Efficacy of in vitro adenosine triphosphate based chemotherapy response assay in gastric cancer

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Efficacy of in vitro adenosine triphosphate based chemotherapy response assay in gastric cancer

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ABSTRACT

Efficacy of in vitro adenosine triphosphate based chemotherapy response assay in gastric cancer

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Purpose: This study was done to investigate efficacy of in vitro adenosine triphosphate based chemotherapy response assay (ATP-CRA) in gastric cancer patients who received adjuvant chemotherapy following curative surgery.

Method: ATP-CRA test was performed in advanced gastric cancer patients between June 2006 and October 2010. Data from 116 patients who underwent curative radical gastrectomy with postoperative adjuvant 5-fluorouracil(5-FU) and Cisplatin chemotherapy were retrospectively reviewed. We analyzed disease free survival and overall survival according to ATP-CRA results and chemotherapy regimens of 5-FU (or UFT or S-1) and Cisplatin regimen. Patients were grouped based on chemosensitivity to 5-FU and Cisplatin. Cell death rate 50% or more was grouped sensitive group whereas less than 50% was resistant group.

Results: The clinicopathologic characteristics between chemotherapy regimen subgroups, ATP-CRA regimen specific sensitive and resistant groups were not statistical different. The three adjuvant chemotherapy regimen subgroups did not showed significant difference in disease free survival rate and overall survival rate. In ATP-CRA results, there were no statistically meaningful difference in disease free survival rate and overall survival rate between sensitive and resistant to 5-FU, Cisplatin, 5-FU or Cisplatin, and both 5-FU and Cisplatin.

Conclusion: To decide adjuvant chemotherapy regimen based on the ATP-CRA in gastric cancer patients may not provide any information to improve prognosis.

Key words : stomach neoplasm, adenosine triphosphate, chemotherapy response assay

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I. INTRODUCTION

Gastric cancer is the 4th most common cause of worldwide cancer death[1] and it is one of the most prevalent cancer in Korea.[2] Due to its high incidence, mass screening program in Korea and Japan detects early stage gastric cancer at the time of diagnosis with over 50 % of stage I cancer. However, still most of the patients except in Japan and Korea are diagnosed at advanced stages with regional or distant metastasis. Patients with advanced stage gastric cancer showed poor prognosis after curative operation. Poor prognosis of patients with advanced gastric cancer is caused by recurrence after surgery and it may be due to lack of proper adjuvant treatment. Thus, more effective adjuvant treatment

following radical surgery for advanced gastric cancer is gaining interest. Adjuvant chemotherapy is one of the most important treatment options for patients with advanced stage gastric cancer.

Several studies showed effect of adjuvant chemotherapy after curative resection of gastric cancer and meta-analysis revealed a significant survival benefit of chemotherapy.[3,4] Even with effective chemotherapy, still many patients are experiencing recurrences after treatment including adjuvant chemotherapy. Treatment failure after curative resection followed by chemotherapy may be caused by heterogeneous response to various chemotherapeutic regimens. Thus, selecting appropriate chemotherapeutic regimen based on individual tumor or patients characteristics is gaining a lot of interest.

To select more efficient chemotherapeutic agent based on the concept of heterogeneous tumor response to chemotherapy, various in vitro chemosensitivity assays were developed and explored for its clinical applications in many types of cancer including stomach cancer.[5-7] An in vitro chemosensitivity assay refers to a diagnostic tool to identify individual drug for better treatment response based on laboratory analyses of tumor growth inhibition. This concept of selecting presumably more effective chemotherapeutic agent prior to treatment appears more fascinating to gastric cancer patients, because no standard adjuvant or neoadjuvant chemotherapy regimens are established for gastric cancer.

There have been many methods of chemosensitivity test. Among them, ATP-CRA was proved to be effective in several cancers, including gastric cancer.[5-12] To our best knowledge, there has been no large size study in a prospective setting for gastric cancer. Moreover, no study evaluated the efficacy of ATP-CRA as a tool for selecting chemotherapeutic agent for adjuvant therapy for gastric cancer. Thus, we tried to evaluate the impact of ATP-CRA as a tool for selecting adjuvant chemotherapy regimen for advanced gastric cancer patients by comparing prognosis of the patients with advanced stage gastric cancer who received 5-FU and Cisplatin regimen as an adjuvant chemotherapy according to the result of ATP-CRA.

II. MATERIALS AND METHODS

1. Patients and treatment

From June 2006 to October 2010, 291 patients were evaluated ATP-CRA test at the Yonsei University, College of Medicine, Severance Hospital. Above 291 patients were treated by radical gastrectomy and adjuvant chemotherapy and they had staged II or III gastric cancer. Among these, patients underwent neo-adjuvant chemotherapy, had a history other cancers or concurrent diagnosed with malignancies of another site were excluded from the analyses. Patients who refused adjuvant chemotherapy or not received the adjuvant

chemotherapy were excluded. Patients who received chemotherapy regimens other than 5-FU and Cisplatin, UFT and Cisplatin, or S-1 Cisplatin were also excluded. Finally, 116 patients who received adjuvant chemotherapy with 5-FU and Cisplatin, UFT and Cisplatin, or S-1 and Cisplatin regimen were included for the analyses.

Our analyses focused on the most popular adjuvant chemotherapy regimen of gastric cancer. The 5-FU and Cisplatin based chemotherapy regimen was divided to 3 subgroups: intravenous(IV) 5-FU with IV Cisplatin group(5-FU+Cisplatin), oral S-1 with IV Cisplatin (S-1+Cisplatin) and oral UFT with IV Cisplatin (UFT+Cisplatin). Written informed consent about ATP-CRA was obtained from all patients. The ATP-CRA result were divided into chemotherapy regimen sensitive and resistant group using a CDR cut-off value 50% (CDR≥50%: sensitive group, CDR<50%: resistant group). Grouping for chemotherapy regimen was 5-FU, Cisplatin, 5-FU or Cisplatin, and 5-FU and Cisplatin group[13].

2. Method of ATP-CRA test

ATP-CRA was performed as described elsewhere[7,11,14]. All tissue specimens were obtained after surgical resection. Immediately after the surgical resection of a tumor, the specimen was sent to a pathology laboratory for confirm of tumor tissue by a pathologist. Then, a 0.5 cubic centimeter piece of the cancer tissue was collected. The tissue specimens were stored in HBSS (GIBCO BRL,

Rockville, MD, USA), containing 100 μg/ml gentamicin (GIBCO BRL, Rockville, MD, USA), 100 IU/ml penicillin (Sigma, St Louis, MO, USA), 100 μg/ml streptomycin (Sigma, St Louis, Mo,USA), 2.5 μg/ml amphotericin B (GIBCO BRL, Rockville, MD, USA) and 5% fetal bovine serum (FBS; GIBCO BRL, Rockville, MD, USA) and promptly transported to the laboratory. These tissue specimens underwent initial washing with 70% ethanol before being quantified and minced to a size less than 1 mm for mechanical disaggregation. Then, for enzymatic disaggregation, they were incubated at 37℃ with 5% CO_2 for 12 to 16 hours with extracellular matrix degrading enzymes such as dispase (Sigma, St Louis, Mo, USA), DNase (Sigma, St Louis, Mo, USA), and pronase (Sigma, St Louis, Mo, USA). Cells were harvested using a cell strainer (BD Falcon, Bedford, MA, USA). To remove red blood cells, normal cells, and excess debris, the cell suspensions were subjected to Ficoll-Hypaque (1077-1, Sigma, St Louis, Mo, USA) gradient centrifugation at 400 g for 15 minutes and anti-CD45 antibody conjugated magnetic beads (Miltenyi Biotech, Auburn, CA, USA). Trypan blue exclusion test was used to determine the viability of isolated cells. After dilution of the separated tumor cells to 2,000~20,000 viable cells/100μl using IMDM (GIBCO BRL, Rockville, MD, USA), including 10% FBS, they were seeded in triplicate to a 96-well ultralow attachment microplate (Costar, Cambridge, MA, USA), which restricts the growth of normal cells. In the treated groups, 100 μl of chemotherapeutic agents were added to the seeded cells; while in the untreated control groups, 100 μl of IMDM without

chemotherapeutic agents was added to 3~6 wells of the microplate. The test drug concentrations were determined based on the peak plasma concentrations according to previous reports and preliminary training set experiments: etoposide (3.57 μg/ml), doxorubicin (1.5 μg/ml), epirubicin (1.2 μg/ml), mitomycin (0.2 μg/ml), 5-FU (10 μg/ml), oxaliplatin (2.9 μg/ml), irinotecan (4.7 μg/ml), docetaxel (3.7 μg/ml), paclitaxel (8.5 μg/ml), MTX (0.37 μg/ml) and cisplatin (2.5 μg/ml)(9-11). Three dilutions (0.2-, 1-, and 5-fold) of the test drug concentration were used in triplicate whenever sufficient number of cancer cell were available. For the purpose of quality control, a negative control group of 3~6 wells of seeding medium without cells and two positive control groups of 3 wells that contained the minimal (105 pg ATP) and the median (280 pg ATP) amounts of ATP, as measured in 1,000 harvested tumor cells were included in the culture plate, respectively. The microplate was cultured for 48 hours at 37℃ in 5% CO_2 with concomitant exposure to drugs. Then, the cells were lysed and the ATP content of each well were measured using the luciferin-luciferase system (Roche, Mannheim, Germany), followed by flash type luminescence measurements on a Victor 3 multi-label counter (PerkinElmer Boston, MA, USA).

Each of the cancer cell death rate (CDR) with luminscence values were calculated by the following formula.

$$\text{CDR (\%)} = \left(1 - \frac{\text{Mean luminescence in treated cells}}{\text{Mean luminescene in untreated control}}\right) \times 100$$

A chemosensitivity index (CI) is calculated as the sum of the percentage inhibition at each concentration tested (CI=300-sum %Inhibition at 0.2-, 1-, and 5-fold of test drug concentration). The higher the value of CI, the greater the resistance to an anti-cancer drug. For every experiment, we calculated the intra assay mean coefficient of variation for quality control. For the calculation of coefficient of variation value, the luminescence values of each specimen were measured 3 times.

The chemosensitivity test of the ATP-CRA was considered a failure when the intra assay mean coefficient of variation for triplicate ATP measurements resulted in any value of over 30 or those of the untreated control which had a measurement less than 105 pg ATP that of the positive control group. When inadequate numbers of cells were harvested or cell culture failed due to microorganism contamination, the test was also regarded as failure.

3. Statistics

Statistical calculations were performed using the “Statistical Package for Social Science(SPSS)” version 18.0 for windows (SPSS Inc., Chicago, IL, USA). The difference of clinicopathologic characteristics between stage II and stage III, sensitive and resistant group to 5-FU, Cisplatin, 5-FU or Cisplatin, 5-FU and Cisplatin on ATP-CRA result were compared using the Student’s t-tests and chi-square tests. The difference of clinicopathologic characteristics between chemotherapy regimen 3 subgroups were compared using chi-square

tests and one-way analysis of variance. The Survival curves were constructed using Kaplan-Meier's method. The log-rank test was used to compare survival probabilities between between sensitive and resistant groups, chemotherapy regimen subgroups. A P-value <0.05 was considered statistically significant.

III. RESULTS

1. Patients clinicopathologic characteristics

The mean age of total patients was 54.7years (range, 24~75 years), and the male to female ratio was 2.1 to 1. The median follow up duration of total patients was 25months (range, 3~56months). During follow up, gastric cancer recurred in 45 patients (38.8%) and 25patients was died. The distribution of the TNM stage according to the 7th AJCC classification included 25 Stage II (20.3%), 91 Stage III (78.4%). (Table 1)

Of all total patients, there are 69 patients (56.1%) who underwent 5-FU+ Cisplatin adjuvant chemotherapy, 36 patients (29.3%) received S-1+Cisplatin, and the other 11 patients (8.9%) received UFT+Cisplatin chemotherapy. These three chemotherapy regimen subgroups did not have any statistically significant difference on age, gender, TNM stages, histologic type, operation method, recurrence and death rate. (Table 2)

Table 1. Clinicopathologic characteristics of total patients and TNM stage subgroups.

Clinicopathologic characteristics		Total (n=116)	TNM stages	
			II (n=25, 20.3%)	III (n=91, 78.4%)
Age†	(Mean±SD)	54.7±11.8	52.7±12.9	55.2±11.6
Gender	Male	79(64.2%)	20(80.0%)	59(64.8%)
	Female	37(30.1%)	5(20.0%)	32(35.2%)
	M: F ratio	2.1:1	4.0:1	1.8:1
T stage	T1b	2(1.6%)	2(8.0%)	0(0%)
	T2	7(5.7%)	5(20.0%)	2(2.2%)
	T3	27(22.0%)	6(24.0%)	21(23.1%)
	T4a	77(62.6%)	12(48.0%)	65(71.4%)
	T4b	3(2.6%)	0(0%)	3(3.3%)
Tumor size‡	(Mean±SD)	56.7±26.2	46.6±21.9	59.4±26.7
Tumor location	upper	16(13.0%)	2(8.0%)	14(15.4%)
	middle	22(17.9%)	3(12.0%)	19(20.9%)
	lower	77(62.6%)	20(80.0%)	58(63.7%)
Proximal margin‡	(Mean±SD)	42.8±32.7	51.4±35.2	40.4±31.7
Distal margin‡	(Mean±SD)	52.9±42.6	42.3±35.7	55.9±44.1
Histology	Differentiated	34(29.3%)	10(40.0%)	24(26.4%)
	Undifferentiated	82(70.7%)	15(60.0%)	67(73.6%)
Lauren classification	Intestinal	52(42.3%)	11(45.8%)	41(45.6%)
	Diffuse	60(48.8%)	13(54.2%)	47(52.2%)
	Mixed	2(1.6%)	0(0%)	2(2.2%)
Retrieved LN§	(Mean±SD)	47.9±16.9	46.1±17.9	48.5±16.6
N stage	N0	14(11.4%)	12(48.0%)	2(2.2%)
	N1	16(13.0%)	6(24.0%)	10(11.0%)
	N2	30(24.4%)	5(20.0%)	25(27.5%)
	N3	56(45.5%)	2(8.0%)	54(59.3%)
Lymphatic invasion		79(64.2%)	13(52.0%)	66(72.5%)
Vascular invasion		78(63.4%)	13(52.0%)	65(71.4%)
Neural invasion		86(69.9%)	15(60.0%)	71(78.0%)
Resection method	RSTG	77(66.4%)	19(76.0%)	58(63.7%)
	RTG	39(33.6%)	6(24.0%)	33(36.3%)
LN dissection	D1+α	1(0.8%)	0(0%)	1(1.1%)
	D1+β	21(17.1%)	6(24.0%)	15(16.5%)
	D2	94(81.0%)	19(76.0%)	75(82.4%)
Chemoregimen	5-FU+Cisplatin	69(56.1%)	14(56.0%)	55(60.4%)
	S-1+Cisplatin	36(29.3%)	7(28.0%)	29(31.9%)
	UFT+ Cisplatin	11(8.9%)	4(16.0%)	7(7.7%)
Chemotherapy cycles	(Mean±SD)	5.4±2.2	5.2±2.2	5.5±2.2
Recurrence rate		45(38.8%)	4(16.0%)	41(45.1%)
Death rate		25(21.6%)	4(16.0%)	21(23.1%)

SD: standard deviation, LN: lymph node, RSTG: radical subtotal gastrectomy, RTG: radical total gastrectomy, 5-FU: 5-fluorouracil

Table 2. Clinicopathologic characteristics of chemotherapy regimen subgroups.

Clinico-pathologic characteristics		Chemotherapy regimen groups			p-value
		5-FU+Cisplatin (n=69, 56.1%)	S-1+Cisplatin (n=36, 29.3%)	UFT+Cisplatin (n=11, 8.9%)	
Age	(Mean±SD(years))	54.5±11.6	53.4±12.4	59.7±10.8	0.295
Gender	Male	48(69.6%)	24(66.7%)	7(63.6%)	0.914
	Female	21(30.4%)	12(33.3%)	4(36.4%)	
	M: F ratio	4.0:1	2.0:1	1.75:1	
T stage	T1b	2(2.9%)	0(0%)	0(0%)	0.129
	T2	3(4.3%)	4(11.1%)	0(0%)	
	T3	13(18.8%)	8(22.2%)	6(54.5%)	
	T4a	50(72.5%)	22(61.1%)	5(45.5%)	
	T4b	1(1.4%)	2(5.6%)	0(0%)	
Tumor size	(Mean±SD(mm))	57.3±26.7	55.2±24.7	57.9±29.6	0.918
Tumor location	upper	10(14.5%)	5(13.9%)	1(9.1%)	0.679
	middle	12(17.4%)	6(16.7%)	4(36.4%)	
	lower	47(68.1%)	25(69.4%)	6(54.5%)	
Proximal margin	(Mean±SD (mm))	42.6±32.9	44.8±35.9	37.0±18.2	0.788
Distal margin	(Mean±SD (mm))	52.3±43.4	55.1±39.3	50.2±51.5	0.925
Histology	Differentiated	19(27.5%)	9(25.0%)	6(54.5%)	0.168
	Undifferentiated	50(72.5%)	27(75.0%)	5(45.5%)	
Lauren classification	Intestinal	30(43.5%)	17(50.0%)	5(45.5%)	0.808
	Diffuse	37(53.6%)	17(50.0%)	6(54.5%)	
	Mixed	2(2.9%)	0(0%)	0(0%)	
Retrieved LN	(Mean±SD)	47.5±15.8	50.5±18.8	42.6±16.6	0.383
N stage	N0	7(10.1%)	5(13.9%)	2(18.2%)	0.442
	N1	9(13.0%)	4(11.1%)	3(27.3%)	
	N2	19(27.5%)	7(19.4%)	4(36.4%)	
	N3	34(49.3%)	20(55.6%)	2(18.2%)	
Lymphatic invasion		50(72.5%)	22(61.1%)	7(63.6%)	0.452
Vascular invasion		50(72.5%)	22(61.1%)	6(54.5%)	0.327
Neural invasion		54(78.3%)	23(63.9%)	9(81.8%)	0.225
TNM Stage	Stage II	14(20.3%)	7(19.4%)	4(36.4%)	0.484
	Stage III	55(79.7%)	29(80.6%)	7(63.6%)	
Resection method	RSTG	49(71.0%)	23(63.9%)	5(45.5%)	0.242
	RTG	20(29.0%)	13(36.1%)	6(54.5%)	
LN dissection	D1+α	0(0%)	1(2.8%)	0(0%)	0.387
	D1+β	15(21.7%)	5(13.9%)	1(9.1%)	
	D2	54(78.3%)	30(83.3%)	10(91.9%)	
Recurrence		30(43.5%)	12(33.3%)	3(27.3%)	0.428
Death		18(26.1%)	5(13.9%)	2(18.2%)	0.339

SD: standard deviation, LN: lymph node, RSTG: radical subtotal gastrectomy, RTG: radical total gastrectomy, 5-FU: 5-fluorouracil.

On the ATP-CRA regimen specific sensitive and resistant group using a CDR cut-off value 50%, the sensitive to 5-FU group was not differ from resistant group about patients clinicopathologic characteristics. To Cisplatin only group, to 5-FU or Cisplatin group, to 5-FU and Cisplatin groups show all similar patterns. S-1+Cisplatin chemotherapy regimen was dominant portion in all kinds of sensitive group, 5-FU+Cisplatin chemotherapy regimen occupied much portion in every resistant group. (Table 3~6)

Table 3. Clinicopathologic characteristics of ATP-CRA regimen specific sensitive and resistant groups to 5-FU

Clinico-pathologic characteristics		ATP-CRA regimen specific sensitive and resistant groups (CDR≥50%: sensitive, CDR<50%: resistant)		
		Semsitive to 5-FU (n=17, 13.8%)	Resistant to 5-FU (n=99, 80.5%)	p-value
Age	(Mean±SD(years))	52.7±12.3	55.0±11.8	0.465
Gender	Male	9(52.9%)	68(68.7%)	0.267
	Female	8(47.1%)	31(31.3%)	
	M: F ratio	1.1:1	2.2:1	
T stage	T1b	0(0%)	2(2.0%)	0.327
	T2	0(0%)	7(7.1%)	
	T3	2(11.8%)	25(25.3%)	
	T4a	14(82.4%)	63(63.6%)	
	T4b	1(5.9%)	2(2.0%)	
Tumor size	(Mean±SD(mm))	59.8±22.2	56.1±26.9	0.595
Tumor location	upper	5(29.4%)	11(11.1%)	0.127
	middle	3(17.6%)	19(19.2%)	
	lower	9(52.9%)	69(69.7%)	
Proximal margin	(Mean±SD (mm))	35.7±35.9	44.0±32.1	0.337
Distal margin	(Mean±SD (mm))	60.6±41.6	51.7±42.9	0.427
Histology	Differentiated	2(11.8%)	32(32.3%)	0.147
	Undifferentiated	15(88.2%)	67(67.7%)	
Lauren classification	Intestinal	7(41.2%)	45(46.4%)	0.850
	Diffuse	10(58.8%)	50(51.5%)	
	Mixed	0(0%)	2(2.1%)	
Retrieved LN	(Mean±SD)	53.9±18.6	47.0±16.4	0.116
N stage	N0	2(11.8%)	12(12.1%)	0.978
	N1	2(11.8%)	14(14.1%)	
	N2	4(23.5%)	26(26.3%)	
	N3	9(52.9%)	47(47.5%)	
Lymphatic invasion		9(52.9%)	70(70.7%)	0.166
Vascular invasion		9(52.9%)	69(69.7%)	0.262
Neural invasion		14(82.4%)	72(72.7%)	0.553
TNM Stage	Stage II	2(11.8%)	23(23.2%)	0.358
	Stage III	15(88.2%)	76(76.8%)	
Resection method	RSTG	9(52.9%)	68(68.7%)	0.267
	RTG	8(47.1%)	31(31.3%)	
LN dissection	D1+α	1(5.9%)	0(0%)	0.120
	D1+β	2(11.8%)	19(19.2%)	
	D2	14(82.4%)	80(80.8%)	
Chemoregimen	5FU+Cisplatin	4(23.5%)	65(65.7%)	<0.001*
	TS-1+Cisplatin	13(76.5%)	23(23.2%)	
	UFT+ Cisplatin	0(0%)	11(11.1%)	
Chemotherapy cycles	(Mean±SD)	5.4±2.8	5.5±2.1	0.859
Recurrence		7(41.2%)	38(38.4%)	>0.999
Death		5(29.4%)	20(20.2%)	0.522

SD: standard deviation, LN: lymph node, RSTG: radical subtotal gastrectomy, RTG: radical total gastrectomy, 5-FU: 5-fluorouracil. *: p-value<0.05

Table 4. Clinicopathologic characteristics of ATP-CRA regimen specific sensitive and resistant groups to Cisplatin

Clinico-pathologic characteristics		ATP-CRA regimen specific sensitive and resistant groups (CDR≥50%: sensitive, CDR<50%: resistant)		
		Sensitive to Cisplatin (n=17, 13.8%)	Resistant to Cisplatin (n=99, 80.5%)	p-value
Age	(Mean±SD(years))	52.4±14.2	55.1±11.4	0.388
Gender	Male	13(76.5%)	66(66.7%)	0.576
	Female	4(23.5%)	33(33.3%)	
	M: F ratio	3.25:1	2.0:1	
T stage	T1b	0(0%)	2(2.0%)	0.090
	T2	3(17.6%)	4(4.0%)	
	T3	1(5.9%)	26(26.3%)	
	T4a	13(76.5%)	64(64.6%)	
	T4b	0(0%)	3(3.0%)	
Tumor size	(Mean±SD(mm))	53.7±21.8	57.2±26.9	0.613
Tumor location	upper	2(11.8%)	14(14.1%)	0.684
	middle	2(11.8%)	20(20.2%)	
	lower	13(76.5%)	65(65.7%)	
Proximal margin	(Mean±SD (mm))	41.6±35.8	43.0±32.2	0.873
Distal margin	(Mean±SD (mm))	47.9±37.1	53.8±43.6	0.597
Histology	Differentiated	2(11.8%)	32(32.3%)	0.147
	Undifferentiated	15(88.2%)	67(67.7%)	
Lauren classification	Intestinal	10(58.8%)	42(43.3%)	0.494
	Diffuse	7(41.2%)	53(54.6%)	
	Mixed	0(0%)	2(2.1%)	
Retrieved LN	(Mean±SD)	49.2±17.3	47.8±16.9	0.754
N stage	N0	1(5.9%)	13(13.1%)	0.257
	N1	1(5.9%)	15(15.2%)	
	N2	3(17.6%)	27(27.3%)	
	N3	12(70.6%)	44(44.4%)	
Lymphatic invasion		12(70.6%)	67(67.7%)	>0.999
Vascular invasion		12(70.6%)	66(66.7%)	0.790
Neural invasion		12(70.6%)	74(74.7%)	0.767
TNM Stage	Stage II	2(11.8%)	23(23.2%)	0.358
	Stage III	15(88.2%)	76(76.8%)	
Resection method	RSTG	13(76.5%)	64(64.6%)	0.415
	RTG	4(23.5%)	35(35.4%)	
LN dissection	D1+α	1(5.9%)	0(0%)	0.120
	D1+β	2(11.8%)	19(19.2%)	
	D2	14(82.4%)	80(80.8%)	
Chemoregimen	5FU+Cisplatin	5(29.4%)	64(64.6%)	0.002*
	TS-1+Cisplatin	12(70.6%)	24(24.2%)	
	UFT+ Cisplatin	0(0%)	11(11.1%)	
Chemotherapy cycles	(Mean±SD)	4.9±2.6	5.5±2.1	0.253
Recurrence		6(35.3%)	39(39.4%)	0.795
Death		2(11.8%)	23(23.2%)	0.358

SD: standard deviation, LN: lymph node, RSTG: radical subtotal gastrectomy, RTG: radical total gastrectomy, 5-FU: 5-fluorouracil. *: p-value<0.05

Table 5. Clinicopathologic characteristics of ATP-CRA regimen specific sensitive and resistant groups to 5-FU or Cisplatin

Clinico-pathologic characteristics		ATP-CRA regimen specific sensitive and resistant groups (CDR≥50%: sensitive, CDR<50%: resistant)		
		Sensitive to 5-FU or Cisplatin (n=26, 21.1%)	Resistant to 5-FU or Cisplatin (n=90, 73.2%)	p-value
Age	(Mean±SD(years))	53.1±12.8	55.1±11.6	0.443
Gender	Male	22(84.6%)	57(63.3%)	0.055
	Female	4(15.4%)	33(36.7%)	
	M: F ratio	5.5:1	1.7:1	
T stage	T1b	0(0%)	2(2.2%)	0.287
	T2	3(11.5%)	4(4.4%)	
	T3	3(11.5%)	24(26.7%)	
	T4a	19(73.1%)	58(64.4%)	
	T4b	1(3.8%)	2(2.2%)	
Tumor size	(Mean±SD(mm))	54.2±21.2	57.4±27.5	0.589
Tumor location	upper	5(19.2%)	11(12.2%)	0.671
	middle	4(15.4%)	18(20.0%)	
	lower	17(65.4%)	61(67.8%)	
Proximal margin	(Mean±SD (mm))	42.2±38.8	42.9±30.9	0.925
Distal margin	(Mean±SD (mm))	54.0±38.6	52.7±43.9	0.889
Histology	Differentiated	3(11.5%)	31(34.4%)	0.028*
	Undifferentiated	23(88.5%)	59(65.6%)	
Lauren classification	Intestinal	14(53.8%)	38(43.2%)	0.527
	Diffuse	12(46.2%)	48(54.5%)	
	Mixed	0(0%)	2(2.3%)	
Retrieved LN	(Mean±SD)	52.6±19.1	46.7±16.0	0.116
N stage	N0	3(11.5%)	11(12.2%)	0.459
	N1	2(7.7%)	14(15.6%)	
	N2	5(19.2%)	25(27.8%)	
	N3	16(61.5%)	40(44.4%)	
Lymphatic invasion		17(65.4%)	62(68.9%)	0.812
Vascular invasion		17(65.4%)	61(67.8%)	>0.999
Neural invasion		19(73.1%)	67(74.4%)	>0.999
TNM Stage	Stage II	4(15.4%)	21(23.3%)	0.434
	Stage III	22(84.6%)	69(76.7%)	
Resection method	RSTG	17(65.4%)	60(66.7%)	>0.999
	RTG	9(34.6%)	30(33.3%)	
LN dissection	D1+α	1(3.8%)	0(0%)	0.122
	D1+β	3(11.5%)	18(20.0%)	
	D2	22(84.6%)	72(80.0%)	
Chemoregimen	5FU+Cisplatin	7(26.9%)	62(68.9%)	<0.001*
	TS-1+Cisplatin	19(73.1%)	17(18.9%)	
	UFT+ Cisplatin	0(0%)	11(12.2%)	
Chemotherapy cycles	(Mean±SD)	4.8±2.6	5.6±2.0	0.132
Recurrence		10(38.5%)	35(38.9%)	>0.999
Death		6(23.1%)	19(21.1%)	>0.999

SD: standard deviation, LN: lymph node, RSTG: radical subtotal gastrectomy, RTG: radical total gastrectomy, 5-FU: 5-fluorouracil. *: p-value<0.05

Table 6. Clinicopathologic characteristics of ATP-CRA regimen specific sensitive and resistant groups to 5-FU and Cisplatin

Clinico-pathologic characteristics		ATP-CRA regimen specific sensitive and resistant groups (CDR≥50%: sensitive, CDR<50%: resistant)		
		Sensitive to 5-FU and Cisplatin (n=8, 6.5%)	Resistant to 5-FU and Cisplatin (n=108, 87.8%)	p-value
Age	(Mean±SD(years))	50.8±14.7	54.9±11.6	0.336
Gender	Male	6(75.0%)	73(67.6%)	0.724
	Female	2(25.0%)	35(32.4%)	
	M: F ratio	3.0:1	2.1:1	
T stage	T1b	0(0%)	2(1.9%)	0.389
	T2	0(0%)	7(6.5%)	
	T3	0(0%)	27(25.0%)	
	T4a	8(100%)	69(63.9%)	
	T4b	0(0%)	3(2.8%)	
Tumor size	(Mean±SD(mm))	65.0±23.5	56.1±26.4	0.354
Tumor location	upper	2(25.0%)	14(13.0%)	0.735
	middle	1(12.5%)	21(19.4%)	
	lower	5(62.5%)	73(67.6%)	
Proximal margin	(Mean±SD (mm))	27.0±18.4	43.9±33.2	0.158
Distal margin	(Mean±SD (mm))	55.0±44.6	52.8±42.7	0.890
Histology	Differentiated	1(12.5%)	33(30.6%)	0.434
	Undifferentiated	7(87.5%)	75(69.4%)	
Lauren classification	Intestinal	3(37.5%)	49(46.2%)	0.760
	Diffuse	5(62.5%)	55(51.9%)	
	Mixed	0(0%)	2(1.9%)	
Retrieved LN	(Mean±SD)	48.3±13.4	47.9±17.2	0.963
N stage	N0	0(0%)	14(13.0%)	0.803
	N1	1(12.5%)	15(13.9%)	
	N2	2(25.0%)	28(25.9%)	
	N3	5(62.5%)	51(47.2%)	
Lymphatic invasion		4(50.0%)	75(69.4%)	0.264
Vascular invasion		4(50.0%)	74(68.5%)	0.435
Neural invasion		7(87.5%)	79(73.1%)	0.678
TNM Stage	Stage II	0(0%)	25(23.1%)	0.198
	Stage III	8(100%)	83(76.9%)	
Resection method	RSTG	5(62.5%)	72(66.7%)	>0.999
	RTG	3(37.5%)	36(33.3%)	
LN dissection	D1+α	1(12.5%)	0(0%)	0.069
	D1+β	1(12.5%)	20(18.5%)	
	D2	6(75.0%)	88(81.5%)	
Chemoregimen	5FU+Cisplatin	2(25.0%)	67(62.0%)	0.041*
	TS-1+Cisplatin	6(75.0%)	30(27.8%)	
	UFT+ Cisplatin	0(0%)	11(10.2%)	
Chemotherapy cycles	(Mean±SD)	6.3±2.6	5.4±2.1	0.275
Recurrence		3(37.5%)	42(38.9%)	>0.999
Death		1(12.5%)	24(22.2%)	>0.999

SD: standard deviation, LN: lymph node, RSTG: radical subtotal gastrectomy, RTG: radical total gastrectomy, 5-FU: 5-fluorouracil. *: p-value<0.05

2. ATP-CRA results

The coefficient variants, 5-FU cell death rate, Cisplatin cell death rate, chemosensitiviry index of ATP-CRA results did not show statistical difference between TNM stages. (Table 7) In chemotherapy regimen subgroup which resulted in high cell death rates of 5-FU and Cisplatin, were S-1+Cisplatin, 5-FU+Cisplatin, UFT+Cisplatin. The highest value of chemosensitivity index was 5-FU+Cisplatin, it was followed by UFT+Cisplatin and then S-1+Cisplatin. The cell death rate and chemosensitivity index of chemotherapy regimen subgroups had statistical difference, but it was not correlated to clinical trend. (Table 8)

In ATP-CRA results in regimen specific sensitive and resistant groups, all sensitive groups had higher mean 5-FU and Cisplatin cell death rate than all resistant groups. All sensitive groups had lower mean 5-FU and Cisplatin chemosensitivity index than all resistant groups. These ATP-CRA results cannot explained any clinical significance or trend.

Table 7. ATP-CRA results of total patients and TNM stage subgroups

ATP-CRA results	Total(n=116)	TNM stage		
		II (n=25,20.3%)	III(n=91,78.4%)	p-value
Mean CV	6.87(1.9~17.9)±2.02	7.00±1.33	6.84±2.17	0.714
5-FU 1x CDR	35.77(0~73.4)±15.01	33.82±13.02	36.31±15.53	0.464
5-FU CI	177.67(73.8~269.3)±41.98	190.51±36.50	173.97±43.00	0.154
Cisplatin 1x CDR	27.88(0~71.5)±19.69	26.28±17.34	28.32±20.35	0.648
Cisplatin CI	206.13(90.1~300.0)±49.86	220.78±33.42	201.91±53.16	0.171

ATP-CRA: In vitro adenosine triphosphate based chemotherapy response assay, CV: coefficient variant, 5-FU: 5-fluorouracil, CDR: cell death rate, CI: chemosentitivity index, SD: standard deviation

Table 8. ATP-CRA results of chemotherapy regimen subgroups.

ATP-CRA results	Chemotherapy regimen subgroups			
	5-FU+Cisplatin (n=69, 56.1%)	S-1+Cisplatin (n=36, 29.3%)	UFT+Cisplatin (n=11, 8.9%)	p-value
Mean CV	6.97±1.74	6.62±1.68	7.08±3.98	0.657
5-FU 1x CDR	32.55±13.46	43.59±15.27	30.38±14.81	0.001*
5-FU CI	188.66±38.02	154.93±42.53	184.40±38.19	0.004*
Cisplatin 1x CDR	24.88±17.18	38.19±21.44	12.96±12.26	<0.001*
Cisplatin CI	216.13±41.10	179.82±59.05	234.70±28.79	0.004*

ATP-CRA: In vitro adenosine triphosphate based chemotherapy response assay, CV: coefficient variant, 5-FU: 5-fluorouracil, CDR: cell death rate, CI: chemosentitivity index, SD: standard deviation, *: p-value<0.05

3. Disease free survival and overall survival

Median disease free survival of total patients was 20 months (range, 2~56 months, mean 24 months), and median overall survival was 25 months (range, 3~56 months, mean 28 months). (Figure 1.(A),(B))

In disease free survival rate, there was no statistical difference between 3chemotherapy regimen subgroups (5-FU+Cisplatin, S-1+Cisplatin, UFT+ Cisplatin) of total patients. In overall survival rate, there was not any significant difference, also. (Figure 2(A),(B)).

No considerable differenc of disease free survival and overall survival was shown between senstive and resistant group to 5-FU, Cisplatin, 5-FU or Cisplatin, and 5-FU and Cisplatin. (Figure 3~6) The sensitive to 5-FU or Cisplatin group had different histological distribution with resistant group.(p-value 0.028, Table 5)

The sensitive group of disease free survival and overall survival was not differ from the resistant group to any kinds of chemotherapy regimen. Such patterns were revealed in total patients, stageII, stage III. (Figure 7~14) Some groups did not exist on total patients; Sensitive group to 5-FU and Cisplatin. (Figure 10.(A), (B))

Figure 1.(A) Disease free survival of total patients

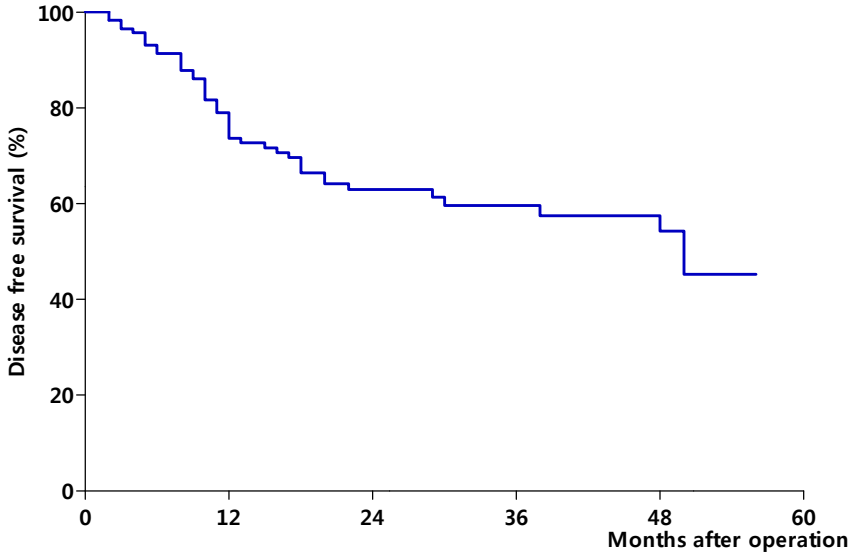


Figure 1.(B) Overall survival of total patients

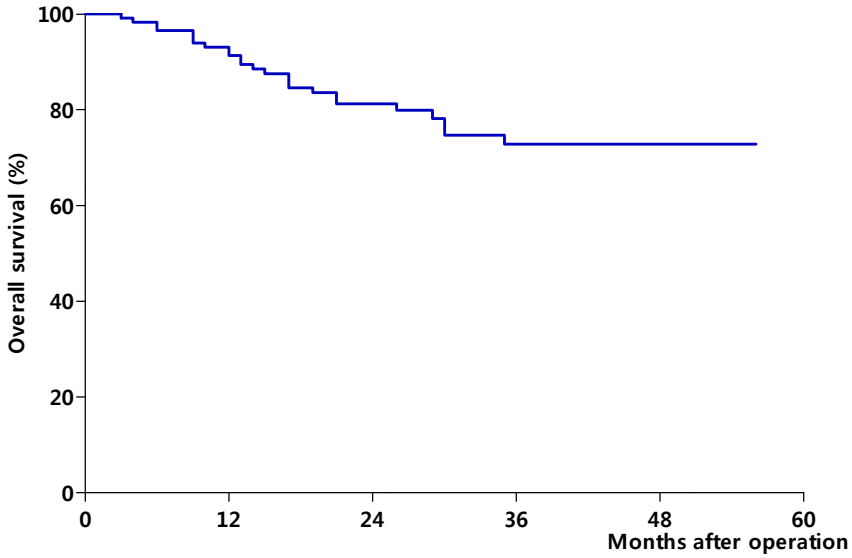


Figure 2.(A) Disease free survival of chemotherapy regimen subgroups

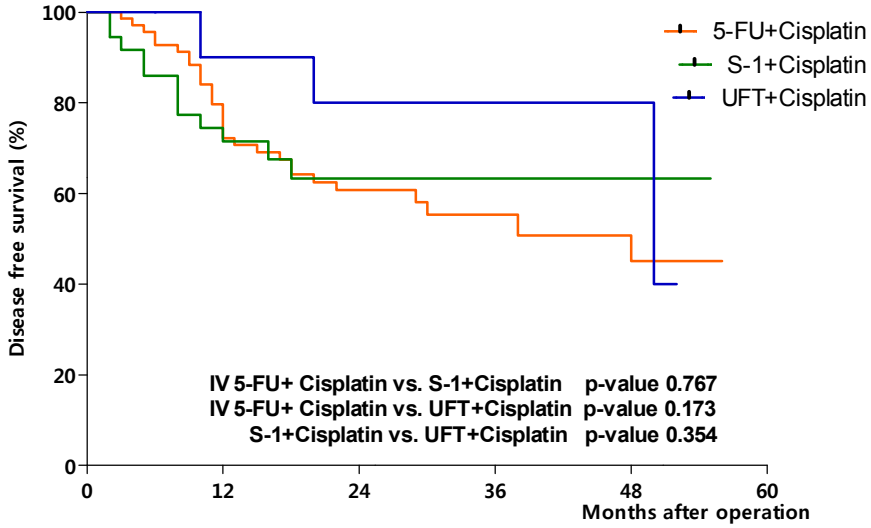


Figure 2.(B) Overall survival of chemotherapy regimen subgroups

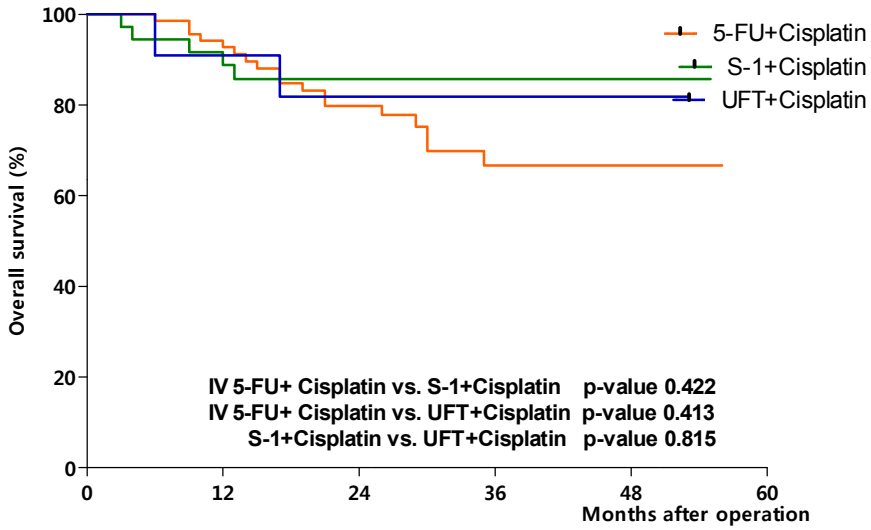


Figure 3.(A) Disease free survival of sensitive/resistant to 5-FU

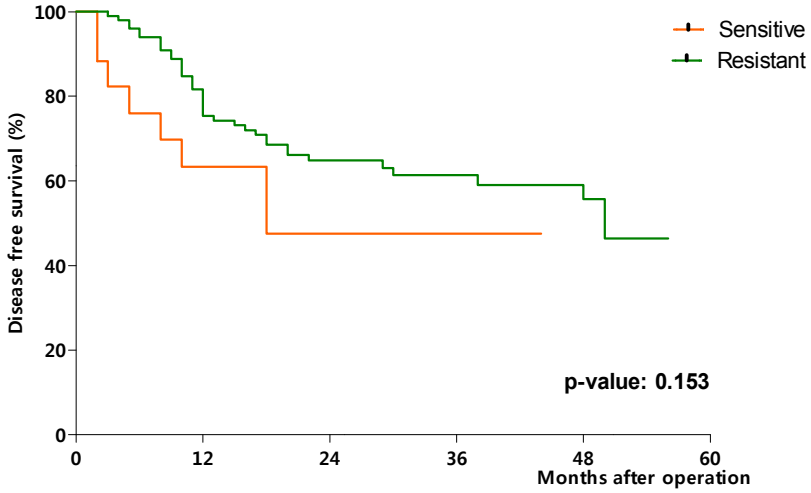


Figure 3.(B) Overall survival of sensitive/resistant to 5-FU

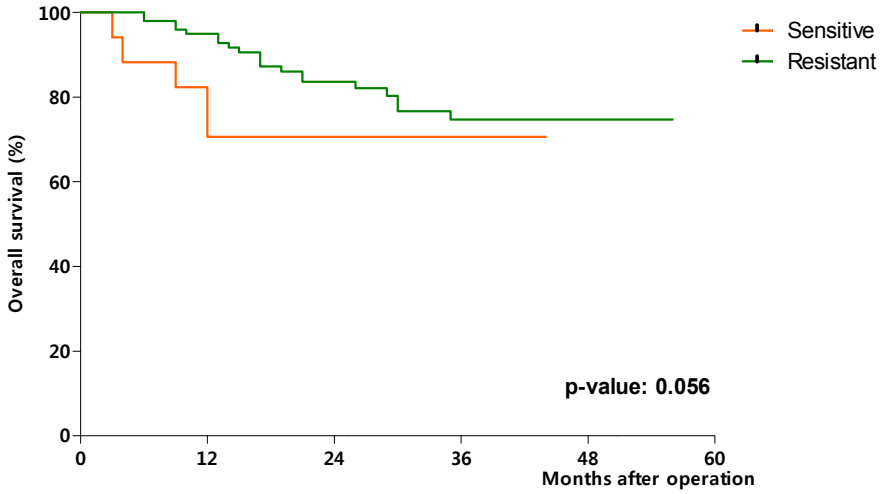


Figure 4.(A) Disease free survival of sensitive/resistant to Cisplatin

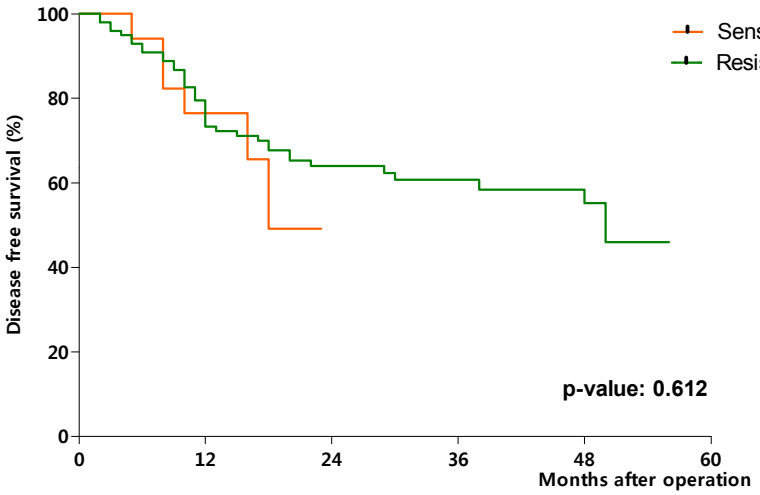


Figure 4.(B) Overall survival of sensitive/resistant to Cisplatin

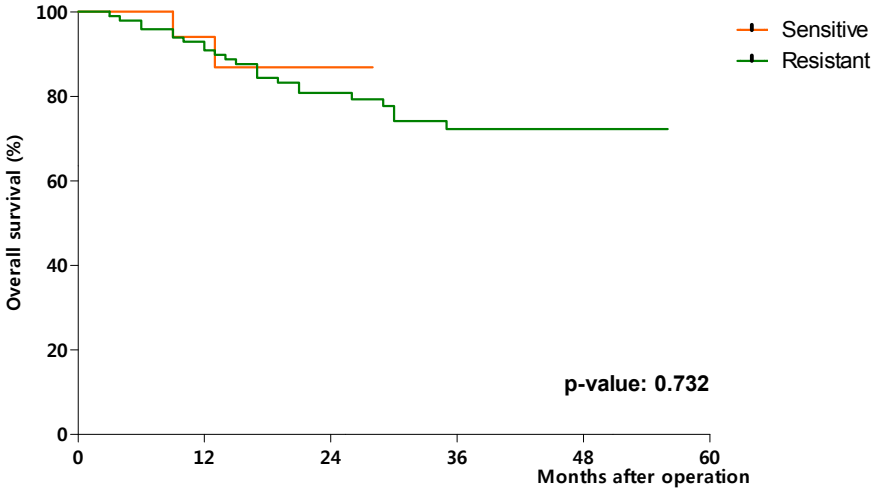


Figure 5.(A) Disease free survival of sensitive/resistant to 5-FU or Cisplatin

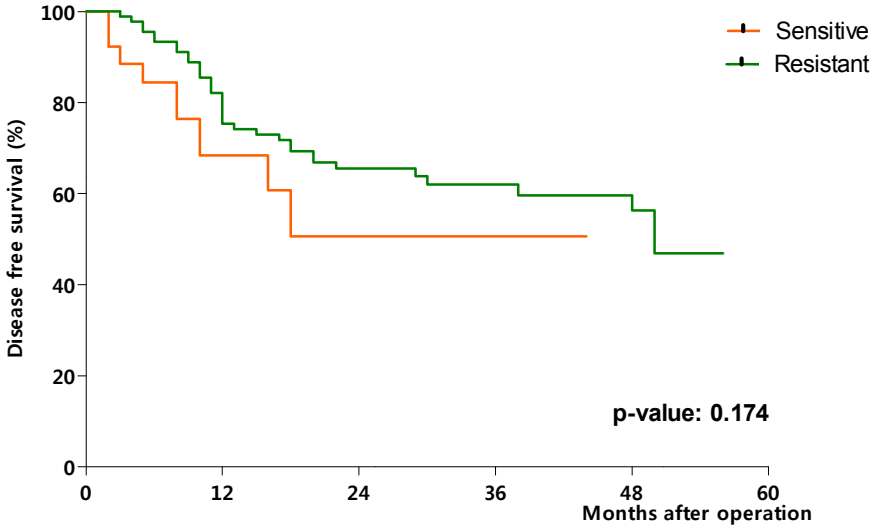


Figure 5.(A) Overall survival of sensitive/resistant to 5-FU or Cisplatin

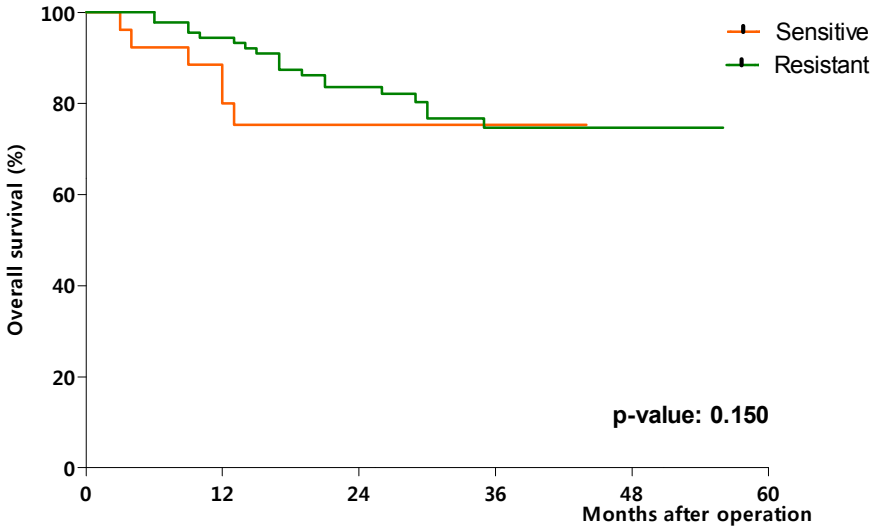


Figure 6.(A) Disease free survival of sensitive/resistant to 5-FU and Cisplatin

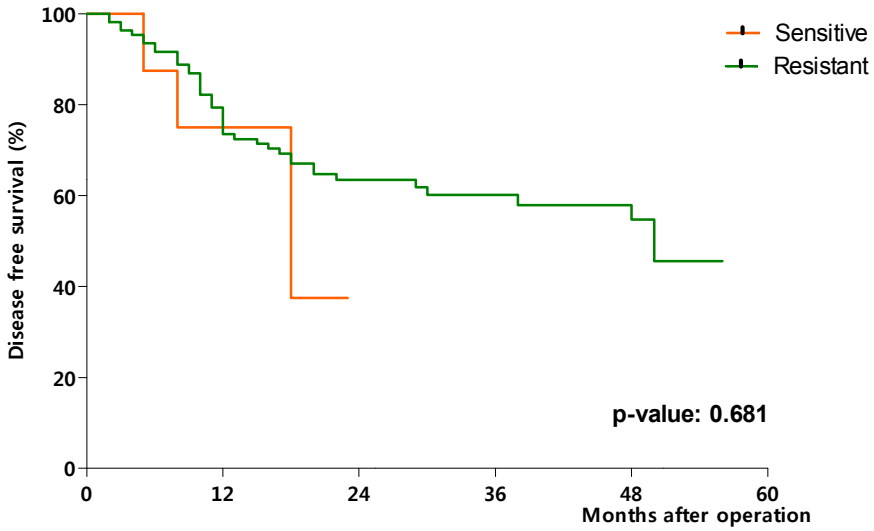


Figure 6.(B) Overall survival of sensitive/resistant to 5-FU and Cisplatin

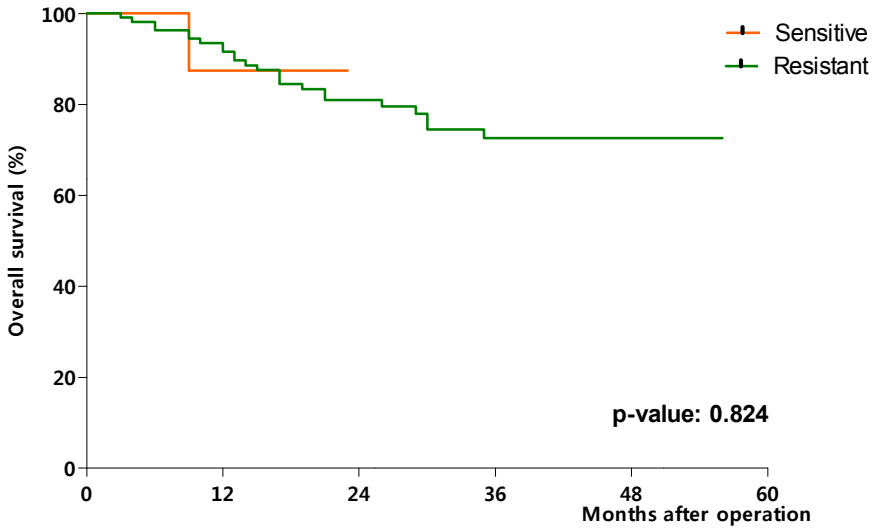


Figure 7.(A) Disease free survival of sensitive/resistant to 5-FU in stage Ⅱ

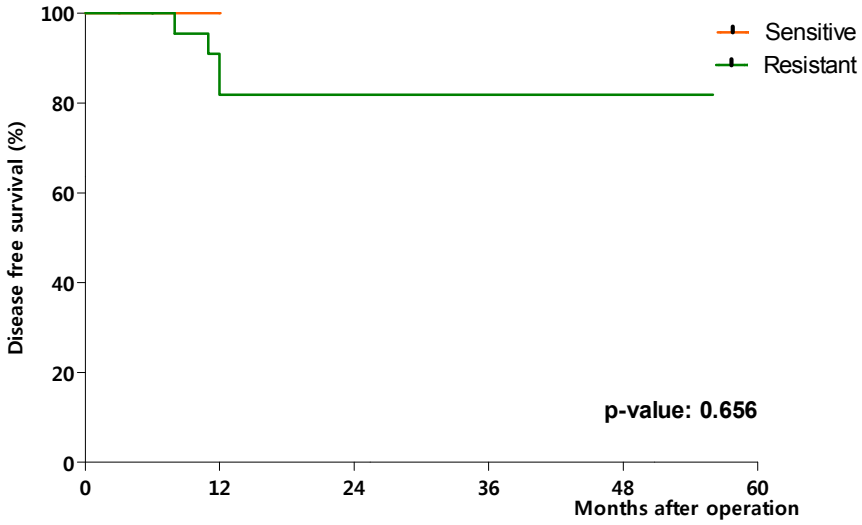


Figure 7.(B) Overall survival of sensitive/resistant to 5-FU in stage Ⅱ

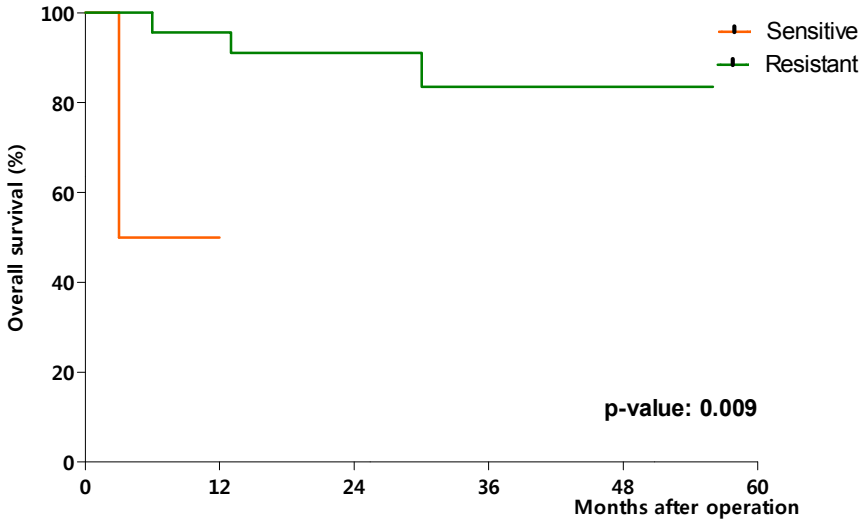


Figure 8.(A) Disease free survival of sensitive/resistant to Cisplatin in stage II

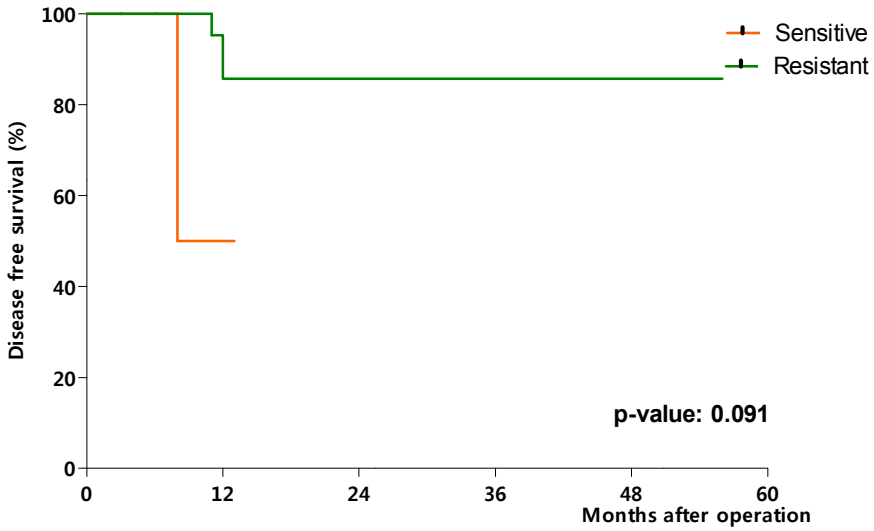


Figure 8.(B) Overall survival of sensitive/resistant to Cisplatin in stage II

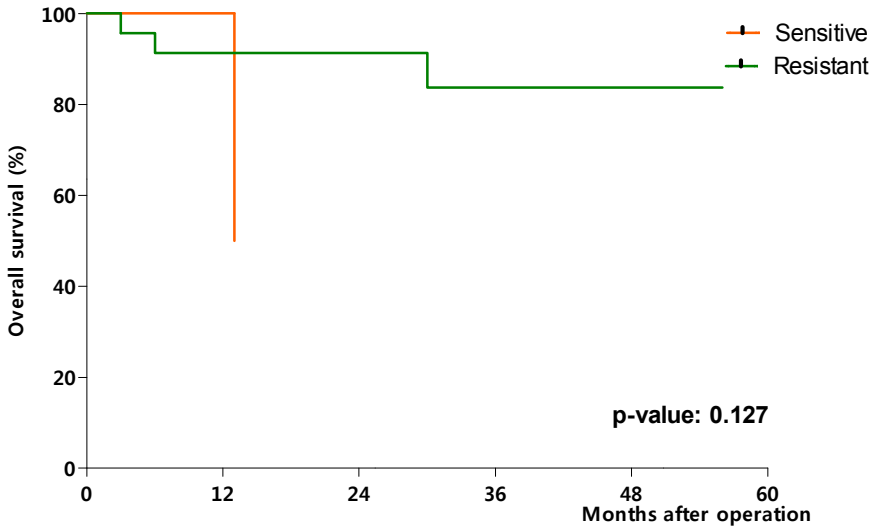


Figure 9.(A) Disease free survival of sensitive/resistant to 5-FU or Cisplatin in stage II

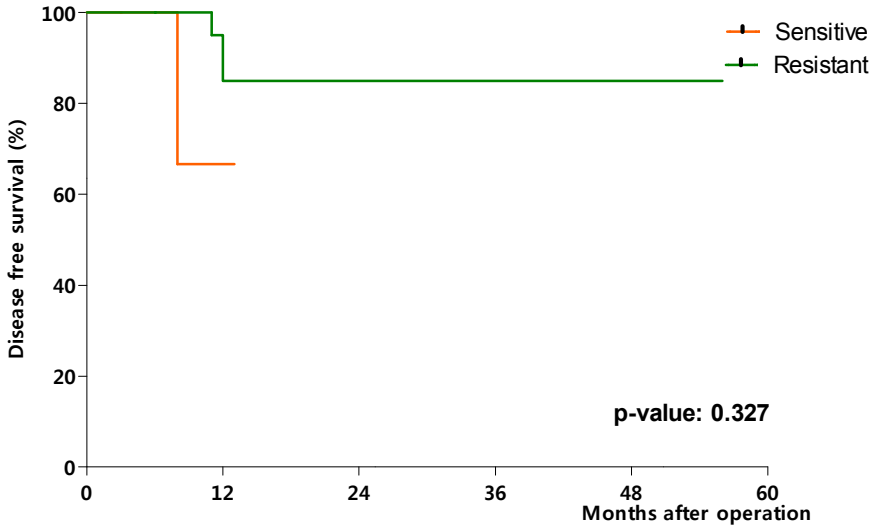


Figure 9.(B) Overall survival of sensitive/resistant to 5-FU or Cisplatin in stage II

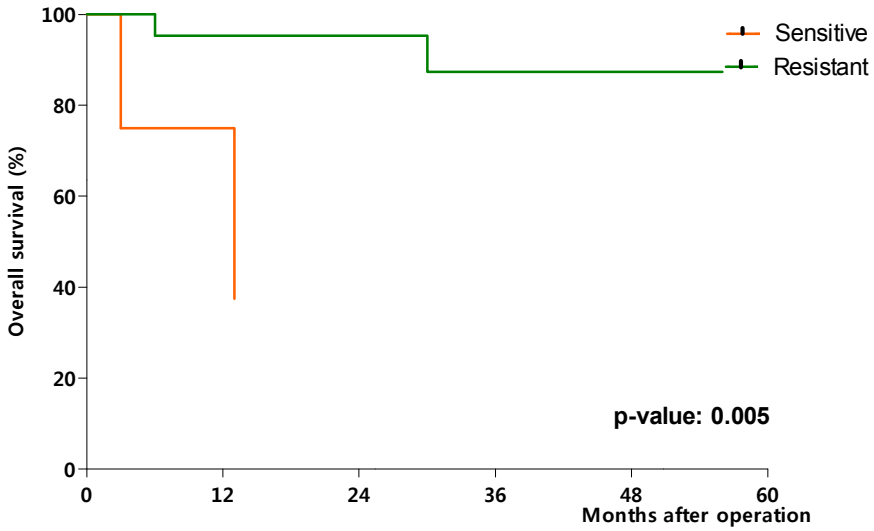


Figure 10.(A) Disease free survival of sensitive/resistant to 5-FU and Cisplatin in stage II

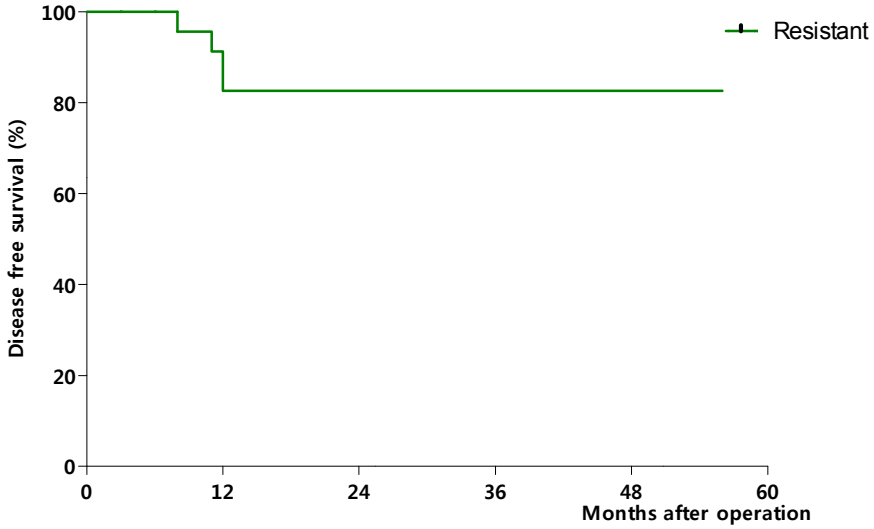


Figure 10.(B) Overall survival of sensitive/resistant to 5-FU and Cisplatin in stage II

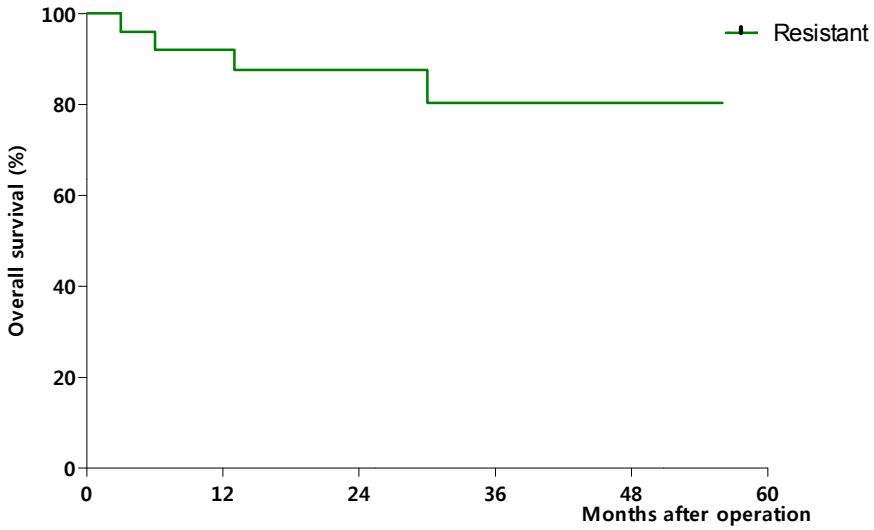


Figure 11.(A) Disease free survival of sensitive/resistant to 5-FU in stage III

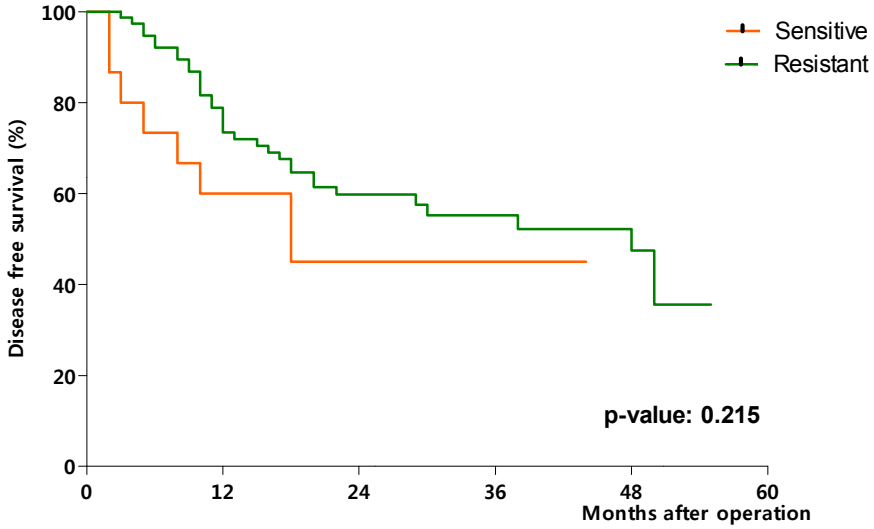


Figure 11.(B) Overall survival of sensitive/resistant to 5-FU in stage III

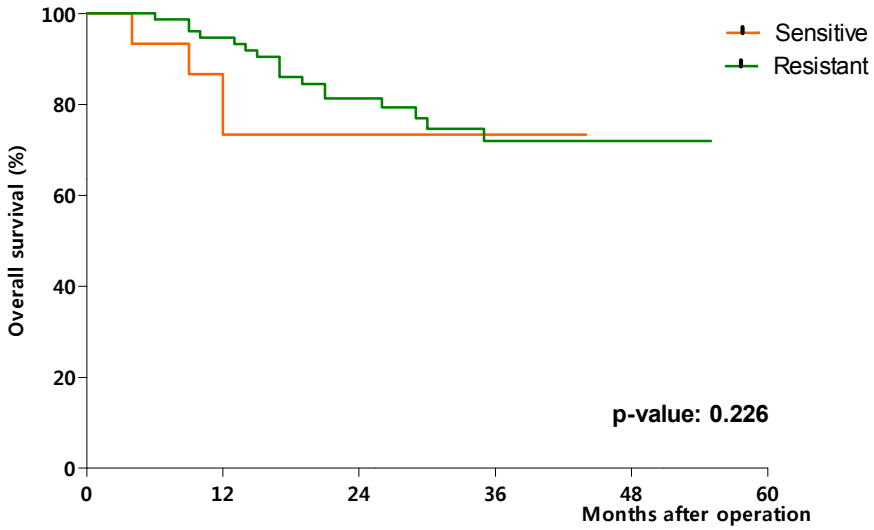


Figure 12.(A) Disease free survival of sensitive/resistant to Cisplatin in stage III

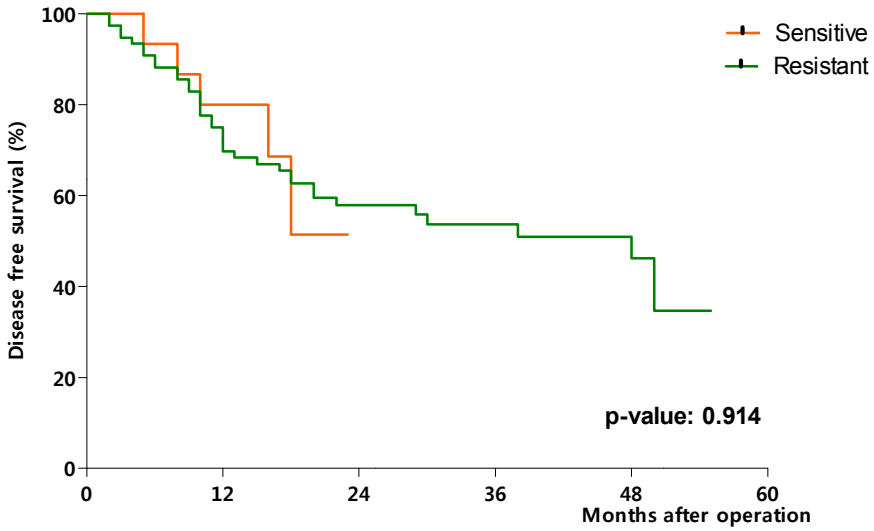


Figure 12.(B) Overall survival of sensitive/resistant to Cisplatin in stage III

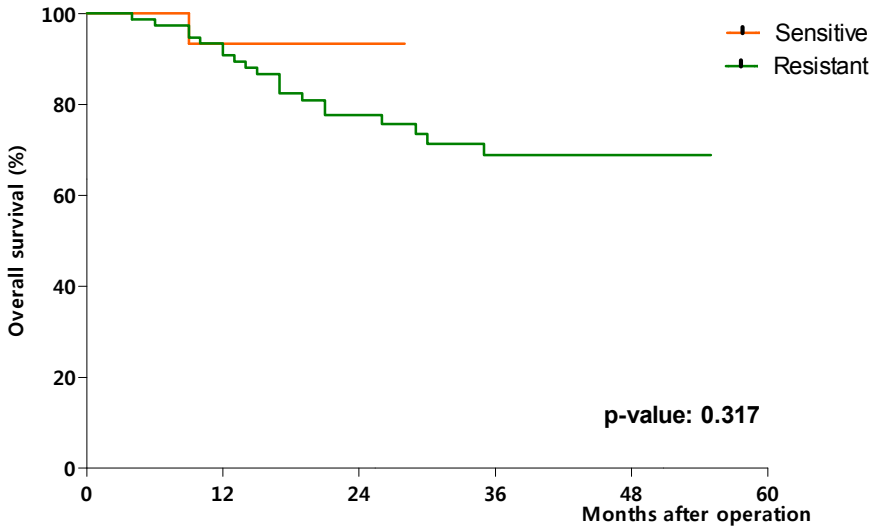


Figure 13.(A) Disease free survival of sensitive/resistant to 5-FU or Cisplatin in stage III

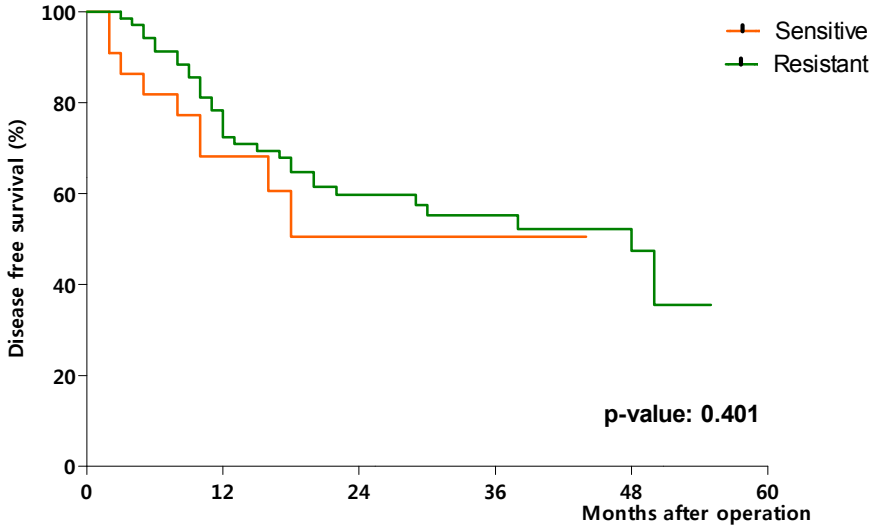


Figure 13.(B) Overall survival of sensitive/resistant to 5-FU or Cisplatin in stage III

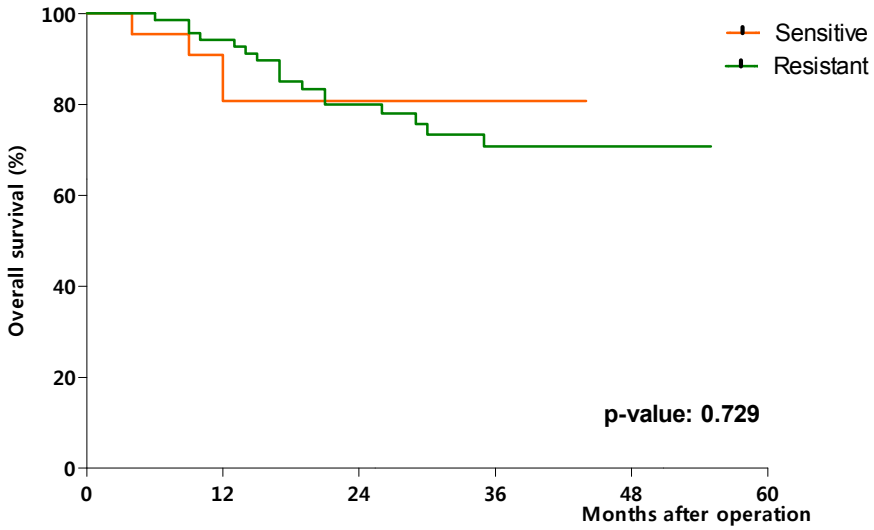


Figure 14.(A) Disease free survival of sensitive/resistant to 5-FU and Cisplatin in stage Ⅲ

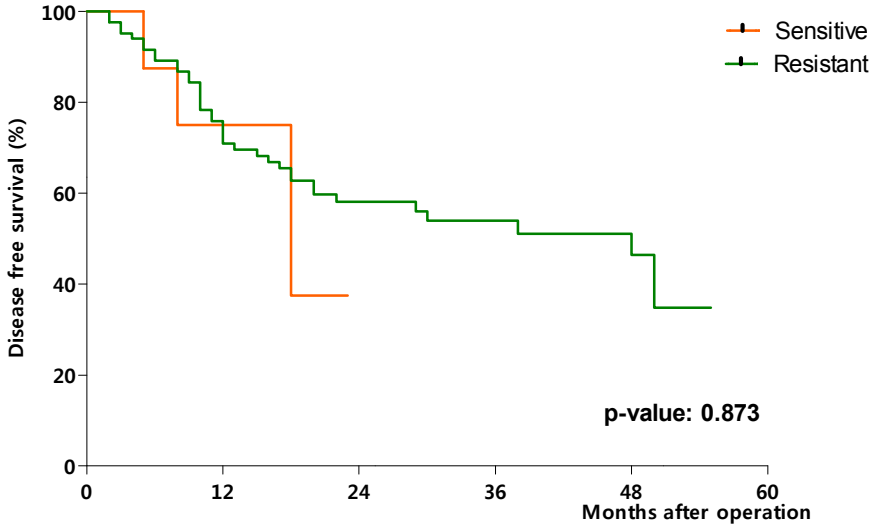
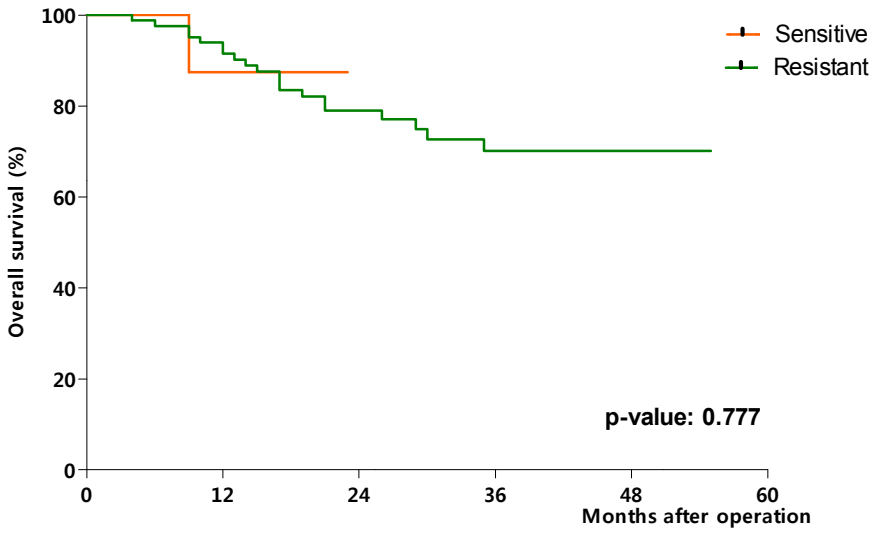


Figure 14.(B) Overall survival of sensitive/resistant to 5-FU and Cisplatin in stage Ⅲ



IV. DISCUSSION

The ATP-CRA can be performed with a very small amount of cancer tissue, effectively eliminates or suppresses normal cells from the tissue specimens, has a higher sensitivity for evaluating viable cells, and is more accurate than previous chemosensitivity tests[15]. ATP-CRA has been explored in many types of cancer as a method of selecting chemotherapy regimens based on individual difference in a variety of anti-cancer drugs[8-11,14,16,17]. However, this study result in that ATP-CRA test is inappropriate for decision of adjuvant 5-FU with Cisplatin based chemotherapy regimen for gastric cancer patients .

The concept of in vitro chemosensitivity test is that it may help to differentiate the response of individual cancer patients to chemotherapeutic agents. The benefits of chemotherapy after gastrectomy for gastric cancer are not fully established, and even though, some phase III randomized prospective clinical trials have shown survival benefits of chemotherapy[3,4,18], the most effective standard chemotherapeutic regimen for gastric cancer was not exist. Therefore, provided that an in vitro chemosensitivity assay could accurately predict the in vivo chemo-responsiveness of the patients, its application may be an ideal method of identifying the most effective patient specific chemotherapy agent.

Although ATP-CRA has the advantage of being just with just 0.5 cubic centimeters sized specimen. This may need to act as a disadvantage that tested small sized specimen was not represent the gastric cancer pathologic character. When the pathologist read the slides, permanent pathology report was described

by 50% or more cells. The tested 0.5 cubic centimeters cancer tissue may not be consistent with the original tumor, and maybe just less than 50% cell type tissue. In clinicopathologic characteristics of regimen specific sensitive and resistant group, sensitive to 5-FU or Cisplatin group had different histological distribution with resistant group.(p-value 0.028, Table 5)

Gastric cancer behavior was too aggressive to control by chemotherapy[18]. Since MacDonald et al reported the results of a study of the FAM(5-FU, doxorubicin, mitomycin C) combination regimen for advanced gastric cancer in 1980, several drugs have been associated with a reduction of more than 50% in measurable tumor mass in over 15% of patient. Complete responses with single agents are rare, the median survival associated with multidrug therapy has generally ranged from 6 to 10 month, and the overall survival effect remains debatable. The gastric cancer character, itself was unresponsive or weakly response to the chemotherapy, complete surgical removal of macroscopic and microscopic tumor (R0 resection) is the only curative treatment for gastric cancer. Thus, the conclusion was reflected that gastric cancer behavior, itself is very aggressive, it did not care the chemotherapy drug sensitivity result.

UFT, S-1, the prodrugs of 5-FU are characterized by a pyrimidine ring with a fluorine atom in position5. They are designed to be well absorbed intact from the gastrointestinal tract and subsequently enzymatically converted into 5-FU in the liver or within the tumor itself. S-1, UFT were followed the IV 5-FU tested dose in this study, because the oral S-1, UFT dose of ATP-CRA test was not

confirmed yet in previous studies. In the pharmacokinetics, these three drugs were different in human body. UFT is the mixture of ftorafur(FTO) and uracil(U) in molar proportions of 1:4. FTO made 5-FU liberation slow, U acts as a modulator to reduced degradation on the catabolism of 5-FU in the organism. S-1 is a combination of a prodrug of 5-FU, FTO, and two compounds, 5-chloro-2,4-dihydroxypyridine(CDHP; gimestat) and potassium oxonate (OXO; otastat). CDHP is a potent and reversible inhibitor of dihydropyrimidine (DPD, the first stage enzyme on catabolic pathway of 5-FU), thereby prolonging high 5-FU concentration in the circulation. OXO is employed to limit the gastrointestinal toxicity of FTO.[19]

5-FU is a small molecule with pK_A(8.0) that should predict excellent absorption and bioavailability. However, the use of oral 5-FU prodrugs was abandoned decades ago because of its irregular absorption. Plasma levels of 5-FU prodrugs are quite unpredictable after oral administration with marked intra and inter-individual differences due to the variable activity of DPD. To overcome the gap between *in vivo* and *in vitro* activity, S-1 or UFT specific tested dose was needed.

Our study has several limitations. This study did not consider of interaction effect of 5-FU and Cisplatin due to technical limitation of ATP-CRA. In addition, this study was investigated disregard of individual dose reduction, chemotherapy cycles.

V. CONCLUSION

For selection of effective adjuvant chemotherapy drug of gastric cancer, One of the tool for chemotherapy drug choice, ATP-CRA test was proved feasibility in many previous studies. In ATP-CRA result , one or two regimens sensitive group and resistant group were not any significant difference in disease free survival and overall survivals in 5-FU with Cisplatin based adjuvant chemotherapy due to advanced gastric cancer .

To decide adjuvant chemotherapy regimen along the ATP-CRA test in gastric cancer patients did not provide help to increase disease free survival rate and overall survival rate. In this study, we apply limited drug concentration, because of there are no drug concentration studies of oral chemotherapy regimen. Other prospective studies with various chemotherapy regimens and many enrolled patients should be evaluated for further evaluation.

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ABSTRACT

위암환자에서 ATP 항암제 감수성 검사의 효용성 연구

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박 슬 기

목적: 본 연구의 목적은 진행성 위암환자에서 수술 후 보조적 항암화학치료약제를 결정시 ATP 항암제 감수성 검사를 이용하여 적절한 항암 화학치료약제 결정의 임상적용 및 효용성을 평가하는 것이다.

방법: 2006년 6월부터 2010년 10월까지 연세대학교 세브란스 병원에서 진행성 위암으로 수술하는 환자를 대상으로 ATP 항암제 감수성 검사를 시행하였다. 그 중 수술 후 보조적 항암화학치료를 시행한 환자 중 5-fluorouracil (5-FU)와 Cisplatin 계열의 항암제를 사용한 환자들을 추적 관찰하여 위암의 재발 및 사망여부에 따른 생존율을 조사하였다. 대상 환자들은 TNM 병기 및 항암제 종류, ATP 항암제 감수성 결과에 따라 분류하여 무병생존율, 전체 생존율의 차이를 비교 분석하였다. ATP-항암제 감수성 결과는 암세포 사멸율 50%이상을 감수성군, 50% 미만을 저항성군으로 분류하였다.

결과: 전체 환자를 TNM 병기 및 항암제 종류, ATP 항암제 감수성 결과에 따라 분류하였을 때 임상병리학적 특징의 차이는 없었다. 항암제 종류 및 항암제 감수성에 따른 무병생존율 및 전체생존율의 의미있는 차이는 없었다.

결론: 진행성 위암환자에서 ATP 항암제 감수성 검사에 따라 5-FU와 Cisplatin에 기반한 항암제를 선택하는 것은 재발 및 생존여부에 큰 영향을 끼치지 못한다.

핵심되는 말 : 위암, 아데노신3인산, 항암제 감수성 검사