Survival rate and prognostic factors in advanced cervical cancer patients accompanied by renal impairment

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Abstrak

Tujuan penelitian ini adalah untuk memperoleh informasi tentang survival kanker servik stadium lanjut dengan gangguan fungsi ginjal (KSSLGFG) serta faktor-faktor yang mempengaruhinya. disamping itu diharapkan dapat ditemukan sistem scoring untuk prediksi kematian pasien KSSLGFG. Rancangan studi yang digunakan adalah retrospektif kohort. Data yang dikumpulkan berasal dari rekam medik penderita KSSLGFG dari 1 januari 1998 sampai 31 Desember 2003 di Rumah Sakit Umum Pusat Nasional Dr Cipto Mangunkusumo, Jakarta, dengan jumlah sampel 70 kasus. Hasil penelitian menunjukkan rerata Survival secara keseluruhan pasien KSSLGFG 8,2 bulan, survival bulan ke-6 sebesar 39%, survival 1 tahun sebesar 3,2%. Median survival 5,3 bulan. Faktor-faktor yang berpengaruh terhadap survival pasien KSSLGFG adalah gambaran histopatologik (sel adenoskuamosa dan diferensiasi sel), ketebalan korteks ginjal < 1 cm dan nefrostomi. ***(Med J Indones 2005; 14: 173-8)***

Abstract

The objective of this study was to obtain information on the survival rate of advanced cervical cancer patients with renal impairment (ACCRI) and its prognostic factors. In addition, it is hoped that by this method the scoring system for predicting the death of ACCRI patients hopetully could be obtained. Design of the study used was retrospective cohort study. Data collected were retrieved from medical records of ACCRI patients from 1 January 1998 to 31 December 2003 at Dr. Cipto Mangunkusumo National Central General Hospital, Jakarta, with a total sample of 70 cases. The results of the study showed that mean survival of all ACCRI patients was 8.2 months, mean survival at sixth month was 39%, and mean survival at one year was 3.2%. Median survival was 5.3 months. Prognostic factors affecting the survival of ACCRI patients included histopathological type (adenosquamous cell and cell differentiation), cortical thickness of the kidney less than 1 cm, and nephrostomy. ***(Med J Indones 2005; 14: 173-8)***

Keywords: *Advanced cervical cancer, renal impairment, nephrostomy, survival, prognostic factor, scoring system*

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A total of 250 cases of advanced cervical cancer (62% of which were stage IIB to IVA)[1] were treated at Dr. Cipto Mangunkusumo General Hospital.

The medical treatment performed on these patients was radiotherapy. However, most of the patients showed a low response.

A survey conducted in the United States in 1978 showed that the primary cause of death in patients with advanced cervical cancer was low response to radiotherapy or local failure (59%). A study conducted at Dr. Cipto Mangunkusumo General Hospital 1994, on the other hand, revealed that 37 cases (30% of advanced cervical cancer patients) suffered from renal failure as a result of ureteral obstruction.[3] Most of the ureteral obstructions in cervical cancers were associated with mass pressure.

This condition made it difficult to overcome the obstruction by cytoscopic retrograde from the bottom. Renal impairment that also followed made it difficult, or almost impossible, to perform radiotherapy. Nephrostomy may become an option to correct renal impairment, and with it the survival rate of ACCRI patients.

The aim of this study was to identify the survival rates and prognostic factors of advanced cervical cancer patients accompanied by renal impairment. The present study also attempted to obtain a scoring system for predicting mortality among ACCRI patients.

METHODS

The present study was a retrospective cohort trial, using data retrieved from medical records of Dr. Cipto Mangunkusumo General Hospital. All patients with advanced cervical cancer admitted to Dr. Cipto Mangunkusumo General Hospital from 1 January 1998 to 31 December 2003 were enrolled. The inclusion criteria were: 1) Cervical cancer stage IIIB, IVA, IVB according to FIGO classification[4]; 2) Recurrent cervical cancer; 3) Renal impairment approved by the consultant of Kidney Hypertension Division, Department of Internal Medicine Dr. Cipto Mangunkusumo National Central General Hospital. The exclusion criteria were patients lost on follow up.

Sample size used the following formula:

$$n = \frac{\left[Z_{1-\alpha 2}\sqrt{2\lambda^2} + Z_{1-\beta}\sqrt{\lambda_1{}^2 + \lambda_2{}^2} \right]}{\left[\lambda_1 - \lambda_2\right]^2}$$

Where:

λ^1 is rate of group 1 (nephrostomy),
λ^2 is rate of group 2 (Conservative)

$\lambda = (\lambda^1+\lambda^2) / 2$

All patients in the present study were monitored until their death.

Factors considered to affect survival rate and prognosis in ACCRI patients were as follows: (A) clinical characteristic factors: 1) age; 2) clinical stage; 3) type of renal impairment; B) histopathological characteristics: 1) histopathological type; 2) cell differentiation; 3) tumor growth pattern; 4) necrosis; 5) lymphvascular reaction; 6) lymphocyte cells surrounding the tumor; C) Characteristic factors of renal pathology: 1) hydronephrosis; 2) cortical thickness/ renal condition; 3) non-visualized kidney; 4) hydroureter; D) Factors of intervention types: 1) conservative; 2) nephrostomy; 3) type of radiation.

Data were analyzed using SPSS and STATA. We used Kaplan Meier test to determine survival rate, while multivariate analysis was used to determine prognostic factors (Table 3). Scoring system was used to predict probability of survival after time (Table 4), and probability of death (Tables 4a and 4b). This study was approved by ethical committee of Dr. Cipto Mangunkusumo National Central General Hospital. We kept the medical records of patients in confidence in accordance with the applicable medical ethics.

RESULTS

Median survival of six months, and one-year survival rate of ACCRI patients were 39% and 3.2% , respectively, while median survival was 5.3 months.

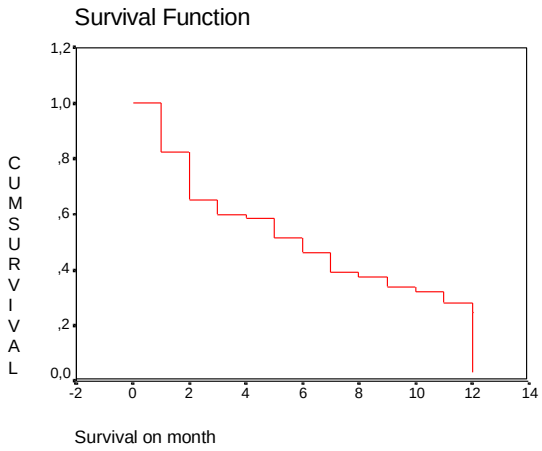

Figure 1. Survival rate of ACCRI patients in month

Multivariate analysis

Multivariate/cox regression analysis showed that risk factors of survival among ACCRI patients were as shown in table 1.

Table 1. Variables included in making of hazard ratio model

Variable	HR	95% CI HR	P value
Age (>= 46 th)	0.73	(0.42;1.25)	0.247
Histopathological type			
adenocarcinoma	0.47	(0.14;1.53)	0.209
Adenosquamous	3.10	(1.07;9.00)	0.037
Small cell	0.35	(0.05;2.58)	0.300
Unknown	2.04	(0.94;4.42)	0.071
Differentiation			
Moderate	1.15	(0.54;2.45)	0.715
Poor	1.35	(0.53;3.42)	0.533
Unknown	1.95	(0.89;4.28)	0.096
Cortical thickness of right kidney (< 1 cm)	1.72	(0.93;3.20)	0.086
(Non)/ conservative nephrostomy	1.78	(1.00;3.16)	0.050
Radiation response			
Partial response	1.64	(0.55;4.87)	0.373
Stable	1.53	(0.68;3.46)	0.305
Progressive	1.15	(0.15;9.10)	0.893
Not performed	2.62	(1.25;5.49)	0.011
Blood creatinine	0.98	(0.95;1.01)	0.249
Hemoglobin level	0.88	(0.76;1.02)	0.081

Table 2. Hazard prediction model

Characteristics	HR	95% CI HR	Coeffi-cient	z	P value	Score
(Non)/ conserva-tive nephrostomy	2.43	(1.10;5.39)	0.8880	2.18	0.029	20
Histopathological type: adenocarci-noma	0.50	(0.11;2.32)	-0.6958	-0.89	0.376	-8
Histopathological type: adenos-quamous	5.21	(1.61;16.80)	1.6500	2.76	0.006	25
Histopathological type: small cell	0.20	(0.02;1.65)	-1.6312	-1.50	0.134	-14
Histopathological type: unknown	1.41	(0.52;3.83)	0.3411	0.67	0.505	6
Moderate differen-tiation	1.05	(0.42;2.67)	0.0534	0.11	0.910	1
Poor differentiation	2.28	(0.76;6.88)	0.8245	1.46	0.143	13
Unknown differen-tiation	4.25	(1.49;12.15)	1.4474	2.70	0.007	25
Cortical thickness of right kidney (< 1 cm)	2.78	(1.39;5.56)	1.0207	2.88	0.004	26

Table 2 showed final model of multivariate analysis and it is evident that factors contributing to survival of ACCRI patients were: nephrostomy (conservative) was not performed, histopathological type of adeno-squamous, unknown cell differentiation, cortical thick-ness of right kidney < 1 cm.

Table 3. Multivariate analysis of prognostic factors among ACCRI patients

Characteristic	HR	95% CI HR	Coefficient	z	*P* values	Scores
1. Nephrostomy						
Yes	1					
No	2.43	(1.10;5.39)	0.8880	2.18	0.029	20
2. Histophatological subtype						
Squamous cell	1					
Adenocarcinoma	0.50	(0.11;2.32)	-0.6958	-0.89	0.376	-8
Adenosquamous	5.21	(1.61;16.80)	1.6500	2.76	0.006	25
Small cell	0.20	(0.02;1.65)	-1.6312	-1.50	0.134	-14
unknown	1.41	(0.52;3.83)	0.3411	0.67	0.505	6
3. Cell differentiation						
Good	1					
Moderate	1.05	(0.42;2.67)	0.0534	0.11	0.910	1
Poor	2.28	(0.76;6.88)	0.8245	1.46	0.143	13
Unknown	4.25	(1.49;12.15)	1.4474	2.70	0.007	25
4. Cortical thickness of right kidney						
>= 1 cm	1					
< 1 cm	2.78	(1.39;5.56)	1.0207	2.88	0.004	26

The present study showed that the difference in the risk or probability between patients who did not undergo nephrostomy and those who underwent nephrostomy after being controlled by other variables. It was evident from the results of multivariate analysis that in the final model, in addition to nephrostomy as a primary variable, there were several confounders, i.e. histopathological type, cell differentiation, and cortex thickness of the kidney. Based on the final model, the probability for patients who did not undergo nephrostomy to die with the same histopathological type, differentiation cell and renal cortex thickness was 2.43 times as high as those undergoing nephrostomy.

Histopathological type of adenosquamous. Compared with squamous type, the mortality risk in ACCRI patients with adenosquamous cell type was 5.21 times (HR 5.21, 95%CIHR 1.61-16.80; p = 0.006) with differetiation cell; intervention and the same cortical thickness.

Cortical thickness of the kidney. Patients with cortical thickness of right kidney less than 1 cm had a mortality risk of 2.78 times (HR 2.78; 95% CIHR; 1.39-5.56; p = 0,004) with intervention and histopathology of the Same cell.

In order to predict survival of patients with advanced stage cervical cancer with renal impairment, we used formula of survival prediction and probability of death as follows:

Formula of survival prediction

$$\text{Survival}_{(t,x)}=[S_0(t)]\ e^{-(0.8880X_1 - 0.6958X_2 + 1.6500X_3 - 1.6312X_4 + 0.3411X_5 + 0.0534X_6 + 0.8245X_7 1.4474X_8 1.0207X_9)}$$

$S_0(t)$ = *Survival base at the –t time*
X_1 = *Conservative(non nephrostomy)*
X_2 = *Histopathological type adenocarcinoma*
X_3 = *Histopathological type adenosquamous*
X_4 = *Histopathological type small cell*
X_5 = *Histopathological type unknown*
X_6 = *Moderate differentiation*
X_7 = *Poor differentiation*
X_8 = *Unknown differentiation*
X_9 = *Cortical thickness of right kidney < 1 cm*

Survival probability patients on 365 th day

$$S_{ACCRI\ (t,x)}=[S_0(t)]\ e^{-(0,8880X_1 - 0,6958X_2 + 1,6500X_3 - 1,6312X_4 + 0,3441X_5 + 0,0534X_6 + 0,8245X_7 + 1,4474X_8 + 1,0207X_9)}$$
$$= (0,8139),x = 0,01016182 = 1,02\%$$

survival probability of ACCRI patients on the 365 th day were 1,02%

Probability of death after 365 thday

$$P = \frac{1}{1 + e^{-(0,8880X_1 - 0,6958X_2 + 1,6500X_3 - 1,6312X_4 + 0,3441X_5 + 0,0534X_6 + 0,8245X_7 + 1,4474X_8 + 1,0207X_9)}}$$

p = 1/1012485342
p = 0,98766862
p =98,8 %

Probability of death after 365 days, were 98,8%

After calculating the probability of survival, we may also calculate the scoring system in a clinically practical way.

Score value was the multiplication of individual characteristic (IC) with index value (1). Thus, each case would have the score that constituted a total of the above multiplication (Σ (IC x I)).

Table 4. Enumeration of probability of survival after time (t)

Characteristics	Individual Values	Coefficient	Amount
	NI	K	NI x K
Nephrostomy			
Yes	0	0	
No	1	0.8880	0.880
Histophatological subtype			
Squamous cell	0	0	
Adenocarcinoma	0	-0.6958	
Adenosquamous	1	1.6500	1.6500
Small cell	0	-1.6312	
unknown/sensor	0	0.3411	
Cell differentiation			
Good	0	0	
Moderate	0	0.0534	
Poor	1	0.8245	0.8245
Unknown/sensor		1.4474	
Cortical thickness of right kidney			
> 1 cm	0	0	
< 1 cm	1	1.0207	1.0207
Total (NI x K)			4.3832

Table 4a. Enumeration of probability of survival after time (t)

Characteristics	Individual Characteristic	Index	Scores
	KI	I	KI x I
Nephrostomy			
Yes	0	0	
No	1	20	20
Histophatological subtype			
squamous cell	0	0	
Adenocarcinoma	0	-8	
Adenosquamous	1	25	25
small cell	0	-14	
Unknown/sensor	0	6	
Cell differentiation			
Good	0	0	
Moderate	0	1	
poor	1	13	13
Unknown/sensor		25	
Cortical thickness of right kidney			
> 1 cm	0	0	
< 1 cm	1	26	26
Total Scores			84

Table 4b. Death prediction conversion of cervical cancer

Total Scores	Death Prediction
≤ -7	67 – 70 %
-1 s.d. 11	71 – 80 %
13 s.d. 31	81 – 90 %
> 39	> 90%

ACCRI patient did not undergo Nephrostomy (conservative) histopathological type : adenosquamous, poor differntiation; cortical thicknes < 1 cm Showed table (4 and 4a) were total score 84.
Since the total score more than 39, death prediction >90% (tabel 4b).

DISCUSSION

Probability of survival in ACCRI patients with renal dysfunction in the 6th month was 39%, while the cummulative probability in the 12th month was 3.2%, and median survival was 5.1 months. As shown in the annual FIGO report, mean survival of cervical cancer patients was 55%. At the advanced stages, i.e. stage III and IV, the five-year survival was still high, i.e. 31.0 % and 7.8 % respectively.

In the present study, with the presence of renal dysfunction the survival rate that the one year survival drops to 3.2%. The study conducted by Gaspari M et.al, showed that survival of ACCRI patients was not influenced by age and renal impairment.[9]

Harrington KJ et.al: found that the median survival in all patients with ureteral obstructions leading to malignancies was ± 133 days (with a range of 7-7-12). Seventeen patients (40%) survived up to 6 months and 5 patients (12%) up to 1 year.[8]

Median survival after nephrostomy was 526 days, with a range of 1-712 days. The study of prostate cancer showed that overall survival rate was 57% for 1 year and 29% for 2 years (median survival was 21 months). Another study of prostate cancer found an overall survival rate of 60% for the 1 year and 32% for 2 years.[9]

With respect to prognostic factors in advanced stage cervical cancer with renal dysfunction, Culkin DJ et. al found that the type of histopathology was the main determining factor for survival in prostate, rectal, and cervical cancer. However, this was not the case

with bladder cancer in which there was no independent factor for significant prognosis.

On the other hand, Roesma J.et.al. found cortical thickness of < 1 cm, showed that the kidney has suffered an irreversible process. However, nephrostomy may be considered for cortical thickness > 1 cm.[10]

The aforementioned studies that supported the results of the present study showed that the prognostic factors in ACCRI patients were: (1) Type of histopathology (Adenosquamous cell); (2) Cell differentiation; (3) cortical thickness (< 1cm), and (4) Nephrostomy.

By taking into consideration the above-mentioned prognostic factors, we might be able to predict patients' survivability using survival prediction scoring.

CONCLUSIONS

1. Median survival among ACCRI patients was 5,31 months, while six months and 1 year survival among ACCRI patients were 39% and 3.2%, respectively. The overall mean of one-year survival of ACCRI patients was 8.2 months, with survival in the sixth month at 39%, and survival in one year at 3.2%. Median survival was 5.31 months.
2. As shown in multivariate analysis, prognostic factors that affected survival among ACCRI patients included: (a) Histopathological subtype, (adenosquamous cells and cell differentiation), (b) cortical thickness <1cm (c) nephrostomy.
3. By using scoring system, we may be able to predict the probability of death in advanced stage cervical cancer patients with renal impairment.

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