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Prognostic Indexes for Renal Cell Carcinoma

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Abstract—*Preoperative and postoperative prognostic indexes concerning nonmetastasized adenocarcinoma of the kidney are derived by use of a multivariate statistical method. Preoperatively, the factors sex, erythrocyte sedimentation rate and, to a certain extent, T-category are important variables predicting survival. Postoperatively, invasion of the renal vein, in addition to sex and sedimentation rate, is found to be a factor of major prognostic importance. The validity of the derived indexes as prognostic indicators is confirmed by application to a second group of comparable patients.*

INTRODUCTION

As IN many other malignant diseases, patients with adenocarcinoma of the kidney show a great variability in survival as the outcome of treatment. The identification of factors associated with the prognosis of these patients, and from which the variability in outcome can be substantially explained, may be of great importance. In this paper, results of a study to investigate the relative prognostic importance of a number of factors concerning nonmetastasized renal cell carcinoma by a multivariate statistical method are presented. Two analyses are performed. One is concerned with preoperatively assessable factors. In the second, tumour characteristics which become evident on histopathological examination of the nephrectomy specimen are also included. This distinction is useful, as the preoperative identification of groups of patients with differing prognosis may facilitate treatment decisions.

Postoperatively, emphasis is on explaining variability in treatment results by consideration of possible mechanisms of the disease.

The preoperative factors studied are (a) sex, (b) age, (c) erythrocyte sedimentation rate (ESR) and (d) radiodiagnostic extent of the tumour. Postoperative tumour characteristics analyzed are (e) histopathological extent of the tumour, (f) invasion of the renal vein, (g) degree of differentiation and (h) cell type. In both analyses, prognostic indexes from which the expected survival of individual patients can be derived are constructed.

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MATERIALS AND METHODS

During the years 1965–1977, 174 patients with nonmetastasized renal cell carcinoma who were considered suitable for simple nephrectomy entered a randomized clinical trial to investigate the value of preoperative irradiation [1]. Of these patients, 89 received preoperative irradiation (TD 3000–4000 rad/3–4 weeks) and 85 were directly nephrectomized.

The i.v. pyelographs and arteriographs performed for the preoperative assessment of the extent of the tumour, the T-category [2], were reviewed by one diagnostic radiologist (R. C. Ledeboer). Renal vein invasion was assessed by histological examination of the nephrectomy specimen. The histological extent of the tumour is expressed by the P-category (P1: tumour surrounded by renal parenchyma; P2: tumour extending to the capsule and/or invading the renal pelvis and/or calyces; P3: perinephric or hilar extension; P4: extension into neighbouring organs and/or fixed to the abdominal wall). Review of all histological specimens was done by one pathologist (R. O. van der Heul). Because of simple nephrectomy local node involvement was not assessed as a routine.

At the time of this analysis, 87 patients had died and 87 were still continuing follow-up. All patients had regular follow-up examinations.

STATISTICAL METHODS

Survival functions of groups of patients are estimated by survival curves according to Kaplan and Meier [3]. For the calculation of P-values in the comparison of survival curves, the log-rank test [4] is used. Because of the limited number of patients and the existing relationships among several factors, the prognostic importance of the factors can be simultaneously investigated by these methods to only a limited extent. A more promising way of making progress here is by adopting a multivariate statistical model. Moreover, such a model may be useful in deriving a rule for prognostic predictions concerning future individual patients. The model which is used here is Cox's proportional hazards model [5]. With this model, a scoring function which relates the expected survival times of individual patients to the values of the prognostic variables can be obtained. The value of the scoring function indicates how strongly the force of mortality (the instantaneous death rate) is related to these factors.

If the number of patients is denoted by n and, if p is the number of prognostic variables, the scoring function for the i-th patient can be written:

$$S_i = a_{i1}\beta_1 + a_{i2}\beta_2 + \ldots + a_{ip}\beta_p. \qquad (1)$$

Here a_{ij} is the value of the j-th prognostic variable ($j=1,\ldots,p$) for the i-th patient ($i=1,\ldots,n$). The parameter β_j denotes the difference in score of patients who differ by one unit in the j-th variable, the other variables being at the same level. Factors with continuous levels such as ESR and discrete factors with two categories such as sex are represented by one variable and one related parameter β. A discrete factor with more than two categories generally needs a number of variables and parameters equal to its number of categories minus one. For instance, the four-categorical factor T-category needed three variables to represent all its levels.

The score S_i is related to the survival outcome by:

$$\lambda_i(t) = \exp(S_i)\lambda_0(t),$$

where $\lambda_i(t)$ denotes the force of mortality of the i-th patient at time t (roughly speaking, $\lambda_i(t)$ gives the probability of dying at month t if the patient is known to be alive at month $t-1$). $\lambda_0(t)$ denotes an arbitrary reference force of mortality function which is unknown. A high score indicates a high death rate and thus a (relatively) poor prognosis. Another interpretation of this scoring system can be obtained by considering its implication for the survival functions. It can be shown that the survival function $F_i(t)$ to which the i-th patient is subjected can be written as:

$$F_i(t) = \{F_0(t)\}^{\exp(S_i)}.$$

Here $F_0(t)$ denotes a reference survival function, that is, the survival function for patients with a score $S=0$.

The unknown parameters $\beta_1, \beta_2, \ldots, \beta_p$ and the function $F_0(t)$ can be estimated from the clinical data by maximum likelihood procedures [6]. This fitting of the model has to be done by a process of successive approximation. Significance tests on subsets of parameters, useful in the assessment of less important prognostic factors, can be obtained by comparisons of fits of models through likelihood ratios.

RESULTS

Extensive analysis of the data showed that the preoperative irradiation had little or no effect on histological variables or survival (5-yr survivals for the preoperatively treated and the surgically treated only group were, respectively, 45 and 54%). This treatment factor is therefore omitted from further consideration. Preoperative factors were first analyzed for their prognostic value.

In Table 1, 3-yr and 5-yr survival percentages are given for the preoperative assessable factors. Considered on its own, sedimentation rate seems to be strongly associated with subsequent survival. Females have a better prognosis than males. Category T4 does more poorly than the lower T-categories. To analyse the effects of the factors sedimentation rate, sex and T-category simultaneously, model (1) is written as:

$$S_i = a_{i1}\beta_1 + a_{i2}\beta_2 + a_{i3}\beta_3 + a_{i4}\beta_4 + a_{i5}\beta_5.$$

Here a_{i1} allows for the factor sedimentation rate and a_{i2} for sex. The three variables a_{i3}, a_{i4} and a_{i5} represent the four categories of the T-classification. Further details on the coding of these variables and the resulting fit to the data are given in Table 2. It appears that each of these three factors contributes significantly to the score. On further examination of the estimated parameters related to the T-category, however, it appears that category

Table 1. Survival according to preoperative factors

Factor	Category	No. of patients	Survival (%) 3 yr	5 yr	Log-rank test
Sex	female	75	66	57	
	male	99	59	43	$P=0.05$
Age	≦55	60	65	60	
	56–65	60	59	38	
	≧66	54	61	50	$P=0.2$
Sedimentation rate	≦12	50	89	80	
	13–29	39	76	57	
	≧30	83	40	27	$P<0.001$
T-category	T1	14	75	48	
	T2	47	58	50	
	T3	66	70	57	
	T4	39	52	36	$P=0.1$
T-categories (combined)	T1, 2, 3	127	66	52	
	T4	39	54	36	$P=0.02$

Missing data: sedimentation rate: 2, T-category: 8.

Table 2. Model including sedimentation rate, sex and T-category

Factor	Variable	β	Estimated β	Likelihood ratio test
Sedimentation rate	$a_{i1}=$ESR	β_1	0.020	$P<0.001$
Sex	$a_{i2}=1$ if male $=0$ if female	β_2	0.51	$P=0.05$
T-category	$a_{i3}=1$ if T1 $=0$ if otherwise	β_3	−0.26	$P=0.01$
	$a_{i4}=1$ if T2 $=0$ otherwise	β_4	−0.39	
	$a_{i5}=1$ if T3 $=0$ otherwise	β_5	−0.95	

T3 has a more favourable prognosis than T2. In turn, T2 is estimated to be somewhat more favourable than T1. As this ranking did not seem to be logical and the differences between the categories T1, T2 and T3 themselves were far from statistical significance, the model was fitted again to the data with T4 contrasted to categories T1, T2 and T3 combined. After assuring that the factor age did not improve the fit of the model, the ultimate preoperative score could be written as:

$$S=0.02\times \text{ESR}+\begin{cases}0.6 \text{ (male)}\\ 0 \text{ (female)}\end{cases} +\begin{cases}0.7 \text{ (T4)}\\ 0 \text{ (T1, T2 or T3)}\end{cases}$$

Now. for each patient, a score according to this prognostic index can be calculated and patients with a similar score can be grouped. After grouping patients with a score between 0 and 1, between 1 and 2, etc., it is shown in Fig. 1 that the observed survival curves of these groups of patients are in reasonably good agreement with the expected survival curves arising from the model. Groups with a relatively good, intermediate and poor prognosis can be clearly distinguished.

Concerning postoperative factors, it appeared that category P4 (inoperable patients) had a very poor prognosis. All seven patients died within 2 yr, most of them within 1 yr. Moreover, as no information was available concerning the histological variables of the tumour in the majority of these patients, they were omitted from the following analysis. In Table 3, survival percentages are given for the remaining operable patients. With increasing P-category, survival becomes worse. Renal vein involvement leads to a considerably poorer prognosis than when no venous invasion is seen. Also with decreasing degree of differentiation of the tumour, survival becomes worse, while the different cell types show similar survival rates. To investigate the prognostic

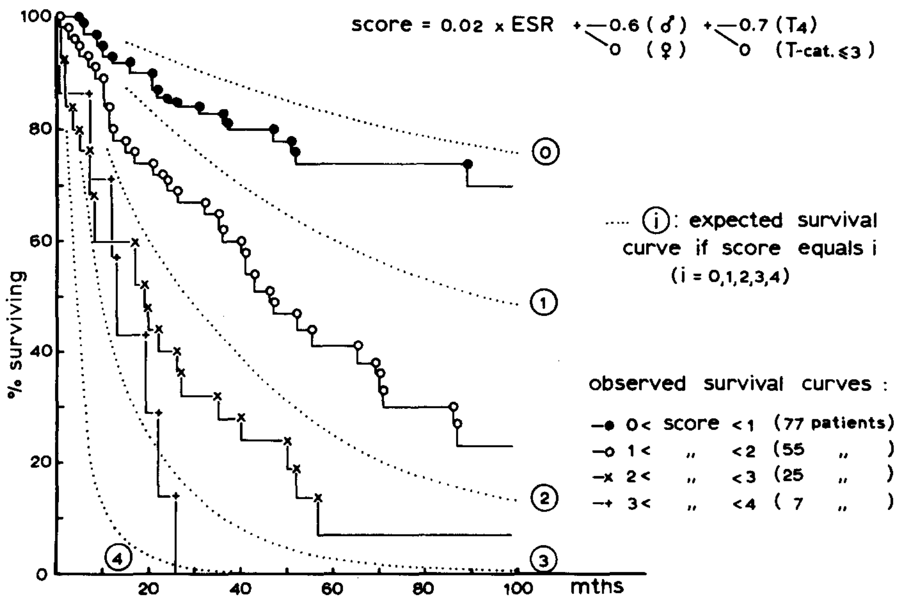

Fig. 1. Observed and expected survival curves according to preoperative score.

Table 3. Survival according to histopathological factors

Factor	Category	No. of patients	Survival (%) 3-yr	5-yr	Log-rank test
P-category	P1	61	81	65	
	P2	38	64	60	
	P3	67	50	33	$P=0.001$
Renal vein invasion	Yes	62	47	28	
	No	105	76	65	$P<0.001$
Degree of differentiation	Low	60	51	39	
	Medium	81	73	57	
	High	21	90	68	$P=0.01$
Cell type	Clear	123	68	52	
	Granular	17	67	52	
	Mixed	22	54	54	$P=0.8$

Missing data: P-category: 1, degree of differentiation and cell type: 5.

importance of the P-category, renal vein invasion and degree of differentiation simultaneously, the following scoring function, which also takes account of sex and sedimentation rate, was fitted to the data:

$$S_i = a_{i1}\beta_1 + a_{i2}\beta_2 + \ldots + a_{i7}\beta_7.$$

The various variables and results of fitting this model are given in Table 4. It appears that, once the factors sex, sedimentation rate and renal vein involvement are known, the factors P-category and degree of differentiation do not contribute significantly to the score. Extending the model with the factors age and cell type also did not improve the fit of the model. The ultimate postoperative score, based on all operable patients except two because of a missing sedimentation rate, can now be written as:

$$S = 0.02 \times \text{ESR} + \begin{cases} 0.8 \text{ (male)} \\ 0 \text{ (female)} \end{cases} + \begin{cases} 0.9 \text{ (renal vein invasion)} \\ 0 \text{ (no renal vein invasion)} \end{cases}$$

After grouping patients with a similar score, Fig. 2 is obtained. Good agreement between observed and expected survival curves is evident.

DISCUSSION

The relatively poor prognosis of patients with invasion of the renal vein is in agreement with general clinical experience [7]. The risk of renal vein involvement increases greatly with increasing P-category; see Table 5. It is conceivable that the prognostic importance of P-categories is mainly derived from renal vein involvement. A similar phenomenon could be observed in the data of McDonald and Priestley [8], who studied survival in relation to renal vein involvement and weight of the diseased kidney.

It has been known for a long time that renal cell carcinoma patients frequently show an elevated sedimentation rate [9]. The importance of the sedimentation rate as a prognostic factor was already stated by Böttiger [10], Ochsner *et al.* [11] and recently by

Table 4. Model including sedimentation rate, sex, P-category, renal vein invasion and degree of differentiation

Factor	Variable	β	Estimated β	Likelihood-ratio test
Sedimentation rate	a_{i1} = ESR	β_1	0.018	$P<0.001$
Sex	a_{i2} = 1 if male = 0 if female	β_2	0.87	$P=0.001$
P-category	a_{i3} = 1 if P1 = 0 otherwise	β_3	−0.48	$P=0.15$
	a_{i4} = 1 if P2 = 0 otherwise	β_4	−0.53	
Renal vein invasion	a_{i5} = 1 if yes = 0 if no	β_5	0.79	$P=0.002$
Degree of differentiation	a_{i6} = 1 if low = 0 otherwise	β_6	0.25	$P=0.3$
	a_{i7} = 1 if medium = 0 otherwise	β_7	−0.14	

Table 5. Numbers of patients according to renal vein invasion and P-category

		P-category P1		P2		P3	
Renal vein invasion	Yes	8	(13%)	15	(39%)	39	(58%)
	No	53		23		28	

Chi-square test: $P<0.001$.

Juusela [12]. In this study, a gradual worsening of prognosis was observed with increasing sedimentation rate. The sedimentation rate showed a strong correlation with the degree of differentiation. With a decreasing degree of differentiation, the sedimentation rate increases. Cumulative frequency distributions of the sedimentation rate are given in Fig. 3 (differences significant at $P=0.01$ by the Krukal–Wallis test). This correlation could explain why the degree of differentiation, while of prognostic value when considered alone (Table 3), is of less value in the postoperative score.

That females have a better prognosis than males was also noted by Meyers *et al.* [13] and Juusela [12]. The greater incidence of renal cell carcinoma among males [14] and the finding that, once metastases have become clinically evident, women respond less to hormonal treatment than men [15], [16] are also suggestive of the involvement of hormonal factors.

The prognostic value of the T-classification was not impressive in this material. Only category T4 was an ominous sign. This observation could readily be explained by comparing T with P-categories. While T4 patients

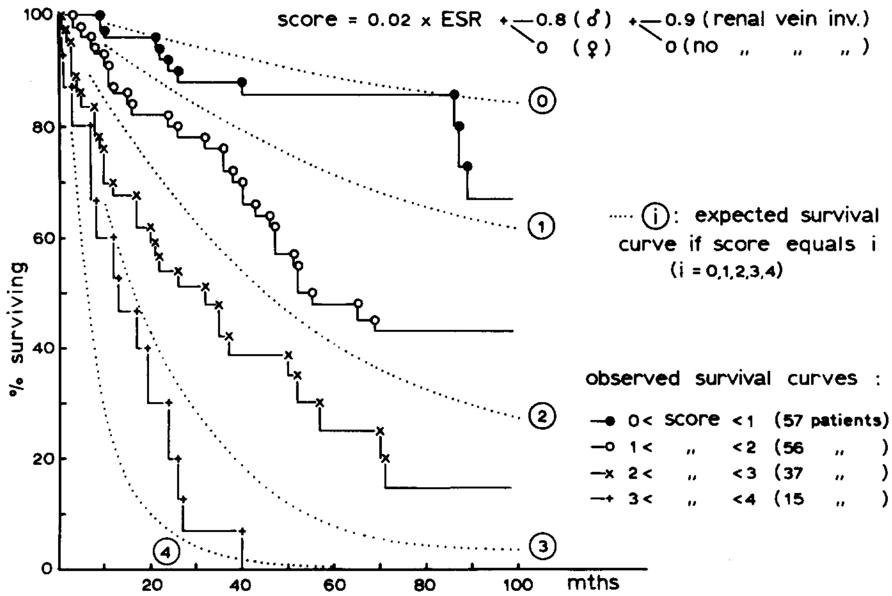

Fig. 2. Observed and expected survival curves according to postoperative score.

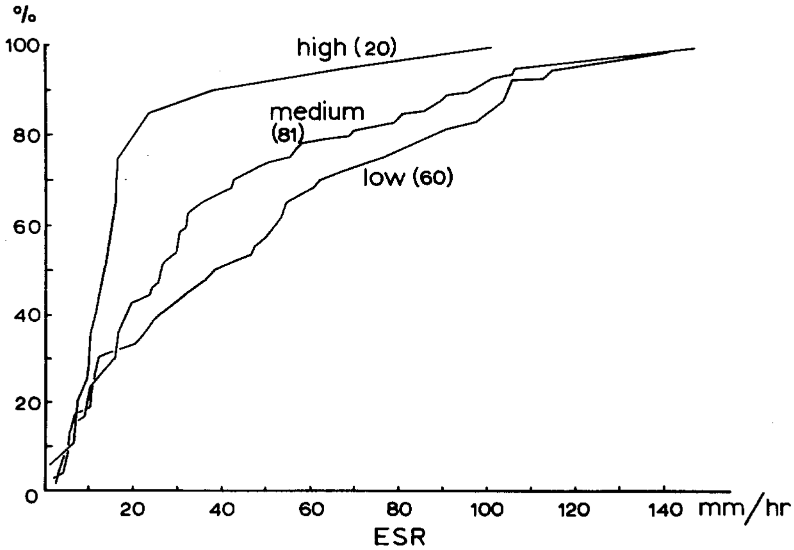

Fig. 3. Cumulative frequency distributions of erythrocyte sedimentation rate by degree of differentiation.

were mainly P3 or P4, there was a minor agreement between T and P-categories for the cases with a lower T-category.

The prognostic indexes derived were broadly similar when a correction was made for the occurrence of intercurrent death. By considering patients (18) withdrawn from study at the moment of death from causes supposedly unrelated to renal cell carcinoma, the estimated parameters in the multivariate models did not appreciably differ from those given.

In comparing observed and expected survival curves (Fig. 1 and 2), good agreement was apparent. The validity of a prognostic index, however, should preferably be tested in another group of comparable patients. Dr. H. Juusela (Helsinki University Central Hospital) kindly evaluated the prognostic indexes by applying them to a comparable group of patients described in his thesis [12]. For patients without evidence of disseminated disease and with a P-category less than 4, intercurrent death corrected survival curves according to postoperative score were obtained as given in Fig. 4 (one patient with a score of 4.4 dying 1 month after operation is not included in that figure). Despite the fact that the groups with the highest scores are less separated, the overall worsening of prognosis with increasing score is satisfactorily confirmed. For the preoperative index a similar validation was obtained.

About uses of the indexes: the preoperative prognostic indicator may possibly be useful as a complementary factor to facilitate making the decision of whether to operate or not in particular patients. Until now, no mode of chemotherapy has been found which can deal effectively with clinically established metastases. In studies of more aggressive hormonal or chemotherapy treatments, the indexes can be useful either as selection criteria or as single stratification factors.

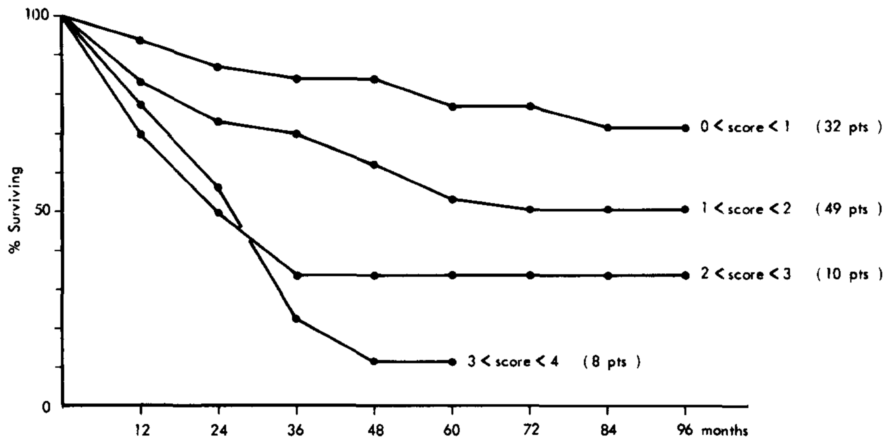

Fig. 4. Survival after extrafascial nephrectomy. Patients are grouped according to postoperative score (courtesy of Dr. H. Juusela).

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