Clinical and Pharmacokinetic Research of the Lung Cancer Chemotherapy Through Pulmonary Artery Pump

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Abstract **Purpose** To investigate an efficient and low side reaction of the chemotherapy method in post operation lung cancer management. **Methods** A subcutaneous pump was inserted into pulmonary artery trunk from the branch of pulmonary artery belong to resected lobe during lung cancer operation. Chemotherapy drug was given via pump after operation. Clinical trial was carry out with 48 unresected cases, 63 uncompleted resected cases and 31 palliative cases. Recurrency, metastatic and survival rate was also observed in 112 complete reseted cases compared with peripheral vein chemotherapy (PVC) group. HD-DAE regimen was adopted in two groups. In order to study the mechanism of pulmonary artery chemotherapy (PAC), we proceeded clinic and animal test. (1) Clinical pharmacokinetic research: before the operation of lung cancer, DDP (40 mg/m^2) was given through pulmonary artery or peripheral vein, and after operation DDP content was tested in resected mass or lymph nodes. (2) Animal pharmacokinetics: 48 mongrel dogs were divided into two groups, DDP (20 mg/m^2) was given through pulmonary artery and peripheral vein respectively. Dogs were killed in different time after operation, and the drug content was tested in different organs. **Results** With PAC method, 1, 3, 5 years survival rate was 51.4%, 31.4% and 12.9% respectively in explosive group, 74.6%, 41.3% and 28.6% in decrement resection group, 83.9%, 76.7% and 45.2% in palliative group, 87.5%, 72.3% and 49.1% in radical resection group; with PVC method, 1, 3, 5 years survival rate was 36.4%, 9.1% and 0 in explosive resection group, 61.8%, 26.5% and 17.6% in decrement resection group, 77.8%, 51.9% and 33.3% in palliative resection group, 81.3%, 61.2% and 40.6% in radical resection group respectively. There was statistics difference between explosive resection group and decrement resection group in 1, 3, 5 years survival rate. There was statistic difference between palliative group and decrement resection group in 3, 5 year survival rate. 3 year recurrence rate was 12.5% in PAC group and 36.7% in PVC group, There was statistic difference between two groups ($P<0.05$). 1, 3, 5 year blood metastatic rate is 11.6%, 22.3% and 27.7% in PAC group and 15.2%, 36.7% and 45.5% in PVC group ($P<0.05$). DDP content of resected masses in PAC group is 5.7 times (tumor center) and 6.6 times (tumor margin) as large as it is in PVC group for peripheral type lung cancer, and it is 6.3 times (tumor center) and 7.4 times(tumor margin) in PAC group as large as it is in PVC group for central type lung cancer; it is 2.3 times (tumor center) and 6.0 times (tumor margin) in PAC group highter than in PVC group for local lymph nodes. Average drug content of target organ (tumor tissue, bronchus, and local lymph node) is higher in PAC group than in PVC group ($P<0.05$), but drug content is 1.15 times and 1.4 times in PVC group greater than in PAC group for liver and kidney ($P<0.05$). **Conclusion** Because of higher drug content in target organs and lower in liver and kidney for PAC group than PVC group, this trial showed satisfied curative effect and low side reaction of PAC.

Key Words Lung tumor; intervention treatment; pulmonary artery; subcutaneous pump; pharmacokinetics

From March 1993 to March 2001, we inserted a pump selectively into pulmonary artery during lung cancer surgical operation for continuous chemotherapy. Treatment result was observed from patients who received explosive operation, decrement operation and palliative operation. For radical resected patients, we recorded recurrence and metastatic state, pharmacokinetic research was also carry out in order to study mechanism of PAC.

MATERIAL AND METHOD

Clinical treatment

Clinic data: From March 1993 to March 2001, We proceeded 655 cases of lung cancer operation.

Of these operation, 70 cases (10.7%) were explosive operation, 97 cases(14.8%) were decrement resection, 58 cases (8.9%) were palliative resection, 430 cases(65.6%) were radical resection. According to operation situation and opinion of patients, we placed a chemotherapy pump into pulmonary artery for 48 explosive operation cases, 63 decrement resection cases and 31 palliative resection cases, these cases were carried out chemotherapy with a pump, the other cases in every group received PVC. In 430 radical resection cases, Ⅰ, Ⅱ phase lung cancer and pneumonectomy were 94 cases totally, the other 336 cases with Ⅲ, Ⅳ phase were performed partial lobectomy, among them, 112 cases were treated with PAC, the other 224 cases were treated with PVC. Of all 561 Ⅲ, Ⅳ phase radical resected cases, 254 cases were treated by PAC, 307 cases were treated with PVC. Detail clinical data shows in table 1.

The PAC method In lung cancer surgical treatment, we dissected a part of segmental pulmonary artery belong to the resected lobe, ligated external part of the artery with a thread and pull it to strain the vessel, block internal part of the artery with a piece of urine tube, cut a small hole in the wall of the artery and inserted the pump tube to pulmonary artery trunk, ensured the position of the pump tube right, and then fixed and ligated the tube, then performed lobectomy. Put a subcutaneous pump for chemotherapy (Fig.1, 2).

Chemotherapy regimen HD-DAE regimen was adopted in PAC group and PVC group, i.e. DDP: 100 mg/m^2, d1; ADM (or E-ADM): 40mg/m^2, d1; Vp-16: 100mg, d1-5, Ⅳ. every 4~6 weeks in a course. Hydrotherapy and anti-vomit treatment was routinely adopted.

Pharmacokinetic research

Clinic pharmacokinetic research 24 cases lung cancer operated were divided into PAC group and PVC group. 6 cases of central type and peripheral type selected from each group for contrastive research. In PAC group, dissect a part of segmental artery belonging to resected lobe, acupuncture it

Table 1 Ⅲ、Ⅳ phase lung cancer cases chemotherapy state via pulmonary artery (234)and via peripheral vein (307)

opreration mode	cases	sex		age	pathology n(%)			phase n(%)		
		male	female		sqamous	adeno	others	Ⅲa	Ⅲb	Ⅳ
explosive resection	70	49	21	53.2	29(41.4)	28(40.0)	13(18.6)	23(32.9)	3.5(50)	12(17.1)
pump chemotherapy	48	32	16	52.3	17(35.4)	20(41.7)	11(22.9)	16(33.3)	24(50)	8(16.7)
vein chemotherapy	22	17	5	54.1	12(54.5)	8(36.4)	2(9.1)	7(31.8)	11(50)	4(18.2)
decrement resection	97	74	23	53.3	47(48.5)	40(41.2)	10(10.3)	42(43.3)	34(35.1)	21(21.6)
pump chemotherapy	63	51	12	54.4	31(49.2)	26(41.3)	6(9.5)	27(42.9)	21(33.3)	15(23.8)
vein chemotherapy	34	23	11	52.2	16(47)	14(41.2)	4(11.8)	15(44.1)	13(38.2)	6(17.6)
palliative resection	58	47	11	52.3	24(41.4)	23(39.7)	11(19.0)	39(67.2)	19(32.8)	
pump chemotherapy	31	26	6	51.4	12(38.8)	13(41.9)	6(19.4)	21(67.7)	10(32.3)	
vein chemotherapy	27	21	5	53.2	12(46.2)	10(37)	5(18.5)	18(66.7)	9(33.3)	
radical resection	336	247	247	52.8	152 (45.2)	133(39.6)	51(15.2)	249(74.1)	87(25.9)	
pump chemotherapy	112	81	81	54.2	46 (41.1)	52(46.4)	14(12.5)	81(72.3)	31(27.7)	
vein chemotherapy	224	166	58	51.4	106(47.3)	81(36.2)	37(16.5)	168(75)	56 (25)	
tatal	561	417	144	52.9	252(44.9)	224(39.9)	85(15.2)	353(62.9)	175(31.2)	33(5.9)

Table 2 Ⅲ、Ⅳphase lung cancer cases survival rate (%) of PAC group(254)and PVC group(307) after operation

opreration mode	PAC group				PVC group				X examination(P-value)		
	cases	1-year	3-year	5-year	cases	1-year	3-year	5-year	1-year	3-year	5-year
explosive resection	70	51.4	31.4	12.9	22	36.4	9.1	0	0.043	0.037	0.032
decrement resection	63	74.6	41.3	28.6	34	61.8	26.5	17.6	0.038	0.046	0.034
palliative resection	31	83.9	67.7	45.2	27	77.8	51.9	33.3	0.055	0.042	0.047
radical resection	112	87.5	72.3	49.1	227	81.3	61.2	40.6	0.147	0.043	0.048

with a needle 10 cm in length to the trunk of pulmonary artery, then inject DDP 20 mg/m^2 with 20 ml saline at a speed of 1ml/m^2/min. Cancer tissue, lymph node, normal lung tissue, bronchus and 5ml blood sample (anticoagulation)were take out and preserve in refrigerator at −40℃ for examination. In PVC group, the same dosage DDP was infused, preserve the samples with same method as in PAC group.

Animal pharmacokinetic research 48 mongrel dogs were divided into PAC group and PVC group, each group (24 dogs) were subdivided into 4 groups. A dogs were general anesthetized, chest were opened, and DDP 20 mg/kg (1ml/kg/min) were injected from pulmonary artery or peripheral vein. After administrated 0.5, 1, 2, 4 hours, dogs were killed, and lung, trachea, bronchus, local lymph nodes, liver, kidney, esophagus, small intestine, blood and bone marrow (5 ml) were taken out and preserved in refrigerator for examination.

Sample examination Sample was treated with auto−control electric hot digest machine, and tested with atom absorb light photometer (United States Varian Specify AA.880z type). Condition of analysis: light electric current was 10.0 mA, the wave-length was 265.9 nm, narrow sews 0.5 Rnm, carry the current of air speed 200 ml/min, break off air 30 ml/min; dry: 85℃~120℃, 70s; the ash turns: 1000℃, 17s; the atom turns; 2700℃, 4.0s; clearance: 2800℃, 3s; examination limit: 0.01μg/ml; precision (RSD): <8%; recovery rate: 90%-95%; related coefficient curve in standard: 0.9938.

Statistics analysis

Exist rate calculation were managed with the life span form method, X^2 examination were adopted to analyse the difference with SPSS10.0 software.

RESULTS

Clinical treatment results

HD-DAE regimen were adopted in all the cases. For explosive resection cases: every cases were treated 3.2 periods (224 periods/70 examples) averagely in PAC group, 3.6 periods (79 periods/22 examples) in PVC group; for decrement resection cases, every cases were treated 3.4 periods (214 periods/63 examples) in PAC group, 3.8 periods(129 periods/34 examples) in PVC group, for palliative resection cases: every cases were treated 4.3 periods (134 periods/31 examples) in PAC group, 4.1 periods(111 periods/27 examples) in PVC group, for radical resection cases: every cases were treated 3.8 periods (425 periods/112 examples) in PAC group, 4.1 periods (918 periods/224 examples) in PVC group. This trial was closed before March 2001, observing period is over 3 years. survival rates of each group shows in table 2.

The symptoms of cancer lump or pleural effusion which appears in the side of surplus lobe, pulmonary hilum, or mediastinal was considered local recurrence, otherwise called blood metastases. In radical resection cases, the local recurrence rate after three years was 12.5% (14/112) in the PAC group and 36.7% (82/224) in PVC group (p<0.05) respectively. 1, 3, 5 years blood metastatic rate was 11.6% (13/112), 22.3% (25/112) and 27.7% (31/112) in PAC group respectively, and it was 15.2% (34/224), 36.7% (82/224) and 45.5% (102/224) in PVC group respectively. The difference of 3 years and 5 years blood metastatic rate between the two groups is significant in statistics (p< 0.05).

Pharmacokinetic examination results

The results of clinical pharmacokinetic examination showed in Fig.3. With different administration method of DDP according to body surface, medicine content was higher in PAC group than that in PVC group. DDP content of tumor tissues in central or peripheral type lung cancers in PAC group is 5.7 times~6.6 times (cancer mass), 3.8 times~11.9 times (bronchus and lung tissue) and 2.3 times~6.0 times (mediastenal, pulmonary hilum and interlobal lymph node) than in PVC group. Drug content in target tissue (lump, bronchus, lung tissue, lymph node) is higher in PAC group than that in PVC group (p<0.01), (t-test, peripheral lung cancer p=0.003, central lung cancer p=0.004). Blood plasma drug content is 2.2~2.6 times in PVC group than that in PAC group.

The result of animal pharmakokinetic showed in Fig.4, Fig.5. DDP was infused into pulmonary artery in PAC group, drug content of the target organ (lump, bronchus, lung tissue, lymph node) is higher in PAC group than that in PVC group, especially in 60 min and 240 min after administration (p<0.05), (t-test, 60 min p=0.0049, 240 min p= 0.0036). For target tissue, the average drug content difference in any time between two group are 1.36 times (tracheal), 4.20 times (bronchus of opposite

side), 10.27 times (resected side), 1.97 times (lobal bronchus, opposite side), 8.19 times (resected side), 1.43 times (lung tissue opposite side), 1.46 times (resected side), 1.32 times (in mediastinal lymph node opposite side), 2.45 times (resected side), 2.18 times (lung hilum lymph node opposite side), 2.6 times (resected side). For non-target tissue (esophagus, stomach, small intestines, liver, kidney, heart, marrow, blood plasma), there was no difference for drug content measurement ($p>0.05$) (t-test, 30min $p=0.433$, 60 min $p=0.878$, 120min, $p=0.399$; 240 min $p=0.398$), but drug average content of liver, kidney in PVC group is 1.15 times and 1.40 times higher than that in PAC group ($p<0.05$).

DISCUSSION

In current surgical treatment of lung cancer, unresected cases is 10%~19.7%[1], remained lump or lymph node seen by naked eye is 13.5%~33%[2,3], bronchus slices positive rate is 28.5%[4]. It is obviously that these cases need to further anti-cancer treatment. Even though in 1/3 radical resected cas-

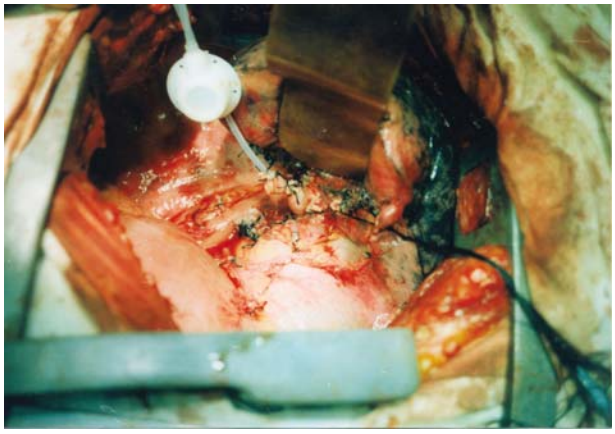

Fig.1 Chemotherapy pump was inserted via dorsal segmental pulmonary artery.

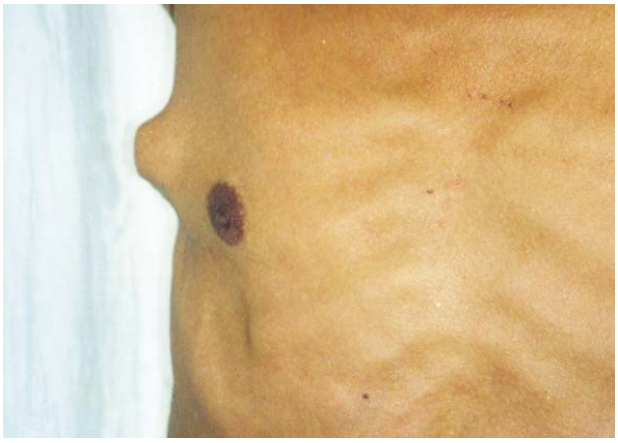

Fig.2 View of a patient who accepted a chemotherapy pump in the anterolateral chest wall.

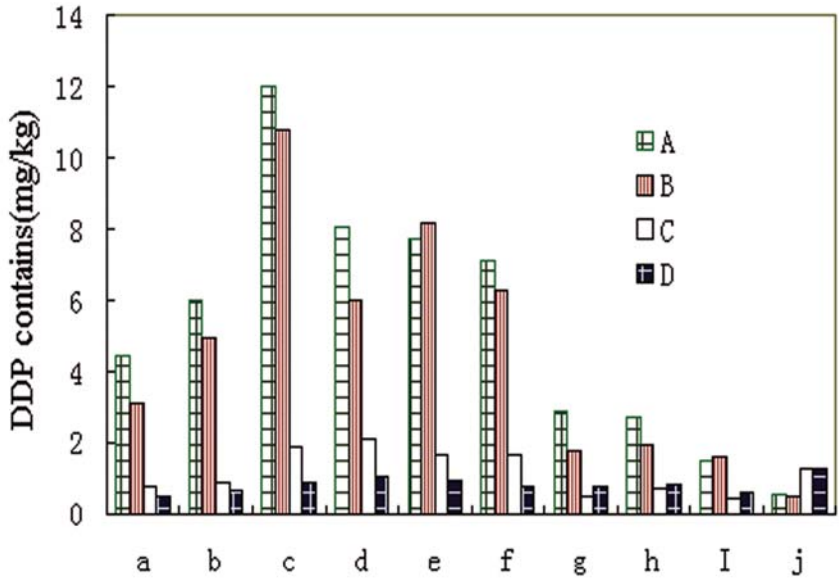

Fig. 3: DDP content of resected side sample administrated via different injection method.
A: pulmonary artery, peripheral type, B: pulmonary artery, center type,
C: peripheral vein, peripheral type, D: peripheral vein, center type.
a: center part of tumor, b: peripheral part of tumor, c: normal lung tissue, d: segment bronchus, e: lobal bronchus, f: main bronchus, g: interlobal lymph node, h: hilum lymph node, I: mediastinal lymph node, j: blood plasma.

es, micro focus remained in surplus lobe[5], it is difficult to prevent from tiny remains transfer focus to mediastinal lymphoid tube net[6,7], and there was already latent distant metastases focus[8], so that local recurrence rate (36.1%~46.7%) and metastases rate (41.7%~46.7%) is higher after resection[9]. Therefore an effective anti-cancer treatment necessary for postoperation pulmonary cancer cases to prolong exist period of patients. Clinical practice proved that chemotherapy can increase exist rate after operation[10]. Selective vascular chemotherapy is a good method because of effective and higher concentration of drug and light side-reaction in target region [11]. In the past bronchus artery chemotherapy was frequently adopted since bronchus artery provide blood supply for lung cancer. In recent research with sulfuric barium or silicones [12,14], pulmonary artery was found to participate in lung cancer blood supply, no mater how inner part or outer part in central type lung cancer or peripheral type lung cancer, pulmonary artery provides the blood supply to them. Because of wider diameter, thin wall of

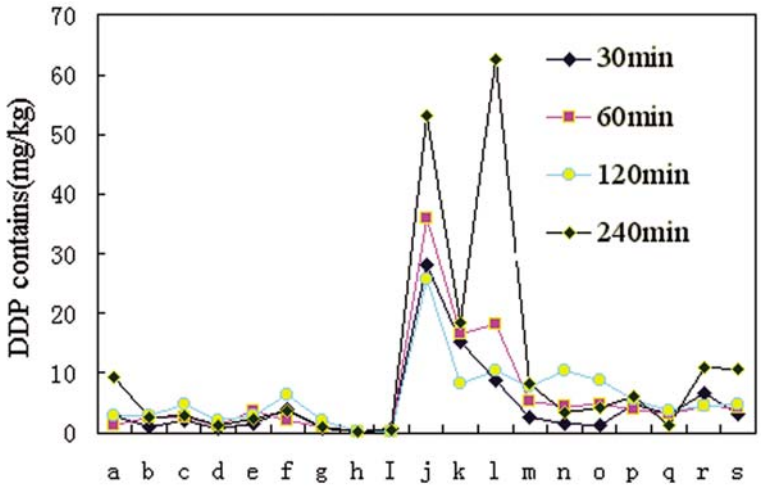

Fig.4: DDP content of dog´s tissure changes with time which administrated via pulmonary artery (mg/kg).
a: tracheal, b: esophagus c: liver, d: mall intestine, e: stomach, f: kidney, g: heart, h: bone marrow I: blood plasma, j: main bronchus, resected side, k: main bronchus, opposite siede, l: lobal bronchus, resected side, m: lobal bronchus, opposite siede, n: lung tissue, resected side, o: lung tissue, opposite siede, p: mediastinal lymph node, resected side q: mediastinal lymph node, opposite siede r: hilum lymph node, resected side, s: hilum lymph node, opposite siede.

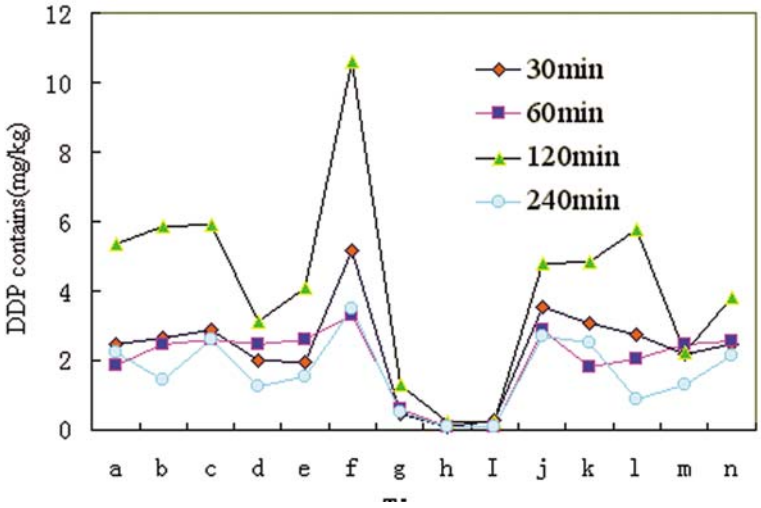

Fig.5: DDP content of dog´s tissue change with time which administrated via peripheral vein (mg/kg)
a:tracheal, b:esophagus, c:liver, d:small intestine, e:stomach, f:kidney, g:heart, h:bone marrow, I:blood plasma, j:main bronchus, k:lobal bronchus, l:lung tissue,m:mediastinal lymph node,n:hilum lymph node.

lung artery, low velocity of blood flow, more time was obtained for drug to kill cancer cell. It was found that pulmonary artery provide blood supply to metastases lymph node of pulmonary hilum and mediastinum especially when vessels was invaded, vascular fistula formed between bronchus artery and pulmonary vein, the pulmonary artery may support blood supply to more area. Clinical experience [15,16] proved that if selective PAC or selective bronchus artery chemotherapy effect is not satisfied, further pulmonary artery perfusion chemotherapy (double blood vascular perfusion chemotherapy)[17,18] treatment can improve chemotherapy effect.

This study revealed that in center type lung cancer or peripheral type lung cancer, drug content of inner or outer part of cancer mass in PAC group 5.7 times as large as it is in PVC group and it is 2.3 times~6.0 times in PAC group higher than it in PVC group for mediastinal, pulmonary hilum, interlobal lymph nodes. When drug concentration increases 1 times, its killing effect can increase 10~20 times[19], this research showed the same results with Shimizu[20] which proved that local lump drug content is 2~6 times in bronchus artery highter than it in PVC, and also proof that both pulmonary artery and broncheal artery provide lung cancer blood supply. This trial first time disclosed mechanism of PAC, replenished and verified the results of lung cancer pathologic anatomy and blood supply system.

The result of animal pharmacokinetic examination revealed that liver and kidney content in PVC group is 1.15~1.40 times as large as it is in PAC group, this is the reason that pulmonary artery perfusion chemotherapy treatment is effective but light side-reaction. Because of high concentration in tumor and local lymph node, this method is more effective for decrement resected cases and unresected cases in PAC group than it in PVC group. There was obvious statistic difference between two groups in 1, 3, 5 years exist rate ($p<0.05$). For palliative resection cases, there was obvious statistic difference between two groups in 3, 5 years exist rate ($p<0.05$). But 1 year exist rate has no difference ($p>0.05$), this is because of remaining cancer cell under microscope had light effect on life in short term. In lung cancer radical resection group, 3, 5 year exist rate had obvious difference between two group ($p<0.05$), this is because of better effect of PAC on local recurrence and metastases in 3, 5 years after resection than PVC, there was obvious difference between two groups ($p<0.05$).

Clinical research proved that lung cancer metastases to lymph node was more frequently found in the same side than opposite side. Lung cancer metastases path is regularly from focus to mediastinal, from interlobal lymph region to mediastinal lymph node [21,22]. Although lobectomy and lymph node resection was performed, metastatic path of lymph net from interlobal lymph region to mediastinal lymph node in surplus lobe is unchangble[6]. In this research, a chemotherapy pump was inserted from resected pulmonary artery to the root of pulmonary artery, chemotherapy medicine was given via the pump, therefore, drug concentration is higher in surplus lobe of lung and lymph node region, this is effective to control second clinical cancer focus in surplus lobe and cancer cell remaining in lymph vessels, nodes or other tissue. If these remaining tiny focus is not controlled, it will increase continuously and become the second spread source, which is the reason that blood metastases frequently occurs after resected 3 years later [23]. Because of this method is effective to second clinical and miro metastases focus in resected side, metastases rate was decreased after operation. Clinical research discovers that 20%~40% lung cancer cases have distance metastases [24], this is the reason why blood metastases occur in earlier period for radical resected cases. According to the entity lump growth obey the mode of Gomppertzian[25] i.e.with the tumor volume increased, double increasing time will prolonged, conversely with volume contracts but shorten. Because of quick growth of the transfer focus after operation, it is seriously affected on the patient´s prognosis. Because of PAC have no advantage on distance metastases than PVC, 1-year metastases rate have no significant differences betweem the two groups ($p>0.05$).

This research showed that PAC almost have the same effect as PVC on metastases beyond local chest before operation. In PAC, right heart catheter can be inserted from subclavian vein or femoral vein, the catheter can be taken out immediately after chemotherapy, or detain for 10 days or more, but long time remaining can cause infection. The second method is connect a subcutaneous pump base on the right heart catheter. But for the two method, catheter must pass through right atrium, right ventricle, tricuspid valve and pulmonary artery valve, long term stimulation can cause or woresen heart disease. The third method is to cut an inci-

sion at left second intercostal space near sternum, cut off left internal thoracic artery, open the pericardium, dissociate the root of pulmonary artery, with the direction of acupuncture, the catheter is inserted to target lung artery, pump is placed under skin for long term chemotherapy. This method avoided the stimulation of catheter to heart. On the other hand, for late term lung cancer cases, it is not very easy to open chest and insert the catheter, so its indication is restricted. In our test, we inserted the pump to lung artery during operation, do not need special equipment, the catheter do not pass through heart, so it is safe and reliable, and has few complication, can be used for a long period. In our research pump was used for 0.5-8.5 years in 254 PAC cases, averagely 6.4 years, 67 pump was take out under local anesthesia, no complication was found for these patients.

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