

Clinical Review of AHCC and GCP on Cancer Therapy: From the Long-Term Follow-Up for Cancer of the Lung, Breast and Large Intestine

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In view of Complementary / Integrative Medicine, clinical review of AHCC and GCP has been made on patients with cancer of the lung, breast and large intestine from the long-term follow-up.

"Clinical Review of AHCC and GCP on Cancer Therapy : From the Long-Term Follow-Up for Cancer of the Breast, Lung and Large Intestine"

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A multidisciplinary therapy with Evidence Based Medicine (EBM) is recognized as a new advance in medical science. New anti-cancer drugs have been developed and the standard chemotherapy with EBM has been recommended. However, repeat trials have brought therapeutic gaps between the standard EBM and QOL of the patients. For the patients who are wishing tumor reduction and extension of survival, both individual EBM and QOL should be considered. For the past 10 years since 1996, more than 300 patients with advanced or recurrent cancer were enrolled in this study.

The evaluation items have been developed to control tumor growth and the standard chemotherapy by Evidence Based Medicine (EBM) is recommended. However, repeat trials have brought therapeutic gaps between the standard EBM and QOL of the patients. For the patients who are wishing tumor reduction and extension of survival, both individual EBM and QOL should be considered.

In view of complementary / integrative medicine, AHCC and GCP have been used for cancer therapy.

Total evaluation of the cancer patients was summarized according to the performance status (PS), progress of Chemotherapy Effect (RECIST), QOL, survival from A to E, and survival terms. Long-term follow-up for the past 10 years was reviewed on cancer of the lung, breast and large intestine.

Table 1 shows total evaluation of the cancer patients. Performance status, progress of therapeutic effect (RECIST), QOL as shown in 5 classes from A to E and finally, survival terms. For proper and objective evaluation," Listen to the patient " focused on the key words is essential.

Table 1. Total Evaluation of the Cancer Patient

Performance Status (P.S.) (0, 1, 2, 3, 4)
(ECOG, Karnofsky Performance, Grading Scale)

Progress of Therapeutic Effect (RECIST) : CR, PR, SD, PD
(RECIST) - Response Evaluation Criteria in Solid Tumors

Quality of Life (QOL)

A: Excellent
B: Good
C: Fair
D: Not Improved
E: Worse

Key words
1. Physical, 2. Mental, Spiritual & Sociality
3. Basic Life: Ryūkaif Home (Appetite, Sleep, etc.)
4. Controlled Medical Problems (Pain, Fear, etc.)

Firstly, let me start from lung cancer. This slide shows survival terms of 35 cases. Five cases of stage 1A in 40 cases were excluded due to no recurrence. Of 35 cases, only one survived 4 years 5 months as the longest survival. Twenty-eight of 35 cases (80%) died within 4 years. Overall survival is 17% (6 / 35) and mortality is 83%.

Table 4. Survival of 35 Cases (Stage 1A excluded)

Survival Term	Case	%	Alive	RECIST	Dead
The Longest					
4Y5M	1	2.9	0		1
3Y ~ 4Y	9	25.7	1	PD	8
2Y ~ 3Y	6	17.1	3	CR+1, PD+2	3
1Y ~ 2Y	8	22.9	1	PR+1	7
< 1Y	9	25.7	1	SD	8
Total Stage 1A	35	6			29
Overall Survival (%)		17.1%			Mortality 82.9%

Of 40 cases including stage 1A, survival (%), numbers of cases alive or dead and RECIST of living cases are shown on each stage. Marked reduction of survival was seen over stage 1B. In stage 4 , survival was 13% (20 / 23) and 2 of 3 living cases are going to critical condition , which suggests 4.3% (1 / 23) survival at worst as a high probability of 4-year-survival.

Table 5. Lung Cancer with AHCC & GCP : 40 Cases

Stage	Case	Alive	RECIST	Dead	Survival (%)
IA	5	5	CR	0	100%
IB	4	1	CR	3	25%
IIA	4	2	PR+1, PR-1	2	50%
IIB	2	0		2	0%
IV	23	3	PR+1, PR-1	20	13.0%
Total	40	11		29	27.5%
Total Stage 1A	35	6		29	17.1%
IV	23	1	PR+1	22	4.3%

① High Probability of 4-yr. Survival in Stage 1A

shows an immunochemotherapy for non-small cell lung cancer at the OPD. Under individual EBD with AHCC and GCP, side effects of chemotherapy could be reduced.

Immunochemotherapy for Non-Small Cell Lung Cancer at the Outpatient Department

AHCC	3 = 6 Pills (2.25 ~ 4.5gm) / D.
1 pack AHCC	0.75gm
GCP	3 = 6 Caps. (0.96 ~ 1.92gm) / D.
10kg GCP	100mg
CaFtials (Fressa)	280mg / D.
Paclitaxel (PTX)	90 ~ 130mg
Doxorubicin (TXT / DOC)	40 ~ 60mg
Carboplatin (CRCA)	100 ~ 180mg
Vincristine (VCR)	10 ~ 20mg
Granisetron (GEM)	600 ~ 800mg

① 20 ~ 40

In order to keep better QOL, it is important to arrange the kinds , dose and interval of anti-cancer drugs.

shows QOL & Stage of 40 patients with lung cancer until terminal admission. Two groups are compared as shown either 1A included (1A~ 4) on the left , or not (1B~4) on the right. On QOL scores, A~C were 80% vs. 77.2%, and A~B were 52.5% vs. 45.7%, respectively. There were small difference between both groups as shown -2.8 points in A~C and -6.8 points in A~B. Although extension of survival was difficult, most cases could save the time of final hospitalization and enjoyed social life at home. Now, lung cancer is the top of the cancer death in Japan , and 60,000 people died in 2004. Except stage 1A, prognosis of lung cancer in an advanced stage or recurrence is still poor. According to the national survey on postop. 5-year-survival of lung cancer in 2004, survivals in stage 4 ranged from 0% to 50%, that disclosed unreliable much difference among the enrolled institutions. Moreover, numbers of stage

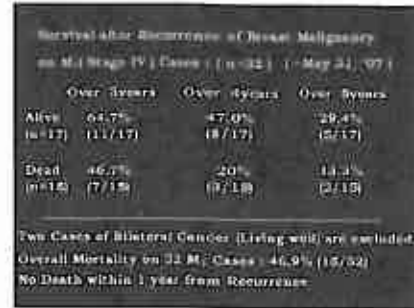
Table 6. QOL & Stage of 40 Patients with Lung Cancer until Terminal Admission

Stage	QOL	IA ~ IV	IB ~ IV
A ~ C		80% (32 / 40)	77.2% (27 / 35)
(A ~ B)		52.5% (21 / 40)	45.7% (16 / 35)
D ~ E		20% (8 / 40)	22.8% (8 / 35)

4 cases are so small as a digit in most institutions. Concerning to the high mortality of stage 4 lung cancer, 0% of 5-year-survival in some cancer centers showed current actual survivals of stage 4.

Now, let me speak on breast cancer. According to the cancer statistics 2004 in Japan, 11,000 patients died of breast cancer, which showed the 5th cancer death of Japanese female. In regard to the long survival, evaluation should be focused on the terms not only from the initial diagnosis but also from the recurrence when encountered.

This slide shows survival after recurrence on 32 M1 (stage 4) cases. Of 32 cases, 17 are alive and 15 are dead. Survival terms were divided into 3 categories over 3 years, over 4 years and over 5 years. No one died within 1 year after recurrence. As shown in this slide, nearly 30% of living cases are alive over 5 years. But, in the dead cases nearly half (46.7%) died over 3 years. Overall mortality on 32 M1 cases are 46.9% (15/32). Improvement of survival over 3 years in M1 cases is the task to be required.



shows survival terms of the living M1 cases. Mean survivals of 17 cases are 5 years 5 months from the recurrence, and 7 years 11 months from the initial diagnosis. As I have reported the effects of AHCC in this meeting, extension of survival with excellent or good QOL is confirmed in comparison with non-AHCC group of breast cancer. The longest survivor (#13) is living well for 13 years 1 month from the recurrence of multiple lung metastasis, and 19 years 10 months from the initial diagnosis. At the end of July 2007, survival reached 20 years.



shows survival terms of the dead M1 cases. Fifteen cases were enrolled. Survival terms are shown from the recurrence (on the left), and from the initial diagnosis (on the right). Mean survival is 3 years 3.4 months and 5 years 4.3 months respectively. The longest survivor (#10) died 9 years 6 months from the recurrence and 14 years 1 month from the initial diagnosis.



shows immunochemotherapy and endocrine therapy for breast cancer at the outpatient department. AHCC and GCP are used as shown in this slide under individual EBM.

Immunotherapy - Endocrine Therapy for Breast Cancer at the Outpatient Department

AHCC 1.2 in 4 Cases (2.20~4.20g) / 1.5
 1 pack AHCC 0.15g
 GCP 1.2 in 4 Cases (1.90~3.90g) / 1.5
 1 pack GCP 0.15g (This includes 1.5g of GCP)

Endocrine Therapy
 TAM or ANK 1.0~2.0g / 1.5
 Clomiphene
 Raloxifene (TRT) 40~60mg / 1.5
 or Fostemsol (FF) 40~60mg / 1.5
 Drostanolone (DR) 10~20mg / 1.5
 Mestranolone (M) 200~400µg (0.2~0.4mg) / 1.5
 Testosterone (Test) 100~200mg / 1.5
 Subcutaneous

Now, let me change to talk on the large intestine. According to the cancer statistics of Japan in 2004, over 40,000 patients died of cancer of the large intestine, which showed the top death of the female and the 5th death of the male in total cancer death. Despite improved health screening, many people died of this cancer in an advanced stage or recurrence, and decreasing tendency of its cancer death is not confirmed. This slide shows the dead cases of stage 4 in my clinic, that survived fairly shortly within 5 years in spite of operation and chemotherapy expect 1 case. They finally died of metastases of the lung and / or liver with peritonitis carcinomatosa. In this group, extensions of survival were difficult, through they underwent cancer chemotherapy and noncurative operation except one. Most of them kept A~B scores of QOL by AHCC against chemotherapy. This fact suggests the actual limit of standard chemotherapy.

Short Survivors under 5 years of Stage IV Cancer of the Colon & the Rectum

Case No.	Age / Sex	Site of Primary	Stage	Survival (yr)	QOL
1	65 / M	Ascending Colon	IV	4	A
2	68 / M	Sigmoid	IV	2	B
3	72 / F	Rectum-sigmoid	IV	4	A
4	75 / M	Sigmoid	IV	3	B
5	78 / F	Sigmoid	IV	2	B
6	80 / M	Ascending Colon	IV	1	A
7	82 / M	Ascending Colon	IV	1	A
8	85 / M	Ascending Colon	IV	1	B

Op: Chemotherapy, AHCC, Ascending Colon
 P.D: Peritonitis Carcinomatosa

shows long survivors over 5 years of stage 4. They underwent operations and no chemotherapy except a case. Survival terms of 4 of 5 cases ranged from 9 years 10 months to 27 years with excellent or good QOL and P.S. For example, case T.K. with diagnosis of stage 4 sigmoid cancer is living well for 27 years. He has had familial multiple polyposis which combined triple cancer as shown in the slide. Since AHCC has been used in cancer therapy, polypoid transformation to cancer has not been identified. Operation is the top strategy for cancer of the large intestine; however, AHCC suggests an important immune-support in cancer therapy. Overall 5-year-survivals of stage 4 and 1 case of stage 3B are 57.5%.

Long Survivors over 5 years of Stage IV Cancer of the Colon & the Rectum

Case No.	Age / Sex	Site of Primary	Stage	Survival (yr)	QOL
9	60 / M	Sigmoid	IV	27	A
10	65 / M	Ascending Colon	IV	10	A
11	70 / M	Ascending Colon	IV	10	A
12	75 / M	Ascending Colon	IV	10	A
13	80 / M	Ascending Colon	IV	10	A
14	85 / M	Ascending Colon	IV	10	A

shows long survivors over 9 years 10 months.

Table 8. Long Survivors after 9 Years 10 Months

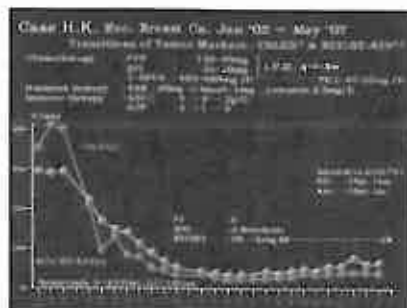
Case	Age Sex	Primary	Site of Recurrence	Stage	PS	QOL	Survival (Years)
HR	60 F	Breast	Lung Met.	IV	0	A	11Y 10M 10D (175)
TR	62 F	Breast	Breast	IV	0	A	10Y 2M 10D (172)
BR	60 F	Breast	Lung Met.	IV	0	A	10Y 10M 10D (170)
HR	60 F	Breast	Lung Met.	IV	0	A	11Y 10M 10D (175)
CR	60 F	Breast	Lung Met.	IV	0	A	11Y 10M 10D (175)
TR	60 F	Breast	Lung Met.	IV	0	A	11Y 10M 10D (175)

is conclusions. Now, let me comment on some cases of long survivors as shown in Table 8.

Conclusions

1. Long survivors (175 months) were enrolled and 8 of them were enrolled in last programs at Stage IV. On 20 cases, survival survival for the last 10 years was 11.7%. On 20 cases of Stage IV, 4 of them survival was 11.7%. All patients (100%) QOL score of 0 on PS and 0 on PS. All patients (100%) QOL score of 0 on PS and 0 on PS. All patients (100%) QOL score of 0 on PS and 0 on PS.
2. Breast (80%) (16/20) cases were enrolled. There are long and well being survivors in Stage IV, which were period by the enrolled survivors. After enrollment, survival terms were 11.7% (2/17) and 11.7% (2/17) and 20.4 years (2/10) and 20.4 years (2/10) and 20.4 years (2/10) and 20.4 years (2/10). No survival within 1 year after enrollment.
3. Clinical features: Forty percent of Stage IV and IV were enrolled. Optimal clinical features were feasible for primary or recurrent cases. Overall 9 of 10 patients (90%) (9/10) in which many long term survivors in Stage IV are enrolled.

This graph shows a recent transition (Jan.'05 ~ May'07) of tumor markers of case H.K. , who has had recurrent breast cancer with lung metastases. Two tumor markers CSLEX and NCC-ST-439 have been followed as positive markers, which showed extraordinary high levels over 2,700 U / mL of CSLEX and over 1,500 U / mL of NCC-ST-439 in Oct.'01. These high levels have decreased to the level of 60 ~ 80 and 30 ~ 40 U / mL, respectively. Current status is Long SD with a score A on QOL and 0 on PS. Survival terms from the recurrence reached 13 years 3 months and 20 years from the initial diagnosis , respectively.

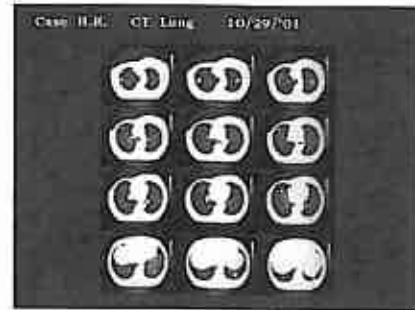


shows immune check on NK activity , Th1 / Th2 ratio , IFN-γ, IL-12 and TNF-α. NK activity and Th1 / Th2 ratio were kept in good levels. IFN-γ and IL-12 were low. TNF-α showed the range from 6 to 19, then down to 0.5 pg / mL in April '07. For evaluation of immune parameters, attention is needed because there is no constantly parallel relation between the parameters and cancer progress. Also , under limited insurance service it is difficult to get early information in advance to other examinations. Immune check is available as retrospective study in current cancer therapy.

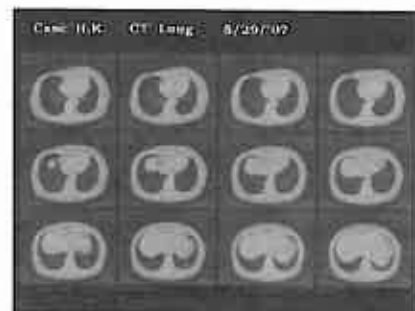
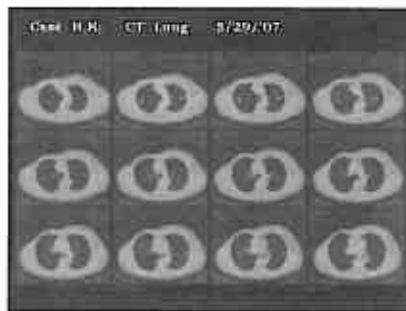
Immune Check

PK Activity	01	02	03	04	05
Th1/Th2	11.1	11.1	11.1	11.1	11.1
IFN-γ	11.1	11.1	11.1	11.1	11.1
IL-12	11.1	11.1	11.1	11.1	11.1
TNF-α	11.1	11.1	11.1	11.1	11.1
CSLEX	11.1	11.1	11.1	11.1	11.1
NCC-ST-439	11.1	11.1	11.1	11.1	11.1

shows chest CT of case H.K. in 2001. Bilateral multiple lung metastases are seen.



CT of case H.K. in May 2007. Tumor reduction and scarring shadows are confirmed.



Photograph of H.K. from the back. Now, she is 69 years old under low dose chemotherapy with 1 / 2 ~ 2 / 3 dose of the standard chemotherapy.



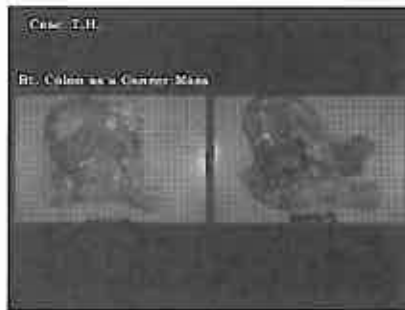
Case Y.O. Giant malignant cystosarcoma phyllodes of the breast. 5 / 20 / '97(preop.) ~ 7 / 4 / '03(postop.)

Photos. from the back and front of the operated area with skin graft 8 / 22 / '06 and 4 / 27 / '07 Survival 10 years 2 months as CR.



Case T.H. The resected specimen of the right hemicolon as a big cancer mass.

She survived 9 years 10 months after the operation up to 101 years of age with the top scores of P.S. and QOL. No chemotherapy done.



Case Y.S. Recurrent breast cancer with liver and lung metastasis. Survived 9 years 6 months from the recurrence and 14 years 1 month from the initial diagnosis. With the best P.S. and QOL she had engaged in her work as a manager of the beauty salon until several days before she expired.



Finally I would like to say that standard EBM is not always the best therapy, but individual EBM focused the each patient should be considered. " Listen to the patient "is a way to an ideal EBM. In view of integrative medicine, AHCC and GCP may have immune support in current cancer therapy.

