

[Research]

Current Progress (As of March 2018)

- Role sharing with affiliated universities

- (a) Clinical Science Section

The Clinical Science Section has started internationalization of the clinical studies in precision external radiotherapy conducted by Professor Quynh-Thu Le, Professor Daniel Chang, Associate Professor Billy Loo, and Assistant Professor Maximilian Diehn at SU. These Professors and clinical research coordinators visited the GI-CoRE and the clinical research and development center at Hokkaido University Hospital before the start of these studies. The role of stereotactic ablative radiotherapy (SABR) in measuring cDNA in the blood, a potentially essential surrogate marker in improving cancer survival rates for lung cancer has been studied. A randomized clinical trial comparing SABR and the standard treatment, trans-arterial embolization for relapsed hepatocellular carcinomas has been conducted by SU. The GSQ has hired clinical research coordinators who are good at English to facilitate the international clinical trials. All English protocols and informed consents were translated into Japanese and accepted by the ethics committee of Hokkaido University Hospital. For these two clinical studies, the Clinical Science Section has made it possible to register patients treated at Hokkaido University Hospital into these studies with the great help of the staff of clinical research at SU. SU has worked closely with HU on highly precise radiotherapy such as image guidance and usage of big data to predict outcomes of cancer treatments. The clinical benefit of proton beam and carbon beam therapies has been discussed extensively with data from HU and other Japanese institutions which utilize particle beam therapy. Linking these clinical studies effectively enables clinical research to realize new treatments aimed at avoiding recurrence and metastasis.

Professor Kohsuke Kudo, Senior Assist. Prof. Noriko Manabe, and Senior Assist. Prof. Khin Khin Tha from the Clinical Science Section of HU and Professor Lei Xing, Assist. Prof. Ruijiang Li, Research Associate Yi Cui, post-doctoral researcher Jeffrey Wang from the Medical Physics Section of SU are conducting collaborative research to identify noninvasive tumor biomarkers through analysis of magnetic resonance (MR) images using radiomics, an innovative quantitative image analysis. The first project was identification of imaging features to predict the overall survival of glioblastoma patients. Using MR imaging datasets of glioblastomas, Drs. Cui, Tha, Wang, Kudo, Xing, Shirato, and Li enabled the extraction of five imaging features, the combination of which predicted the overall survival of glioblastoma patients with superior performance over existing prognostic indicators (Fig. 1) (*Radiology* 2016; 278: 546-553). Drs. Cui, Tha, Shirato, and Li further extended the work to identify MR imaging features which could differentiate glioblastoma molecular subtypes (Fig. 2) — this differentiation is important as treatment responses and prognoses varied greatly among the subtypes. Through a few modifications of the radiomic analytics they developed, the researchers could distinguish the proneural subtype of glioblastoma from other molecular subtypes (*Eur Radiol* 2017; 27: 3583-3592). Using a similar approach, Drs. Wang, Manabe, Li, Cui, Tha, Kudo, and Shirato also identified MR imaging features that could differentiate triple-negative breast cancer (*PLoS One* 2015; 10: e0143308). Currently, these researchers are working on prediction of hypoxic regions within glioblastomas (Drs. Kudo, Tha, Cui, and Shirato), and on distinguishing pseudo-progression and pseudo-regression of diffuse gliomas from true tumor progression and responses (Drs. Tha, Xing, and Shirato), through radiomics and deep learning analytics of MR images. Hypoxic tumor areas are often resistant to standard doses of radiation therapy and require adaptation of treatment regimes. Distinguishing pseudo-progression and regression from true tumor progression and response is essential since treatment regimens differ for these conditions, but the performance of currently available imaging techniques is not satisfactory.

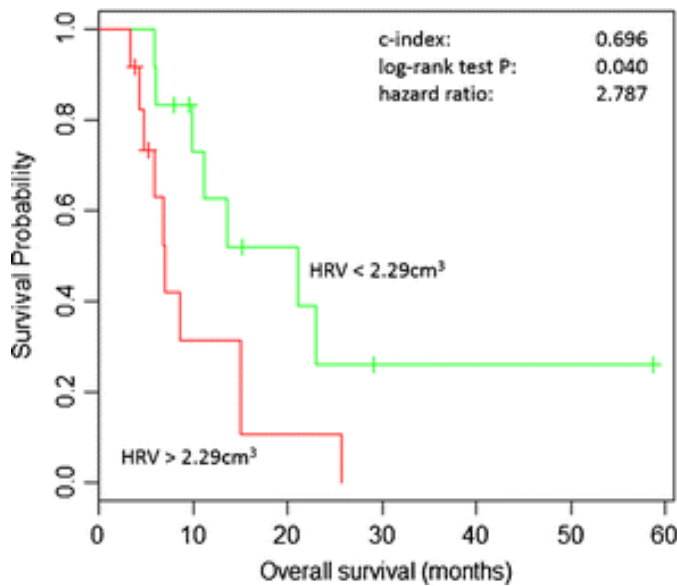


Fig.1 Kaplan-Meier curves showing the performance of MR imaging features extracted by radiomic analytics in distinguishing patients based on overall survival period (Radiology 2016; 278: 546-553)

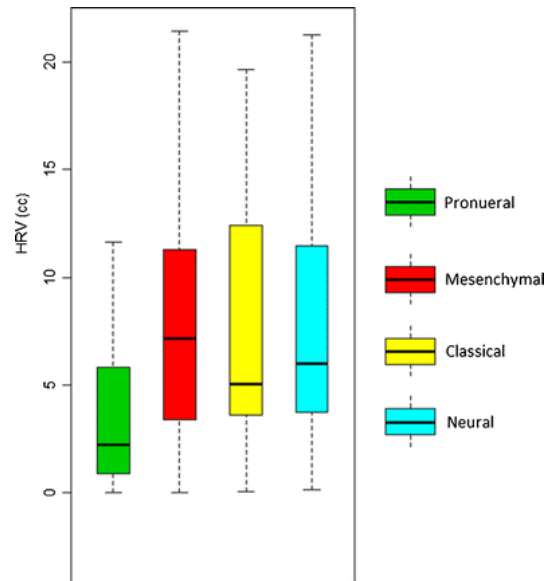


Fig.2 Boxplots showing smaller high-risk volume (HRV) MR images for the proneural glioblastoma molecular subtype (HRV was derived from the MR images) (Eur Radiol 2017; 27: 3583-3592)

(b) Medical Physics Section

The Medical Physics Section and researchers of SU have conducted research to visualize two dimensional (2D) gold concentration distributions in objects by observing the amount of fluorescence X-rays emitted when proton beams collided with gold, using the proton beam line at HU (M. Bazalova et al., *Med. Phys.* 2015). The team has also been engaging in the development of technology to determine proton ranges in real-time by observing ultrasonic waveforms emitted from the irradiated target during treatment (M. Ahmad et al., *Med. Phys.* 2015). Furthermore, working with Dr. Ruud Vinke, a doubly appointed Stanford researcher who stayed at HU for three months in 2015, the team developed technology to enable CBCT acquisition with multiplex X-ray energy levels which is better than the existing single energy cone beam CT technology. For the research into proton beam irradiation technology, the team also developed a device to decrease the duration of irradiation when the target moves due to respiration (T. Matsuura et al., *Phys. Med. Biol.* 2016). Another SU researcher, Cesare Jenkins, came to HU and performed the first experimental study of proton range verification using phosphor coated phantom and the preliminary data was presented at the 2016 Annual Meeting of AAPM. Anastasia Makarova, a post-doctoral researcher at HU between 2016 and 2017, worked together with Associate Professor Taeko Matsuura and Assistant Professor Kenneth Lee Sutherland. They evaluated energy absorption by bystander gold nanoparticles. Through Monte Carlo simulation, the efficiency of electron shielding by tumor-surrounding clusters of gold nanoparticles was examined. The study was presented at the 2017 Annual Meeting of AAPM. Dr. Hao Peng of SU works in pursuit of several projects together with Dr. Jeffrey Wang and other HU researchers. With Dr. Peng's vast experience in PET and MRI technologies, projects concerning development of detector designs are underway, investigating circuit multiplexing strategies, signal encoding, and optimization of systems using machine learning techniques. Dr. Peng also has been investigating characterization of a new imaging technique to improve accuracy of breast cancer diagnosis with Dr. Wang. The X-ray-induced acoustic (XA) imaging technique (pioneered by Prof. Lei Xing) has shown great promise as a technique able to produce tomographic images as well as act as a method of radiation therapy dose calculation. Dr. Peng was awarded a 3-year

Grant-in-Aid for Young Scientists from the Japan Society for the Promotion of Science (JSPS) which started in 2017, to develop a system to hybridize breast tomosynthesis and XA to improve diagnostic accuracy of mammography (Fig. 3). Specifically, the project aims to develop a comprehensive framework to characterize the performance of such a system, with respect to image quality and detection limit, as well as to build a prototype to demonstrate feasibility through phantom and in-vivo animal studies. Dr. Qiong Xu of SU visited between 2016 and 2018, during which time she advanced to become Assist. Prof. of HU. She has been investigating reconstruction of low-dose thoracic CT using dictionary learning of region-specific structures within organ compartments. The strategy successfully takes into account inherent regional differences inside reconstructed objects and lead to improved images. The results of this study have been submitted to the IEEE's Transactions on Medical Imaging (Fig. 4). Dr. Xu is currently working on a deep learning-based method of CT reconstruction with Dr. Wang. The technique exploits a deep convolutional decoder-encoder network learned prior to restore images corrupted by metal artifacts. The initial study has been submitted to the 2018 Annual Meeting of AAPM. Dr. Mehmet Burcin Unlu is the latest scholar to visit from SU, an expert in the topics of photoacoustic imaging and inverse problems, also pursuing interests in radiation-induced acoustic imaging. At first, evaluation of an analytical model for acoustic signal induction is being performed against simulations and has been submitted to AAPM 2018. Several projects involving characterizing proton beam- and X-ray- induced acoustics experimentally are also underway.

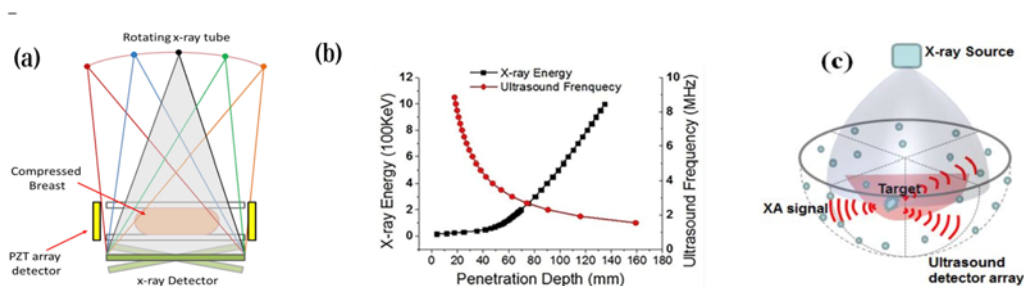


Fig.3 (a) Schematic drawing of a hybrid X-ray induced acoustic breast imaging system (not to scale). (b) The penetration depth of X-ray in different energies vs. the penetration depth of ultrasound wave in different frequencies, which are much larger compared to optical photons. (c) The acoustic signal emission from the target hit by a pulsed X-ray allows for 3D volumetric imaging (Xing et al., Scientific Reports 2016).

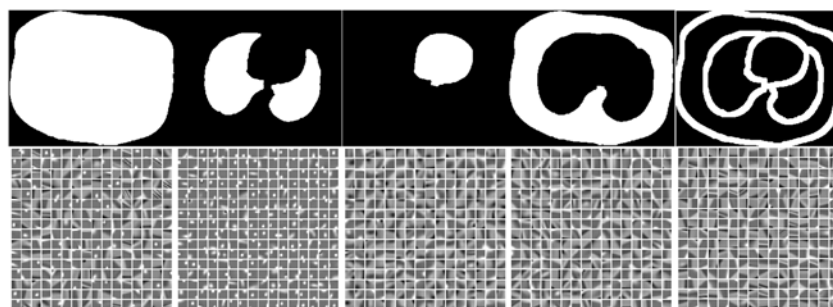


Fig. 4 Learned dictionaries for region-specific low-dose CT reconstruction (bottom) and their represented regions (top). The 1st column at left corresponds to the thorax region mask and represents the conventional single dictionary. The 2nd-5th columns are the lung, heart, surrounding tissue, and juncture region masks respectively, corresponding to the respective region-specific dictionaries (submitted by Xu et al., IEEE TMI 2018).

(c) Radiation Biology Section

Since 2014, the Radiation Biology Section has worked to develop a work environment, including wet laboratory space, an office, and research facilities on the 4th floor of the Graduate School of Medicine of HU that enables carrying out of collaborative radiation biology research between SU and HU. The research of the Radiation Biology Section led by Professor Amato J. Giaccia of SU, and the team including Senior Assist. Prof. Jin-Min Nam, Assist. Prof. Erinn B. Rankin, research fellow Yu Miao, and post-doctoral researchers Frances C. Recuenco and Chi-Che Hsieh have conducted collaborative research at HU. The team has been investigating the molecular mechanism of radiation effects to improve the efficacy of radiation treatment on cancer cells.

Dr. Giaccia has given three state-of-the-art special lectures on radiation biology and the tumor microenvironment at the annual GI-CoRE International Symposium. For education of students, Dr. Giaccia and Dr. Le will give a lecture series on radiation biology in the Hokkaido Summer Institute 2018/ GI-CoRE Summer School for Radiation Biology 2018. Dr. Nam has been giving lectures and research training to graduate students at HU of the Graduate School of Medicine and Graduate School of Biomedical Science and Engineering. Drs. Rankin and Miao gave talks at the annual GI-CoRE International Symposium. The SU members stayed and conducted discussions with lab members at HU.

In educational activities, under the supervision of Dr. Nam, Ping-Hsiu Wu (M.D.), a graduate student of the Graduate School of Medicine of HU, is engaged in research related to the application of sensitizers targeting certain cell surface receptors which regulate cancer cell invasion. Dr. Wu presented the research at international conferences: The ASCB Annual Meeting (San Diego, 2015), The 3rd GI-CoRE Medical Science and Engineering Symposium (Sapporo, 2016), ASTRO (Boston, 2016), JCA (Yokohama, 2016), JASTRO (Osaka, 2017), and will present at AACR 2018 (Chicago, 2018) sponsored by Drs. Giaccia and Le. Dr. Wu also visited the laboratories of Drs. Giaccia and Graves at SU to learn how to conduct *in vivo* experiments in mice. By the supervision of Dr. Nam and Dr. Giaccia, Dr. Wu published work about gold nanoparticles and radiation sensitization in the International Journal of Nanomedicine (Wu et al., *Int J Nanomedicine*, 2017, Fig.5). Dr. Recuenco has mastered the experimental system of *in vivo* imaging to analyze the effects of radiation using animal models. Dr. Recuenco provided training in animal work for students and technicians.

In addition to the original work, researchers of the GSQ Stanford

University unit have been actively collaborating with other faculty groups in the Graduate School of Medicine to understand the molecular mechanisms of cancer cell invasion (Hashimoto et al., *J Cell Biol.*, 2016; *Cell Commun Signal.*, 2016), Nik-related kinase signaling on placental development (Morioka et al., *PLoS One*, 2017), and cell competition (Kon et al., *Nat Cell Biol.*, 2017). The GSQ Stanford University unit has also been working with an immunologist in collaborative research showing that the Toll-like receptor 3 signal augments radiation-induced tumor growth retardation in a murine model (Yoshida et al., *Cancer Sci.*, 2018). Drs. Le, Giaccia, Koong, and Shirato have put together a review on an emerging treatment paradigm in radiation oncology in a prestigious American Association for Cancer Research journal (Le QT et al., *Clin Cancer Res* 2015). Drs. Rankin, Nam, and Giaccia published a review of Hypoxia and metastatic cascade (Rankin et al. *Trends Cancer*, 2016).

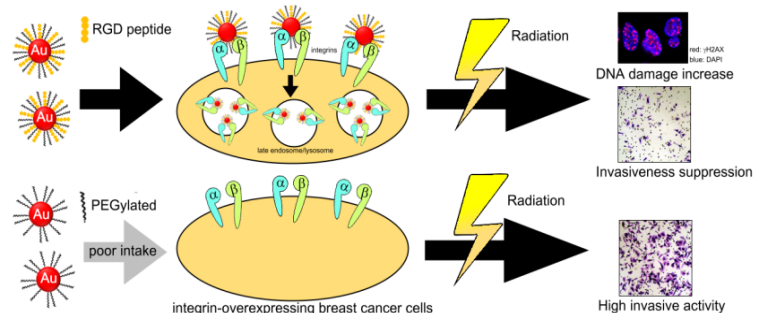


Fig.5 RGD-conjugated gold nanoparticles in radiotherapy

● Role sharing between faculty members at HU

(a) Clinical Science Section

At the Clinical Science Section, Professor Hiroki Shirato has published summaries of the GI-CoRE

4th and 5th symposium with the co-editor Prof. Quynh-Thu Le of SU in a special edition of the Journal of Radiation Research, the official journal of the Japanese Society of Radiation Oncology (JASTRO). The aim of the symposium was to establish international consensus in the way to select external radiotherapy technology for individual patients and featured lecturers from the Netherlands, USA, and Japan. The special issue contains all peer-reviewed papers including those from distinguished researchers such as the Mayo Clinic, the MD Anderson Hospital, and the National Institute for Radiological Science in addition to HU and SU. Drs. Shirato, Le, and other professors at HU and SU have published a keynote review for this issue. A consensus statement from all of the speakers in the symposium has been published in the journal. Professor Shinichi Shimizu has led research to develop state-of-the-art, minimally invasive, advanced radiotherapy technology using proton beam therapy. Dr. Shimizu has published papers and made presentations at academic conferences related to the development of proton beam therapy with the real-time tumor tracking technology and numerical simulations of clinical applications. Assistant Prof. Tetsuya Inoue has started two international clinical studies to measure cDNA (cancer cell genes in the blood) conducted by Assist. Prof. Maximilian Diehn at SU to improve survival rates of lung cancer. Assistant Prof. Norio Katoh and Senior Assist. Prof. Daisuke Abo, have become involved in the randomized trial conducted by Professor Daniel Chang at SU to compare the effect of stereotactic ablative body radiotherapy (SABR) with the standard treatment, intra-arterial embolization, for the relapse of hepatocellular carcinomas. Dr. Abo studied at Stanford University Hospital for 3 months before the start of this study. These two international collaborative studies have been successful in recruiting patients from Japan to the studies in the USA making the value of the studies international. Assist. Prof. Kentaro Nishioka has analyzed clinical results of real-time-image gated proton therapy (RGPT) and published the results in the journal. Senior Assist. Prof. Noriko Manabe has developed innovative quantitative image analysis technology for cardiac imaging with international colleagues.

Drs. Kudo and Tha have recently initiated a collaboration with Professor Miki Haseyama of the Graduate School of Information Science and Technology, who also belongs to the Global Station for Big Data and Cybersecurity (GSB), to develop a system that would allow automatic detection of small brain metastases. Development of such a system would be helpful in reducing the workload of radiologists involved in identifying these lesions from hundreds of images and also increase the diagnostic accuracy. Promising preliminary results have been obtained (Sugata et al., A note on the classification of brain metastases from MR images based on machine learning), and the researchers are currently planning to proceed with the data analysis by incorporating larger volumes of image data. Members of the GSQ and Drs. Yasuda, Kudo, and Haseyama of GSB are planning to evaluate whether the system would also allow automatic detection of vertebral metastases. As a separate project, Drs. Tha and Manabe have initiated research to determine the usefulness of electric properties tomography — a new MR imaging technique, in evaluations of lung and liver tumors. Drs. Tha, Kudo, and Shirato have previously explored the role of this imaging technique in evaluations of brain tumors and observed that electrical conductivity measurable by this technique can differentiate glioblastomas from lower grade gliomas (*Eur Radiol* 2018; 28: 348-355). Dr. Wang of the Medical Physics Section is currently investigating multiparametric MRI, especially using new machine learning techniques, for diagnosis of breast cancer and prognosis of its treatment therapy with Dr. Manabe. Incorporation of the advanced Diffusion Kurtosis Imaging method, already shown to increase diagnostic specificity significantly, is expected to improve upon current models of predicting breast cancer outcomes with the radiomics approach. Along with Dr. Tha, Dr. Wang is also studying diagnosis of early Parkinson's Disease and prognosis in brain tumor radiotherapy using deep generative neural network learning of biomarkers seen on Diffusion Tensor Imaging.

(b) Medical Physics Section

The Medical Physics Section has worked on developing new technology to improve the treatment

accuracy of proton therapy, something that has attracted a great deal of public attention in recent years. Assoc. Prof. Taeko Matsuura of HU and Instructor Magdalena Bazalova (currently serving as an Assistant Professor at University of Victoria) developed technology to depict and outline the two dimensional gold concentration distributions in objects using the proton beam therapy system of HU (M. Bazalova et al., *Med. Phys.* 2015). Many specialists have pointed out the importance of developing technology to verify the proton beam range during treatment, and the team led by Dr. Matsuura and post-doctoral researcher Moiz Ahmad at SU has engaged in developing technology to determine the range of the proton beam in real-time using ultrasonic waveforms emitted by the irradiated target during treatment (M. Ahmad et al., *Med. Phys.* 2015). Since 2015, a team led by Assist. Prof. Seishin Takao, Professor Kikuo Umegaki, and post-doctoral researcher Ruud Vinke, who joined HU for three-months, has been engaging in the development of technology to make it easier to acquire CBCT with multiplex X-ray energy levels compared to the existing single energy approach. We can expect that this technology will improve resolution of the obtained CT images and enable more accurate calculations of dose. The Matsuura team has also developed a device to decrease the duration of irradiation needed when the target moves due to respiration (T. Matsuura et al., *Phys. Med. Biol.* 2016). In addition to these research activities, as previously mentioned in the Clinical Science Section, researchers in Medical Physics Section, Assist. Prof. Ruijiang Li who spent 6 months at HU and post-doctoral researcher Yi Cui (currently serving as a Research Associate at SU) who spent 12 months in the GSQ at HU, performed radiomics studies using the clinical imaging data of brain and pancreatic tumors treated at SU and HU. They published their results in the top journal in this field (*Radiology*, 2015). Professor Masayori Ishikawa and Assist. Prof. Kenneth Lee Sutherland at HU are engaging in the summer school sessions at HU as a part of the global educational outreach in collaboration with SU. With the growing presence of artificial intelligence, in efforts described above and all other industries, the GSQ, Global Station for Big Data and Cybersecurity (GSB), and the Institute for Genetic Medicine (IGM), held a joint symposium in July 2017. Topics of quantum science, informatics, biology, medicine, and the emerging “Internet of Things” were covered between interdisciplinary experts, spurring many discussions and further initiating collaborative efforts. Drs. Matsuura and Takao have investigated the impact of real-time image gating on spot scanning proton therapy for lung tumors, through simulation. For the purpose of studying the effectiveness of real-time image gated proton beam therapy for lung tumors, a novel respiratory model was developed employing 4DCT to express regular volumetric variations of respiration (Fig. 6, T. Kanehira et al., *Intl. Journal of Rad. Onc. Bio. Phys.* 2017). They have also developed an analytical dose-averaged-linear energy transfer (LETd)-calculation algorithm, which considers off-axis enhancement by secondary protons in proton therapy to evaluate the biological effects of proton beams as part of daily clinical routine. Large improvements of LETd accuracy were seen compared with the previous analytical approach based on the pencil-beam algorithm. This work has been submitted to *Medical Physics*. Dr. Kanehira, a graduate of HU, is currently visiting the Netherlands Institute for Cancer as a post-doctoral researcher investigating image-guided radiotherapy using MRI. Under the supervision of Drs. Matsuura, Makarova, Peng, Umegaki, and Shirato, Jihun Kwon, a student of HU's Graduate School of Medicine evaluated the energy absorption of gold nanoparticles (GNP). This work was presented at the 2017 annual meeting of AAPM. Mr. Kwon is currently on a one-year visit to the Dana-Farber Institute of

Brigham and Women's Hospital and Harvard Medical School. With local experts in the use of GNP, he conducts research investigating them as a vascular disrupting agent, focusing on a method to non-invasively quantify a "signature" of the disruption using ultrasound and MRI. In parallel, he also investigates prediction of treatment outcome using microvascular imaging. The first presentation of the work was presented at the North England chapter of AAPM 2018.

In addition to these original works, researchers of the GSQ Hokkaido University unit have been actively collaborating with other faculty groups in the Graduate School of Medicine to develop quantitative imaging techniques and the radiomics approach of data analysis. The details of these collaborative works and the publications to which they led have been listed above in the Clinical Sciences Sections.

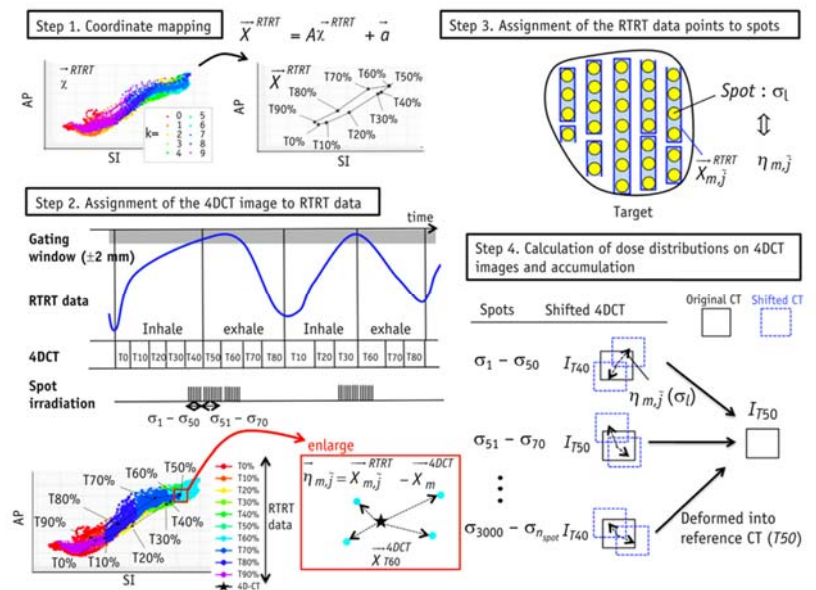


Fig. 6 Study workflow for the 4-dimensional dose calculation in studying impact of real-time image gating on spot scanning proton therapy for lung tumors (Kanehira et al. 2017)

(c) Radiation Biology Section

For the collaborative project in radiation biology, a number of studies with different themes have been conducted to find novel molecular targets to improve the efficacy of radiation therapy with the faculty of HU and the GSQ Stanford University unit. The collaborative team focused on vesicular trafficking of cell-surface receptors, cancer stemness, immune responses, and the extracellular microenvironment. The collaborative studies including experiments have mainly been conducted by postdoctoral fellows, graduate students, and technicians of HU in the lab of the Graduate School of Medicine under supervision of SU members, Faculty members of HU and the GSQ Stanford University unit. To conduct the collaborative research, Senior Assist. Prof. Yasuhito Onodera and Dr. Nam installed a 200 m² laboratory for radiation biology in 2014 (Fig.7). Faculty members of HU and SU have set up the *in vivo* imaging work equipment in the animal facility of the Faculty of Medicine (Fig. 8).



Fig.7 Set-up of the laboratory for biology

Dr. Onodera has been in discussions with members of the GSQ Stanford University unit and fellows about education and collaboration in research. Dr. Onodera has also been working with Drs. Shirato and Nam on a project of mitochondrial dynamics and cancer invasion (Onodera et al., *Nature communications*, 2018, Accepted).

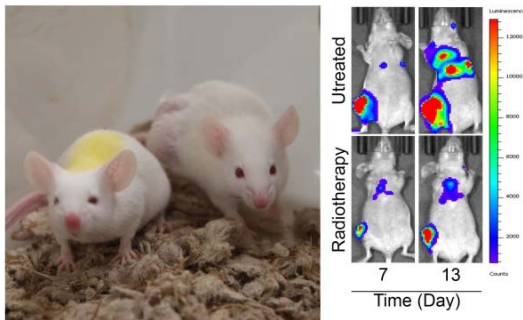


Fig. 8 *In vivo* Imaging

Assist. Prof. Koichi Yasuda visited the Rankin lab at SU for five months in 2015 to carry out collaborative research focusing on enhancing tumor radiosensitivity. For education of undergraduate and graduate students, faculty members of the GSQ have been organizing a monthly journal club with the topics of radiation biology in English. In addition, faculty members at HU have

been teaching graduate HU students of the Graduate School of Medicine and the Graduate School of Biomedical Science and Engineering. They will hold the Hokkaido Summer Institute/GI-CoRE Summer School for Radiation Biology in 2018.

[International Collaborative Research]

- Current progress in meeting initial research goals (As of March 2018)

(a) Clinical Science Section

We have conducted international collaborative research in the Clinical Science Section between HU and SU as follows.

a. International clinical trials

- a-1. Phase II trial of individualized lung tumor stereotactic ablative radiotherapy (iSABR) P.I. Maximilian Diehn, and Billy Loo, M.D., Ph.D. (Fig. 9)

An official agreement was reached, as of September 1, 2015, by and between Hokkaido University and the BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, a body having corporate powers under the laws of the State of California for this International Multi-Site Clinical Trial.

From Hokkaido University, three patients have been successfully registered up to March 2018.

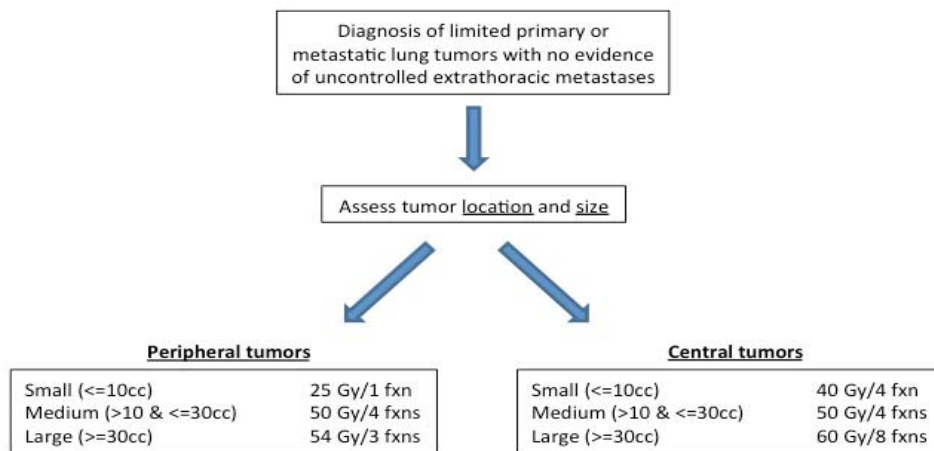


Fig.9 Schema of Phase II trial of individualized lung tumor stereotactic ablative radiotherapy (iSABR).

- a-2. International Randomized Study of Transarterial Chemoembolization (TACE) versus Stereotactic Body Radiotherapy (SBRT) / Stereotactic Ablative Radiotherapy (SABR) for Residual or Recurrent Hepatocellular Carcinomas after Initial TACE. P.I. Daniel Chang, Protocol Number: IRB-35937 (Fig. 10)

From Hokkaido University, one patient has been successfully registered up to March 2018.

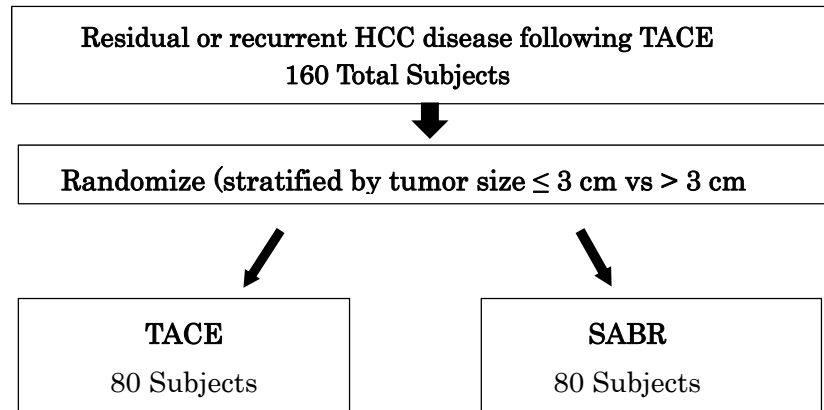


Fig.10 Schema of International Randomized Study of Transarterial Chemoembolization (TACE) versus Stereotactic Body Radiotherapy (SBRT) / Stereotactic Ablative Radiotherapy (SABR) for Residual or Recurrent Hepatocellular Carcinomas after Initial TACE.

b. Radiomics

A biomarker has been developed by Dr. Li of SU in collaboration with Dr. Tha based on radiomics. Dr. Cui, started working as a post-doctoral researcher of the GSQ and currently holds a double appointment between SU and HU, started clinical data analysis with Dr. Li of SU who has also once been hired at the GI-CoRE.

b-1. Glioblastomas

1. Cui Y, Tha KK, Terasaka S, Yamaguchi S, Wang J, Kudo K, Xing L, Shirato H, Li R. Prognostic Imaging Biomarkers in Glioblastoma: Development and Independent Validation on the Basis of Multiregion and Quantitative Analysis of MR Images. *Radiology*. 2016 Feb;278(2):546-53. doi: 10.1148/radiol.2015150358.
2. Cui Y, Ren S, Tha KK, Wu J, Shirato H, Li R. Volume of high-risk intratumoral subregions at multi-parametric MR imaging predicts overall survival and complements molecular analysis of glioblastoma. *Eur Radiol*. 2017 Sep;27(9):3583-3592. doi: 10.1007/s00330-017-4751-x

b-2. Breast cancer

1. Wang J, Kato F, Oyama-Manabe N, Li R, Cui Y, Tha KK, Yamashita H, Kudo K, Shirato H. Identifying Triple-Negative Breast Cancer Using Background Parenchymal Enhancement Heterogeneity on Dynamic Contrast-Enhanced MRI: A Pilot Radiomics Study. *PLoS One*. 2015 Nov 24;10(11):e0143308. doi: 10.1371/journal.pone.0143308.
2. Wang J, Kato F, Yamashita H, Baba M, Cui Y, Li R, Oyama-Manabe N, Shirato H. Automatic Estimation of Volumetric Breast Density Using Artificial Neural Network-Based Calibration of Full-Field Digital Mammography: Feasibility on

Japanese Women With and Without Breast Cancer. *J Digit Imaging*. 2017. doi: 10.1007/s10278-016-9922-9

3. Wu J, Sun X, Wang J, Cui Y, Kato F, Shirato H, Ikeda DM, Li R. Identifying relations between imaging phenotypes and molecular subtypes of breast cancer: Model discovery and external validation. *J Magn Reson Imaging*. 2017 Oct;46(4):1017-1027. doi: 10.1002/jmri.25661.

c. Overview of radiotherapy

Based on the discussion at the GI-CoRE symposium, HU and SU have written a review article about the state-of-art of radiotherapy and the selection of external beam radiotherapies for precise and accurate cancer treatments.

1. Le QT, Shirato H, Giaccia AJ, Koong AC. Emerging Treatment Paradigms in Radiation Oncology. *Clin Cancer Res*. 2015 Aug 1;21(15):3393-401. doi: 10.1158/1078-0432.CCR-14-1191.
2. Shirato H, Le QT, Kobashi K, Prayongrat A, Takao S, Shimizu S, Giaccia A, Xing L, Umegaki K. Selection of external beam radiotherapy approaches for precise and accurate cancer treatment. *J Radiat Res*. 2018 Jan 24. doi: 10.1093/jrr/rrx092

(b) Medical Physics Section

We have conducted international collaborative research in the Medical Physics Section between HU and SU as follows.

- a. Several novel imaging techniques are being investigated, including proton-induced X-ray fluorescence CT, X-ray-induced acoustic imaging, and Multi-energy Cone Beam CT.
 1. Bazalova-Carter M, Ahmad M, Matsuura T, Takao S, Matsuo Y, Fahrig R, Shirato H, Umegaki K, Xing L: "Proton-induced x-ray fluorescence CT imaging.", *Med Phys.*, 2015 Feb;42(2):900-7 (2015)
 2. 3-year Kakenhi Grant-in-Aid for Young Scientists from the JSPS awarded to Dr. Hao Peng toward "Development of a hybrid tomosynthesis and acoustic imaging modality for early detection of breast cancer."
 3. 2-year Kakenhi Grant-in-Aid for Young Scientists from the JSPS awarded to Dr. Jeffrey Wang toward "Development of an acoustic imaging modality for absolute and real-time radiotherapy dosimetry."
- b. Developments concerning characterization of the impact of novel radiation and proton therapy techniques are also underway in parallel, including use of acoustics methods for range verification, devices to decrease duration of irradiation during movement, real-time image gating on spot scanning proton therapy, analytical models of dose-averaged-linear energy transfer, phosphor-coated phantoms, and gold nanoparticles.
 1. Ahmad, M., Xiang, L., Yousefi, S., & Xing, L. (2015). Theoretical detection threshold of the proton-acoustic range verification technique. *Medical Physics*, 42(10), 5735–5744.
 2. Matsuura T, Fujii Y, Takao S, Yamada T, Matsuzaki Y, Miyamoto N, Takayanagi T, Fujitaka S, Shimizu S, Shirato H: "Development and evaluation of a short-range applicator for treating superficial moving tumors with respiratory-gated spot-scanning proton therapy using real-time image guidance.", *Phys Med Biol.*, 61(4):1515-31 (2016)
 3. Kanehira, Matsuura, Takao et al., "Impact of Real-Time-Image gating on Spot Scanning Proton Therapy for Lung Tumors: A Simulation Study," *International Journal of Radiation Oncology Biology Physics* 97.1 (2017): 173-181.

4. Hirayama, Matsuura, Ueda et al., "An Analytical Dose-Averaged LET-Calculation Algorithm Considering the Off-Axis LET Enhancement by Secondary Protons for Spot-Scanning Proton Therapy," *Med. Phys.* submitted (2018)

(c) Radiation Biology Section

International collaborative research in radiation biology has been conducted between HU and SU to find novel molecular targets and radiation sensitizers to improve the efficacy of radiation therapy.

1. RGD-conjugated gold nanoparticles (AuNPs) in radiotherapy decrease the invasive activity of breast cancer cells: The work has been conducted mainly at HU (Drs. Nam, Onodera, and Shirato) by collaboration with SU (Drs. Rankin and Giaccia) and companies (Aisin Seiki Co., Ltd., Aichi, Japan and IMURA America, Inc., Ann Arbor, MI). The study suggests that RGD/P-AuNPs can target integrin-overexpressing cancer cells to improve radiation therapy by suppressing invasive activity in addition to providing sensitization. The findings provide a possible clinical strategy for using AuNPs to treat invasive breast cancer following radiotherapy. Further studies are needed for a detailed understanding of the molecular mechanism. (Fig. 11)

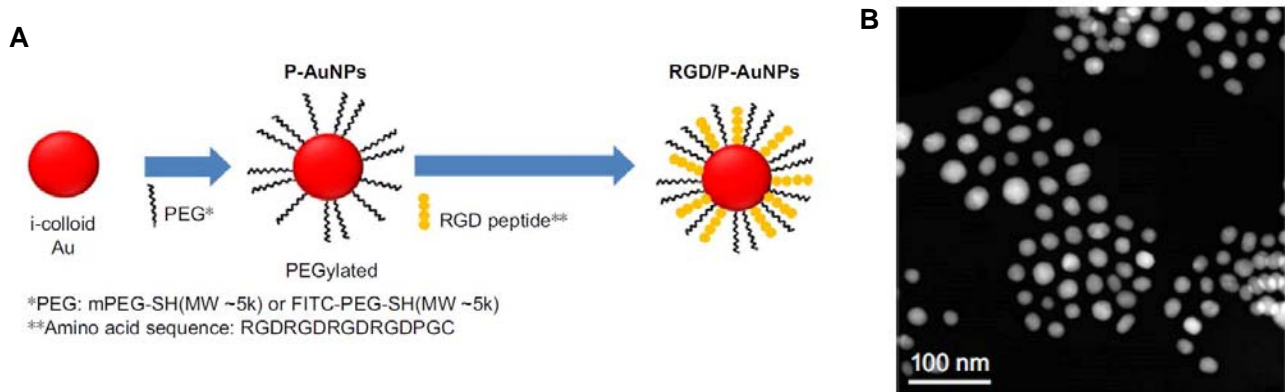


Fig.11 (A)Schematic diagram of RGD/P-AuNPs. (B) Dark-field TEM image of synthesized AuNPs.

- Wu PH, Onodera Y, Ichikawa Y, Rankin EB, Giaccia AJ, Watanabe Y, Qian W, Hashimoto T, Shirato H, Nam JM. Targeting integrins with RGD-conjugated gold nanoparticles in radiotherapy decreases the invasive activity of breast cancer cells. *Int J Nanomedicine*. 2017 Jul 14;12:5069-5085. doi: 10.2147/IJN.S137833.

2. Radiation increases the invasive activity of breast cancer cells by altering the lysosome exocytosis: To find novel molecular targets and understand the mechanism of the activity, the exocytosis pathway in cells has been analyzed by Dr. Wu under supervision of staff at HU and SU, Drs. Shirato, Nam, Onodera, Giaccia, and Le. Dr. Wu, a graduate student at HU, found that radiation enhances lysosome exocytosis in breast cancer cells, an activity that can lead to increases in the invasive activity. The work will focus on providing details of a novel mechanism to understand cancer invasion after radiotherapy and suggest novel approaches to counteract this undesirable effect of radiotherapy.

- Wu PH, Onodera Y, Giaccia AJ, Le QT, Shirato H, Nam JM. Radiation increases invasive activity of breast cancer cells via altering lysosome exocytosis. *ACR Annual Meeting 2018*. Chicago, 2018. 4. 14-18.

HU=Hokkaido University, SU=Stanford University