

นิพนธ์ต้นฉบับ

ปัจจัยที่มีผลต่ออัตราการรอดชีพของผู้ป่วยโรคมะเร็งท่อน้ำดีภายในตับ หลังจากได้รับการรักษาด้วยวิธีการผ่าตัด ของผู้ป่วยที่เข้ารับการรักษา ในโรงพยาบาลร้อยเอ็ด จังหวัดร้อยเอ็ด

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บทคัดย่อ

ที่มาของปัญหา: โรคมะเร็งท่อน้ำดีทางเดินน้ำดีเป็นปัญหาสำคัญทางด้านสาธารณสุขในภาคตะวันออกเฉียงเหนือของประเทศไทย ผู้ป่วยที่ได้รับการรักษาด้วยวิธีการผ่าตัดอาจช่วยเพิ่มระยะเวลารอดชีพได้

วัตถุประสงค์: เพื่อศึกษาปัจจัยที่มีผลต่อการรอดชีพของผู้ป่วยโรคมะเร็งท่อน้ำดีทางเดินน้ำดีภายในตับที่ได้รับการรักษาด้วยการผ่าตัด

วิธีการศึกษา: เป็นการศึกษาแบบ cohort โดยเก็บรวบรวมข้อมูลจากเวชระเบียนผู้ป่วยโรคมะเร็งท่อน้ำดีทางเดินน้ำดีภายในตับทั้งหมดที่ได้รับการรักษาด้วยการผ่าตัดที่โรงพยาบาลร้อยเอ็ด ระหว่างวันที่ 1 เดือนมกราคม พ.ศ.2553 ถึง วันที่ 31 เดือนธันวาคม พ.ศ. 2557 และติดตามการมีชีวิตจนถึงวันที่ 31 เดือนมีนาคม พ.ศ. 2559 สถิติที่ใช้ในการวิเคราะห์ข้อมูลได้แก่ สถิติเชิงพรรณนา การวิเคราะห์ระยะปลอดเหตุการณ์โดยใช้โค้งปลอดเหตุการณ์ของแคปแลนและไมเยอร์ log-rank test และสถิติ cox proportional hazard model

ผลการศึกษา: จากผู้ป่วยโรคมะเร็งท่อน้ำดีทางเดินน้ำดีภายในตับรายใหม่จำนวน 92 ราย เป็นเพศชาย

ร้อยละ 60.87 อายุเฉลี่ย 59.54 ปี (\pm SD = 8.63) มีระยะติดตาม 1,486 คนต่อเดือน อัตราตาย 4.8 ต่อ 100 คนต่อเดือน ผู้ป่วยหลังผ่าตัดส่วนมากมีชีวิตรอด 12.1 เดือน โดยมีอัตราการรอดชีพ 3 เดือน 6 เดือน 1 ปี และ 3 ปี คือ ร้อยละ 84.8, 72.8, 51.1 และ 23.3 ตามลำดับ ปัจจัยที่มีผลต่ออัตราการรอดชีพของผู้ป่วยมะเร็งท่อน้ำดีทางเดินน้ำดีภายในตับได้แก่ การแพร่กระจายของมะเร็ง (HR_{Adj} 5.3:95%CI; 3.00 - 9.34), การเป็นโรคมะเร็ง Stage IV (HR_{Adj} 1.3:95%CI; 1.15 - 2.65) และ Unknown stage (HR_{Adj} 1.4:95%CI; 1.24-2.25) ส่วนผู้ป่วยที่ได้รับการรักษาด้วยเคมีบำบัดพบมีอัตราการรอดชีพมากกว่ากลุ่มที่ไม่ได้รับการรักษาด้วยเคมีบำบัด (HR_{Adj} 0.3:95%CI; 0.26-0.69)

สรุป: การแพร่กระจายของมะเร็งและระยะของการเกิดโรคมีผลต่ออัตราการรอดชีพของผู้ป่วยโรคมะเร็งท่อน้ำดีทางเดินน้ำดีภายในตับ ผู้ป่วยที่ได้รับการรักษาด้วยเคมีบำบัดพบมีอัตราการรอดชีพมากกว่ากลุ่มที่ไม่ได้รับการรักษาด้วยเคมีบำบัด

คำสำคัญ: มะเร็งท่อน้ำดีทางเดินน้ำดี; อัตราการรอดชีพ; การรักษาด้วยการผ่าตัด; โรงพยาบาลร้อยเอ็ด

Original article

Factors Effecting to Survival of Intrahepatic Cholangiocarcinoma after Surgical Treatment among Admitted Patients in Roi Et Hospital, Roi Et Province

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Abstract

Background: Intrahepatic Cholangiocarcinoma (ICHCA) is a frequent malignancy found in the northeast of Thailand. Surgical treatment may support ICHCA patients having long time survival.

Objective: To investigate factors effecting to survival of ICHCA patients after surgical treatment.

Material and Methods: A retrospective cohort study. Data was collected from medical records of ICHCA patients who had surgical treatment at Roi Et Hospital during 1 January, 2013 to 31 December, 2015. All cases were followed up the vital status until 31 March, 2016. The data were analyzed using Kaplan-Meier method, log-rank test and Cox proportional hazard models.

Results: 92 patients were new diagnosed for ICHCA and most of them were male (60.87 percent), mean age was 59.54 years (\pm SD=8.63). The total follow-up times were 1,486 person-

months. The mortality rate was 4.8 per 100 person-months, median survival time after surgeries was 12.1 months. The cumulative 3 month 6 months, 1 year 3 years survival rate were 84.8 percent, 72.8 percent, 51.1 percent, and 23.3 percent respectively. After adjusted data, the metastasis (HR_{Adj} 5.3:95%CI; 3.00- 9.34), Stage IV (HR_{Adj} 1.3:95%CI; 1.15- 2.65) and unknown stage (HR_{Adj} 1.4:95%CI; 1.24- 2.25) were the factors effected to survival of ICHCA patients. Patients who receive chemotherapy had survival rate better than non-chemotherapy therapy patients (HR_{Adj} 0.3:95%CI; 0.26-0.69).

Conclusion: The metastasis and stage of diseases were the important factors effecting to survival of ICHCA patients. Patients who receive chemotherapy had survival rate better than non-chemotherapy therapy patients.

Keyword: Cholangiocarcinoma; survival rate; surgical treatment; Roi Et hospital

Introduction

Cholangiocarcinoma (CHCA) is the major cause of death of malignancy in the northeast of Thailand. The incidence of CHCA among male is higher than female¹. The Age Standardized Rate (ASR) of CHCA from 1985 to 2009 was 16.8 to 62.0 per 100,000 for males and 4.8 to 25.6 per 100,000 for females. The overall ASR from 1985 to 2009 of male was 44.3 per 100,000 and female was 17.6 per 100,000.²

Previous studies showed the mortality rate of CHCA patients who has supportive treatment was 10.8 per 100 person-years and the median survival time was 4 months³. The overall 5-year survival rate of patients who received curative resection for perihilar CHCA was 20.6 percent and the median survival time was 19.9 months. Meanwhile patients achieving R0 led to 58 percent reduction to the chance of mortality compared to R1⁴ and some study found 4 years survival rate of CHCA after R0 resection was 100 percent⁵.

Although the incidence of CHCA in northeast Thailand was high but few studies reported on the factors effecting to survival of ICHCA after the surgery treatment. The aim of this study was to investigate the factors effecting to survival of ICHCA after surgical treatment

Methods

Study subjects

A retrospective Cohort study data were

collected from medical records and from the Cancer Registry Unit, Roi Et Hospital, Roi Et Province. All patients were newly diagnosed for Intrahepatic Cholangiocarcinoma (ICHCA) and received surgical treatment at Roi Et Hospital, Roi Et Province during 1 January, 2013 to 31 December, 2015. All subjects were followed-up vital status until death or the end of study (31 March, 2016).

The criteria of cases

The clinical suspicions for ICHCA include patients having obstructive jaundice, hepatomegaly, palpable gall bladder. The initial data of subjects include demographic data, medical history, presented symptom, radiographic, tumor maker and clinical of tumor. Of 92 ICHCA patients who received surgical treatment and had pathological confirmation. The diagnosis was made according to The International Classification of Diseases for Oncology (ICD-O 3rd). The variables of interest included demographic data, treatment data, operative data and pathological reports.

Cases follow-up

The classical end point of this study is survival time of ICHCA, and this study measured survival length from the date at first diagnosis to date of death or date of the end of study. The vital status of patients was checked from medical records and by link with the death registry of the Thai National Statistical Data Base. The end point of follow-up was patient's death. For those who lost to follow-up

or death from other causes were considered as censored. The end of study was 31 March, 2016.

Variables of interests

The variables of this study including demographic variables and the explanatory variable were chemotherapy, histology type, histology grading, staging of diseases and surgeries. All variables were categorical variables.

Ethical consideration

This study was approved by the Ethical committee of Roi Et Hospital, Roi Et Province, Thailand. The certificate number is 004/2560.

Statistical analyses

The baseline characteristics of patient were described using descriptive statistics. The categorical data and mean with standard deviation (SD) were used to describe continuous data. The observed survival curves were estimated by Kaplan-Meier method. The log-rank test was used to compare survival curve between groups of variables. The univariate and multivariate were described by using Cox proportional hazard models to present crude hazards ratios (HRc) and adjusted hazards ratios (HRa) and their 95% CI. The statistical significant was set at $p\text{-value} < 0.05$.

Results

The general characteristics of patients with Intrahepatic cholangiocarcinoma

Of 92 patients, the total follow-up times

were 1,486 person-months and the mortality rate was 4.8 per 100 person-months. Most of them were male 60.87 percent mean age 59.54 years (\pm SD = 8.63), histology grading was highest with moderately differentiated 36.96 percent, Direct extension was 33.70 percent. The stage of diseases was highest with unknown 72.83 percent stage followed by Stage IV, Stage III, stage II and Stage I (11.96 percent, 6.52 percent, 5.43 percent, 3.26 percent) respectively. Data shows in Table 1.

The survival time and survival rate of Intrahepatic cholangiocarcinoma after surgical treatment

The median survival time of ICHCA patients after surgical treatment was 12.1 months, data was shown in Figure 1. Figure 2 shows the median survival time of stage of disease. The stage I, II, III, IV and unknown stage were 38.1, 38.3, 19.4, 11.2 and 11.8 months respectively. Figure 3-4 shows the median survival time of metastasis of diseases and chemotherapy treatment. For metastatic patients it was 3.7 months and for non metastatic was 18.7 months. For patients received chemotherapy the time was 17.0 months and for non-received it was 6.2 months. Table 2 shows median survival time and cumulative survival rate of ICHCA after surgery treatment. The cumulative survival 3, 6 months, 1, 3 years survival were 84.8 percent, 72.8 percent, 51.1 percent, and 23.3 percent respectively.

Table 1 The general characteristic of patients

Variables	Number (n=92)	Percent
Gender		
Male	56	60.87
Female	36	39.13
Age		
<60	44	47.83
≥ 60	48	52.17
Mean \pm SD	59.46 \pm 8.63	
Min: Max	36:79	
Histology grading		
Well differentiated	28	30.43
Moderately differentiated	34	36.96
Poorly differentiated	5	5.43
Undifferentiated	25	27.17
Staging of diseases		
Stage I	3	3.26
Stage II	5	5.43
Stage III	6	6.52
Stage IV	11	11.96
Stage unknown	67	72.83
Extent		
In situ.	1	1.09
Localized	8	8.70
Direct extension	31	33.70
Regional lymph node	27	29.35
Distant metastasis	7	7.61
Unknown	18	19.57
Metastasis		
No	63	68.5
Yes	29	31.5

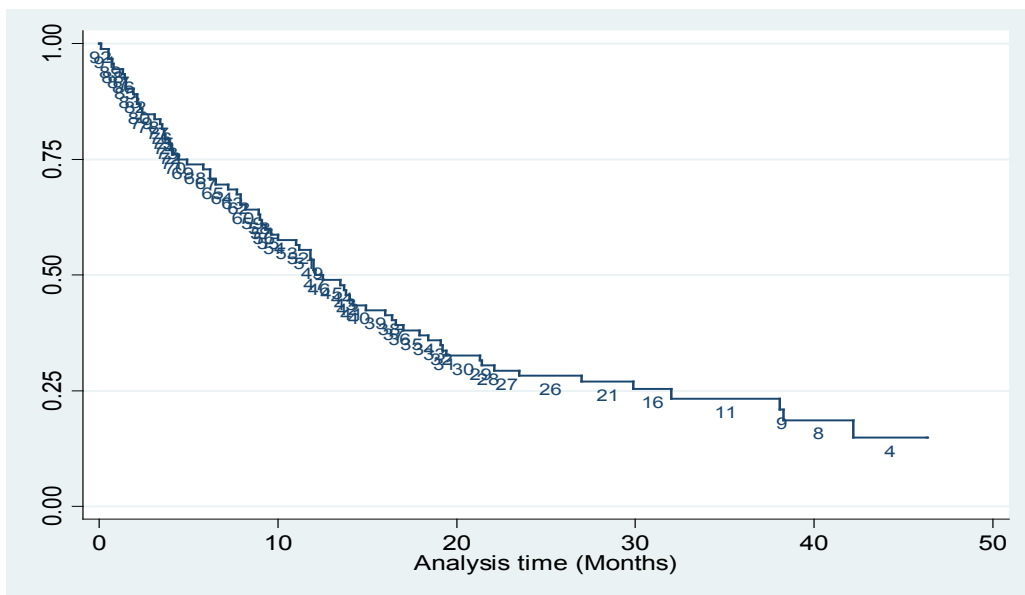


Figure 1 The survival time of Intrahepatic Cholangiocarcinoma after surgery

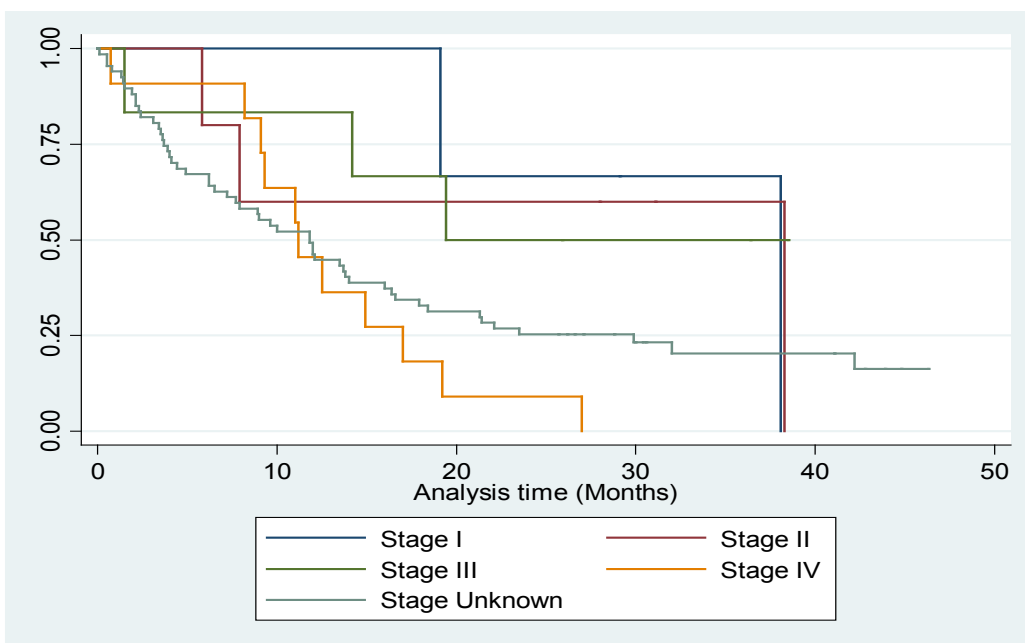


Figure 2 The survival time of stage of Intrahepatic Cholangiocarcinoma

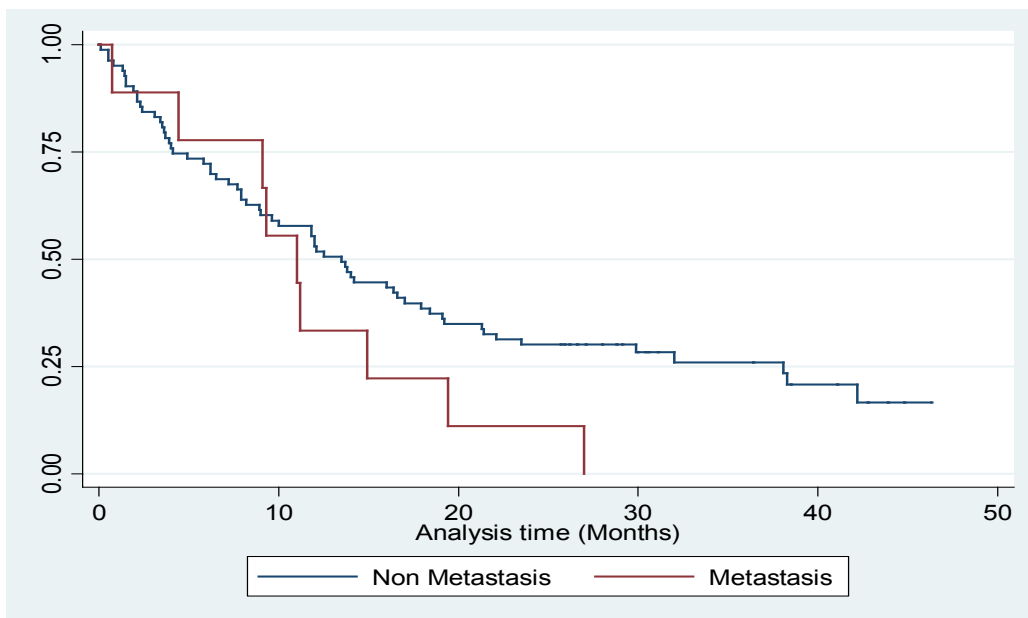


Figure 3 The survival time of metastasis of Intrahepatic Cholangiocarcinoma

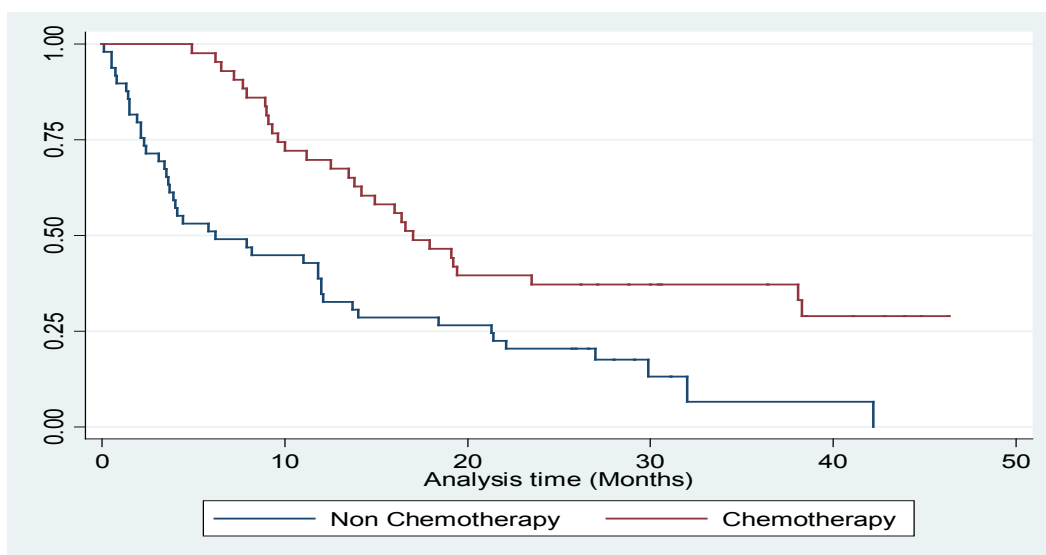


Figure 4 The survival time of chemotherapy of Intrahepatic Cholangiocarcinoma

Table 2 The survival rate of Intrahepatic Cholangiocarcinoma after surgery treatment

Survival time	Median time (Months)	95% CI	Survival rate (percent)	95% CI
3 Months	1.4	0.50-2.10	84.8	75.66-90.69
6 Months	3.9	3.40-4.40	72.8	62.50-80.74
1 Year	9.0	7.70-11.00	51.2	40.47-60.73
3 Years	29.9	19.40-42.20	23.3	14.75-32.94

The factors affected to survival of Intrahepatic Cholangiocarcinoma patients.

The multivariate analysis were statistically significant with the metastasis of diseases (HR_{Adj.} 5.3:95%CI; 3.00 - 9.34), diseases Stage IV (HR_{Adj.} 1.3:95%CI; 1.15-2.65) and Unknown stage (HR_{Adj.} 1.4:95%CI; 1.24 - 2.25). Meanwhile, Chemotherapy treatment was the factor protecting for ICHCA patients (HR_{Adj.} 0.3:95%CI; 0.26 - 0.69).

Discussion

The aim of this study was to investigate the factors effecting to survival of intrahepatic cholangiocarcinoma (ICHCA) patients were received surgical treatment at Roi Et Hospital. The data analysis showed the median survival time of ICHCA after surgeries was 12.1 months and the factors effecting to survival of ICHCA were metastasis of diseases, cancer Stage IV and Unknown

stage. The chemotherapy was the factor protecting hazard of death of patients after surgical treatments.

This study found the median survival time of ICHCA after surgery treatment was 12.1 months and cumulative survival 3, 6 months, 1, 3 years survival were 84.8 percent, 72.8 percent, 51.2 percent, and 23.3 percent respectively. It is comparative with previous studies finding, which they found the median survival time of ECHCA after resection was 15 months and 1-, 3-, and 5-year survival rates were 62.1 percent, 21.7 percent and 10.8 percent, respectively⁶ and consistency with study with the median survival time after resection of ICHCA was 12.4 months and the cumulative 1, 3, and 5 year survival rates were 52.1 percent, 21.7 percent, and 11.2 percent, respectively.⁷

Table 3 The univariable and multivariate analysis of factors effected to hazard of death of Intrahepatic Cholangiocarcinoma

Variables	Median time (Months)	Person times	IR/100	HR _c	HR _A	95%CI	p-value
Gender							0.917
Male	13.7	906	0.49	1	1		
Female	11.8	579	0.48	1.1	1.2	(0.63-1.65)	
Age							0.911
<60	12.1	726	0.48	1	1		
≥60	12	760	0.49	1.2	1.2	(0.65-1.63)	
Metastasis							<0.001
No	18.7	1293	0.34	1	1		
Yes	3.7	192	1.45	4.3	5.3	(3.00- 9.34)	
Chemotherapy							<0.001
No	6.2	556	0.77	1	1		
Yes	17	925	0.31	0.4	0.3	(0.26-0.69)	
Histology grading							0.535
Well differentiated	14.2	538	0.43	1	1		
Moderately diff.	4.0	535	0.49	0.9	0.9	(0.51-1.72)	
Poorly diff.	4.9	78	0.38	0.6	0.7	(0.21-2.43)	
Undifferentiated	3.9	333	0.60	1.3	1.4	(0.79-2.27)	
Staging of diseases							0.047
Stage I	38.1	86	0.02	1	1		
Stage II	38.3	111	0.27	0.5	0.6	(0.17-1.77)	
Stage III	19.4	135	0.22	0.4	0.4	(0.13-1.29)	
Stage IV	11.2	140	0.79	1.4	1.3	(1.15-2.65)	
Stage unknown	11.8	1012	0.52	1.3	1.4	(1.24-2.25)	
Extend							0.633
In situ.+ Localized	32	206	0.24	1	1		
Direct extension	19.2	677	0.29	0.4	0.3	(0.21-1.60)	
Lymph node	11.8	339	0.68	0.7	0.6	(0.35-1.14)	
Distant metastasis	11	83	0.84	0.8	1.3	(0.46-1.12)	
Unknown	4.4	150	1.13	1.5	1.4	(0.42-4.37)	

***Adjusted for Age and Gender, HR_c = Crude Hazard Ratio, HR_A = Adjusted Hazard Ratio, 95%CI= 95%

confident interval and p-value from Partial likelihood ratio test.

In term of factors effecting to survival of ICHCA, previous studies they found patients with stage III, stage IV and Unknown stage were higher mortality rate than stage I and II it is consistency with ours study finding.^{3, 8} However this study might differ from previous

studies, which they found patients were presented of jaundice, ascites, positive serum carcinoembryonic antigen, macroscopic classification and positive resection margin were increases hazard of death.^{6, 7, 8} But this study was not considered those factors.

In conclusion, this study shown the median survival time of ICHCA after surgeries was 12.1 months. The factors effecting to survival of ICHCA were metastasis of diseases, cancer stage IV and unknown stage. Patients who receive chemotherapy had survival rate better than non-chemotherapy therapy patients.

Limitation

The unknown stage of ICHCA of this study was high. In this case might effect to the outcome from data analysis. The specific study on stage of diseases needs to verify ours study finding.

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