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NEURO-ONCOLOGY ADVANCES

Abstracts

INVITED LECTURES

SL-1

ACTIVITY ON NATIONWIDE CANCER GENOME SCREENING PROJECT FOR ADVANCED SOLID TUMORS; SCRUM-JAPAN GI-/MONSTAR-SCREEN

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Advances in precision oncology have made genotyping mandatory for most advanced solid tumors to ensure proper therapy selection. However, the innovations remains limited by the realities of patient identification-actionable targets are present in only a small fraction of patients. We initiated a nationwide cancer genome screening project, SCRUM-Japan GI- (from 2015 to 19)/MONSTAR-SCREEN (since 2019) with the purpose of matching patients with interventional IND trials. We revealed requirement for tissue samples hampers recruitment, and genotyping using archival tumor samples provides information only at a single spatial and temporal point and fail to detect chronological tumor evolution and intratumoral heterogeneity, both of which are obstacles for proper therapy selection. We also demonstrated circulating tumor DNA (ctDNA) analysis using next-generation sequencing (NGS)-based methods have the potential of ctDNA analysis for genomic profiling as an alternative for tissue genotyping. Recently, gut microbiome has the promise in predictive value of therapy. Serial analyses with ctDNA and microbiome at pre- and post- cancer therapies are ongoing. Updated results will be presented.

SL-2

BREAST CANCER TREATMENT SYSTEM

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Surgery under general anesthesia for breast cancer was performed for the first time in Japan. Hormone therapy (bilateral ovariectomy, selective estrogen receptor modulator, LHRH analog, aromatase inhibitor, selective estrogen receptor down-regulator) has been developed for more than 120 years. Radiation therapy also has a history of more than 100 years. Anti-cancer chemotherapy has a history of about 50 years. It has been about 20 years since the development of molecular-targeted therapy began, and we have succeeded in developing therapeutic methods targeting HER2, mTOR, CDK4 / 6, PARP, PI3K, etc.in breast cancer, and immunotherapy is currently the biggest topic. Breast cancer is a highly heterogenous cancer, and multidisciplinary treatment and individualized treatment are the central concepts of treatment. Recent trends in multidisciplinary treatment are measures to promote treatment escalation, and de-escalation, 'Do More and Do Less', to maximize treatment benefits and minimize treatment-related toxicity and quality of life reduction. On the other hand, individualization of treatment has made great progress in the last 20years with the generalization of high-standard pathological diagnosis, characterization of tumor subtypes and prediction of prognosis and therapeutic outcomes using multi-gene assay / expression profiles. Recently, it has become possible to test pathogenic variants of breast cancer-related genes such as BRCA1 / 2 in clinical practice, and it has been applied to surgery for patients with primary breast cancer, preventive resection for reducing contralateral breast cancer, and to indicate PARP inhibitor as companion diagnostics for patients with recurrent breast cancer. These current situations and prospects will be described.

SS-1

THERAPEUTIC CHALLENGES FOR GLIOBLASTOMA: TEMOZOLOMIDE AND ITS ISSUES?

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Glioblastoma (GBM), the most malignant form (WHO grade IV) of gliomas, remains incurable despite recent advances in medical technologies and molecular knowledge, with 5-year survival rate being just beyond 10%, thus undoubtedly leaving unmet needs to develop effective therapeutics to improve outcome. Current standard of care for patients with newly diagnosed GBM is maximum safe resection of the enhancing tumor bulk, followed by involved-field radiotherapy with temozolomide (TMZ) given concomitantly and as an adjuvant therapy thereof with or without Tumor-Treating Fields (TTF). The efficacy of TMZ for GBM was proved in 2005 by a randomized phase III trial (EORTC25981) for the first time ever in history, since then, however, any other agents have failed to show benefit to improve survival until now. *O6*-methylguanine-DNA methyltransferase (MGMT), a specific DNA repair enzyme, has been shown to restore the cytotoxic *O6*-methylguanine lesion induced by TMZ to normal, responsible for a major reason of TMZ resistance. Expression of MGMT is tightly regulated by methylation of the promoter region of the *MGMT* gene, where promoter methylation results in suppression of its expression. Accordingly, the promoter methylation of the *MGMT* gene (meth-MGMT) has been consistently associated with a better response to and outcome by TMZ treatment, and furthermore a favorable prognostic factor for patients with newly diagnosed GBM in a number of prospective clinical trials. In this line, efforts have been made to overcome TMZ resistance including intensifying dose schedulings of TMZ, one of which has been currently tested in a multi-institutional prospective phase III trial in Japan (JCOG1308C). TMZ has also been investigated in lower grade gliomas. A major issue in treating lower grade glioma with TMZ is potential development of the hypermutated tumors by virtue of *O6*-methylguanine-induced mutagenesis. The clinical and molecular consideration related to TMZ in glioma treatment will be presented.

SS-2

CURRENT STATUS AND FUTURE PERSPECTIVE OF RADIOMICS IN GLIOMA IMAGING

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Qualitative imaging, primarily focusing on brain tumors' genetic alterations, has gained traction since the introduction of molecular-based diagnosis of gliomas. This trend started with fine-tuning MRS for detecting intracellular 2HG in IDH-mutant astrocytomas and further expanded into a novel research field named "radiomics". Along with the explosive development of machine learning algorithms, radiomics became one of the most competitive research fields in neuro-oncology. However, one should be cautious in interpreting research achievements produced by radiomics as there is no "standard" set in this novel research field. For example, the method used for image feature extraction is different from research to research, and some utilize machine learning for image feature extraction while others do not. Furthermore, the types of images used for input vary among various research. Some restrict data input only for conventional anatomical MRI, while others could include diffusion-weighted or even perfusion-weighted images. Taken together, however, previous reports seem to support the conclusion that IDH mutation status can be predicted with 80 to 90% accuracy for lower-grade gliomas. In contrast, the prediction of MGMT promoter methylation status for glioblastoma is exceptionally challenging. Although we can see sound improvements in radiomics, there is still no clue when the daily clinical practice can incorporate this novel technology. Difficulty in generalizing the acquired prediction model to the external cohort is the major challenge in radiomics. This problem may derive from the fact that radiomics requires normalization of qualitative MR images to semi-quantitative images. Introducing "true" quantitative MR images to radiomics may be a key solution to this inherent problem.

SS-3

TUMOR TREATING FIELDS: FROM THE PETRI DISH TO THE PATIENT

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Tumor Treating Fields (TTFields) are a non-invasive, loco-regional, antineoplastic treatment modality targeting rapidly dividing cancer cells using low intensity, alternating electric fields at cell-type-specific intermediate frequencies (100–500 kHz). TTFields therapy is approved for the treatment of newly-diagnosed and recurrent glioblastoma as well as malignant pleural mesothelioma, following clinical trials demonstrating efficacy and a favorable safety profile. Using novel in vitro and in vivo systems for TTFields application, research activities are being conducted to extend the understanding of the underlying mechanisms of action (MoA) and to assess additional means to improve treatment outcomes. The demonstrated

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