Print ISSN: 2434-9186 Online ISSN: 2434-9194

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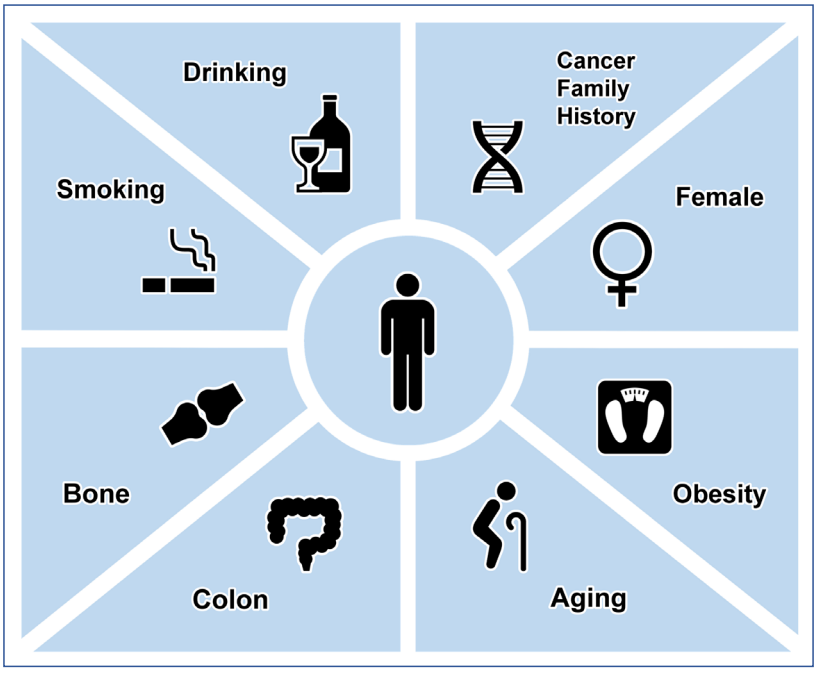
Global Health & Medicine

Volume 4, Number 1
February, 2022



Ningen Dock: Rubric for selecting optional tests and examinations to undergo as part of a personalized medical examination (Page 11)

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Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
Language: English

Global Health & Medicine

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Print ISSN: 2434-9186
Online ISSN: 2434-9194
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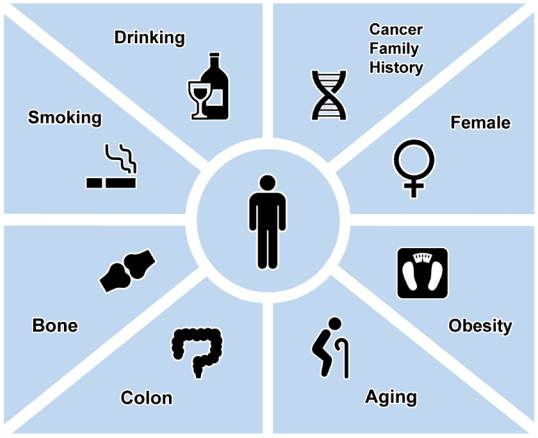

Ningen Dock: Rubric for selecting optional tests and examinations to undergo as part of a personalized medical examination. As an example, the general condition and risk of a 45-year-old smoker could be evaluated by adding a colonoscopy, brain examination, heart examination, lung examination, and test for arteriosclerosis. The idea is to be able to perform a tailored examination that is better suited to the individual (Page 11).

Global Health & Medicine. 2022; 4(1):1-8. REVIEW
DOI: 10.35772/ghm.2021.01120

AIDS at 40th: The progress of HIV treatment in Japan

Shinichi Oka*

AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Forty years have passed since the first five AIDS cases in Los Angeles were reported in 1981. Looking back at the history, these 40 years could be divided into 3 phases. During the first 15 years, when there was little efficacious therapy against HIV, clinical research was directed to develop diagnosis and treatment for opportunistic infections, mainly *Pneumocystis jirovecii* pneumonia. When combination antiretroviral therapy (cART) became available in 1996, taking cART had been troublesome to most patients following 10 years because some of them had severe side effects, diet restrictions, high pill burdens, drug interactions, *etc.* It was not easy for patients to keep high adherence and, therefore, the virus easily obtained drug resistance. Although the prognosis has been dramatically improved, patients had been still living with hard times during the second phase. Along with advancement of anti-retroviral drugs that have allowed simple treatment possible, their life expectancy has further improved and is reaching almost nearly the general population in the following 15 years. However, some patients have recently faced an additional load to treat life-related comorbidities and non-AIDS defining malignancies. The problem is that these diseases start to occur in the 40s- or 50s-year-old generations and that means HIV-infected persons are suffering from pre-mature aging. AIDS no longer signifies death. However, we still have a lot to improve for their quality of life.

***Keywords*:** *Pneumocystis jirovecii* pneumonia, drug resistance, combination antiretroviral therapy, tailor-made therapy, prevention, pre-mature aging

The beginning of AIDS era: the first phase for 15 years

In 1981, adult homosexual male cases of rare pneumonias and tumors were reported from Los Angeles and New York City (*1-3*). After that, additional cases were reported from many cities in the United States (US), all of these cases exhibited severe cellular immunodeficiency (*4,5*), and then the disease was named acquired immunodeficiency syndrome, AIDS. T-lymphotropic retrovirus was isolated from AIDS patients in 1983 and named human immunodeficiency virus (HIV) (*6*). Diagnosis of AIDS equaled death at that time, spreading strong stigma and prejudice in society. Even in a hospital, medical professionals refused to care for and treat HIV patients.

Under such dark years, Japanese researchers managed to develop the first anti-HIV drug, zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor (NRTI) (*7*), and the first neutralizing monoclonal antibody, named 0.5β (*8*). However, because of rapid and continuous replicating properties of HIV in infected patients (*9*), the virus can obtain drug resistance soon after treatment with one- or two- drugs (*10*) and escape variants can easily appear (*11*), keeping the prognosis still poor until three-drug combination antiretroviral treatments (cART) became possible in 1996 (*12,13*). Instead, pathogenesis of HIV infection was able to be learned watching the natural course of the disease.

In Japan, an HIV history started in hemophiliacs who had been transfused concentrated but contaminated blood products mostly imported from US until 1986. Pathogenesis of HIV and histories of Japanese hemophiliacs infected with HIV were described previously (*14*). In this first phase, 15 years, the clinical focus was directed to diagnosis and treatment of rare opportunistic infections before AIDS era such as *Pneumocystis jirovecii* pneumonia that was the leading cause of death in AIDS patients.

Diagnosis and treatment of *Pneumocystis jirovecii* (*P. jirovecii*, formerly *carinii*) pneumonia (PCP)

PCP was very rare before AIDS era. Therefore, clinical experience of diagnosis and treatment of PCP was very limited at that time. *P. jirovecii* cannot be isolated by *in vitro* culture. Therefore, diagnosis was done by direct staining of pulmonary specimens obtained from invasive methods such as bronchial endoscopy in hypoxemic patients, although sensitivity

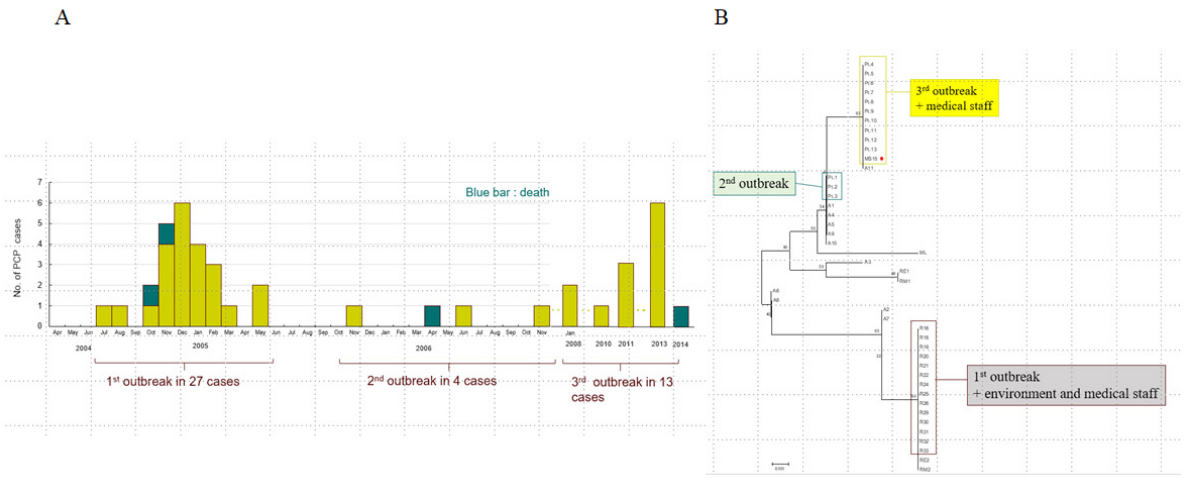

Figure 1. PCP is not the endogenous but exogeneous infection. (A) Three outbreaks of PCP in out-patient unit of renal transplant recipients; **(B)** Phylogenetic tree analysis of *P. jiroveci*. PCP, *Pneumocystis jiroveci* (*P. jiroveci*) pneumonia.

of the method was sometimes not clinically enough. Then, PCR was applied for the diagnosis of PCP amplifying 5S ribosomal DNA (*15*) that enabled us to diagnose PCP rapidly and sensitively with noninvasive specimens by using induced sputum, and follow direct monitoring of the treatment possible. Another group also developed PCR diagnosis of PCP independently (*16*). *P. jirovecii* was thought to be an infection in childhood, colonized in the lung dormantly, and developed PCP endogenously if the patient became an immunocompromised state (*17*). However, along with advancement of immunosuppressive agents, outbreaks of PCP in organ transplant recipients have been reported frequently from European countries since 2000 (*18-21*). Three outbreaks of PCP were also documented, which started in 2004 at out-patient units of renal transplant recipients and lasted for 10 years, that proved human-to-human transmission and possibly airborne, indicating *P. jirovecii* is highly contagious to susceptible hosts (*22*). The genotype of *P. jirovecii* in each outbreak was identical but different from each other (Figure 1). An environment survey revealed contamination with *P. jirovecii* around PCP patients and an oral swab from a healthy medical staff using PCR. PCP prophylaxis with oral trimethoprim-sulfamethoxazole (TMP-SMX) was strongly recommended and the outbreak has been finally mitigated since 2014 (*22*).

As PCP was to be a most common opportunistic infection in AIDS patients, basic research for *P. jirovecii* accelerated in 1980s. Morphological and ultrastructural observations concluded that the organism was a protozoan. Actually, treatment with an anti-protozoan drug, pentamidine, was documented as highly effective against PCP for treatment (*23*) and prophylaxis (*24*). However, advancement of molecular techniques and phylogenetic analysis of Pneumocystis 16S rRNA demonstrated that *P. jirovecii* is a fungi (*25*). If *P. jirovecii* was the fungi, the cell wall was thought to

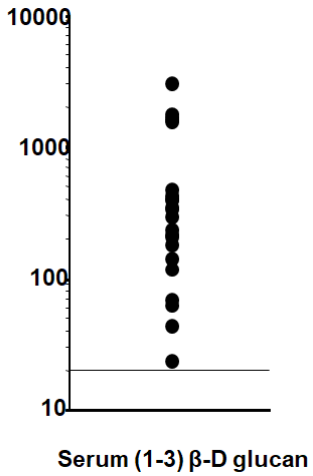

Figure 2. Serum (1→3) β-D-glucan in 22 HIV patients with PCP. Serum (1→3) β-D-glucan was elevated in all 22 patients and mean ± SD was 607 ± 771 ng/mL.

contain (1→3) β-D-glucan (*26*). Then, it was measured in PCP patients and first found that the serum titer in PCP patients was elevated (Figure 2) and it was higher than that in deep seated mycosis (*27*). Furthermore, clinical usefulness of measurement of serum (1→3) β-D-glucan was confirmed as an adjunctive diagnosis of PCP with a sensitivity of 96.4% and specificity of 87.8 % when the cutoff value was 23.2 pg/mL (*28*). Serum (1→3) β-D-glucan has been widely using clinically for diagnosis of PCP in daily practice in Japan since then.

In Japan, as the number of HIV infected patients was still not large in 1990s, most primary physicians were not familiar with diagnosis and treatment of PCP. PCP was not listed in the differential diagnosis of community acquired severe pneumonia. Then, a certain number of severe PCP cases with delayed diagnosis were referred to our hospital. If undiagnosed, PCP is a fatal disease (the mortality is 100%). Therefore, it could be supposed

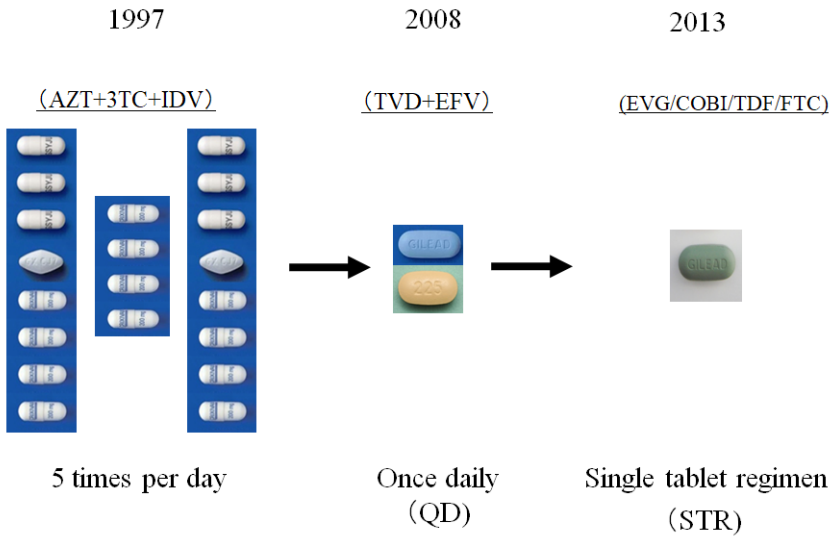

Figure 3. Advancement of cART in Japan. AZT, zidovudine; 3TC, lamivudine; IDV, indinavir; TVD, Truvada; EFV, efavirenz; EVT, elvitegravir; COB, cobicistat; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine.

that there might be a lot of undiagnosed cases with PCP during the first phase. However, if diagnosed at early to moderate stages, all cases can be cured by standard treatment with TMP-SMX or alternative treatment with Pentamidine or Atovaquone in Japan. At present, effective treatment and prophylaxis for PCP have been established (*29*) and primary physicians have been getting experience. Subsequently, PCP is no longer fatal once diagnosed. From this point of view, establishment of PCR diagnosis with noninvasive specimens and adjunctive diagnosis with serum (1→3) β-D-glucan, can both be outsourced to commercial laboratories from any hospital, and have contributed greatly to improve prognosis of PCP in Japan.

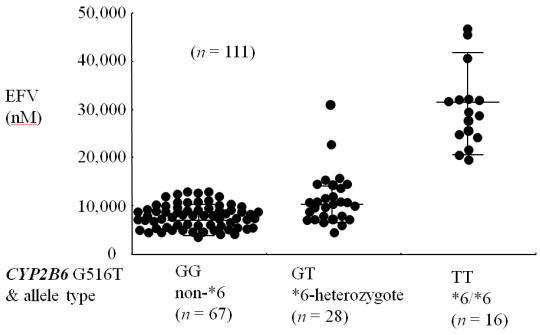

Figure 4. Genotypes of CYP 2B6 and serum efavirenz concentrations in Japanese. If patients had CYP 2B6 *6 homozygote, serum concentrations of efavirenz were elevated without exception. CYP, cytochrome P450.

The second phase of the history from 1996 to 2005

Since new classes of antiretroviral drugs, protease inhibitor (PI) including saquinavir, indinavir (IDV), ritonavir, and non-nucleoside reverse transcriptase inhibitor (NNRTI) including efavirenz (EFV) and nevirapine, have been developed (*30-32*) around 1995-1998, three-drug combination therapy (cART) has been the main strategy for HIV infection. cART consists of 2 components: key drug (PI or NNRTI) plus backbone (2 NRTIs). Especially, IDV-containing cART demonstrated strong anti-HIV activity, suppressed viremia to a undetectable level, and improved prognosis (*13*). However, patients on the IDV-containing regimen (mostly IDV plus lamivudine (3TC) plus ZDV) had to take a total of 20 tablets/day and 5 times/day (twice before and three times after meals) with 1.5 L water/day to prevent nephrotoxicity (Figure 3). In addition, patients taking the first-generation PI suffered from gastrointestinal side effects and the complicated medication patterns with high pill burdens. Then, it was very difficult to keep high adherence until a once daily regimen became possible in 2008 (Figure 3). Then, drug resistance easily occurred (*33,34*). A Japanese drug resistance surveillance network was also established in this period (*35*). Besides drug resistance, patients on the PI-containing regimen had some metabolic complications (*36-38*) and, consequently, had higher risk of cardiovascular diseases under prolonged therapy (*39,40*).

As to the other key drug of NNRTI, efavirenz (EFV), induces central nerve system (CNS) side effects such as vertigo, insomnia, nightmares, and finally depression. It was found that some patients suffered from very strong CNS side effects due to high concentrations of serum EFV because those patients, who were slow metabolizer of EFV, had cytochrome P450 2B6 *6 homozygote (Figure 4) (*41*). EFV dose was reduce from 600 mg/day to 200 mg/day with sufficient clinical efficacy and reduce the CNS side effects by checking their genotype beforehand, achieving the first tailor-made therapy in

HIV infection (*42*).

In the second phase, long term use of d-drug, especially stavudine (d4T), resulted in mitochondrial toxicities such as lipodystrophy and lactic acidosis (*43*). A combination of the generic d4T/3TC/EFV was the most widely used cART worldwide because of its low cost and combined formulation in a single tablet easy to take. Then, it contributed greatly to improve prognosis of HIV-infected patients in developing countries. However, WHO guidelines advised to stop using d4T because of irreversible and unacceptable mitochondrial toxicities of the drug (*44*) and recommended using tenofovir (TDF) in 2010 (*45*). Use of d4T has been phasing out even in developing countries and TDF/3TC/EFV was replaced thereafter (*46*).

In terms of efficacy of cART, it dramatically improved prognosis of HIV-infected patients, especially after 2000 (*47*). Life expectancy of the patients was expected to be nearly only 10 years less than the general population if not co-infected with hepatitis C. However, under these better situations, the biggest clinical question at that time was when to start cART because, as described, long term treatment caused severe side effects and complications, problems of adherence, and drug resistance. A couple of observational studies reported outcome comparisons between the early or deferred cART in asymptomatic HIV infected-patients and demonstrated that an initiation threshold of CD4 counts was around 200/mm^3 to 350/mm^3 (*48-51*). A large international randomized study, the Strategies for Management of Anti-Retroviral Therapy study (SMART study), was conducted to explore whether cART could be interrupted when CD4 counts elevated over 350/mm^3. Our clinic participated in this study as the Japan site. In this study, patients with CD4 counts > 350/mm^3 were randomly assigned to the continuous use of cART (viral suppression group) or CD4 count-guided interruption group (the drug conservation group). In the drug conservation group, patients restarted cART if CD4 counts decreased to < 250/mm^3 and then interrupted it if CD4 increased again to > 350/mm^3. The result was that patients in the drug conservation group had significantly increased the risk of opportunistic diseases or death as compared with those in the viral suppression group (*52*). After this study, it was strongly recommended that cART should continue while their CD4 counts were under 350/mm^3 and never interrupted if patients had some difficulties continuing cART. Apart from the efficacy of cART, development of better drugs or better combinations of ART such as easy to take, less toxic, and no drug-drug interactions were still desired during the second phase.

The third phase of the history from 2006 to present

The first integrase inhibitor (INSTI), raltegravir (RAL), was approved and the first once daily cART (TDF/3TC + EFV) was available in Japan in 2008. The second INSTI, elvitegravir (EVG), enabled us to treat with a single tablet regimen (STR) in 2013 (Figure 3). A simple treatment for HIV infection has become possible in this phase. However, when to start cART was still a major clinical issue around 2010. Benefits and risks of early treatment for asymptomatic HIV infection with CD4 count > 350/mm^3 were not proved by randomized trials. To explore this issue, the Strategic Timing of Anti-Retroviral Treatment (START) study was conducted. In this study, patients with CD4 counts > 500/mm^3 were randomly assigned to start cART immediately (immediately-initiation group) or to defer it until CD4 counts decreased to < 350/mm^3 (deferred-initiation group). The result was the immediately-initiation group had a better outcome over the deferred-initiation group (*53*). The issue of when to start cART was concluded in this study that it should start as soon as possible irrespective of CD4 counts even in asymptomatic HIV-infected patients.

In parallel with when to start issue, HIV prevention trial network (HTPN) study group conducted the HTPN 052 study. It enrolled 1,763 serodiscordant heterosexual couples. HIV-infected subjects with CD4 counts between 350/mm^3 and 540/mm^3 were randomly assigned to receive cART either immediately (early therapy group) or after a decline in CD4 counts (delayed therapy group). An interim analysis of this study showed that cART prevented more than 96% of genetically linked infections in the serodiscordant couples (*54*). The study continued for more than 5 years follow up to assess durability of prevention of HIV transmission and concluded that no linked infections were observed when HIV was stably suppressed by cART in the index cases (*55*). The data indicated that both personal and public health benefits from early therapy. Another important prevention study was done in serodiscordant gay couples (PARTNER study). In this study, 782 couples reported 76,088 times condom less sex for median follow up of 2.0 years, but none were genetically linked within-couple transmission. The result was similar with HPTN 052, strongly indicating that when viral load is suppressed, HIV transmission risk is suppressed to zero (*56*). These findings support the message of 'the undetectable equals untransmittable (U=U)" campaign.

Another big advancement of prevention of HIV transmission was that efficacy of pre-exposure prophylaxis (PrEP) for high-risk populations such as men and transgender women who have sex with men (MSM) was demonstrated in many clinical trials (*57,58*) and now operation of PrEP entered into the implementation phase worldwide. In theory, how to mitigate or conclude new HIV transmission can be listed: treat all for infected person to decrease viral load to undetectable level (U=U) and PrEP for high-risk populations. Taking the evidence into account, WHO

published the consolidated guidelines for treatment and prevention of HIV infection for a public health approach in 2016 (*59*). Looking back to Japanese status of treatment and prevention of HIV infection, approved antiretroviral drugs are almost the same as US and Europe, treatment cost is covered by the national health insurance plus the disabled person's coverage system, resulting that all people living with HIV can be treated with adequate treatment with affordable medical cost. In the point of treatment, the goal has arrived at some success. However, looking at prevention wise, to obtain the disabled person's coverage, patients often have to wait until their CD4 counts decrease below 500/mm^3, and that means not all patient can be treated because CD4 counts at diagnosis with more than 500/mm^3 exist at around 20%-30% of patients. Furthermore, PrEP was not approved yet as of December 2021. Above all, countermeasures to HIV prevention are almost 10 years behind the world. Implementation of the treat-all strategy and PrEP is crucial to mitigate HIV infection in Japan.

Along further improvement of the prognosis (*60*), the aging issue of patients has been getting more important in this decade. Causes of death have been changing over time. The number of deaths caused by non-AIDS defining malignancies (NADM) and related mental health issues exceeded that of AIDS-related (*61*). As an example, causes of death in my hospital in 2020 are listed in Table 1. Among 16 cases of death, 50% of patients died of NADM. The mean age of patients with NADM was 55 years old in my hospital, whereas so called cancer age in the general population is 60 years or older in Japan. Not only NADM, but also co-morbidities such as cardiovascular diseases and diabetes mellitus occurred in earlier ages than general population, indicating pre-mature aging in HIV-infected patients (*62*). Reasons for pre-mature aging are not understood clearly. One possibility might be that current cART completely suppresses plasma viral load to an undetectable level, whereas recoveries of CD4 count, CD4 percent, and CD4/CD8 ratio were not sufficient (*63*). Incomplete immune recovery might cause continuous intravascular inflammation that could cause pre-mature aging. Further clinical and basic research should be employed to answer why HIV-infected patients have pre-mature aging.

Table 1. Causes of death in 2020 in patients registered at AIDS Clinical Center

No.	Age	Sex	Category	Cause	Stage
1	30s	M	Mental health	Suicide	AC
2	30s	M	Unknown	unknown	AC
3	40s	F	NADM	Ovarian ca	AIDS
4	40s	M	Mental health	Suicide	AC
5	40s	M	NADM	Colon ca	AC
6	50s	M	Accident	Slip down at mountain	AC
7	50s	M	Mental health	Alcoholic toxication	AIDS
8	50s	M	NADM	Esophageal ca	AIDS
9	60s	M	NADM	Colon ca	AIDS
10	60s	M	NADM	Pharyngeal ca	AIDS
11	60s	M	NADM	Anal ca	AC
12	60s	M	AIDS	Wasting	AIDS
13	60s	M	CCVD	Cardiac arrest	AC
14	70s	M	NADM	Pancreas ca	AC
15	70s	M	CCVD	Cerebral infarction	AIDS
16	80s	M	NADM	Prostate ca	AC

NADM, non-AIDS defining malignancies; CCVD, cerebrocardiovascular diseases; ca, cancer.

Conclusions and Future

Treatment for HIV infection has progressed rapidly for 40 years from dark years to bright future. In the first 15 years, there had been virtually nothing that could save patients and just avoided fatal opportunistic infections. In the second phase of the subsequent 10 years, it had considered what to use, when to start, and how to treat patients with effective but troublesome ART. And in the third phase of the next 15 years, HIV-infected patients are now well recognized as people living with HIV. Their life expectancy is getting much longer with simple and much safer cART. Long-acting ART of once a month or longer is becoming a reality in the near future (*64*) in Japan. However, they have a disproportionally high incidence of comorbidities and therefore reduced health-related quality of life (*65*). For a better future of people living with HIV, broader ranges of care and comprehensive treatment are necessary for them.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received December 6, 2021; Revised January 26, 2022; Accepted February 2, 2022.

Released online in J-STAGE as advance publication February 7, 2022.

**Address correspondence to*:
Shinichi Oka, AIDS Clinical Center, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: oka@acc.ncgm.go.jp

Global Health & Medicine. 2022; 4(1):9-13.
MINI-REVIEW
DOI: 10.35772/ghm.2021.01109

Ningen Dock: Japan's unique comprehensive health checkup system for early detection of disease

Jun Lu*

Medical Examination Center, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Japan's comprehensive health checkup – Ningen Dock – is a unique system for early detection of disease that has developed over the years along with the country's universal health insurance system. Ningen Dock is currently offered at 1,727 facilities nationwide, involving about 3.7 million people annually. The development of the comprehensive health checkup system may be one reason for Japan's long life expectancy. The major purpose of the comprehensive health checkup system is to maintain health in three main ways: early detection of cancer, detection of lifestyle-related diseases, and confirmation of health status. Here, the history and current status of Ningen Dock in Japan, tests and examinations included in the comprehensive health checkup system, the effectiveness of those checkups, and their advantages and disadvantages are described.

***Keywords*:** Ningen Dock, comprehensive health checkups, Japan

Introduction

Japan's comprehensive health checkup – Ningen Dock – is a unique system for early detection of disease that has developed over the years along with the country's universal health insurance system. "Ningen" means human in Japanese, "Dock" is derived from the dockyard for inspecting and repairing ships. "Ningen Dock" is similar to the medical checkup system in which people visit a facility for a medical checkup. As a comprehensive health checkup system, Ningen Dock have advanced in Japan and are currently offered at 1,727 facilities nationwide, involving about 3.7 million people annually (*1*).

The development of the comprehensive health checkup system may be one reason for Japan's long life expectancy (*2*). The major purpose of the comprehensive health checkup system is to maintain health in three main ways: early detection of cancer, detection of lifestyle-related diseases, and confirmation of health status. Although the cost of such an examination is borne by the examinee, this system will help to reduce the country's overall health care expenditures through early detection and early treatment.

Symptom-based medical care is being major developed around the world, so there is limited public awareness of the comprehensive health checkup system. Facilities perform comprehensive health checkups in countries such as China (*3*), Thailand (*4*), Singapore (*5*), and Vietnam (*6*). Here, the history and current status of Ningen Dock in Japan, tests and examinations included in the comprehensive health checkup system, the effectiveness of those checkups, and their advantages and disadvantages are described.

History of Ningen Dock

In Japan, July 12 is "Ningen Dock Day". The first systematic Ningen Dock was created at the National Tokyo Daiichi Hospital – now the National Center for Global Health and Medicine (NCGM) – on July 12, 1954. At the time, the examination was called "a detailed physical examination involving short-term hospitalization", and a full-scale medical examination was conducted over 6 days. This is the origin of comprehensive medical examinations in Japan (*7*).

In 1955, an outpatient health checkup over five days, mainly involving internal medicine, was instituted at the Aichi Prefectural Central Health Counseling Center. On 1958, a health checkup involving short-term hospitalization for one night and two days was devised at St. Luke's Hospital, and it widely served as the basic format for a health checkup (*8*). This multi-day health checkup was undergone by about 300,000 people annually in 1994. Checkups have taken less and less time, and one-day health checkups are now possible. Today, one-day health checkups are the mainstream, and one-day and multi-day health checkups are undergone by more than 3.7 million people annually (Figure 1).

Current status of Ningen Dock

Currently, Japanese medical examinations are roughly divided into legally mandated medical examinations and voluntary medical examinations (Table 1). Legally mandated medical examinations include medical examinations of local residents conducted by local governments, regular medical examinations conducted by companies and employee organizations, tuberculosis and lung cancer examinations, and health examinations based on the Maternal and Child Health Act and the School Health Act. Health checkups for the elderly have been conducted since 2008 for all participants in public medical insurance ages 40 to 74 (*9*).

In addition, voluntary medical examinations such as Ningen Dock are also conducted. Within the voluntary medical examination market in FY2016, "general health checkups" represented a market of 420 billion yen while "specialized health checkups" such as breast cancer screening and brain examinations represented a market of 45 billion yen. Over the past few years, the market for general health checkups has changed little, amounting to 484 billion yen in 2013, 464 billion yen in 2014, and 464 billion yen in 2015 (average 471 billion yen) (*10,11*).

Tests and examinations that are part of a comprehensive health checkup

Each facility has some basic tests and examinations and optional tests and examinations, although there are some differences.

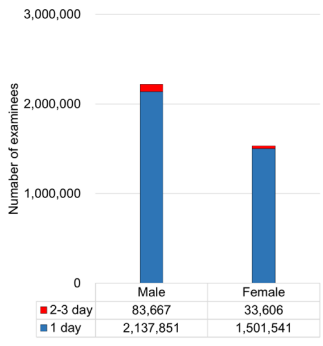

Figure 1. Average number of people who undergo Ningen Dock health checkup in Japan. (Apr. 2017-Mar. 2019). Source: Reference (*1*) 2017/2018 Report on a survey of member facilities (2021/3/31), with modifications.

Basic tests and examinations

Basic tests and examinations include an upper gastrointestinal tract test, physical measurements, medical examination, physiological function test, urine test, stool test, X-ray examination, abdominal ultrasound, blood test (general blood test, liver function test, renal function test, lipid metabolism test, pancreatic function test, sugar metabolism, test for gout, serology, thyroid test, test for tumor markers, and an immunological test), gynecological examination, *etc.* (*12*) (Table 2).

Optional tests and examinations

Various examinations and tests are conducted by each facility, including a lower gastrointestinal tract examination, breast examination, test for arteriosclerosis, brain examination, heart examination, pancreas examination, liver examination, bone examination, test for lifestyle-related diseases, test for Helicobacter pylori infection, test for human papillomavirus infection, PET-CT scan, *etc.*.

Ningen Dock at the NCGM

To provide tailored comprehensive health checkups suitable for everyone, the NCGM is striving to offer options to examinees beyond the basic tests and examinations (Figure 2).

Since 2010, encouraging medical tourism has been a key policy of the Japanese Government. The number of facilities catering to medical tourism has increased. Given that context, the current authors' facility – Ningen Dock at the NCGM – has endeavored to become an international medical facility since 2016. Various efforts have been made to enhance the facility's ability to cater to foreign examinees by translating explanations, test and examination guides, and consent forms, by providing guidance before tests and examinations and on-site interpretation for tests and examinations, and by publishing reports on the number of examinees and their country of origin. As a result of these efforts, the total number of foreign examinees as of March 2017 had increased about 10-fold compared to the previous year. The number

Table 1. Comparison of legally mandated and voluntary medical examinations conducted annually in Japan

	Legally mandated medical examinations	Voluntary medical examination (Comprehensive health checkup)
Purpose	Maintain public health	Maintain personal health
Contents	Anthropometry, eyesight, hearing, blood pressure, chest X-ray, blood test (hemoglobin, red blood cell count, ALT, AST, γ-GTP, triglycerides, HDL-C, LDL-C, fasting blood glucose, HbA1c), urinalysis (protein, sugar), electrocardiogram, doctor's consultation, *etc.*	Includes the same tests/examinations as the legally mandated medical examination
Number of examinees	About 28,000,000	About 3,700,000
Market size	About 445 billion yen	About 471 billion yen

Table 2. Tests and examinations that are part of Ningen Dock health checkups

Test/examination	Details
Upper Gastrointestinal exam	Gastric camera (gastroscopy) or barium meal (stomach X-ray)
Physical measurements	Height, weight, obesity index (BMI), body fat percentage, abdominal circumference
General consultation	History taking, auscultation and percussion of the heart and lungs, palpation
Physiological function test	Blood pressure, electrocardiogram (at rest), hearing test (simple), visual acuity, intraocular pressure, ocular fundus, lung function test (FVC, FVC%, FEV_1%)
Bloodwork	
General	White blood cell count (differential count of leucocyte), red blood cell count, hemoglobin level, hematocrit, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)
Liver function	Total protein, albumin, total bilirubin, AST, ALT, γ-GTP, ALP
Kidney function	Urea nitrogen, creatinine, electrolytes (Na, K, Cl, Ca, P, Mg)
Lipid metabolism	Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides
Pancreatic function	Amylase
Glycometabolism	Fasting blood glucose, glycohemoglobin (HbA1c)
Gout	Uric acid
Serological tests	Hs-CRP, syphilis reaction, hepatitis virus test (HBs antigen and antibody, HCV antibody), blood type (ABO, Rh type)
Thyroid gland	TSH, FT4
Tumor marker	PSA (male only), CA125 (female only), CEA
Rheumatoid	RF (Rheumatoid factor)
Urine analysis	Urine specific gravity, pH, protein, glucose, occult blood, sediment, urine microalbumin
Stool analysis	Occult blood reaction (samples to be collected on 2 separate times)
X-ray examination	Chest X-ray (2 directions)
Abdominal ultrasonography	Liver, gallbladder, pancreas, kidneys, spleen, and other organs
Gynecology (female only)	Pelvic exam, speculum exam, transvaginal ultrasonography, Pap smear (cervical screening)

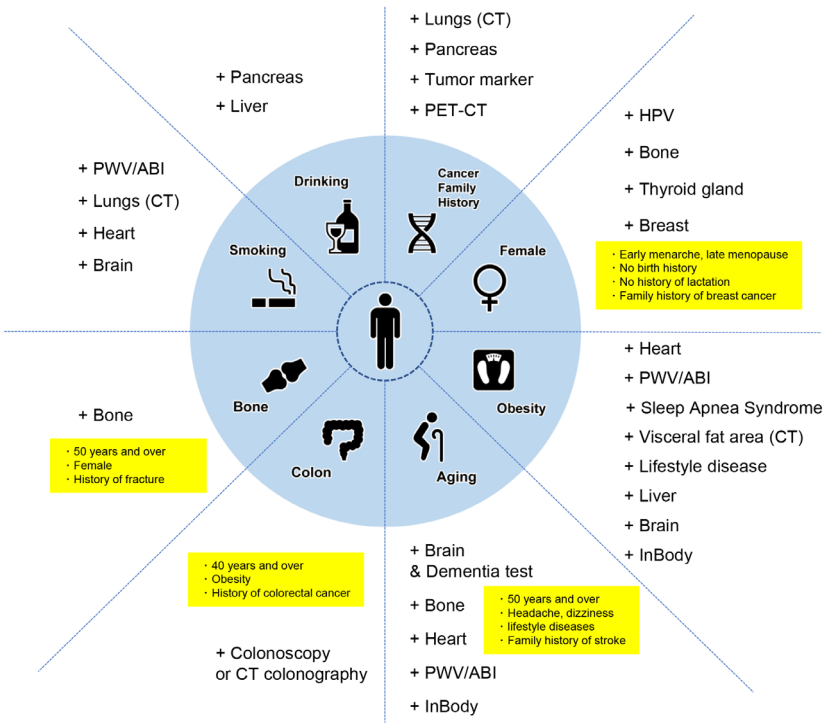

Figure 2. Ningen Dock: Rubric for selecting optional tests and examinations to undergo as part of a personalized medical examination. As an example, the general condition and risk of a 45-year-old smoker could be evaluated by adding a colonoscopy, brain examination, heart examination, lung examination, and test for arteriosclerosis. The idea is to be able to perform a tailored examination that is better suited to the individual.

of Vietnamese examines increased rapidly after September 2017. Prior to 2019, the number of foreign examinees totaled 3,385, accounting for 28% of all examinees, and foreign examinees accounted for more than 50% of the facility's total revenue (Figure 3).

Effectiveness, advantages, and disadvantages of Ningen Dock

Two year of data from the latest survey on the five major cancers by the Japan Society of Ningen Dock

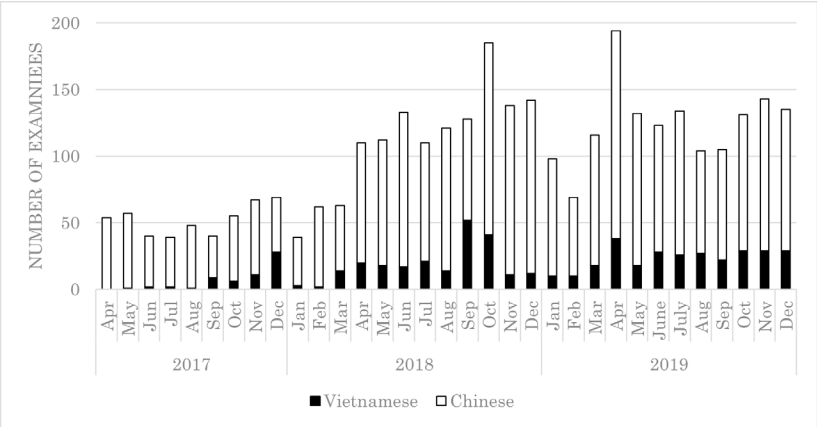

Figure 3. Changes in the number of foreigners visiting the Ningen Dock at the NCGM.

Table 3. Number of cancers found in individuals undergoing Ningen Dock health checkups (Apr. 2016 ~Mar. 2018)

Examination	Number of examinees	Number of cancers found (including suspected)	Cancer confirmed
Lung cancer	6,395,860	26,367	1,754
Gastric cancer	5,681,805	39,828	4,526
Colorectal cancer	6,107,352	83,587	4,239
Breast cancer	2,055,693	27,490	4,463
Cervical cancer	1,772,270	9,746	772

Data source: Reference (*1*) 2017/2018 Report on a survey of member facilities (2021/3/31), with modifications.

indicated that the rate of cancer detection, including suspected lung cancer, in comprehensive health checkups was approximately 0.41%. In 6.65% of examines, lung cancer was definitively diagnosed. The rate of detection of gastric cancer was 0.7%, and gastric cancer was confirmed in 11.36% of examines. The rate of detection of breast cancer is the highest, with a rate of detection of 1.34%, and cancer was confirmed in 16.23% of examinees (Table 3).

The biggest advantage of comprehensive health checkups is preserving life through early detection and early treatment. Since there is a high possibility that the patient can be cured at an early stage and the treatment is often less burdensome, the patient generally has less of a physical, financial, or temporal burden. Regular medical examinations are required so that disease can be found at an early stage.

A disadvantage of comprehensive health checkups is that the determination/results of the medical examination are not 100% correct. Although testing and examination accuracy and technology have made remarkable progress, there are still some situations in which disease may be overlooked. A comprehensive health checkup can also result in a "false positive" (*13*) and, as a result, "overdiagnosis" leading to unnecessary testing and treatment. Unnecessary tests and examinations may strain the body physically (pain, radiation exposure, *etc.*) and psychologically. One should undergo a comprehensive health checkup after considering its advantages and disadvantages.

Conclusion

There are still various aspects of the global problem of aging that still need to be addressed, such as early detection and treatment of disease and tests and examinations suited to the individual, but Japan's unique comprehensive health checkup system – Ningen Dock – should help in that regard. Even though the cost of such tests and examinations is born by individual examines themselves, this approach should help to reduce national health care costs through early detection and treatment.

Funding: None.

Conflict of Interest: The author has no conflicts of interest to disclose.

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Received October 18, 2021; Revised February 4, 2022; Accepted February 16, 2022.

Released online in J-STAGE as advance publication February 24, 2022.

**Address correspondence to*:
Jun Lu, Medical Examination Center, National Center for Global Health and Medicine, Toyama 1-21-1, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: j-lu@hosp.ncgm.go.jp

Global Health & Medicine. 2022; 4(1):14-20.
MINI-REVIEW
DOI: 10.35772/ghm.2021.01015

Present status and perspective of perioperative chemotherapy for patients with resectable pancreatic cancer in Japan

Yasuhide Yamada*

Comprehensive Cancer Center, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Adjuvant chemotherapy is the standard treatment for patients with resectable pancreatic ductal carcinoma. Perioperative chemotherapy has been given in less than 50% of patients with potentially resectable pancreatic cancer in Japan. A modified combination regimen of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX; oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2 on day 1, and 5-fluorouracil 2,400 mg/m^2 over 46 hours every 14 days for 12 cycles) is now preferred worldwide because it mitigates concerns regarding toxicity and tolerance. Adjuvant chemotherapeutic regimens employ S-1 in East Asia, whereas other areas use FOLFIRINOX, capecitabine plus gemcitabine, or gemcitabine monotherapy. Adjuvant chemoradiotherapy is not recommended because randomized controlled trials and meta-analyses revealed no survival benefit compared with chemotherapy. Preoperative chemotherapy with S-1 and gemcitabine combination chemotherapy for patients with resectable/borderline resectable pancreatic cancer significantly increased survival compared to upfront surgery in a recent clinical trial. Perioperative outcomes, including R0 resection rate and post-operative morbidity, were not significantly different between groups. When compared to upfront surgery, neoadjuvant S-1 and gemcitabine treatment significantly reduced the number of pathological nodal metastases in patients who underwent resection. Japanese guidelines therefore recommend neoadjuvant chemotherapy for patients with resectable pancreatic cancer. Preoperative chemotherapy can increase R0 cases by down-staging with higher relative dose intensity of chemotherapy. In contrast, patients who do not respond to chemotherapy may miss resection opportunities and would therefore be at a disadvantage. Therefore, it is critical for both patients and doctors that predictive markers for the response to chemotherapy are identified.

***Keywords*:** FOLFIRINOX, gemcitabine, S-1, oxaliplatin, excision repair cross-complementing gene 1 (ERCC1)

Introduction

Pancreatic cancer is the seventh leading cause of cancer-related deaths worldwide; in 2020, there were 496,000 new cases of pancreatic cancer and 466,000 deaths due to the disease (*1*). The number of cancer deaths in 2019 in Japan was approximately 370,000 (*2*). The number of male cancer deaths was 1.5 times greater than that of female cancer deaths. Lung was the leading site (24.2%) for males in mortality, followed by stomach (12.7%), colon/rectum (12.4%), pancreas (8.2%), and liver (7.6%). The leading site for females was colon/rectum (15.4%), followed by lung (14.1%), pancreas (11.7%), stomach (9.5%), and breast (9.5%). In Japan, 18,124 males and 18,232 females died of pancreatic cancer in 2019, making this malignancy the fourth leading cause of cancer-related deaths in the country (*2*). The proportions of patients in Japan with clinical stage I, II, III, and IV disease in 2018 were 24.5%, 11.9%, 13.1%, and 44.3%, respectively (*2*). The 5-year overall survival rates of patients with pathological stage I, II, III, and IV disease were 39.9%, 16.4%, 5.8%, and 1.3%, respectively. The number of patients with pancreatic cancer has increased steadily since 1955 (*3*). Surgery alone, chemotherapy alone, surgery plus chemotherapy, and no therapy underwent: 25.9%, 10.0%, 43.7%, 14.8% in preoperative clinical stage I, 18.9%, 20.9%, 36.0%, 18.4% in stage II, and 1.8%, 59.6%, 7.0%, 20.8% in stage III in Japan. Regardless of disease stage, fewer than 50% of patients with resectable pancreatic cancer in Japan receive adjuvant chemotherapy (*2*). Perioperative chemotherapy has been given in less than 50% of patients with potentially resectable pancreatic cancer.

In this review, present status and perspective of perioperative chemotherapy in Japan and overseas for pancreatic cancer are described.

Prognosis in resectable pancreatic cancer

Based on the results from several phase III trials (*4,5*), adjuvant chemotherapy has become the standard

treatment for patients with resectable pancreatic ductal carcinoma (Figure 1). However, data from the Medicare database shows that only 7% of 2,440 patients who underwent upfront resection for pancreatic cancer completed adjuvant chemotherapy; 65% of the patients received no adjuvant chemotherapy and 28% received incomplete therapy. Factors that were significantly associated with chemotherapy completion were nodal metastases, comorbidities, and treatment at a National Cancer Institute-designated cancer center (*6*). The median overall survival (OS) was 14 months for patients who received no adjuvant chemotherapy, 17 months for those receiving incomplete chemotherapy, and 22 months for those who completed the chemotherapy regimen. Therefore, completion of adjuvant chemotherapy should be the goal after upfront resection, and neoadjuvant chemotherapy may ensure that patients then receive systemic chemotherapy (*6*).

Meta-analysis of 27 studies suggested neoadjuvant chemotherapy prolonged survival compared with an upfront surgery approach [Hazard ratio 0.72 (95% CI, 0.69-0.76)]. In addition, R0 resection rates were significantly higher in patients who received neoadjuvant chemotherapy (*7*). Of 35,599 patients with stage I to III pancreatic adenocarcinoma in the National Cancer Database, 3,395 (9%) underwent neoadjuvant chemotherapy, 19,865 (56%) received adjuvant chemotherapy, and 12,299 (35%) underwent surgery alone. Cox-regression analysis showed superior OS in the neoadjuvant chemotherapy group compared with patients receiving adjuvant chemotherapy or surgery alone (26 *vs.* 23 *vs.* 14 months, $p < 0.001$) (*8*). Analysis of data in the National Cancer Data Base (1998-2011) from 18,243 patients with Stage I or II pancreatic adenocarcinoma who underwent pancreaticoduodenectomy revealed that 1,375 (7.5%) received neoadjuvant therapy. Over this time frame, the use of neoadjuvant therapy increased from 4.3% to 17.0%. Patients receiving neoadjuvant therapy were more likely to receive treatment at an academic facility (64.4% *vs.* 51.4%, $p < 0.001$). Patients who received neoadjuvant therapy were more likely to have negative margins (77.8% *vs.* 85.5%, $p < 0.001$) and negative lymph nodes (42.9% *vs.* 59.3%, $p < 0.001$) (*9*).

In the European Study Group for Pancreatic Cancer (ESPAC)-3 randomized controlled trial, the median OS was 24.9 (22.9-27.2) months for 646 (56.1%) patients with resection margin negative (R0 > 1 mm) tumors, 25.4 (21.6-30.4) months for 146 (12.7%) patients with R1 < 1 mm positive resection margins, and 18.7 (17.2-21.1) months for 359 (31.2%) patients with R1-direct positive margins ($p < 0.001$) (*10,11*). Multivariate analysis indicated that overall R1-direct tumor margins, poor tumor differentiation, and positive lymph node status were all independently and significantly associated with reduced OS and recurrence-free survival (RFS). Resection margin involvement was also associated with an increased risk for local recurrence (*10*). Patients with borderline resectable/locally advanced pancreatic ductal adenocarcinoma

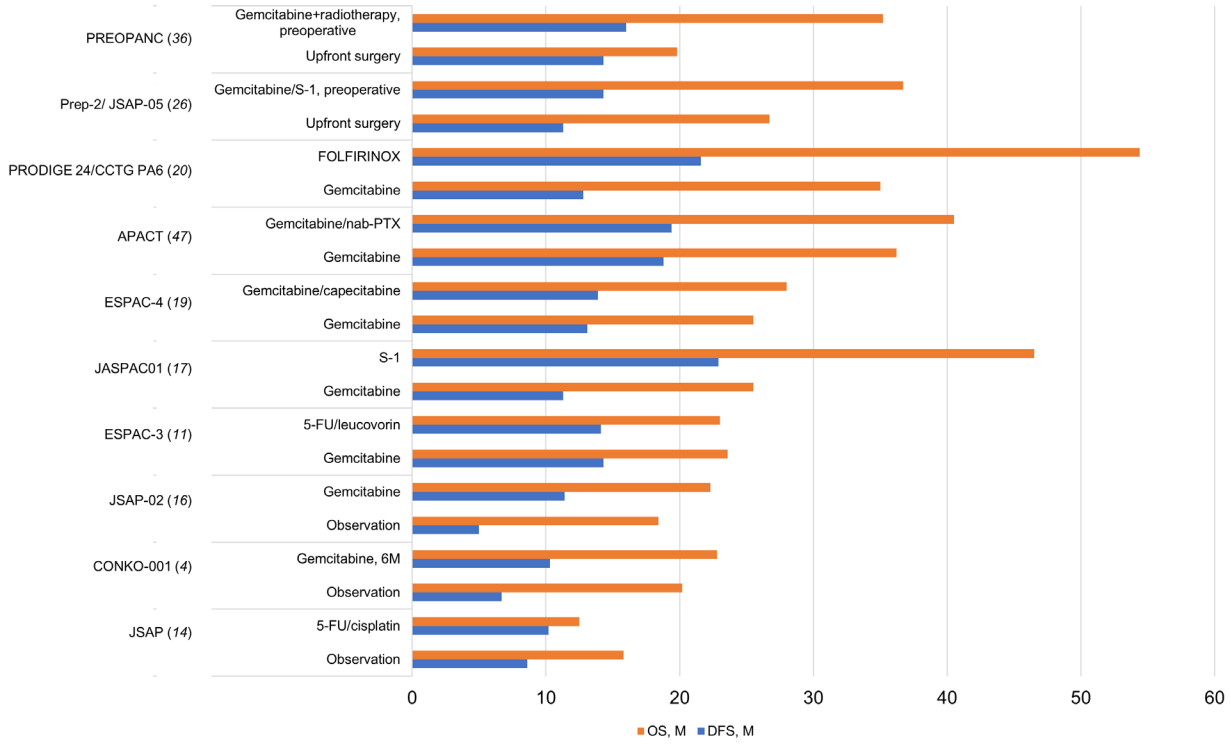

Figure 1. Overall survival (OS) and disease-free survival (DFS) of resectable pancreatic cancer in clinical trials of adjuvant and neoadjuvant chemotherapy. 5-FU, 5-fluorouracil; nab-PTX, nab paclitaxel; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; M, months.

are often treated with 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) to obtain a margin-negative resection, yet selection of patients for resection remains challenging. One hundred and forty-one patients underwent exploratory surgery (borderline, 49%; locally advanced, 51%) and 110 (78%) underwent tumor resection in Massachusetts General Hospital. Although resected patients had lower preoperative CA 19-9 levels (21 *vs.* 40 U/mL, $p = 0.03$) and smaller tumors on preoperative computed tomography scan (2.3 *vs.* 3.0 cm, $p = 0.03$), no predictors of resectability were identified. Disease-free survival (DFS) and OS were significantly better for borderline resectable/locally advanced pancreatic cancer patients treated with neoadjuvant FOLFIRINOX compared with upfront resected patients (DFS, 29.1 *vs.* 13.7, $p < 0.001$; OS, 37.7 *vs.* 25.1 months from diagnosis, $p = 0.01$) (*12*).

The updated American Society of Clinical Oncology (ASCO) clinical practice guidelines state that all patients with resected pancreatic adenocarcinoma who did not receive preoperative therapy should be offered 6 months of adjuvant chemotherapy in the absence of medical or surgical contraindications (*13*). The modified combination regimen of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX; oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2 on day 1, and 5-fluorouracil 2,400 mg/m^2 over 46 hours every 14 days for 12 cycles) is now preferred to mitigate concerns regarding toxicity or tolerance; alternatively, doublet therapy with gemcitabine and capecitabine or monotherapy with gemcitabine alone or fluorouracil plus leucovorin alone can be offered (*13*).

Clinical trials of adjuvant chemotherapy

The Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP) conducted a randomized controlled trial in patients who underwent surgical resection of pancreatic cancer with clear histological margin between 1992 and 2000. The aim was to evaluate the efficacy of adjuvant chemotherapy with 5-fluorouracil plus cisplatin compared to observation alone (*14*). Adjuvant 5-fluorouracil plus cisplatin provided no survival benefit, and lymph node involvement and moderately or poorly differentiated tubular adenocarcinoma versus well-differentiated tubular or papillary adenocarcinoma were factors associated with significantly worse prognosis (*14*). However, a meta-analysis suggested that adjuvant fluorouracil-based chemotherapy provided some survival benefit (*15*).

S-1 is considered a standard adjuvant therapy in Japan based on the results of a randomized trial (*16*) that showed oral S-1 (a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine drug) with gemcitabine was superior (in terms of OS) to observation alone in the Charité Onkologie (CONKO)-001 and JSAP-02 trials (*4,17*) . While S-1 can be used in Caucasian populations, it has only been approved in a limited number of western countries (*18*). While direct comparisons of S-1 efficacy in combination with gemcitabine in western populations are therefore not possible, the European ESPAC-3 trial demonstrated that gemcitabine was not superior to a combination of leucovorin with fluorouracil, a fluoropyrimidine (*11*). Capecitabine plus gemcitabine showed superiority to gemcitabine monotherapy in the ESPAC-4 study (*19*). Furthermore, FOLFIRINOX showed significantly superior activities to gemcitabine in phase III trials (PRODIGE [Partenariat de Recherche en Oncologie Digestive] 24-ACCORD [Actions Concertées dans les Cancers Colorectaux et Digestifs] 24 and CCTG PA [Canadian Cancer Trials Group Pancreatic Adenocarcinoma] 6) that were conducted in France and Canada (*20*). The modified FOLFIRINOX regimen consisted of oxaliplatin (85 mg/m^2) delivered as a 2-hour intravenous infusion, followed by leucovorin (400 mg/m^2) given as a 2-hour intravenous infusion, and after 30 minutes, the addition of irinotecan (180 mg/m^2) administered as a 90-minute intravenous infusion, immediately followed by fluorouracil (2400 mg/m^2) administered by continuous intravenous infusion over a period of 46 hours, every 14 days for 24 weeks (12 cycles).

Because of the morbidity and vulnerability often observed in patients after pancreatectomy, bolus fluorouracil was not administered; this allowed the maintenance of FOLFIRINOX dose intensity and avoided severe or prolonged neutropenia. After the enrollment of 162 patients, however, the dose of irinotecan was reduced to 150 mg/m^2 due to incidences of neutropenia, in accordance with protocol-specified interim safety analysis. In cases of febrile neutropenia or delays in treatment administration due to neutropenia, the use of granulocyte colony-stimulating factor, G-CSF, was advised for the following cycles. Irinotecan-induced severe neutropenia is associated with homozygosity at the *UGT1A1*28* or *UGT1A1*6* alleles. The allele frequency of *UGT1A1*28* is lower in Asians than in Caucasians, and grade 3 or more neutropenia is associated with *UGT1A1*6* polymorphisms in Asians (*21*). The homozygotes and double heterozygotes of *UGT1A1*6* and **28* (**6/*6*, **28/*28* and **6/*28*) were significantly associated with severe neutropenia in patients who received irinotecan monotherapy (*21,22*). Additional dose reduction of irinotecan in the adjuvant FOLFIRINOX setting is required in patients with *UGT1A1* alleles that are associated with poor metabolism of the drug. The most highly quoted adjuvant trials (PRODIGE 24-ACCORD 24-CCTG PA 6, CONKO-001, and ESPAC-4) enrolled between 0.6 and 1.5 patients per center per year, and the number of eligible patients (at each center) should be given the most attention (*23*).

Adjuvant chemotherapeutic regimens have commonly used S-1 in East Asia whereas FOLFIRINOX, capecitabine plus gemcitabine, or gemcitabine monotherapy are used in Western countries. Adjuvant chemoradiotherapy is not recommended because randomized controlled trials and meta-analyses indicated that they provided no additional survival benefit compared with chemotherapy (*15,24*).

Neoadjuvant chemotherapy

Many patients fail to complete courses of postoperative adjuvant chemotherapy due to postoperative complications, poor oral intake, or poor PS. In regard to tumor excision, pancreatic cancer is classified into three groups; resectable, borderline resectable, and unresectable. Even clinically localized pancreatic cancer is associated with the highest probability of harboring radiographically occult metastatic disease. Preoperative chemotherapy with S-1 and gemcitabine (NAC-GS) for patients with resectable and borderline resectable pancreatic cancer significantly increased survival compared to upfront surgery in the Prep-02/JSAP-05 phase II/III trial (*25-28*). The median OS was 36.7 months in the NAC-GS group and 26.6 months in patients who received upfront surgery (HR 0.72, 95% CI 0.55-0.94, $p = 0.015$). Although grade 3 or 4 adverse events of leucopenia and neutropenia were frequently (73%) observed in the NAC-GS group, there was no significant difference between groups with respect to perioperative outcomes including R0 resection rate and post-operative morbidity (*26,29*). A significant decrease in pathological nodal metastases in the NAC-GS group (60%) was noted compared to upfront surgery (82%) for resected patients ($p < 0.01$). The frequency of hepatic metastasis after surgery was significantly reduced in the NAC-GS group (30%) compared to upfront surgery (48%) (*28*). Hence, Japanese guidelines recommend neoadjuvant chemotherapy for patients with resectable pancreatic cancer (*30*).

Preoperative chemotherapy can increase R0 cases by down-staging with higher relative dose intensity of chemotherapy, while non-responders are disadvantaged since they miss resection opportunities during chemotherapy. Outside Japan, many clinical trials of preoperative chemotherapy have been conducted but not completed due to low accrual rates. The low enrollment is due to the reluctance of surgeons to risk disease progression while patients are receiving chemotherapy, as progression can render the patients ineligible for tumor resection. The Southwest Oncology Group (SWOG) S1505 was a randomized phase II trial of perioperative mFOLFIRINOX compared with gemcitabine plus nab-paclitaxel in patients with either resectable or borderline resectable pancreatic cancer. Eighty-two percent of patients completed all intended neoadjuvant chemotherapy and surgery; the resectability rate in the group with resectable disease was 92%, and R0 resection rates were 47% and 48% in the FOLFIRINOX and gemcitabine plus nab-paclitaxel arms, respectively. The median OS and DFS were 23.2 and 10.9 months in the FOLFIRINOX arm, and 23.6 and 14.2 months in the gemcitabine plus nab-paclitaxel arm; there was thus no significant difference in clinical outcomes between the two treatment regimens (*31*). In total, 11 out of 68 patients had postoperative grade 3 or 4 adverse events. The most common postoperative adverse events included anemia ($n = 6$), abnormal liver function tests ($n = 5$), anorexia/nausea/vomiting ($n = 5$), and dehydration/diarrhea ($n = 3$). A total of 61 patients started postoperative adjuvant therapy and 46 completed adjuvant therapy in SWOG S1505. A021806, a phase III trial of perioperative *vs.* postoperative FOLFIRINOX, and NEPAFOX, a phase II/III trial of perioperative FOLFIRINOX *vs.* postoperative gemcitabine, and are ongoing (*32,33*).

The benefit of adjuvant chemotherapy after resection of pancreatic cancer following neoadjuvant combination treatment with FOLFIRINOX is unclear. A retrospective cohort study showed no survival difference for patients who received adjuvant chemotherapy *vs.* those who did not (median OS, 29 *vs.* 29 months; HR 0.99, $p = 0.93$) (*34*). In patients with pathologically node-positive disease, adjuvant chemotherapy was associated with improved survival (median OS, 26 *vs.* 13 months; multivariable HR 0.41, $p = 0.004$).

Neoadjuvant chemoradiotherapy

In the National Cancer Database, data regarding use of neoadjuvant and adjuvant therapies was available for 8,472 of 9,795 patients (86%) who underwent surgery for clinical T1 or T2 pancreatic head adenocarcinoma. Seven hundred and seventy-four (9.1%) received neoadjuvant and 435 (5.1%) received chemoradiotherapy. Neoadjuvant chemotherapy was found to lower positive margin rates from 21.8 to 15.5% ($p < 0.0001$), and when radiotherapy was added this rate dropped to 13.4%. Positive margins were associated with worse overall survival (14.9 *vs.* 23.9 months; HR 1.702, $p < 0.0001$) (*35*).

In the recent PREOPANC trial, neoadjuvant chemoradiotherapy with gemcitabine did not prolong overall survival compared with upfront surgery for patients with resectable or borderline resectable pancreatic cancer. Patients were randomly assigned to one of two groups. In the first group, patients received preoperative chemoradiotherapy consisting of 3 courses of gemcitabine (the second course was combined with 15 × 2.4 Gy radiotherapy) followed by surgery, then received 4 courses of gemcitabine as adjuvant setting. In the second group, patients received 6 courses of adjuvant gemcitabine after upfront surgery. The median OS was 16.0 months with neoadjuvant

chemoradiotherapy and 14.3 months with upfront surgery (HR 0.78, 95% CI 0.58-1.05, $p = 0.096$). The R0 resection rate was 71% (51/72) in patients who received preoperative chemoradiotherapy and 40% (37/92) in patients assigned to upfront surgery ($p < 0.001$) (*36*).

Future perspectives

Neoadjuvant chemotherapy will become standard therapy for resectable pancreatic cancer. Mutations in *BRCA1/2* and *PALB2* genes are present in approximately 5% to 10% of patients with pancreatic cancer (*37*). The presence of DNA damage repair gene mutations such as *ATM*, *BRCA1/2*, *CHEK2*, *PALB* are associated with improved OS in metastatic pancreatic cancer patients treated with FOLFIRINOX (*38-40*). Cisplatin and gemcitabine combination therapy is an active regimen in advanced germline *BRCA1/2* and *PALB2* pancreatic cancer. The addition of veliparib to cisplatin and gemcitabine was not superior to cisplatin and gemcitabine, and the triplet combination was notable for increased hematologic toxicity relative to the doublet. The median OS was 15.5 months for the triplet therapy and 16.4 months for the doublet. The response rate for the triplet was 74% and 65% for the doublet ($p = 0.55$). The small increase in response rate with triplet therapy does not offset the negative effects of increased hematotoxicity, and therefore the triplet regimen may not be the optimal choice in the current neoadjuvant setting.

Patients and doctors would greatly benefit from a panel of factors that predict the response to chemotherapy. DNA repair systems allow cells to overcome the DNA damage induced by chemotherapy. DNA interstrand, intrastrand, and DNA-protein crosslinks caused by cisplatin and oxaliplatin are repaired by the nuclear excision repair pathway, of which excision repair cross-complementation group 1 (ERCC1) is an essential part. In the JCOG9912 trial involving patients with advanced gastric cancer, low ERCC1 expression was a significant independent favorable prognostic factor in those who received first-line chemotherapy, regardless of treatment regimen (*41*). FOLFIRINOX was more effective in metastatic pancreatic cancer patients with lower expression of ERCC1 mRNA than in those with higher expression (*42*). The median OS in "ERCC1 low" *vs.* "ERCC1 high" patients was 16 *vs.* 8 months (HR 0.23, 95% CI 0.12-0.46, $p < 0.0001$), and disease control rate was 93% *vs.* 50% ($p = 0.00006$). These data indicate that ERCC1 could therefore be an effective predictor of response to FOLFIRINOX also in pancreatic cancer. In an animal model, high ERCC1 expression led to cisplatin resistance and restored the ability of cells to displace cisplatin from DNA. Fluoropyrimidines can induce a variety of DNA damage in human cancer cell lines due to its functional interaction with enzymes involved in DNA repair, leading to the activation of downstream factors such as p53. The expression of wild-type p53 was a strong predictor of sensitivity to 5-FU in cell lines of the National Cancer Institute's Anticancer Drug Screen panel *in vitro* (*43*).

Positive circulating tumor (ct) DNA indicated significantly poorer OS in patients with resectable pancreatic cancer (at baseline, HR 2.27, 95%CI 1.13-4.56; postoperative, HR 3.66, 95% CI 1.45-9.28). Patients with detectable ctDNA tended to have a higher risk for disease recurrence than those without detectable ctDNA (at baseline, HR 1.96, 95% CI 0.65-5.87; postoperative, HR 2.20, 95% CI 0.99-4.87). The results were consistent regardless of whether ctDNA was detected pre- or post-operation. Intensive chemotherapy is required for ctDNA positive resectable pancreatic cancer, however, the number of patients who can complete a full course of FOLFIRINOX is limited (*44-46*).

In summary, the current strategies used against pancreatic cancer need to be modified with regard to innovative treatments with current drugs and/or novel patient selection strategies. Such approaches will be facilitated by correlating "omic" data from clinical samples with patient clinical characteristics and drug responses, and will lead to improved survival and quality of life.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received February 8, 2021; Revised September 7, 2021; Accepted October 1, 2021.

Released online in J-STAGE as advance publication October 15, 2021.

**Address correspondence to*:
Yasuhide Yamada, Comprehensive Cancer Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: yayamada@hosp.ncgm.go.jp

Global Health & Medicine. 2022; 4(1):21-25.
MINI-REVIEW
DOI: 10.35772/ghm.2021.01077

The current status of robotic surgery for endometrial cancer in Japan

Tomoko Gota*, Kensuke Tomio, Taichi Kurose, Risa Saito, Ryoken Nara, Sohmi Kin, Minami Hoshiba, Yuri Ogata, Misao Nakanishi, Maya Takamoto, Miyuki Sadatsuki, Hajime Oishi

Department of Obstetrics and Gynecology, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: The da Vinci® surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA) was approved in 2009 by the Japanese Ministry of Health, Labor, and Welfare. In gynecology, robotic surgery for hysterectomy for benign indications and early-stage endometrial cancer has been covered by National Health Insurance since 2018. In a context where the da Vinci surgical system has prevailed in urology departments in Japan, gynecological robotic surgery has spread rapidly once it was covered by insurance. Although minimally invasive gynecologic surgery (minimally invasive surgery, or MIS) in Japan has a specific context, there are several problems with its safety, surgeon education, and cost in Japan. To maximize the many advantages of robotic surgery, its effectiveness needs to be carefully evaluated and this new technology needs to be safely incorporated in practice.

***Keywords*:** endometrial cancer, robotic surgery, minimally invasive surgery

Introduction

The da Vinci S, Si, and Xi surgical systems were respectively approved by Japanese Ministry of Health, Labor, and Welfare in 2009, 2012 and 2015, and their use has rapidly spread in urology. The da Vinci provides the surgeon with an enlarged three-dimensional view and motion scaling, it eliminates instrument tremors, and it allows the performance of accurate surgical procedures with articulated arms. The short learning curve in also a merit of robotic surgery (*1,2*). The pelvic cavity is deep and narrow. In spite of these advantages of robotic surgery at that site, the problem of high costs has prevented robotic surgery from becoming standard treatment. Nevertheless, 12 new procedures were covered by National Health Insurance in Japan in April 2018. Hysterectomy for benign indications and early-stage endometrial cancer has been approved in gynecology. Since 2018, facilities have increasingly adopted a robotic approach to gynecological disease.

The current article reviews the current status of, problems with, and prospects of robotic surgery for patients with endometrial cancer in Japan.

The history of minimally invasive gynecologic surgery in Japan

The da Vinci surgical system was first introduced in Asia at Keio University in March 2000. Robot-assisted hysterectomy was first performed in Japan in March 2009 at Tokyo Medical University Hospital. Although the gynecological organs that are locate in the deep and narrow pelvic cavity are ideal for a robotic approach, high costs and the lack of evidence indicating the superiority of robotic surgery initially prevented the da Vinci system from being approved by the Japanese Ministry of Health, Labor, and Welfare.

In contrast, MIS was greatly needed for young female patients, and the small number of Japanese patients was suitable for a laparoscopic approach. In Japan, gynecological laparoscopic surgery was initially performed for benign indications by clinicians in reproductive medicine and endocrinology, and most gynecologic oncologists preferred open surgery to laparoscopic surgery. As a result, the introduction of MIS for gynecological malignancies was delayed.

The LAP2 study was a multicenter randomized controlled trial, the results of which were published in 2012 (*3*). The LAP2 study indicated the feasibility and inferiority of oncologic outcomes of MIS for patients with early-stage endometrial cancer compared to conventional laparotomy. According to that study, the estimated hazard ratio for the 3-year recurrence rate was 1.14 (95% CI = 0.92 to 1.46), and the estimated 5-year overall survival rate was 89.9% in each group. After the LAP2 study, laparoscopic surgery for patients with stage IA endometrial cancer was covered by National Health Insurance in 2014, and it has gradually spread to many facilities. The Japan Gynecologic and Obstetric Endoscopy Database (JOE-D) indicated that gynecologic laparoscopic surgeries increased from 56,233 in 2014 to 80,678 in 2016. Moreover,

laparoscopic surgeries for gynecological malignancy increased approximately 1.8-fold (from 1,898 to 3,490 cases) from 2014 to 2016 (*4*). Thus, laparoscopic surgery had already become the standard treatment in gynecology departments in Japan, while robotic surgery was adopted slowly and in limited instances.

However, that situation changed after 12 new procedures were covered by Japan's National Health Insurance in April 2018. In gynecology, hysterectomy for benign uterine disease and endometrial cancer was covered. In April 2020, robot-assisted sacrocolpopexy for pelvic organ prolapse was added to the list. Since the da Vinci surgical systems were already installed in urology at many facilities, robotic gynecological surgery has spread rapidly over the past few years. There are now approximately 350 da Vinci surgical systems installed in Japan, which is nearly half of the number in Asia.

Education in robotic surgery

The Japan Society of Gynecologic Robotic Surgery (JSGRS) was established in January 2019, and the JSGRS instituted the trainer system in order to safely introduce robotic surgery. Trainers need practical experience as well as knowledge of the three different da Vinci systems: Si, X, and Xi. The demand for trainers is increasing, and the lack of trainers is a problem in Japan.

Current status of and problems with MIS for patients with endometrial cancer

The number of patients with endometrial cancer has increased in Japan, and the Japan Society of Obstetrics and Gynecology (JSOG) reported that there were 11,230 patients with endometrial cancer in 2018 (*5*). Endometrial cancer was diagnosed in its early stages in most of those patients, and the demand for MIS has also been increasing. According to a survey by the Japan Society for Endoscopic Surgery (JSES), the usage of laparoscopic surgery for endometrial cancer increased from 210 in 2011 to 4,045 in 2019 (Figure 1), respectively accounting for 0.67% and 4.68% of gynecological endoscopic surgeries (*6*).

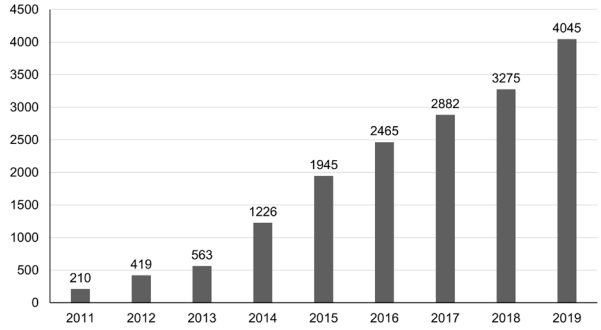

Figure 1. The number of laparoscopic surgeries for endometrial cancer in Japan. Data adapted from (*6*).

A point worth noting is that the rate of discrepancy between preoperative and postoperative staging varies between 6.8% and 41.2%. A high rate of upstaging has been reported at some medium-volume facilities (*7-12*). Lymphadenectomy for low-risk disease was omitted from the Japanese treatment guidelines for neoplasms of the uterine corpus, which was updated by the Japan Society of Gynecologic Oncology (JSGO) in 2018. In contrast, pelvic and para-aortic lymphadenectomy were performed in 91.5% of patients undergoing a laparoscopy and in 95.8% of those undergoing a laparotomy in the LAP2 study (*3*).

There is a possibility that preoperative underdiagnosis, differences in surgical techniques, and differences in the treatment results of high-volume centers and low- to mid-volume center may affect oncologic outcomes. Further studies of the clinical prognosis of MIS need to be conducted in patients with endometrial cancer nationwide. Precise enrollment of MIS candidates is essential for accurate preoperative diagnosis.

Robotic hysterectomy for endometrial cancer

A few randomized controlled trials (RCTs) have assessed the clinical outcomes of robotic surgery for gynecological malignancies, and to the extent known no RCTs have reported the oncologic outcomes of robotic surgery alone. Initial concern about robotic surgery limited its cost effectiveness, but recent studies have reported that the cost of robotic surgery is similar to or less than that of a laparotomy specifically for oncologic indications (*13-16*). Operating time has also been a disadvantage of robotic surgery compared to conventional laparoscopic surgery, but this might be solved by a surgical team with sufficient experience (*17-19*). Moreover, several studies have indicated that robot-assisted hysterectomy yields favorable outcomes in terms of the rate of conversion, intraoperative blood loss, the duration of hospitalization, and complications compared to laparoscopic hysterectomy (*17-18,20*). Retrospective Japanese studies of robotic surgery for endometrial cancer have indicated similar favorable perioperative outcomes even in the early phase (Table 1). In a retrospective study at a single institution, the selection criteria for a laparoscopic approach or a robotic approach were based on the patient's wishes; robotic surgery tended to be chosen by obese patients and patients with cancer in a more advanced stage (*24*). According to the annual report on treatment for 2018, patients with endometrial cancer underwent 344 robotic surgeries, which accounted for 3.2% of all procedures for endometrial cancer (*5*). JSES reported the number of complications of robotic surgery for malignant uterine disease from 2018 to 2019, and it noted the feasibility of robotic gynecologic procedures in Japan (Table 2).

Table 1. Robotic hysterectomy for patients with endometrial cancer in recent studies

Author (*Ref.*)	Year	Number of patients	Surgical procedure	Operating time (min)	Blood loss	Conversion	Hospitalization (days)	Transfusion (%)
Salehi S, *et al.* (*13*)	2017	48	RAH + PLND + PALND	233 (166-320)	78 mL (20-300)	1	2 (1-5)	0
Maenpaa M, *et al.* (*18*)	2016	50	RAH + PLND	139 (86-197)	50 mL (5-500)	0	1 (1-4)	12
Ono K, *et al.* (*21*)	2016	1	RAH	243.5	86.3 mL	-	7.3	-
		3	RAH + PLND					
Baba T, *et al.* (*22*)	2019	8	RAH	304.6	91.9 g	-	5.4	-
		33	RAH + PLND	319.9	41.8 g		5.3	
		38	RAH + PLND + PALND	484.3	153.3 g		6.9	
Aoki T, *et al.* (*23*)	2020	21	RAH	233 (160-346)	0 mL (0-141)	1	4 (4-6)	0
		9	RAH + PLND					
		1	Conversion					
Aiko K, *et al.* (*24*)	2020	30	RAH + PLND + PALND	178	237 mL	1	8	0
		91	RAH + PLND + PALND					

RAH, robot-assisted hysterectomy; PLND, pelvic lymph node dissection; PALND, para-aortic lymph node dissection.

Table 2. Perioperative complications of robotic surgery for malignant uterine disease, excluding radical hysterectomy and radical trachelectomy, in Japan from 2018-2019

Variables	RAH (*n* = 617)	RAH + PLND (*n* = 341)	RAH + PLND + PALND (*n* = 22)	RMRH (*n* = 184)	RMRH + PLND (*n* = 66)	RMRH + PLND + PALND (*n* = 40)	Total number (*n* = 1,270)
Conversion to laparotomy	0	0	0	0	1 (1.52)	0	1 (0.08)
Intraoperative complication							
Blood loss > 500 mL	0	1 (0.29)	0	0	1 (1.52)	1 (2.5)	3 (0.24)
Vascular injury	0	0	0	0	0	0	0
Urinary tract injury	0	0	0	0	1 (1.52)	0	1 (0.08)
Bladder injury	0	0	0	0	0	0	0
Bowel injury	0	0	0	0	0	0	0
Others	1 (0.16)	6 (1.76)	1 (4.55)	1 (0.54)	0	0	9 (0.71)
Postoperative complication							
Intraperitoneal bleeding/Hematoma	0	1 (0.29)	0	0	0	0	1 (0.08)
Peritonitis	3	0	1 (4.55)	0	0	0	4 (0.31)
Surgical site infection	0	1 (0.29)	0	0	0	0	1 (0.08)
Vaginal cuff dehiscence	1 (0.16)	1 (0.29)	0	0	1 (1.52)	0	3 (0.24)
Bowel complication	0	0	0	0	0	0	0
Urinary tract injury	0	0	0	0	0	0	0
Bladder injury	0	0	0	0	0	0	0
Respiratory complication	0	0	0	0	0	0	0
Other	1 (0.16)	4 (1.17)	2 (9.09)	1 (0.54)	3 (4.55)	0	11 (0.87)

RAH, robot-assisted hysterectomy; RMRH, robotic modified radical hysterectomy; PLND, pelvic lymph node dissection; PALND, para-aortic lymph node dissection. Data are presented as *n* (%). Data were adapted from (*6*).

The future prospects of robotic surgery

The da Vinci surgical system is the most popular system for robotic surgery. Recently, several venture companies, including domestic companies, have been planning to start developing robotic surgical systems. As a result, reduced costs and technological innovation will promote the introduction of robotic surgery in clinical practice. Advances in techniques will improve surgical performance as well as outcomes.

Currently, the dearth of surgeons and medical disparities between urban and rural areas are urgent problems in Japan. Robotic surgery is a useful way to efficiently utilize human resources. Laparoscopic surgery requires at least 3 surgeons and a laparotomy requires at least 2 surgeons, whereas robotic surgery is performed almost solo. Moreover, the learning curve for robotic surgery is shorter than that for other approaches, and the surgeon is likely to feel less fatigue with robotic surgery than conventional laparoscopic surgery because of the ergonomic design of surgical systems (*25*).

In the future, remote surgery and artificial intelligence-guided surgery might overcome regional disparities, but there are still problems with the protection of personal information, costs, and the management of emergencies.

Preoperative registration in the National Clinical Database (NCD) has become mandatory in gynecology since July 2020, and the safety of robotic surgery will be evaluated. In conclusion, gynecologic robotic surgery has several advantages in solving many problems peculiar to Japan. We need to aware of its risks and medical economics in order to safely introduce this new technology to benefit patients.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received June 22, 2021; Revised September 24, 2021; Accepted October 1, 2021.

Released online in J-STAGE as advance publication October 7, 2021.

**Address correspondence to*:
Tomoko Gota, Department of Obstetrics and Gynecology, Center Hospital of the National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: tgota@hosp.ncgm.go.jp

Global Health & Medicine. 2022; 4(1):26-36.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2021.01037

Burden of cancer attributable to modifiable factors in Japan in 2015

Manami Inoue[1,2,*], Mayo Hirabayashi[1], Sarah Krull Abe[1], Kota Katanoda[3], Norie Sawada[2], Yingsong Lin[4], Junko Ishihara[5], Ribeka Takachi[6], Chisato Nagata[7], Eiko Saito[3], Atsushi Goto[8], Kayo Ueda[9], Junko Tanaka[10], Megumi Hori[3], Tomohiro Matsuda[11]; the Cancer PAF Japan Collaborators

[1] Division of Prevention, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan;
[2] Division of Cohort Research, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan;
[3] Division of Cancer Statistics Integration, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan;
[4] Department of Public Health, Aichi Medical University School of Medicine, Nagakute, Aichi, Japan;
[5] School of Life and Environmental Science, Department of Food and Life Science, Azabu University, Kanagawa, Japan;
[6] Department of Food Science and Nutrition, Graduate School of Humanities and Sciences, Nara Women's University, Nara, Japan;
[7] Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan;
[8] Yokohama City University, Department of Health Data Science, Graduate School of Data Science, Yokohama, Japan;
[9] Environmental Health Sciences, Graduate School of Global Environmental Studies, Kyoto University, Kyoto, Japan;
[10] Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan;
[11] National Cancer Registry Section Center for Cancer Registries Center for Cancer Control and Information Services/Office of International Affairs, Strategic Planning Bureau National Cancer Center, National Cancer Center, Tokyo, Japan.

Abstract: The This study estimated the cancer burden attributable to modifiable factors in Japan in 2015 using the best available epidemiological evidence and a standard methodology. We selected the following factors for inclusion in the estimates, namely tobacco smoking (active smoking and secondhand smoking), alcohol drinking, excess bodyweight, physical inactivity, infectious agents (*Helicobacter pylori*, hepatitis C virus, hepatitis B virus, human papilloma virus, Epstein-Barr virus, and human T-cell leukemia virus type 1), dietary intake (highly salted food, fruit, vegetables, dietary fiber, red meat, processed meat), exogenous hormone use, never breastfeeding and air pollution, given that these were considered modifiable, in theory at least. We first estimated the population attributable fraction (PAF) of each cancer attributable to these factors using representative relative risks of Japanese and the prevalence of exposures in Japanese around 2005, in consideration of the 10-year interval between exposure and cancer outcomes. Using nationwide cancer incidence and mortality statistics, we then estimated the attributable cancer incidence and mortality in 2015. We finally obtained the PAF for site-specific and total cancers attributable to all modifiable risk factors using this formula, with statistical consideration of the effect of overlap between risk factors. The results showed that 35.9% of all cancer incidence (43.4% in men and 25.3% in women) and 41.0% of all cancer mortality (49.7% in men and 26.8% in women) would be considered preventable by avoidance of these exposures. Infections and active smoking followed by alcohol drinking were the greatest contributing factors to cancer in Japan in 2015.

***Keywords*:** cancer, modifiable factor, population attributable fraction, Japan

Introduction

The structure of disease in Japan has changed drastically over the past decades, largely due to changes in economics, demographics and lifestyle. Together with rapid aging, the transition from communicable diseases such as tuberculosis and pneumonia to non-communicable diseases such as cancer has challenged domestic health systems and public health.

Cancer has been the leading causes of death in Japan since 1981 (*1*). Recent statistics show that cancer accounted for 27.3% of all deaths (n = 1,381,093) (31.1% of men and 23.2% of women) in 2019 (*1*). The national cancer registry documented 980,856 newly diagnosed cases of cancer (558,874 men and 421,964 women) in 2018, suggesting that 65.0% of men and 50.2% of women will be diagnosed with cancer at least once in their lifetime (*2*). For 2035, it is estimated that over 1,172,000 Japanese will be diagnosed with cancer, and 382,000 will die from it (*3*). Thus, effective cancer prevention and control is crucial to reducing the burden of cancer in Japan.

It has long been known that many cancers are caused by lifestyle and environmental factors that could potentially be prevented (*4*), suggesting the possibility of reducing the cancer burden caused by such exposures. However, the pattern of such modifiable factors and pattern of cancer differ among countries and regions, and cancer control policies should accordingly be tailored to reflect the local burden of cancer.

The proportion of preventable cancers is often referred to as the population attributable fraction (PAF). The first quantitative assessment of attributable causes of cancer mortality was reported in 1981 for the US by Doll and Peto (*5*). More recently, country-specific attributable causes of cancer using PAF have been reported in the US (*5-7*), Nordic countries (*8,9*), France (*10-12*), China (*13*), South Korea (*14*), UK (*15,16*), Australia (*17*), Canada (*18*), Germany (*19*), Brazil (*20*), Chile (*21*) and Vietnam (*22*) as well as Japan (*23*). In Japan, the burden of cancer attributable to known preventable risk factors was first assessed for the year 2005 (*23*), in which 55% of cancer among men and nearly 30% among women was attributed to preventable risk factors. That study also showed that tobacco smoking and infections were the major causes of cancer in Japan. Of note, the study applied to the prevalence of exposures occurring 15 years before, *i.e.* around 1990, based on a 15-year time lag between exposure and cancer outcome. This process was hampered by the limited availability of data sources for many exposures around 1990, which obliged the researchers to use less representative data or to exclude such exposures from analysis. Likewise, the number of Japanese epidemiological studies of risk assessment at that time was also limited, which led to insufficient evidence for PAF estimates. The subsequent decade saw the accumulation of additional epidemiological evidence and data on exposures of interest, and national representative data became available for many factors. In addition, the prevalence of many modifiable risk factors in Japan was shown to have dramatically changed by birth cohort. Accordingly, analysis to determine the burden of cancer attributed to such factors should be done with consideration to prevalence among birth cohorts at the time of exposure.

Hence, in this report, we estimated the cancer burden attributable to modifiable factors in Japan in 2015, using the most recent epidemiological evidence.

Methods

PAF in this project is defined as the fraction of cancer incidence or mortality that is attributable to a particular exposure and that could be avoided if the exposure were eliminated or reduced to an alternative scenario that would result in the lowest risk; or in other words, the theoretical minimum risk exposure distribution. We took several steps to accomplish this goal (Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=43*), namely I. Selection of risk factors with definitions of their theoretical minimum risk exposures and target cancers; II. Acquisition of essential data, namely *i*) cancer incidence and mortality statistics in Japan, *ii*) prevalence of risk factors in Japan, and *iii*) representative relative risks for each risk factors; and III. Estimation of PAF of cancer attributable to modifiable factors in Japan in 2015. Estimation of PAF was conducted first by risk factor, by specific cancer site. By adding up the obtained PAF of each factor related to each site, with statistical control of the effect of overlap between risk factors, we finally obtained the PAF for total cancers attributable to modifiable factors.

I. Selection of risk factors with definitions of their theoretical minimum risk exposures and target cancers

Selection of risk factors and related cancer sites

Risk factors included in the present PAF estimation were basically selected based on agents classified by the International Agency for Research on Cancer (IARC) as group 1 (carcinogens in humans) (*24*) and risk factors that were judged as "convincing", with the exception of "convincing" or "probable" for dietary factors, from the Third Expert Report, Diet, Nutrition, Physical Activity and Cancer: a Global Perspective (*25*). Related cancer sites were also selected from these expert reports, as well as from a report of the US Surgeon General in 2014 (*26*) for tobacco smoking. Additionally, we referred to domestic comprehensive evaluations, including a report by the Japanese Committee on Smoking and Health in 2016 (*27*), and a risk assessment by the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan (*28*).

Risk factors meeting the following criteria, as applied in a previous estimate (*23*), were adopted into the present estimate: 1) there was evidence of a causal association between the factor and at least one type of cancer; 2) prevalence was available from national representative surveys; and 3) there were achievable alternative exposure levels that would reduce the risk.

Some established carcinogens, including some types of infectious agents such as *Schistosoma hematobium*, *Opisthorchis viverrini*, human immunodeficiency virus (HIV), and aflatoxin, were not included due to their extremely low prevalence in Japan. Furthermore, we did not include occupational exposures, or ultraviolet or radiation exposure, due to a lack of reliable prevalence data in Japan.

Theoretical minimum risk exposure level

We defined a theoretical minimum risk exposure level for each risk factor included in this estimate. Details are described in the following companion reports, with a focus on the PAF of cancer by each risk factor.

Risk factors, theoretical minimum risk exposure levels, and cancer sites considered in this estimate are

described in Table 1.

II. Acquisition of essential data

i) Cancer incidence and mortality statistics in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan Project (MCIJ) on the basis of data collected from population-based cancer registries in Japan (*29*). Estimation was done using an age and period spline model, a type which is used for short-term projections of cancer incidence in Japan (*30*). For some of the cancer sites, subsites, or histological subtypes which were not included in this published database, we further asked the MCIJ project to provide such detailed data, with permission for this purpose.

The sex- and age-specific incidence data for target cancers were coded by the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10) (*31*), with the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3) (*32*).

The statistical data on cancer mortality from 2015 were obtained from the vital statistics of Japan (*33*). We obtained sex- and age-specific mortality data by cause of death from available data sources from the Health, Labour, and Welfare Statistics Association (*34*). As was done for the cancer incidence data, 4-digit ICD-10 codes were used to classify the cause of death.

Table 2 shows the summary of incidence and mortality of cancer data used in this estimate in Japan in 2015.

ii) Prevalence of risk factors in Japan

The current incidence or mortality of cancer reflects the cumulative effect of past exposures. For most cancers and risk factors, the latent period between "exposure" to the risk factor and the increase in risk of the relevant cancer has not been well established. We assumed that this would be 10 years on average, and thus examined the effects of cancers occurring in 2015 from exposure to risk factors in 2005. We collected prevalence data

Table 1. Risk factors considered, theoretical minimum risk exposure level, and cancer sites considered

Risk factors	Theoretical minimum risk exposure level		Cancer site
Tobacco smoking	Never		
1. Active smoking			lung; oral cavity and pharynx; nasal; esophagus; stomach; colon; rectum; liver; pancreas; bladder; cervix; acute myeloid leukaemia
2. Secondhand smoking			lung
Alcohol drinking	None		oral cavity, pharynx, esophagus, stomach, colorectum, liver, larynx, and breast*
Excess body weight	BMI < 23 kg/m^2		esophageal adenocarcinoma, stomach (cardia), colorectum, liver, gallbladder, pancreas, breast* (pre- and post- menopausal), ovary*, endometrium*, advanced prostate**, kidney
Physical activity	Regular exercise		colorectum, breast*, endometrium*
Infection	No infection		
1. *Helicobacter pylori*			stomach (non-cardia); MALT lymphoma
2. Hepatitis C virus (HCV)			liver
3. Hepatitis B virus (HBV)			liver
4. Human papilloma virus (HPV)			oral cavity; oropharynx; anus; penis; vulva; vagina; cervix uteri
5. Epstein-Barr virus (EBV)			nasopharynx; Burkitt lymphoma; Hodgkin lymphoma
6. Human T-cell Leukemia Virus Type 1 (HTLV-1)			adult T-cell lymphoma/leukemia (ATL)
Dietary intake			
1. Highly salted food	None		stomach
2. Fruit			lung
3. Vegetables			stomach (distal)
4. Dietary fiber	Age (yrs)	Men/Women	colon
	5-9	≥ 11.5 g/ ≥ 11 g	
	10-14	≥ 15 g/ ≥ 14.5 g	
	15-19	≥ 19.5 g/ ≥ 17.5 g	
	20-69	≥ 20 g/ ≥ 18 g	
	70+	≥ 19 g/ ≥ 17 g	
5. Red and processed meat	< 500 g/week		colon; rectum
Breast feeding	Ever		breast*; ovary*; endometrium*
Exogenous hormone use	Never		
1. Menopausal hormone therapy			breast*; ovary*
2. Oral contraceptive use			breast*; ovary*; endometrium*
Air pollution	Ambient PM 2.5 ≤ 10 μg/cm^3		lung

*Calculated for women only. **Calculated for men only.

Table 2. Incidence[a] and mortality[b] of all and selected sites of cancer in Japan (2015)

Cancer site	ICD-10	Men		Women		Both sexes	
		Incidence	Death	Incidence	Death	Incidence	Death
Base of Tongue	C01	654	26	38	2	692	28
Oral and mouth	C02-C06	6,409	1,844	4,544	1,467	10,954	3,311
Tonsil and Oropharynx	C09-C10	2,033	798	475	167	2,509	965
Nasopharynx	C11	581	224	277	75	858	299
Other oral pharynx	C00, C07-C08, C12-C14	4,802	2,366	1,150	411	5,952	2,777
Esophagus	C15	19,390	9,774	3,540	1,965	22,930	11,739
Stomach	C16	91,883	30,809	42,203	15,870	134,087	46,679
Colon	C18	50,394	17,063	44,310	17,275	94,703	34,338
Rectum	C19-C20	30,433	9,755	16,401	5,606	46,835	15,361
Anus	C21	521	209	472	202	993	411
Liver	C22	28,222	19,008	15,087	9,881	43,308	28,889
Gallbladder	C23	3,721	2,532	5,190	3,716	8,911	6,248
Pancreas	C25	19,523	16,186	18,524	15,680	38,046	31,866
Sino-nasal	C30-31	1,333	392	705	245	2,038	637
Larynx	C32	4,630	899	360	72	4,990	971
Lung	C33-C34	83,169	53,208	40,025	21,170	123,194	74,378
Breast	C50			84,709	13,584	84,709	13,584
Vulva	C51			867	262	867	262
Vagina	C52			363	151	363	151
Cervix	C53			11,253	2,813	11,253	2,813
Endometrium	C54			15,372	2,322	15,372	2,322
Ovary	C56			10,166	4,676	10,166	4,676
Penis	C60	412	141			412	141
Prostate	C61	82,896	11,326			82,896	11,326
Kidney	C64	13,471	3,182	5,954	1,584	19,426	4,766
Renal pelvis & ureter	C65-66	5,292	2,353	3,008	1,558	8,300	3,911
Bladder	C67	15,280	5,582	5,168	2,548	20,448	8,130
Hodgkin disease	C81	805	102	446	58	1,251	160
Non-Hodgkin Lymphoma	C82-C85, C96	15,195	6,568	12,581	5,140	27,776	11,708
Burkitt's lymphoma	C837	170	36	138	20	308	56
Adult T-cell Lymphoma/Leukemia	C915	912	446	663	506	1,575	952
Acute Myeloid leukemia	C920, C924, C925	2,970	2,968	1,983	1,808	4,953	4,776
All sites	C00-C96, C97[c]	549,241	219,508	408,572	150,838	957,813	370,346

[a]Derived from Monitoring of Cancer Incidence in Japan project. [b]Derived from the vital statistics of Japan. [c]C97 is included in death only.

of exposure to each risk factor from different sources, prioritizing Japanese national representative surveys. For exogenous hormone use (hormone replacement therapy and oral contraceptive use), the latency period was not considered since cancer risk decreases rapidly after cessation (*35*).

iii) Representative relative risk for each risk factor

Relative risk (RR) data were obtained from epidemiological studies identified from different sources, including PubMed, *Ichushi-web*, and other literature searches, either in English or Japanese. We used studies that reported RR and corresponding 95% confidence intervals (CIs). We employed priority ranking for the inclusion and selection of representative RRs. Among these studies, meta-analyses that included pooled analyses of Japanese populations were the most preferred source of RR. When such meta-analyses were not available, RR was derived from the most comprehensive Japanese studies. Cohort studies were prioritized over case-control studies. If no RR derived from Japanese population sources were available, the data from other Asian populations were used, followed by non-Asian populations. Within meta- and pooled analyses where multiple RRs were available, RRs were selected based on characteristics that were most relevant to the evidence.

III. Estimation of PAF of cancer attributable to modifiable factors in Japan in 2015

Cancer site-specific PAF estimation by each risk factor

Cancer site-specific PAFs of each risk factor were calculated separately by sex and age groups and the age-specific attributed cases or deaths were aggregated to obtain the total number of attributed cases or deaths. In this study, we estimated PAF by a couple of methods. When exposure to a risk factor was dichotomous, a standard PAF formula proposed by Levin (*36*) was applied:

$$PAF = \frac{P(RR-1)}{P(RR-1)+1}$$

where *P* is prevalence and RR is relative risk.

When there are multiple categories to be considered in the PAF calculation, the modified formula for κ multiple categories by Hanley was used (*37*):

$$PAF = \frac{\sum_{\kappa=1}^{K} P_\kappa(RR_\kappa - 1)}{\sum_{\kappa=1}^{K} P_\kappa(RR_\kappa - 1) + 1}$$

$$\kappa = 1, 2, \ldots, K$$

where *P* is prevalence, R is relative risk, and K is the number of categories for the risk factor.

For some risk factors, risk of cancer per unit increase in exposure and average RR for the whole population based on the average exposure, with the assumption of a log-linear relationship between exposure and risk, was calculated using the following formula (*11*):

$$PAF = \frac{Risk - 1}{Risk}$$

$$Risk = exp^{[\ln(\text{risk per unit}) \times \text{average exposure level}]}$$

For some infectious agents, PAF was calculated using the prevalence of the infectious agent in cases only and the RR associated with that infection (*37*):

$$PAF = Pc \times \frac{RR - 1}{RR}$$

where Pc is prevalence among cases.

Total cancer PAF estimation by individual risk factors

Cancer site-specific PAF was multiplied by the number of incidence or mortality of site-specific cancer to obtain the site-specific number of attributable cancer incidence and mortality. By summing these site-specific attributed numbers of cancer incidence and mortality, we obtained the attributed number of total cancer incidence and mortality. Total cancer PAF was then obtained by dividing the number of attributed total cancer incidence and mortality by the number of observed total cancer incidence and mortality.

Site-specific and total cancer PAF estimation considering all modifiable risk factors

Risk factor-specific PAF of each site of cancer and total cancers was further aggregated to estimate total PAF with consideration of all modifiable risk factors. Most cancers are caused by multiple risk factors, and PAF for individual risk factors for the same cancer sites can therefore overlap and add up to over 100%. To obtain the PAF of total modifiable risk factors, we took into account the degree of overlap of PAF under the assumption of independence of exposures and risk (*38*). Combined PAF for the two risk factors A and B can be calculated by the following formula (*38*):

$$PAF_{AB} = 1 - (1 - PAF_A) \times (1 - PAF_B)$$

This formula can be generalized to more than two risk factors.

We finally obtained the PAF for site-specific and total cancers attributable to all modifiable risk factors using this formula with statistical consideration of the effect of overlap between risk factors. These PAFs were then used to estimate the number of attributable incident cases and deaths of site-specific and total cancer.

Sensitivity analysis of PAFs

Calculation of the PAF is determined by the choice of estimated exposure prevalence at the population level and the RR associated with the risk factor. Use of a point estimate of RR involves uncertainty. To account for differences in PAF due to uncertainty in the RR estimation, we performed sensitivity analyses on the PAFs by using the lower and upper bounds of the 95% CIs for the RR estimates.

Results

The estimated PAFs of total and associated cancer sites for each modifiable factor were reported in separate articles in detail (*39-48*), and are summarized in Table 3. Table S1 (cancer incidence) and S2 (cancer mortality) (online data, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=42*) describe the PAF estimates for relevant cancer sites and types and total cancers for each modifiable factor. Overall, 35.9% of all cancers diagnosed in Japan in 2015 (43.4% in men and 25.3% in women) were attributable to modifiable risk factors of cancer. The corresponding figure for cancer mortality was 41.0% for both sexes (49.7% in men and 26.8% in women). Infections and active smoking are the most important modifiable factors for cancer in Japan, followed by alcohol drinking, given that 16.6% of cancer incidence is explained by infections, 15.2% by active smoking, and 6.2% by alcohol drinking. Cancer mortality showed similar figures, among which 19.6% of cancer deaths were explained by active smoking, 17.7% by infections, and 6.5% by alcohol drinking. There was a difference in the pattern of PAF by sex (Figure 1), with the major attributable factors for men being active smoking (23.6% for incidence and 29.8% for mortality), infections (18.1% for incidence and 18.5% for mortality) and alcohol drinking (8.3% for incidence and 8.8% for mortality), versus infections (14.7% for incidence and 16.5% for mortality), alcohol drinking (3.5% for incidence and 3.0% for mortality) and active smoking (4.0% for incidence and 4.7% for mortality) for women. In both sexes, other factors such as secondhand smoking, excess body weight, physical

Table 3. Number and population attributable fraction (PAF, %) of cancer incidence and mortality attributable to selected modifiable risk factors in Japan in 2015

Risk factor	Theoretical minimum risk exposure level	Incidence		Mortality	
		PAF (%)	number	PAF (%)	number
Men					
Total Number			549,241		219,508
Active smoking	Never	23.6	129,502	29.8	65,417
Secondhand smoking	Never	0.2	1,095	0.3	735
Alcohol drinking	None	8.3	45,360	8.8	19,406
Excess body weight	BMI < 23 kg/m^2	1.0	5,539	1.0	2,197
Physical inactivity	Regular exercise	1.0	5,509	0.9	1,942
Infections	No infection	18.1	99,481	18.5	40,580
Highly salted food consumption	No intake	3.0	16,249	2.5	5,571
Vegetable consumption	≥ 350 g/day	0.3	1,667	1.0	2,197
Fruit consumption	≥ 100 g/day	0.1	570	0.1	253
Dietary fiber consumption	sufficient consumption*	1.2	6,837	1.0	2,124
Red and processed meat consumption	< 500 g/week	0.0	75	0.0	16
Air pollution	Ambient PM 2.5 ≤ 10 μg/cm^3	1.6	8,788	2.6	5,682
Above all risk factors (adjusted for overlaps)		43.4	238,497	49.7	109,151
Women					
Total Number			408,572		150,838
Active smoking	Never	4.0	16,263	4.7	7,105
Secondhand smoking	Never	0.9	3,483	1.3	1,932
Alcohol drinking	None	3.5	14,477	3.0	4,522
Excess body weight	BMI < 23 kg/m^2	0.3	1,228	0.3	429
Physical inactivity	Regular exercise	1.6	6,521	0.8	1,153
Infections	No infection	14.7	59,893	16.5	24,935
Highly salted food consumption	No intake	1.6	6,497	1.7	2,510
Vegetable consumption	≥ 350 g/day	0.1	564	0.3	429
Fruit consumption	≥ 100 g/day	0.0	69	0.0	18
Dietary fiber consumption	sufficient consumption*	0.8	3,143	0.9	1,370
Red and processed meat consumption	< 500 g/week	0.0	0	0.0	0
Breastfeeding	Ever	0.3	1,232	0.1	202
Exogenous hormone use	Never	0.4	1,454	0.2	279
Air pollution	Ambient PM 2.5 ≤ 10 μg/cm^3	0.7	3,014	1.0	1,582
Above all risk factors (adjusted for overlaps)		25.3	103,237	26.8	40,495
Both sexes					
Total Number			957,813		370,346
Active smoking	Never	15.2	145,765	19.6	72,521
Secondhand smoking	Never	0.5	4,579	0.7	2,667
Alcohol drinking	None	6.2	59,838	6.5	23,929
Excess body weight	BMI < 23 kg/m^2	0.7	6,767	0.7	2,625
Physical inactivity	Regular exercise	1.3	12,030	0.8	3,095
Infections	No infection	16.6	159,374	17.7	65,515
Highly salted food consumption	No intake	2.4	22,746	2.2	8,081
Vegetable consumption	≥ 350g/day	0.2	2,231	0.7	2,625
Fruit consumption	≥ 100g/day	0.1	640	0.1	271
Dietary fiber consumption	sufficient consumption*	1.0	9,979	0.9	3,494
Red and processed meat consumption	< 500 g/week	0.0	75	0.0	16
Breastfeeding	Ever	0.1	1,232	0.1	202
Exogenous hormone use	Never	0.2	1,454	0.1	279
Air pollution	Ambient PM 2.5 ≤ 10 μg/cm^3	1.2	11,922	2.0	7,264
Above all risk factors (adjusted for overlaps)		35.9	344,230	41.0	151,672

*Theoretical minimum risk exposure level for dietary fiber consumption by age group: Men 5-9: ≥ 11.5 g, 10-14: ≥ 15 g, 15-19: ≥ 19.5 g, 20-69: ≥ 20 g, 70+: ≥ 19 g; Women 5-9: ≥ 11 g, 10-14: ≥ 14.5 g, 15-19: ≥ 17.5 g, 20-69: ≥ 18 g, 70+: ≥ 17 g. The number of both sexes is not equal to the sum of men and women due to rounding.

inactivity, highly salted food intake, fruit intake, vegetable intake, dietary fiber intake, red and processed meat intake, breast feeding, exogenous hormone use, and air pollution accounted for a small share of both cancer incidence and mortality.

Estimated PAFs of all modifiable factors aggregated for cancer sites/types associated with one or more modifiable factors are shown in Table 4. Cancer of the uterine cervix and adult T-cell leukemia/lymphoma had the highest fractions of potentially modifiable factors (100%) for which the infectious agents were considered necessary causal factors. Other cancer sites/types with

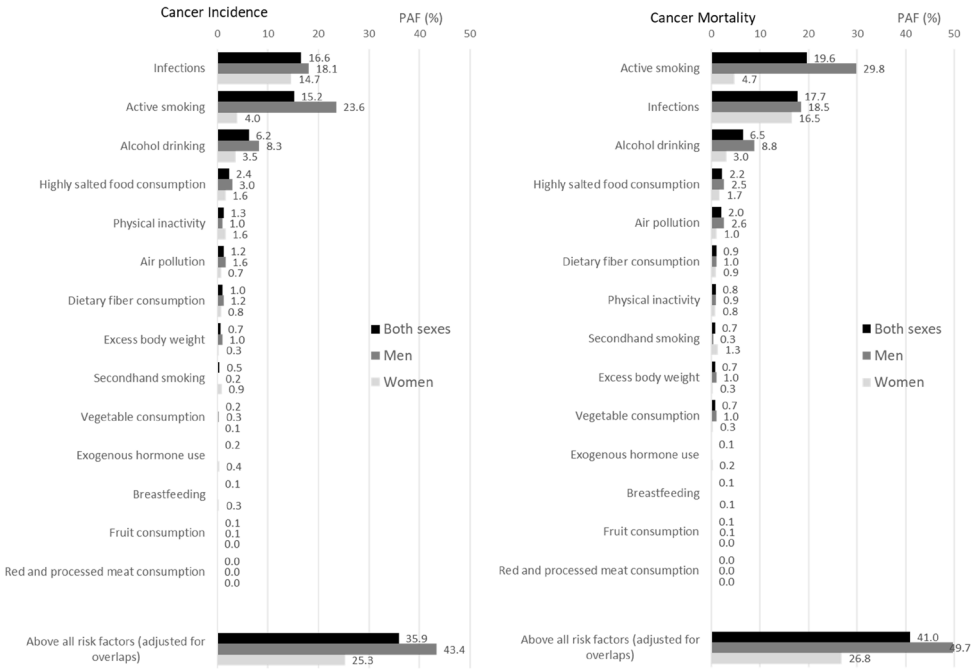

Figure 1. Population attributable fraction (PAF, %) of cancer incidence and mortality in Japan in 2015 by exposure.

Table 4. Summary table of population attributable fraction of cancer incidence and mortality in Japan in 2015 by cancer site

Site	ICD-10	Population Attributable Fraction (%)					
		Men		Women		Both sexes	
		Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
Base of Tongue	C01	72.3	71.8	58.4	56.0	68.9	68.3
Oral and mouth	C02-C06	59.8	58.6	27.6	22.9	50.8	49.4
Tonsil and Oropharynx	C09-C10	72.3	71.8	58.4	56.0	68.9	68.3
Nasopharynx	C11	82.4	82.6	83.5	83.1	83.6	83.8
Other oral pharynx	C00, C07-C08, C12-C14	58.6	57.2	24.5	19.5	48.9	47.4
Esophagus	C15	82.4	81.4	42.9	40.2	77.8	76.2
Stomach	C16	85.0	86.6	87.1	90.1	86.0	88.0
Colon	C18	42.0	40.7	15.1	15.1	31.3	33.1
Rectum	C19-C20	34.1	33.2	9.7	8.8	25.0	23.4
Anus	C21	88.0	88.0	88.0	88.0	88.0	88.0
Liver	C22	74.3	75.3	70.0	72.6	73.8	75.3
Gallbladder	C23	3.1	2.7	0.9	0.8	1.8	1.6
Pancreas	C25	26.8	26.7	7.7	7.2	17.5	17.1
Sinonasal	C30-31	48.9	48.4	19.7	17.1	38.8	36.4
Larynx	C32	77.0	75.4	13.5	11.8	73.0	71.3
Lung	C33-C34	66.3	65.6	33.2	31.2	55.2	55.4
Breast	C50			14.0	14.2	14.0	14.2
Vulva	C51			48.0	48.0	48.0	48.0
Vagina	C52			78.0	78.0	78.0	78.0
Cervix	C53			100.0	100.0	100.0	100.0
Endometrium	C54			16.1	18.5	16.1	18.5
Ovary	C56			1.0	1.1	1.0	1.1
Penis	C60	51.0	51.0			51.0	51.0
Prostate	C61	1.4	3.0			1.4	3.0
Kidney	C64	28.1	26.5	3.1	2.7	20.6	18.6
Renal pelvis & ureter	C65-C66	66.1	64.7	2.8	2.4	43.2	39.9
Bladder	C67	41.6	40.7	9.5	8.0	33.5	30.5
Hodgkin disease	C81	56.0	56.0	56.0	56.0	56.0	56.0
Non-Hodgkin Lymphoma	C82-C85, C96	3.7	3.7	3.7	3.7	3.7	3.7
Burkitt's lymphoma	C837	30.0	30.0	30.0	30.0	30.0	30.0
Adult T-cell Lymphoma/Leukemia	C915	100.0	100.0	100.0	100.0	100.0	100.0
Acute Myeloid leukemia	C920, C924, C925	20.6	21.2	5.3	4.4	14.5	14.8
All sites	ALL	43.4	49.7	25.3	26.8	35.9	41.0

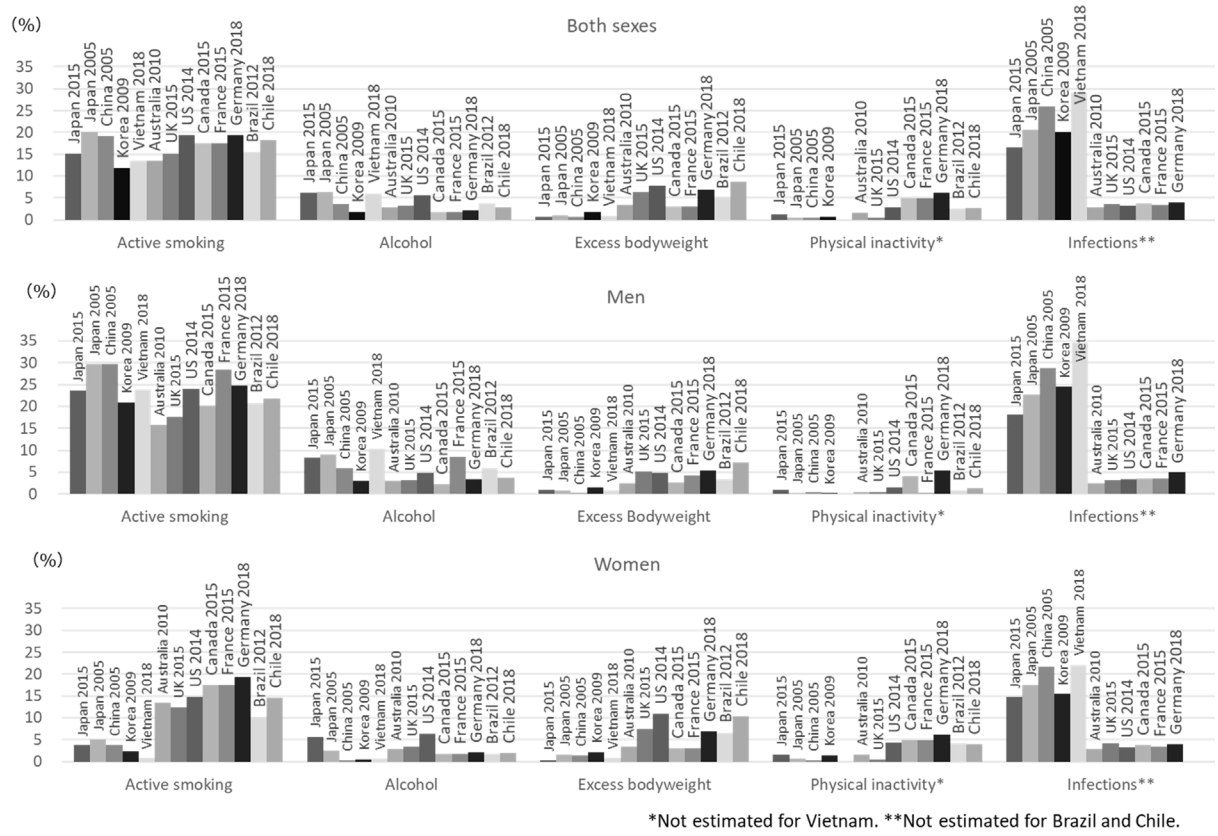

Figure 2. Major attributable causes of cancer incidence-international comparison. Japan 2015 (the present estimate), Japan 2005 (*23*), China 2005 (*13,52-55*), South Korea 2009 (*14,56-59*), Vietnam 2018 (*22*), Australia 2010 (*60*), UK 2015 (*16*), US 2014 (*7*), Canada 2015 (*18*), France 2015 (*12*), Germany 2018 (*19, 61-63*), Brazil 2012 (*20*), Chile 2018 (*21*).

higher fractions tended to be associated with infectious agents and smoking.

Discussion

This report provides the latest estimates of the cancer burden attributable to modifiable factors in Japan in 2015. Compared with the first assessment for the year 2005, when data sources for the PAF estimates for many exposures occurring around 1990 were generally limited, more epidemiological evidence and data on exposures of interest have since been accumulated, and nationally representative data for the prevalence of many factors have become available. Further, the prevalence of many modifiable risk factors in Japan has dramatically changed with birth cohort; accordingly, use of appropriate prevalence by birth cohort at the time of exposure to these factors allows a more precise estimation of cancer burden.

Compared with the first PAF estimate for 2005 (*23*), we observed a nearly 5% reduction in the PAF of cancer incidence and mortality attributable to active smoking in men. This reduction is partly attributable to the decreased prevalence of active smoking in men over these decades (*49*). A similar reduction was also observed for the PAF attributable to infections. Infections such as *Helicobacter pylori* and hepatitis C and B viruses appear to be the major contributors to cancer in Japan. Improvements in socioeconomic and hygiene status at the time of infection has definitely contributed to a reduction in prevalence, and prevalence rates estimated by birth cohort rather than age group might accordingly provide more precise estimates. In contrast, however, a notable increase in PAF was attributed to alcohol drinking in women.

International comparison clearly indicates that the PAF of infections is relatively high among Asian countries, namely Japan, China, South Korea and Vietnam; but relatively low among European countries and their migration countries, such as UK, US, France, Germany, Australia and Canada (Figure 2). Compared with the previous Japanese estimate for 2005, prevalence of major infectious agents in Japan has decreased, especially in younger birth cohorts (*50,51*). This decrease will in turn lead to drastic reductions in gastric and liver cancers - the major infection-related cancers in Japan - in the next couple of decades. PAF of other modifiable factors were generally similar among different countries. Of note, however, the larger difference in PAF by active smoking between men and women observed for Japan, China, and South Korea may reflect the difference in smoking rates by sex in East Asia.

Attribution of modifiable factors other than infections, active smoking, and alcohol drinking to

cancer in Japan was generally small (< 3%). Excess bodyweight, which is regarded as an important risk factor of cancers, was attributed a very small portion (≤ 1 %), in spite of the use of a more severe cut-off point (BMI < 23) as a theoretical minimal risk exposure level due to the average BMI levels being less than 25.

There are several limitations for these estimates. We did not include factors with insufficient exposure or relative risk data, such as solar ultraviolet radiation exposure and ionizing radiation. Also, we could not include occupational exposures due to a lack of adequate prevalence data in the Japanese general population. Given that occupational exposure in Japan is expected to be non-negligible, its inclusion would improve the PAF estimates. Furthermore, a multivariate approach is more realistic considering the multifactorial etiology of cancer in general. We took a statistical approach to account of the overlapping effect of exposures, due to the substantial lack of information for most interactions and the joint prevalence of multiple exposures.

Even though we used the best estimates of prevalence and relative risks available for Japanese and the most suitable methodology, the current estimates are focused on modifiable factors, and did not include unmodifiable factors such as genetic, socioeconomic disparity and reproductive factors which cannot be changed at the individual level. Inclusion of these factors could help provide more comprehensive estimates of attributable causes of cancer, both modifiable and non-modifiable.

In addition to the inclusion of attributable fractions of modifiable factors, national cancer control policy will be further strengthened by the inclusion of economic burden and burden of disability-adjusted life years (DALYs) under these modifiable factors. Inclusion of these variables in combination will aid understanding of the effective population intervention for each factor, and in turn lead to appropriate cancer control policy measures at the national level.

Conclusions

We estimated the cancer burden attributable to modifiable factors in Japan in 2015 using the best available epidemiological evidence. From our estimates, around 40% of cancer incidence and mortality may be preventable by avoiding exposure to known modifiable factors. Our findings clearly indicate that infections and active smoking followed by alcohol drinking are the greatest contributing factors and should be the most highly prioritized targets in current cancer control actions.

Funding: This study was supported by JSPS KAKENHI Grant Number 16H05244.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received April 8, 2021; Revised December 9, 2021; Accepted December 27 2021.

Released online in J-STAGE as advance publication December 30, 2021.

**Address correspondence to*:
Manami Inoue, Division of Prevention, Center for Public Health Sciences, National Cancer Center, 5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045, Japan.
E-mail: mnminoue@ncc.go.jp

Global Health & Medicine. 2022; 4(1):37-44.
BRIEF REPORT
DOI: 10.35772/ghm.2021.01097

Report on the nature, characteristics, and outcomes of the Japanese healthcare system

Tatsuya Kondo*; MEJ Four Dimensional Health Innovation Group

Medical Excellence JAPAN, Tokyo, Japan.

Abstract: In Japan, healthcare takes a "patient-centeredness" approach to prioritize providing rational medicine for patients under the initiative of medical doctors. This approach to healthcare is based on the concept that patients should receive the correct diagnosis and optimal treatment. The present report aims to provide an overview of the specific characteristics of healthcare in Japan to healthcare management professionals in other countries. We introduce the systems within Japan's healthcare framework, particularly "medical team approach", "nutrition management", and "infection controls", as well as treatment results in Japan using objective data to inform medical doctors in management positions in other parts of the world. Collectively, these three healthcare systems comprise the "patient-centeredness" philosophy through which Japanese healthcare professionals perceive ideal patient care and act accordingly. These healthcare systems are unique to Japan and were developed in accordance with the specific framework of Japanese history, systems, and culture. This report presents the effects of "patient-centeredness" healthcare based on treatment results and performance data by making a quantitative and qualitative comparison with healthcare in Europe and the USA. Further objective evaluation revealed that Japan demonstrates positive treatment results that are comparable to those of Europe and the USA due to its "patient-centeredness" rational medical system and the availability of the "correct diagnosis and optimal treatment". These findings introduce Japan's "patient-centeredness" medical and healthcare system with a view of informing and guiding improvements in the healthcare quality of other countries and promoting future international collaborations.

***Keywords*:** patient-centeredness, healthcare system, Japan

Introduction

The health insurance system in Japan provides universal health coverage that is funded by both taxes and individual contributions. All residents, including expatriates, are obliged to join either the employment-based or residence-based health insurance (*1*). Additional private health insurance is common to complement the universal health insurance and prepare for unforeseen expenses.

Insured residents pay 30% (children, elderly, and low-income citizens have lower coinsurance rates) of their medical and pharmaceutical costs and the insurer covers the rest, up to monthly and annual maximum limits (*1*). The government defines the benefits and sets the fee schedule, which is renewed every 2 years. The universal health insurance fundamentally works on a piecework system and is not compatible with treatments outside of the system. We believe that the Japanese healthcare system aims at providing rational medicine based on "patient-centeredness" to best provide correct diagnoses and optimal treatments. The system uses meticulous on-site improvements to provide patients with adequate services.

This report introduces three aspects within the system as specific examples, namely "medical team approach", "nutrition management", and "infection control". Outcomes of distinctive diseases are presented and compared with those of some European countries and the USA. This study aims to convey the noteworthy characteristics of the Japanese healthcare system to healthcare management professionals worldwide.

Materials and Methods

A survey of 131 medical doctors and healthcare professionals across 48 Japan International Hospitals, medical institutions accredited by the Medical Excellence Japan for their readiness to take in foreign patients in Japan, was conducted online between October and December 2019 to collect data on the strengths and advantages of the Japanese healthcare system. The information was narrowed down to 10 aspects: team approach, speed, quality and safety, medical education, nutrition support, infrastructure, nationwide equal accessibility, preventative and

advanced medicine, leadership of physicians, and home doctors.

Six medical doctors with international backgrounds were interviewed to determine the strengths that could be shared internationally to promote better patient care and support. Three characteristics, "medical team approach", "nutrition management", and "infection control" were selected as noteworthy characteristics, and four healthcare professionals were interviewed regarding these specific aspects.

Results and Discussion

Healthcare in Japan

In Japan, healthcare focuses on providing treatment and care based on "patient-centeredness", prioritizing the provision of rational medicine to patients as a team under the initiative of medical doctors. In this report, "patient-centeredness" is defined as the attitude of healthcare professionals to provide ideal and beneficial care depending on the decision of the patient throughout their treatment based on the principle that patients should always receive the "correct diagnosis and optimal treatments".

Japan has nationwide training facilities for healthcare professionals and the network of university hospitals, small and large specialized hospitals, and clinics in urban and rural areas are well organized. Many large-scale hospitals are equipped with the facilities, systems, and skills that healthcare providers of a comparable standard would deliver in other medically advanced regions, such as Europe and North America. The universal healthcare reimbursement system evaluates the services provided by each facility so that services are maintained at a high level across the country. Universal health insurance ensures that these factors enable the equal availability of healthcare services nationwide. Furthermore, the low mortality rate of ischemic cerebral infarction (*2*) and high five-year survival rate of all carcinomas (*3*) show small regional differences within Japan.

The following sections will introduce the three characteristics, namely "medical team approach", "nutrition management", and "infection controls", of the healthcare system in Japan that support the foundation of healthcare and contribute indirectly to treatment results.

Unique features of Japan's medical and healthcare system

Medical team approach

The medical team approach is defined in Japan as "sharing goals and information of the patient, cooperating with and complementing each other while serving each of their roles, and providing flexible care depending on patients' situations *via* a wide variety of healthcare staff engaged in medical and healthcare on the premise of a high level of their expertise" (*4*).

Cooperation among disciplines is essential for delivering adequate treatment and care due to the increased specialization of each field and the subdivision of occupations. The Japanese national government certifies a diverse range of healthcare professionals and their professionalism is nurtured via continual training provided under the initiative of the academic societies in addition to hands-on training within the hospitals (Table 1).

An example that highlights this approach is the "clinical pathway", which has evolved independently in Japan and penetrated deep into the healthcare system. The idea of the clinical pathway originated in the USA as the "critical pathway", which began as a manufacturing process control technique. It was later introduced to the field of healthcare to optimize resources in hospitals by forecasting and managing the human resources necessary in each patient's treatment phase (*5*). Healthcare providers in Japan developed this process control technique into a tool to provide the best care for patients based on the concept of "patient-centeredness" using optimal resources. In Japan, the clinical pathway involves creating customized treatment plans for each patient and setting goals in each treatment phase (*6*). The members of the medical care team clearly understand their individual roles as well as the overall targets and goals so the development and implementation of the ideal care programs are unified. In other words, the clinical pathway is a tool for practicing a "medical team approach" that is customized to individual patients by facilitating information shared among the team.

These clinical pathways are constantly updated and improved. Hospitals establish clinical pathway committees and perform operational management activities associated with these such as developing, promoting, and reviewing the procedures (*6*). Moreover, academic societies and communities, such as the Japanese Society for Clinical Pathway, continually facilitate improvement in clinical pathways at associated hospitals by conducting exchanges of opinions on a

Table 1. Healthcare professionals certified with national qualifications in Japan

Doctors	Physiotherapists	Health laboratory technicians
Dentists	Occupational therapists	Clinical engineers
Pharmacists	Orthoptists	Dental hygienists
Health nurses	Speech therapists	Dental technicians
Midwives	Prosthetists	Emergency medical technicians
Nurses	Radiological technologists	Registered dieticians
Clinical laboratory technicians		

nationwide basis (*6*).

The Japan Council for Quality Health Care sets interdisciplinary cooperation as one of the rating indices for hospitals with independent evaluations for in-hospital cooperation based on "patient-centeredness". This serves as an external driving force to promote patient-centered cooperation.

In the USA, specialization in healthcare professionals' expertise is promoted from the perspective of management rationalization by healthcare organizations (*7*). There is a history of new occupations complementing traditional professionals and the healthcare delivery system has been built based on the combination of professionals with definite roles, centering on doctors.

In France, some medical procedures that are traditionally conducted by medical doctors have been authorized to be carried out by nurses to promote specialization in doctors' expertise due to increasingly sophisticated treatments and to control healthcare costs. The roles of nurses with and without expertise is stipulated by law (*8*) and a healthcare delivery system has been established in which multiple disciplines cooperate based on individual roles.

The "medical team approach", in Japan involves the division of labor, provides efficient healthcare services, has a comprehensive approach that includes patients in the team, and provides tailor-made goals for each patient. Furthermore, responsibilities of healthcare professionals overlap so that there are more opportunities for contingencies.

Nutrition management

"Nutrition management" refers to developing and implementing nutrition management plans for individual patients before and after treatment based on information obtained from the patients' physical condition and laboratory data to improve their prognosis. Appropriate nutrition management before and after treatment has been confirmed to stabilize patients' conditions and reduce mortality (*9*).

Many Japanese hospitals have set up systems to perform the same level of nutritional care as in Europe and the USA to ensure suitable nutrition management before and after treatment. Hospitals aim to provide treatment as well as customized nutrition care for each patient, with a focus on improving quality of life (QOL) after their discharge from hospital, based on the concept of "patient-centeredness".

A feature of "nutrition management" in Japan is that registered dieticians actively intervene in patients' nutrition management to improve their prognosis. This means individual patients receive the optimal nutrition management that considers nutrients, allergies, food forms that are easy to eat, and patients' taste and flavor preferences that are appropriate for the clinical conditions.

Registered dieticians coordinate with medical doctors to tailor the nutrition management for each individual patient. Registered dieticians check the patients' nutritional intake and use that information to make suggestions to the doctors about the content and forms of the meals and intravenous nutrition administration plans. They also talk with patients to relieve anxieties about meals after treatment and provide dietary instructions after discharge from hospital. They aim to improve the patients' prognosis and QOL following discharge (*10*).

One example of customized care to patients is thickening liquids. Post-stroke patients have a greater risk of developing pneumonia due to aspirating liquid. Registered dieticians thicken water to make it easier to drink. Since the required thickness differs according to each patient, the thickness of the water is carefully and gradually reduced as each patient recovers (*11*).

In Japan, registered dieticians are keenly aware of deferring to and supporting patients' wishes when they want to consume food orally. They emphasize the aspect of a hospital diet as a clinical diet to boost the nutritional intake as well as making meals enjoyable. For example, meals are provided at temperatures at which patients can enjoy them by using serving wagons with heat insulation and a cooling function (*11*). Moreover, some hospitals promote enjoyable meals using decorative ingredients and colors and incorporating seasonal ingredients to stimulate the appetites of patients who are reluctant to eat (*11*). Studies have shown that food intake increases and the effects of treatment improve when patients are willing to consume meals (*12*).

In Japan, "nutrition management" is supported by on-site activities, such as nutrition screening, development and review of nutrition management plans, and establishment of nutrition support teams, that are conducted at each hospital. There is a reimbursement system for "nutrition management" to promote these efforts. The same nutrition management system has been adopted by hospitals across the country since this system has come to serve as a guideline for hospitals to promote "nutrition management".

Many registered dieticians support "nutrition management" in Japan. In December 2019, the total number of registered dieticians in Japan was 244,487. The number of registered dieticians in Japan is 193/100,000 people (*13*) and is significantly higher than that in the USA (32/100,000 people), which is considered an advanced country in terms of nutrition management (*14*) (Figure 1).

Due to their abundance, registered dieticians are able to provide highly individual nutrition care for each patient. This could deliver benefits such as improved prognosis for recovery and greater patient satisfaction. An example of improved prognosis is the case of outcomes for intensive care unit (ICU) patients who require fast and meticulous nutrition management. Organizing a nutrition management system that includes

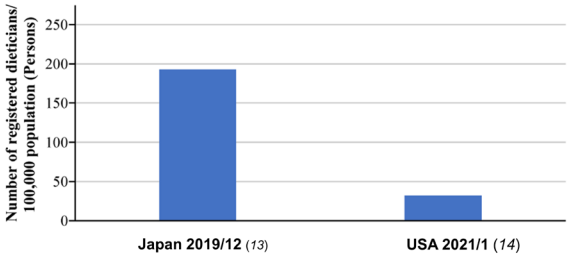

Figure 1. Comparison of the numbers of registered dieticians per 100,000 people in Japan and the USA. Compared to the USA, one of the most advanced countries in the world, the number of registered dietician per capita is significantly higher in Japan. Data source: *Reference 13 for Japan, and Reference 14 for the USA.*

early administration of enteral nutrition to ICU patients improves prognosis and significantly reduces the length of stay in the ICU and the length of hospitalization (*9*). Greater patient satisfaction is also seen. At least 85% of patients answered "satisfied" in a meal satisfaction survey conducted after registered dieticians collected and analyzed data from patients regarding meals, checking patients' dietary intake and taste preferences, and improving the menus (*11*).

"Nutrition management" is a system that is unique to Japan, where healthcare professionals' desire for patients to enjoy a safe, appetizing, and nutritious diet as part of Japan's excellent healthcare system is reflected. This can be considered an additional characteristic of Japan's healthcare system based on "patient-centeredness".

Infection control

The Ministry of Health, Labor, and Welfare defined healthcare-associated infections as: *i*) infections which patients are newly affected apart from the primary diseases in the healthcare facilities; *ii*) infections which healthcare professionals, *etc.* have acquired in the healthcare facilities". We now present an outline of the measures against healthcare-associated infections concerning the first category.

Infection control refers to preventing the occurrence of infections and reducing the spread of infections when they do occur. It includes thoroughly implementing standard sterilization and launching countermeasures according to specific pathogens and clinical conditions as well as improving the hospital environment. These items are listed in the Centers for Disease Control and Prevention guidelines (*15*).

Infection controls were developed in Europe and the USA in response to an increase in antibiotic-resistant bacteria. Japan's countermeasures have been incorporated alongside those in Europe and the USA and have evolved into Japan's own system. Japan is working toward a system of infection control based on the concept of "patient-centeredness" in which countermeasures are made according to patients' respective conditions.

In Japanese hospitals, a special team comprising members from multiple disciplines is assembled to prevent infections and to implement anti-infection measures for the organization. Rather than uniformly following one standard guideline, each hospital customizes the guidelines to match its human resources, financial condition, and patient demographics. These guidelines incorporate efforts to improve work in clinical practice and are updated regularly. For example, a patient's shoes are removed and placed in a bag when they are put on a stretcher to prevent bacteria present on the soles of their shoes from coming into contact with the bed they lie on.

However, rather than making adherence to guidelines the primary goal, responses should be based on the guidelines while considering patients' needs. In some cases, hospitals even consider which zones should allow flowers to be brought in as get-well gifts for patients due to conditions such as immunosuppression. Even when such situations are not described in the guidelines, they are considered, according to the best healthcare service for patients in view of safety and patient satisfaction.

Thus, a flexible approach to infection control is taken in Japan with the best interests of the patients in mind. Consequently, accumulating the small efforts mentioned above has led to an appropriately hygienic environment unique to Japan. Many hospitals conduct surveillance regarding healthcare-associated infections in hospitals and have adopted a feedback system to improve their guidelines (*16,17*). As a result of these infection controls in each hospital, the incidence of healthcare-associated infections (bloodstream infections/urinary tract infections/ventilation-related pneumonia) is low in Japan compared with European countries, which are considered to be advanced in this field (*17,18*) (Figure 2).

In addition to the above-mentioned infection prevention measures, the proper use of antibiotic agents is promoted in Japan to reduce post-surgery deaths resulting from infections. In some cases, efforts are made to resolve delays in reporting test results, implementing appropriate treatments, and diminishing adverse events by cooperation among doctors, nurses, pharmacists, and clinical laboratory technicians and monitoring patients with culture-positive results for 24 hours a day, 365 days a year, based on the guidance published by the Ministry of Health, Labor and Welfare (*10*).

There is a reimbursement system for infection controls to promote these efforts. Since this system stipulates the measures against healthcare-associated infections to be taken as a requirement for calculating medical fees, each hospital across the country takes the appropriate measures against infection according to each situation. Some countries penalize medical institutions for not implementing infection control, while Japan evaluates the implementation of infection controls and provides additional remuneration as incentives that lead to quality improvement.

Consequently, Japan's system of "infection control"

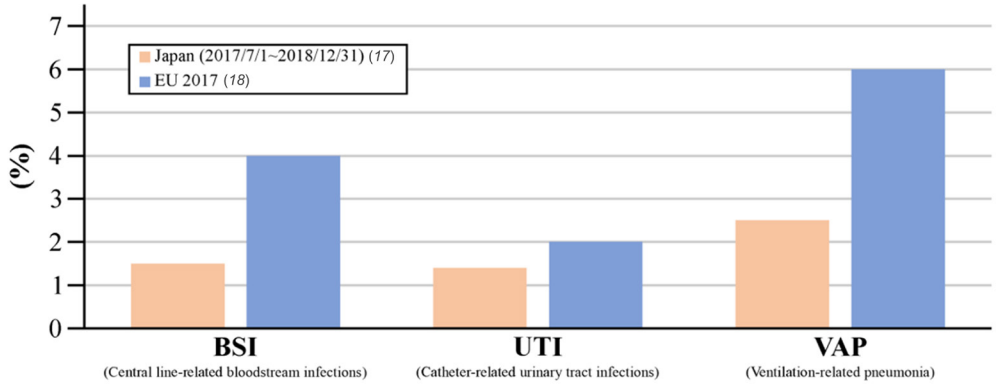

Figure 2. Comparison of the incidence of healthcare-associated infections according to clinical conditions in Japan and Europe. A comparison of the incidence of surgical site infections has been omitted due to a lack of comparable data. BSI, central line-related bloodstream infections; UTI, catheter-related urinary tract infections; VAP, ventilation-related pneumonia. Data source: *Reference 17 for Japan, and Reference 18 for European countries.*

Table 2. Comparison of 5-year survival rates for cancer treatments in the USA, Europe, and Japan

Categories	Comparison of 5-year survival rates (%)*				
	Japan	USA	Germany	France	UK
Lung cancer	33	21	18	17	13
Gastric cancer	60	33	34	27	21
Esophageal cancer	36	20	21	14	16
Colon cancer	68	65	65	64	60
Hepatic cancer	30	17	13	18	13

*5-year survival rates for each type of carcinoma (including all stages) from 2010 to 2014. Data source: Reference *3*.

is the most unique in the world as each hospital has repeatedly established their individual system based on systems adopted from Europe and the USA. This system could be regarded as a key characteristic of Japan's healthcare system based on the concept of "patient-centeredness".

Excellent treatment results from Japan's medical and healthcare system based on "patient-centeredness"

This report has discussed the nature of Japan's medical and healthcare system based on "patient-centeredness". Excellent treatment results for many diseases have also been observed in Japan based on the "correct diagnosis and optimal treatment". Here, we discuss the results of cancer treatments and minimally invasive medicine for cardiovascular diseases as specific examples.

Cancer treatments

Japan has strong outcomes in cancer treatment. Table 2 shows the five-year survival rates for various carcinomas in Japan, the USA, and some European countries (*3*). The five-year survival rates for treatment of major carcinomas are higher in Japan than those in the USA and the listed European countries. Many types of cancer treatments are available in Japan (Table 3).

Minimally invasive medicinal treatment for cardiovascular diseases

Japan also has excellent treatment results for minimally invasive medical treatment of cardiovascular diseases. Table 4 shows the 30-day mortality after treatment of ischemic heart diseases in Japan and in other countries as reference. The number of deaths due to cardiac arrest per 100,000 people in Japan, the USA, Germany, and France was 171, 256, 314, and 182, respectively (*2*). The number of deaths due to cardiac arrest per 100,000 people is lower in Japan than in other countries.

Minimally invasive medical treatments for a variety of cardiovascular diseases are also available in Japan (Table 5). Japan has better treatment results than Europe and the USA, particularly for cancer treatments and minimally invasive medical procedures for cardiovascular diseases. This is attributed to the excellent characteristics of Japan's medical and healthcare system, as well as the independently developed advanced healthcare system adopted from Europe and the USA based on "patient-centeredness" and ingenuity in clinical practice.

Conclusion

This report details examples of the systems within Japan's healthcare framework, namely "medical team approach," "nutrition management," and "infection controls," as well as treatment results using objective data. These three healthcare systems manifest the philosophy of "patient-centeredness," by which healthcare professionals always consider the ideal care and act accordingly. Another characteristic is that these healthcare systems are unique to Japan and were developed with the history, systems, and the culture of Japan.

Japan demonstrates positive treatment results comparable to Europe and the USA due to its rational medical system based on "patient-centeredness" and the pursuit of the "correct diagnosis and optimal treatment".

Table 3. Cancer treatment methods and their results

Treatment methods	Number of cases (year)*
Laparoscopic surgery for cancers (minimally invasive treatment for the digestive system)	Stomach: 15,000 per year (2018) (*19*) Lung: 39,000 per year (2018) (*19*)
Endoscopy/Endoscopic therapy	
ESD	Stomach: 47,045 per year (2017) (*20*) Large intestine: ≥ 6,000 (2017) (*20*)
EMR (including polypectomy)	Stomach: 3,824 per year (2017) (*20*)
Hepatic cancer treatment (RFA)	30,000 per year or more (2014) (*21*)
IMRT	25,000 per year (2017) (*22*)
Particle-beam radiation therapy	4,800 per year (2017) (*22*)

*The number of cases for each treatment method for Japan's population (126,020,000, as of 1/1/2020) is listed. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; IMRT, intensity-modulated radiotherapy; RFA, radiofrequency ablation.

Table 4. The 30-day mortality after treatment for cardiac diseases in Japan compared with that in other countries

Treatment	Mortality in Japan (year)	Mortality in other countries (year)
Cardiac catheterization treatment	0.05-0.2% (*23*) (2006)	USA: 1.20% (*24*) (2005-2016)
Surgery for valvular heart diseases (TAVI)	2.0% (*25*) (October 2013-July 2015)	Germany: 2.40% (*26*) (2012-2015)
Aortic stent grafting		
Thoracic	Descending part: 1.40% (*27*) (fiscal 2017) Arch: 3.0% (*28*) (fiscal 2017)	USA & Canada: 8.40%* (*28*) (2013-2014)
Abdominal	0.90 (*27*) (fiscal 2014)	USA & Canada: 1.20%** (*29*) (2006-2015)

*Analysis of 2,542 patients registered in the Vascular Quality Initiative compared with the mortality in Japan. **Analysis of 30,076 patients registered in the American College of Surgeons National Surgical Quality Improvement Program compared with the mortality in Japan.

Table 5. Treatment methods for cardiovascular diseases and their results

Treatment methods	Number of cases performed*
Cardiac catheterization treatment	Elective PCI: 192,670 per year (2018) (*30*)
Catheter ablation	10,590 (August-December 2017) (*31*)
Surgery for valvular heart disease (TAVI)	6,850 per year (2018) (*30*)
Aortic stent grafting	
Thoracic	4,177 per year (2018) (*30*)
Abdominal	9,410 per year (2018) (*30*)

*The number of cases for each treatment method for Japan's population (126,020,000, as of 1/1/2020). PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.

This report intends to introduce Japan's medical and healthcare system based on "patient-centeredness" to healthcare providers worldwide for the global improvement of the quality of healthcare.

Acknowledgments

We would like to express our sincere gratitude to all participants who contributed to the study.

We received professional inputs from the following members including medical doctors in the management bracket in hospitals overseas: Dr. Minoru Akiyama (Medical Excellence JAPAN); Dr. Tianyuan Guo (Juntendo University Hospital); Dr. Masao Hashimoto (National Center for Global Health and Medicine); Dr. Dongcun Jin (Tsuyama Chuo Hospital International Medical Support Center); Dr. Takashi Karako (National Center for Global Health and Medicine); Dr. Dongmei Ma (University of Tsukuba Hospital); Dr. Tetsuya Matsumoto (International University of Health and Welfare); Dr. Yasushi Miyazawa (Tokyo Medical University); Dr. Itaru Nakamura (Tokyo Medical University); Dr. Jun Oda (Tokyo Medical University); Dr. Haoying Shi (SinoUnited Health); Dr. Pham Tuan Anh (National Cancer Hospital of Viet Nam); and Dr. Zhaoqi Zhang (Meishen Medical Center).

Furthermore, we received valuable advice from the following members: Dr. Takao Aizawa (Japan Hospital Association), Dr. Yasuhiro Fujiwara (Pharmaceuticals and Medical Devices Agency), Dr. Kiyotaka Hoshinaga (Fujita Academy), Dr. Satoshi Imamura (Japan Medical Association), Dr. Yuko Kitagawa (Keio University), Dr. Norihiro Kokudo (National Center for Global Health and Medicine), Dr. Morito Monden (The Japanese Association of Medical Sciences), Dr. Yasuyuki Seto (The University of Tokyo), and Dr. Kotaro Yokote

(National University Hospital Council of Japan).

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received August 24, 2021; Revised December 14, 2021; Accepted December 22, 2021.

Released online in J-STAGE as advance publication January 17, 2022.

**Address correspondence to*:
Tatsuya Kondo, Medical Excellence JAPAN, Ichibancho Hougenzaka Bldg. 3F, 13 Ichibancho, Chiyoda-ku, Tokyo 102-0082, Japan.
E-mail: yojigen@me-jp.org

Global Health & Medicine. 2022; 4(1):45-51.
BRIEF REPORT
DOI: 10.35772/ghm.2021.01019

Preprocedural frailty is strongly associated with symptoms after balloon pulmonary angioplasty

Nobutaka Ikeda[1,*], Raisuke Iijima[1], Hidehiko Hara[1], Yukio Hiroi[2], Masato Nakamura[1]

[1] Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan;
[2] Division of Cardiovascular Medicine, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Balloon pulmonary angioplasty (BPA) has improved the survival rate of patients with chronic thromboembolic pulmonary hypertension (CTEPH). The resolution of symptoms is one of the remaining goals of BPA. Frailty affects the outcome of cardiovascular diseases or treatments. The aim of this study is to assess the association between frailty and outcome of BPA. The resolution of symptoms is evaluated by the post-BPA World Health Organization functional class (WHO-FC). A total of 54 patients with CTEPH were divided into 2 groups by post-BPA WHO-FC (WHO-FC I group; $n = 34$ *vs.* WHO-FC ≥ II group; $n = 20$). Frailty was assessed by physicians using the clinical frailty scale (CFS) at the point of patient admission for their first BPA sessions. Compared to the WHO-FC ≥ II group, the WHO-FC I group was younger (65.6 ± 13.9 years *vs.* 74.3 ± 8.0 years) and had a lower CFS (3 [3, 4] *vs.* 4 [4, 6]) (median [25th, 75th percentiles]). The WHO-FC I achievement rates for each CFS score were CFS 3: 82.8%; 4: 53.8%; 5: 25.0%; 6: 33.3%; and 7: 20.0%. Logistic regression analysis showed that CFS was an independent predictor of WHO-FC I achievement (odds ratio 0.50, $p = 0.012$), but pre-BPA hemodynamic parameters and age were not independent predictors. Whether WHO-FC I can be achieved is predicted by pre-BPA patient frailty but not by pre-BPA hemodynamic parameters and age.

Keywords: chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, frailty, WHO functional class

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a Group 4 pulmonary hypertension (PH) caused by organized thrombi, and prognosis is very poor if these patients are not treated properly (*1,2*). Balloon pulmonary angioplasty (BPA) is emerging as a promising complement to pulmonary endarterectomy (PEA), especially in patients with distal type or inoperable CTEPH (*3-7*). In 2017, multicenter registry results from Japan showed that the improvements in hemodynamic status and survival rates after BPA were excellent (*8*). However, many patients still had symptoms of World Health Organization functional class (WHO-FC) II or more at the follow-up periods, even though they underwent BPA (*8,9*). Currently, the resolution of symptoms is one of the biggest remaining goals of BPA. Even in the last few years, with innovations in techniques and technologies of BPA, certain patients still fail to reach WHO-FC I (*3,7,10-14*).

Compared to those with Group 1 PH, patients with CTEPH are older and have many comorbidities (*5,6*). Patients who are elderly and patients with comorbidities have reduced physiological reserve and increased vulnerability to stress. Recently, the concept of frailty has become increasingly used when evaluating the general condition of patients, especially in patients who are elderly. High frailty is associated with an increased risk of dependency and poor life prognosis, and frailty affects the outcome of cardiovascular diseases or treatments (*15-19*).

The purpose of this study is to assess the association between frailty, hemodynamic status, and outcome of BPA.

Materials and Methods

Study patients

The study subjects were 54 consecutive patients with CTEPH who underwent BPA from April 2016 to March 2020 at Toho University Ohashi Medical Center and were evaluated pre- and post-BPA to determine their WHO-FC using questionnaires. CTEPH was diagnosed based on the presentation of organized thrombi in pulmonary arteries by pulmonary angiography or contrast computed tomography, perfusion lung scintigraphy, pulmonary function tests, blood tests,

echocardiography and right heart catheterization (mean pulmonary artery pressure 25 mmHg or more and pulmonary artery wedge pressure 15 mmHg or less). Other causes of PH were ruled out. Patient characteristics, frailty, pre and post-BPA hemodynamic parameters, 6-minute walk distance (6MWD), and BPA results were retrospectively collected from their medical records. Exclusion criteria were lack of data before and after BPA, and patients who refused use of their data refused to use the data. Study patients were divided into two groups (WHO-FC I group *vs.* WHO-FC ≥ II group). The definition of WHO-FC is shown in supplemental Table 1.

Evaluation of frailty

Frailty was assessed by physicians using the clinical frailty scale (CFS) at the point of patient admission for their first BPA sessions (Figure 1). The CFS level (1: Very Fit to 9: Terminally Ill) was determined by a validation study and revised in 2008 (*20*).

BPA procedures

The BPA procedure was as follows. An 8.2-Fr sheath was inserted into the femoral or right internal jugular vein. From the sheath, a 70-cm-long 6-Fr guiding sheath (ParentPlus60®, Medikit Co. Ltd, Tokyo) was advanced to the right or left main pulmonary arteries. Through the guiding sheath, a 6-Fr guiding catheter was advanced to the segmental or subsegmental pulmonary arteries. Contrast media was injected to visualize the angiographic features of the target lesions. Under fluoroscopic guidance, a 0.014-inch wire was advanced distal to the target lesions, and the lesions were dilated using adequate size balloons (from 1.2 mm to 8.0 mm). The sizes of balloons were selected mainly by angiography. The goal of BPA at our institution is to properly treat all lesions accessible by catheters, and repeated BPA sessions are performed to achieve this goal.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normality of variable distributions. Continuous variables are presented as the means ± SDs or medians and the interquartile ranges [25th, 75th percentiles]. Categorical variables are presented as counts or proportions (percentages). To evaluate the predictive values of patient characteristics and pre-BPA status for achievement of WHO-FC I, logistic regression analysis was used, and odds ratios and 95% confidence intervals (95% CIs) are presented. Variables with a p-value < 0.1 were included in the multivariable analysis. All of the tests were two-sided, and p-values < 0.05 were considered significant. SPSS (IBM Japan, Tokyo) software package (ver. 23) was used for the analyses.

Ethical considerations

This study was performed in accordance with the Code of Federal Regulations and the Declaration of Helsinki. The present study was approved by the Ethics Committee of Toho University Ohashi Medical Center (approval number: H20001). Written informed consent for comprehensive agreement was obtained from all patients, and an opt-out form on the website of Toho University Ohashi Medical Center provided the target

Table 1. Patient characteristics and the effect of BPA on haemodynamic parameters and 6-minute walk distance

Variables	Pre-BPA	Post-BPA	p value
Total number of patients	54		
Age (y)	68.8 ± 12.7		
Male sex	17 (31.5%)		
Body weight (kg)	57.5 ± 14.3		
Duration from onset (y)	2.9 ± 0.4		
Pulmonary vasodilator	22 (40.7%)		
Endothelin receptor antagonist	3 (5.6%)		
Phosphodiesterase type 5	2 (3.7%)		
Prostacyclin	9 (16.7%)		
Soluble guanylate cyclase	17 (31.5%)		
Deep vein thrombosis and/or Pulmonary embolism	29 (53.7%)		
Coronary artery disease	2 (3.7%)		
Chronic obstructive pulmonary disease	6 (11.1%)		
Clinical frailty scale	3 [3, 4]	–	–
6MWD (m)	296 ± 132	424 ± 150	< 0.0001
sPAP (mmHg)	60.1 ± 18.5	37.1 ± 11.5	< 0.0001
dPAP (mmHg)	20.4 ± 5.9	13.4 ± 4.6	< 0.0001
mPAP (mmHg)	35.4 ± 9.0	22.2 ± 6.0	< 0.0001
CI (L/min/m^2)	2.7 ± 0.7	3.0 ± 0.8	0.028
PVR (dyne·s/cm^5)	497 ± 236	225 ± 107	< 0.0001

mean ± SD, median [25th, 75th percentiles]; 6MWD: six-minute walk distance; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

Figure 1. Clinical frailty scale (*Data source*: permission received from Dalhousie University).

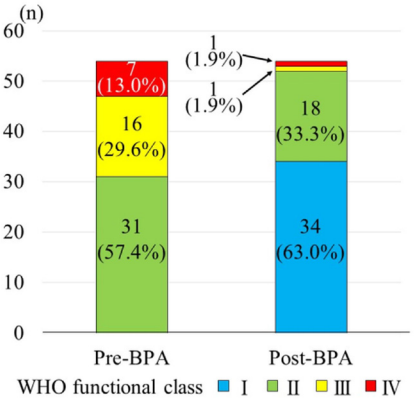

Figure 2. Change of WHO-functional class. WHO-functional class pre- and post- balloon pulmonary angioplasty (BPA).

patients with the opportunity to refuse participation in the present study.

Results and Discussion

Effects of BPA

In 54 patients who underwent BPA, 34 (63%) achieved post-BPA WHO-FC I, and 20 (37%) achieved post-BPA WHO-FC ≥ II (Figure 2). BPA significantly improved hemodynamic parameters and the 6MWD (Table 1).

WHO-FC I achievement and pre-BPA status

Regarding pre-BPA status, compared to the WHO-FC ≥ II group, the WHO-FC I group was significantly younger (65.6 ± 13.9 years *vs.* 74.3 ± 8.0 years) and had lower CFS scores (3 [3, 4] *vs.* 4 [4, 6]) (Table 2). Figure 3 shows the WHO-FC I achievement rate for each CFS score (CFS 3: 82.8%; 4: 53.8%; 5: 25.0%; 6: 33.3%; and 7: 20.0%).

WHO-FC I achievement and post-BPA status

Regarding post-BPA status, the WHO-FC I group showed significantly lower post-BPA systolic and mean pulmonary artery pressure (sPAP: 34.1 ± 8.6 mmHg *vs.* 42.6 ± 14.2 mmHg; mPAP: 20.8 ± 5.0 mmHg *vs.* 24.7 ± 6.9 mmHg), lower pulmonary vascular resistance (PVR: 197 ± 76 dyne·s/cm^5 *vs.* 272 ± 134 dyne·s/cm^5) and longer post-BPA 6MWD (475 ± 140 m *vs.* 331 ± 123 m) (Table 2). However, WHO-FC I achievement rate stratified by quartiles of post-BPA mPAP reached a plateau (post-BPA mPAP 1st quartile 11-18 mmHg: 76.9% [10/13]; 2nd quartile 19-20 mmHg: 75% [9/12]; 3rd quartile 21-23 mmHg: 60% [9/15]; and 4th quartile 24-42 mmHg: 42.9% [6/14]) (Figure 4).

Predictors of WHO-FC I achievement

Multivariable logistic regression analysis showed that CFS was an independent predictor of WHO-FC I achievement, but pre-BPA hemodynamic parameters and age were not independent predictors (Table 3).

Main findings

In daily clinical practice, we tend to have the impression that both the improvement of patient hemodynamic parameters and pre-BPA status affect patient symptoms after BPA. The principle finding of our study is that frailty, not age, is a limitation for the improvement of symptoms after BPA. Although post-BPA hemodynamic status was associated with the WHO-FC I achievement rate, not all hemodynamically well-improved patients reached WHO-FC I. Figure 4 shows an upward trend and plateau of the WHO-FC I ratio with decreasing post-BPA mPAP. Pre-BPA patient conditions also strongly affected post-BPA patient symptoms.

Table 2. Patient characteristics, 6-minute walk distance and haemodynamic parameters of pre/post balloon pulmonary angioplasty

Variables	WHO-FC I	WHO-FC II or more	*p* value
Total number of patients	34	20	–
Age (y)	65.6 ± 13.9	74.3 ± 8.0	0.006
Male sex	11 (32.4%)	6 (30.0%)	1.00
Body weight (kg)	59.6 ± 13.8	54.0 ± 14.7	0.16
Duration from onset (y)	2.6 ± 3.2	3.6 ± 3.2	0.15
Pulmonary vasodilator	13 (38.2%)	9 (45.0%)	0.78
Clinical frailty scale	3 [3, 4]	4 [4, 6]	< 0.0001
Total number of BPA sessions	4.8 ± 2.1	4.5 ± 2.6	0.60
Total amount of contrast medium (mL)	836 ± 378	880 ± 544	0.76
eGFR, Pre-BPA/Post-BPA (mL/min/1.73m^2)	59.6 ± 12.9/62.6 ± 13.5	51.9 ± 15.3/55.7 ± 13.2	0.12/0.15
Mixed venous blood oxygen saturation, Pre-BPA/Post-BPA (%)	67.4 ± 5.9/72.4 ± 4.6	57.8 ± 9.0/64.6 ± 10.6	0.003/0.11
Pre-BPA			
6MWD (m)	312 ± 145	239 ± 131	0.096
sPAP (mmHg)	58.6 ± 19.3	63.5 ± 16.3	0.34
dPAP (mmHg)	20.6 ± 6.0	19.8 ± 5.6	0.65
mPAP (mmHg)	35.1 ± 10.0	35.9 ± 7.2	0.75
CI (L/min/m^2)	2.8 ± 0.6	2.7 ± 0.8	0.56
PVR (dyne·s/cm^5)	456 ± 219	566 ± 254	0.10
Post-BPA			
6MWD (m)	475 ± 140	331 ± 123	0.002
sPAP (mmHg)	34.1 ± 8.6	42.6 ± 14.2	0.016
dPAP (mmHg)	12.7 ± 4.4	14.7 ± 4.7	0.14
mPAP (mmHg)	20.8 ± 5.0	24.7 ± 6.9	0.030
CI (L/min/m^2)	3.0 ± 0.9	2.8 ± 0.8	0.49
PVR (dyne·s/cm^5)	197 ± 76	272 ± 134	0.030

BPA: balloon pulmonary angioplasty; mean ± SD, median [25th, 75th percentiles]; BPA: balloon pulmonary angioplasty; eGFR: estimated glemerular filtration rate; 6MWD: six-minute walk distance; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

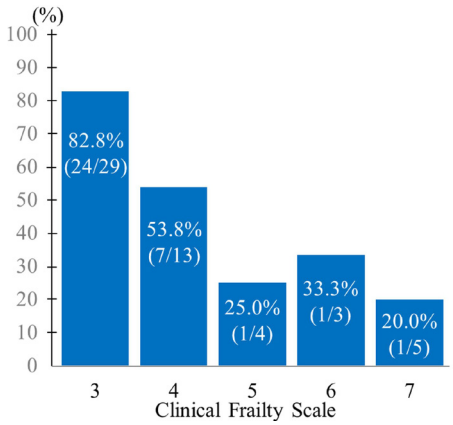

Figure 3. WHO-functional class I achievement and frailty. Achievement rate of WHO-functional class I at each level of the clinical frailty scale (CFS).

Development of BPA

The results of the multicenter registry of Japan reported by Oagawa in 2017 indicated acceptable hemodynamic improvement and survival rates (*8*). However, the accumulation of previous expert center findings, plus the participation of catheter interventionalists, has led to the application of percutaneous coronary intervention (PCI) and peripheral arterial endovascular therapy (EVT) techniques and technologies to improve the outcomes of contemporary BPA. Today, the expected clinical goals of BPA are even higher, as new technologies have improved the results and safety of BPA (*3,4,7,10-14,21-24*). The BPA performed in Japan, which is based on catheter intervention techniques, has improved hemodynamics compared to other countries (*3,4,7,21,22*). Retrograde approach or intravascular ultrasound-guided BPA for completely occluded lesions and gadolinium BPA for patients allergic to contrast media are particularly noteworthy (*10,11,13*).

In terms of a target mPAP, "the lower, the better" has been considered (*7*). In addition, Inami *et al.* reported excellent results with BPA in chronic thromboembolic pulmonary disease without PH (*23,24*). These refined BPAs have markedly improved the hemodynamics and quality of life of patients. Ikeda *et al.* reported a case in which a patient with severe CTEPH was able to carry a child with planned BPA and anticoagulation (*12*). At our institution, more than 60% of the patients who underwent contemporary BPA achieved WHO-FC I, but a certain proportion still had symptoms, even when all accessible lesions were treated. Pre-BPA patient status is one of the limitations to relieving symptoms.

Frailty and results of BPA

Frailty is a phenotype of a multidimensional state of vulnerability that includes a complex of biological, cognitive and social factors (*15,16,20,25-27*). Therefore, highly frail patients potentially have many internal medical or orthopedic disorders, and the improvement

Table 3. The odds ratios for achievement of WHO-functional class I

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age	0.93 (0.88-0.99)	0.024	0.95 (0.89-1.02)	0.14
Male sex	1.12 (0.34-3.69)	0.86	-	-
Body weight	1.03 (0.99-1.08)	0.16	-	-
Duration from onset	0.91 (0.77-1.08)	0.91	-	-
Pulmonary vasodilator	0.76 (0.25-2.32)	0.63	-	-
Clinical frailty scale	0.44 (0.25-0.76)	0.003	0.50 (0.29-0.86)	0.012
eGFR	1.04 (0.99-1.10)	0.12		
Pre-BPA				
6MWD (each 10 m)	1.04 (0.99-1.09)	0.10	-	-
sPAP	0.99 (0.96-1.02)	0.34	-	-
dPAP	1.02 (0.93-1.13)	0.64	-	-
mPAP	0.99 (0.93-1.05)	0.75	-	-
CI	1.29 (0.56-2.99)	0.56	-	-
PVR (each10 dyne·s/cm^5)	0.98 (0.96-1.00)	0.11	-	-

BPA: balloon pulmonary angioplasty; 6MWD: six-minute walk distance; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

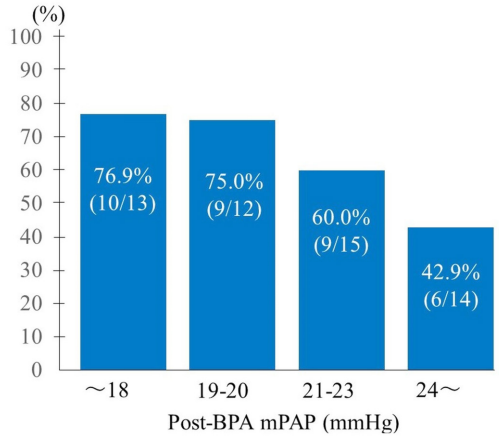

Figure 4. WHO-functional class I achievement and mean pulmonary artery pressure (mPAP). Achievement rate of WHO-functional class I, stratified by post-BPA mean pulmonary artery pressure (mPAP).

of cardiopulmonary function by BPA in such patients may not directly lead to improvement of symptoms. Frail patients show a high rate of comorbidities such as ischemic heart disease, chronic obstructive pulmonary disease and other diseases that are not CTEPH but cause cardiopulmonary dysfunction, cerebrovascular disorders, muscle weakness, *etc.* Such patients remain symptomatic, even if their pulmonary circulation is improved by BPA.

In our study, 8 of the 54 patients failed to complete all planned BPA procedures due to the patient's decision (n = 3) or due to the discovery or worsening of malignancy or problems of general conditions (n = 4). Five of the 8 patients who failed to complete all planned BPA procedures had frailty with a CFS score of 5 or more. Frail patients are less active, and may wish to discontinue BPA if relieved from their dyspnea at rest, especially in cases with malignancy, in whom a long survival period is not expected. We included all patients who underwent BPA, even for one session, in the study because dropout by various reasons is also one of the limitations of BPA. Further discussion is needed on how aggressively BPA should be performed for highly frail patients. Furthermore, multifactorial interventions for frailty, such as nutrition guidance and rehabilitation, need to be considered.

Age and hemodynamic status

Age did not independently prevent the achievement of WHO-FC I. For elderly patients with CTEPH, BPA is a less invasive and attractive treatment option. It is clear that "the lower the mPAP the better," as the first quartile (mPAP 11-18 mmHg) showed the highest WHO-FC I rate (Figure 4). However, the upward trend of achievement rate of WHO-FC I looks as if it reached a plateau. Frailty, not age, should be considered in selecting BPA candidates and deciding how much to treat.

Limitations

Our study has some important limitations. First, the number of patients in this study was relatively small. Second, the results of this study were based on an analysis of BPA outcomes at a single institution (Toho University Ohashi Medical Center, Tokyo, Japan). In our institution, the strategy of BPA using PCI/EVT techniques was aggressive, and all lesions accessible by catheters were treatment targets. These strategies should be considered in the interpretation of our results. Third, the pre-BPA hemodynamic parameters were relatively mild. The patients with severely high pulmonary artery pressures were intensively treated with a combination of oral pulmonary vasodilators before BPA. Intensive combination therapy affected

baseline hemodynamic parameters. Fourth, WHO-FC was tabulated based on patient self-reports using questionnaires. Patients accustomed to dyspnea from effort might have underestimated their symptoms after BPA. Fifth, the results of respiratory function tests could not be presented because of the large number of missing post BPA tests. Sixth, patients receiving oxygen prior to BPA were included in the study. Mixed venous blood oxygen saturation was not included in the logistic regression analysis, because it was strongly influenced by oxygen administration.

Conclusions

Whether WHO-FC I can be achieved is predicted by pre-BPA patient frailty, not pre-BPA hemodynamic parameters and age. The selection of BPA candidates should be carried out according to frailty rather than age.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received February 13, 2021; Revised September 18, 2021; Accepted October 5, 2021.

Released online in J-STAGE as advance publication October 16, 2021.

Address correspondence to:
Nobutaka Ikeda, Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, 2-22-36 Ohashi, Meguro-ku, Tokyo153-8515, Japan.
E-mail: nobu@oha.toho-u.ac.jp

Global Health & Medicine. 2022; 4(1):52-56.
BRIEF REPORT
DOI: 10.35772/ghm.2021.01100

Demonstration of the right-side boundary of the caudate lobe in a liver cast

Masamitsu Kumon[1], Tatsuya Kumon[1], Yoshihiro Sakamoto[2,*]

[1] Noichi Central Hospital, Konan, Kochi, Japan;
[2] Department of Hepato-Biliary-Pancreatic Surgery, Kyorin University Hospital, Mitaka, Tokyo, Japan.

Abstract: There have been historical arguments about the boundary of the caudate lobe of the liver. Kumon M first advocated the definition of the caudate lobe based on the portal segmentation of the liver in 1985, and classified it into three parts, Spiegel lobe, paracaval portion and caudate process. Prof. Couinaud defined the dorsal liver as a union of segments I and IX in 1994, based on the spatial position to the major hepatic veins, hilar plate and inferior vena cava. In Couinaud's classification, right-side of the dorsal liver is supplied by the branches from the posterior and anterior sections. In the present study using a liver cast, we found a paracaval branch of the portal vein branching from the right portal vein on the dissecting plain along the Rex-Cantlie's line. We also found several branches from the posterior portal vein to the right-side of the paracaval portion, but they should be defined to belong to the posterior sections.

***Keywords*:** liver cast, caudate lobe, paracaval portion

Introduction

The caudate lobe of the liver is generally considered as the deepest area of the liver in front of the inferior vena cava (IVC) surrounded by the major hepatic veins and the hilar plate. However, there have been historical arguments on the boundary of the caudate lobe.

In 1985, Kumon M proposed to define the caudate lobe based on the portal segmentation and classified it into three parts, Spiegel lobe, paracaval portion and the caudate process (*1-3*). On the other hand, this deep area of the liver in front of the IVC had been also called dorsal liver by Prof. Couinaud. Prof. Couinaud, a famous French anatomist, classified the dorsal liver based on the spatial position against the major hepatic veins and IVC, and classified it into segment I and IX and then, placed these two segments into several alternatives (*4-8*).

Right-side boundary of the caudate lobe is clinically important in the surgical treatment of liver cancer or hilar cholangiocarcinoma. Curative surgical resection of perihilar cholangiocarcinoma requires total caudate lobectomy to obtain negative surgical margins, because the biliary branches in the caudate lobe is involved with cancer in more than 40% of cases (*9*).

In the present study, we revealed the right-side boundary of the caudate lobe of a liver cast, discovering the paracaval branches of the portal vein and bile duct in a liver cast.

Materials and Methods

A liver cast was made after injecting colored epoxy resin into the portal vein (blue) and bile duct (yellow) of the whole liver, while the hepatic artery and hepatic vein were left as they were without injecting resin. This method follows Healey and Schroy's (*10*). Although the author prepared 75 human liver casts between July 1, 1981 and October 2, 1990 (*3*), there was only one Healey and Schroy's type cast, which is suitable for observing the anatomy of the portal vein and bile duct. The specimen was fixed in water to preserve the natural hepatic shapes, as they would be in the body. The liver tissue was corroded completely using potassium hydroxide.

After fixation, we dissected the liver cast using forceps with fine tips and extracted the small Glissonean and venous branches, gently piece by piece. The right portal vein was divided at the proximal site of the bifurcation of the anterior and posterior portal branches. After meticulous dissection, we observed the portal and biliary branches of the paracaval portion of the caudate lobe.

The information on the study's approval by the Institutional Review Board/Research Ethics Committee has been described in previous study (*3*).

Results and Discussion

Before dissection of the liver, the whole liver was observed from the cranial ventral side of the liver (Figure 1). Because the liver cast did not have the

hepatic arteries and veins including the IVC, dissection and observation were simple and easy without any consideration on the variation of the hepatic arteries and veins. The whole liver was divided along the Rex-Cantlie line, and the right Glissonean pedicle, composed of the right portal vein and the right bile duct, was found on the dissecting plane (Figures 2 and 3). The right portal vein and the bile duct were divided at the proximal site of the bifurcation of the anterior and posterior sections (Figures 3 and 4). The cut surface of the liver coincided the plane including right edge of the IVC. The root of the paracaval portal vein was found on the proximal side of the cut point of the right portal vein. The cut edge of the right portal vein and posterior bile duct revealed the portal branches and bile ducts in the paracaval portion of the liver (Figures 4 and 5). The paracaval portal vein branched from the right and left portal veins (Figure 5), while the paracaval branch of the bile duct branched from the posterior bile duct (Figure 4). There were found some branches from the posterior portal veins behind the posterior portal vein, going to the right-side of the paracaval portion along the IVC (Figure

Figure 1. Cranial view of the liver cast from ventral position. Three arrows indicate the orifices of the major hepatic veins. L, left hepatic vein; M, middle hepatic vein; R, right hepatic vein.

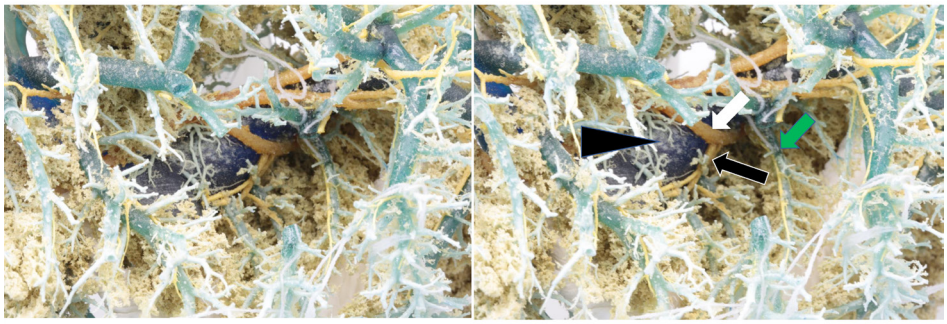

Figure 2. Cranial view of the hilar plate of the right Glissonean pedicle. Arrow head indicates the right portal vein. White arrow indicates the posterior bile duct. Black arrow indicates the paracaval branch of the bile duct. Green arrow indicates 1st portal branch of anterior portal vein.

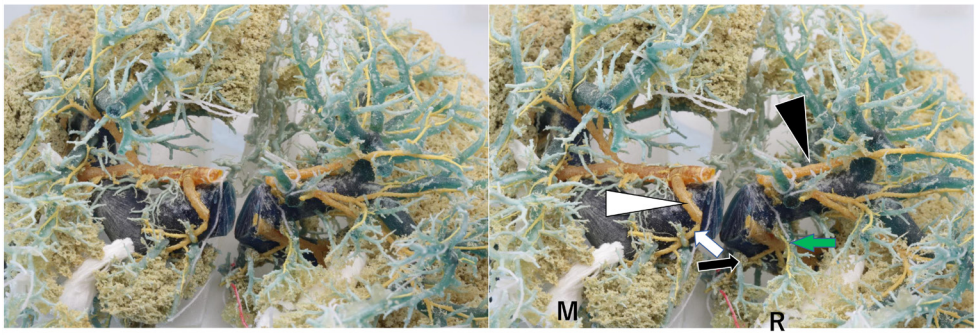

Figure 3. Cranial view of the division of the right Glissonean pedicle. The right and posterior hepatic duct and the right portal vein are divided. The paracaval bile duct (white arrow) branching from the posterior bile duct (white arrow head) is indicated. Black arrow head indicates anterior branches of the bile duct. Black and green arrows indicate the d-vein (Couinaud) and 1st branch of anterior portal vein, respectively. Red line indicates the right edge of IVC.

6), which correspond to the c and d branches of segment IX in Couinaud's classification.

In the present study, we found the definitive portal and biliary branches to the paracaval portion of the liver in a divided liver cast. The paracaval branch of the portal vein branched from the right and left portal vein, a first-order branch of the main portal vein, thus this could be the paracaval portion based on the concept of portal segmentation. On the other hand, we confirmed that there were some accessory branches from the posterior portal vein along the IVC (Figure 6), which cannot be included in the paracaval portion. These portal veins should be included in the posterior section. As the biliary trees have considerable numbers of variants, it would be

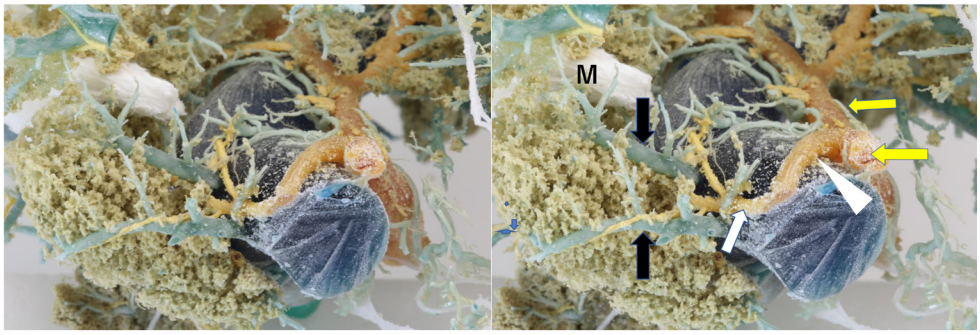

Figure 4. Lateral view of the paracaval branch of the portal vein and the bile duct. The black arrows indicate paracaval branches of the portal vein branching from the right portal vein. The white arrow indicates the paracaval branch of the bile duct and the white arrow head indicates the posterior branch of the bile duct.

Figure 5. Caudal view of the branches from the main portal vein and common bile duct. Black arrows indicate paracaval branches of portal veins. Yellow arrow indicates the superior portal branch of Spiegel lobe. Blue and yellow arrow head indicate the trunk of portal vein and common hepatic duct, respectively.

Figure 6. Caudal view of the branches from the anterior and posterior portal veins. The inside portal branches from the posterior portal vein are shown behind the posterior portal vein along the inferior vena cava, which should belong to the posterior section, not paracaval potion, in our classification. The black arrow and white arrow head correspond to d-vein and c-vein in segment IX in Couinaud's classification, respectively. A and P indicate the anterior and posterior portal veins, respectively. Green arrow indicates the first branch of anterior portal vein. P6 and P7 indicate portal veins of segment 6 and 7, respectively. Red line indicates the right marginal line of the inferior vena cava.

confusing to classify the hepatic segments based on the biliary segmentation as Ishiyama did (*11,12*).

The caudate lobe was first described as the "lobus exiguous" by Adrian van der Spiegel in 1622. Healey and Schroy first classified the liver into four sections, the lateral, medial, anterior and posterior segment. They defined the caudate lobe as areas that did not belong to the above four segments, and classified the caudate lobe into right portion, left portion and the caudate process (*9*). However, Kumon M was the first who classified the caudate lobe of the liver into three parts, Spiegel lobe, paracaval portion and caudate process, based on a study using 23 human liver casts (*1,2*). He has sustained the dogma that any hepatic segment should be defined based on portal segmentation.

On the contrary, Couinaud's definition of the caudate lobe, dorsal liver in his work varied with the times. He first described it on the dorsal liver and divided it into segment Il and Ir along the plain including middle hepatic vein in 1989 (*4*). He changed segment Il&Ir to segment I and IX in 1994 (*5*), and divided segment IX into three parts, subsegments b (between middle and right hepatic veins), c (inferior area of the right hepatic vein) and d (posterior area of the right hepatic vein) in 1998 (*6*). Then, he replaced segment IXb into IXL, and segment IXd to IXR (*7*), but finally abandoned his idea on classification of the caudate lobe in 2002 (*8*). As shown in the above transition, Couinaud had great difficulty defining the caudate lobe as a monosegment.

Ishiyama followed the concepts of Kumon and Couinaud. He supported the concept of dorsal liver by Couinaud from the viewpoint of biliary system, and advocated that 92.5% of the right-side area of the dorsal liver (dorso-lateral paracaval portion, dl-PCP) could not be covered only by the concept of Kumon's portal segmentation, analyzing 54 liver casts (*11,12*). He found that the bile ducts in the dl-PCP were supplied by the branches from the anterior and posterior bile ducts. He also mentioned that the biliary branches to the dorsal liver should include the branches from the posterior or anterior bile ducts in order to increase the curability of perihilar cholangiocarcinoma requiring left hemihepatectomy plus bile duct resection, and criticized the concept of Kumon's classification based on portal segmentation.

However, anatomical boundary of the liver should be determined based on anatomical landmarks, not on the surgeon's preference. First, Couinaud's dorsal liver is a concept of spatial position of the deep liver surrounded by the IVC and the right hepatic vein. This classification is not based on portal segmentation, and thus will cause some confusion on discriminating anatomical segments. Second, Ishiyama's concept is based on biliary segmentation. Portal branches in dl-PCP apparently carries the portal flow in the anterior or posterior portal branches, and could be better included in anterior or posterior sections based on the concept of portal segmentation.

Gadzijev *et al.* studied the difference between segment I and IX using 61 human liver corrosion casts. They also accepted the concepts of Couinaud's dorsal liver and defined segment IX as the dorsal part of the liver located about 2cm away from the IVC (*13*). His concept is also not based on portal segmentation and supported the concept of dorsal liver by Prof. Couinaud. Prof. Makuuchi, a legend of liver surgeons, commented that Couinaud's segment IX corresponds to the paracaval portion of the liver on Kumon's classification (*14*), however we regret that his explanation cannot be accepted.

Conclusion

Anatomical right-sided boundary of the paracaval portion of the caudate was studied in a liver cast containing colored resin in the portal vein and bile duct. The paracaval branch of the portal vein and bile duct was demonstrated on the cut surface along the Rex-Cantlie's line. The boundary of the caudate lobe should be decided based on the portal segmentation, not by biliary segmentation.

Funding: This study was supported by Grants-in-Aid for Scientific Research. Grant Number JP20K09019.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received September 18, 2021; Revised October 22, 2021; Accepted November 10, 2021.

Released online in J-STAGE as advance publication November 28, 2021.

Address correspondence to:
Yoshihiro Sakamoto, Department of Hepato-Biliary-Pancreatic Surgery, Kyorin University Hospital, 6-20-2 Shinkawa, Mitaka-city, Tokyo 186-8611, Japan.
E-mail: yosakamo@ks.kyorin-u.ac.jp

Global Health & Medicine. 2022; 4(1):57-60.

COMMENTARY

DOI: 10.35772/ghm.2021.01102

Proposal of new treatment algorithm for gastric cancer liver metastases: Up-front surgery or conversion surgery?

Nobuyuki Takemura[1,*], Akio Saiura[2], Hiromichi Ito[3], Kyoji Ito[1], Fuyuki Inagaki[1], Fuminori Mihara[1], Shusuke Yagi[4], Naoki Enomoto[4], Kyoko Nohara[4], Yosuke Inoue[3], Yu Takahashi[3], Kazuhiko Yamada[4], Norihiro Kokudo[1]

[1] Department of Surgery, Hepato-Biliary Pancreatic Surgery Division, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Department of Hepatobiliary Pancreatic Surgery, Juntendo University Hospital, Tokyo, Japan;
[3] Department of Hepatobiliary and Pancreatic Surgery, Cancer Institute Hospital, Tokyo, Japan;
[4] Department of Surgery, Upper Abdominal Surgery Division, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Hepatectomy for gastric cancer liver metastases (GCLM) has a 5-year survival rate of 9-42%; however, indications for hepatectomy remain unclear. Many researchers have reported prognostic factors for GCLM after hepatectomy, but surgical indications vary according to the literature. Furthermore, the indication for optimal candidates for neoadjuvant chemotherapy and intensive chemotherapy is also unclear. To understand the indications for surgery and chemotherapy intended for hepatectomy for GCLM, a new treatment algorithm was created based on previously reported evidence from the viewpoint of hepatic surgeons.

***Keywords*:** gastric cancer liver metastases, treatment algorithm, conversion surgery, up-front surgery

Introduction

The prevalence of gastric cancer has been reported to have declined in recent decades (*1,2*); however, it is still the third leading cause of death in Japan (*2*), has the sixth highest incidence rate of all cancers, and is the third leading cause of death worldwide (3). The liver is one of the most frequent sites of distant metastasis from gastric cancer (*4,5*). In the past, gastric cancer liver metastasis (GCLM) has been regarded as a contraindication for surgery because of its poor prognosis (*6*). Conversely, the recent literature has reported a 9-42% 5-year survival rate and 12-41 months median survival time after hepatectomy for GCLM with curative resection (*5,7-15*). Based on these reports, prognostic factors after hepatectomy of GCLM have been reported to include large tumours (*5,8,11,15*), multiple tumours (*8,10,13-15*), depth of the primary gastric cancer (*5,8,9,13,14*), lymph node metastasis of the primary gastric cancer (*10*), age (*15*), non-curative resection (*9,15*), and disease-free interval after resection of the primary gastric cancer (*15*) in multivariate analyses.

Although few reports have evaluated the effect of neoadjuvant chemotherapy (NAC) for the treatment of GCLM, Fukuchi *et al*. and Yamaguchi *et al*. reported the usefulness of NAC for stage IV gastric cancer, including patients with peritoneal metastasis and/or hepatic metastasis (*16,17*). Yoshida *et al*. proposed that multiple GCLM, GCLM greater than 5 cm, and GCLM with vascular invasion can be categorized as marginally resectable metastases and are indications for intensive chemotherapy (*18*). If metastatic diseases are technically resectable, metastasectomy is recommended. They categorized solitary GCLM less than 5 cm without vascular invasion as marginally resectable; however, its condition is neither a poor prognostic risk factor nor marginally resectable unless it infiltrates the hepatic hilum. From the perspective of hepatic surgeons, there is a discrepancy between their indications and previously reported prognostic factors for GCLM. To solve this discrepancy, we created a new treatment algorithm for GCLM based on previously reported prognostic factors.

Previous evidence of gastric cancer liver metastases

There are many reports discussing the significance of hepatic resection for GCLM; however, all of them are retrospective studies and no randomized studies have been conducted in this setting. Although the evidence is limited, reports including more than 50 patients with GCLM who underwent hepatectomy were selected (*5,8-15*). The reported prognostic factors for overall survival among these studies include the depth of the primary tumour (*5,8,9,13,14*) (most studies identified serosal invasion (*i.e*. T4) of the primary tumour (*5,8,14*)), tumour size (*5,8,11,15*) (two of them are more than 5 cm (*5,8*) and the others are 3 cm (*11,15*), multiple tumours (*7-10,13-15*) (two of which are more than three nodules

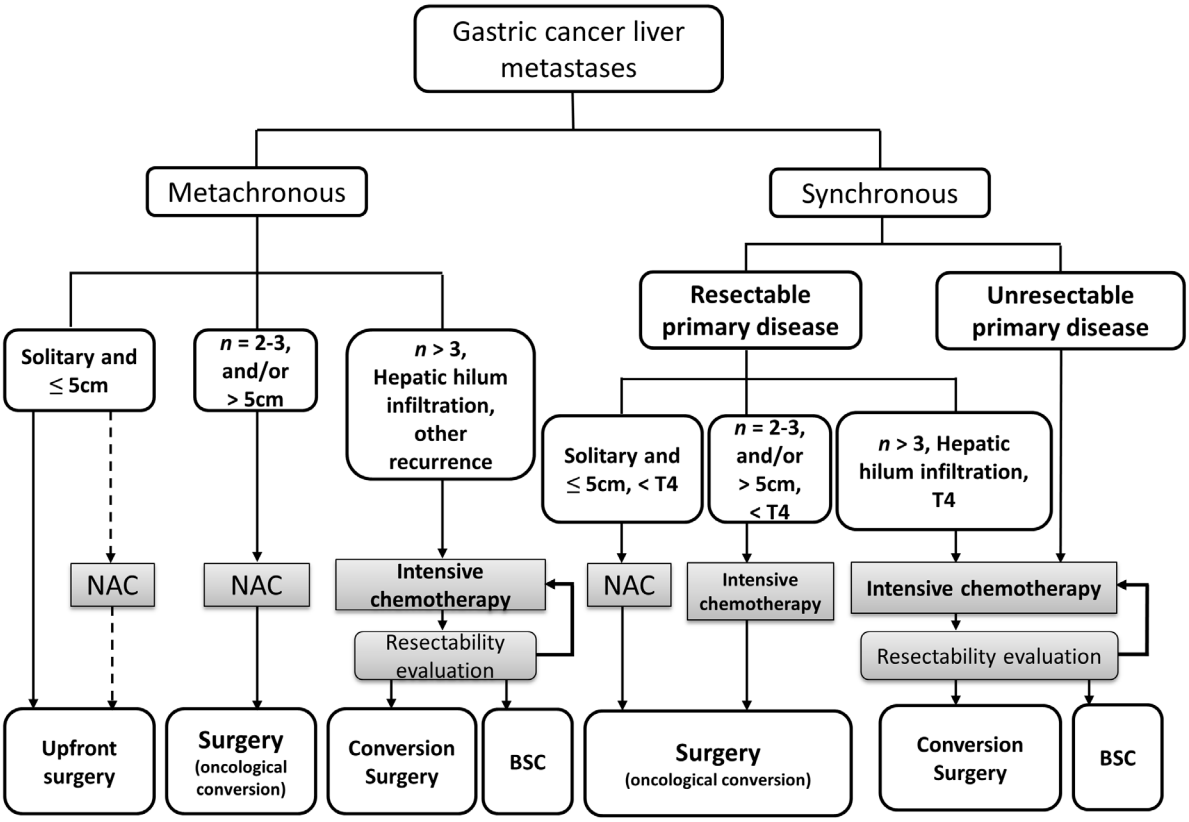

Figure 1. Suggestion of treatment algorithm for GCLM. T4 means serosal invasion of the primary gastric cancer. *Abbreviations*: GCLM, gastric cancer liver metastases; NAC, neoadjuvant chemotherapy; BSC, best supportive care.

(*8,15*)), non-curative resection (*9,15*), lymph node metastasis of the primary tumour (*10*), age (*15*), and disease-free interval (*15*). Prognostic factors for survival reported in two or more studies were included in the treatment algorithm for GCLM.

Proposal of treatment algorithm for gastric cancer liver metastases

Based on the evidence mentioned above, a treatment algorithm for GCLM was created (Figure 1). The best candidate for hepatectomy is a metachronous solitary small GCLM less than 5 cm in diameter that does not have any poor prognostic factors. In these patients, up-front surgery or occasional NAC followed by surgery are suggested. NAC is suggested for patients with one or two poor prognostic risk factors in the metachronous group, that is, two or three tumours and/or solitary large tumours without hepatic hilum invasion. In patients with more than three GCLM and/or GCLM with hepatic hilum infiltration or with other sites of metastasis, chemotherapy is the first treatment choice; if chemotherapy leads to remarkable tumour shrinkage, conversion surgery can be considered as a treatment option. Regarding synchronous primary gastric cancer with liver metastasis, chemotherapy is first suggested both in a neoadjuvant setting and as intensive chemotherapy according to the standard treatment for stage IV gastric carcinoma, even if the tumour is resectable. If the patients have only one poor prognostic factor, that is, solitary synchronous GCLM less than 5 cm in diameter without serosal invasion (< T4), surgery followed by NAC is suggested. In patients with synchronous GCLM with fewer than three tumours without serosal invasion, surgery followed by intensive chemotherapy is the suggested indicated therapy. Patients with multiple poor prognostic factors, including more than three tumours, hepatic hilum infiltration, serosal invasion (T4), or unresectable primary gastric cancer are candidates for standard intensive chemotherapy same to that for stage IV gastric cancer.

Discussion

Yoshida *et al*. first created a treatment algorithm for stage IV gastric cancer in 2018 (*18*). It is simple and easy to apply in daily clinical practice for patients with stage IV gastric cancer; however, considering the treatment choice, especially for GCLM, the structure of their algorithm is partly not based on the previously reported evidence for GCLM. As a result, we created a new treatment algorithm especially for GCLM based on the previously presented evidence from the perspective of hepatic surgeons. In this algorithm, risk factors that were reported to be prognostic factors two or more times in relatively large cohort studies including more than 50

patients were used to create the algorism. Candidates for hepatectomy for GCLM are highly limited; it has been reported that 10-20% of all patients with GCLM because of a coexisting advanced cancer condition, such as peritoneal metastases, para-aortic lymph node metastases, or locally advanced primary disease (*4,12*). However, some of these patients can be cured using hepatectomy (*5,7-15*). With the recent advances in chemotherapy for gastric cancer (*16-18*), regulation of the indications for up-front surgery, neo-adjuvant chemotherapy, and intensive chemotherapy with the aim of conversion surgery (if remarkable tumor shrinkage is achieved) is needed. Consequently, we created a new treatment algorithm for GCLM according to previously reported evidences.

In Yoshida's algorithm for stage IV gastric cancer, GCLM with vascular invasion was selected for algorithm branching and was considered an inoperable factor. From the standpoint of a hepatic surgeon, vascular invasion of metastatic liver tumour is not considered a contraindication for hepatectomy unless the tumour has deeply invaded the hepatic hilum or the estimated volume of future liver remnant is insufficient for safe hepatectomy. To date, few reports have detected vascular invasion as a prognostic factor for GCLM. Unlike vascular invasion, multiple GCLM, large GCLM, and synchronous GCLM are technically resectable, but they are often considered oncologically unresectable due to the high malignant potential of advanced gastric cancer. In these situations, postoperative recurrences occur frequently because of the accompanying poor prognostic factors. However, chemotherapy might change these difficult situations to better ones, where long-term survivals is expected due to the effect of chemotherapy itself and having time to confirm the absence of new lesions. We use the term "oncological conversion" to explain these situations.

In patients with synchronous GCLM, the treatment strategy of this algorithm is similar to that of Yoshida's algorithm. Chemotherapy is proposed to control the primary disease, whether its role is as NAC or intensive chemotherapy. Picado *et al*. reported a relatively better prognosis in patients who underwent preoperative chemotherapy for synchronous GCLM (*19*). Therefore, the first branching of this algorithm was set as whether GCLM was diagnosed as synchronous or metachronous metastasis. Uggeri *et al*. recently conducted a systematic review of GCLM and indicated two prognostic factors; < 5 cm in size and single or > 3 metastases (*20*). This algorithm contains these two factors as branches.

Given the recent advancements in chemotherapy for gastric cancer, further prognostic improvements for patients with GCLM are expected. However, disease cure with chemotherapy alone has rarely been achieved, even in the recent era. Attention should be paid to not miss the best timing for surgery, which is the only potentially curative treatment. This algorithm is not based on the results of a randomized controlled study, which is quite difficult to conduct in patients with GCLM; therefore, the evidence level is not very high. Treatment selections are not recommended but are suggested in the algorithm. Validation studies of this algorithm are needed in the future. Since the treatment of GCLM is highly limited, further discussion motivated by this study will be expected to better understanding the surgical indications for GCLM and to improve patients' prognosis.

Funding: This work was partly supported by a Grant-in-Aid for Research from the National Center for Global Health and Medicine (21A1019 to N.T.)

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received September 23, 2021; Revised October 7, 2021; Accepted October 12, 2021.

Released online in J-STAGE as advance publication October 15, 2021.

**Address correspondence to*:
Nobuyuki Takemura, Department of Surgery, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjyuku-ku, Tokyo 162-8655, Japan.
E-mail: ntakemura@hosp.ncgm.go.jp

Global Health & Medicine. 2022; 4(1):61-63.

LETTER

DOI: 10.35772/ghm.2021.01090

Interleukin-6 is upregulated and may be associated with myocardial injury in some patients who have recovered from COVID-19

Hiromasa Hayama[1,*], Satoshi Ide[2], Yui Kitami[1], Hisao Hara[1], Satoshi Kutsuna[2], Yukio Hiroi[1,*]

[1] Department of Cardiology, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Coronavirus disease (COVID-19) causes myocardial injury by inducing a cytokine storm in severe cases. Studies have reported that myocardial injury persists for a prolonged period during COVID-19 recovery, and cardiac troponin is a useful indicator of myocardial injury. The interleukin-6 (IL-6) level is known to be associated with the morbidity and mortality of COVID-19, but this association has not been studied during recovery. The current study examined the association between IL-6 levels and myocardial damage during COVID-19 recovery. Four of 209 patients (1.9%) who recovered from COVID-19 had elevated IL-6 levels. All 4 patients tested positive for high-sensitivity troponin T, and 3 patients had subclinical left ventricular (LV) dysfunction according to echocardiography. Positivity for IL-6 during COVID-19 recovery suggests ongoing myocardial damage due to inflammation.

***Keywords*:** COVID-19, interleukin-6, cardiac troponin, myocardial damage, echocardiography

Coronavirus disease (COVID-19) continues to be prevalent worldwide, and in severe cases, it induces a cytokine storm that causes myocardial damage. In addition, studies have reported that myocardial damage is prolonged even during the recovery period as a result of elevated troponin levels and abnormalities in cardiac imaging studies (*1,2*). However, no studies have reported an association between cytokines and myocardial injury in patients who have recovered from COVID-19. The current study examined the relationship between the level of interleukin-6 (IL-6) and myocardial damage during COVID-19 recovery.

Subjects were patients who participated in the COVIPLA study of convalescent plasma therapy in Japan from April to September 2020 (*3*). Patients who had recovered from COVID-19 underwent blood tests and echocardiography at least 3 weeks after the onset of infection. All data were retrospectively collected at the National Center for Global Health and Medicine. IL-6 and high-sensitivity troponin T (hsTnT) were measured in stored frozen serum. An IL-6 level ≥ 8 pg/mL and a hsTnT level ≥ 0.003 ng/mL were considered to be a positive result (Roche Diagnostics, Tokyo, Japan).

Echocardiography was performed using Canon Artida, and standard guidelines were used as a reference for abnormal values of left and right ventricular function (*4*). Tricuspid annular plane systolic excursion (TAPSE) of 17 mm or more was regarded as normal. Left ventricular global longitudinal strain (LVGLS) was determined from the average of the 4-chamber, 3-chamber, and 2-chamber views, and LVGLS was analyzed using TOMTEC. A LVGLS value of < -20 was regarded as abnormal (*5*).

This study complied with the Declaration of Helsinki and was approved by the Hospital Ethics Committee. Informed consent was obtained in an opt-out format.

Subjects were 209 patients from the COVIPLA registry who underwent echocardiography and blood tests between April and September 2020. IL-6 could not be measured in 3 patients due to insufficient sample volume. The mean age (± standard deviation) was 44 ± 12 years (range: 36-55 years), and the proportion of males was 51%. Of 74 patients (35.4%) with hsTnT below the limit of detection, all had an IL-6 level below the limit of detection. hsTnT levels were above the limit of detection (> 0.003 ng/mL) in 135 patients (64.6%), and the IL-6 level exceeded the sensitivity threshold in 4 patients (3.0%). Those 4 patients had high peak CRP levels of 10.03 mg/dL, 18.91 mg/dL, 17.24 mg/dL, and 8.99 mg/dL during their hospitalization for COVID-19 (Table 1).

Of the IL-6-positive patients, all 4 had no history of hypertension, diabetes, or cardiovascular disease, and their echocardiographic ejection fraction was greater than 50%. Patient 1 received oxygen therapy during hospitalization, with slightly reduced left ventricular function (LVGLS -19.3%) and normal right ventricular function (TAPSE 23.1 mm). Patient 2 did not need oxygen therapy and had slight left ventricular and right ventricular dysfunction (LVGLS -18.9%, TAPSE 16.7

Table 1. Patient characteristics including myocardial troponin T and echocardiographic data for IL-6-positive patients

Patients No.	Age (years)	Sex	BMI (kg/m^2)	Period from onset to testing (days)	COVID-19 severity during hospitalization	Medication for COVID-19	Peak CRP during infection (mg/dL)	CRP during recovery (mg/dL)	IL-6 (pg/mL)	hsTnT (ng/mL)	Left ventricular function LVGLS	Right ventricular function TAPSE
1	57	Male	21.5	65	Oxygen required	Remdesivir, steroid	10.03	0.02	14	0.004	-19.3%	23.1 mm
2	42	Male	27.2	27	No oxygen therapy	Remdesivir	18.91	0.06	14	0.004	-18.9%	16.7 mm
3	53	Male	28.9	28	Oxygen required	Remdesivir, steroid, Tocilizumab	17.24	0.04	103	0.005	-17.7%	14.2 mm
4	46	Male	29	24	Intubation	Remdesivir, steroid	9.0	0.43	12	0.004	-20.0%	18.4 mm

BMI: body mass index; IL-6: interleukin-6; hsTnT: high-sensitivity troponin T; LVGLS: left ventricular global longitudinal strain; TAPSE: tricuspid annular plane systolic excursion.

mm). Patient 3 required oxygen and had the highest IL-6 level (103 pg/mL) during recovery. The patient had marked left ventricular and right ventricular dysfunction (LVGLS -17.7%, TAPSE 14.2 mm). Patient 4 had previously been on mechanical ventilation but had no left ventricular or right ventricular hypofunction (LVGLS -20.0%, TAPSE 18.4 mm). All 4 patients with elevated IL-6 during COVID-19 recovery were positive for hsTnT. Of the 4, 3 had impaired left ventricular function, 2 had impaired right ventricular function, and 2 had both impaired left and right ventricular function.

Previous studies have reported the presence of subclinical myocardial damage with positive hsTnT in about 70% of patients recovering from COVID-19 (*1*). A recent study in Japan reported that 65% of patients who recovered from COVID-19 had a hsTnT level exceeding the limit of detection (*6*), and another study reported that a hsTnT level is associated with decreased LVGLS (*7*).

In the current study, all 4 patients who were positive for IL-6 were also positive for hsTnT, and all of the CRP tests performed during recovery were negative, suggesting that myocardial injury due to different inflammatory mechanisms may occur during COVID-19 recovery.

A recent study found that significantly elevated IL-6 levels in patients hospitalized for COVID-19 were associated with worse clinical outcomes such as ICU admission and death (*8*). In an analysis of risk factors for ARDS and death by Wu *et al.* (*9*), IL-6 was significantly elevated in patients with COVID-19 who developed ARDS (median 7.4 pg/mL, IQR 5.6-10.9 *vs.* median 6.3 pg/mL, IQR 5.4-7.8, $p = 0.03$). Ruan *et al.* (*10*) found that IL-6 levels were significantly higher in patients who died of COVID-19 compared to those who survived (11.4 ± 8.5 pg/mL *vs.* 6.8 ± 3.6 pg/mL, $p < 0.001$).

Among the patients with elevated IL-6 who recovered from COVID-19, 3 had impaired left and right ventricular function, suggesting that cytokine-induced inflammatory mechanisms persist and may contribute to impaired cardiac function even during COVID-19 recovery. Patients positive for IL-6 and with impaired cardiac function should be carefully monitored for a further decline in cardiac function. Two limitations of this study were the lack of data on cytokine levels and the lack of echocardiography images during hospitalization.

Funding: This work was supported by a donation from the National Center for Global Health and Medicine and supported by the Health, Labour, and Welfare Policy Research Grants, Research on Emerging and Re-emerging Infectious Diseases and Immunization (grant number 20HA1006). The funders/sponsors have had no role in the design and/or implementation of the study.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received August 2, 2021; Revised September 22, 2021; Accepted September 28, 2021.

Released online in J-STAGE as advance publication October 7, 2021.

**Address correspondence to*:
Hiromasa Hayama and Yukio Hiroi, Department of Cardiology, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo, Japan.
E-mail : hhayama@hosp.ncgm.go.jp (HH), yhiroi@hosp.ncgm.go.jp (YH)

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(*As of January 2022*)

Global Health & Medicine
National Center for Global Health and Medicine,
1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan
URL: *www.globalhealthmedicine.com*
E-mail: *office@globalhealthmedicine.com*

Print ISSN: 2434-9186 Online ISSN: 2434-9194

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Global Health & Medicine

Volume 1, Number 1
October, 2019

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