated with antacids or anti-ulcer drugs before a diagnosis has been established by examination (Lawrence, 1991; Moreaux, 1993). Such treatment may mask the symptoms of gastric cancer and lead to a delay in diagnosis (Allum, 1989; Craen, 1994; Sue-Ling, 1992). It is reported that in half of patients the reason for delayed diagnosis was poor interpretation of symptoms or incorrect diagnosis at the first evaluation (Arvanitakis, 1992). Pain and dyspepsia, specially if persistent, should make one consider the possibility of the cancer and the need of more profound investigation (Correa, 1988; Correa, 1992; Sobala, 1993; Stalnikowicz, 1990; *paper V*).

2. Tumor related prognostic factors

After curative gastrectomy in patients without peritoneal dissemination or hematogenous distant metastasis, gastric wall invasion and lymph node involvement have proved to be the most important pathological predictors of tumor recurrence (Baba, 1989a; Kaijtani, 1981; Maruyama, 1989). Our study showed that the prognosis of gastric cancer patients depends on three features of the tumor: depth of invasion, lymph node status and histologic type. In addition, the relatively high 5-year survival rates may be also caused by the high frequency of the differentiated histological types and lower or middle location of the tumor observed in this study.

Depth of invasion

Depth of tumor infiltration through the stomach wall is not only one of the most important prognostic factors in gastric cancer but also of major weight in the

decision process of the surgeon once he has opened the abdomen (Rohde, 1987). In general, because the disease tends to present at an advanced stage in most cases, the pessimism and surgical conservatism is prevailing among Western surgeons (Macintyre, 1991; McCulloch, 1994).

This study has demonstrate a significant association between depth of gastric wall invasion and survival rates. The total 5-year survival rate after surgery for early gastric cancer was 80.7%, for T2 tumors 54.0%, for T3 tumors 44.0% and for T4 tumors 34.0% (Table 3.16). Based on our data the muscularis propria or deeper invasion is really a predictor of relatively poor prognosis for gastric cancer patients and only the early cases are associated with satisfactory survival rate. The risk of death was 2.04 times higher in T2 cases, 2.27 times higher in T3 cases, and 3.24 times higher in T4 cases compared with early gastric cancer (Table 3.19). A further analysis of our data show that although the probability of the peritoneal dissemination of cancer cells and nodal involvement is reported to be high in T3–T4 cases, our patients with these tumors had a relatively favourable 5-year survival rates, especially when there were no lymph node metastases (56.6% and 51.9% respectively).

Concerning the early cases of gastric cancer, the question remains whether it is an entity different from invasive gastric carcinoma or an early stage of the same disease. There are many arguments in favour of both propositions. The long duration of expressive preoperative clinical symptoms just as it has been noticed also in other series and the different pathologic features of early and advanced gastric cancer (Table 3.3, Table 3.4., Table 3.7) make it impossible to exclude absolutely the possibility that early gastric cancer might be an independent form of malignance. On the other hand transitions between early and invasive carcinomas are often met (Lawrence, 1991; Moreaux, 1993).

The overall incidence of early gastric cancer in our series was 7.6% compared with 3 to 21% in other European studies (Akoh, 1992; Arveaux, 1992; Bollschweiler, 1992). In Japan the developments in diagnosis and the introduction of mass screening programmes have allowed increased detection of early gastric cancer, leading to an excellent survival prospect.

Lymph node metastases

Lymph node involvement is often stated to be one of the prognostic factors for patients with gastric cancer (Baba, 1989a; Jatzko, 1992a; Mishima, 1987; Msika, 1989). In our study it was the most important independent prognosticator followed by the depth of invasion and the histological type of cancer. The risk of death was 1.57 times higher in N1 cases, 2.48 times higher in N2 cases, and 3.98 times higher in N3 cases compared with patients without lymph node metastases (Table 3.19). Lymph node involvement was found in one hundred and eighty one patients (44.6%).

The extent of lymph node involvement among our patients showed the dependence on the T-stage. Univariate analysis shows the significantly different distribution of node negative and node positive cases only when the T1 and advanced tumors were compared — a high incidence of lymph node metastases is accompanied with the proper muscular layer or deeper involvement (*paper II*). The survival rates in T2 cases come also closer to the rates for T3 than for T1 cases and therefore it is reasonable to consider the T2-tumors to be advanced ones, as it is prescribed by the Japanese surgeons (Kaijtani, 1981; Maruyama, 1987b; Maruyama, 1989).

We found the survival rate of early gastric cancer with lymph node metastases to be significantly lower compared to the rate of early cancer without nodal involvement (*paper I*). Therefore we agree with Inoue, 1991 that the definition of early gastric cancer may need some revision — it might be modified to "carcinoma with invasion confined to the mucosa or submucosa but without evidence of lymph node metastases" (Inoue, 1991).

It is relevant here that in addition to the depth of tumor invasion the extent of lymph node involvement also correlated significantly with the Borrmann type and tumor size, but not with the histologic type or the location of the cancer.

The discrepancy among the Japanese Joint Committee (JJC) and International Union Against Cancer (UICC) classifications of the staging of gastric cancer has caused confusion (Noguchi, 1989). The UICC TNM classification defines the perigastric lymph nodes and nodes along the left gastric, common hepatic, splenic, and celiac arteries as regional lymph nodes; involvement of hepatoduodenal, retropancreatic, mesenteric, or para-aortic nodes is regarded as distant metastasis. According to the recommendations of the Japanese surgeons (Kaijtani, 1981; Maruyama, 1987b; Maruyama, 1989) the latter nodes are classified as regional (N3–N4) and in addition to the cancer-free resection margin only the R2, or more extensive lymphadenectomy is the pre-requisite of the curative gastric cancer surgery. In our patients the muscularis propria layer or deeper invasion was associated with the high incidence of lymph node metastases and with lower survival rates. Those it is extremely important in our opinion to interpret the hepatoduodenal, retropancreatic and mesenteric nodes, or the nodes at the splenic hilus as regional (N3) and all cases with involvement of these nodes as curative.

A Cox model, including all prognostic variables, indicated that the depth of gastric wall invasion and presence of lymph node metastases were the more important independent predictors of death. According to the results of 5-year survival analysis in different T and N categories all cases were divided into three prognostic groups. We can define the T1N0–2 and T2N0–1 tumors as cases with good prognosis, T3N0–1 and T4N0 tumors as cases with inter-

mediate prognosis, and T2N2–3, T3N2–3 and T4N1–3 tumors as cases with poor prognosis (see Table 3.18. and Figure 6.).

Histology

Multivariate analysis showed that the histological type of cancer is an independent and important prognostic factor. The high frequency of the intestinal types (differentiated types) is connected with a high-risk population and also a better prognosis of survival (Bollschweiler, 1993; Mishima, 1987). In our series the differentiated types: non-differentiated types ratio was 1.06 (171:161) which is comparable to that in most of the reports on the high risk areas (Jatzko, 1992a; Lauren, 1993; Maruyama, 1993; Roukos, 1990). When the incidence of different histologic types was also comparable, the frequency of cases with signet cell carcinoma was relatively lower (7.4%) than it was reported in other series (Bollschweiler, 1993; Jatzko, 1992a; Maruyama, 1987b). In 68.7% of all cases the tumors had histological patterns with higher 5-year survival rates than the overall 5-year survival rate was. Beside the relatively well-differentiated types (papillary and tubular carcinomas) the poorly differentiated adenocarcinoma with the 5-year survival rate of 47.2% also complete this group.

The non-differentiated gastric carcinomas (poorly differentiated adenocarcinoma, signet ring cell, mucinous and undifferentiated carcinomas) tend to spread more extensively in the gastric wall (Heberer, 1988; Ikeda, 1994; Janssen, 1991). We found these types of gastric cancer more often in T3–T4 stages than in the early cases. In addition, most of the non-differentiated cancers had infiltrative macroscopic type of grow and larger tumor size. These findings clearly show that the non-differentiated gastric carcinomas are clinically silent for a longer time than the differentiated-types and the early detection of the former is more difficult. It might be also possible that the non-differentiated types tend to grow more rapidly and that the alteration of the predominant histologic type alter with growth of tumor. On the other hand we did not observed differences in the lymph node involvement by the histological types. Accordingly, especially the resections of primary tumors should be recommended to be more extensive in patients with the non-differentiated cancers.

Some studies point out the fact that differentiated tumor is more frequent in men and older patients, whereas the diffuse type is more common in women and in the younger age groups (Lauren, 1965; Haugstvedt, 1992; Mecklin, 1988). We did not observed those associations in our material. It can be explained by the supposition that most of the young patients with non-differentiated did not undergone radical surgery because of the too advanced tumors.

Location

We found carcinomas in the upper third of the stomach only in 10.3% of the cases. There was no increased incidence of cancer of this location in radically operated on patients, also it has been pointed out in many other reports (Cuschieri, 1989; Maruyama, 1987b; Bollschweiler, 1993; Meyers, 1987). Some authors have showed that proximal tumors tend to penetrate into the serosa and have lymph node metastases more often than those of the distal stomach (Bollschweiler, 1993; Meyers, 1987). Because of the high percentage of cardial tumor in advanced stages (between 50 and 75%) the need for adequate screening programs is especially felt in the diagnosis of this location of gastric cancer (deCalan, 1988; Husemann, 1989; Kawaura, 1988; Moreaux, 1988; Rohde, 1991). There was 38.1% of N0 cases in cardial tumors in our study compared with 56.5% and 60.7% in antral and corporal tumors respectively, although these differences were not significant (p=0.081). A possible explanation for this finding is the unique anatomic situation in the proximal third having lymph drainage directly into left paraaortic (N3) nodes.

Some authors have reported that carcinoma of the cardia is characteristic for older patients (deCalan, 1988; Husemann, 1989; Kawaura, 1988; Moreaux, 1988; Rohde, 1991), when others have found more young with proximal cancers than those with distal cancers (deCalan, 1988; Husemann, 1989; Kawaura, 1988; Moreaux, 1988; Rohde, 1991; Welvaart, 1980). In our patients the incidence of cardial tumors was higher in less than 60 years of age (p=0.013), but no significant differences in the sex of patients was found (p=0.919).

The traumatic thoracoabdominal approach with combined gastrectomies in the treatment of cardial tumors also contributes to the high frequency of inoperable cases in particular with elderly patients who frequently suffer from concomitant diseases. This also accounts for the number of operable cases of cardial cancer being low. On the other hand the overwhelming majority of tumors were located in the lower (49.3%) and middle (34.5%) part of the stomach, where the radicality of resection should be better guaranteed. In our study, in cases of non-cardial carcinomas the survival rates are really about two times higher than in the cases with cardial location or total involvement of the stomach. 5-year survival rate for our patients with gastric cardia cancers was 28.6% compared with 51.5% for patients with antral cancers and 47.9% for patients with tumors located in the middle part of the stomach (p=0.005). This can partly be explained by the low rate of early cancers in this area and T1 tumors of the proximal gastric third also have a worse prognosis than T1 tumors of the distal stomach. Although the tumor location was not a significant prognostic parameter in the multivariate analysis because of the close connection with others, mainly with the extent of gastrectomy, we still think that distribution of both the tumor locations and histological types may be linked to the relatively good cure results in our study.

Borrmann type

By the results of the univariate analysis the infiltrative types of gastric cancer were more frequently associated with deeper gastric wall invasion, cardial location or total involvement of the stomach, larger tumor size, non-differentiated histologic types and lymph node involvement. Although the Borrmann type was not a prognostic factor in the multivariate model, it is closely related to the other pathologic variables. The 5-year survival rates also differed significantly between circumscribed and infiltrative types of tumor — 61.0% *versus* 39.0%. Considering these associations in clinical situation, as preoperatively as at the time of operation, the macroscopic appearance of a tumor may be a simple and easy method to indicate the prognosis in patients with gastric cancer.

3. Treatment related prognostic factors

In addition to the predetermined prognostic factors, surgical strategy also has a marked impact on the prognosis for gastric cancer patients. A planned, properly executed gastric resection offers the only hope for cure in patients whose disease is confined to the stomach and regional lymph nodes. There are three considerations in planning the extent of a resection for gastric carcinoma: 1) the extent of stomach resection; 2) the scope of lymphadenectomy, and 3) the need for *en bloc* resection of adjacent organs. In contrast to surgery for peptic ulcer disease, the perigastric tissues need to be widely dissected and removed, and resection margins at the duodenum, stomach, oesophagus, and other neighbouring organs need to be widely cleared of tumor to avoid recurrence in the tumor bed (Maruyama, 1987a; Shiu, 1987b).

Curative surgery was possible for 58.8% (n 406) of the 690 patients with primary gastric cancer treated at the Tartu Hospital of Oncology, Estonia during the 10-year period from 1978 to 1987.

Gastrectomy

According to the data from this study of the three surgical treatment factors found to be prognostically significant by univariate analysis, the Cox model confirmed that only the type of gastrectomy was the important prognostic indicator. The total as opposed to subtotal gastrectomy was associated with higher postoperative mortality higher risk of death (Table 3.14 and 3.19). The big differences in the 5-year survival rates after total and subtotal gastrectomies (34.4% versus 55.9%) were not only determined by the extent of surgical invasion but they also depended on various tumor parameters, mainly the Borrmann type of growth, the maximal diameter and the depth of invasion of the primary tumor. We performed total gastrectomy mainly in case of

infiltrative types and deep invasion and subtotal gastrectomies in case of limited tumors. The high percentage of differentiated carcinomas located in the gastric antrum and corpus also enabled us to carry out a high rate of subtotal gastrectomy. Considering the favourable oncological situation necessary to perform a subtotal gastrectomy, it follows logically that total gastrectomies have a much worse prognosis.

In conclusion, the extent of the primary tumor and the technical requirements must dictate the need for total gastrectomy in individual patients and the policy of applying total gastrectomy in case of any gastric cancer even when it can be widely resected with a subtotal gastrectomy is not justified. Dissection of the left and right paracardial nodes as well the retropancreatic nodes is technically possible without carring out a total gastrectomy, and only the question about jeopardising of the vascularisation by the skeletonizating of the upper part of the stomach and distal oesophagus remains (Hüscher, 1992). No ischeamic complications in the gastric stump was documented in our study. Furthermore, our data show that the choice between total and subtotal gastrectomy was made not only on the site and extent of the primary lesion in the stomach, but also on the desired extent of nodal dissection. If the extensive nodal involvement or extranodal spread existed, the total gastrectomy was preferred.

The small number of proximal subtotal gastrectomies — 10 (2.5% of the cases) — can be accounted for by the operation on principle being performed only in cases of small circumscribed tumors, the incidence of which in cardial region, partly due to diagnostic problems, is very low.

Splenectomy

The effect of splenectomy on survival after resection for gastric cancer is not generally agreed upon. Removal of the spleen *en bloc* with the gastric specimen has traditionally been part of a standard radical gastric resection for cancer in many centres, although is reported to be associated with higher postoperative complications and mortality in others (Furukawa, 1988; Maehara, 1991b; Noguchi, 1989). In our study most of the splenectomies were performed with resections associated with a higher postoperative complications and a lower survival rates of itself — total gastrectomy and R3-lymphadenectomy — because these procedures were used in cases of more advanced carcinomas. Significant differences between the cases with and without splenectomy existed in our study with respect to tumor size, location and gross appearance, serosal invasion, and lymph node metastasis. For patients subjected to splenectomy the non-antral location of primary cancer (85.1%), deeper (T3–T4) invasion (85.8%) and infiltrative type of growth (72.3%) were more frequent. There was no significant correlation with the extent of the lymph node involvement although we have decided about the need of splenectomy mostly by the accidental biopsies of the lymph nodes before gastrectomy.

The postoperative mortality in our patients was 11.3% and the 5-year survival rate was 30.5% compared with 3.0% and 54.3% respectively in patients without splenectomy. Despite the differences in the survival rates the splenectomy was not the independent prognostic factor in the Cox model. Higher complications and mortality after splenectomy was mainly due to infectious complications. We concluded that the splenectomy was the cause of higher postoperative mortality induced by the infectious complications, but not the cause of lower 5-year survival rates more strongly conditioned by the prognostic factors associated with primary tumor. In our opinion splenectomy should not be performed routinely and should be reserved for tumors with non-antral location of the stomach or for antral tumors with N2 node involvement. In addition the adequate technique of the lymph node dissection in the splenic artery and splenic hilus regions without splenectomy is described by the Japanese authors (Maruyama, 1993).

Resection of adjacent organs

During the operation in many cases the surgeons are faced with the necessity of extending the resection to adjacent organs. This should prompt careful intra-abdominal exploration and sampling of suspected areas of invasion for microscopic frozen section analysis, especially when suspicion rests on parechymal organs where clinical assessment is less precise and biopsy less dangerous than in case of hollow viscera. Nevertheless, the clinical suspicion of infiltration of these organs was confirmed by the postoperative histological examination only in 39.1% in our study.

We are of the opinion that direct invasion to adjacent organs is not an indicator of incurability when compared with factors such as peritoneal dissemination or liver metastasis. In cases of quaternary nodal involvement the postoperative mortality rate and incidence of early recurrence is extremely high and we consider these cases also as non-curative.

Tumors with invasion of contiguous structures (T4) had also good cure results (34.0% at 5-year) in our study, particularly in cases without nodal involvement. Therefore we think that combined resection of neighbouring organs directly invaded by gastric cancer is a very effective method of therapy. The importance of combined resections of neighbouring organs has been also reported by many others (Bozzetti, 1990; Jatzko, 1992a; Korenaga, 1988a; Maruyama, 1987b). They emphasise that surgeons should be aggressive in performing gastrectomy with *en bloc* removal of invaded organs in all cases when cancer appears to be in a potentially curable cases.

We consider that the current operative mortality rate of 10.0% and 11.7% after combined operations is acceptable and compares favourably with figures of 0% to 28.0% reported in other Western countries, even if it is still far from the figure of 3% reported by Japanese authors (Bozzetti, 1990; Korenaga, 1988a; Macintyre, 1991).

Extensive lymphadenectomy

The extent of lymphadenectomy remains a controversial issue in the management of gastric cancer. In Japan the standard treatment policy for all potentially curable patients with gastric carcinoma is radical resection, including extensive lymphadenectomy. This policy is applied to early as well as advanced gastric cancer and substantial increases in survival time have always been reported (Korenaga, 1988a; Maruyama, 1987b; Noguchi, 1989).

Jaehne, 1992 reported that according to a European questionnaire a radical lymphadenectomy is performed in only 50% of all cases and concluded that this may, in part, explain the disappointingly low survival rates after potentially curative resections in the Western hemisphere. Candela, 1990 found that the surgical therapy in the form of extended R2 or R3 lymphadenectomy in Japan may be more effective than the generally applied standard R1 lymphadenectomy in the United States. The heterogeneity of techniques in gastric cancer surgery and a small percentage of dissections similar to the Japanese R2 dissection in the United States is reported (Wanebo, 1993). In our hospital the dissection of at least N2 nodes was routinely performed in all cases.

Although it is widely recognised that lymph node metastases affect survival of early gastric cancer as well as that of advanced cancer, the incidence and extent of nodal involvement in early cases is always lower. In cases of early gastric cancer the lymph node involvement rate always correlate with the depth of invasion: in patients with intramucosal carcinoma the lymph node metastases are observed in single cases, when in patients with extensive submucosal involvement the incidence if nodal deposits may be up to 50% (Sue-Ling, 1992; Hioki, 1990; Inoue, 1991; Iriyama, 1989; Lauren, 1965; Maehara, 1992d; Moreaux, 1993; Sakita, 1989). If the patients had not been divided by nodal status, early gastric cancer treated by subtotal gastrectomy with R0–R1 lymphadenectomy showed only a slightly lower survival rate than those undergoing total gastrectomy with R2 lympadenectomy (Guardagni, 1993; Hioki, 1990; Iriyama, 1989; Moreaux, 1993; Sakita, 1989). Therefore it would seem logical to carry out a more conservative (R1) resection with complete excision of only perigastric (N1) nodes in cases of early gastric cancer where it is confined to the mucosa, reserving the more radical (R2) resection for the cases where the tumor has penetrated to the submucosa and the incidence of lymphogenic metastases is higher. Nevertheless, preoperative assessment of the depth of invasion of early gastric cancer would require the use of endoscopic endoluminal ultrasound, which is not yet routinely available in most European centres (Sue-Ling, 1992). Even if it is available, accurate distinction between mucosal and submucosal tumors is not always achieved. The surgeons do not know the exact TNM stage of the tumor before the operation and the diagnosis of early gastric cancer is usually made in retrospect. Secondly, data from Japan (Kaijtani, 1981; Maruyama, 1987a; Maruyama, 1989; Shiu, 1987b) have

consistently supported the view that the "R" number (0–3) of resection should exceed the "N" number (0–3) of nodal metastases if absolute curative resection is to be achieved. As the metastases to N1 nodes are not rare for early gastric cancer, it follows that R2 resection should be the treatment of choice. Thus, we think an aggressive surgical approach including extended (at least R2) lymphadenectomy should be used for all early gastric cancers as Japanese authors continue to advocate (Boku, 1989; Eriguchi, 1991; Guardagni, 1991; Hioki, 1990; Inoue, 1991; Korenaga, 1988a; Maruyama, 1987b; Noguchi, 1989).

Significant differences existed in survival rates relative to the nodal status. Despite the extensive lymphadenectomy used in all cases, the cure results in N3 positive cases were quite modest (12.0%). However, the frequency of metastases in N2 (24.4%) and N3 (6.2%) nodes determined the necessity of N3 node dissection. Univariate survival analysis showed the better 5-year survival rate after R2-lymphadenectomy (52.7%) than after R3-dissection (34.3%). These results are likely to reflect the extent of the disease: the R2-lymphadenectomies were more frequently associated with subtotal gastrectomies and limited (N0–N1) lymph node involvement, while most of the R3-lymphadenectomies were performed in cases of extended nodal disease and were associated with simultaneous total gastrectomy. The scope of lymphadenectomy in multivariate analysis showed no significant difference in survival because the extensive lymph node dissection was used in all patients.

The concept of lymphadenectomy being beneficial only when it widely encompasses the disease is not new (Shiu, 1987). This study showed that extensive lymph node dissection (R2 or R3) offers more benefit to the patients with either no or limited (N0–N1) nodal disease, that is in these cases where the dissected area was at least one nodal level wider than the actual lymphatic spread of the tumor. The second lymph node group (N2) should be removed with the extensive lymphadenectomy if no lymph node involvement is found. If there are clear macroscopic changes in the perigastric nodes, R3-lymphadenectomy is indicated. In the absence of palpable abnormalities in lymph nodes, the cure results of gastric cancer can be improved by a wide prophylactic node dissection, particularly in the patients with elevated risk to lymph node metastases.

We have attempted to determine the extent of nodal disease before gastrectomy by the frozen-section examination of the macroscopically suspicious nodes around the stomach. Unfortunately, the postoperative histological examination of the removed lymph nodes proves that accidental biopsies and evaluation of nodes by palpation during operation is not always reliable because of the large number of false-negative and false-positive results. The histological examination of lymph nodes in the observed period implied only the investigation of one-step sectioning of enlarged nodes and therefore some micrometastases might remain undetected. At present all removed nodes undergo microscopical examination and the three-step-sectioning method is being intro-

duced to make data processing concerning the lymphogenic spread of cancer more precise.

Postoperative complications and mortality

A decline in operative mortality rates after radical gastric cancer surgery over the past 30 years has been demonstrated over the world, but it is still regarded as unacceptably high by many practitioners (Akoh, 1992). The overall 30-day postoperative mortality for our patients — 5.9% — is higher than the one reported after comparable surgery in Japan, but it is equal to or lower than the rates published in non-Japanese series (Gouzi, 1988; Jatzko, 1992a; Kaibara, 1990; Lindahl, 1988; Roukos, 1990; Shiu, 1987a; Viste, 1988). It is also lower than in a number of hospitals where the extensive lymph node dissection was not used (Akoh, 1992; Allum, 1989; Wanebo, 1993). The postoperative mortality was higher after R3 lymphadenectomy and total gastrectomy (11.0% and 10.6% respectively). Although we have achieved the higher radicality partly at the cost of higher mortality, we can not consider these mortality rates extensively high to make us refrain from extensive surgery in gastric cancer therapy as there are no effective alternative methods at our disposal. Aggressive surgery with extensive lymphadenectomy can safely be performed on young patients, on elderly patients with concomitant systemic disorders this approach must have a selective use.

We also may conclude that the use of prophylactic measures against infection, and the standardisation of surgical techniques in specialised hospitals should reduce the operative complications and mortality following extensive gastric resections.

4. Extended *versus* conventional surgery for gastric cancer

Adequate surgical resection offers the only chance for long-term survival for a patient who has potentially curable gastric carcinoma and the surgeon's choice and manner of execution of surgery can have a significant effect on prognosis (Akoh, 1992; Jatzko, 1992; Maruyama, 1987b; Pacelli, 1993; Shiu, 1987a, Stipa, 1994). In Finland and in Estonia the treatment policy of gastric cancer is quite different. The patients in Finland are treated by the general surgeons with conventional methods of surgery. In contrast there is the network of specialised oncological aid for cancer patients In Estonia and the more extensive surgery has been in use. In this part of discussion the two operative procedures with different radicality will be compared (*papers I, III and VI*).

The mean age for patients who underwent curative treatment was 63.0 years in Oulu (range 27 to 81) and 62.4 years in Tartu (range 31 to 85 years). Relatively more male patients were found among curable gastric cancer patients in Oulu study (59.1% versus 48.8% in Tartu study).

The 5-year survival rates following surgery for cure was 45.5% in the Oulu study. It was approximately the same as in our study (46.1%) and it seemed that the extensive methods of surgery were not essential in the reduction of the mortality after gastric cancer surgery. Further analysis of the data from both studies show that this conclusion is not correct. In Table 4.1 the comparative data of prognostic factors and survival rates after curative gastric cancer surgery in Oulu University Hospital and Tartu Hospital of Oncology are. Relative frequencies of prognostic factors differed significantly ($p<0.05$) in T stages, N stages and Borrmann types. Although higher incidence of cardial cancer was observed in Oulu, the overall difference in locational distribution between two groups was not significant. Histologic types were not comparable because different grading systems were used in two centres: WHO classification in Tartu and the Lauren classification in Oulu (Devessar, 1990; Lauren, 1965; Oota, 1977).

Comparative analysis of the 5-year survival rates shows no differences in the survival rates for T1 and T2 cases in two groups, but it was highly different for T3 tumors. Moreover, patients in Tartu had higher incidence of T3 tumors and no patients with T4 tumors were operated on with curative intention in Oulu. The 34.0% 5-year survival rate of T4 patients in the Tartu study is unquestionably high and confirms the importance of combined resections of neighbouring organs in gastric cancer surgery.

In Oulu only patients with N0–N1 involvement were subjected to the curative surgery. In Tartu 124 (30.6% of all cases) patients with metastases in N2 and N3 nodes were also curatively operated on with subsequent 5-year survival 25.3% and 12.0% respectively.

Borrmann type III–IV tumors were found only in 21.6% of curative cases in Oulu compared with the equal distribution of expansive and infiltrative types in Tartu and also in the overall material from Oulu (Table 4.1, Table 3.16). Despite of the fact that the distribution of Borrmann types within two Hospitals was different, the survival rate was significantly higher after extensive surgery only in infiltrative Borrmann types of gastric cancer. In general these results show that differences in survival rates are more noticeable in more advanced stages (T2–T3, N2–N3, Borrmann type III–IV). Within both series the sex of patients had little influence on the survival rate but younger patients had better survival curves. These differences can be explained by a more aggressive approach to combined organ resection and extensive lymph node dissection. Otherwise we may conclude that the patients in Oulu are more carefully selected for curative surgery than the patient in Tartu Hospital of Oncology.

Table 4.1

Frequencies of prognostic factors and survival rates after curative gastric cancer surgery

Variable	No. and percentages of curative cases		5-year survival rates	
	Tartu study	Oulu study	Tartu study	Oulu study
All cases	406 (100.0)	88 (100.0)	46.1	45.5
Sex				
male	198 (48.8)	52 (59.1)	46.9	48.1
female	208 (51.2)	36 (40.9)	45.2	41.7
Age				
< 70	281 (69.3)	56 (63.6)	50.9	50.0
> 69	125 (30.8)	32 (36.4)	35.2	37.5
T stage				
T1	31 (7.6)	20 (22.7)	80.7	85.0
T2	63 (15.5)	31 (35.3)	54.0	48.4
T3	218 (53.7)	37 (42.0)	44.0	21.6
T4	94 (23.2)	0	34.0	–
N stage				
N0	225 (55.4)	67 (76.1)	60.0	49.3
N1	57 (14.0)	21 (23.9)	42.1	33.3
N2	99 (24.4)	0	25.3	–
N3	25 (6.2)	0	12.0	
Location				
Lower	200 (49.3)	49 (45.4)	51.5	55.0
Middle	140 (34.5)	22 (25.0)	47.9	50.0
Upper	42 (10.3)	22 (25.0)	28.6	31.8
Total	24 (5.9)	4 (4.5)	20.8	0.0
Borrmann				
I–II	193 (47.5)	69 (78.4)	59.1	53.6
III–IV	213 (52.5)	19 (21.6)	34.3	15.8
Size				
< 4 cm	57 (14.0)	27 (30.7)	71.9	81.5
4–7 cm	192 (47.3)	47 (53.4)	44.3	29.8
8–12 cm	123 (30.3)	12 (13.6)	43.1	33.3
> 12 cm	34 (8.4)	2 (2.3)	23.5	0.0

Simple resectional procedures, that is the excision of the primary tumor, including perigastric nodes, guarantee the fair prognosis only in cases without serosal invasion and lymph node metastases (Korenaga, 1991; Santoro, 1991). According to our data gastric cancer, if operated during the early phase, is curable without extensive lymph node dissection, resulting in Finland in a 5-year survival rate 85%. Nevertheless, the comparative analysis of survival rates after radical gastric cancer surgery in conditions of limited and extended

lymphadenectomy confirm that in cases of nodal involvement the latter is instrumental in effecting the cure. As determining of the extent of excision may present a problem in the absence of palpable abnormalities in lymph nodes or without obvious invasion into adjacent structures, the standardisation of operative policy in gastric cancer surgery is essential (deAretxabala, 1987; Korenaga, 1991; Maruyama, 1987b). The extensive lymphadenectomy made in the absence of palpable abnormalities in lymph nodes may also be important in establishing N stages more accurately and may result in a higher prevalence of patients with (micro)metastases. A relationship between the number of nodes dissected and the proportion of patients with lymph node metastases has been reported also by others (deAretxabala, 1987; Maruyama, 1989; Soga, 1988).

Table 4.2

Surgical complications and mortality after curative surgery

Type of operation	No. of cases	Surgical complications	Postoperative mortality	5-year survival
Curative gastrectomy				
in Oulu:	88	14 (15.9)	9 (10.2)	45.5
total	59	13 (22.0)	6 (10.2)	39.0
subtotal	29	1 (3.4)	3 (10.3)	58.6
curative gastrectomy				
in Tartu:	406	59 (14.5)	24 (5.9)	46.1
total	170	37 (21.8)	18 (10.6)	32.3
subtotal	226	22 (9.7)	5 (2.2)	56.2
proximal	10	0 (0.0)	1 (10.0)	50.0

Not only in Japanese studies (deAretxabala, 1987; Jatzko, 1992a; Maruyama, 1989) a low rate of postoperative mortality (1.7–4.8%) is observed after radical gastric cancer surgery and it is not affected by the extent of node dissection performed. In this comparative study the postoperative surgical complications rate was similar in two hospitals (Table 4.2). It had the same rate after total gastrectomy and was lightly higher after subtotal gastrectomy with R2–R3 lymphadenectomy compared with conventional subtotal gastrectomy. Therefore we can conclude that the extensive surgery can safely be performed without adverse effect on postoperative complications and mortality.

Thus, we found that the same overall survival rate after curative gastric cancer surgery may be the result of different selection of patients. It is caused by the more or less aggressive approach to the dissection of cancer.

The conservative techniques in gastric cancer surgery in the United States and in Europe may, in part, explain the low number of curative cases and the disappointing survival rates after potentially curative resections (Candela, 1990; Jaehne, 1992; McCulloch, 1994; Wanebo, 1993). As it was already

pointed out, the reports from centres with a special interest show results that are clearly superior to those (Buyse, 1991; Diggory, 1985; Green, 1988; Irvin, 1988; Jatzko, 1992a; *paper I*). The authors emphasised that the treatment of cancer patients by few surgeons specialising in oncological surgery improve the outcome (Allum, 1989; McCulloch, 1994; Wanebo, 1993). In Estonia there is the relatively well operating network of specialised oncological aid, where most of the gastric cancer patients are operated on by surgical oncologist with the similar concept of resection policy as has been described in this study. In Tartu most of the operations analysed in this study were performed by one experienced surgeon — professor Karl Kull. Our results demonstrate high 5-year survival rates even in cases of more advanced tumors (T2N3, T3N2, T4N0). Therefore it is concluded that special education of surgeons in the requisites for adequate gastrectomy and the use of such resection techniques which have demonstrated more adequate control over the locoregional disease may increase the survival of patient with gastric cancer.

In conclusion it is extremely important to analyse the survival rates in different hospitals and its associations with prognostic factors. As we can see from the present study the same overall survival rate after curative gastric cancer surgery may be the result of different selection of patients or different treatment policy. However, caution must still be exercised in drawing conclusions from retrospective studies in which results from different hospitals are compared. A prospective randomised trial comparing the results of the gastric cancer surgery with different extension might be initiated in the future. Despite the suspicions, the results obtained from this study support the concept that extensive methods of surgery have a role in the treatment of gastric cancer.

*

The incidence rate of gastric cancer in Estonia is relatively high, the percentage of early gastric cancer is extremely low, and the great differences between survival rates of patients with early and advanced tumors exist. In addition, the high incidence of precancerous changes in Estonians already in their early decades of life (Rätsep, 1976; Villako, 1991), expressive clinical symptomatology and the long duration of preoperative symptoms is characteristic for patients with gastric cancer in Estonia.

We look forward to the day when effective non-surgical therapies will make gastrectomy and lymphadenectomy obsolete surgical procedures (Jatzko, 1992a). But for now, adequate surgical resection offers the best chance for long-term survival for a patient who has potentially curable gastric carcinoma. Even though only some prospective randomised trials have been performed to study the use of radical gastrectomy with wide lymphadenectomy, a preponderance of cure results in Japan support its therapeutic merit. In the Western world the surgery of gastric cancer is covered with pessimism. The surgeons

perform palliative procedures because they believe that gastric cancer is nearly incurable at presentation (McCulloch, 1994). Many Western surgeons incline to conservatism also because of the concern over the potential complications associated with more radical operations. In addition, extensive gastric lymphadenectomy does require extra time and effort in performing a gastrectomy.

Our study indicates that extensive surgery with systemic lymph node dissection and combined organ resections is a surgical procedure that allows a precise TNM staging, offers the possibility of improving the survival in certain patients (particularly in those with limited lymph node metastases), and helps to define the risk groups for early tumor recurrences. It should form the basis for further studies to improve the prognosis of gastric carcinoma. We agree with Jatzko, 1992a that the extended radical surgery for gastric cancer should no longer be a controversial topic in Europe. At present a decrease in the mortality for the gastric cancer can be achieved only by these methods. We also believe that the cure results might be much better when the radical surgery will be combined with successful program of screening for early disease.

CONCLUSIONS

1.1. Univariate analysis of prognostic factors for curative gastric cancer brought forth as favourable factors the age below 70, tumor location in the lower or middle part of the stomach, Borrmann I–II type, tumor size less than 4 cm, differentiated histological type, T 1–2 stage, limited (N0–N1) lymph node involvement, subtotal gastrectomy, R2 versus R3 lymphadenectomy and the extent of lymphadenectomy more than one N-group from the involved lymph nodes. The year of operation and the sex of patients did not have a significant influence on the survival.

1.2. By the multivariate analysis five prognostic variables for our patients were identified that independently influenced the risk of death. Among these, lymph node involvement was the most important independent prognostic factor, followed by the extent of gastrectomy, the depth of invasion, the histological type of cancer and the age of patients.

1.3. According to the results of 5-year survival analysis of the two more important independent predictors of death — depth of gastric wall invasion and presence of lymph node metastases — all cases can be divided into three prognostic groups: 1) tumors with good prognosis (T1N0–2 and T2N0–1); 2) tumors with intermediate prognosis (T3N0–1 and T4N0); and 3) tumors with poor prognosis (T2N2–3, T3N2–3 and T4N1–3).

Because the survival rate of T1 tumors with lymph node metastases is significantly lower compared to the rate of early cancer without nodal involvement, only the T1 cases without evidence of lymph node metastases might be defined as early cancers.

1.4. As there was relatively fewer male patients capable of undergoing radical surgery, we conclude that men tend to care less for their health and need more attention in cases of gastrointestinal disorders. The age of the patients is not a contraindication to radical resection for gastric cancer. Aggressive surgery with extensive lymphadenectomy can safely be performed on young patients, on elderly patients with concomitant systemic disorders this approach must have a selective use. The long duration of expressive clinical symptoms is characteristic for gastric cancer.

2. The results of this study support the value of extensive surgery for gastric carcinoma. We are positive, that there must be three considerations in planning the extent of a resection for gastric adenocarcinoma: 1) the extent of stomach resection; 2) the scope of lymphadenectomy, and 3) the need for en bloc resection of adjacent organs.

2.1. All the tumor related factors must dictate the extent of gastrectomy in individual patients. Total gastrectomy is indicated when the proximal distance from the cardia is less than required (5 cm in circumscribed and 8 cm in infiltrative tumors), in Borrmann types 3 and 4, and in cases with non–

differentiated histological pattern. The policy for applying total gastrectomy in case of any gastric cancer when it can be widely resected with a subtotal gastrectomy is not justified.

2.2. As the N2 nodes are frequently involved, even in T1 cases, group 1 and 2 nodes should be removed in all cases. To achieve adequate lymph node dissection and to avoid the recurrence of the disease at least one uninvolved nodal level should be resected. In this connection it is extremely important in our opinion to interpret the hepatoduodenal, retropancreatic and mesenteric nodes, as well the nodes at the splenic hilus as regional (N3) and all cases with involvement of these nodes as curative.

2.3. Direct invasion to adjacent structures is not an indicator of incurability. These tumors had good cure results in our study, particularly in cases without nodal involvement. Therefore we think that combined resection of neighbouring organs directly invaded by gastric cancer is a very effective method of therapy. Curative gastric resection should also be regularly combined with en bloc resection of neighbouring organs to achieve the better lymphatic tissue dissection.

2.4. We conclude that the splenectomy is the cause of higher postoperative mortality induced by the infectious complications, but it does not influence the 5–year survival rates more strongly conditioned by the prognostic factors associated with primary tumor. Nevertheless, splenectomy is indicated to achieve better lymphadenectomy.

3. Similar overall survival rates after curative gastric cancer surgery in different hospitals may be the result of different selection of patients for radical surgery. The differences in the distribution of clinicopathological factors of gastric cancer between two hospitals observed in this study can be explained by the different extent of tumor resections. More aggressive approach to combined organ resection and extensive lymph node dissection in Tartu enlarged the relative amount of potentially curable patients.

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RADIKAALSELT OPEREERITUD MAOVÄHI-HAIGETE ELULEMUST MÕJUTAVAD TEGURID

Kokkuvõte

Haigestumusnäitajate üldisele langustendentsile vaatamata on maovähk üks juhtivaid pahaloomulistest kasvajatest tingitud surmapõhjusi kogu maailmas. Ka Eestis on maovähi esinemissagedus viimastel aastakümnetel pidevalt vähenenud, jäädes aga kiiruselt märgatavalt alla meie läänepoolsete naaberriikide omadele (Cancer Society of Finland, 1990; Cancer Society of Finland, 1992; Craanen, 1992; Holleb, 1991; Lauren, 1993; Lindahl, 1988; Tekkel, 1992; Thomson, 1994). Euroopas ja Põhja-Ameerikas on maovähk enamasti tuntud kui haigus, mis seostub suure hilisjuhtude osatähtsuse, ravis kasutatavate operatsioonimeetodite heterogeensuse, kõrge operatsioonijärgse suremuse ja ebarahuldavate ravitulemustega (Akoh, 1991; Allum, 1989; Guardagni, 1993; Inoue, 1993; Sano, 1992; Wanebo, 1993).

Maovähi ravi tunduvalt paremad tulemused Jaapanis on tingitud ühelt poolt edukalt tehtavatest sõeluuringutest, teiselt poolt aga ühtse metoodikaga laiendatud ja kombineeritud operatsioonide järjekindlast rakendamisest (deAretxabala, 1988; Maruyama, 1987b; Maruyama, 1989; Soga, 1988). Et suhteliselt madalate haigestumusnäitajate tõttu ei ole sõeluuringud Euroopas poolehoidu leidnud, on maovähi ravitulemusi siin võimalik parandada vaid õiget kirurgilist ravitaktikat kasutades. Samas lähevad arvamused nii kasvaja algkolde kui magu ümbritsevate lümfisõlmede eemaldamise ulatusest tublisti lahku (Allum, 1989; Bonenkamp, 1993; Jatzko, 1992a; McCulloch, 1994; Roukos, 1990; Sigal, 1991; Wanebo, 1993).

Eespool öeldust tulenesid käesoleva töö eesmärgid:

1. Analüüsida maovähi radikaalse kirurgilise ravi tulemusi Tartu Ülikooli Kliinikumi Onkoloogiahaiglas ja selle kaudu selgitada Eestis radikaalselt ravitavate maovähihaigete prognoosi mõjutavad tegurid.
2. Määrata elundite ja lümfisõlmede eemaldamise näidustused ja sobilik ulatus maovähi radikaalses kirurgilises ravis.
3. Võrrelda maovähi kirurgilise ravi taktikat ja kaugtulemusi üldkirurgilises ja spetsialiseeritud onkoloogilises raviasutuses.

Käesolev retrospektiivne uurimus on valminud 406 Tartu Ülikooli Kliinikumi Onkoloogiahaiglas (endises Tartu Linna Onkoloogiadispanseris) aastatel 1978–1987 radikaalselt opereeritud maovähihaige haigusloo analüüsi tulemusena. Kõikidel juhtudel rakendati raviks gastrektoomiat või subtotaalset maoresektsiooni koos lümfisõlmede laiendatud eemaldamisega (R2- või R3-lümfadenek-

toomia). Radikaalne ravi on sellistel põhimõtetel meie haiglas kasutusel 1970. aastate lõpust. Võrdlemaks maovähi kirurgilises ravis kasutatavaid operatsioonitaktikaid, on hinnatud ka 203 üldkirurgilises raviasutuses — Oulu Ülikooli Haigla kirurgiaosakonnas — ravitud maovähihaige prognostilisi tegureid. Selles osakonnas kasutatakse maovähi radikaalse ravi meetodina konventsionaalset gastrektoomiat koos R1-lümfadenektoomiaga.

Statistiliseks andmeanalüüsiks koguti haiguslugudest 38 erinevat haige, kasvaja ja raviga seotud näitajat, mis võiksid olla prognostilise väärtusega. Kõiki haigeid jälgiti viie aasta vältel, elulemusnäitajad on kogutud vastavalt Eesti ja Soome Vähiregistritest.

Vaadeldud perioodil tehti Tartu Ülikooli Kliinikumi Onkoloogiahaiglas 170 radikaalset gastrektoomiat ja 236 radikaalset subtotaalset maoresektsiooni, 260 R2-lümfadenektoomiat ja 146 R3-lümfadenektoomiat. 30-päevane operatsioonijärgne suremus oli 5,9% ja üldine suhteline viie aasta elulemus 46,1%.

Haigete keskmine vanus oli 62,5 (ulatus 31–85) aastat. Leidsime, et kuigi alla 40 aasta vanuseid haigeid oli radikaalselt opereeritute hulgas vähe, olid nende ravitulemused head (viie aasta elulemus 71,4%). Vanemaealistel haigetel oli operatsioonijärgseid üldtüsistusi sagedamini, nende elulemusnäitajad olid keskmisest madalamad ja seda osalt ulatuslikuma lümfogeense metastaseerumise tõttu.

Kui kõikide maovähihaigete hulgas oli Eestis meeste ja naiste suhe 1,35, siis radikaalselt opereeritute seas oli see näitaja 0,95 ja varajase vähi juhtudel vaid 0,48. Selliseid erinevusi ei saa seletada ei erineva sümptomatoloogia ega kasvaja iseloomuga; põhjusi tuleb otsida meeshaigete suhtumisest neil esinevatesse haigusnähtudesse.

Haiguse anamneesi keskmine pikkus oli 11,1 kuud, varajase maovähiga haigetel oli see isegi mõnevõrra pikem. Nii varajase kui ka radikaalselt ravitava mittevarajase maovähiga haigetel olid sagedasemateks haigusnähtudeks epigastraalne valu (vastavalt 77,4% ja 70,2%), kaalulangus (45,2% ja 61,8%), düspeptilised vaevused (19,4% ja 39,2%) ja üldine halb enesetunne (nõrkus, väsimus jms.; 25,8% ja 33,3%).

Kolmekümne ühel (7,6%) haigel oli tegemist T1-, kuuekümne kolmel (15,5%) T2-, kahesaja kaheksateistkümnel (53,7%) T3- ja üheksakümne neljal (23,2%) T4-kasvajaga. Seega on varajase maovähi osatähtsus radikaalselt opereeritud haigete hulgas äärmiselt madal. Saja kaheksakümne ühel juhul (44,6%) leiti lümfisõlmede metastaatiline kahjustus, mille ulatus oli statistiliselt oluliselt määratud kasvaja algkolde invasioonisügavuse, makroskoopilise kasvuvormi ja läbimõõduga. Prognoosi seisukohalt kahe kõige olulisema maovähi patoloogilis-anatoomilise omaduse — invasioonisügavuse ja lümfisõlmede kahjustuse ulatuse alusel oli võimalik moodustada kolm prognostilist gruppi: hea (T1N0-2, T2N0-1), rahuldav (T3N0-1, T4N0) ja halb (T2N2-3, T3N2-3, T4N1-3). Selgus, et sageli on olulisem just lümfisõlmede seisund.

Maovähi diferentseerumata histoloogilised vormid olid diagnoosimise hetkel sügavama invasiooniga, infiltratiivsema kasvuvormi ja suurema läbimõõduga ning seetõttu prognostiliselt halvemad. Diferentseerunud vormide tagasihoidlik ülekaal (1,06 korda) näitab muuhulgas, et kuulume kõrge maovähiriskiga piirkondade hulka.

Töö tulemused näitasid, et haige ja kasvajaga seotud prognostiliste tegurite kõrval on maovähihaigete prognoosile suur mõju kirurgilisel ravitaktikal. Selgus, et mao antrumis või korpuses lokaliseeruvate piirdunud vähikollete ravis ei ole gastrektoomial eelist subtotaalse maoresektsiooni ees. Samas oli oluline mao naaberelundite resetseerimine, andes T4-kasvajate korral haigete hea viie aasta elulemuse (34,0%). Heade ravitulemuste saavutamiseks oli oluline ka lümfikoestiku eemaldamine piisavas kauguses vähist kahjustatud lümfisõlmedest, mille eelduseks omakorda oli laiendatud lümfadenektoomia kasutamine.

Selgus ka, et viie aasta elulemus pärast radikaalseid operatsioone oli kahes võrreldud haiglas sarnane (vastavalt Oulus 45,5% ja Tartus 46,1%). Samas opereeriti Oulu Ülikooli Kliinikus radikaalselt vaid 43,3% kõikidest maovähihaigetest, Tartus oli radikaalsus 58,8%. Kahe võrreldud haigerühma prognostiliste tegurite suhtelised sagedused erinesid oluliselt ($p<0,05$) T- ja N-astmete ning Borrmanni tüüpide osas. Tartus oli opereeritud tunduvalt rohkem T3-kasvajaid ja T4-juhud olid Oulus arvatud radikaalselt mitteopereeritavateks. Ka N1-sõlmedest ulatuslikuma metastaseerumisega kasvajaid Oulus radikaalselt ei opereeritud, Tartus oli selliseid haigeid aga 30,6% kõikidest juhtudest. Piirdunud ja infiltratiivsete kasvuvormide suhe oli Tartus 0,9 ja Oulus 3,6. Seega võib järeldada, et sarnane viie aasta elulemus pärast maovähi radikaalset ravi erinevates haiglates oli haigete erisuguse valiku tulemus. Patoloogiliste näitajate jaotumuse lahknevus kahes vaadeldud haiglas on seletatav kasvajate eemaldamise erineva ulatusega. Ekstensiivse, naaberorganite resektsioonide ja laiendatud lümfadenektoomiaga kombineeritud maooperatsiooni tähtsus muutus oluliseks just lokaalselt või lümfogeenselt levinud kasvajate (T3–4, N2–3, Borrmanni III–IV tüüp) puhul. Et just need kasvajad moodustasid suurema osa haigusjuhtudest, võimaldas selline metoodika suurendada potentsiaalselt ravitavate haigete hulka Tartus.

Vastavalt üksiktunnusanalüüsi tulemustele olid radikaalselt ravitavate maovähihaigete seisukohalt soodsad järgmised prognostilised tegurid: vanus alla 70 aasta (viie aasta elulemus 51,9% 35,2% vastu), T1–T2 staadium (viie aasta elulemus 67,8% 41,0% vastu), piirdunud (N0–N1) lümfisõlmede kahjustus (viie aasta elulemus 56,4% 22,6% vastu), diferentseerunud histoloogiline ehitus (viie aasta elulemus 55,0% 39,6% vastu), I–II tüüpi kasvuvorm Borrmanni klassifikatsiooni järgi (viie aasta elulemus 59,1% 34,3% vastu), kasvaja asetsus mao alumises või keskmises kolmandikus (viie aasta elulemus 50,0% 25,8% vastu), distaalne subtotaalne maoresektsioon (viie aasta elulemus 55,0% 32,4% vastu), R2-lümfadenektoomia (viie aasta elulemus 52,7% 34,3% vastu) ja roh-

kem kui ühe lümfogeense metastaseerumise taseme profülaktiline eemaldamine (viie aasta elulemus 58,1% 27,2% vastu).

Hulgitunnusanalüüs Coxi mudeli järgi, milles on arvestatud kõiki muutujate omavahelisi mõjusid, selgitas viis sõltumatut prognostilist tegurit radikaalselt ravitavate maovähihaigete jaoks. Toime tugevuse järjekorras loetletuna on need järgmised: lümfisõlmede kahjustuse ulatus, mao eemaldamise ulatus, kasvaja invasiooni sügavus, kasvaja histoloogiline ehitus ja haige vanus. Seega oli lümfogeenne metastaseerumine maovähi taaspuhkemise kõige olulisem riskitegur. Kirurgilise raviga seotud näitajad olid tihti tugevasti mõjutatud kasvaja patoloogilis-anatoomilisest iseloomust. Nii oli näiteks gastrektoomia sagedamini tehtud infiltratiivse ja lümfogeenselt ulatuslikult metastaseerunud kasvaja korral. Ka R3-tüüpi laiendatud lümfadenektoomia oli enamasti sooritatud koos gastrektoomiaga ja seotud ulatuslikuma kasvaja või selle mitteantraalse lokalisatsiooniga.

Töö tulemuste põhjal võib väita, et kirurgide seas vaidlusi põhjustanud kombineeritud ja laiendatud operatsioonide vajalikkus maovähi radikaalses kirurgilises ravis leidis kinnitust. Gastrektoomia või distaalne subtotaalne maoresektsioon koos kasvajast haaratud naaberelundite resektsiooni ja lümfisõlmede laiendatud eemaldamisega peaks olema maovähi radikaalse kirurgilise ravi valikmeetodiks kõikidel kaugmetastaasideta haigusjuhtudel. Mao naaberelundite eemaldamine on õigustatud ka lümfadenektoomia parema teostamise eesmärgil. Laiendatud lümfadenektoomia peaks alati haarama vähemalt teist lümfogeense metastaseerumise taset, metastaaside esinemisel lümfisõlmedes tuleks lisaks eemaldada vähemalt ühe kahjustamata taseme sõlmestik.

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PUBLICATIONS

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FACTORS INFLUENCING SURVIVAL OF PATIENTS AFTER RADICAL SURGERY FOR GASTRIC CANCER

A regional study of 406 patients over a 10-year period

ANDRUS ARAK and KARL KULL

The present retrospective report presents a review of prognostic factors influencing the survival of 406 gastric cancer patients radically operated on in the Tartu Oncology Hospital, Estonia in 1978–1987. All patients underwent total (n = 170) or subtotal (n = 236) gastrectomies with extensive lymphadenectomy (260 R2- and 146 R3-resections) according to the General Rules for the Gastric Cancer Study in Surgery and Pathology established by the Japanese Research Society for Gastric Cancer, introduced in our hospital at the end of the 1970s and now used as the unavoidable procedure for curative gastric cancer surgery. The 30-day postoperative mortality was 5.9% and the overall 5-year survival 46.1%. The male : female ratio was 0.95 and the mean age 62.4 years. Only 7.6% of all our patients operated on had early gastric cancer with a 5-year survival of 80.7% whereas 76.8% had T3–T4 tumours with a 5-year survival of 41.0%. Lymph node involvement was found in 44.6% of the patients. Independent favourable prognostic factors were (the 5-year survivals are presented within parentheses): limited (N0–N1) lymph node involvement (56.4 vs. 22.6%), pT 1–2 stage (62.8 vs. 41.0%), papillary, tubular or poorly differentiated histological pattern (51.9 vs. 33.1%), subtotal gastrectomy (55.9 vs. 32.4%) and age below 70 years (51.9 vs. 35.2%). Sex of patients, Borrmann type, size and site of tumour were not statistically associated with prognosis at multivariate analysis. Our results also suggested that besides predetermined prognostic factors, the surgical policy had a great impact on the prognosis of gastric cancer patients. We conclude that gastrectomy with combined resections of neighbouring organs directly invaded and with extensive lymphadenectomy at least up to the second node group might be the procedure of choice for advanced gastric cancer.

Marked variability of the gastric cancer incidence is observed as well as a general tendency to decrease. In Estonia this decline has been less expressed than in most of the neighbouring North-European countries (1–4). The morbidity rate in our country has changed from 53.1 in males and from 39.4 in females per 100 000 in the 1970s to 41.9 in males and 32.0 in females in the 1980s (5, 6). Most cases of gastric cancer were detected in advanced stages, and only very rare cases were operated in early stages. It is thus essential to analyse the results of gastric cancer treatment and improve the results of therapy.

The high survival rates in Japan are attributed to a successful screening programme for the detection of early gastric cancer, better staging and more aggressive surgical treatment with extended lymphadenectomy (7). Extended lymph node dissection (so-called R2 and R3 resections) became standard treatment in Japan for all cases of advanced gastric cancer in the middle of the 1970s and most of the Japanese authors have pointed out the relationship between extensive lymph node dissection and better cure

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results (8–11). In the opinion of many authors adjuvant chemotherapy has offered no significant benefit in curative treatment of gastric cancer (12–14).

In Europe, extensive screening programs have not been established and the therapeutic results can be improved only by using extensive surgical techniques. Thanks to the good results shown in Japanese studies the practice of extended lymphadenectomy has gained increased acceptance in many European hospitals in recent years (1, 16, 17).

In our hospital the principles of extended lymphadenectomy were introduced at the end of the 1970s and we consider this procedure necessary in curative gastric cancer surgery. In the present retrospective report we have analysed the influence of different prognostic factors on the survival of gastric cancer patients with reference to the effectiveness of extensive surgical procedures.

Material and Methods

Among 690 patients with primary gastric cancer (with the exception of stomach stump cancer), treated surgically at the Department of Oncosurgery, Tartu Hospital of Oncology, Estonia during the 10-year period from 1978 to 1987, 406 (58.8%) underwent curative resection (18) with extended (R2 or R3) lymphadenectomy. The following cases were excluded from the present study: patients who underwent bypass procedures or palliative resections due to distant metastases or technical inoperability; those who underwent gastrectomies with only group 1 lymph node dissection (R1 lymphadenectomy) because of high operative risk, i.e. non-curative procedures in our conception; and some of those who underwent R4 lymphadenectomy (i.e. dissection of N4, mainly the para-aortal lymph nodes) with very high postoperative mortality or early recurrence of malignancy. All the clinico-pathological data were collected from case histories and from the database of the Estonian Cancer Registry.

Depth of invasion was classified as pT1 (tumour confined to mucosa and submucosa), pT2 (invasion of proper muscle layer and subserosa), pT3 (invasion into serosa) and pT4 (invasion of contiguous structures) according to the UICC rules (19). Advanced gastric cancer was defined as "invasion or deeper invasion of the tumour into muscularis propria by histopathological examination" (18). Tumour location was divided into upper, middle and lower third or total involvement of the stomach. Histology was classified as papillary and well or moderately differentiated tubular adenocarcinoma, interpreted as the intestinal type, and poorly differentiated adenocarcinoma, signet-ring cell or mucinous tumours, interpreted as the diffuse type, and undifferentiated carcinomas (18). The macroscopical types of tumour were classified according to Borrmann's classification as type 1—polypoid, type 2—ulcerated, type 3—ulcerated with partially diffuse infiltrating border, and type 4—diffusely invading tumour. Lymph nodes from different anatomical positions (lymph node stations 1–16) were divided into 4 N-groups (N1, N2, N3 and N4) according to the location of the primary tumour (18). In each case only the most distant lymph node station affected is mentioned.

The operative procedures were performed according to the recommendations of Japanese surgeons (8, 9, 18). Operation with curative intention was defined as "removal of all macroscopic cancer i.e., primary tumour with margins histologically free of cancer and all involved lymph nodes" (18). The required cancer-free distance at the proximal margin was more than 5 cm in circumscribed tumours and more than 8 cm in infiltrative tumours. Total gastrectomy was regarded as indicated when the proximal distance from the cardia was less than required or in Borrmann types 3 and 4 (8). Extended lymph node dissection was carried out according to the recommendations of the Japanese Research Society for Gastric Cancer (18). Dissection, called R2 lymphadenectomy, always included the perigastric nodes, excluding the left cardial nodes in distal gastrectomy and nodes located along the left gastric, common hepatic, splenic and coeliac arteries. In cases of non-antral location the nodes in the splenic hilum were also removed. The nodes of group 3 (R3 lymphadenectomy) from the hepatoduodenal ligament, behind the pancreatic head and the root of mesenterium were dissected in cases of palpable changes in the perigastric lymph nodes. If needed, frozen sections were examined before making decisions about the extent of lymphadenectomy. In cases of lymph node metastases, the aim was to obtain a margin of at least one uninvolved group of lymph nodes distal to the most peripherally involved group. The lymph nodes were always removed en bloc with the stomach and surrounding fatty tissue.

The statistical data analysis was made in the SPSS system, using uni- and multivariate (Cox regression) analyses of variance, the significances were calculated by the χ^2-method and Student's t-tests.

Results

The 30-day postoperative mortality for all radically operated patients was 5.9 (24 of 406); it was highest for R3 lymphadenectomy (11.1%), followed by total gastrectomy (10.6%) and proximal subtotal gastrectomy (10.0%), and was relatively low for R2 lymphadenectomy (3.1%) and for distal subtotal gastrectomy (2.2%). Table 1 shows the distribution of the prognostic factors and the 5-year survival rates for the patients who underwent curative surgery and Table 2 presents the results of the univariate analysis of the influence of these factors on survival. Univariate analysis showed as favourable factors age below 70 years, tumour location in the lower or middle part of the stomach, Borrmann I–II type, tumour size less than 4 cm, intestinal histological type, pT 1–2 stage, limited (N0–N1)

Table 1

5-year survival rates in relation to different prognostic factors

Prognostic factor	Patients		5-year survival	
	n	(%)	n	(%)
Sex				
Male	198	48.8	93	46.9
Female	208	51.2	94	45.2
Age, years				
30–39	7	1.7	5	71.4
40–49	49	12.2	22	44.9
50–59	106	26.1	59	55.7
60–69	119	29.3	57	47.9
70–79	115	28.3	42	36.5
>79	10	2.5	2	20.0
Location				
Antrum	200	49.3	103	51.5
Corpus	140	34.5	67	47.9
Cardia	42	10.3	12	28.6
Total	24	5.9	5	20.8
Borrmann type				
I	17	4.2	13	76.5
II	176	43.3	101	57.4
III	105	25.9	40	38.1
IV	108	26.6	33	30.6
Tumour diameter (cm)				
<4	57	14.0	41	71.9
4–7	192	47.3	85	44.3
8–12	123	30.3	53	43.1
>12	34	8.4	8	23.5
Histologic type				
Papillary adenocarcinoma	7	1.7	4	57.1
Tubular adenocarcinoma				
well differentiated	52	12.8	33	63.5
moderately differ.	112	27.6	57	50.9
Poorly differentiated adenocarcinoma	108	26.6	51	47.2
Mucinous adenocarcinoma	23	5.7	7	30.4
Signet ring cell carcinoma	30	7.4	11	36.7
Undifferentiated carcinoma	74	18.2	24	32.4
pT category				
pT1	31	7.6	25	80.7
pT2	63	15.5	34	54.0
pT3	218	53.7	96	44.0
pT4	94	23.2	32	34.0
pN category				
pN0	225	55.4	135	60.0
pN1	57	14.0	24	42.1
pN2	99	24.4	25	25.3
pN3	25	6.2	3	12.0
Gastrectomy				
Distal subtotal	226	55.7	127	56.2
Proximal subtotal	10	2.5	5	50.0
Total	170	41.8	55	32.4
Lymph node removal				
R2	260	64.0	137	52.7
R3	146	36.0	50	34.3
Extent of lymphadenectomy relative to nodal stage (R minus N)				
0	81	20.0	19	23.5
1	77	19.0	24	31.2
2	195	48.0	115	59.0
3	53	13.0	29	54.7

Table 2

Univariate analysis of prognostic factors influencing the 5-year survival of gastric cancer patients

Prognostic factor	Favourable (5-year survival)	Unfavourable (5-year survival)	p-value
Sex			NS[1]
Age	< 70 (51.9%)	> 70 (35.2%)	< 0.01
T	1–2 (67.8%)	3–4 (41.0%)	< 0.0001
N	0–1 (56.4%)	2–3 (22.6%)	< 0.00001
Histologic type	intestinal (55.0%)	diffuse (39.6%)	< 0.01
Borrmann type	I–II (59.1%)	III–IV (34.3%)	< 0.0001
Size of tumour	< 4 cm (71.9%)	≥ 4 cm (41.8%)	< 0.0001
Site of tumour	antrum and corpus (50.0%)	cardia and total (25.8%)	< 0.0001
Gastrectomy	subtotal (55.0%)	total (32.4%)	< 0.00001
Lymphadenectomy	R2 (52.7%)	R3 (34.3%)	< 0.00001
R minus N[2]	2–3 (58.1%)	0–1 (27.2%)	< 0.00001

[1] Not significant, [2] Extent of lymphadenectomy relative to nodal stage

lymph node involvement, subtotal gastrectomy, R2 versus R3 lymphadenectomy and an extent of lymphadenectomy more than one N-group from the involved lymph nodes. The influence of age of patient at operation, tumour sites, and different histological types were statistically less marked than other factors. The year of operation and the sex of patients did not significantly influence survival. The overall 5-year survival was 46.1% including the 30-day postoperative mortality. The male:female ratio was 0.95 (198:208) and the mean age was 62.4 years (range 31–80 years). We observed a decreased survival with increasing age of the patients at time of the operation. Of our patients 49.3% had cancer with antral location and only 10.3% with cardial location. During the observed 10-year period we did not notice significant changes in the locational distribution of tumours. The survival rates were nearly two times higher in the cases with antral or middle location than in those with cardial location or total involvement of the stomach. The ratio of the circumscribed and the infiltrative macroscopic types of tumours according to the Borrmann classification was 1:1 and the difference of the 5-year survival rates between these two groups was significant. The 5-year survival rates diminished with increasing tumour size. Significantly different survival rates were found only between tumours smaller than 4 cm and larger ones. The mean diameter of the removed tumours was 6.2 cm and ranged from 1 to 23 cm.

The most common histologic types were moderately differentiated tubular adenocarcinoma (27.6%) and poorly differentiated adenocarcinoma (26.6%). The survival rates were noticeably higher in cases of papillary and well or moderately differentiated adenocarcinoma. The 5-year survival rate was also relatively high (47.2%) in cases of poorly differentiated adenocarcinoma that one might suspect to have poor prognosis. The 5-year survival rate was 30.4–36.7% for patients with the cancers of mucinous, signet-ring cell type or undifferentiated structure.

Only 7.6% of all our patients operated on had early (T1) gastric cancer with a 5-year survival rate of 80.7% whereas 76.8% had T3–T4 tumours with a 5-year survival of 41.0%. Lymph node involvement was found in 44.6% of the patients and in 31% of the node-positive cases it extended to N1-nodes, in 54.7% to N2-nodes and in 13.8% to N3-nodes. The 5-year survival rates differed much depending on the presence of lymph node metastases and were strongly correlated with the extent of the nodal involvement.

In this material 226 distal subtotal, 170 total and 10 proximal subtotal gastrectomies were performed. Neighbouring organs were resected in 176 cases (42.9%), most frequently the spleen (141 cases) and the distal part of the pancreas (28 cases). In 64.0% of the cases the patients underwent dissection of N1 and N2 nodes (R2-resection) and in 36.0% so-called R3-resections. The 5-year survival rate 52.7% for R2-resections and 34.3% for R3-resections. Comparing the lymphadenectomies with different extension as to the extent of lymph node involvement (R minus N), extensive lymphadenectomy had a favourable effect only when it encompassed more than one uninvolved group of lymph nodes. The 5-year survival was 27.2% when R minus N was equal to 0 or 1 and 58.1% when it was equal to 2 or 3.

In the multivariate analysis using Cox's regression model (Table 3), all factors tested by the univariate analysis were used. This analysis identified 5 prognostic variables that significantly influenced the risk of death. Among these, lymph node involvement was the most important independent prognostic factor, followed by extent of gastrectomy, depth of invasion, histological type of cancer and age of patients.

Table 4 shows the relationship between the 5-year survival rate and the presence of lymph node metastases and the level of intramural cancer invasion. In general, the 5-year survival rate correlated well with both the extent of

Table 3

Results of the Cox regression multivariate analysis of prognostic factors after curative surgery

Variable	Relative risk of death (95% confidence interval)	p-value to remove
Nodal involvement		0.0000
N0	1.0	
N1	1.57 (1.04–2.37)	
N2	2.48 (1.81–3.41)	
N3	3.98 (2.45–6.48)	
Extent of gastrectomy		0.0003
Subtotal	1.0	
Total	1.68 (1.27–2.23)	
Depth of invasion		0.0098
T1	1.0	
T2	2.04 (0.84–4.96)	
T3	2.27 (0.99–5.23)	
T4	3.24 (1.38–7.62)	
Histologic type		0.017
Papillary or tubular	1.0	
Poorly differentiated	1.01 (0.70–1.43)	
Others[1]	1.51 (1.09–2.09)	
Age, years		0.017
< 70	1.0	
> 69	1.42 (1.07–1.88)	
Did not significantly improve model		p-value to enter
Borrmann type		0.11
Location		0.24
Size		0.52
Extent of lymphadenectomy		0.059
R minus N factor		0.47
Sex		0.46

[1] Mucinous, signet-ring cell and undifferentiated carcinomas

Table 4

Incidence of cases with lymph node metastases and the 5-year survival rates in relation to pT stage (number of cases and 5-year survival rates)

	T1		T2		T3		T4		Total	
	n	5-yr survival	n	5-yr survival	n	5-yr survival	n	5-yr survival	n	5-yr survival
N0	28	82.1	37	64.9	106	56.6	54	51.9	225	60.0
N1	0		7	71.4	45	42.2	5	0.0	57	42.1
N2	3	66.7	10	30.0	57	28.1	29	13.8	99	25.3
N3	0		9	22.2	10	10.0	6	0.0	25	12.0
Total	31	80.7	63	54.0	218	44.0	94	34.0	406	46.1

lymph node metastases and the depth of tumour penetration. There was a significant difference of the 5-year survival rates between the node-positive and the node-negative groups, 28.7% and 60.0% respectively, and also between the early and the advanced cases of cancer, 80.7% and 43.2% respectively. The highest 5-year survival rate was found in patients with early gastric cancer without lymph node metastases (82.1%) and the lowest rate in patients with T3–T4 tumours with N3-positive nodes (6.3%). The extent of lymph node involvement showed a correlation with the T stage.

Discussion

A decline in operative mortality rates after radical gastric cancer surgery over the past 30 years has been demon-

strated throughout the world (20), but it is still regarded as unacceptably high by many practitioners. The overall 30-day postoperative mortality for our patients—5.9%—is higher than the one reported after comparable surgery in Japan, but it is equal to the rates published in non-Japanese series (2, 12, 15, 16, 21). The postoperative mortality was high after R3 lymphadenectomy and total gastrectomy (11.0% and 10.6% respectively). Although we achieved the higher radicality partly at the cost of a higher mortality, we do not consider these mortality rates as reasons to avoid extensive surgery, the more so as there are no effective alternative methods.

Differences in the incidence of early gastric cancer, in the extent of surgical resections and in the epidemiological factors are considered responsible for the variation in the survival rates of patients who have undergone curative surgical treatment of gastric carcinoma (4, 20, 22). In our study, however, multivariate analysis indicated that extent of lymphadenectomy (R2 or R3) by itself or relative to the stage of nodal involvement, as well as location, size and Borrmann type of tumour were not independent prognostic factors. This study included only patients in whom extensive (R2 or R3) lymphadenectomy was performed and therefore this factor could not influence the survival rates in the analysed cases. Size and Borrmann type of tumour had a strong correlation with prognosis. However, since these factors are closely related to depth of invasion and lymph node metastases, they had no independent prognostic significance when the analysis was adjusted for other variables. Multivariate analysis identified five prognostic factors as independent and important predictors of recurrence and death of patient. Three of these important factors—depth of invasion, nodal involvement and histological pattern—are inherent pathologic features of the tumour at the time of operation.

After curative gastrectomy in patients without peritoneal dissemination or liver metastasis, gastric wall invasion and lymph node involvement have proved to be the most important predictors of tumour progression (9, 18). Lymph node involvement is often stated to be one of the main prognostic factors (16, 23, 24) and our data confirm this statement. The extent of lymph node involvement among our patients showed the dependence on the T stage. Significant differences existed in survival rates relative to the nodal status. Despite the extensive lympha-denectomy used in all cases, the cure results in N3 positive cases were quite modest. However, the frequency of metastases in N2 and N3 nodes determined the necessity of extensive node dissection. In the present study the R2-lymphadenectomy had a significantly more favourable effect on the prognosis than R3-lymphadenectomy by the univariate but not by multivariate analysis. This result can be explained by the fact that R2-lymphadenectomy was more frequently associated with subtotal gastrectomies and limited (N0–N1) lymph node involvement (78.5% of the R2-cases), while most R3-lymphadenectomies were performed in combination with total gastrectomy and only 53.4% of these cases were associated with limited nodal involvement. The concept that lymphadenectomy is bene-ficial only when it widely encompasses the disease is not new (12). The present study suggested that extensive lymph node dissection (R2 or R3) offered more benefit to patients with no or limited (N1) nodal disease and that the distal distance of lymphadenectomy to the metastatic nodes was important.

We have attempted to determine the extent of nodal disease before gastrectomy by frozen-section examination of macroscopically suspicious nodes around the stomach. However, the postoperative histological examination of the removed lymph nodes showed that incidental biopsies during the operation cannot be relied on because of large number of false-negative and false-positive results. The histological examination of lymph nodes during the observed period implied only one-step sectioning of enlarged nodes and therefore some micrometastases might have remained undetected. At present all removed nodes undergo microscopical examination and the three-step-sectioning method has been introduced to make the data concerning lymphogenic spread more precise.

Serosal invasion is considered to be a predictor of poor prognosis for gastric cancer involvement (2, 22). From the results of the present study we may conclude that a proper muscular layer (pT2) is associated with a high incidence of lymph node metastases and the survival rates in these cases come closer to the rates for T3 than for T1 cases. Therefore we agree with the Japanese surgeons and consider the pT2-tumours to be advanced. Patients with serosal invasion (pT3) had a relatively favourable prognosis, especially when there were no lymph node metastases—the 5-year survival rate for those patients was 56.6%. Tumours with invasion of contiguous structures (pT4) had also good survival (34.0% at 5-years) particularly cases without nodal involvement. Therefore we think that combined resection of neighbouring organs directly invaded by gastric cancer is an effective method. We do not know exactly how splenectomy influences the postoperative course. Most splenectomies were associated with total gastrectomies and R3-lymphadenectomies with a high postoperative morbidity and low survival rates because of the advanced carcinomas.

Multivariate analysis showed that the histological type of cancer was an independent and important prognostic factor. A high frequency of the intestinal type is connected with a high-risk population and a higher survival rate (23). In our series the intestinal types : diffuses types ratio was 1.06 (171 : 161) which is comparable to that in most reports from high-risk areas (4, 9, 15, 16). The frequency of cases with signet-cell carcinoma was relatively low in our series (7.4%) compared to other series reported (8, 16, 22). In 68.7% of all cases the tumours had histological patterns

(papillary, tubular or poorly differentiated adenocarcinoma) with higher 5-year survival rates than the overall rate.

Contrary to most reports (7, 8, 22, 26) we found carcinomas in the upper third of the stomach only in 10.3% of our cases. Proximal tumours have penetrated into the serosa and have lymph node metastases more often than tumours in the distal stomach (22, 26). For early diagnosis of cancer of the upper third of the stomach there is a special need for screening programs as asymptomatic course of the disease is common. The traumatic thoracoabdominal approach with combined gastrectomy in the treatment of cardial tumours also contributes to the high frequency of inoperable cases, particularly in elderly patients who frequently suffer from concomitant diseases. This also accounts for the low number of operable cardial cancer. The overwhelming majority of tumours in our series were located in the lower (49.3%) and middle (34.5%) part of the stomach, where it is easier to guarantee radicality of resection. The survival rate in cases of non-cardial carcinoma was in our series twice as high compared to cases with cardiac location or total involvement of the stomach. Although the tumour location was a prognostic indicator in the univariate analysis, it was not a significant factor in the multivariate analysis because of the close connection with other parameters, perhaps mainly the extent of gastrectomy. We still think that distribution of both tumour locations and histological types may be closly linked to the relatively good survival results in our study. In addition to the predetermined prognostic factors, the surgical strategy probably also had an impact on the prognosis. Of the three surgical treatment factors found to be prognostically significant by univariate analysis, only the type of gastrectomy remained as an important prognostic indicator at the Cox analysis. Total gastrectomy was associated with a much higher risk of death than subtotal gastrectomy (5-year survival 34.4% vs. 49.9%). This large difference is probably mainly explained by various tumour parameters, as Borrmann type of growth, and size and invasion of the primary tumour. We performed total gastrectomy mainly in cases with infiltrative types and deep invasion while subtotal gastrectomy was peferred in limited tumours. In our study the extent of lymph node involvement also correlated significantly with the depth of tumour invasion. Borrmann type and tumour size. However, it did not correlate with the histologic type or the location of the cancer. The small number of proximal subtotal gastrectomies – 10 – (2.5% of the cases) can be accounted for by the fact that this operation in principle was performed only in cases with small circumscribed tumours and the incidence of such tumours in the cardial region was very low, partly because of diagnostic problems.

The high 5-year survival rate for patients in the 30–39-year group (71.4%) after extensive radical surgery requires a special comment. Because of the more aggressive course of the disease in young people, the number of curatively operated patients in this age group was relatively low (1.7%) and the overall prognosis was worse than in other age groups. On the other hand, the results suggest that it is the young patients who benefit most from extensive surgery. 30.8% of our patients were over 70 years old. We found a rather low 5-year survival rate in the old (35.2% in patients > 70 years) and the very old (20% in patients > 80 years) age groups. Recurrent gastric cancer is probably the dominating official cause of death among elderly patients operated on for gastric cancer. However, too few autopsies are made in these patient groups and the real cause of death may be other than gastric cancer. Aggressive surgery with extensive lymphadenectomy does not always seem to contribute to a favourable prognosis in elderly patients, who usually have concomitant systemic cardiovascular and respiratory disorders and who are therefore at high risk for postoperative complications.

The male–female rate of gastric cancer patients in Estonia is 1.35, while in most reports it is said to be 1.5 or more (3, 8, 9, 10, 16, 22). The male–female ratio in the radically operated cases was 0.95 (198:208). That means that there were relatively fewer male patients suitable for radical surgery as males tend to come less for their health and turn later to doctors than females.

To conclude, the present study showed that the prognosis of gastric cancer patients depended on three pathologic features of tumour: lymph node metastasis, depth of invasion and histologic type. Our results demonstrate rather high 5-year survival rates, in some relatively advanced tumour groups (T2N3, T3N2, T4N0). One possible explanation for this outcome may be the relatively well functioning network of specialized oncological care in Estonia, where most gastric cancer patients are operated on by surgical oncologists with similar concept of operative policy. We think that combined en bloc resection of neighbouring organs directly invaded by gastric cancer is an effective treatment method. We would like to emphasize that curative gastric resection should be regularly combined with extensive lymphadenectomy up to the second lymph node group when no lymph node involvement is found. When there are clear macroscopic changes in the perigastric nodes, R3-lymphadenectomy is indicated. When metastases in non-perigastric nodes are found on the frozen-sections examination before gastrectomy, the lymph node dissection should ideally have a margin of at least one uninvolved group of lymph nodes distal to the most peripheral involved group of node stations, although it does not always gaurantee a favourable prognosis. In our patients the muscularis propria layer or deeper invasion was associated with a high incidence of lymph node metastases and low survival rates. Therefore we favour extensive lymph node dissection in all cases of advanced cancers of the stomach. Aggressive surgery with extensive lymphadenectomy can safely be performed in

young patients, whereas in elderly patients with concomitant systemic disorders this approach must be used more selectively.

The relatively high 5-year survival rates preseneted in our study may, at least partly, be due to the high frequency of intestinal histological types and lower or middle location of the tumours in the stomach. The incidence of early gastric cancer among radically operated patients in Estonia is extremely low. We are of the opinion that a screening program for early detection of gastric cancer should be started. At present a decrease in the mortality of the gastric cancer can be achieved only by extensive surgery.

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Correlation of lymph node metastases with other prognostic factors of curative gastric cancer

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Correlation of lymph node metastases with other prognostic factors of curative gastric cancer

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SUMMARY

This retrospective analysis of data about 361 patients with gastric cancer, who underwent curative surgery with extensive lymphadenectomy from 1978 to 1986 at the Hospital of Oncology, Tartu, Estonia, was performed to define the prognostic factors for genesis of the lymph node metastases. The nodal involvement was found in 46.3 % of cases. The overall 5-year survival rate was 48.5 %. We observed the decreasing survival rates associated with increase of the extent of nodal involvement. According to univariate analysis the lymph node metastases of gastric cancer occured more frequently in elderly patients, in cases of infiltrative type of primary tumor, muscularis propria or deeper invasion and when tumor size was more than 4 cm. Multiple regression analysis revealed the Borrmann type, age of patients and the extent of lymph node dissection as statistically indipendent prognostic factors.

INTRODUCTION

The extent of lymph node metastases has previously been shown to be one of the most important prognostic factors in gastric cancer without distant metastases and the presence of lymph node metastases adversely affects the cure rate (1,2,3,4). Unfortunately the pattern of lymphatic spread is reported to be unpredictable in many cases and evaluation of nodes by palpation is believed to be unreliable (5). On the other hand there are some expected prognostic factors for lymph node metastasis of gastric cancer (larger tumor size, deeper tumor invasion, diffuse histologic pattern, young age of patients) reported in the

literature (5,6,7). This retrospective study was performed to evaluate the incidence of lymph node metastases in gastric cancer and to assess the influence of other clinocopathological variables on nodal involvement.

PATIENTS AND METHODS

For this retrospective study, we used data on 361 patients who underwent curative surgery for primary gastric cancer at the Tartu Hospital of Oncology, Tartu, Estonia from 1978 through 1986. All the data were collected from case histories and from the database of the Estonian Cancer Registry. Macroscopic and microscopic evaluations were made according to the Japanese General Rules for the Gastric Cancer Study (8). There were 174 men and 187 women in our study. The mean age was 62.3, ranged from 31 to 85.
134 (37.1%) total and 227 (62.9%) subtotal gastrectomies were performed. In all cases the extensive lymph node dissection was used: R2 lymphadenectomy in 239 (66.2 %) and R3 lymphadenectomy in 122 (33.8 %) cases. When the palpable changes in lymph nodes occured, the aim of the dissection was to have a margin of one uninvolved group of lymph nodes distal to the most peripheral involved group of node station.
The univariate analysis of variance and multiple regression analysis by the "Statgraphics" program was used to determine the prognostic variables.

RESULTS AND CONCLUSIONS

In the present study the nodal involvement was found in 167 (46.3 %) patients. Metastases limited with perigastric (N1) nodes presented in 51 (14.1 %) patients, the involvement up to N2 nodes was found in 89 (24.7 %) and up to N3 nodes in 27 (7.5 %) cases. Lymph node involvement was diagnosed in 65.4 % of patients who survived less than one year, in 57.8 % of patients who survived less than three years and in 26.9 % of cases with five year survival time ($p<0.00001$). The overall 5-year survival rate was 48.5 %. 5-year survival rate was 65.5 % for patients without lymph node metastases, 43.1 % for patients with metastases in perigastric nodes, 24.7 % for patients with metastases in N2 nodes and 11.1 % for patients with metastases in N3 nodes. The survival rates for both node positive and node negative cases are comparable with those reported in literature (2,3,9,10).
Table 1 shows the incidence of node negative and node positive cases for other clinical and pathological variables according to the univariate analysis. Lymph node metastases occured more frequently in cases of muscularis propria or deeper invasion, tumor size more than 4 cm and infiltrative macroscopic type. The metastasizing potential of gastric cancer is reported to be more active in the young (7), but we found the node positive cases more frequently in elderly (over 70 year of age) people than in younger ones. Multiple regression analysis indicated that the age of patients, Borrmann type and the extent of lymph node dissection were statistically the indipendent prognostic factors (Table 2). Although the Borrmann type is closely related to the degree of gastric wall invasion and tumor size, it was the only independent pathologic prognostic factor associated with lymph node status. In our study the univariate analysis shows the significantly different distribution of node negative and node positive cases only when the T1 and T>1 tumors were compared. So we may conclude that the muscularis propria or deeper invasion of primary tumor is associated with higher frequency of nodal involvement and the extensive lymphadenectomy is advisable

Table 1. The distribution of cases without lymph node metastases and with lymph node metastasis for different clinicopathological variables

Variable	No. of all cases	Without lymph node metastasis (%)	With lymph node metastasis (%)	p-value
Age				<0.001
<50	50	58.0	42.0	
50-59	94	63.4	36.6	
60-69	104	57.0	43.0	
70-79	103	41.7	58.3	
>79	10	40.0	60.0	
Sex				NS
Men	174	53.4	46.6	
Women	187	55.1	44.9	
T stage				<0.001
T1	29	89.7	10.3	
T2	54	53.7	46.3	
T3	190	47.4	52.6	
T4	88	58.0	42.0	
Borrmann type				<0.005
I-II	177	61.1	38.9	
III-IV	184	46.5	53.5	
Location				NS
lower third	187	54.0	46.0	
middle third	116	60.3	39.7	
upper third	15	40.5	59.5	
total	10	47.6	52.4	
Histologic type				NS
differentiated	152	57.9	42.1	
undifferentiated	209	51.7	48.3	
Size				<0.005
< 4 cm	54	85.2	14.8	
≥ 4 cm	307	48.9	51.1	
Gastrectomy				NS
total	134	49.3	50.7	
subtotal	227	57.3	42.7	
Lymphadenectomy				<0.00001
R2	239	61.9	38.1	
R3	122	41.3	58.7	

in all these cases to prevent local recurrence. The incidence of lymph node metastases in early gastric cancer is commonly reported as less than 15 % (11,12). In present study there was 10.3 % of early tumors with nodal involvement.

The distribution of lymph node negative and positive cases differed significantly in two groups of lymphadenectomy but not in patients who undewent gastrectomy with different extension. There was 38.1 % of node positive cases in the group of R2-lymphadenectomy and 58.7 % in the group of R3-lymphadenectomy. Survival analysis showed the better 5-year survival rate after R2-lymphadenectomy (59.6

Table 2. Multiple regression analysis of variables associated with lymph node metastases

Variable	Regression coefficient	Standard error	P-value
Age	0.01	0.01	0.0399
Borrmann type	0.11	0.06	0.0023
Lymphadenectomy	1.04	0.13	0.0000

%) than after R3-dissection (30.8 %). These results likely are reflective of the extent of disease: most of the R3-lymphadenectomies were performed in cases of extended nodal disease and were associated with more advanced primary tumors. Conclusions. The extensive (R2 or R3) lymph node dissection offers more benefit to the patients with either no or limited (N1) nodal disease. When tumors are large, invasive, and have infiltrative type of growth, extensive lymph node dissection is essential. In the absence of palpable abnormalities in lymph nodes, the cure results of gastric cancer can be improved by a wide prophylactic node dissection, particularly in the patients with elevated risk to lymph node metastases. In patients with all these risk factors close follow-up is necessary.

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III

Annales Chirurgiae et Gynecologiae (submitted for publication)

GASTRIC CANCER: SURGICAL MANAGEMENT AND PROGNOSIS

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Summary

The experience of the Department of Surgery of Oulu University Hospital, Finland in the treatment of 203 consecutive patients (129 men and 74 women, mean age 64.9 years) with primary gastric cancer during the 5-year period from 1983 to 1987 is reviewed.

196 (96.6 %) patients underwent surgery: radical gastrectomy with limited lymphadenectomy in 88 (43.3 %) cases, palliative gastric resections in 47 (23.2 %) cases and symptomatic bypass-procedures in 27 (13.3 %) cases. Postoperative complications occurred more frequently after total than after subtotal gastrectomy. Overall postoperative mortality was 9.2 %. The 5-year survival was 21.1 % for all patients and 45.5 % for curatively operated patients. Univariate analysis indicated that tumor size, location, gross appearance, degree of gastric wall invasion, presence of lymph node and/or distant metastases, and operative procedures were the significant prognostic factors of survival. In a Cox multivariate analysis only the T stage and presence of distant metastases independently affected survival.

Our results show that beside the early detection the standardization of surgical procedures (extent of gastrectomy and lymphadenectomy) as well as the substantial decrease of postoperative complications and mortality rates have importance in the improvement of the outcome of surgery for gastric cancer.

Introduction

Also the incidence of gastric cancer has markedly decreased during recent decades in Finland as in most industrialised countries, it still represents one of the leading causes of death from malignant disease. The population-based incidence of gastric cancer in Finland in 1955 was 65.4 per 100 000 in the male population and 37.7 per 100 000 in the female population, and in 1985 it was 21.4 and 11.0 per 100 000 respectively (11).

The disappointingly low survival rates even after potentially curative in the Western world are attributed to the late diagnosis and less aggressive surgery compered with approach used in Japan (7, 13, 14, 21). Only half the patients present with resectable tumor, and less than half of these are suitable for curative resection (3). Besides, the treatment of gastric carcinoma by general surgeons have shown results considerably poorer than those reported by special referral centres and the proportion of the patients who underwent apparently curative resection have been low (15 %) (1, 15).

This analysis of our institutional experience was performed to evaluate the influence of clinicopathological factors and operative procedures on the prognosis of patients with gastric cancer in general surgical practice in Oulu, Finland.

Patients and Methods

The current study is based on all 203 consecutive patients with histologically proved primary gastric cancer treated at the Department of Surgery of Oulu University Hospital during the 5-year period from 1983 to 1987. All the clinicopathological data were collected from case histories. The data about survival come from the database of the Finnish Cancer Registry. There were 129 men and 74 women in our study with the male:female ratio of 1.74. The mean age was 64.9 and the median age 68, the age range was from 27 to 88.

The histopathologic TNM staging was determined according to the UICC 1987 year classification (6). Tumor location scale included the upper, middle and lower third or total location, involving more than two thirds of the stomach. Histologically, tumors were either of intestinal or diffuse type according to Lauren´s classification (10), or of mixed type, representing patterns of both types. All pathologic specimens were re-examined by the same pathologist (H.T.). Macroscopical Borrmann types were described as circumscribed (polypoid or ulcerated types) and infiltrative (ulcerated tumor with partially infiltrating border or diffusely infiltrating tumor).

Conventional resection performed for gastric cancer at Oulu University Hospital was either the total or subtotal removal of the stomach and perigastric lymph nodes - nodes along the lesser and greater curvature, paracardial and parapyloric nodes, and nodes along the left gastric artery, i.e. R1-

lymphadenectomy according to the Japanese General Rules for the Gastric Cancer Study (8). Roux-en-Y method was applied to reconstruct the alimentary tract. In this study the gastric resection was classified radical if the lymph node involvement was restricted to the perigastric (N1) nodes, no tumor was left following the surgery, and no microscopical invasion in the resection margins was found on the postsurgical histological examination. The minimal distance of the upper resection margin in radical cases was 5 cm, however in infiltrative cases total gastrectomy was always performed. Postoperative mortality was defined as the number of deaths within the 30 days after surgery.
All clinical, surgical and pathological data of the patients were stored in a personal computer and the statistical data analysis was performed with the SPSS program of univariate and multivariate Cox regression analysis, the significance level was calculated with the chi-square distrubution formula.

Results

No data about preoperative symptoms were available in seven case histories. The average duration of symptoms presence was 6.5 months. Abdominal pain, dyspepsia and weight loss were the most commonest presenting symptoms (Table 1). The initial diagnosis for one patient was gastric perforation. The laboratory analyses showed serum haemoglobin level lower than 120 g/l in 76 (37.4 %) and hypoproteinaemia (serum albumin level lower than 40 g/l) in 92 (45.3 %) patients.
The clinicopathological data of all the cases discussed are presented in Table 2. The lower third of the stomach appeared to be the most common location, invaded in 44.3 % of the cases, followed by the upper third (22.7 %), the middle third (21.1 %) and the total involvement (11.8 %). The distribution of macroscopic types of tumors showed the prevalence of infiltrative cases. The pathological examination found Lauren´s intestinal type in 50.2 %, diffuse type in 35.0 % and mixed type in 14.8 % % of the cases. The ratio of the intestinal type to the diffuse type was 1.43. T1 was found in 9.9 %, T2 in 16.8 %, T3 in 32.5 % and T4 in 39.4 % of the cases. The lymph nodes were involved in 49.3 % of the cases. In 12.3 % of the cases the extent of nodal involvement could not be retrospectively established. Distant metastases were diagnosed in 23.7 % of the patients.
196 (96.6 %) patients of 203 underwent surgery (Table 3). Radical gastrectomy was performed in 88 (43.3 %), palliative gastric resections in 47 (23.2 %) and bypass-procedures in 27 (13.3 %) cases. Lymphadenectomy up to the nodes along the left gastric artery was performed in all radical cases. In addition to the 91 splenectomies other neighbouring organs had to be resected in 16 cases (the distal part of pancreas in 6 cases, the abdominal part of oesophagus in 5 cases, mesocolon in 2 cases, liver in 2 cases and colon transversum in 1 case). Six patients with the postoperative histological examination showing microscopic

residual tumors at the resection margins made up the subgroup of the palliative surgery. Chemotherapy (5-FU alone or FAM-combination) was administered in 6 cases and radiotherapy (up to 40 Gy) in 8 cases, but only when relapse occurred.

Thirty two patients (16.3 %) had postoperative complications. General complications were recorded in 6 cases and surgical complications in 27 cases, anastomotic insufficiency (n=10), wound infection (n=5), intra-abdominal infection (n=4) and postoperative acute pancreatitis (n=4) were frequent. The complications occurred more frequently after total than after subtotal gastrectomy (Table 3). Overall postoperative mortality was 9.2 % (n=18), with 10.2 % (n=9) after the radical operations and 17.0 % (n=8) after the palliative operations (Table 3). Splenectomy, preoperative anaemia, hypoalbuminaemia or weight loss had no significant influence on the postoperative course of our patients.

Table 2 shows the clinical and pathological data of the 88 patients radically operated on and the 108 patients not radically operated on. Those two groups differed significantly in depth of invasion, nodal status, Borrmann type and tumor size. However, the groups did not differ significantly as to the age and sex of the patients.

The overall 5-year survival for all patients was 21.1 %. The mean survival time was 34.5 months after curative resections, 15.7 months after palliative resection, 5.0 months after bypass procedures, 5.8 months after explorative laparotomy and 3.0 months after conservative treatment. There were only four patients alive after a year from a non-resective operations. The total gastrectomy adversely influenced the 5-year survival rates of patients both in curative and in palliative cases (Table 3). The 5-year survival rates influenced by the clinicopathological variables are shown in Table 2. Univariate analysis indicated that tumor size, location, gross appearance, degree of gastric wall invasion, presence of lymph node and distant metastases, and radicality of operative procedures were the significant prognostic factors of survival. No significant relationship was found between the survival rates and the age or sex of patients, Lauren histopathological type or splenectomy performed with gastrectomy. In a Cox multivariate analysis of the eleven clinicopathological and treatment variables analysed by univariate analysis only T stage and presence of distant metastases independently affected survival (Table 4).

Discussion

The mean age of patients with new cases of gastric cancer registered in Finland in 1985 was 68.4 years for males and 72.2 years for females (11). In comparison our male patients were 4.0 and female patients 6.7 years younger. There was no significant differences in the 5-year survival rates relative to the

age and sex of patients. The elderly patients in our study tolerated operation well, as it has also been reported by other researchers (4, 19).

Although by univariate analysis all the pathologic features of gastric cancer excepted Lauren type did have significant influence on the survival rates, multivariate analysis using the Cox model identified only two variables - T stage and M stage - as independent predictors of survival. The study has again demonstrated that the depth of gastric wall invasion is the most important factor predicting survival.

Comparison of the curability and resectability rates in our study with those in other European hospitals revealed that our approach to gastric cancer therapy was justifiably aggressive (12, 15, 16, 22). Although only 3.4 % of the patient did not undergo surgery, in more than half of those who did, potentially curative resection was not feasible. Considering the 5-year survival rate in T1 (85.0 %) and T2 cases (50.0 %) our results seem to be satisfactory, however the results with T3 and T4 cases (5-year survival 12.1 % and 1.3 % respectively) leave much room for improvement. Moreover, the cases with a good prognosis represented a small proportion of all cases and therefore both the diagnosis and treatment of gastric cancer remains an important problem.

The prognosis for patients who had undergone total gastrectomy was worse compared with subtotally gastrectomized patients both in curative and in palliative cases (Table 3). However, it is not necessary caused by the type of operation but rather by the fact that the tumors were more advanced in these patients. On the other hand the surgical technique chosen significantly influences the complication and mortality rates. The high complication rates by palliative or curative total gastrectomy (28.6 % and 22.0 % respectively) and the high mortality rate after pallitive total gastrectomy (17.9 %) are matters of serious concern. Too much anastomotic leakages and infectious complications were associated with these procedures. Nevertheless we consider that the overall postoperative mortality rate of 9.2 % is acceptable as it compares favourably with figures of 7 to 26.9 % in other Western countries (1, 22).

Limited lymphadenectomy was routinely performed. Our results are easily comparable to those in contemporary Western hospitals where gastrectomy is performed without extended lymphadenectomy, but they are inferior to those in centres where extensive lymph node dissection is routinely practised (1, 2, 4, 5, 12, 15, 18, 20). In our study there were no lymph node metastases in the T1 cases, which correlates well with the high cure rate of those cases. The survival rates for limited node dissection in node positive cases, also low, are comparable with those reported in literature, but the 5-year survival in node negative cases (43.6 %) might be higher. The results confirm that for both the cases with and without nodal involvement more extensive lymphadenectomy might be instrumental in effecting a cure. Besides, extensive lymphadenectomy made in the absence of palpable abnormality may by of importance in

establishing N stages accurately and may results in a higher prevalence of patients with lymph node micrometastases. However, it is difficult to analyse the importance of lymph node dissection in this retrospective study.

Although palliative resection for gastric cancer is mainly indicated to improve the quality of the patients remaining life by reducing the danger of complications (17), it also offers a possibility of longer survival for patients who cannot undergo radical surgery. In our study 6.4 % of the patients were alive five years after palliative resection. We agree with D.Korenaga, et al., 1988 (9), who think that the resection palliative due to the presence of various incurable factors still seems preferable to laparotomy alone or gastrojejunostomy.

The effect of splenectomy on survival after resection for gastric cancer is not generally agreed upon (18). The results of our study indicate that splenectomy, performed with curative or palliative gastrectomy, did not significantly influence the postoperative complications, neither did not increase the survival rates as possible warrantor of more radical lymphadenectomy. The latter fact may be caused by the limited dissection in other nodal groups. So at present we have preferred to save the spleen by radical gastrectomies whenever possible.

Conclusions

For all patients with gastric cancer the T stage and presence of distant metastases were the most important factors predicting. Our results indicate that to decrease the complications rate, subtotal resection should be preferred in cases of circumscribed tumors with location in the distal or middle third, total gastrectomy should be reserved for infiltrative tumors. To evaluate the importance of lymphadenectomy with different extention the prospective randomized study should be initiated. Palliative resection is to be preferred to gastrojejunostomy for incurable cases as it results in a longer mean survival.

Table 1. Symptoms and findings at admission

Symptom	No. of cases	%
Pain	123	62.8
Dyspepsia	107	54.6
Weight loss	80	40.8
Bleeding	49	25.0
Vomiting	46	23.5
General dyscomfort	40	20.4
Palpable tumor	28	14.3
Dysphagia	17	8.7
Anorexia	11	5.6
Gastric perforation	1	0.5

Table 2. Association of clinicopathological variables with curability and 5-year survival

Variable	Cases No. (%)	Curative No. (%)	Non-curative No. (%)	p†	5-y. surv. (%)	p‡
Sex				NS*		NS
male	129 (63.5)	52 (59.1)	71 (65.7)		20.2	
female	74 (36.5)	36 (40.9)	37 (34.3)		23.0	
Age				NS		NS
< 70	116 (57.1)	56 (63.6)	57 (52.8)		25.0	
> 69	87 (42.9)	32 (36.4)	51 (47.2)		16.1	
T stage				<0.01		<0.01
T1	20 (9.9)	20 (22.7)	0		85.0	
T2	34 (16.8)	31 (35.3)	3 (.2.8)		50.0	
T3	66 (32.5)	37 (42.0)	29 (26.9)		12.1	
T4	80 (39.4)	0	76 (70.3)		1.3	
N stage				<0.01		<0.01
N0	78 (38.4)	67 (76.1)	11 (12.4)		43.6	
N1	32 (15.8)	21 (23.9)	11 (12.4)		21.9	
N2	68 (33.5)	0	68 (75.2)		2.9	
M stage				<0.01		<0.01
M0	153 (75.4)	88 (100.0)	64 (59.3)		28.1	
M1	48 (23.7)	0	44 (40.7)		0.0	
Location				NS		<0.05
Lower	90 (44.3)	40 (45.5)	49 (45.4)		25.6	
Middle	43 (21.1)	22 (25.0)	20 (18.5)		27.9	
Upper	46 (22.7)	22 (25.0)	20 (18.5)		17.4	
Total	24 (11.8)	4 (4.5)	19 (17.6)		0.0	
Borrmann				<0.01		<0.01
I-II	92 (45.3)	69 (78.4)	22 (20.4)		43.5	
III-IV	111 (54.7)	19 (21.6)	86 (79.6)		2.7	
Size				<0.01		<0.01
<4 cm	27 (13.3)	27 (30.7)	0		81.5	
4–7 cm	66 (32.5)	12 (13.6)	20 (42.6)		15.6	
>12 cm	10 (4.9)	2 (2.3)	8 (17.0)		0.0	
Lauren				NS		NS
Intestinal	102 (50.2)	52 (59.1)	50 (43.5)		24.5	
Diffuse	71 (35.0)	24 (27.3)	47 (40.9)		15.5	
Mixed	30 (14.8)	12 (13.6)	18 (15.6)		23.3	

(continued)

Variable	Cases No. (%)	Curative No. (%)	Non-curative No. (%)	p†	5-y. surv. (%)	p‡
Splenectomy				NS		NS
yes	91 (67.4)[a]	63 (71.6)	28 (59.6)		29.4	
no	44 (32.6)[a]	25 (28.4)	19 (40.4)		36.4	
Resection				—		<0.01
curative	88 (43.3)	88 (100.0)	—		45.5	
palliative	47 (23.2)	—	47 (43.5)		6.4	
no	68 (33.5)	—	61 (56.5)		0.0	

† - significance for curability; ‡ - significance for 5-year survival rates; * - not significant; [a] - % from all the resections

Table 3. 5-year survival, postoperative complications and mortality after different types of surgery.

type of operation	No. of cases	complications	postoperative mortality	5-year survival (%)
curative resection	88	14 (15.9 %)	9 (10.2 %)	45.5
total gastrectomy	59	13 (22.0 %)	6 (10.2 %)	39.0
subtotal gastrectomy	29	1 (3.4 %)	3 (10.3 %)	58.6
palliative resection	47	11 (23.4 %)	8 (17.0 %)	6.4
total gastrectomy	28	8 (28.6 %)	5 (17.9 %)	3.6
subtotal gastrectomy	19	3 (15.8 %)	3 (15.8 %)	10.5
bypass procedures	27	1 (3.7 %)	1 (3.7 %)	0.0
exploratory laparotomy	34	1 (2.9 %)	0 —	0.0

Table 4. Cox regression analysis of factors affecting survival

Variable	Relative risk of death	P-value to remote
T stage		0.0000
T1	1.0	
T2	4.73 (1.39-16.16)	
T3	12.37 (3.83-39.96)	
T4	16.16 (4.68-55.81)	
M stage		0.0065
M0	1.0	
M1	3.18 (1.51-6.70)	
Did not significantly improve	model:	P-value to enter
Age		0.3998
Sex		0.4173
Borrmann type		0.0561
N stage		0.1361
Tumor size		0.2511
Location		0.8123
Lauren type		0.8238
Curability		0.0931
Splenectomy		0.6996

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IV

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ÜLEVAATED

Laiendatud lümfadenektoomia maovähi kirurgilises ravis

Andrus Arak Karl Kull

maovähk, regionaalne metastaseerumine, laiendatud lümfadenektoomia

Mitme vähilokalisatsiooni puhul on edukas kemo- ja immunoteraapia, hormoon- ja kiiritusravi vähendanud ulatuslike kirurgiliste manipulatsioonide vajadust. Radikaalses maovähi ravis on need ainult täiendmeetoditeks, kuid ainsaks edu tagavaks raviviisiks on siiski jäänud kasvaja täielik eemaldamine. Epiteliaalsete pahaloomuliste kasvajate puhul on onkoloogiliste operatsioonide põhinõudeks haiguse algkolde laialdane ekstsisioon tervete kudede piires koos regionaalse lümfisoonte ja -sõlmede võrgustiku eemaldamisega ühtse blokina. Üldtunnustatud seisukoha järgi tuleb maovähi algkolle eemaldada piisavas kauguses kasvaja makroskoopilisest piirist ja kasvajarakkudest vaba resektsioonijoon on üks olulisi haigete prognoosi mõjutavaid faktoreid. Nii peetakse maovähi infiltratiivsete vormide korral radikaalseks operatsiooniks ainult gastrektoomiat, kuna antrumi eksofüütsete kasvajate ravis on õigustatud ka mao distaalne subtotaalne resektsioon (12, 29). Ka magu ümbritsevate lümfisõlmede eemaldamise vajaduses ollakse enamasti veendunud, kuid selle ulatuse osas lähevad arvamused tublisti lahku. Kuigi maovähki haigestumine kogu maailmas järjekindlalt väheneb, on ta kasvajatest tingitud surma põhjustest esimeste seas enamikus lääneriikides, kus seda haigust põdejate viie aasta elulemus püsib 5...10% piires (12). Radikaalselt opereeritute väljavaated on pisut paremad: neist elab üle 5 aasta Euroopas 35...40% ja Jaapanis 60...75%, varase maovähi opereerimisel on elulemus aga 100% lähedane (2, 9, 29, 31, 34). Tabelis 1 on näitena esitatud 100 maovähihaige elulemust käsitleva artikli ülevaade (2).

Tabel 1. Maovähihaigete radikaalne kirurgiline ravi Jaapanis ja teistes riikides

Uurimisandmed	Jaapan	Teised riigid	Kokku
Uuringuseeriaid	15	85	100
Haigeid kokku	19048	80738	99786
neist opereeritud (%)	99,8	74,1	79,0
Radikaalseid operatsioone (%)	58,6	17,8	25,6
viie aasta elulemus pärast radikaalseid operatsioone (%)	60,5	39,4	52,2

Jaapan on ainus riik, kus maovähisuremuse vähendamine on kiirem kui -haigestumuse vähenemine (12). Võimalikke bioloogilisi erinevusi Jaapanis ja Läänes esineva maovähi vahel on raske määratleda. Mõnel pool esitatud intestinaalse ja difuusse vormi esinemissageduse mõningane erinevus eri geograafilistes piirkondades ei mõjuta ravitulemusi nii olulisel määral, kui need tegelikult erinevad (22, 25). Samal ajal on aga täheldatud maovähipuhuse lümfisõlmede metastaatilise kahjustuse sarnasust Jaapanis ja Euroopa riikides (28).

Maovähi ravi tunduvalt paremad tulemused Jaapanis on tingitud ühelt poolt edukalt tehtavatest sõeluuringutest, mis on seal viimase 15 aastaga tõstnud varajase maovähi osatähtsuse 5%-lt peaaegu 50%-ni (23, 34), teiselt poolt aga ühtse metoodikaga laiendatud lümfadenektoomia järjekindlast kasutamisest rohkem kui 20 aasta vältel (20, 29).

Jaapanlased toovad olulise eelisena esile oma haigete suhteliselt noorema eluea

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ja väiksema kehakaalu. Kõhnadel ja «madala» kõhuõõnega haigetel on võimalik hea juurdepääs magu ümbritsevatele lümfiteedele; noorematel haigetel esineb harvem raskeid kaasnevaid elutähtsate elundite häireid. Kõik see võimaldab julgemini teha laiendatud operatsioone, mille puhul ka operatsioonijärgne letaalsus on minimaalne, mitte üle 2...3% (2, 29). Haigete suurema kehakaaluga kaasnev pikem operatsiooniaeg, keskmisest suurem verekaotus ja komplikatsioonide arv ning sagedam kaasnevate haiguste esinemine põhjustavad suurema suremuse pärast operatsiooni ja on põhjuseks, miks laiendatud lümfadenektoomia põhimõtted on läänemaailmas visad juurduma (5, 8, 10, 28). Suures operatsioonijärgses letaalsuses ei ole «süüdi» ainult haiged. On leitud, et ravitulemuste erinevus sõltub ka sellest, kas laiendatud lümfadenektoomia metoodika on omandatud omal käel või kogenud (Jaapani) kirurgide juhendamisel (8).

Ulatuslikul morfoloogilisel materjalil põhinev ja kõikides Jaapani kirurgiakeskustes ühesugustel põhimõtetel kasutatav lümfadenektoomia metoodika maovähi kirurgilises ravis on veenvalt tõestanud oma efektiivsust eemaldatud lümfisõlmede hulga suurenemise ja ravitulemuste paranemise omavahelise sõltuvuse kaudu (vt. tabel 2) (3, 34).

Tabel 2. Lümfisõlmede eemaldamise ja ravitulemuste paranemise seos

Lümfadenektoomiat iseloomustav näitaja	Ajavahemik 1961...1970	1971...1975	1976...1980	1981...1985
Lümfisõlmede arv preparaadis (keskmiselt)	29,7	31,1	33,8	37,9
Metastaasidega lümfisõlmi (%)	16,0	13,6	9,0	6,1
Lümfogeensete metastaasidega radikaalselt opereeritud haigete viie aasta elulemus (%)	35,2	42,1	49,6	–

Lümfisõlmede süsteemikindla eemaldamise aluseks on lümfivoolu iseärasuste tundmine ning metastaseerumise põhjalik ja ulatuslikul kliinilisel materjalil põhinev analüüs (29). Magu ümbritsevad lümfisõlmed on süsteemselt rühmitatud. Meie kliinilises praktikas kasutusel oleva TNM-süsteemi N-kategooria kõrval on teine enam kasutatav ja tunduvalt täpsem jaotus esitatud Jaapani Maovähi Uuringute Ühingu (*Japan Research Society of Gastric Cancer* — JRSGC) poolt (18). Selle järgi jaotatakse magu ümbritsevad lümfisõlmed 16 gruppi (vt. tabel 3, joonis 1), millest suur osa langeb kokku magu toitvate arteritega. Need grupid koondatakse nelja N-rühma vastavalt nende kaugusele kasvaja algkoldest ja sõltuvalt viimase lokalisatsioonist on grupi asukoht N-süsteemis erinev (vt. tabel 3).

Tabel 3. Maoümbruse lümfisõlmede rühmitus

Lümfisõlmede grupp	Kasvaja algkolde asukoht maos: antrum	korpus	kardia	totaalne
Parem parakardiaalne	N2	N1		
Vasak parakardiaalne	N3	N2	N1	
Väike maokõverik	N1			
Suur maokõverik	N1			
Suprapüloorne	N1		N2	N1
Infrapüloorne	N1		N2	N1
Gastrica sin. p/k	N2			
A. hepatica comm. p/k	N2			
Truncus coeliacus'e p/k	N2			
Põrnavärat	N3	N2		
A. lienalis'e p/k	N3	N2		
Hepatoduodenaalne	N3			
Retropankreaatiline	N3			
A. mesenterica sup. p/k	N3			
A. colica med. p/k	N4			
Paraaortaalne	N4			

Esitatud JRSGC-klassifikatsioonis peetakse kaugmetastaasideks N3-sõlmedest kaugemal paiknevaid (N4) lümfogeenseid metastaase, TNM-klassifikatsioonis aga on nendeks kõik intraabdominaalsed metastaasid, mis ei paikne perigastrilistes, *a. gastrica sinistra*, *a. hepatica communis*'e, *a. lienalis*'e või *truncus coeliacus*'e piirkonna lümfisõlmedes (13, 18). Seegi erinevus tundub olevat lümfadenektoomia ulatusse erineva suhtumise väljenduseks.

1...6. grupi lümfisõlmi nimetatakse perigastrilisteks ja nende kahjustus on otse-

ses sõltuvuses kasvaja lokalisatsioonist maos. Nii on 1. ja 2. grupi lümfisõlmedes metastaase vastavalt kuni 25%-l ja 10%-l haigetest, valdavalt kardiavähi korral, kuid ka kuni 10% mao antraalosa kasvajatest annab sinna metastaase. 3. grupi puhul olulist erinevust sõltuvalt lokalisatsioonist ei ole, siirdeid on kuni pooltel haigetest. 4. grupi kahjustust esineb 1/3-l haigetest, kardiavähi puhul üle kahe korra harvemini kui teiste lokalisatsioonide puhul. 5. ja 6. grupi lümfisõlmed on küll antrumivähi metastaseerumise eelispaigaks, vastavalt kuni 20%-l ja 50%-l juhtudest, kuid ka kuni 5% kardia- ja 15% korpusekasvajatest võivad sinna siirdeid anda.

7. grupi lümfisõlmede kahjustust esineb kuni 35%-l haigetest; nende metastaaside algkoldeks on peaaegu võrdväärselt kõik lokalisatsioonid; metastaase esineb seal 85%-l haigetest, kellel on metastaase väikese maokõveriku lümfisõlmedes, ja 7. grupi metastaasidega juhtudest omakorda on 43%-l siirdeid ka 9. grupi lümfisõlmedes. 8. grupi kahjustusi täheldatakse umbes 25%-l juhtudest, algkoldeks on 50%-l antrumi-, 35%-l korpuse- ja 15%-l kardiavähk. 9. grupi kahjustust esineb 20%-l haigetest, metastaaside algkoldeks võivad võrdselt olla kõik lokalisatsioonid.

10. ja 11. grupi lümfisõlmedes esinevad metastaasid 10...12%-l juhtudest, enamasti on need pärit võrdselt kas mao kardia- või korpuseosast, kuid ka 4...6% antrumivähkidest annab siia siirdeid. Metastaaside esinemine neis gruppides on prognostiliselt halb näitaja. 12. grupi lümfisõlmede kahjustust tuleb ette alla 10%-l juhtudest, algkoldeks enam kui 60%-l on antraalosa vähk; 8. grupi metastaaside korral on seal siirdeid 70%-l juhtudest; see piirkond on sageli vaheetapiks 3-ndast 13. gruppi. Prognostiliselt peetakse 12. gruppi paremaks kui 10...11. gruppi ja seetõttu on siit lümfisõlmede eemaldamine väga oluline. 13...15. grupis on metastaase kuni 5%-l haigusjuhtudest, 13. grupile on iseloomulik sage korreleerumine 6. grupiga. 16. grupp, s.o. paraaortaalsed lümfisõlmed, on viimane resetseeritav intraabdominaalne lümfisõlmede grupp, kuhu koonduvad maolt tulevad lümfiteed piki *truncus coeliacus*'e, *a. mesenterica superior*'i ja teiste arterite kulgu. Kahjustusi esineb seal kuni 8%-l radikaalselt opereeritutest elulemusega kuni 2 aastat (3, 6, 28, 30, 32).

Lümfogeenseid metastaase perigastriliste lümfisõlmede kahjustuseta leitakse vaid mõnel protsendil juhtudest, enamasti *a. gastrica sinistra, a. hepatica communis*'e ja *a. lienalis*'e piirkonnas. Nähtavasti ei ole sellistel juhtudel tegemist tõeliste nn. *skip**-metastaasidega, nagu seda on kirjeldatud mõne muu vähilokalisatsiooni puhul, vaid nende levik on toimunud *aa. gastricae breves*'eid või *a. gastrica posterior*'i saatvate lümfiteede kaudu (28). Seega on maovähi lümfogeense metastaseerumise puhul valdavalt tegemist kindlate seaduspärasustega, mida teadlikult ära kasutades on võimalik ravi tulemusi parandada.

Edukalt kasutatakse lümfadenektoomia operatsioonieelset planeerimist personaalarvutil, kus patsiendi sugu ja vanust, samuti kasvajat iseloomustavaid näitajaid ning varasemate operatsioonileidude analüüsi arvestades koostatakse igal haigusjuhul oletatava metastaseerumise skeem ja haiget opereeritakse sellele vastavalt (21). Sellise analüüsi kasutamine annab võimaluse makroskoopiliste metastaaside puudumise korral mitte pidada rangelt kinni lümfadenektoomia tüüpoperatsioonide printsiipidest ja eemaldada vaid need lümfisõlmede grupid, millesse metastaseerumine on tõenäoline. Enamasti on niisugused katsetused siiski tiivustatud rohkem soovist püüda operatsiooni ulatuse vähendamisega vähendada kõrget operatsioonijärgset suremust, kui parandada ravitulemusi.

Metastaaside olemasolu määramist

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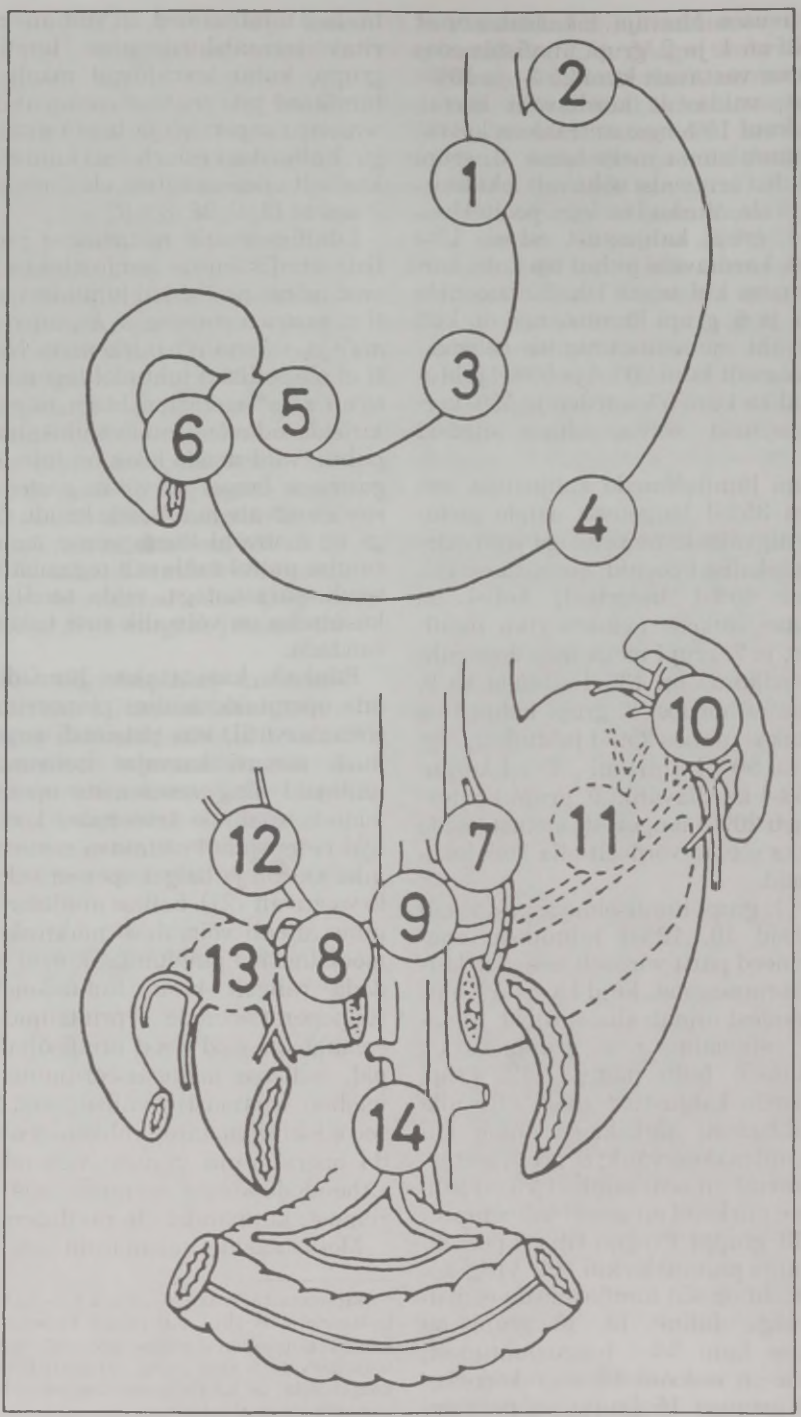
* **skip**-metastaas: skip (inglise k.) — ülehüpe, vahelejätmine; s. o. siire, mis esineb kasvaja algkoldest kaugel lümfisõlmes samaaegse vahetult kasvajat ümbritsevate (antud juhul perigastriliste) sõlmede kahjutuseta; on lümfisõlmede barjäärfunktsiooni arvestades raskesti seletatav.



Joonis. Mao regionaalsete lümfisõlmede grupid.

palpatsiooni teel ei peeta kuigi usaldusväärseks ja soovitatavaks meetodiks nii valepositiivse kui valenegatiivse leiu suure tõenäosuse tõttu (3). Lümfisõlmede kahjustuse täpsemaks määramiseks kasutatakse laialdaselt operatsiooniaegset kiiruuringut. Seda ei pea mitmed autorid samuti õigeks ühelt poolt kasvajarakkude leviku ohu tõttu (6, 33), teiselt poolt annab niisugune metastaaside juhuslik otsimine väga suure eksimise võimaluse mikrometastaaside esinemise tõttu makroskoopiliselt muutumatutes lümfisõlmedes — neid võib olla kuni 20%-l haigusjuhtudest (15, 20). Oluline on meeles pidada, et samal ajal kui lümfisõlmede metastaase esineb keskmiselt 50...60%-l hematogeensete kaugmetastaasideta haigetest, piirdub kasvajarakkudega lümfisõlmede arv enamasti 2...8-ga (6, 27, 32, 34). Lihtne loogika ütleb, et mida rohkem lümfisõlmi eemaldada, seda rohkem varjatud metastaase on võimalik avastada. Tehes näiliselt varajase (makroskoopiliselt vaikese algkoldega) maovähi puhul laiendatud lümfadenektoomia, võime avastada hoopiski II staadiumi vähi (T1 N2 M0 — UICC TNM-klassifikatsiooni järgi).

Laiendatud lümfadenektoomia all mõistetakse kõikide maost lähtuvate lümfiteede ja -sõlmede eemaldamist koos kogu neid ümbritseva rasvkoega ühtse blokina kasvajast haaratud maoga (või selle osaga), arvestades magu ümbritsevate fastsiate ja serooskelmete struktuuri (30). Lümfadenektoomia ulatusest ehk radikaalsusest (R) sõltuvalt jaotatakse maovähi puhul tehtavad operatsioonid viide kategooriasse: R0 on operatsioon, mille puhul eemaldatakse osaliselt N1-lümfisõlmed, R1 tähistab N1-sõlmede, R2 — N1- ja N2-sõlmede, R3 — N1-, N2- ja N3-sõlmede ja R4 — N1-, N2-, N3- ja N4-sõlmede täielikku eemaldamist. Radikaalseks peetakse operatsioone lümfadenektoomia ulatusega R2-st kuni R4-ni ja need on Jaapanis maovähi ravis kasutatavate operatsioonide obligatoorseks koostisosaks. R0- ja R1-resektsioonid on õigustatud ainult eakatel, suure riskiga haigetel ja neid ei peeta radikaalseks (18).

Laiendatud lümfadenektoomiat alustatakse *lig. gastrocolicum*'i eemaldamisega koos *mesocolon transversum*'i pindmise lestmega. Mao ülemist poolt toitva, *lig. gastropancreaticum*'is kulgeva *a. gastrica sinistra* ligeerimine vahetult tema väljumiskohas *truncus coeliacus*'est võimaldab eemaldada selle, metastaseerumise seisukohalt nii ohtliku sideme täielikult. Mao alumise osa verevarustus toimub peamiselt *a. hepatica communis*'e kaudu. Selles piirkonnas on oluline eemaldada *lig. hepatogastricum*'i ja *lig. hepatoduodenale* kogu koestik, säilitades *a. hepatica communis*'e, *v. portae* ja ühissapijuha. Duodeenumi mobiliseerimine ja *foramen* Winslow laiendamine annavad hea võimaluse põhjalikuks lümfadenektoomiaks. Edasi eemaldatakse pankreast kattev *peritoneum* (nn. omentobursektoomia). Järgmiseks sammuks on kõhunäärme distaalosa ja põrna mobiliseerimine mesenteriaaltüve, *a. linealis*'e ja põrnavärati piirkonna lümfisõlmede eemaldamiseks. Paljud, eriti Jaapani autorid, soovitavad põhjaliku lümfadenektoomia huvides eemaldada lisaks veel põrna ja kõhunäärme distaalosa. See on vajalik ka juurdepääsuks paraaortaalsetele lümfisõlmedele R4-resektsiooni korral. Põrna eemaldamine on tekitanud rohkeid vaidlusi, selle põhjuseks on mõnel pool leitud splenektoomiaga kaasnev madal elulemus. Siiski ei ole elulemust vähendavaks teguriks neil juhtudel mitte splenektoomia ise, vaid asjaolu, et see manipulatsioon võetakse ette rohkem ulatuslike, põrnaväratisse metastaseerunud kasvajate korral. Lisaks nendele piirkondadele tuleb kindlasti eemaldada ka mõlemapoolselt parakardiaalne kude, mis on tehniliselt võimalik nii gastrektoomia kui ka distaalse subtotaalse maoresektsiooni korral (14, 16, 26, 29, 30).

Oluline on seos maovähi algkolde invasioonisügavuse ja lümfogeense metastaseerumise ning lümfadenektoomia vahel. Varajase maovähi puhul on tähele pandud, et submukooskoe invasiooni korral on metastaaside esinemissagedus suurem kui limaskestaga piirduva vähi korral, ol-

les vastavalt 20% ja alla 5% (31, 34). Sellise erinevuse morfoloogiliseks aluseks peetakse metastaseerumiseks piisava laiusega lümfiteede paiknemist maoseina submukooskoes ja sügavamal, kuna limaskesta pindmine ja keskmine kiht lümfikapillaare ei sisalda (24). Ravitaktika valik sel juhul aga eeldab kasvaja invasioonisügavuse määramist endosonograafiliselt koos morfoloogilise materjali ülitäpse võtmisega, mis isegi paljude arenenud riikide juhtivates ravikeskustes ei ole veel rutiiniks muutunud (11, 31, 35, 36). Selliste võimaluste olemasolul võiks ainsaks erandiks olla limaskestaga piirduv nn. kergitatud intestinaalset tüüpi varajane maovähk, mille korral lümfogeenseid metastaase tuleb ette üliharva ja ravitulemused R1- ja laiendatud resektsioonide korral oluliselt ei erine (17, 23). Muudel juhtudel on ka varajase maovähi korral kasvaja taastekke peamise põhjusena hematogeensete maksametastaaside kõrval täheldatud ebapiisavast lümfadenektoomiast säilinud lümfogeensete mikrometastaaside arengut (6). Seetõttu peetakse ka sel juhul vajalikuks vähemalt R2-resektsiooni (6, 15, 19, 35).

Vaidlusaluseks küsimuseks on laiendatud lümfadenektoomia otstarbekus kasvaja invasiooni korral mao serooskihisse. Juhtudel, kui operatsiooni eel või ajal on tekkinud serooskihi kahjustuse kahtlus, soovitatakse peritoneaalvedelikku tsütoloogiliselt uurida. Selleks pestakse kõhuõõnt kohe pärast avamist 100...200 ml füsioloogilise lahusega temperatuuril 37°C, tagasi aspireeritakse 50 ml loputusvedelikku, mis kohe tsentrifuugitakse ja sademest valmistatakse äigepreparaadid kiiruuringuks. Selline meetod näitab intraperitoneaalsete vabade vähirakkude olemasolu umbes 20%-l haigetest, kellel makroskoopiliselt mao serooskihi kahjustust ei täheldata (7). Lümfogeensete metastaaside esinemissagedus suureneb koos serooskihi kahjustuse ulatusega. Niisugune seos kehtib kõikides 16 lümfisõlmede grupipides ja ka kõikides N-etappides (4, 28). Nii on mao serooskihi algava invasiooni korral metastaase lümfisõlmedes leitud 53...65%-l juhtudest, märgatava invasiooni korral umbes 80%-l ja naaberelunditesse sissekasvu korral üle 90%-l haigetest (7, 32, 34). Serooskihi kahjustuse korral peetakse haiguse operatsioonijärgse varajase taastekke peamiseks põhjuseks peritoneaalseid implantatsioonimetastaase, mis jäävad väljapoole kirurgilist ravimeetodit ja sel juhul kaheldakse lümfadenektoomia otstarbekuses. Siiski näitavad ravitulemused selle meetodi efektiivsust juhtudel, kui mao serooskihi invasioon kasvajast on algjärgus ja lümfisõlme kahjustus piirdub N1-rühmaga (20,34). Ulatuslikumal maoseina väliskihi haaratusel (üle 3 cm) (1,7) aga lümfadenektoomia enam ravitulemusi ei paranda. Sellise maovähi ravis pannakse suuri lootusi operatsiooniaegsele ja varajasele operatsioonijärgsele intraperitoneaalsele kemoteraapiale (37).

Andmed muude maovähki iseloomustavate näitajate (makroskoopiline kasvuvorm, histoloogiline ehitus, kasvaja suurus) mõju kohta lümfogeensele metastaseerumisele on vastukäivad (21, 23, 27, 28, 29, 30, 31, 34) ja lümfadenektomia ulatuse planeerimine nendest lähtuvalt ei ole õigustatud.

Järeldused.

1. Et kemoteraapia ja muud mittekirurgilised ravimeetodid ei ole maovähihaigete elulemust oluliselt parandanud, jääb selle haiguse ravi valikmeetodiks kasvaja radikaalne eemaldamine.

2. Et lümfogeense metastaseerumise hindamine ravi eel ja ajal on raske, kuid samal ajal on haiguse retsidiveerumise peapõhjuseks regionaalsed metastaasid, tuleb laiendatud lümfadenektoomiat pidada maovähi kirurgilise ravi lahutamatuks osaks ja ravitulemuste peamiseks parandajaks.

3. Magu ümbritseva lümfivõrgustiku rikkaliku anastomoseerumise ja metastaaside põhjustatud takistusest tingitud retrograadse lümfivoolu tõttu peab laiendatud lümfadenektoomia haarama kõiki lümfogeense metastaseerumise piirkondi.

sõltumata kasvaja algkolde asukohast maos.

4. Enamikus Euroopa riikides ja ilmselt ka Eestis on laiendatud lümfadenektoomiast hoidutud kõrge operatsioonijärgse letaalsuse tõttu. Seda on võimalik vähendada haigete operatsioonieelse ettevalmistamise parandamisega ühelt poolt, teisalt selle operatsiooni sooritamisega ainult kõrge professionaalsusega, operatsioonitehnikat hästi valdavate kirurgide poolt.

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Summary

Extended lymphadenectomy in gastric cancer surgery. In this review of publications the therapeutic value of extended regional lymphadenectomy for gastric cancer has been analysed. Japan is the only country where the decline of mortality due to gastric cancer is faster than the decline of incidence. Japanese surgeons consider their success to be in early detection and extended lymphadenectomy.

The Japanese classification (JRSGC) of gastric regional lymph node stations, the frequency of their metastatic involvement and the systemic lymph node dissection technique have been shortly described.

Most of the studies indicate that the extensive lymphadenectomy improves the results of gastric cancer treatment and can be safely performed in all cases by propely trained surgeons without increasing surgical mortality.

Kommentaar

Ülevaateartiklis käsitlemist leidev probleem on ülimalt aktuaalne, kuna maovähi kirurgiline ravi on otsustavaks ravivõimaluseks. Operatsiooni metoodika ja radikaalsus määravad haige elulemuse. Autorid on analüüsivalt esitanud nüüdisaja kirjanduse seisukohad selles küsimuses, eriti hinnatav on jaapani koolkonna ülevaatlik esitamine, mis on nimetatud probleemi alal juhtiv maailmas.

Väino Rätsep — Eksperimentaalse ja Kliinilise Meditsiini Instituudi onkoloogiaosakond

V

Eesti Arst (Estonian Physician) 1994; 6: 476–483

Summary

Adaption with removable dentures: the clinical study. An investigation of removable dentures (RD) wearers with protheses covering of hard palate after one year using period were examined clinically, including biomechanical parameters and adaptional difficulties. Only correlation between above mentioned sign groups, the negative relation of general stability of denture to shewing ability was found. Correlation between occlusal stability and retention would be interpreted as the necessity to the construct of bilaterally balanced occlusion for dentures with free-end saddles, for preservation of retention ability. The relation of patients with signs of erythema in some type of edentulism/denture is caused rather by denture design with worse hygien contition then construction difference.

Teade

«Eesti Arsti» 1994. aasta 4. numbris ilmus Tartu Ülikooli Füüsilise Antropoloogia Keskuse teade jaoskonnaarstidele (perearstidele), et TÜ Arstide ja Proviisorite Täienduskeskuse kaudu hakkab Füüsilise Antropoloogia Keskus korraldama täienduskursusi «Meditsiinilise ja antropomeetrilise andmestiku töötlus arvutil».

Nüüd on koostatud TÜ Arstide ja Proviisorite Täienduskeskuse tööplaan järgmiseks aastaks. Need kursused toimuvad 6...10. märtsini 1995 (I tsükkel) ja 6...10. novembrini 1995 (II tsükkel) Tartus. Sellel kursusel saadakse kogemusi igapäevase arstitöö andmete töötlemiseks, antropomeetrilisteks mõõtmisteks ja arvuti kasutamiseks.

Eesti Arst, 1994, 6, 476—483

ÜLEVAATED

Mao kartsinogenees

Andrus Arak Karl Kull

intestinaalne ja difuusne maovähk, etioloogilised tegurid, limaskesta vähieelsed muutused, preventsioon

1980-ndate aastateni oli maovähk üks sagedamini esinevaid pahaloomulisi kasvajaid maailmas, andes igal aastal ligikaudu 700 000 uut juhtu (3). Viimastel aastakümnetel on selle kasvaja esinemissagedus kõikjal pidevalt vähenenud, kuigi selle languse kiirus on piirkonniti olnud väga erinev. Jaapani kui erandi kõrval on maovähi esinemissagedus jäänud suhteliselt suureks madala sotsiaal-majandusliku standardiga riikides, selle kiire vähenemine on aga olnud üldise heaolu järkjärgulise paranemise peegelduseks (3, 13).

Ka Eestis on maovähi esinemissagedus viimastel aastakümnetel pidevalt vähenenud, jäädes aga kiiruselt märgatavalt alla meie läänepoolsetele naaberriikidele (9, 13, 34). Samal ajal on mitme rikka ühiskonna statistika näidanud, et maovähi esinemissageduse vähenemine ei ole piiramatu. Nii on maovähijuhtude absoluutarv Ameerika Ühendriikides viimastel aastatel pidevalt suurenenud ja seni ei ole lõplikult selgunud, kas selle peamiseks põhjuseks on elanikkonna vananemine, kõrge maovähiriskiga piirkondadest pärit immigrantide arvu suurenemine või kardiavähi sagenemine (3).

Intestinaalne ja difuusne maovähk. Epidemioloogilistes uuringutes on mao-

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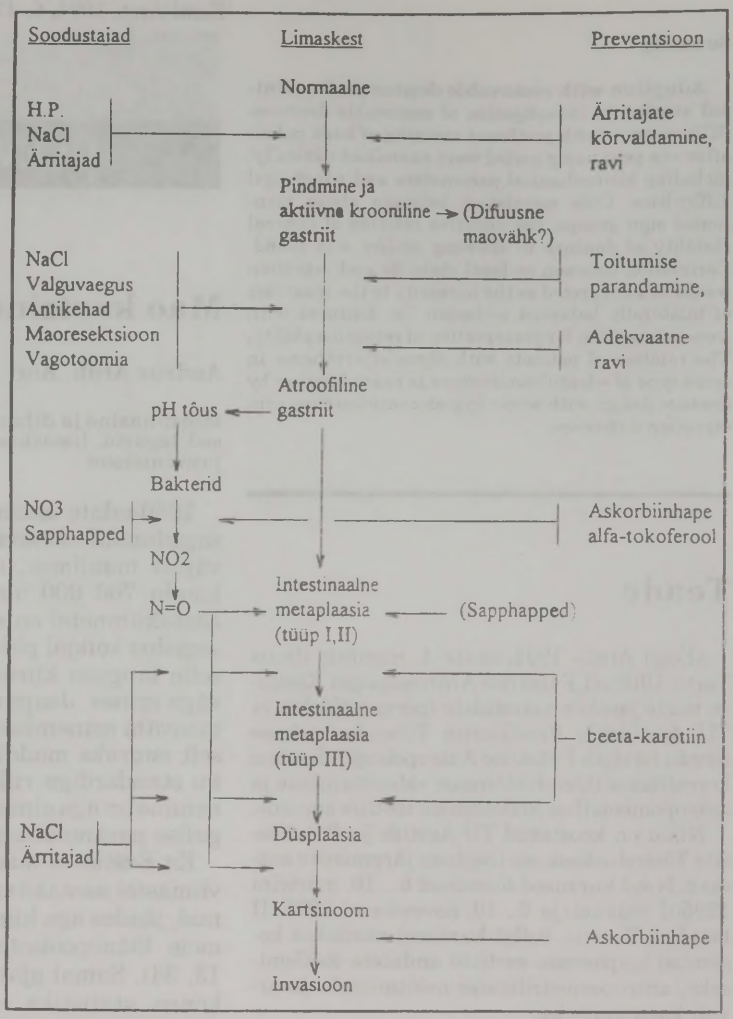

Joonis. Intestinaalset tüüpi maovähi tekkes osalevad keskkonnategurid ning limaskesta muutused. Koostatud P. Correa (3, 4, 6), M. E. Craaneni (7), L.-E. Hanssoni (11), P. Sipponeni (31) ja G. M. Sobala (35) järgi.

vähk jaotatud kaheks peamiseks histoloogiliseks tüübiks — intestinaalseks ja difuusseks — enamasti Laureni klassifikatsiooni järgi (11). Lisaks morfoloogilistele omadustele on selline jaotus õigustatud ka kliinilise ja epidemioloogilise laadi tõttu, mis viitavad nende kahe tüübi pato- ja histogeneesi võimalikule erinevusele (12). Kõikjal, kus on täheldatud maovähihaigestumuse kiiret vähenemist, on see toimunud peamiselt intestinaalse tüübi arvel. Difuusne tüüp on jäänud nendest muutustest peaaegu puutumata ja tema suhtosa on seetõttu pidevalt suurenenud (5, 13).

Intestinaalset tüüpi maovähki on nimetatud ka epideemiliseks (2) tema tiheda seose tõttu eksogeensete kantserogeensete teguritega ja märgatavate esinemissageduse muutuste tõttu. Oma sarnasuse tõttu jämesoolevähi morfoloogilise ehitusega on seda ka diferentseerunuks nimetatud (19). Kliiniliselt esineb intestinaalset maovähki rohkem vanematel meestel, ta on sagedamini ek-

sofüütse kasvuga ja ravijärgne elulemus tema puhul on tavaliselt parem (12, 19).

Difuusset tüüpi maovähki nimetatakse endeemiliseks (2, 12, 19) tema stabiilsema esinemissageduse ja arvatava tugevama pärilike teguritega seostatuse tõttu. Morfoloogiliselt on difuusse maovähi puhul näärmeline struktuur vaid aimatav, kuigi funktsionaalselt (näiteks limaproduktsioon) võib ta olla küllalt hästi diferentseerunud (4, 12, 19). Kliiniliselt on talle iseloomulikum infiltratiivne kasvuvorm ja halvem prognoos kui intestinaalse tüübi puhul (19). Tugevamale seosele geneetiliste teguritega viitavad just selle maovähi-tüübi sagedam esinemine perekonniti (15, 33), esinemine noortel (9, 18) ja naistel (13), A-veregrupiga inimestel (2, 18) ja ühemunarakukaksikutel (17), samuti stabiilsus ka nendes piirkondades, kus eksogeensete teguritega seostatud intestinaalset tüüpi maovähi juhud on kiiresti vähenenud (9, 13). Pärilikkusele viitab ka selle maovähivormi sagedam esinemine koos mõne päriliku haigusega, nagu autosoomdominantse Lynch II sündroomi, päriliku hüpogammaglobulineemiaga (7, 8).

Difuusset tüüpi maovähi puhul ei ole suudetud leida selgelt eristatavaid ega üksteisele järgnevaid vähieelseid muutusi ja see vorm näib tekkivat kas täiesti normaalse limaskesta või äärmisel juhul pindmise gastriidi foonil (12, 25, 26). Maovähi erinevate histoloogiliste tüüpide morfogeneesi eristumine võibki toimuda pindmise või aktiivse kroonilise gastriidi vältel — difuusne maovähk saab alguse atroofiliste muutusteta limaskestast, kuna intestinaalne vorm peab läbi tegema mitmed eelastmed (26).

Kindlasti ei saa ka difuusse maovähi korral välistada eksogeensete kantserogeensete faktorite ja intestinaalse maovähi korral geneetiliste tegurite soodustavat osa. Siiski, kui on näiteks püütud maovähi sagedamat perekondlikku esinemist seostada sarnaste eksogeensete teguritega, ei ole enamasti tehtud vahet selle kahe histoloogilise tüübi vahel; pärilike teguritega seotud autoimmuunsele atroofilisele gastriidile järgnev maovähk on küll enamasti intestinaalset tüüpi, kuid pärilik seos on siin pigem prekantseroossetel muutustel kui vähil endal (14, 15, 23, 33).

Etioloogilised faktorid. Mao limaskesta vähieelseid muutusi on ikka ja jälle seostatud väliskeskkonna tegurite mõjuga. Magu on elund, mis esimesena, sageli ja pikka aega järjest puutub kokku toidus sisalduvate ainetega nende muutumatul kujul ja järkjärguliste progresseeruvate muutuste aastakümneid kestev jada näib sobivat nende tegurite pideva toimega (29). Samuti on just muutused toitumistavades kõige tugevamini mõjutanud intestinaalse maovähi esinemissagedust (3). Mao kartsinogeneesi uurimise eksperimentaalmudelites on efektiivsemaks osutunud otsese toimega kantserogeenid, kuna metaboolset aktivatsiooni vajavad prekantserogeenid on sarnase efektiivsusega ka teiste, näiteks jämesoolevähi tekkes (19).

Teadmata aine toimemehhanismi, ei saa selle vähi teket soodustavas toimes siiski veel kindel olla. Toidu termilisel töötlemisel tekib tuhandeid pürolüüsiprodukte, mille koguhulk arvatakse olevat umbes 2000 mg inimese kohta päevas ja tass kohvi sisaldab vähemalt 10 mg selliseid aineid, mis eksperimendis on osutunud närilistele kantserogeenseks (1). Meie igapäevases taimses toidus olevatest, enamasti kantserogeenseteks peetud pestitsiididest on kaaluliselt 99% looduslikud (s.o. toodetud taimede poolt enesekaitseks) ja olnud inimese toidu koostisosadeks aastatuhandeid (1). Võib oletada, et looduslikus olelusvõitluses looma- ja taimeriigi vahel on muu hulgas ka inimese mao limaskest omandanud mingisuguseid kaitsemehhanisme selliste ainete vastu.

Keedusool (NaCl) on üks olulisemaid maovähi tekkes osalevaid eksogeenseid tegureid, mille ülemäärane tarvitamine põhjustab limaskesta kahjustust ja esialgu pindmise põletiku teket. Pikaajaline soola liigtarvitamine aga viib juba kroonilise gastriidini koos hilisemate atroofiliste muutuste lisandumisega (5). Põletikuga kaasnev hoogne rakustiku uuenemine

kergendab ka teiste kantserogeensete ainete toimimist ja suurendab sellega mutatsioonide tekke võimalust (1, 5). NaCl-i lämmastikuühendite mutageense toime potentseerimine on tähtis mao kartsinogeneesiahela hilisemates etappides — düsplaasia ja ka invasiivse kartsinoomi tekkes (5). Intestinaalse maovähi esinemissageduse kiiret vähenemist oma sotsiaalset seisundit parandanud riikides on suuresti seostatud just soolatud toitudest loobumise ja toiduainete teiste säilitamisvõimaluste (külmikud) kättesaadavamaks muutumisega (13).

Ka nitraadid on meie toidu lahutamatud koostisosad, mida saame koos juurvilja, säilitamiseks töödeldud lihasaaduste ja joogiveega. Kuigi andmed lämmastikuühendite osast mao kartsinogeneesis on kohati vasturääkivad, on siiski mitmed epidemioloogilised vaatlused näidanud nende ainete rohkemat kasutamist kõrge maovähiriskiga piirkondades, näiteks Kostariikas, Hiinas, Kolumbias (3, 5). Nende toime viib esialgu intestinaalse metaplaasia ja hiljem vähi tekkeni. Nitroühendite kantsero- ja mutageensust potentseerivad lisaks NaCl-ile ka sapphapete lisandumine ja askorbiinhappe defitsiit; nende teke on soodustatud alahappelises maos, mis on heaks keskkonnaks reduktaase tootvatele anaeroobsetele mikroobidele (3, 5).

Limaskesta atroofia ja maosisese pH tõusuni viivat kroonilist põletikku tekitab peale *Helicobacter pylori* tegevuse, autoimmuunse reaktsiooni ja keemiliste põletikutekitajate ka toimunud vagotoomia või maoresektsioon (31). 15...20 aastat pärast neid manipulatsioone, eriti Billroth II-tüüpi resektsiooni, suureneb vähirisk 7...8 korda: duodenogastriline refluks võib põhjustada limaskesta erosioonideni ulatuva kahjustuse ja sellega kaasnev proliferatsiooniprotsess võib muutunud tingimustes lõppeda intestinaalse metaplaasia tekkega (19, 30, 31). Kartsinogeensete nitrosoühendite moodustamisest vahetult limaskestal võtavad osa ka põletikulise infiltraadi rakulised elemendid, nagu aktiveeritud makrofaagid, polümorftuumsed leukotsüüdid (5).

Geenitoksiliste ainete toime ei piirdu tavaliselt ühe kindla elundi kasvaja tekkega. Maovähi põhjustajatena geneetiliste häirete kaudu võiksid arvesse tulla nitroühendid, loomsete valkude pürolüüsil tekkivad heterotsüklilised amiinid, vähem mükotoksiinid või taimsed alkaloidid (5, 32).

Helicobacter pylori infektsiooni on täheldatud kõikjal üle kogu maailma mõnesuguste variatsioonidega geograafilises esinemissageduses ja nakatumise eas (29). Arenenud tööstusriikides on ta lapseeas harva esinev, kuid sageneb koos vanusega ja vanuses üle 60 aasta on nakatunud üle 50% inimestest. Arengumaades seevastu on nakatunud pooled lastest ja täiskasvanutel võib *Helicobacter pylori* esinemissagedus olla väga suur — üle 90% (16). Sarnaseid erinevusi on ilmnenud ka ühe piirkonna erinevate sotsiaalsete klasside vahel. Epidemioloogilised uuringud on näidanud selle mikroobi ja maovähi esinemissageduse kokkulangevust (26). Et *Helicobacter pylori* on peaaegu ilma kahtluseta umbes 80%-l juhtudest seotud vähemalt pindmise ja aktiivse kroonilise gastriidi tekkega, need aga limaskesta järgnevate muutuste kaudu intestinaalse maovähiga, siis ongi *Helicobacter pylori*'t püütud paigutada maovähi etioloogiliste faktorite hulka (25).

Kirjeldatud on maovähi mõnevõrra sagedamat esinemist varem *Helicobacter pylori*'ga nakatunud inimestel võrreldes nendega, kellel seda infektsiooni ei ole esinenud (21, 22). Siiski on need uuringud tehtud piirkondades, kus *Helicobacter pylori* nakkus on väga sage ka neil inimestel, kes maovähki kunagi ei haigestu. Leitud on ka *Helicobacter pylori* infektsiooni võrdselt nii intestinaalse kui ka difuusse maovähi ümbrusest (21, 22), kuigi viimase teket eelnevate limaskesta muutustega ei seostata. Kõige sagedamini on seda mikroobi leitud koos (antrumi) pindmise gastriidiga, vähem aktiivse kroonilise gastriidiga, atroofiliste muutuste lisandumisel tema esinemissagedus järsult väheneb ja intestinaalse metaplaasiaga epiteelis puudub ta enamasti täielikult (6, 28, 38). Arvatakse, et limaskesta muutus-

tega kaasnev mao sisekeskkonna muutus (peamiselt pH tõus) võib olla *Helicobacter pylori* elutegevuseks ebasoodne, kuigi H2-blokaatorite tekitatud hüpoklorhüüdria suhtes on ta resistentne (28).

Spontaanset *Helicobacter pylori* infektsiooni paranemist ei ole kirjeldatud ja saanud alguse lapseeas, on ta üks pikema ekspositsiooniajaga etioloogilisi tegureid (22). Arvestades *Helicobacter pylori* teadaolevaid toimemehhanisme, võib ta aastakümneid maos püsides tõesti vähi tekkeni viia. Mao kartsinogeneesiga seotud *Helicobacter pylori* võimalike toimemehhanismidena on kirjeldatud: 1) tsütotoksiliste või põletikumediaatorite ultserogeenset kaskaadi käivitava toimega ainete (atseetaldehüüd, fosfolipaas-A2 jt.) produktsiooni; 2) kõrget ureaasi aktiivsust, mis uureaga reageerides annab tugeva mukolüütilise toimega ammoniaagi kontsentratsiooni tõusu maos; 3) hüperproliferatsiooni indutseerimist põletikukoldes, mis soosib epiteeli metaplastilist progressiooni ja võimalik, et ka maliignsete rakuliinide teket; 4) üldise ja lokaalse immuunreaktsiooni stimuleerimist, mille tagajärjeks võib muu hulgas olla ka ristreaktsioon mao limaskesta vastu; 5) epidermaalse kasvufaktori stimuleerimist; 6) askorbiinhappe kontsentratsiooni vähendamist maoõõnes (9, 20, 26, 36). Otseste kantserogeensete ainete tootmist *Helicobacter pylori* poolt ei ole leitud. Lisaks sellele on põletikuline limaskest ise tundlik kantserogeensete ainete toime suhtes, näiteks vabade radikaalide põhjustatud oksüdatiivse stressi suhtes, alludes kergemini mutatsioonidele ja maliignsele transformatsioonile (22). Peab aga ütlema, et suur osa eespool nimetatud mehhanismidest on kindlaks tehtud *in vitro* ja seostub ka haavandi tekkega. Mainitud mikroobi osa maovähi tekkes saab tõestada vaid siis, kui on näidatud, et selle infektsiooni raviga on võimalik vähki haigestumist vältida (4, 25).

Väliskeskkonna tegurid toimivad enamasti kindlal vähitekke etapil, vastavat limaskesta muutust kas soodustades, takistades või regressioonile viies. Arvatakse, et kantserogeenide ekspositsiooniaeg peab olema pikk — kogu kartsinogeneesiprotsess saab alguse juba inimese elu esimesel veerandil ja kestab aastakümneid (9).

Prekantseroosne protsess maos. Intestinaalse vähiga lõppev protsess mao limaskestas arvatakse üldjoontes kulgevat järgmise skeemi järgi: pindmine gastriit — aktiivne krooniline gastriit — krooniline atroofiline gastriit — intestinaalne metaplaasia — (III tüüpi intestinaalne metaplaasia) — düsplaasia — (võimalik vähk) — vähk — invasioon (vt. joonis) (2, 3, 5, 6, 27). Sellise skeemi paikapidavust kinnitavad vaatluse tulemused, kus on leitud gastriidi raskusastmete korreleerumine intestinaalse metaplaasia sagedusega ja viimase erinevate raskusastmete korreleerumine düsplastiliste muutuste esinemissagedusega (2). Eestis kui küllalt suure maovähihaigestumusega riigis on vaatlused näidanud progresseeruvate muutustega gastriidi väga sagedat esinemist ja seda ka noortel (37).

Teistest maohaigustest on kõrget vähiriski seostatud adenomatoosse polüübiga, mao limaskesta limarakulise hüperplaasia — Menetrier' tõvega. Kroonilise maohaavandi korral ei ole vähi esinemissagedus oluliselt suurem kui kahjustamata maos; eksperimendis on kroonilise haavandiga mao limaskest küll vastuvõtlikum kantserogeensete ainete toimele, mõned haavandi tekkes olulised faktorid (näiteks maohape) aga kaitsevad magu pahaloomulise kasvaja tekke eest (19, 22, 24).

Pikaajalist ja progresseeruvat **gastriiti** peetakse intestinaalse maovähi tekke eelduseks (3). Varajasemad arvukad gastriidi klassifikatsioonid on ühendatud nn. Sydney süsteemi, kus eristatakse ägedat ja kroonilist põletikku, kusjuures viimane jaotatakse omakorda aktiivseks ja atroofiliseks (27). Selline jaotus sobib hästi ka maovähi prekantseroositeooriaga. Topograafiliselt võib gastriit Sydney klassifikatsiooni järgi esineda antraalse, korpuse või pangastriidina (27). P. Correa on neid gastriite nimetanud hüpersekretoorseteks, autoimmuunseteks ja keskkonnategurite tingitud vormideks (3). Neist esi-

mesele on iseloomulik krooniline (pindmine) põletik enamasti mao antraalosas (ka nn. difuusne antraalne gastriit), maohappe ja pepsiini suurenenud sekretsioon ning ta on seotud peamiselt duodeenumi või pülooruse piirkonna peptilise haavandi tekkega, kuna tema vähirisk on väike (27). Hüpersekretoorne gastriit on 80...90%-l juhtudest seotud *Helicobacter pylori* infektsiooniga (3).

Mõnevõrra suurema maovähiriskiga autoimmuunne gastriit on seotud parietaalrakkudevastaste antikehade ja pernitsioosse aneemia sündroomiga. See gastriit lokaliseerub tavaliselt mao korpuseosas, temaga kaasnev näärmekoeatroofia on difuusne ja põhjustab aklorhüüdria teket (23, 27). Peamiselt keskkonna toksilistest teguritest põhjustatud mitmekoldeline metaplastiline gastriit algab pindmise põletikuna maokorpuse ja -antrumi piiril ja levib hiljem mõlemas suunas (27). Põletikule lisanduvad esialgu koldelised ja hiljem omavahel laatuvad atroofilised muutused. Näärmekoeatroofia ei ole siin täielik, kuid tekkivast hüpoklorhüüdriast piisab nitraate redutseerivate bakterite elutegevuseks (14). Just see gastriidivorm arvatakse olevat peamine maovähi eelkäija (3, 29).

Kroonilistele atroofilistele muutustele lisanduva **intestinaalse metaplaasia** korral asendub mao limaskest vastavat tüüpi soole omaga, saades kaasa ka selle omadused (19). Peensoole tüüpi intestinaalset metaplaasiat nimetatakse ka täielikuks ja I tüüpi intestinaalseks metaplaasiaks, millele on iseloomulik peensoole tüüpi rakustiku ja sialomutsiinide produktsioon, lisanduda võib ka peensoole limaskestale iseloomulik alkaalse fosfataasi ja mõne seedeensüümi (disahharidaas, peptidaas) produktsioon (3, 19). Jämesoole tüüpi metaplaasiat aga nimetatakse mittetäielikuks ja ka III tüüpi metaplaasiaks, millele on omane vastav ehitus ja sulfomutsiinide produktsioon (19). Nende kahe tüübi kõrvale jääb veel üks — II tüüpi ehk ka karikrakuline, olles ehituselt lähedane jämesooleepiteelile, kuid produtseerides peaasjalikult sialomutsiine (29).

Neid mao limaskesta muutuste vorme peetakse üksteisele järgnevateks lülideks intestinaalse maovähi tekke ahelas. Samas on aga leitud (peamiselt I ja II tüüpi) intestinaalset metaplaasiat ka suuremal osal mao kroonilise haavandiga haigetel ja vaid III tüüp seostub maovähiga kindlamalt kui teiste maohaigustega (6). Nii ongi avaldatud arvamust, et III tüüpi intestinaalne metaplaasia võib olla hoopiski paraneoplastiline muutus ja peensoole tüüpi metaplaasia on vanemas eas niivõrd sage muutus, et kliiniliselt on tema prekantseroosne potentsiaal võrdne kroonilise atroofilise gastriidi omaga (19).

Kõikide eespool nimetatud mao limaskesta patoloogiliste muutuste puhul võib nende vähieelsuses kahelda nende suure esinemissageduse ja väikese vähiriski tõttu. Düsplaasia on juba niisugune muutus, millel on maovähiga kindel seos. Raske astme düsplaasiat on enamasti leitud koos kasvajaga või küllalt lühikest aega (aasta) enne varajase vähi avastamist.

Kui düsplaasia laiemas mõttes tähendab abnormset kasvu üldse, siis vähi tekke protsessis on ta premaliignsuse sünonüümiks ja teda on defineeritud kui koe niisugust patoloogilist seisundit, mille puhul rakulised ja struktuursed muutused näitavad ilmekalt kalduvust pahaloomulisusele (19). Düsplastiliste rakkude DNA polü- ja aneuploidsus, rakutsükli pikenemine ja rakkude eluea lühenemine, kartsinoembrüonaalse antigeeni ja teiste onkogeneesiproduktide esinemine viitavad kindlale seosele maliignsete rakkudega. Tihti ongi piiri tõmbamine düsplaasia ja vähi vahele võimatu, mille tõttu on ka kasutusel mõiste «võimalik vähk» (19). Taaspöördumine arvatakse olevat võimalik kuni kergetest düsplastilistest muutustest (3, 19, 21).

Preventsioon. Primaarse maovähi preventsioon sisaldab kontrolli selle tekkes oluliste faktorite üle. Suitsetamisest, kangetest alkohoolsetest jookidest ja kantserogeeniderikastest toitudest loobumine ning rohke toores taimne toit seostuvad intestinaalse maovähi esinemissageduse kiire vähenemisega (13). Maovähi primaarse preventsiooniga seostub ka

suur hulk keskkonnakaitseprobleeme, kuigi näiteks pestitsiidide osas on vaieldud selle üle, kas mitte neist saadav kasu taimse toidu rohkusena ei kaalu üles arvatavat vähiriski (1).

Arvestades aklorhüüdria ja hüpoklorhüüdria olulisust mao kartsinogeneesis, peaks üks maovähi vältimise võimalusi olema normaalse happesuse säilitamine atroofilise gastriidi tekkepõhjuste kontrolli ja haavandtõve adekvaatse ravi kaudu (24). *Helicobacter pylori* infektsiooni puhul on oluline silmas pidada üldist hügieenitaset ja kindlaks määrata selle ravi näidustused ja otstarbekus (5, 16).

Vähivastasteks aineteks peetakse värskes taimetoidus sisalduvat askorbiinhapet, β-karotiini, α-tokoferooli, samuti mikroelemente (seleen), mis kui tugevad antioksüdandid pärsivad hapniku vabade radikaalide (siin peamiselt nitrosoühendite) mao limaskesta kahjustavat toimet, seejuures üksteist potentseerides (3, 35). Lisaks sellele osaleb askorbiinhape stresshormoonide tootmises, aitab immuunsüsteemi stimuleerimisega tõsta organismi resistentsust mikroobide (ka HP) ja kasvajate suhtes, takistab nitritite amiinimist maos, aitab kõrvaldada mitme (näiteks tubakasuitsus sisalduvate) kantserogeense aine toimet (9). Tubakasuits sisaldab lisaks paljudele muudele kantserogeensetele ainetele ka hulgaliselt vabu radikaale, mis võivad olla oksüdatiivse stressi indutseerijateks suitsetajatel, ja nii on suitsetajatel täheldatud tunduvalt suuremat vitamiinivajadust mittesuitsetajatega võrreldes (35). C-vitamiin on vajalik ka sidekoevalgu kollageeni sünteesi juures, osaledes nii juba tekkinud vähi mikrokollete piiramises ja progresseerumise pidurdamises (3, 35).

Sekundaarne maovähi preventsioon peaks seisnema kõikide kartsinogeneesiprotsessist hõlmatud haigete praktiliselt ebareaalses väljaselgitamises, jälgimises ja ravimises. Varajase maovähi avastamise suur sagedus Jaapanis näitab sõeluuringute efektiivsust suure riskiga piirkondades küll vähi puhul (3), kuid prekantseroossete muutuste suure esinemissageduse tõttu tuleb siin, erinevate tegurite koosmõju arvestades, uuritavaid selekteerida. Määratavad on mao limaskesta muutustele viitavad bioloogilised markerid: pepsinogeenid, intestinaalse metaplaasiaga kaasnevad limaproduktsiooni muutused ja soolestiku ensüümide esinemine maos, anomaalse Lewis-A-antigeeni ilmumine mao limaskestas jt. (2, 5, 10, 29). Düsplastiliste muutuste korral leitavad ja malignisatsioonile viitavad markerid (CEA jt.) ei ole enam maovähispetsiifilised (19).

Kokkuvõte. Esitatud ülevaates on tähelepanu pööratud viimastel aastatel esitatud täiendustele maovähi tekke etioloogiliste ja patomorfoloogiliste aspektide osas. Intestinaalset tüüpi maovähi esinemissageduse kiire vähenemine kõrge sotsiaal-majandusliku standardiga riikides on arengumaadega võrreldes andnud võimaluse selgitada nende muutuste põhjusi. Üldine hügieenitase ja toitumisharjumused seostuvad kindlalt suurema osa teadaolevate etioloogiliste teguritega, millest praegu peetakse olulisemaks *Helicobacter pylori* infektsiooni, ülemäärast soola tarbimist ja mao kartsinogeneesi pidurdavate antioksüdantse toimega A-, C- ja E-vitamiini defitsiiti.

Nagu sellise multifaktorilise põhjuslikkuse puhul ikka, arvatakse siingi välistele soodustajatele lisanduvat geenitoksiliste kantserogeensete ainete toime ja pärilik eelsoodumus. Viimase osa eksogeensete tegurite nõrgema toime kõrval peetakse oluliseks difuusse maovähi puhul, mille geneesi selgitamisele hakatakse lähitulevikus ilmselt tunduvalt suuremat tähtsust omistama. Seal aga, kus maovähi esinemissagedus on veel küllalt suur just intestinaalse vähitüübi arvel, on võimalik teiste kogemustest omandatud teadmisi haigestumise vähendamise eesmärgil ära kasutada. Intestinaalse maovähi tekkeks peavad väliskeskkonna tegurite pideval toimel arenema mao limaskesta järjestikused progresseeruvad muutused pindmise ja aktiivse kroonilise pangastriidi ning atroofiliste, metaplastiliste ja düsplastiliste muutustena, kuna difuusse vähi tekkeks atroofia eelnemise olulisust ei ole leitud.

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Summary

Gastric Carcinogenesis. In this article a review of publications of recent years about the morphological and aetiological aspects of gastric cancer is presented. The incidence of the gastric cancer has been declining, more rapidly in affluent societies than in developing countries. The decline has been observed mainly for the so-called intestinal type, when the incidence of the other, diffuse type has been changed less notoriously. The latter type seems to have a more obvious relationship to the hereditary aetiology and a little is known about the precancerous process of it. The intestinal type is considered to be the end result of a prolonged precancerous process in which superficial gastritis, atrophy, intestinal metaplasia and dysplasia appear in sequential steps. This changes are chiefly caused by the environmental factors (*Helicobacter pylori*, different carcinogenic and genotonic chemical agents) in combination with hereditary and aquared genetic alterations. So the cause of this disease is almost certainly multifactorial and the multidisciplinary approach is needful to resolve the problem of castric cancer. Screening of the gastric precancerous changes in high risk areas, anti-Helicobacter and adequate anti-ulcer therapy, use of micronutrient antioxydants with low salt intake are possible measures of prevention of this malignance.

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MAOVÄHI RADIKAALNE KIRURGILINE RAVI

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Autorid tänavad Soome ja Eesti Vähiregistreid koostöö eest ja Pentti Niemineni Oulu Ülikoolist abi eest andmete statistilisel töötlemisel.

Võtmesõnad: maovähk, kirurgiline ravi, operatsiooni radikaalsus

Kasvaja algkolde invasioonisügavus ja lümfogeense metastaseerumise ulatus on kaks kõige olulisemat maovähihaigete prognoosi mõjutavat tegurit (9). Seetõttu on nende tegurite arvestamine oluline ka radikaalse kirurgilise ravi planeerimisel (9,12). Olemas on kaks erinevat arusaama maovähipuhuse operatsiooni radikaalsusest. Ühe järgi peetakse piisavaks nn. konventsionaalset ehk sarnaselt nii mao hea- kui halvaloomuliste haiguste ravis kasutatavat, kuna teine eeldab mao eemaldamise kombineerimist naaberorganite resektsioonide ja laiendatud lümfadenektoomiaga (2,3,9,12).

Käesoleva töö eesmärgiks oli võrrelda nende kahe erineva operatsioonimetoodika mõju maovähihaigete ravitulemustele prognostiliste tegurite ja elulemusnäitajate alusel.

Uurimismaterjal ja -metoodid. Töös on vaadeldud 88 aastatel 1983 - 1987 Oulu Ülikooli Kliiniku kirurgiaosakonnas ja 406 aastatel 1978 - 1987 Tartu Ülikooli Kliinikumi Onkoloogiahaiglas radikaalselt opereeritud maovähihaiget. Võrreldavate haiglate valikus osutus määravaks erinevus kirurgilise ravi taktikas ning sarnasus nii haigestumuses kui kasvajate patoloogilistes näitajates Põhja-Soomes ja Eestis (1,4,13).

Soomes puuduvad spetsialiseeritud haiglad onkoloogiliste haiguste kirurgiliseks raviks. Oulu Ülikooli Kliinikus opereeritakse maovähihaigeid gastrektoomia või subtotaalse maoresektsiooni teel koos perigastriliste lümfisõlmede eemaldamisega. Radikaalseid operatsioone ei peeta võimalikuks kasvaja invasioonil mao naaberkudedesse (T4) ja N1 sõlmedest ulatuslikuma lümfogeense leviku korral. Oluline on kasvajavaba resektsiooni-joone olemasolu, selle minimaalseks kauguseks on 5 cm kasvaja makroskoopilisest piirist. Infiltratiivsete kasvajate korral eelistatakse gastrektoomiat.

Eesti onkoloogiahaiglates on maovähi radikaalses ravis oluliseks peetud kombineeritud naaberorganite resektsioone ja laiendatud lümfadenektoomiat. Seda metoodikat on varem lähemalt kirjeldatud (1). Need on ka peamised

erinevused radikaalsuse mõistes epiteliaalsete pahaloomuliste kasvajate kirurgias Soomes ja Eestis.

Retrospektiivseks analüüsiks on kogutud andmed mõlema kliiniku haiguslugudest. Kasvajad on klassifitseeritud TNM klassifikatsiooni 1987. aasta väljaande alusel, N-kategooria Jaapani Maovähi Uuringute Ühingu klassifikatsiooni alusel (5,7). Makroskoopilised kasvuvormid Borrmanni järgi on koondatud eksofüütseteks (polüpoidne, haavanduv) ja infilitratiivseks (infiltratiiv-haavanduv, infiltratiivne). Histoloogilised tüübid jaotatakse Soomes P. Laureni järgi, Eestis aga ÜTO klassifikatsiooni alusel, ja ei ole seetõttu antud uuringus võrreldavad (8,11). Elulemusnäitajad on arvutatud Soome ja Eesti Vähiregistrist saadud andmete põhjal.

Statistiliseks andmetöötluseks SPSS programmis on kasutatud üksiktunnusanalüüsi ja Cox'i hulgitunnuselist regresioonimudelit, statistikud on leitud χ^2-testiga.

Uurimistulemused ja arutelu. Haigete keskmine vanus oli Oulus 63,0 (27 kuni 81) ja Tartus 62,4 (31 kuni 85) aastat. Suhteliselt rohkem oli meeshaigeid Oulu rühmas (59,1% Tartu 48,8% vastu) kuigi haigestumuse järgi sellist erinevust ei esine. Ühise joonena võib välja tuua haigete soo ja vanuse mõju puudumise 5-aasta elulemusele.

Kõikide haigete 5-aasta suhteline elulemus oli Oulus 45,5%. See näitaja on väga lähedane 46,1%-sele elulemusnäitajale Tartus ja jätab esmapilgul mulje, et laiendatud operatsioonidel ei ole eelist konventsionaalse metoodika ees. Kahe haigeterühma lähem võrdlus näitab siiski sellise järelduse ennatlikkust. Tabelis 1 on toodud tähtsamate prognostiliste tegurite ja nendega seotud suhteliste 5-aasta elumuste võrdlevad andmed. Selgus, et Oulu ja Tartu Ülikooli kliinikutes opereeritud haigete prognoosi mõjutavate tegurite sagedused erinesid oluliselt ($p<0,05$) T ja N kriteeriumi ning makroskoopilise tüübi jaotumuse osas.

Konservatiivsema ravitaktika tõttu on Oulus haiged valitud radikaalseteks operatsioonideks tunduvalt hoolikamalt ja mitmed potentsiaalselt ravitavad haiged (so. T1-3N2-3, T4N0-3) on sellest rühmast välja jäänud. Tartus moodustasid sellised haiged märkimise osa - 45,1% (n=183). Sel põhjusel oligi radikaalsus kahes kliinikus erinev - Oulus 43,3%, Tartus 58,8%.

Tartus opereeriti suhteliselt sagedamini ulatuslikumate (T3-T4) kasvajatega haigeid (76,9% Oulu 42,0% vastu), sest naaberkudede invasioon välistas Oulus radikaalse operatsiooni. T1-T2 kasvajate kirurgilise ravi tulemused ei sõltunud oluliselt erineva operatsioonimetoodika kasutamisest. Samas võis märgata erinevust T3 kasvajate puhul ja T4 kasvajate radikaalne opereerimine andis Tartus maovähi jaoks märkimisväärse elulemuse (34,0%).

Kui Oulus rakendati radikaalset ravi vaid N0-N1 kahjustuse korral, siis Tartus moodustasid N2 ja ulatuslikuma levikuga tuumorid 30,6% kõikidest juhtudest. Sõltumata kasvaja algkolde invasiooni sügavusest oli haigete 5-aasta suhteline

elulemus N2 kahjustusel 25,3% ja N3 kahjustusel 12,0%. Et, kasvaja invsiooni sügavus korreleerub enamasti makroskoopilise ehitusega, siis oli ka infiltratiivsete vähitüüpidega haigeid Oulus radikaalselt opereeritute hulgas vaid 21,6%. Kõikidest maovähkidest moodustavad need enamasti ikka ligikaudu poole ja nii on see olnud ka Tartus ravitute ning kogu Oulu kliiniku teeninduspiirkonna haigete puhul (2,3,9,12). Eksofüütsete vähivormide ravitulemused osutusid sarnasteks, erinesid aga oluliselt infiltratiivsete kasvajate korral - Oulus 15,8%, Tartus 34,3%.

Olles tagasihoidlikud kombineeritud operatsioonides ja lümfadenektoomias, eelistatakse Oulu haiglas gastrektoomiat maoresektsioonile sagedamini kui Tartus (tabel 2). Kuigi meie materjal ja ka kirjanduse andmed näitavad, et piisava resektsiooni-kauguse korral on maokönt kasvaja taaspuhkemise kohaks harva (väide gastrektoomia parema radikaalsuse vastu), on mao täielik eemaldamine mitmel põhjusel õigustatud (2,3). Esiteks on operatsiooni eelselt kasvaja tegelikku levikut adekvaatselt raske hinnata ja see võib olla ebaõige kuni 2/3-l juhtudest (10). Nii on haiguskolde ulatuslikul eemaldamisel on ka diagnostiline eesmärk - võimalike mikrometastaaside või naaberorganitesse sissekasvu avastamine. Teiseks tagab gastrektoomia parema juurdepääsu eemaldamist vajavatele lümfisõlmedele (näiteks parakardiaalsed, a. lienalis'e ümbruse jt.). Eriti oluline on see mitte-varajaste, infiltratiivsete või madala diferentseerumisastmega kasvajate korral, kus lisaks suurele erinevusele vähikolde mikro- ja makroskoopilise piiri vahel tuleb arvestada ka metastaseerumisega kõikidesse võimalikesse lümfikollektoritesse (6,9).

Meie andmetel ei ole põhjendatud arvamus laiendatud ja kombineeritud maovähi-operatsioonide seosest suurema operatsiooni-järgsete tüsistuste ja letaalsuse sagedusega. Kirurgiliste tüsistuste arv ja letaalsus olid kahes vaadeldud haiglas üsna sarnased, laiendatud subtotaalsed maoresektsioonid andsid aga isegi madalama suremuse (tabel 2). Seega võime kinnitada, et tüsistuste oht ei ole selliste operatsioonide sooritamise takistuseks (6).

Järeldused.

1. Sarnased elulemusnäitajad võivad olla haigete erineva selektsiooni tulemus. Patoloogiliste näitajate jaotumuste erinevused kahes vaatluse all olnud kliinikus opereeritud maovähijuhtudel on seletatavad vaid erineva agressiivsusega kasvaja algkolde ja metastaatiliste lümfisõlmede suhtes.

2. Ekstensiivse, naaberorganite resektsioonide ja laiendatud lümfadenektoomiaga kombineeritud mao-operatsiooni tähtsus muutub oluliseks just lokaalselt või lümfogeenselt levinud kasvajate (T2-T3(T4), N2(N3), Borrmanni III-IV tüüp) puhul. Et just need kasvajad moodustavad suurema osa haigusjuhtudest, võimaldab selline metoodika rahuldavate tulemustega radikaalselt ravida tunduvalt rohkem maovähihaigeid.

Tabel 1. Tähtsamate prognostiliste tegurite esinemissageduste ja 5-aasta suhteliste elulemuste võrdlus

Näitaja	Haigete arv ja %		5-aasta suhteline elulemus	
	Tartu grupp	Oulu grupp	Tartu grupp	Oulu grupp
Kõik juhud	406 (100,0)	88 (100,0)	46,1	45,5
1.Sugu				
mehed	198 (48,8)	52 (59,1)	46,9	48,1
naised	208 (51,2)	36 (40,9)	45,2	41,7
2.Vanus				
< 70 aasta	281 (69,3)	56 (63,6)	50,9	50,0
> 69 aasta	125 (30,8)	32 (36,4)	35,2	37,5
3.T aste				
T1	31 (7,6)	20 (22,7)	80,7	85,0
T2	63 (15,5)	31 (35,3)	54,0	48,4
T3	218 (53,7)	37 (42,0)	44,0	21,6
T4	94 (23,2)	0	34,0	-
4.N aste				
N0	225 (55,4)	67 (76,1)	60,0	49,3
N1	57 (14,0)	21 (23,9)	42,1	33,3
N2	99 (24,4)	0	25,3	-
N3	25 (6,2)	0	12,0	
6.Lokalisats.				
alumine	200 (49,3)	49 (45,4)	51,5	55,0
keskmine	140 (34,5)	22 (25,0)	47,9	50,0
ülemine	42 (10,3)	22 (25,0)	28,6	31,8
totaalne	24 (5,9)	4 (4,5)	20,8	0,0
7.Borrmann				
I-II	193 (47,5)	69 (78,4)	59,1	53,6
III-IV	213 (52,5)	19 (21,6)	34,3	15,8
8.Suurus				
< 4 cm	57 (14,0)	27 (30,7)	71,9	81,5
4-7 cm	192 (47,3)	47 (53,4)	44,3	29,8
8-12 cm	123 (30,3)	12 (13,6)	43,1	33,3
> 12 cm	34 (8,4)	2 (2,3)	23,5	0,0

Tabel 2. Kirurgilised tüsistused ja letaalsus radikaalsete operatsioonide järgselt

Haigla, operatsioon	Haigeid	Kirurgilisi tüsistusi	Op.-järgne letaalsus	5-aasta elulemus
Oulu Ülikooli Kliinik	88	14 (15,9)	9 (10,2)	45,5
gastrektoomia	59 (67,1)	13 (22,0)	6 (10,2)	39,0
subtot. resektsioon	29 (32,9)	1 (3,4)	3 (10,3)	58,6
Tartu				
Onkoloogiahaigla	406	59 (14,5)	24 (5,9)	46,1
gastrektoomia	170 (41,9)	37 (21,8)	18 (10,6)	32,3
subtot. resektsioon	236 (58,1)	22 (9,3)	6 (2,5)	55,9

KIRJANDUS

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Summary

Radical surgery for gastric cancer

Although close in the incidence and pathological features of gastric cancer Finland and Estonia have different policy of surgical treatment of this malignance. We performed a retrospective comparative study to analyse the causes of similar survival rates in different hospitals (Oulu University Hospital and Tartu Hospital of Oncology) and its associations with prognostic factors.

We found that the same overall survival rate after curative gastric cancer surgery may be the result of different selection of patients. Frequences of prognostic factors vary significantly ($p<0.05$) in T stages, N stages and Borrmann types. These differences can be explained by a more or less aggressive approach to combined organ resections and lymph node dissection.

Thus, the results obtained from this study indicate that the extensive surgery with systemic lymphadenectomy is a safe surgical procedure that gives good cure result and offers the possibility of increasing the number of potentially curable patients.

CURRICULUM VITAE

Andrus Arak was born on August 7, 1960, in Tallinn, Estonia. In 1986, he graduated from the Medical Faculty of the University of Tartu. After one-year residental study he obtained Surgeon's qualification and after that he practised at the Central Hospital of Jõgeva County as a General Surgeon and an Oncologist. From 1990 to 1992 he worked as an Assistant at the Department of Radiology and Oncology, University of Tartu and practised as a Surgical Oncologist in Tartu Hospital of Oncology. Since 1992, he is a Doctoral Student at the same Department.

Andrus Arak has passed study courses in 1988, in Kharkov, Ukraine and in 1992, at the Medical Faculty, University of Amsterdam. In 1994, he worked 4 months as a Visiting Scientist at the Department of Gastroenterology, Oulu University Hospital.

Andrus Arak is a member of the Estonian Cancer Union and Tartu Society of Surgeons.

The main areas of his scientific interest are the prognostic factors and surgical treatment of gastric cancer. He has 20 scientific publications.

ELULOOKIRJELDUS

Andrus Arak on sündinud 7. augustil 1960. aastal Tallinnas. 1978. aastal lõpetas ta Tallinna 1. Keskkooli ja 1986. aastal Tartu Ülikooli arstiteaduskonna raviosakonna. Pärast aastast internatuuri kirurgia erialal Tartu Kliinilises Haiglas töötas Jõgeva Rajooni Keskhaiglas kirurgi ja onkoloogina. Aastatel 1990–1992 oli ta Tartu Ülikooli arstiteaduskonna radioloogia ja onkoloogia kliiniku assistent, praktiseerides samal ajal pidevalt ka kirurgilise onkoloogina Tartu Onkoloogiahaiglas. Alates 1992. aastast on ta sama kliiniku doktorant.

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Andrus Araku teaduslikuks uurimisvaldkonnaks on olnud peamiselt maovähi prognostilised tegurid ja radikaalne kirurgiline ravi. Ta on avaldanud 20 publikatsiooni.

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