BIOGRAPHICAL SKETCH

NOTE: Follow the format and instructions provided by the NIH.

NAME: Soulen, Michael C.

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

POSITION TITLE: Professor of Radiology

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
Yale University, New Haven, CT	BS	05/1979	Biology
University of Pennsylvania, Philadelphia, PA	MD	05/1984	Medicine
Johns Hopkins Hospital, Baltimore, MD	Residency	06/1989	Radiology
Thomas Jefferson University Hospital	Clinical & Research Fellowships	06/1991	Interventional Radiology

A. Personal Statement

My major clinical and research focus for the past 30 years has been image-guided cancer therapy (interventional oncology), with a specific focus on embolotherapy and ablative therapy of solid tumors in the liver and kidney. Animal research includes swine, rabbit, and rat models for liver-directed therapies, investigating novel embolic agents, novel ablation devices, and ultrasound-mediated drug delivery using novel drug-loaded microbubble contrast agents. Clinic trials focus on embolotherapies for primary liver cancers, liver metastases from colorectal and neuroendocrine tumors, and renal cell carcinomas. Current clinical investigations focus on synergy between locoregional and systemic therapies, including 1) pharmacologic modulation of the metabolic stress response under conditions of embolic ischemia; 2) integration of radiation, drugs, and embolization to enhance oncologic outcomes; 3) serial biopsy for tumor cell culture, rapid drug screening, and testing in PDX mice, with the goal of personalized precision medicine; and 4) the first international randomized trial comparing embolotherapy techniques for neuroendocrine tumor liver metastases.

B. Positions and Honors

Positions and Employment

2004 - present Professor of Radiology and Surgery, University of Pennsylvania School of Medicine
1997-2004 Associate Professor of Radiology and Surgery, University of Pennsylvania School of Medicine
1991-1996 Assistant Professor of Radiology and Surgery, University of Pennsylvania School of Medicine

Certification & Licensure

Board Certified, Vascular & interventional Radiology
Pennsylvania Medical License MD-044138-E

Honors

Alpha Omega Alpha Medical Honor Society
Fellow, Society of Interventional Radiology 1997
Fellow, Cardiovascular & Interventional Radiology Society of Europe 2002
26th Charles T. Dotter Lecture, Society of Interventional Radiology, 2010
4th Sid Wallace Memorial Lecture, MD Anderson Cancer Center, Houston TX, December 2017
Gold Medal, Society of Interventional Radiology, 2020
Excellence in Research Teaching, University of Pennsylvania Department of Radiology, 2020.

C. Contributions to Science

1) Neuroendocrine Tumors

Neuroendocrine tumors are the 2nd-most common gastrointestinal malignancy (after colorectal cancer), with a prevalence greater than most other GI cancers combined. Ninety percent of these patients develop liver metastases, which is the foremost determinant of survival. Embolization is the mainstay of therapy for NET liver metastases. NET patients make up most of my clinical practice. Since survival in this disease measures years to decades, the integration and sequencing of the multiple surgical, radiation, medical, and interventional oncologic therapies requires expert multidisciplinary care to achieve optimal long-term outcomes. I work with the North American Neuroendocrine Tumor Society, the Commonwealth Neuroendocrine Tumor Society, and the Society of Nuclear Medicine to develop guidelines for imaging and treatment of NETs. In terms of clinical trials, I have evaluated integration of peptide receptor radiotherapy with other standard of care treatments, identifying patients at increased risk from this novel therapy. I completed a feasibility and safety trial of integrated capecitabine-temozolomide chemotherapy with Y90 radioembolization for intermediate grade NETS, demonstrating improved (synergistic) oncologic outcomes with only additive toxicity, and am now PI of a multicenter phase 2 trial. I am the global PI for the first international multicenter randomized trial of bland vs. chemoembolization, with outcome measures for oncologic benefit, toxicities, and patient-reported outcomes.

a. **Soulen MC**, van Houten D, Teitelbaum UR, Damjanov N, Cengel KA, Metz DC. Safety and Feasibility of Integrating Yttrium-90 Radioembolization With Capecitabine-Temozolomide for Grade 2 Liver-Dominant Metastatic Neuroendocrine Tumors Pancreas 2018 Sep;47(8):980-984.
b. Chen JX, Wileyto EP, **Soulen MC**. Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver (RETNET): study protocol for a randomized controlled trial. Trials 2018;19:390.
c. Chen JX, Rose S, White SB, El-Haddad G, Fidelman N, Yarmohammadi H, Hwang W, Sze DY, Kothary N, Stashek K, Wileyto EP, Salem R, Metz DC, **Soulen MC**. Embolotherapy for Neuroendocrine Tumor Liver Metastases: Prognostic Factors for Hepatic Progression-Free Survival and Overall Survival. Cardiovasc Intervent Radiol. 2017 Jan;40(1):69-80.
d. Kipnis ST, Hung M, Kumar S, Heckert JM, Lee H, Bennett B, **Soulen MC**, Pryma DA, Mankoff DA, Metz DC, Eads JR, Katona BW**.** Laboratory, Clinical, and Survival Outcomes Associated With Peptide Receptor Radionuclide Therapy in Patients With Gastroenteropancreatic Neuroendocrine Tumors. JAMA Netw Open 2021;4(3):e212274.

2) Hepatocellular Carcinoma

One of the most common lethal malignancies worldwide, and a major component of Interventional Oncology practice, HCC is treated with ablative and embolotherapies at early, intermediate, and advanced stages. I have collaborated with other international experts to codify optimal treatment techniques and expectations for safety and efficacy. Sophisticated imaging and serial biopsy in our laboratory has shown that residual viable tumor is frequently present despite apparent complete response on conventional imaging. We have developed an autochthonous rat model of induced HCC amenable to survival percutaneous embolization in order to evaluate tumor metabolism and resistance mechanisms to ischemia-mediated cell death, and identified three protective mechanisms: autophagy, unfolded protein response, and HIF activation. Current animal and Phase 1-2 clinical trials are evaluating pharmacologic adjuncts (e.g., hydroxychloroquine to suppress autophagy) targeted to these escape pathways and combination of SBRT with TACE prior to transplantation. HCC patients treated with TACE undergo serial biopsies for genomic, metabolomic, and proteomic analysis to evaluate characteristics of baseline and survival cells post-TACE, then screening with CRISPR and rapid-drug assay to identify personalized targets which can be tested in PDX mice created from cultures of HCC cells from each patient.

a. Gade TPF, Tucker E, Nakazawa MS, Hunt SJ, Wong W, Krock B, Weber CN, Nadolski GJ, Clark TWI, **Soulen MC**, Furth EE, Winkler JD, Amaravadi RK, Simon MC. Ischemia Induces Quiescence and Autophagy Dependence in Hepatocellular Carcinoma. Radiology. 2017 Jun;283(3):702-710.
b. Kiefer RM, Hunt SJ, Pulido S, Pickup S, Furth EE, **Soulen MC**, Nadolski GJ, Gade TP. Translational Rat Model of Diethylnitrosamine-Induced Hepatocellular Carcinoma and Transarterial Embolization.J Vasc Interv Radiol. 2017 Jul;28(7):1043-1050

c. Tischfield DJ, Ackerman D, Noji M, Chen JX, Johnson O, Perkons NR, Nadolski GJ, Hunt SJ, **Soulen MC**, Furth EE, Gade TP: Establishment of hepatocellular carcinoma patient-derived xenografts from image-guided percutaneous biopsies. Scientific Reports 9(1): 10546, Jul 2019.

d. Lencioni R, de Baere T, **Soulen MC**, Rilling WS, Geschwind JF. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: A systematic review of efficacy and safety data.Hepatology. 2016 Jul;64(1):106-16.

3) Renal Cell Carcinoma

Small renal masses are detected with increasing frequency in the aging population and present multiple clinical conundrums. A sizeable minority are benign, yet percutaneous biopsy is non-diagnostic in 20% and in error in 10%. For malignant small masses (Stage T1a), cancer-specific survival is close to 100% since most progress slowly if ever, rarely metastasize, and death from other causes is the rule. Hence clinical challenges include accurate diagnosis, triage between surveillance and active intervention, and assessment of effectiveness of ablation. Past work includes identifying imaging criteria for adequate ablation and optimal surveillance strategies following treatment. Current efforts include develop of novel deep learning tools for histologic characterization and prediction of tumor behavior, and Phase 1 trials of ablation and embolization as immunostimulants.

a. Chen JX, Maass D, Guzzo TJ, Bruce Malkowicz S, Wein AJ, **Soulen MC**, Clark TWI, Nadolski GJ, William Stavropoulos S. Tumor Growth Kinetics and Oncologic Outcomes of Patients Undergoing Active Surveillance for Residual Renal Tumor following Percutaneous Thermal Ablation.J Vasc Interv Radiol. 2016 Sep;27(9):1397-1406.

b. Ge BH, Guzzo TJ, Nadolski GJ, **Soulen MC**, Clark TW, Malkowicz SB, Wein AJ, Hunt SJ, Stavropoulos SW. Percutaneous Renal Cryoablation: Short-Axis Ice-Ball Margin as a Predictor of Outcome.J Vasc Interv Radiol. 2016 Mar;27(3):403-9

c. Choi JW, Hu R, Zhao Y, Purkayastha S, Wu J, McGirr AJ, Stavropoulos SW, Silva AC, **Soulen MC**, Palmer MB, Zhang PJL, Zhu C, Ahn SH, Bai HX. Preoperative prediction of the stage, size, grade, and necrosis score in clear cell renal cell carcinoma using MRI-based radiomics. Abdom Radiol 2021 Jan 2.doi: 10.1007/s00261-020-02876-x

d. Xi IL, Zhao Y, Wang R, Chang M, Purkayastha S, Chang K, Huang RY, Silva AC, Vallières M, Habibollahi P, Fan Y, Zou B, Gade TP, Zhang PJ, **Soulen MC**, Zhang Z, Bai HX, Stavropoulos SW. Deep Learning to Distinguish Benign from Malignant Renal Lesions Based on Routine MR Imaging. Cancer Res 2020 Apr 15;26(8):1944-1952.

Complete List of Published Work in Google Scholar:
https://scholar.google.com/citations?user=2d6Op1oAAAAJ&hl=en

4) Clinical Trials

Interventional Oncology (IO) is fast becoming the fourth pillar of cancer care, alongside Medical, Surgical, and Radiation Oncology. Local injection, ablation, and intra-arterial therapies have been used to treat cancer for over 50 years. Despite this, the evidence basis for integration of Interventional Oncology into multidisciplinary care is lagging. The dearth of guidelines for image-guided therapies is a barrier to access to care and a critical unmet need in the cancer community.

As Director of Interventional Oncology at the Abramson Cancer Center and founder and past President of the Society of Interventional Oncology, I have devoted the past 30 years to the science of IO and its translation into the clinic. Through innovative multidisciplinary collaborations, considerable progress has been made in the preclinical and translational science underlying locoregional therapies and advancing clinical trials in interventional oncology. Research has elucidated the mechanisms of cancer cell death from percutaneous therapies and illuminated synergistic interactions with systemic agents and with the immune system. This understanding has guided development of an exciting and diverse array of novel clinical trials. Areas ripe for investigation include potentiation of ischemia-based therapies by targeting HIF activation, autophagy, the unfolded protein response, and free radical generation; potentiation of selective internal radiation via co-administration of radiosensitizers; potentiation of thermal-based therapies to achieve curative ablation margins; use of ablation and embolization as immunostimulants to potentiate immune

checkpoint inhibition; delivery of CAR-T cells into solid tumors; direct injection and intralymphatic administration of vaccine-based agents; and novel nanoplatforms for delivery of therapeutic agents.

Efforts to foster IO clinical trials include 1) chairing the Radiological Society of North America Clinical Trials Methodology Workshop, which trains 25 junior faculty annually in an intensive 6-day bootcamp; 2) chairing the ECOG-ACRIN Interventional Oncology Working Group, which has generated over a dozen trial concepts integrating image-guided and systemic therapies across the spectrum of solid tumors; and 3) chairing the Penn IR Research Committee, which has a strong portfolio of collaborative trials with medical, radiation and surgical oncology and with hepatology.

Representative current investigator-initiated trials include:

1. Randomized Embolization Trial for NET Metastases to the Liver (RETNET). (Soulen PI). International multicenter randomized trial comparing bland to chemoembolization. Safety readouts from this trial have already led to changes in NCCN guidelines.
2. Multicenter Phase 2 Study Of Capecitabine-Temozolomide(Captem) With Yttrium-90 Radioembolization In The Treatment Of Patients With Unresectable Metastatic Grade 2 NET. (Soulen PI). A pilot study at Penn led to this current multicenter phase 2 trial.
3. Multicenter Randomized Trial of Transarterial Chemoembolization with or without SBRT for HCC Patients Awaiting Liver Transplantation. (Soulen PI). Multi-center trial of the impact of adding SBRT to TACE on imaging and pathologic response rate.
4. Phase 1 study of ipilumumab/nivolumab plus immunostimulatory embolization for Stage 4 renal cell carcinoma. (Soulen PI). Phase 1 study examining immune synergy via serial blood and tissue sampling in patients on immune checkpoint therapy getting embolization.
5. Multicenter phase 1 study of ipilumumab/nivolumab plus immunostimulatory cryoablation for Stage 4 renal cell carcinoma. (author/steering committee). This trial investigates the combination of cryoablation and immune checkpoint inhibition in metastatic RCC.
6. Phase I Study of Hepatic Chemoembolization with Irinotecan-Loaded Drug-Eluting Microspheres Plus Axitinib and Hydroxychloroquine for Liver-Dominant Metastatic Adenocarcinoma of the Colon and Rectum. (Soulen PI). First human trial combining embolization with dual blockade of both autophagy and VEGF pathways.
7. Ablation with Confirmation of Colorectal Liver Metastases (ACCLAIM) Prospective Trial for Microwave Ablation as a Local Cure. (author/steering committee). This international multicenter trial employs novel software to confirm an adequate margin for complete pathologic response.
8. Interventional Oncology Clinical Outcomes Registry (IO-CORE) (chairman/author/steering)
   While controlled clinical trials offer the highest level of evidence, they are often not feasible in interventional oncology. Limited case volume, disease heterogeneity, competing treatment strategies, and the sequencing of therapies are all obstacles to controlled trials of any specific intervention. The IO-CORE provides real world data to determine current outcomes and identify future research opportunities. Data elements address multiple domains including imaging, AI, oncologic outcomes, PRO’s and financial toxicity.