CHAPTER V

RESULT

1. Patient Characteristics

26 patients were included into this study. Two patients were withdrawn from this study because they had inappropriate sampling blood time. Data of 24 patients were therefore available.

From the remaining 24 patients, twenty patients had been treated for colon cancer, three for rectal cancer and one of them had unknown primary tumor site. All of them had undergone surgery to confirm diagnosis. Two of them had recurrence colorectal cancer and two from 24 has family history died from cancer. Characteristics of the patients are shown in Table 5. There were 16 men and 8 women. The mean age was 55.3 $\pm$ 14.5 years old (range 31 to 84). By TNM staging, six patients had stage II, nine had stage III and nine had stage IV cancer. Only two patients had performance status 0, 15 had status 1 and 8 had performance status 2. The common metastases found at lymph node and liver. Nine patients had metastases to lymph node, four of patients had metastases to liver, three of patients had metastases to lung, two of patients had metastases to appendix and one of them had metastases to rectum. Each patient was different cycle in collecting blood sample. There were 11 patients collected blood on the first cycle of chemotherapy, 9 patients were collected on the third cycle of chemotherapy, 2 patients were collected on the tenth cycle of chemotherapy, 1 patient was collected on the fifth cycle of chemotherapy and 1 patient was collected on the sixth cycle of chemotherapy.

All patients received standard mayo regimen of folinic acid 20 mg/m^2/day intravenous infusion in 15 min followed by 5-FU 425 mg/m^2/day infusion in 15 min. Average dose of folinic acid was 34.37 $\pm$ 6.96 mg/day (range from 30-40 mg/day) while average dose of 5-FU was 684.79 $\pm$ 55.18 mg/day (range from 610-800 mg/day).There

were two patients had received 5-FU lower than 425 mg/m^2/day that may effected to AUC and response of therapy. Table 6 shows dosage of folinic acid and 5-FU of individual patients.

2. The standard curve of 5-FU plasma concentration.

Sensitivity and specificity

Sensitivity was tested by spiking 5-FU and 5-BU stock solution into six different of drug free plasma and the concentrations in these spiked plasma samples were analyzed. Chromatogram of 5-FU and 5-BU in plasma are shown in Fig. 5. Each chromatogram run required 20 min. The retention times were approximately 7.3 min for 5-FU and 14.8 min for 5-BU. Extraction and chromatogram of blank plasma samples confirmed that there were no interfering peaks that found at the retention time of 5-FU and BU.

Linearity

The calibration curve was estimated by plotting drug concentration of 5-FU spikes plasma against peak area ratio between 5-FU and internal standard with a correlation coefficient of $r^2 > 0.995$. Calibration solutions were prepared on the same day by using the same stock solution. All calibration concentrations were back-calculated to recheck expected concentration.

Precision and accuracy

Data for precision and accuracy of within and between days was shown in table 7. For within-day precision and accuracy, five control samples of four 5-FU concentrations were extracted and injected for 3 days. For between-day assessment, same concentrations used for within day precision and accuracy tests were extracted and injected on each of 3 days. The within- day percent of coefficient variation (%CV) varied between 6.67-12.35% and between-day precision varied between 4.96-9.85%. The accuracy at the testes concentrations range from 91.38-105.99%

Table 5 Patient characteristics

Patient number	Gender	Age	Primary tumor site	TNM staging	Performance status	Cycle	Metastases site	Concomittant disease	Drug Interaction	Allergy
1,kk	M	35	unknown	II	0	C3	appendix	-	-	-
2,ib	M	52	rectum	II	1	C3	-	-	-	-
3,ys	M	34	colon	IV	1	C3	appendix	-	-	-
4,ps	M	54	colon	III	1	C3	LN	-	-	-
5,jl	M	62	colon	III	1	C3	LN	-	-	-
6,ss	F	65	colon	IV	2	C1	lung	-	-	-
7,sw	M	56	colon	III	2	C10	LN	-	-	-
8,pn	M	44	rectum	IV	1	C3	liver	-	-	-
9,js	M	74	colon	IV	1	C1	lung	HTN, IHD	-	-
10,cj	F	76	colon	III	1	C3	LN	HTN	-	-
11,pa	F	57	colon	III	0	C1	LN	HTN	-	-
12,no	M	84	colon	III	2	C1	LN	-	-	-
13,tc	F	67	colon	II	1	C1	-	-	-	-
14,ws	M	55	rectum	IV	1	C10	liver	-	-	-

Patient number	Gender	Age	Primary tumor site	TNM staging	Performance status	Cycle	Metastases site	Concomittant disease	Drug Interaction	Allergy
15,pf	M	47	colon	III	1	C1	LN	-	-	-
16,st	M	68	colon	IV	2	C1	liver	-	-	-
17,ss	M	43	colon	II	2	C1	-	-	-	-
18,yk	M	39	colon	II	1	C3	-	-	-	-
19,sp	M	45	colon	III	2	C1	LN	-	-	-
20,bc	F	72	colon	IV	1	C1	lung	-	-	-
21,jv	F	31	colon	IV	1	C1	rectum	-	-	-
22,gl	F	69	colon	III	1	C3	LN	HTN,DM	-	-
23,ls	M	72	colon	II	1	C5	-	HTN	-	-
24,wn	F	41	colon	IV	2	C6	liver	-	-	-

Abbreviation : M = male, F = female, C = cycle, LN = lymph node, HTN = hypertension, IHD = ischemic heart disease, DM = diabetic mellitus, - = not found

Table 6 5-FU and LV dose from calculation and actual data

Pat ient number	Weight (kg)	Height (cm)	BSA (m^2)	5-FU dose cal. (mg)	LV dose cal. (mg)	5-FU dose act. (mg)	LV dose act. (mg)
1	64	173	1.75	743.75	30.8	750	40
2	65	165	1.72	731	29.8	745	35
3	59.6	177	1.71	726.75	29.4	750	50
4	58.8	153	1.58	671.5	25	655	30
5	78	159	1.85	786.25	34.4	750	40
6	83	152	1.87	794.75	35	750	40
7	61	175	1.72	731	30.6	650	30
8	73.8	173	1.88	799	35.4	790	50
9	72.1	163	1.80	765	32.6	750	30
10	50	159	1.48	629	22	620	30
11	47.5	152	1.42	603.5	20	610	30
12	51.3	160	1.50	637.5	22.8	640	30
13	54.1	147	1.49	633.25	22	620	30
14	65	160	1.70	722.5	28.8	650	30
15	59	167	1.65	701.25	27.4	705	50
16	53.9	165	1.57	667.25	24.8	670	35
17	51.2	171.5	1.56	663	24.4	680	30
18	53	168	1.57	667.25	24.8	680	30
19	40	165	1.35	573.75	18.4	600	30
20	62	153	1.62	688.5	26.4	680	30
21	48	160	1.46	620.5	21.4	650	30
22	74	151	1.76	748	31	720	30
23	59.4	163	1.64	697	26.8	700	35
24	47.5	160	1.45	616.25	21.2	620	30

Abbreviation : cal. = calculation act. = actual

Table 7 Precision and accuracy of the method

Actual concentration (mg/L)	Within-day		Between-day		
	Measured concentration (mean ± SD)	RSD (%)	Measured concentration (mean ± SD)	RSD (%)	Accuracy (%)
0.05	0.053±0.006	12.35	0.053±0.005	5.99	105.99
0.2	0.194±0.016	8.29	0.194±0.015	2.87	97.13
5	4.884±0.424	8.69	4.884±0.242	2.32	97.68
50	45.690± 3.049	6.67	45.690±2.538	8.62	91.38

Recovery

The absolute analytical recovery of 5-FU and 5-BU was calculated in three analytical runs, by comparing peak areas obtained by direct injection of a standard solution 5-FU and 5-BU in mobile phase, to those obtained in extracted plasma samples of validation. The mean recovery of 5-FU were 82.26, 66.98 and 73.62% of the concentration 0.2, 5 and 50 mg/L. The recovery of internal standard, 5-BU, measured at the concentration 30 mg/L was 84.20%.

Stability

The stability of 5-FU in human plasma was established during three consecutive freeze thawing cycle. In plasma samples spiked with 0.2 and 50 mg/L, the percent recovery were 96.87 % of 0.2 mg/L 5-FU 97.26 % of 50 mg/L of 5-FU. The stability was also tested after room temperature incubation of the samples for 12 hrs. The percent recovery were 99.32 and 97.77% of 0.2 mg/L and 50 mg/L of 5-FU respectively.

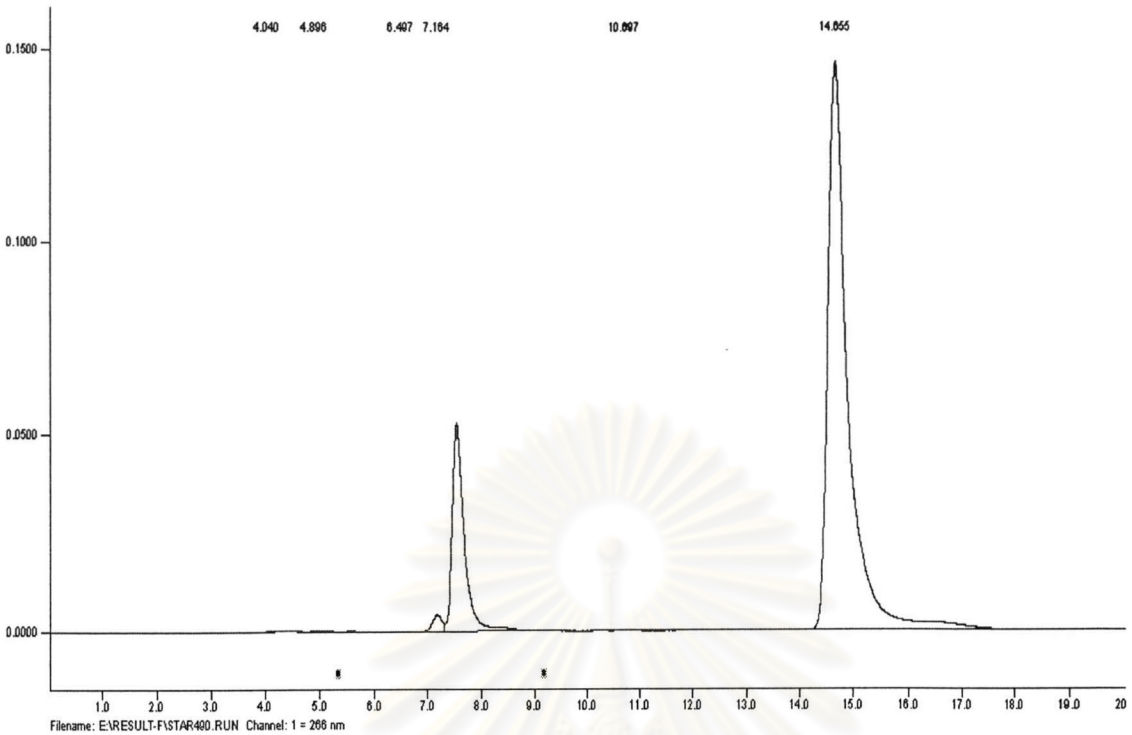

Fig. 5a Chromatogram of standard solution 5-FU 5 μg/ml and internal standard

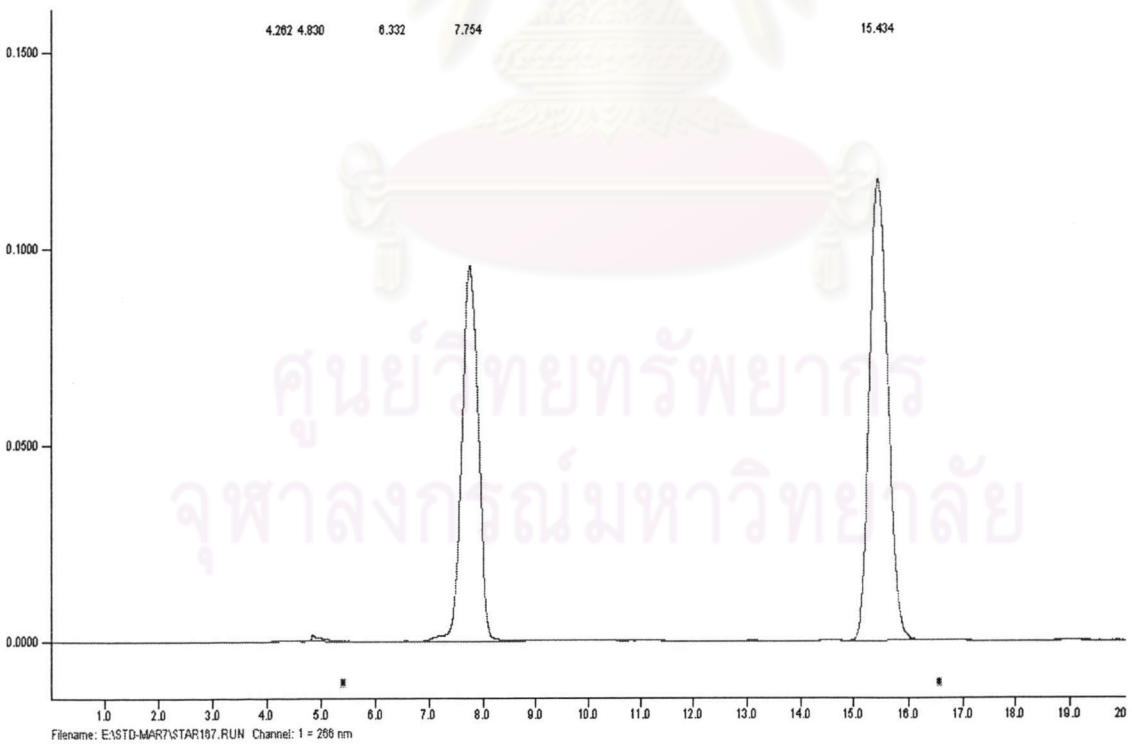

Fig. 5b Chromatogram of plasma spiked with 5-FU 25 μg/ml and internal standard

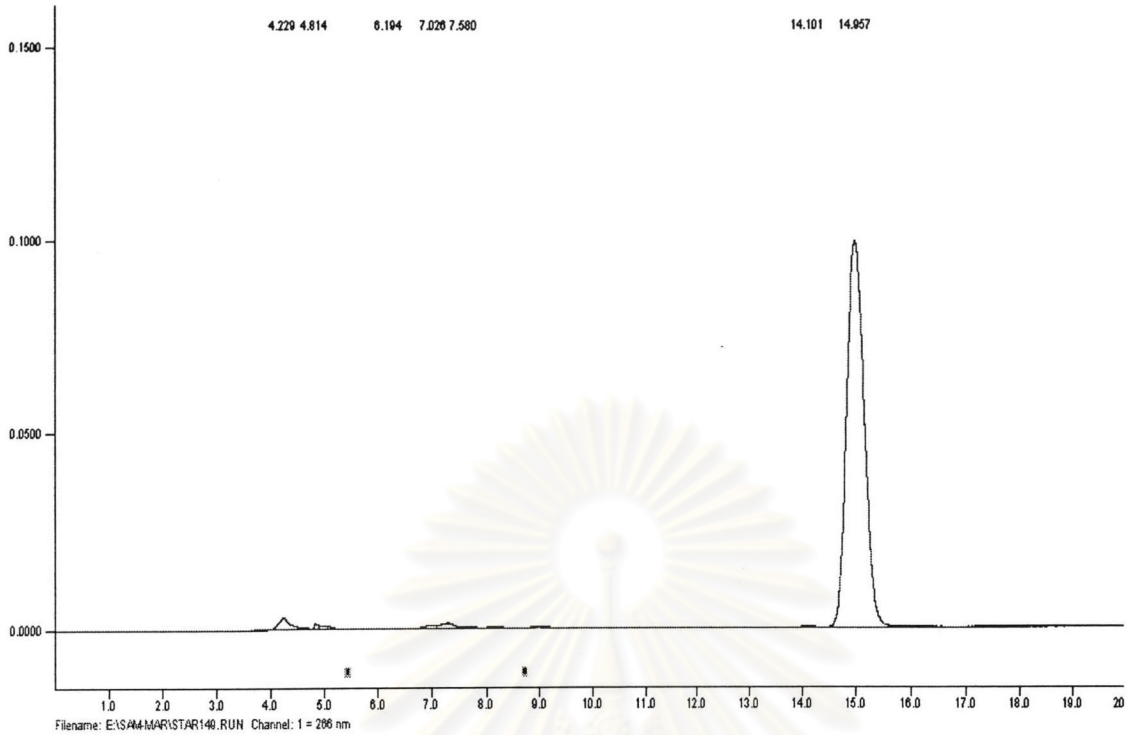

Fig. 5c Chromatogram of blank plasma spiked with internal standard

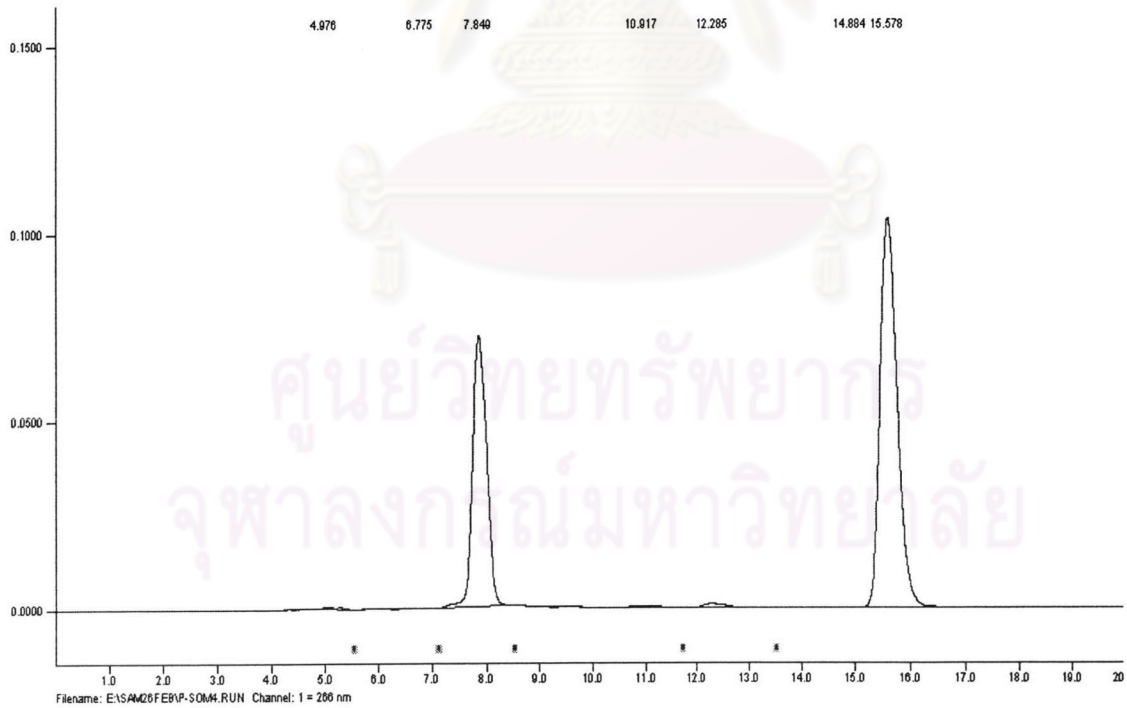

Fig. 5d Chromatogram of sample plasma with internal standard

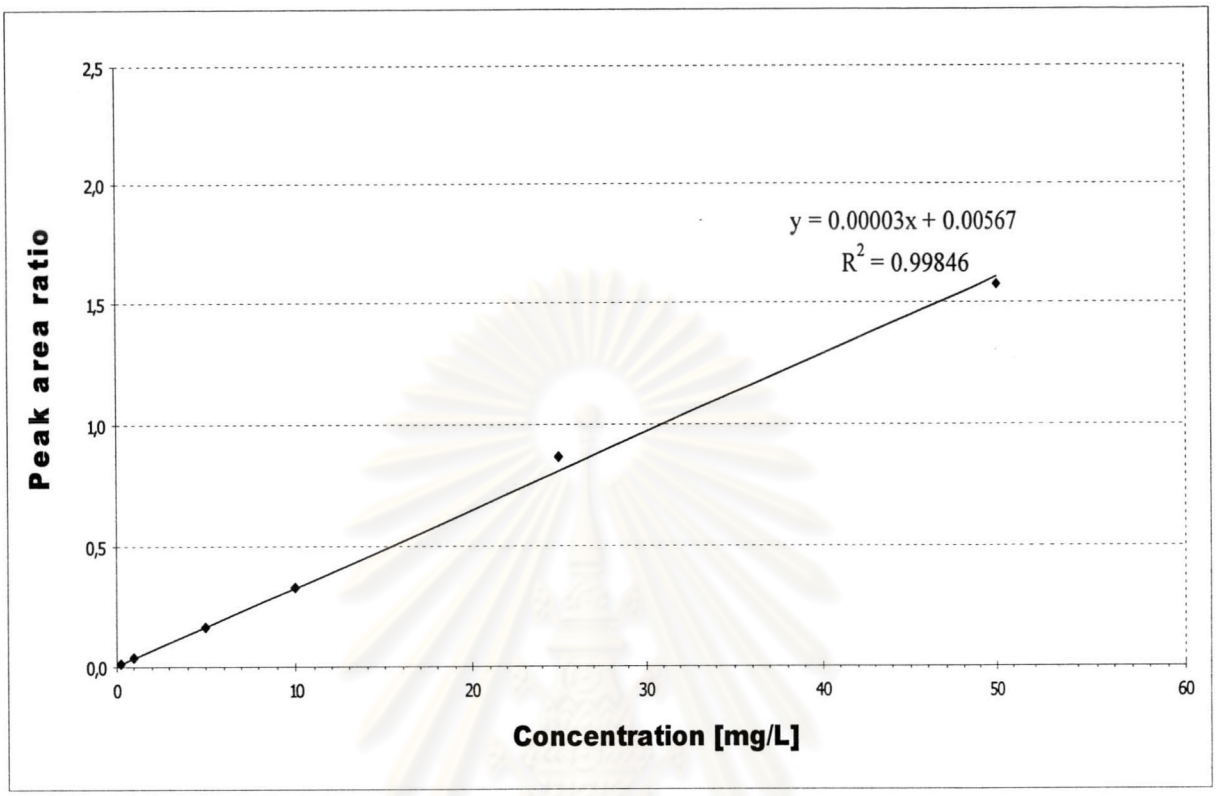

Fig.6 The standard curve of plasma 5-FU concentration-time

3. 5-FU plasma concentration of patients

Interpatient variations of plasma concentrations were found. Fig. 7a-7x were shown plasma concentrations-time curve of 5-FU. Mean and semi-log plot plasma concentration were shown in Fig. 8. and 9.

Patient number: 1

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	1.48	8.66	18.59	21.12	9.74	1.63	(-)

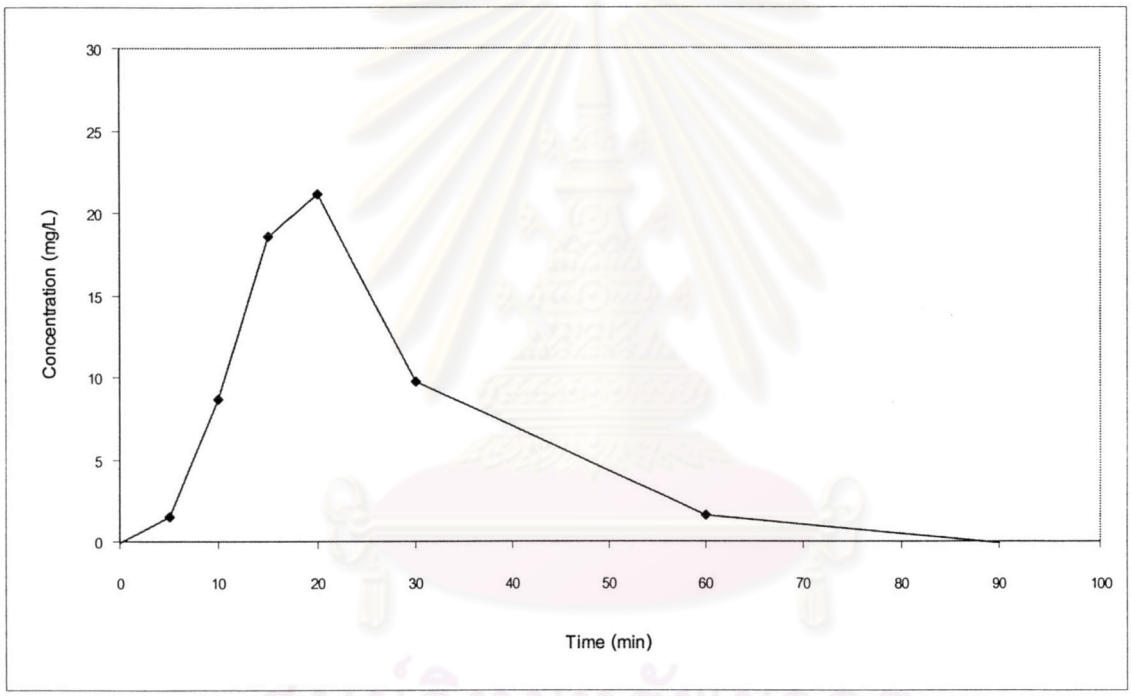

Fig 7a 5-FU Plasma concentration profiles of patients no. 1

Patient number : 2

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	16.51	19.46	22.46	12.55	6.19	0.31	0.19

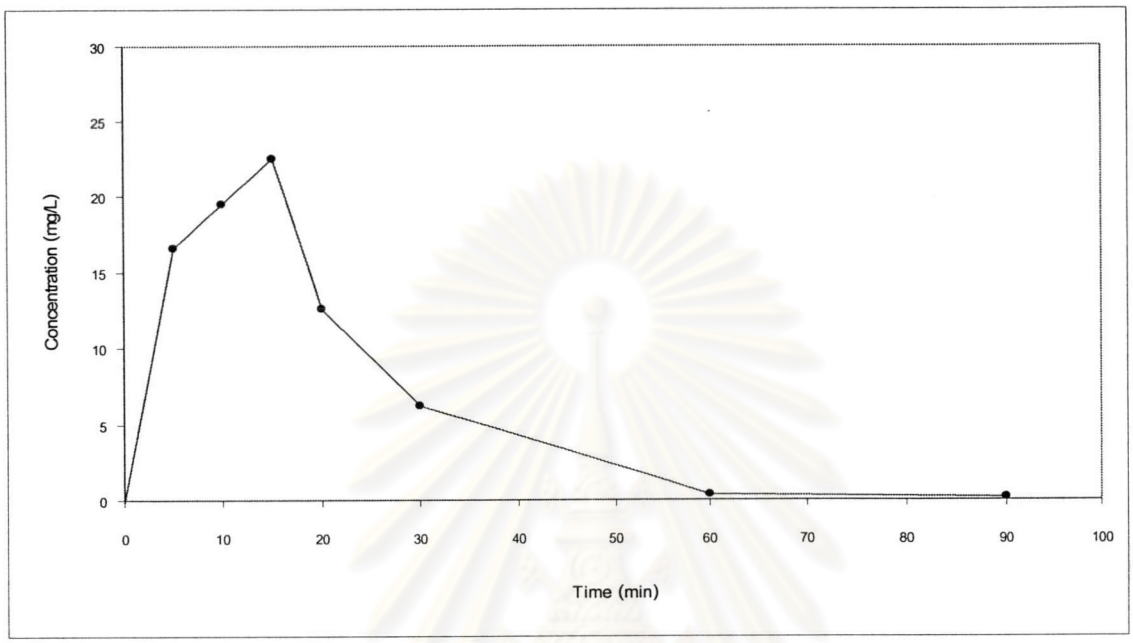

Fig 7b 5-FU Plasma concentration profiles of patients no. 2

Patient number : 3

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	5.94	10.63	13.93	8.71	2.86	0.19	(-)

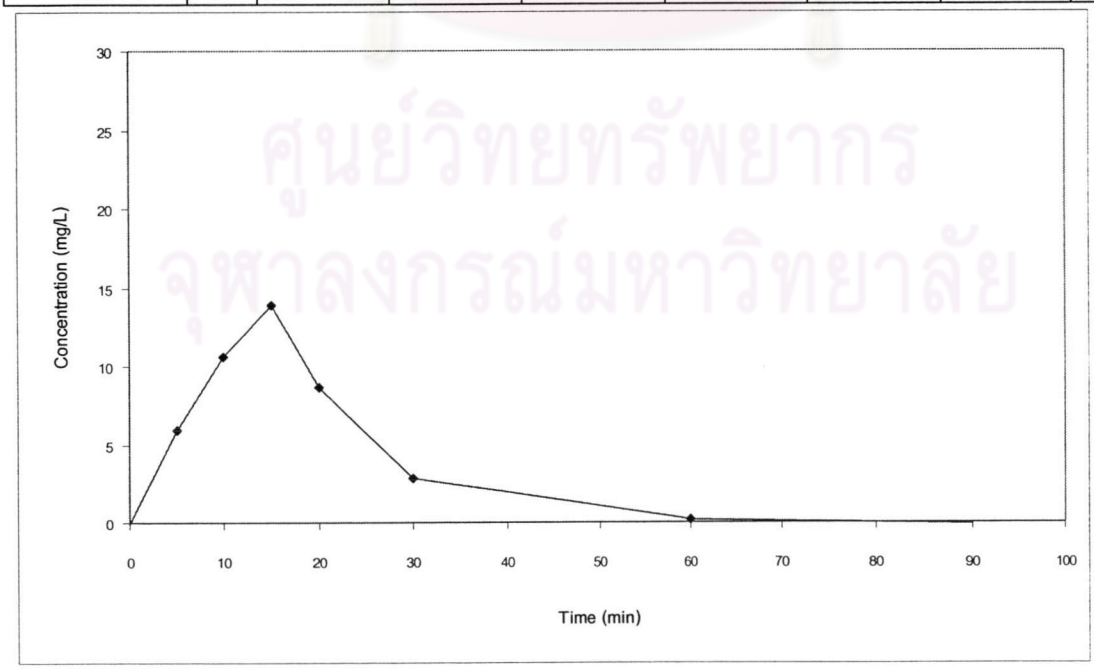

Fig 7c 5-FU Plasma concentration profiles of patients no. 3

Patient number : 4

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	7.76	15.96	16.57	15.77	7.39	0.89	(-)

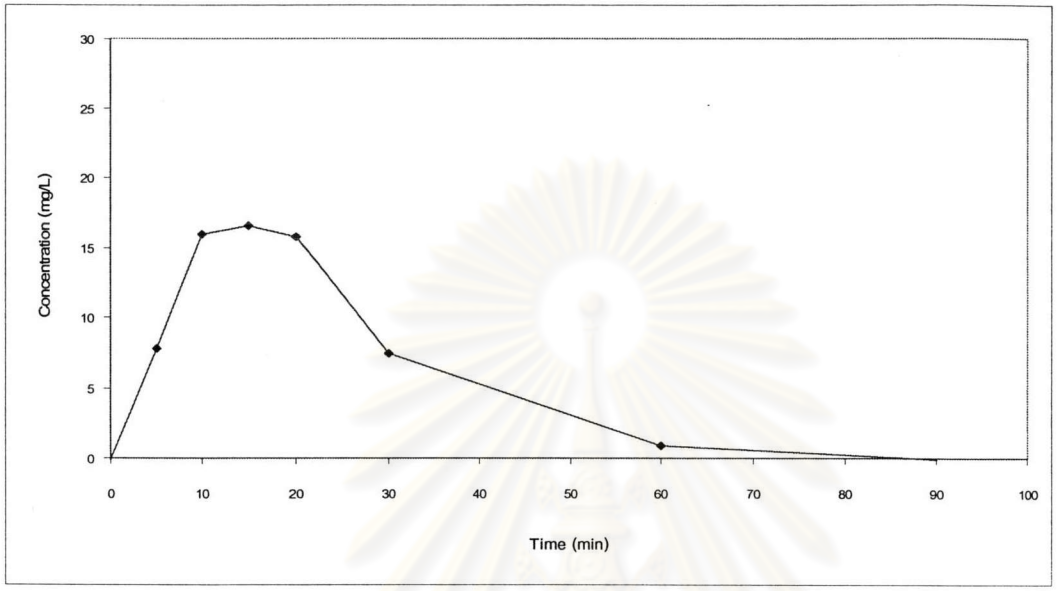

Fig 7d 5-FU Plasma concentration profiles of patients no. 4

Patient number : 5

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	1.04	5.94	7.86	9.15	4.66	0.30	(-)

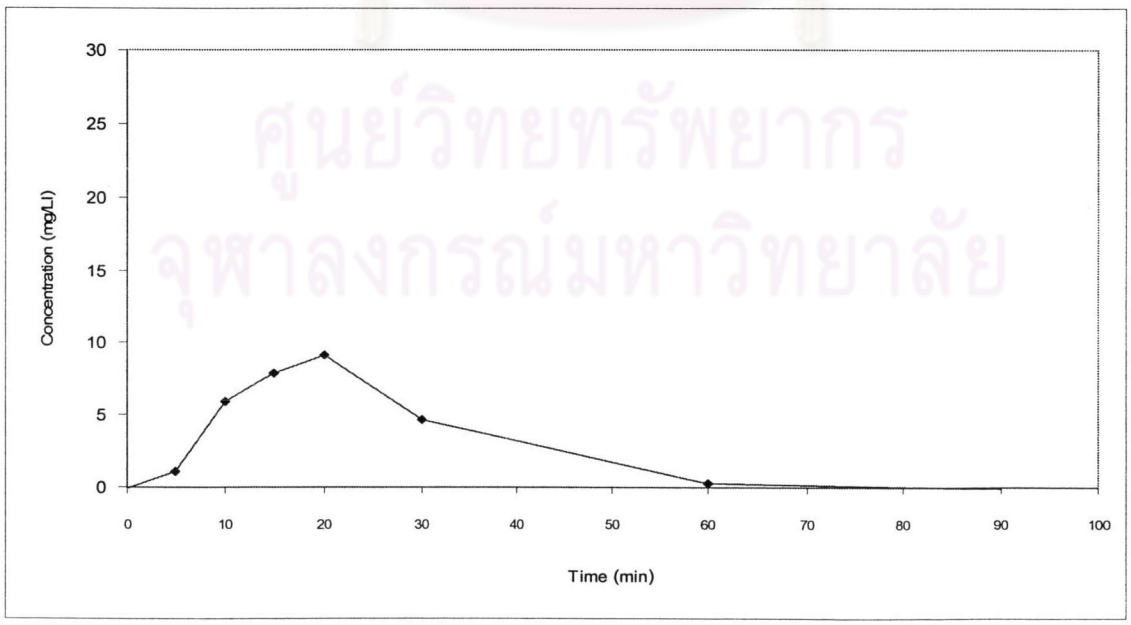

Fig 7e 5-FU Plasma concentration profiles of patients no. 5

Patient number : 6

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	15.92	21.40	23.16	15.02	2.59	0.73	(-)

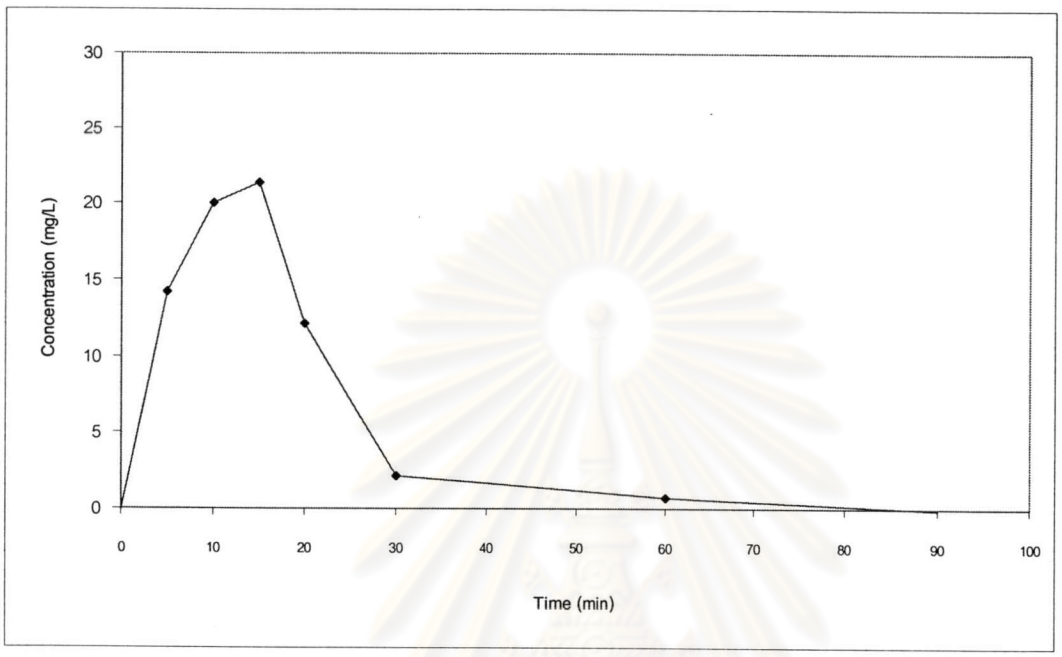

Fig 7f 5-FU Plasma concentration profiles of patients no. 6

Patient number : 7

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	2.96	5.09	8.54	5.62	3.08	0.33	(-)

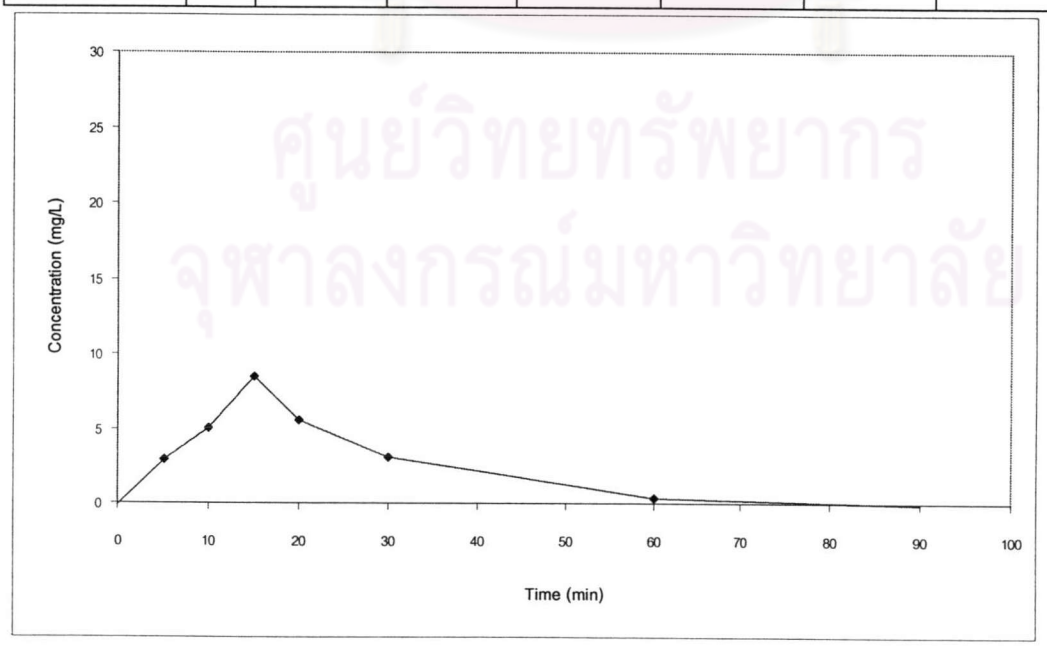

Fig 7g 5-FU Plasma concentration profiles of patients no. 7

Patient number : 8

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	15.89	16.69	24.96	13.59	4.45	0.27	(-)

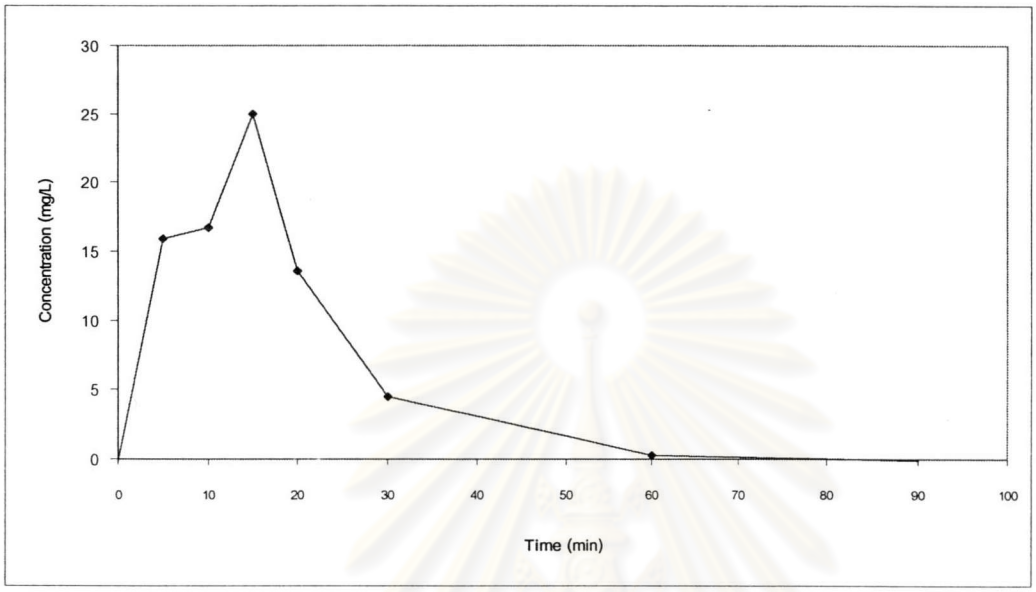

Fig 7h 5-FU Plasma concentration profiles of patients no. 8

Patient number : 9

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	6.75	12.56	16.83	9.57	4.34	0.53	(-)

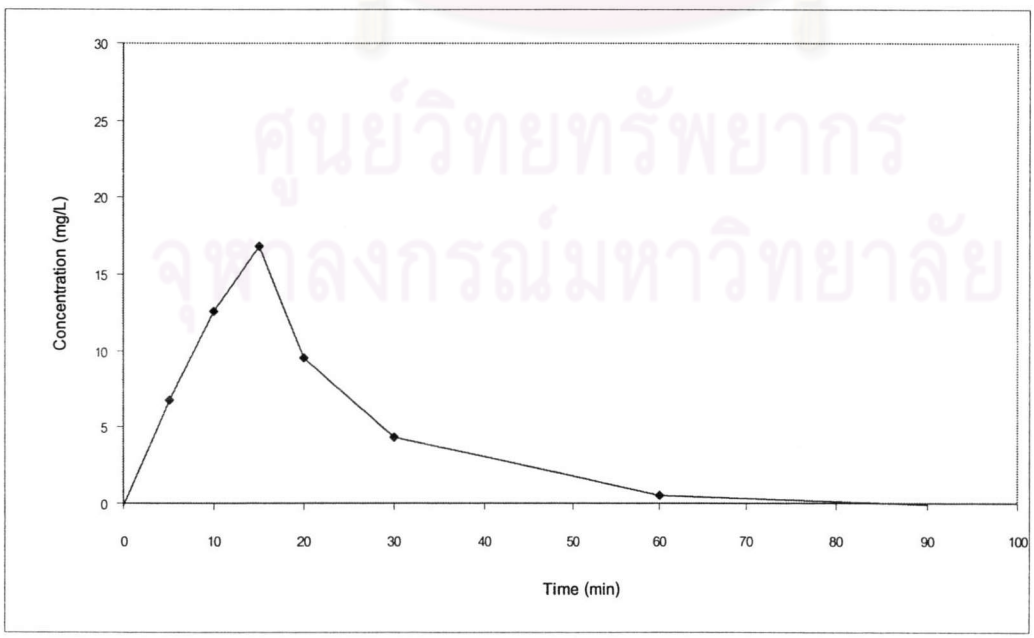

Fig 7i 5-FU Plasma concentration profiles of patients no. 9

Patient number : 10

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	7.36	18.03	19.43	18.24	7.39	0.11	(-)

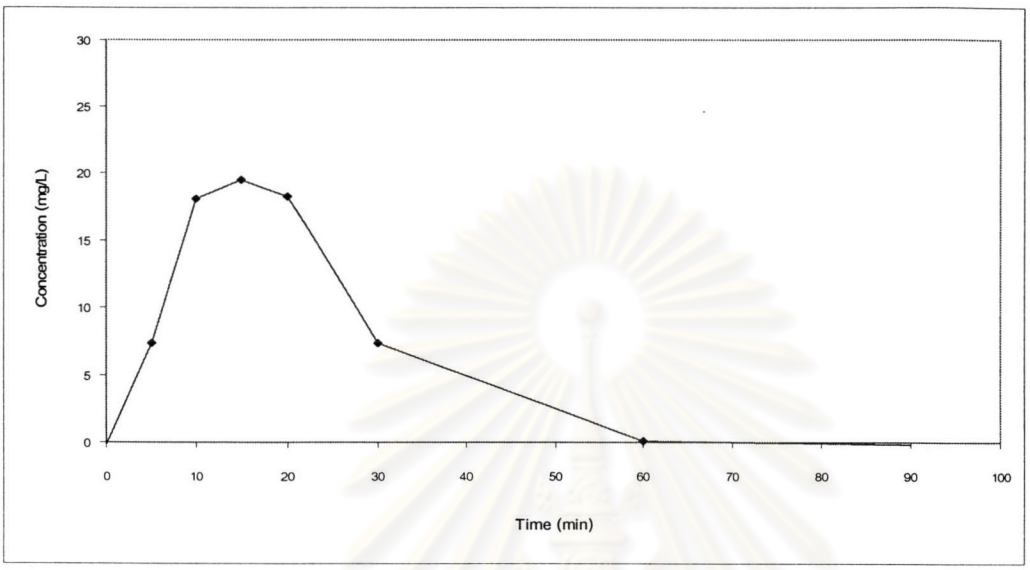

Fig 7j 5-FU Plasma concentration profiles of patients no. 10

Patient number : 11

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	(-)	0.40	12.91	16.06	13.27	1.45	(-)

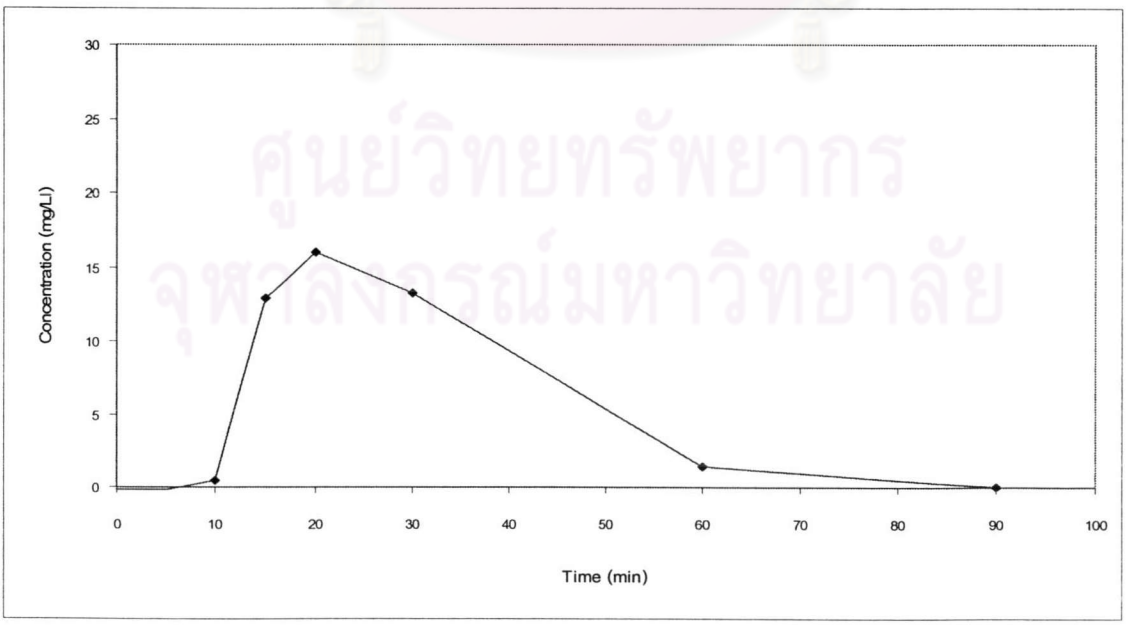

Fig 7k 5-FU Plasma concentration profiles of patients no. 11

Patient number : 12

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	6.37	13.30	14.99	21.30	4.18	0.82	(-)

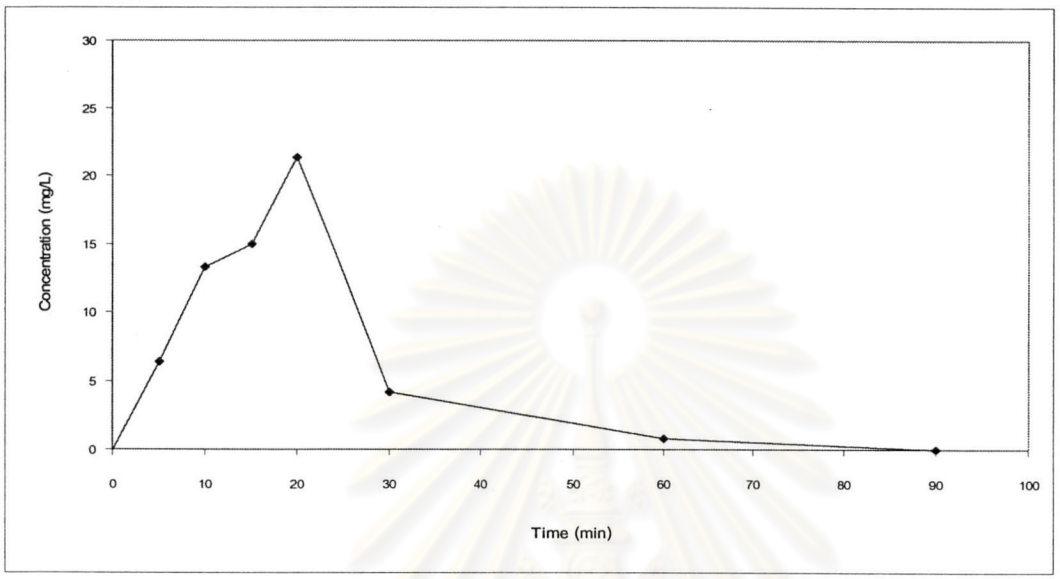

Fig 7l 5-FU Plasma concentration profiles of patients no. 12

Patient number : 13

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	3.44	14.42	18.31	20.63	9.04	1.60	(-)

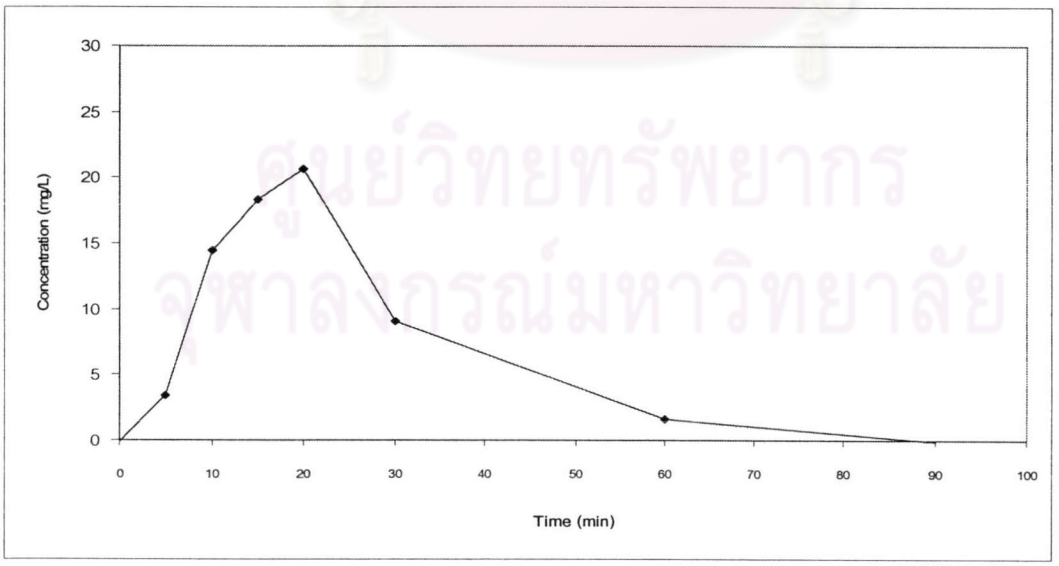

Fig 7m 5-FU Plasma concentration profiles of patients no. 13

Patient number : 14

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	0.46	11.90	14.15	10.20	3.09	(-)	(-)

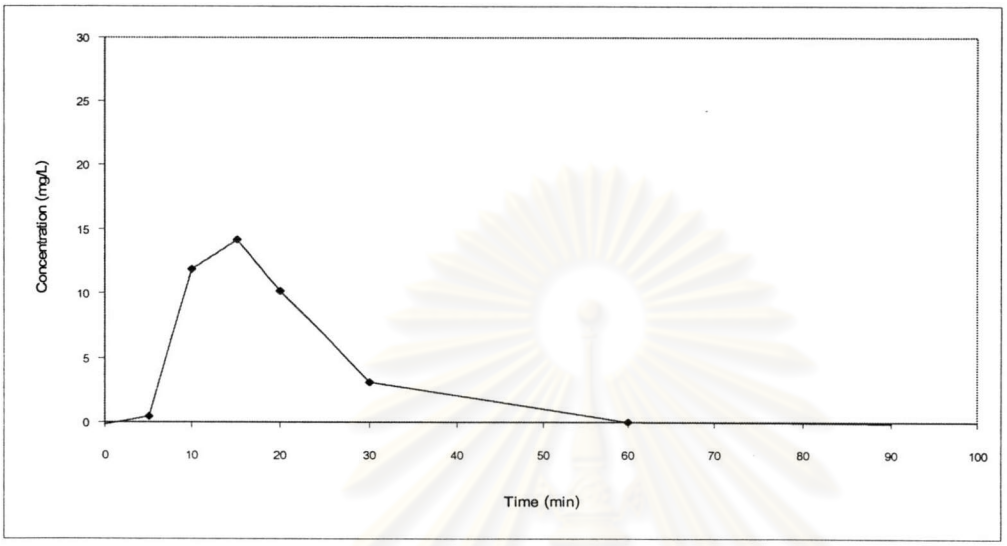

Fig 7n 5-FU Plasma concentration profiles of patients no. 14

Patient number : 15

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	10.03	17.36	20.20	13.35	3.73	(-)	(-)

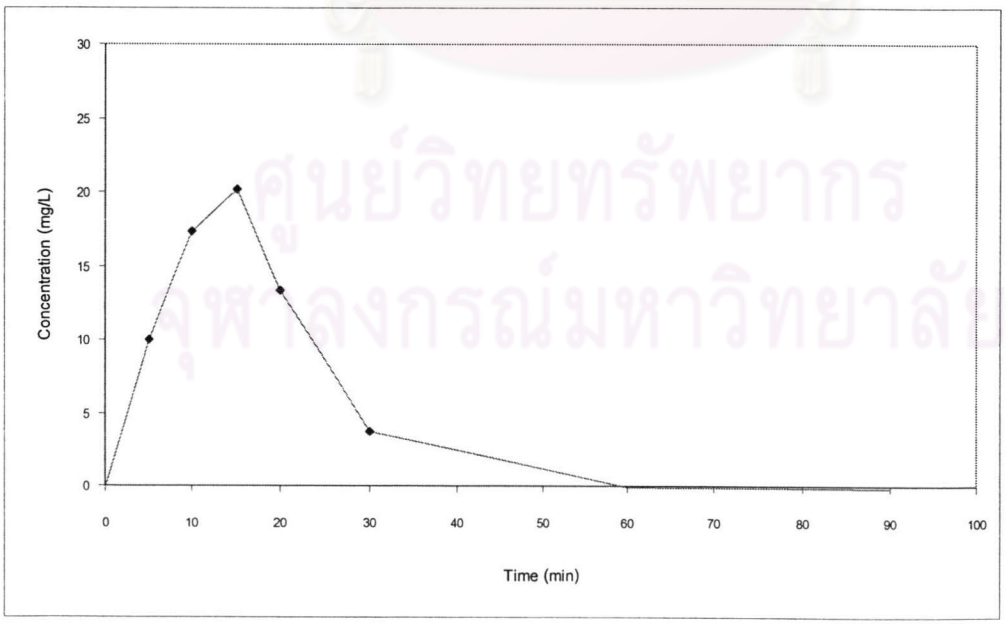

Fig 7o 5-FU Plasma concentration profiles of patients no. 15

Patient number : 16

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	3.83	9.70	13.72	8.95	3.76	1.54	0.05

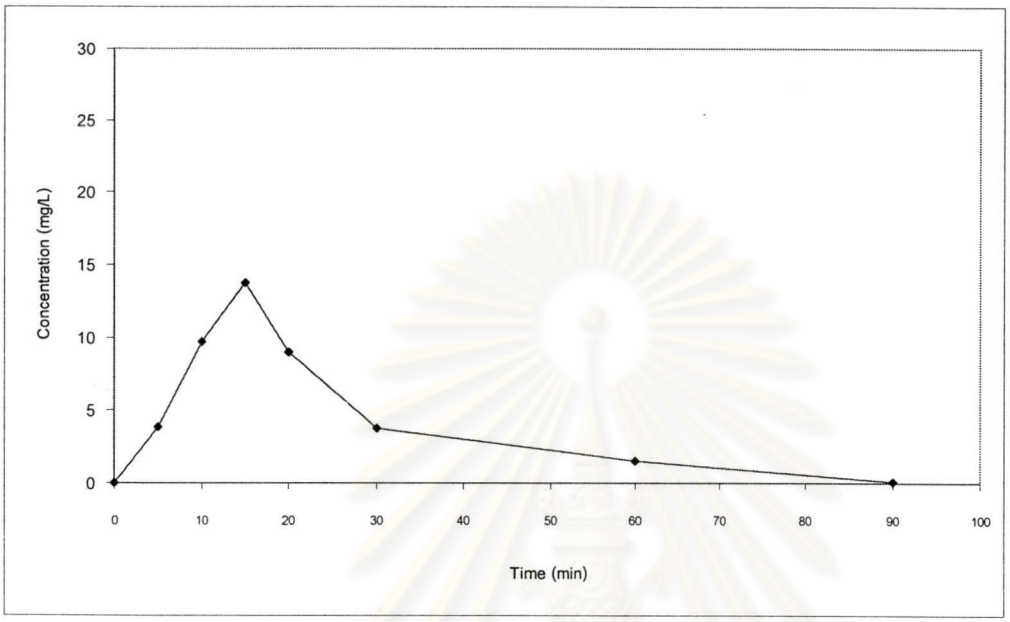

Fig 7p 5-FU Plasma concentration profiles of patients no. 16

Patient number : 17

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	5.41	14.67	19.30	12.21	7.17	0.55	(-)

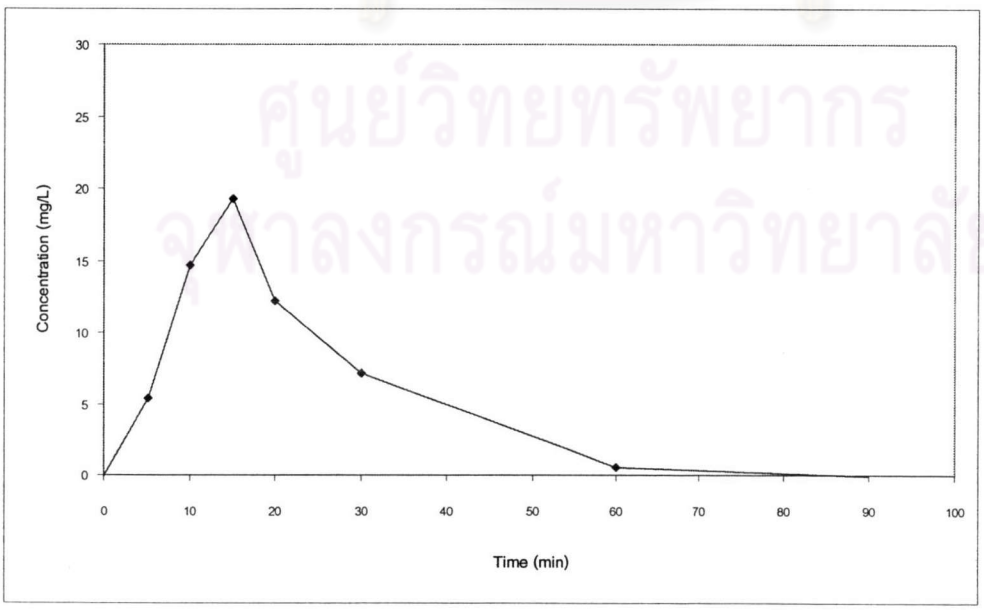

Fig 7q 5-FU Plasma concentration profiles of patients no. 17

Patient number : 18

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	8.90	22.56	30.83	22.26	9.34	0.96	0.26

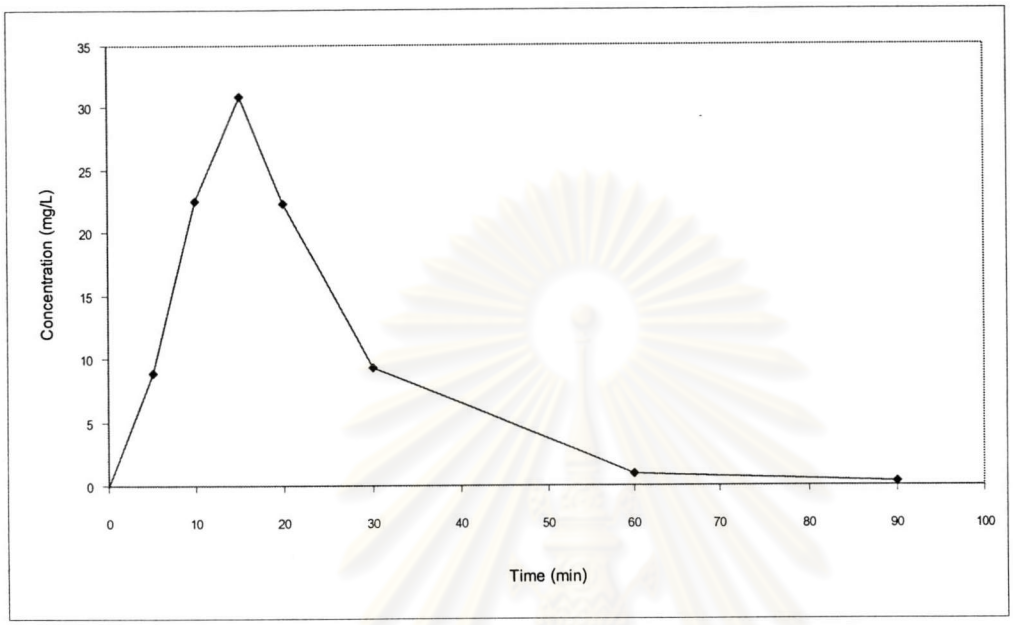

Fig 7r 5-FU Plasma concentration profiles of patients no. 18

Patient number : 19

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	12.56	17.86	22.19	9.85	1.21	(-)	(-)

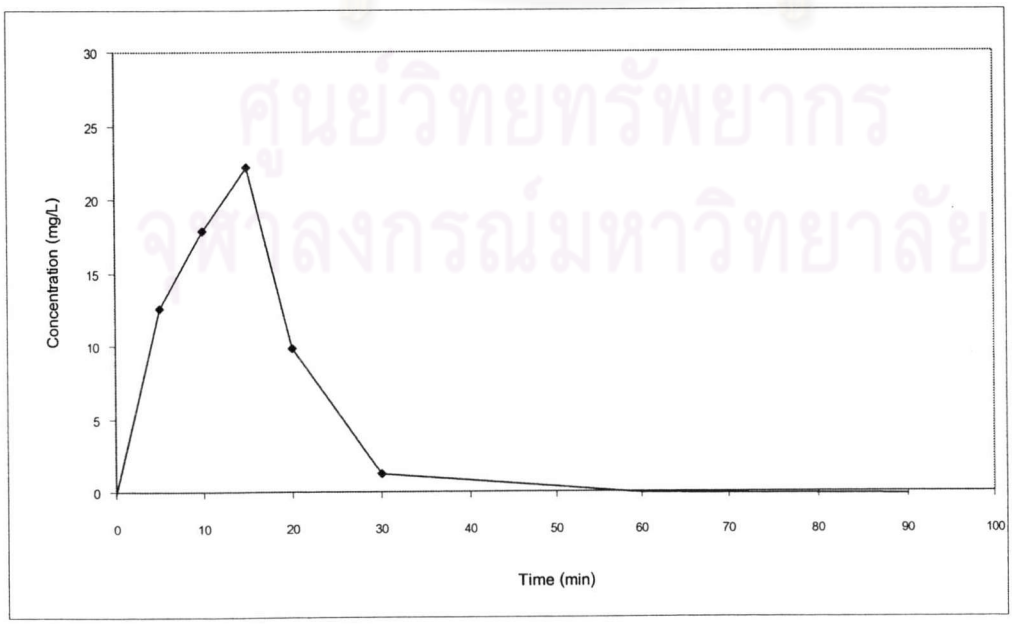

Fig 7s 5-FU Plasma concentration profiles of patients no. 19

Patient number : 20

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	4.09	24.71	13.65	12.03	5.94	1.45	0.23

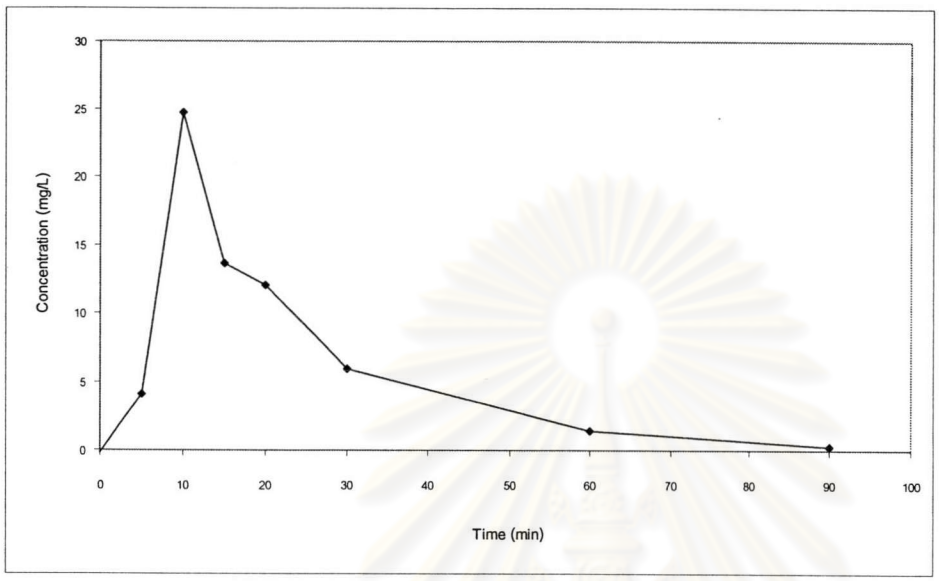

Fig 7t 5-FU Plasma concentration profiles of patients no. 20

Patient number : 21

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	3.03	6.49	11.72	11.17	9.2	0.82	(-)

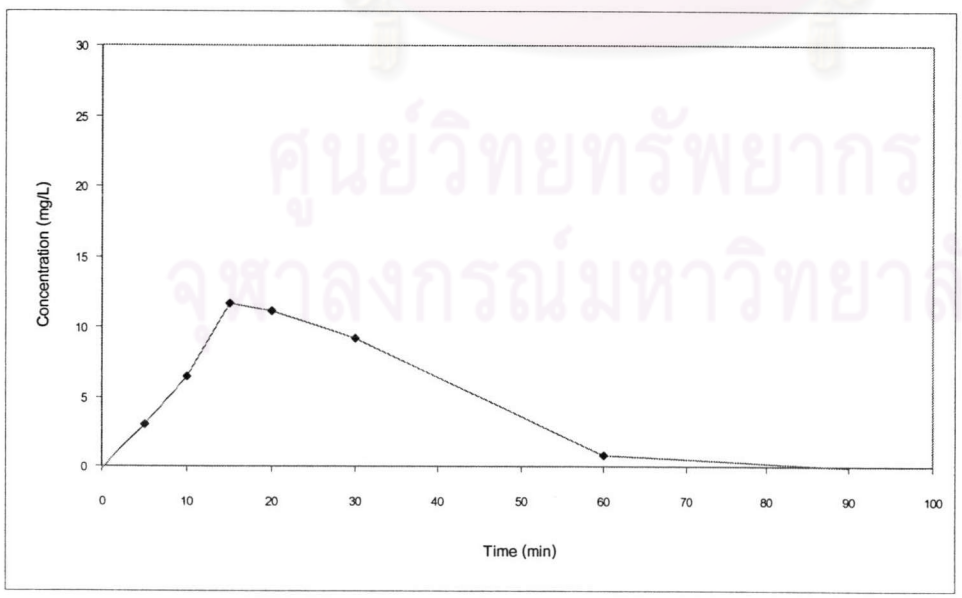

Fig 7u 5-FU Plasma concentration profiles of patients no. 21

Patient number : 22

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	0.68	13.2	15.77	8.47	5.27	0.21	(-)

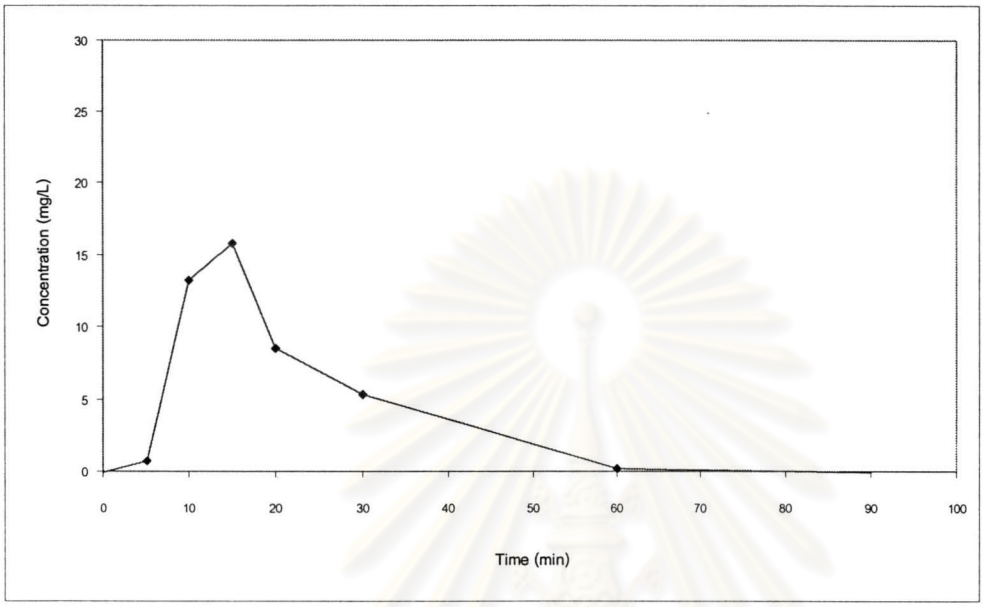

Fig 7v 5-FU Plasma concentration profiles of patients no. 22

Patient number : 23

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	0.36	6.37	11.93	8.23	2.93	0.14	0.06

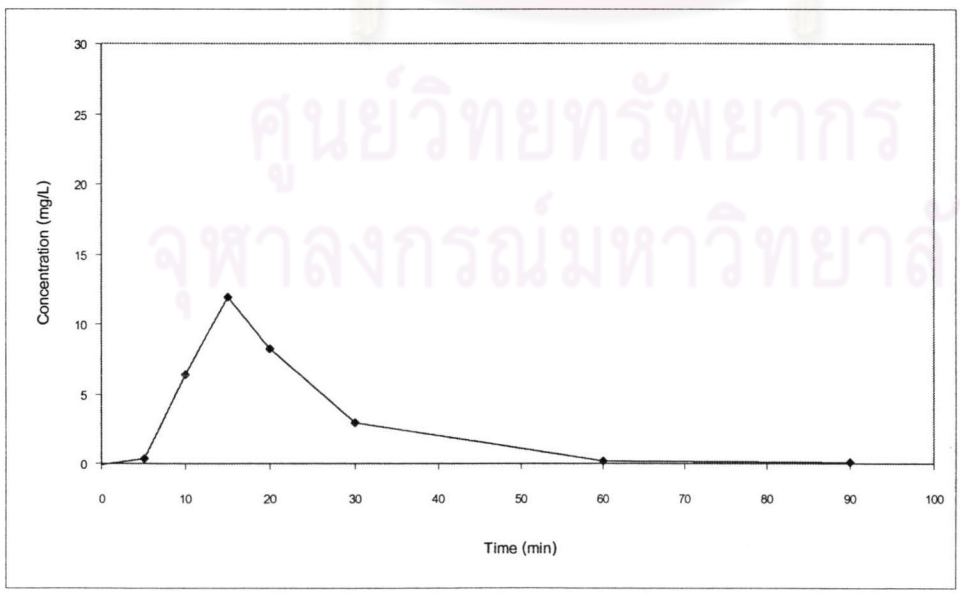

Fig 7w 5-FU Plasma concentration profiles of patients no. 23

Patient number : 24

Time	C1	C2	C3	C4	C5	C6	C7	C8
Conc(mg/L)	(-)	1.56	6.36	9.43	15.97	9.52	2.22	0.06

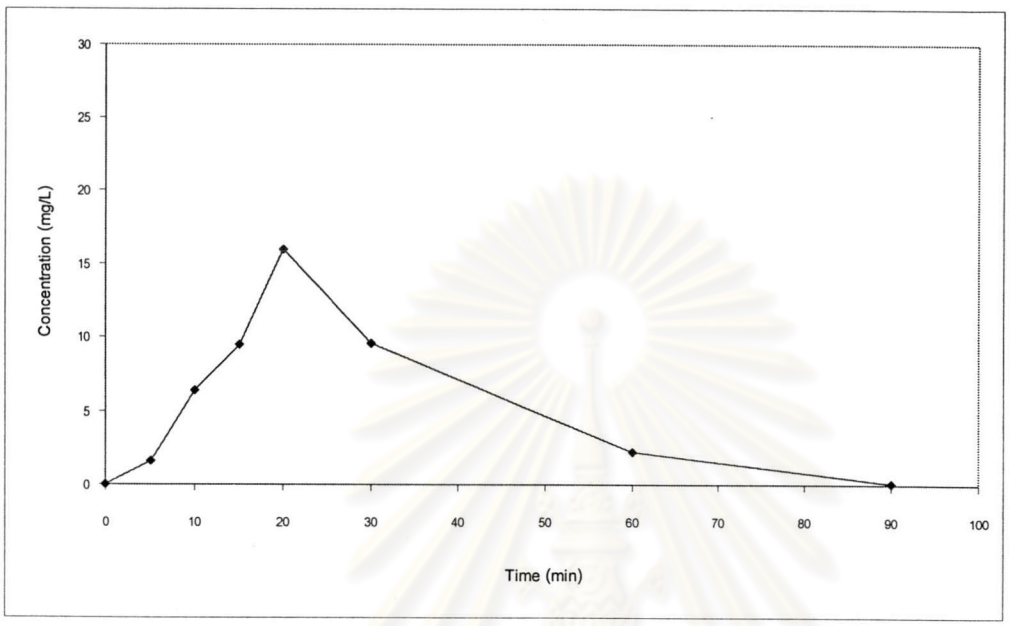

Fig 7x 5-FU Plasma concentration profiles of patients no. 24

Abbreviation ; (-) = not detectable

Table. 8 Average plasma concentration of 5-FU

Patient number	C1 (mg/L)	C2 (mg/L)	C3 (mg/L)	C4 (mg/L)	C5 (mg/L)	C6 (mg/L)	C7(mg/L)	C8(mg/L)
1	(-)	1.48	8.66	18.59	21.12	9.74	1.63	(-)
2	(-)	16.51	19.46	22.46	12.55	6.19	0.31	0.19
3	(-)	5.94	10.63	13.93	8.71	2.86	0.19	(-)
4	(-)	7.76	15.96	16.57	15.77	7.39	0.89	(-)
5	(-)	1.04	5.94	7.86	9.15	4.66	0.30	(-)
6	(-)	15.92	21.40	23.16	15.02	2.59	0.73	(-)
7	(-)	2.96	5.09	8.54	5.62	3.08	0.33	(-)
8	(-)	15.89	16.69	24.96	13.59	4.45	0.27	(-)
9	(-)	6.75	12.56	16.83	9.57	4.34	0.53	(-)
10	(-)	7.36	18.03	19.43	18.24	7.39	0.11	(-)
11	(-)	(-)	0.40	12.91	16.06	13.27	1.45	(-)
12	(-)	6.37	13.30	14.99	21.30	4.18	0.82	(-)
13	(-)	3.44	14.42	18.31	20.63	9.04	1.60	(-)
14	(-)	0.46	11.90	14.15	10.20	3.09	(-)	(-)

Patient number	C1 (mg/L)	C2 (mg/L)	C3 (mg/L)	C4 (mg/L)	C5 (mg/L)	C6 (mg/L)	C7(mg/L)	C8(mg/L)
15	(-)	10.03	17.36	20.20	13.35	3.73	(-)	(-)
16	(-)	3.83	9.70	13.72	8.95	3.76	1.54	0.05
17	(-)	5.41	14.67	19.30	12.21	7.17	0.55	(-)
18	(-)	8.90	22.56	30.83	22.26	9.34	0.96	0.26
19	(-)	12.56	17.86	22.19	9.85	1.21	(-)	(-)
20	(-)	4.09	24.71	13.65	12.03	5.94	1.45	0.23
21	(-)	3.03	6.49	11.72	11.17	9.2	0.82	(-)
22	(-)	0.68	13.2	15.77	8.47	5.27	0.21	(-)
23	(-)	0.36	6.37	11.93	8.23	2.93	0.14	0.06
24	(-)	1.56	6.36	9.43	15.97	9.52	2.22	0.06
Mean ± SD	(-)	5.93±5.12	13.07±6.16	16.38±5.52	13.33±4.74	5.84±3.00	0.71± 0.63	0.14 ± 0.09

Abbreviation C1= 0±1 min, C2= 5±1 min, C3= 10±1 min, C4= 15±1 min, C5= 20±1 min, C6=30±1 min, C7=60±1 min, C8= 90±1 min, (-) = not detectable

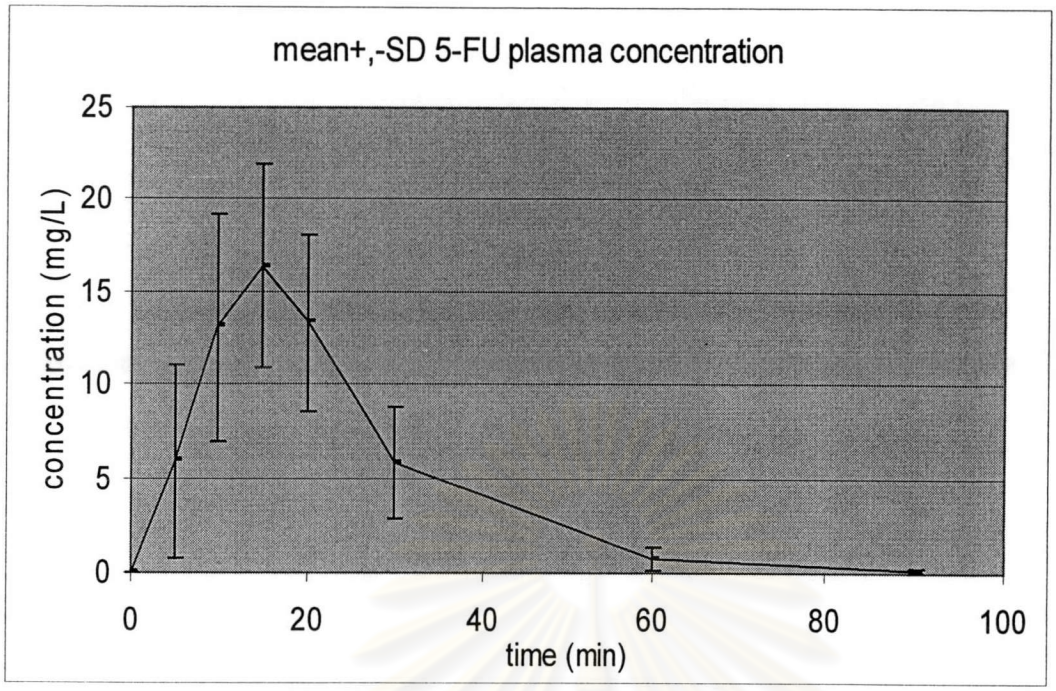

Fig. 8 Mean concentration plasma of 5-FU from SPSS calculated

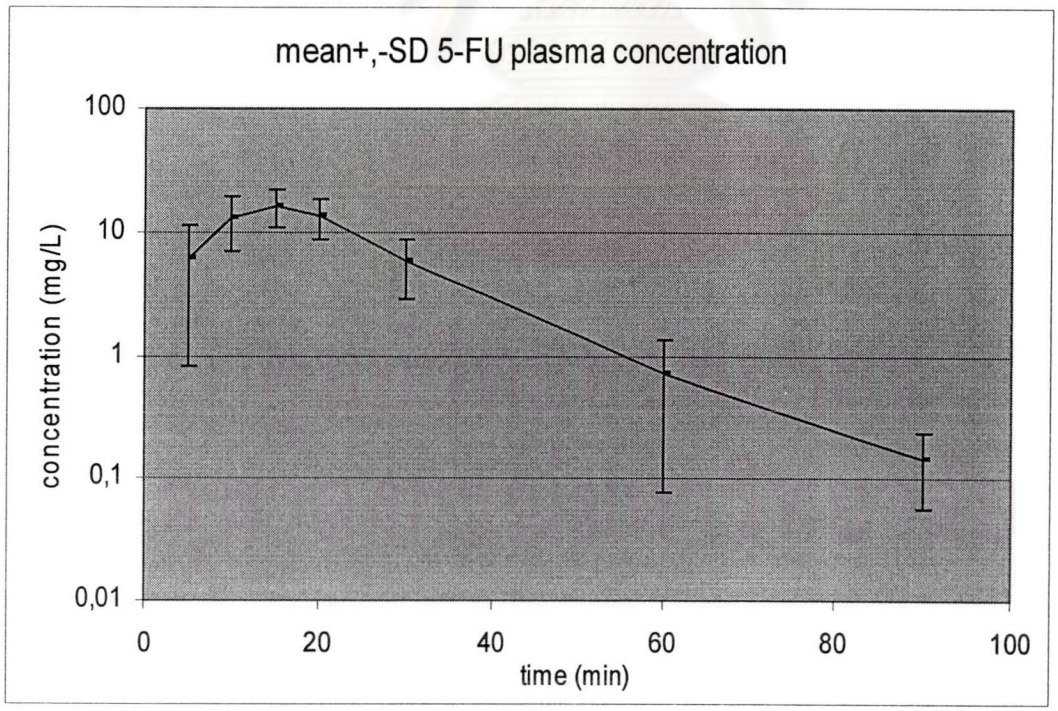

Fig. 9 Semi-log plot mean concentration plasma of 5-FU from SPSS calculated

Pharmacokinetic data of 5-FU

Pharmacokinetic parameters including Tmax, Cmax of 5-FU were determined by using winnonlin software version 4.1. Mean ± SD of these parameters were shown in Table 9. Time to maximum concentration was observed at 15-20 min. Only one patient had a peak 5-FU concentration at 10.2 min. Other pharmacokinetic parameters were highly variable. Mean± SD of maximum concentration was 18.04± 5.33 mg/L (range 8.53-30.83 mg/L), mean± SD observe clearance, volume of distribution and elimination constant were 1.72± 0.69 L/min (range 0.31-3.31 L/min), 23.05±8.85 L (range 8.76-46.16 L) and 0.08 ± 0.03 min^{-1} (range 0.05-0.2 min^{-1}), respectively.

Area under the 5-FU plasma concentration-time curves were also calculated in manually. AUC of 5-FU in 24 patients were shown in Fig.10. Average manually calculated AUC was 415.2±121.80 mg/L.min(95%CI = 363.65 – 466.20 mg/L.min).

Table 9 Pharmacokinetics data of patients

Patient number	$Tmax_{cal}$ (min)	$Cmax_{cal}$ (mg/L)	$t_{1/2,\ cal}$ (min)	Ke_{cal} (1/min)	Vd_{obs} (L)	Cl_{obs} (L/min)	AUC_{cal} (mg/L.min)
1	20	21.12	11.00	0.06	21.75	1.37	547.18
2	15	22.46	10.31	0.07	21.10	1.42	525.05
3	15	13.93	7.29	0.10	28.17	2.68	279.95
4	15	16.57	9.67	0.07	18.52	1.33	493.19
5	20	9.15	7.95	0.09	35.28	3.07	243.90
6	15	21.35	9.58	0.07	23.92	1.73	433.50
7	15	8.54	9.67	0.07	46.16	3.31	196.31
8	15	24.96	7.16	0.10	16.82	1.63	485.62
9	15	16.83	9.68	0.07	29.53	2.11	354.87
10	15	19.49	5.32	0.13	9.30	1.21	511.44
11	20	16.06	11.09	0.06	19.57	1.22	499.04
12	20	21.30	9.22	0.08	19.35	1.45	439.96
13	20	20.63	11.08	0.06	17.52	1.10	565.81
14	15	14.15	6.66	0.10	24.58	2.56	254.23

Patient number	$Tmax_{cal}$ (min)	$Cmax_{cal}$ (mg/L)	$t_{1/2,\ cal}$ (min)	Ke_{cal} (1/min)	Vd_{obs} (L)	Cl_{obs} (L/min)	AUC_{cal} (mg/L.min)
15	15	20.20	6.04	0.11	15.78	1.81	389.22
16	15	13.72	10.03	0.07	29.69	2.05	326.37
17	15	19.30	8.80	0.08	19.31	1.52	447.01
18	15	30.83	10.58	0.06	14.79	0.97	701.56
19	15	22.19	3.53	0.20	8.76	1.72	349.10
20	10.2	24.71	12.70	0.05	26.39	1.44	472.33
21	15	11.72	10.09	0.07	23.76	1.63	398.32
22	15	15.77	7.29	0.10	23.49	2.23	322.48
23	15	11.93	9.27	0.07	42.63	3.19	219.64
24	20	15.97	8.84	0.08	17.01	1.33	464.92
Mean ± SD	16.05 ± 2.52	18.04± 5.33	8.87± 2.11	0.08±0.03	23.05±8.85	1.72± 0.69	415.2±121.80

Abbreviation Cal = calculated from winnonlin sofeware, obs = observe from winnonlin software

Calculated pharmacokinetic parameters formula from winnonlin software were

Ke = (ln C_1-ln C_2)/(t_2-t_1), $t_{1/2}$=0.693/Ke, Vd = Dose/Ke x $AUC_{0-\tau}$, Cl = Dose/$AUC_{0-\tau}$, [,AUC_{0-t}] $_0^t$ =Σ (C_{n-1}+C_n)(t_n+t_{n-1})/2

Ke from winnonlin calculated may not equal to in manual calculated because in winnonlin software used more than 2 point of concentration to select the best fit of calculated value

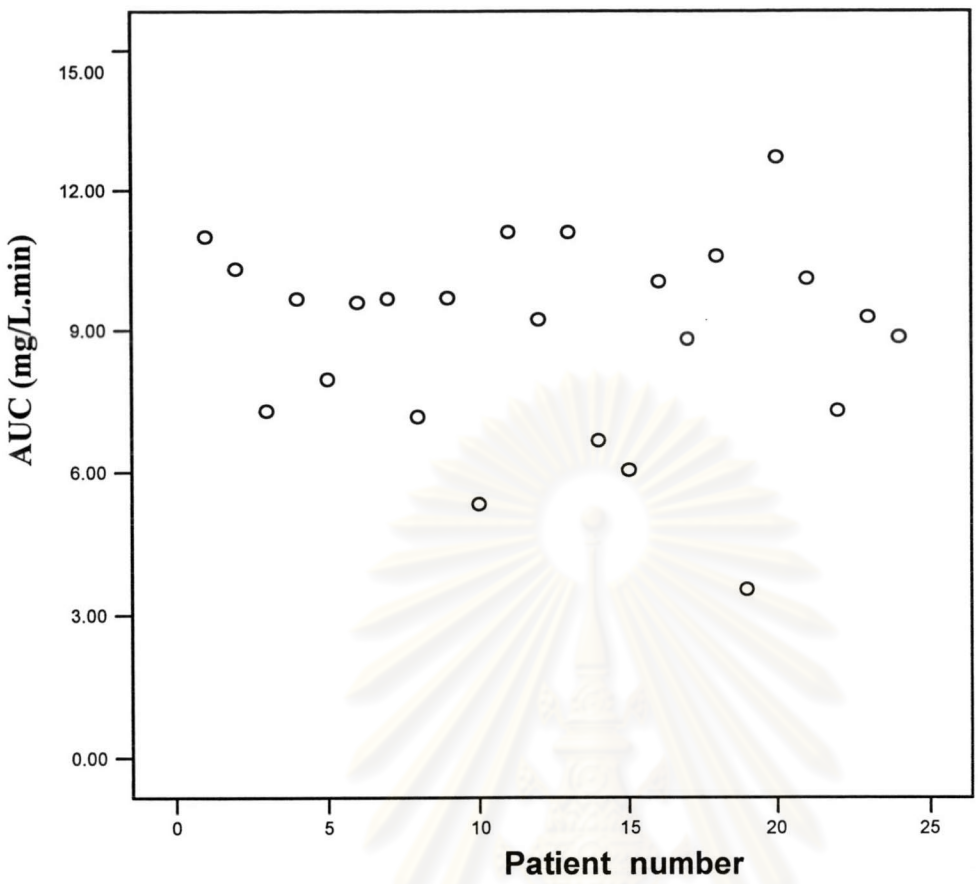

Fig.10 AUC distribution of patients

5. Toxicity of chemotherapy

All patients were followed for toxicity monitoring by using the National Cancer Institute (NCI) of America guidelines. However, only hematological problems, hand-foot syndrome,diarrhea and oral mucositis were monitored in this study. There were two patients suffered from grade I hematologic toxicity and four patients from grade II hematologic toxicity after receiving chemotherapy. None of patients were suffered from hand-foot syndrome, diarrhea and oral mucositis. Table 10 and 11 had shown parameters followed for toxicity monitoring.

Table 10 Hematological toxicity monitoring parameters

Patient number	cycle	WBC before ($x10^3$ g/dL)	WBC after ($x10^3$ g/dL)	Plt before (/μL)	Plt after (/μL)	Hb before (g/dL)	Hb after (g/dL)	%ANC before	%ANC after
1	C3	7.9	9.5	314	295	12.1	12.4	10.37	6.36
2	C3	4.38	4.61	191	179	14.7	14.5	2.45	2.67
3	C3	10.0	9.8	228	168	13.0	14.1	4.0	5.78
4	C3	4.5	6.14	337	241	9.5	14.2	2.74	3.00
5	C3	5.7	4.6	232	226	11.4	11.5	3.31	3.13
6	C1	6.85	14.03	222	241	13.5	14.3	2.88	9.26
7	C10	9.8	11.69	277	276	8.6	5.4	7.05	5.01
8	C3	4.29	4.6	207	194	14.1	12.9	1.63	1.38
9	C1	7.3	6.11	179	198	13.3	13.4	3.36	1.83
10	C3	7.3	4.71	205	197	11.2	10.6	4.60	1.46
11	C1	6.42	6.6	311	260	11.6	12.9	3.98	3.76
12	C1	6.1	6.8	254	245	10.5	12.6	0.67	2.52
13	C1	6.8	4.6	264	200	10.8	10.9	3.26	1.29
14	C10	6.7	5.5	186	194	13.2	12.6	3.55	2.42
15	C1	11.04	10.73	716	331	10.6	11.6	6.96	5.15
16	C1	17.4	7.3	173	163	10.7	13.4	15.49	4.38
17	C1	4.5	4.6	289	223	12.4	11.4	1.89	1.47
18	C3	5.85	14.7	222	210	13.2	14.7	2.05	4.2
19	C1	5.96	7.4	194	188	10.7	11.2	3.75	3.40
20	C1	7.4	7.0	331	290	11.5	11.5	4.51	4.2
21	C1	6.0	5.1	315	383	10.4	11.7	3.36	1.58
22	C3	8.1	8.4	194	227	10.9	10.6	4.94	5.04
23	C5	9.4	7.0	321	267	16.2	15.6	6.20	3.99
24	C6	3.13	3.01	202	191	12.2	11.9	1.47	1.73

Table 11 Grading toxicity monitoring parameters

Patient number	Hematological grade	Diarrhea grade	Hand-foot syndrome grade	Mucositis grade
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	2	0	0	0
7	0	0	0	0
8	2	0	0	0
9	1	0	0	0
10	0	0	0	0
11	0	0	0	0
12	0	0	0	0
13	2	0	0	0
14	0	0	0	0
15	0	0	0	0
16	0	0	0	0
17	2	0	0	0
18	0	0	0	0
19	0	0	0	0
20	0	0	0	0
21	0	0	0	0
22	0	0	0	0
23	0	0	0	0
24	1	0	0	0

6. Response to therapy

The tumor size was assessed by computed tomography before the beginning of chemotherapy and compared to the size after chemotherapy courses were finished, evaluating by WHO criteria. Of 24 patients in this study, nine stage IV patients were assessed for response of therapy from their remaining tumor. There were one patient had partial response (AUC 7.74 mg.h/L), four had stable disease (AUC range from 4.51-7.80 mg.h/L), one had disease progress (AUC 5.92 mg.h/L), one had no recurrence of liver metastases after 6 months after resection of tumor before start chemotherapy (AUC 5.43 mg.h/L) and two had not assessed because they had not finished chemotherapy course. (AUC 4.68 and 7.24 mg.h/L).