Hiroshima J. Med. Sci.
Vol.40, No.2, 55~62, June, 1991
HIJM 40-10

Analyses of Survival Rate of Unresectable Pancreatic Adenocarcinoma in Aspect of Data Analyses

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ABSTRACT

Using Cox's proportional hazard model and Weibull's proportional hazard model and taking into account the covariates involved, estimation of survival time was made on 94 confirmed deceased cases of unresectable pancreatic adenocarcinoma (excluding cases of cystadenocarcinoma) from the data of their admission for confirmation of diagnosis. The following results were obtained:

1)The covariates which were related to the prognosis of unresectable pancreatic adenocarcinoma were presence or absence of metastasis to the liver and lung, type of treatment for obstructive jaundice, and whether in such treatment, chemotherapy, or radiotherapy was conducted.

2)Estimation of the survival time after adjusting these factors showed that the median survival time was 57 days in untreated cases with metastasis, 107 days in untreated cases without metastasis, 284 days in cases with metastasis in which surgical tratment for obstructive jaundice, chemotherapy, and radiotherapy was administered, and 350 days in cases without metastasis in wihch the same positive tratment was administered. It can therefore be deduced that multidisciplinary treatment is effective in prolonging life.

Key words: *Unresectable pancreatic adenocarcinoma, Proportional hazard model, Survival rate*

Despite the remarkable advances made in diagnostic techniques it is difficult even at present to make an early diagnosis of small pancreatic cancer and thus the number of resectable pancreatic cancer cases is small. Various types of therapy are provided for unresectable pancreatic cancer, but it cannot be said that an adequate evaluation has been made of the effect of such therapy on extending survival time. This is attributable to differences in basic factors in each pancreatic cancer case i.e. sex, age, size, and location of the tumor, presence or absence of metastasis, and therapy.

In the present study on unresectable pancreatic cancer cases, the various types of treatment were evaluated taking into account all the possible factors involved (covariates). Proportional hazard models were applied in the estimation of survival time, and the validity of these models for such estimation was examined. In addition, the treatment methods for unresectable pancreatic cancer cases were evaluated, and an estimation of survival time was attempted.

SUBJECTS AND METHODS

From the 124 cases admitted to Hiroshima University Hospital or to its affiliated hospitals from January 1985 to October 1988 who were diagnosed to have duct cell carcinoma (excluding cystadenocarcinoma), 94 cases confirmed to have deceased as of June 1990 were selected as subjects of the present study. Of these, the diagnosis had been histologically confirmed in only 53 cases. By sex, 60 were males and 34 were females. Metastasis to either the liver or lung was confirmed in 48 cases by chest x-ray, ultrasound or computed tomography. The sites of tumor involvement were head in 48 cases, body or tail in 41 cases, and others in 5 cases. Figure 1 shows with Q-Q plot[4] the distribution of age, primary tumor size (measurement made by abdominal ultrasound or abdominal CT), serum CEA level, and serum CA19-9 level.

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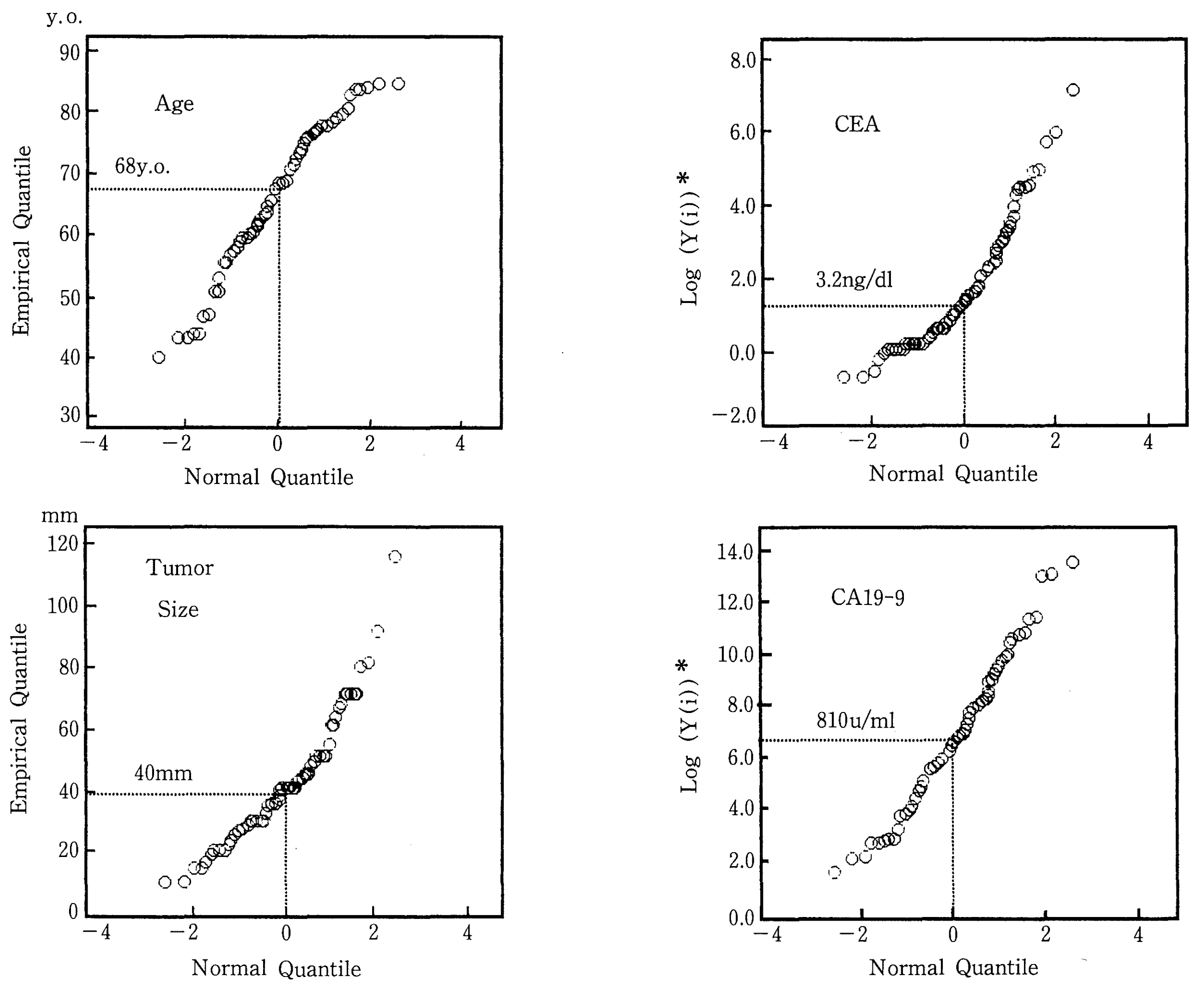


Fig. 1. Distribution of age, maximum tumor size, serum CEA level, and serum CA19-9 level (Q-Q plot); *: Ordinate shows log converted values of CEA level and CA19-9 level. 0 point of normal quantile corresponds to median.

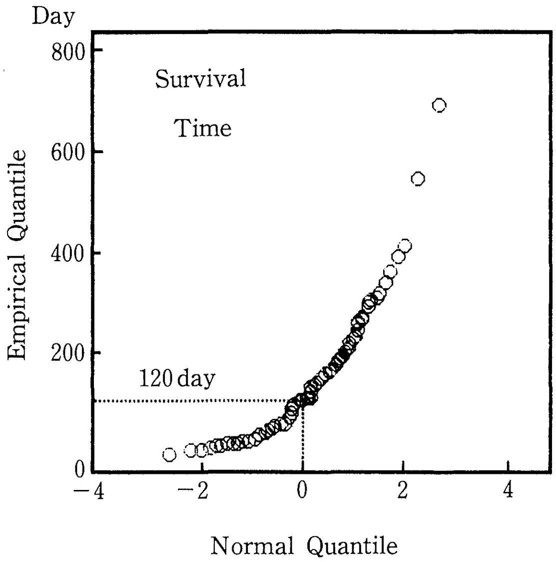
Chemotherapy was conducted in 34 cases, that is, intravenous chemotherapy[15] by FAM or FAM-S. Immunotherapy using OK 432 was administered in 18 cases. Intraarterial chemotherapy using 5-FU or MMC was provided in 13 cases. Radiotherapy involving intraoperative radiotherapy and/or postoperative external irradiation was given in 18 cases.

For the estimation of the distribution of survival time in which covariates were not taken into account, Weibull's probability paper method, a type of Q-Q plot, was employed. To examine the possible effect of each of the covariates on survival time, a test of the difference of cumulative survival function was made with the use of a Log-rank test. In this process, age, maximum tumor size, serum CEA level, and serum CA19-9 level were cut into two levels based on the median of these variables and classification was made into five groups: treatment of obstructive jaundice not executed, exploratory laparotomy alone, percutaneous transhepatic biliary drainage (PTBD), percutaneous transhepatic biliary endoprosthesis (PTBE), and operative bypass.

To determine the effect of various types of therapy on survival time in which covariates are taken into account and to estimate adjusted survival rate, Cox's proportional hazard model[7] and Weibull's proportional hazard model[13] which are a type of multivariate analysis were used. In the selection of covariates, factors which significantly influence survival time and tumor size were employed and the Akaike's information criteria (AIC) model was adopted as the final model.

Furthermore, in the use of Cox's proportional hazard model, Cook's distance[5] was used to check the outliers, stratified plots of log-log (survival density function) was used to check the proportionality of the effect of covariates, and the Bootstrap method[10] was used to check the validity of the hazard models themselves. The stability of the regression coefficients thus obtained was examined (See supplementary explanation). Finally, for the covariates the method of Kalbfleisch and Prentice[13] was employed to determine the adjusted cumulative survival function.

The data of admission for confirmation of diagnosis was employed as the date of entry in the study to determine survival time. In the analyses of the data, programs developed by the authors



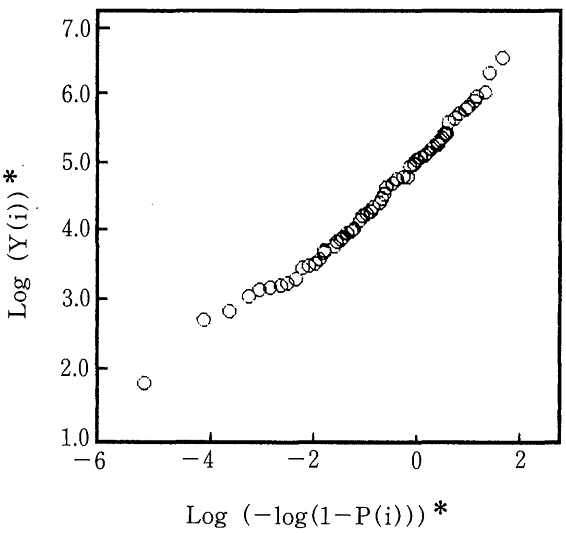


Fig. 2. Distribution of survival time of entire sample (Q-Q plot); Left figure is when the theoretical distribution is normal distribution and right figure is when the theoretical distribution is Weibull's distribution. *: Ordinate shows log converted values of survival time and abscissa shows converted values of cumulative probability P(i). If the data fall on a straight line, they conform to Weibull's distribution.

Table 1. Effect of background factors and therapeutic factors on survival time (Log-rank test)

Categories	Cut Level	P-Value
Sex	Male, Female (63.8%) (36.2%)	0.20
Age	< =68, >68*	0.01
Tumor Size	< =40, >40*	0.41
Location of Tumor	Head, Body & Tail, Combined (51.1%) (43.6%) (5.3%)	0.63
Metastasis	(−), (+) (48.9%) (51.1%)	<0.01
CEA Level	< =3.2, >3.2*	0.88
CA19-9 Level	< =810, >810*	0.19
Treatment of Jaundice	Five Levels**	0.01
Treatment of Jaundice	Two Levels***	<0.01
Chemotherapy	none, executed (63.8%) (36.2%)	0.01
Intraarterial Chemotherapy	none, executed (80.9%) (19.1%)	0.36
Immunotherapy	none, executed (70.2%) (29.8%)	0.11
Radiotherapy	none, executed (86.2%) (13.8%)	0.04

*: Classified into two groups by the median; **: Classified into not conducted (46.8%), only exploratory laparotomy (6.4%), percutaneous transhepatic biliary drainage (22.3%), percutaneous transhepatic biliary endoprosthesis (6.4%) and operative bypass (18.1%); ***: Classified into surgical treatment (only exploratory laparotomy + operative bypass) and others; Significant ($p<0.05$) variables were age, presence or absence of metastasis, type of treatment of obstructive jaundice, and whether such treatment, chemotherapy, or radiotherapy was conducted or not.

were employed. The reliability of most of the results was confirmed by BMDP[9], SAS[16] and S[2] statistical software packages.

RESULTS

1) Distribution of survival time of entire sample

A Q-Q plot (normal probability paper method) of the distribution of survival time of the entire sample is shown on the left on the assumption that the theoretical distribution is normal distribution and a Q-Q plot (Weibull's probability paper method) of the same is shown on the right on the assumption that the theoretical distribution is Weibull's distribution (Fig. 2). The figure on the left shows that the median survival time of the entire sample was 120 days, 25%-tile was 56 days, and 75%-tile was

191 days. The plot in the figure on the right is almost linear on Weibull's probability paper. The distribution of survival time not adjusted for covariates showed Weibull's distribution.

2) Effect of covariates (background and therapeutic factors) on survival time

The results of a Log-rank test are shown in Table 1. The factors which had a significant effect on survival time were age, presence or absence of metastasis to the liver and lung, type of treatment for obstructive jaundice, and whether in such treatment, chemotherapy, or radiotherapy was conducted.

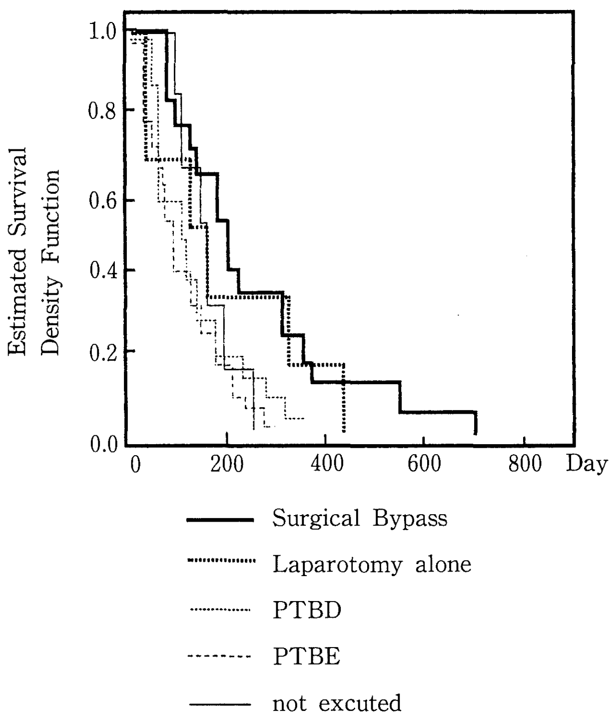


Fig. 3. Estimated survival density function by type of treatment of obstructive jaundice and absence of treatment (Product-limit method); PTBD: Percutaneous transhepatic biliary drainage; PTBE: Percutaneous transhepatic biliary endoprosthesis: When it ended only with surgical bypass and exploratory laparotomy, the prognosis is more favorable than the other groups.

Figure 3 shows the estimated survival density function by type of treatment for obstructive jaundice and absence of treatment determined by Product-limit method. As the survival rate of the group given surgical treatment differed from that of the other groups, the cases were divided into two groups and the following analyses were conducted.

3) Study by proportional hazard models

Using a model with age, presence or absence of metastasis, type of treatment for obstructive jaundice as therapeutic factor, and whether in such treatment, chemotherapy, or radiotherapy was conducted as factors found in the Log-rank test to significantly influence survival time together with

Table 2. List of variables applied to proportional hazard model

	Name of Variables	Level
x1	Age	1: >68 y.o. 0: <=68
x2	Tumor Size	1: >40mm 0: <=40
x3	Metastasis	1: (+) 0: (−)
x4	Surgical Treatment*	1: executed 0: none
x5	Chemotherapy	1: executed 0: none
x6	Radiotherapy	1: executed 0: none

*: Classified into surgical treatment (only exploratory laparotomy + operative bypass) and two other groups.

Table 3. Results by Cox's proportional hazard model

$$\hat{\lambda}(t,x1,x2,x3,x4,x5,x6) = \hat{\lambda}0(t)\exp(\hat{\beta}1x1+\hat{\beta}2x2+\hat{\beta}3x3+\hat{\beta}4x4+\hat{\beta}5x5+\hat{\beta}6x6)$$

	Coefficients	S.E.	P-Value
$\hat{\beta}1$	-6.47×10^{-2}	2.76×10^{-1}	0.82
$\hat{\beta}2$	1.64×10^{-1}	2.36×10^{-1}	0.49
$\hat{\beta}3$	7.33×10^{-1}	2.45×10^{-1}	<0.01
$\hat{\beta}4$	-1.13×10^{0}	3.56×10^{-1}	<0.01
$\hat{\beta}5$	-5.19×10^{-1}	2.49×10^{-1}	0.04
$\hat{\beta}6$	-9.94×10^{-1}	3.45×10^{-1}	<0.01
		AIC=613.2	

$$\hat{\lambda}(t,x3,x4,x5,x6) = \hat{\lambda}0(t)\exp(\hat{\beta}3x3+\hat{\beta}4x4+\hat{\beta}5x5+\hat{\beta}6x6)$$

	Coefficients	S.E.	P-Value
$\hat{\beta}3$	7.32×10^{-1}	2.45×10^{-1}	<0.01
$\hat{\beta}4$	1.16×10^{0}	3.21×10^{-1}	<0.01
$\hat{\beta}5$	-4.67×10^{-1}	2.42×10^{-1}	0.06
$\hat{\beta}6$	-9.59×10^{-1}	2.59×10^{-1}	<0.01
		AIC=609.8	

$\hat{\lambda}$ is estimated hazard and $\hat{\lambda}0(t)$ is base line hazard. The upper table shows results when all variables were included and the lower table shows results by the model selected by minimum AIC. Significant were presence or absence of metastasis and whether surgical treatment or radiotherapy was conducted or not.

tumor size, Cox's proportional hazard was applied. With the results thus obtained, a selection of variables was made which is shown in the upper part of Table 3 while the selected minimum AIC model is shown in the lower part. Quantification of these factors was based on the data given in Table 2. The model finally selected was a model in which presence or absence of metastasis, type of treatment for obstructive jaundice, and whether in such treatment, chemotherapy, or radiotherapy was conducted were included as covariates. Of these, all the variables excluding presence or absence of chemotherapy (p=0.06) showed a probability value

Table 4. Results by Weibull's proportional hazard model

$\hat{\lambda}(t,x1,x2,x3,x5,x6)=\hat{\lambda}\hat{\gamma}t^{\hat{\gamma}-1}\exp(\hat{\beta}1x1+\hat{\beta}2x2+\hat{\beta}3x3+\hat{\beta}4x4+\hat{\beta}5x5+\hat{\beta}6x6)$

$Y=\hat{\alpha}+(\hat{\beta}^*1x1+\hat{\beta}^*2x2+\hat{\beta}^*3x3+\hat{\beta}^*4x4+\hat{\beta}5x5+\hat{\beta}^*6x6)+\hat{\delta}\omega$:Linear Model

	Coefficients	S.E.	P-Value
$\hat{\beta}^*1$	-9.51×10^{-3}	1.64×10^{-1}	0.95
$\hat{\beta}^*2$	-2.13×10^{-1}	1.40×10^{-1}	0.13
$\hat{\beta}^*3$	-3.71×10^{-1}	1.50×10^{-1}	0.01
$\hat{\beta}^*4$	4.70×10^{-1}	1.93×10^{-1}	0.01
$\hat{\beta}^*5$	2.72×10^{-1}	1.44×10^{-1}	0.06
$\hat{\beta}^*6$	5.05×10^{-1}	1.99×10^{-1}	0.01
$\hat{\alpha}$	5.63×10^{0}	3.91×10^{-1}	<0.01
δ	6.20×10^{-1}	4.97×10^{-2}	
		AIC=221	

$\hat{Y}=\hat{\alpha}+(\hat{\beta}^*3x3+\hat{\beta}^*4x4+\hat{\beta}^*5x5+\hat{\beta}^*6x6)+\hat{\delta}\omega$:Linear Model

	Coefficients	S.E.	P-Value	
$\hat{\beta}^*3$	-3.30×10^{-1}	1.51×10^{-1}	0.03	$\hat{\beta}3 = 5.30\times10^{-1}$
$\hat{\beta}^*4$	5.12×10^{-1}	1.79×10^{-1}	<0.01	$\hat{\beta}4 = -8.03\times10^{-1}$
$\hat{\beta}^*5$	2.46×10^{-1}	1.45×10^{-1}	0.09	$\hat{\beta}5 = -3.86\times10^{-1}$
$\hat{\beta}^*6$	4.89×10^{-1}	1.74×10^{-1}	<0.01	$\hat{\beta}6 = -7.67\times10^{-1}$
$\hat{\alpha}$	5.78×10^{0}	2.77×10^{-1}	<0.01	
$\hat{\delta}$	6.38×10^{-1}	5.01×10^{-2}		
		AIC=215.3		

The results were resolved by use of linear model.
λ and γ are parameters of Weibull's distribution, ω follows extreme value distribution, and Y is survival time. The upper table shows results when all variables were included and the lower table shows results by the model selected by minimum AIC. Significant variables were the same as the results obtained by Cox's proportional hazard model.

of 5% or less.

A study made of outliers, proportional hazard, and stability of regression coefficients is presented in the supplementary explanation.

Weibull's proportional hazard model was applied to the variables shown in Table 2. The results of the full model resolved by the linear model are shown in the upper part of Table 4 and the results of the final model selected by AIC are presented in the lower part. Covariates similar to Cox's proportional hazard model were selected and the regression coefficients were almost the same.

4) Estimation of adjusted survival time

Figure 4 shows the adjusted survival density function obtained by the method of Kalbfleisch and Prentice. The figure shows that the median estimated survival time was 57 days when metastasis to the liver and lung was observed but no positive treatment was administered and was 350 days when metastasis was not observed but multidisciplinary treatment was provided including surgical bypass for obstructive jaundice, chemotherapy, and radiotherapy.

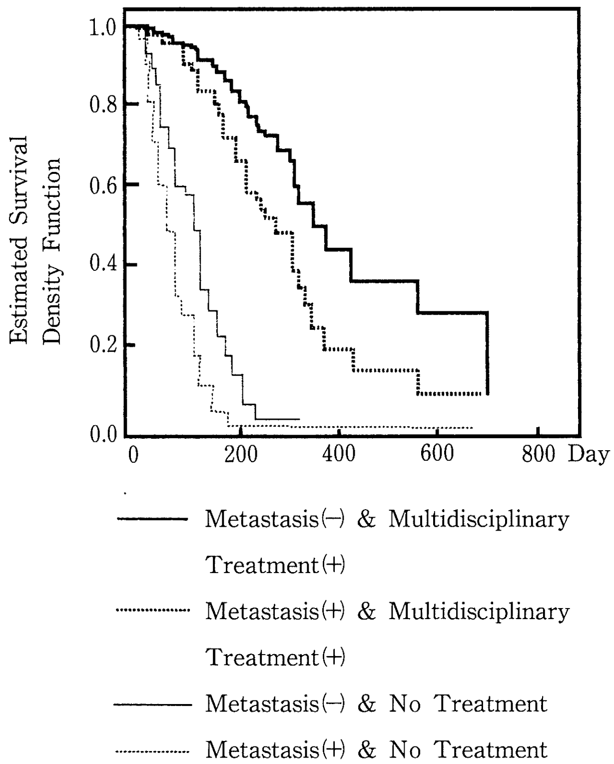


Fig. 4. Estimated adjusted survival density function (method of Kalbfleish and Prentice): Estimated adjusted survival density function was computed by presence or absence of metastasis and by whether multidisciplinary therapy was provided or not. Conduct of multidisciplinary therapy extended survival time more than twofold.

DISCUSSION

It is apparent that the survival rate of resectable cases is higher than that of unresectable cases, but the reported resectability rate ranges from 5% to 25%[5] and in our cases there were 14 surviving cases or 13% among the 108 cases of excluding cases of cystadenocarcinoma. During our period of study, 10 cases of cystadenocarcinoma were observed, but as the prognosis of these cases is considered to be generally favorable[17], they were excluded from the analyses. According to the Japan Pancreatic Cancer Registration Survey[12] conducted over seven years from 1981 to 1987, of the 5631 cases of pancreatic cancer there were 1818 resectable cases and the median survival time of the unresectable cases was about 4 months. The median survival time of our unresectable cases was also 120 days or about 4 months. It is assumed that the estimated cumulative survival function of these unresectable cases follows Weibull's survival distribution function. As there are thought to be many factors involved (covariates) which influence survival time, it cannot be said to be a true estimate of survival distribution function of individual pancreatic cancer patients with these covariates. The Product-limit method (also referred to as Kaplan Meier method) enables computation of the nonparametric cumulative survival function. However, comparison of cumulative survival function by independent combinations of these covariates is difficult because of the massive number of available combinations. On the assumption that differences in mean values of the background factors between two groups or between a number of groups cannot be observed (this is generally referred to as mean matching technique[1].), many reports have been published on the tests made by the Log-rank method, Cox Mantel method, and generalized Wilcoxon method on the comparison of the cumulative survival function curves between the groups, but in these tests adjustment was not made of the bias arising from covariates. It is considered that a limit can be set on demonstrating differences between the groups by the Product-limit method alone. As methods for estimating therapeutic effects and pancreatic cancer survival function curves with consideration given to covariates, Cox's proportional hazard model and the method of Kalbfleisch and Prentice for the estimation of pancreatic cancer cumulative survival function curves based on the Cox proportional hazard model were employed.

First, the effect (bias) of various background factors and therapeutic factors on cumulative survival function was studied with the use of the Log-rank test. The results thus obtained suggested that age, presence or absence of metastasis to the liver and lung, type of treatment for obstructive jaundice, and whether in such treatment, chemotherapy, or radiotherapy was conducted significantly influenced the cumulative survival function. According to Petrek et al[18] presence or absence of metastasis and tumor size significantly affected the cumulative survival function, while Brandabur et al[3] have reported that no difference could be demonstrated in their comparison of the effect of endoscopic treatment and that of surgical treatment in treating obstructive jaundice of unresectable pancreatic cancer. Our results showed that maximum tumor size did not show a significant effect, but type and conduct of treatment of obstructive jaundice had a significant effect. Therefore, the following analyses were conducted on all the significant variables including maximum tumor size.

The treatment methods considered to have a significant effect on hazard (effect on hazards is ultimately demonstrated as effect on the cumulative survival function) were the type of treatment for obstructive jaundice and whether in such treatment chemotherapy or radiotherapy was conducted only. Intravenous chemotherapy brought about slight but not significant elevation of the cumulative survival function. Cullinan et al[8] have questioned the value of combination chemotherapy and Kawai[14] who analyzed the survival rate of 423 cases of pancreatic cancer with use of Cox's model reported that the survival rate of cases given immunotherapy and anti-cancer agents was slightly superior to that in the cases in which the patients followed a natural course without any therapy, but nonetheless 50% of the cases died in five months. Thus, in the case of advanced cancers, cost-benefit and cost-effectiveness cannot be ignored. However, many workers[11,19] have reported the usefulness of radiotherapy and its combination with chemotherapy. This is in agreement with our results. Which show it to be effective in reducing tumor size, in improving the quality of life by reducing pain, and in extending survival time.

Cox's model has been recommended in evaluating therapeutic results, but little has been reported on its validity and on base line hazard. We have therefore used estimated cumulative survival function computed according to the method of Kalbfleisch and Prentice in order to estimate the base line hazard. The results suggested that conduct of multidisciplinary therapy would extend survival time more than twofold.

It is proposed that through randomized control study evaluation be conducted in the future with consideration also given to quality of life.

The results of the present analyses were reported in part at the 31st annual meeting of the Japanese Society of Gastroenterology held in Asahikawa in 1989.

SUPPLEMENTARY EXPLANATION

1) CEA level, CA19-9 level, and tumor size (Table 5)

Spearman's correlation coefficients of CEA level, CA19-9 level as tumor markers, and tumor size are presented in Table 5. Other than the correlation of CEA level and CA19-9 level, no significant

Table 5. Correlation of maximum tumor size, serum CEA level and serum CA19-9 level (Spearman's correlation coefficients)

	Tumor Size	CEA	CA19-9
Tumor Size	—	0.08 (P=0.44)	0.02 (P=0.82)
CEA	—	—	0.43 (P<0.01)

Correlation between CEA level and CA19-9 level was observed, but correlation between tumor size and tumor markers could not be demonstrated.

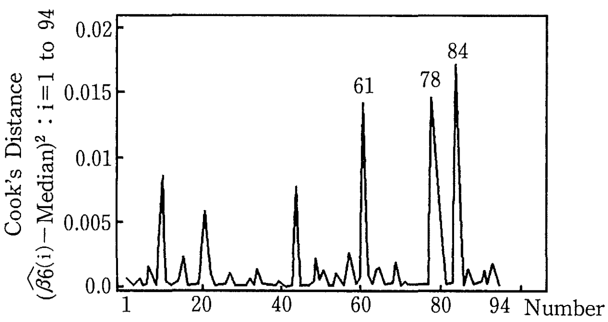


Fig. 5. Detection of outliers by Cook's distance; Cook's distance is shown by coefficient $\hat{\beta}6$(i) (i=1 to 94) whether radiotherapy was conducted or not. Addition of cases #61, #78 and #84 brought about a large variation in regression coefficients. Similar results were obtained for coefficients of other variables though not shown in the figure. In the following analyses these cases were excluded.

correlation could be observed. These three did not have a significant effect on survival time, but as many reports have been made that tumor size is involved in survival time, tumor size was included in proportional hazard model.

2) Problem points in the application of Cox's proportional hazard model

It is common for medical data to contain outliers and therefore Cook's distance was applied for the detection of outliers (Fig. 5). The results showed a high possibility of outliers in cases #61, #78, and #84 and in the following analyses these three cases were excluded.

The results of study made on proportional hazard are shown in Fig. 6. It cannot be said that the presence or absence of metastasis and whether in surgical treatment of obstructive jaundice, chemotherapy, or radiotherapy was conducted are results which would deny proportional hazard.

A total of 1000 bootstraps were prepared and the ultimate results of application of the bootstrap method to Cox's model are shown as a distribution of coefficients in Fig. 7. Skewness could not be ob-

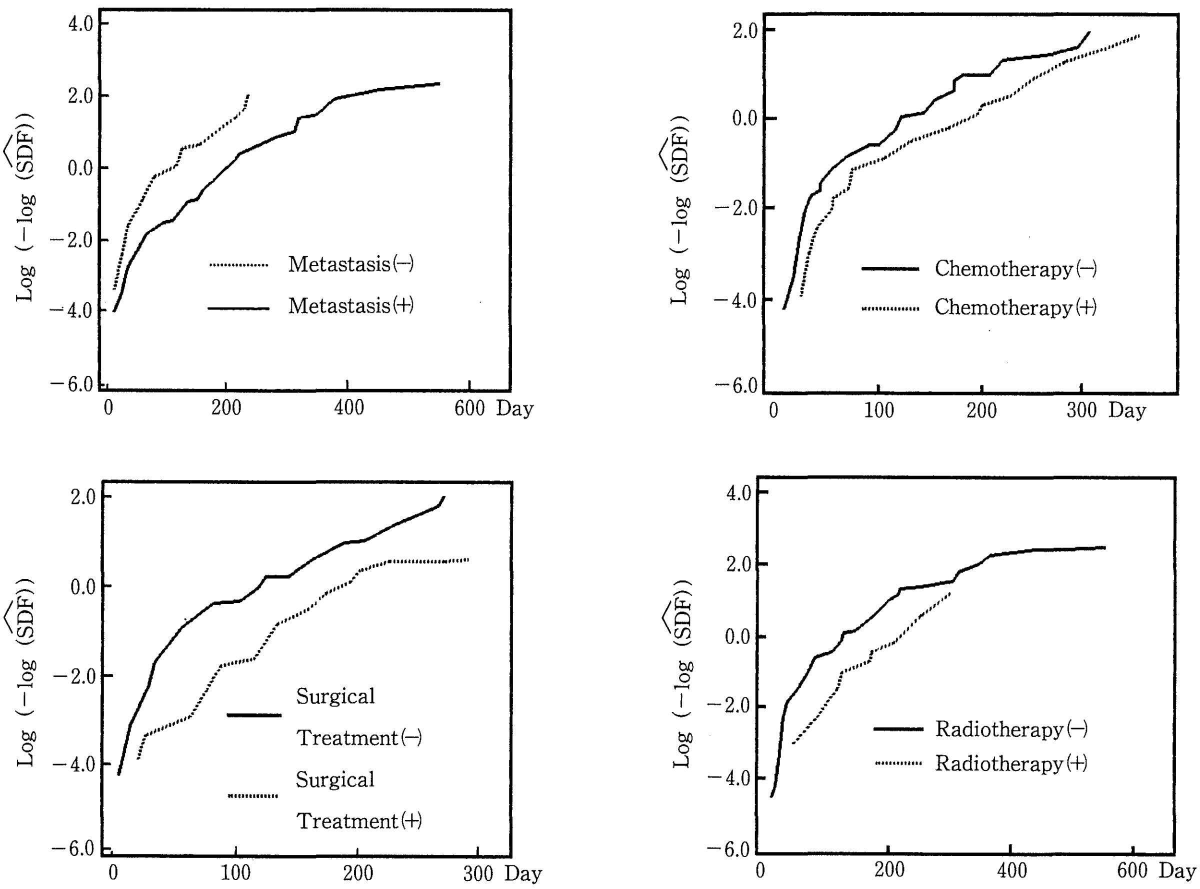


Fig. 6. Study of proportional hazard: If proportional hazard is established, the curves become parallel by stratified plots. Results of the stratified plots could not deny proportional hazard.

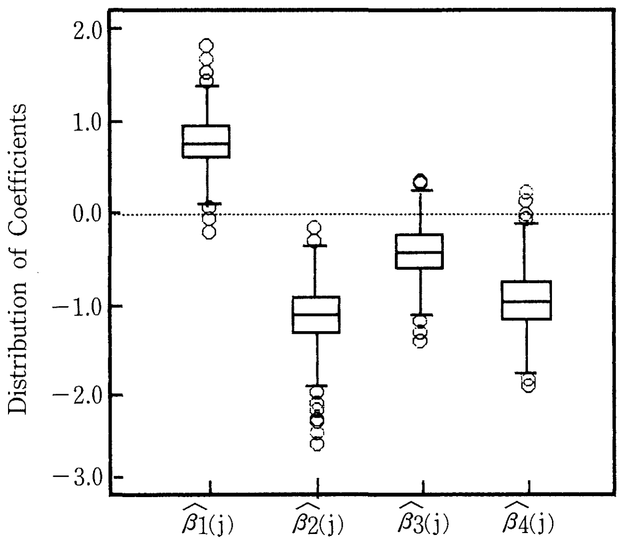


Fig. 7. Distribution of regression coefficients (Bootstrap method): Shown is the distribution of regression coefficients of 1000 Bootstrap samples (j = 1 to 1000). $\hat{\beta}1$(j): coefficient of presence or absence of metastasis; $\hat{\beta}2$(j): coefficient whether surgical treatment was conducted or not; $\hat{\beta}3$(j): coefficient whether chemotherapy was conducted or not; $\hat{\beta}4$(j): coefficient whether radiotherapy was conducted or not: In all cases distribution without any skewness was observed. The median is almost equal to the regression coefficient of the results of analysis by Cox's proportional hazard model.

served in the distribution of any of the coefficients. Their medians are almost equal to the results shown in the bottom part of Table 3.

The foregoing results suggest that Cox's model which was applied in this study provided valid results.

ACKNOWLEDGMENTS

The authors wish to express their profound appreciation to the Hiroshima Gastrointestinal Cancer Group for kindly providing their cases to this study and to Megu Otaki, P.H.D. and Masaki Munaka, M.D. of the Department of Biometrics, Research Institute for Nuclear Medicine and Biology, Hiroshima University for their invaluable suggestions on data analyses.

(Received March 6, 1991)
(Accepted April 30, 1991)

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