Acute Tumor Inflammation with CD4/8+ and CD11+ Enhanced Long Survival Time in Advanced Stages of all Solid tumors by Ultra Minimum Incision Personalized Intratumoral Chemoimmunotehrapy

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1. Abstract

1.1. Aim: The objective of study reported here was to evaluate the clinical efficacy, side effects and long survival time in the advanced stages of all solid tumors after the treatment of UMIPIC.

1.2. Methods: 581 patients with solid tumors in late stages were collected for retrospect analysis of their clinical efficacy, adverse reactions, survival time and survival rate of patients after treated with UMIPIC.

1.3. Results: It was found that the main adverse reactions were a mine fever, tolerable pain after treatment, followed by hemoglobin reduction and leucopenia come from previous post chemotherapy, there was not found any adverse reactions such as rash, neurotoxicity and hair loss; The clinical benefit rate of 316 patients was 95.89%; the average survival time was 22.96 months and the median survival time was 11.40 months; The 1year, 2 years, 3 years and 5 years survival rate of various cancer is that the lung cancer is 47.70%, 16.67%, 13.79% and 10.34%; the esophageal cancer is 34.41%, 23.12%, 18.82% and 16.67%; the liver cancer is 20.78%, 11.69%, 9.09% and 7.79%; the pancreatic cancer is 13.04%, 8.79%, 8.70% and 8.70%; and the gastric cancer is 34.78%, 30.43%, 30.435 and 30.43%.

1.4. Conclusion: Patients with tumors in late stages has reached the high clinical benefit rate and low adverse reactions by UMIPIC treatment because the UMIPIC therapy with effective in the killing tumor and promotion of immunological response through releasing tumor antigens which modified through penicillin as hapten, also without any side effect, so that it indicated UMIPIC is a novel eclectic approach for cancer therapy and valuable method for widely clinical application.

2. Introduction

In 2019, 1,762,450 new cancer cases and 606,880 cancer deaths are projected to occur in the United States. In the past decade of data, the cancer incidence rate (2006-2015) was stable in women and declined by approximately 2% per year in men, whereas the cancer death rate (2007-2016) declined annually by 1.4% and 1.8%, respectively [1]. High-Income Countries (HIC) continue to have the highest incidence rates for all sites, as well as for lung, colorectal, breast, and prostate cancer, although some Low and Middle Income Countries (LMIC) now count among those with the highest rates. Mortality rates from these cancers are declining in many HICs while they are increasing in LMICs. LMICs have the highest rates of stomach, liver,

esophageal, and cervical cancer [2]. Example for lung cancer, Lung cancer is the leading cause of cancer-related death and the second most diagnosed cancer in the United States. Surgical intervention is most applicable to early-stage lung cancer diagnoses and considered the best curative option. Multiple surgical techniques are now available, including wedge resection, segmentectomy, lobectomy and pneumonectomy. Robotics and video-assistance are commonly used in wedge resection and sometimes used for segmentectomy. Regardless of the technique, focused clinical management of the patient following lung cancer surgery by nurses and nurse practitioners remains a priority. Future innovations affecting the surgical treatment of lung cancer include immunotherapy and oncogenomics [3]. Many of trial evidence supports cisplatin-based adjuvant therapy either after surgical resection or concurrently with radiotherapy. Consensus guidelines support neoadjuvant chemotherapy in lieu of adjuvant chemotherapy and carboplatin-based regimens for patients who are ineligible for cisplatin. In 2018, the anti-PD-L1 antibody durvalumab was approved for patients with stage III lung cancer after concurrent chemoradiotherapy. Since then, the study of targeted therapies and immunotherapies in patients with early-stage lung cancer has rapidly expanded [4]. For others cancers, esophageal cancer is one of the most fatal malignancies worldwide, with a dramatic increase in incidence in the Western world [5], liver cancer is the most frequent fatal malignancy; in the United States, it ranks fifth [6], globally, number of pancreatic cancer is about 338000 people in 2012, making it the 11th most common cancer [7]. Chemotherapy and immunotherapy are the best options for therapy, new treatment options are necessary. However, they still exhibit toxicities and have limitations due to the differences in the molecular and histological profiles of many cancers. Use of natural compounds and/or nanotechnology may provide patients with better outcomes with lower systemic toxicity and fewer side effects. Improved treatments can lead to better prognoses. UMIPIC is a new option for cancer treatment with eclectic approach is not only killing tumor cells but also stimulating whole body immunological response against tumor cells, as it integrates local chemotherapeutic effect with systemic antitumor immunity by intratumoral drug delivery. We have applied UMIPIC in the treatment of advanced many kind of cancer with a compounded solution including three components: an oxidant, a cytotoxic drug (cytosine arabinoside [Ara-C]), and hapten: penicillin [8]. Previous clinical and animal studies showed that a clinically approved oxidant can effectively coagulate tumor mass thoroughly by denaturation, which kills more than 90% of the tumor mass, reduces blood flow, and entraps the injected cytotoxic drugs at a high concentration within the coagulated tumors (>10× than conventional chemotherapy) for sustaining drug release. The cytotoxic drug Ara-C can continue to kill tumor cells that were not destroyed by coagulation. At the same time, autologous tumor-associated antigens that are also released from the dead tumor can trigger immune response as a self-vaccination. Meanwhile, hapten binds to the tumor-associated antigens to increase the specificity of these antigens and further boost systematic hormonal and cellular immunity for the suppression and eradication of tumor recurrence and metastasis. In the last decade, we have tried this treatment using combination of drugs with or without hapten in patients with advanced many kind of cancer including lung cancer, esophageal cancer, liver cancer, gastric and pancreatic cancer [9-11]. These data had approved that cancer treated with a single drug with hapten can enhance clinical therapeutic effective. Today we report using penicillin as hapten with two chemotherapy drugs to enhance a long survival time of lung cancer, esophageal cancer, liver cancer, pancreatic cancer, gastric cancer and others which followed up to 5 years.

3. Data and Methods

3.1. General Information

581 patients with malignant solid tumors hospitalized in our hospital from January 2011 to December 2011 were selected as the research objects, including 399 males and 182 females; The average age was (61.33 ± 11.84) years; There were 6 cases in stage I, 29 cases in stage II, 163 cases in stage III, 179 cases in stage IV and 204 cases without stage. There were 174 patients with lung cancer, 186 patients with esophageal cancer, 77 patients with liver cancer, 23 patients with pancreatic cancer, 23 patients with gastric cancer and 98 patients with other cancer; All patients signed the treatment consent form, treated according to the UMIPIC treatment guidelines, evaluated the efficacy of the patients and followed up. 179 patients with lost follow-up and survival time of less than three months 33 patients excluded and the remaining 369 patients were excluded for survival rate analysis.

3.2 Inclusion Criteria

① All patients were diagnosed as solid tumors by case diagnosis outside the hospital, and were confirmed to diagnosed as solid tumors by comprehensive, symptom, cytological examination, imaging examination and other methods in our hospital; ② There was no contraindication for UMIPIC treatment; ③ Have complete treatment records; ④ Patients or family members know about the study and sign the treatment consent form.

3.3 Exclusion Criteria

① Patients with non-solid tumors; ② Non hospitalized patients; ③ Patients admitted without umipic treatment; ④ Severe cachexia; ⑤ Major organ dysfunction; ⑥ Serious bleeding tendency; ⑦ Diffuse liver cancer, severe jaundice and ascites, active stage of hepatitis B and pulmonary tuberculosis; ⑧ Periampullary carcinoma with obstruction of duodenal carcinoma, unable to eat; ⑨ The patients with esophageal cancer in each segment without pre perforation signs and unable to tolerate gastroscopy detection and treatment.

3.4 UMIPIC Preparation

Preparation of the agents: Fine-needle biopsy is performed in clinical practice, and it is used to diagnose and evaluate the treatment of pancreatic organs, which requires a fine needle with a sharp tip. At the same time, 25 gauge of spinal needles and inflators (inflation device,

30 atm/bar)) were purchased. The UMIPIC solutions are freshly prepared at the clinical site before each injection. UMIPIC contains oxidative agents [12] that oxidize tumor stromal tissue, cytotoxic drugs (Cytarabine Hydrochloride (Ara-C) or Adriamycin Hydrochloride (Dox)), and penicillin (used as hapten that binds the antigen to enhance antigenicity.

3.5 Treatment Delivery

All patients had a lung computed tomography (CT) scan as a pre-treatment baseline. Routine examination of cardiopulmonary function was also done. Prior to UMIPIC, the patients were asked to fast without water for 14 hours prior to this therapy in order to avoid side effects and infections from this therapy.

After routine disinfection, draping, and local anesthesia with 2% lidocaine, a 25-gauge spinal needle was inserted into the tumor under CT guidance, and the needle tip in the tumor was monitored by CT. The core of the needle was taken out and the inflator was connected and used as a high-pressure syringe (inflation device, 30 atm/bar; Merit Medical Systems, West Jordan, UT, USA), then the injection of solution was performed.

UMIPIC has the same therapeutic procedure, which is minimally invasive and simple like a needle biopsy. The UMIPIC was delivered by a spinal needle inserted into the tumor, as just described, and the solution was pressurized (at the level of atmospheric pressure) to obtain the full distribution of the clinically approved regimens in the tumor under CT imaging guidance. A Picker IQ CT unit was used for single-slice scanning and monitoring of the density changes in CT value at a point or area of interest in the lung cancer tumor. Special attention was needed for monitoring the density changes in CT value at the tumor margins to ensure the complete distribution of the drugs. The drugs in the solution are water soluble, which is better than an oil-drug emulsion, which is sticky and hard to distribute in tumors. Under high pressure, the combination of drugs in UMIPIC can penetrate the full matrix of the tumor, even into tumor cells, providing sustained drug release for a long time.

The average time the whole procedure took was approximately 30–45 minutes. Patients with severe cough during the treatment were unable to have the procedure completed on them and were excluded from data analysis. The volume of the injection was calculated as the diameter of tumor (Dt) $\times 2$ for 1–5 cm tumors and Dt $\times 1.5$ for tumors not smaller than 6 cm; good practice is the key to a successful treatment in all cases according to this calculation in order to deliver enough dosage into tumors (Figure 1).

Having injected the combined solution, the physicians would observe the density values by CT at a point or area of interest of the tumor (indicating drug diffusion in the tumor) and related complications such as hemorrhage around the needle track by CT scan imaging. Second and third cycles of treatment are usually required for better efficacy compared with one cycle of treatment. The patients should be re-examined by CT 4–6 weeks after the last therapy, and some patients in our study were treated with a second cycle of treatment. For esophageal cancer, we used endoscopy for same injection.
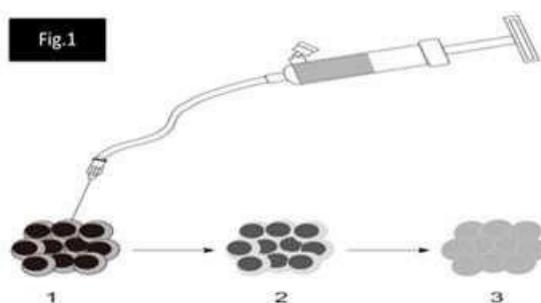
Figure 1: The ultra-minimum incision personalized intratumoral chemoimmunotherapy procedure.

Notes: 1) Guided by computed tomography, the needle is inserted into the tumor, connected to the inflator, and introduced int ratumorally with the optimal route and angle; 2) the regimen is slowly delivered into the tumor; 3) with high pressure supplied by the inflator, the solution penetrates the extracellular matrix of the tumor and facilitates diffusion.

4. Assessment

The treatment response to solid tumors was evaluated according to the evaluation criteria of EROTC (European Organization for Research and Treatment of Cancer) and RECIST (NCI, the United States and Canada) [13] in October 1998. All Case Report Forms (CRF) were filled out by the attending physicians. In every hospital, all physicians were trained in standard procedures.

5. Statistical Methods

The data were collected by SPSS23.0 statistical software package for data statistics. In the study, the quantitative data are expressed in the form of mean ± standard deviation, the counting data are expressed in the rate (%), and the general data are expressed in χ^2 inspection; Kaplan Meier survival curve was used to analyze the survival data. The effective rate=(Cr + PR)/number of effective cases*100%, and the benefit rate=(Cr + PR + SD)/number of effective cases*100%. Survival rate=number of survivors/number of effective cases*100%. The difference was statistically significant ($P < 0.05$).

6. Results

6.1 Adverse Reactions

According to the statistics of adverse reactions after UMIPIC treat-

ment, the main adverse reactions were fever 31.43% (182 / 579), followed by hemoglobin reduction 15.09% (86 / 570), tolerate pain 12.56% (73 / 581), leucopenia 5.08% (29 / 571), nausea 4.30% (25 / 581), thrombocytopenia 2.62% (15 / 572), liver function damage 2.14% (12 / 561), renal function damage 1.60% (9 / 561), and no rash neurotoxicity and hair loss are not adverse reactions. According to the statistics of moderate and severe adverse reactions, only fever was 7.94%, and other moderate and severe adverse reactions is a few. The adverse reactions were less than 2%. The detailed results are shown in Table 1.

Table 1: Adverse reaction of all solid tumor after UMIPI treatment.

Type of Adverse Reaction	No. cases	No. effective cases		Adverse reaction(AR)		Moderate and severe AR	
		Cases	%	Cases	%	Cases	%
Fever	581	579	99.66%	182	31.43%	46	7.94%
Pain	581	581	100.00%	73	12.56%	9	1.55%
Leucopenia	581	571	98.28%	29	5.08%	1	0.18%
Hemoglobin reduction	581	570	98.11%	86	15.09%	9	1.58%
Thrombocytopenia	581	572	98.45%	15	2.62%	1	0.17%
Liver function	581	561	96.56%	12	2.14%	7	1.25%
Renal function damage	581	561	96.56%	9	1.60%	6	1.07%
Nausea	581	581	100.00%	25	4.30%	7	1.20%
Vomit	581	581	100.00%	12	2.07%	5	0.86%
Rash	581	581	100.00%	0	0.00%	0	0.00%
Neurotoxicity	581	581	100.00%	0	0.00%	0	0.00%
Alopecia	581	581	100.00%	0	0.00%	0	0.00%

6.2. Clinical efficacy evaluation

The clinical benefit rate from analysis of 316 patients was 95.89% while the clinical efficient rate was only 7.6% and the detailed results are shown in Table 2.

6.3 Clinical overall survival time

After follow up to 5 years and analyse from the available 369 patient's data, it was found that the average survival time after receiving UMIPIC treatment was 26.888 months and the median survival time was 14.20 months. The detailed results are shown in Table 3 and Figure 2.

Table 2: Efficacy Evaluation of UMIPIC in the treatment of patients with solid tumors

CR	PR	SD	PD	Efficient	benefit rate
1	23	279	13	7.6	95.89

Table 3: Mean and median survival time after UMIPIC treatment.

Group	Average (Month)				Median (Month)			
	EST (M)	SE	95% confidence interval		EST (M)	SE	95% confidence interval	
			L limit	U limit			L limit	U limit
Lung cacner	23.155	1.969	19.296	27.014	14.87	0.585	13.724	16.016
Esophageal cancer	32.731	2.728	27.384	38.078	19.03	2.759	13.623	24.437
Liver cancer	17.219	3.065	11.212	23.226	7.6	0.849	5.937	9.263
Pancreatic cancer	14.229	4.406	5.593	22.866	6.7	1.13	4.485	8.915
Gastric cancer	37.566	8.529	20.848	54.284	14.8	.	.	.
Others	31.733	3.635	24.609	38.858	17.83	3.668	10.641	25.019
General	26.861	1.372	24.172	29.55	14.2	0.617	12.991	15.409

a. If the survival analysis time has been checked, the estimation will be limited to the maximum survival analysis time.

Note: Estimate (EST), Standard error (SE), L limit: Lower limit, U limit:up limit.

6.4 Survival rate

By calculating and analyzing the survival rate of all patients followed up to 5 years after treatment with the available 369 patient's data, it is concluded that the 1year, 2 years, 3 years and 5 years survival rate of various cancer is that that is 66.94%, 23.39%, 19.35% and 16.13% for lung cancer; 64.65%, 43.43%, 35.35% and 31.31% for the esophageal cancer; 32.00%, 18.00%, 14.00% and 14.00% for the liver cancer; 25.00%, 12.5%, 12.5% and 12.5% for the pancreatic cancer; and 53.33%, 46.67%, 46.67% and 46.67% for the gastric cancer (Table 4-5, Figure 2-1, 2-2).

7. Discussion

Worldwide, cancer is still one of the major deadly diseases. Local treatment, like surgery and radiotherapy, is the major primary curative therapy for patients in the early stages of all solid tumor. Metastasis is considered the latest stage of cancer development, approximately 54% of patients present a metastasis at diagnosis time due to lack of clinical symptoms at the early stages, which tends to result in an extremely poor prognosis with an overall 5-year survival rate of lower than the 5%.

For most advanced of late stages cancers, standard chemotherapy involving 5-FU [14], pemetrexed [15], oxaliplatin [16] and docetaxe and

gemcitabine [17] is generally the mainstream of management, but apparently this has reached a plateau with disappointing outcomes. Despite the introduction of a series of targeted drugs for patients with epidermal growth factor receptor mutations (gefitinib or erlotinib) [18, 19] and ALK rearrangement (crizotinib) [20] in the past decade, the survival rate still has not been significantly improved. Today, immunotherapeutic interventions, including vaccine therapy derived from lung cancer cell lines (or tumor-associated antigens) and immune-stimulatory checkpoint antibodies, although traditionally not considered possible treatments for tumors, may improve outcomes in lung cancer. Moreover, the combination of immunotherapy and chemotherapy, or "chemoimmunotherapy", has been successfully applied clinically [21, 22].

"UMIPIC", described in this clinical study, is a patented therapeutic method for treating solid tumors, and was explored patients from this hospital with personalized dosages based on tumor size while utilizing patient-specific in vivo modified autologous tumor antigens as a self-vaccination to tumor-specific response. The regimen is a personalized and freshly prepared compound solution containing an oxidant, a cytotoxic drug, and hapten. Each component plays a vital role in the therapy.

"Intratumoral therapy", characterized as high local drug concentrations with minimal systematic toxicity, is an outstanding and attractive alternative to systematic treatment, with increasing evidence of its clinical benefits [23, 24]. The intratumoral delivery approach, integrated with the coagulation induced by the oxidant, can significantly increase the local accumulation of drugs (up to 10 to 100x that of systemic administration [8, 27] Intratumoral therapy the oxidant acts as the main force in the debulking of the fibronectin, proteoglycans, hyaluronic acid, and other large molecules, creating a soft, semisolid, or solid mass with destroyed metabolism and induced fibrosis generation. It may also destroy the environmental conditions for tumor cell growth which was found in our previous animal experiment [28]. More importantly, we not only found lymphocyte infiltration in the tumors, but also more positive cluster of differentiation CD8+ in the animals studied; and recently, we also found dendritic cells (DC11 and DC86) and debris of tumor cells under electron microscopy (Figure 3). Therefore, coagulation is one of the major ways of improving drug utilization by extending the duration of drug action, as well as systematic drug exposure through sustained drug release, with greatly reduced toxicity [27] and the induction of a possible immune capability against cancer cells in the body.

In view of the optimistic survival advantage of UMIPIC therapy, we further analyzed the data for 95.89% benefit rate for all of patients while the efficient rate is only

7.60% (Table 2). The average OS of patients in the UMIPIC treatments was 20.526 months and the median OS of patient was 9.733 months (Table 3). the 1 year, 2 years, 3 years and 5 years survival rate of various cancer is that is 66.94%, 23.39%, 19.35% and 16.13% for lung cancer; 64.65%, 43.43%, 35.35% and 31.31% for the esophageal cancer; 32.00%, 18.00%, 14.00% and 14.00% for the liver cancer; 25.00%, 12.5%, 12.5% and 12.5% for the pancreatic cancer; and 53.33%, 46.67%, 46.67% and 46.67% for the gastric cancer (Table 4-5, Figure 2-1, 2-2), it is significant better survival rate than published data, it indicated that combination of drugs and hapten could give a better survival rate of 5 years for advanced stages of all solid tumor. The moderate to severe adverse with good survival rate of patients, only fever is 31.43% to 7.94%, pain is 12.56 to1.55%, and the survival rate of patients with solid tumor with moderate to severe adverse reactions was 23%, tolerate pain is accepted for all of patients, it indicated that this therapy of UMIPIC is less of side effect (Table 1).

In the past years reports, lung cancer is the leading cause of cancer-related death in the United States, with an average five-year survival rate of 15 percent [28], esophageal cancer in the United States carries a poor prognosis with overall 5 year survival rate of approximately 10% [29], for liver cancer survival rates of liver cancer from three 15-year periods of 1972-1986, 1987-2001, and 2002-2016 have increased significantly, with 5-year OS rates of 2.02%, 4.40%, and 10.76% [30], for pancreatic cancer age standardised one-year and five-year net survival increased from 17.9% and 3.6%, respectively, for 2000-2009, to 21.6% and 4.2% during 2010-2013, 29% were classified as "early gastric cancers [31]. Our data here has showed that 5-years survival time is better than above reported therapy, special for advances stages of lung cancer, esophageal cancer, pancreatic cancer and gastric cancer, UMIPIC treatment showed a advantage achievement.

This may be attributed to the long-term immunological memory induced by the constitutive release of antigens, leading to a more effective anti-tumor response. The debulking effect of UMIPIC resulted in less tumor load, then control better of the residual cancer cells by immunological cells.

It is confirmed that the inflammatory response, induced by coagulation and hapten, may also be involved with the antitumor immunity. The migration of APCs to the inflammatory tissue can enhance the capture and processing of tumor-associated antigens released from dead tumor cells to draining lymph nodes by APCs. This drives a desired antigen-specific immune response to further eradicate cancer cells at distant sites [32].

Table 4: survival rate of classified cancer patients after UMIPIC treatment (%)

Type	Cases	1 year %	2 years %	3 years %	5 years %
Lung cancer	124	66.94	23.39	19.35	16.13
Esophageal cancer	99	64.65	43.43	35.35	31.31
Liver cancer	50	32	18	14	14
Pancreatic cancer	16	25	12.5	12.5	12.5
Gastric cancer	15	53.33	46.67	46.67	46.67
Other cancer	65	55.38	40	36.92	32.31

Table 5: Overall survival rate of all solid tumor patients after UMIPIC treatment (%)

Cases	1 year %	2 years %	3 years %	5 years %
369	57.18 （211/369）	31.44 （116/369）	26.83 （99/369）	23.85 （88/369）
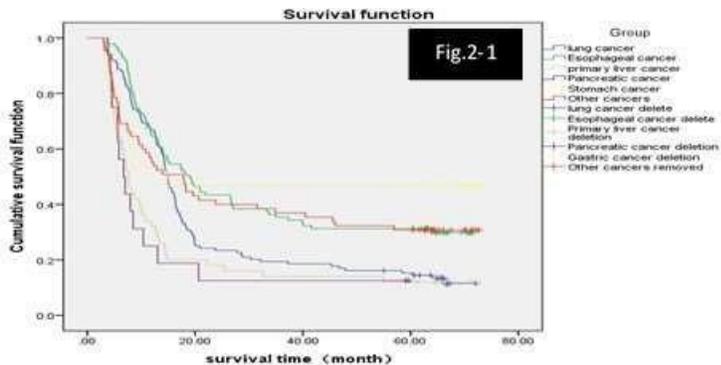
Figure 2-1: Survival rate of different cancer
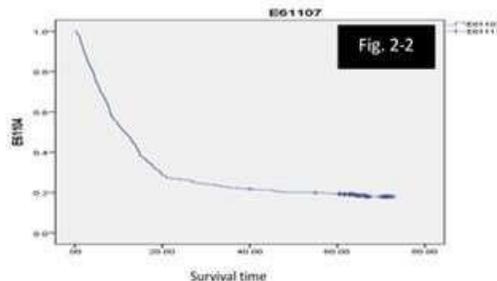
Figure 2-2: Survival curve of all patients with UMIPIC therapy solid tumor
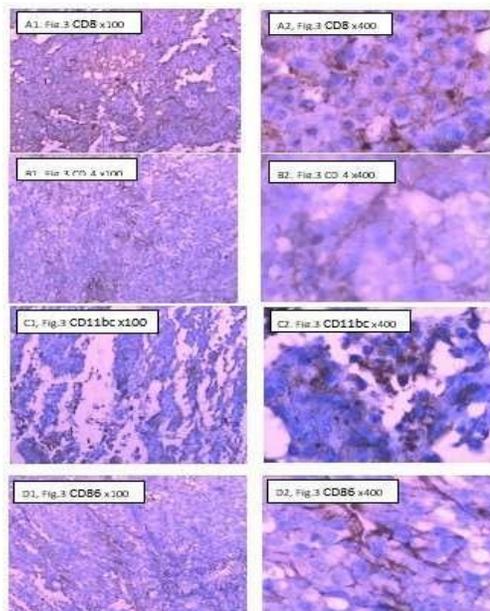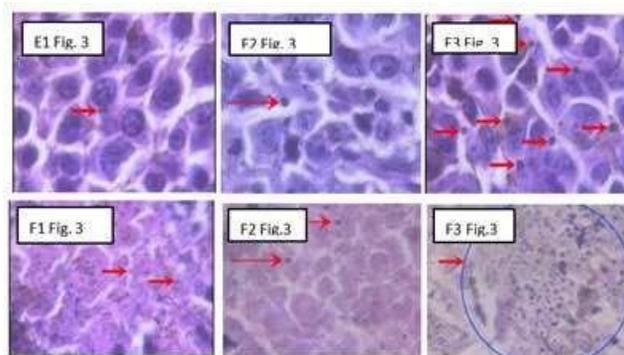
Figure 3: Localized inflammation with lymphocyte and dendritic cell (DC) infiltration in tumors with histochemical staining for CD 8, CD11, CD 86.
Notes: A1 and A2 showed cluster of differentiation (CD) 8+ increase in tumors with lymphocyte infiltration after the ultra-minimum incision personalized intratumoral chemoimmunotherapy (UMIPIC); B1 and B2 showed cluster of differentiation (CD) 4+ increase in tumors with lymphocyte infiltration after UMIPIC. C1, C2 and D1, D2 showed cluster of differentiation (CD11) and CD86+ increase in tumors with lymphocyte infiltration after UMIPIC. E1, E2 and E3 showed that inflamation with lymphocyte under general microscopy. F1, F2 and F3 showed that tumor cell necrosis and debris without lymphocytes under microscopy since without hapten in UMIPIC treatment.
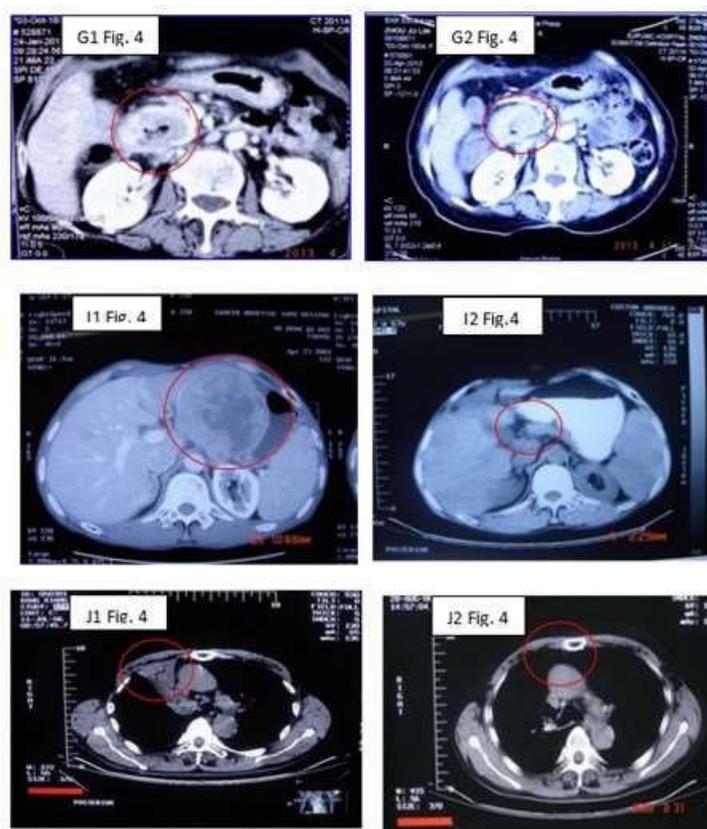
Figure 4: Clinical response of ultra-minimum incision personalized intratumoral chemoimmunotherapy (UMIPIC) in lung cancer.
Notes: G1 and G2 showed that response to UMIPIC therapy in pancreatic cancer, after two time UMIPIC therapy tumor start to necrosis and smaller. I1 and I2 showed that big liver tumor mass regressed to complete remission (CR)after UMIPIC treatment. J1 and J2 showed that response to UMIPIC therapy in lung tumor location at side of chest wall, it is impossible to to cut off, so that UMIPIC was executed and tumor disappeared.

8. Conclusion

This clinical study showed that UMIPIC can induce more inflammatory responses in local tumors and showed a significantly prolonged survival time for patients with advanced cancer (Tables 2 to 4), and the addition of hapten in UMIPIC demonstrated a significant role as an immunological booster in terms of prolonged survival time (11, 12, 26).

In summary, UMIPIC for all of solid tumor is a noninvasive and potentially effective therapy with a satisfying profile of high specificity and prolonged survival time. It offers the prospect of tailoring treatments much more precisely and could lead to a better response, especially in patients with advanced-stage inoperable or drug-resistant types of all solid cancer.

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