

Contents

Foreword: Clinical Trials in Surgical Oncology	xiii
Timothy M. Pawlik	
Preface: Clinical Trials in Surgical Oncology	xv
Syed A. Ahmad and Shishir K. Maithel	
Fundamentals of Conducting Cooperative Group Trials Through the National Clinical Trials Network	1
Rebecca A. Snyder and Matthew H.G. Katz	
This review discusses the benefits of performing multidisciplinary trials through the cooperative group mechanism, outlines the process from trial concept to activation, and discusses opportunities for surgeons to become involved in cancer cooperative trials.	
The Development of Investigator-Initiated Clinical Trials in Surgical Oncology	13
Hannah G. McDonald, Emily B. Cassim, Megan M. Harper, Erin E. Burke, Emily F. Marcinkowski, Michael J. Cavnar, Prakash K. Pandalai, and Joseph Kim	
Investigator-initiated trials (IITs) are designed by principal investigators who identify important, unaddressed clinical gaps and opportunities to answer these questions through clinical trials. Surgical oncologists are poised to lead IITs due to their multidisciplinary clinical practice and substantial research background. The process of developing, organizing, and implementing IITs is multifaceted and involves important steps including (but not limited to) navigating regulatory requirements, obtaining funding, and meeting enrollment targets. Here, the authors explore the steps, methodology, and barriers of IIT development by surgical oncologists and highlight the importance of IITs in oncology.	
Clinical Trials That Have Informed the Modern Management of Breast Cancer	27
Laura K. Krecko, Meeghan A. Lautner, and Lee G. Wilke	
Randomized controlled trials have informed the historical evolution of breast cancer management, distilling operative and nonoperative treatments to achieve disease control and improve survival while maximizing quality of life and minimizing complications. The authors describe landmark trials investigating and influencing the following aspects of breast cancer care: extent of breast surgery; axillary management; neoadjuvant and adjuvant therapies; and selection of chemotherapy versus endocrine therapy via application of genomic assays.	
Clinical Trials in Melanoma: Margins, Lymph Nodes, Targeted and Immunotherapy	47
Cimarron E. Sharon, Georgia M. Beasley, and Giorgos C. Karakousis	
Multiple randomized controlled trials have influenced the current standard of care for patients with cutaneous melanoma. Since the development of	

targeted and immune therapy, studies of adjuvant therapy for patients with resected stage III/IV melanoma have led to the approval of combined B-raf proto-oncogene (BRAF) and mitogen-activated protein kinase kinase inhibitors for patients with a BRAF mutation, and cytotoxic T-lymphocyte associated protein-4 or antiprogrammed cell death-1 therapy for patients without a BRAF mutation. This article discusses the details of the trials that have influenced these treatment decisions, in addition to discussing ongoing trials and possible future directions.

The Perioperative and Operative Management of Esophageal and Gastric Cancer

65

Amn Siddiqi and Fabian M. Johnston

Optimal management of esophageal and gastric cancer during the perioperative period requires a coordinated multidisciplinary treatment effort. Accurate staging guides treatment strategy. Advances in minimally invasive surgery and endoscopy have reduced risks associated with resection while maintaining oncological standards. Although the standard perioperative chemo- and radiotherapy regimens have not yet been established, randomized control trials exploring this subject show promising results.

Past, Present, and Future Management of Localized Biliary Tract Malignancies

83

Janet Li, Flavio G. Rocha, and Skye C. Mayo

Most of the patients with gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (iCCA), and peri-hilar cholangiocarcinoma (pCCA) present with advanced disease. Complete staging with multiphasic liver imaging is essential to determine the extent of disease. Operative goals should include a margin-negative resection, portal lymphadenectomy for staging, and sufficient remnant liver volume. Biliary tract malignancies have distinct mutational drivers (GBC and pCCA = ERBB2 in 20%; iCCA = fibroblast growth factor receptor 2 or isocitrate dehydrogenase 1 in 20%) amenable to therapy with inhibitors. Clinical trials assessing neoadjuvant, peri-operative, and adjuvant treatments continue to evolve and now include targeted inhibitors and the integration of hepatic arterial infusion.

An Overview of Clinical Trials in the Treatment of Resectable Hepatocellular Carcinoma

101

Nicole M. Nevarez, Gloria Y. Chang, and Adam C. Yopp

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related death worldwide. Partial hepatectomy, one of a few curative therapeutic modalities, is plagued by high recurrence rate of up to 70% at 5 years. Throughout the past 3 decades, many clinical trials have attempted to improve HCC recurrence rate following partial hepatectomy using adjuvant and neoadjuvant treatment modalities such as antiviral therapy, brachytherapy, systemic chemotherapy, immunotherapy, transarterial chemoembolization and radioembolization, and radiotherapy. The goal of this review is to discuss the clinical trials pertaining to resectable HCC including surgical technique considerations, adjuvant, and neoadjuvant treatment modalities.

Colorectal Cancer Liver Metastases: Multimodal Therapy 119

Berk Aykut and Michael E. Lidsky

Despite a steady decline in incidence and mortality rates, colorectal cancer (CRC) remains the second most common cancer diagnosis in women and the third most common in men worldwide. Notably, the liver is recognized as the most common site of CRC metastasis, and metastases to the liver remain the primary driver of disease-specific mortality for patients with CRC. Although hepatic resection is the backbone of curative-intent treatment, management of CRLM has become increasingly multimodal during the last decade and includes the use of downstaging chemotherapy, ablation techniques, and locoregional therapy, each of which are reviewed herein.

Surgeon-Led Clinical Trials in Pancreatic Cancer 143

Akhil Chawla and Cristina R. Ferrone

The review also highlights key landmark adjuvant, neoadjuvant and perioperative trials with an emphasis on surgeon-run clinical trials that have helped to define the pancreatic cancer treatment paradigms.

Primary Colorectal Cancer 153

Alexander Dowli, Alessandro Fichera, and James Fleshman

Over the last few decades, the colorectal surgery world has seen a paradigm shift in the care of patients. The introduction of minimally invasive techniques led to the development of procedures resulting in reduced patient morbidity and hospital stay. The vetting process of minimally invasive colorectal surgery involved rigorous studies to ensure that oncologic outcomes were not being compromised. In this chapter, we discuss the most relevant randomized controlled trials that support the practice of minimally invasive colorectal surgery. The multimodal treatment of rectal cancer has developed rapidly, resulting in improved survival and decreased morbidity and mortality. In this review, we also present the latest evidence behind the multidisciplinary approach to rectal cancer.

Evidence for the Current Management of Soft-tissue Sarcoma and Gastrointestinal Stromal Tumors and Emerging Directions 169

Fahima Dossa and Rebecca A. Gladdy

Soft-tissue sarcoma (STS) is not a single entity but, rather, a family of diseases with differing biologic behaviors and anatomic site- and histotype-specific responses to treatment. Whereas surgery remains the mainstay of treatment of primary, localized disease, evolving evidence is establishing the role of multimodality treatment of these tumors. This article summarizes prospective evidence to date informing our treatment of STS. Key future directions will include advancing our understanding of fundamental tumor biology and mechanisms of response and recurrence, as well as defining the optimal provision of regional, systemic, and targeted therapies, including the role of immunotherapy. Ongoing global collaborations will be integral to progress in treating these rare tumors.

The Evolving Landscape of Neuroendocrine Tumors**185**

Ashley Russo and Alexandra Gangi

Neuroendocrine tumors (NETs) represent a heterogeneous group of tumors, with variable presentation based on the location of origin and degree of metastatic spread. There are no randomized control trials to guide surgical management; however, surgery remains the mainstay of treatment for most gastroenteropancreatic NETs based on retrospective studies. Metastatic disease is common at the time of presentation, particularly in the liver. There is a role for cytoreduction for improvement of both symptoms and survival. Robust prospective randomized data exists to support the use of medical therapies to improve progression-free and overall survival in patients with advanced, metastatic, and unresectable NETs.

Advances in Endocrine Surgery**199**

Michael S. Lui, Aditya S. Shirali, Bernice L. Huang, Sarah B. Fisher, and Nancy D. Perrier

Recent changes in the landscape of endocrine surgery include a shift from total thyroidectomy for almost all patients with papillary thyroid cancer to the incorporation of thyroid lobectomy for well-selected patients with low-risk disease; minimally invasive parathyroidectomy with, and potentially without, intraoperative parathyroid hormone monitoring for patients with well-localized primary hyperparathyroidism; improvement in the management of parathyroid cancer with the incorporation of immune checkpoint blockade and/or targeted therapies; and the incorporation of minimally invasive techniques in the management of patients with benign tumors and selected secondary malignancies of the adrenal gland.

Diversity, Equity, and Inclusion in Clinical Trials**221**

Grace Keegan, Angelena Crown, and Kathie-Ann Joseph

Minority groups are vastly underrepresented in clinical trial participants and leadership. Because these studies provide innovative and revolutionary treatment options to patients with cancer and have the potential to extend survival, it is imperative that public and private stakeholders, as well as hospital and clinical trial leadership, prioritize equity and inclusion of diverse populations in clinical trial development and recruitment strategies. Achieving equity in clinical trials could be an important step in reducing the overall cancer burden and mortality disparities in vulnerable populations.