Intratumoral injection chemo-immunotherapy of 5-FU and recombinant interferon-gamma for hepatocellular carcinoma

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HCC survival: comparison between screened and not screened cases
Spiral Liver CT Scan

PEIT or RFA
Operative Resection or Liver Transplantation
Prognosis

Operability

HCC

TNM

CLIP

Child/MELD

Resectability

Severity

Prognosis

ICG

Resectability

Operability

Severity

Prognosis

BCLC/JIS

≤Milan’s criteria

≤2cm, single

Curable

20% 40% 40%

Palliative

TACE  TAC  RT  SC

Hospice

Any + PST-4,5

Hopeless

TNM-III

PST-0,1,2

TNM-III or IV

+ PST-3

LT  Op  RFA
간세포암성장 속도

5.7.
6.30 (54일후) 10.10 (156일후)

성장속도: 2배/1.5개월 9배/5개월

\[ y = 0.0892x^2 + 0.2283x + 3.3 \]

\[ y = 1E-04x^2 + 0.0076x + 3.3 \]
간세포암 성장 (Vol.) 속도

<3cm

\[ y = 0.0093x^3 - 0.2766x^2 + 2.0356x + 0.0588 \]
\[ R^2 = 0.9956 \]

\[ y = 0.0006x^3 - 0.0142x^2 + 0.1297x + 0.5007 \]
\[ R^2 = 0.9993 \]

>3cm - <6cm

\[ y = 0.1x^2 + 0.3x + 3 \]
\[ R^2 = 1 \]

\[ y = 7.7977x^2 - 5.9137x + 14.13 \]
\[ R^2 = 1 \]
70/female

Intrahepatic Metastasis 3 months later, and sizes are increasing

Intrahepatic Metastasis 6 months later, and sizes are increasing

1 year later: multifocal, both

HCC. single 1st. detected Not treated
The larger the size, the more the malignant: malignant behavior aspect

\[ y = 5.8307e^{0.1331x} \]

Metastasis ↑↑
Vascular Invasion ↑↑

\[ y = 14.285e^{-0.004x}, // late phase (stage IV phase) \]
(overlapping point = tumor diameter 6.6cm) ;
// stage III phase
\[ y = -7.133\ln(x) + 43.929; // early phase stage I-II (early III) phase \]

\[ y = 2E^{-09x^4} - 2E^{-06x^3} + 0.0009x^2 - 0.1873x + 19.102 \]
\[ R^2 = 0.9881 \]

\[ y = -7.133\ln(x) + 43.929; // early phase stage I-II (early III) phase \]
Differentiation grade

- in viewpoint of the tumor size,
- the opportunity of dedifferentiation process from WD to PD in cancer stem cells is increasing in correlation with tumor size.

  accompanied by microenvironmental changes:
  - nutritional supply
  - O2 supply
  - Free radicals

<table>
<thead>
<tr>
<th>Differentiation Grade</th>
<th>DN</th>
<th>G-I</th>
<th>G-II</th>
<th>G-III</th>
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<tr>
<td></td>
<td>17.73±5.76</td>
<td>27.76±9.57</td>
<td>42.38±20.61</td>
<td>56.56±23.13</td>
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(P < 0.001)
Comparison of the pathological prognostic features between grade III and I/II

<table>
<thead>
<tr>
<th></th>
<th>I (N=33)</th>
<th>II (N=40)</th>
<th>III (N=74)</th>
<th>Sum (%)</th>
<th>p-value*</th>
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</thead>
<tbody>
<tr>
<td>Capsular formation</td>
<td>11 (33.3%)</td>
<td>17 (42.5%)</td>
<td>58 (78.4%)</td>
<td>86 (58.5%)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Capsular infiltration</td>
<td>1 (9.1%)</td>
<td>7 (41.2%)</td>
<td>24 (41.4%)</td>
<td>32 (21.8%)</td>
<td>0.0813</td>
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<tr>
<td>Microvascular invasion</td>
<td>3 (9.1%)</td>
<td>28 (70.0%)</td>
<td>65 (87.8%)</td>
<td>96 (65.3%)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Portal vein invasion</td>
<td>0</td>
<td>4 (10.0%)</td>
<td>14 (18.9%)</td>
<td>18 (12.2%)</td>
<td>0.0042</td>
</tr>
<tr>
<td>Satellite nodules</td>
<td>0</td>
<td>7 (17.5%)</td>
<td>22 (29.7%)</td>
<td>29 (19.7%)</td>
<td>0.0002</td>
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</tbody>
</table>
Comparison of the predictive survival curves (solid line) and the observed survival curves (broken line) in the validation sample

(a) LCSGJ-T

(b) AJCC-T

Legend:
- predictive survival curves
- observed survival curves
Anti-cancer agents: chemotherapy, gene therapy, immune therapy, target therapy
Slow releasing agents: epinephrine gel (CDDP), bead (Adr. Epi)
Necrotizing agents: ethanol, acetic acids.
Anti-cancer vaccine: in-situ vaccination, dendritic cell injection
Device: RFA, laser (for solid tissue), microwave
Combination with: TAC, Radiation therapy, RFA

INTRATUMORAL INJECTION
Figure 1. Shows the needle inserted vertically into an endo-luminal polypoid or exophitic mass.

Figure 2. Shows the removal of tumor residues (debridements) by mechanical resection with forceps. The locally injected drug kills the malignant cells but does not remove them. The necrotic residues are therefore removed by mechanic debridement with forceps and facilitates delivery of additional cytotoxic drugs further into the tumoral mass if necessary.

Figure 3. Shows the injection of the drug into tumor infiltrating the bronchial wall after removal of the endo-luminal component of the tumor mass.

Figure 4. Shows the injection of cytotoxic drug into a tumor that causes a compressive airway obstruction with intact bronchial mucous membrane. No bronchial fistula develops after intratumoral chemotherapy.
Multicenter Phase I Study of Repeated Intratumoral Delivery of Adenoviral \textit{p53} in Patients With Advanced Non–Small-Cell Lung Cancer

Toshiyoshi Fujiwara, Noriaki Tanaka, Susumu Kanazawa, Shoichiro Ohtani, Yasuo Saijo, Toshihiro Nukiwa, Kunihiko Yoshimura, Tetsuo Sato, Yoshikatsu Eto, Sunil Chada, Haruhiko Nakamura, Harubumi Kato

From the Center for Gene and Cell Therapy, Okayama University Hospital; Departments of Surgery and Radiology, Okayama University Graduate School of Medicine and Dentistry, Okayama; Department of Molecular Medicine, Tohoku University Graduate School of Medicine; Department of Respiratory Oncology and Molecular Medicine, Institute of Developing, Aging, and Cancer, Tohoku University, Sendai; Department of Gene Therapy, Institute of DNA Medicine, Department of Respiratory Medicine, Jikei University School of Medicine; Department of Surgery, Tokyo Medical University, Toyko, Japan; and Introgen Therapeutics Inc, Houston, TX

Ad5CMV-p53 (ADVEXIN; Introgen Therapeutics Inc, Houston, TX),
In Situ Vaccination With a TLR9 Agonist Induces Systemic Lymphoma Regression: A Phase I/II Study


Abstract

Purpose
Combining tumor antigens with an immunostimulant can induce the immune system to specifically eliminate cancer cells. Generally, this combination is accomplished in an ex vivo, customized manner. In a preclinical lymphoma model, intratumoral injection of a Toll-like receptor 9 (TLR9) agonist induced systemic antitumor immunity and cured large, disseminated tumors.

Patients and Methods
We treated 15 patients with low-grade B-cell lymphoma using low-dose radiotherapy to a single tumor site and—at that same site—.injected the C-G enriched, synthetic oligodeoxynucleotide (also referred to as CpG) TLR9 agonist PF-3512676. Clinical responses were assessed at distant, untreated tumor sites. Immune responses were evaluated by measuring T-cell activation after in vitro restimulation with autologous tumor cells.

Results
This in situ vaccination maneuver was well-tolerated with only grade 1 to 2 local or systemic reactions and no treatment-limiting adverse events. One patient had a complete clinical response, three others had partial responses, and two patients had stable but continually regressing disease for periods significantly longer than that achieved with prior therapies. Vaccination induced tumor-reactive memory CD8 T cells. Some patients’ tumors were able to induce a suppressive, regulatory phenotype in autologous T cells in vitro; these patients tended to have a shorter time to disease progression. One clinically responding patient received a second course of vaccination after relapse resulting in a second, more rapid clinical response.

Conclusion
In situ tumor vaccination with a TLR9 agonist induces systemic antilymphoma clinical responses. This maneuver is clinically feasible and does not require the production of a customized vaccine product.
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Conclusion In situ tumor vaccination with a TLR9 agonist induces systemic antilymphoma clinical responses. This maneuver is clinically feasible and does not require the production of a customized vaccine product.
Metastatic Renal Cell Carcinoma: CT-guided Immunotherapy as a Technically Feasible and Safe Approach to Delivery of Gene Therapy for Treatment

Robert D. Suh, MD, Jonathan G. Goldin, MD, Amanda B. Wallace, BS, Ramon E. Sheehan, MD, Stefan B. Heinze, Barbara J. Gitlitz, MD and Robert A. Figlin, MD

Abstract

PURPOSE: To assess the technical feasibility and safety of weekly outpatient percutaneous computed tomographic (CT)-guided intratumoral injections of interleukin-2 (IL-2) plasmid DNA in a wide variety of superficial and deep tumor sites.

MATERIALS AND METHODS: Twenty-nine patients with metastatic renal cell carcinoma and a total of 30 lesions measuring 1.0 cm² or greater in accessible thoracic (n = 15) or abdominal (n = 15) locations underwent up to three cycles of six weekly intratumoral IL-2 plasmid DNA injections. CT was used to guide needle placement and injection. After injection cycle 1, patients whose tumors demonstrated stable (≤25% increase and ≤50% decrease in product of lesion diameters) or decreased size (>50% decrease in product of lesion diameters) advanced to injection cycle 2. Patients whose lesions decreased in size by more than 50% over the course of injection cycle 2 were eligible to begin injection cycle 3. An acceptable safety and technical feasibility profile for this technique was deemed to be (a) a safety and feasibility profile similar to that of single-needle biopsy and (b) an absence of serious adverse events (as defined in Title 21 of the Code of Federal Regulations) and/or unacceptable toxicities (as graded according to the National Cancer Institute Common Toxicity Criteria).

RESULTS: A total of 284 intratumoral injections were performed, with a mean of 9.8 injections (range, 6–18 injections) received by each patient. Technical success (needle placement and injection of gene therapy agent) was achieved in all cases. Complications were experienced after 42 (14.8%) of the 284 injections. The most common complication was pneumothorax (at 32 [28.6%] of 112 intrathoracic injections), for which only one patient required catheter drainage. Complications occurred randomly throughout injection cycles and did not appear to increase as patients received more injections (P = .532). No patient experienced serious adverse events or unacceptable toxicities.

CONCLUSION: Percutaneous CT-guided intratumoral immunotherapy injections are technically feasible and can be safely performed.
Transverse thin-section CT scans used to guide intratumoral injection of IL-2 plasmid DNA show injection at various target sites, including (a) the lung, (b) the liver, (c) a lymph node, and (d) an adrenal gland.
The promise of gene therapy in gastrointestinal and liver diseases
J Prieto, M Herraiz, B Sangro, C Qian, G Mazzolini, I Melero, J Ruiz

Abstract

Gene therapy consists of the transfer of genetic material to cells to achieve a therapeutic goal. In the field of gastroenterology and hepatology gene therapy has produced considerable expectation as a potential tool in the management of conditions that lack effective therapy including non-resectable neoplasms of the liver, pancreas and gastrointestinal tract, chronic viral hepatitis unresponsive to interferon therapy, liver cirrhosis, and inflammatory bowel disease.
Interferon-gamma (IFN-γ):
a homodimeric glycoprotein
• immune modulator
• anti-cancer proliferative effect
• anti-angiogenic effect
• increases chemo-sensitivity of 5-FU

INTERFERON- GAMMA
Fig. 2: interferon-γ (IFN-γ) controls Th immune and allergic responses. IFN-γ is produced by different cell sources. It may counteract Th2 immune responses (by suppressing the development of Th2 lymphocytes), induce Th1 differentiation (by enhancing IL-12 production by APC or skewing naive Th lymphocytes toward the Th1 phenotype), and control several steps of allergic responses (by inducing eosinophil apoptosis and blocking IgE isotype switch in B cells).
IFN-γ Signal Transduction Pathway

MHC class I

IFN-γ Signal Transduction

1. IFN-γ binds to the IFNγ-Rα and IFNγ-Rβ receptors.
2. The receptors dimerize, activating Jak1 and Jak2.
3. Jak1 and Jak2 phosphorylate Stat1, leading to its dimerization.
4. Phospho-Stat1 (pY132/136) binds to Stat1, promoting its dimerization and activation.
5. pY701 of Stat1 is also phosphorylated, leading to its nuclear translocation.
6. pY701 of Stat1 binds to PIAS, which in turn binds to GAS (eg. IRF-1, SOCS) binding sites.
Anticancer mechanism of 5-FU

5-fluorouracil (5-FU)
Activation of p53 by 5-fluorouracil
Mechanism of thymidylate synthase inhibition by 5-fluorouracil
Mechanism of thymidylate synthase inhibition by 5-fluorouracil
Modulation of 5-fluorouracil activity
IFN-γ Enhances Anti-cancer Effects of 5-FU

In IFNγ knockout (IFNγ -/-) mice, the inhibitory effects of 5FU/celecoxib on angiogenesis and tumor growth were significantly impaired compared with that in wild type mice. <Irie, et al., International Journal of Cancer Volume 121 Issue 4, Pages 878 - 883>

IFNγ enhances the cytotoxicity of 5FU and 5'DFUR against human bladder cancer cells through induction of PD-ECGF/TP. The results imply that an IFNγ /5FU or IFNγ /5'DFUR combination therapy may be applicable to clinical bladder cancers. <Li, et al., Anticancer Res. 2002 Sep-Oct;22(5):2607-12>

By adding 12.5 U/ml of IFNγ, which is a concentration that does not affect cell proliferation, the TP expression significantly increased by 1.5 to 3.4 times in the 4 RCC cell lines. Susceptibility to 5-FU and 5'-DFUR was also significantly induced by 1.42 to 2.36 times and 2.9 to 5.71 times, respectively, in the 4 cell lines. <Ikemoto, et al., Anticancer Res. 2002 Nov-Dec;22(6C):4023-7>

Total thymidylate synthase was decreased by triple combination therapy (5-FU, IFNα/β and IFNγ, P = 0.0019) and combination therapy (5-FU and IFNγ, P = 0.0018) compared to 5-FU alone. <Ishii, et al., Int J Urol. 2004 Nov;11(11):993-1000.>

In vitro studies in HT29 cells demonstrated that clinically relevant IFNγ concentrations (1 to 10 U/ml for 6.5 h) with 5-FU/LV upregulated Fas expression 3.5-fold. <Turner, et al., Cancer Chemother Pharmacol. 2004 Mar;53(3):253-60.>

The pharmacokinetic parameters of IFNγ correlated with a 2-3-fold up-regulation of Fas expression at 24 h in CD15+ cells in peripheral blood samples. Furthermore, clinically relevant IFNγ concentrations up-regulated Fas expression and sensitized HT29 colon carcinoma cells in vitro to FURA/LV cytotoxicity. <Schwartzberg, et al., Clin Cancer Res. 2002 Aug;8(8):2488-98.>
Interferon-\(\gamma\) sensitizes hepatitis B virus-expressing hepatocarcinoma cells to 5-fluorouracil through inhibition of hepatitis B virus-mediated nuclear factor-\(\kappa\)B activation

CANCER SCI 2007
NF-κB in Hepatocarcinogenesis

Key Role in Inflammation
Carcinogenesis:
- promotion

Growth factors (e.g., TGF-β)

Oncogenes (e.g., Ras)

Cell Survival ↑

NF-κB ↑

HBV (HBx)

Cell Proliferation
Immune Response
Angiogenesis
Metastasis
Anti-apoptosis
Drug Resistance
Non-canonical NF-κB Pathway, HBV and IFNγ

LTα → TRAF2

NIK: NF-κB Inducing Kinase; IKKα homodimer; NF-κB: P52, p100; RelB; IFN γ: Interferon-gamma; GADD: growth arrest and DNA damage-inducible transcription factors

TRAF2: TNFR associated factor 2; NIK: NF-κB Inducing Kinase; IKKα homodimer; NF-κB: P52, p100; RelB; IFN γ: Interferon-gamma; GADD: growth arrest and DNA damage-inducible transcription factors
Efficacy of a cocktail of 5-FU and IFN-γ for the growth inhibition of Huh7 and Hep3B cell lines

MTT ASSAY
### 24H

#### 5-Fu (ug/ml) vs Hep3B

- **Treat**
  - IFN-\( \text{r} \)
  - **Conc**
    - 0 u/ml
    - 1000 u/ml
    - 2000 u/ml
    - 3000 u/ml
    - 4000 u/ml

- **5-Fu**
  - 0 ug/ml
  - 50 ug/ml
  - 100 ug/ml
  - 200 ug/ml
  - 300 ug/ml

### 48H

#### IFN-\( \text{r} \) (U/ml) vs 5-Fu (ug/ml)

- **Treat**
  - IFN-\( \text{r} \)
  - **Conc**
    - 0 u/ml
    - 1000 u/ml
    - 2000 u/ml
    - 3000 u/ml
    - 4000 u/ml

- **IFN-\( \text{r} \)**
  - 0 u/ml
  - 1000 u/ml
  - 2000 u/ml
  - 3000 u/ml
  - 4000 u/ml
**Hep3B**

### 24H

- **IFN-r (U/ml)**
  - Treat: 0, 2000

### 48H

- **IFN-r (U/ml)**
  - Treat: 0, 2000

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<th>Conc</th>
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<tr>
<td>5-FU</td>
<td>100ug/ml</td>
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<tr>
<td>5-FU</td>
<td>150ug/ml</td>
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<td>5-FU</td>
<td>200ug/ml</td>
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<th>IFN-r</th>
<th>Conc</th>
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<td>IFN-r</td>
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<tr>
<td>IFN-r</td>
<td>1500u/ml</td>
</tr>
<tr>
<td>IFN-r</td>
<td>2000u/ml</td>
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**5-Fu (ug/ml)**

- **24H**
- **48H**
24H

Hep3B

IFN-r (U/ml)

Treat | Conc
---|---
5-FU | 0ug/ml
5-FU | 12.5ug/ml
5-FU | 25ug/ml
5-FU | 50ug/ml
5-FU | 100ug/ml

48H

5-Fu (ug/ml)

IFN-r (U/ml)

Treat | Conc
---|---
IFN-r | 0u/ml
IFN-r | 500u/ml
IFN-r | 1000u/ml
IFN-r | 1500u/ml
IFN-r | 2000u/ml
Huh7

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24H

5-Fu(ug/ml)  IFN-r(U/ml)

48H

5-Fu(ug/ml)  IFN-r(U/ml)
Efficacy of combination therapy of PICT-IF and TAC-EC for HCC

CHEMOTHERAPY SHOULD BE EFFECTIVE.
57/F

2004-7-14

Hemoperitoneum
TAE-Adr for bleeding control: x1
Additional Treatment

PIC-IF

Protocol treatment

• TAC-EC: x5
• PIC-IF: x8
CR state, DFI = 7 years

2011-5-18: cross section

vertical section
66/M


TAE for bleeding control
Additional Treatment

PIC-IF

Protocol Treatment

• TAC-EC: x4
• PIC-IF: x3
Pulmonary recurrence: n1

Op resected. DFI = 3 years

Pulmonary recurrence: DFI = 4.5 years
Total survival = 8 years
(recurrences * 2 times: lung and liver)

Liver: recurrence S6

PIC-IF, x2, DFI = 5 months
56/F

2001.5.16: Hemoperitoneum

TAE-Adr for bleeding control
Recurrence in spleen and lung:
DFI = 22 months

Spleen metastasis: 2003.4.30
CR by systemic ECF therapy, 2 cycles

lung metastasis: 2003.5.7.

2009.11.20.
Total survival time: 11 years
DFI after CR by systemic ECF = 8 years

Lung.free: 2010.12.23

Recurrence in liver: 2011.6.23
2003.11.15 : 60/female visit to ER: hemoperitoneum single, 7.5cm TAE and Operative resection

2007.2.27 visit to ER: terminal state multiple extrahepatic huge metastasis

2005.8 – 2007.12 post-operative recurrence TACE 3 times but no response at all
47/m: 2003.3.7 – 2007.7.13
(pass due to traffic accident: survival = 4.4 years)

Spleen metastasis: CR

PICT-IF. for spleen lesion
43/m, alcoholic LC, small multiple

before treatment: arterial phase

after treatment: arterial phase
Repeated PIC-IF for small multiple nodules

before treatment: arterial phase

after treatment: arterial phase
Repeated PIC-IF for small multiple nodules

before treatment: arterial phase

after treatment: arterial phase
Repeated PIC-IF for small multiple nodules

before treatment: delayed phase

after treatment: delayed phase
Example of PICT in this case

before PIC-IF

after PIC-IF
56/M: survival = 7 years after PIC-IF
single 3cm HCC to multiple marginal recurrence after RFA

Marginal recurrence after RFA:
DFI = 5 months

CT after TAC-EC/PIC-IF: 2 times of single marginal recurrence
Survival = 36 months
Survival = 10 years
48 Female: multiple recurrence after Operation and resistance to the conventional TACE: Survival = 18 months after TAC-EC/PIC-IF
32/male

“TAC + PIC” combination treatment protocol

2008.6.3
massive: 20cm
dultiple, both lobe
no major vascular invasion

2008.6.3
HBV DNA: not detectable
no hepatitis
no diabetes

2009.7.1
PR: still remained
dultiple, both lobe

2009.7.28
reactivation of hepatitis B
severe flare-up
diabetes developed
60 M
67 M
66 M
PATIENTS and METHODS

• Total of 43 HCCs was treated with this protocol (with informed consent) (M:F=31:12; 29 HBV, 7 HCV, 6 alcoholic, and 1 NBNC; age, 61±10 years old). Number of cases in each TNM II, III, and IV group was 19, 20, and 4, respectively.

• A mixture of rIFNγ (6 to 10 mega unit, LG Biochem. Pharm., Korea) and 5-FU (Choongwae Pharm., Korea; 500mg to 1500mg according to the number and size of the tumor nodule) was injected into each HCC nodule under the ultrasonography guidance 1 to 4 days after TAC with epirubicin and cisplatin (TAC-EC) and lipiodol.
**Treatment Protocol**

- **TAC**
- **PIC**

**Time interval between TAC and PIC:** 1 to 4 days

**Epirubicin:** 50mg/m²  
**Cisplatin:** 60mg/m²  

Repeated every 4-6 weeks  

Until non-visualization on TAC

**Mixture of**  
**5-FU 1000~1500mg**  
**IFNγ 10 MU**

**TAC dose adjustment by:**  
- Age  
- Wbc count  
- Body surface area (BSA)  
- Pugh-Child score
The PIC technique
SUMMARY OF RESULTS

- The initially complete response (CR) rate was 98% (n=43), but recurrence rate was 42% (n=18).
- Survival time was $28.9 \pm 12.5$ months, time to recurrence was $14.8 \pm 10.1$ months, and disease free interval (DFI) = $22 \pm 13$ months.
- Six were died of PD-associated (n=3), cirrhosis-associated hepatic failure (n=2) and accident (n=1).
- All cases were well tolerable:
  - flu-like symptoms (grade I-II)
  - leukocytopenia (grade II-III)
  - mild-to-moderate increase of AST and ALT (grade I-II).
Applications of PIC-IF

Various clinical situations
- Almost all intrahepatic HCC lesions with nodular or infiltrative features
- Intrahepatic regions of the major vascular invasion (*, but not for bile duct invasion)
- Extrahepatic metastatic lesions (palliative): adrenal gland, spleen, abdominal wall, and bone.
- Large exophitic growth of HCC

Benefits
- various targeted applications
- sometimes surprising therapeutic effects
- tolerable toxicity: pain (grade 1~2) and fever/chill (grade 1~2)
- no serious complications when carefully performed by experts
- cases with stabilized decompensation
  - platelet: 15,000 ~ 20,000/mm³
  - PT(%): 40%~50%
  - Ascites (not too small liver size)
CONCLUSIONS

◆ PIC with 5-FU and IFN-γ:
  is very safe (when performed by experts).
  is synergistic with TAC-EC (Epirubicin and Cisplatin).
  is useful for HCC cases with vascular invasion (± shunt).
  is technically very flexible for various agents:
    – anti-angiogenic injectable agent: (humanized anti-VEGF monoclonal antibody, such as Bevacizumab)
    – other chemotherapeutic agents: epinephrine-gel CDDP, Beaded adriamycin, gel-coated epirubicin
    – gene/immuno therapy: Dendritic cell therapy, p53 gene therapy

  is possible to administer the gene/immuno/chome agentes into the portal vein