Eur J Cancer Clin Oncol, Vol. 21, No. 6, pp. 655–658, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Perspectives and Commentaries

Prognostic Significance of Pathological Staging in Gastrointestinal Tumors

H. BLEIBERG

Service de Médecine et Laboratoire d'Investigation Clinique H. Tagnon, Unité de Gastroentérologie, Institut Jules Bordet, Brussels, Belgium

(A COMMENT ON: Kayser K, Burkhardt H-U, Bleyl U *et al.* Volume, staging and grading of gastrointestinal carcinoma—a population-based study. *Eur J Cancer Clin Oncol* 1984, **20**, 1127–1134.)

THE MAIN reason for pathologic examination of gastrointestinal organs resected for adenocarcinomas is to determine prognostic factors. Differences in prognostic factors are responsible for the large variation in survival observed among the same histologic type of cancer and are even more substantial than improvement due to therapy. It is thus of paramount importance to recognize these factors for the design of therapeutic trials and interpretation of the results.

Among the different categories of prognostic factors possibly affecting the patient outcome, anatomic staging and histology are correlated to survival [1, 2]. We shall briefly review the current data establishing this correlation in primary colorectal and gastric cancer.

LOCATION OF THE TUMOR

The 5-yr survival in rectal carcinoma is 10–15% lower than in colon cancer [3]. This difference has been confirmed [4] or denied [5] in other series. Carcinoma of the right colon, especially the caecum, may also have a less favorable prognosis [4]. In gastric cancer, carcinoma of the cardia has a worse prognosis than tumors at other sites [6].

TUMOR SIZE

Most of the available data indicate that the size of the tumor has little relationship to prognosis. The statement, "the larger the tumor the worse the prognosis," is generally not true for gastrointestinal cancers. No correlation is found between measurements of resected carcinomas and the 5-yr survival rates or the percentage with concomitant metastases [7]. Some authors even found significantly higher 5-yr survival rates after resection of large tumors [8]. Similarly, in gastric cancer large- and medium-sized tumors appear to have a better prognosis than those less than 2 cm [6].

PENETRATION

In 1932 Dukes described a remarkably simple system for the pathologic staging of carcinoma of the rectum [9]. In his original paper the criteria for three stages of extension of tumor were described: A, growth limited to wall of rectum; B, extension of growth to extrarectal tissues but no metastases in regional lymph nodes; C, metastases in regional lymph nodes. Although Dukes' work was intended for carcinomas of the rectum, his staging system has been widely applied to tumors of the colon and extrapolation seems reasonable. Numerous studies have established an inverse relationship between the local extent of carcinoma of the colon and rectum and 5-yr survival rates [10–12]. During the past decades several changes in Dukes' staging system were proposed. Data from reports classifying local spread in terms of specific layers of the wall of the involved intestine showed that the most dramatic decrease in survival rate occurred with penetration of the muscularis propria, suggesting that the muscular layers may form an important barrier to invasion [11]. However, patients with carcinoma limited to the mucosa represent less than 1% and subclassification for other wall layers does not seem to offer any advantage over the original Dukes

Accepted 20 November 1984.

classification [12]. In gastric cancer longer survival belongs to tumors confined to the mucosa. The rate of 5-yr survivors for pT_1, pT_2 and pT_{3-4} is 80, 38 and 9% respectively. These low survival rates once the muscular layer is involved indicate that node and visceral metastases occur very soon [6].

METASTASES TO LYMPH NODES

Multiple studies of large numbers of patients leave no doubt that the presence of metastases to lymph nodes in a resected specimen greatly decreases the probability of cure. Reported 5-yr survival rates range from less than 30 to 45% for patients with involved lymph nodes [9] and from 52 to well over 80% for those without [13]. Some of the variability in survival data is probably due to the selection of patients. However, the differences in results may also be due to variations in the proportion of instances in which metastases were detected. Nodal involvement ranges between 32 and 68% of resected specimens and these variations mainly result from dissimilarities in the procedure used to detect them [14]. The number and location of lymph node metastases is also of prognostic significance. In patients with less than five nodes involved the 5-yr survival rate was 24% compared to 9% when more than five nodes were involved. Moreover, when only regional nodes are involved the survival rate is 53%, as compared with 15% for more extensive lymphatic spread involving nodes at the point of ligature of blood vessels. The presence of venous invasion significantly reduces the survival rate [13], and although invasion of the perineural lymphatics has been far less studied, available evidence indicates that they affect prognosis adversely [7]. However, for colon cancer the extent of penetration remains significantly related to survival, whether or not veins and lymphatics are involved [5, 13]. In gastric cancer the 5-yr survival rate was 40.5% for patients without lymph node metastases and 11.8% for those with node metastases. Here also evidence is available to support the hypothesis that survival is related to the proportion of local nodes involved and is not a function of the absolute presence or absence of secondary spread to lymph nodes. Patients with fewer than five nodes involved may have a 5-yr survival comparable to patients without lymph node involvement [6].

HISTOLOGY, GRADING AND CELLULAR INFILTRATIONS

Studies of histologic structure have shown that patients with colorectal carcinoma classified as less differentiated have a significantly smaller chance of cure than patients with well-differentiated tumors [13]. Unfortunately the criteria used for determining grades are not easily specified [11]. More than 50 yr ago it was shown that the presence of lymphocytic infiltration was of greater significance, in terms of survival, than the degree of cellular differentiation. Carcinomas with an intact margin surrounded by an inflammatory infiltration of plasma cells and lymphocytes may become large and spread locally but will not metastasize while those with an infiltrating margin and no inflammatory infiltration metastasize frequently [15]. More recent studies confirm that the presence of a lymphoplasmocytic infiltration in the center of or around the tumor has a favorable effect on survival [5]. In gastric carcinoma there is a great variability in the degree of differentiation in different parts of the same tumor. There is a significant difference in the percentage of 5-yr survivors with anaplastic or poorly differentiated carcinomas compared with differentiated tumors, but it is not very great. The degree of lymphocytic and plasma cell infiltration of the carcinoma seems to be a favorable prognostic sign. Indeed, about 40% of the patients survived for more than 5-yr compared with about 18% for those with tumors which showed little or no lymphocytic and plasma cell infiltration [6].

A great number of tumor and patient characteristics have been tested as prognostic variables. Tumor markers could not be correlated to survival. Conclusions regarding age, sex, race, socioeconomic status or even symptoms were often contradictory [11, 16]. Pathologic staging was reliably correlated to survival. The paper of Kaiser *et al.* [17] gives interesting information regarding the extension of gastrointestinal tumors at the time of surgical resection for a European population. Unfortunately due to the data protection law in West Germany these characteristics could not be correlated with survival. This makes the interpretation of results difficult. Most of the information on survival is based on data published in American series. Considering the possible influence of environmental factors, survival rates might be different in European and American series. Confrontation of pathologic staging with survival is also a way of controlling the methods used to determine the stage. This might be even more important in multicenter studies. Differences in the death rate of Dukes B, for example, would suggest, for a homogeneous population, differences in techniques used for identifying lymph nodes [14]. Moreover, in his studies Kaizer correlated positively invasiveness and tumor size. The prognostic value of penetration is well known while tumor size is generally not correlated with

survival [6-8]. Survival studies could have clarified this point.

Identification of prognostic factors is important in the analysis of studies comparing treatments because before evaluating the effect of treatment one must first ensure that the groups compared are in fact comparable with respect to important prognostic factors. As far as pathological staging is concerned this is not equally feasible for all gastrointestinal tumors. In colorectal cancer there is a sequence of stop-points, i.e. the muscular layer, the intestinal wall, the lymph nodes and the liver, which in most cases seem to cause a delay in tumor progression leading to a stratification in what looked like a homogeneous group of patients. Even when the liver is invaded, the disease may remain for long periods of time in that localization before disseminating to other sites. For this type of cancer the pathologic staging correlates satisfactorily with survival [5, 7-9, 13].

Gastric cancers appear to be much more aggressive. Once the tumor grows beyond the submucosa, progression occurs very quickly and dissemination in multiple sites may be observed very soon after curative surgery. Sixty percent of the patients operated with a curative aim will die and have therefore, to various degrees, generalized cancer. Pancreatic and esophageal cancers are probably generalized at the time of diagnosis since most of the patients operated with a curative aim will die within 1 or 2 yr. In these tumor types the pathologic staging underestimates tumor dissemination and cannot give precise information on tumor burden. No anatomic criteria can be found and new prognostic factors should be investigated.

One may speculate what might be the nature of these new prognostic factors. Cell kinetic parameters have been said to be correlated with Dukes' classification in colon cancer. Studies undertaken on small numbers of patients are contradictory [18]; however, the idea of linking one or several proliferative parameters to tumor aggressivness is worthwhile to be tested on larger series of patients.

Gastrointestinal tumors are currently considered as a single cell population. In colon cancer three different cell lines have been identified in cell culture [19], suggesting that gastrointestinal tumors might be heterogeneous. The poor results of chemotherapy in these cancers might be explained, at least partially, by the lack of stratification according to different cell subpopulation. Identification of these cell lines should now be a major field of research.

REFERENCES

1. Byar DP. Identification of prognostic factors. In: Buyse EM, Staquet MJ, Sylvester RJ, eds. *Cancer Clinical Trials. Methods and Practice*. Oxford, Oxford University Press, 1984, 423-443.
2. Zelen M. Importance of prognostic factors in planning therapeutic trials. In: Staquet MJ, ed. *Cancer Therapy: Prognostic Factors and Criteria of Response*. New York, Raven Press, 1975, 1-5.
3. Moertel CG. Carcinoma of the stomach: prognostic factors and criteria of response to therapy. In: Staquet MJ, ed. *Cancer Therapy : Prognostic factors and Criteria of Response*. New York, Raven Press, 1975, 229-253.
4. Falterman KW, Hill CB, Markey JC, Fox JW, Cohn I. Cancer of the colon, rectum and anus: a review of 2313 cases. *Cancer* 1974, **34**, 951-959.
5. de Mascarel A, Coindre JM, de Mascarel I, Trojani M, Marie D, Hoerni B. The prognostic significance of specific histologic features of carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1981, **153**, 511-514.
6. Hawley PR, Westerholm P, Morson BC. Pathology and prognosis of carcinoma of the stomach. *Br J Surg* 1970, **57**, 877-883.
7. Spratt JS, Spjut HJ. Prevalence and prognosis of individual clinical and pathologic variables associated with colorectal carcinoma. *Cancer* 1967, **20**, 1970-1985.
8. Osnes S. Carcinoma of the colon and rectum; a study of 353 cases with special reference to prognosis. *Acta Chir Scand* 1955, **110**, 378-383.
9. Dukes CE. The classification of cancer of the rectum. *J Pathol Bacteriol* 1932, **35**, 323-329.
10. Newland RC, Chapuis PH, Pheils MT, MacPherson JG. The relationship of survival to staging and grading of colorectal carcinoma. A prospective study of 503 cases. *Cancer* 1981, **47**, 1424-1429.
11. Buckwalter JA, Kent TH. Prognosis and surgical pathology of carcinoma of the colon. *Surg Gynecol Obstet* 1973, **136**, 465-472.
12. Roseman DL, Straus AK. Staging of carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1980, **151**, 93-95.

13. Copeland EM, Miller LD, Jones RS. Prognostic factors in carcinoma of the colon and rectum. *Am J Surg* 1968, **116**, 875-881.
14. Grinnell RS. The spread of carcinoma of the colon and rectum. *Cancer* 1950, **3**, 641-652.
15. MacCarty WC. Principles of prognosis in cancer. *JAMA* 1931, **96**, 30-32.
16. Polissar L, Sim D, Francis A. Survival of colorectal cancer patients in relation to duration of symptoms and other prognostic factors. *Dis Colon Rectum* 1981, **24**, 364-367.
17. Kayser K, Burkhardt H-U, Bleyl U *et al.* Volume, staging and grading of gastrointestinal carcinoma a population based study. *Eur J Cancer Clin Oncol* 1984, **20**, 1127-1134.
18. Bleiberg H, Buyse M, van den Heule B, Galand P. Cell cycle parameters and prognosis of colorectal cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 391-396.
19. Brattain MG, Fine WD, Khaled FM, Thompson S, Brattain DE. Heterogeneity of malignant cells from a human colonic carcinoma. *Cancer Res* 1981, **41**, 1751-1756.