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**Preface: The Management of Esophagogastric Cancers Enters a New Era** xiii

Manish A. Shah

## Tumor Biology

**The Gastric Microbiome and Its Influence on Gastric Carcinogenesis: Current Knowledge and Ongoing Research** 389

Chao Zhang, Sarah Ellen Powell, Doron Betel, and Manish A. Shah

Gastric malignancies are a leading cause of cancer-related death worldwide. At least 2 microbial species are currently linked to carcinogenesis and the development of cancer within the human stomach. These include the bacterium *Helicobacter pylori* and the Epstein-Barr virus. In recent years, there has been increasing evidence that within the human gastrointestinal tract it is not only pathogenic microbes that impact human health but also the corresponding autochthonous microbial communities. This article reviews the gastrointestinal microbiome as it relates primarily to mechanisms of disease and carcinogenesis within the upper gastrointestinal tract.

**Barrett Esophagus and Intramucosal Esophageal Adenocarcinoma** 409

Shanmugarajah Rajendra and Prateek Sharma

Barrett esophagus (BE) is a precursor lesion for esophageal adenocarcinoma (EAC). Developments in imaging and molecular markers, and endoscopic eradication therapy, are available to curb the increase of EAC. Endoscopic surveillance is recommended, despite lack of data. The cancer risk gets progressively downgraded, raising questions about the understanding of risk factors and molecular biology involved. Recent data point to at least 2 carcinogenic pathways operating in EAC. The use of p53 overexpression and high-risk human papillomavirus may represent the best chance to detect progressors. Genome-wide technology may provide molecular signatures to aid diagnosis and risk stratification in BE.

## Management

**Staging in Esophageal and Gastric Cancers** 427

Thomas Hayes, Elizabeth Smyth, Angela Riddell, and William Allum

Gastric and esophageal tumors have a poor prognosis; approximately 15% of patients are alive at 10 years following diagnosis. Surgical resection plus adjunctive chemotherapy or chemoradiotherapy is curative in approximately 50% of patients with operable disease, but is also associated with significant morbidity. Therefore, accurate preoperative staging is required to spare patients unnecessary toxicity and futile surgery. This review evaluates the sensitivity and specificities of the modalities used to stage patients with gastroesophageal cancer. Staging techniques

reviewed include CT, PET, MRI, EUS, and laparoscopy. The article concludes with suggestions on appropriate staging tools according to site and stage of disease.

**Management of Locally Advanced Gastroesophageal Cancer: Still a Multidisciplinary Global Challenge?**

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Salah-Eddin Al-Batran and Sylvie Lorenzen

The outcome of patients with locally advanced, resectable gastric cancer, or adenocarcinoma of the gastroesophageal junction is poor. In clinical trials, multimodality therapy, such as perioperative chemotherapy, preoperative or postoperative chemoradiation, or adjuvant chemotherapy led to significant increments in survival. Therefore, experts agree that patients with stage II or III disease should be offered a multidisciplinary treatment approach. However, patients are treated somewhat differently in the different regions of the world and survival rates remain far from being satisfactory. Efforts to further improve outcome are highly warranted.

**The Role of Radiotherapy in Localized Esophageal and Gastric Cancer**

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John Ng and Percy Lee

Multimodality management has become a core treatment principle for locally advanced esophageal, gastroesophageal junction (GEJ), and gastric cancer. Radiotherapy serves an important role for optimizing patient outcomes. This article reviews the evolving role of radiotherapy in the multidisciplinary management of esophageal, GEJ, and gastric cancer, summarizing the results of recent clinical trials leading to contemporary accepted treatment approaches. A major theme is the evidence supporting the role of radiotherapy in combined modality management, particularly the trend toward its delivery in the neoadjuvant setting. Also reviewed are novel radiotherapy paradigms and newer radiation technologies such as image-guided radiotherapy and MRI-guided radiotherapy.

**Management of Metastatic Gastric Cancer**

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Radka Obermannová and Florian Lordick

Metastatic gastric cancer is an incurable disease. Systemic chemotherapy prolongs survival, improves symptom control, and helps maintain a better quality of life of patients with metastatic gastric cancer. HER2 testing of the primary tumor and/or the metastases is warranted before initiation of first-line treatment. This review article outlines the indication and clinical data of medical treatment of advanced gastric cancer and highlights aspects of quality of life.

**Emerging Targeted Therapies**

**The Evolving Role of Checkpoint Inhibitors in the Management of Gastroesophageal Cancer**

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Adrian G. Murphy and Ronan J. Kelly

The connection between inflammation and malignancy has long been recognized in gastric and esophageal cancers. Given the considerable

success of immune checkpoint inhibitors in other tumor types, for example, lung cancer and melanoma, much attention is being paid to furthering their role in gastric and esophageal cancers. The Cancer Genome Atlas has provided further details of the molecular heterogeneity of these tumors, which may help predict responsiveness to immune checkpoint inhibitors. This article discusses the rationale for investigating these agents in gastroesophageal cancer and summarizes the relevant clinical trial data and ongoing studies.

### **Antiangiogenic Therapy in Gastroesophageal Cancer**

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Zhaohui Jin and Harry H. Yoon

Antiangiogenesis therapy is one of only 2 biologically targeted approaches shown to improve overall survival over standard of care in advanced adenocarcinoma of the stomach or gastroesophageal junction (GEJ). Therapeutic targeting of vascular endothelial growth factor receptor 2 improves overall survival in patients with previously treated advanced gastric/GEJ adenocarcinoma. No antiangiogenesis therapy has demonstrated an overall survival benefit in patients with chemo-naïve or resectable esophagogastric cancer or in patients whose tumors arise from the esophagus. Promising ongoing clinical investigations include the combination of antiangiogenesis therapy with immune checkpoint inhibition and anti-human epidermal growth factor receptor 2 therapy.

### **Update on Gastroesophageal Adenocarcinoma Targeted Therapies**

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Steven B. Maron and Daniel V.T. Catenacci

Gastroesophageal cancer (GEC) remains a major cause of cancer-related mortality worldwide. Although the incidence of distal gastric adenocarcinoma (GC) is declining in the United States, proximal esophagogastric junction adenocarcinoma (EGJ) incidence is rising. GC and EGJ, together, are treated uniformly in the metastatic setting as GEC. Overall survival in the metastatic setting remains poor, with few molecular targeted approaches having been successfully incorporated into routine care to date—only first-line anti-HER2 therapy for *ERBB2* amplification and second-line anti-VEGFR2 therapy. This article reviews aberrations in epidermal growth factor receptor, *MET*, and *ERBB2*, their therapeutic implications, and future directions in targeting these pathways.

### **Emerging Novel Therapeutic Agents in the Treatment of Patients with Gastroesophageal and Gastric Adenocarcinoma**

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Gayathri Anandappa and Ian Chau

With further understanding of the biology of gastric and gastroesophageal adenocarcinomas, strides are being made to find effective treatments through novel trial designs. This article focuses on the ongoing trials of drugs targeting specific hallmarks of gastric and gastroesophageal cancers, including oncogene addiction proliferative pathways (fibroblast growth factor receptor 2 amplified tumors), stem cell inhibition, apoptotic induction through claudin inhibitors, and matrix metalloproteinase inhibition. In developing novel therapeutics in treatment of patients with gastroesophageal adenocarcinomas, parallel research efforts to refine target

population and biomarkers are crucial, and targeting the tumor genomics and microenvironment may be key in improving overall survival.

**Future Directions in Improving Outcomes for Patients with Gastric and Esophageal Cancer**

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Manish A. Shah

*This issue of Hematology/Oncology Clinics of North America provides an update to the current understanding of the physiology of gastric and esophageal cancers and the state-of-the-art management of disease. Over the past 10 years, we have witnessed dramatic changes in both our understanding of the disease and its management. We have 2 new biological agents approved to treat advanced disease, with several more prospects under development. In this article, the author looks to the future, attempting to answer the question of which advancements will play the biggest role in improving patient outcomes in this still-devastating disease.*

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