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SPECIAL ARTICLE

The evolution of surgical treatment for gastrointestinal cancers

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Abstract

Introduction According to the latest Japanese nationwide estimates, over a million Japanese people are newly diagnosed with cancer each year. Since gastrointestinal cancers account for more than 40% of all cancer-related deaths, it is imperative to formulate effective strategies to control them.

Materials and methods, and results *Basic drug discovery research* Our research has revealed that the abnormal expression of regulators of chromosomal stability is a cause of cancers and identified an effective compound against cancers with chromosomal instability. We revealed the molecular mechanism of peritoneal dissemination of cancer cells via the CXCR4/CXCL12 axis to CAR-like cells and identified an MEK inhibitor effective against these tumors. Residual tumor cells after chemotherapy in colorectal cancer are LGR5-positive cancer stem cells and their ability to eliminate reactive oxygen species is elevated. *The development of surgical procedures and devices* In cases of gastric tube reconstruction for esophageal cancer, we determined the anastomotic line for evaluating the blood flow using ICG angiography and measuring the tissue O2 metabolism. We established a novel gastric reconstruction method (book-binding technique) for gastric cancer and a new rectal reconstruction method focusing on the intra-intestinal pressure resistance for rectal cancer. We established a novel tissue fusion method, which allows contact-free local heating and retains tissue viability with very little damage, and developed an understanding of the collagen-related processes that underpin laser-induced tissue fusion. *Strategy to prevent carcinogenesis* We succeeded in cleaving hepatitis B virus DNA integrated into the nucleus of hepatocytes using genome editing tools. The development of HCC from non-alcoholic steatohepatitis (NASH) may be prevented by metabolic surgery.

Conclusion We believe that these efforts will help to significantly improve the gastrointestinal cancer treatment and survival.

Keywords Gastrointestinal cancers · Drug discovery · Chromosomal instability · Reconstruction after gastrointestinal surgery · Biomaterial collagen · Cancer odors · Metabolic surgery

Introduction

Thank you very much for the very kind and flattering introduction, Professor Kitagawa. It is truly a great honor for me to be awarded the Prof. Komei Nakayama Prize of the Japan Society of Clinical Oncology. I am delighted to be given this opportunity today to deliver a lecture. Its title is "The Evolution of Surgical Treatment for Gastrointestinal Cancers".

I would like to start with the definition of the term "biological evolution" in the headline here. According to the Japanese dictionary *Daijirin*, it is a process of historical change based on the idea that living organisms are not immutable and change gradually in their form, function, and action to adapt to the environment, producing the diverse species found worldwide, and this change is not necessarily an improvement. Accordingly, it is for future generations to

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judge whether or not the changes brought about in the field of surgery in our time represent improvements.

Surgery is a field that entails subjecting patients to artificial invasive procedures. In addition to the knives used in surgical operations, anticancer drugs and gene therapies are also considered types of knives that are invisible and invasive. Surgery involves understanding biological reactions to surgical invasions and ensuring the control of such reactions, and also clarifying the molecular mechanisms of diseases and establishing novel diagnostics and therapeutics using tissues resected from living bodies, with the aim of overcoming and preventing illness.

Here are the flow of surgical care and the roles of surgeons (Fig. 1). Surgical treatment itself is a single-day procedure. It is preceded by weeks of preoperative diagnostics and evaluations and is followed by months of postoperative management and treatment and then years of follow-up, during which we surgeons keep in touch with our patients. It is also our important role to provide information on the prophylactic measures for surgical diseases to educate society and people in this regard.

The ideal relationship between clinical surgery and surgical research is shown in Fig. 2. That is to clarify the molecular mechanisms of underlying diseases and pathological conditions using resected organs, and tissues, and to strive for novel diagnostics, drug discovery and development, and innovative technologies, to benefit surgical medicine. In the clinical setting, it is essential for us surgeons to keep accurate records of our practices to look back on when necessary and to nurture ourselves as healthcare providers who are able to support patients to make changes in their lives, while as researchers, we are required to be creative and innovative.

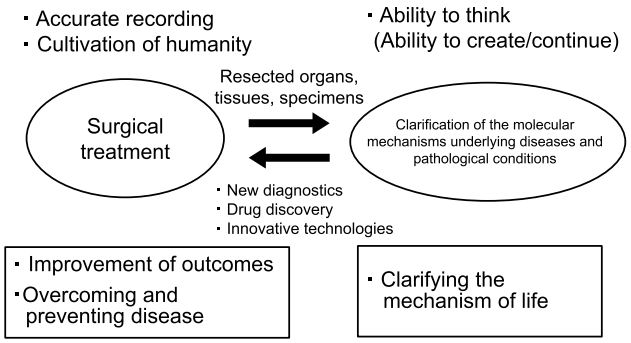


Fig. 2 Ideal clinical surgery and surgical research

Basic drug discovery research and clinical trials

Currently, no treatment is available for the peritoneal dissemination of cancer, and it is associated with a very poor prognosis because the molecular mechanism of this condition is unknown.

We identified the presence of CXCL12-abundant reticular cells (CAR cells) that support hematopoietic stem cells in the murine peritoneal mesentery (Fig. 3). The chemokines produced by CAR cells draw cancer cell spheroids, resulting in their engraftment, eventually leading to peritoneal dissemination. Similar histology was demonstrated in a human model as well. Treatment with a chemokine receptor antagonist or MEK inhibitor potently inhibited peritoneal dissemination [1].

There are anticancer drug-resistant cells that survive after colorectal cancer treatment; what properties do such cells have? We found that they are LGR5-positive and have high stemness properties [2]. Without drugs that are effective against such cells, cancer is certain to relapse. In an attempt to address this problem, we successfully subcultured stemness-high cells isolated from colon cancer tissue. Those cells ceased to proliferate when exposed to an anticancer

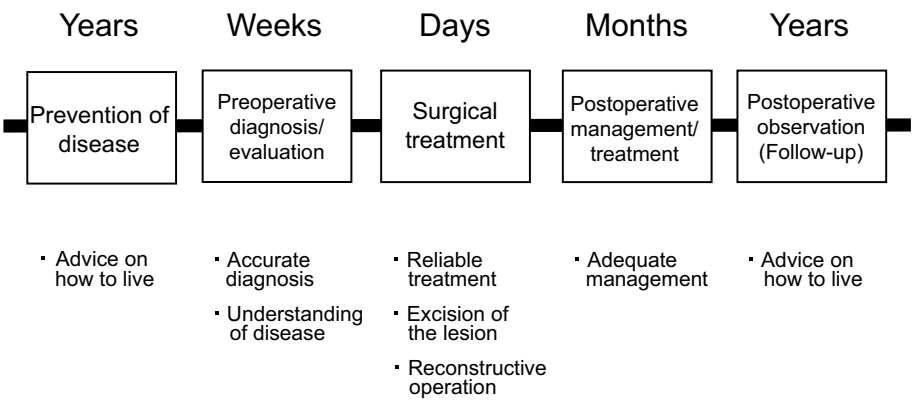


Fig. 1 The flow of surgical care and roles of surgeons

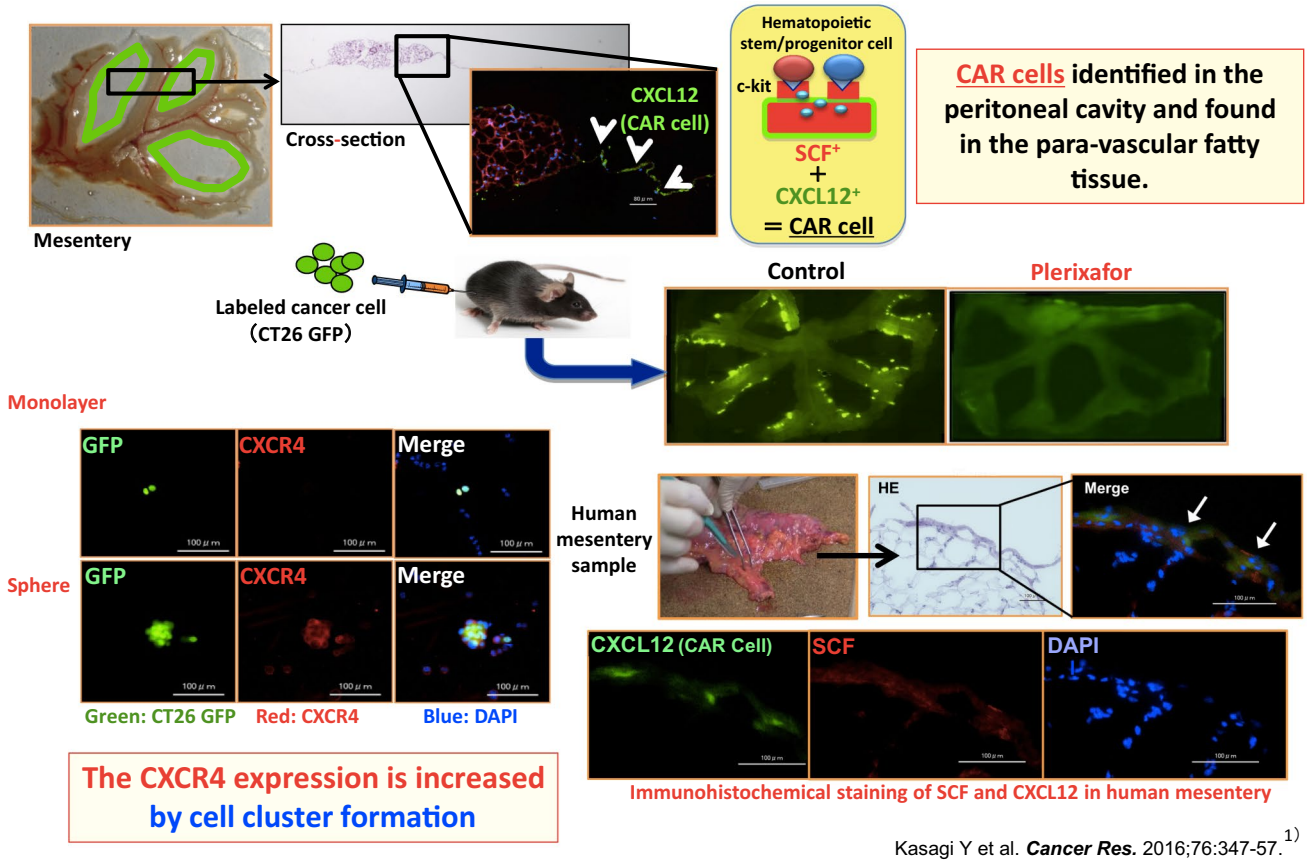


Fig. 3 CXCR4-dependent "Niche Directivity" of dissemination

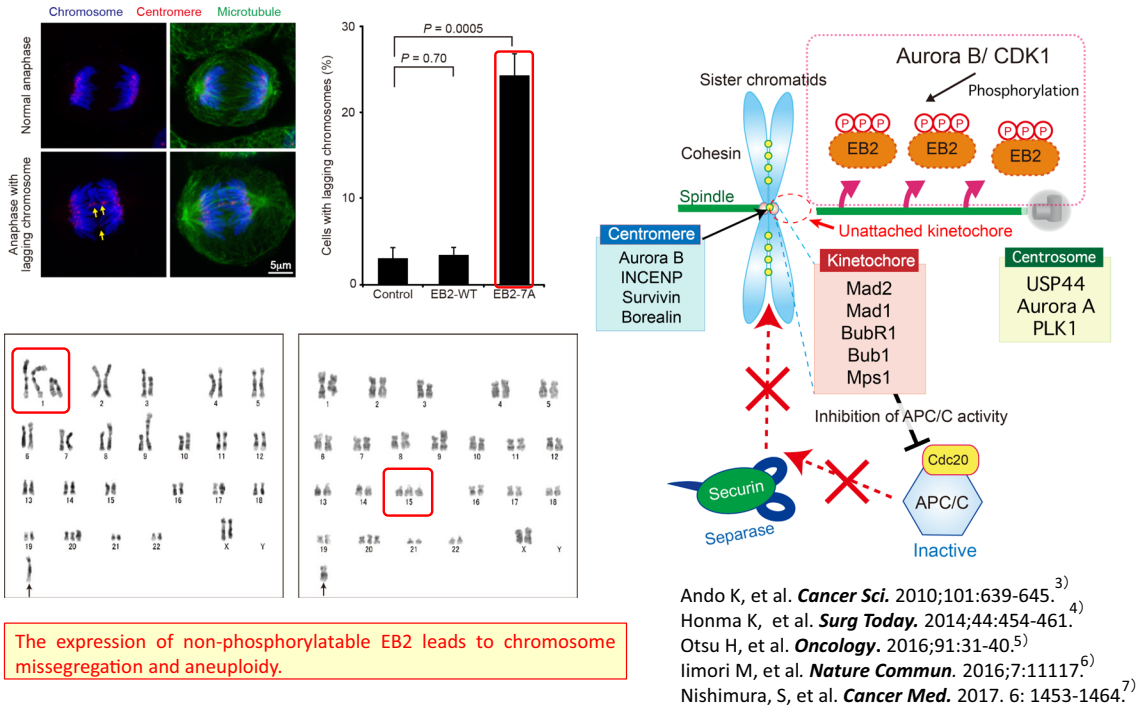
drug and started to regrow when the drug was eliminated. In their regrowth phase, the cells formed an intestinal organoid structure. As regrowth proceeded, LGR5 was expressed. In those cells, the expression of anti-oxidant molecules was increased. The cell regrowth was suppressed by anti-reactive oxygen species (ROS) inhibitors. New approaches to handling such stemness-high cells are awaited.

Chromosomal instability (CIN) is one of the most prominent features in tumor cells. It is well known that sister chromatids are segregated into two daughter cells in mitosis and that CIN tumor cells exhibit an elevated rate of chromosome missegregation. An abnormal number of chromosomes (aneuploidy) is found in most solid tumors, including gastrointestinal cancer.

We demonstrated the relationship between aneuploidy and the expression levels of BubR1 and Aurora B (known as a regulatory factor in mitotic checkpoints) or USP44, PLK1 and Aurora A (known as a regulatory factor of centrosome positioning during mitosis) in clinical gastric cancer specimens [3–6]. Furthermore, we found that the phosphoregulation of microtubule end-binding protein 2 (EB2) was required for genome stability, and its control failure induced aneuploidy. Based on a model in which high rates of chromosome missegregation lead to cell death and tumor suppression, the EB2 phosphorylation pathway may be a potential therapeutic target for aneuploid cells [7] (Fig. 4).

UFT and S-1 are orally administrated antitumor drugs that were clinically developed in Japan. Both are based on the biochemical modulation of 5-fluorouracil (5-FU). UFT is a combination of tegafur (FT), a prodrug of 5-FU—as an active component—and uracil at a molar ratio of 1:4. Uracil suppresses dehydro-pyrimidine dehydrogenase (DPD) activity, which degrades 5-FU [8]. S-1 is a combination of FT, gimeracil (CDHP) and oteracil potassium (Oxo) at a molar ratio of 1:0.4:1. CDHP is a more potent DPD inhibitor than uracil. Oxo, an inhibitor of orotate phosphoribosyltransferase (OPRT), inhibits the phosphorylation and activation of 5-FU at the alimentary canal mucosa and suppresses mucosal disorder [9] (Fig. 5).

Clinical studies have proven the effectiveness of UFT and S-1. In Japan, UFT has received approval for the treatment of 11 cancers since 1983 and S-1 received approval for the treatment of 7 cancers since 1999. Furthermore, UFT and S-1 have been approved in 6 countries and 45 countries, respectively, including Japan [10–13].



The expression of non-phosphorylatable EB2 leads to chromosome missegregation and aneuploidy.

Ando K, et al. ***Cancer Sci.*** 2010;101:639-645.[3)]
Honma K, et al. ***Surg Today.*** 2014;44:454-461.[4)]
Otsu H, et al. ***Oncology.*** 2016;91:31-40.[5)]
Iimori M, et al. ***Nature Commun.*** 2016;7:11117.[6)]
Nishimura, S, et al. ***Cancer Med.*** 2017. 6: 1453-1464.[7)]

Fig. 4 Molecular mechanisms that prevent genome instability in mitosis

In 2005, we launched a new clinical study group in the Kyushu and Okinawa area called the Kyushu Study group of Clinical Cancer (KSCC), for the purpose of providing clinical evidence with high-quality global accounting standards. KSCC has conducted 34 clinical studies, mainly for gastrointestinal cancer. The 140 institutions and 152 clinical departments who have agreed with the concept of the studies, have cooperated on the studies. KSCC has published 23 articles until now.

For example, a retrospective multicenter cohort study (KSCC1302) indicated that surgical treatment might be associated with improved survival in gastric cancer patients with single liver metastasis [14]. Result of a phase II study of SOX plus trastuzumab (T-SOX) for HER2-positive advanced gastric cancer (KSCC1501B) has been quoted by Japanese Gastric Cancer Treatment Guidelines 2018 [15] (Fig. 6).

Trifluridine (FTD) is a key component of the anti-cancer drug FTD/TPI. Tipiracil (TPI) inhibits FTD degradation in the liver. In tumor cells, FTD is successively phosphorylated by thymidine kinase 1 (TK1), thymidylate kinase (TMPK) and nucleotide diphosphate kinase (NDK). FTD-resistant colorectal cancer (CRC) cells (DLD1-FTD) completely lost TK1 protein and showed impaired ability to incorporate FTD into DNA [16]. FTD triphosphate (F3dTTP) is incorporated into DNA during replication. FTD in the DNA causes DNA dysfunction, activates p53 and causes growth arrest [17] (Fig. 7).

Oxaliplatin activates p53 and reduces dUTPase, which causes the accumulation of dUTP accumulation. In addition, oxaliplatin also induces miR-34a and suppresses the expression of thymidylate synthesis factors, which suppresses dTTP biosynthesis. These effects possibly enhance 5-FU cytotoxicity [18]. In a clinical situation, oxaliplatin should have a combined effect with 5-FU against p53-wild gastrointestinal cancers (Fig. 8).

Myeloid-derived suppressor cells (MDSCs) has been reported to be associated with tumor refractoriness to anti-VEGF treatment [19]. We found that capecitabine efficiently reduced intratumor MDSCs both by the suppression of its recruitment via the reduction of G-CSF and by the direct elimination of TP-expressing MDSCs. Capecitabine reversed the tumor escape from anti-VEGF, leading to superior anti-tumor activity, suggesting that it is a favorable chemotherapeutic agent that should be combined with bevacizumab [20] (Fig. 9).

In breast cancer, E-cadherin and vimentin are regarded as major conventional canonical markers of the epithelial–mesenchymal transition. It is commonly assumed that E-cadherin is uniformly lost during the process of epithelial–mesenchymal transition. Breast tumor cells typically invade as a cohesive multicellular unit in a process called collective invasion. The aim of this study was to reveal the clinical importance of the expression pattern of E-cadherin and vimentin in breast cancer. The therapeutic targeting of aggressive subpopulation may, therefore, have a positive

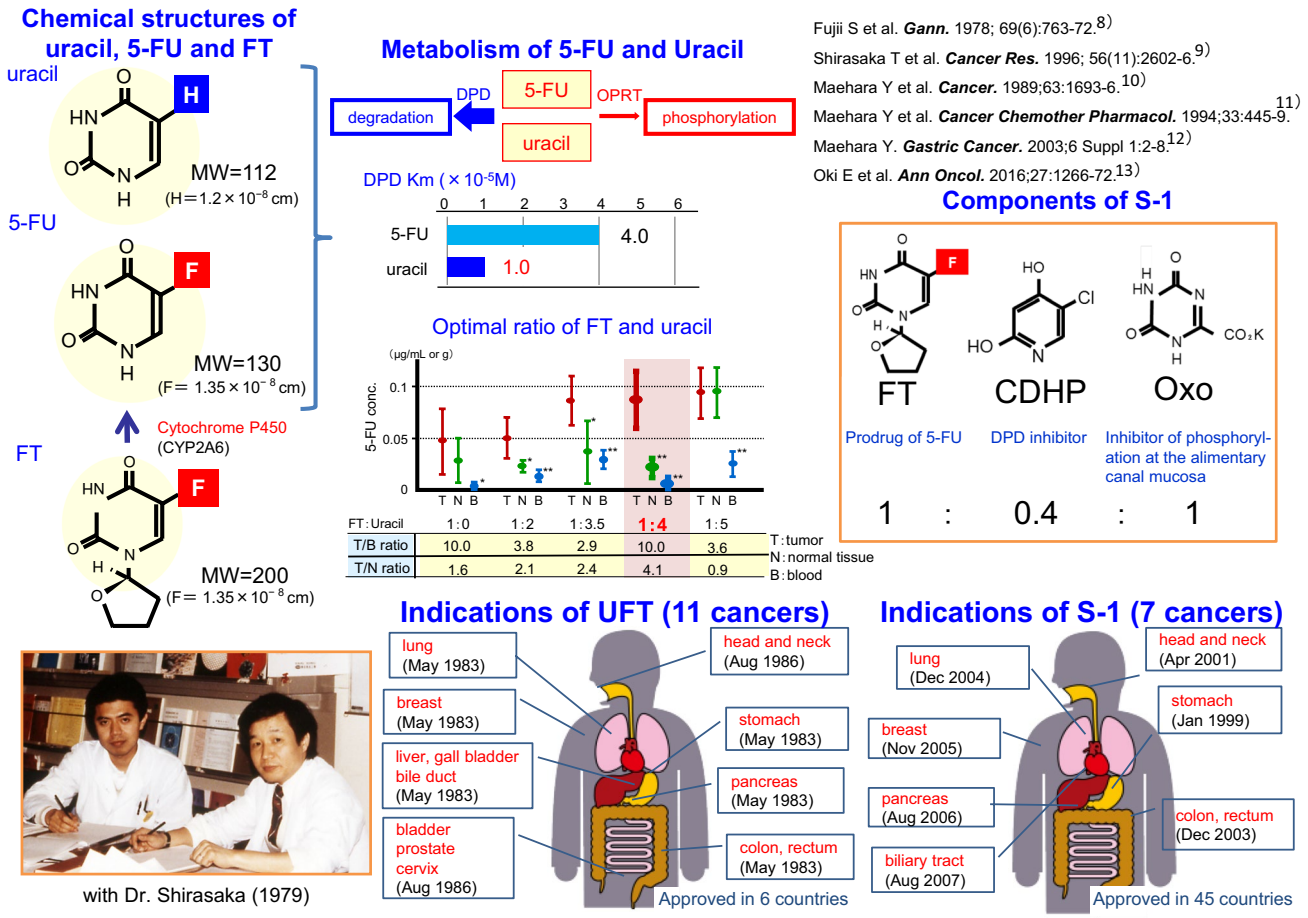


Fig. 5 Basic research and clinical development of UFT and S-1

impact on improving the outcomes of breast cancer patients [21] (Fig. 10).

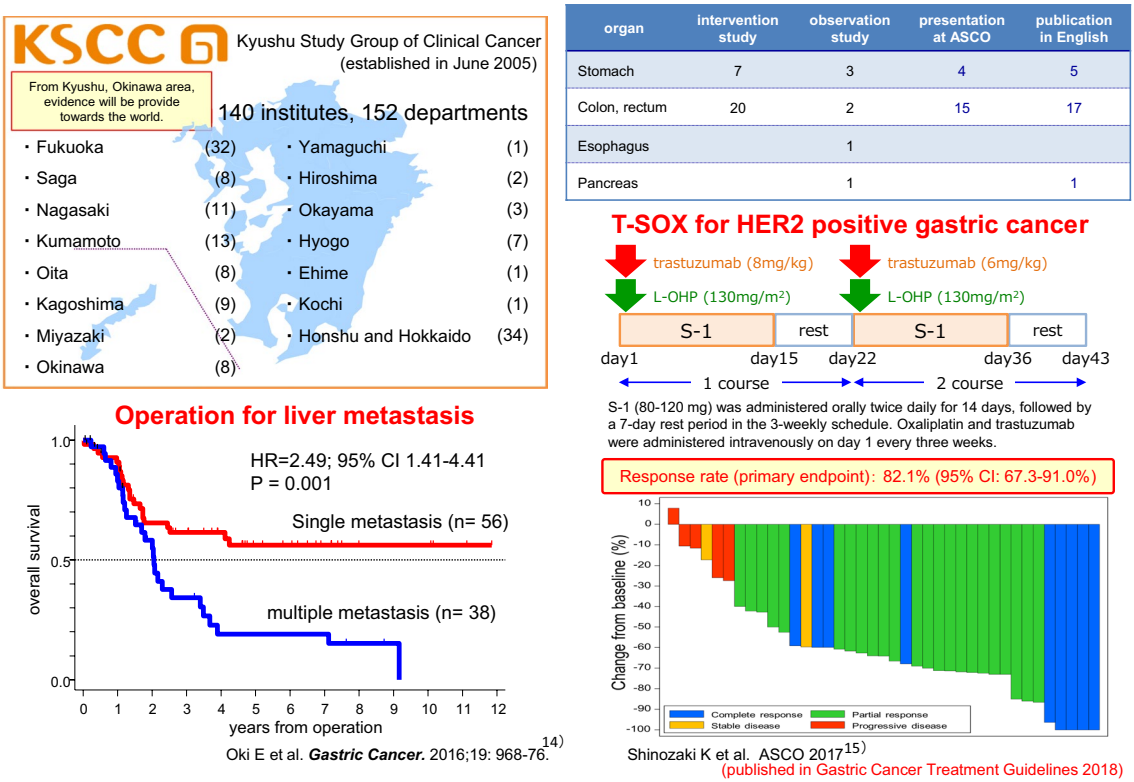
The development of surgical procedures and devices

In the area of surgical treatments, we have been working on the development of surgical procedures for gastrointestinal reconstruction.

After esophageal cancer resection, the remaining esophageal segment and a reconstructed gastric tube are connected. For secure anastomosis, the evaluation of blood perfusion in the reconstructed gastric tube is essential. Indocyanine green (ICG) is a fluorescence dye, and imaging of intravenously injected ICG is employed for tissue blood flow visualization using a censor that detects a specific wavelength [22, 23]. Furthermore, the tissue O_2 saturation and the amount of Hb in the gastric tube just before esophagogastric anastomosis were evaluated using a multispectral tissue quantitative imaging device. The site of anastomosis was decided according to the quantitative values and patterns of both the tissue O_2 saturation and the amount of Hb. The method of quantitatively imaging the tissue O_2 saturation and Hb level in real-time and non-invasively using a multispectral device allows for the instantaneous determination of conditions of the anastomotic site, thereby contributing to determining the appropriate treatment direction [24] (Fig. 11).

For patients undergoing partial gastrectomy for gastric cancer resection, we developed the book binding technique. This technique enables safe and secure anastomosis and reconstruction, with ischemic gastric and duodenal areas removed [25, 26] (Fig. 11).

After rectal cancer is resected, anastomosis is usually performed by the double stapling technique (DST). In this case, the resulting anastomosis is capable of resisting pressure of not more than 11 mmHg. We developed the circular side stapling technique (CST), to create anastomoses that can withstand five times higher pressure. With the CST, side-to-side colorectal anastomosis is made on the remaining rectum and colon [27, 28]. However, even with this technique, the constructed anastomosis is far from being able to resist the pressure of flatulence, which can be as high as 90 mmHg



organ	intervention study	observation study	presentation at ASCO	publication in English
Stomach	7	3	4	5
Colon, rectum	20	2	15	17
Esophagus		1		
Pancreas		1		1

Fig. 6 Clinical study on gastrointestinal cancer

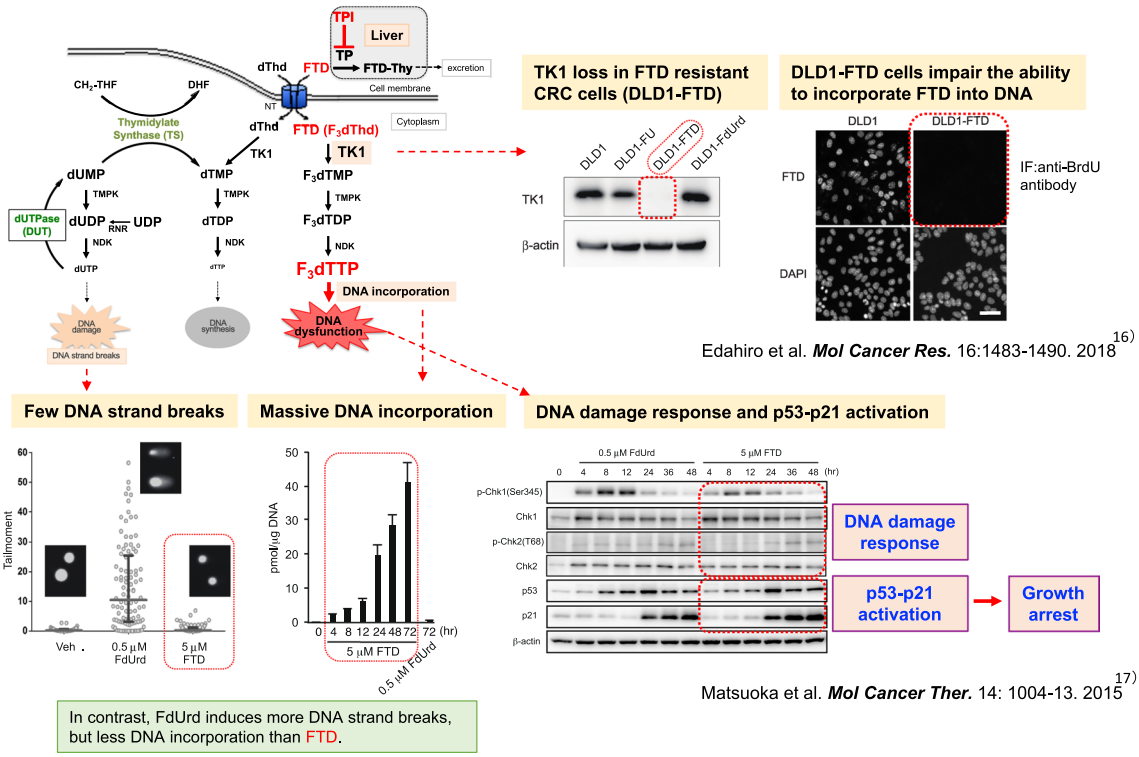
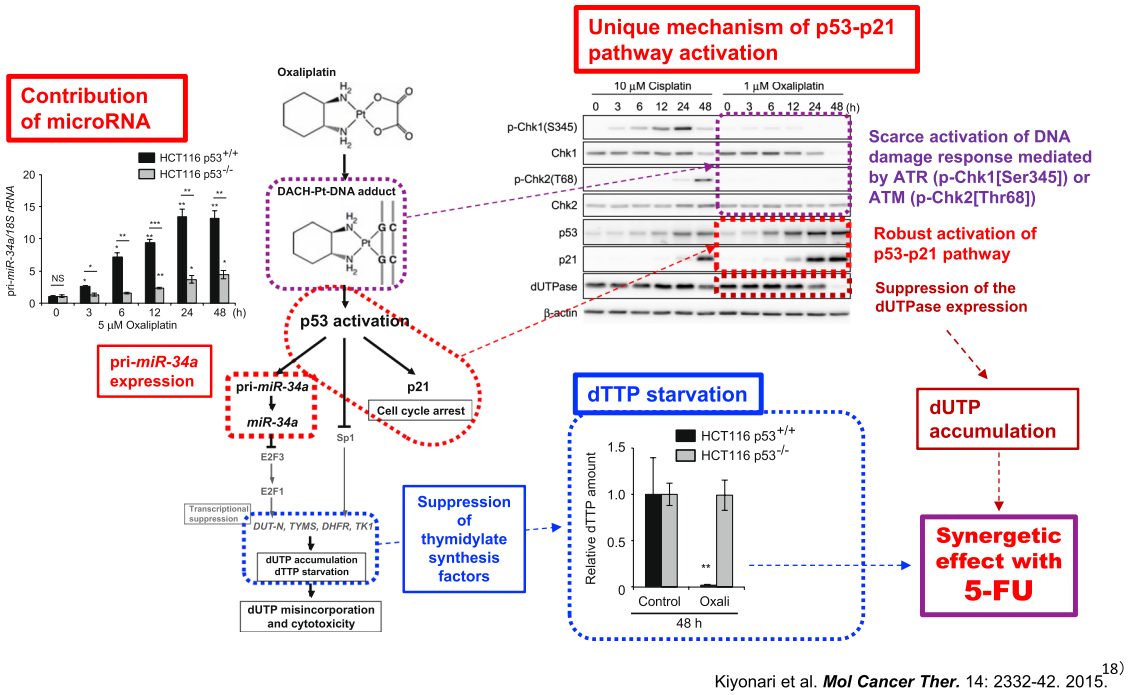
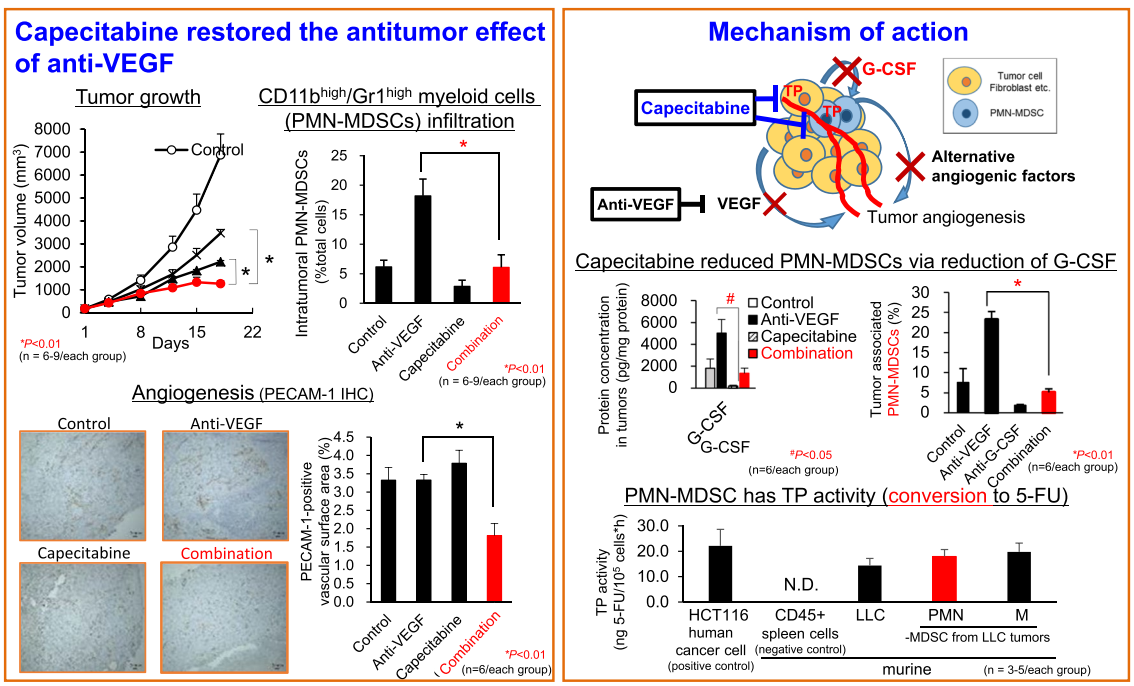


Fig. 7 The mechanism of action of trifluridine



Kiyonari et al. ***Mol Cancer Ther.*** 14: 2332-42. 2015.[18)]

Fig. 8 The mechanism of action of oxaliplatin that enhances 5-FU cytotoxicity

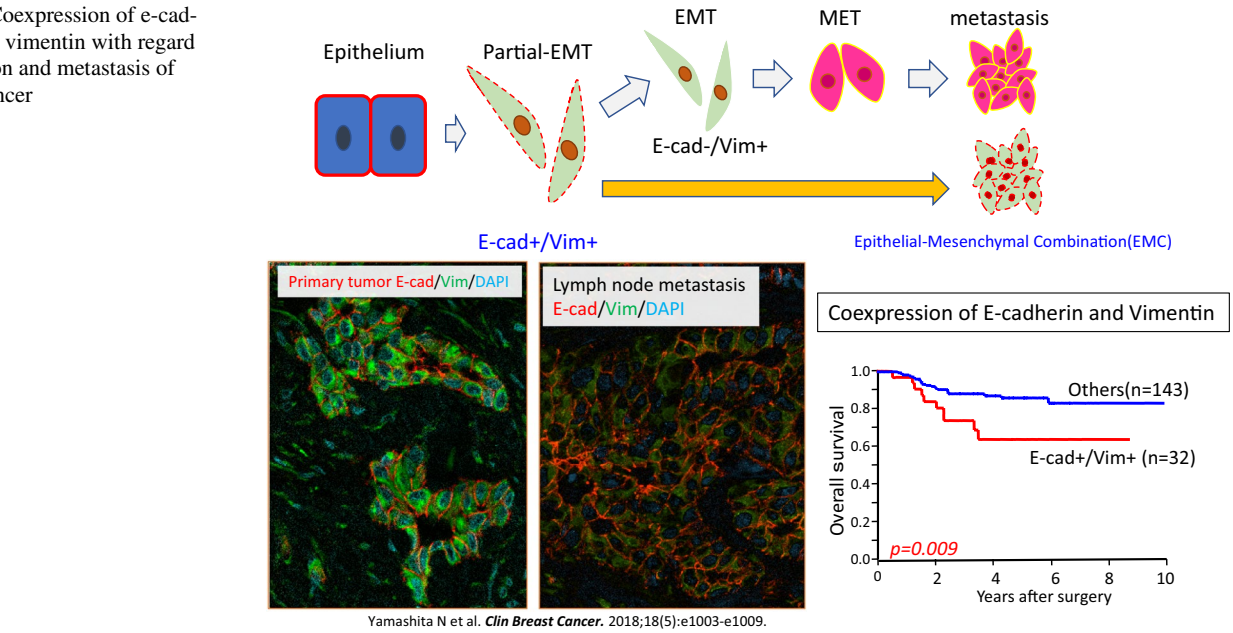


Shojaei F et al. **Nat Biotechnol.** 2007; 25:911–20.[19)]
Iwai T et al. **Oncotarget.** 2018;9(25):17620-17630.[20)]

Fig. 9 Capecitabine reverses tumor escape from anti-VEGF through the elimination of CD11bhigh/Gr1high myeloid cells

[29]. A critical issue is how to secure sufficient strength of the affected tissue (Fig. 11).

We tackled this issue, focusing on collagen in tissues (Fig. 12). Synthesis of collagen is said to be what caused the



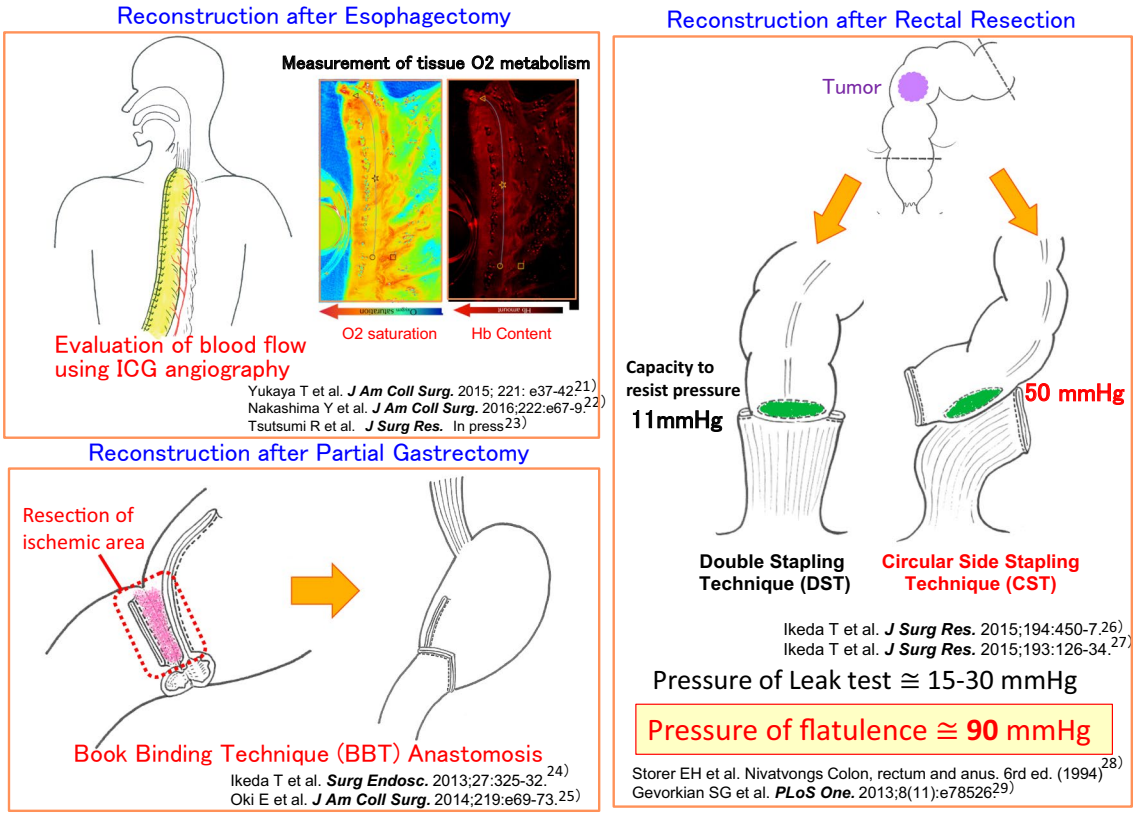


Fig. 10 Coexpression of e-cadherin and vimentin with regard to invasion and metastasis of breast cancer

Fig. 11 Reconstruction after gastrointestinal surgery

evolution of single-celled organisms to three-dimensional multicellular creatures. Collagen, which accounts for 30% of protein in the human body, forms a triple spiral helix consisting of glycine–proline–hydroxyproline repeats [30, 31]. Due to its highly unbalanced amino acid composition, collagen fibers loosen and swell at or above temperatures above 40 °C, and each triple helix is degraded into three gelatin molecules. It is said, in an analogy to building structures,

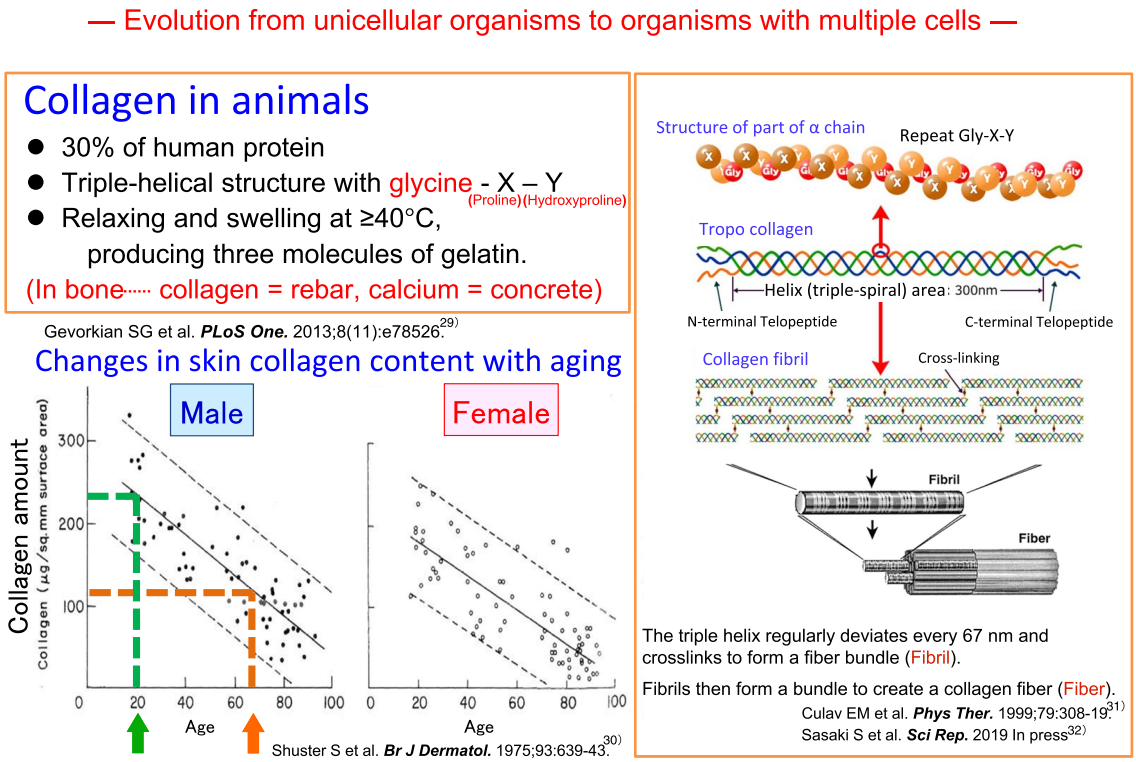


Fig. 12 Formation of tissue skeleton

that collagen in the bone corresponds to rebar and calcium to concrete. Since the tissue collagen content decreases with age, the elderly are considered to be at greater risk of developing anastomotic insufficiency [32].

This is why we attempted to strengthen the site of anastomosis by covering it with biomaterial collagen. A bovine internal carotid artery sample was severed. The severed site was covered with biomaterial collagen, pressed, heated with hot water (approximately 50 °C) to cause the loosening and swelling of collagen fibers, and then re-cooled to achieve interdigitation. Optic and electron microscopic observation revealed intertwining of biological collagen fibers with biomaterial ones at the site of anastomosis, and the site was able to resist pressures of over 300 mmHg [33].

Adequate postoperative management

The relationship between family-associated factors and the postoperative prognosis was elucidated in patients with non-small cell lung cancer (NSCLC). Additionally, we investigated whether having children was associated with the postoperative maintenance of the nutritional status. Nutritional indices, including the prognostic nutritional index (PNI) and sarcopenia, were used to estimate the change in the nutritional status for 1 year after surgery. The overall survival (OS) and disease-free survival (DFS) of partner-present and partner-absent patients did not differ to a statistically significant extent, while childless patients showed significantly shorter OS and DFS in comparison patients with children. The postoperative exacerbation of PNI and sarcopenia in childless patients were significantly greater than those in patients with children [34] (Fig. 13).

Approach for detecting early-stage cancer

For the detection of early-stage cancer, we pay special attention to cancer odors in our research. It has long been believed that cancer has a specific odor (Fig. 14). Dogs are considered to have a sense of smell that is 15 thousand times more accurate than that of humans. Odor-based detection of cancer by trained dogs has been reported in multiple high impact factor journals [35–38]. We performed a study to evaluate the ability of a cancer detection dog to detect cancer odors using exhaled breath and watery stool samples from patients with early to advanced colorectal cancer [39]. The result was that the dog detected colorectal cancer with high probability. This result indicates the presence of compounds that are produced in cancer-specific metabolism.

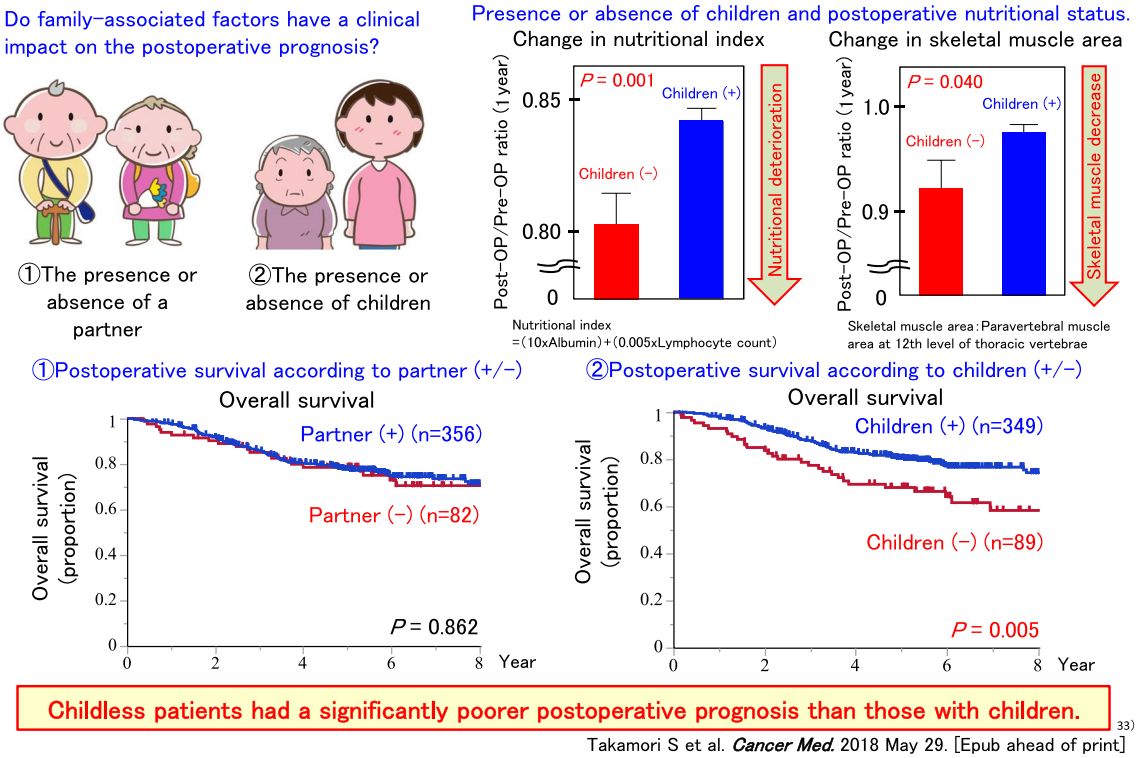
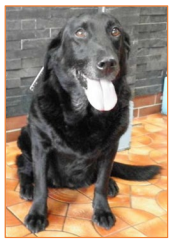


Fig. 13 The relationship between family associated factors and the postoperative prognosis in non-small cell lung cancer patients



- Williams H et al. 1989 Lancet. (IF : 53.3)
- Willis CM et al. 2004 BMJ. (IF:23.3)
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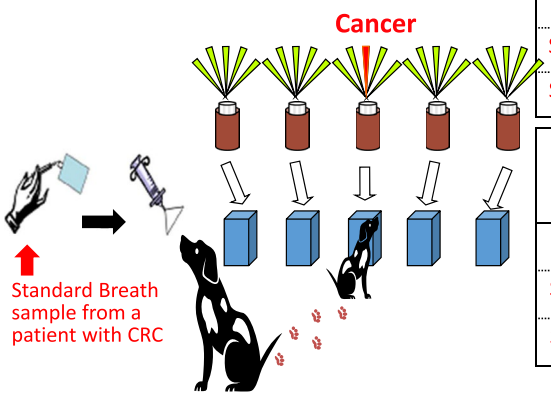
- We examined exhaled breath and watery stool samples obtained from patients with colorectal cancer (CRC) using a cancer-detecting dog.
- CRCs, including early-stage cancers, were detected with ≥91% sensitivity and 99% specificity.
- The cancer detection dog did not respond to odors resulting from benign polyps, inflammation, necrosis, or bleeding.

For a single test,
24 controls and 1 cancer sample were used.
Watery stool 200 µl/sample × 5 = A total of 1ml/bottle



CRC Stage	Exhaled Breath 0	I	II	III	IV	Total
Total	4/4	6/8	7/7	9/10	7/7	33/36
Sensitivity	1	0.67	1	0.89	1	0.91
Specificity	1	0.92	1	1	1	0.99

CRC Stage	Watery Stool 0	I	II	III	IV	Total
Total	6/6	5/6	9/9	11/11	6/6	37/38
Sensitivity	1	0.8	1	1	1	0.97
Specificity	1	0.95	1	1	1	0.99

Sonoda H et al. Gut. 2011;60:814-9.

Fig. 14 Presence of cancer odors has been demonstrated

Given this result, we next attempted to identify substances linked to cancer odors, starting with breast cancer. It is deemed that this cancer tends to generate greater levels of odor with increased proliferation. We analyzed GC–MS cultured cell lines of breast cancer and fibroblasts to identify volatile compounds that differed in quantity between cancer patients and healthy controls and detected medium-chain fatty acid (MCFA). High levels of MCFA were found in the urine of breast cancer patients, but to our disappointment, the cancer detection dog did not react to this compound. While we are still searching for substances to which the dog reacts, a mechanism by which MCFA levels increase was reported by other researchers: beta-oxidation of MCFA is suppressed, resulting in the enhancement of the glycolytic system, which is associated with cancer advancement [40].

What is interesting is that medium-chain acyl-CoA dehydration deficiency, an autosomal recessive genetic disorder in young children, is the only human disease that elevates MCFA levels [41]. The prevalence of this disorder is estimated to be one in 130 thousand. Its symptoms include impaired consciousness, respiratory problems, muscle weakness, hepatomegaly, and skeletal muscle damage, which match the symptoms of cancer cachexia. This may suggest that the pathological conditions of cancer cachexia need to be comprehended as a lipid metabolism abnormality.

Strategies for preventing carcinogenesis

We have been proactively engaged in the surgical treatment of hepatocellular carcinoma (HCC) since 1985. Patient survival rates have been increasing [42–46] (Fig. 15). Currently, we perform laparoscopic surgery for early-stage HCC, but this is not an optimal operation for the liver, which is protected by the ribs and diaphragm. We came up with a patient position that enables safe and secure laparoscopic surgery of the liver and reported on this procedure. The left semi-prone position creates space between the diaphragm and the liver, facilitating laparoscopic manipulation [47].

We had a case of unresectable huge HCC that spread through the entire liver. For this patient, we devised an operative procedure applying a living liver transplant operation. The patient's father was standing by for liver transplantation in case the transplanted liver segment would not function. The removed tumor weighed 2,050 g, the normal liver segment weighed 400 g, and the blood loss amounted to 25,000 mL. It took 19 h 22 min to complete the surgery [48]. This patient has been alive and recurrence free for 11 years and 2 months since the operation and is now a mother of two children (Fig. 15).

Now let me discuss strategies for HCC prevention. There seem to be four main causes of HCC development (Table 1).

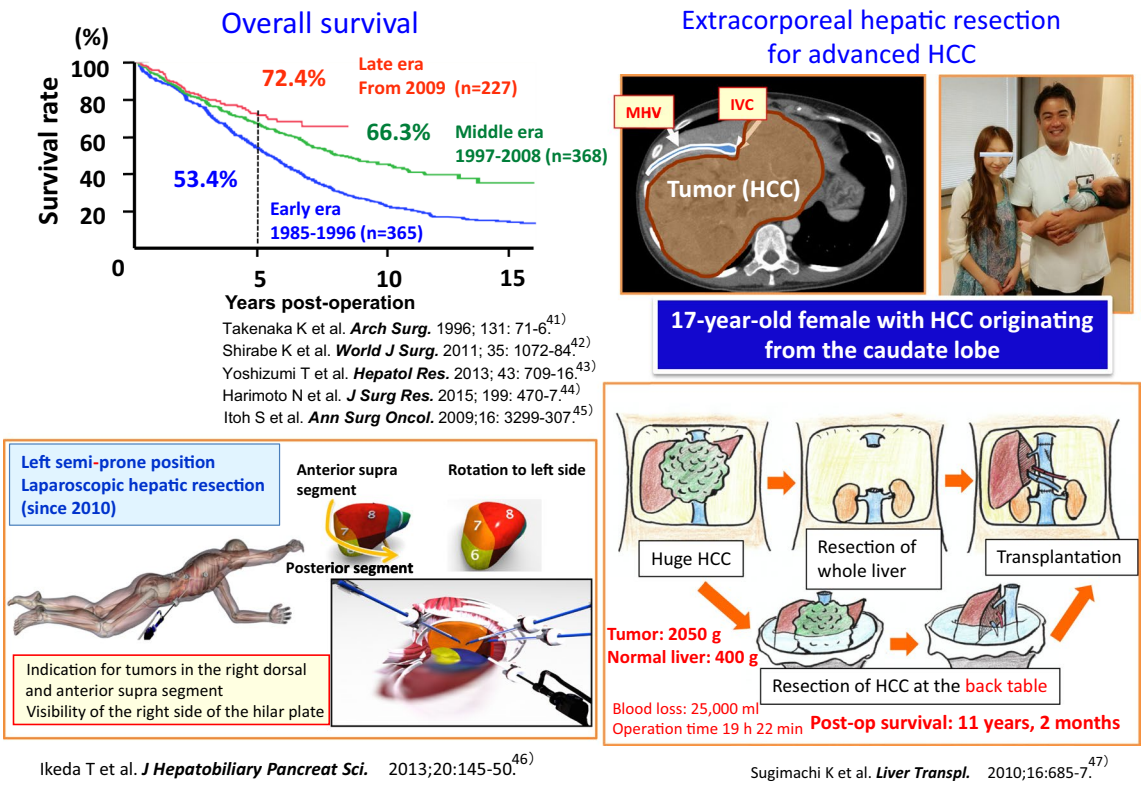


Fig. 15 Surgical treatment of hepatocellular carcinoma

Table 1 Causes and preventive approaches for HCC

Causes	Concrete measures for prevention
Alcohol	Lifestyle guidance Advice on how to drink
HCV	Treatment with nucleic acid synthesis inhibitors (direct-acting antivirals; DAAs)
HBV	Trial of viral DNA cleavage using genome-editing technology
NASH (due to DM, obesity)	Lifestyle guidance Improvement in condition via metabolic surgery

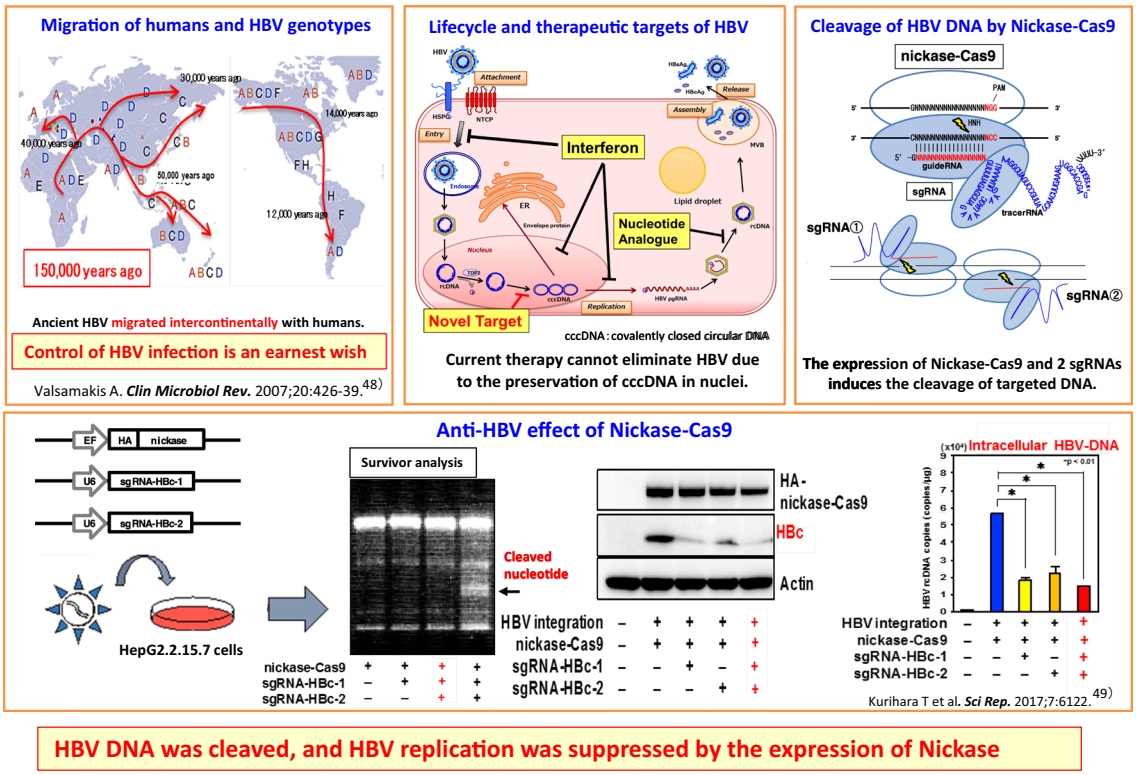


Fig. 16 Establishment of novel anti-HBV treatment (Nickase-Cas9 System)

The alcohol intake increases in the US as well, and this constitutes a social problem. To combat this issue, lifestyle guidance and advice on how to drink (how to live your life) should be offered. HCV-related cancer is expected to decrease since nucleic acid synthesis inhibitors have become available. Regarding HBV-associated cancer, it seems that it can only be addressed by eliminating the hepatitis B viral DNA incorporated into the cell DNA by genome editing technology. The prevalence of non-alcoholic steatohepatitis (NASH) (due to diabetes or obesity) increases worldwide. For individuals with this condition, we have been providing lifestyle guidance and currently we also offer metabolic surgery.

Since the dawn of humankind in Africa 150 thousand years ago, HBV has been migrating with humans over the course of our evolution and infecting us repeatedly throughout history (Fig. 16). It is estimated that worldwide, 240 million people are infected with HBV and that 800 thousand people die annually of cirrhosis or HCC [49]. We employed genome editing technology with a pair of single-guide RNAs and nickase-Cas9 to successfully achieve viral DNA cleavage and suppression of viral protein synthesis and viral replication in experimentally HBV-infected cells [50]. These techniques may potentially serve as a therapeutic modality that can prevent HBV-related hepatocarcinogenesis.

We have been engaging in metabolic surgery as a treatment for type 2 diabetes and obesity (Fig. 17). Removing part of the stomach to make it smaller and thinner has been observed to be associated with modified transit time of food and gastrointestinal hormonal secretion. As a result, the termination of insulin treatment for diabetes and improvement

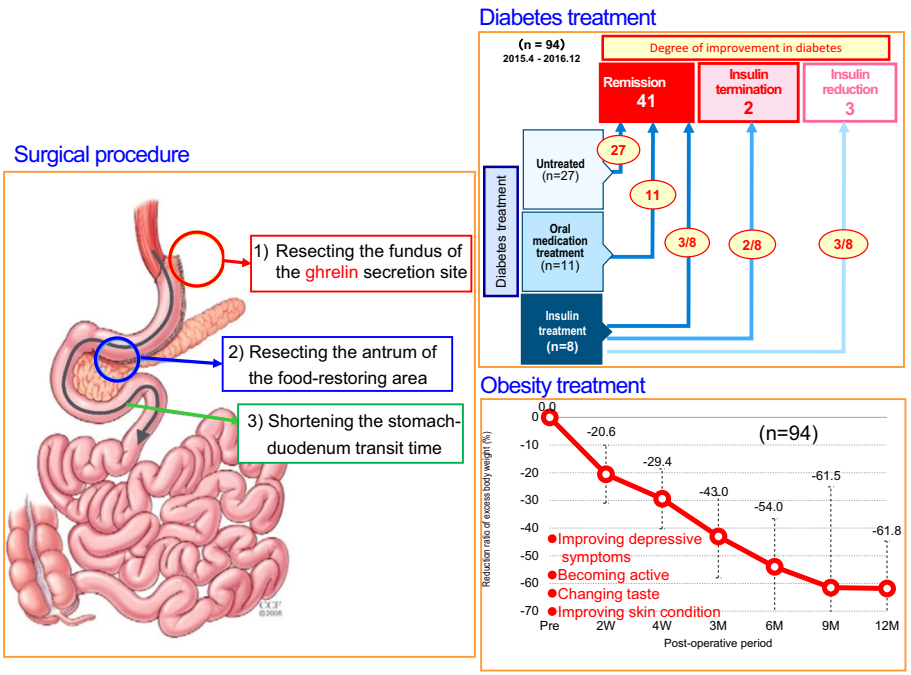


Fig. 17 Metabolic surgery for diabetes mellitus and obesity

Fig. 18 International cooperation in the field of surgery

in the obesity level, accompanied by an alleviated state of depression, have been achieved. Interestingly, the intestinal flora has been found to be drastically altered and increasingly normalized along with symptomatic improvement, namely, the stool condition approached that of a normal healthy adult. This finding appears to indicate that normalization of the intestinal flora may lead to the improvement of diabetes and obesity.

Table 2 Collaborative Research Institutes

Department of Surgery and Science, Kyushu University
Emergency & Critical Care Center, Kyushu University
Department of Advanced Medical Initiatives, Kyushu University
Department of Surgery and Molecular Targeting Therapy, Kyushu University
Department of Innovative Applied Oncology, Kyushu University
Department of Surgery and Multidisciplinary Treatment, Kyushu University
Department of Molecular Oncology, Kyushu University
Department of Molecular Cancer Biology, Kyushu University
R&D Laboratory for Innovative Biotherapeutics, Kyushu University
Research and Development Center for Taste and Odor Sensing, Kyushu University
Department of Molecular Virology, Osaka University
Endoscopy and Endoscopic Surgery, Fukuoka Dental College
Taiho Pharmaceutical Co., Ltd
Chugai Pharmaceutical Co., Ltd
Yakult Honsha Co., Ltd
Ono Pharmaceutical Co., Ltd

International cooperation in the field of surgery

Regarding international cooperation in the field of surgery, Dr. Naoyuki Kawahara, who joined our department in 1992, founded a nonprofit organization (NPO) called Rocinantes in 2006. This NPO is chiefly dedicated to the provision of medical services in Sudan, Africa (Fig. 18). They interact with universities nationwide in Japan and dispatch personnel where needed. Earlier in this month, Japanese government officials and the President of Sudan met to discuss medical device support for Sudan. In this country, a liver transplantation center is under construction and is slated to be completed in 2019.

Big Real-World Data Project in Japanese Foundation for Multi-disciplinary Treatment of Cancer (JFMC)

I would like to talk about the database project by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JMFC). Since 1980, the Foundation has sponsored 51 large-scale clinical studies, in which the total enrollment surpasses 40 thousand patients. Ten of these studies were on postoperative adjuvant chemotherapy; 13,816 colorectal cancer patients were enrolled. The latest ACHIEVE study is pooled analysis with six international joint studies. This study made new standard of the world postoperative adjuvant chemotherapy for colon cancer [51, 52]. The JMFC is working on compiling the data from these patients into a database. This database is advantageous in that the obtained data are validated in clinical investigations and are, therefore, highly reliable and accurate and that the survival status and relapsing event data are also available as these patients were followed up after the study. It is also possible to perform additional analyses to assess, for instance, differences in drug effects and adverse event profiles by subset analyses according to age, sex, concurrent disease, and other factors; the frequency of cancer development secondary to chemotherapy; and the selection of endpoints for clinical studies. The JFMC also seeks to integrate their database with those abroad. The resulting database is expected to contribute to clarifying regional differences by race or country. Accordingly, a long-standing question, on whether or not colorectal cancer in the Japanese is biologically the same as that in Westerners, can be answered.

Conclusion

In conclusion, it is our belief that the steady advancement being made in the field of surgery will greatly contribute to improved outcomes of gastrointestinal cancer treatments and control and preventive measures of the cancer.

With this, I would like to end my lecture. Thank you very much for your attention.

Here are 16 research institutes with which we are collaborating (Table 2).

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Compliance with ethical standards

Conflict of interest We disclose the following conflicts of interest. We offer our heartfelt gratitude to the cooperation extended by the research institutes of these four companies: Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, and Yakult Honsha.

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