

BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME: YANG, JONATHAN

eRA COMMONS USER NAME (credential, e.g., agency login): YANGJONATHAN

POSITION TITLE: Assistant Member, Assistant Attending Radiation Oncologist, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of North Carolina- Chapel Hill, NC	B.S.	06/2003	Radiologic Science
Yale University School of Medicine, New Haven, CT	M.D.	06/2011	Medicine
Vrije Universiteit Amsterdam, Amsterdam, Netherlands	Ph.D.	09/2016	Medicine
Memorial Sloan Kettering Cancer Center, (MSKCC) New York, NY	Intern	07/2012	Transitional Year
MSKCC, New York, NY	Certificate	04/2015	NIH Research Methodology
MSKCC, New York, NY	Resident	06/2016	Radiation Oncology

A. Personal Statement

Overview: I am a Radiation Oncologist at Memorial Sloan Kettering Cancer Center (MSKCC) where I hold appointments in the Department of Radiation Oncology and the Early Drug Development Service. I lead the effort at MSKCC for the study and treatment of leptomeningeal metastases (LM) using proton therapy. With multidisciplinary collaboration, I have successfully led and completed a phase I study on proton craniospinal irradiation for solid tumor LM (NCT03520504). MSKCC is the leading clinical and research center of solid tumor LM worldwide.

Medical school & residency: After studying Radiologic Science as an undergraduate and working 3 years as a radiation therapist, providing daily radiation therapy to patients with cancer, I decided to pursue a career in medicine. During medical school, I pursued a research fellowship at the Netherlands Cancer Institute, which led to several first-authored publications on the subject of imaged-guided radiation therapy. After medical school, I pursued a Radiation Oncology residency at MSKCC, where I also served as Chief Resident. During this time, I completed my Ph.D. work through Vrije Universiteit Amsterdam, received training in research methodology, and completed a research fellowship at the Lewis Cantley laboratory, which led to development of novel cancer therapy and publications in *Cell Report* and *Cell Chemical Biology*.

Faculty position: In 2016 I began a faculty position at MSKCC as an Assistant Attending and immediately developed a clinical practice caring for patients with metastatic cancer including LM using therapeutic radiation with both x-ray-based photon therapy and proton particle therapy. Given my clinical and academic advancement in the treatment of metastatic cancer, I was appointed Director of Metastatic Disease in the Department of Radiation Oncology at MSKCC in 2017. I have published on our unique service as the senior and corresponding author in *JAMA Oncology*. I also developed a research focus on formulating novel and rational treatments using radiation alone or in combination with first-in-human systemic therapy for patients

with brain tumors and leptomeningeal disease. Using proton therapy, I successfully evaluated the safety of craniospinal irradiation in patients with solid tumor LM, leading to a first and corresponding author publication in *Neuro-Oncology*. Our group also published our experience of cerebrospinal fluid circulating tumor cells as a biomarker for proton craniospinal irradiation for LM in *Neuro-Oncology Advances*, for which I am the senior and corresponding author. This work has also been presented for oral presentation at the annual American Society of Clinical Oncology meeting and was awarded the Merit Award. I have also gained widely recognized clinical expertise in the treatment for solid tumor brain metastases and LM and am contributing review articles to *Frontiers Neurology* and *Current Oncology Report*. I currently treat the largest cohort of adult patients with solid tumor LM with proton therapy in the United States. I am Principal Investigator on five protocols investigating brain metastases and LM.

Clinical trials experience: I have been the Principal Investigator and co-Principal Investigator of 10 clinical trials since joining the MSKCC faculty. These have had successful enrollment, execution, and publications. I led the phase I trial of proton craniospinal irradiation for solid tumor LM; Promising results in disease control, quality of life preservation, and long-term survival have led to the proposed phase II trial. In addition, I am currently leading 2 additional phase I trials of first-in-human systemic therapy in combination with radiation therapy for patients with LM by targeting radiation resistance, such as the phosphatidylinositol-3-kinase (PI3K) pathway, which has led to presentation at American Association of Cancer Research annual meeting. I also served on the MSKCC Institutional Review Board.

Ongoing and recently completed projects that I would like to highlight include:

SK2018-0108 (Yang) 3/14/2018- 3/14/2023
AstraZeneca

D6940C00002: A Phase I, Multicenter Study to Assess the Safety, Tolerability, and Pharmacokinetics of Ascending Doses of AZD1390 in Combination with Radiation Therapy in Patients with Glioblastoma Multiforme and Brain Metastases from Solid Tumors

The goal of this project is to assess the tolerability and pharmacokinetics of AZD1390, a CNS penetrating ATM inhibitor, in combination with radiation therapy for patients with recurrent glioblastoma, newly diagnosed glioblastoma, or brain metastases and/or leptomeningeal disease from solid tumors.

Role: Principal Investigator

GC241385 (Yang) 10/01/2018–11/30/2022
Cycle for Survival

A Prospective Study of Proton Craniospinal Irradiation for Patients with Leptomeningeal Metastases from Solid Tumors with Quantitative and Qualitative Biomarkers Assessment of Cerebrospinal Fluid Circulating Tumor Cells and Tumor-Derived Cell-Free DNA

The goals of this project are to assess the safety and efficacy of proton craniospinal irradiation in patients with leptomeningeal metastasis (LM) from solid tumors; to evaluate whether quantitative assessment of cerebrospinal fluid circulating tumor cells can be used to monitor treatment response after proton CSI; and to investigate changes in the genetic profile of LM before and after proton CSI by sequencing cerebrospinal fluid tumor-derived cell-free DNA through MSK-IMPACT.

Role: Principal Investigator

SK2019-0646 (Yang) 6/10/2019–06/10/2024
Kazia Therapeutics

A Phase I Study with Expansion Cohort of Concurrent GDC-0084 with Radiation Therapy for Patients with Solid Tumor Brain Metastases or Leptomeningeal Metastases Harboring PIK3CA Mutations

The goal of this project is to find the highest dose of GDC-0084 that can be given safely in patients with PIK3CA-mutated cancers that have spread to the brain and/or leptomeningeal metastases and to examine if the combination of GDC-0084 is effective against these cancers.

GC260930 (Yang) 10/01/2020-9/30/2022
Center for Mechanism Based Therapy

Biomarkers for Concurrent GDC-0084 with Radiation Therapy for Patients with Solid Tumor Brain Metastases or Leptomeningeal Metastases Harboring PIK3CA Mutations

The goal of this project is to develop biomarkers of response of GDC-0084 in combination with radiation therapy in patients with brain metastases and leptomeningeal metastases

Role: Principal Investigator

Citations:

- a. Lockney A, Wang D, Pei X, Goldman D, Zhang Z, Lin A, Chan TA, Yamada Y, Beal K, **Yang TJ**. Phosphatidylinositol-3-kinase Mutations are Associated with Increased Local Failure in Brain Metastases Treated with Radiation. *International Journal of Radiation Oncology*Biography*Physics* 2018; 101(4):833-844. PMID: 29976496
- b. Tsai CJ, Gomez DR, **Yang TJ**. Metastatic Disease as a Distinct Discipline in Radiation Oncology. *JAMA Oncology*. 2021;7(1):21–22. PMID: 33057693
- c. **Yang TJ**, Wijetunga NA, Yamada J, Wolden S, Mehallow M, Goldman DA, Zhang Z, Young RJ, Kris MG, Yu HA, Gavrilovic IT, Lin A, Santomasso B, Grommes C, Piotrowski AF, Schaff L, Stone JB, DeAngelis LM, Boire A, Pentsova E. Clinical Trial of Proton Craniospinal Irradiation for Leptomeningeal Metastases. *Neuro Oncol*. 2021; 23(1):134-143. PMID: 32592583
- d. Wijetunga NA, Boire A, Young RJ, Yamada Y, Wolden S, Yu H, Kris M, Seidman A, Betof-Warner A, Diaz M, Reiner A, Malani R, Pentsova E, **Yang JT**. Quantitative Cerebrospinal Fluid Circulating Tumor Cells are a Potential Biomarker of Response for Proton Craniospinal Irradiation for Leptomeningeal Metastasis. *NeuroOncol Adv*. Epub 12/4/2021. PMID: 34993483

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020-Present Co-Director, Multidisciplinary Bone Metastases Team, MSKCC, New York, NY
2018-Present Member, Multidisciplinary Brain Metastases Team, MSKCC, New York, NY
2018-2022 Member, Institutional Review Board, MSKCC, New York
2017-Present Director, Metastatic Disease, Department of Radiation Oncology, MSKCC, New York, NY
2017-Present Radiation Oncologist, New York Proton Center, New York, NY
2017-Present Assistant Attending, Early Drug Development Service, Department of Medicine, MSKCC, New York, NY
2017-Present Member, Society of Palliative Radiation Oncology
2016-Present Assistant Member, MSKCC, New York, NY
2016-Present Assistant Attending Radiation Oncologist, MSKCC, New York, NY
2016-Present Member, Society for Neuro-Oncology
2015-Present Member, Radiologic Society of North America
2015-2016 Chief Resident, Department of Radiation Oncology, MSKCC, New York, NY
2014-2016 Research Fellow, Lew Cantley Laboratory, Weill Cornell Medical College, New York, NY
2012-Present Member, American Society of Clinical Oncology
2012-Present Member, American Society for Therapeutic Radiation Oncology
2010-Present Member, American Association for Cancer Research
2008-2009 Research Fellow, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Honors

2021 American Society of Clinical Oncology 2021 Annual Meeting Merit Award
2020 MSKCC Center for Mechanism Based Therapy Award
2018 Cycle for Survival Equinox Innovation Award in Rare Cancer
2015 National Comprehensive Cancer Network Fellows Recognition Program
2014 Conquer Cancer Foundation of the American Society of Clinical Oncology Merit Award
2009 Yale University School of Medicine Farr Scholar Award
2008 James G. Hirsh, M.D. Endowed Medical Student Fellowship
2007 NIH CTSA T32 Research Fellowship
2007 Yale Cancer Center Etta S. Chidsey Award in Cancer Research

C. Contribution to Science

1. **Evaluation of treatment outcomes and toxicities after radiation therapy for brain metastases and leptomeningeal metastases (LM):** Radiation therapy is essential in the management of brain metastases and LM. Nevertheless, prognostic factors of treatment outcome have not been fully delineated. I have determined new therapeutic approaches and identified unique patient and tumor characteristics that correlate with disease control and survival outcomes in patients who received radiation therapy for brain metastases and LM, allowing clinicians to make evidence-based recommendations for individual patients.
 - a. **Yang TJ**, Oh JH, Folkert M, Gupta G, Shi W, Zhang Z, Morikawa A, Seidman A, Brennan C, Yamada Y, Chan TA, Beal K. Outcomes and Prognostic Factors in Women with 1 to 3 Breast Cancer Brain Metastases Treated with Definitive Stereotactic Radiosurgery. *Int J Radiat Oncol Biol Phys*. 2014;90(3):518–525. PMID: 24736317
 - b. Brennan C*, **Yang TJ***, Hilden P, Zhang Z, Chan K, Yamada Y, Chan TA, Lymberis SC, Narayana A, Tabar V, Gutin PH, Ballangrud A, Lis E, Beal K. A Phase 2 Trial of Stereotactic Radiosurgery Boost After Surgical Resection for Brain Metastases. ***Co-first Authors.** *Int J Radiat Oncol Biol Phys*. 2014;88(1):130–136. PMID: 24736310
 - c. Casey DL, Pitter KL, Imber BS, Chan TA, Beal K, Yamada Y, Feldman DR, **Yang TJ**. High-dose Radiation Therapy is Needed for Intracranial Control and Long-term Survival in Patients with Non-seminomatous Germ Cell Tumor Brain Metastases. *J Neurooncol*. 2019;142(3):523–528. PMID: 3143359
 - d. **Yang TJ**, Wijetunga NA, Yamada J, Wolden S, Mehallow M, Goldman DA, Zhang Z, Young RJ, Kris MG, Yu HA, Gavriloic IT, Lin A, Santomaso B, Grommes C, Piotrowski AF, Schaff L, Stone JB, DeAngelis LM, Boire A, Pentsova E. Clinical Trial of Proton Craniospinal Irradiation for Leptomeningeal Metastases. *Neuro Oncol*. 2021; 23(1):134-143. PMID: 32592583
2. **Evaluation of survival outcomes in patients with lung cancer brain metastases and LM:** Patients with lung cancer who develop brain metastases tend to have poor survival. However, in the era of molecular classifications, patients with epidermal growth factor receptor (EGFR) mutated or anaplastic lymphoma kinase (ALK) fusion oncogene positive lung cancers have prolonged survival due to targeted therapies for these genetic mutations. The impact of EGFR and ALK mutations and the use of targeted inhibitors in patients with lung cancer with brain metastases is not well understood. Through multi-institutional collaborations, I was able to examine survival outcomes in this population.
 - a. Sperduto PW, **Yang TJ**, Beal K, Pan H, Brown PD, Bangdiwala A, Shanley R, Yeh N, Gaspar LE, Braunstein S, Sneed P, Boyle J, Kirkpatrick JP, Mak K, Shih HA, Engleman A, Roberge D, Arvold ND, Alexander B, Awad MM, Contessa J, Chiang V, Hardie J, Ma D, Lou M, Sperduto W, Mehta M. The Effect of Gene Alterations and Tyrosine Kinase Inhibition on Survival and Cause of Death in Patients with Adenocarcinoma of the Lung and Brain Metastases. *Int J Radiat Oncol Biol Phys*. 2016;96(2):406–413. PMID: 26575932
 - b. Sperduto PW, **Yang TJ**, Beal K, Pan H, Brown PD, Bangdiwala A, Shanley R, Yeh N, Gaspar LE, Braunstein S, Sneed P, Boyle J, Kirkpatrick JP, Mak K, Shih HA, Engleman A, Roberge D, Arvold ND, Alexander B, Awad MM, Contessa J, Chiang V, Hardie J, Ma D, Lou M, Sperduto W, Mehta M. Improved Survival and Prognostic Ability in Lung Cancer Patients with Brain Metastases: An Update of the Graded Prognostic Assessment for Lung Cancer using Molecular Markers. *JAMA Oncol*. 2017;3(6):827–831. PMID: 2824323
 - c. Magnuson W, Lester-Coll NH, Wu AJ, **Yang TJ**, Lockney NA, Beal K, Amini A, Patil T, Kavanagh BD, Camidge DR, Braunstein SE, Boreta LC, Balaubramanian S, Ahluwalia MS, Rana NG, Attia A, Gettinger SN, Contessa JN, Yu JB, Chiang VL. Management of Brain Metastases in TKI-naïve EGFR – mutant NSCLC: A Multi-Institutional Analysis. *J Clin Oncol*. 2017;35(10):1070–1077. PMID: 28113019
 - d. Sener U, Matin N, Yu H, Lin A, **Yang TJ**, Malani R. Radiographic Appearance of Leptomeningeal Disease in Patients with EGFR-mutated Non-Small Cell Lung Carcinoma Treated with Tyrosine Kinase Inhibitors: a Case Series. *CNS Oncol*. 2019;8(4):CNS42. PMID: 312846
3. **Determination of genetic biomarkers for radiation treatment response:** While tumors may respond to radiation therapy differently, little is known of the genetic drivers of radiation treatment response in patients.

Knowing the genetic alterations that predict the effectiveness of radiation therapy is valuable as it allows us to personalize radiation treatments for patients. As an example, I have found that tumors harboring phosphatidylinositol-3-kinase (PI3K) mutations are innately more resistant to radiation therapy. With this information, I am in the process of designing a clinical study of combination radiation therapy with PI3K inhibitor to improve disease control in patients harboring PI3K mutations. In addition, I have worked with the Cantley laboratory in developing a novel PI3K pathway target as potential cancer therapy.

- a. Lockney A, **Yang TJ**, Barron D, Gelb E, Gelblum D, Yorke E, Shi W, Zhang Z, Rimner A, Wu AJ. PIK3CA Mutation is Associated with Increased Local Failure in Lung Stereotactic Body Radiation Therapy. *Clin Transl Radiat Oncol*. 2017;7:91–93. PMID: PMC5830173
- b. Lockney A, Wang D, Pei X, Goldman D, Zhang Z, Lin A, Chan TA, Yamada Y, Beal K, **Yang TJ**. Phosphatidylinositol-3-kinase Mutations are Associated with Increased Local Failure in Brain Metastases Treated with Radiation. *Int J Radiat Oncol Biol Phys*. 2018;101(4):833–844. PMID: 29976496
- c. Wang DG, Paddock MN, Lundquist MR, Sun JY, Mashadova O, Amadiume S, Bumpus TW, Hodakoski C, Hopkins BD, Fine M, Hill A, **Yang TJ**, Baskin JM, Dow LE, Cantley LC. PIP4Ks Suppress Insulin Signaling Through a Catalytic-Independent Mechanism. *Cell Reports* 2019; 27(7):1991-2001. PMID: PMC6619495
- d. Sivakumaren SC, Shim H, Zhang T, Ferguson FL, Lundquist MR, Browne CM, Seo HS, Paddoc MN, Manz TD, Jiang b, Hao MF, Krishnan P, Wang DG, **Yang TJ**, Kwiatkowski NP, Ficarro SB, Cunningham JM, Marto JA, Dhe-Paganon S, Cantley LC, Gray NS. Targeting the PI5P4K Lipid Kinase Family in Cancer Using Novel Covalent Inhibitors. *Cell Chemical Biol*. 2020;27(5):525–537.e6. PMID: PMC7286548

4. **Determination of radiographic biomarkers for radiation treatment response:** In addition to genomic biomarkers of response, I also have dedicated efforts in developing reliable radiographic biomarker for predicting treatment response and disease status monitoring after radiation. Traditional radiographic determination of treatment response is particularly difficult after radiation therapy given radiation-induced changes. I have collaborated with Radiology investigators to develop more robust assessments of treatment response after radiation therapy for brain tumors.

- a. Hatzoglou V*, **Yang TJ***, Omuro A, Gavrilovic I, Ulaner G, Rubel J, Schneider T, Woo K, Zhang Z, Beal, K, Young R. A Prospective Trial of Dynamic Contrast Enhanced (DCE) MRI Perfusion and Flourine-18 FDG PET-CT in Differentiating Brain Tumor Progression From Radiation Injury After Cranial Irradiation. *Neuro-Oncology* 18 (6): 873-80 (2016). ***Co-first Authors**. PMID: PMC4864262
- b. Bhatia A, Birger M, Veeraraghavan H, Um H, Tixier F, McKenney AS, Cugliari M, Caviasco A, Bialczak A, Malani R, Flynn J, Zhang Z, **Yang TJ**, Santomaso BD, Shoushtari AN, Young RJ. MRI Radiomic Features are Associated with Survival in Melanoma Brain Metastases Treated with Immune Checkpoint Inhibitors. *Neuro Oncology* 21(12): 1578-1586 (2019). PMID: PMC7145582
- c. Miloushev V, Granlund K, Boltyanskiy R, Lyashchenki S, DeAngelis L, Mellinghoff I, **Yang TJ**, Holodny A, Sosa R, Guo Y, Chen A, Tropp J, Fraser R, Keshari K. Metabolic Imaging of the Human Brain with Hyperpolarized 13C Pyruvate Demonstrates 13C Lactate Production in Brain Tumor Patients. *Cancer Research* 78(14):3755-3760 (2018). PMID: PMC Metabolic Imaging of the Human Brain with Hyperpolarized 13C Pyruvate Demonstrates 13C Lactate Production in Brain Tumor Patients.6050093
- d. Imber BS, Lin AL, Zhang Z, Murthy KNK, Deipolyi AR, Beal K, Cohen MA, DeAngelis LM, Geer EB, Tabar V, **Yang TJ***, Young RJ*. Comparison of Radiographic Approaches to Assess Treatment Response in Pituitary Adenomas: is Using RECIST or RANO good enough? *Journal of the Endocrine Society* 3(9):1693-1706 (2019). ***Co-senior Authors** PMID: PMC6735764\

