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Prognostic Indicators in Rectal Carcinoma. An evaluation of Clinicopathological Variables, Tumour Markers and Tumour Stage

Minireview based on a doctoral thesis

Elisabeth Ståhle

Department of Surgery, University Hospital, Uppsala, Sweden

INTRODUCTION

Colorectal cancer is today the most common malignant disease in Sweden, (Cancer Incidence of Sweden, 1984), considering both sexes combined. Thirty-five to forty per cent of all tumours in the large bowel are situated in the rectum or rectosigmoid, where 95-96 % are adeno-carcinomas. In a few per cent (3-4 %) the tumour originates from the epithelium of the anal canal. In rare cases a carcinoid, sarcoma or malignant lymphoma may occur in the rectum.

At present, surgical resection is the only effective method for treating patients with colorectal cancer. Surgery for cure is initially possible, however, in only 60 % of the patients (4,56) and even after a potentially radical surgical procedure, 50 % of the patients will die of the disease. In patients operated upon for a rectal carcinoma the relapse of the disease is often local. In contrast, the major problem for patients operated upon for an adenocarcinoma of the colon is predominantly distant metastases.

In rectal cancer, perioperative radiotherapy decreases the incidence of local recurrences (7,57,60) and might improve survival (69). Hitherto all efforts to improve survival in patients with colorectal carcinoma with postoperative adjuvant chemotherapy have been unsuccessful (47). Recent data suggest, however, that pre- or peroperatively initiated additional cytotoxic therapy may represent a possible way of improving the survival rates (62,79). Also, experience from other tumour types indicates that pre- or peroperative initiation of such treatment may be more successful than postoperative (52).

The question of additional therapy commenced pre- or peroperatively causes much concern, however, since there is no way of excluding from therapy subgroups of patients with a low risk of recurrence. Moreover, in patients with disseminated disease discovered at surgery, the value of adjuvant therapy in the form available at present is limited.

It is thus of utmost importance to find potent prognostic predictors that are available prior to, or at least in certain instances during surgery so that patients suitable for additional therapy can be selected.

REVIEW OF THE LITERATURE

PROGNOSIS

Surgical curability and prognosis

The surgical curability rate, i.e. the proportion of patients with a radically removed rectal tumour and with no known distant metastases, is approximately 60 % in an unselected patient material (56).

The corrected 5-year survival of patients with a "potentially cured" rectal tumour is about 30-70 % (61,86) The cancer mortality is highest within the first two years, but not until seven to ten years is the mortality rate negligible for cancer of the colon and rectum (19).

An important factor in the overall result is the early postoperative mortality. After an apparently curative resection the postoperative mortality is 5 % (8,56,69). With modern anaesthetic methods the mortality rate has decreased substantially and this is probably the most likely explanation for the slight improvement in prognosis during the last two decades (19).

Local recurrence

The rate of local tumour recurrence after curative surgery varies considerably in different series of patients, but in the majority of unselected series it is often high (30-50 %) (4,54). Local recurrence usually means an incurable disease. Attempts to

perform extended resection of local recurrences are associated with high morbidity and mortality (65,85). Radiotherapy may have a good palliative effect and results in 5-year survival in a few cases (11).

Generalized disease

If the tumour shows generalized spread, the median survival is six to eight months and very few patients survive five years (4,51,61). One report claims that the presence of occult hepatic metastases at surgery is the single feature that is responsible for a poor long-term outcome after potentially curative surgery for large bowel cancer (22).

SURGERY

In patients with a tumour located lower than five cm from the anal verge, an abdominoperineal resection (29) is probably the most widely used technique. When the tumour lies more than 12 cm above the verge, an anterior resection with a hand-sewn anastomosis is today most generally preferred. For tumours located in between, the introduction of the stapling technique has strongly promoted sphincter-saving surgery (35,70). In order to achieve locally radical surgery it is of great importance that a wide en bloc resection of the bowel be performed, including the perirectal fat laterally, the mesocolorectum dorsally and the anal canal inferiorly together with considerable parts of the levator ani muscles, and lymph nodes along the superior haemorrhoidal vessels (36). The adoption of stapling devices and the increased proportions of sphincter-saving procedures have further raised the question as to the most appropriate distal margin of clearance. A distal margin of 3 cm has been considered adequate (87).

Surgical resection of hepatic and pulmonary metastases synchronously or metachronously with the primary procedure might improve the 5-year survival rates in carefully selected groups of patients (64).

ADJUVANT RADIOTHERAPY

In rectal cancer, radiotherapy given in an adequate dose in addition to surgical treatment decreases the incidence of local

recurrence (7,25,57,60) and might improve survival (69). The minimum dose required to kill micrometastases is about 45 Gray (Gy) using conventional fractionation, or a comparable dose with other fraction schedules (23) if given prior to surgery. Postoperatively, hypoxic areas due to vascular derangement may render the tumour cells more resistant to the radiation. Data indicate that in this situation higher dose levels are required to kill micrometastases with a high probability (23).

ADJUVANT CHEMOTHERAPY

Until now all efforts to improve survival in colorectal carcinoma with postoperative adjuvant chemotherapy have been unsuccessful (47). Recent findings suggest, however, that some new chemotherapeutic combinations, such as a combination of sequentially administered methotrexate and 5-fluorouracil (5-FU), together with leucovorin rescue, have a promising antitumoural effect in patients with metastatic colorectal disease and may also prolong survival in such patients (26, personal communication). There are also reports that 5-FU combined with a high dose of leucovorin has given improved response rates as indicated by preliminary results from two controlled clinical trials (15,20). No chemotherapeutic regime has yet altered the survival, as properly evaluated in a controlled study, in patients with metastases from colorectal cancer.

In a controlled study on patients recently reported by Taylor et al. (79), intraoperative and immediately postoperative portal vein infusion of 5-FU led to improved survival (79). Another approach is to administer the chemotherapeutic agent intraperitoneally in order to reduce the risk of liver metastases and/or peritoneal implants (33,77).

NEOADJUVANT CHEMOTHERAPY - THEORETICAL CONSIDERATIONS

In all adjuvant settings, the main issue is the treatment of sub-clinical disease, which may include micrometastases. Micrometastases usually have a higher growth fraction, which should thus make these cells more sensitive to cytotoxic therapy than cells in large tumours (14). The timing of the introduction of systemic treatment is perhaps one of the most important determinants of the therapeutic outcome. The majority of animal

experiments and the results of retro- spective analyses in several clinical trials suggest that delay in starting adjuvant therapy even by a short time period may abolish the benefits that are documented to be gained with early treatment (53,62).
In theory, the objectives of preoperative chemotherapy in colorectal cancer are:
- to prevent possible acceleration of the cell duplication rate after non-curative surgery, a phenomenon observed in experimental studies;
- to prevent tumour cell duplication beyond the number that can be killed by chemotherapy;
- to prevent or diminish the risk of resistance to chemotherapy; studies of resistance have shown that even a short delay in commencing chemotherapy may adversely affect the outcome (29), as during this delay, the first resistance cells may appear, thus eliminating the probability of cure;
- to reduce the viability of tumour cells that may be shed into the circulation and/or into the peritoneal cavity during surgery.

It is therefore logical, at least on a theoretical basis, to use a promising combination of cytotoxic drugs and to apply this new approach of scheduling, i.e. preoperative initiation of chemotherapy, in a strong effort to improve the overall survival in patients undergoing surgery for colorectal cancer. Hitherto only one adjuvant trial has shown improved survival and in this trial, therapy was initiated peroperatively (79).
The principal aim of all therapy additional to surgery should of course be to increase the proportion of cured patients, and not solely to prolong disease-free survival time. As mentioned above, in (neo)adjuvant settings it is a question of treating subclinical disease. The tumour cell burden in patients "potentially cured by surgery" may, however, vary between 0 and 10^9 cells (14). The extent to which chemotherapeutic agents available today against colorectal cancer may reduce this tumour cell burden is not yet fully established, but it is clearly limited. Even if it may be postulated that micrometastases are more sensitive to cytostatic drugs than macroscopic disease, data from studies on advanced disease indicate that the cytoreduction properties are at most in the order of 100- to 10,000-fold cell

kill (47). It is reasonable to assume that patients dying of late cancer-specific death are predominantly those with a minimum of tumour cells left after surgery (see also below).

PROGNOSTIC PREDICTION

General considerations

There are many reasons for attempting to identify prognostic factors: 1/ They may provide insight into the nature of a disease; 2/ they facilitate comparison between different groups of patients regarding the outcome of a disease; 3/ they may help in deciding what treatment and/or follow-up schedule should be used in an individual patient or a group of patients.

The response variable (the dependent variable) is a measure of the future health or illness of the patient and its value is usually dependent on one or more prognostic factors. The response might be dichotomous (i.e. relapse of disease or not, cancer-specific death or not), ordinal (i.e. a certain tumour stage at surgery) or a measure of time (with the possibility of censored observations). In addition, the explanatory variables can be of different kinds, e.g. dichotomous, categorized or continuous. This must be taken into account when choosing an appropriate statistical model for identifying and evaluating prognostic factors.

Statistical models

The prognostic value of different factors is usually assessed by creating a model relating the response in some way to the factors in question. The following examples constitute a brief survey over such models.

The standard multiple regression model

The best known version is multiple regression, in which the response variable is continuous with an expected value which is a linear or a more complicated function of the prognostic variables (16).

The logistic regression model

When the response variable is dichotomous (e.g. survival or death), the standard regression model is not suitable. Instead

the logistic regression model has been used. If p denotes the probability of dying, for example, the logistic regression model implies that the natural logarithm of the odds ratio of dying (ln p/(1-p)) is a function (usually linear) of the explanatory variables (40).

Walker & Duncan regression model
If the response is an ordinal variable, this also makes a standard regresssion model unsuitable, and here a generalization of the logistic model can be used (83).

Life table method
A particularly common situation is that the response variable is the survival time but the maximum follow-up time is of different lengths for different individuals. The usual way to analyse data of this type is by life table analysis (39). One method is to subdivide the data according to prognostic variables, and perform life table analyses separately for each subgroup, using the median survival time or the proportion of individuals surviving for some fixed time. This approach is tedious, especially if there are many prognostic variables, and it is not generally useful for examining several prognostic variables at the same time.

Cox proportional hazards model
The Cox proportional hazards model is the model most commonly used for analysing the effects of several variables on survival. One advantage of this model is that the baseline hazard function need not be specified, which means that the model is more general than models based on specific distributions (43).

Prognostic indicators: clinical features
Sex has been claimed to influence survival; women are more often found to have a slightly better outcome than men (4,46). A lack of correlation with sex has recently been reported, however (18). The level of the lesion in the rectum is of prognostic importance in patients operated upon for cure (18,86). In all patients the mobility of the tumour has proved to be of great prognostic importance, as has the number of quadrants involved (18). In several, but not all series it has been found that the duration

of symptoms and certain specific symptoms such as a history of rectal bleeding, abdominal pain and bowel obstruction contain prognostic information (8,13,24).

Prognostic indicators: tumour stage

In patients with colorectal carcinoma it is still the histological examination of the surgical specimen, with the use of different tumour staging systems, that provides most prognostic information. Dukes' staging system, i.e. classification according to the degree of penetration of the tumour through the bowel wall, is the system most frequently employed. The corrected 5-year survivals related to Dukes' stage are 80-100 % for stage A; 40-65 % stage B; 20-35 % stage C; 0-5 % stage D (17). All tumour staging systems, e.g. the Astler/Coller system (3), the pTNM system (78) and the Australian clinico-pathological staging system (12) are relatively specific in predicting survival. The rate of false positive prediction is low. However, the rate of false negative predictions is relatively high in all systems. Dukes' system is comparable to the others concerning sensitivity and specificity (50). Recently Jass et al. (37) have described an alternative classification of the surgical specimen, including the number of lymph nodes with metastatic spread, the character of the invasive margin, peritumoural lymphatic infiltration and local spread, and consider it to be superior to other systems (38).

Radiological methods such as preoperative computed tomography (CT) (1) and ultrasonography (55) have been evaluated for their ability to disclose tumour growth into or through the bowel wall and/or to disclose lymph node metastasis, but their accuracy is not yet sufficiently high.

Prognostic indicators: tumour differentiation

The histological differentiation of the tumour reveals prognostic information which, at least to some extent, is independent of that given by tumour stage (37). However, tumour differentiation is known to be very subjective and to vary considerably both inter- and intraindividually (66,80). The majority of cases are referred to the moderately differentiated group. The degree of

differentiation is also known to vary considerably between different parts of the tumour; the correlation between the differentiation in the diagnostic biopsy and in the definitive pathological examination is poor (9,66).

Prognostic indicators: serum markers

Alterations in blood constituents have been used as indicators of the presence of malignancy, the stage of the disease and the prognosis (44). These substances may be produced by normal cells as a reaction against the tumour. For example, acute phase reactant proteins have been claimed to provide prognostic information in patients with colorectal carcinoma (83).

Alternatively, the tumour cells may produce the substances themselves, so-called tumour markers. Human chorionic gonadotropin for chorio-carcinoma, alpha-fetoprotein in the detection of hepatic or testicular malignancy, and the specific blood hormone levels for a specific endocrine tumour (44), provide the sensitivity and the specificity needed for a definite diagnosis of a specific tumour type. To date, the usefulness of most other specific tumour markers is limited to evaluation of a patient's response to therapy, and as a prognostic indicator.

Thymidine kinase

The serum level of thymidine kinase, which is a marker of cell proliferation, has been found to correlate with the stage of the disease and to be of prognostic importance in patients with malignant lymphomas (31) and small cell carcinomas of the lung (32).

Neuron-specific enolase

Neuron-specific enolase, which is normally present in high concentrations in neurons and neuroendocrine cells, has been introduced as a marker for tumours with neuroendocrine properties, but is also expressed in certain non-neuroendocrine tumour cells (58).

Carcinoembryonic antigens (CEA)

CEA is perhaps the tumour-associated antigen that has been most investigated clinically in cancer, and it is claimed to provide

information not only in colorectal cancer but also concerning other malignancies (bladder: 52, stomach: 68, bronchogenic cancer: 63).
This oncofetal glycoprotein (27) is present in fetal tissues and in human colonic cancer. It is thought to be a product of a fetal gene, a gene which is normally repressed in the adult individual but derepressed as a consequence of malignant transformation. However, CEA is also present in normal epithelial cells and the differences in CEA derived from normal and malignant tissues are quantitative rather than qualitative. Significantly increased concentrations of this substance have been found in the plasma of patients with a variety of benign diseases (81). CEA has been reported to correlate with disease recurrence in patients who have undergone resection of colorectal cancer (21,30,85) and also to correlate with survival (67). However, it has also been reported that poorly differentiated tumours seem to produce less CEA (30).

Tissue polypeptide antigen (TPA)
The elevated levels of circulating TPA antigenicity (5) that are present in the sera of patients with carcinoma, correspond to soluble proteolytic fragments from a particular ceratinine subgroup, which are known cytoskeletal components in epithelial cells. Hence, TPA cannot be considered to be a tumour-specific antigen, and an increase in circulating TPA probably reflects cell destruction and/or cell shedding.
Most neoplasms except those derived from stratified epithelial cells or mesenchymal cells might be expected to be positive for TPA. However, the percentage of patients showing elevated TPA levels are highest for adenocarcinomas of different sites (6).
The serum level of TPA has been claimed to correlate with the tumour stage in colorectal cancer (2). It has also been found to give information concerning a variety of other malignancies (5,63,49).

Carbohydrate antigen (CA-50)
CA-50 is a carbohydrate antigen which is expressed in the cell membrane of tumour cells and which is identified by a monoclonal antibody called C-50 (45). The CA-50 antigens are present in the cell membrane in a lipid-bound form (ganglioside) and in a high

molecular weight protein-bound form (glycoprotein). The CA-50 antigens are shed into the circulation, where they can be measured. The C-50 monoclonal antibody identifies two different carbohydrate structures which make the test independent of the Lewis status. Another monoclonal antibody, 19-9 (41), reacts with one of these two antigenic determinants. Smokers have elevated serum levels of CA-50, as do patients with cirrhosis of the liver and inflammatory bowel diseases (45).
CA-50 is claimed to be of value in staging and postoperative management of patients with colorectal carcinoma (34), and in other gastrointestinal malignancies (42).

AIMS OF THE INVESTIGATION

The main purpose of this investigation was to identify a scoring system which, by the use of preoperatively available predictors only, could classify patients with primary rectal carcinoma into prognostic categories that would be clinically useful in the selection of patients for additional therapy.

The specific aims were:
1. to select a number of serum markers, representing different aspects of the tumour/tumour cell characteristics, that could be of prognostic relevance in rectal cancer;
2. to evaluate the use of the selected markers (CEA, TPA and CA-50) in preoperative staging and prognostication in patients with a rectal tumour;
3. to determine the amount of prognostic information present in preoperatively available clinical and histopathological variables, individually or in combination, in patients with carcinoma of the rectum;
4. to select the set of these preoperatively available variables that best predicted survival and evaluate their discriminatory power; and
5. to assess the ability of these variables to identify patients who will have a late cancer-specific death.

RESULTS

SELECTION OF TUMOUR MARKERS

In a first screening attempt we tested a number of possible serum markers, i.e. thymidine kinase, neuron-specific enolase, different acute phase reactants (orosomucoid, haptoglobin, $Æ_1$ antitrypsin), IgG, IgM, IgA and TPA in preoperative sera from patients with a carcinoma of the rectum. Extremely few patients (4/107) had elevated serum levels of TK, although several of the patients had generalized disease. Analyses of the sera from 30 patients did not show any correlations between levels of NSE, acute phase reactants or immunoglobulins, on the one hand, and tumour stage or prognosis, on the other. Thus none of these markers were considered appropriate for further testing. The preoperative serum level of TPA, however, was found to be correlated to the presence of rectal cancer, the stage of the disease and the prognosis in this screening analysis (data not presented separately).

In a separate screening procedure (59), one newer so called "tumour-specific" marker, namely CA-50, was also considered. Determinations of the CA-50 levels in sera from presumedly healthy blood donors gave a mean value of 7.7 U/ml; the mean value + 2 SD was 16.5 U/ml. In a material consisting of 266 non-consecutive patients with carcinoma of the colon or rectum, 47 % (126 patients) had elevated serum levels of CA-50. Very few patients (5 %) with benign colorectal disease had an elevated level. Among patients from whom serum was taken 6-36 months after curative resection, 62 % of those with known recurrence had elevated levels. The corresponding figure for patients with no evidence of disease was 25 %. Among 139 patients from whom both a preoperative and a postoperative (6-9 months after surgery) serum sample was taken, 12 patients showed a clear rise in CA-50 (>15 U/ml). None of these patients displayed clinical signs of disease at the time that the serum sample was taken, but they all had recurrence during the prolonged follow-up.

We therefore chose to further evaluate the preoperative serum levels of CA-50 and TPA. In addition, CEA was included as representing the most extensively used tumour marker in

colorectal cancer.

PREDICTION OF TUMOUR STAGE

S-CEA showed a clear correlation to tumour stage in that the proportion of patients with elevated levels increased with each successive stage. However, S-CEA did not become truly discriminatory either for a locally advanced tumour or for metastatic spread.

The serum level of TPA was clearly correlated to the tumour burden. This stage-dependent correlation was demonstrated both by significant differences in mean levels of TPA and by the probability of predicting the tumour stage as calculated from the logistic regression model. Patients with low S-TPA had a very high probability of having a localized tumour (stage A). An increase in the level of S-TPA was associated with a decreased probability of having a tumour in stage A and with an increased probability of having a tumour first in stage B and then in C. Finally, patients with a clearly elevated serum level were most likely to have metastatic spread.

Also, S-CA-50 showed a statistically significant relationship to the tumour stage. Although there was no true correlation with the extent of local tumour growth, S-CA-50 was able to discriminate between patients with and without metastatic disease.

Hence, all three tumour markers were found to be clearly related to Dukes' staging system and the presence of metastatic spread (72). They also yielded information additional to that provided by stage when tested in a multivariate approach. TPA showed the strongest association with the stage of the disease and when TPA was taken into account, S-CEA and S-CA-50 contributed further. TPA was also the most informative marker concerning metastatic spread, but S-CA-50 also yielded significant additional information.

PREDICTION OF PROGNOSIS by the use of the preoperative serum levels of CEA, TPA and CA-50

A strong correlation was found between a single preoperative determination of either S-CEA, S-TPA or S-CA-50 and prognosis, both in terms of crude survival in the total patient material and

of disease-free survival in "potentially cured" patients (73).

S-TPA appeared to have a logarithmic relationship to prognosis, i.e. prognostic information was provided even by low levels and by moderately elevated levels, with a more pronounced increase in the relative hazard for clearly elevated levels. S-CEA and, especially, S-CA-50 seemed to have a somewhat different kind of relationship to survival in that only clearly increased levels influenced the risk. However, the results showed that the use of tumour markers in their natural logarithmic form in the Cox proportional hazards model was appropriate.

The results of the analysis suggested that the use of a combination of markers provided more information than one alone. The model for and the clinical usefulness of the combination are at present difficult to decide. We tried to combine different cut-off levels that appeared clinically useful. The use of normalized ranges was of limited value. A finding that all tumour markers were within the normal range was not a universal sign of long-term survival, and similarly, a finding that they were all beyond the normal range was not equivalent to a poor prognosis. Neither was the elevation of one or two tumour markers of apparent prognostic value. The critical serum level, as calculated by the Cox regression model, that best separated the patients with regard to prognosis resulted in too few patients in one of the two subgroups, and was thus of limited clinical relevance.

Using a generalized version of the basic Cox model where the effects of variables were assumed to be constant within the time intervals 0-1, 1-2 and >2 years, but were allowed to change between the intervals, it was found that the preoperative serum level of each tumour marker was closely associated with the risk of dying of rectal cancer during the first year after surgery ($p<0.001$) in patients "potentially curable by surgery" and, among this group, in those "potentially cured" (76). During the second year after surgery the prognostic information given by any tumour marker was reduced, although still statistically significant. S-CEA and S-CA-50 gave very little or virtually no prognostic information in patients who survived two years from diagnosis. S-

TPA, however, provided some prognostic information in these patients also.

PREDICTION OF PROGNOSIS by the use of preoperatively available clinical and routine pathological variables

Two variables indicating surgical non-curability, i.e. immobility of the tumour and the presence of metastatic spread diagnosed prior to surgery, gave the greatest prognostic information ($p<0.001$) concerning crude survival in all patients (71). Patients with a polypoid tumour had a better survival ($p<0.01$). Abnormal liver function tests indicated a poor prognosis, as did tumour ulceration, tumour stricture, a large tumour and an anterior tumour location. Patients with a poorly differentiated lesion as discovered by routine analysis of the preoperative biopsy showed decreased survival, whereas the difference in survival between patients with a highly and those with a moderately differentiated tumour was not so apparent.

The same variables as were found to be of prognostic importance regarding crude survival in the whole material, except the two indicating surgical non-curability and abnormal liver function tests, also gave statistically significant ($p<0.05$) information in patients "potentially curable by surgery". In addition, age provided statistically significant prognostic information in this group (a high age was associated with a poorer prognosis).

Analysis of cancer-specific survival gave results comparable to those for crude survival both for the whole material and for those "potentially curable" by surgery. The set of preoperatively available clinical variables that had the best prognostic value in patients "potentially curable" by surgery was the knowledge of whether the tumour was polypoid or not combined with the age of the patient at the time of diagnosis.

Using the alternative version of the standard Cox model where the estimates were allowed to change between certain time intervals, patients with a polypoid tumour seemed to have a good prognosis also beyond two years after diagnosis. The tumour size, tumour stricture and ulceration gave limited information, but this was of the same magnitude for all time periods (tumour size $\beta_{0-1\ year}=0.004$, $\beta_{1-2\ year}=0.002$, $\beta_{>2\ years}=0.003$, $\beta_{tot}=0.003$);

tumour stricture $\beta_{0-1\ year}=0.65$, $\beta_{1-2\ year}=0.31$, $\beta_{>\ 2\ years}=0.57$, $\beta_{\ tot}=0.48$; tumour ulceration $\beta_{0-1\ year}=1.02$ $\beta_{1-2\ years}=1.17$, $\beta_{>\ 2\ years}=1.05$, $\beta_{\ tot}=1.05$).

PREDICTION OF PROGNOSIS by histopathological findings in the diagnostic biopsy

The majority of the tumours in patients "potentially curable" by surgery were classified as tubular (67 %), had an irregular tubular configuration (76 %) and showed a small or moderately large nuclear size (81 %) as judged from the biopsy material (74). Polypoid structures were present in 53 cases (21 %). Most tumours were considered to be moderately differentiated (57 %), but a remarkably large number were judged to be poorly differentiated (27 %). There was no correlation between these histopathological features as displayed in the biopsy and the definitive tumour stage.

Patients with a well differentiated tumour had a better prognosis ($p<0.04$) than those with a less well differentiated lesion. In 43 % of the patients the over-all subjective impression was an "aggressive" tumour pattern. These patients had worse survival prospects ($p<0.04$).

However, even if some of these easily identifiable variables correlated with the prognosis, the prognostic information provided was limited.

PREDICTION OF PROGNOSIS by the best combination of preoperatively available predictors

Using all the preoperatively available variables in the Cox regression model and in a multivariate way, the preoperative serum levels of the three tumour markers combined with the knowledge about preoperatively diagnosed metastases and polypoid tumour growth constituted the set of variables that best predicted the outcome concerning all patients (75).

The same variables, except the one representing generalized disease, also represented the set of variables that best predicted cancer- specific survival in patients "potentially curable by surgery" and, among this group, those "potentially cured".

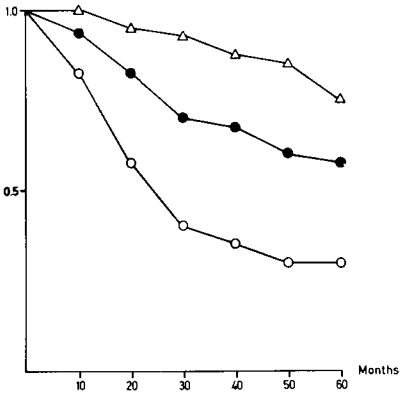

Fig. 1. Cancer-specific survival by risk groups defined on the basis of the best set of preoperatively available variables
(△ low-risk group;
● medium-risk group;
○ high-risk group).

This set of variables and their associated regression coefficients were used to divide the patients into groups with different prognoses. The 24 % of the "potentially curable" patients with the best prognosis had a cancer-specific mortality rate of 15 % and for the 26 % with the worst prognosis this rate was 57 % (Fig. 1). The corresponding figures for all patients were 18 % and 68 %, and for the "potentially cured" of the "potentially curable" 14 % and 47 %, respectively.

As mentioned above, this prognostic model was defined by a multivariate analysis in which the variables were selected stepwise. In the first step S-TPA was included. The preoperative serum level of S-TPA alone was used for dividing the patients in the same way as above (i.e. the 25 % of the patients with the "best" prognosis (low-risk group), the 25 % with the "worst" (high-risk group) and the 50 % in between (medium-risk group), and with a median follow-up of 47 months, range 20-80 months). In patients "potentially curable" by surgery this resulted in a low-risk and a high-risk group in which the cancer-specific mortality rates were 21 % and 51 %, respectively.
In the next step S-CA-50 was included (p value for improvement <0.001). When the same patients were divided on the basis of this two-variable model, the mortality rates in the low- and high-risk groups were actually the same as when S-TPA was used. However, the patients referred to a certain risk group as defined by S-TPA alone were not identical to those referred to the same risk group as defined by both S-TPA and S-CA-50.

In the third step, S-CEA was selected for inclusion (p value for improvement = 0.007), and this resulted in a cancer-specific mortality of 16 % in the "best" quartile and 56 % in the "worst" quartile. Polypoid tumour growth was the last variable to be included (p value for improvement = 0.016) and resulted in corresponding cancer-specific mortality rates of 15 % and 57 %, respectively (Fig. 1). Almost all patients with a polypoid tumour were found in the low-risk groups. The preoperative level of any tumour marker increased with "increased" risk group, but the ranges clearly overlapped and no obvious cut-off point was recognizable.

PREDICTION OF PROGNOSIS by Dukes' staging system

The prognosis was strongly correlated to the stage of the tumour (73,75). After a mean follow-up of 49 months (median 47, range 20-80), the cancer- specific mortality rate in patients with a tumour in stage A was 7 % (5/75), in stage B 32 % (33/102) and in stage C 51 % (44/86). When the tumour was generalized at surgery, i.e. in stage D, the mortality rate was 89 % (47/53) (75). These patients had a median survival of 10 months. When Dukes' staging system was estimated in the Cox regression model and permitting the estimates to change with time, it was found that the prognostic effect of the tumour stage was not reduced from the first to the second year of follow-up (76). However, the prognostic information given by Dukes' staging system then seemed to diminish, although it was still highly statistically significant later than two years after diagnosis.

PREDICTION OF PROGNOSIS by Dukes' stage in combination with the preoperatively available variables

With Dukes' staging system already in the Cox regression model, and with consideration paid to the preoperatively available clinico-pathological variables, additional information was provided by polypoid tumour growth, the age of the patient and tumour growth anteriorly, in patients "potentially curable" by surgery (71). If the tumour markers were also considered, the preoperative serum level of CA-50 and polypoid growth gave additional information in the same patient category (75). In order to compare the best set of preoperatively available predictors with Dukes' staging system, tests were carried out to see whether the preoperative variables contained extra

information given that the information from Dukes' staging system had been taken into account, and vice versa. In both cases the hypothesis of no extra information was rejected, but the significance was stronger in the cases with Dukes' staging system. This means that Dukes' staging system gave most information (75).

GENERAL DISCUSSION

In order to obtain new prognostic information, statistical analyses are required. It is essential to choose the appropriate statistical model and to be aware of its potentialities and limitations. This could mean, for example, that clinical data have to be transformed to suit the statistical model. After statistical inference the information obtained, e.g. chi-square values, p values and β estimates, may have to be reconverted to a form suitable for clinical use.

The standard Cox regression model is one of the most widely used statistical models in prognostic studies. However, in the traditional formulation it involves two major assumptions, 1/ that the relationship between the logarithm of the hazard and the independent variable is linear, and 2/ that the relative hazards are constant over time, but both these assumptions can be corrected for.

Using the Cox proportional hazards model, many studies have resulted in identification of a number of prognostic variables and information concerning their statistical significance. It is always important to remember, however, that even strong statistical significance need not be equivalent to clinically useful information.

Further, no sophisticated statistical analysis will compensate for a deficiency in the patient material. In order to be representative of patients with a rectal carcinoma, it is desirable that the patients be unselected and subjected to basically the same treatment protocol. In this study we therefore included all patients with a primary rectal carcinoma from a defined population consecutively referred to one hospital, which meant that the patient selection was minimized and lower than in

many hospital-based series. In many previous studies patients with tumours of the colon and the rectum have been analysed together. This implies a limitation in the interpretation of the results, as the natural history of a carcinoma of the rectum differs in many essential ways from that of a carcinoma of the colon.

In the present investigation virtually all patients received radiotherapy in addition to surgery as part of a controlled study. An interim analysis showed no difference in survival rates between the two treatment categories. Several investigators consider that radiotherapy should be given as adjuvant treatment in the clinical management of a patient with a rectal carcinoma. Thus, a basic protocol already including radiotherapy may increase the validity of future applications of the results from this study.

Furthermore, differences in prognostic situations have to be considered. Our primary aim was to classify patients prior to surgery with respect to the risk of dying from their disease. For this reason we were restricted to variables that were available at that point in time. We found that a number of clinical variables that were easily identified and preoperatively available, and the preoperative serum level of three selected tumour markers (CEA, TPA and CA-50), correlated with the prognosis in patients with adenocarcinoma of the rectum. A combination of the preoperative serum level of the three tumour markers and polypoid tumour growth made it possible to divide patients into prognostic groups. Patients "potentially curable" by surgery with a median follow-up of 47 months (mean 49 months, range 20-80 months) were divided into three groups: the "best" quartile of the patients with a cancer-specific mortality of 15 % (low-risk group), and the "worst" quartile with 57 % (high-risk group); the cancer-specific death rate in the remaining 50 % of the patients was 36 %. It must be emphasized that this result refers to the same material as that from which the model was derived, which means that the figures given above probably exaggerate the usefulness of the model.

Is this prediction sufficiently good to permit allocation of

patients for adjuvant treatment? All such treatment available today is attended with complications. An aggressive therapeutic policy aiming at cure, in particular, may involve a risk of morbidity and even mortality among the patients. Hypothetically, therefore, the "best" prognostic group would represent a patient category in which the justification of at least potentially toxic adjuvant therapy would be clearly doubtful, as it would mean definite overtreatment of 85 % of the patients. It thus seems as if one quartile of the patients could be excluded from additional therapy on the basis of this model. In the remaining 75 %, almost every second patient will die of cancer. Whether this outcome is "poor enough" for initiating adjuvant therapy would depend, however, upon the efficacy of this therapy and its toxicity. Hypothetically, if we had a form of therapy for colorectal cancer that was at least as effective as the CMF (cyclophosphamide-methotrexate-5-FU) regime in breast cancer (i.e. with a response rate in advanced disease of about 50 % with a median duration of responses of 6-8 months, compared to 20 % with a median duration of 3-5 months in colorectal regimes) without being more toxic, the model would seem useful in allowing us to select a group for which this therapy might be of value. Postoperatively, when the pathological stage is also known, even better selection is possible, as some patients in whom adjuvant therapy has been initiated pre/peroperatively can then be excluded from prolonged postoperative treatment. If, for example, patients who were found to have a tumour in stage A were withdrawn, a further 17 % of the patients, with an excellent prognosis, could be excluded from postoperative therapy. In this way, those patients who received no therapy besides surgery would run a 15 % (9/60) risk of dying of cancer, those who received pre- or peroperative or immediately postoperative therapy a 9 % (4/43) risk and those who received both pre-, per- and postoperative therapy a 52 % (77/148) risk. This hypothetical discussion could also be continued further for the group in whom no therapy is started preoperatively: in patients referred to the "low-risk" group and with a tumour in stage B-C, the cancer-specific mortality rate was 26 % (8/31).

Other aspects apart from the over-all expected survival must also be considered. Taking the cytotoxic properties of available

chemo-therapeutic agents into account, the patients who can be cured are most probably only those with a truly minimal tumour cell burden left after surgery; or alternatively those with rapidly growing tumour cells - or both.
We have proposed that the patients with a truly minimal tumour cell burden are predominantly those dying of late cancer-specific deaths. Since, however, the doubling-time of the tumour cell population varies considerably, this proposal may be wrong. The time that elapses before recurrence (or death) is also dependent upon this population-doubling time. Some patients with metastatic disease can survive for several years after diagnosis, while in others the disease seems to have a more aggressive course. The median survival time for patients with primarily advanced or recurrent disease is in the order of 6-8 months. Patients with a tumour in stage D at surgery in the present series had a median survival time of ten months.

In this study patients with high serum titres of the three selected markers had a high risk of dying early after surgery. Even if our results indicate that the high serum titres may be a result of a large tumour burden, they may also be associated with an aggressive and rapidly growing tumour. In analogy, patients dying of cancer several years after surgery may represent those with a minimal number of cells left after surgery or those with a slow net growth of tumour cells, or both.
We found that the preoperative serum level of two of the tumour markers did not predict the late outcome. Therefore, late deaths of cancer are just as likely, hypothetically, to occur in our "low-risk" group as among the "high-risk" patients.

Our model for prognostic scoring required a somewhat advanced calculation of the relative hazard from the formula exp (β_1 ln(S-TPA) + β_2 ln (S-CA-50) + β_3 ln(S-CEA) + β_4 polypoid tumour (1 = present; 0 = absent)), which may be too complicated a prognostic model to be of value in clinical practice. However, if the calculated risk were proved to give reliable and clinically useful prognostic information, this difficulty would surely be overcome by the clinicians. As no obvious and clinically valuable cut-off levels were found in the calculated hazards, the patients were simply divided so as to get comparable numbers in each

group. Furthermore, the outcome of our prognostic model has as yet only been demonstrated in the same patient material as that from which it was derived, and thus the prognostic importance of the predictors may have been exaggerated. If our results can be reproduced in another patient material and by others, and if the information is considered to influence the patient care in one way or another, new attempts to simplify the scoring system will be appropriate. For example, it is not yet established that all selected variables should be used in a prognostic model, even if the additional information provided is statistically significant (see above). The preferred model was obtained by a stepwise selection procedure. In such a procedure a large number of significance tests are performed, which will increase the chance of making a type I error (the problem of mass significance). The resulting exact significance level cannot be stated with certainty in such situations. The practical conclusion to be drawn from this is that one should be aware of the problem and interpret the results with some caution for variables showing "not very strong" significance. Before the final design of a prognostic model is decided upon, this aspect must be further analysed.

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Address for reprints:

Dr Elisabeth Ståhle

Department of Surgery

University Hospital

Uppsala University

S-751 85 Uppsala

Sweden