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Research Article
Diagnosis and Treatment of Non-Small Cell Lung Cancer: Adenosine Triphosphate Tumor Chemosensitivity Assay

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Abstract

Background and Objective: In recent years, domestic and foreign scholars have carried out a large number of clinical trials with adenosine triphosphate tumour chemosensitivity assay *in vitro* (ATP-TCA). This study explores the guiding significance of ATP-TCA in the treatment of Non-Small Cell Lung Cancer (NSCLC) patients with pleural effusion in our hospital. **Materials and Methods:** In the experiment group, the cancer cells in patients with pleural effusion were tested for ATP-TCA and the sensitivity of the drug results would be sent to the clinicians who would adjust the medication based on the results. In the control group, the clinician used traditional treatment, without intervention. After the treatment and discharge, the patients were followed up once a month to observe the difference in survival rate and quality of life between the 2 groups. At last, we perform statistical analysis on laboratory data and patient clinical data. **Results:** The sensitivity of the cancer cells in the pleural effusion was significantly different and the use rates of the drugs had significant differences. Meanwhile, the above 2 sets of data did not show a good correlation. Besides, the survival rate of patients in the experimental group was significantly higher than that of patients in the control group but there was no significant difference in the quality of life between the 2 groups after treatment. **Conclusion:** The choice of anti-tumour drugs by clinicians was relatively random. ATP-TCA had clinical guiding significance for the choice of anti-tumour drugs for NSCLC patients combined with pleural effusion.

Key words: ATP-TCA, NSCLC, pleural effusion, guiding significance, therapy

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Chemotherapy is a treatment that uses chemical drugs to prevent cancer cells from proliferation, infiltration, metastasis and ultimately kill cancer cells. It is a systemic treatment. Due to the individual differences in the tumour itself, the selectivity of chemotherapy drugs is not strong. Even in tumours of the same histological type and the same degree of differentiation, the sensitivity of that to the drugs are significantly different[1], the efficacy of tumour chemotherapy is not uniform. That is a major challenge that oncologists have been dealing with. Some scholars have proposed that detecting the sensitivity of the patient's tumour cells to drugs before chemotherapy can screen relatively effective chemotherapy drugs for patients and improve clinical treatment effects. Therefore, tumour drug sensitivity detection technology has become the main research object of scientists.

ATP-TCA attracts the attention of scientists. It is an advanced drug susceptibility detection technology for tumours *in vitro*. The endogenous ATP content of cells is used as an indicator of cell activity and the effects of drugs on tumour cells in each cycle can be reflected. This technique is sensitive and reliable, with an evaluable rate of more than 90% on specimens and is suitable for tumour drug susceptibility testing[2]. A recent report from the *in vitro* cytotoxicity assessment center also showed that endogenous ATP analysis in cells is the most predictive test method for detecting cytotoxicity.

At present, ATP-TCA has been widely used in the treatment of ovarian cancer, breast cancer[3,4], gastrointestinal tumours[5] and leukaemia[6]. It has also been reported in the United States for the treatment of NSCLC[7], in China, most studies use it for *in vitro* research on non-small cell lung cancer. Hospitals have also carried out this research and conduct *in vivo* research on non-small cell lung cancer. Now, this study researched its use in NSCLC patients in our hospital for reference by colleagues.

MATERIALS AND METHODS

Clinical data: The study is divided into 2 groups: Experimental group and control group. The specimens of the experimental group were recruited from June, 2017 to May, 2019 in NSCLC patients with pleural effusion and physical performance status (ECOG) scores of 0-2, who can accept chemotherapy. All patients were confirmed by pathological and imaging examinations that it is primary NSCLC with pleural effusion. The data of the control group were the clinical data of patients with NSCLC and pleural effusion who were admitted to our hospital during the same period (without ATP-TCA). This study was the 3 new projects approved by the hospital in 2015. The research plan was reviewed and approved by the Medical Ethics Committee of Yijishan Hospital of Wannan Medical College.

Reagents and instruments: ATP-TCA kit (Huzhou Haichuang Biotechnology Co., Ltd.), HBC-1000-A/B3 biological safety cabinet (Sujing Group Antai Company), HH-CP-7W carbon dioxide incubator (Shanghai Lishen Scientific Instruments) Co., Ltd.), BHP9504 microplate luminescence analyzer (German BERTHOLD company), ECLIPSE TS100/100-F Nikon inverted biological microscope (Shanghai Hengjie Instrument Co., Ltd.), BCD-254 refrigerator (Hefei Meiling Co., Ltd.), TGL-16G high-speed centrifuge (Shanghai Lu Xiangyi) used in this study.

Methods

Tumour susceptibility test of experimental group: Collect the sterile pleural effusion (including cancer cells) from patients with advanced NSCLC through closed thoracic drainage. According to the ATP-TCA procedure, the cancer cells in the specimens were subjected to the drug sensitivity test and the drug used in the test were 8 anti-tumour drugs commonly used in NSCLC chemotherapy. The 8 drugs were Cisplatin (DDP), Carboplatin (CBP), Nedaplatin (NDP), Docetaxel (TXT), Paclitaxel (PTX), Gemcitabine (GEM), vinorelbine (Navelbine, NVB), etoposide (Etoposide, VP-16). Follow the instructions of the ATP-TCA Kit (Huzhou Haichuang Biotechnology Co., Ltd.). The specific experimental procedures were as follows:

- Took a sample of pleural effusion, centrifuge at 2000 rpm for 5 min, remove the supernatant and collect the remaining cells
- Counting and culturing the cells
- Operating following the standard operating procedures of drug dilution and sample addition in the Haichuang Bio-ATP-TCA operating standards. Drug concentration setting: The final concentration is the Plasma Peak Concentration (PPC) value corresponding to a certain clinical drug dose. Each drug was set to 200, 100, 50, 25 and 12.5% PPC, 5 concentration gradients in total and then calculated each tumour growth inhibition rate for each concentration of each drug, drew the drug concentration-inhibition rate curve and calculated the IC_{90} and IC_{50} of each drug (IC_{90} = the drug concentration when the inhibition rate was 90%, IC_{50} = the drug concentration when the inhibition rate was 50%)

- ATP-TCA result judgment based on Index. The index calculation method was: Index = 500 the sum of 5 TGI (tumour growth inhibition rate) caused by 5 TDC (test drug concentration), these 5 concentrations were 200, 100, 50, 25 and 12.5% of drug PPC

At last, the test results of the experimental group were sent to the clinician who would adjust the patient's medication after referring to the results.

Control group data collection: NSCLC patients combined with pleural effusion who was admitted to hospital during the same period (ATP-TCA) outside the experimental group served as the control group. The clinical data of the patients were consulted, the clinical selection and use of anti-tumour drugs were retrospectively analyzed and their medication was analyzed.

Data analysis: The sensitivity of the cancer cells in pleural effusion to anti-tumour drugs was compared with the usage rate of the same drugs in the control group. Observe whether there was a correlation between the above 2 groups of data to preliminary predict the guiding significance of the ATP-TCA on the clinical treatment of NSCLC patients. After the patients were discharged from the hospital, regular follow-up surveys were carried out to analyze the survival rate and quality of life of the 2 groups of patients to confirm finally determine the guiding significance of the ATP-TCA on the clinical treatment of NSCLC patients.

Follow-up survey: Followed up the discharged patients every month after they were discharged from the hospital. The follow-up time was 1-27 months. Patients in both groups were followed up by telephone. A Follow-up survey mainly understood the similarities and differences in the survival status and quality of life of the 2 groups of patients.

Statistical methods: Graph pad statistical software was used to compare and analyze the count data. The statistical analysis of demographic characteristics used the χ^2 test, the correlation analysis was used for the anti-tumour drug sensitivity in the experimental group and the anti-tumour drug usage rate in the control group and also the χ^2 test was used to analyze the survival rate of patients. All inspection levels are $\alpha = 0.05$. If $p \geq 0.05$, the difference is not statistically significant and $p<0.05$ indicates that the difference is statistically significant.

RESULTS

Demographic characteristics in the 2 groups: The patients were divided into 2 groups, the experimental group and the control group. A total of 36 patients were recruited in the experimental group and 79 patients in the control group were patients outside the experiment group with primary NSCLC with pleural effusion. The 2 group's patients were in the same period. The demographic characteristics of the patients in the 2 groups were statistically analyzed. It was found that the 2 groups of patients were mostly elderly people over 60 years old, of which 28 were in the experimental group and 63 were in the control group and most of them were male patients. There were 25 male patients in the experimental group and 52 male patients in the control group. In addition, most of them were adenocarcinoma patients. There were 29 adenocarcinoma patients in the experimental group and 61 adenocarcinoma patients in the control group. As a result, the age composition of each group, the proportion of males and females and the proportion of cancer types showed no significant difference. It showed that there was no significant difference in the basic data of the 2 groups of patients, which layed the foundation of the accuracy and objectivity for the follow-up research. The specific data was shown in Table 1.

Analysis of tumour drug sensitivity results in the experimental group: The results in Table 2 show the sensitivity of cancer cells in the pleural effusion in the experimental group to 8 anti-tumour drugs. The sensitivity to GEM is up to 80.56%, followed by PTX and CBP, with a sensitivity of 63.89%. The sensitivity rate of cancer cells to VP-16 and TXT was 52.78% and the lowest sensitivity rate to NVB was 50%. That is, the sensitivity of cancer cells in the pleural effusion to 8 anti-tumour drugs is significantly different.

Selection and use of anti-tumour drugs in the control group: Statistically analyzed the use of anti-tumour drugs in NSCLC patients combined with pleural effusion in the control group. It was found that the highest usage rate was NDP, with a utilization rate of 31.65% and the lowest usage rate was CBP and NVB 0.00%. The usage rate of other drugs was between that of the above 2 drugs. There were significant differences in the utilization rate of the 8 drugs. The specific results were shown in Table 3.

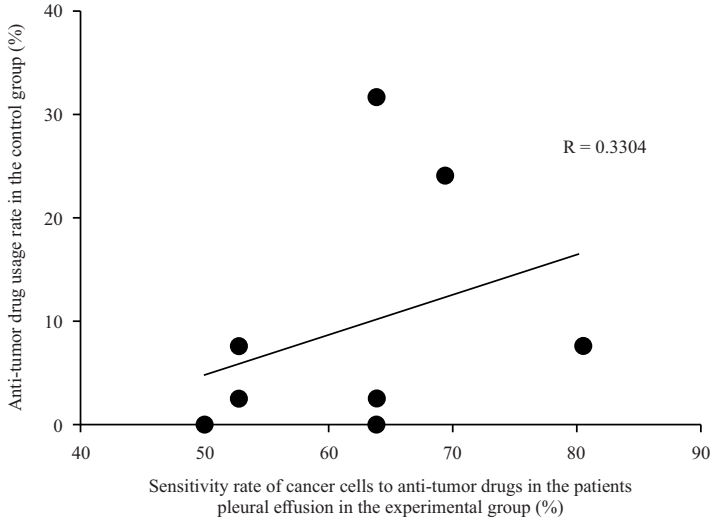

Fig. 1: Correlation analysis between the sensitivity rate of cancer cells to anti-tumour drugs

Each point in the figure represents a drug. These drugs are from left to right (from bottom to top if the abscissa is in the same position): NVB, VP-16, TXT, CBP, PTX, NDP, DDP and GEM

Table 1: Demographic characteristics of patients

		Age (year)		Sex		Types	
Groups	Cases	<60	>60	Males	Female	Scc	Ade
Experiment	36	8	28	25	11	7	29
Control	79	16	63	52	27	18	61
χ^2		0.05806		0.1466		0.1622	
p-value		0.8096		0.7018		0.6871	

SCC: Squamous cell carcinoma, ADE: Adenocarcinoma, analyzed the differences in the clinic data between the experimental group and the control group from the perspectives of age composition, gender ratio and pathological type ratio

Table 2: Drug sensitivity of anti-tumour drugs in the experimental group

Drugs	Cases	Highly sensitive cases	Moderately sensitive cases	Sensitivity (%)
CBP	36	15	8	63.89
DDP	36	16	9	69.44
NDP	36	16	7	63.89
GEM	36	16	13	80.56
TXT	36	13	6	52.78
NVB	36	13	5	50.00
PTX	36	15	8	63.89
VP-16	36	12	7	52.78

Counted the sensitivity of eight anti-tumour drugs commonly used in hospital

Correlation analysis: Analyzed the correlation between the sensitivity of the 8 drugs in the experimental group and the use rate of the 8 drugs in the control group. As shown in Fig. 1, the X-axis represented the sensitivity rate of the anti-tumour drugs in the experimental group and the Y-axis represented the use rate of anti-tumour drugs in the control group. The 8 points on the Figure represent 8 different anti-tumour drugs, from left to right were NVB, VP-16, TXT, CBP, PTX, NDP, DDP and GEM. There was no correlation between the 2 group's data, indicating that the clinical medication was relatively random. The reason may be that every doctor had their medication habits, so the choice of drugs by clinicians was relatively random. Thus, we got preliminary inference that ATP-TCA had clinical guiding significance for chemotherapy in patients with NSCLC and pleural effusion.

Analysis of survival rate and quality of life: Scored the survival curve and quality of life according to the follow-up results of the 2 group's patients. As shown in Fig. 2, the X-axis

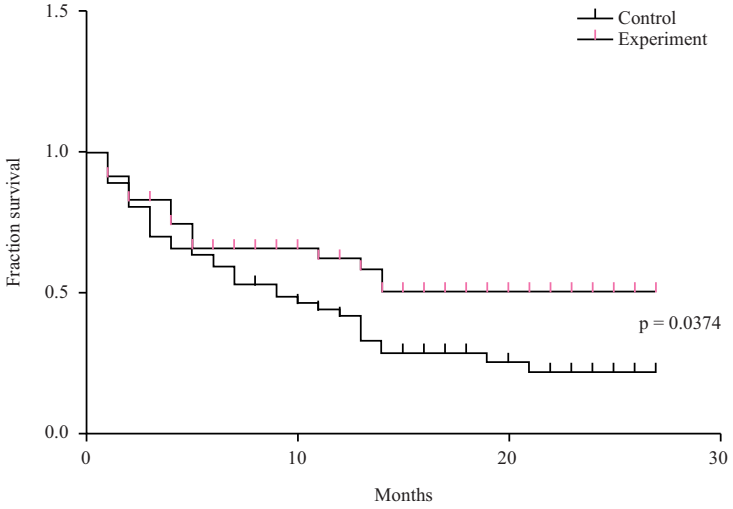

Fig. 2: Survival curve analysis of patients in experimental group and control group after follow-up
Statistical significance was defined as p<0.05

Table 3: Usage of anti-tumour drugs in the control group

Drugs	Cases	Usage rate (%)
CBP	0	0.00
DDP	19	24.05
NDP	25	31.65
GEM	6	7.59
TXT	6	7.59
NVB	0	0.00
PTX	2	2.53
VP-16	2	2.53

Counted the usage rates of 8 anti-tumour drugs commonly used in hospital

Table 4: Evaluation and analysis of the quality of life of the experimental and control group

Life quality dimension	Experiment groups	Control groups	t	p-value
Body dimension	1.4±0.49	1.18±0.34	1.156	0.2636
Role dimension	1.33±0.71	1.3±0.48	0.1211	0.905
Emotional dimension	0.11±0.18	1.2±0.33	0.5843	0.5667
Cognitive dimension	1.17±0.5	1.1±0.33	0.3513	0.7297
Social function	1.39±0.51	1.3±0.48	0.3765	0.7112
General health	5.22±0.75	5.85±1.05	1.475	0.1584
Fatigue score	1.41±0.64	1.267±0.38	0.5562	0.5854
Nausea and vomiting score	1±0	1.2±0.42	1.419	0.174
Pain score	1.33±0.56	1.4±0.57	0.2574	0.7999
Shortness of breath score	1.33±0.71	1.2±0.42	0.5056	0.6196
Insomnia score	1.33±0.5	1.3±0.67	0.1211	0.905
Loss of appetite score	1.44±0.53	1.3±0.48	0.6235	0.5413
Constipation score	1.11±0.33	1.3±0.48	0.9804	0.3406
Diarrhea score	1±0	1.2±0.42	1.411	0.1763
Financial hardship score	2.22±0.83	1.8±0.92	1.045	0.3108

Scored it from 15 aspects, there is no significant difference in each set of data

represented patient's follow-up time after their discharge, the Y-axis represented the patient's survival rate. In the experimental group, 27 patients died and 9 patients survived. While 69 patients died and 10 patients survived in the control group. The results showed that the survival rate of the experimental group was significantly higher than that of the control group. It was proved that ATP-TCA had clinical guiding significance for the treatment on the NSCLC patients combined with pleural effusion as it enables clinicians to choose anti-cancer drugs more precisely. However, there were no significant differences in the scores of quality of life in the 2 group's patients as shown in Table 4. Therefore, concluded

that ATP-TCA had guiding significance for the clinical treatment of patients with NSCLC combined with pleural effusion but it had little effect on the quality of life of patients after treatment.

DISCUSSION

At present, the traditional method for the treatment of malignant tumours is chemotherapy. However, different types of tumours or different patients of the same tumour type or even different cancer disease stages of the same patient, have significantly different treatment characteristics and therapeutic effects[8,9]. Therefore, it is necessary to establish a relatively reliable anti-tumour chemotherapeutic drug sensitivity test to select chemotherapeutic drugs accurately to achieve individualized clinical treatment. In addition, from the perspective of the dose-effect relationship of drug effects, clinicians need to adjust the dose of chemotherapy based on the results of the drug sensitivity test to achieve individualization of the chemotherapy dose.

The principle of ATP-TCA technology is that under aerobic conditions, luciferase can combine with luciferin to catalyze the conversion of ATP into AMP and release fluorescence (wavelength at 562 nm). ATP-TCA uses luciferase-luciferin catalytic reaction to measure intracellular ATP content to reflect the number of living cells. It can also be used to compare the different inhibition rates of drugs with series concentrations on cultured cells and refer to the corresponding judgment indicators, to evaluate the killing effect of the chemotherapy drug on tumour cells. At present, this technology has been used in the domestic anti-tumour drug susceptibility testing of ovarian cancer, haematological tumours[6] and cervical cancer[10].

It can be seen from Table 1 that the majority of patients were over 60 years old, most of which were adenocarcinoma and the proportion of male patients was significantly higher than that of female patients. This was consistent with the previous scientific research conclusions[11]. It can be seen from Table 2 that the sensitivity rate of cancer cells in the pleural effusion in the experimental group to GEM was as high as 80.56%, while the sensitivity rate to VP-16 and TXT was 52.78%. It showed that the sensitivity of tumour cells in the pleural effusion in patients to different drugs was significantly different. This provided a theoretical basis for the individualized treatment of NSCLC in our hospital.

Currently, ATP-TCA technology has been used to predict the susceptibility of various cancers to anti-tumour drugs. However, the treatment programs examined by researchers[12] included combination medications, which was more convincing than study individual medications, because most of the treatment regimens for patients were combination medications. At the same time, studied the sensitivity of Squamous cell carcinoma and adenocarcinoma to drugs, which was what we lack. The most sensitive rate of their research results was PTX (51.7%) while the highest sensitivity rate in current research results was GEM (80.56%). The inconsistency may be related to the doctor's medication habits. However, currently studied the direct correlation between the use rate of drugs and the sensitivity of cancer cells to drugs and did follow-up work that the data was more complete. Also, studies had found that the activity of anti-tumour drugs was related to the expression of drug pumps, DNA repair enzymes and other genes. So ATP-TCA and genetic testing could be combined to predict the sensitivity and resistance of tumour cells to drugs, to guide individualized chemotherapy for lung cancer. This was an innovation compared to current research[7]. ATP-TCA was also used for individualized medication guidance for other cancers. In addition, other studies found that ATP-TCA guided ovarian cancer treatment had triple the response rate and double the survival time compared with empirical chemotherapy regimes. The median overall survival was extended by 3.8 months. It had the same clinical effect as current research results[13]. This study expanded the scope of ATP-TCA for cancer sensitivity prediction[3]. However, some studies had found that the progression-free survival of ovarian cancer patients treated with ATP-TCA was not significantly different from that of the control group[14]. Zhi-qiang Ling *et al.*[15] used ATP-TCA technology as a guideline for the diagnosis and treatment of esophageal cancer. They examined the sensitivity of each regimen in multiple samples and were able to obtain the sensitivity of each regimen but it could not be correlated with the clinical effect which was not meaningful. There were also studies on the use of ATP-TCA for the guided treatment of cervical cancer. The treatment programs investigated were all combination medications. The results found that the survival rate of the experimental group was significantly higher than that of the control group, proving that it was also suitable for the treatment of cervical cancer patients[11]. There were also studies using ATP-TCA to guide the treatment of acute myeloid leukaemia and it was found that 66.2% of patients guided by cytarabine sensitivity achieved complete remission and multiple logistic regression analysis revealed that the sensitivity of cytarabine was one of the significant risk factors for complete relief. It was suggested that ATP-TCA detection technology could become a useful tool for optimizing the treatment of acute myeloid leukaemia. Compared with current results, this study had done multiple logistic regression

analysis, which was more sufficient than current evidence[6]. Besides, breast cancer was found more sensitive to paclitaxel and its combination regimen and the treatment effect of adriamycin+paclitaxel was better. However, this study did not study the survival rate and the evidence was insufficient[4]. There were also studies using ATP-TCA for rectal cancer. However, its research was limited to the evaluation of the sensitivity of cancer cells to anti-tumour drugs *in vitro* and had not been applied to the clinic. Compared with our research, its content was too simple[2]. At present, the research of ATP-TCA used to guide the use of anti-tumour drugs has not achieved significant clinical effects and most of them stay in the study of *in vitro* sensitivity rate and current research has achieved clinical effects and has certain clinical value.

At present, the commonly used 1st-line chemotherapy for NSCLC was CE (CBP+VP-16), NP (NVB+DDP), PC (PTX+CBP), DP (TXT+DDP), DN (TXT+NVB), PP (ALI+DDP), GP (GEM+DDP) and GN (GEM+NVB). Studies have shown that platinum drugs induce tumour cell death through DNA damage, thus exerting anti-tumour effects[16,17]. In China, platinum-based combined with other chemotherapy drugs is the main chemotherapy regimen for the treatment of advanced NSCLC. The data in Table 3 suggested that the use rata of anti-tumour drugs in our hospital was highest in NDP, followed by DDP, which was consistent with the above theory. CBP and NVB were almost not used. This did not show any correlation with the sensitivity rate results in Table 2. It was suggested that there is no correlation between the clinical use rata of anti-tumour drugs and the sensitivity of anti-tumour drug sensitivity, indicating that the clinical use of drugs was relatively random as shown in Fig. 1. Figure 2, found that the survival rate of patients in the experimental group was significantly higher than that of the control group, that is, ATP-TCA detection technology had guiding significance for the selection and use of clinical anti-tumour drugs. The current study showed that there was no significant difference in the quality of life in the 2 groups of patients after treatment, that is, the quality life of patients with NSCLC was not closely related to the treatment plan and maybe related to clinical nursing work[18], education level[19] and social support[20]. Currently, the World Health Organization has issued guidelines for the clinical application of anti-tumour drugs to provide a reference for clinicians to choose drugs to treat diseases. However, due to specific clinical conditions, most doctors have their medication habits and make the use of clinical drugs not reasonable enough. The results of ATP-TCA can provide very strong reference evidence for the clinic and bring challenges to traditional chemotherapy concepts. Based on the drug susceptibility results, ATP-TCA is of great significance for the individualized medication of NCSLC.

CONCLUSION

The sensitivity rate of tumour cells in the experimental group to anti-tumour drugs and the use rate of anti-tumour drugs in the control group failed to show a good correlation, which showed that doctors were relatively random in medication. It was preliminarily proved that ATP-TCA had clinical guiding significance for the choice of anti-tumour drugs in chemotherapy regimens for NSCLC patients combined with pleural effusion. In addition, the survival rate of patients in the experimental group was significantly higher than that in the control group, confirming that ATP-TCA technology could guide individualized treatment of NSCLC patients combined with pleural effusion.

SIGNIFICANCE STATEMENT

This study discovered the ATP-TCA had clinical guiding significance for the choice of anti-tumour drugs for NSCLC patients combined with pleural effusion. That can be beneficial for doctors. This study will help the researchers to uncover the critical areas of individualized guidance that many researchers were not able to explore. Thus a new theory on the treatment of NSCLC patients combined with pleural effusion guided by ATP-TCA improves the survival rate of patients may be arrived at.

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