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A Review on Palliative Care of Stomach Cancer with KAMPO (漢方) Medication in Japan

by

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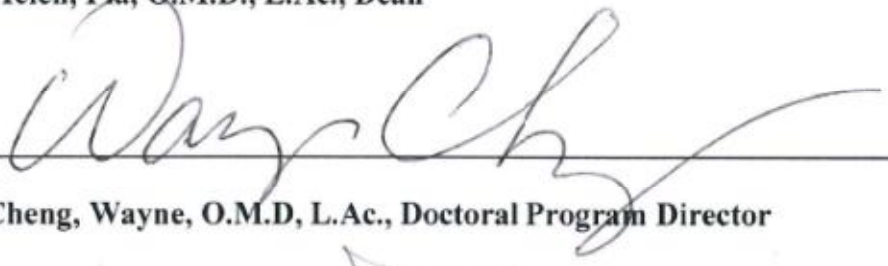

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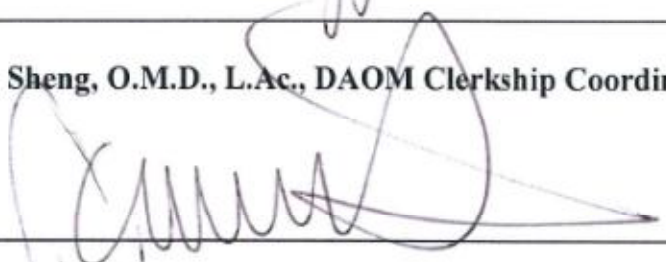

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A Review on Palliative Care of Stomach Cancer with KAMPO （漢方）Medication in Japan

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ABSTRACT

Stomach cancer is diagnosed as cancer cells that have started from the mucosa and spread to other layers in the stomach. Cancer cells invasively spread from the stomach to the lymph nodes and other surrounding organs in the human body. The growing cancer is called metastasis or metastatic disease. This stage is called stage IV gastric cancer, and it is a very serious medical condition at stage IV gastric cancer patient who receives an operation will remove parts of the stomach or even the entire stomach known as gastrectomy.

After gastrectomy, they have to receive radiotherapy or chemotherapy. These treatments have a several side effects to the patient. These potential side effect include reflex esophagitis, dumping syndrome, malnutrition, weight loss, osteoporosis, and depression due to fear of death. The stage IV patients recognize that one day their doctors will no longer be able to treat them any more with chemotherapy or radiotherapy. These patients

are coming to the final stage of terminal cancer, and are looking for an effective or alleviative treatments as a last chance for their survivals.

Kampo medicine is corresponding and integrating treatments for these terminal patients. This review is geared to analyze the evidence from randomized controlled trials and systemic reviews of Japanese Kampo herbal medicine treatment on palliative care of stomach cancer symptoms and to discuss the safety and efficacy of Kampo medicine versus the common pharmacotherapy in treating the stage IV gastric cancer symptoms. The key words were used to search the lines of evidence found in the databases PubMed. No limit was used on date of publication from the U.S. and Japan. Conclusively, Kampo medicine can help the terminal care for the patients. There is using with the western medication as the combined therapy, as a result their immune system increase and their spontaneous cure start by the corresponding and integrating Kampo medications.

KEYWORDS: Kampo medicine, palliative care, stomach cancer, reflex esophagitis, dumping syndrome, gastrectomy, chemotherapy, radiotherapy, metastasis, and gastric syndromes.

TABLE OF CONTENTS

I. INTRODUCTION

According to the calculation of Japanese National Cancer Center in 2015, the annual death number 49,400 of Japanese patient with stomach cancer was the second highest in the all cancer disorders[1]. Presently, Japan has about 133,000 stomach cancer patients. This fact can compare with the death/patients' number in the U.S (10,720/24,590). The Japanese death is much higher than the U.S, it shows that today's Japanese people have a serious cancer regarding stomach cancer[2]. The 5-year survival rate of stage IV patients was 7.3 %[3]. The World Health Organization (WHO) advocates "Palliative Care" as a means of improving the quality of life (QOL) for the patients with life-threatening illness and their families[4]. Almost all of stage IV gastric tumor patients who need the palliative care, do not choose Japanese traditional Kampo medication, rather they chose special organic food for their terminal care[5]. Japanese medical field has a high quality of advancing medical technology in the world. Even though Japan has a high level medical insurance system which can admit all Japanese people. The government allows Kampo medication for Japanese, it is still not widely used by the Japanese common people. If Kampo traditional herbal medication is used in combination with the Western medication, the terminal patients will alleviate the side effect of chemotherapy / radiotherapy or the metastasis of cancer. The combination increases the immune system and the spontaneous cure. This new paragraph proposed review will discuss the medical principles behind the monitoring of the common pharmacotherapy versus the Kampo herbal therapy. It will evaluate how precise

each monitoring is and how effective in reaching results for stage IV terminal stomach cancer patients.

1. **Stomach Cancer: Definition and Classification**

   Stomach cancer has been defined by the Free Dictionary[5]

   A disease of the cells forming the inner lining of the stomach became abnormal and start to divide uncontrollably, forming a mass called a tumor.

   National Cancer Institute (NCI)[7] defined as follows: *Gastric (stomach) cancer is a disease in which malignant (cancer) cells form in the lining of the stomach*[6].

   According to The International Gastric Cancer Association and The Japanese Gastric Cancer Association[8], it has eleven disorders in histological tumor findings; tumor location, macroscopic type, size, histological type, depth of invasion, cancer-stroma relationship, pattern of infiltration, lymphatic invasion, venous invasion, lymph node metastasis, and resection margins. Gastric carcinoma is also classified four Stages (TNM classification).

   1) Stage I: Tumor confined to the mucosa (M) or submucosa (SM)
   2) Stage II: Tumor invades the muscularis propria (MP)
   3) Stage III: Tumor invades the subserosa (SS)
   4) Stage IV: Tumor invasion is contiguous or exposed beyond the serosa (SE) or tumor invades adjacent structures (SI)

   Stage IV is the most serious stage of stomach cancers. This stage has four treatment possibilities: surgery, chemotherapy, radiotherapy and symptomatic treatment. The appropriate treatment is specific to each symptom and condition

of each unique patient.

2. Different Symptoms of Stomach Cancer:

Stomach cancer has different symptoms by different stages[9] as follow:

1) Stage IA: asymptomatic
2) Stage IB: gastric pain, vomiting, and belching
3) Stage II: gastric pain, abdominal pain, and back pain
4) Stage IIIA: difficulty swallowing, palpitation, fatigue, weight loss, anemia, and dark stools
5) Stage IIIB: abdominal dropsy, pleural fluid, and constant pain of stomach area
6) Stage IV: hard tumor, anorexia, strong body pain, strong abdominal dropsy, and strong pleural fluid

Stomach cancer symptoms vary patient by patient:

a. Pre-Gastrectomy: abdominal pain, vomiting, belching, and sense of abdominal distention
b. Post-Gastrectomy(side effect): weight loss, dumping syndrome, anemia, reflux esophagitis, alkaline gastritis, constipation, and finally-malnutrition
c. Post-Chemotherapy(side effect): vomiting, belching, loss of appetite, canker sore, diarrhea, constipation, general malaise, numbness of extremities, loss of hair, leukopenia, anemia, thrombopenia, and impairment of KD/LV/HT/LU functions.

d. Post Radiotherapy (side effect): vomiting, belching, loss of appetite, canker sore, diarrhea, constipation, loss of hair, numbness of extremities

3. The Risk of Stomach Cancer:

The risk factor of stomach cancer, which is increasing a diseases of stomach cancer. According to National Cancer Institute (NCI), the risk factor of stomach cancer has some medical conditions and reasons[7].

Medical Conditions

1) Helicobacter pylori (H. pylori) infection of stomach
2) Chronic gastritis (information of stomach)
3) Pernicious anemia
4) Intestinal metaplasia
5) Familial adenomatous polyposis (TAP), or gastric polyps

Reasons

a. Eating a diet high in salt, smoked foods. Eating a diet that is low in fruits and vegetables
b. Eating foods that have not been prepared or started properly (no cooking foods)
c. Being older (over 60 years old)or male
d. Smoking cigarettes
e. Having the family members who have had stomach cancer

Particularly, Japanese people have four main risk factors of stomach cancer[10] (by Diamond Online in Japan)

a) Foods that are high in salt

In Japanese foods, the highest risk factor is eating: many kinds of foods that have high in salt content the common traditional foods: miso soup, Japanese pickles, processed meats, smoked meats, dried fish, and broiled meats.

b) Smoking cigarettes;

Many Japanese males enjoy smoking cigarettes daily. Because of the habitual smoking, they may not only have a high risk factor of stomach cancer, but also the high risk factor of lung cancer and other various cancers.

c) Helicobacter pylori Contaminated Water

The third main risk factor of stomach cancer is Helicobacter pylori. Over 65 years old Japanese people infected helicobacter pylori by contaminated water after WWII. Because they lost their food, clothing and shelters, and they had no waterworks after damaging their environment so that they used to drink well or river contaminated water which infected helicobacter pylori. In Japan, the typical stomach diseases include: gastric polyps, stomach ulcer, or chronic gastritis. Chronic gastritis appears like pre-stomach cancer, because chronic gastritis is the first stage which may lead to stomach cancer after infection of Helicobacter pylori.

d) Stress

The fourth risk factors of stomach cancer is stress many. Japanese people have many stresses in their daily life so has a stressful; home life, social life, school life, professional life, or medical treatment. Stress affects the blood stream, and

increases incidence of active organs. As a result, impatience (the stress) becomes gastritis → stomach ulcer which leads to stomach cancer

4. Mechanism for Stomach Cancer Symptoms:

Stomach cancer is an asymptomatic disease. During the early stage of stomach cancer, the patient has no subjective signs of the disease manifesting in their body, stomach cancer develops in three stages[9].

1) Early Stage Symptoms: Common symptoms are such as indigestion, stomach discomfort, loss of appetite, stomach pain, heartburn, and mild nausea, which are similar to gastritis or stomach ulcer. The tumor develops in the mucosa of the stomach
    a. For a few years, tumor grows at a slow pace in the wall of stomach.
    b. Tumor is makes small dots on the surface of stomach.
    c. Tumors remain in the mucosa or the layer of mucosa in the stomach.
2) Second Stage Symptoms: Stomach cancer develops from the mucosa to the muscularis, then to the deeper serosa area. In the second stage, symptoms include lack of appetite, vomiting, weight loss, general malaise (fatigue), hematemesis, diarrhea or constipation, stomachache, backache, and bloody stools.
3) Third Stage-Terminal Stage Symptoms: This stage is called the stage IV stomach cancer, the terminal condition of the malignant gastric carcinoma. Symptoms in the most severe cases, include: body pain, malnutrition, ascites (cancerous peritonitis), potential bleeding with severe anemia, metastasis, and

more. This last stage indicates that a patient has no reasonable option of chemotherapy/radiotherapy treatment or other therapies for survival.

5. Palliative Care of Stomach Cancer:

In 2002, World Health Organization defined about palliative care[4]:

"Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."

Palliative care is a medical activity of holistic care from the initial diagnosis to the after care. Holistic care is given to the precise evaluation problem treatment for the patient and families who have life-threatening diseases. Common experience, they have many forms of pain, for example physical, psychological, social, and spiritual problems.

Holistic care is to improve quality of life (QOL) of patients and their families totally.

4) **The Palliative Care of Stomach Cancer**:

Stomach cancer patients need to care for side effects and some problems after gastrectomy, chemotherapy, or radiotherapy. Side effect of stomach cancer has many different kind of symptoms. Side effect of gastrectomy has reflex esophagitis, dumping syndrome, loss of appetite, malnutrition, weight loss, anemia, and osteoporosis. Side effect of chemotherapy includes combing, canker sore, vomiting/belching, loss of white

blood cell and platelet. Side effect of radiotherapy includes combing, gastritis, low appetite, vomiting/belching, fatigue, soft stools, abdominal pain, and GI problems[9].

5) Palliative Care in Japan:

Palliative care is not only for terminal care, but also the definitive treatment →conservative treatment → improvement of condition treatment. This purpose expands the role of palliative care with each step[11].

1) Mental care for the patient, once they are informed of their cancer, and the ascertainment of support for making the decision by the patient.
2) Information of choices for developed treatment plan and place of treatment.
3) Throbbing pain management.
4) Cleansing care and preventing of decubitus.
5) Controlling abdominal dropsy and pleural fluid.
6) Nutritional support when patient has difficult with oral nutrient intake.
7) The measure of the terminal stage: Does the patient have not resuscitate. (DNR)
8) Consideration of terminal stage patients and their families after the death of terminal stage patient. [physical, psychosocial, social, and spiritual care]

6. Stomach Cancer Treatment by Western Medication:

Surgical therapy, chemotherapy and radiotherapy are possible options for stomach cancer treatment through Western medication[12].

1) Surgical Therapy: Gastrectomy

Gastrectomy is to remove the cancer, and to protect the stomach from recurrence of the cancer. The goal of the gastric surgery is a removal of the primary cancer and the lymphatic problems of the cancer in the stomach completely. Stomach therapy has three main treatments:

a. Abdominal Surgery for Stomach Cancer;

   It is used to operate for late stage (stage II-IV) patients of stomach cancer by lancing the abdominal area directly. Patients opting surgery have a long term hospital stay and a long term recover time.

b. Laparoscopic Gastrectomy

   It is used to operate on early stage (stage I) of stomach cancer patients by laparoscope through opening of keyholes in the abdomen indirectly.

   This surgery is less intrusive and a phenomenal recovery is highly possible scars of the keyholes, incisions and there is a quick return to normal life.

c. Endoscopic Surgery

   It is used to operate on the early stage (stage 0-I) patient of stomach cancer by using an endoscope through the inside of the stomach indirectly. This surgery also a rapid recovery to normal life.

2) Chemotherapy

   a. Before the surgery, chemotherapy is used to decrease the growth of cancer cell although the entire cancer cell cannot be entirely removed, or repressed of metastasis from recurring.

b. It is used when stomach cancer is inoperable, the growth of stomach cancer is impossible the surgery.

c. It is used when stomach cancer had metastasized to other organs or returned to other organs.

3) Radiotherapy

a. It is used to alleviate the symptoms where the growth of stomach cancer is inoperable.

b. It is used to prevent metastasis or recurrence of stomach cancer

7. Side Effect of Gastrectomy, Chemotherapy and Radiotherapy:

A large-term study by the Site of Organized Information about Gastric Cancer Treatment (SOIGCT) is following thousands of stomach cancer patient to see what effect stomach cancer therapy might have on risk of dumping syndrome (early stage=dizziness, cold sweat, headache, bloating, palpitation, vertigo, lassitude, diarrhea, red/pale face: late stage=dizziness, lassitude, sweatness, tremor), reflex esophagitis (heartburn), anorexia, nausea/vomiting, lassitude, fatigue/malaise, malnutrition, nutritional disorder, anemia, weight loss, combing, osteoporosis, and more. There are three areas of the SOIGCT study: gastrectomy, chemotherapy, and radiotherapy. Each care has different side effects to each of them[12].

1) Side Effect of Gastrectomy

Gastrectomy is divided into four surgery types (by National Cancer Center):

a. Total gastrectomy: dumping syndromes, reflex esophagitis, diarrhea

b. Distal gastrectomy: dumping syndrome, dyspepsia, abdominal pain, diarrhea
c. Pylorus preserving gastrectomy: sense of repletion, abdominal distention, heavy on stomach
d. Proximal gastrectomy: reflex esophagitis, heartburn

2) Side Effect of Chemotherapy: combing, canker sore, vomiting/belching, diarrhea, loss of White Blood Cell, loss of platelet
3) Side Effect of Radiotherapy: combing, gastritis low appetite, vomiting, belching, diarrhea, fatigue, abdominal pain, intestinal obstruction, duodenitis, intestinal necrosis, renal impairment, liver damage

8. Complementary and Alternative Treatment for Stomach Cancer:

Complementary and alternative treatment (CAT) research started by Ministry of Health and Welfare in 2001, Japan. In the U.S, National Center for Complementary and Alternative Medicine defined complementary and alternative medicine[13] (CAM) as follow:

> *Complementary and alternative medicine is a group of diverse medical and health care system, practices, and products that are not generally considered part of conventional medicine. (2013)*

The different Complementary and Alternative Treatments[9]:

1) Traditional Treatment; Kampo medicine, acupuncture, moxibustion
2) Chiropractic; massage, finger pressure therapy
3) Foods therapy; supplement, health foods, herbs

4) Psychosomatic therapy; Yoga, Qi gong, Tai qi, art therapy, music therapy, aroma therapy,

5) Other therapy; magnetic therapy, animal therapy, hot spring therapy

Among Japanese people, especially stage IV stomach cancer patients often rely on nutritional foods therapy (total 96.2%, 2005); Agaricus (66.6%), Propolis (28.8%), and Fucoidan[9]. These terminal patients complement the treatment with Western medication (Gastrectomy, Chemotherapy, and Radiotherapy), in addition, they hope to extend their life-expectancy. However, nutritional foods therapy has some serious issues[17].

a. Nutritional foods therapy does not have sufficient evidences to suggest it has any benefit.

b. Stomach cancer patient typically do not have enough knowledge of nutritional foods therapy information.

c. Western medical doctors are not educated enough about Complementary and Alternative Treatment when they were medical students or trainees of Western medical school in Japan.

9. History of Kampo Traditional Medicine:

1) The introduction of Chinese medicine

Between the 5th and 6th Century A.D., Chinese medicine was introduced to Japan, and disseminated to the Japanese people between the 8th to 12th century. The Chinese medical system became the standard medical system in Japan. In the 9th century, the first Japanese medical book named Daidoruijuho (大同類聚方)

written by Abe Masanao (808), encompassed a collection of Japanese traditional therapies. Even though Chinese medical knowledge was adapted to Japan's climate and people, not all necessary medical materials were available. Consequently Japanese doctors modified the original materials of China to Japan's own herbs and minerals[14].

2) The development of Kampo medicine

The most developmental century for Kampo medicine was in the Edo period (16-18 A.D.). Kampo medicine was based on the Shang Han Lun (傷寒論), a single classical medical book in old China (Han Dynasty). Kampo medicine used Shang Han Lun as the foundational principles and concepts. Japanese physician Todo Yoshimasa emphasized that an appropriate treatment is "matching of pattern and formula" (Todo's Koho school) as used in Shang Han Lun. Since then, many Japanese physicians digested and assimilated about Shang Han Lun, and they expanded from acute treatment method to the original chronic treatment method[14].

Presently, modern Japanese Kampo medicine continues to be influenced by the Shang Han Lun theory among many Kampo physicians.

3) The decline of Kampo medication

Kampo medicine declined rapidly in Meiji period (19th Century), because the Meiji government embraced only the German medical system until 1940, and only recognizes the Western doctor license to this date. The Meiji government had a plan for enriching the nation and building up the defense against Western countries. Consequently Kampo medicine was retracted, and the medical licenses of existing

Kampo practitioners that were revoked lost legal standing. Although a small number of these Kampo practitioners continued to practice privately in the local area in Japan, they did so without legal recognition[15]. Since then, Kampo practitioners have needed to obtain many kinds of alternative recognized licenses to apply their medical knowledge: a practitioner of acupuncture and moxibustion, a massagist, a bodywork therapist, a bonesetter, a Kampo pharmacist, among others.

4) Recovery of Kampo medicine

In the Showa period (20th Century), Kampo medicine became popular, and widely recognized among Japanese people after World War II. The Japanese people had no access to Western medicine and they had to rely on folk medicine or Japanese traditional Kampo medicine since 1945. In 1957, a Japanese medical company started to manufacture high-quality extracted herbal granules of Kampo. It was until 1976 that the Japanese government decided to add Western medicine with Kampo herbal medicine into Japanese Health Insurance Plan, encompassing 147 Kampo medical formulas[18].

Current 21st century Kampo medicine combines with Western medical treatment medication.

Kampo medicine uses Western medicine is four folds[16]:

a. Kampo medicine reduces the level of serious side effects when combined with Western medication.

b. Modern medical doctors in Japan are more specialized today in compared to the past.

c. Western doctors generally have a more impersonal relationship with their patients compared to Kampo practitioners, whose premise for treatment is a connection with the patients' conditions holistically.

d. The continual changes and developments in many chronic illnesses and many cancers has resulted in less effective Western medical treatments because of the frequent changes illness patterns.

10. Evidence from Studies of Kampo Medication:

According to Current Kampo Oncology (2012), the reasons for placing Kampo medical therapy in Japanese cancer medical treatment[17] include:

1) Personal Kampo medical therapy was recognized under health insurance and made Kampo medicine changing from a decoction to an extract granule.
2) Manufacturing of Kampo medicine extract unfirming ingredient could be used supply it as well as in a Western medical site.
3) Kampo medicine's use of cancer therapy is based on two reasons:
    a. Progress in physiological activity of compound medicine and the efficacy of the medicine
    b. Recommendation for to certificate for clinical medicine
4) Revaluation of insurance medicine are also performed. Random comparable tests for scientific resemblance of Western medicine are also performed. As a result, the medicinal evaluation is scientifically supporting the use of Kampo medicine.

Western Medical Treatment Faces with Improvement of Some Cancer Therapies[17]

a. Keeps disease from becoming chronic
b. Benefits an aging cancer patient by the aging society
c. Various lifestyle-related diseases and illnesses of a disease aggregate which involve a complication
d. Unidentifiable complaints which are difficult diagnosis increased by the social structural changing. As a result, Western medication has limited for the holistic or complete physical treatment. Doctors prescribed their patients many kinds of Western medicines which were each on a cases by case basis.

Kampo extract medicine may be used with various systemic therapies. The side effects are minimal. Palliative care of the various symptoms include the same side effects and symptoms of terminal cancer. Kampo medicine, as the respective drugs, is validated safe because has been basis is thoroughly tested in clinical tests that have been accumulated via a long history[17]. It is comparable with Western medicine for Kampo medicine and blended Kampo herbal medicines.

The clinical significance of using Kampo medication in palliative care:

Kampo medication in palliative care Kampo medicine complements the treatment for clinical purposes subsequent effects of Western therapy for palliative care[18].

a) Improved immunity
b) Improved quality of life (QOL) for the patient

c) Individually/symptomatically uses Kampo medicine liquid form treatment and by each symptom of the patient.

d) To check the overall history of a patient; of growth, examines of the state of body and the whole body, questioning, inspection, and examines pulse, tongue, and abdomen.

Consequently, Kampo medication becomes an appropriate choice for a patient.

11. Kampo Medication for Stomach Cancer:

Stomach cancer patient have six processes of cancer treatment[12] (Figure 1):

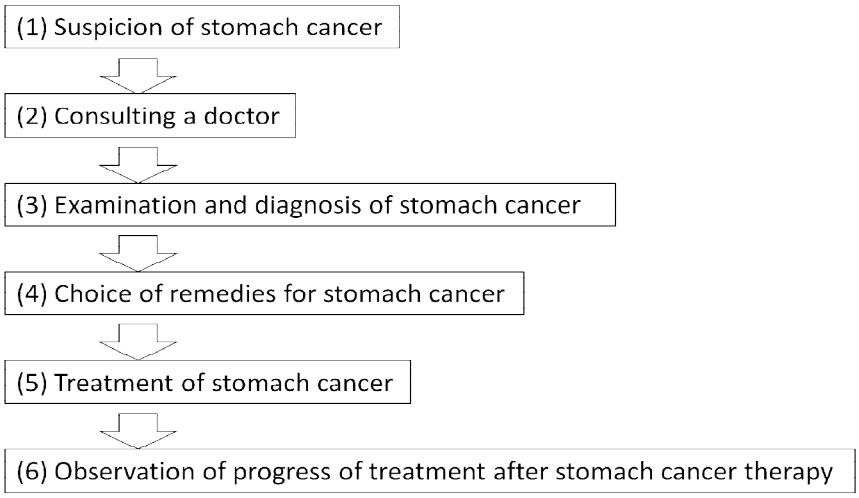

Figure 1. Six processes of cancer Treatment

In 2006, the "Cancer Prevention Act" was approved by Japanese government[19].

Before this act was enabled, three Western therapies were recognized (surgical therapy, chemotherapy, and radiotherapy). A Western doctors could include palliative care for pain control and mental care. Furthermore, they could use Kampo medicine for both pain/mental care as the complementary medication.

According to the research of the National Cancer Center of Japan (2013), 64.3% of Western doctors are using Kampo medicine with Western treatment. The doctors employing them use Kampo medication[20] (Table 1):

Table 1. Doctors' agreement answer rate of using Kampo medicine

Therapy	Effective rate
Big advantage of Kampo therapy	72.0 %
Other therapy (Common medicines) not enough effect	64.5 %
Other correct therapy (chemotherapy) not enough effect	63.5 %

Presently, stage IV stomach cancer patients receive the benefit of Kampo medicine for their holistic palliative cares.

Some examples of the use Kampo medications for terminal care[17] include:

a. For General fatigue --- Shi Quan Da Bu Tang (十全大補湯), Bu Zhong Yi Qi Tang(補中益氣湯)
b. For Anorexia --- Liu Jun Zi Tang (六君子湯), Fu Ling Yin (茯苓飲), Bu Zhong Yi Qi Tang (補中益氣湯)
c. For Nausea/Vomiting --- Liu Jun Zi Tang (六君子湯), Fu Ling Yin (茯苓飲)
d. For Side Effects of Western Therapy --- Shi Quan Da Bu Tang(十全大補湯), Ban Xia Xie Xin Tang (半夏瀉心湯), Liu Jun Zi Tang (六君子湯)
e. For Fermentative Diarrhea --- Ban Xia Xie Xin Tang (半夏瀉心湯)
f. For Constipation --- Da Jian Zhong Tang (大建中湯)

g. For Muscle clamp/pain --- Shao Yao Gan Cao Tang (芍薬甘草湯)

These cases show that Juzentaihoto, Rikkunsito, and Hangesyasinnto are very useful for terminal stomach cancer patients. In review of the research, three Kompo medicines strand out as important for palliative care in trials (Table 2):

Table 2. The efficacy of three formulas for palliative care

Name	Efficacy
Shi Quan Da Bu Tang (十全大補湯)	immune enhancement, suppression of recurrence and metastasis, protection of blood formation dysfunction, improvement of appetite and a physical strength
Liu Jun Zi Tang (六君子湯)	increased appetite and body weight/function, and restraint of gastrointestinal dysfunction
Ban Xia Xie Xin Tang (半夏瀉心湯)	prevention of loose bowels, prevention of nausea and vomiting, and prevention of canker sores

12. Kampo Medicine Theory about Stomach Cancer Syndromes:

1) The history of the name of Kampo：

The name of Kampo has two meanings. *Kan* or *Kam* means the Han dynasty in China, and *ho* or *po* means the medical method. Kampo signifies the medical method of the Han dynasty, reflected in the works of Shan Han Lun. During the Meiji period, the Japanese government decided to allow only the Dutch Western medical system instead of Japanese traditional medicine. In order to distinguish between Ram-po (蘭方) medicines, Western medicine and Kampo (漢

方) traditional Japanese medicine, Western doctors are referred to as Traditional Kampo or Kampo practitioner[21-22].

2) The Kampo concept of "*Sho*" (証) and the Kampo pattern of "Qi-Blood-Water (氣, 血,水) "：*Sho* means the concept of Kampo diagnosis. Sho diagnosis method is different from Western diagnosis method. Sho is based on the patient's symptoms and patterns of disease. Kampo medicine can use the same disease and different Kampo prescriptions by different sho. Similarly the same Kampo formulas can be applied to different diseases by the same sho diagnosis method to the patient[22].

   The Kampo patterns are: Kyo-Zitu (虛, 実), Hyo-Ri (表, 裏), Kan-Netu (寒, 熱), and Ki-Ketu-Sui (氣,血,水). Kyo-zitu (deficiency-excess) and Ki-ketu-sui (Qi-blood-Water). These patterns are always used for the combination of Kampo diagnosis. For example, one use of the patterns would be Ki-kyo (氣虛), Ketu-kyo (血虛), or Ki-utu (氣鬱).

3) The abdominal examination, *Fukushin* (腹診) in Kampo four examinations (四診)

   Kampo medicine has four methods of examinations (四診)； (1) inspection (望診), (2) inquiry (聞診), (3) audio-olfactory assessment (問診), and (4) abdominal observation, *Fukusin* (腹診). Tongue and pulse diagnosis are very important for traditional Chinese medicine (TCM). In contrast, abdominal diagnostic pattern, *Fukusho* (腹証) is one of the core component of Kampo medicine for chronic illness.

Abdominal examination, *Fukushin* (腹診) examines the tension, pain point, or opposition of the whole abdomen. Practitioners provide patients diagnosis through the special information from reflection of the various body constitutions[22].

8 abdominal examinations (腹診):

a. Stuffiness and rigidity below the heart (心下痞鞕)

b. Fullness in the chest and hypochondrium (胸脇苦満)

c. Stomach splashing sound (胃部振水音)

d. Palpitations above/besides/below the umbilicus (臍上/傍/下悸悸)

e. Rectus tension (腹直筋攣急)

f. Blood stasis signs (瘀血)

g. Lower abdominal numbness (小腹不仁)

h. Lower abdominal contracture (小原拘急)

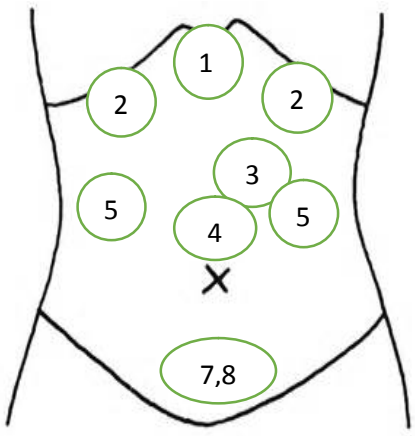

Fig 2. Fukushin

Kampo diagnosis for palliative care of terminal (stage IV) stomach cancer

In Kampo diagnosis, the Stage IV stomach cancer symptoms are called Ki-kyo (氣虛), Ki-utu (氣鬱), Ketu-kyo (血虛), or Sui-doku (水毒)[17].

a) Ki-kyo (氣虛) means Qi deficiency. A patient is diagnosed with a terminal stomach cancer by a doctor, and a patient experienced a loss of appetite because of psychological and spiritual stress. In addition, the whole body became weak after gastrectomy. Furthermore, it also became weak to the inferior of oral consumption after chemotherapy, or radiotherapy.

b) Ki-utu (氣鬱) means stagnation of Qi, or mental depression. Terminal cancer patients feels no hope, a person mystic view of the future, and their families had psychological or spiritual stresses as well. In additionally patients often have insomnia, loss of motivation or interests.

c) Ketu-kyo (血虛) refers to a blood deficiency. There are anemia with hemorrhage after gastrectomy, repression of bone marrow with side effect of chemotherapy/radiotherapy, bloodless with malnutrition, pale face, dizziness, extreme fatigue, loss of hair, and skin or nail problems.

d) Sui-doku (水毒) means an abnormal deficiency or excess of body fluids. Terminal cancer patients have dehydration or abdominal dropsy, edema of extremities/trunk of the body. These symptoms include the problems of saliva/ tears/snivel/sweat, thirst, stiffness, diarrhea, palpitation, ears ringing, bloating, and a feeling of heaviness in the body.

4) Kampo Prescriptions for Palliative Care of Terminal Stomach Cancer:

In Kampo medication, Western doctors use Kampo formulas as the complementary benefit agents with Western drugs for terminal stomach cancer[17]. (Table 3)

Table 3. Kampo formulas as the complementary benefit agents

Prescription	Formulas
Ki-kyo (氣虛)	Si Jun Zi Tang (四君子湯), Liu Jun Zi Tang (六君子湯), Bu Zhong Yi Qi Tang(補中益氣湯)
Ki-utu (氣鬱)	Xiao Chai Hu Tang (小柴胡湯), Chai Hu Gui Zhi Tang (柴胡桂枝湯), Yi Gan San (抑肝散), Chai Hu Gui Zhi Gan Jiang Tang (柴胡桂枝乾姜湯), Chai Hu Jia Long Gu Mu Li Tang (柴胡加竜骨牡蠣湯)
Ketu-kyo (血虛)	Shi Quan Da Bu Tang (十全大補湯), Ren Shen Yang Ying Tang (人参養栄湯)
Ki/ketu-kyo (氣血虛)	Shi Quan Da Bu Tang (十全大補湯), Ren Shen Yang Yong Tang (人参養栄湯)
Sui-doku (水毒)	Si JunZi Tang (四君子湯), Liu Jun Zi Tang (六君子湯), Bu Zhong Yi Qi Tang (補中益氣湯), Shi Quan Da Bu Tang (十全大補湯), Ban Xia Xie Xin Tang (半夏瀉心湯)

In Table 3 shows that Shi Quan Da Bu Tang (十全大補湯), Liu Jun Zi Tang (六君子湯), and Ban Xia Xie Xin Tang (半夏瀉心湯) are important Kampo formulas for terminal stomach cancer treatment as the palliative care..

13. Combination of Western/Kampo Medication for Stomach Cancer:

From 1960 to 2000, the Japanese medical field has developed three main cancer Therapies: surgical therapy, chemotherapy, and radiotherapy.

The palliative care treatment started in 2006 by the regulation of Cancer Prevention Act. The holistic therapy was established as a direction of integrative medication[17]. Each hospital and clinic established their own Palliative Care Team (Fig 3). Hospitals are including Kampo medication as Complementary and Alternative Medicine.

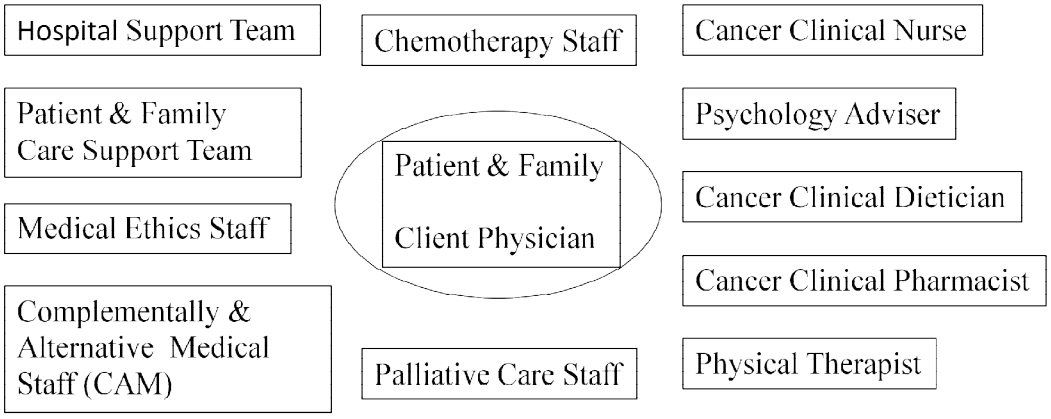

Fig 3. Palliative Care Team

At the present time, almost all Japanese hospitals and clinic doctors are using Kampo medicine as the CAM for preventing side effects of Western therapies[17].

In the case of stomach cancer, Western doctors use four kinds of Western drugs with Kampo medicines as the combination treatment.

1) Weatern drugs with Kampo medicines as the combination therapies:

   a. **Oxaliplatin (**Platinum**)**; to treat diarrhea, nausea/vomiting, numbness of extremities, pharynx/larynx tightness, bone marrow suppression:

      Niu Qi Shen Qi Wan (牛耆腎气丸)

b. **Prodrugs of Fluorouracil system(**antimetabolites**)**; severe diarrhea, bloody enteritis, dehydration, bone marrow suppression, hemorrhage colitis, loss of appetite, malaise, nausea/vomiting, canker sore, hair loss, hand-foot syndrome: Shi Quan Da Bu Tang(十全大補湯), Bu Zhong Yi Qi Tang (補中益氣湯), Ren Shen Yang Yong Tang (人参養栄湯), Liu Jun Zi Tang (六君子湯), Ban Xia Xie Xin Tang (半夏寫心湯)

c. **Paclitaxel (**alkaloid**)**; fever, joint/muscle pain, hair loss, bone marrow suppression: Shao Yao Gan Cao Tang (芍薬甘草湯)

d. **Sispratinn (**Platinum**);** kidney problem, nausea/vomiting, loss of appetite, bone marrow suppression: Chai Ling Tang (柴苓湯), Shi Quan Da Bu Tang (十全大補湯), Wu Ling San (五苓散), Liu Jun Zi Tang(六君子湯)

As the complementary and alternative medicine (CAM), the trial of three formulas ---Shi Quan Da Bu Tang (十全大補湯), Liu Jun Zi Tang (六君子湯) and Ban Xia Xie xin Tang (半夏瀉心湯) --- are using with Western medication by Western doctors.

14. Kampo Medicine---Relationship of Herbs and Human Health:

Kampo medicine is compounded from many different ingredients of herbs, and each herb has its own role in the Kampo formula as Chinese herbs. Kampo medicine is based on the principle of "Qi-Blood- Water" (氣、血、水) and Kyo –Zitu (虛実) elwments[24]:

1) Ki-kyo (氣虛); making up energy by condition of gastrointestine:

Ren Shen (人参), Huang Qi (黄耆), Bai Zhu (白朮), Cang Zhu (蒼朮), Shao Yao (芍薬), Da Zao(大棗), Fu Ling (茯苓)

2) Ki-utsu (氣鬱); recovery of body function from Qi stagnation: Chen Pi (陳皮), Xiang Fu Zi (香附子), Mu Xiang (木香), Su Ye (蘇葉), Bo He (薄荷), Chai Hu (柴胡)

3) Ketu-kyo (血虚); rising up the resistance of the body by improving of nutrition Dang Gui (当帰), Shao Yao(芍薬), Sheng Di Huang (生地黄), E Jiao (阿膠), Long Yan Rou (竜眼肉), Gou Qi Zi (枸杞子)

4) O-ketu (瘀血); Rising up of blood circulation: Tao Ren (桃仁), Mu Dan Pi(牡丹皮), Shao Yao (芍薬), Hong Hua (紅花), Niu Xi (牛膝), E Zhu (莪朮), Dan Shen (丹参)

5) Sui=doku (水毒); making up the fluids circulation in the body

Zhu Ling (猪苓), Ze Xie (泽瀉), Fang Ji (防已), Huang Qi (黄耆), Cang Zhu (蒼朮), Bai Zhu (白朮), Fu Ling (茯苓)

These herbs shows that the trail of three formulas of Shi Quan Da Bu Tang (十全大補湯), Liu Jun Zi Tang (六君子湯), and Ban Xia Xie Xin Tang (半夏瀉心湯) are included as the Ingrediants of herbs.

15. Effect of Herbs for Stomach Cancer Syndromes:

According to Dr. M. Niimi, Kampo medicine can be applied as the insurance, not only extract formulation but also decoct formulation. Stage IV stomach cancer patients, especially, sometimes need to drink Kampo medicine as a decoction[25].

The side effects of chemotherapy or radiotherapy are influenced very drastically for the terminal cancer patient. Many doctors use Kampo medicine with combination of herbs[24]. These herbs are very effective, they recover appetite, decrease side effect syndromes, strengthening energy/immunity, and cause a smooth flow of the body fluid and blood circulation by herbs (table 4)

Table 4. The syndromes of side effect by chemotherapy and radiotherapy with using herbs

Syndromes	Herbs
Loss of appetite	Bai Zhu (白朮), Chen Pi (陳皮), Da Zao (大棗), Gan Cao (甘草), Sheng Jiang (生姜)
Nausea/vomiting	Ban Xia (半夏), Fu Ling (茯苓), Sheng Jiang (生姜)
Fermentative diarrhea	Fu Ling (茯苓), Bai Zhu (白朮), Sheng Jiang (生姜),Huang Lian (黄連)
Low energy/malaise	Korea Ren Shen (高麗人参), Wu Wei Zi (五味子), Gou Qi Zi (枸杞子)
Low WHC/immunity	Korea Ren Shen (高麗人参), Zhu Ling (猪苓)
Anemia/low platelet	Dang Gui (当帰), Shao Yao (芍薬), Chuan Xiong (川弓), Shu Di Huang (塾地黄)
Swelling	Cang Zhu (蒼朮), Fu Ling (茯苓), Ze Xie (泽瀉), Zhu Ling (猪苓)

The three special formulas (table 5) previously mentioned inTable2. However they are important in trials for palliative care of stage IV stomach cancer patients. When we compare the herbs of Table 5 to the herbs of Table 4, they are almost same ingredients of

herbs. This shows that the three formulas of Table 5 has strong evidence using in fever of these formulas/herbs for terminal care of stomach cancer treatment with Western medicine as the complementary and alternative medicine (CAM).

Table 5. Tree formulas of palliative care of stomach cancer

Formulas	Herbs
Liu Jun Zi Tang (六君子湯)	Cang Zhu(蒼朮), Ren Shen (人参), Ban Xia (半夏), Fu Ling (茯苓), Da Zao (大棗), Chen Pi (陳皮), Gan Cao (甘草), Sheng Jiang (生姜)
Ban Xia Xie Xin Tang (半夏瀉心湯)	Ban Xia (半夏), Huang Qin (黄芩), Gan Jiang (乾姜), Ren Shen (人参), Gan Cao (甘草), Da Zao (大棗), Huang Lian (黄連)
Shi Quan Da Bu Tang (十全大補湯)	Dang Gui (当帰), Chuan Xiong (川弓), Shao Yao (芍薬), Shu Di Huang (熟地黄), Bai Zhu (白朮), Fu Ling (茯苓), Ren Shen (人参), Gui Zhi (桂皮), Huang Qi (黄耆), Gan Cao (甘草)

16. Kampo Medicine vs Special Organic Food:

According to National cancer center[12], 40% of stomach cancer patients are taking some supplements as complementary and alternative medication. The percentage breakdown of the patients taking complementary and alternative medication is as foll0ws: 60 % are taking Agaricus (mushroom), about 30% are taking Propolis (bee glue), 10 % are taking Fucoidan (seaweed extract) as the special foods or supplements.

1) Agaricus (mushroom)

Mushrooms are a very commonly-used ingredients in Japanese cooking. For example, the type of mushrooms used include Shiitake, Matsutake, Maitake, Shimeji, Enoki, among others. Agaricus has three Japanese names,

Mematsutake, Kawariharatake, or Himematsutake. Agaricus contains β-glucan. The function of β-glucan is to increase immune system, lower cholesterol, decrease HBP, and regulate liver/intestinal environment. As a result, Agaricus may become a powerfull cancer inhibiter[27].

2) Propolis (bee glue)

Propolis originates in Brazil. Japanese bees do not prodice bee glue. Brazil bee contains Bioflavonoids in Propolis. A variety of Bioflavonoids are the substance of a strong anti-oxidant. The function of this Bioflavonoids is to boosts the immune system, and control the spread of cancer cells. Propolis strengthens the natural healing power in the human body. Propolis works to prevent of various diseases because Propolis includes various vitamins, minerals, and amino acid chains[26].

3) Fucoidan (seaweed extract)

Seaweed is very popular in Japan. People is enjoy many seaweed rrecipies as their daily meals. Some popular meals include Kombu, Wakame,
Hijiki, Nori, Aosa, Mozuku, Mekabu, Tengusa, Akamoku, among others.
Seaweed contains Fukoidan, which is sticky fiber, and constitutes with
U-Fucoidan, F-Fucoidan, and G-Fucoidan. Fucoidan strengthens the immune system in fighting or preventing cancer, lowers cholesterol, lowers high blood pressure, and is an anti-many virus[12].

In section 11-15, the trial of three Kampo formulas--- Shi Quan Da Bu Tang (十全大補湯), Liu Jun Zi Tang (六君子 湯), and Ban Xia Xie Xin Tang (半夏瀉心湯) --- as discussed

a. Section 11; efficacy of Kampo medicine
b. Section 12; complementary benefit agents of Kampo medicine
c. Section 13; complementary and alternative medicine of Kampo
d. Section 14; relationship of herbs and human health in Kampo medicine
e. Section 15; efficacy of each herbs in trial of three formulas

In the view of the three Kampo formulas, Western doctors try to study Kampo medicine in a more scientific and experimental way. In 2001, Western medical students begun to study Japanese Kampo traditional medicine in their medical schools[15]. Therefore, Western doctors are still the early stage scientific verification. The special Japanese publications or online of experimental trials are few in numbers.

17. Kampo Medication Study Design:

In the Japanese medical field, even though Western doctors make many kinds of trials, the trials of stomach cancer combined with Kampo medicine therapy have resulted very little findings. One possible explanation for the limited findings is that the Kampo medical education for medical students began only 15 years ago[15].There are presently only 12 articles findings[29-38]; 10 clinical trials, and 2 systemic reviews. (Table 6)

Table 6. Types of articles for three formulas

Articles	Shi Quan Da Bu Tang (十全大補湯)	Liu Jun Zi Tang (六君子湯)	Ban Xia Xie Xin Tang (半夏寫心湯)
Controlled Study		1	1
Prospective Single-arm study		2	
Randomized Controlled Trials (RCT)	2	2	2
Systemic review		2	

In the Kampo medication study design, if RCT is chosen as the only research method, there will be very few results or outcomes. The limited number of articles were consequently used for this study. On the other hand, the trials of three special organic foods (Agaricus, Propolis, and Fucoidan) were not found anywhere in the information of National Institute of Health and Nutrition in Japan[27].

Japanese doctor seems to still favor nonclinical study or clinical trials for combination therapy. Based on the limited availability of existing research of Western medical studies in this field, Kampo medication study was the main focus this review paper.

II. MATERIALS & METHODS

1. Search method

Using key search words “Kampo and (stomach cancer or gastric cancer)”, resulted in

1201 articles on PubMed. I narrowed down the search, entering key words: “Kampo and three of the 9 articles were from Japan; Among them, 10 clinical trial studies and 2 reviews which were identified and used[29-38]. The articles include Kampo clinical trial report, related systemic reviews, and correlated studies. The articles excludes studies focused on the special organic food, traditional remedies, or immunotherapy, and others, for gastric cancer syndromes. The purpose of this article is to review the available evidence regarding Kampo medicine for palliative care of stomach cancer. In addition to provide more information about the effectiveness and high quality research issues to be addressed in the next step.

2. Study selection

All articles were based on controlled study, prospective study, Randomized Controlled Trial (RCT), and systemic review, in which the stage IV terminal stomach cancer patients with the side effects of Western treatment (gastrectomy, chemotherapy, and radiotherapy) due to reflex esophagitis, dumping syndrome, metastasis, and gastric syndromes of any persons were treated with Kampo herbal medication. Kampo medicine was created by taking Kampo extract formation, the ready-to-use formation, and the dosage of about 15-50g as the extract formation. The diagnosis is made by Western medical doctors who are

licensed from Japanese Ministry of Health, Labour, and Welfare. This diagnosis is based on Western diagnostic systems[40] Traditional trials which test other forms of Kampo medicine; such as the individual formulation like China, or extract decoction, were excluded. The trials compared Kampo medication with various forms of other treatments, in parallel or cross-over design, before and after Kampo medical treatment. Articles and abstracts were provided which contained sufficiently details. Quality and validity assessment, information was extracted from the articles according to pre-defined criteria to show data extraction. The modified Jadad score was calculated by assessing three criteria: description of randomization, blinding, and withdrawal, with the score ranging from 0 to 5 points. The selected articles for detailed review score 3 or more points on Jadad scales.

3. The Jadad scale score

In 1996 an appendix paper, Jadad *et al.* (Scientist Physician of University of Oxford UK) published a 3 point questionnaire from which the answers were used to formulate a basic Jadad score.

1. *Was the study described as randomized?*
2. *Was the study described as double blind?*
3. *Was there a description of withdrawals and dropouts?*

An article of the Jadad scale score describes the number of withdrawals and dropouts corresponding to the response to question #3 for each of the study groups. There underlying reason were also given.

Additional points are awarded for other features: the method of randomization was described in the paper, and that method was appropriate because this method is easy to use, and contains plenty of the important elements, and also has known reliability/external validity. The method of blinding was described, and it was appropriate because this method uses the tablet with similar looks but different taste. Points would be withheld if: the method of randomization was described, but was inappropriate. The method of blinding was described, but was inappropriate. Because these methods lack accuracy.

Reporting a clinical trial could receive a Jadad score of between 0-5. The Jadad scale involves 3 questions but responses are spread over a 5-point scale.

Jadad scores are most used in three ways:

1) To evaluate the general quality of medical research in a particular field.
2) To set a minimum standard for papers' results to be included in a meta-analysis.
3) A researcher conducting a systemic review, for example might elect to exclude all papers on the topic with a Jadad score of 3 or less; or critical analysis of an individual paper.

4. Stomach Cancer evaluation

The following are the measurements for stomach cancer stages in Japan. The most frequently used method is the Japanese Classification of Gastric Carcinoma (JCGC or JC).

In 2010, the Japanese Gastric Cancer Association (JGCA) published new versions of JCGC and JG.

Japanese Articles Center Focus on JCGC and Symptoms [30]

The stage or type is the same stage grouping as that in the UICC/TMN 7th edition has been adopted in the new Japanese Classification of Gastric Carcinoma (JCGC or JC). The UCGC/TMN is based on "Evaluation of the seventh American Joint Committee on Cancer/International Union Against Cancer classification of gastric adenocarcinoma in comparison with the sixth classification. "Cancer, 2010; 116:5592-8" by Ahn HS, Lee Hj, Hahn S, et al… According to the basic classification of UICC/TMN, gross tumor morphology is categorized from type X (TX) to type I-4 (TI-4), as follows:

TX: Depth of tumor unknown; asymptomatic

T0: no evidence of primary tumor: asymptomatic

TI is divided Tia and TIb that tumor confined to the mucosa (M) or submucosa (SM).

Tia: tumor confined to the mucosa (M), asymptomatic

TIb: tumor confined the submucosa (SM), belch, anorexia, vomit

T2 is invades the muscularis propria (MP), gastric pain, abdominal pain

T3 is tumor invades the subserosa (SS), fatigue, palpitation, weight loss, anemia

T4 is divided T4a and T4b that tumor invasion is contiguous to or exposed beyond

the serosa (SE) or tumor invades adjacent structures (SI).

T4a: tumor invasion is contiguous in the serosa or penetrates serosa and is exposed to the peritoneal cavity (SE), abdominal constant pain/dropsy, pleural fluid

T4b: tumor invades adjacent structures (SI), hard tumor feeling, anorexia, strong body pain, abdominal dropsy, and pleural fluid

III. RESULTS

There are a total of 12 original clinical research trials. The trials are summarized in a few different forms: Two studies included are controlled studies for gastrointestinal symptoms after gastrectomy. The other two studies included are prospective studies (single-arm assessments) for gastrointestinal symptoms and ghrelin levels after gastrectomy. The six studies included are Randomized Controlled Trials (RCT) for treating the stomach cancer symptoms. The two studies included are a systemic review of gastrointestinal dysfunction and anorexia syndromes.

1. 12 clinical research trials

Table 7. Controlled study trials: Ban Xia Xie Xin Tang (半夏瀉心湯), Liu Jun Zi Tng (六君子湯)

	Ban Xia Xie Xin Tang (半夏寫心湯)	Liu Jun Zi Tang (六君子湯)
Authors	Akira Aichi, Syuhei Hirose, *et al.*	Akira Aichi, Syuhei Hirose, *et al.*
Source	Nishogaikaishi 28 (4) 961-965	Nishogaikaishi (4) 961-965
Group, and Treatment	Age 62.3, n= 29 (M 21, F 8) HST> once/d, 4wks + drugs	Age 62.7, n= 37 (M28, F 9) RT> once/d, 4wks + drugs
Result	Improvement rate. (after 4 wks) Loss of appetite= 70.6 %	Improvement rate. (after 4 wks) Loss of appetite= 71.4%

	Heavy stomach= 62.5% Heartburn= 65.0% Nausea/vomiting= 62.5%	Heavy stomach= 65.2% Heartburn= 65.4% Nausea/vomiting= 75.0%
Conclusion	Patients Loss of appetite, Bloated feeling , Heartburn, and Nausea/Vomiting improved.	Patients Loss of appetite, Bloated feeling, Heartburn, and Nausea/Vomiting improved.

There are two controlled study trials on two Kampo medical treating for gastrointestinal symptoms after gastrectomy. These both formulas' results are showed the positive and hopeful outcomes. However, these trials need to arrange the same age/number group in patients, and also need to use the same Western anti-cancer drugs in all the patients.

Table 8. Prospective (Single arm) study trials: Liu Jun Zi Tang (六君子湯)

	Liu Jun Zi Tang (六君子湯) 1	Liu Jun Zi Tang (六君子湯) 2
Authers	Shuji Takiguchi, Yuichiro hiura, *et al*.	Gunji, S., Ueda, S. *et al*
Source	Gastric Cancer (2013) 16: 167-174	Journal Surgical Research (2013)
Group, and Treatment	Age 61.9, n= 25 (M= 16, F= 9) TG=17, DG=8 RT> 3/d, 4wks, (rest 4wks), 4wks= 8wks	n= 19 , PG, PG> 6 mo before entry RT > 2.5g 3/d, 4wks Before & after 4-wk administration of RT by GSRS

		Exam: ghrelin levels, body weight, appetite, and GSRS for QOL
Result	Improvement points (after 4 wks) LS= $p<0.05$ LBE,GRD,LBS, and NV= $p<0.05$ QOL= $p<0.05$ Ghrelin level= $p=0.0026$ > (after rest p= o.oo15)	Improvement points (after 4 wks) GSRS=after 1.9 ± 0.7,(before 2.6±0.6 (For abdominal pain, acid reflux, diarrhea, and constipation) Ghrelin levels= affected Body weight= increased Appetite= increased
Conclusion	Patients changed to increase active ghrelin, weight, and appetite. There are also control of gastrointestinal problems, and progress of body functions so that it improves patients QOL.	Patients changed to increase active Ghrelin, weight, and appetite. There is a baseline GSRS score of ≥2. RT effect plasma ghrelin functions so that it improves patients QOL.

There are two single-arm clinical trials on Kampo medical treating gastrointestinal symptoms and ghrelin levels. Japanese doctors have noticed low QOL, which is a loss of appetite and weight loss after gastrectomy, cause of dysfunction of ghrelin. In two trials, active ghrelin showed that it leads to improve patients' quality of life (QOL).

Table 9. Randomized Controlled Trials (RCT): Shi Quan Da Bu Tang (十全大補湯)

	Shi Quan Da Bu Tang (十全大補湯) 1	Shi Quan Da Bu Tang (十全大補湯) 2
Authors	Takuya Yamada	Hiroyuki Imano, Yuuzi Maruo et al
Source	Progress in Medicine (2004) 24: 2746-7	Nihon Toyo Gakkai (2004)
Group	Arm 1 n=43 5-FU + JT Arm 2 n= 51 5-FU	Arm 1 n= 11, UFT+ JT Arm 2 n= 12, UFT
Measurement/ Data/Times	Arm 1: FU 200mg/d + JT 7.5g/d clinical stage terms Arm 2: FU 200mg/d, 2years 5/clinical stages year-survival rate	Arm 1: UFT 300mg/d + JT 7.5g/d Arm 2: UFT 300mg/d (both14 wks) Blood components (after 1/3/6/12 ms); low appetite, general malaise
Result	5 year-survival rate: Arm 1: 73.5%, Arm 2: 74.3% Clinical stage year rate Arm 1: I,II= 2ys 92%, 5ys 90% Arm 2: I,II- 2ys 91%, 5ys 83% Arm 1: III,IV= 2ys 87%, 5ys 25% Arm 2: III,IV= 2ys 22%, 5ys 0%	Hemoglobin, WBC/ lymphocyte count: No meaningful Sub presser T cell %: ↓ Arm 1, after I month, $p<0.05$ Cytotoxicity T cell%: ↑ Arm 1 after 1 month, $p= 0.076$
Conclusion	Patients survival rate showed that Median value of stage III and IV patients is 14.2 years (2ys), and 35.1ys (5ys) by taking FU/JT. Combination of JT therapy is effective for terminal ST cancer.	Sub presser T cell of Arm 1 reduced during 3 months, and Cytotoxicity T cell increased after 1 month. Low appetite and malaise were improved. Combination of JT is effective for terminal ST cancer.

There are two randomized controlled clinical trials which compared with combined and non-combined therapy after gastrectomy. The first trial showed survival rate of combined therapy is higher than non-combined therapy. Especially, a 5 year survival-rate of stage III/IV stomach cancer patients at a significant rate Arm 1 (25%) compare with Arm 2 (0%). The second trial showed differentiate of blood components after gastrectomy. As a side effect of stomach surgery, patients have loss of appetite and general malaise overall. Unlike the immune system of a healthy body condition which including a good appetite and well-being of the body. Acceding to the trial, Cytotoxicity T cell increased and Sub presser T cell decreased. This indicates that ST cancer cell decreased by Cytotoxicity T cell (killer cell), and continue to attack the cancer cells by decreasing the Sub presser T cell (stopper of Cytotoxicity T cell's function). Both combination of JT therapies reflect good results for terminal stomach cancer patients.

Table 10. Randomized Controlled Trials (RCT): Liu Jun Zi Tang (六君子湯)

	Liu Jun Zi Tang (六君子湯) 1	Liu Jun Zi Ta g (六君子湯) 2
Authors	Ohno, T., Yanai, M. *et al.*	Takahashi, T., Endo, S. *et al.*
Source	Clin Exp Gastroenterol, 2011	Journal of Surgical Research, 2013
Group	n= 10 (current or unrecectable of ST cancer patients)	n= 11 (M= 8, F= 3,Pylorus-Preserving Gastrectomy: PPG patients)
Measure-Ment &	Arm 1: n= 5, S-1 + RT 7.5g/d 3wks, (rest 2wks), no take 3wks Arm 2: n= 5, S-1 + RT 7.5g/d	Arm 1: n=4, RT 2.5g ×3/d 4wks, (rest 4wks) Arm 2: n=7, Rt 2.5g ×3/d (rest 4wks), 4wks

Data/Times	Don't take 3wks, (rest 2wks) 3wks Anorexia, nausea/vomit by S-1	GIQLI, SRSS, Sigstad score, and ACES
Result	Plasma acyl ghrelin: ↑ RT intake Food intake score : p= 0.0496 During RT administration: Plasma acyl ghrelin: ↓ nausea= ↓ Plasma acyl ghrelin: ↓ appetite= ↑ Anorexia grade: p= 0.0441	GIQLI: no significant difference SRSS: decreased on RT treatment. Sigstad score: no significant difference ACES: decreased on RT treatment.
Conclusion	Patients nausea decreased, and appetite increased by taking RT. RT therapy is good for side effect of Cisplatin in terminal ST cancer.	Patients SRSS (Stasis related symptom score) and ACES (Alimentary Canal Excretion Scintigraphy) decreased. RT therapy is to promote the excretion.

There are two randomized controlled trials which compare combined and non-combined therapy for three types of patients: (1) who are current ST cancer, (2) ineffective gastrectomy, or (3) PPG (Paylous-Preserving Gastrectomy) patients. The first trial showed that the side effects of chemotherapy (used Cisplatin) are anorexia and nausea/vomiting. After taking RT, plasma acyl ghrelin decreased and food intake (appetite) score increased. Therefore, RT combined therapy is more effective than non-combined therapy for the terminal ST cancer (current ST cancer or ineffective gastrectomy) patients. The second trial showed that PPG patient has delay excretory, which is a delay in urination and bowel movements (both liquid and solid in the body) because of one of dumping syndromes. Both of SRSS (Stasis Related Symptom Score) and ACES (Alimentary Canal Excretion

Scintigraphy) a decrease so that the rate of hangover of ST decreased. RT therapy is effective for side effects of gastrectomy and chemotherapy.

Table 11. Randomized Controlled Trials (RCT): Ban Xia Xie Xin Tang (半夏瀉心湯)

	Ban Xia Xie Xin Tang (半夏寫心湯) 1	Ban Xia Xie Xin Tang (半夏寫心湯) 2
Authors	Aoyama, T., Nishikawa, K. *et al.*	Hibino, S., Ina, K. *et al.*
Source	Cancer Chemother Phamacol, 2014	Nissyogaikaishi, 2014
Group	Age 61.9 (36-89), n= 91 (M 91) chemotherapy patients	n= 20 (M= 12, F= 8) metastasis ST or colorectal cancer
Measurement Data/Times	Double-blind, placebo-controlled Arm 1: n= 45, HST 7.5g/d (×3/d) Arm 2: n=46, Placebo Usage: Both of them in 50ml of drinking water and rinse their oral cavity for 10 s. COM (by CTCAE grade)	Arm 1: n= 10, CPT-11 ×1/2w+ HST 2wks + HST 7.5g/3d, (rest 2wks) Arm 2: n= 10, CPT-11, 100-125mg Antitumor effect (by RECIST), CTCAE, and QOL Exam: each 1-15-29/d (3 times)
Result	COM: ≥ grade2, Arm 1=18 (40%) Arm 2=19 (41.3%) Median duration of any grade of COM: Arm 1= for 9 days Arm 2= for 17 days	Antitumor effect: no difference CTCAEt: Arm 1< Arm 2 QOL: Arm 1= no decline (n= 10) Arm 2= decline (n= 7, -2 pts)

Conclusion	Short period of Chemotherapy-induced oral mucositis (COM). HST rinse therapy is effective to reduce side effects many types of chemotherapy drugs.	Patients decreased adverse event and a maintained non-declined quality of life (QOL). Therefore, HST therapy is useful for terminal ST cancer patients.

There are two randomized controlled clinical trials which compare combined and non-combined therapy for chemotherapy or metastasis ST cancer patients. The non-combined therapy includes placebo in double-blind, placebo-controlled randomized phase II study. The first trial shows oral mucositis as the side effect of chemotherapy (S-1, paclitaxel, irinotecan, cisplatin, etc.) is oral mucositis. After using HST, the median duration of any grade of Chemotherapy- induced Oral Mucositis (COM) is shorter than non-combined therapy. The duration of Oral Mucositis is 9 days, compared to 17 days of non-combined therapy. HST rinse therapy is effective to reduce the side effects of any Western chemotherapy medications.

The second trial showed that adverse event include diarrhea, nausea and vomiting, anorexia, ST pain and more. One of prominent side effect of Irinotecan (CPT-11) is delayed-onset of diarrhea. The purpose this trials is to evaluate the usefulness of HST for delayed-onset of diarrhea. In Chinese medicine, Ban Xia Xie Xin Tang (半夏寫心湯) is used for epigastric focal distention, fullness/tightness with very slight or no pain, or dry heaves[45]. Japanese Kampo HST is used only for fermentative diarrhea or carbohydrate malabsorption[47], not for water soluble diarrhea[48]. The HST symptoms are difficulty in swallowing at solar plexus, a

tendency to have soft stools or diarrhea, acute or chronic gastroenteritis, stomach weakness, hangover (二日酔), or heartburn[46]. In the second trials, patients could maintain their QOL by using HST therapy so that patients were also protected from delayed-onset of diarrhea of side effect of chemotherapy.

Table 12. Systemic review trials: Liu Jun Zi Tang (六君子湯)

	Liu Jun Zi Tang (六君子湯) 1	Liu Jun Zi Tang (六君子湯) 2
Authors	Mogami, S., Hattori, T.	Fijitsuka, N., ,Uezono, Y.
Source	Hidwei Pubrishing Corporation 2014	Froriters in PHARMACOLOGY 2004
Highlight Point	A small number of patients in each control group (10 or 19).	Both research cases of humans or animals.
Summary	The physiology & clinical benefits of RT with a special focus on RT-Western drug combination therapies	As a ghrelin potentiator, the effects of RT and its mechanisms of action on anorexia-cachexia for improving QOL in patients
Limitation	Limited by two publications of RCTs and reviews. There is evidence from RCTs that RT-Western drug combination therapy improving and anorexia symptom improve.	Limited by two publications of RCT/single arm studies and reviews. Despite the evidence from different cases of patients. Patients QOL improved.

Conclusion	Used Western drug (docetaxel/S-1/5-FU) and RT and measured sufficient plasma ghrelin levels and QOL score.	Used an sufficiently large group, measurements. Need for both RCT studies and chose for only terminal ST cancer cases.

For the above two reviews, the common conclusions were as follows:

1) Kampo medicine reduced the side effects of combination of Western drug therapies.
2) There is not enough evidence to support that, in Japan, Kampo medicine is more effective than a special organic food diet.
3) Based on current trials, most of them have limitations with data collections, symptoms of observation, research design methodology, and duration of follow-up observation.
4) Two reviews suggest a future direction for RCT research in thesis of quality and quantity of trial design, better data collection and symptoms observation, larger samples, well-chosen control groups, and longer follow-up observation,.

2. Benefits and Harms a special organic food diet

National Institute of Health and Nutrition (NIHN) is introducing the three special organic foods (Agaricus, Propolis, and Fucoidan) as the health foods or supplements[27]. Acceding to Japanese Pharmaceutical Affairs Law, government does not allow to be classified as the medicine[42]. NIHN is also introducing the information of experiments of

each food. However, no evidence of research trials for these three foods is available. In order to discuss Kampo medicine vs special organic foods, we need to list up compare benefits and harms of three organic foods[27,40,44].

Table 13. The benefits and hams of three special organic foods.

	Benefits	Harms
Agaricus (mushroom)	B-glucan; increase the immune system, lower cholesterol, decrease HBP, and regulate LV/Intestinal environment	There is no evidence by clinical experiments. Many animal/cultured cells experiments were reported with not enough evidence of cancer.
Propolis (bee glue)	Bioflavonoids: boost immune System, control the multiplication of cancer cell	Side effects: gastrointestinal problem, ST discomfort, diarrhea, and allergy by body condition or constitution
Fucoidan (seaweed)	U/F/G- Fucoidan: strengthen immune system for cancer, lower Cholesterol/HBP, and anti-virus	Fucoxanthin is reported more effects than U/F/G-Fucoidan for cancer cells, but, they have no studies to perform evidence of humans (only animals).

IV. DISCUSSION

This work includes 6 Randomized Controlled Trials (RTC), 2 single arm trials, 2 contr0lled studies, and 2 systemic reviews. The reviews titles are conducted in Japan and North America ranging from 2000 to 2016.

There are three main Kampo herbal medications' studies[29-38], which include "Shi Quan Da Bu Tang" [十全大補湯] (3trials). "Liu Jun Zi Tang" [六君子湯] (7trials), and "Ban Xia Xie Xin Tang" [半夏瀉心湯] (2 trials). There studies compared three special organic foods, which include Agaricus, Propolis, and Fucoidan as the common pharmacotherapy showing consistent results in all three[27]. The Kampo herbal medication studies showed that the Japanese Kampo medicine was more significantly suitable than the special organic foods in ameliorating the multiple gastric cancer syndromes for the stage IV stomach cancer patients[3]. This effecteness includes alleviating or improving from reflex esophagitis, anorexia, fatigue/malaise, dumping syndrome, weight loss, anemia, and osteoporosis. Recently, Japanese doctors have a used many kinds of Kampo formulas properly with patients of special cases. Particularly, above 3 Kampo herbal formulas are able to reduce the side effects of the terminal care treatment. The stage IV stomach cancer patients healing powers, strengthened immune system, increased appetite, all these inhibit cancer benefits of Kampo use, and has progresses, and they enjoy a long term survival possibilities.

The three special organic foods are not sufficient evidence by formal experiments to date[27].The special food can be considered as one of the herbal categories in the formulas of Kampo. According to Chinese medical concept in English, "医食同源" (Isyokudougen)

means that healthy food both prevents and cures, in other words, medicine and food have same roots, Medicine and foods are equals[41]. In Kampo herbal medication considered more important than special organic food. Kampo herbal medicine includes so many ingredients from the whole earth in Japan. The stage IV stomach cancer patients have many different conditions and serious feelings. Their aim is life extension more than patients in their stages. In the clinical trial studies, Kampo medication is a means to treat safely without many side effects adaptable to each patient, changing formulas or modifying of the each different case of patient. Therefore, to design clinical trials studying Kampo medicine for stomach cancer symptoms, we should measure both Health Related Quality of Life (HRQOL) and functional capacities measures. Another benefit of Kampo medicine is rarely reported risks or side effects. Kampo medicine may save as a valuable and alternative treatment for the many different types of tumors or cancers[17].

This review is based upon recent clinical trials and systemic reviews. Through evidence from randomized controlled trials (RCT), Kampo Japanese traditional herbal medicine is the palliative care. Kampo combined with Western medication as combined therapy for the terminal stomach cancer patients that is a neutral and gentle treatment. Kampo medicine has yet to gain the full recognition and acceptance by Japanese people so that more advanced research of Kampo medication will be widely accepted.

V. CONCLUSION

The following are the general conclusion throughout the studies:

1. *There is wide agreement that Kampo traditional herbal medicine can relieve the intolerable pain and problems from the side effect of Western treatments.*
2. *Kampo traditional herbal medicine can be used a natural and healing treatment.*
3. *Kampo uses special organic food in its traditional herbal medicine formulas to reduce terminal stage of stomach cancer symptoms. Patients may use as"薬膳" (healthy medicinall cooking) for palliative care of daily meals*[41].
4. *Kampo traditional herbal medicine can reduce the symptoms of the terminal care in stomac cancer better than special organic food.*
5. *Japanese Kampo traditional herbal medicine can be used as a transformation to the holistic therapy. Kampo herbal medicine can be integrated with Western and Eastern medicine for a holistic therapy. Therefore, Japanese Kampo combined with Western medicine can take its role as one of the significant medical fields for the worldwide medical society.*

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APPENDIX

JT: Shi Quan Da Bu Tang, RT: Liu Jun Zi Tang, HST: Ban Xia Xie Xin Tang

TG: Total Gastrectomy, DG: Distal Gastrectomy

PPG: Pylous-Preserving Gastrectomy

GS: Gastrointestinal Symptoms, GSRS: Gastrointestinal Symptom Rating Scale

GIQLI: Gastrointestinal QOL Index, GRD: Gastroesophageal Reflux Disease

5-FU: Fluorouracil, UFT: Tegafur/Uracil, S+1Cisplatin, CPI=11: Irinotecan

COM: Chemotherapy- Induced oral mucositis

SRSS: Stasis Rerated Symptoms Score

LBD: Low Body Energy, LBS: Low Blood Sugar

ACES: Alimentary Canal Excretion Scintigraphy

CTCAE: Common Terminology Criteria for Adverse Events