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Leonidas C. Platanias

SECTION I: RADIATION ONCOLOGY

Opportunities and Advances in the use of Proton Radiotherapy for Management of Central Nervous System and Base of Skull Tumors, *1*

Bansi Savla, Gregory Alexander, Ariel E. Pollock, Justin Cohen, and Mark V. Mishra

Advances in managing central nervous system (CNS) malignancies have led to improved survival outcomes and therefore an increased need to reduce the risk of treatment-related toxicities. Precise dose delivery through advanced radiation techniques can spare radiation dose to critical structures while maintaining adequate target coverage. This review discusses potential clinical applications of proton beam therapy for treatment of tumors of the central nervous system and reviews the emerging clinical data supporting use of proton beam therapy and ongoing clinical trial efforts.

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Breast Cancer-Related Lymphedema: Causes, Detection, Prevention, and Treatment, *13*

Jonathan B. Strauss, Sumanas W. Jordan, George E. Naoum, Megan E. Fracol, Jennifer Bai, and Ann Marie Flores

Lymphatic fluid is composed of water, protein, and other debris emitted from capillary beds into the interstitium. Under normal conditions lymphatic fluid is absorbed by lymphatic capillaries and pumped towards the thoracic duct, ultimately re-entering the venous circulation. Damage to lymphatic structures leads to accumulation of protein-rich lymphatic fluid in the interstitium leading to edema, inflammation, and ultimately the irreversible changes of fibrosis and adipose deposition. The major risk factors for the development of breast cancer-related lymphedema are: extent of axillary surgery, increasing BMI, and receipt of regional nodal irradiation. Exclusion of the dissected axilla from the radiotherapy field during regional nodal irradiation appears to be associated with a lower risk of lymphedema.

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Updates in Adjuvant Therapy for High-Risk and Locally Advanced Endometrial Cancer, 25

Anjali L. Saripalli, Anna C. Griffin, Dylan Ross, John C. Roeske, William Small Jr., and Matthew M. Harkenrider

Paradigms of adjuvant therapy for endometrial cancer continue to evolve, and there is no standard of care adjuvant therapy for locally advanced endometrial cancer patients. Several recently published clinical trials attempted to provide clarity on adjuvant therapy recommendations. The role of adjuvant radiation therapy may need to be re-evaluated as treatment delivery techniques have improved and evolved. The role of adjuvant therapy has and will continue to evolve as molecular-based treatment recommendations continue to be investigated. The aim of this manuscript is to review the evolution of recently published data to inform patient-centered decision making in the adjuvant treatment of high-risk and locally-advanced endometrial cancer.

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Updates on Neoadjuvant Therapy for Resectable and Borderline Resectable Pancreatic Adenocarcinoma, 35

Gregory C. Wilson, Sameer H. Patel, and Syed A. Ahmad

Mortality after the diagnosis of pancreatic ductal adenocarcinoma remains high for all patients. The role of multimodal therapy, including surgical resection and systemic chemotherapy, has been well established. Neoadjuvant treatment strategies continue to be used in resectable and borderline resectable PDAC. Results from ongoing or recently completed trials will continue to provide valuable insight into the management of patients with resectable and borderline resectable PDAC. Advances in the outcomes for this difficult disease and therefore the focus of futures studies should include a better understanding of tumor biology and markers, novel treatment agents, and combination treatment strategies.

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Neoadjuvant Chemotherapy for Nonmetastatic Breast Cancer: How Response Impacts Locoregional and Adjuvant Systemic Therapy Decision Making, 47

Giacomo Montagna, Emanuela Ferraro, and
Melissa L. Pilewskie

Neoadjuvant chemotherapy is now considered standard of care for most of the patients with clinically node-positive disease, and for a large proportion of triple-negative breast cancer and HER2-positive tumors. Here we reviewed the benefit of neoadjuvant chemotherapy on surgical de-escalation, the prognostic role of pathologic complete response, new therapeutic strategies across subtypes, and ongoing studies assessing locoregional treatment de-escalation according to treatment response. Thanks to the integration of new biomarkers, new ways to detect minimal residual disease after neoadjuvant chemotherapy, and new targeted therapies, the landscape of neoadjuvant therapy is evolving rapidly, and our ability to personalize breast cancer treatment is improving.

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Contemporary Multimodal Management of Primary Retroperitoneal Sarcomas, 63

Rachel Hae-Soo Joung and Jeffrey D. Wayne

Retroperitoneal sarcoma is composed of a heterogeneous group of mesenchymal neoplasms that has poor prognosis. Although surgery remains the mainstay of treatment, achieving complete surgical resection with adequate margins is challenging, given anatomic constraints. Evidence on the use of adjunctive treatment modalities for retroperitoneal sarcoma is sparse, with the treatment rationale often based on data extrapolated from other soft tissue sarcomas. Recent studies demonstrate some benefits of neoadjuvant radiotherapy for histologic subtypes with high locoregional recurrence rates. Ongoing studies are evaluating various novel adjunctive treatment modalities.

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NTRK Inhibitors in Adult Patients with Solid Tumors, 71

Meghan DioGuardi, Rachel Evans, and
Christos Fountzilas

TRK receptors are primarily involved in neuronal growth and survival. NTRK gene fusions involving the receptor and a 5' partner are oncogenic drivers in multiple cancer types. They are most often found as recurrent low-frequency events, although they can be the primary mutation in select cancer types. Larotrectinib and entrectinib are first-generation NTRK inhibitors and demonstrate potent antitumor efficacy across fusion gene type and cancer type.

Development of second-generation inhibitors to assess on-target resistance mechanisms is ongoing. Off-target resistance causing alterations downstream from NTRK receptors will likely require a combinatorial approach.

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Vidit Kapoor and Sukeshi Patel Arora
 The incidence of cancer among the elderly is increasing worldwide. Older adults with cancer are at an increased risk of adverse events and disease- or treatment-related complications. Incorporation of geriatric assessments as part of the routine care of such patients can help predict and minimize these adverse events and lead to improved outcomes. A comprehensive geriatric assessment includes an evaluation of a patient’s functional status, comorbidities, medications, cognitive and psychological status, nutritional status and social support systems. With consistent implementation of geriatric assessments into practice and incorporation of principles of geriatrics into oncology, every oncologist can optimize the care for older adults with cancer.

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McKenzie Foxall and Rebecca Arend

Gynecologic malignancies are a heterogenous group of tumors driven by a wide variety of molecular alterations. Molecular profiling has become increasingly useful in the development of novel biomarkers, screening tools, and targeted therapeutic agents. The purpose of this article is to provide an overview of the current usage of personalized medicine in the field of gynecologic oncology.

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Emma C. Rossi

The surgical staging of endometrial cancer has changed in recent years to include sentinel lymph node (SLN) biopsy as a tool to replace regional lymphadenectomy. This has afforded surgeons the ability to preserve surgical staging information, valuable for adjuvant therapy prescription, while minimizing associated morbidities, such as lymphedema. Although SLN biopsy has been established as being highly accurate in detecting metastatic disease, including in patients with high-grade cancers, future studies should focus on establishing the value of this technique with respect to patient survival and its role in concert with

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Allison Grubbs, Emma L. Barber, and Dario R. Roque

Disparities in the treatment, incidence and outcomes of women with gynecologic malignancies are multifactorial. A significant amount of the literature on health disparities in gynecologic cancer care has focused on descriptively identifying disparities with a particular focus on the dichotomous care received by black and white patients. Although there are actionable improvements that can be made to improve research within this field as it is currently conceived, it is critical to broaden the academic approach to these difficult issues in order to develop frameworks in which both the medical factors and social and environmental factors are treated as an integrated system.

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Circulating Tumor Cells and Cell-free Tumor DNA in Evaluation and Management of Gliomas: Current Evidence and Potential Future Clinical Use, 129

Kathryn Nevel

Liquid biopsy (LB) is the real-time sampling of tumor cells or tumor nucleotides from biofluids such as

serum and cerebrospinal fluid (CSF). In systemic malignancies, LB is established as a useful clinical tool, but its role in central nervous system (CNS) tumors is less clear. Gliomas are primary brain tumors that are generally incurable; the most common malignant brain tumor in adults is glioblastoma which carries a dismal prognosis. LB holds promise in the clinical care of gliomas, particularly as it could enable tumor assessment without requiring invasive tissue biopsy or reliance on imaging which is subject to misleading results. Circulating tumor cells (CTCs) are released from the primary tumor site into the circulation and cell-free tumor DNA (ctDNA) are fragments of tumor DNA released from the breakdown of tumor cells into the biofluids. Both have been explored as diagnostic, prognostic, and predictive tools in gliomas. This review explores the potential future clinical applications of LB in glioma and the limitations to the current research.

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Madison L. Shoaf and Katherine B. Peters

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Benjamin A. Derman and Andrzej J. Jakubowiak

Controversy swirls around the concept of cure in multiple myeloma (MM) – how to define it, how to identify it, and whether it can be achieved at all. Measurable residual disease (MRD) negativity can be used to define the absence of disease, but it is sustained MRD-negativity over time that is key to establishing the definition of a cure in MM. There is a substantial minority of patients who are exceptional responders to contemporary therapies who may have a mortality rate similar to a normal age-matched population. Interventions that drive an increase in MRD-negativity may improve the cure fraction in MM.

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Optimizing Hematopoietic Cellular Transplantation in Older Adults with Hematologic Malignancies, 171

Samuel J. Yates and Mariam T. Nawas

Older adults undergoing hematopoietic cellular transplantation (HCT) with steadily increasing frequency, and carefully selected older patients experience favorable outcomes with this therapy. However, HCT remains heavily underutilized in patients over age 60. The evaluation of older adults for HCT is evolving beyond a simple assessment of chronological age, performance status and comorbidities. The Geriatric Assessment (GA) is a comprehensive battery of health testing that confers prognostic value when applied to older HCT candidates and guides impactful interventions. Work remains to address barriers to widespread adoption of the GA, and to reduce excess transplantation-associated toxicity in older adults.

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Lisa Chu and Kristen Pettit

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by dysregulated myeloid cell production and proliferation, increased proinflammatory cytokine production, and propensity to transform to acute myeloid leukemia. Although the clinical spectrum of

disease behavior across MPN subtypes is broad, they share a common pathogenic driver: excess activation of Janus kinase 2 (JAK2) signaling. JAK inhibitors have emerged as the cornerstone of treatment for MPNs given their ability to improve symptoms and splenomegaly in a subset of patients; however, their potential to modify the natural history of the disease is modest.

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Ming Yin, Lauren Pomerantz, Ryan Vaca, Petros Grivas, and Monika Joshi

The intact deoxyribonucleic acid (DNA) damage response (DDR) is critical to guard against DNA damage and maintain genomic integrity/stability. DDR

defects have been involved in cancer initiation, progression, and have been associated with anticancer treatment response and outcomes. A better understanding of the role of DDR alterations in cancer development has led to the utilization of DDR defects as relevant therapeutic targets and putative biomarkers, which is the focus of our review, focusing on genitourinary (GU) cancers. Poly-ADP ribose polymerase inhibitors (PARPi) have become a crucial tool for targeting this pathway in the treatment of certain cancers, including prostate cancer. Unfortunately, resistance to PARPi is common and this primarily drives the investigation of multiple combination strategies with other agents. Novel agents targeting the DDR pathway, in addition to PARPi constitute a promising therapeutic approach, while translational research aiming to refine patient selection and prove the clinical utility of putative biomarkers across various cancer types remains crucial.

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Clinical Trial Considerations for Bladder Preservation in Muscle-Invasive Bladder Cancer, 213

Benjamin Miron, Jessica E. Hawley,
 Daniel M. Geynisman, Kent W. Mouw,
 John P. Sfakianos, Emily S. Weg, Fady Ghali,
 Jonathan Wright, Petros Grivas, and Ali Raza Khaki

Although the most common curative-intent approach for muscle-invasive bladder cancer is radical cystectomy, bladder preservation approaches have become desired by many patients, given the morbidity and quality-of-life implications of this procedure. In this review, the authors define the contemporary methods of bladder preservation including trimodality therapy (with or without [neo]adjuvant systemic therapy) and approaches of biomarker-based treatment allocation. They review examples of ongoing clinical trials and discuss relevant trial design considerations, including patient selection/eligibility, stratification, optimal endpoints, use of randomization with appropriate control arms, and relevant putative biomarkers.

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Dustin A. Deming

Locally advanced rectal cancer (LARC) is a common clinical problem, which is growing in incidence in younger populations. This disease often requires multi-modality treatment including chemotherapy,

radiation, and surgery. The treatment options for patients with LARC are evolving rapidly with multiple studies now indicating significant benefit from a total neoadjuvant approach, instead of the recently more common sequencing whereby only chemoradiation was given neoadjuvantly. Additionally, there are now alternative options that can be used in different sequences as part of a total neoadjuvant approach, including chemotherapy and radiation options. There is also a growing interest in a nonoperative approach for patients who have achieved a clinical complete response to their neoadjuvant therapy. Here we review these differing approaches and outline the evolving treatment options for patients with LARC. Through multidisciplinary management of these patients, we can enhance treatment outcomes, while also aligning patient-care goals and minimizing treatment-related toxicities.

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The Changing Demographics of Colorectal Cancer: Rising Incidence in Younger Individuals, 237

Justin H. Lo and Kristen K. Ciombor

The incidence of early-onset colorectal cancer (EOCRC) has been rising in the United States in recent decades, with disparities based on race/ethnicity, sex, and geography. Risk factors associated with EOCRC include inflammatory bowel disease, obesity, smoking, heavy alcohol intake, and poor diet. EOCRC cases differ from late-onset cases

on a clinical, histologic, and molecular level. They are more likely to present at advanced stages, affect the distal colon or rectum, exhibit adverse histologic features, and arise due to germline mutations.

Recent changes to CRC screening guidelines may help address the rising trend in EOCRC, and studies are starting to shed light on the optimal management of EOCRC.

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