Revisiting Barrett's Esophagus

Giuseppe Galloro
Editor

Springer

Revisiting Barrett's Esophagus

Giuseppe Galloro
Editor

Revisiting Barrett's Esophagus

Springer

Editor
Giuseppe Galloro
Department of Clinical Medicine and Surgery
University of Naples Federico II
School of Medicine
Naples
Italy

ISBN 978-3-319-92092-4 ISBN 978-3-319-92093-1 (eBook)
https://doi.org/10.1007/978-3-319-92093-1

Library of Congress Control Number: 2018955193

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Barrett's esophagus (BE) is among the most common conditions encountered by the endoscopist, diagnosed in people who have long-term gastroesophageal reflux disease (GERD) and other risk factors (more than 50 years old, male, Caucasian, current or past smoking). Despite only a small percentage of people with GERD developing BE, its link with an increased risk of developing esophageal cancer requires a higher attention to this condition.

Nowadays, BE is very well studied in tertiary centers where the patients are often referred. Nevertheless, most of the endoscopists are not at ease with this disease, and, sometimes, they are not up to date about how to manage it. For these reasons, too often patients with GERD are endoscopically studied superficially and BE cases are not recognized. Then, if it is justified to send a patient with BE to a reference center for the most appropriate therapy, it is mandatory that all endoscopists would know how to recognize it in the best way.

The purpose of this book is to review the definition, epidemiology, diagnostic procedures, and therapeutic techniques of BE, providing a pragmatic framework for the care of such patients.

Structured in four parts (morphologic backgrounds, epidemiology and natural history, diagnosis, and treatments), this handbook benefits from the contributions of some of the world's leading experts on the management of BE, and, I hope, it will be able to transfer their knowledge to the reader.

Naples, Italy — Giuseppe Galloro

Acknowledgments

I would like to thank all the coauthors and contributors of the book: with their efforts they have been able to share and communicate their scientific knowledge and enthusiasm to all those who will read and study this volume. Without them the result would not have been the same.

Secondly, my thanks to the Springer editorial team, who believed in this endeavor and followed it with professionalism.

Finally, my thoughts go to all my collaborators. Without their care, dedication, skill, and professionalism my work could not be the same, and, probably, this volume would have never been realized.

Thanks again to everyone.

Contents

Contributors

Seiichiro Abe Digestive Endoscopy Unit, Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

Gabrio Bassotti Gastroenterology and Hepatology Section, Department of Medicine, University of Perugia—School of Medicine, Perugia, Italy

Raf Bisschops Department of Gastroenterology and Hepatology, Catholic University of Leuven (KUL), TARGID, University Hospitals Leuven, Leuven, Belgium

Carlo Calabrese Department of Medicine and Surgery, University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

Clotilde Castaldo Department of Public Health, Section of Human Anatomy, University Federico II—School of Medicine, Naples, Italy

Filippo Catalano Emergency Surgical Endoscopy Unit, Piastra Endoscopica, Polo Confortini, Ospedale Borgo Trento, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

Kenneth J. Chang Division of Gastroenterology and Hepatology, H. H. Chao Comprehensive Digestive Disease Center, University of California, Irvine Medical Center, Orange, CA, USA

Jean Marc Chevallier Service de Chirurgie Digestive, Hôpital Européen Georges Pompidou, Paris, France

Sonja Chiappetta Department of Obesity and Metabolic Surgery, Sana Klinikum Offenbach, Offenbach am Main, Germany

Massimo Conio Department of Gastroenterology, General Hospital, Sanremo (IM), Italy

Mattia Crespi Department of Gastroenterology, General Hospital, Sanremo (IM), Italy

Alessandra D'Alessandro Gastroenterology Unit, Department of Clinical Medicine and Surgery, University Federico II—School of Medicine, Naples, Italy

Antonella De Ceglie Department of Gastroenterology, General Hospital, Sanremo (IM), Italy

Franca Di Meglio Department of Public Health, Section of Human Anatomy, University Federico II—School of Medicine, Naples, Italy

De Palma Giovanni Domenico Department of Clinical Medicine and Surgery, Digestive Surgical Endoscopy Unit, University of Naples Federico II—School of Medicine, Naples, Italy

Jose-Miguel Esteban Endoscopy Unit, Hospital Clínico San Carlos, Madrid, Spain

Giuseppe Galloro Surgical Digestive Endoscopy Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II—School of Medicine, Naples, Italy

Karel Geboes Department of Pathology, University Hospitals Leuven, KU Leuven, Leuven, Belgium

Karen Geboes Department of Gastroenterology, Universitair Ziekenhuis Gent, Ghent, Belgium

Cassese Gianluca Department of Clinical Medicine and Surgery, Endoscopic Surgery Unit, University of Naples Federico II, Naples, Italy

Takuji Gotoda Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

Anne Hoorens Department of Pathology, Universitair Ziekenhuis Gent, Ghent, Belgium

Paola Iovino Gastrointestinal Unit, Department of Medicine and Surgery, University of Salerno—School of Medicine, Salerno, Italy

David Lee Division of Gastroenterology and Hepatology, H. H. Chao Comprehensive Digestive Disease Center, University of California, Irvine Medical Center, Orange, CA, USA

Gaetano Luglio Department of Clinical Medicine and Surgery, Digestive Surgical Endoscopy Unit, University of Naples Federico II—School of Medicine, Naples, Italy

Raffaele Manta Gastroenterology and Digestive Endoscopy Unit, NOCSAE Hospital of Modena, Modena, Italy

Stefania Montagnani Department of Public Health, Section of Human Anatomy, University Federico II—School of Medicine, Naples, Italy

Mario Musella General Surgery Unit, Department of Advanced Biomedical Sciences, University Federico II—School of Medicine, Naples, Italy

Nico Pagano Gastroenterology and Digestive Endoscopy Unit, Department of Medical and Surgical Sciences (DIMEC), University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

Andrea Parodi Gastroenterology Unit, Galliera Hospital, Genoa, Italy

Fernando Rizzello Department of Medicine and Surgery, University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

Uberto Fumagalli Romario General Surgery 2 Unit, ASST Spedali Civili, Brescia, Italy

Alessandra Romiti Department of Medical and Surgical Sciences, University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

Teresa Russo Surgical Digestive Endoscopy Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II—School of Medicine, Naples, Italy

Yutaka Saito Digestive Endoscopy Unit, Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

Marco Salice Department of Medicine and Surgery, University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

Tiziana Salviato Department of Pathology, University of Trieste—School of Medicine, Trieste, Italy

Jason Samarasena Division of Gastroenterology and Hepatology, H. H. Chao Comprehensive Digestive Disease Center, University of California, Irvine Medical Center, Orange, CA, USA

Giovanni Sarnelli Gastroenterology Unit, Department of Clinical Medicine and Surgery, University Federico II—School of Medicine, Naples, Italy

Dolores Sgambato Gastroenterology and Digestive Endoscopy Unit, NOCSAE Hospital of Modena, Modena, Italy

Donato Alessandro Telesca Surgical Digestive Endoscopy Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II—School of Medicine, Naples, Italy

Antonello Trecca Gastroenterology and Operative Endoscopic Units, I-Salus Project Group, Rome, Italy

Endoscopy Unit, USI Center, Rome, Italy

Nigel J. Trudgill Department of Gastroenterology, Sandwell General Hospital, West Bromwich, UK

Vincenzo Villanacci Institute of Pathology, Spedali Civili, Brescia, Italy

Rocco Maurizio Zagari Department of Medical and Surgical Sciences, University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

Part I

Morphologic Backgrounds

Macroscopic Anatomy of Esophagus

1

Stefania Montagnani and Clotilde Castaldo

1.1 The Esophagus

The esophagus is a muscle-membranous tube connecting the pharynx with the stomach and extending from the sixth cervical vertebra, at the level of the laryngeal cricoid cartilage, to the eleventh thoracic one. In the newborn, its position is lightly higher than in the adult, from the fourth cervical vertebra to the ninth thoracic. It descends anterior to the vertebral column, following its curves in the neck and in the posterior superior mediastinum and then crosses the diaphragm to reach the gastric cardia portion [1]. The esophagus generally lies in the median plane, but at the root of the neck and then at the level of the seventh thoracic vertebra, it deviates to the left moving towards the diaphragm (Fig. 1.1).

Some constrictions characterize its length: the first is at the pharyngeal junction, where the inferior pharyngeal constrictor muscle acts as a functional sphincter (it can be damaged by catheters). The second constriction is at the level of the aortic arch, which crosses the esophagus; the third is due to the cross of left principal bronchus. Finally, the fourth is caused by the compression of the diaphragm when the esophagus passes through the *esophageal hiatus* [2]. Food descends through the esophagus rapidly because of its musculature and gravity only helps this phenomenon. The presence of food in the esophagus is the stimulus for the muscle contraction, through tactile receptors and motor impulses along the vagal efferent fibers. The peristaltic waves of swallowing cause relaxation of the lower esophagus part, sometimes considered as a physiological sphincter, when bolus reaches the stomach.

This organ extends in the cervical, thoracic, and abdominal anatomical regions; in everyone, the esophagus has important and characteristic relationships [3].

S. Montagnani (✉) · C. Castaldo
Department of Public Health, Section of Human Anatomy, University Federico II—School of Medicine, Naples, Italy
e-mail: montagna@unina.it

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_1

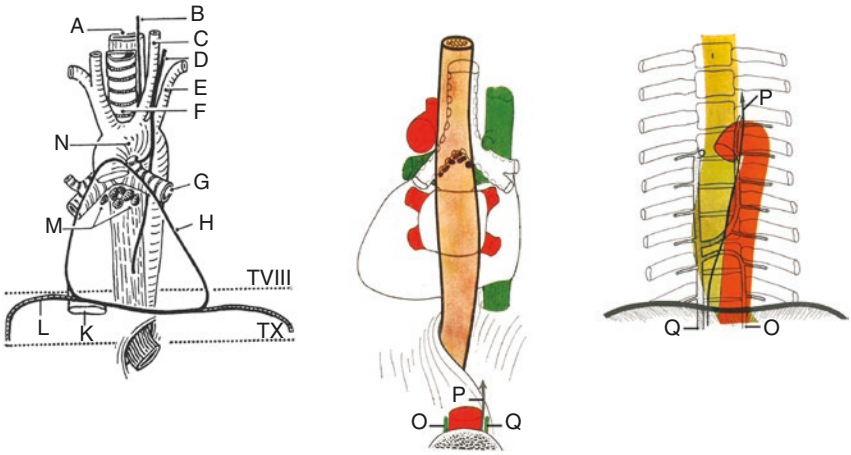

Fig. 1.1 Relationships of the esophagus with mediastinal structures: *A*—esophagus, *B*—left laryngeal recurrent nerve, *C*—common carotid artery, *D*—vagus nerve, *E*—left subclavian artery, *F*—trachea, *G*—left bronchus, *H*—pericardium, *L*—diaphragm, *K*—inferior vena cava, *M*—carina lymph nodes, *N*—aortic arch, *O*—hemiazygos vein, *P*—thoracic duct, *Q*—azygos vein

Traditionally we divide it in cervical, thoracic, and abdominal esophagus: this is of particular interest for the aim of this volume, because only the distal part of the organ is generally interested in the Barrett's esophagus alterations.

The periesophageal connective tissue forms different compartments in the different regions that it crosses. In the cervical region we can distinguish the alar fascia, which runs from the left to the right carotid posteriorly to the esophagus, and the visceral fascia which surrounds trachea and esophagus: in this compartment we find recurrent laryngeal nerves, lymph nodes, and the thyroid gland. In the esophageal portion up to the aortic arch, two connective layers from aorta to esophagus merge with the outer connective tissue of the esophagus [4]. In particular, the connective tissue coursing from aorta to esophagus delineates a periesophageal compartment, containing esophagus, carinal lymph nodes and both vagus nerves, and a para-aortic compartment, which is located posteriorly and contains the thoracic duct and the azygos vein (Fig. 1.2).

In the portion between tracheal bifurcation and diaphragm, connective tissue links aorta and the left lateral side of the esophagus merging with the peri-aortic and the periesophageal connective tissue and sometimes with the pleural reflection in both sides. The major number of lymph nodes are positioned anteriorly to the connective tissue layer between aorta and esophagus, while the thoracic duct and the azygos vein are always located posteriorly. In these regions of the esophagus, it is not accurate by the anatomical point of view the term of "meso" which was sometimes adopted to define these connective layers, because "meso" is usually defined as a structure made of two peritoneal layers with connective tissue inside, for example mesocolon or mesentery.

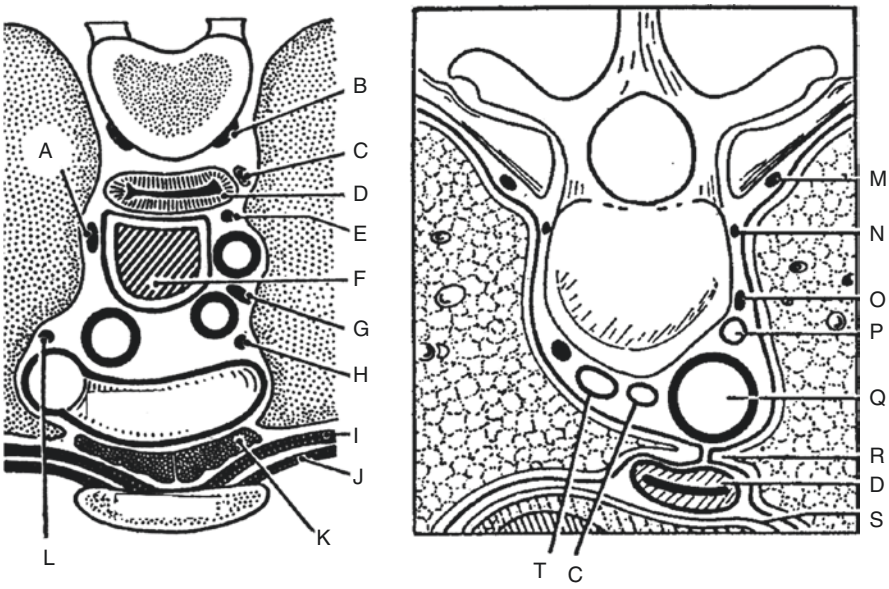

Fig. 1.2 Cross sections in the mediastinum. On the left, superior mediastinum; on the right, posterior compartment. *A*—right vagus nerve, *B*—neck muscle, *C*—thoracic duct, *D*—esophagus, *E*—left laryngeal nerve, *F*—trachea, *G*—left vagus nerve, *H*—phrenic nerve, *I*—sternothyroid muscle, *J*—sternohyoid muscle, *K*—thymus, *M*—Sympathetic fibers, *N*—lesser splanchnic nerve, *O*—greater splanchnic nerve, *P*—hemiazygos vein, *Q*—aorta, *R*—connective tissue, *S*—pericardium, *T*—azygos vein

The abdominal portions of the esophagus is the only portion that has a partial serosal lining, as, crossing the diaphragm, the esophagus enters the abdominal cavity where the visceral pertoneum covers most of the abdominal organs.

1.1.1 The Cervical Esophagus

The cervical part of esophagus is strictly connected with the posterior part of the trachea by smooth muscle and connective tissue: in this portion, it has a median position but it moves towards left in the distal cervical tract, and this deviation becomes more evident in the thoracic tract. The esophagus is anterior to the vertebral column; the vascular-nervous support of the neck (common carotid artery, jugular vein, and vagus nerve) and the lateral lobes of the thyroid gland are positioned laterally in each side. On the left side, esophagus related to the subclavian artery and the end of the thoracic duct, which ascends on its left surface also in the thoracic part after crossing it posteriorly.

Branches of the inferior thyroid arteries provide the blood supply for the cervical part of the esophagus, and the recurrent laryngeal nerves, which ascend laterally to the organ on each side, innervate this portion.

The venous drainage is in the inferior thyroid vein. Sympathetic fibers for the vessels origin from the thoracic spinal cord neuromeres (fourth to sixth);

preganglionic fibers reach the middle and inferior cervical ganglia and take contact with postganglionic fibers for vessels in the cervical and in the upper thoracic part of esophagus. Afferent visceral pain fibers are transported by sympathetic fibers to the spinal cord in the same segments which receive fibers from the heart, so it may be difficult to distinguish esophageal and heart pain.

1.1.2 The Thoracic Esophagus

The thoracic part of the esophagus descends lightly on the left in the superior and then in the posterior mediastinum, with the trachea ahead and the vertebral column behind. It returns on the midline at T5 level and then moves on the left to reach the esophageal opening in the diaphragm.

From above downwards, we can observe its relations with different structures.

Anteriorly it has relations with the tracheal bifurcation and the left bronchus, which causes a constriction in its diameter, the pericardium and finally the diaphragm. The aortic arch and the thoracic duct are on its left while the azygos vein arches forwards on its right.

Posteriorly there is the thoracic column, the thoracic duct (ascending towards the left and crossing the esophagus posteriorly), the azygos vein with its tributary vessels, and the descending aorta.

On the left side, its relations are with the left subclavian artery, the descending part of the aortic arch, the left recurrent laryngeal nerve, the thoracic duct, and the left pleura. The thoracic aorta descends on the left and posteriorly to the esophagus in the posterior mediastinum and reaches the diaphragm.

On the right, there are the pleura and the azygos vein; at the root of the lung, the vagus nerves form a nervous plexus with the left vagus ahead and the right vagus behind the esophagus.

The thoracic esophagus vessels derived from the bronchial and esophageal branches of the thoracic aorta: they origin from the anterior surface of the aorta and form a mesh with the branches of the thyroid arteries in the upper part and with the left phrenic and gastric arteries below.

Blood drains into a submucosa plexus and then in a periesophageal one: esophageal veins arise from it and reach mainly the azygos vein, only for a minor part the hemiazygos or the bronchial and intercostal veins.

1.1.3 The Abdominal Esophagus

The abdominal esophagus is the shortest part of the organ (1–2 cm in length), crosses the diaphragm through the esophageal aperture, descends to the left of the midline, and ends at the esophago-gastric junction. This orifice is named cardias because it is very near to the pericardium, being separated only by the diaphragm.

This portion of the esophagus lies in a groove posteriorly to the left hepatic lobe, with the left inferior phrenic vessels and the greater splanchnic nerve, and is covered

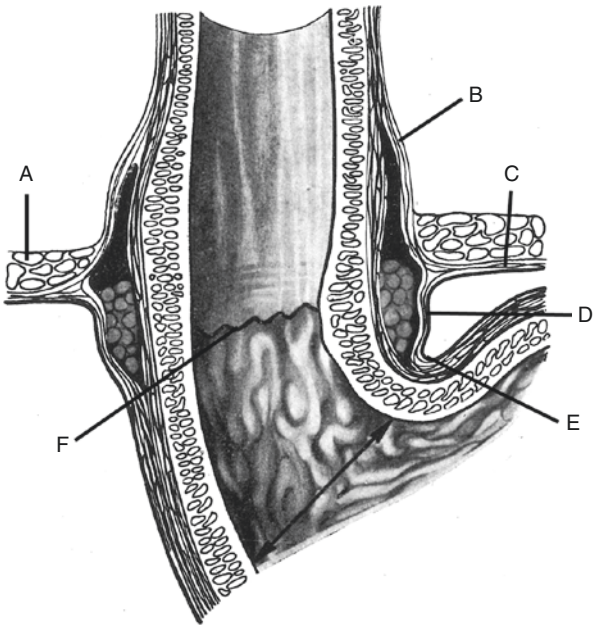

Fig. 1.3 The abdominal esophagus. *A*—diaphragm; *B* and *E*—upper and lower limbs of the phrenico-esophageal ligament; *C*—endoabdominal fascia; *D*—peritoneum; *F*—Z-line, the boundary between esophagus and stomach

by peritoneum containing both vagus nerves and branches of left gastric vessels. The anterior vagus is often composed from multiple branches and strictly connected with muscle fibers of the esophagus, while the posterior vagus is a single trunk whose relation with muscle fibers of the esophagus is mediated by connective tissue.

The phrenic-esophageal ligament keeps the esophagus in the diaphragmatic orifice and is divided in an ascending limb, up to the diaphragm, which is an extension of subpleural fascia, and a descending limb, often rich in adipose tissue, which is in continuity with the fascia transversalis. The ligament allows to both the esophagus and the diaphragm a certain independence in their movements during breathing and swallowing (Fig. 1.3).

This adipose tissue in the inferior portion of the phrenic-esophageal ligament is a constant report and may be useful to individuate the esophago-gastric junction. Here the peritoneum reflects on the anterior and lateral portions of the abdominal esophagus, while the posterior part is shorter and coated by connective tissue.

The peritoneal portion is named gastro-phrenic ligament: it contains the esophageal branches of left gastric vessels and the coeliac trunks of the posterior vagus and is often considered as a short mesentery for the abdominal esophagus.

Esophageal branches of the left gastric artery reach the abdominal esophagus following the peritoneum, while the short posterior surface can use branches of the upper short gastric arteries as well as vessels from thoracic aorta and sometimes of the posterior gastric artery.

The blood from the lower esophagus drains in the submucosa plexus, then in the periesophageal veins using perforating veins and finally in the left gastric vein and into the portal venous system. At the same time, some submucosal veins from this

esophageal portion drain in the systemic venous system and enter the azygos vein: this region can be considered like an anastomotic link between portal and systemic veins. In some conditions like deep breathing or Valsalva manoeuvers, blood can change its direction through perforating veins.

The relation with portal system can influence this circle in some heart or liver pathologies and cause the dilation of the deeper vein supply of the lower esophagus, with the evidence of varices easily visible in endoscopy as they are in the lamina propria.

1.1.4 The Lymphatic Drainage

The esophagus has a rich and continuous lymphatic vessels mesh: lymphatic vessels from the cervical portion reach the cervical or the paratracheal nodes, those from the thoracic one go to the mediastinal nodes. Lymphatic drainage of the abdominal esophagus goes to left gastric nodes, to paracardial nodes in both sides or, for the posterior surface, to para-aortic nodes. Sometimes even mediastinal nodes receive lymph from the abdominal esophagus [5].

The lymphatic drainage is organized in a network localized in the submucosal layer and in another one that is in the musculature layer: these two networks maintain poor communications.

It is interesting to note that lymphatic networks which origin in the submucosal layer rapidly develop during embryonic growth in a longitudinal way from proximal to distal part of the thoracic esophagus, passively following the development of pharynx, trachea, and heart. So, the submucosal lymphatics drain in a longitudinally oriented route, towards their proximal or towards their distal ends. The lymphatic route in the cervical esophagus keeps the direction of the inferior thyroid arteries and the recurrent laryngeal nerves, which are inside the "mesentery" of the proximal esophagus. The lower parts of the esophagus drain the lymph into paracardial and then celiac nodes, following the left gastric or the left phrenic arteries, which are instead components of the dorsal mesentery.

The lymphatic network of the muscle layer usually drains in the paraesophageal nodes and towards the superior mediastinum for the proximal portion and towards paracardial nodes for the distal portion.

The significance of the lymphatic drainage is important to understand the metastatic cancer spread from esophagus. The anatomic aspects of the esophagus lymphatic network support the finding of "skip metastasis" in anatomically distant lymph nodes, even supraclavicular nodes [6]. In addition, not infrequently lymphatic vessels from the right and the posterior part of the thoracic esophagus drain directly into the thoracic duct without any node relay, hence lymph from the right and posterior parts of the organ might reach cervical nodes swiftly. This "direct drainage route" originates mainly from vessels of the submucosal layer crossing the two muscle layers through complete gaps between muscle cells. These vessels are thick, their wall contains smooth muscle cells, and the lumen is expanded: their exit points were located in the dorsal or in the right portion of the esophagus and can easily drain in the thoracic duct.

Lymphatic vessels from the musculature often cross incomplete gaps and their wall is more thin.

1.1.5 The Motor and Sensory Innervation

The gastrointestinal system is innervated with sensory neurons which are related with the enteric nervous system and interact to regulate mucosal transport, blood flow, secretion, and motility.

Esophageal functions are coordinated by an intrinsic innervation composed by Auerbach's and Meissner's plexuses and, in addition, by an extrinsic innervation whose preganglionic neurons are located in the brain stem for the parasympathetic component and in the spinal cord for the sympathetic one. The vagal preganglionic neurons are in the dorsal motor nucleus (DMN) and in the ambiguous nucleus of the vagus. Interestingly, neurons that inhibit and neurons which excite the myenteric plexus coexist in the DMN and are probably involved in deglutition, in deglutition inhibition as well as in peristalsis. Neurons of the ambiguous nucleus control skeletal muscles of the pharynx, esophagus, and palate.

As the upper esophagus has somatic innervation, the organ has a dual nervous support and this complex convergence leads to referred pain or to visceral hyperalgesia. Short lasting and low intensity stimuli activate *N*-methyl-D-aspartate receptors in the esophagus, in contrast with the somatic sensory fibers [7].

The sympathetic fibers originate in the spinal lateral horn from D4 to D6. As the afferent fibers transport sensory information to the dorsal horn in the spinal cord, they can influence preganglionic efferent cells.

The afferent fibers from the esophagus are stimulated by mechanical stretch, thermic alteration, or acidity. Patients report discomfort and pain when the esophagus is involved in diseases as well as in inflammation. Mucosal damage or inflammatory mediators as histamine, H+ ions, or adenosine triphosphate can induce the pain sensation due to cation channels transduction.

Esophageal pain can be caused by various pathologic conditions and is often referred as originating from heart or skin or chest. Visceral sensory fibers mediating conscious sensations from esophagus end in the spinal dorsal horn in a diffuse arrangement, complicated by somatic afferent fibers and by autonomic nervous system afferents like vagal fibers, which mediates non-noxious sensations like nausea or satiety.

Recent studies demonstrated an higher sensitivity of the proximal esophagus as compared to the distal one, with the evolutionary significance of a protective role to prevent the aspiration of gastric content or residual food. In this condition, reverse transportation may be observed during vomiting.

Nevertheless, the less serious sensitivity of the distal esophagus is altered in case of erosion or Barrett's esophagus: also if BE patients seem more resistant to pain for acidity if compared with patients suffering for erosive esophagitis, it is commonly accepted that their sensitivity is increased if compared with normal controls. Probably the activation of autonomous nervous system is responsible for this

increasing acid sensitivity from healthy controls to BE patients to erosive esophagitis, and reflects the different degree of mucosal inflammation and cytokines involvement.

1.2 The Development of the Esophagus

The development of the esophagus is strictly connected with those of the larynx and the trachea, in a special way for its cervical portion. In fact, the anterior part of the gut begins with a cul de sac in the embryo, and will form the trachea and the esophagus by dividing into two parts. The trachea origins from the respiratory diverticulum, which appears in the anterior portion of the gut at fourth week of the embryo and is divided into two parts, the tracheal diverticulum and the cervical esophagus, by the tracheo-esophageal septum. Both organs are formed by splanchnopleural mesenchymal cells, which rapidly diverge in two different tubes. The mesenchymal cells of esophagus form the submucosal zone and the muscular coat, whereas in the trachea they form the cartilage. The perforation of the oropharyngeal membrane provides the communication between oral cavity and pharynx.

At the end of its development, the cervical part of esophagus exhibits skeletal muscle fibers, and its innervation is due to the recurrent laryngeal nerves while the other portions have parasympathetic fibers from the vagus nerve, through the esophageal plexuses.

The esophagus development is rapid and its length reaches 8–10 cm at birth; the diameter of the esophagus is on the contrary one of the less in the whole digestive system.

Acknowledgements The authors are grateful to Idelson Gnocchi editors for their permission to use macroscopic images from their volumes.

References

1. Standring. Gray's anatomy. 40th ed; 2008. p. 1745–54.
2. Harold E. Clinical anatomy. 11th ed. Hoboken: Blackwell; 2006. p. 42–5.
3. Moore KL, Dalley AF, AMR A. Clinically oriented anatomy. 6th ed. Baltimore: Lippincott Williams & Wilkins; 2010. p. 229–31.
4. Weijs TJ, Goense L, van Rossum PSN, Meijer GJ, van Lier ALHM, Wessels FJ, et al. The periesophageal connective tissue layers and related compartments: visualization by histology and magnetic resonance imaging. J Anat. 2017;230:262–71.
5. Tachimori Y. Pattern of lymph node metastases of squamous cell esophageal cancer based on the anatomical lymphatic drainage system: efficacy of lymph node dissection according to tumor location. J Thorac Dis. 2017;9(Suppl 8):S724–30.
6. Kuge K, Murakami G, Mizobuchi S, Hata Y, Aikou T, Sasaguri S. Submucosal territory of the direct lymphatic drainage system to the thoracic duct in the human esophagus. J Thorac Cardiovasc Surg. 2003;125(6):1343–9.
7. Brock C, Gregersen H, Gyawali P, Lottrup C, Furnari M, Savarino E, et al. The sensory system of the esophagus-what do we know? Annals N Y Acad Sci. 2016;1380:91–103.

Microscopic Anatomy and Histology of Esophagus

2

Stefania Montagnani and Franca Di Meglio

2.1 The Microscopic Structure of the Esophagus

The microscopic structure of the esophagus is similar to other parts of the digestive system, as it is composed by four layers whose properties permit the passage of the content and the return to the previous dimension and morphology as soon as this transit is finished. Four layers give to the esophagus its characteristics.

2.2 The Mucosal Layer

The **mucosa** is the inner portion of the esophagus: here the mucosal layer acquires the tri-stratified structure which will continue in all the intestinal tract until the distal portion of the rectum. The esophageal mucosa is smooth and pink-grey color, with deep longitudinal grooves which can unfold when the lumen contains food. When the lumen is empty, the grooves give it a star-like and partially obliterated aspect [1].

The **epithelium** is thick, squamous, and stratified: this type of epithelium is the result of the changes of the ciliated columnar epithelium during the fetal life [2]. Several signaling molecules like BMPs and transcription factors like NOTCH, SOX, and NKX2.1 are involved in the separation of trachea from esophagus in the embryo, in the transition from columnar into stratified epithelium, and in the maintenance of epithelium in the adults. At the birth sometimes it has some areas which maintain such columnar aspect, but they rapidly disappear (Fig. 2.1). As sometimes it happens during the development of various pathologies in human tissues, the embryonic-like columnar epithelium can reappear in EB and in other alterations and

S. Montagnani (✉) · F. Di Meglio
Department of Public Health, Section of Human Anatomy, University Federico II—School of Medicine, Naples, Italy
e-mail: montagna@unina.it

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_2

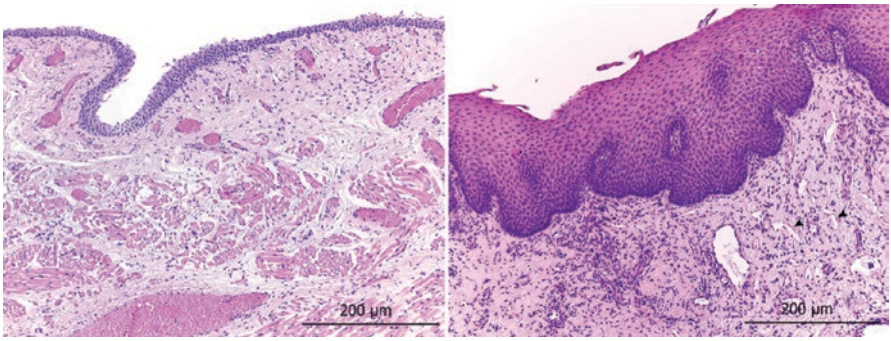

Fig. 2.1 Sections from fetal esophagus (on the left, 8 months) and from adult esophagus (on the right). Note the transition from the fetal columnar to the stratified epithelium. Arrows indicate some lymphatic vessels in the lamina propria (EE staining, ×10)

the changes in the level of these factors play an important role in this phenomenon. As the conversion of simple columnar into stratified epithelium during the development of the esophagus involves dynamic changes in the expression of differentiation markers, abnormal expression of transcription factors or signaling pathway disrupts the equilibrium of the stratified epithelium in the adult esophagus and is often associated with the pathogenesis of several common esophageal diseases, from esophagitis to Barrett's to cancer [3, 4].

In human esophagus, we can observe several layers of basal proliferating cells and almost 20 layers of suprabasal and then squamous cells, without any acellular layer of keratin like in rodents.

SOX2 is crucial for self-renewal of progenitor cells in the basal stratum, while bone morphogenetic proteins play an important role in the differentiation of suprabasal cells, with a stage-dependent role in the epithelial morphogenesis of the esophagus. NOTCH signaling pathway can regulate cell fate and differentiation through cell–cell communication: the inhibition promotes a switch from normal squamous to columnar cell type, with induction of columnar keratins K8 and K18 and mucins, instead of normal expression of squamous K5 and K13. It is intriguing that a BMP increase has been demonstrated in Barrett's esophagus, while SOX2 is decreased: on the contrary, increased SOX2 is often found in poorly differentiated squamous cell carcinoma.

The epithelium of the esophagus, as in other sites of our body, has the basal proliferating layer positioned on the basal lamina, and parabasal and flattened squamous cells going towards the surface. These superficial cells contain keratin filaments and keratohyalin granules; the epithelium is not keratinized, nevertheless its thickness defends it from damages due to the progression of food and liquids. This protection has a limited value if the irritating stimuli are repeated, as well as in case of gastric reflux, of course [5]. This can cause fibrosis, ulcerations of the mucosa, and pain, but in normal conditions the cardias structure prevents all these damages. The name of Barrett's mucosa indicates the metaplastic gastric-like aspect which is typical of this pathological condition.

Langerhans cells are present in this epithelium and act as antigen-presenting cells as usual, so helping in immunoactivation of T-cells and immunodefense of the esophagus. As all the epithelia in the digestive system, also the epithelium of the esophagus is completely self-renewing but this process is slower than in other parts of the system and employs about 3 weeks. The esophageal squamous cells are rich in claudins, a family of proteins typical of tight junctions, and in particular they are rich in Claudin-4 which confers resistance to paracellular transport of ions. On its surface, the esophageal epithelium is protected by the so-called pre-epithelial barrier, composed by the secretion of both salivary glands and submucosal glands. The secretion of salivary glands is released on the esophageal surface during swallowing, while the products of the submucosal gland of the esophagus are secreted with the help of the mechanical compression exerted by the food on the submucosal connective tissue. This barrier utilizes mucin, bicarbonate, and proteins but also EGF and PGE, and the rate of these components varies during the most common esophageal pathologies, like RE and BE. The esophageal mucosal barrier neutralizes acid and proteolytic activity of pepsin by buffers, mucus, mucins, ion transport, peptide growth factors like EGF and PGE; cells defend themselves with apical junction complexes and with self-renewal proliferation. Acid and pepsin, with sometimes the contribution of bile acids, are the aggressive factors which could damage the barrier: so, the morphological integrity of the mucosa is based on the equilibrium between aggressive factors and protective mechanisms. The esophageal pre-epithelial barrier creates a viscoelastic mucus-buffer layer on the surface of epithelial cells: it is continuously exposed to the erosive power of gastric acids especially in the distal portion of the esophagus, where the hydrogen ions concentration is higher and can lead to a gradual digestion of mucus, mucins, and proteins. Nevertheless, the various components of the barrier are always renewed at its base by fresh secretion and by swallowing salivary secretion, with a special stimulation by heartburn [6]. In fact, cholinergic and adrenergic chemoreceptors linked to parasympathetic and sympathetic afferent sensory fibers transport to the interneurons of CNS the stimuli for the esophago-salivatory reflex, inducing an increase in salivary inorganic (PS effect) and organic (S effect) components which increase the protective function of the barrier. Salivatory secretion is of great value because its mucin and proteins are viscous and easily attaching to the mucous layer covering the epithelium. The impact of mastication on the rate of salivatory protective factor secretion is very important. The esophago-gastric junction is characterized by a dramatic change in the epithelium, which is squamous stratified in the esophagus and simply columnar in the stomach: this change is visible on the surface of the cardial esophagus as a zig-zag line and marked from the passage from the pink color of the esophagus to the reddened epithelium of the stomach.

Connective permanent papillae protrude in the epithelial basal lamina: they serve to feed epithelial cells and act as an anchorage to the **lamina propria**, the second mucosal layer which connective origin permits to act as a clivage layer. It contains lymphocytes, vessels and nerves, and can be pressed during the lumen dilation. Some tubular complex glands are present in this layer, mainly in the distal tract of the esophagus, and contribute to prepare the microenvironment to

the stomach conditions: their mucous production, together with the epithelium thickness, protects the mucosa from mechanical and thermic damage. If these glands are present in the upper part of the esophagus they are considered as an aberration, or an heterotypic report if the epithelium is columnar like in the stomach. The extracellular matrix of the lamina propria plays a role in modulating cellular functions as it affects tissue elasticity and architecture and cellular responses [7].

Tenascins, a family of large adhesive glycoproteins, and fibronectin are particularly interesting because both of them are differently expressed during the development, the normal conditions and the pathological alterations. Tenascin-C, which plays an important role in morphogenesis but is usually reduced in adult normal conditions, can reappear in various diseases and is associated to invasive and metastatic potential: its expression is low in metaplasia but gradually increases towards high-grade dysplasia.

Fibronectin is strongly expressed not only in embryonic tissue but also during wound healing and inflammation. Both tenascin-C and fibronectin are normally expressed in the lamina propria of adult esophageal mucosa, in the subepithelial layer and occasionally around the glands, but both molecules, and Tenascin-C in particular, can increase significantly from metaplasia towards adenocarcinoma presumably by their increased synthesis by myofibroblasts.

In our experience, in the normal human adult tenascin-C is mainly present in a subepithelial line (Fig. 2.2) while fibronectin surrounds vessels and muscle fibers bundles (Fig. 2.3).

The **muscularis mucosae** underlie the lamina propria. It is formed from longitudinally oriented smooth muscle cells and its thickness is typically increased near the passage to the stomach, the gastro-esophageal junction. In the upper cervical part of the organ, the muscularis mucosae is absent or poorly organized: its complete formation is considered the boundary between the pharyngeal portion of esophagus and the cervical esophagus, at the level of the cricoid cartilage.

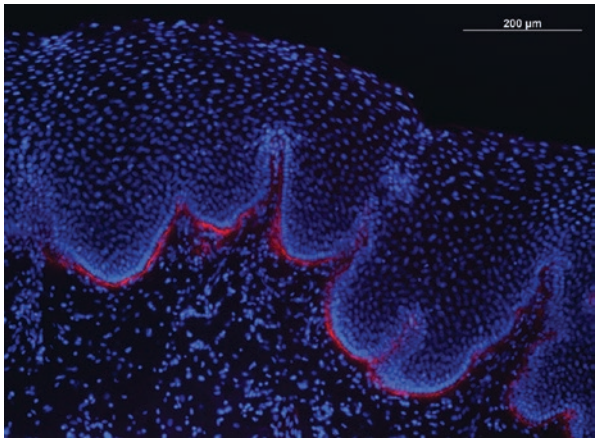

Fig. 2.2 In the normal adult esophagus, tenascin-C (red) borders the epithelial basal lamina and delineates the boundary with lamina propria. Nuclei are blue stained with DAPI (IF, ×10)

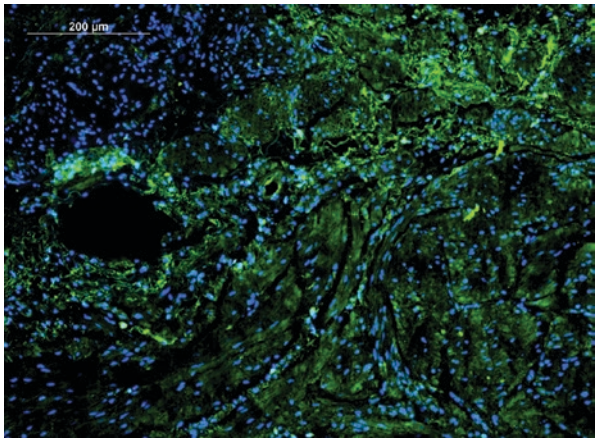

Fig. 2.3 In the normal adult esophagus, fibronectin (green) surrounds vessels as well as muscle fibers. Nuclei are blue stained with DAPI (IF, ×10)

2.3 The Submucosal Layer

The **submucosal layer** is made of connective tissue, contains blood vessels and nerves and the submucosal plexuses (the Meissner plexus in the inner layer and the Henle plexus in the outer layer) which contribute to calibrate the blood supply to submucosal and mucosal layer.

Mucous tubular and branched glands, rich in myoepithelial cells and producing glycoproteins, mucins and bicarbonate, are present in this layer. They may also contain cells producing lysozyme, in a special way near the pharynx, perhaps continuing the antibacterial function that this enzyme has in the saliva. During the development, residual columnar epithelium remains and growth inside the mesenchyme forming the submucosal glands, whose ducts are made from cuboidal cells and reach the inner surface of the esophagus. These glands are mainly positioned in the proximal and in the distal part of the esophagus, but they are present in all the esophagus. Their secretory ducts are lined by columnar epithelium that becomes squamous near the surface and their goal is the secretion when the esophagus dilation due to the passage of food presses them: in this way, the inner surface of the organ is covered by glycoproteins when it is necessary.

Near the stomach, esophageal glands are very similar to the gastric cardia glands and they are sometimes considered aberrant.

The lymphatic supply has a lesser extent in respect with other tract of the digestive system; nevertheless, we can observe some lymphatic nodules and many lymphatic vessels.

2.4 The Muscular Layer

The **muscular layer** has a particular interest because it is composed by striated muscle cells in the proximal tract, where it continues the pharyngeal musculature, and by smooth muscle in the distal two-thirds of the organ. This phenomenon

implies a different innervation, with the autonomic nervous system regulation of the distal part by the vagus nerve and the voluntary control of the proximal one through the pharyngeal skeletal muscles. An intermediated zone has both kinds of muscle cells; this reflects the transdifferentiation which happens during the fetal passage from smooth to striated muscle cells. When the embryonal esophagus divides from the trachea, the mesenchyme under the epithelium differentiates into smooth muscle cells initially in the whole organ; only during the 4–5 week of gestation, the smooth muscle is replaced by striated muscle in a proximal-to-distal direction [8].

The function of the esophagus is largely mechanical as swallowed food and liquids need to be transported from the pharynx to the stomach, and this function is due to the contraction of this tunica. The muscle layer is organized in two differently oriented zones, a circular one inside and a longitudinal one outside. The longitudinal fibers form a continuous coat but under the cricoid cartilage they diverge to ascend in the anterior part of the organ and insert in a tendon on the back of the cricoid. In this way, a V-shaped portion of the organ is here coated only by the circular fibers and by the pharyngeal inferior constrictor muscle: this is the more common site of perforation of the esophagus.

At the level of esophago-gastric junction, the muscle layer is elliptically oriented and functions as a physiological sphincter structure together with the diaphragmatic musculature. This arrangement helps to maintain the food inside the stomach, due both to the His angle and the air content of the gastric fundus.

The myenteric plexus is positioned between circular and longitudinal layers and regulates their contraction. The submucosal and the myenteric plexuses are interconnected and have a great independence from the Central Nervous System, which nevertheless reaches them with its fibers. Cajal interstitial cells (ICCs) are involved in the interrelation of CNS and autonomic nervous system with the plexuses which are globally indicated with the name of enteric nervous system. In the same time, ICCs can act as enteric pacemaker cells to generate peristaltic waves.

Occasionally we can observe some smooth muscle fibers connecting esophagus with bronchi, pericardium or aorta; they facilitate the maintenance of topographic relations in this anatomical region. Mechanosensitive receptors of afferent nerves are located mainly in the myenteric plexus, embedded in its complex structure, and their stimulation end to the dorsal horn of the spinal cord often reflecting on efferent fibers located in the ventral horn. Esophageal distension activates many areas of the cortex, from prefrontal to cingulate cortex, and thalamus as well. Limbic structures are probably activated when the stimulus is disagreeable.

Near the stomach, the circular layer of the esophageal muscular layer continues with the oblique layer in the gastric muscle wall.

2.5 The Adventitial Layer

The esophagus is linked to adjoining structures through most of its length, so its outer layer represents the **adventitial layer** made up from connective tissue with abundance of elastic fibers to connect esophagus to other organs. The relation with the tracheal posterior aspect is ensured by tracheo-esophageal muscle.

Only after entering the abdominal cavity, the anterior and the lateral portions of the organ are covered by visceral peritoneum, while the posterior portion retains the connective adventitia in continuity with the same coat of the gastric fundus. This ensures the loss of mobility which is needed for normal position of the angle of His.

Acknowledgements The authors are grateful to prof. Giuseppe Terzi, Department of Pathology, Hospital of Cosenza, Italy, for his kind permission to use his histological specimen.

References

1. Moore KL, Dalley AF, Agur AMR. Clinically oriented anatomy. 6th ed. Baltimore: Lippincott Williams & Wilkins; 2010.
2. Ross MH. Histology text and atlas with correlated cell and molecular biology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
3. Zhang Y, Jiang M, Kim E, Lin S, Liu K, Lan X, et al. Development and stem cells of the esophagus. Semin Cell Dev Biol. 2017;66:25–35.
4. Vega ME, Giroux V, Natsuizaka M, Liu M, Klein-Szanto AJ, Stairs DB, et al. Inhibition of Notch signaling enhances transdifferentiation of the esophageal squamous epithelium towards a Barrett's-like metaplasia via KLF4. Cell Cycle. 2014;13(24):3857–66.
5. Jovov B, Shaheen NJ, Orlando GS, Zorka D, Orlando RC. Defective barrier function in neo-squamous epithelium. Am J Gastroenterol. 2013;108(3):1–14.
6. Sarosiek J. Does the healing of the esophageal mucosa improve the function of the esophageal submucosal and salivary glands? Ann N Y Acad Sci. 2016;1380:155–61.
7. Leppanen J, Bogdanoff S, Lehenkari PP, Saarnio J, Kauppila JH, Karttunen TJ, et al. Tenascin-C and fibronectin in normal esophageal mucosa, Barrett's esophagus, dysplasia and adenocarcinoma. Oncotarget. 2017;8(40):66865–77.
8. Que J. The initial establishment and epithelial morphogenesis of the esophagus: a new model of tracheal-esophageal separation and transition of simple columnar into stratified squamous epithelium in the developing esophagus. Wiley Interdiscip Rev Dev Biol. 2015;4(4):419–30.

Part II

Epidemiology and Natural History

Definition and Epidemiology of Barrett's Esophagus

3

Alessandra Romiti and Rocco Maurizio Zagari

3.1 Definition

Barrett's esophagus (BE) is a condition characterized by presence of metaplastic columnar epithelium in the distal esophagus for at least 1 cm above the gastro-esophageal junction [1, 2]. The development of metaplastic columnar epithelium is a complication of gastro-esophageal reflux disease (GERD) [1]. In the esophagus, chronic inflammation due to acid reflux damages squamous cells and allows for their replacement by mucus-secreting columnar cells [1]. BE is a precancerous condition associated with an increased risk of esophageal adenocarcinoma; thus, a diagnosis of BE can have a negative impact on patients' quality of life causing psychological stress.

There are still areas of controversy surrounding the definition of BE, in particular as concern the histological type of metaplastic epithelium that establishes a definitive diagnosis of BE [3]. According to American guidelines, the presence of intestinal metaplasia with goblet cells (also called specialized intestinal metaplasia) is necessary for a definitive diagnosis of BE as this condition clearly predisposes to malignancy [4]. The carcinogenic sequence may occur through a sequential progression from intestinal metaplasia to low-grade dysplasia, then to high-grade dysplasia and eventually to adenocarcinoma [5]. On the other hand, for the British Society of Gastroenterology the presence of cardiac mucosa (comprising mucus-secreting columnar cells) without goblet cells in esophagus should lead to the diagnosis of BE [6]. Although the risk for malignancy of cardia-type epithelium in esophagus remains unclear, there is some evidence supporting its premalignant potential [7]. A recent case-report showed that esophageal adenocarcinoma developed from cardia-type columnar mucosa without goblet cells [8]. Kelty et al. reported that patients with BE without intestinal metaplasia had a similar cancer risk of

A. Romiti · R. M. Zagari (✉)
Department of Medical and Surgical Sciences,
University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy
e-mail: roccomaurizio.zagari@unibo.it

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_3

those with specialized intestinal metaplasia [9]. Additional studies showed that non-goblet columnar epithelium may have similar molecular abnormalities to cells of intestinal metaplasia [10]. However, a recent population-based study carried out in Northern Ireland found that the annual risk of developing high-grade dysplasia or esophageal cancer was significantly higher in patients with specialized intestinal metaplasia than in those with only cardiac-type epithelium (0.38% vs. 0.07%) [11].

3.2 Incidence and Prevalence

In line with the increasing prevalence of gastro-esophageal reflux disease [12], the incidence of Barrett's esophagus has raised dramatically over the last decades, in particular in Europe [13]. A population-based study showed an increase in the incidence rate of BE of about three times between 1993 and 2005 in Netherland [14]. Similarly, Coleman et al. reported in Northern Ireland a rise in the average annual incidence of BE from 23.9 per 100,000 persons during 1993–1997 to 62 per 100,000 persons during 2002–2005 [15]. In both studies, the increase in the incidence of BE was independent from the increase of endoscopies and esophageal biopsies over the same time period [14, 15].

Despite the increased incidence of BE, the prevalence of BE in the general population seems to be still low. Three endoscopic studies conducted in Sweden (Kalixanda study) [16], Italy (Loiano-Monghidoro study) [17], and China (SILC study) [18] have estimated the prevalence of BE in unselected samples of the general population. The prevalence of BE with or without intestinal metaplasia in the general population was 10.3% in the Swedish study and 3.6% in the Italian study, and lower, 1.8%, in the Chinese study. However, BE with intestinal metaplasia was reported only in 1.6% and 1.3% of individuals in the community in Sweden and Italy, respectively.

A systematic review showed an increase in prevalence of BE over the last two decades also in Eastern Asian countries with a pooled prevalence of endoscopic BE (with or without intestinal metaplasia) of 7.8% and of BE with intestinal metaplasia of 1.3% [19].

The endoscopic studies carried out in the general population in Europe reported that the prevalence of BE with intestinal metaplasia in subjects with typical reflux symptoms (heartburn or acid regurgitation) was around 1–2% [16, 17]. However, a large prospective study carried out in a cohort of 1058 patients in the USA showed a prevalence of BE with intestinal metaplasia in patients with gastro-esophageal reflux symptoms of 14.1% [20].

A substantial proportion of subjects with BE does not have reflux symptoms. Overall, 60 and 46.2% of subjects with BE did not report reflux symptoms in the Swedish and Italian studies, respectively [16, 17].

3.3 Risk Factors

Several demographic, environmental, and genetic factors are associated with an increased risk of BE (Table 3.1). The main risk factors for BE are older age (<50 years), white race, male sex, chronic heartburn, and smoking. The risk of BE

Table 3.1 Risk factors for Barrett's esophagus

Age > 50 years
White race
Male sex
Obesity with abdominal adiposity
Chronic symptoms (heartburn) of reflux
Smoking
Hiatal hernia
Erosive esophagitis
Low birth weight
Obstructive sleep apnea
Family history of Barrett's esophagus or esophageal adenocarcinoma

is twice higher in men than women [21]. It is not clear when BE develops, but most cases are diagnosed in adults aged more than 50 years old [22]. In patients with chronic gastro-esophageal reflux symptoms, the risk of BE is six times higher than in the general population [23]; the risk seems to depend on frequency and duration of GERD symptoms [4]. Rubenstein et al. observed that BE was associated with weekly GERD symptoms (OR: 2.33, 95% CI: 1.34, 4.05) and the risk to develop BE was higher for a duration of symptoms longer than 5 years (OR: 2.02, 95%CI: 1.05–3.86) [24].

Epidemiological data suggest that weight gain is in the first place associated with an increased risk of BE. Several studies have shown an association of BE with body mass index and abdominal obesity [25]. A recent meta-analysis of 17 studies showed that the risk of BE was about twice higher in individuals with abdominal adiposity (OR: 1.98, 95%CI: 1.52–2.57) [26]. Abdominal adiposity seems to be an independent risk factor for BE as the association still remains statistically significant after adjustment for body mass index and GERD. Visceral fat is metabolically active and it is associated with low serum levels of adiponectin and increased production of leptin and insulin-like growth factors, which promote cell proliferation and lead to the development of metaplastic tissue in esophagus [27], and pro-inflammatory cytokines, such as IL-6 and TNF-alpha, which can modify gastro-esophageal motility [28].

There is a strong association between tobacco use and BE [13]. A recent meta-analysis of 39 studies, including 7069 patients with BE, showed that smokers had an increased risk of BE when compared with no-smokers (OR: 1.44, 95% CI: 1.20–1.74) [29]. On the other hand, there is no evidence that alcohol intake increases the risk of developing BE [30]. Conversely, a recent meta-analysis of five studies from the international BEACON consortium observed a borderline significant inverse correlation between BE and any degree of alcohol intake (OR: 0.77, 95% CI: 0.60–1.00) [31].

Several studies have been carried out in order to find out other possible conditions which may be associated with BE. A recent population-based case-control study carried out in Sweden reported that the risk for developing BE in the adulthood was higher in infants born with low birth weight (<2500 g) in comparison with those with normal birth weight (3000–3900 g) (OR: 8.22, 95% CI: 2.83–23.88) [32]. Moreover,

a case-control study in Minnesota reported that patients with obstructive sleep apnea have a significantly higher risk of BE (OR: 1.8, 95% CI: 1.1–3.2) [33].

The relationship between *Helicobacter pylori* infection and BE is still controversial. However, there is supporting evidence for a protective role of *Helicobacter pylori* infection. A pooled analysis of 49 studies showed a negative association between *Helicobacter pylori* infection and BE (RR: 0.46, 95%CI: 0.35–0.6) [34]. Additionally, an ecological analysis using data from population-based studies showed a negative linear association between the prevalence of *Helicobacter pylori* and the prevalence of BE in the community ($r = -0.95$) [35]. *Helicobacter pylori* infection may lower the risk of BE causing in a subgroup of subjects corpus gastritis, thus reducing acid secretion and preventing a pathological gastro-esophageal reflux [36].

However, the changing epidemiology of BE seems to be correlated with the changing epidemiology of obesity and *Helicobacter pylori* infection over the last decades. As a consequence of the continuous increasing prevalence of obesity [37] and the declining of *Helicobacter pylori* infection [38], BE may keep rising dramatically in the next future.

References

1. Spechler SJ, Souza RF. Barrett's esophagus. N Engl J Med. 2014;371:836–45.
2. Tan WK, Di Pietro M, Fitzgerald RC, et al. Past, present and future of Barrett's oesophagus. Eur J Surg Oncol. 2017;43:1148–60.
3. Amadi C, Gatenby P. Barrett's oesophagus: current controversies. World J Gastroenterol. 2017;23:5051–67.
4. Shaheen NJ, Falk GW, Iyer PG, et al. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111:30–50.
5. Martinucci I, De Bortoli N, Russo S, et al. Barrett's esophagus in 2016: from pathophysiology to treatment. World J Gastrointest Pharmacol Ther. 2016;7:190–206.
6. Fitzgerald RC, Di Pietro M, Ragunath K, et al. British society of gastroenterology guidelines on the diagnosis and management of Barrett's esophagus. Gut. 2014;63:7–42.
7. Macias-Garcia F, Dominiguez-Munoz JE. Update on management of Barrett's esophagus. World J Gastrointest Pharmacol Ther. 2016;7:227–34.
8. Lavery DL, Martinez P, Gay LJ, et al. Evolution of oesophageal adenocarcinoma from metaplastic columnar epithelium without goblet cells in Barrett's oesophagus. Gut. 2016;65:907–13.
9. Kelty CJ, Gough MD, Van Wyk Q, et al. Barrett's oesophagus: intestinal metaplasia is not essential for cancer risk. Scand J Gastroenterol. 2007;42:1271–4.
10. Liu W, Hahn H, Odze RD, et al. Metaplastic esophageal columnar epithelium without goblet cells shows DNA content abnormalities similar to goblet cell-containing epithelium. Am J Gastroenterol. 2009;104:816–24.
11. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst. 2011;103:1049–57.
12. Eusebi LH, Ratnakumaran R, Yuan Y, et al. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut. 2017;0:1–11.
13. Runge TM, Abrams JA, Shaheen NJ. Epidemiology of Barrett's esophagus and esophageal adenocarcinoma. Gastroenterol Clin N Am. 2015;44(2):203–31.

14. Van Soest EM, Dieleman JO, Siersema PD, et al. Increasing incidence of Barrett's oesophagus in the general population. Gut. 2005;54:1062–6.
15. Coleman HG, Bath S, Murray LJ, et al. Increasing incidence of Barrett's oesophagus: a population-based study. Eur J Epidemiol. 2011;26:739–45.
16. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology. 2005;129:1825–31.
17. Zagari RM, Fuccio L, Wallander MA, et al. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the italian Loiano-Monghidoro study. Gut. 2008;57:1354–9.
18. Zou D, He J, Chen J, et al. Epidemiology of symptom-defined gastroesophageal reflux disease and reflux esophagitis: the systematic investigation of gastrointestinal diseases in China (SILC). Scand J Gastroenterol. 2011;46:133–41.
19. Shiota S, Singh S, Anshasi A, et al. Prevalence of Barrett's esophagus in asian countries: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2015;131:907–18.
20. Balasubramanian G, Singh M, Gupta N, et al. Prevalence and predictors of columnar lined esophagus in gastroesophageal reflux disease (GERD) patients undergoing upper endoscopy. Am J Gastroenterol. 2012;107:1655–61.
21. Asanuma K, Iijima K, Shimosegawa T. Gender difference in gastro-esophageal reflux diseases. World J Gastroenterol. 2016;22:1800–10.
22. Ford AC, Forman D, Reynolds PD, et al. Ethnicity, gender, and socioeconomic status as risk factors for esophagitis and Barrett's esophagus. Am J Epidemiol. 2005;162:454–60.
23. Kroep S, Lansdorp-Vogelaar I, Rubenstein JH, et al. An accurate cancer incidence in Barrett's esophagus: a best estimate using published data and modeling. Gastroenterology. 2015;149:577–85.
24. Rubenstein JH, Morgenstern H, Appelman H, et al. Prediction of Barrett's esophagus among men. Am J Gastroenterol. 2013;108:353–62.
25. Camilleri M, Malhi H, Costa A. Gastrointestinal complications of obesity. Gastroenterology. 2017;152:1656–70.
26. Singh S, Sharma AN, Murad MH, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11:1399–412.
27. Greer KB, Thompson CL, Brenner L, et al. Association of insulin and insulin-like growth factors with Barrett's oesophagus. Gut. 2012;61:665–72.
28. El Serag H. The association between obesity and GERD: a review of the epidemiological evidence. Dig Dis Sci. 2008;53:2307–12.
29. Andrici J, Cox MR, Eslike GD, et al. Cigarette smoking and the risk of Barrett's esophagus: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2013;28:1258–73.
30. Sharma N, Yu HK. Risk factors for Barrett's esophagus. Gastrointest Tumors. 2016;3:103–8.
31. Thrift AP, Cook MB, Vaughan TL, et al. Alcohol and the risk of Barrett's esophagus: a pooled analysis from the international BEACON consortium. Am J Gastroenterol. 2014;109:1586–94.
32. Forssell L, Cnattingius S, Bottai M, et al. Increased risk of Barrett's esophagus among individuals born preterm or small for gestational age. Clin Gastroenterol Hepatol. 2013;11:790–4.
33. Leggett CL, Gorospe EC, Calvin AD, et al. Obstructive sleep apnea is a risk factor for Barrett's esophagus. Clin Gastroenterol Hepatol. 2014;12:583–8.
34. Fischbach LA, Nordenstedt H, Kramer JR, et al. The association between Barrett's esophagus and Helicobacter pylori infection: a meta-analysis. Helicobacter. 2012;17(3):163–75.
35. Zagari RM, Eusebi LH, Rabitti S, et al. Prevalence of upper gastrointestinal endoscopic findings in the community: a systematic review of studies in unselected samples of subjects. J Gastroenterol Hepatol. 2016;31:1527–38.
36. Graham DY. Helicobacter pylori update: gastric cancer, reliable therapy, and possible benefits. Gastroenterology. 2015;148:719–31.
37. Wang YC, McPherson K, Marsh T, et al. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet. 2011;378:815–25.
38. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of Helicobacter pylori infection. Helicobacter. 2014;19(Suppl 1):1–5.

4 Pathophysiology of Gastroesophageal Reflux Disease and Natural History of Barrett's Esophagus

Paola Iovino, Antonella Santonicola, and Nigel J. Trudgill

4.1 Gastroesophageal Reflux Disease

The most widely accepted definition of gastroesophageal reflux disease (GERD) is "a condition that develops when stomach contents cause troublesome symptoms and/or complications" [1].

The pathophysiology of GERD is multifactorial and complex and determined by interactions among multiple aggressive mechanisms and defensive factors.

Some mechanisms play a role in the provocation of GERD, schematically at the level of the esophagogastric junction (EGJ) such as Transient Lower Esophageal Sphincter Relaxations (TLESRs, low LES pressure, hiatus hernia (HH), and increased distensibility of the EGJ), above the EGJ in the esophageal body such as prolonged esophageal clearance, and below the EGJ such as acid pocket, delayed gastric emptying, and increased intragastric pressure. A number of other factors, indeed, may influence the intensity-frequency of GERD symptoms, including the phenomenon of peripheral (primary afferents) and central (spinal dorsal horn neurons) sensitization, as well as the characteristics of refluxate (acidity, the presence of gas, the presence of bile acids, the proximal extent), the longitudinal muscle contraction, and the mucosal integrity.

The EGJ, that play a central role because it is the main defense against GERD, anatomically consists of the LES, the crural diaphragm, and the anatomical flap

P. Iovino (✉)
Gastrointestinal Unit, Department of Medicine and Surgery, University of Salerno—School of Medicine, Salerno, Italy
e-mail: piovino@unisa.it

A. Santonicola
Gastrointestinal Unit, Department of Medicine, Surgery & Dentistry Scuola Medica Salernitana, University of Salerno—School of Medicine, Salerno, Italy

N. J. Trudgill
Department of Gastroenterology, Sandwell General Hospital, West Bromwich, UK

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_4

valve, and acts as an antireflux barrier. LES, a short segment of tonically contracted smooth muscle at the very end of the esophagus, is considered the intrinsic sphincter and is surrounded by oblique gastric fibers that are fastened to the striated muscle of the crural diaphragm by the phreno-esophageal ligament, while the right crus of the diaphragm forms a sling that surrounds the distal esophagus (the extrinsic sphincter) augmenting the high-pressure zone of the LES [2, 3]. When these protective components are compromised, the deleterious effects are additive, resulting in abnormal esophageal reflux exposure.

TLESRs [4] by definition are characterized by complete prolonged (>10 s) LES relaxations not caused by swallowing and accompanied by inhibition of the crural diaphragm (CD) [5].

The dominant trigger for TLESR is distension of the proximal stomach, which stimulates afferent vagal innervation that input to the nucleus tractus solitarii in the brainstem and subsequently to the dorsal motor nuclei of the vagus. Dorsal motor nucleus neurons send motor outputs of the reflex circuit to inhibitory neurons localized into the myenteric plexus of the distal esophagus and an integrated motor response involving LES relaxation through reflex inhibitory responses, longitudinal muscle contraction that reduces EGJ obstruction through tension-mediated LES relaxation and repositioning of the LES above the crura, crural diaphragmatic inhibition, and contraction of the costal diaphragm as the final effector state of the TLESR reflex [6]. Compelling evidence has demonstrated that TLESR is the most frequent mechanism associated with gastroesophageal reflux episodes and essentially the only operant mechanisms during period of normal LES pressure (>10 mmHg) [4, 7]. Although TLESR is a major mechanism of gastroesophageal reflux, patients with GERD do not have more frequent TLESRs than controls. However, the frequency of acid reflux during TLESRs has been reported to be greater in GERD patients [8, 9]. It is therefore not the frequency of TLESRs which cause GERD but alterations in the complex processes comprising TLESRs.

LES pressure measured by conventional esophageal manometry (including mean basal and end-expiratory LES pressures) continues to be reported and utilized [10]. However, LES pressure has been described consistently low only in small number of GERD patients [11, 12]. These parameters are descriptive terms and cannot be used to evaluate the LES and CD separately, and so cannot provide an accurate picture of EGJ function. In fact, the resting tone varies also in healthy individuals during the day reaching lower pressure in the postprandial state [13]. LES tone is under regulation of multiple myogenic and neurogenic factors that are modified by gastric distension, intraabdominal pressure, hormones, and medication [14]. Recently, the new technique of high resolution manometry (HRM) introduced new parameters that incorporate EGJ length and respiratory variability such as LES pressure integral [15] or EGJ contractile integral [16] and it has been demonstrated that these parameters are significantly decreased in GERD patients. The EGJ-CI is evaluated using the distal contractile integral (DCI) value at the EGJ during three complete respiratory cycles with a threshold of 2 mmHg above the gastric baseline, and the recorded value is divided by the respiratory cycle duration. The magnitude of contractility can be integrated over time and EGJ length, which are fundamental

for EGJ barrier function. The clinical utility of the EGJ-CI has been further investigated to diagnose GERD [17] and recently it has been suggested its clinical utility after surgical intervention in patients with GERD and achalasia [18].

A HH is present when a spatial dissociation of the antireflux barrier at the EGJ into the intrinsic sphincter and extrinsic sphincter crural diaphragm exists [19], which is likely caused by the weakening or rupture of the phreno-esophageal ligament [20]. Old studies in animal models demonstrated that severing the phreno-esophageal ligament reduced the LES pressure, and that the subsequent repair of the ligament restored the LES pressure to levels similar to baseline [21].

By using HRM it is now easily seen the spatial dissociation of the antireflux barrier into intrinsic sphincter and hiatal canal pressure components, and it has been demonstrated that each of these components was of lower magnitude than the EGJ pressure of a comparator group of healthy individuals [22].

It has been accurately established that patients with HH have more reflux episodes and greater esophageal acid exposure than patients without HH [23, 24]. When the LES lies constantly above the diaphragm, the swallow-associated re-reflux from the hiatal sac impairs esophageal clearance [25], allowing a prolonged acid exposure of the mucosa. In fact, patients with large HH show a severe alteration in the clearance of refluxate [26]. Furthermore, prolonged acid clearance correlates with the severity of esophagitis and the presence of Barrett's metaplasia [27, 28]. However, the threshold for these responses and complications vary and is likely to be influenced by the integrity of the epithelium [27, 28].

Traditionally the assessment of esophageal clearance has therefore focused on pH measures, and esophageal acid clearance time is determined by the time where the esophageal lumen is acidified to a pH of less than 4 after a reflux event. Recently, new methodologies such as impedance analyze bolus presence and clearance [29] and other parameters such as post-reflux swallow-induced peristaltic wave index and nocturnal baseline impedance parameters have been demonstrated to improve the diagnostic yield of impedance-pH monitoring and might identify subpopulations that will respond to acid suppression [30].

Peristaltic dysfunction is considered a potential cause of prolonged reflux exposure and acid clearance and an important contributor to the severity of esophagitis.

Delayed gastric emptying and altered motor function of the proximal stomach have often been described in GERD. It is uncertain, however, how much these alterations contribute to the increased gastroesophageal reflux [31]. The acid pocket was firstly described in 2001 as layer of unbuffered acidic, gastric juice sits on top of the meal, close to the cardia, ready to reflux in the postprandial period [32]. The acid pocket is present in GERD patients and controls. However, alterations in its location and/or distribution may favor acid reflux from the pocket and partially explain the difference between GERD patients and controls [33].

Central obesity increases the intragastric pressure [34] and the gastroesophageal pressure gradient. Both of them favor reflux of gastric content [35] and are also predictors of HH development [36]. Interestingly, it has been demonstrated that small decrease in weight (approximately 10–15 lbs) can reduce GERD symptoms, possibly reducing the pressure gradient and burden on the antireflux barrier [37].

The severity of esophageal acid exposure to gastric content does not directly correlate to the severity of symptoms. It is a matter of fact that patients with non-erosive reflux disease (NERD) and patients with PPI refractory symptoms are hypersensitive to minor stimuli while patients with severe esophagitis and Barrett are often hyposensitive or even asymptomatic [38]. In the last decade, a number of patient-related factors such as peripheral and central sensitization, impaired mucosal barrier function and possibly genetic factors together with the acidity, the proximal extent, the presence of bile acids and the presence of gas in the refluxate have been taken into account to explain the differences in perception in specific subtypes of GERD symptoms [39]. At peripheral level, nerve endings in the submucosal layer are belived that mediate the sensitivity to refluxed gastric contents. A loss of mucosal barrier function has been demonstrated in GERD that might allow components of refluxate can easily reach nerve endings and increase symptoms [40, 41].

Dilated intercellular spaces studied by histology or, most accurately, by electron microscopy of esophageal biopsies have been demonstrated in GERD as expressions of the loss of mucosal barrier integrity [42]. Recently, another technique, baseline impedance, has been used to evaluate the mucosal integrity [43, 44].

Acid and bile reflux have been involved in causing the dilation of intercellular spaces and increase in mucosal permeability suggesting that luminal aggressive refluxate activate receptors on submucosal nerve endings, then inducing symptoms [40, 45]. In last decade it has been suggested that refluxed gastric material stimulated esophageal epithelial cells to secrete cytokines that attracted immune cells, which ultimately damaged the mucosa [46] and, in 2016 a preliminary study of 12 patients with severe esophagitis successfully treated with PPI therapy, the interruption of PPI results in submucosal infiltration by T cells and dilated intercellular spaces in the basal layer without loss of surface cells [47].

The presence and density of reflux-sensing receptors such as transient receptor potential vanilloid type-1 (TRPV1), acid-sensitive ion channels, and the protease-activated receptor 2 (PAR2), which are all expressed in human esophageal mucosa might also determine symptom occurrence during reflux events and possibly determining esophageal hypersensitivity to reflux [48, 49].

The pathogenesis of esophageal hypersensitivity, however, could involve also central mechanisms that increase sensitivity of incoming signals from the esophagus affecting spinal cord excitability and altered descending modulation of nociceptive processing. These are regulated by factors that affect central mechanisms, such as stress, anxiety, and personality traits [50]. Stress is often presumed to alter central processing of afferent signals, such as heartburn, but animal studies showed that acute stress led to dilation of intercellular spaces in the esophagus, which could also account for the increased sensitivity to reflux [51].

GERD patients show reduced quality of life [52]. In presence of depression and especially anxiety, GERD patients have more symptoms and lower quality of life compared to GERD patients without anxiety and similar reflux parameters [53].

However, more studies are mandatory to explain how intensity-frequency of GERD symptoms could be modulated.

4.2 Natural History of Barrett's Esophagus

Following the original description in 1950 by Normal Barrett of the condition that came to bear his name [54], it has been subsequently established from animal studies that Barrett's oesophagus (BO) is an acquired condition due to gastroesophageal reflux, leading to the replacement of the normal squamous epithelium of the lower esophagus with a columnar lined mucosa [55].

BO is commonly defined endoscopically as an esophagus in which a variable proportion of the distal normal squamous epithelial lining has been replaced by visible metaplastic columnar epithelium above the gastroesophageal junction, usually defined by the proximal margin of the gastric folds, and confirmed histologically on endoscopic biopsy [56].

In 1952, a patient was reported who developed an adenocarcinoma in an esophageal mucosa of intestinal type goblet cells, consistent with BO [57]. Given the poor prognosis of many patients presenting with symptomatic esophageal adenocarcinoma, endoscopic screening of patients with BO has been widely practiced over the past three decades, though not without some controversy.

Endoscopic surveillance of BO is based on the histological progression in subjects with esophageal adenocarcinoma from non-dysplastic to low grade dysplasia and then high grade dysplasia before developing adenocarcinoma. Detecting dysplasia potentially allows endoscopic intervention with endoscopic mucosal resection or radio-frequency ablation to prevent progression to adenocarcinoma.

4.3 Natural History of Non-dysplastic Barrett's Esophagus

The annual risk of developing esophageal adenocarcinoma in non-dysplastic BO is a key factor in determining the cost-effectiveness of endoscopic surveillance for BO and the recommendations we make to our patients concerning its value. A recent meta-analysis of the risk of esophageal adenocarcinoma in BO without dysplasia included 57 cohort studies involving over 11,000 BO subjects and over 58,000 years of follow-up and suggested that the annual esophageal adenocarcinoma risk in BO is 0.33% [58]. However, although there was no evidence of publication bias reported in this meta-analysis, many of the case series included are prone to a number of other biases, particularly selection bias. Two subsequent large population based studies suggest that the annual esophageal adenocarcinoma risk in BO is significantly lower [59, 60]. In a population based study of 8522 BO subjects in Northern Ireland with no dysplasia at study entry, the annual risk of esophageal adenocarcinoma was 0.1% [59]. In a nationwide study based on histopathology records of 11,028 Danish BO subjects with no dysplasia at study entry, the annual risk of EAC was 0.1% [60].

It is important to point out that other risk factors for esophageal adenocarcinoma in BO need to be taken into account when assessing the individual annual risk of esophageal adenocarcinoma, in particular the length of the Barrett's segment. In a Dutch cohort study of 713 BO subjects, the risk of progression to esophageal

adenocarcinoma increased by a factor of 1.11 for each extra centimeter of BO segment length [61]. The length of BO segment was only available in 20% of subjects in the Northern Ireland population based study and in none of the Danish population based study, since it was based on histopathology records [59, 60]. In Northern Irish subjects with short segments less than 3 cm of BO, the annual risk of esophageal adenocarcinoma was 0.07% and was 0.22% in longer segment Barrett's [60]. Both population based studies are likely to have included a majority of BO subjects with short segments, since they are more common than long segment BO, thereby lowering their estimates of the annual risk of esophageal adenocarcinoma compared with cohort studies largely from surveillance programs, which would predominantly include subjects with longer BO segments.

In conclusion, subjects with BO with no dysplasia at index endoscopy are at lower overall risk of developing EAC than previously thought, with two recent population based studies suggesting this is around 0.1% per year.

4.4 Natural History of Barrett's Esophagus Indefinite for Dysplasia

Indefinite for dysplasia is used for BO cases where the morphological features differentiating between true dysplasia and regenerative/inflammatory atypia are not clear [62]. The degree of agreement among histopathologists for a diagnosis of indefinite for dysplasia has been reported to be very poor and even lower than the known poor agreement for low grade dysplasia, with kappa values of 0.18 and 0.35, respectively [63]. There is very limited data on the natural history of BO subjects indefinite for dysplasia. The rate of progression to esophageal adenocarcinoma in BO subjects indefinite for dysplasia has been reported to be similar to non-dysplastic BO patients, unless the areas that were indefinite for dysplasia were multifocal, when the rate of progression to carcinoma seemed as high as in patients with low grade dysplasia [64].

It has therefore been recommended that patients with a diagnosis of indefinite for dysplasia should be managed with optimization of their medical therapy and a further surveillance endoscopy in 6 months [56]. If no dysplasia is found on biopsies at that stage, then the patient's risk is thought to be the same as non-dysplastic BO, with the need and timing of future surveillance determined by segment length and patient factors such as age and co-morbidity.

4.5 The Natural History of Barrett's Esophagus with Low Grade Dysplasia

Despite the recognized limitations of a diagnosis of low grade dysplasia, with the poor inter-observer agreement among histopathologists described above, recognition of low grade dysplasia appears of critical importance to the management of BO and prevention of esophageal adenocarcinoma. In cohort studies and two large

population based studies it was the most important predictor of subsequently developing esophageal adenocarcinoma, with BO subjects with low grade dysplasia five times more likely to develop esophageal adenocarcinoma than subjects without dysplasia [60, 61, 65]. In contrast, BO subjects who do not have low grade dysplasia at baseline and do not develop it during endoscopic follow-up appear to be at much lower risk of esophageal adenocarcinoma. Among a cohort of 3515 BO subjects, the risk of esophageal adenocarcinoma progressively fell in subjects who had an increasing number of surveillance endoscopies up to five that did not reveal dysplasia, from 0.32% per year to 0.11% per year [66].

Important data on the risk of progression of low grade dysplasia to esophageal adenocarcinoma has been provided by a retrospective analysis of 293 subjects with low grade dysplasia diagnosed at a number of community hospitals [67, 68]. Following a new consensus review, the original diagnosis of low grade dysplasia was confirmed in 27% of cases and downgraded to no dysplasia or indefinite for dysplasia in the others. Subjects with confirmed low grade dysplasia had a high risk of progression to high grade dysplasia or esophageal adenocarcinoma of 9.1% per year. Subjects whose diagnosis was down-staged, to either non-dysplastic BO or indefinite for dysplasia, had much lower rates of progression to high grade dysplasia or esophageal adenocarcinoma of 0.6 and 0.9% per year, respectively. This is supported by the results of a meta-analysis that reported that cohort studies with a lower ratio of low grade dysplasia to non-dysplastic BO cases, suggesting more stringent criteria for low grade dysplasia, reported a higher annual incidence of esophageal adenocarcinoma (0.76%) compared to studies with higher ratios (0.32%) [69]. Furthermore, in a trial of radio-frequency ablation for low grade dysplasia in BO, over a 3 year period 26.5% of subjects undergoing surveillance only progressed to high grade dysplasia or esophageal adenocarcinoma, compared with only 1% in the radio-frequency ablation arm ($p < 0.001$) [70]. To be eligible for inclusion in this study, the diagnosis of low grade dysplasia had to be confirmed by a central pathologist with extensive experience in BO.

Due to the variability among histopathologists in diagnosing low grade dysplasia, it is recommended that low grade dysplasia should be diagnosed on at least two endoscopies and confirmed by a histopathologist with expertise in BO. BO patients with low grade dysplasia should therefore have a repeat endoscopy in 6 months. If low grade dysplasia is reported at any follow-up endoscopy and confirmed by an expert gastrointestinal histopathologist, the patient should be offered endoscopic ablation therapy following multi-disciplinary team discussion given the high risk of progression to adenocarcinoma under these circumstances [70, 71].

4.6 The Natural History of Barrett's Esophagus with High Grade Dysplasia

Historically, high grade dysplasia was regarded as an indication for esophagectomy, given the high rate of carcinoma reported in resection specimens in surgical series for high grade dysplasia [72]. However, careful intensive endoscopic follow-up

tempered this approach. The reported esophageal adenocarcinoma risk in subjects with high grade dysplasia seems to be highly variable between different series and is likely to reflect that patients are not usually just followed up when high grade dysplasia has been diagnosed, that there is variation in histopathological diagnosis of high grade dysplasia between different centers and that the endoscopic appearances of early esophageal adenocarcinoma were not as well appreciated in published studies as they are today.

In a cohort study in 50 BO subjects, 5 out of 8 high grade dysplasia subjects developed adenocarcinoma on repeat endoscopies within 1 year [73]. Among a cohort of 1099 subjects, 79 initially had high grade dysplasia or subsequently developed it, without evidence of adenocarcinoma. Of the 75 high grade dysplasia subjects who remained without detectable adenocarcinoma after 1 year of intensive searching, 12 developed cancer (16%) during a mean 7.3-year surveillance period [74]. In a recent multi-center, sham-controlled study of radio-frequency ablation in BO with dysplasia, 21 subjects with high grade dysplasia underwent sham treatment and were followed up for 12 months with endoscopy and biopsies at 3-month intervals. Progression to adenocarcinoma occurred in 19% of subjects, while disappearance of HGD was seen in 19%, implying that even in the carefully controlled conditions of a clinical trial, high grade dysplasia can still regress to lower grades or no dysplasia, as well as progress to adenocarcinoma [75].

Although there may be visible abnormalities at endoscopy in high grade dysplasia, these can often be subtle and overlooked. It is therefore essential that there is an immediate repeat high quality endoscopy to look for any visible lesions suitable for endoscopic mucosal resection and map the extent of any dysplastic changes prior to any management decisions [56]. More than 80% of patients referred for further management of HGD or early esophageal adenocarcinoma, apparently without visible abnormalities, have at least one visible lesion detected in their BO segment on expert endoscopic assessment [76]. All patients with high grade dysplasia for which therapy is being considered, should be discussed at the specialist MDT for esophagogastric cancer [56]. This team should include an interventional endoscopist, upper GI cancer surgeon, radiologist, and a GI pathologist. Increasingly endoscopic therapy with endoscopic mucosal resection and radio-frequency ablation is the mainstay of treatment in patients with high grade dysplasia. A systematic review showed a mortality of 1.2% in the esophagectomy group compared with 0.04% in the endoscopic group [77] and radio-frequency ablation has been shown to be more cost-effective than esophagectomy for high grade dysplasia [78].

References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900–20.
2. Mittal RK, Balaban DH. The esophagogastric junction. N Engl J Med. 1997;336:924–32.
3. van Herwaarden MA, Samsom M, Smout AJ. The role of hiatus hernia in gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol. 2004;16:831–5.

4. Mittal RK, Holloway RH, Penagini R, Blackshaw LA, Dent J. Transient lower esophageal sphincter relaxation. Gastroenterology. 1995;109:601–10.
5. Roman S, Holloway R, Keller J, Herbella F, Zerbib F, Xiao Y, Bernard L, Bredenoord AJ, Bruley des Varannes S, Chen M, Fox M, Kahrilas PJ, Mittal RK, Penagini R, Savarino E, Sifrim D, Wu J, Decullier E, Pandolfino JE, Mion F. Validation of criteria for the definition of transient lower esophageal sphincter relaxations using high-resolution manometry. Neurogastroenterol Motil. 2017;29(2):e12920.
6. Tack J, Pandolfino JE. Pathophysiology of gastroesophageal reflux disease. Gastroenterology. 2018;154(2):277–88. https://doi.org/10.1053/j.gastro.2017.09.047.
7. Dent J, Holloway RH, Toouli J, et al. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. Gut. 1988;29:1020–8.
8. Trudgill NJ, Riley SA. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. Am J Gastroenterol. 2001;96:2569–74.
9. Sifrim D, Holloway R, Silny J, Tack J, Lerut A, Janssens J. Composition of the postprandial refluxate in patients with gastroesophageal reflux disease. Am J Gastroenterol. 2001;96:647–55.
10. Pandolfino JE, Kahrilas PJ. AGA technical review on the clinical use of esophageal manometry. Gastroenterology. 2005;128:209–24.
11. De Giorgi F, Palmiero M, Esposito I, Mosca F, Cuomo R. Pathophysiology of gastro-oesophageal reflux disease. Acta Otorhinolaryngol Ital. 2006;26(5):241–6.
12. Iovino P, Mohammed I, Anggiansah A, Anggiansah R, Cherkas LF, Spector TD, Trudgill NJ. A study of pathophysiological factors associated with gastro-esophageal reflux disease in twins discordant for gastro-esophageal reflux symptoms. Neurogastroenterol Motil. 2013;25(8):650–6. https://doi.org/10.1111/nmo.12137. Epub 2013 May 26.
13. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. J Clin Invest. 1980;65:256–67.
14. Goyal RK, Rattan S. Nature of the vagal inhibitory innervation to the lower esophageal sphincter. J Clin Invest. 1975;55:1119–26.
15. Hoshino M, Sundaram A, Mittal SK. Role of the lower esophageal sphincter on acid exposure revisited with high-resolution manometry. J Am Coll Surg. 2011;213:743–50.
16. Nicodeme F, Pipa-Muniz M, Khanna K, Kahrilas PJ, Pandolfino JE. Quantifying esophagogastric junction contractility with a novel HRM topographic metric, the EGJ-contractile integral: normative values and preliminary evaluation in PPI non-responders. Neurogastroenterol Motil. 2014;26:353–60.
17. Tolone S, De Bortoli N, Marabotto E, et al. Esophagogastric junction contractility for clinical assessment in patients with GERD: a real added value? Neurogastroenterol Motil. 2015;27:1423–31.
18. Wang D, Patel A, Mello M, et al. Esophagogastric junction contractile integral (EGJ-CI) quantifies changes in EGJ barrier function with surgical intervention. Neurogastroenterol Motil. 2016;28(5):639–46. NGM 2015.
19. Sloan S, Rademaker AW, Kahrilas PJ. Determinants of gastroesophageal junction incompetence: hiatal hernia, lower esophageal sphincter, or both? Ann Intern Med. 1992;117(12):977–82.
20. Curci JA, Melman LM, Thompson RW, Soper NJ, Matthews BD. Elastic fiber depletion in the supporting ligaments of the gastroesophageal junction: a structural basis for the development of hiatal hernia. J Am Coll Surg. 2008;207:191–6.
21. Michelson E, Siegel C. The role of the phrenico-esophageal ligament in the lower esophageal sphincter. Surg Gynecol Obstet. 1964;118:1291–129.
22. Kahrilas PJ, Lin S, Manka M, et al. Esophagogastric junction pressure topography after fundoplication. Surgery. 2000;127:200–8.
23. Pandolfino JE, Kim H, Ghosh SK, Clarke JO, Zhang Q, Kahrilas PJ. High-resolution manometry of the EGJ: an analysis of crural diaphragm function in GERD. Am J Gastroenterol. 2007;102:1056–63.

24. Patti MG, Goldberg HI, Arcerito M, Bortolasi L, Tong J, Way LW. Hiatal hernia size affects lower esophageal sphincter function, esophageal acid exposure, and the degree of mucosal injury. Am J Surg. 1996;171:182–6.
25. Sloan S, Kahrilas PJ. Impairment of esophageal emptying with hiatal hernia. Gastroenterology. 1991;100:596–605.
26. Jones MP, Sloan SS, Jovanovic B, Kahrilas PJ. Impaired egress rather than increased access: an important independent predictor of erosive oesophagitis. Neurogastroenterol Motil. 2002;14:625–31.
27. Gillen P, Keeling P, Byrne PJ, et al. Barrett's oesophagus: pH profile. Br J Surg. 1987;74:774–6.
28. Karvelis KC, Drane WE, Johnson DA, et al. Barrett esophagus: decreased esophageal clearance shown by radionuclide esophageal scintigraphy. Radiology. 1987;162:97–9.
29. Frazzoni L, Frazzoni M, de Bortoli N, Tolone S, Furnari M, Martinucci I, Bertani H, Marchi S, Conigliaro R, Fuccio L, Savarino V, Savarino E. Postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance can link PPI-responsive heartburn to reflux better than acid exposure time. Neurogastroenterol Motil. 2017;29(11):e13116. https://doi.org/10.1111/nmo.13116.
30. Frazzoni M, Savarino E, de Bortoli N, et al. Analyses of the post-reflux swallow-induced peristaltic wave index and nocturnal baseline impedance parameters increase the diagnostic yield of impedance-pH monitoring of patients with reflux disease. Clin Gastroenterol Hepatol. 2016;14:40–6.
31. Penagini R, Bravi I. The role of delayed gastric emptying and impaired oesophageal body motility. Best Pract Res Clin Gastroenterol. 2010;24:831–45.
32. Fletcher J, Wirz A, Young J, et al. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. Gastroenterology. 2001;121:775–83.
33. Beaumont H, Bennink RJ, de Jong J, et al. The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and patients with GORD. Gut. 2010;59:441–51.
34. Iovino P, Angrisani L, Galloro G, Consalvo D, Tremolaterra F, Pascariello A, Ciacci C. Proximal stomach function in obesity with normal or abnormal oesophageal acid exposure. Neurogastroenterol Motil. 2006;18(6):425–32.
35. Iovino P, Angrisani L, Tremolaterra F, Nirchio E, Ciannella M, Borrelli V, Sabbatini F, Mazzacca G, Ciacci C. Abnormal esophageal acid exposure is common in morbidly obese patients and improves after a successful lap-band system implantation. Surg Endosc. 2002;16(11):1631–5.
36. de Vries DR, van Herwaarden MA, Smout AJ, Samsom M. Gastroesophageal pressure gradients in gastroesophageal reflux disease: relations with hiatal hernia, body mass index, and esophageal acid exposure. Am J Gastroenterol. 2008;103:1349–54.
37. Jacobson BC, Somers SC, Fuchs CS, et al. Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med. 2006;354:2340–8.
38. Savarino E, Tutuian R, Zentilin P, Dulbecco P, Pohl D, Marabotto E, Parodi A, Sammito G, Gemignani L, Bodini G, Savarino V. Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. Am J Gastroenterol. 2010;105(5):1053–61.
39. Weijenborg PW, Bredenoord AJ. How reflux causes symptoms: reflux perception in gastroesophageal reflux disease. Best Pract Res Clin Gastroenterol. 2013;27:353–64.
40. Barlow WJ, Orlando RC. The pathogenesis of heartburn in nonerosive reflux disease: a unifying hypothesis. Gastroenterology. 2005;128(3):771–8.
41. van Malenstein H, Farré R, Sifrim D. Esophageal dilated intercellular spaces (DIS) and nonerosive reflux disease. Am J Gastroenterol. 2008;103(4):1021–8.
42. Solcia E, Villani L, Luinetti O, Trespi E, Strada E, Tinelli C, Fiocca R. Altered intercellular glycoconjugates and dilated intercellular spaces of esophageal epithelium in reflux disease. Virchows Arch. 2000;436(3):207–16.
43. Farré R, Blondeau K, Clement D, Vicario M, Cardozo L, Vieth M, Mertens V, Pauwels A, Silny J, Jimenez M, Tack J, Sifrim D. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. Gut. 2011;60(7):885–92.

44. Frazzoni M, de Bortoli N, Frazzoni L, Furnari M, Martinucci I, Tolone S, Farioli A, Marchi S, Fuccio L, Savarino V, Savarino E. Impairment of chemical clearance and mucosal integrity distinguishes hypersensitive esophagus from functional heartburn. J Gastroenterol. 2017;52(4):444–51.
45. Farré R, van Malenstein H, De Vos R, Geboes K, Depoortere I, Vanden Berghe P, Fornari F, Blondeau K, Mertens V, Tack J, Sifrim D. Short exposure of oesophageal mucosa to bile acids, both in acidic and weakly acidic conditions, can impair mucosal integrity and provoke dilated intercellular spaces. Gut. 2008;57(10):1366–74.
46. Souza RF, Huo X, Mittal V, et al. Gastroesophageal reflux might cause esophagitis through a cytokine-mediated mechanism rather than caustic acid injury. Gastroenterology. 2009;137(5):1776–84.
47. Dunbar KB, Agoston AT, Odze RD, Huo X, Pham TH, Cipher DJ, Castell DO, Genta RM, Souza RF, Spechler SJ. Association of acute gastroesophageal reflux disease with esophageal histologic changes. JAMA. 2016;315(19):2104–12.
48. Matthews PJ, Aziz Q, Facer P, Davis JB, Thompson DG, Anand P. Increased capsaicin receptor TRPV1 nerve fibres in the inflamed human oesophagus. Eur J Gastroenterol Hepatol. 2004;16(9):897–902.
49. Kandulski A, Wex T, Mönkemüller K, Kuester D, Fry LC, Roessner A, Malfertheiner P. Proteinase-activated receptor-2 in the pathogenesis of gastroesophageal reflux disease. Am J Gastroenterol. 2010;105(9):1934–43.
50. Knowles CH, Aziz Q. Visceral hypersensitivity in non-erosive reflux disease. Gut. 2008;57(5):674–83.
51. Farré R, De Vos R, Geboes K, Verbecke K, Vanden Berghe P, Depoortere I, Blondeau K, Tack J, Sifrim D. Critical role of stress in increased oesophageal mucosa permeability and dilated intercellular spaces. Gut. 2007;56(9):1191–7.
52. Iovino P, Pascariello A, Limongelli P, Tremolaterra F, Consalvo D, Sabbatini F, Amato G, Ciacci C. The prevalence of sexual behavior disorders in patients with treated and untreated gastroesophageal reflux disease. Surg Endosc. 2007;21(7):1104–10.
53. Kessing BF, Bredenoord AJ, Saleh CM, Smout AJ. Effects of anxiety and depression in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2015;13(6):1089–95.e1.
54. Barrett NR. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. Br J Surg. 1950;38(150):175–82.
55. Bremner CG, Lynch VP, Ellis FH Jr. Barrett's esophagus: congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. Surgery. 1970;68:209–16.
56. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014;63:7–42.
57. Morson BC, Belcher JR. Adenocarcinoma of the esophagus and ectopic gastric mucosa. Br J Cancer. 1952;6:127–30.
58. Desai TK, Krishnan K, Samala N, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut. 2012;61:970–6.
59. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst. 2011;103(13):1049–57.
60. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011;365:1375–83.
61. Sikkema M, Looman CW, Steyerberg EW, et al. Predictors for neoplastic progression in patients with Barrett's esophagus: a prospective cohort study. Am J Gastroenterol. 2011;106(7):1231–8.
62. Odze RD. Barrett esophagus: histology and pathology for the clinician. Nat Rev Gastroenterol Hepatol. 2009;6:478–90.
63. Sonwalkar SA, Rotimi O, Scott N, et al. A study of indefinite for dysplasia in Barrett's oesophagus: reproducibility of diagnosis, clinical outcomes and predicting progression with AMACR (alpha-methylacyl-CoA-racemase). Histopathology. 2010;56:900–7.
64. Younes M, Lauwers GY, Ertan A, et al. The significance of "indefinite for dysplasia" grading in Barrett metaplasia. Arch Pathol Lab Med. 2011;135:430–2.

65. Theron BT, Padmanabhan H, Aladin H, Smith P, Campbell E, Nightingale P, Cooper BT, Trudgill NJ. The risk of oesophageal adenocarcinoma in a prospectively recruited Barrett's oesophagus cohort. United European Gastroenterol J. 2016;4(6):754–61.
66. Gaddam S, Singh M, Balasubramanian G, et al. Persistence of nondysplastic Barrett's esophagus identifies patients at lower risk for esophageal adenocarcinoma: results from a large multicenter cohort. Gastroenterology. 2013;145(3):548–53.
67. Curvers WL, ten Kate FJ, et al. Low-grade dysplasia in Barrett's esophagus: over diagnosed and underestimated. Am J Gastroenterol. 2010;105(7):1523–30.
68. Duits LC, Phoa KN, Curvers WL, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut. 2015;64(5):700–6.
69. Singh S, et al. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. Gastrointest Endosc. 2014;79(6):897–909.
70. Phoa KN, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. 2014;311(12):1209–17.
71. di Pietro M, Fitzgerald RC; BSG Barrett's guidelines working group. Revised British Society of Gastroenterology recommendation on the diagnosis and management of Barrett's oesophagus with low-grade dysplasia. Gut. 2018;67(2):392–3. doi: https://doi.org/10.1136/gutjnl-2017-314135. Epub 2017 Apr 7
72. Dar MS, Goldblum JR, et al. Can extent of high grade dysplasia in Barrett's oesophagus predict the presence of adenocarcinoma at oesophagectomy? Gut. 2003;52(4):486–9.
73. Hameeteman W, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. Gastroenterology. 1989;96(5):1249–56.
74. Schnell TG, Sontag SJ, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. Gastroenterology. 2001;120(7):1607–19.
75. Shaheen NJ, Sharma P, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009;360:2277–88.
76. Curvers WL, Singh R, Song LM, et al. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut. 2008;57:167–72.
77. Menon D, Stafinski T, Wu H, et al. Endoscopic treatments for Barrett's esophagus a systematic review of safety and effectiveness compared to esophagectomy. BMC Gastroenterol. 2010;10:111.
78. Boger PC, Turner D, Roderick P, et al. A UK-based cost-utility analysis of radiofrequency ablation or oesophagectomy for the management of high-grade dysplasia in Barrett's oesophagus. Aliment Pharmacol Ther. 2010;32:1332–42.

Obesity: Barrett's Esophagus and Esophageal Cancer Risk

5

Jean Marc Chevallier, Sonja Chiappetta, and Mario Musella

5.1 Introduction

The gastro-esophageal reflux disease (GERD) is the passage of gastric content into the esophagus. It can lead to non-erosive or erosive esophagitis due to acid and/or bile.

The frequency of upper gastrointestinal symptoms like abdominal pain, vomiting, diarrhea, and actually GERD is highly increased in obese patients (BMI > 30 kg/m^2).

The association between obesity and GERD reflux has been demonstrated in the United States where obesity rates are the highest and have also been seen in Europe and Eastern Asia [1].

A study on 10,545 American nurses showed that the relative risk of frequent GERD (more than once a week) is linearly correlated with the BMI to reach 2.9 for obese patients [2]. A similar link was seen in the results from 80,110 insurance members from the Kaiser Permanente Multiphasic Health Check-up cohort [3]. The association between BMI and GERD was stronger among whites compared with black members, with ORs of 1.58 and 1.33, respectively.

The high prevalence of GERD was confirmed by a study on 24 h-pH testings performed on 100 obese patients waiting for bariatric surgery [4]. An increase of

J. M. Chevallier (✉)
Service de Chirurgie Digestive, Hôpital Européen Georges Pompidou, Paris, France
e-mail: jean-marc.chevallier@aphp.fr

S. Chiappetta
Department of Obesity and Metabolic Surgery, Sana Klinikum Offenbach, Offenbach am Main, Germany

M. Musella
General Surgery Unit, Department of Advanced Biomedical Sciences, University Federico II—School of Medicine, Naples, Italy
e-mail: mario.musella@unina.it

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_5

time exposure of the lower esophagus to acid was observed in 46% of the cases. The pH testing was altered according to the BMI.

The effect of weight change on GERD symptoms has been studied. Jacobson [2] studied select individuals from the Nurses' Health Study and found that an increase of BMI by more than 3.5 kg/m^2 when compared with no weight change was associated with an increased risk of frequent symptoms of reflux.

Based on a systematic review, the prevalence rate of GERD in Europe was estimated to be 15% for the period 2005–2009 [5]. The epidemiologic relation between obesity and GERD has been observed in Europe as well. The German National Health Interview and Examination Survey found the OR for GERD to be 1.8 for overweight and 2.6 for obese individuals [6]. In England, the Bristol Helicobacter Project found that obese individuals had an OR of 2.91 for heartburn and an OR of 2.23 for regurgitation [7]. In a cohort of 1001 Swedish patients representing the whole population and having had an endoscopy, the patients who had a BMI > 30 kg/m^2 had an esophagitis in 26.5% of the cases compared with 9.3% in nonobese patients [8].

5.2 Factors Leading to GERD

The factors leading to GERD are mechanical or related to changes in esophageal motility.

The existence of a hiatal hernia, especially if it is a huge one, is associated with an increase in the seriousness of the GERD symptoms. The reason is that the hiatal hernia alters the function of the lower esophageal sphincter (LES) and increases the time during which the esophageal mucosa remains in contact with gastric acid. Stene-Larsen showed in a prospective study in 2019 patients that the overweight patients had a higher prevalence of hiatal hernia than the patients with normal weight [8]. This was even more correlated with patients having associated esophagitis. An other case-control study [9] showed that overweight (BMI between 25 and 30 kg/m^2) is associated with 2.5 times more risk of hiatal hernia (IC 95%: 1.5–4.3) compared with slim patients and the risk is 4.2 times more (IC 95%: 2.4–7.6) in obese patients.

The association between hiatal hernia and esophagitis was almost ten times more frequent in obese patients compared with control patients (OR: 9.9; IC 95%: 8.8–11.1).

In a series of patients with a BMI equal to or above 35 kg/m^2, a hiatal hernia was found in 39.4% and an esophagitis in 6.4%. Suter and colleagues [10] studied morbidly obese patients with history of reflux symptoms with upper endoscopy, 24-h pH monitoring, and manometry. They observed that of 345 subjects approximately half had a hiatal hernia.

These studies suggest that the increase of BMI is associated with a higher risk of hiatal hernia.

The impairment of the esophageal motility or the lower esophageal sphincter (LES) could lead to GERD in overweight or obese patients. Deficiency of the LES is frequently associated with GERD as demonstrated by this systematic manometric study on motility disorders in 100 patients waiting for bariatric surgery [11].

Decrease of the LES pressure is noted in 69% of the patients. Two similar studies have reported multiple motility disorders in morbidly obese patients waiting for bariatric surgery. In one [12] 54% of the patients had abnormal manometric findings: in 33 patients out of 61, ten had a defective LES whereas eleven had a hypertensive LES, two had diffuse esophageal spasm, three had nutcracker esophagitis, one presented ineffective esophageal disorder, and fourteen had nonspecific esophageal motility disorder. Some patients had more than one disorder.

In the other study, Jaffin [13] showed in 111 patients with mean BMI of 50.7 ± 9.4 kg/m^2 that there is no correlation between BMI and LES pressure. But 61% of the patients had esophageal motility disorders (25% defective, 14% nutcraker, 14% nonspecific, 7% diffuse spasm, and 1% achalasia). These authors noted that 59% of these patients having esophageal motility disorders did not suffer from any symptom (heartburn, dysphagia, or chest pain), suggesting that obesity might be accompanied by an alteration of the sensation of the visceral pain.

Central obesity seems also to be related with GERD. Central obesity has an effect on esophago-gastric junction even without creating a hiatal hernia. Pandolfino [14] performed high-resolution manometries in three groups of patients (normal weight, overweight, obese). Compared to both other groups, the obese group showed an increase of intragastric and intraesophageal pressure and an increase of the gastro-esophageal gradient. Abdominal obesity increases intra-abdominal pressure. Lambert and colleagues studied morbidly obese patients with a urinary catheter as a surrogate for intra-abdominal pressure and found that obese patients compared with nonobese patients had higher intra-abdominal pressures [15].

The increase of the intra-abdominal pressure deteriorates also the LES. A Chinese team [16] combined a 2 h-long postprandial manometry to a 24 h pH testing after a standard meal in three groups of patients (normal weight, overweight, and obese). The LES basal pressure was similar in the three groups, but transient LES relaxation was particularly frequent in the last two groups, with association between LES relaxation and GERD. The postprandial increase of transient LES relaxation in overweight and obese patients was considered as related to the increase of the intragastric pressure.

In conclusion, the potential pathogenic mechanisms in the obese leading to GERD are:

- Increase of intra-abdominal and intragastric pressures.
- Increase of transient relaxation of lower esophageal sphincter.
- Hiatal hernia.
- Decrease of lower esophageal sphincter pressure.
- Esophageal dysmotility.

5.3 Obesity, Barrett's Ulcer, and Risk of Cancer

The main complication of GERD is the occurrence of a Barrett's esophagus (BE). It is a typical endoscopic pattern presenting glandular mucosa above the esophago-gastric junction and histologically a specialized mucosa with

intestinal metaplasia. The odds-ration of BE increases with the BMI: 2.43 (Confidence Interval 95%: 0.68–4.2, $p = 0.261$) for overweight patients to 4.0 (CI 95%: 1.4–11.1, $p = 0.008$) for obese patients, independently from sex and ethnicity [17].

The link between obesity and esophageal neoplasia may be via altered secretion of adipokines such as adiponectin and leptin. Adiponectin is a protein that has anti-inflammatory and immunomodulatory functions and stimulates apoptosis. Secretion of adiponectin decreases with obesity. In a case-control study, Rubenstein [18] found an inverse association between plasma adiponectin levels and the presence of BE. Leptin is secreted by adipocytes and gastric chief cells. Leptin levels correlate directly with obesity [19]. Leptin has been shown to have mitogenic properties and induce proliferation in human cell lines including esophageal cancer cells [20].

Abdominal diameter index is a stronger predictor of prevalent Barrett's esophagus than BMI or waist-to-hip ratio [21]. In a recent study, 31 BE patients have been compared to 27 control patients. The BE cohort were older and had a higher rate of hiatal hernia. The mean abdominal diameter index for patients with BE was 0.65 ± 0.07 and without BE was 0.60 ± 0.07 ($p = 0.01$). The abdominal diameter index appeared to be the only significant predictor of BE in multivariate analysis.

A meta-analysis including seven studies [22] found an increased risk of lower esophageal adenocarcinoma in overweight patients (OR: 1.52: CI 95%: 1.15–2.01) and in obese patients (OR: 2.78; CI 95%:1.85–4.16).

The recent increase of the incidence of the adenocarcinoma of the cardia has been related to the increase of obesity.

The acid attack on the esophagus is the main trigger for BE but bile reflux has its own role. In BE reflux is mostly mixt, presenting both acid and bile. A long history of GERD and a deficient LES can lead to an extended BE (more than 3 cm long) and there is a relation between the length of the BE and the exposure of the esophagus to acid and/or bile.

The main complication of BE is its conversion into adenocarcinoma. Incidence reported in older series is between 0.2 and 2.1% patient/year of follow-up, which represents an increased risk of cancer by 30 or 50 times more than the general population [23]. Most of the studies have been done for long BE, the risk of cancer after short BE seems to be lower but not well known.

The prevalence of the dysplasia depends on the length of the BE [24]: around 8.5% for short BE (<3 cm), between 15 and 25% in long BE. The evolution of a non-dysplastic mucosa to a cancer can take at least 4 years. The probability for a low dysplasia to progress to a high dysplasia is between 6 months and 4 years. When the BE contains high dysplasia, the risk to evolve to a cancer is great. In a series of 76 patients endoscopically surveyed for high dysplasia, the cumulative incidence of cancer was between 60 and 80%, respectively, 4 and 6 years after the diagnosis of the dysplasia compared with patients without dysplasia or with low dysplasia where the incidence of cancer was only 10% after 10 years.

5.4 Bariatric Surgery and the Risk of GERD

The typical manifestations of gastro-esophageal reflux disease (GERD) are heartburn and/or regurgitation. GERD can be further classified into erosive and non-erosive GERD based on endoscopic appearance of esophageal mucosa. The recognized sequelae of GERD include Barrett's esophagus and esophageal adenocarcinoma. Obesity, defined as a Body Mass Index (BMI) ≥ 30, is common in the Western world and is increasing in other parts of the world, particularly Asia. Epidemiologic data demonstrate that overall obesity is a risk factor for both GERD [25] and esophageal adenocarcinoma [26]. There is evidence that central abdominal obesity, including increased abdominal pressure, is the most important factor associated with Barrett's esophagus [1].

Cross-sectional epidemiological studies have demonstrated a higher prevalence of GERD in obese individuals compared to the nonobese. Jacobsen et al. used a supplemental GERD questionnaire to show that subjects that reported at least weekly symptoms had a near linear increase in the adjusted odds-ratio for reflux symptoms for each BMI strata [2].

Approximately one-half of morbidly obese patients have objectively documented GERD (by either endoscopy or esophageal pH monitoring), even though some patients with these abnormalities do not report reflux symptoms. While fundoplication is the mainstay for the treatment of severe GERD, the outcomes and durability in the setting of obesity are poor [27]. Bariatric surgery is an effective approach to weight loss, and the data has generally shown that this weight loss can have positive effects on GERD [28].

5.5 GERD Following Restrictive Procedures

5.5.1 Laparoscopic Adjustable Gastric Banding

Laparoscopic adjustable gastric banding (LAGB) has gained increasing acceptance throughout the world because of its relative simplicity, safety, efficacy, and its low complication rate [29, 30]. Although it has proven effective in weight reduction, the effect on esophageal function and gastro-esophageal reflux is still unclear and published data on the effects of gastric banding on GERD reveal conflicting results [31, 32].

A review of the current literature on gastric banding shows a pattern of short-term improvement of GERD after band positioning, which can reverse course to an eventual worsening of this pathology. Although there is some symptom data supporting improvement of pre-existing GERD after 3 years [33], different studies suggest a relapse after several years: Himpens et al. [34] recorded 20.5% of de novo GERD 3 years after LAGB and Gutschow et al. [35] found pathologic reflux rates both on endoscopy and with pH-metry 3–4 years after LAGB. Moreover, a case of Barrett's esophagus has been communicated as late complication of this procedure by Varela [36].

The anti-reflux effect of the band is thought to be related to augmentation of the lower esophageal sphincter (LES) by creating a longer intra-abdominal pressure zone. On the other side, the incidence of esophageal dilation after gastric banding is significant and can worsen GERD postoperatively: this is probably due to the inflated band which reduces trans-stomal flow by narrowing the esophageal outlet, leading to reduced esophageal clearance, stasis of ingested food and refluxed material, and exerting physical expansion of the distal esophagus [37, 38]. Due to these and other long-term complications (slippage, intragastric migration, band and weight loss failure), the numbers of performed LAGB are decreasing worldwide [39].

Considering the adverse outcomes in relation to GERD in the long term, obese patients with GERD or esophageal dysmotility should be cautioned on receiving LAGB.

5.5.2 Laparoscopic Sleeve Gastrectomy

Laparoscopic sleeve gastrectomy (LSG) is nowadays the most performed bariatric procedure worldwide, which underlines the importance of the increasing discussion about the incidence of de novo GERD after LSG. Tai et al. [40] found a significant increase in the prevalence of GERD symptoms (47%) and erosive esophagitis (66.7%) 1 year after LSG. Of the population analyzed by Howard and colleagues [41], 18% were noted to have new-onset GERD on their postoperative upper gastrointestinal swallow test after their LSG procedure. Furthermore, in a recent long-term evaluation of the impact of LSG on Indian population, Garg et al. [42] found new-onset GERD in 2.8% and a worsened pre-existing GERD in 11.4% of patients at 7 years follow-up. Indeed, Nocca et al. reported GERD as the most common late complication after LSG in 39.1% of the patients [43] and Himpens et al. described de novo GERD in a follow-up of 6+ years in 21% of patients [44].

A worsening of the disease was also seen by Weiner et al. [45] who reported that 16% patients having postoperative GERD were healed by conversion to laparoscopic Roux-en-Y gastric bypass (RYGB). Lacy [46] in his paper of post sleeve revisional surgery, mentioned persistent reflux as cause of reoperation between 5 and 36%, and 15% had to be converted to bypass due to intractable reflux.

There are multiple factors that may explain the worsening of GERD after sleeve gastrectomy: first is the alteration of the angle of His which normally acts as a valve to prevent reflux of stomach contents into the esophagus; moreover, the transection near the angle of His during gastrectomy may hesitate in a decrease of LES pressure as reported by Burgerhart et al. [47]. LSG induces a significant elevation in intragastric pressures and gastro-esophageal pressure gradient [48]. Finally, in an effort to avoid fistulas, surgeons can also leave excess fundus at the time of operation, which then results in a sleeve-tube with a conical shape and the creation of a neo-fundus; the neo-fundus may serve as a reservoir for food and it may determine gastric stasis and increased acid production [49].

Another important aspect related to development of GERD is the appraisal of Barrett's esophagus. One year after LSG, Braghetto and Csendes found [50], among

their 231 patients operated, reflux symptoms in 57 (23.2%), erosive esophagitis in 38 patients (15.5%), and histological examination confirmed Barrett's esophagus (BE) in 3/231 cases (1.2%) with presence of intestinal metaplasia. A higher percentage of BE was found by Felsenreich et al. [51] from a total of 43 patients over a period of 130 months, six of them (14.0%) were converted to RYGB due to intractable reflux. De novo hiatal hernia was found in 45% of the patients and Barrett's metaplasia in 15%.

Finally, Genco et al. in a total of 110 patients with a mean follow-up of 58 months, found an increased incidence of GERD symptoms compared with preoperative values (68.1% versus 33.6%), at upper endoscopy. The group demonstrated an upward migration of the "Z" line and a biliary-like esophageal reflux in 73.6 and 74.5% of cases. At same time, authors found a significant increase in non-dysplastic Barrett's esophagus, which was newly diagnosed in 19 patients (17.2%) [52].

The fifth international consensus conference indicates pH and manometry study pre-laparoscopic sleeve gastrectomy [53]. Although sleeve gastrectomy is now considered an effective weight loss surgery, considering the consistent data regarding development and worsening of GERD, it generally is not recommended in patients with pre-existing reflux.

5.6 GERD Following Gastric Bypass Procedures

5.6.1 Laparoscopic Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) is still the gold standard in bariatric surgery despite its complex surgical technique and potential complications, due to its excellent outcomes in weight loss and its metabolic impact.

In his study on 55 patients with preoperative GERD, Schauer et al. [54] demonstrated that no patient had aggravation of the disease and 96% showed improvement or resolution of symptoms.

In a large multicenter study on 130,796 patients with 1-year follow-up, Sudan and colleagues compared outcomes from LAGB, LSG, RYGB, and biliopancreatic diversion with duodenal switch (BPD/DS). They found RYGB being the best procedure for resolution of GERD, and odds of resolution were 1.5 higher compared with other surgical techniques; this is probably due to the dimensions of the stomach pouch which after RYGB is smaller than in the other procedures, and acid and bile are directed downstream to help improve GERD symptoms [55].

Also, Pallati et al. [56] analyzed GERD score after various bariatric procedures in a cohort of 116,136 patients, 36,938 of which had evidence of GERD preoperatively; the review underlines an improvement of GERD symptoms significantly highest in RYGB patients (56.5%), followed by LAGB (46%) and LSG patients (41%). Worsening of GERD was seen in a small number of patients, mostly in LSG (4.6%), followed by RYGB (2%) and LAGB (1.2%).

There are small case-series examining the effect of RYGB on Barrett's esophagus. Houghton et al. found complete or partial regression in four of five Barrett's

esophagus patients following RYGB at an average of 34 months postoperatively [57]. Moreover, Csendes et al. studied 15 patients with long- and short-segment Barrett's esophagus; they found a 100% resolution of reflux and erosive esophagitis with a variable complete regression rate [58].

The superior efficacy of RYGB in morbidly obese patients with GERD is likely due to the anatomic configuration of a low-acid producing pouch, a low-pressure system and diversion of bile reflux by a Roux-en-Y re-construction, and the intra-abdominal pressure changes related to postoperative weight loss. By this point of view, RYGB is currently recommended for morbidly obese patients with GERD or Barrett's esophagus given the superior reflux control of both acid and non-acid events compared to other bariatric surgeries [59].

5.6.2 Mini/One Anastomosis Gastric Bypass

Since its introduction by Rutledge in 1997 [60], the Mini Gastric Bypass, named as One Anastomosis Gastric Bypass in the Spanish variant [61], (MGB/OAGB), has encountered the favor of a large number of surgeons, becoming the fourth most performed surgery in Europe and in the Asia/Pacific area [39].

Despite first skepticism in this technique, different authors have reported interesting results in terms of weight loss, low rate of mid- and long-term postoperative complications, and resolution of obesity-related comorbidities [62]. Moreover, compared with other bariatric procedures, MGB/OAGB has the advantage of being technically simple and easy to learn with less morbidity and mortality rate, especially in super obese patients with high operative risk [63].

In a recent Italian multicenter study on 2678 patients [64], a retrospective analysis was conducted to define the complication rate following the MGB in the short- and mid-term period. The risk of postoperative GERD, or better duodenal-gastro-esophageal reflux (DGER), was analyzed too. Despite a preoperative diagnosis of GERD present in 122/2678 patients (4.5%), Musella and colleagues found a GERD/DGER at 5-year follow-up in 28/683 patients (4.0%). Among them, on 18 patients presenting preoperative GERD, 4 (22.2%) worsened following MGB/OAGB, 10/18 (55.5%) reported a decrease in proton pump inhibitors (PPI) usage, while 4/18 (22.2%) experienced a documented improvement. Conversely, a total de novo GERD/DGER globally occurred in 14/683 patients in the follow-up (2.0%).

Tolone et al. [65] in a recent article have demonstrated, with usage of high-resolution impedance manometry (HRiM), that MGB/OAGB, in contrast with LSG, did not compromise the esophago-gastric junction function and that MGB/OAGB statistically diminishes intragastric pressures and gastro-esophageal pressure gradient.

Revising literature on this bariatric procedure, the incidence of bile reflux in MGB has been deeply discussed. Interesting results have been reported in the experimental setting by Chevallier [66], while retrospective studies with large numbers of patients have stated a rate of reflux much lower than 1%. Lee et al. [67] have described three cases out of more than 1300 MGBs (0.2%) with severe bile reflux

that had to be converted to RYGB whereas in another study from Italy, Musella et al. [68] have found a rate of 0.9% during upper endoscopy in almost 1000 MGB patients. Finally, Plamper et al. have found a comparable rate of 0.6% in his MGB patients [69]. The statistical correlation of postoperative duodenal-gastro-esophageal reflux (DGER) with a gastric pouch shorter than 9 cm [64] underlines the importance of performing the right anatomical technique to minimize bile reflux.

The advantages of MGB/OAGB include the low-pressure system and the intra-abdominal pressure changes related to postoperative weight loss. Further studies remain however necessary to define the positive effects of MGB/OAGB on GERD/DGER control.

References

1. Chang P, Friedenberg F. Obesity and GERD. Gastroenterol Clin N Am. 2014;43:161–73.
2. Jacobson BC, Somers SC, Fuchs CS, et al. Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med. 2006;354:2340–8.
3. Corley DA, Kubo A, Zhao W. Abdominal obesity, ethnicity and gastrooesophageal reflux symptoms. Gut. 2007;56(6):756–62.
4. Aro P, Ronkainen J, Talley NJ, et al. Body-mass index and chronic unexplained gastrointestinal symptoms: an adult endoscopic population based study. Gut. 2005;54:1377–83.
5. Von Ruesten A, Steffen A, Floegel A, et al. Trend in obesity prevalence in European adult cohort populations during follow-up since 1996 and their predictions to 2015. PLoS One. 2011;6(11):e27455.
6. Nocon M, Labenz J, Willich SN. Lifestyle factors and symptoms of gastrooesophageal reflux-a population-based study. Aliment Pharmacol Ther. 2006;23(1):169–74.
7. Murray L, Johnston B, Lane A, et al. Relationship between body mass and gastro-oeosophageal reflux symptoms : the Bristol Helicobacter Project. Int J Epidemiol. 2003;32(4):645–50.
8. Stene-Larsen G, Weberg R, Froyshov Larsen I, et al. Relationship of overweight to hiatus hernia and reflux oesophagitis. Scand J Gastroenterol. 1988;23:427–32.
9. Wilson LJ, Ma W, Hirschowitz BI. Association of obesity with hiatal hernia and esophagitis. Am J Gastroenterol. 1999;94:2840–4.
10. Suter M, Dorta G, Giusti V, et al. Gastro-oesophageal reflux and esophageal motility disorders in morbidly obese patients. Obes Surg. 2004;14(7):959–66.
11. Merrouche M, Sabate JM, Jouet P, et al. Gastro-esophageal reflux and esophageal motility disorders in morbidly obese patients before and after bariatric surgery. Obes Surg. 2007;17:894–900.
12. Hong D, Khajanchee YS, Pereira N, et al. Manometric abnormalities and gastroesophageal reflux disease in the morbidily obese. Obes Surg. 2004;14:744–9.
13. Jaffin BW, Knoepfelmacher P, Greenstein R. High prevalence of asymptomatic esophageal motility disorders among morbidly obese patients. Obes Surg. 1999;9:390–5.
14. Pandolfino JE, El-Serag HB, Zhang Q, et al. Obesity: a challenge to esophagogastric junction integrity. Gastroenterology. 2006;130:639–49.
15. Lambert DM, Marceau S, Forse RA. Intra-abdominal pressure in the morbidly obese. Obes Surg. 2005;15(9):1225–32.
16. Wu JC, Mui LM, Cheung CM, et al. Obesity is associated with increased transient lower esophageal sphincter relaxation. Gastroenterology. 2007;132:883–9.
17. El-Serag HB, Kyapil P, Kacken-Bitar J, et al. Abdominal obesity and the risk of Barrett's esophagus. Am J Gastroenterol. 2005;100:2151–6.
18. Rubenstein JH, Kao JY, Madanick RD, et al. Association of adiponectin multimers with Barrett's oesophagus. Gut. 2009;58(12):1583–9.

19. Weigle DS. Leptin and other secretory products of adipocytes modulate multiple physiological functions. Ann Endocrinol (Paris). 1997;58(2):132–6.
20. Ogunwobi O, Mutungi G, Beales IL. Leptin stimulates proliferation and inhibits apoptosis in Barrett's esophageal adenocarcinoma cells by cyclooxygenase-2-dependant, prostaglandin-E2-mediated transactivation of the epidermal growth factor receptor and c-Jun NH2-terminal kinase activation. Endocrinology. 2006;147(9):4505–16.
21. Baik D, Sheng J, Schlaffer K, et al. Abdominal diameter index is a stronger predictor of prevalent Barrett's esophagus than BMI or waist-to-hip ratio. Dis Esophagus. 2017;30(9):1–6.
22. Singh S, Sharma AN, Murad MH, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(11):1399–412.
23. Whiteman DC, Kendall BJ. Barrett's oesophagus: epidemiology, diagnosis and clinical management. Med J Aust. 2016;205(7):317–24.
24. Krishnamoorthi R, Lewis JT, Krishna M, et al. Predictors of progression in Barrett's oesophagus with low-grade dysplasia: results from a multicenter prospective BE Registry. Am J Gastroenterol. 2017;112(6):867–73.
25. El-Serag H. The association between obesity and GERD: a review of the epidemiological evidence. Dig Dis Sci. 2008;53(9):2307–12.
26. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. Lancet. 2014;384(9945):755–65.
27. Prachand VN, Alverdy JC. Gastroesophageal reflux disease and severe obesity: fundoplication or bariatric surgery? World J Gastroenterol. 2010;16(30):3757–61.
28. Tutuian R. Effects of bariatric surgery on gastroesophageal reflux. Curr Opin Gastroenterol. 2014;30(4):434–8.
29. Belachew M, Belva P, Desaive C. Long-term results of laparoscopic adjustable gastric banding for the treatment of morbid obesity. Obes Surg. 2002;12:564–8.
30. Carlin AM, Zeni TM, English WJ, Hawasli AA, Genaw JA, Krause KR, Schram JL, Kole KL, Finks JF, Birkmeyer JD, Share D, Birkmeyer NJ. The comparative effectiveness of sleeve gastrectomy, gastric bypass, and adjustable gastric banding procedures for the treatment of morbid obesity. Ann Surg. 2013;257:791–7.
31. Tolonen P, Victorzon M, Niemi R, Makela J. Does gastric banding for morbid obesity reduce or increase gastroesophageal reflux? Obes Surg. 2006;16:1469–74.
32. Rebecchi F, Rocchietto S, Giaccone C, et al. Gastroesophageal reflux disease and esophageal motility in morbidly obese patients submitted to laparoscopic adjustable silicone gastric banding or laparoscopic vertical banded gastroplasty. Surg Endosc. 2011;25:795–803.
33. Pilone V, Vitiello A, Hasani A, Di Micco R, Monda A, Izzo G, Forestieri P. Laparoscopic adjustable gastric banding outcomes in patients with gastroesophageal reflux disease or hiatal hernia. Obes Surg. 2015;25:290–4.
34. Himpens J, Dapri G, Cadière GB. A prospective randomized study between laparoscopic gastric banding and laparoscopic isolated sleeve gastrectomy: results after 1 and 3 years. Obes Surg. 2006;16:1450–6.
35. Gutschow CA, Collet P, Prenzel K, Hölscher AH, Schneider PM. Long-term results and gastroesophageal reflux in a series of laparoscopic adjustable gastric banding. J Gastrointest Surg. 2005;9:941–8.
36. Varela JE. Barrett's esophagus: a late complication of laparoscopic adjustable gastric banding. Obes Surg. 2010;20:244–6.
37. de Jong JR, van Ramshorst B, Timmer R, Gooszen HG, Smout AJ. The influence of laparoscopic adjustable gastric banding on gastroesophageal reflux. Obes Surg. 2004;14:399–406.
38. Milone L, Daud A, Durak E, Olivero-Rivera L, Schrope B, Inabnet WB, Davis D, Bessler M. Esophageal dilation after laparoscopic adjustable gastric banding. Surg Endosc. 2008;22:1482–6.
39. Angrisani L, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric surgery worldwide 2013. Obes Surg. 2015;25(10):1822–32.

40. Tai CM, Huang CK, Lee YC, Chang CY, Lee CT, Lin JT. Increase in gastroesophageal reflux disease symptoms and erosive esophagitis 1 year after laparoscopic sleeve gastrectomy among obese adults. Surg Endosc. 2013;27:1260–6.
41. Howard DD, Caban AM, Cendan JC, Ben-David K. Gastroesophageal reflux after sleeve gastrectomy in morbidly obese patients. Surg Obes Relat Dis. 2011;7:709–13.
42. Garg H, Aggarwal S, Misra MC, Priyadarshini P, Swami A, Kashyap L, Jaiswal R. Mid to long term outcomes of laparoscopic sleeve gastrectomy in Indian population: 3-7 year results - a retrospective cohort study. Int J Surg. 2017;48:201–9.
43. Nocca D, Loureiro M, Skalli EM, Nedelcu M, Jaussent A, Deloze M, Lefebvre P, Fabre JM. Five-year results of laparoscopic sleeve gastrectomy for the treatment of severe obesity. Surg Endosc. 2017;31(8):3251–7.
44. Himpens J, Dobbeleir J, Peeters G. Long-term results of laparoscopic sleeve gastrectomy for obesity. Ann Surg. 2010;252(2):319–24.
45. Weiner RA, Theodoridou S, Weiner S. Failure of laparoscopic sleeve gastrectomy—further procedure? Obes Facts. 2011;4(Suppl 1):42.
46. Lacy A, Ibarzabal A, Pando E, et al. Revisional surgery after sleeve gastrectomy. Surg Laparosc Endosc Percutan Tech. 2010;20:351–6.
47. Burgerhart JS, Schotborgh CA, Schoon EJ, Smulders JF, van de Meeberg PC, Siersema PD, Smout AJ. Effect of sleeve gastrectomy on gastroesophageal reflux. Obes Surg. 2014;24:1436–41.
48. Yehoshua RT, Eidelman LA, Stein M, Fichman S, Mazor A, Chen J, et al. Laparoscopic sleeve gastrectomy--volume and pressure assessment. Obes Surg. 2008;18(9):1083–8.
49. Laffin M, Chau J, Gill RS, Birch DW, Karmali S. Sleeve gastrectomy and gastroesophageal reflux disease. J Obes. 2013;2013:741097.
50. Braghetto I, Csendes A. Prevalence of Barrett's esophagus in bariatric patients undergoing sleeve gastrectomy. Obes Surg. 2016;26(4):710–4.
51. Felsenreich DM, Kefurt R, Schermann M, Beckerhinn P, Kristo I, Krebs M, Prager G, Langer FB. Reflux, sleeve dilation, and Barrett's esophagus after laparoscopic sleeve gastrectomy: long-term follow-up. Obes Surg. 2017;27(12):3092–101. https://doi.org/10.1007/s11695-017-2748-9.
52. Genco A, Soricelli E, Casella G, Maselli R, Castagneto-Gissey L, Di Lorenzo N, Basso N. Gastroesophageal reflux disease and Barrett's esophagus after laparoscopic sleeve gastrectomy: a possible, underestimated long-term complication. Surg Obes Relat Dis. 2017;13(4):568–74.
53. Gagner M, Hutchinson C, Rosenthal R. Fifth international consensus conference: current status of sleeve gastrectomy. Surg Obes Relat Dis. 2016;12(4):750–6.
54. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg. 2000;232:515–29.
55. Sudan R, Maciejewski ML, Wilk AR, Nguyen NT, Ponce J, Morton JM. Comparative effectiveness of primary bariatric operations in the United States. Surg Obes Relat Dis. 2017;13(5):826–34.
56. Pallati PK, Shaligram A, Shostrom VK, Oleynikov D, McBride CL, Goede MR. Improvement in gastroesophageal reflux disease symptoms after various bariatric procedures: review of the bariatric outcomes longitudinal database. Surg Obes Relat Dis. 2014;10(3):502–7.
57. Houghton SG, Romero Y, Sarr MG. Effect of Roux-en-Y gastric bypass in obese patients with Barrett's esophagus: attempts to eliminate duodenogastric reflux. Surg Obes Relat Dis. 2008;4(1):1–4.
58. Csendes A, Burgos AM, Smok G, et al. Effect of gastric bypass on Barrett's esophagus and intestinal metaplasia of the cardia in patients with morbid obesity. J Gastrointest Surg. 2006;10(2):259–64.
59. Kindel TL, Oleynikov D. The improvement of gastroesophageal reflux disease and Barrett's after bariatric surgery. Obes Surg. 2016;26(4):718–20.
60. Rutledge R. The mini gastric bypass: experience with the first 1274 cases. Obes Surg. 2001;11:276–80.

61. Carbajo M, García-Caballero M, Toledano M, Osorio D, García-Lanza C, Carmona JA. One-anastomosis gastric bypass by laparoscopy: results of the first 209 patients. Obes Surg. 2005;15(3):398–404.
62. Chevallier JM, Arman GA, Guenzi M, Rau C, Bruzzi M, Beaupel N, Zinzindohoué F, Berger A. One thousand single anastomosis (omega loop) gastric bypasses to treat morbid obesity in a 7-year period: outcomes show few complications and good efficacy. Obes Surg. 2015;25(6):951–8.
63. Taha O, Abdelaal M, Abozeid M, Askalany A, Alaa M. Outcomes of omega loop gastric bypass, 6-years experience of 1520 cases. Obes Surg. 2017;27(8):1952–60.
64. Musella M, Susa A, Manno E, De Luca M, Greco F, Raffaelli M, Cristiano S, Milone M, Bianco P, Vilardi A, Damiano I, Segato G, Pedretti L, Giustacchini P, Fico D, Veroux G, Piazza L. Complications following the mini/one anastomosis gastric bypass (MGB/OAGB): a multi-institutional survey on 2678 patients with a mid-term (5 years) follow-up. Obes Surg. 2017;27(11):2956–67.
65. Tolone S, Cristiano S, Savarino E, et al. Effects of omega-loop bypass on esophagogastric junction function. Surg Obes Relat Dis. 2016;12:62–9.
66. Bruzzi M, Duboc H, Gronnier C, Rainteau D, Couvelard A, Le Gall M, Bado A, Chevallier JM. Long-term evaluation of biliary reflux after experimental one-anastomosis gastric bypass in rats. Obes Surg. 2017;27(4):1119–22.
67. Lee WJ, Lee YC, Ser KH, Chen SC, Chen JC, Su YH. Revisional surgery for laparoscopic minigastric bypass. Surg Obes Relat Dis. 2011;7(4):486–91.
68. Musella M, Susa A, Greco F, De Luca M, Manno E, Di Stefano C, et al. The laparoscopic mini-gastric bypass: the Italian experience: outcomes from 974 consecutive cases in a multicenter review. Surg Endosc. 2014;28(1):156–63.
69. Plamper A, Lingohr P, Nadal J, Rheinwalt KP. Comparison of mini-gastric bypass with sleeve gastrectomy in a mainly super-obese patient group: first results. Surg Endosc. 2017;31(3):1156–62.

Part III

Diagnosis

First Level Endoscopy in Barrett's Esophagus: Endoscopic Pictures, Praga Classification, and Biopsy Protocols

6

Massimo Conio, Antonella De Ceglie, and Mattia Crespi

6.1 Endoscopic Pictures

Endoscopy is considered the gold standard to diagnose Barrett's esophagus (BE). The term endoscopy is generally referred to as standard trans-oral endoscopy.

Trans-nasal endoscopy has shown a sensibility and specificity of 100% for endoscopic diagnosis of BE when compared with standard endoscopy; it was better tolerated and preferred by patients. However, standard endoscopy showed a better optical quality than that of trans-nasal endoscopy ($p < 0.0001$) [1].

The advent of high-resolution endoscopes (HRE) has significantly improved the quality of endoscopic images, making easier the identification of the landmarks. Better morphological details of the mucosa are obtained with magnification endoscopy and virtual chromoendoscopy [2].

At the time of endoscopy, three important landmarks must be recognized for a correct diagnosis of BE:

1. The gastro-esophageal junction (GEJ).
2. The diaphragmatic pinch.
3. The squamo-columnar junction (SCJ) or Z-line.

In Western guidelines, the upper end of the gastric folds (GF) is the landmark for the GEJ. The position of most proximal margin of the GF is assessed in deflate condition because air insufflation or deep inspiration may change its positions and mislead the diagnosis [3].

In Japanese guidelines, only the distal end of the lower esophageal palisade vessels (PVs) is considered as the endoscopic landmark of the GEJ [4]. PVs are longitudinal vessels running in the mucosal layer of the lower esophagus, descending into the submucosa once entering the cardia. PVs are most easily assessed when the

M. Conio (✉) · A. De Ceglie · M. Crespi
Department of Gastroenterology, General Hospital, Sanremo (IM), Italy

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_6

lower esophagus is adequately distended. Their identification may be disturbed by several factors, such as mucosal inflammation, dysplastic changes, and a thick double muscularis mucosa [5].

In Scholvinck et al. study, PVs were located at a median of 1 cm distal of the GF in 63% of patients with BE and in 27% of cases, intestinal metaplasia was present in this discordant zone [6].

However, Amano et al. reported that PVs criteria showed an overall poor diagnostic reproducibility with a *k* value of 0.14 when compared with GF, and the level of agreement was independent of endoscopic experience [7].

The diaphragmatic pinch is the point at which the diaphragmatic crura constricts or "pinches" the esophagus; this landmark is important to denote the presence of a hiatal hernia.

The SCJ is the transitional point between stratified squamous and columnar epithelium of the esophagus and stomach, respectively. In normal esophagus, the GEJ and SCJ coincide [8] (Fig. 6.1).

BE has been traditionally defined as the presence of at least 1 cm of metaplastic columnar epithelium that replaces the stratified squamous epithelium normally lining the distal esophagus. Therefore, endoscopic presence of BE is suspected when the SCJ lies ≥1 cm above the GEJ at the level of its more proximal extension [9–11].

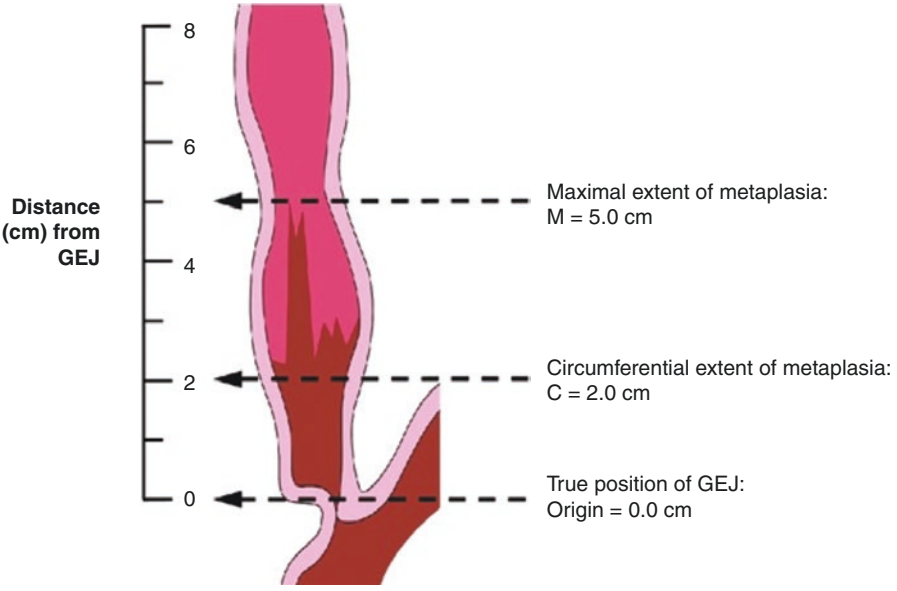

Fig. 6.1 Diagrammatic representation of endoscopically identified Barrett's esophagus showing an area classified as C2M5 according to Prague classification. *GEJ* gastroesophageal junction, *M* maximal extent of the metaplasia, *C* extent of circumferential metaplasia. (Adapted from *Sharma P* et al. [3] by permission from Elsevier and Copyright Clearance Center. License number 4233801225643-Nov 21, 2017)

Upward displacement of the SCJ is concealed if severe esophagitis is present, and the correct diagnosis of BE may be difficult [12].

BE should only be diagnosed when there is a clearly endoscopically visible change from squamous to columnar epithelium in the distal esophagus, starting at GEJ. In patients with esophagitis (Los Angeles Classification B, C, D), endoscopic examination should be repeated after 8–12 weeks of therapy with PPI [9].

Metaplastic columnar epithelium is characterized by the typical salmon color and coarse texture. Histologically, three distinct types of cells are involved: gastric fundic type, cardiac type, and specialized intestinal metaplasia (SIM) characterized by the presence of goblet cells [13].

Disagreement remains in guidelines as to the histological features of the columnar mucosa necessary to define BE: pathologists in Europe and the United States require intestinal metaplasia within columnar-lined mucosa (CLM) in the tubular esophagus to diagnose BE, whereas in the United Kingdom and Japan only the presence of CLM is required [9–11, 14].

However, intestinal metaplasia has been considered as the most biologically instable type of metaplastic columnar epithelium with the greatest risk of neoplastic progression through dysplasia to adenocarcinoma [15].

An irregular Z-line/columnar-lined esophagus <1 cm (ultra-short BE) should be ignored because of the lack of an established cancer risk of intestinal metaplasia at this level and, being a common finding especially in patients with reflux disease, the excessive demands if they were put under surveillance [16–18].

Endoscopists should also avoid to take biopsies from the gastric cardia or at GEJ when there is no visible columnar epithelium, as the presence of IM is a common pathological finding, occurring up to 18% of people undergoing elective endoscopic examination, irrespective of indication, without an increased risk of developing cancer [19].

Also islands of columnar metaplasia in the proximal esophagus should not be confused with BE; these are cervical inlet patches that very rarely have intestinal metaplasia and more rarely develop cancer [20].

6.2 Prague Classification

In the presence of BE, endoscopic evaluation should be carried out using the Prague criteria which considers circumferential (C) and maximum (M) extent of endoscopic visible columnar-lined esophagus in centimeters (Fig. 6.2).

"C" is considered as the difference in endoscope insertion distance between the positions recorded for the GEJ and the proximal margin of the circumferential Barrett's epithelium; "M" is considered as the difference in endoscope insertion distance between the positions recorded for the GEJ and the proximal margin of the longest tongue-like segment of Barrett's epithelium.

The presence and location of visible lesions should also be reported according to the Paris classification [10, 11, 21] (Fig. 6.3).

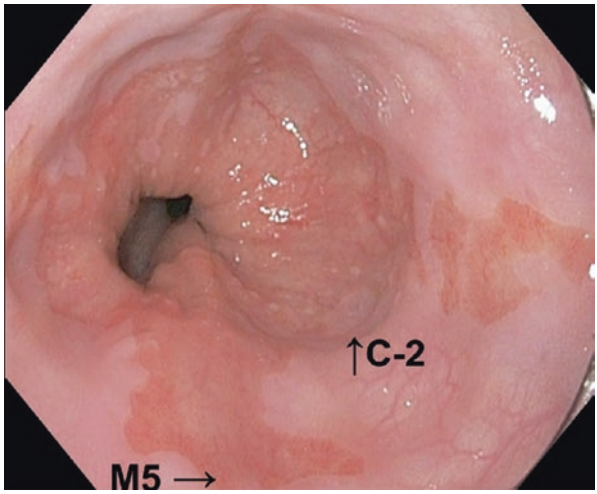

Fig. 6.2 Endoscopic aspect of Barrett's esophagus (Praga C2 M5)

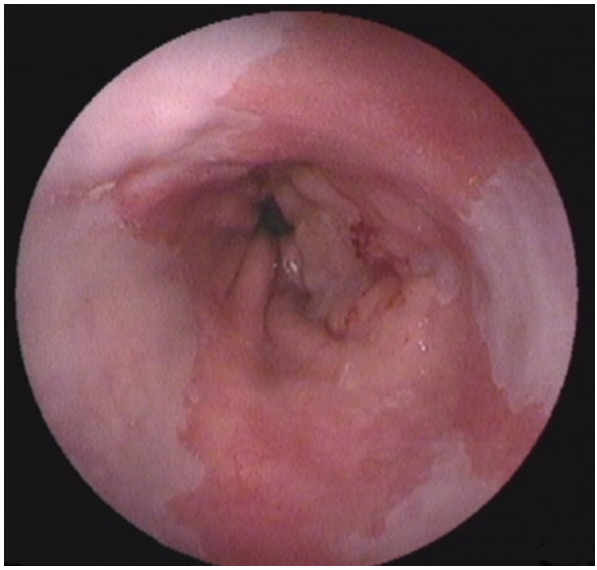

Fig. 6.3 C0M4 Barrett's esophagus containing a 15 × 13 mm (Paris 0-IIa) lesion at 4 o'clock in white light

The presence or absence of erosive esophagitis using the Los Angeles classification should also be reported [11].

The Prague C&M classification is based on validated, explicit, consensus-driven criteria developed by The International Working Group for Classification of Oesophagitis (IWGCO) [3].

Video recordings were scored by an international panel of 29 endoscopists, and the overall reliability coefficients for endoscopic recognition of BE ≥1 cm was 0.72 (0.91 for C and 0.66 for M), whereas for BE ≤1 cm, it was 0.22. These results demonstrated that the C&M grading system could be easily understood; it has been validated by endoscopists with different experience levels [22, 23].

This classification uses the top of GF as landmark for the distal BE segment because in the most patients with BE, the PVs are not visible with the standard endoscopic imaging and may be less clear if esophagitis is present [3].

All guidelines recommend to describe the extent of BE using the Prague criteria avoiding to define endoscopic segment of BE as "long," "short," and "ultra-short" without an established cut-off for any of these categories [9–11].

In this classification, segments of Barrett's epithelium shorter than 1 cm are not considered, due to inability of endoscopists to reliably measure it.

Epstein A et al. analyzing data coming from two prospective patient cohorts found metaplastic-appearing mucosa in islands in 40.7% of entire cohort, specialized intestinal metaplasia confirmed in 10.8% of cases, and 18% of island extended farther than the Prague M segments by a mean distance of 2.3 cm. The prevalence of dysplasia in these islands was 3.4%, so the authors concluded that excluding columnar islands from Prague endoscopic classification could lead to an underestimation of the presence of BE as well as a falsely low-grade dysplasia [22].

British Society of Gastroenterology guidelines suggest a modification of the Prague classification in future, providing an easier system for recording columnar-lined epithelium not continuous with the GEJ [10].

6.3 Biopsy Protocol

The diagnosis of BE requires both endoscopic findings and histologic confirmation; it becomes necessary to adopt a standard bioptic sampling protocol. SIM and dysplasia have a patchy distribution into the columnar epithelium, and, Eloubeidi et al. study, reported that the diagnostic yield of SIM decreased with the declining length of BE: >65% (>5 cm), 50% (3–5 cm), 25% (<3 cm) [24].

Therefore, diagnostic yield increases with an increased number of biopsies and an aggressive biopsy protocol of four quadrant biopsies every 1–2 cm has been recommended.

The Seattle Protocol involves 4-quadrant biopsy sampling every 2 cm throughout the columnar-lined esophagus. Furthermore, every mucosal irregularity should be sampled since it is more likely to hide dysplastic tissue [25, 26].

Target biopsy samples from visible lesions should be taken before random biopsies; distal area should be biopsied first starting 1–2 cm above GEJ and advancing proximally to minimize obscure view from bleeding [10]. This method is actually recommended by the American Gastroenterological Association [27].

In patients with previous diagnosis of dysplasia history, a 4-quadrant biopsies every 1 cm protocol should be performed, due to the "mosaic pattern" with which dysplasia is manifested [9].

A prospective study demonstrated a significant increase in the detection of early lesions when the Seattle bioptic protocol was applied [28].

However, this protocol only samples up to 5% of BE epithelium and can miss up to 40% of treatable neoplasia [29].

The adherence to this protocol is limited, especially in long segment of BE; many practicing gastroenterologists take a smaller number of biopsies at

unspecified intervals. Ishaq et al. in a study involving 228 gastroenterologists in the United Kingdom indicated that the average number of biopsies taken was four [30].

Harrison et al. evaluated the number of biopsies needed to identify SIM in 125 patients (BE mean length: 4.9 cm; range: 1–11 cm). Their data pointed out that at least eight random biopsies were required to diagnose SIM. In contrast, if only four biopsies were obtained, goblet cells were diagnosed in only 34.7% of cases [31].

When it is not possible to perform eight biopsies, given the small length of columnar epithelium, four biopsies per cm of circumferential BE (one on each quadrant) and one biopsy per cm in tongues of BE should be obtained [32].

It has been demonstrated that BE without dysplasia was more frequently located in the posterior wall of the esophagus (38.4%) rather than in the right (28.8%), anterior and left wall (22.6% vs. 10.2%, respectively). Dysplastic lesions were more commonly detected in the posterior (39.3%) than in the anterior (35.8%), right (21.4%), and left wall (3.5%).

Thus, during endoscopic assessment of BE, more attention should be focused at the right hemisphere and at the posterior wall of the lower esophagus where advanced lesions may occur with higher frequency [33–37].

When endoscopic findings are suggestive for BE but histology doesn't confirm the diagnosis, it is recommended to repeat biopsies after 1–2 years, since about 30% of these patients are going to get a BE diagnosis at one of the following exams [38].

In order to help pathologists to distinguish between true BE and IM of the cardia, the endoscopist should label the site from which the samples are taken (esophagus, proximal stomach/cardia) [10, 39].

The development of advanced endoscopic imaging techniques that increase the detection of both IM and dysplasia in BE has been the focus of intense research. The aim of such imaging modalities is the possibility to identify dysplasia without the need for biopsy or with the ability to focus biopsies to areas most likely to contain dysplastic epithelium.

Modern endoscopes with a high-resolution charged-coupled device (CCD), combined with high-definition television monitors, provide excellent image quality, having a high number of pixels (up to one million). HRE are also equipped with an electronic zoom system that provides magnification, allowing the identification of mucosal patterns and microvessels. The maximal efficiency of these systems is in combination with chromoendoscopy (CE) [40, 41].

Dyes are used in CE to enhance endoscopic detection. Methylene blue (MB) is a vital dye absorbed by columnar intestinal-type cells and has been used to improve the yield of MI and dysplasia in BE. Its absorption is reduced in areas of high-grade dysplasia (HGD) and early cancer due to the paucity of goblet cells in the setting of dysplasia, while the behavior of low-grade dysplasia is unpredictable. Biopsies could be targeted on suspicious areas only. Conflicting data come from literature regarding the utility of MB in detecting MI and dysplasia when compared with conventional 4-quadrant random biopsy [42]. In addition, the combination of methylene blue and white-light illumination has recently been reported to increase the genetic damage in Barrett's tissue [43].

Indigo carmine (IC) is a contrast agent not absorbed by cells. It enhances the mucosal irregularities of the mucosa and can help in the identification of BE. Sharma et al. used indigo carmine combined with high-magnification endoscopy to identify and described three patterns of BE: ridged/villous, circular, and irregular/distorted. The ridged/villous pattern had a sensitivity of 71% for IM, while the distorted pattern had a specificity of 88% in the identification of HGD/early cancer [44].

Instillation of acetic acid (AA) on the esophageal mucosa, in conjunction with high-resolution and magnifying endoscopy has been investigated to identify IM and dysplasia in BE.

AA results in reversible alterations of the proteins in the cell, modifying their optical properties, allowing the clear demarcation of BE and the identification of mucosal pit-patterns. When 1–3% AA is sprayed on BE epithelium, there is an initial aceto-whitening reaction for a few minutes, improving the examination of BE epithelium: dysplastic areas tend to lose aceto-whitening faster than non-dysplastic areas.

Guelrud et al. were the first to describe this method in BE patients, and they identified four pit-patterns: type I-round pits, type II-reticular, type III-villous, type IV ridged with a cerebriform appearance of the mucosa. Only types III and IV were highly predictive of the presence of SIM [45].

Data coming from literature about the usefulness of AA in predicting the presence of SIM in BE are conflicting.

Hoffman et al. evaluated the diagnostic yield of magnifying endoscopy with AA targeted biopsies compared with random biopsies in patients with BE greater than 2 cm. The authors simplified the Guelrud's classification: type I–II (gastric epithelium) and type III–IV (BE). Magnifying endoscopy predicted BE with a sensitivity and specificity of 100% and 66%, respectively. AA biopsies allowed a diagnosis of SIM in 78% of patients, while in the random group was 57%. The number of biopsies needed to confirm BE was half when AA was used. Only types III and IV were predictors of BE with a sensitivity of 100%, specificity of 64%, and accuracy rate of 83%. However, the authors stated that the combined approach cannot be recommended in daily clinical practice [46].

Pech et al. in their prospective study showed similar positive results: when AA (balsamic vinegar) without magnification endoscopy was used to study surface pattern in 20 patients with BE, the reliability of predicting the presence of specialized columnar epithelium was high [47].

Coletta et al. meta-analysis evaluating 13 prospective studies showed that AA had a high sensitivity for SIM characterization, but a poor specificity, suggesting that histological confirmation is necessary when AA is positive.

In contrast, non-magnification AA chromoendoscopy had an overall high diagnostic accuracy for detecting HGD/early cancer, comparable to that of more advanced imaging techniques such as narrow-band imaging with magnification [48].

Similar data have been reported in ASGE Technology Committee systematic review and meta-analysis: the pooled sensitivity, NPV, and specificity for AA chromoendoscopy (96.6%, 98.3%, and 84.6%, respectively), as well as for

narrow-band imaging and confocal laser endomicroscopy, into detection of dysplasia in BE met the thresholds set by the American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) initiative on imaging in BE, who recommends that a new imaging technology with target biopsy should have a per-patient sensitivity ≥90%, specificity ≥80%, and a NPV ≥98% in order to eliminate the need for random biopsy during surveillance [49, 50].

Bhandari et al. have showed that histology on AA-target biopsies was more cost-effective than the Seattle protocol in high-risk population [51] (Figs. 6.4 and 6.5).

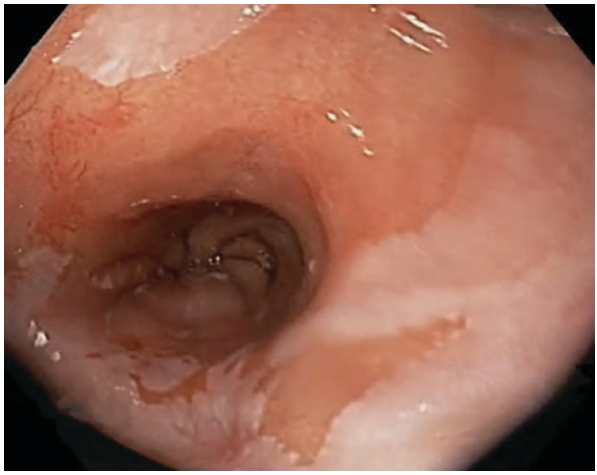

Fig. 6.4 Barrett's esophagus on white-light endoscopy

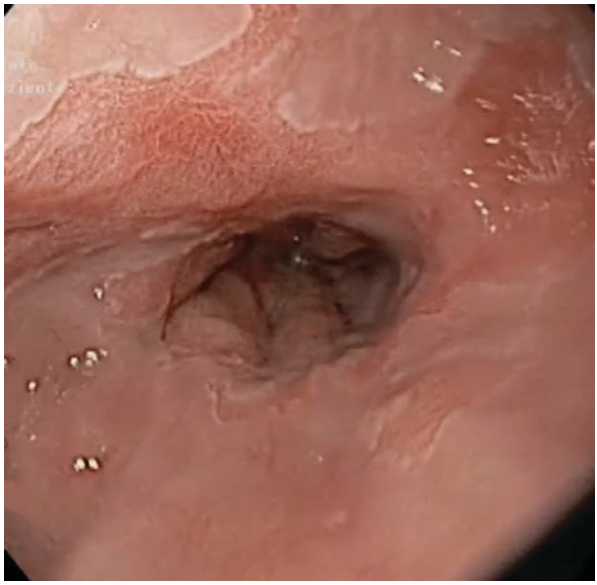

Fig. 6.5 Same patient as Fig. 6.4 after acetic acid chromoendoscopy showing normal Barrett's esophagus with an area of HGD highlighted by differential loss of aceto-whitening

Recently, a new classification system known as PREDICT (the Portsmouth acetic acid classification) for the diagnosis of Barrett's neoplasia using AA has been developed and validated.

This classification is based on two criteria: focal loss of aceto-whitening and surface patterns of Barrett's mucosa. The application of PREDICT improved the sensitivity and NPV for the identification of Barrett's neoplasia [52].

Although chromoendoscopy, in comparison to other endoscopic imaging modalities, is relatively inexpensive, requiring only a spray catheter and contrast agent, it has not gained widespread clinical use because it is considered time consuming, requiring careful execution of the all necessary steps, and it is strictly dependent on the operator, with high inter-observer and intra-observer variability, as reported by Meining et al. [53]

Except for PREDICT classification, published in September 2017, no previous standardized classification criteria of mucosal patterns have been established for dye-based chromoendoscopy. Therefore, advanced imaging modalities have been considered not superior to standard white-light endoscopy in BE surveillance and not recommend for routine use [10, 28, 32].

The unquestionable advantage of CE is that it obliges endoscopists to spend more time inspecting the esophagus, improving the detection of tiny mucosal abnormalities [12].

Gupta et al. study reported that endoscopists with an average inspection time lasting more than 1 min/cm on BE were more likely to detect HGD/EAC than endoscopists with shorter inspections times, suggesting that high quality BE examination should incorporate inspection of the mucosa at a rate of 1 min/cm or slower [54].

Conclusions

During index endoscopy when BE is suspected or in known BE endoscopic surveillance, a careful inspection of the BE mucosa is recommended, cleaning the mucosal surface of mucus, saliva, and food debris using mucolytic agents or antifoaming agent. Endoscopic characteristic of the metaplastic epithelium must be described according to the Praga C&M criteria, reporting the site of the landmarks and the presence and location of visible lesions according to the Paris classification. The Seattle biopsy protocol and target biopsy samples from visible lesions are recommended at the time of diagnosis and at subsequent surveillance.

In our Unit, we perform the endoscopic surveillance of BE patients using HRE under deep sedation with propofol in order to perform an adequate inspection.

In addition, we use an EMR or ESD cap on the tip of the scope that allows a better examination of cardia region, smoothing GF.

References

1. Shariff MK, Varghese S, O'Donovan M, et al. Pilot randomized crossover study comparing the efficacy of transnasal disposable endosheath with standard endoscopy to detect Barrett's esophagus. Endoscopy. 2016;48:110–6.

2. Bennett C, Vakil N, Bergman J, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. Gastroenterology. 2012;143:336–46.
3. Sharma P, Dent J, Armstrong D, Bergman JJ, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. Gastroenterology. 2006;131:1392–9.
4. Aoki T, Hanyu N, Mukai H. Gastroesophageal reflux disease and Barrett's esophagus: inspection in Japan. Sogo Rinsho. 2005;50:2005–8. (in Japanese).
5. Ishimura N, Amano Y, Kinoshita Y. Endoscopic definition of esophagogastric junction for diagnosis of Barrett's esophagus: importance of systematic education and training. Dig Endosc. 2009;21:213–8.
6. Schölvinck DW, Goto O, Seldenrijk CA, et al. Detection of palisade vessels as a landmark for Barrett's esophagus in a western population. J Gastroenterol. 2016;5:682–90.
7. Amano Y, Ishimura N, Furuta K, et al. Which landmark results in a more consistent diagnosis of Barrett's esophagus, the gastric folds or the palisade vessels? Gastrointest Endosc. 2006;64:206–11.
8. Tan WK, di Pietro M, Fitzgerald RC. Past, present and future of Barrett's oesophagus. Eur J Surg Oncol. 2017;43:1148–60.
9. Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;11:30–50.
10. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014;63:7–42.
11. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017;49:191–8.
12. Conio M. Esophageal chromoendoscopy in Barrett's esophagus: "cons". Gastrointest Endosc. 2006;64:9–12.
13. Paull A, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RK. The histologic spectrum of Barrett's esophagus. N Engl J Med. 1976;295:476–80.
14. Salimian KJ, Waters KM, Eze O, et al. Definition of barrett esophagus in the United States: support for retention of a requirement for goblet cells. Am J Surg Pathol. 2018;42(2):264–8.
15. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst. 2011;103:1049–57.
16. Ishimura N, Amano Y, Appelman HD, et al. Barrett's esophagus: endoscopic diagnosis. Ann N Y Acad Sci. 2011;1232:53–75.
17. Dickman R, Levi Z, Vilkin A, Zvidi I, Niv Y. Predictors of specialized intestinal metaplasia in patients with an incidental irregular Z line. Eur J Gastroenterol Hepatol. 2010;22:135–8.
18. Kim JB, Shin SR, Shin WG, et al. Prevalence of minimal change lesions in patients with nonerosive reflux disease: a case-control study. Digestion. 2012;85:288–94.
19. Spechler SJ, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK. Prevalence of metaplasia at the gastro-oesophageal junction. Lancet. 1994;344:1533–6.
20. Chung CS, Lin CK, Liang CC, Hsu WF, Lee TH. Intentional examination of esophagus by narrow-band imaging endoscopy increases detection rate of cervical inlet patch. Dis Esophagus. 2015;28:666–72.
21. Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy. 2005;37:570–8. Review.
22. Epstein JA, Cosby H, Falk GW, Khashab MA, et al. Columnar islands in Barrett's esophagus: do they impact Prague C&M criteria and dysplasia grade? J Gastroenterol Hepatol. 2017;32:1598–603.
23. Vahabzadeh B, Seetharam AB, Cook MB, et al. Validation of the Prague C & M criteria for the endoscopic grading of Barrett's esophagus by gastroenterology trainees: a multicenter study. Gastrointest Endosc. 2012;75:236–41.

24. Eloubeidi M, Provenzale D. Does this patient have Barrett's esophagus? The utility of predicting Barrett's esophagus at the index endoscopy. Am J Gastroenterol. 1994;94:937–43.
25. Levine DS, Blount PL, Rudolph RE, et al. Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus. Am J Gastroenterol. 2000;95:1152–7.
26. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011;140:1084–91.
27. Reid BJ, Blount PL, Feng Z, et al. Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. Am J Gastroenterol. 2000;95:3089–96.
28. Fitzgerald RC, Saeed IT, Khoo D, Farthing MJ, Burnham WR. Rigorous surveillance protocol increases detection of curable cancers associated with Barrett's esophagus. Dig Dis Sci. 2001;46:1892–8.
29. Kariv R, Plesec TP, Goldblum JR, et al. The Seattle protocol does not more reliably predict the detection of cancer at the time of esophagectomy than a less intensive surveillance protocol. Clin Gastroenterol Hepatol. 2009;7:653–8.
30. Ishaq S, Harper E, Brown J, et al. Survey of current clinical practice in the diagnosis, management and surveillance of Barrett's metaplasia: a UK national survey. Gut. 2003;53:A32.
31. Harrison R, Path FRC, Perr I, et al. Detection of intestinal metaplasia in Barrett's esophagus: an observational comparator study suggests the need for a minimum of eight biopsies. Am J Gastroenterol. 2007;102:1154–61.
32. Abela JE, Going JJ, Mackenzie JF, McKernan M, O'Mahoney S, Stuart RC. Systematic four-quadrant biopsy detects Barrett's dysplasia in more patients than nonsystematic biopsy. Am J Gastroenterol. 2008;103:850–5.
33. Pera M. Trends in incidence and prevalence of specialised intestinal metaplasia, Barrett's esophagus and adenocarcinoma of the gastroesophageal junction. World J Surg. 2003;27:999–1008.
34. Csendes A, Smok G, Burdiles P, et al. Prevalence of intestinal metaplasia according to the length of specialised columnar epithelium lining the distal esophagus in patients with gastroesophageal reflux. Dis Esophagus. 2003;16:24–8.
35. Spechler SJ. Intestinal metaplasia at the gastroesophageal junction. Gastroenterology. 2004;126:567–75.
36. Bibbò S, Ianiro G, Ricci R, et al. Barrett's oesophagus and associated dysplasia are not equally distributed within the esophageal circumference. Dig Liver Dis. 2016;48:1043–7.
37. Savarino E, Villanacci V. Barrett's esophagus detection: multiple biopsies are useful, even better if you have an "X" on your map. Dig Liver Dis. 2016;48:1041–2.
38. Khandwalla HE, Graham DY, Kramer JR, et al. Barrett's esophagus suspected at endoscopy but no specialized intestinal metaplasia on biopsy, what's next. Am J Gastroenterol. 2014;109:178–82.
39. Srivastava A, Odze RD, Lauwers GY, Redston M, Antonioli DA, Glickman JN. Morphologic features are useful in distinguishing Barrett esophagus from carditis with intestinal metaplasia. Am J Surg Pathol. 2007;31:1733–41.
40. Kara MA, Peters FP, Rosmolen WD, Krihnadath KK, ten Kate FJW, Fockens P, Bergman JJGHM. High-resolution endoscopy plus chromoendoscopy or narrow-band imaging in Barrett's esophagus: a prospective randomized crossover study. Endoscopy. 2005;37:929–36.
41. Elta GH, Wang KK. Enhanced endoscopic imaging. Preface. Gastrointest Endosc Clin N Am. 2009;19:xiii–xiv.
42. Ngamruengphong S, Sharma VK, Das A. Diagnostic yield of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in Barrett's esophagus: a meta-analysis. Gastrointest Endosc. 2009;69:1021–8.
43. Olliver JR, Wild CP, Sahay P, et al. Chrmoendoscopy with methylene blue and associated DNA damage in Barrett's oesophagus. Lancet. 2003;362:373–4.
44. Sharma P, Marcon N, Wani S, et al. Non-biopsy detection of intestinal metaplasia and dysplasia in Barrett's esophagus: a prospective multicenter study. Endoscopy. 2006;38:1206–12.

45. Guelrud M, Herrera I, Essenfeld H, Castro J. Enhanced magnification endoscopy: a new technique to identify specialized intestinal metaplasia in Barrett's esophagus. Gastrointest Endosc. 2001;53:559–65.
46. Hoffman A, Kiesslich R, Bender A, et al. Acetic acid-guided biopsies after magnifying endoscopy compared with random biopsies in the detection of Barrett's esophagus: a prospective randomized trial with crossover design. Gastrointest Endosc. 2006;64:1–8.
47. Pech O, Petrone MC, Manner H, et al. One-step chromoendoscopy and structure enhancement using balsamic vinegar for screening of Barrett's esophagus. Acta Gastroenterol Belg. 2008;71:243–5.
48. Coletta M, Sami SS, Nachiappan A, Fraquelli M, Casazza G, Ragunath K. Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Gastrointest Endosc. 2016;83:57–67.
49. ASGE Technology Committee, Thosani N, Abu Dayyeh BK, Sharma P, et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE preservation and incorporation of valuable endoscopic innovations thresholds for adopting real-time imaging-assisted endoscopic targeted biopsy during endoscopic surveillance of Barrett's esophagus. Gastrointest Endosc. 2016;83:684–98.
50. Sharma P, Savides TJ, Canto MI, et al. ASGE Technology and Standards of Practice Committee. The American Society for Gastrointestinal Endoscopy PIVI (preservation and incorporation of valuable endoscopic innovations) on imaging in Barrett's esophagus. Gastrointest Endosc. 2012;76:252–4.
51. Bhandari P, Kandaswamy P, Cowlishaw D, Longcroft-Wheaton G. Acetic acid-enhanced chromoendoscopy is more cost-effective than protocol-guided biopsies in a high-risk Barrett's population. Dis Esophagus. 2012;25:386–92.
52. Kandiah K, Chedgy FJQ, Subramaniam S, et al. International development and validation of a classification system for the identification of Barrett's neoplasia using acetic acid chromoendoscopy: the Portsmouth acetic acid classification (PREDICT). Gut. 2017. https://doi.org/10.1136/gutjnl-2017-314512. pii: gutjnl-2017-314512 [Epub ahead of print] PubMed PMID: 28970288.
53. Meining A, Rosch T, Kiesslich R, et al. Inter- and intra-observer variability of magnification chromoendoscopy for detecting specialized intestinal metaplasia at the gastroesphageal junction. Endoscopy. 2004;36:160–4.
54. Gupta N, Gaddam S, Wani SB, Bansal A, Rastogi A, Sharma P. Longer inspection time is associated with increased detection of high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus. Gastrointest Endosc. 2012;76:531–8.

7 Augmented Endoscopy in Barrett's Esophagus: Zoom Endoscopy, Traditional and Virtual Chromoendoscopy

Giuseppe Galloro, Raffaele Manta, Nico Pagano, Teresa Russo, Donato Alessandro Telesca, Andrea Parodi, and Cesare Formisano

7.1 Introduction

Barrett's Esophagus diagnosis starts from an endoscopic suspect and requires histological confirmation of biopsies showing intestinal metaplasia. The accepted protocols and current guidelines recommend four biopsies in each quadrant every centimeter out of the total Barrett's Esophagus mucosa length [1, 2]. Nevertheless, three are the pivotal problems, about this topic:

G. Galloro (✉) · T. Russo · D. A. Telesca
Surgical Digestive Endoscopy Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II—School of Medicine, Naples, Italy
e-mail: giuseppe.galloro@unina.it

R. Manta
Gastroenterology and Digestive Endoscopy Unit, NOCSAE Hospital of Modena, Modena, Italy

N. Pagano
Gastroenterology and Digestive Endoscopy Unit, Department of Medical and Surgical Sciences (DIMEC), University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

A. Parodi
Gastroenterology Unit, Galliera Hospital, Genoa, Italy

C. Formisano
Department of Clinical Medicine and Surgery, Surgical Colo-Proctology Unit, University Federico II—School of Medicine, Naples, Italy

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_7

– Standard endoscopic images provide poor details of the mucosal surface,
– Using white-light endoscopy, we don't have endoscopic markers of intestinal metaplasia and, even less, of dysplasia to target biopsies,
– Random biopsies, using white-light endoscopy, show only around 4–5% of epithelium [3],

The most commonly accepted Seattle biopsies protocol requires biopsies in all the visible lesions, and random four-quadrant samples at every centimeter of suspected Barrett's areas from the gastro-esophageal junction up to 1 cm above the proximal extent of Barrett's mucosa. However, this procedure is expensive, time-consuming, uncomfortable for the patient and imprecise because bleeding impairs adequate vision of the mucosa [4].

Moreover, the distribution of metaplasia and early dysplasia is usually irregular and, sometimes, multi-focal: this is why the random biopsies protocol, even though suggested by several studies and guidelines, is a non-optimal method [5].

In the last 15 years, many advanced endoscopic technologies have been developed to improve detection of intestinal metaplasia and dysplasia but only some of them have, nowadays, an application in clinical practice.

Here, we analyze and evaluate the role of chromoendoscopy, magnifying or zoom endoscopy and virtual chromoendoscopy in improving detection of suspected areas and in targeting biopsies to allow an early diagnosis of Barrett's Esophagus and perform less invasive treatments to improve prognoses.

7.2 Traditionl Chromoendoscopy

Chromoendoscopy is a well-known technique in which dyes are sprayed on the mucosal surface of the gastrointestinal tract to better evaluate the endoscopic aspect of the mucosa by enhancing the contrast of raised and deepened areas. This procedure can improve endoscopic detection of surface patterns and recognition of minimal mucosal changes that may predict the presence of lesions otherwise very difficult to detect with standard endoscopic technique. So, those that may seem just vague ordinary endoscopic observations can be well defined with dye, resulting in accurate lesions detection and precise qualitative diagnosis.

Usually, chromoendoscopy is combined with magnifying endoscopy for best results.

7.2.1 Chromoendoscopy Technique

A good preparation is a crucial condition for chromoendoscopy in each digestive segment [6]. For this reason, the suspected area has to be treated by water and simethicone, to eliminate foam, and *N*-acetylcysteine, to eliminate mucus, from the mucosal surface. Twenty milliliters of 10% solution of acetylcysteine can be enough to dissolve any mucus to ensure homogenous uptake of dye by epithelial cells.

One to two minutes after mucolytic agent application, the esophagus has to be washed with 100 cc water to remove the dissolved mucinous layer.

At this point, the stain can be applied injecting it directly through the working channel of the scope or using a spray catheter. These devices, passed through the accessory channel of the endoscope, are disposable, with a luer lock and metal nozzle tip. The amount of staining solution required depends on the extension of surface area but the smallest amount necessary should be applied to avoid dye pooling. Excessive dye is removed by suction after a staining time of about 1 min.

7.2.2 Stains

7.2.2.1 Methylene Blue

It is a vital stain absorbed by small intestinal and colonic epithelium and not absorbed by non-absorptive mucosa such as squamous or gastric epithelium. For the study of Barrett's Esophagus, a 0.5% concentration of methylene blue is suggested.

Endoscopic biopsied should be targeted at specific areas [7]:

- High stained areas, suspected for intestinal metaplasia,
- Heterogeneously or lower stained areas, suspected for high grade dysplasia or early cancers absorbing lower degree of dye, due to loss in goblet cells and decreased cytoplasm.

Methylene blue is safe but, sometimes, it might induce oxidative damage of DNA in the epithelial stained cells [8]. Up to now, no increased risk of cancer has been proved in patients undergone methylene blue dying. Anyway many centers prefer to use indigo carmine (see below) to avoid any potential teratogenic activity.

Chromoendoscopy using methylene blue may also cause a transient blue discoloration of urine and feces [7, 8].

Use of methylene blue in endoscopic practice of Barrett's surveillance shows disagreeing results; anyway most of papers conclude that, in detection of specialized intestinal metaplasia and dysplasia, it is comparable, but not superior to random biopsies protocol [9].

7.2.2.2 Indigo Carmine

Indigo carmine is a contrast dye that neither reacts with nor is absorbed by the mucosa, but simply pools in the mucosal grooves, enabling the visualization of the pattern formed by mucosal folds and pits, allowing better topographic definition. For this cause, it is also defined the contrast dye.

A small volume of 0.4% solution of indigo carmine is applied by spray catheter on the suspected areas to avoid excess dye accumulation.

Chromoendoscopy by indigo carmine is propaedeutic to magnifying or zoom endoscopy to define the arrangements of the mucosal pit patterns in Barrett's Esophagus suspected areas (see below) that may correlate with histology

[10–12]. These combined techniques are able to detect intestinal metaplasia up to 100% of the cases but not to distinguish dysplasia from non-dysplastic intestinal metaplasia [11, 12].

Unlikely methylene blue, patients dyed by indigo carmine do not seem to induce an increased DNA damage [13].

7.2.2.3 Acetic Acid

Acetic acid is not actually a stain but an enhancer: it does not have coloring activity but, breaking the disulfide bridges of mucus glycoproteins, induces a reversible denaturation of proteins enhancing the structural surface pattern, similarly to a contrast agent.

Pre-treatment of the mucosa with mucolytic agents is not required. Twenty milliliter of 1.5–3% solution of acetic acid are usually sprayed onto the esophageal mucosa inducing a whitish discoloration of superficial layer, in few seconds. In association with magnification or zoom endoscopy, this method is useful to evaluate the mucosal pit pattern to predict the presence of specialized columnar-lined epithelium [11, 12]. Some papers suggest that acetic acid is also helpful applied to standard white-light endoscopy [14]. Moreover, staining with the naturally brownish-colored balsamic vinegar combines the advantage of chromoendoscopy with surface structure enhancement by the acetic acid [15].

On the other hand, there are papers showing that acetic acid-enhanced chromoendoscopy is more cost-effective than protocol-guided biopsies in the study of a high-risk Barrett's population [16].

7.3 High-Definition, Zoom, and Magnifying Endoscopy

The new trend of industrial technology is to provide the endoscopists with instrumentations able to realize more detailed endoscopic pictures.

High-resolution endoscopes magnify the endoscopic images 30–35 times. Zoom endoscopes are defined by the capacity to perform optical zoom by using a movable lenses system in the tip of the endoscope [17]. The optical zoom provides a closer image of the target while maintaining image display resolution. This is distinguished from electronic magnification, which simply moves the image closer on the display and results in a decreased number of pixels composing the area of display, with no improvement in resolution [18]. With a suitable processor, conventional endoscopes provide an electronic magnification of 1.5–2. Although standard endoscopes magnify images 30–35 times, zoom endoscopes can optically magnify images up to 150 times, depending on the size of the monitor [19].

7.3.1 Pit Pattern Classifications Zoom/Magnifying Endoscopy Based

The target of zoom and magnifying endoscopy is a correct qualitative diagnosis based on the study of the so-called pit pattern (the superficial orifices of the

glandular crypts on the digestive mucosal surface) because a lot of researches and papers show that, in expert hands, there is a wide agreement between zoom/magnify endoscopic findings and histological results [20–22]. This achievement (based on stereomicroscopic analysis of the pit pattern in a large case-number of digestive lesions) is oriented to predict the histologic diagnosis starting from endoscopic morphological data (color, size, and shape of lesions, presence and severity of depression) and mucosal pit pattern.

In the study of the esophagus, two are the pit pattern classifications widely accepted: the Guerlrud and the Endo classifications.

7.3.1.1 Guelrud Classification

This protocol provides a preparation by 10–15 mL of 1.5% acetic acid and irrigation with 3–5 mL of water by using the lens-cleaning water channel of the endoscope.

The codified mucosal patterns are the following:

- Pattern I—regular: With round and regular pits, orderly arranged,
- Pattern II—reticular: With circular or oval and pits, regular in shape and arrangement,
- Pattern III—villous: Without evidence of pits but with a fine villiform appearance, regular in shape and arrangement,
- Pattern IV—ridged: Without evidence of pits but with a thick villous convoluted shape with a cerebriform appearance with regular shape and arrangement,

In the Guelrud experience, specialized intestinal metaplasia is associated with biopsy specimens of pattern II in 11%, of pattern III in 87%, and of pattern IV in 100% of the cases. By using histology as the main outcome, the sensitivity, specificity, positive predictive value, and negative predictive value of acetic acid-enhanced magnification endoscopy for patterns III and IV in detecting specialized intestinal metaplasia are 96.5%, 88.7%, 87.5%, and 96.9%, respectively. The overall accuracy of this classification is 92.2% [23].

7.3.1.2 Endo Classification

This protocol provides a previous stain by methylene blue.

The codified mucosal patterns are the following:

- Type I: With roundish and small pits of relatively uniform size and shape,
- Type II: With long straight lines, of relatively uniform size and shape,
- Type III: With long oval and curved pits, larger than those of the type 1,
- Type IV: With tubular pits, complicated and twisted similar to a branch or gyrus-like structure,
- Type V: With villous pits with flat, finger-like projections,

In the Endo experience, specialized intestinal metaplasia is associated with biopsy specimens of pit pattern I in 6%, of pit pattern II in 0%, of pit pattern III in 40%, and of pit pattern IV and V in 100% of the cases. Moreover, the histological

evaluation of the biopsy specimens shows a relationship between pit pattern IV and V with intestinal-type mucin phenotype respectively of 87.5% and 100% [12].

7.4 Computed Virtual Chromoendoscopy

Computed virtual chromoendoscopy is a real-time, on-demand endoscopic imaging technology able to enhance visualization of the superficial submucosal vascular network, also improving surface texture of the mucosa to improve tissue characterization and differentiation.

The computed virtual chromoendoscopy systems are NBI (Narrow Band Imaging, Olympus, Tokyo, Japan), FICE (Fujinon Intelligent Color Enhancement, Fujinon, Tokyo, Japan), and iScan system (Pentax, Tokyo, Japan). All these three systems are based on the observation that selected narrowed light wavelengths maximize the relative intensity of blue light. Because blue light is highly absorbed by hemoglobin, images from computed virtual chromoendoscopy systems result in higher vascular contrast compared with standard white-light endoscopic images. These modifications are available at the push of a button and have dramatic effects on image quality, with increased vascular contrast and some improvement of mucosal topography [20].

NBI alters the spectrum of wavelengths by optical filters situated in the light source and illuminates tissues with modified light. In contrast, FICE is based on a computed spectral estimation technology that processes the reflected photons of an ordinary illuminated tissue to reconstitute virtual images. FICE has the potential advantage of allowing the endoscopist to choose up to ten different filters, each providing a virtual image with a dedicated wavelength pattern for optimal observation of the targeted tissue. Despite these differences, applications of FICE and NBI produce similar imaging, with increased vascular contrast, and so far, studies have shown broadly similar results [20, 24].

Computed virtual chromoendoscopy is used in combination with zoom/magnifying endoscopy to maximize the endoscopic observation of the superficial submucosal microvascular architecture associating these data with those deriving from the study of the mucosal pit pattern. This way, an expert endoscopist can perform an advanced endoscopy able to detect the most early mucosal and vascular changes underpinning preneoplastic conditions or early neoplasms. Obviously, these methods are not prime-time techniques and have to be performed by dedicated endoscopists in high-volume referral centers [25].

NBI, in association with zoom/magnifying endoscopy, has been applied in Barrett's Esophagus to improve the detection of both intestinal metaplasia and dysplasia and four classification systems have been proposed: the Kansas, the Amsterdam, the Nottingham, and the BING classification.

7.4.1 Kansas Classification

Endoscopic images are graded according to mucosal and vascular pattern, as above reported:

– Mucosal pattern circular uniform and regular dots,
– Ridge/villous longitudinal darker and lighter ridges, with uniform distribution
– Irregular/distorted non-uniform, irregular, and distorted pattern
– Vascular pattern normal thin vessels with a uniform branching pattern, Abnormal dilated, corkscrew vessels with increased vascularity and Abnormal, non-uniform branching pattern

Normal mucosa is characterized by circular mucosal pattern and normal vascular pattern.

Intestinal metaplasia is characterized by ridged/villous mucosal pattern and normal vascular pattern.

Dysplasia is characterized by irregular/distorted mucosal pattern and abnormal vascular pattern.

The sensitivity, specificity, and positive predictive value of mucosal and vascular pattern for diagnosis of IM without high grade dysplasia are 93.5%, 86.7%, and 94.7%, respectively. The sensitivity, specificity, and positive predictive value of mucosal and vascular pattern for high grade dysplasia are 100%, 98.7%, and 95.3%, respectively [26].

7.4.2 Amsterdam Classification

Endoscopic images are graded on the ground of mucosal and vascular pattern, according to the following ten points:

1. The type of mucosal pattern (flat mucosa, circular/oval/tubular pattern, longitudinal pattern, villous/gyrus-like pattern, and disrupted mucosa).
2. The regularity of the mucosal pattern (regular, focally irregular/disrupted, diffusely irregular/disrupted).
3. The presence of a vascular pattern.
4. The regularity of the vascular pattern (regular, focally irregular, or diffusely irregular).
5. Whether the vasculature formed honeycomb structures.
6. Whether all blood vessels were situated between/alongside the mucosal folds.
7. The presence of blood vessels crossing over mucosal folds (the so-called mucosal bridging).
8. In the case of a flat mucosa, whether the vasculature consisted of normal-appearing long branching vessels.
9. The presence of abnormal blood vessels.
10. The description of the observed abnormal vessels.

Normal mucosa is characterized by regular flat mucosal pattern and regular vascular pattern without abnormal blood vessels.

Intestinal metaplasia is characterized by regular villous/gyrus-like mucosal pattern and regular vascular pattern without abnormal blood vessels.

Dysplasia is characterized by irregular/disrupted mucosal pattern and irregular vascular pattern with evidence of abnormal blood vessels.

The sensitivity, specificity, positive predictive value, and negative predictive value for high grade dysplasia are 94%, 76%, 64%, 98%, respectively [27].

7.4.3 Nottingham Classification

Endoscopic images are graded on the ground of mucosal and vascular pattern, classified into four easily distinguishable types:

A, round/oval pits with regular microvasculature.
B, villous/ridge pits with regular microvasculature.
C, absent pits with regular microvasculature.
D, distorted pits with irregular microvasculature.

Normal mucosa is characterized by round/oval pits with regular microvasculature.

Intestinal metaplasia is characterized by villous/ridge pits with regular microvasculature (type B) or absent pits with regular microvasculature (type C).

Dysplasia is characterized by distorted pits with irregular microvasculature.

The positive predictive value and negative predictive value for type A pattern (columnar mucosa without intestinal metaplasia) is 100% and 97%, respectively; for types B and C (intestinal metaplasia) are 88% and 91%, respectively, and for type D (high grade dysplasia) 81% and 99%, respectively [28].

7.4.4 BING (Barrett's International NBI Group) Classification

This is the most recent, simple, and validated classification system to discriminate neoplastic from non-neoplastic Barrett's Esophagus using NBI and near-focus technology, but not formal magnification endoscopy.

Endoscopic images are graded according to mucosal and vascular pattern, as above reported:

- Mucosal pattern regular circular, ridged/villous, and tubular surface pattern,
  Irregular absent or irregular surface pattern
- Vascular pattern regular normal blood vessels with long, branching pattern regularly situated.
  Along or between mucosal ridges
  Irregular anarchic blood vessels with focal or irregular distribution not following
  The normal mucosal ridges

Non-dysplastic intestinal metaplasia is characterized by a circular or ridge/villous mucosal pattern arranged in an orderly fashion and blood vessels that clearly follow the architecture of the mucosal pattern or are distributed between the mucosal ridges.

Dysplasia is characterized by irregular mucosal pattern and anarchic blood vessels with focal or diffuse distribution, not following the normal mucosal ridges.

The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of BING criteria for diagnosis of dysplasia are 91%, 93%, 89%, 95%, and 92%, respectively [5, 29].

In conclusion, the new augmented endoscopic techniques, compared with standard definition and white-light endoscopic exploration, represent a big improvement in the study of Barrett's Esophagus patients. In details, zoom/magnifying and new lighting methods, emphasizing the imaging of endoscopic features such as mucosal crypt and submucosal superficial vascular patterns, show a very good diagnostic value for intestinal metaplasia and dysplasia when used for the advanced study of targeted areas of interest [30–32].

Several classification systems have been proposed by the use of augmented endoscopic technologies. However, these classifications involve different criteria, some complicated, some other easier and simplified, making them useful in expert hands of dedicated and trained endoscopist but difficult to use in clinical practice by general gastroenterologists.

For these reasons, further validation studies in widely practical endoscopy setting are needed. Moreover, to realize all the benefits from these technologies we need robust evidence as to their effectiveness, diagnostic reproducibility, and accuracy.

References

1. Mannath J, Ragunath K. Era of Barrett's surveillance: does equipment matter? World J Gastroenterol. 2010;16:4640–5.
2. Shaheen NJ, Falk GW, Iyer PG, et al. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111:30–50.
3. Sharma P, Falk GW, Weston AP, et al. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's oesophagus. Clin Gastroenterol Hepatol. 2006;4:566–72.
4. Verna C, Feyles E, Lorenzi L, et al. I-SCAN targeted versus random biopsies in Barrett's oesophagus. Dig Liver Dis. 2014;46:131–4.
5. Nogales O, Caballero-Marcos A, Clemente-Sánchez A, et al. Usefulness of non-magnifying narrow band imaging in EVIS EXERA III video systems and high-definition endoscopes to diagnose dysplasia in Barrett's esophagus using the Barrett International NBI Group (BING) classification. Dig Dis Sci. 2017;62:2840–6.
6. Pohl J, Pech O, May A, et al. Incidence of macroscopically occult neoplasias in Barrett's esophagus: are random biopsies dispensable in the era of advanced endoscopic imaging? Am J Gastroenterol. 2010;105:2350–6.
7. Trivedi PJ, Braden B. Indications, stains and techniques in chromoendoscopy. QJM. 2013;106(2):117–31.

8. Olliver JR, Wild CP, Sahay P, et al. Chromoendoscopy with methylene blue and associated DNA damage in Barrett's oesophagus. Lancet. 2003;362:373–4.
9. Ngamruengphong S, Sharma VK, Das A. Diagnostic yield of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in Barrett's esophagus: a meta-analysis. Gastrointest Endosc. 2009;69:1021–8.
10. Sharma P, Weston AP, Topalovski M, et al. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's oesophagus. Gut. 2003;52:24–7.
11. Guelrud M, Herrera I, Essenfeld H, et al. Enhanced magnification endoscopy: a new technique to identify specialized intestinal metaplasia in Barrett's esophagus. Gastrointest Endosc. 2001;53:559–65.
12. Endo T, Awakawa T, Takahashi H, et al. Classification of Barrett's epithelium by magnifying endoscopy. Gastrointest Endosc. 2002;55(6):641–7.
13. Davies J, Burke D, Olliver JR, et al. Methylene blue but not indigo carmine causes DNA damage to colonocytes in vitro and in vivo at concentrations used in clinical chromoendoscopy. Gut. 2007;56:155–6.
14. Longcroft-Wheaton G, Duku M, Mead R, et al. Acetic acid spray is an effective tool for the endoscopic detection of neoplasia in patients with Barrett's esophagus. Clin Gastroenterol Hepatol. 2010;8:843–7.
15. Pech O, Petrone MC, Manner H, et al. One-step chromoendoscopy and structure enhancement using balsamic vinegar for screening of Barrett's esophagus. Acta Gastroenterol Belg. 2008;71:243–5.
16. Bhandari P, Kandaswamy P, Cowlishaw D, et al. Acetic acid-enhanced chromoendoscopy is more cost-effective than protocol-guided biopsies in a high-risk Barrett's population. Dis Esophagus. 2012;25:386–92.
17. Bruno MJ. Magnification endoscopy, high resolution endoscopy, and chromoscopy; towards a better optical diagnosis. Gut. 2003;52(Suppl 4):iv7–11.
18. Kwon RS, Adler DG, Chand B, et al. High-resolution and high-magnification endoscopes. Gastrointest Endosc. 2009;69:399–407.
19. Galloro G. High technology imaging in digestive endoscopy. World J Gastrointest Endosc. 2012;4(2):22–7.
20. Galloro G, Ruggiero S, Russo T, et al. Recent advances to improve the endoscopic detection and differentiation of early colorectal neoplasia. Color Dis. 2015;17(Suppl 1):25–30.
21. Galloro G, Magno L, Diamantis G, et al. Multiple primary malignancies: role of advanced endoscopy to identify sincronous and metacronous digestive tumours. In: Renda A, editor. Multiple primary malignancies. Milan: Springer; 2008. p. 221–30.
22. Galloro G, Magno L, Ruggiero S, et al. Contribution of new technologies to endoscopic imaging. In: Trecca A, editor. Ileoscopy: technique, diagnosis, and clinical applications. Milan: Springer; 2012. p. 21–9.
23. Guelrud M, Herrera I, Essenfeld H, et al. Enhanced magnification endoscopy: a new technique to identify specialized intestinal metaplasia in Barrett's esophagus. Gastrointest Endosc. 2001;56(6):559–65.
24. East JE, Vleugels JL, Roelandt P, et al. Advanced endoscopic imaging: European Society of Gastrointestinal Endoscopy (ESGE) technology review. Endoscopy. 2016;48(11):1029–45.
25. Curvers WL, van Vilsteren FG, Baak LC, et al. Endoscopic trimodal imaging versus standard video endoscopy for detection of early Barrett's neoplasia: a multicentre, randomised cross-over study in general practice. Gastrointest Endosc. 2011;73:195–203.
26. Sharma P, Bansal A, Mathur S, et al. The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. Gastrointest Endosc. 2006;64:167–75.
27. Kara MA, Ennahachi M, Fockens P, et al. Detection and classification of the mucosal and vascular patterns (mucosal morphology) in Barrett's esophagus by using narrow band imaging. Gastrointest Endosc. 2006;64:155–66.
28. Singh R, Anagnostopoulos GK, Yao K, et al. Narrow-band imaging with magnification in Barrett's esophagus: validation of a simplified grading system of mucosal morphology patterns against histology. Endoscopy. 2008;40:457–63.

29. Sharma P, Bergman JJ, Goda K, et al. Development and validation of a classification system to identify high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus using narrow-band imaging. Gastroenterology. 2016;150:591–8.
30. Singh R, Shahzad MA, Tam W, et al. Preliminary feasibility study using a novel narrow-band imaging system with dual focus magnification capability in Barrett's esophagus: is the time ripe to abandon random biopsies? Dig Endosc. 2013;25(Suppl 2):151–6.
31. Kato M, Goda K, Shimizu Y, et al. Image assessment of Barrett's esophagus using the simplified narrow band imaging classification. J Gastroenterol. 2017;52:466–75.
32. Matsuhashi N, Sakai E, Ohata K, et al. Surveillance of patients with long-segment Barrett's esophagus: a multicenter prospective cohort study in Japan. J Gastroenterol Hepatol. 2017;32:409–14.

8 Confocal Laser Endomicroscopy in Barrett's Esophagus: Is It a Clinical Resource or Still a Research Procedure?

Giovanni Domenico De Palma, Gianluca Cassese, and Gaetano Luglio

8.1 Confocal Laser Endomicroscopy: Theoretical and Practical Bases

Confocal laser endomicroscopy (CLE) is a relatively recent endoscopic technique, regarded among the enhanced endoscopic procedures; it was developed to obtain very high magnification and resolution images of the mucosal layer of the gastrointestinal (GI) tract. Confocal microscopy was invented by a neuroscientist, Dr. Minsky, in 1955, in order to study neuronal connections and architecture [1]. The main principle of this technique is to collect the light emitted by a single focal plane, in order to keep in perfect focus that portion of the sample and eliminate the light noise coming from the layers above and below. In this way, it is possible to magnify the image hundreds of times without blur and with great spatial resolution, allowing an evaluation of the histologic and cellular architecture [2, 3]. To achieve this aim, a filter called pinhole is necessary to get the image magnification. The light emitted by an argon blue laser (488 nm) passes through the pinhole and is focused on the focal plan of interest. The reflected light is then refocused into the detection system by the same lens; the term confocal refers to the alignment of both illumination and collection systems in the same focal plane [4, 5]. All the signals from the illuminated plane are captured by a detector and measured by creating a grayscale image of the tissue, that is digitized and reconstructed by measuring the light returning to the detector from successive points; the brightness of each pixel corresponds to the relative intensity of the fluorescent light detected at the corresponding point of the magnified tissue. Moving along the vertical axis after each scan through the actuators that set the various scanning planes, it is possible to perform a series of successive scans, on focal planes at various depths. These scans are called optical sections

G. D. De Palma (✉) · G. Cassese · G. Luglio
Department of Clinical Medicine and Surgery, Endoscopic Surgery Unit, University of Naples Federico II, Naples, Italy
e-mail: giovanni.depalma@unina.it; gianluca.cassese@unina.it; gaetano.luglio@unina.it

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_8

and their ordered overlap, performed by a software, allows to reconstruct an overall image. These images are defined *Optical Biopsies* and the main differences compared with traditional histology is that this optical sectioning is direct, non-invasive, real time and, above all, in vivo.

CLE systems can use "through-the-scope" probes or dedicated endoscopes with integrated CLE systems. The probe-based CLE (pCLE) involves miniprobes inserted through the accessory channel of standard endoscopes; it has a fixed focal length so it can only scan in a single plane, without the possibility of obtaining cross-sectional images at different depths. Confocal miniprobes created for GI tract applications (Cellvizio Mauna KeaTechnologies, Paris, France) include Colo-Flex UHD, GastroFlex UHD, and CholangioFlex. It has a depth of imaging of 70–130 μm for the GI tract, and 55–65 μm for the ultrahigh-definition probes [6]. The lateral resolution of pCLE is 1 μm, which is a 43% decrease in resolution compared to the endoscopy-integrated CLE (eCLE) [7]. In endoscopy-integrated CLE (eCLE; Pentax, Tokyo, Japan), a confocal probe is integrated in the tip of the endoscope. This reduces the maneuverability of the endoscope, thus inhibiting some maneuvers and reducing the visibility of some sections in the digestive tract. The field of view is 475 × 475 μm, with a lateral resolution of 0.7 μm and axial resolution of 1 μm [6]. Nowadays, the eCLE system is no longer available in commerce.

Confocal imaging can be based on tissue reflectance or fluorescence [8]. Confocal devices based on tissue reflectance do not require any contrast agents, but they currently have low resolution, that doesn't allow their use in clinical practice. CLE implemented with fluorescence contrast agents, instead, generates high resolution images, which are usually referred as in vivo *histology* [9, 10]. Contrast agents can be administered intravenously or topically. Intravenous sodium fluorescein is the most widely used contrast agent in endomicroscopy. Despite its safety has been documented in literature, it is still considered off-label for the endomicroscopy use [11]. Self-limiting yellowing of the skin and eyes and a more pronounced coloring of the urine occur in all the patients. So it is important to disclose these side effects within the informed consent. Fluorescein binds to serum albumin; on the other hand, the free portion spreads in the capillary system, permeates the tissues, and contrasts the extracellular matrix, the surface of the epithelium, and the lamina propria, for about 30 min [12]. The identifiable mucosal structures after the administration of fluorescein include epithelial cells, cellular infiltrates, enterocytes, vessels, and erythrocytes. Cell nuclei and mucins are not colored by fluorescein, so they appear dark. The acriflavine, which is used topically, is a highly specific acid dye that colors the nuclei and the most superficial layers of the mucosa. The visualization of the nuclei allows an easier differentiation between intraepithelial neoplasia and invasive cancer. Furthermore, fluorescein and acriflavine can also be used simultaneously to obtain an optimal view of the extracellular matrix, other than the cells and their nuclei. Anyway, there are concerns about the possible mutagenicity of acriflavin and for this reason its use in humans is currently limited [13]. Another topical agent, cresyl violet is a cytoplasmic stain used to outline the nucleus. Moreover, cresyl violet has a limited depth of penetration in the esophageal mucosa. A newer topical agent, 2-[*N*-(7-nitrobenz-2-oxa-1,3-diaxol-4-yl) amino]-2-deoxyglucose (2-NBDG) is a

glucose analog that is transported into cells with high metabolic activity, like neoplastic cells [9] and becomes fluorescent after cellular incorporation [14]. Ex vivo studies showed a high specificity for dysplastic BE cells [15] so it is now being evaluated for in vivo endomicroscopy [16].

8.2 CLE in the Management of Barrett's Esophagus: Technical Notes

Despite CLE is usually considered technically feasible and safe, one theoretical issue is the need for additional time compared to standard endoscopy. Startup/calibration time with the most recent versions have been shortened to less than 2–3 min, so that the total startup including the need for the dedicated equipment, powering, probe insertion, and user interface setup typically takes at least 5–10 min. The patient must be obviously adequately informed. The confocal miniprobe is inserted in the instrumentation channel of the endoscope. The tip of the probe appears on the endoscope screen. The endoscopist chooses the area that deserves this investigation and places the tip *in contact* with the mucosa, after having turned on the laser light. The images are viewed and captured in real time using a foot pedal, in the form of video at a frequency of 12 frame/s and it is also possible to see a "mosaic" with the collected frames. There is also a real-time or post-acquisition image reconstruction software that reconstructs an enlarged image (4 × 2 mm) from the dynamic sequences, thus allowing to obtain the mosaics (and also the single images in offline mode), improves contrast, and eliminates motion artifacts. The adequate contact of the actual probe in pCLE with the esophageal mucosa is critical in order to obtain high quality images although there is a software for stabilizing movement artifacts. There are some tricks that can be used to stabilize the target area: you can apply a slight suction, you can position the probe within an endoscopic cap, you can infuse scopolamine methyl bromide. Acquisition of targeted biopsies can be achieved with extreme precision with CLE systems. In pCLE, an area adjacent to the area of interest should be marked using other devices. The miniprobe is then removed to allow for biopsy acquisition through the instrument channel. The endoscopist must adjust for this discrepancy by targeting sites to the left of the suction channel using a suction mark as a reference point. Current knowledge recommends the use of pCLE in addition to other advanced endoscopic techniques in order to improve the diagnostic yield and to focus the right target area. The eCLE technique is not described here because of its unavailability at the moment this chapter is written.

8.3 CLE for Barrett's Esophagus Management

The role of CLE has been widely investigated in the field of both neoplastic and preneoplastic lesions of gastrointestinal tract [17], other than in the setting of inflammatory bowel disease [18].

Several studies also focused the role of CLE in the evaluation of suspicious lesions within Barrett's esophagus. The first study on CLE in BE was carried out by Kiesslich and colleagues in 2006 with eCLE, involving 63 patients [19]. Vascular and cellular architecture were analyzed and described with endomicroscopy and compared with histology from targeted biopsies. These authors described morphological patterns to distinguish between gastric-type epithelium, Barrett epithelium, and neoplasia: normal gastric epithelium was characterized by a regular, columnar-lined epithelium with round, glandular openings, typical cobblestone appearance, and regular-shaped capillaries visible in the deeper mucosa (Fig. 8.1); BE showed columnar-lined epithelium with dark mucin in goblet cells, a villiform pattern, and regular-shaped capillaries in the upper and deeper mucosa (Fig. 8.2); neoplastic BE, instead, was characterized by black cells with irregular borders and shapes, high dark contrast to the surrounding tissue, and irregular leaking capillaries in the upper

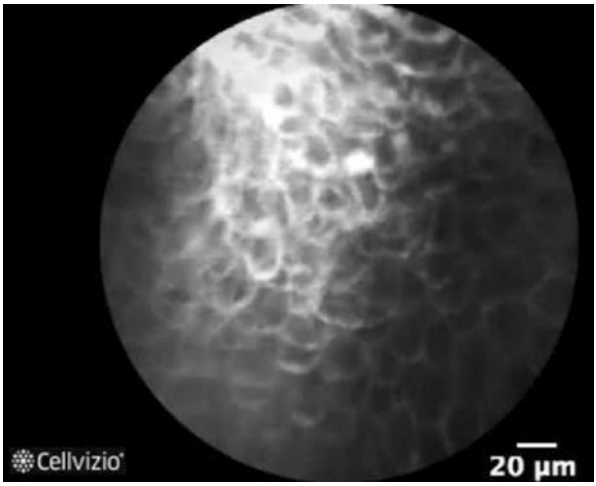

Fig. 8.1 Normal squamous epithelium

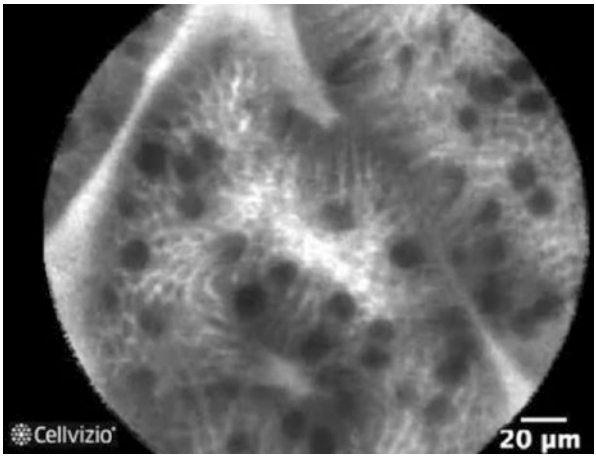

Fig. 8.2 Barrett's esophagus

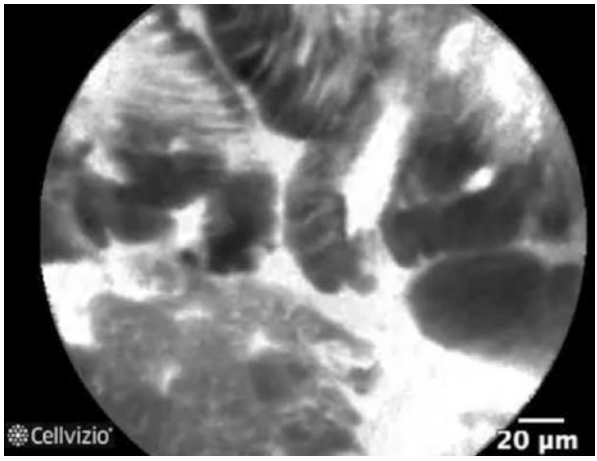

Fig. 8.3 Cancer in Barrett's esophagus

and deeper mucosa (Fig. 8.3). These features were organized and called Mainz criteria for endomicroscopic diagnosis of Barrett's esophagus. With expert image acquisition and interpretation, use of the Mainz criteria demonstrated, with an investigator-masked evaluation, a sensitivity and specificity of 98% and 94% for BE and 93% and 94% for BE-associated dysplasia, respectively, in predicting in vivo histology. In addition, inter- and intra-observer agreement with this classification system was significantly high, with *k* value of 0.84 and 0.89, respectively.

A prospective randomized double-blinded crossover trial compared the diagnostic efficiency of eCLE with targeted biopsies to a standard endoscopy biopsy acquisition protocol [20]. The results of this study showed an improvement of the diagnostic yield for high-grade dysplasia compared to random biopsies (33.7% versus 17.2%), other than a reduction of the mean number of required mucosal biopsy specimens (9.8 versus 23.7). This study did not allow to assess the diagnostic accuracy because the biopsies at eCLE were only performed for suspected BE lesions with high-grade dysplasia. Similar results were also confirmed by a recent multicentric randomized controlled trial; in this paper, Canto colleagues compared high-definition white-light endoscopy with random biopsies at endoscopy plus eCLE with targeted biopsies [21]. The combination of high-definition white-light endoscopy and eCLE increased the diagnostic yield for neoplasia (22% versus 6%) and significantly lowered the number of required biopsies. These studies demonstrated that eCLE can help in vivo decision-making and improve endoscopic outcomes, being able to change the treatment plan in 36% of patients.

Compared to eCLE, probe-based CLE has substantial differences, making it impossible to use the same classification system. In 2008 Pohl and colleagues published the first prospective multicenter trial study on BE using pCLE [22]. In this study, they tried to establish the criteria for the diagnosis of BE neoplasia based on 95 biopsies obtained from 15 patients, testing these criteria on 201 biopsies from the remaining patients without visible focal changes. Five neoplastic criteria suggestive of BE neoplasia were identified: irregular epithelial lining, variable width of the

epithelial lining, glandular fusion, presence of dark areas and an irregular vascular pattern. The pCLE diagnosis of neoplasia was based on the presence of at least two of these criteria. The sensitivity and specificity found by two independent investigators were 75% and 88.8%, and 75% and 91%, respectively, showing a positive predictive value of 44.4% and a negative predictive value of 98.8%; the interobserver agreement shows a *k* value of 0.6.

The pCLE criteria for the diagnosis of BE neoplasia were further refined in the Miami Classification and the KC (Kansas City) Confocal Criteria. The Miami Classification system is based on a consensus among the leading experts during a meeting held in Miami in 2009 [23]. According to these criteria, high-grade dysplasia in BE is characterized by villiform structures, dark irregularly thickened epithelial borders, and dilated irregular vessels, whereas adenocarcinoma in BE is characterized by disorganized or complete loss of villiform structures and crypts, dark columnar cells, and dilated irregular vessels. The consensus meeting emphasized how the sensitivity and specificity for the detection of dysplasia were 88% and 96%, respectively, with a significant inter-observer agreement (*k* value 0.72). The KC Confocal Criteria, instead, were proposed and validated by the Kansas City group [24]. These criteria are based on 50 pCLE videos collected with newer high-definition miniprobe during the "DON'T BIOPCE" study. They include non-equidistant glands, unequal size and shape of glands, saw-toothed epithelial surfaces, non-easily identifiable goblet cells, enlarged cells, and irregular and non-equidistant cells: dysplasia can be diagnosed with the presence of at least two criteria. These criteria showed a positive and negative predictive values of 76% and 85%, respectively, with an overall accuracy in diagnosing dysplasia of 81.5% and a good interobserver agreement ($k = 0.61$), with no differences between experts and non-experts after a structured teaching session, suggesting a short learning curve [25]. Nevertheless, these criteria have not undergone to in vivo validation.

Other than for diagnostic purposes, the role of CLE has also been investigated with regard to surveillance programs in patients with Barrett's esophagus. A multicenter non-inferiority study, with a 3-month post-procedurally follow-up, involving 68 patients with 670 pairs of biopsies, showed a specificity and a negative predictive value for excluding neoplasia of 0.97 and 0.93 in the blinded evaluation, and 0.95 and 0.92 for the on-site assessment, respectively [26]. The authors concluded that pCLE is non-inferior to standard biopsy surveillance. The interesting result was also a significant decreasing of the specificity from 95% to 59% on a per-patient basis when investigators were blinded to the endoscopic findings. These results suggested that an adequate image interpretation requires the simultaneous evaluation of endoscopic and confocal images.

The aforementioned "DON'T BIOPCE" randomized trial compared high-definition endoscopy, narrow band imaging and pCLE with matching biopsies considered as reference standard [27]. The aim of this prospective randomized controlled multicentric trial was to evaluate the sensitivity and specificity of pCLE added to white-light endoscopy (WLE) for the detection of high-grade dysplasia (HGD) and early cancer (EC). The specificity and sensitivity for the detection of high-grade dysplasia using high-definition endoscopy alone was 34% and 93%, respectively, compared to

68% and 88% when used in combination with pCLE. The authors conclude that the addition of pCLE is more than twice as specific as WLE alone, and 1.3 times as sensitive as WLE and NBI to detect dysplasia. Furthermore, the use of pCLE allowed the detection of all HGD/EC patients, with the use of pCLE in addition to WLE and NBI resulting in a theoretical reduction of the need for biopsies of 39%. CLE can potentially even guide BE therapy by providing real-time evaluation of esophageal mucosa, allowing to discern between dysplastic areas to treat or to spare. A retrospective case series by Johnson et al. reported four cases of endoscopic mucosal resection and ablation therapy pCLE guided [28]. In this study, pCLE was also used to evaluate post-treatment margins, with one patient showing non-complete resection and requiring a repeated endoscopic treatment. In another case-series study reporting outcomes in seven patients with HGD endoscopically treated, pCLE led to additional endoscopic mucosal resections in one patient, whereas a dysplastic area was not immediately recognized at WLE [29]. Anyway, randomized controlled trials are required to fully establish the role of CLE in such situations.

A multicenter randomized-controlled trial also investigated the role of endomicroscopy in post-radiofrequency ablation of BE: white-light endoscopy or high-definition white-light endoscopy plus pCLE were compared in patients under surveillance [22]. Patients with suspected dysplasia underwent biopsy plus ablation while patients with no suspected dysplasia underwent biopsy alone. The trial demonstrated no statistically significative difference in the proportion of optimally treated patients between groups, concluding that there is no current evidence of improved treatment outcomes with the addition of pCLE to high-definition white-light endoscopy in post-ablation patients.

8.4 Current Limitations and Possibilities for Future Development

The most important remarks regarding the actual role of CLE in clinical management of Barrett's esophagus probably come from a meta-analysis endorsed by the American Society of Gastrointestinal Endoscopy [30]. In this paper, Thosani et al. stated that high-definition white-light endoscopy associated with confocal laser endomicroscopy targeted biopsies meets the Preservation and Incorporation of Valuable Innovation (PIVI) threshold for adopting real-time imaging-assisted endoscopic targeted biopsy during the endoscopic surveillance of Barrett's esophagus. The performance thresholds established in the PIVI document is a per-patient sensitivity of ≥90% and a negative predictive value (NPV) of ≥98% for detecting HGD or early EAC, other than a sufficiently high specificity (>80%); these thresholds would allow a reduction in the number of required biopsies (compared with random protocols). For "pCLE," the pooled sensitivity and specificity was 90.3% and 77.3%, respectively; despite very encouraging, these results do not fully meet the established PIVI thresholds yet. Nevertheless, with regard to the "eCLE," these thresholds are satisfied (with a sensitivity of 90.4% and a specificity of 92.7%), but unfortunately this device is no longer available in commerce.

The principal limitation of pCLE probe is the small field of mucosa you can capture and the difficulty in performing targeted biopsy of mucosa at the exact site visualized by pCLE; this would make the endoscopist prone to sampling error.

Current evidence is probably not sufficient to allow the pCLE to replace standard biopsies with histopathology; on the other hand, definitely it can be considered as a *red flag technique*, improving BE surveillance thanks to a real-time evaluation of the mucosa and the ability to recognize suspected focal areas of dysplasia for targeted biopsy.

A novel excellent opportunity to further increase the diagnostic accuracy in BE is represented by the development of topical fluorescent peptides with high affinity to BE dysplasia [31] together with newer endoscopes with fluorescence capability. These peptides can be marked with fluorescein or other agents and can guide endoscopic procedures, as already showed for colonic dysplasia [32, 33].

Future perspectives also include the possibility to perform a comprehensive wide-field examination of the esophagus with a volumetric laser endomicroscopy (VLE), a novel imaging technology similar to optical coherence tomography [29]. The use of VLE alongside CLE may provide the dual advantage of both wide-field imaging and a narrow high magnification of dysplastic mucosa in vivo.

Conclusions

Confocal laser endomicroscopy has demonstrated to facilitate the diagnosis of BE and associated dysplasia in vivo. Its accuracy in detecting high-grade dysplasia is comparable to conventional biopsies, despite its routine use in clinical practice still needs to be implemented and further investigated. The role of CLE in BE surveillance and treatment is evolving. The high resolution point-imaging capability of CLE may be an excellent adjunct to newer imaging technologies capable of achieving a comprehensive view of the esophagus.

Technical advances and novel available contrast agents will also potentially enhance the interpretation of confocal imaging and the agreement among endoscopists specialized in the management of Barrett's esophagus and early esophageal cancers.

References

1. Minsky M. Memoir on inventing the confocal scanning microscope. Scanning. 1988;10(4):128–38.
2. Wang TD, Van Dam J. Optical biopsy: a new frontier in endoscopic detection and diagnosis. Clin Gastroenterol Hepatol. 2004;2:744–53.
3. Aisenberg J. Gastrointestinal endoscopy nears "the molecular era". Gastrointest Endosc. 2008;68(3):528–30.
4. Kiesslich R, Goetz M, Vieth M, Galle PR, Neurath MF. Confocal laser endomicroscopy. Gastrointest Endosc Clin N Am [Internet]. 2005;15(4):715–31. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16278135.
5. Kiesslich R, Goetz M, Neurath MF. Confocal laser endomicroscopy for gastrointestinal diseases. Gastrointest Endosc Clin N Am [Internet]. 2008;18(3):451–66, viii. Available from

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18674696.
6. Neumann H, Kiesslich R, Wallace MB, Neurath MF. Confocal laser endomicroscopy: technical advances and clinical applications. Gastroenterology. 2010;139(2):388.
7. Bisschops R, Bergman J. Editorial: Probe-based confocal laser endomicroscopy: scientific toy or clinical tool? Endoscopy. 2010;42(6):487–9.
8. Yoshida S, Tanaka S, Hirata M, Mouri R, Kaneko I, Oka S, et al. Optical biopsy of GI lesions by reflectance-type laser-scanning confocal microscopy. Gastrointest Endosc. 2007;66(1):144–9.
9. Inoue H, Cho JY, Satodate H, Sakashita M, Hidaka E, Fukami S, et al. Development of virtual histology and virtual biopsy using laser-scanning confocal microscopy. Scand J Gastroenterol Suppl. 2003;38(237):37–9.
10. Kiesslich R, Neurath MF. Chromoendoscopy and other novel imaging techniques. Gastroenterol Clin N Am. 2006;35:605–19.
11. Wallace MB, Meining A, Canto MI, Fockens P, Miehlke S, Roesch T, et al. The safety of intravenous fluorescein for confocal laser endomicroscopy in the gastrointestinal tract. Aliment Pharmacol Ther. 2010;31(5):548–52.
12. Becker V, von Delius S, Bajbouj M, Karagianni A, Schmid RM, Meining A. Intravenous application of fluorescein for confocal laser scanning microscopy: evaluation of contrast dynamics and image quality with increasing injection-to-imaging time. Gastrointest Endosc. 2008;68(2):319–23.
13. Bruce WR, Heddle JA. The mutagenic activity of 61 agents as determined by the micronucleus, Salmonella, and sperm abnormality assays. Can J Genet Cytol. 1979;21(3):319–34.
14. O'Neil RG, Wu L, Mullani N. Uptake of a fluorescent deoxyglucose analog (2-NBDG) in tumor cells. Mol Imaging Biol. 2005;7(6):388–92.
15. Thekkek N, Maru DM, Polydorides AD, Bhutani MS, Anandasabapathy S, Richards-Kortum R. Pre-clinical evaluation of fluorescent deoxyglucose as a topical contrast agent for the detection of Barrett's-associated neoplasia during confocal imaging. Technol Cancer Res Treat. 2011;10(5):431–41.
16. Leggett CL, Sun G, Chowdhury S, Gorospe EC, Sharma AN, Buttar N. Topical esophageal delivery of a fluorescent marker of dysplasia in barrett's esophagus: a feasibility study [Internet]. Gastroenterology. 2013;144:S694. Available from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed15&NEWS=N&AN=71118366.
17. De Palma GD. Confocal laser endomicroscopy in the "in vivo" histological diagnosis of the gastrointestinal tract. World J Gastroenterol. 2009;15(46):5770–5.
18. De Palma GD, Rispo A. Confocal laser endomicroscopy in inflammatory bowel diseases: dream or reality? World J Gastroenterol. 2013;19(34):5593–7.
19. Kiesslich R, Gossner L, Goetz M, Dahlmann A, Vieth M, Stolte M, et al. In vivo histology of Barrett's esophagus and associated neoplasia by confocal laser endomicroscopy. Clin Gastroenterol Hepatol. 2006;4(8):979–87.
20. Dunbar KB, Okolo P, Montgomery E, Canto MI. Confocal laser endomicroscopy in Barrett's esophagus and endoscopically inapparent Barrett's neoplasia: a prospective, randomized, double-blind, controlled, crossover trial. Gastrointest Endosc. 2009;70(4):645–54.
21. Canto MI, Anandasabapathy S, Brugge W, Falk GW, Dunbar KB, Zhang Z, et al. In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). Gastrointest Endosc. 2014;79(2):211–21.
22. Pohl H, Rosch T, Vieth M, Koch M, Becker V, Anders M, et al. Miniprobe confocal laser microscopy for the detection of invisible neoplasia in patients with Barrett's oesophagus. Gut [Internet]. 2008;57(12):1648–53. Available from: http://gut.bmj.com/cgi/doi/10.1136/gut.2008.157461.
23. Wallace M, Lauwers GY, Chen Y, Dekker E, Fockens P, Sharma P, et al. Miami classification for probe-based confocal laser endomicroscopy. Endoscopy. 2011;43:882–91.
24. Gaddam S, Mathur SC, Singh M, Arora J, Wani SB, Gupta N, et al. Novel probe-based confocal laser endomicroscopy criteria and interobserver agreement for the detection of dysplasia in barrett's esophagus. Am J Gastroenterol. 2011;106(11):1961–9.

25. Tofteland N, Singh M, Gaddam S, Wani SB, Gupta N, Rastogi A, et al. Evaluation of the updated confocal laser endomicroscopy criteria for Barrett's esophagus among gastrointestinal pathologists. Dis Esophagus. 2014;27(7):623–9.
26. Bajbouj M, Vieth M, Rösch T, Miehlke S, Becker V, Anders M, et al. Probe-based confocal laser endomicroscopy compared with standard four-quadrant biopsy for evaluation of neoplasia in Barretts esophagus. Endoscopy. 2010;42(6):435–40.
27. Sharma P, Meining AR, Coron E, Lightdale CJ, Wolfsen HC, Bansal A, et al. Real-time increased detection of neoplastic tissue in Barrett's esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial. Gastrointest Endosc. 2011;74(3):465–72.
28. Johnson EA, De Lee R, Agni R, Pfau P, Reichelderfer M, Gopal DV. Probe-based confocal laser endomicroscopy to guide real-time endoscopic therapy in Barrett's esophagus with dysplasia. Case Rep Gastroenterol. 2012;6(2):285–92.
29. Konda VJ, Chennat JS, Hart J, Waxman I. Confocal laser endomicroscopy: potential in the management of Barrett's esophagus. Dis Esophagus [Internet]. 2010;23(5):E21–31. Available from http://www.ncbi.nlm.nih.gov/pubmed/20626448.
30. Thosani N, Abu Dayyeh BK, Sharma P, Aslanian HR, Enestvedt BK, Komanduri S, et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE preservation and incorporation of valuable endoscopic innovations thresholds for adopting real-time imaging-assisted endoscopic targeted biopsy during endoscopic surveillance. Gastrointest Endosc. 2016;83(4):684–698.e7.
31. Li M, Anastassiades CP, Joshi B, Komarck CM, Piraka C, Elmunzer BJ, et al. Affinity peptide for targeted detection of dysplasia in barrett's esophagus. Gastroenterology. 2010;139(5):1472–80.
32. De Palma GD, Colavita I, Zambrano G, Giglio MC, Maione F, Luglio G, et al. Detection of colonic dysplasia in patients with ulcerative colitis using a targeted fluorescent peptide and confocal laser endomicroscopy: a pilot study. PLoS One. 2017;12(6):e0180509.
33. Hsiung PL, Hardy J, Friedland S, Soetikno R, Du CB, Wu AP, et al. Detection of colonic dysplasia in vivo using a targeted heptapeptide and confocal microendoscopy. Nat Med. 2008;14(4):454–8.

Histology: The Different Points of View on Barret's Esophagus

9

Vincenzo Villanacci, Karel Geboes, Tiziana Salviato, and Gabrio Bassotti

Barrett's esophagus (BE) is an endoscopically recognized pathological condition determined by the replacement of the esophageal squamous epithelium with gastrointestinal epithelium [1, 2].

Factors for the development of BE in patients with gastroesophageal reflux disease (GERD) include hiatal hernia and duodenogastric reflux (LES) [3–7].

The importance of BE diagnosis is related to its association with the possible development of esophageal adenocarcinoma [8, 9], the frequency of which has rapidly increased over the last decades [10, 11].

9.1 The Normal Esophagus

A precise diagnosis of BE is based on the understanding of the normal anatomy and histology of the esophago-gastric junction (EGJ). Endoscopically, the muscular EGJ can correspond to the proximal margin of the gastric folds [12]. The mucosal EGJ, also known as the mucosal squamocolumnar junction (SCJ) or Z-line, is the site at which the squamous mucosa of the esophagus meets the columnar-lined mucosa [13–15].

The most proximal portion of the stomach is termed "cardia," and it is composed by surface foveolar mucinous epithelium and either underlying pure mucous or

V. Villanacci
Institute of Pathology, Spedali Civili, Brescia, Italy

K. Geboes
Department of Pathology, University Hospitals Leuven, KU Leuven, Leuven, Belgium

T. Salviato (✉)
Department of Pathology, University of Trieste—School of Medicine, Trieste, Italy

G. Bassotti
Gastroenterology and Hepatology Section, Department of Medicine, University of Perugia—School of Medicine, Perugia, Italy

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_9

mixed mucous and oxyntic glands. In some individuals, only oxyntic glands are present in the cardia; therefore, the histologic features of this small anatomic area are variable. There is ongoing controversy regarding the origin and nature of "cardiac" mucosa (mucous glands) of the EGJ region in normal individuals (e.g., whether it is congenital or metaplastic).

The actual existence of the gastric cardia as a normal finding has been a source of great debate. In reference manuals [16, 17], the gastric cardia is described as a narrow strip of mucosa separating the most distal portion of the esophageal squamous mucosa from the acid-producing fundic mucosa [18]. However, several studies suggest that gastric cardia (cardiac-type mucosa) is metaplastic [13–15, 19].

Kilgore et al. evaluated the entire EGJ in 30 pediatric autopsies from patients younger than 18 years with no known history of GERD or BE [20]. The squamocolumnar junction and its relationship to the EGJ were noted: in all cases, cardiac mucosa was present on the gastric side of the EGJ, with a length of only 1–4 mm. These results support the concept that the gastric cardia is present from birth as a normal structure although the possibility that cardiac-type mucosa can arise in the distal esophagus as a metaplastic phenomenon is not precluded. In a study of 48 fetal autopsy specimens De Hertogh et al. found that the distal esophagus was lined by simple columnar epithelium from 12-week gestational age (GA). The proximal part of this segment consisted of mucus-producing epithelium, devoid of parietal cells. Similarities between the fetal and adult EGJ and stomach cytokeratin expression patterns supported the conclusion that adult cardiac-type mucosa has an identifiable precursor in the fetus [21].

9.2 The Endoscopic and Microscopic Diagnosis of Barrett's Esophagus

BE is defined as columnar metaplasia of the esophagus that is visible endoscopically (endoscopically suspicious esophageal metaplasia, ESEM) and confirmed histologically. Pathologists are often asked to evaluate EGJ biopsies in patients who have been found an irregular endoscopic Z-line suggesting the presence of ultra-short-segment BE.

Endoscopically, it may be difficult to confidently recognize BE for several reasons [22, 23]. First, the presence of a hiatal hernia, often associated to BE, makes the identification of muscular EGJ more difficult. In addition, there are no anatomic landmarks that clearly define the borders of the LES [23]. Thus, it may be unknown where the biopsy specimens have precisely been obtained in relation to the EGJ. A biopsy with intestinal metaplasia obtained near the EGJ could either represent BE or intestinal metaplasia of the most proximal portion of the stomach.

Histologically, specialized columnar epithelium is characterized by two cell types: goblet cells and columnar cells. Cytologically, goblet cells have distended, mucin-filled cytoplasm with a barrel-shaped configuration. Histochemically, these cells contain acid mucins (both sialo- and sulfated mucins) which stain positively with alcian blue at pH 2.5. The columnar cells may resemble either gastric foveolar

cells or intestinal absorptive cells: unlike normal gastric foveolar cells, which contain neutral mucin, the columnar cells in BE may contain alcian blue-positive acid mucin ("the columnar blues" or "pseudogoblet" cells) although the intensity of staining is not as strong as that of the goblet cells [35]. These cells should not be used as definitive evidence of BE since unequivocal goblet cells are required for this diagnosis.

In 1976, Paull et al. described three different types of epithelium in BE: fundic-type, cardiac-type (junctional), and specialized columnar epithelium [24].

The cardiac and fundic types of Barrett's epithelium resemble their normal counterparts in the stomach, except for the presence of some degree of mucosal distortion, glandular atrophy, and mild inflammation [24, 25]. A biopsy from the "distal esophagus" with the presence of either of these findings is not diagnostic of BE since, as stated earlier, these mucosal types are frequently found in the distal esophagus in the absence of intestinal metaplasia [13–15]. If the endoscopic feeling is clearly that of BE, the absence of intestinal metaplasia may be merely a consequence of sampling errors. Thus, although the pathologist may not be able to make a definitive diagnosis of BE in these situations, the endoscopic suspicion may still suggest this diagnosis. Weinstein et al. found non-intestinal tongues of columnar epithelium extending more than 2 cm into the lower esophagus in less than 1% of 250 cases of studied BE [26].

A recent international, multidisciplinary group defined BE by the presence of columnar mucosa of the esophagus and noted that the pathology report of biopsies of the esophagus should always state whether goblet cells are present in tissue samples obtained from above the EGJ [27]. The statement is similar to the one proposed by the Montreal Definition in 2006, saying that "when biopsies of ESEM show columnar epithelium, it should be called Barrett's esophagus and the presence or absence of intestinal metaplasia specified" [28].

Another term which was introduced is the "histologic squamo-oxyntic gap" [29, 30]. Patients who have oxyntocardiac ± cardiac ± intestinal epithelia between the squamous epithelium proximally and the proximal limit of gastric oxyntic mucosa distally are defined as having a squamo-oxyntic gap. Classically, the distribution of the epithelia in the gap is constant with intestinal metaplasia, when present, mainly in the proximal region of the gap, cardiac epithelium intermediate and oxyntocardiac epithelium in the most distal segment of the gap. This is similar to what has been described historically for BE by Paull et al. [24], and to the so-called columnar-lined esophagus and its development is linked to reflux [29].

The presence of "intestinal-type" metaplasia can be confirmed or recognized by alcian-blue stain (pH 2.5) which easily highlights isolated goblet cells in areas that otherwise resemble cardiac or fundic-type mucosae [24] (Fig. 9.1).

The presence of specialized columnar epithelium and acid mucin containing goblet cells has been accepted as diagnostic of BE, regardless of the precise site of the biopsy within the tubular esophagus [25, 26].In fact, the American College of Gastroenterology provided a definition of BE as "**a change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have intestinal metaplasia by biopsy**" [27, 31–33]. This definition was proposed

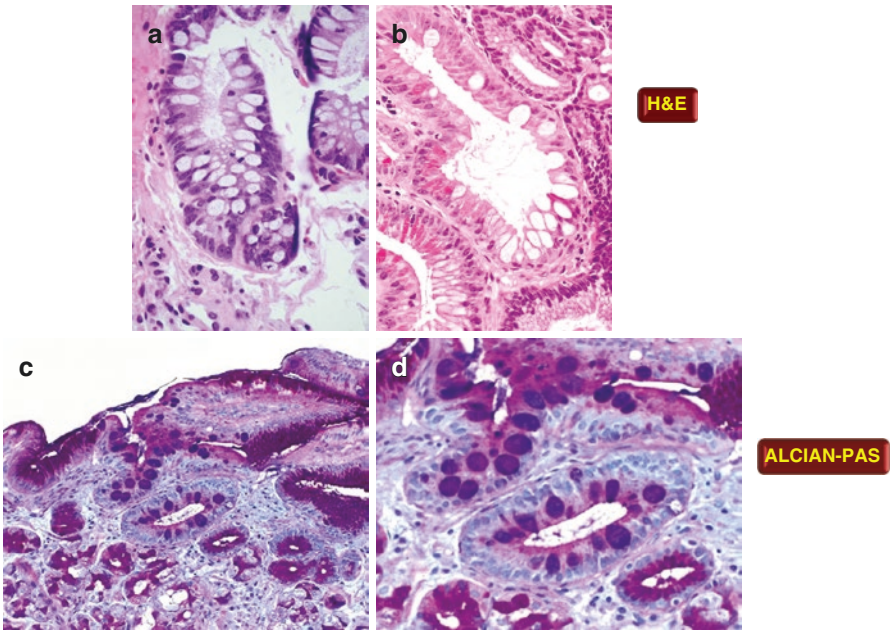

Fig. 9.1 Intestinal metaplasia in BE (**a**, **b**) H&E ×40 (**a**, **b**); Alcian-PAS ×20 (**c**) ×40 (**d**)

because the presence of "intestinal metaplasia" is linked to the development of cancer and hence implies that the patients need surveillance.

For this reason, and presuming a sufficient esophageal sampling, it is currently reasonable for the pathologist to abide by the dictum "No goblets No Barrett's" [34].

9.3 Is All Intestinal Metaplasia Equivalent to Barrett's Esophagus?

Spechler and colleagues were the first to report that adults frequently have unrecognized segments of intestinal metaplasia in the EGJ area [35, 36]. Among 142 patients without endoscopically apparent BE (defined as greater than 3 cm of specialized columnar epithelium above the EGJ), 26 (18%) were found to have intestinal metaplasia in this site. Subsequent studies reported a prevalence of intestinal metaplasia near the EGJ ranging from 9 to 36% [34, 37, 38] with an average of approximately 18%. While some investigators have found intestinal metaplasia in this location to be associated with symptoms of GERD [37] others found it to be associated with increased age [6, 38, 39].

It should be emphasized that intestinal metaplasia near the EGJ does not necessarily mean BE. Histologically, intestinal metaplasia of the upper stomach and distal esophagus are indistinguishable by light microscopy and histochemical methods

[39, 40]. Furthermore, the endoscopist may not be entirely sure of whether the biopsy specimen with intestinal metaplasia has been obtained from above or below the EGJ, given the difficulty in locating this landmark. Thus, the issue whether cardiac intestinal metaplasia (CIM) in the gastric cardia has the same etiology and significance as BE becomes central to establish whether the distinction between these two conditions is important.

Over the past years, there had been increasing evidence that CIM is a relatively common finding, with a prevalence rate ranging from 5.3% [40] to 23% [41] of adults undergoing upper endoscopy. Differences in patient populations and number of biopsy specimens may account for the variability in the prevalence of CIM reported in these studies. For instance, in the experience of Morales et al., in which five biopsy specimens from the cardia were obtained in each patient, the prevalence rate of CIM was 23% [42], whereas in a study from the Cleveland Clinic Foundation, only two biopsy specimens were obtained from cardia, resulting in a prevalence of CIM of 9% [43]. Thus, if CIM distribution is patchy, then it would be logical to assume a higher yield if more biopsy specimens are obtained.

There are conflicting data on the relationship of *H. pylori* infection and GERD in the development of CIM. Oberg et al. found that intestinal metaplasia in this location was strongly associated with the hallmarks of GERD, including increased esophageal acid exposure, hiatal hernia, defective LES, and erosive esophagitis [15]. Only 17% of patients with CIM had *H. pylori* infection documented in the cardia, and only 6.9% had intestinal metaplasia in other portions of the stomach. In contrast, Hackelsberger and colleagues found that patients with an endoscopically unremarkable squamocolumnar junction and intestinal metaplasia frequently had *H. pylori* infection as well as intestinal metaplasia in other parts of the stomach [7]. However, in patients with endoscopic features of BE, intestinal metaplasia near the EGJ was associated with male sex and hallmarks of GERD [7]. Similar results were reported in a large study by Hirota et al. including over 1000 patients [41]. In this study, CIM was more common among controls (22%) than GERD patients (3%); all patients with CIM had carditis, and the majority had evidence of *H. pylori* infection as well as of intestinal metaplasia in other portions of the stomach. The significance of intestinal metaplasia near the EGJ in a single patient should be evaluated in the context of endoscopic findings, histologic and serologic data for *H. pylori* infection, and information obtained from biopsies of the distal stomach.

However, the presence of one or more of the following morphologic features, such as squamous epithelium overlying crypts (buried columnar epithelium), severe diffuse crypt atrophy and disarray, multilayered epithelium, and esophageal glands and/or ducts are indicative of an esophageal origin of the columnar mucosa in the biopsy sample and thus are significantly associated with BE.

Although many studies have been performed evaluating ancillary techniques in BE, mucin-histochemical or intestine specific biomarker stains are not routinely used in this setting. Markers such as DAS1, CDX2, Hep Par 1, villin, CK7/20, or any of the MUC molecules that are known to be specific for intestinal columnar epithelium are equally common or not specific to columnar epithelium of the distal esophagus compared with the proximal stomach.

9.4 Dysplasia in Barrett's Esophagus

Dysplasia can be defined as the presence of neoplastic epithelium that is confined within the basement membrane of the gland within which it arises [44].

Unlike inflammatory bowel disease-associated dysplastic lesions, most cases of Barrett's-related dysplasia do not closely resemble colonic adenomas. Rather, the typical form of Barrett's-related dysplasia often arises in glands which retain their normal configuration, and often lack nuclear stratification.

Using the criteria defined by Riddell et al. for dysplasia arising in inflammatory bowel disease, dysplasia in BE can be classified as either low-grade or high-grade based upon the degree of the abnormality present. Thus, the possibilities include (1) negative for dysplasia; (2) positive for dysplasia, either low-grade or high-grade; or (3) indefinite for dysplasia.

In **low-grade dysplasia** (LGD), crypt architecture tends to be preserved with only minimal distortion, and cytologically atypical nuclei are limited to the basal half of the crypts. The nuclei tend to show variable hyperchromasia, overlapping cell borders with nuclear crowding and irregular nuclear contours. Dystrophic goblet cells may be seen although typically the number of goblet cell is markedly reduced in dysplastic foci. Separation of LGD from regenerative changes will be discussed below (Fig. 9.2).

High-grade dysplasia (HGD) shows more severe cytologic atypia and architectural complexity than are present in LGD, and in some cases this distinction is quite difficult. Architecturally, crypt complexity in HGD is more pronounced, sometimes with a villiform configuration of the mucosal surface and/or branched

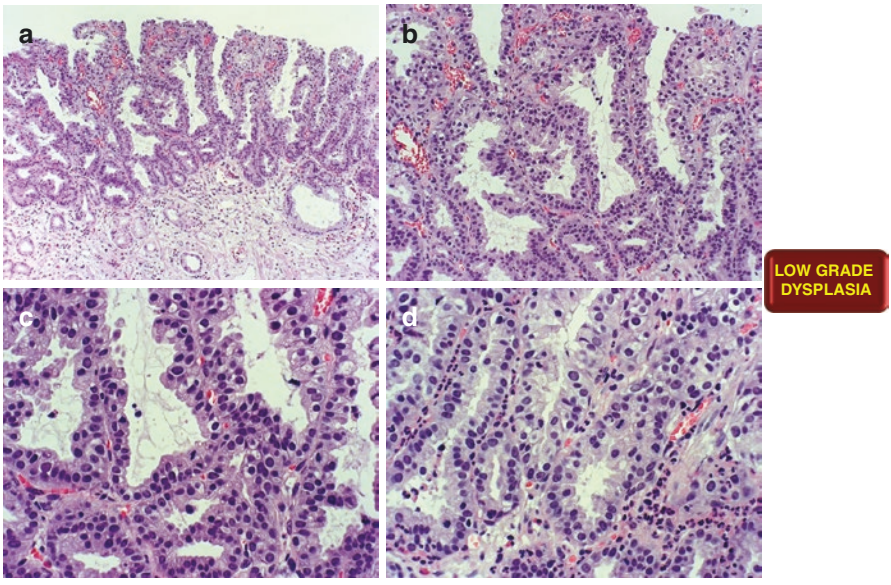

Fig. 9.2 Low-grade dysplasia H&E (**a**) ×10, (**b**) ×20, (**c**, **d**) ×40

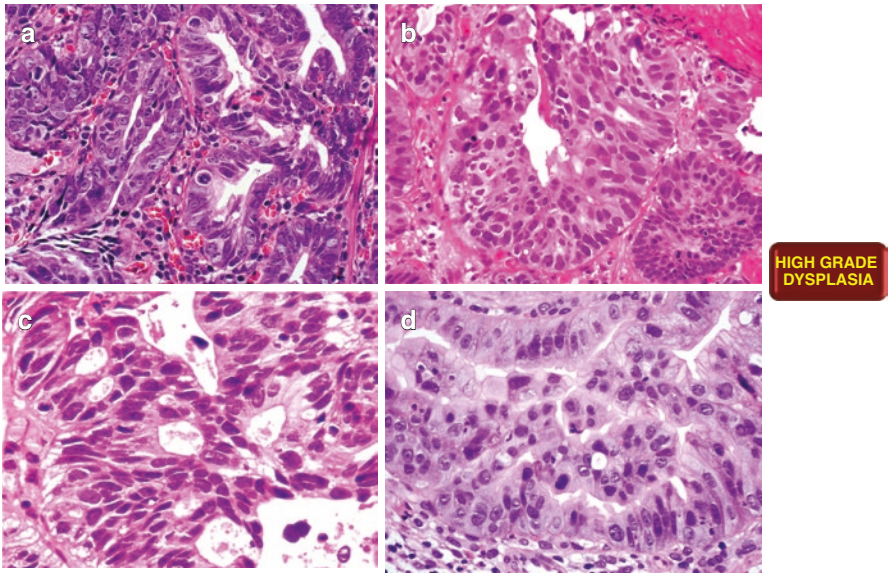

Fig. 9.3 High-grade dysplasia H&E (**a**) ×10, (**b**) ×20, (**c**, **d**) ×40

crypts. Cytologically, the cells show more nuclear pleomorphism and hyperchromatism than in LGD, and there is often nuclear stratification to the crypt luminal surface (Fig. 9.3).

Separation of intramucosal adenocarcinoma (IMC) from HGD is important, but in some cases this is exceedingly difficult. By definition, in IMC, neoplastic cells have penetrated through the basement membrane and infiltrate into the lamina propria, typically as single cells or in small clusters. Given the presence of lymphatic channels within the esophageal mucosa, there is a small but definite risk of regional lymph node metastasis in patients with IMC [45, 46]. Therapeutic strategies based upon the histologic separation of HGD from IMC are debatable given the great difficulty in their microscopic assessment [47].

A diagnosis of "**indefinite for dysplasia,**" is only a temporary diagnosis. The differentiation of regenerative changes from true dysplasia, particularly in a background of inflammation or ulceration, may be very challenging or suffering from an irreducible bias. Thus, if the pathologist is not sure as to whether the epithelial changes are regenerative or truly dysplastic, a diagnosis of indefinite for dysplasia should be made. In some cases, architectural atypia may be striking in the absence of definitive cytologic atypia of the surface epithelium: under these circumstances, a diagnosis of indefinite for dysplasia is acceptable as well (as described further below).

Because Barrett's mucosa is metaplastic, there is a "baseline atypia" which is always present, and this fact in a certain sense must be overlooked in order to make a diagnosis of dysplasia. This baseline atypia is most pronounced in the glands at the base of the mucosa and does not involve the surface epithelium. In addition,

biopsies from Barrett's mucosa are not infrequently inflamed, often with the presence of both acute and chronic inflammatory cells. As in case of active chronic inflammatory bowel disease, neutrophil-mediated epithelial injury can induce regenerative changes that may be difficult to differentiate from dysplasia. There are some general rules that are useful in distinguishing between these conditions, as outlined below.

The low-magnification appearance of the mucosa is extremely important. True dysplasia usually draws attention at low magnification due to the consistent presence of nuclear hyperchromasia. Obviously, configuration of cytologic atypia at higher magnification is necessary. In addition, the cytologic alterations should be present on the surface epithelium, not merely in the glandular compartment. In a well-oriented specimen, it is fairly straightforward to determine whether these cytologic alterations involve the surface epithelium. Yet, in a tangentially sectioned biopsy specimen, this evaluation can be difficult.

Cytologically, dysplastic epithelium tends to show variable nuclear hyperchromasia and pleomorphism. In other words, cells tend to look different from each other, with some of them showing nuclear hyperchromasia and irregular nuclear contours when compared to surrounding cells within the same crypt. In contrast, although both nuclear hyperchromasia and pleomorphism may be seen during repair, the changes tend to be less severe and more uniform throughout. Thus, the cytologic atypia associated with repair is more uniform than in true dysplasia. Dysplastic cells tend to have a higher nuclear-to-cytoplasmic ratio as well as irregular nuclear contours. Although regenerative cells may have nuclear size similar to those seen in dysplasia, they tend to have a proportional increase of cytoplasm amount such that the nuclear-to-cytoplasmic ratio is normal or only mildly increased. In addition, regenerative cells tend to have round regular nuclear contours.

In any case, dysplasia may be diffusely distributed throughout a BE segment, or the changes may be focal [48], sometimes limited to a small area of one of the multiple fragments from a patient. When dysplasia is diffuse, the 4-quadrant biopsy technique has usually a high diagnostic yield. However, small foci of dysplasia can be missed even using this rigorous sampling technique. The need for thorough sampling is further emphasized by the fact that many cases of HGD or early adenocarcinoma arising in BE are not associated with a grossly recognizable lesion [49, 50]. Given this sampling error, once a diagnosis of dysplasia is made, subsequent biopsies without dysplasia should not reassure the gastroenterologist into a false sense of security, provided that the original diagnosis was correct.

Another major issue is represented by the intra- and interobserver variation in the diagnosis of dysplasia. Given the subtle range of changes from baseline atypia to LGD to HGD, it is not surprising that this variation exists. Reid et al. found this variation to be most striking at the lower end of the histologic spectrum—that is, distinguishing negative for dysplasia from LGD or indefinite for dysplasia [50]. The study by Reid et al. describes observer variation in terms of percentage agreement, which does not account for agreement that is likely to occur by chance alone. A study by Montgomery et al. using kappa statistical analysis (which does account for agreement that occurs by chance alone) confirmed a high degree of intra- and

interobserver variation in the separation of these diagnoses, even among gastrointestinal pathologists [51].

In addition, in real-life situations may further worsen. In a recent study carried out outside the formal strict rules of research trials, we have shown that a second look by an experienced gastro-intestinal pathologist revealed almost 80% of diagnostic discordance, and in more than 60% of cases the initial diagnosis of dysplasia in BE was not confirmed [52].

Given the difficulty to determine the precise site of a biopsy specimen and the histologic resemblance of intestinal metaplasia in both of these locations, it would be of clinical importance to localize the intestinal metaplasia to either the distal esophagus or proximal stomach. Immunohistochemical stains for Cytokeratin (CK) subsets may be useful in this regard. Ormsby et al. evaluated CK7 and 20 immunoreactivity patterns in resection specimens with LSBE and compared them to distal gastric resection specimens with intestinal metaplasia [53]. Virtually all cases with LSBE were characterized by superficial and deep CK7 immunoreactivity, with only superficial CK20 staining. In contrast, distal gastric intestinal metaplasia was characterized by patchy superficial and deep CK20 staining in areas of incomplete intestinal metaplasia, strong superficial and deep CK20 staining in areas of complete intestinal metaplasia, and patchy or absent CK7 staining in either type of gastric intestinal metaplasia. Although all patients with BE are at increased risk for developing adenocarcinoma, certain patients are at higher risk than others. For instance, epidemiologic data suggest that most patients with BE-associated adenocarcinoma are elderly white males [1, 54, 55]. There is also evidence to support the claim that only patients with specialized columnar epithelium have an increased risk of developing Barrett's-related adenocarcinoma [27, 56–58]. The presence of epithelial dysplasia, particularly high-grade dysplasia (HGD), is also a risk factor for synchronous or metachronous adenocarcinoma [58–60]. Several retrospective studies have noted the frequency with which dysplasia is seen both adjacent to and distant from Barrett's-related adenocarcinomas [1]. Prospective studies have also documented the progression from specialized columnar epithelium to HGD and eventually invasive adenocarcinoma [58, 61]. Thus, dysplasia is not only a marker of adenocarcinoma, but also represents the pre-invasive lesion [62]. Finally, although it is known that adenocarcinoma can arise in extremely short segments of BE [63] some investigators have proposed that there is an increased risk of adenocarcinoma related to the increase of the length of BE [40, 64].

Although available prospective data are scattered, a few studies have indicated a much lower risk of CIM progression to dysplasia or carcinoma when compared to either SSBE or LSBE. For example, Sharma et al. found only one out of 34 patients with CIM progressing to dysplasia (low-grade) during the follow-up period [65]. Morales et al. found dysplasia (low-grade) in only 1 out of 28 patients with follow-up periods ranging from 12 to 46 months (mean 2.5 years) [66]. Among 85 patients with CIM, Goldstein reported that only 10 had CIM on repeated biopsy, and none developed dysplasia [67].

These data reiterate the importance of attempting to distinguish CIM from intestinal metaplasia of esophageal origin in biopsy specimens, given the apparent differences in the risk of progression to dysplasia or carcinoma.

Although cancer surveillance is started in most institutions once a diagnosis of BE is made, the true cost/benefit ratio of this endeavor is still essentially unknown. Although this issue has yet to be resolved, patients are placed into a cancer surveillance program once a diagnosis of BE has been clearly established, with the surveillance goal being the identification of epithelial dysplasia in a biopsy specimen, before carcinoma has developed. The protocol proposed by Reid et al. [68] with 4-quadrant biopsies taken at intervals of 2 cm or less throughout the length of the Barrett's segment, with additional biopsies of any endoscopic lesions, using jumbo forceps, is mandatory [49, 69–73].

In most institutions, a diagnosis of dysplasia is reached with endoscopic biopsies. The size of the samples remains however limited although the diagnostic yield can be increased with multiple biopsies. The introduction of endoscopic mucosal resection (EMR) which produces larger samples can improve diagnostic reliability and consistency in addition to being a staging and therapeutic procedure [74]. Furthermore, several other endoscopic techniques allowing better detection and biopsy procedures such as esophageal-guided biopsy with laser endomicroscopy are currently being developed or tested and may modify the clinical approach in the future.

References

1. Spechler SJ, Goyal RK. Barrett's esophagus. N Engl J Med. 1986;315:362–71.
2. Jankowski J, Barr H, Wang K, Delaney B. Diagnosis and management of Barrett's oesophagus. BMJ. 2010;341:c4551.
3. Collen MJ, Lewis JH, Benjamin SB. Gastric acid hypersecretion in refractory gastroesophageal reflux disease. Gastroenterology. 1990;98:654–61.
4. Mulholland MW, Reid BJ, Levine DS, Rubin CE. Elevated gastric acid secretion in patients with Barrett's metaplastic epithelium. Dig Dis Sci. 1989;34:1329–34.
5. Shaheen NJ, Richter JE. Barrett's oesophagus. Lancet. 2009;373:850–61.
6. Dixon MF, Mapstone NP, Neville PM, Moayyedi P, Axon AT. Bile reflux gastritis and intestinal metaplasia at the cardia. Gut. 2002;51:351–5.
7. Hackelsberger A, Gunther T, Schultze V, Manes G, Dominguez-Munoz JE, Roessner A, Malfertheiner P. Intestinal metaplasia at the gastro-oesophageal junction: helicobacter pylori gastritis or gastro-oesophageal reflux disease? Gut. 1998;43:17–21.
8. Haggitt RC, Tryzelaar J, Ellis FH, Colcher H. Adenocarcinoma complicating columnar epithelium-lined (Barrett's) esophagus. Am J Clin Pathol. 1978;70:1–5.
9. Villanacci V, Rossi E, Zambelli C, Galletti A, Cestari R, Missale G, Casa DD, Bassotti G. COX-2, CDX2, and CDC2 immunohistochemical assessment for dysplasia-carcinoma progression in Barrett's esophagus. Dig Liver Dis. 2007;39:305–11.
10. Blot WJ. Esophageal cancer trends and risk factors. Semin Oncol. 1994;21:403–10.
11. Haggitt RC. Adenocarcinoma in Barrett's esophagus: a new epidemic? Hum Pathol. 1992;23:475–6.
12. Bombeck CT, Dillard DH, Nyhus LM. Muscular anatomy of the gastroesophageal junction and role of phrenoesophageal ligament; autopsy study of sphincter mechanism. Ann Surg. 1966;164:643–54.
13. Chandrasoma PT, Lokuhetty DM, Demeester TR, Bremmer CG, Peters JH, Oberg S, Groshen S. Definition of histopathologic changes in gastroesophageal reflux disease. Am J Surg Pathol. 2000;24:344–51.

14. Der R, Tsao-Wei DD, Demeester T, Peters J, Groshen S, Lord RV, Chandrasoma P. Carditis: a manifestation of gastroesophageal reflux disease. Am J Surg Pathol. 2001;25:245–52.
15. Oberg S, Peters JH, DeMeester TR, Chandrasoma P, Hagen JA, Ireland AP, Ritter MP, Mason RJ, Crookes P, Bremner CG. Inflammation and specialized intestinal metaplasia of cardiac mucosa is a manifestation of gastroesophageal reflux disease. Ann Surg. 1997;226:522–30; discussion 30–2.
16. Adler DG, Farraye FA, Crawford JM. Gastrointestinal tract endoscopic and tissue processing techniques and normal histology. In: Odze RD, Goldblum JR, editors. Odze and Goldblum surgical pathology of the GI tract, liver, biliary tract, and pancreas. 3rd ed. Philadelphia: Elsevier Saunders; 2015. p. 4–33.
17. Rege TA, Noffsinger AE. The nonneoplastic esophagus. In: Noffsinger A, editor. Fenoglio-Presiser's gastrointestinal pathology. 4th ed. Philadelphia: Wolters Kluwer; 2008. p. 11–95.
18. Owen DA. Stomach. In: Sternberg SS, editor. Histology for pathologists. New York: Raven Press; 1992. p. 533–45.
19. Chandrasoma PT, Der R, Ma Y, Dalton P, Taira M. Histology of the gastroesophageal junction: an autopsy study. Am J Surg Pathol. 2000;24:402–9.
20. Kilgore SP, Ormsby AH, Gramlich TL, Rice TW, Richter JE, Falk GW, Goldblum JR. The gastric cardia: fact or fiction? Am J Gastroenterol. 2000;95:921–4.
21. De Hertogh G, Van Eyken P, Ectors N, Geboes K. On the origin of cardiac mucosa: a histological and immunohistochemical study of cytokeratin expression patterns in the developing esophagogastric junction region and stomach. World J Gastroenterol. 2005;11:4490–6.
22. Spechler SJ, Goyal RK. The columnar-lined esophagus, intestinal metaplasia, and Norman Barrett. Gastroenterology. 1996;110:614–21.
23. Chandrasoma P, Wijetunge S, Ma Y, Demeester S, Hagen J, Demeester T. The dilated distal esophagus: a new entity that is the pathologic basis of early gastroesophageal reflux disease. Am J Surg Pathol. 2011;35:1873–81.
24. Paull A, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RK. The histologic spectrum of Barrett's esophagus. N Engl J Med. 1976;295:476–80.
25. Haggitt RC. Barrett's esophagus, dysplasia, and adenocarcinoma. Hum Pathol. 1994;25:982–93.
26. Weinstein WM, Ippoliti AF. The diagnosis of Barrett's esophagus: goblets, goblets, goblets. Gastrointest Endosc. 1996;44:91–5.
27. Costamagna G, Battaglia G, Repici A, Fiocca R, Rugge M, Spada C, Villanacci V. Diagnosis and endoscopic management of Barrett's esophagus: an Italian Experts' opinion based document. Dig Liver Dis. 2017;49:1306.
28. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900–20; quiz 43.
29. Chandrasoma P, Wijetunge S, Demeester SR, Hagen J, Demeester TR. The histologic squamo-oxyntic gap: an accurate and reproducible diagnostic marker of gastroesophageal reflux disease. Am J Surg Pathol. 2010;34:1574–81.
30. Lenglinger J, See SF, Beller L, Cosentini EP, Asari R, Wrba F, Riegler M, Schoppmann SF. Review on novel concepts of columnar lined esophagus. Wien Klin Wochenschr. 2013;125:577–90.
31. Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol. 1998;93:1028–32.
32. Sharma P. Short segment Barrett esophagus and specialized columnar mucosa at the gastroesophageal junction. Mayo Clin Proc. 2001;76:331–4.
33. Weston AP, Krmpotich P, Makdisi WF, Cherian R, Dixon A, McGregor DH, Banerjee SK. Short segment Barrett's esophagus: clinical and histological features, associated endoscopic findings, and association with gastric intestinal metaplasia. Am J Gastroenterol. 1996;91:981–6.
34. Batts KP. Barrett esophagus—more steps forward. Hum Pathol. 2001;32:357–9.
35. Offner FA, Lewin KJ, Weinstein WM. Metaplastic columnar cells in Barrett's esophagus: a common and neglected cell type. Hum Pathol. 1996;27:885–9.

36. Spechler SJ, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK. Prevalence of metaplasia at the gastro-oesophageal junction. Lancet. 1994;344:1533–6.
37. Johnston MH, Hammond AS, Laskin W, Jones DM. The prevalence and clinical characteristics of short segments of specialized intestinal metaplasia in the distal esophagus on routine endoscopy. Am J Gastroenterol. 1996;91:1507–11.
38. Nandurkar S, Talley NJ, Martin CJ, Ng TH, Adams S. Short segment Barrett's oesophagus: prevalence, diagnosis and associations. Gut. 1997;40:710–5.
39. Trudgill NJ, Suvarna SK, Kapur KC, Riley SA. Intestinal metaplasia at the squamocolumnar junction in patients attending for diagnostic gastroscopy. Gut. 1997;41:585–9.
40. Ormsby AH, Goldblum J, Richter JE, Falk GW, Gramlich TL. The sensitivity and specificity of histologic features in the diagnosis of Barrett's esophagus on routine endoscopic biopsy specimens. Am J Clin Pathol. 1999;112:A533.
41. Hirota WK, Loughney TM, Lazas DJ, Maydonovitch CL, Rholl V, Wong RK. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. Gastroenterology. 1999;116:277–85.
42. Morales TG, Sampliner RE, Bhattacharyya A. Intestinal metaplasia of the gastric cardia. Am J Gastroenterol. 1997;92:414–8.
43. Goldblum JR, Vicari JJ, Falk GW, Rice TW, Peek RM, Easley K, Richter JE. Inflammation and intestinal metaplasia of the gastric cardia: the role of gastroesophageal reflux and H. pylori infection. Gastroenterology. 1998;114:633–9.
44. Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, Ahren C, Correa P, Hamilton SR, Morson BC, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Hum Pathol. 1983;14:931–68.
45. Goseki N, Koike M, Yoshida M. Histopathologic characteristics of early stage esophageal carcinoma. A comparative study with gastric carcinoma. Cancer. 1992;69:1088–93.
46. Sabik JF, Rice TW, Goldblum JR, Koka A, Kirby TJ, Medendorp SV, Adelstein DJ. Superficial esophageal carcinoma. Ann Thorac Surg. 1995;60:896–901; discussion 2.
47. Ormsby AH, Petras RE, Henricks WH, Riche TW, Richter JE, Goldblum JR. Interobserver variation in the diagnosis of superficial adenocarcinoma in Barrett's esophagus. Mod Pathol. 1998;11:386A.
48. Lavery DL, Martinez P, Gay LJ, Cereser B, Novelli MR, Rodriguez-Justo M, Meijer SL, Graham TA, McDonald SA, Wright NA, Jansen M. Evolution of oesophageal adenocarcinoma from metaplastic columnar epithelium without goblet cells in Barrett's oesophagus. Gut. 2016;65:907–13.
49. Falk GW, Rice TW, Goldblum JR, Richter JE. Jumbo biopsy forceps protocol still misses unsuspected cancer in Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc. 1999;49:170–6.
50. Reid BJ, Haggitt RC, Rubin CE, Roth G, Surawicz CM, Van Belle G, Lewin K, Weinstein WM, Antonioli DA, Goldman H, et al. Observer variation in the diagnosis of dysplasia in Barrett's esophagus. Hum Pathol. 1988;19:166–78.
51. Montgomery E, Bronner MP, Goldblum JR, Greenson JK, Haber MM, Hart J, Lamps LW, Lauwers GY, Lazenby AJ, Lewin DN, Robert ME, Toledano AY, Shyr Y, Washington K. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol. 2001;32:368–78.
52. Villanacci V, Salemme M, Stroppa I, Balassone V, Bassotti G. The importance of a second opinion in the diagnosis of Barrett's esophagus: a "real life" study. Rev Esp Enferm Dig. 2017;109:185–9.
53. Ormsby AH, Goldblum JR, Rice TW, Richter JE, Falk GW, Vaezi MF, Gramlich TL. Cytokeratin subsets can reliably distinguish Barrett's esophagus from intestinal metaplasia of the stomach. Hum Pathol. 1999;30:288–94.
54. de Jonge PJ, van Blankenstein M, Looman CW, Casparie MK, Meijer GA, Kuipers EJ. Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study. Gut. 2010;59:1030–6.
55. Sjogren RW Jr, Johnson LF. Barrett's esophagus: a review. Am J Med. 1983;74:313–21.

56. Hamilton SR, Smith RR. The relationship between columnar epithelial dysplasia and invasive adenocarcinoma arising in Barrett's esophagus. Am J Clin Pathol. 1987;87:301–12.
57. Lee RG. Dysplasia in Barrett's esophagus. A clinicopathologic study of six patients. Am J Surg Pathol. 1985;9:845–52.
58. Reid BJ, Blount PL, Rubin CE, Levine DS, Haggitt RC, Rabinovitch PS. Flow-cytometric and histological progression to malignancy in Barrett's esophagus: prospective endoscopic surveillance of a cohort. Gastroenterology. 1992;102:1212–9.
59. Schmidt HG, Riddell RH, Walther B, Skinner DB, Riemann JF. Dysplasia in Barrett's esophagus. J Cancer Res Clin Oncol. 1985;110:145–52.
60. Smith RR, Hamilton SR, Boitnott JK, Rogers EL. The spectrum of carcinoma arising in Barrett's esophagus. A clinicopathologic study of 26 patients. Am J Surg Pathol. 1984;8:563–73.
61. Hameeteman W, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. Gastroenterology. 1989;96:1249–56.
62. Smith J, Garcia A, Zhang R, DeMeester S, Vallone J, Chandrasoma P. Intestinal metaplasia is present in most if not all patients who have undergone endoscopic mucosal resection for esophageal adenocarcinoma. Am J Surg Pathol. 2016;40:537–43.
63. Schnell TG, Sontag SJ, Chejfec G. Adenocarcinomas arising in tongues or short segments of Barrett's esophagus. Dig Dis Sci. 1992;37:137–43.
64. Menke-Pluymers MB, Hop WC, Dees J, van Blankenstein M, Tilanus HW. Risk factors for the development of an adenocarcinoma in columnar-lined (Barrett) esophagus. The Rotterdam Esophageal Tumor Study Group. Cancer. 1993;72:1155–8.
65. Sharma P, Weston AP, Morales T, Topalovski M, Mayo MS, Sampliner RE. Relative risk of dysplasia for patients with intestinal metaplasia in the distal oesophagus and in the gastric cardia. Gut. 2000;46:9–13.
66. Morales TG, Camargo E, Bhattacharyya A, Sampliner RE. Long-term follow-up of intestinal metaplasia of the gastric cardia. Am J Gastroenterol. 2000;95:1677–80.
67. Goldstein NS. Gastric cardia intestinal metaplasia: biopsy follow-up of 85 patients. Mod Pathol. 2000;13:1072–9.
68. Reid BJ, Weinstein WM, Lewin KJ, Haggitt RC, VanDeventer G, DenBesten L, Rubin CE. Endoscopic biopsy can detect high-grade dysplasia or early adenocarcinoma in Barrett's esophagus without grossly recognizable neoplastic lesions. Gastroenterology. 1988;94:81–90.
69. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, Trudgill N, Patel P, Kaye PV, Sanders S, O'Donovan M, Bird-Lieberman E, Bhandari P, Jankowski JA, Attwood S, Parsons SL, Loft D, Lagergren J, Moayyedi P, Lyratzopoulos G, de Caestecker J, British Society of Group. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014;63:7–42.
70. Naik AD, El-Serag HB. Endoscopic ablation of low-grade dysplasia in Barrett's esophagus: have all the boxes been checked for us to move on? Gastrointest Endosc. 2017;86:130–2.
71. Nguyen T, Thrift AP, Yu X, Duan Z, El-Serag HB. The annual risk of esophageal adenocarcinoma does not decrease over time in patients with Barrett's esophagus. Am J Gastroenterol. 2017;112:1049–55.
72. Petras RE, Sivak MV Jr, Rice TW. Barrett's esophagus. A review of the pathologist's role in diagnosis and management. Pathol Annu. 1991;26(Pt 2):1–32.
73. Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111:30–50; quiz 1.
74. Mino-Kenudson M, Hull MJ, Brown I, Muzikansky A, Srivastava A, Glickman J, Park DY, Zuckerberg L, Misdraji J, Odze RD, Lauwers GY. EMR for Barrett's esophagus-related superficial neoplasms offers better diagnostic reproducibility than mucosal biopsy. Gastrointest Endosc. 2007;66:660–6; quiz 767, 9.

The Role of Molecular Biology in Diagnosis and Follow-Up of Barrett's Esophagus

10

Karen Geboes and Anne Hoorens

Molecular pathways leading to the development of Barrett's esophagus (BE) and to the progression from Barrett's esophagus to esophageal adenocarcinoma (EAC) have been the focus of recent research. Surveillance of patients with BE relies on regular endoscopic surveillance to detect dysplasia and to diagnose carcinoma in an early treatable stage. Poor adherence to the recommended surveillance protocols with extensive sampling, as well as interobserver variability in evaluating dysplasia are, however, major drawbacks in this context, emphasizing the need for molecular biomarkers that may help in risk stratification of BE patients.

Definitions of BE vary between countries. In the USA, a diagnosis of Barrett's esophagus is only withheld when normal stratified squamous epithelium of the esophagus is replaced by an intestine-like columnar epithelium with goblet cells (specialized intestinal metaplasia), whereas in Japan and the United Kingdom BE is often used for any columnar mucosa found in the tubular esophagus.

There are different theories concerning the origin of BE and no consensus has been reached [1]. Multiple cell sources that may have undergone molecular reprogramming can be at the origin of BE. Transdifferentiation is a process in which one mature (differentiated) somatic cell type transforms directly into another type of mature somatic cell without undergoing an intermediate pluripotent state or progenitor cell type. It seems less probable that this is the origin of BE because it is unlikely that a nonproliferating differentiated squamous cell could sustain BE tissue indefinitely. Moreover, full phenotypic conversion of a cultured mature squamous cell has not yet been demonstrated. Transcommitment, in which undifferentiated

K. Geboes (✉)
Department of Gastroenterology, Universitair Ziekenhuis Gent, Ghent, Belgium
e-mail: karen.geboes@uzgent.be

A. Hoorens
Department of Pathology, Universitair Ziekenhuis Gent, Ghent, Belgium
e-mail: anne.hoorens@uzgent.be

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_10

progenitor cells in the esophagus that would normally differentiate into squamous cells instead differentiate into columnar cells, seems to be the more likely hypothesis.

Gene expression arrays showed that expression of genes of both gastric and intestinal epithelium can be found in Barrett epithelium. One hypothesis suggests an evolution from esophageal squamous epithelium to cardiac type glands and further into intestinal glands [2]. Another concept may be the evolution of Barrett glands from metaplasia of the stem cells of the proximal columnar gastric or cardiac epithelium [3]. In addition, circulating bone marrow-derived multi-potential stem cells have been shown to migrate to the esophagus and contribute to regeneration and metaplasia of esophageal epithelium following injury induced by irradiation or reflux [4, 5].

Whether its source are esophageal progenitor cells, residual embryonic cells at the squamo-columnar junction (SCJ), proximally shifting columnar progenitor cells from the gastric cardia, progenitor cells in the submucosal glands or ducts, circulating bone marrow-derived stem cells or esophageal differentiated squamous cells, the cells at the origin of BE would have to undergo molecular reprogramming with altered expression of key developmental transcription factors leading to a change in the cell's phenotypic committement [6]. Data exist to support each of these possible origins—progenitor cells in the esophagus, progenitor cells proximally shifting from the SCJ or cardia or progenitor cells circulating in the bloodstream, as a reaction upon injury—and none can be completely excluded. Esophageal squamous epithelial progenitor cells retain the embryonic capacity to switch between squamous and columnar phenotype, but must still undergo molecular reprogramming to give rise to specialized intestinal metaplasia. Pathways responsible for columnar differentiation, intestinalization, and mucus differentiation from epithelial cells with biphenotypic potential are described in the next paragraph.

10.1 Development of BE and Dysplasia

10.1.1 Molecular Pathways Implicated in Development of BE

The esophagus is derived from the embryological foregut. Four main signaling pathways in the differentiation of the embryological foregut have been identified thus far: the Bone morphogenetic protein (BMP), Hedgehog (HH), Wingless-Type MMTV Integration Site Family (WNT), and Retinoic acid (RA) signaling pathways (Fig. 10.1) [7]. It has been suggested that dysregulation of these embryological signaling pathways is involved in the development of BE.

Bone morphogenic proteins (BMPs) are members of the transforming growth factor-β (TGFB) superfamily of ligands [8]. SHH (Sonic hedgehog) is one of the three ligands of the HH signaling pathway. The SHH protein is a secretory protein that regulates the expression of many genes, among which BMP genes. SHH-BMP cell signaling is essential for the development of many organ systems and their function is highly conserved between species. The three key transcription factors

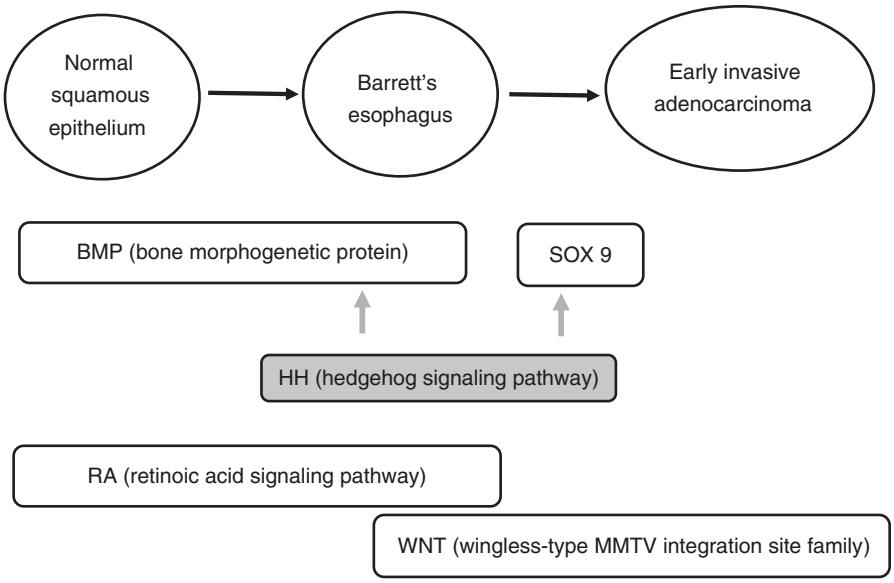

Fig. 10.1 Molecular pathways leading to the progression from normal squamous epithelium to Barrett's esophagus and adenocarcinoma

expressed by these pathways for the regulation of differentiation of foregut epithelium toward a squamous or columnar type are SOX2, p63, and NKX2.1. SOX2 and p63 induce squamous differentiation, while NKX2.1 expression is required for columnar differentiation [9].

Known risk factors for development of BE are chronic gastroesophageal reflux disease (GERD) and obesity. In normal squamous epithelium, the BMP pathway is not active [7]. In case of inflammation—as may be caused by GERD—the BMP pathway is activated with stromal BMP4 expression, contributing to a columnar transdifferentiation of squamous esophageal cells. In vitro studies showed that BMP4 induced a shift in the gene expression profile of squamous cells toward that of columnar cells, including an important shift of the cytokeratin (CK) expression pattern [10]. In BE, CK7 and CK20, markers for glandular differentiation, are highly expressed [11]. It is likely that HH signaling also contributes to BE development as expression of SHH was found to be increased in biopsies of BE and in a mouse model of BE [7]. The HH signaling pathway, as stated above, can activate BMP signaling. Furthermore, the HH pathway can also act by inducing epithelial SOX9 expression. SOX9 is a transcription factor of columnar-type genes, found to induce the expression of columnar-type cytokeratin 8 (CK8) in squamous cells, independent of BMP4 [12].

Where SHH and BMP4 are key players for the formation of a simple columnar epithelial lining, WNT as well as Notch signaling are subsequently implicated in the further differentiation of the intestinal mucosa into crypts and villi [13]. SOX9 protein is a WNT target expressed in the intestine, where it represses CDX2 and MUC2

expression and may therefore contribute to the WNT-dependent maintenance of a progenitor cell phenotype [14]. CDX1 and CDX2 are homeobox genes playing a critical role in differentiation and maintenance of intestinal epithelial functions. CDX2 is normally not expressed in the normal esophagus, but nuclear CDX2 as well as CDX1 expression can be found in intestinal-type metaplasia [15]. CDX2 alone is insufficient to induce columnar metaplasia in squamous cells. CDX2 and MUC2 expression appear to be late events in columnar cells which already have an upregulated BMP4/pSMAD pathway and seem to be mediated by a pSMAD-CDX2 interaction, and in later stage WNT and Notch signaling [16, 17].

Activity of the retinoic acid (RA) signaling pathway is increased in the development of BE [7]. In incubation experiments, RA failed to induce complete columnar differentiation in a squamous cell line, but it did increase the expression of MUC2. During embryological development, in contrast, RA signaling contributes to squamous differentiation. These opposing effects might be related to differences in retinoid receptor subtype expression [7].

10.1.2 Molecular Markers for the Diagnosis of BE

Despite increasing knowledge of the molecular pathways leading to development of BE, no markers known to be specific for intestinal columnar epithelium, such as DAS1, CDX2, Hep Par 1, Villin, CK 7/20, or any of the MUC molecules (MUC2, MUCAC, MUC6), are helpful to distinguish between columnar epithelium of the distal esophagus and the proximal stomach [1]. Good communication between gastroenterologists and pathologists remains crucial in the identification of patients with short- or ultrashort-segment BE. Biopsies of the stomach may help in determining whether a biopsy with goblet cells in a patient suspicious for ultrashort-segment BE is indeed indicative of BE. Documentation of chronic gastritis with intestinal metaplasia (IM) in the stomach could indicate that the goblet cells in the biopsy may be secondary to diffuse chronic gastritis and not be due to BE.

10.1.3 Markers for the Diagnosis of Dysplasia

Several markers have been investigated, such as surface expression of cyclin A by immunohistochemistry, the proliferation marker Ki67, DNA content (aneuploidy/tetraploidy), telomerase activity, genetic mutations (p53, p16, KRAS, APC, β-catenin), growth factors, apoptosis inhibitors, cyclooxygenase 2, and alpha-methylacyl-CoA racemase (AMACR) immunohistochemistry [1, 18–20].

P53 is a transcription factor expressed from the tumor suppressor gene TP53. TP53 inactivation is the most common genetic alteration in dysplasia and early adenocarcinoma. Biallelic mutation of this gene will result in aberrant p53 immunohistochemical staining properties and in theory should provide an excellent diagnostic tool. Inactivating mutations of the p53 gene can be detected by immunohistochemistry, and this has been the most extensively studied marker in dysplasia in BE. The frequency of p53 mutation

increases in BE neoplasia [21, 22]. However, studies investigating p53 immunohistochemistry suffered from high rates of both false positivity and false negativity and thus seemed not appropriate for the confirmation of a histologic diagnosis of dysplasia in patients with BE. The fact that studies failed to show unequivocal results may be due to different protocols and antibodies used. Recent data however, re-emphasize the value of p53 as an ancillary marker in BE. Quality assessment of p53 immunohistochemistry and recognition of complete absence of p53 staining as an indication of an inactivating mutation of the p53 gene, next to the more common pattern of p53 overexpression, may have contributed to better recognition of the value of p53 immunohistochemistry. If there is unequivocal dysplasia, p53 immunohistochemistry is not required. Dysplasia in BE in a minority of cases occurs without abnormal p53 staining and a definite morphological diagnosis of dysplasia should not be altered in case of normal p53 expression. P53 immunohistochemistry, however, appears to be a very useful marker in difficult cases as it improves the reproducibility of definite dysplasia in BE. Unfortunately, p53 is generally expressed aberrantly in both low- and high-grade dysplasia, so while appearing a very useful marker of dysplasia, its role in the grading of dysplasia is less clear [23].

The WNT signaling pathway is responsible for promoting the intestinal architecture. Activation of the WNT signaling pathway can be observed by overexpression of the WNT targets cyclin D1, SOX-9 and c-myc. WNT signaling appeared to play a role in progression to dysplasia, especially high-grade dysplasia [24].

Telomere shortening is correlated with cellular senescence and apoptosis. Cancer cells can escape apoptotic pathways by activating mechanisms involved in telomere elongation and stabilization. Telomerase is responsible for telomere maintenance. Inhibition of telomerase leads to shorter telomeres, reduced cell growth, and apoptosis. Higher telomerase activity may be an early event in maintaining genomic instability, even in the premalignant phase [25].

The frequency of AMACR-immunohistochemical positive staining increases in BE neoplasia [26, 27]. This enzyme is found in mitochondria and in peroxisomes. It has been described in low- and high-grade dysplasia, as well as in adenocarcinoma. Results of two studies were only moderately consistent in their findings [28].

10.1.4 Genome-Wide Association Studies for the Development of Barrett's Esophagus

There is a substantial overlap in the set of genes contributing to the risk of BE and adenocarcinoma of the esophagus. Genome-wide association studies have identified 8 loci within or near *MHC*, *FOXF1*, *GDF7*, *TBX5, CRTC1*, *BARX1*, *FOXP1,* and *ALDH1A2* associated with the development of BE [29–31].

10.2 Progression to Adenocarcinoma in BE

10.2.1 Molecular Pathways Implicated in the Transition of Barrett's Esophagus to Early Adenocarcinoma

Because BE is common in the population and only a minority of patients develop esophageal carcinoma, specific markers for the transition of BE to early adenocarcinoma are needed.

The signaling pathways implicated in the differentiation of the embryological foregut—the Bone morphogenetic protein (BMP), Hedgehog (HH), Wingless-Type MMTV Integration Site Family (WNT), and Retinoic acid (RA) signaling pathways—may be implicated in the progression from BE to EAC [7]. During the progression of BE toward malignancy, the SHH and WNT signaling pathways are upregulated while the RA and probably the BMP signaling pathways are downregulated. Further research however is required to further elucidate these issues since modulation of these pathways may be an option in the management of development of EAC in BE.

10.2.2 Molecular Biology of Progression to Adenocarcinoma

C-myc and cyclins have been implicated as oncogenes, inducing hyperproliferation [32]. C-myc is a transcription factor essential for the expression of genes necessary for cell proliferation. The incidence of c-myc amplification was reported to increase with worsening histopathology [33]. Tumors with c-myc amplification in addition were found to show overexpression of COX2 and VEGF, genes involved in angiogenesis, a process essential for carcinoma development [34]. Cyclins have varying expression levels during cell cycle. Dysregulation of key players in the cell cycle can lead to tumor growth [32].

The mitogen-activated protein kinase (MAPK) RAS-RAF signaling pathway may be implicated in development of BE EAC. However, the phosphatidylinositol 3-kinase (PI3K) pathway has recently been identified by exome and whole-genome sequencing as the most frequently altered oncogenic pathway in esophageal adenocarcinoma development [35, 36]. ErbB-2 mutations have been detected, but the role of erbB-2 (also called HER2/Neu) in the development of BE and EAC remains controversial [37]. The prevalence of HER2 amplification or overexpression has been reported to be high in BE and adenocarcinoma of the esophagus [38]. It was however also shown that the majority of HER2-amplified gastric as well as esophageal adenocarcinomas harbor secondary oncogenic alterations that can confer resistance to HER2-directed therapy [39]. HER2 and EGFR for example are frequently co-amplified and may dimerize with one another [39].

The TGF-β signaling pathway regulating growth inhibition and suppression of genomic instability requires the transcription factors SMAD proteins and

Runt-related transcription factor 3 (RUNX3). SMAD4 alterations may be stage specific and although BE and EAC share a common mutational landscape, SMAD4 mutations are confined to the malignant stage of the disease [40].

Inactivation of tumor suppressor genes p53, p16, p27, and APC has been implicated in the progression of BE to adenocarcinoma. Inactivation of p53 is thought to be a mechanism to avoid apoptosis of DNA damaged cells. Overexpression of cyclo-oxygenase-2, expression of NF-κβ, and downregulation of 15-lipoxygenase-1 have also been described, as well as expression of the anti-apoptotic proteins Bcl-2 and Bcl-XL and the pro-apoptotic protein Bax [41–43].

Aneuploid cells are at risk for neoplastic progression and in progression of BE to EAC epithelial cells were demonstrated to express aneuploidy [19].

Enhanced expression of both tumor necrosis factor receptor 1 (TNFR1) and TNF-α, its ligand, has been described [44].

Epigenetic changes can lead to altered gene expression without the occurrence of mutations or structural variation. Hypermethylation of tumor suppressor genes such as APC, CDKN2A, CDH1, transcription factor ESR1 and REPRIMO—involved in the p53-mediated cell cycle arrest—has been demonstrated.

Small non-coding microRNAs (miRNAs) capable of degrading target mRNA via sequence complementarity have been the subject of many studies as well. miR-21 is one of the most expressed microRNAs in EAC [45]. miRNA-375 may be downregulated and is associated with c-myc and TP53 regulation [46]. Other frequently reported miRNAs are miR-192, -194, and -96A, that are more expressed with progression to malignancy, whereas miR-200 and miR-203 are downregulated [47]. miRNA could have unique expression profiles in different stages of malignant progression making them potential diagnostic indicators. miR-25, -99a, -133a, and -133b are purely diagnostic and miR-21, -27b, -126, -143, and-145 as a panel can be valuable both in diagnosis and prediction of progression [48].

10.2.3 Molecular Markers for the Diagnosis of Progression to EAC

Accumulation of aberrant chromosomal events resulting in aneuploidy, chromosomal rearrangements, tumor suppressor inactivation, and activation of oncogenes are associated with progression to carcinoma. Especially inactivation of the tumor suppressor gene p53, methylation markers, and DNA content (aneuploidy/tetraploidy) have been examined as potential markers to help to identify high-risk patients [18–21]. Aberrant p53 expression is associated with an increased risk of neoplasia, both overexpression and loss of expression [49]. In the overexpression pattern, an intense nuclear staining will be seen because of the accumulation of abnormal amounts of the p53 protein, due to mutations creating a protein product that is resistant to degradation. Complete lack of p53 labeling can be the result of homozygous deletion of the TP53 locus or can be caused by mutations in the TP53 transcript, accelerating its degradation.

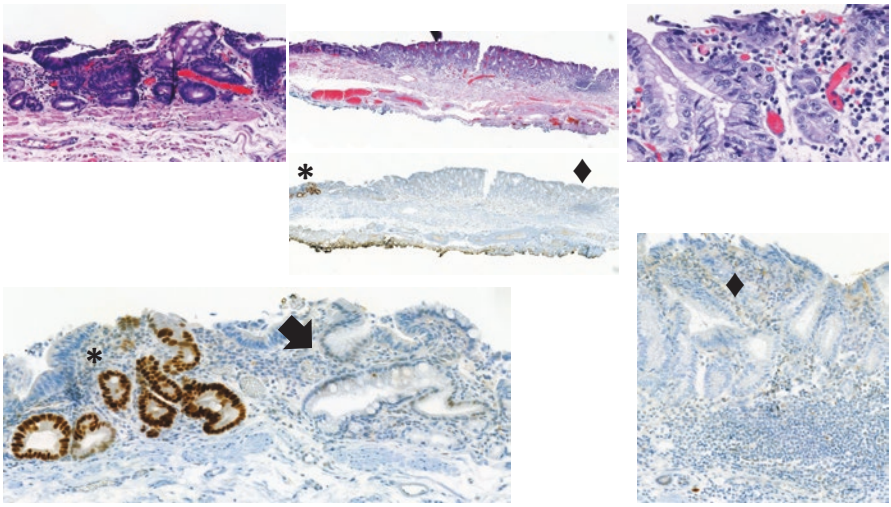

Fig. 10.2 Tissue section from an EMR (endoscopic mucosal resection) specimen—HE and p53 immunohistochemistry—with higher magnification of the regions indicated on the right (asterisk) and left (filled diamond) end. At the left end, there is an area of p53 overexpression (asterisk) corresponding with glands showing high-grade intestinal type dysplasia, while at the right end (filled diamond) we can observe an area of complete absence of p53 staining, corresponding in this case with glands showing foveolar type dysplasia. Next to the area of p53 overexpression, we recognize glands with intestinal metaplasia showing wild-type p53 expression (arrow)

Normal epithelium—both squamous and non-dysplastic columnar epithelium—invariably express a low background amount of p53 protein because of ongoing DNA surveillance mechanisms, thus providing an internal p53 staining control. It is estimated that between 10 and 20% of BE with dysplasia show the so-called null mutation pattern with complete absence of staining. P53 function is altered or lost by mutation or loss of heterozygosity (LOH). Combination of biomarkers, such as DNA content and LOH of p53 and p16 appeared to be a good indicator of neoplastic progression [49–51]. Recent data show that aberrant expression of p53 in BE appears to be associated with a significantly increased risk of neoplastic progression also in non-dysplastic and low-grade dysplastic BE (Fig. 10.2).

10.2.4 Genetic Changes Involved in the Progression From BE to EAC

The concept that the evolution of cancer proceeds through a stepwise accumulation of genetic alterations in a predictable, linear manner has existed for a long time. It fits with phenotypic observations of changes in cell and structure, such as the progression from metaplastic BE over dysplastic BE to EAC. Consequently, for a long time, it was believed that specific genetic alterations would be present at different stages of neoplastic progression.

Joint efforts such as The Cancer Genome Atlas and the International Cancer Gene Consortium helped us to understand somatic genetic and epigenetic alterations leading to the development of cancer by carrying out whole-genome and/or whole-exome sequencing in different cancer types.

These studies have demonstrated that there are more pathways to develop a malignancy by showing the heterogeneity of gene mutations that can occur in cancers in the population. We also learned that a tumor does not consist of one type of cancer cells, but that there is also intratumoral heterogeneity. With the exception of TP 53, few genes appear to be altered in a high number of cancer samples—and a large number of genes appear to be altered in only a minority of cases.

It remains hard to identify genetic changes responsible for driving certain events in the development of a specific cancer type. In BE associated EAC loci found near CRTC1, BARX1, FOXP1, and ALDH1A2 have been associated with development of both BE and esophageal adenocarcinoma [29–31]. These observations sustain a genetic component of BE and EAC associated with BE.

The mutational load in esophageal adenocarcinoma is high and microsatellite instability is rare [52]. Despite a very high mutational load, very few genes were altered in more than 20% of cancers. The extensive copy number alterations and structural rearrangements found indicate a variety of mutational mechanisms active during progression to EAC. The small number of studies that examined BE around EAC found clonally related alterations in the precursor and the cancer, indicating that the evolution of somatic genomic alterations found in EAC begins in BE [52, 53].

10.2.5 Biomarker Development

Biomarkers with high specificity and sensitivity are needed for a reliable diagnosis of carcinoma in its earliest stage and for the identification of patients at risk. Most of the preclinical findings are not yet ready for clinical implementation.

As stated before, recent data show that aberrant expression of p53 in BE appears to be associated with a significantly increased risk of neoplastic progression also in non-dysplastic and low-grade dysplastic BE. If there is unequivocal dysplasia, p53 immunohistochemistry is not required. Dysplasia in BE in a minority of cases occurs without abnormal p53 staining and a definite morphological diagnosis of dysplasia should not be altered in case of normal p53 expression. P53 immunohistochemistry, however, appears to be a very useful marker in difficult cases, as aberrant expression in this context implies that these patients are at high risk of progression and should be managed as such. However, quality assurance of p53 immunohistochemistry is needed to improve staining method and interpretation. Also, further confirmation of these findings are needed, before this can be implemented in daily practice [23, 28].

Some other biomarker panels have been validated in large prospective cohorts. A set of methylation markers (p16, RUNX3, HPP1, NELL1, TAC1, SST, AKAP12, and CDH13) showed to have a good specificity, but low sensitivity [54]. A

chromosomal abnormality panel can include TP53, CDNK2A (p16), LOH, and DNA content abnormality [55].

Attempts are made to combine molecular biomarkers with imaging techniques, in order to target biopsies more properly [56]. The cytosponge is an example of a tool developed to acquire reliable material in a minimally invasive way [57]. Coupled with immunohistochemistry for Trefoil Factor 3 it may identify patients with reflux symptoms who warrant endoscopy to diagnose BE. miRNA panels could be useful because the tissue-specific gene regulation may allow the development of a test based on a noninvasive blood collection [58].

None of these biomarker panels are ready for routine use. Studies evaluating reproducibility, specificity, and sensitivity are warranted. Biomarkers need to address the issues of under- and overdiagnosis and have to be validated for specific stages during progression to EAC.

Conclusions

Barrett's esophagus probably develops as a result of transcommitment, in which progenitor cells in the esophagus that normally would differentiate into squamous cells instead differentiate into columnar cells. The pathways responsible for columnar differentiation, intestinalization, and mucus differentiation from epithelial cells have largely been described. However, there are still many issues at the molecular level that need to be resolved in order to allow to develop novel molecular therapies.

Molecular markers for the diagnosis of dysplasia and early adenocarcinoma have been described, p53 being the most intensively studied. However, all markers suffer from high rates of both false positivity and negativity. Studies failed to show unequivocal results, possibly due to different protocols and antibodies used. More and more data confirm that aberrant expression of p53 in BE is associated with a significantly increased risk of neoplastic progression also in non-dysplastic and low-grade dysplastic BE. Prospective validation studies are still warranted, even for the most promising markers, before they may be used as reliable biomarkers. Quality assurance of p53 immunohistochemistry is needed to improve staining method and interpretation, before this can be implemented in daily practice.

References

1. Naini BV, Souza RF, Otze RD. Barrett's esophagus: a comprehensive and contemporary review for pathologists. Am J Surg Pathol. 2016;40:e45–66.
2. Chandrasoma PT, Der R, Dalton P, et al. Distribution and significance of epithelial types in columnar-lined esophagus. Am J Surg Pathol. 2001;25:1188–93.
3. McDonald SAC, Lavery D, Wright NA, Jansen M. Barrett esophagus: lessons on its origins from the lesion itself. Nat Rev Gastroenterol Hepatol. 2015;12:50–60.

4. Epperly MW, Guo H, Shen H, et al. Bone marrow origin of cells with capacity for homing and differentiation to esophageal squamous epithelium. Radiat Res. 2004;162:233–40.
5. Sarosi G, Brown G, Jaiswal K, et al. Bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus. Dis Esophagus. 2008;21:43–50.
6. Wang D, Souza R. Transcommitment: paving the way to Barrett' metaplasia. In: Jansen M, Wright NA, editors. Stem cells, pre-neoplasia, and early cancer of the upper gastrointestinal tract. Advances in experimental medicine and biology 908. Basel: Springer; 2016. p. 183–212.
7. Pavlov K, Meijer C, van den Berg A, Peters FT, Kruyt FA, Kleibeuker JH. Embryological signaling pathways in Barrett's metaplasia development and malignant transformation; mechanisms and therapeutic opportunities. Crit Rev Oncol Hematol. 2014;92:25–37.
8. Fukuda K, Yasugi S. Versatile roles for sonic hedgehog in gut development. J Gastroenterol. 2002;37:239–46.
9. Litingtung Y, Lei L, Westphal H, et al. Sonic hedgehog is essential to foregut development. Nat Genet. 1998;20:58–61.
10. Milano F, van Baal JW, et al. Bone morphogenetic protein 4 expressed in esophagitis induces a columnar phenotype in esophageal squamous cells. Gastroenterology. 2007;132:2412–21.
11. El-Zimaity HMT, Graham DY. Cytokeratin subsets for distinguishing Barrett's esophagus from intestinal metaplasia in the cardia using endoscopic biopsy specimens. Am J Gastroenterol. 2001;96:1378–82.
12. Clemons NJ, Wang DH, Croagh D, et al. SOX9 drives columnar differentiation of esophageal squamous epithelium: a possible role in the pathogenesis of Barrett's esophagus. Am J Physiol Gastrointest Liver Physiol. 2012;303:G1335–46.
13. Elliott EN, Kaestner KH. Epigenetic regulation of the intestinal epithelium. Cell Mol Life Sci. 2015;72:4139–56.
14. Blache P, van de Wetering M, Duluc I, et al. SOX9 is an intestine crypt transcription factor, is regulated by the Wnt pathway and represses the CDX2 and MUC2 genes. J Cell Biol. 2004;166:37–47.
15. Guo RJ, Suh ER, Lynch JP. The role of Cdx proteins in intestinal development and cancer. Cancer Biol Ther. 2004;3:593–601.
16. Mari L, Milano F, Parikh K, et al. A pSMAD/CDX2 complex is essential for the intestinalization of epithelial metaplasia. Cell Rep. 2014;7:1197–210.
17. Krishnadath KK, Wang KK. Molecular pathogenesis of Barrett esophagus: current evidence. Gastroenterol Clin N Am. 2015;2:233–47.
18. Rioux-Leclercq N, Turlin B, Sutherland F, et al. Analysis of Ki-67, p53 and Bcl-2 expression in the dysplasia-carcinoma sequence of Barrett's esophagus. Oncol Rep. 1999;6:877–82.
19. Fritcher EG, Brankley SM, Kipp BR, et al. A comparison of conventional cytology, DNA ploidy analysis and fluorescence in situ hybridization for the detection of dysplasia and adenocarcinoma in patients with Barrett's esophagus. Hum Pathol. 2008;39:1128–35.
20. Younes M, Lebovitz R, Lechago L, et al. P53 protein accumulation in Barretts metaplasia, dysplasia and carcinoma: a follow-up study. Gastroenterology. 1993;105:1637–42.
21. Kaye PV, Haider SA, James PD, et al. Novel staining pattern of p53 in Barrett's dysplasia—the absent pattern. Histopathology. 2010;57:933–5.
22. Bhargava P, Eisen GM, Holterman DA, et al. Endoscopic mapping and surrogate markers for better surveillance in Barrett esophagus. A study of 700 biopsy specimens. Am J Clin Pathol. 2000;114:552–63.
23. Janmaat V, van Olphen S, Biermann K, et al. Use of immunohistochemical biomarker as independent predictor of neoplastic progression in Barrett's oesophagus surveillance: a systematic review and meta-analysis. PLoS One. 2017;12:e0186305. https://doi.org/10.1371/journal.pone.0186305.
24. Moyes LH, Mc Ewan H, Radulescu S, et al. Activation of Wnt signaling promotes development of dysplasia in Barrett's oesophagus. J Pathol. 2012;228:99–112.

25. Lord RV, Salonga D, Danenberg KD, et al. Telomerase reverse transcriptase expression is increased early in the Barrett's metaplasia, dysplasia, adenocarcinoma sequence. J Gastrointest Surg. 2000;4:135–42.
26. Dorer R, Odze RD. AMACR immunostaining is useful in detecting dysplastic epithelium in Barrett's esophagus, ulcerative colitis and Crohn's disease. Am J Surg Pathol. 2006;30:871–7.
27. Scheil-Betram S, Lorenz D, Ell C, et al. Expression of alpha-methylacyl coenzyme A racemase in the dysplasia carcinoma sequence associated with Barrett's esophagus. Mod Pathol. 2008;21:961–7.
28. Kaye PV, Ilyas M, Soomro I, et al. Dysplasia in Barrett's oesophagus: p53 immunostaining is more reproducible than haematoxylin and eosin diagnosis and improves overall reliability, while grading is poorly reproducible. Histopathology. 2016;69:431–40.
29. Su Z, Gay LJ, Strange A, et al. Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett's esophagus. Nat Genet. 2012;44:1131–6.
30. Palles C, Chegwidden L, Li X, et al. Polymorphisms near TBX5 and GDF7 are associated with increased risk for Barrett's esophagus. Gastroenterology. 2015;148:367–78.
31. Levine DM, Ek WE, Zhang R, et al. A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus. Nat Genet. 2013;45:1487–93.
32. Souza RF, Spechler SJ. Concepts in the prevention of adenocarcinoma of the distal esophagus and proximal stomach. CA Cancer J Clin. 2005;55:334–51.
33. Sarbia M, Arjumand J, Wolter M, et al. Frequent c-myc amplification in high-grade dysplasia and adenocarcinoma in Barrett esophagus. Am J Clin Pathol. 2001;115:835–40.
34. von Rahden BH, Stein HJ, Pühringer-Oppermann F, Sarbia M. c-myc amplification is frequent in esophageal adenocarcinoma and correlated with the upregulation of VEGF-A expression. Neoplasia. 2006;8:702–7.
35. Sommerer F, Vieth M, Markwarth A, et al. Mutations of BRAF and KRAS2 in the development of Barrett' adenocarcinoma. Oncogene. 2004;23:554–8.
36. Dulak AM, Stojanov P, Peng S, et al. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. Nat Genet. 2013;45:478–86.
37. Gowryshankar A, Nagaraja V, Eslick GD. HER2 status in Barrett's esophagus and esophageal cancer: a meta analysis. J Gastrointest Oncol. 2014;5:25–35.
38. Langer R, Rauser S, Feith M, Nährig JM, et al. Assessment of ErbB2 (Her 2) in oesophageal adenocarcinomas: summary of a revised immunohistochemical evaluation system: bright field double in situ hybridization and fluorescence in situ hybridization. Mod Pathol. 2011;24:908–16.
39. Kim J, Fox C, Peng S, et al. Preexisting oncogenic events impact trastuzumab sensitivity in ERBB2-amplified gastro-esophageal adenocarcinoma. J Clin Invest. 2014;124:5145–58.
40. Weaver JM, Ross-Innes CS, Shannon N, et al. Ordering of mutations in preinvasive disease stages of esophageal carcinogenesis. Nat Genet. 2014;46:837–43.
41. Wilson KT, Fu S, Ramanujam KS, et al. Increased expression of inducible nitric oxide synthase and cyclooxygenase-2 in Barrett's esophagus and associated adenocarcinomas. Cancer Res. 1998;58:2929–34.
42. Shureiqi I, Xu X, Chen D, et al. Nonsteroidal anti-inflammatory drugs induce apoptosis in esophageal cancer cells by restoring 15-lipoxygenase-1 expression. Cancer Res. 2001;61:4879–84.
43. Katada N, Hinder RA, Smyrk TC, et al. Apoptosis is inhibited early in the dysplasia-carcinoma sequence of Barrett esophagus. Arch Surg. 1997;132:728–33.
44. Tselepis C, Perry I, Dawson C, et al. Tumour necrosis factor-alpha in Barrett's oesophagus: a potential novel mechanism of action. Oncogene. 2002;21:6071–60081.
45. Feber A, Xi L, Luketich JD, et al. MicroRNA expression profiles of esophageal cancer. J Thorac Cardiovasc Surg. 2008;135:255–60.
46. Garman KS, Owzar K, Hauser ER, et al. MicroRNA expression differentiates squamous epithelium from Barrett's esophagus and esophageal cancer. Dig Dis Sci. 2013;58:3178–88.

47. Revilla-Nuin B, Parilla P, Lozano JJ, et al. Predictive value of MicroRNAs in the progression of Barrett esophagus to adenocarcinoma in a long-term follow-up study. Ann Surg. 2013;257:886–93.
48. Sakai NS, Samia-Aly E, Barbera M, Fitzgerald RC. A review in the current understanding and clinical utility of miRNAs in esophageal cancer. Semin Cancer Biol. 2013;23:512–21.
49. Kastelein F, Biermann K, Steyerberg EW, et al. Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus. Gut. 2013;62:1676–83.
50. Bird-Lieberman EL, Dunn JM, Coleman HG, et al. Population-based study reveals new risk-stratification biomarker panel for Barrett's esophagus. Gastroenterology. 2012;143:927–35.
51. Wang JS, Guo M, Montgomery EA, et al. DNA promoter hypermethylation of p16 and APC predicts neoplastic progression in Barrett's esophagus. Am J Gastroenterol. 2009;104:2153–60.
52. Agrawal N, Jiao Y, Bettegowda C, et al. Comparative genomic analysis of esophageal adenocarcinoma and squamous cell carcinoma. Cancer Discov. 2012;2:899–905.
53. Streppel MM, Lata S, DelaBastide M, et al. Next-generation sequencing of endoscopic biopsies identifies ARID1A as a tumor suppressor gene in Barrett's esophagus. Oncogene. 2014;33:347–57.
54. Jin Z, Cheng Y, Gu W, et al. A multicenter, double blinded validation study of methylation biomarkers for progression prediction in Barrett's esophagus. Cancer Res. 2009;69:4112–5.
55. Galipeau PC, Li X, Blount PL, et al. NSAIDs modulate CDNK2A, TP53 and DNA content risk for progression to esophageal adenocarcinoma. PLoS Med. 2007;4:e67. https://doi.org/10.1371/journal.pmed.0040067.
56. Di Pietro M, Boerwinkel DF, Shariff MK, et al. The combination of autofluorescence endoscopy and molecular biomarkers is a novel diagnostic tool for dysplasia in Barrett's oesophagus. Gut. 2015;64:49–65.
57. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, et al. BEST2 Study Group. Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case control study. PLoS Med. 2015;12:e1001780. https://doi.org/10.1371/journal.pmed.1001780.
58. Bansal A, Lee IH, Hong X, et al. Discovery and validation of Barrett's esophagus microRNA transcriptome by next generation sequencing. PLoS One. 2013;8:e54240. https://doi.org/10.1371/journal.pone54240.

11 Timing and Protocols of Clinical and Endoscopic Surveillance of Barrett's Esophagus

Carlo Calabrese, Marco Salice, Nico Pagano, Raffaele Manta, and Fernando Rizzello

Barrett's esophagus (BE) is a premalignant lesion in which normal squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium of any histological subtype [1]. Several guidelines for diagnosing and managing BE have been published; however, they differ significantly among and within countries [1–3]. Only few large well-designed trials have been conducted so far [4–6].

BE affects 2% of the adult population [7], particularly those with heartburn and those undergoing endoscopy [8–11]. BE-related esophageal adenocarcinoma (EA) develops from chronic esophagitis through benign BE and dysplasia [11–14]. The incidence of EA has increased in recent decades in developed countries [15, 16], and a large retrospective study [17] reported an annual mortality rate from EA of only 0.14%. In a population-based cohort study [18], the overall mortality rate in patients with BE was similar to that of an age- and sex-matched control population. EA accounted for only a small proportion of deaths in these patients, most deaths being due to other causes. From these data and several other studies, EA is an uncommon cause of death in patients with BE, and the mortality rate due to EA is low, whether or not patients undergo endoscopic surveillance (Fig. 11.1).

Surveillance of patients with confirmed BE is recommended by all guidelines although strategies and time intervals may differ [1, 19–22] (Table 11.1).

C. Calabrese (✉) · M. Salice · F. Rizzello
Department of Medicine and Surgery, University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy
e-mail: carlo.calabrese2@unibo.it

N. Pagano
Gastroenterology and Digestive Endoscopy Unit, Department of Medical and Surgical Sciences (DIMEC), University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

R. Manta
Gastroenterology and Digestive Endoscopy Unit, NOCSAE Hospital of Modena, Modena, Italy

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_11

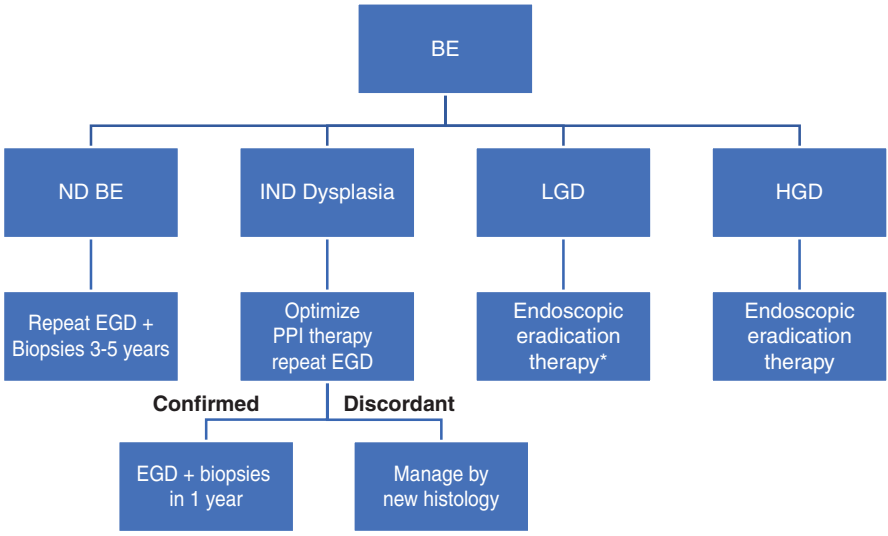

Fig. 11.1 Algorithm of BE surveillance. *Although endoscopic eradication therapy is associated with a decreased rate of progression, surveillance upper endoscopy at 1-year intervals is an acceptable alternative

The BOB CAT study [19] was either unclear or negative on the proposition that surveillance, with its associated potential harms and costs, decreases mortality from EA.

There are currently no tightly defined and accepted criteria to differentiate the risk of progression in patients with non-dysplastic BE, and there are no data available yet from randomized controlled trials (RCTs) that demonstrate benefits from scheduled surveillance in terms of a decrease in mortality due to EA. In the absence of this information, the decision to carry out surveillance should be based on risk factors of progression of BE. A guide for targeted surveillance in high-risk groups with non-dysplastic BE (above >50 years of age, male sex, length of BE segment, longer duration, higher frequency and severity of symptoms, presence of central obesity, and tobacco smoking) has been proposed [23].

There is not an overall consensus on the management of patients with lower risk BE compared with those with potentially higher risk BE such as indefinite for dysplasia (IND), or low-grade dysplasia (LGD) persistent in two consecutive endoscopies, in a long BE segment.

In the case of LGD found on a single occasion, if not treated, endoscopic follow-up with biopsy should be close (6–12 months) since it may lead to HGD.

The diagnosis of IND should be considered temporary and should prompt further close follow-up with adequate biopsy sampling. Patients with persistent and confirmed LGD should be treated with ablative therapy, which decreases the progression to neoplasia [24]. In all cases, the risks and benefits of surveillance should be taken into account with the patient's input, particularly in those patients with comorbidities or short life expectancy.

Table 11.1 Screening interval in BE according to the different guidelines

	ACG [21]	BOB CAT [19]	BSG [1]	ASGE [20]	AGA [22]
Gastric metaplasia compatible with BE diagnosis	No	No	Yes	No	No
Length of BE	No	No	Yes	No	No
NDBE <3 cm	3–5 year	[a]No consensus	3–5 year	3–5 year	3–5 year
NDBE >3 cm	3–5 year	No consensus	2–3 year	3–5 year	3–5 year
IND	Repeat endoscopy after 3–6 months: Confirmed 12 months	6–12 months If persists: ablative therapy	Repeat endoscopy after 6 months: Not confirmed: surveillance as for NDBE	Not specified	Not specified
LGD	Endoscopic treatment or 12 months surveillance	No consensus If persistent LGD: ablative therapy	6 months	[a]Repeat endoscopy after 6 months. [a]Then every year	6–12 months
HGD	Endoscopic treatment	Endoscopic treatment	Endoscopic treatment	Treatment. Continued surveillance in absence of therapy	3 months in the absence of eradication therapy

[a]In the absence of agreement on surveillance vs. no surveillance for reduction of mortality from EA, there was no consensus on intervals for surveillance

The influence of intestinal metaplasia (IM) is unclear; the study by Bhat et al. [25] in 2011 stated that the risk of cancer was statistically significantly elevated in patients with, vs. without IM at index biopsy [0.38% per year vs. 0.07% per year; HR = 3.54, 95% CI = 2.09–6.00, $p < 0.001$).

Current literature shows that it is unclear if goblet cells are necessary for the development of all EAs in the distal esophagus [26]. On the other hand, the available data also imply that if goblet cells are present, BE has a higher risk for malignant transformation (~0.12% per year) [27].

The high mortality in EA partially results from late detection. A high proportion of patients present with advanced disease [28] but patients who undergo surveillance are often diagnosed at an earlier stage [28–30].

However, the low incidence of EA in patients with BE largely limits the expected benefit of surveillance [31]. Based upon a cancer incidence of 0.5% [32], surveillance is cost-effective every 5 years for non-dysplastic BE and every 3 years for

LGD in long-segment BE [33]. In regions where the cancer incidence is lower, the usefulness of surveillance is questioned [19, 27, 34, 35].

One of the problems that compromises the cost-effectiveness of surveillance is the fact that most of the cancers are not detected during surveillance but at the time or within a year of the index endoscopy [27, 32].

Hvid-Jensen et al. [27] performed a cohort study using population data from the Danish pathology registry and Danish Cancer Registry. During the follow-up period, 197 of the 11,028 patients with BE received a new diagnosis of EA, of whom 131 (66.5%) patients were diagnosed during the first year of follow-up. The authors suggested that the high incidence rate during the first year may be due to missed diagnosis of EA during the index endoscopy, for example, by biopsy sampling error.

Sharma et al. [32] also conducted a cohort study pooling patient from four US centers. At first endoscopy in 1376 patients with BE, 91 patients (6.6%) were diagnosed with EA, 42 (3%) with HGD, and 101 patients (7.3%) with LGD. These findings indicate that the majority of the neoplastic lesions are detected at the initial endoscopy. Of 618 patients that were followed up at least 1 year, 12 patients developed EA during follow-up. Of these 12 patients, 7 had HGD before cancer development, 2 had only LGD, and 3 developed EA from non-dysplastic BE. Of the 34 patients developing either HGD and/or cancer during follow-up, 18 patients (53%) had at least 2 initial consecutive endoscopies documenting non-dysplastic BE. So, although there is an increased risk of developing neoplasia in dysplastic BE, HGD and EA can develop in patients without dysplasia, even at two consecutive endoscopies, highlighting the need for better risk stratification [31]. Also, in that study, 80% of patients with EA and HGD were detected at the index endoscopy, hence not due to surveillance, again indicating that better risk stratification for screening is necessary.

In conclusion, due to conflicting evidence it remains unclear whether surveillance leads to a benefit in terms of reduced mortality [19, 30, 31, 36]. Further studies are required to determine the optimal time of surveillance intervals and if and when surveillance can be stopped.

Some studies have suggested that PPIs exert a protective effect against the progression from BE to EA. However, a recent meta-analysis [37] that included a total of 5712 patients with non-dysplastic BE or LGD, of whom 501 progressed to EA and/or HGD, showed that PPIs therapy does not have a protective effect on prevention of dysplasia or cancer. These results conflict with previous studies, most of which reported an inverse relationship between PPI use and the risk of neoplastic progression, as well as a decreased risk of neoplastic progression with prolonged PPI use [38]. In conclusion, PPI usage should be restricted to symptom control according to current guidelines.

11.1 Protocol

Seattle protocol has been broadly used in the characterization of lesions compatible with BE, and there is evidence that its adoption increases the success rate of the endoscopic diagnosis, in particular the detection of dysplastic changes [39].

This protocol is accepted as the standard for surveillance in BE and is recommended by all guidelines.

The protocol consists in performing biopsies in the four quadrants at each 2 cm. In agreement with the histological findings, the follow-up should be the following:

- In Barrett's esophagus without dysplasia, it is recommended to perform biopsies of the four quadrants at each 2 cm every 3–5 years.
- In Barrett's esophagus with low-grade dysplasia, it is recommend performing biopsies of the four quadrants at each 1–2 cm every 6–12 months.
- In Barrett's esophagus with high-grade dysplasia, it is recommended to perform biopsies of the four quadrants each 1 cm every 3 months, in the absence of treatment for its eradication.

Short segments (<3 cm) without intestinal metaplasia should not be followed after a second endoscopy confirming the absence of metaplasia.

Nevertheless, this protocol has some disadvantages such as its duration, the risk of bleeding, the poor adherence, and the costs for the health care.

Endoscopic surveillance and the Seattle biopsy protocol are the standard for surveillance in BE. The biopsies are however random and cover only a small surface of the Barrett mucosa, whereas dysplastic and cancerous lesions in BE tend to have a patchy distribution. Advanced imaging techniques may enable targeted biopsies and improve accuracy of endoscopic surveillance [30]. Surveillance should be performed with high-definition/high-resolution white light endoscopy.

The majority of patients with BE will never develop EA. Hence, there is an interest in biomarkers that identify patients with a higher risk of developing neoplasia that should be included in surveillance programs. A meta-analysis investigated if 16 immunohistochemical (IHC) biomarkers could be used as independent predictors for neoplastic progression in BE surveillance [30, 40]. The meta-analysis showed that only five of these biomarkers proved to be useful in predicting neoplastic progression. Aberrant p53 expression was associated with a significantly increased risk of neoplastic progression in both non-dysplastic BE patients and those with LGD BE. Out of the other four IHC biomarkers, AOL appeared to be most promising in predicting neoplastic progression, whereas Cyclin A, Cyclin D, and alpha-methylacyl-CoA racemase are still of limited value.

Conclusions

- Patients should only undergo surveillance after adequate counseling regarding risks and benefits of surveillance.
- Surveillance should be performed with high-definition/high-resolution white light endoscopy.
- Endoscopic surveillance should employ four-quadrant biopsies at 2 cm intervals in patients without dysplasia and 1 cm intervals in patients with prior dysplasia (Seattle protocol).
- For BE patients without dysplasia, endoscopic surveillance should take place at intervals of 3–5 years.

- Patients diagnosed with BE on initial examination with adequate surveillance biopsies do not require a repeat endoscopy in 1 year for dysplasia surveillance.
- For patients with IND for dysplasia, a repeat endoscopy after optimization of acid-suppressive medications for 3–6 months should be performed. If the IND for dysplasia reading is confirmed on the repeat examination, a surveillance interval of 12 months is recommended.
- For patients with confirmed LGD and without life-limiting comorbidity, endoscopic therapy is considered as the preferred treatment modality although endoscopic surveillance every 12 months is an acceptable alternative.
- Patients with BE and confirmed HGD should be managed with endoscopic therapy unless they have life-limiting comorbidity.

References

1. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014;63:7–42.
2. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ, American Gastroenterological A. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology. 2011;140:18–52.
3. Bennett C, Vakil N, Bergman J, Harrison R, Odze R, Vieth M, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. Gastroenterology. 2012;143:336–46.
4. Das D, Chilton AP, Jankowski JA. Chemoprevention of oesophageal cancer and the AspECT trial. Recent Results Cancer Res. 2009;181:161–9.
5. Jankowski J, Barr H, Wang K, Delaney B. Diagnosis and management of Barrett's oesophagus. BMJ. 2010;341:c4551.
6. Jankowski J, Barr H. Improving surveillance for Barrett's oesophagus: AspECT and BOSS trials provide an evidence base. BMJ. 2006;332(7556):1512.
7. Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology. 2005;129:1825–31.
8. Ford AC, Forman D, Reynolds PD, Cooper BT, Moayyedi P. Ethnicity, gender, and socioeconomic status as risk factors for esophagitis and Barrett's esophagus. Am J Epidemiol. 2005;162:454–60.
9. Malfertheiner P, Lind T, Willich S, Vieth M, Jaspersen D, Labenz J, et al. Prognostic influence of Barrett's oesophagus and Helicobacter pylori infection on healing of erosive gastro-oesophageal reflux disease (GORD) and symptom resolution in non-erosive GORD: report from the ProGORD study. Gut. 2005;54:746–51.
10. Coleman HG, Bhat S, Murray LJ, McManus D, Gavin AT, Johnston BT. Increasing incidence of Barrett's oesophagus: a population-based study. Eur J Epidemiol. 2011;26:739–45.
11. Taylor JB, Rubenstein JH. Meta-analyses of the effect of symptoms of gastroesophageal reflux on the risk of Barrett's esophagus. Am J Gastroenterol. 2010;105:1729–37.
12. Ronkainen J, Talley NJ, Storskrubb T, Johansson SE, Lind T, Vieth M, et al. Erosive esophagitis is a risk factor for Barrett's esophagus: a community-based endoscopic follow-up study. Am J Gastroenterol. 2011;106:1946–52.
13. Erichsen R, Robertson D, Farkas DK, Pedersen L, Pohl H, Baron JA, et al. Erosive reflux disease increases risk for esophageal adenocarcinoma, compared with nonerosive reflux. Clin Gastroenterol Hepatol. 2012;10:475–80.

14. Malfertheiner P, Nocon M, Vieth M, Stolte M, Jaspersen D, Koelz HR, et al. Evolution of gastro-oesophageal reflux disease over 5 years under routine medical care--the ProGERD study. Aliment Pharmacol Ther. 2012;35:154–64.
15. Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. CA Cancer J Clin. 2013;63:232–48.
16. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87–108.
17. Solaymani-Dodaran M, Card TR, West J. Cause-specific mortality of people with Barrett's esophagus compared with the general population: a population-based cohort study. Gastroenterology. 2013;144:1375–83.
18. Anderson LA, Murray LJ, Murphy SJ, et al. Mortality in Barrett's oesophagus: results from a population based study. Gut. 2003;52:1081–4.
19. Bennett C, Moayyedi P, Corley DA, Den Caestecker J, Falck-Ytter Y, Falk G, et al. BOB CAT: a large-scale review and Delphi consensus for management of Barrett's esophagus with No Dysplasia, indefinite for, or low-grade Dysplasia. Am J Gastroenterol. 2015;110:662–82.
20. Evans J, Early D, Fukami N, Ben-Menachem T, Chandrasekhara V, Chathadi K, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc. 2012;76:1087–94.
21. Shaheen NJ, Falk GW, Iyer PG, Gerson L. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2015;111:30–50.
22. American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American gastroenterological association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011;140:1084–91.
23. Sikkema M, Looman CW, Steyerberg EW, Kerkhof M, Kastelein F, van Dekken H, et al. Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. Am J Gastroenterol. 2011;106:1231–8.
24. Phoa KN, van Vilsteren FG, Weusten BL, Bisschops R, Schoon EJ, Ragunath K, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. 2014;311:1209–17.
25. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst. 2011;103:1049–57.
26. Nunobe S, Nakanishi Y, Taniguchi H, et al. Two distinct pathways of tumorigenesis of adenocarcinomas of the esophagogastric junction, related or unrelated to intestinal metaplasia. Pathol Int. 2007;57:315–21.
27. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011;365:1375–83.
28. Bisschops R. Optimal endoluminal treatment of Barrett's esophagus: integrating novel strategies into clinical practice. Expert Rev Gastroenterol Hepatol. 2010;4:319–33.
29. Fountoulakis A, Zafirellis KD, Dolan K, Dexter SPL, Martin IG, Sue-Ling HM. Effect of surveillance of Barrett's oesophagus on the clinical outcome of oesophageal cancer. Br J Surg. 2004;91:997–1003.
30. Lerut T, Coosemans W, Van Raemdonck D, Dillemans B, De Leyn P, Marnette JM, et al. Surgical treatment of Barrett's carcinoma. Correlations between morphologic findings and prognosis. J Thorac Cardiovasc Surg. 1994;107:1059–65.
31. Sharma P, Falk GW, Weston AP, Reker D, Johnston M, Sampliner RE, et al. Dysplasia and Cancer in a large multicenter cohort of patients with Barrett's Esophagus. Clin Gastroenterol Hepatol. 2006;4:566–72.
32. Sharma P. Barrett's esophagus. N Engl J Med. 2009;26361:2548–56.
33. Kastelein F, van Olphen S, Steyerberg EW, Sikkema M, Spaander MCW, Looman CWN, et al. Surveillance in patients with long-segment Barrett's oesophagus: a cost-effectiveness analysis. Gut. 2015;64:864–71.
34. Rubenstein JH, Scheiman JM, Sadeghi S, Whiteman D, Inadomi JM. Esophageal adenocarcinoma incidence in individuals with gastroesophageal reflux: synthesis and estimates from population studies. Am J Gastroenterol. 2011;106:254–60.

35. Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. Am J Gastroenterol. 1999;94:2043–53.
36. Corley DA, Levin TR, Habel LA, Weiss NS, Buffler PA, McKinney A, et al. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. Gastroenterology. 2002;122:633–40.
37. Hu Q, Sun T-T, Hong J, Fang J-Y, Xiong H, Meltzer SJ. Proton pump inhibitors do not reduce the risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a systematic review and meta-analysis. PLoS One. 2017;12:e0169691.
38. Singh S, Garg SK, Singh PP, Iyer PG, El-Serag HB. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut. 2014;63:1229–37.
39. Levine DS, Blount PL, Rudolph RE, et al. Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus. Am J Gastroenterol. 2000;95:1152–7.
40. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, Walker E, Varghese S, Lao-Sirieix P, et al. Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case-control study. PLoS Med. 2015;12:1–19.

Part IV

Treatments

Lifestyles, Medical Therapy, and Chemoprevention

12

Giovanni Sarnelli, Alessandra D'Alessandro, and Raf Bisschops

12.1 Physical Activity and Diet

Obesity and weight gain, as described in Chap. 5, are considered risk factors for gastro-esophageal reflux disease (GERD), Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC). Indeed, many studies have demonstrated a strong relationship between GERD and BMI [1–4], suggesting that obesity may facilitate recurrent acid reflux in the esophagus, eventually leading to BE development. In addition, obesity is associated with a persistent low-grade inflammatory status [5], which may promote the switch from esophagitis to intestinal metaplasia and cancer. Visceral fat (VAT) has a higher metabolic activity, while subcutaneous fat (SAT) causes a prevalent increase of abdominal pressure. El-Sarag et al. investigated the different roles of SAT and VAT on BE, showing that the ratio of VAT/SAT was significantly greater in BE patients compared to controls. This data suggests that the metabolic activity of adipose tissue and low-grade systemic inflammation associated with obesity generates a procarcinogenic environment, promoting the development of BE and neoplastic transformation. In addition, genetic factors such as Caucasian race and male gender seem to play an important role in cancer development [6]. Because of the importance of obesity, physical activity and low calorie diet represent the main lifestyles modifications to reduce the cancer risk.

Indeed, physical activity has been associated with a lower incidence of BE and EAC. This protective effect is not only associated with weight reduction but is likely mediated by improving insulin sensitivity, decreasing systemic inflammation

G. Sarnelli (✉) · A. D'Alessandro
Gastroenterology Unit, Department of Clinical Medicine and Surgery, University Federico II—School of Medicine, Naples, Italy
e-mail: Giovanni.Sarnelli@unina.it

R. Bisschops
Department of Gastroenterology and Hepatology, Catholic University of Leuven (KUL), TARGID, University Hospitals Leuven, Leuven, Belgium

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_12

and favoring immunomodulation. A recent meta-analysis showed that physical activity can reduce the risk of EAC by 24% [7]. Similar results have been found for colon and gastric cancer risk, suggesting a key role of adipokines and cytokines released by visceral fat in gastrointestinal carcinogenesis. Indeed, physical activity, especially aerobic exercise, may reduce insulin-resistance, pro-inflammatory mediators, and oxidative stress, improving tissue integrity, immune response, and DNA repair [8].

In keeping with this, weight reduction in obese people should be encouraged, and a hypocaloric diet may be suggested in these subjects. On the other hand, also specific dietary regimen may improve the outcome of BE also in normal weighted people. Indeed, an Irish study demonstrated that foods with a lower inflammatory index is protective against BE and, interestingly, neoplastic evolution in EAC. In particular, regular consumption of fruits, vegetables, fish (rich in vitamins and omega-3), and some phytochemicals such as resveratrol and curcumin is associated with a lower risk of EAC [9]. Data on different dietary regimens have been summarized in a recent review, concluding that higher consumption of leafy green and raw vegetables showed an inverse relationship with development of BE and EAC, which may be attributable to the high concentration of fiber, anti-oxidants, as selenium, A, C, and E vitamins. In addition, an American meta-analysis on ten relevant case-control studies confirmed the protective effects of dietary fiber against BE and EAC [10].

In conclusion, although current guidelines [11] do not define specific changing in lifestyles, physical activity, and daily consumption of fruits and vegetables may be encouraged in BE patients.

12.2 Smoking and Alcohol Intake

Smoking represents another potentially modifiable risk factor for BE; however, the role of cigarettes consumption in BE is still debated. Several studies have found a positive association, while others failed to find any significant relationship between smoking and risk of BE. In particular, a large community-based case-control study [12] demonstrated that smoking influences the development of BE only in a subgroup of high risk patients, such as abdominal obese people and alcohol users. Conversely, a recent meta-analysis [13], comprising 39 studies and 7069 BE patients, revealed that cigarette smoking is strongly associated with BE. In particular, the more and the longer a person uses tobacco, the higher the risk for BE is. Moreover, this analysis showed that the higher risk persists and raises in former-smokers. This data may to some extend be explained by the fact that smoking cessation is associated with increased health-seeking and hence with a greater likelihood of BE diagnosis. In addition, smoking cessation is often associated with weight gain, which itself is a known risk factor. Interestingly, the effects of cigarette smoking seem to be less significant in the subgroup of GERD patients compared to non-GERD, supporting the idea that gastric refluxate represent the main condition predisposing to BE. However, some reports have demonstrated that cigarette

smoking may decrease the lower esophageal sphincter pressure, promoting gastroesophageal reflux [14]. In conclusion, cigarette smoking represents a risk factor for BE, while smoking cessation does not reduce the risk to the level observed in never-smokers. Therefore, primary prevention of smoking remains a priority. In addition, while the association between smoking and BE is debated, a clear association has been found between smoking and neoplastic progression of BE, indeed smokers have a significant twofold increased risk of progressing to esophageal or gastric cardia adenocarcinoma or esophageal HGD. However, the role of smoking cessation in cancer risk reduction remains debated, with several studies supporting that former-smokers have a similar or higher risk of neoplastic evolution [15–17]. The pro-cancerogenic role of tobacco is well known, and it has been demonstrated that smoke may induce DNA damage in BE epithelium, leading to cancer progression [16, 17]. The persistence of cancer risk in former-smoker supports the hypothesis that tobacco plays a key role in the early stage of neoplastic transformation.

Alcohol represents a well-known risk factor for several cancers, including squamous esophageal cancer. Several studies have investigated the relationship between alcohol consumption and both BE and EAC. However, although initial data were controversial, recent meta-analysis failed to find any association between alcohol and BE or EAC. Conversely, some evidence suggested an inverse relationship between moderate alcohol intake and EAC, maybe due to the consumption of red wine, which is rich in resveratrol [18, 19].

12.3 Chemoprevention

BE is considered a non-reversal condition that does not require any specific therapy. However, some evidence supports the idea that antisecretory agents may decrease the risk of progression and could be considered in EAC chemoprevention. Epidemiological data have indicated that the use of proton pump inhibitors (PPIs) may prevent or delay progression of dysplasia in BE. However, these studies were methodologically weak and the causal relation between acid-suppressive therapy and EAC risk reduction is still a matter of debate and investigation.

In keeping with this, the latest guidelines indicate that PPI therapy is limited to symptom control and esophageal mucosal healing. In this paragraph, we summarize the pro and cons of acid-suppressive therapy in BE and discuss the results from a recent meta-analysis.

Evidence favoring PPI chemoprevention comes from the fact that acid is strongly involved in the pathogenesis of esophageal metaplasia. In particular, in vitro studies demonstrated that acid reflux induces a chronic esophageal inflammation which promotes columnar cells replacing squamous cells. This mechanism has been suggested as an adaptive response of esophageal mucosa to gastric reflux. Indeed, the metaplastic columnar cells of BE are more resistant to acid-induced injury than the native squamous cells [20–22]. Moreover, acid plays a key pro-inflammatory role on esophageal mucosa, stimulating secretion of specific cytokines, such as IL-8, leading to a chronic inflammatory status [23]. It has also been demonstrated that

acid induces DNA double-strand breaks and promotes cell proliferation, favoring cell transformation [24–26].

The main role of acid in BE is not only suggested by in vitro studies, but also by the clinical evidence that the length of BE correlates with the percent of time that esophageal pH is <4 and that patients with longstanding and severe reflux symptoms are at increased risk for EAC [27, 28]. Accordingly, acid-suppressive therapy has been suggested in BE patients for years.

In addition, recent studies showed that PPIs are able to alter the bacterial content of the distal esophagus, increasing the number of "good bacteria" (Lachnospiracea, Comamonadeaceal). However, the clinical significance of this finding is still under evaluation [29]. Some authors also suggest that PPIs have anti-oxidant and anti-inflammatory properties, distinct from acid inhibition.

The abovementioned findings, combined with low risk profile and low cost, make the use of PPIs in preventing BE neoplastic evolution logic and justifiable. However, in the latest years some authors suggested that PPIs may promote progression to dysplasia and cancer. Indeed, acid-suppressive therapy increases gastrin levels, modifies COX-2 expression, and may favor bile salts/acids toxicity in the esophagus [30, 31]. Also, despite the wide use of PPIs, the incidence of esophageal adenocarcinoma is still increasing. While the chronic acid suppression reduces acid injury on esophageal mucosa, it may also affect GI physiology by altering the secretion of gastrointestinal hormones secretion and bile acids conjugation, which may favor BE onset and its neoplastic progression.

It has been demonstrated that gastrin serum levels correlate with cells' proliferation in non-dysplastic Barrett's esophagus [32]. The pro-cancerous effects of gastrin seem to depend on the activation of cholecystokinin-type 2 receptor (CCK-2R), which results twofold upregulated in human BE tissues [32]. In particular, it has been proposed that gastrin, via CCK-2R, may activate the PKB/Akt antiapoptotic pathway, amplifying cells proliferation and, hence, favoring the metaplasia-dysplasia-cancer progression. Interestingly, some authors suggested that there is a cut-off level beyond which gastrin becomes dangerous; however, since gastrin secretion during PPIs therapy showed a great inter-individual variability, these authors suggest to regulate PPIs dosage in relation to gastrin levels.

Since four main signaling pathways are involved in esophageal mucosal differentiation, in particular the bone morphogenetic protein (BMP), Hedgehog (Hh), wingless-type MMTV integration site family (WNT), and retinoic acid (RA) [33, 34], their involvement in BE development and progression has been claimed.

There is evidence that non-steroidal anti-inflammatory drugs (NSAIDs) are able to decrease WNT activity, and that the combination of ursodeoxycholic acids and aspirin is also able to inhibit the Hh-pathway. Since these drugs are already available, they appear an attractive and innovative therapeutic approach for BE.

In addition, a systematic review and meta-analysis by Singh et al showed that statins are associated with reduced risk of esophageal cancer, especially in BE patients [35]. In keeping with this, Choi et al. evaluated the cost-effectiveness of aspirin, statin, and combination chemoprevention for BE management [36], suggesting that aspirin therapy is the most cost-effective chemoprevention strategy for

patients with BE, while combination of aspirin and statins may be useful in high risk patients. However, a recent matched case-control study failed to find any significant association among PPIs, statins, or aspirin and reduction of BE-related adenocarcinoma [37].

To date, aspirin seems to represent the best candidate for chemoprevention, due to the well-known risk profile and low cost. In order to clarify the cost-effectiveness and risk-benefit of aspirin treatment for chemoprevention in BE patients, a large RCT is ongoing. The final answer can be expected from the ASPECT trial in which patients are randomized between PPIs and placebo with or without aspirin, the results of this trial will be available in 2018 (https://www.oncology.ox.ac.uk/trial/aspect).

References

1. Nocon M, Labenz J, Jaspersen D, Meyer-Sabellek W, Stolte M, Lind T, et al. Association of body mass index with heartburn, regurgitation and esophagitis: results of the Progression of Gastroesophageal Reflux Disease study. J Gastroenterol Hepatol. 2007;22(11):1728–31. https://doi.org/10.1111/j.1440-1746.2006.04549.x.
2. Aro P, Ronkainen J, Talley NJ, Storskrubb T, Bolling-Sternevald E, Agréus L. Body mass index and chronic unexplained gastrointestinal symptoms: an adult endoscopic population based study. Gut. 2005;54(10):1377–83. https://doi.org/10.1136/gut.2004.057497.
3. Dore MP, Maragkoudakis E, Fraley K, Pedroni A, Tadeu V, Realdi G, et al. Diet, lifestyle and gender in gastro-esophageal reflux disease. Dig Dis Sci. 2008;53(8):2027–32. https://doi.org/10.1007/s10620-007-0108-7.
4. Ebrahimi-Mameghani M, Saghafi-Asl M, Arefhosseini S, Khoshbaten M. Is there any association between overweight, obesity and symptoms of reflux disease? Pak J Biol Sci. 2008;11(3):443–7.
5. Heilbronn LK, Campbell LV. Adipose tissue macrophages, low grade inflammation and insulin resistance in human obesity. Curr Pharm Des. 2008;14(12):1225–30.
6. El-Serag HB, Kvapil P, Hacken-Bitar J, Kramer JR. Abdominal obesity and the risk of Barrett's esophagus. Am J Gastroenterol. 2005;100(10):2151–6. https://doi.org/10.1111/j.1572-0241.2005.00251.x.
7. Singh S, Manickam P, Amin AV, Samala N, Schouten LJ, Iyer PG, Desai TK. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. Gastrointest Endosc. 2014 Jun;79(6):897–909. https://doi.org/10.1016/j.gie.2014.01.009.
8. Wolin KY, Tuchman H. Physical activity and gastrointestinal cancer prevention. Recent Results Cancer Res. 2011;186:73–100. https://doi.org/10.1007/978-3-642-04231-7_4.
9. Shivappa N, Hebert JR, Anderson LA, Shrubsole MJ, Murray LJ, Getty LB, Coleman HG. Dietary inflammatory index and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma: a population-based case-control study. Br J Nutr. 2017 May;117(9):1323–31. https://doi.org/10.1017/S0007114517001131.
10. Coleman HG, Murray LJ, Hicks B, Bhat SK, Kubo A, Corley DA, et al. Dietary fiber and the risk of precancerous lesions and cancer of the esophagus: a systematic review and meta-analysis. Nutr Rev. 2013;71(7):474–82. https://doi.org/10.1111/nure.12032.
11. Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of Gastroenterology. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111(1):30–50.; quiz 51. https://doi.org/10.1038/ajg.2015.322.
12. Kubo A, Levin TR, Block G, et al. Cigarette smoking and the risk of Barrett's esophagus. Cancer Causes Control. 2009;20(3):303–11. https://doi.org/10.1007/s10552-008-9244-4.

13. Andrici J, Cox MR, Eslick GD. Cigarette smoking and the risk of Barrett's esophagus: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2013 Aug;28(8):1258–73. https://doi.org/10.1111/jgh.12230.
14. Kahrilas PJ, Gupta RR. Mechanisms of acid reflux associated with cigarette smoking. Gut. 1990 Jan;31(1):4–10.
15. Jung KW, Talley NJ, Romero Y, Katzka DA, Schleck CD, Zinsmeister AR, et al. Epidemiology and natural history of intestinal metaplasia of the gastroesophageal junction and Barrett's esophagus: a population-based study. Am J Gastroenterol. 2011;106(8):1447–55. https://doi.org/10.1038/ajg.2011.130.
16. Sikkema M, Looman CW, Steyerberg EW, Kerkhof M, Kastelein F, van Dekken H, et al. Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. Am J Gastroenterol. 2011 Jul;106(7):1231–8. https://doi.org/10.1038/ajg.2011.153.
17. Coleman HG, Bhat S, Johnston BT, McManus D, Gavin AT, Murray LJ. Tobacco smoking increases the risk of high-grade dysplasia and cancer among patients with Barrett's esophagus. Gastroenterology. 2012;142(2):233–40. https://doi.org/10.1053/j.gastro.2011.10.034.
18. Thrift AP, Cook MB, Vaughan TL, Anderson LA, Murray LJ, Whiteman DC, et al. Alcohol and the risk of Barrett's esophagus: a pooled analysis from the International BEACON Consortium. Am J Gastroenterol. 2014;109(10):1586–94. https://doi.org/10.1038/ajg.2014.206.
19. Lou Z, Xing H, Li D. Alcohol consumption and the neoplastic progression in Barrett's esophagus: a systematic review and meta-analysis. PLoS One. 2014;9(10):e105612. https://doi.org/10.1371/journal.pone.0105612.
20. Quante M, Bhagat G, Abrams JA, Marache F, Good P, Lee MD, et al. Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. Cancer Cell. 2012;21(1):36–51. https://doi.org/10.1016/j.ccr.2011.12.004.
21. Wang X, Ouyang H, Yamamoto Y, Kumar PA, Wei TS, Dagher R, et al. Residual embryonic cells a precursors of a Barrett's-like metaplasia. Cell. 2011;145(7):1023–35. https://doi.org/10.1016/j.cell.2011.05.026.
22. Sarosi G, Brown G, Jaiswal K, Feagins LA, Lee E, Crook TW, et al. Bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus. Dis Esophagus. 2008;21(1):43–50. https://doi.org/10.1111/j.1442-2050.2007.00744.x.
23. Souza RF, Huo X, Mittal V, Schuler CM, Carmack SW, al ZHY e. Gastroesophageal reflux might cause esophagitis through a cytokine-mediated mechanism rather than caustic acid injury. Gastroenterology. 2009;137(5):1776–84. https://doi.org/10.1053/j.gastro.2009.07.055.
24. Zhang HY, Hormi-Carver K, Zhang X, Spechler SJ, Souza RF. In benign Barrett's epithelial cells, acid exposure generates reactive oxygen species that cause DNA double-strand breaks. Cancer Res. 2009;69(23):9083–9. https://doi.org/10.1158/0008-5472.CAN-09-2518.
25. Fitzgerald RC, Omary MB, Triadafilopoulos G. Dynamic effects of acid on Barrett's esophagus. An ex vivo proliferation and differentiation model. J Clin Invest. 1996;98(9):2120–8.
26. Souza RF, Shewmake K, Terada LS, Spechler SJ. Acid exposure activates the mitogen-activated protein kinase pathways in Barrett's esophagus. Gastroenterology. 2002;122(2):299–307.
27. Fass R, Hell RW, Garewal HS, Martinez P, Pulliam G, Wendel C, Sampliner RE. Correlation of oesophageal acid exposure with Barrett's oesophagus length. Gut. 2001;48(3):310–3.
28. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825–31.
29. Wang Z-K, Yang Y-S. Upper gastrointestinal microbiota and digestive diseases. World J Gastroenterol. 2013;19(10):1541–50. https://doi.org/10.3748/wjg.v19.i10.1541.
30. Alsalahi O, Dobrian AD. proton pump inhibitors: the culprit for Barrett's esophagus? Front Oncol. 2015;4:373. https://doi.org/10.3389/fonc.2014.00373.
31. Spechler SJ. Does Barrett's esophagus regress after surgery (or proton pump inhibitors)? Dig Dis. 2014;32(1–2):156–63. https://doi.org/10.1159/000357184.
32. Green DA, Mlynarczyk CM, Vaccaro BJ, Capiak KM, Quante M, Lightdale CJ, Abrams JA. Correlation between serum gastrin and cellular proliferation in Barrett's esophagus. Therap Adv Gastroenterol. 2011;4(2):89–94. https://doi.org/10.1177/1756283X10392444.

33. Pavlov K, Meijer C, van den Berg A, Peters FT, Kruyt FA, Kleibeuker JH. Embryological signaling pathways in Barrett's metaplasia development and malignant transformation; mechanisms and therapeutic opportunities. Crit Rev Oncol Hematol. 2014;92(1):25–37. https://doi.org/10.1016/j.critrevonc.2014.05.002.
34. Schoofs N, Bisschops R, Prenen H. Progression of Barrett's esophagus toward esophageal adenocarcinoma: an overview. Ann Gastroenterol. 2017;30(1):1–6. https://doi.org/10.20524/aog.2016.0091.
35. Singh S, Singh AG, Singh PP, Murad MH, Iyer PG. Statins are associated with reduced risk of esophageal cancer, particularly in patients with Barrett' esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(6):620–9. https://doi.org/10.1016/j.cgh.2012.12.036.
36. Choi SE, Perzan KE, Tramontano AC, Kong CY, Hur C. Statins and aspirin for chemoprevention in Barrett's esophagus: results of a cost-effectiveness analysis. Cancer Prev Res (Phila). 2014;7(3):341–50. https://doi.org/10.1158/1940-6207.CAPR-13-0191-T.
37. Masclee GM, Coloma PM, Spaander MC, Kuipers EJ, Sturkenboom MC. NSAIDs, statins, low-dose aspirin and PPIs, and the risk of oesophageal adenocarcinoma among patients with Barrett's oesophagus: a population-based case-control study. BMJ Open. 2015;5(1):e006640. https://doi.org/10.1136/bmjopen-2014-006640.

Endoscopic Treatments: Photodynamic Therapy

13

Raffaele Manta, Dolores Sgambato, Nico Pagano, and Giuseppe Galloro

13.1 Introduction

Photodynamic therapy (PDT) is a technique developed in 1990 for reducing the severity of tumor symptoms and cancer size. It acts through a non-thermal mechanism utilizing the activation of a photosensitizer—administrated by intravenous, topical, or oral route—with a specific wavelength of light. The excited photosensitizer generates oxygen radicals which induces localized necrosis and cellular damage in the site of photoactivation. Site and depth of injury depended on several factors, including oxygen concentration, type of sensitizing agent, waiting time between dosing and light stimulation, energy per unit area, intensity of light dosimetry, wavelength, and time of irradiation.

PDT may be used in the tissues accessible to light exposure, such as skin, retina, bronchial tree, and the gastrointestinal tract, for either palliative approach (namely lumen obstruction by lung and esophageal tract cancer) [1] or curative therapy. In the gastrointestinal tract, PDT is thought to be effective in the treatment of Barrett's esophagus with high-grade dysplasia. Further investigational applications include palliative approach to unresectable cholangiocarcinoma [2] and treatment of

R. Manta (✉) · D. Sgambato
Gastroenterology and Digestive Endoscopy Unit, NOCSAE Hospital of Modena, Modena, Italy

N. Pagano
Gastroenterology and Digestive Endoscopy Unit, Department of Medical and Surgical Sciences (DIMEC), University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

G. Galloro
Surgical Digestive Endoscopy Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II—School of Medicine, Naples, Italy
e-mail: giuseppe.galloro@unina.it

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_13

duodenal or colon adenomas associated to FAP syndrome [3]. Finally, there are few data on ablation of gastric superficial tumors [4].

This review focused on PDT tools, indications, limits, and contraindications in the treatment of Barrett's esophagus.

13.2 Technique

The main actors of PDT technique are:

- Photosensitizer (PS)
- Light

13.2.1 Photosensitizers

PSs are prodrug used in PDT which, activated by a suitable wavelength light, produce reactive oxygen species. Production of oxygen radicals causes local non-thermal cellular damage, vascular thrombosis, and necrosis. Ideal characteristics of a PS should be molecular stability, no adverse pharmacological effect after administration, no longer photosensitivity, and rapid clearance. Moreover, an optimal PS should be as selective as possible for tumor tissue binding, which is relevant for therapy outcome. It should be conceivable as a water-soluble structure, but a lipophilic PS (little or no overall charge) could be desirable for a rapid diffusion into tumoral cells [5]. PS may be classified as porphyrin (based on the structure similarity with the protoporphyrin prosthetic group contained in hemoglobin) and non-porphyrin photosensitizers. Although the mechanism is unknown, the tumoral tissues capturing the photosensitizer agents actively express LDL receptors. Likely, both porphyrin and non-porphyrin photosensitizers are absorbed by cells with a strong metabolic activity, as cancer cells [6].

The first prodrug used in PDT was porfimer sodium, sold as Photofrin, an oligomer mixture of hematoporphyrin which is found directly in nature. It has a strong absorption band at around 400 nm, and it may be used only for treating superficial tumor. After reconstitution, the prodrug should be kept away from light and administered immediately at dose of 2 mg/kg intravenous. Porfimer sodium is discharged from the healthy tissue over 40–72 h while it is retained for longer from tumor cells [7]. Unfortunately, it owns some drawbacks, such as prolonged photosensitivity, lack of specificity, and a weak absorption in the therapeutic window [8].

Instead, the second-generation porphyrin PSs, such as chlorins and bacteriochlorins, is used to treat deep-seated tumors, and it absorbs light of longer wavelengths than porfimer sodium. These PSs are cleared from tissue faster when compared to first generation, reducing duration of patient photosensitivity [9].

Aminolevulinic acid (ALA) is a PS of second generation which is converted to protoporphyrin IX (PpIX) after administration. It is used topically in the treatment of cutaneous conditions in the USA, while intravenous administration has been employed

for PDT therapy of Barrett's esophageal with or without dysplasia [10]. The advantage of ALA is a higher mucosal than submucosal concentration leading to a more superficial injury, a characteristic useful for Barrett treatment. Moreover, ALA PS has much shorter half-life, with reduction of photosensitivity-associated reactions [11].

The third generation of porphyrin PSs includes molecules linked to carrier or packaged within it for a selective accumulation in the tumor tissue [12]. Carriers may be an antibody, a molecule with a rapid cellular uptake (as sugars) or elements which selectively bound an overexpressed target in cancer cells (oligonucleotides, folic acid, peptides, and amino acids) [13].

Recently, a new class has been generated through the link of porphyrin prodrugs to nanomaterials functionalized with cancer-surface targeting (CST) agents. It has a specific therapeutic effect through the link between CST agents and their receptors overexpressed on the surface of tumor tissue. Main advantages include safety towards the health tissue and reduction of photoexposition time [9].

13.2.2 Light

The light plays an important role in PDT because of the efficacy depends on the type of light used. The choice among the different light sources available for PDT may depend on tumor site and the PS used. Moreover, the grade of light penetration correlates with the optical properties of tissues (reflection, transmission, scattering, and absorption), and with the wavelength of the light.

Usually the depth of penetration is 3–8 mm when light ranging from 630 to 800 nm [14]. This interval of wavelength has been defined as "therapeutic window." Lower wavelengths (as blue light which ranges from 450 to 495 nm) obtain poor tissue penetration, while higher wavelengths have an insufficient energy to produce singlet oxygen species [15].

Another determinant feature of light is the dosimetry which consists of fluence (energy received by a surface per unit area—J/cm^2) and fluence rate (incident energy per second across a sectional area—W/cm^2). Usually light doses applied in PDT are within 60–200 J/cm^2. Although higher fluence rates could reduce treatment time, a lower photodynamic effect due to oxygen depletion has been observed [16]. Conversely, fluence rates over 150 mW/cm^2 could induce hyperthermia because light absorption leads to heat generation [17].

Regarding the gastrointestinal tract, there are several laser light sources which deliver appropriate wavelength light [18]. Diomed 630 PDT Laser Model 2TUSA is the only one currently cleared by FDA and marketed for use with Photofrin porfimer sodium. It is a 43 pound-portable device with a 630 nm red light laser system and operates on standard 115 V AC current.

Diomed characteristics are follows:

- Internal forced air cooling (it does not require plumbing).
- Semiconductor diodes as a light source (it avoids the need for laser alignment and dye replenishment or disposal).

– An energy up to 2000 mW at the tip of the delivery fiber.
– An automated program for dosimetry (light power and duration) associated with the operators input of the target organ, pathology, and fiber length to be used.

The light dose for treatment of esophageal carcinoma using porfimer sodium is 300 joules (J)/cm of diffuser length (for treatment duration of 12 min and 30 s), while higher doses are necessary for high-grade dysplasia in Barrett's esophagus (130 J/cm of diffuser length, administered over 8 min). Regarding the Diomed laser, autoclavable sterile cuvettes for calibration of the light output are available, and they can be sterilized and reused up to ten times.

13.3 Data of Literature

In the last, the PDT efficacy for treatment of Barrett has been evaluated in either placebo-controlled studies or comparative studies. Overholt et al. [19] reported mucosal ablation and squamous re-epithelialization in 75–80% on 100 patients with metaplastic esophageal mucosa using sodium porfimer. In 43 cases there was a complete elimination, but healing was associated with stricture formation in 34% of patients. The association of oral steorids to treatment with PDT was not sufficient to reduce the incidence of strictures [20]. In 2000, Ackroyd et al. [10] reported data of the first prospective, double-blind, placebo-controlled trial on PDT with ALA for treating patients with low-grade dysplasia on Barrett's esophagus. After four hours from orally random administration of 30 mg/kg ALA dissolved in 50 ml of orange juice or placebo, laser endoscopy was performed with green light (514 nm). Sixteen out of 8 patients of ALA group showed a decrease of the Barrett's area until to 60%, and a reduction of 10% was observed in further 2 patients, while no change was observed in 16 ($p < 0.001$). However, in the placebo group, persistent low grade dysplasia was found in 12 patients ($p < 0.001$). Neither short- nor long-term major side-effects were observed, and the success was maintained for up to 24 months.

Other studies found that PDT with porfimer sodium plus omeprazole was more effective than omeprazole alone in ablating high-grade dysplasia (HGD) on Barrett's metaplasia, also reducing the incidence of esophageal adenocarcinoma [21]. In detail, at 1-year follow-up, the HGD was eradicated in 77% out of 208 patients as compared to 39% of controls, and complete remission of metaplasia was achieved in 52% of patients treated with PDT. Adverse effects included photosensitivity reactions (69%), esophageal strictures (36%), vomiting (32%), noncardiac chest pain (20%), pyrexia (20%), and dysphagia (19%). A long-term (median follow-up: 37 months) observational study [22] on 66 patients treated with PDT reported a complete response in as many as 97% of patients with HGD and 100% of those with early adenocarcinoma, with a disease-free survival of 89% and 68%, respectively. The calculated 5-year survival was 97% for HGD patients and 80% for cancer patients, with no death related to Barrett's neoplasia. In another study with Photofrin, 77% of patients achieved a response at 5-year follow-up, without relevant adverse effects [23].

ALA and Photofrin are the most used for PDT in Barrett's esophagus. In a head-to-head comparison [24], the efficacy was similar, with a complete HGD reversal achieved in 16 (47%) out of 34 treated with ALA and in 12 (40%) out of 30 patients receiving Photofrin. However, ALA was found to be safer than Photofrin, stricture occurring 6% and 30%, respectively ($P = 0.018$), most likely due to the lacking of action of ALA on deeper muscle layers. Moreover, skin photosensitivity was significantly more frequent with Photofrin.

Since the introduction of radiofrequency ablation (RFA) technique in Barrett's esophagus treatment, some studies comparing RFA and PDT have been performed. The first head-to-head comparison [25] showed a complete remission of dysplasia in 54.5% and 88.7% ($P = 0.001$) of patients treated with PDT and RFA, respectively. Moreover, side-effects occurred more frequently following PDT (one esophageal perforation, two photosensitivity, and nine strictures) than RFA (two strictures). In addition, dysplasia recurred in eight (one HGD, seven LGD) patients treated with PDT group and in none in the RFA group, while the development of subsquamous intestinal metaplasia did not differ. Finally, the PDT treatment was approximately 5-fold more costly than RFA. In a recent retrospective study [26], results of 342 patients who underwent endoscopic therapy for Barrett's esophagus, including RFA therapy alone (119 pts), RFA after EMR for visible nodules (98 pts), and Ps-PDT (125 pts) were reported. The complete remission of intestinal metaplasia, defined as lack of visible columnar-lined esophagus at endoscopy and absence on two consecutive biopsy specimens after treatment, was the primary end point. Data found a higher remission rate following Ps-PDT than RFA or EMR-RFA, with a similar recurrence rate at a median follow-up of 14.2 months. However, strictures were less frequent in RFA patients (2.4%) as compared to EMR-RFA (13.3%) and Ps-PDT (10.4%), whereas bleeding events similarly occurred among three groups.

13.4 Limits

13.4.1 Adverse Effects

The main limit of PDT approach is the incidence of different side-effects, classified as short-, medium-, and long-term.

At short-term, patients frequently (20–30%) complain of odynophagia, chest pain, abdominal pain, nausea, vomiting, or fever. Moreover, asymptomatic pleural effusions are common (33–75%). On the contrary, bleeding for mucosal ulcerations, esophageal perforation, atrial fibrillation, and respiratory symptoms rarely develop [27].

At medium-term, near a third of patients experience cutaneous phototoxicity, which occurs within 90 days after treatment, and it is characterized by a sunburn-like reaction (particularly in the face, the hands, and the neck). In the 69% of cases, phototoxicity is mild, moderate in the 24%, and severe in the 7% [21]. Unfortunately, sunscreens do not protect against photofrin-related phototoxicity.

At long-term, esophageal stricture may develop in 15–58% of patients. Higher light doses, focused pretreatment of localized lesions, such as nodular lesions, and repetition of treatments on the same segment have been found to be predictive factors. The use of centering balloons did not induce a statistically significant reduction in the risk of stricture formation [28]. The stricture may be successfully treated with esophageal dilation [29].

13.5 Contraindication

There are some contraindications to PDT treatment, including allergies/intolerance to porphyrins, porphyria or any porphyria form disease, esophageal vessel eroded by tumors or esophageal or gastric varices, esophageal ulcers, tracheaesophageal or broncho-esophageal fistula. Concomitant therapy with other potential photosensitizing agents, such as fluoroquinolones, griseofulvin, some hypoglycemic agents, phenothiazines, sulfonamides, sulfonylurea, tetracyclines, and thiazides are contraindicated. Finally, because porphyrin sodium is not dialyzable, it should be not used in patient's renal failure.

13.6 State of Art

The use of PDT technique progressively disappeared from the International recommendations. According to the most recent ACG guidelines [30], the PDT approach would be too expensive and with a low safety profile compared with data supporting the safety and efficacy of RFA. In the last ESGE Position Statement [31], the PDT technique was no more mentioned.

References

1. Lightdale CJ. Role of photodynamic therapy in the management of advanced esophageal cancer. Gastrointest Endosc Clin N Am. 2000;10:397–408.
2. Moole H, Tathireddy H, Dharmapuri S, et al. Success of photodynamic therapy in palliating patients with nonresectable cholangiocarcinoma: a systematic review and meta-analysis. World J Gastroenterol. 2017;23(7):1278–88.
3. Mlkvy P, Messmann H, Debinski H, et al. Photodynamic therapy for polyps in familial adenomatous polyposis: a pilot study. Eur J Cancer. 1995;31A:1160–5.
4. Deprez PH, Aouattah T, Piessevaux H. Endoscopic removal or ablation of oesophageal and gastric superficial tumours. Acta Gastroenterol Belg. 2006;69(3):304–11.
5. Hamblin MR, Newman EL. On the mechanism of the tumour-localising effect in photodynamic therapy. J Photochem Photobiol B. 1994;23:3–8.
6. Webber J, Herman M, Kessel D, Fromm D. Current concepts in gastrointestinal photodynamic therapy. Ann Surg. 1999;230:12–23.
7. Petersen BT, Chuttani R, Croffie J, et al. Photodynamic therapy for gastrointestinal disease. Gastrointest Endosc. 2006;63(7):927–32.

8. Josefsen LB, Boyle RW. Photodynamic therapy and the development of metal-based photosensitisers. Met Based Drugs. 2008;(2008):276109.
9. Fakayode OJ, Tsolekile N, Songca SP, Oluwafemi OS. Applications of functionalized nanomaterials in photodynamic therapy. Biophys Rev. 2018;10(1):49–67.
10. Ackroyd R, Brown NJ, Davis MF, et al. Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomised, placebo controlled trial. Gut. 2000;47: 612–7.
11. Barr H. Barrett's esophagus: treatment with 5-aminolevulinic acid phtotodynamic therapy. Gastrointest Endosc Clin N Am. 2000;10:421–37.
12. Sibani SA, McCarron PA, Woolfson AD, Donnelly RF. Photosensitiser delivery for photodynamic therapy. Part 2: systemic carrier platforms. Expert Opin Drug Deliv. 2008;5: 1241–54.
13. Balaz M, Steinkruger JD, Ellestad GA, Berova N. 5'-Porphyrin-oligonucleotide conjugates: neutral porphyrin-DNA interactions. Org Lett. 2005;7:5613–6.
14. Bashkatov AN, Genina EA, Kochubey VI, Tuchin VV. Optical properties of human skin, subcutaneous and mucous tissues in the wavelength range from 400 to 2000 nm. J Phys D Appl Phys. 2005;38:2543.
15. Castano AP, Demidova TN, Hamblin MR. Mechanisms in photodynamic therapy: part one—photosensitizers, photochemistry and cellular localization. Photodiagn Photodyn Ther. 2004;1:279–93.
16. Seshadri M, Bellnier DA, Vaughan LA, Spernyak JA, Mazurchuk R, Foster TH, Henderson BW. Light delivery over extended time periods enhances the effectiveness of photodynamic therapy. Clin Cancer Res. 2008;14:2796–805.
17. Svaasand LO. Photodynamic and photohyperthermic response of malignant tumors. Med Phys. 1985;12:455–61.
18. Panjehpour M, Overholt BF, Haydek JM. Light sources and delivery devices for photodynamic therapy in the gastrointestinal tract. Gastrointest Endosc Clin N Am. 2000;10:513–32.
19. Overholt BF, Panjehpour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: follow-up in 100 patients. Gastrointest Endosc. 1999;49:1–7.
20. Panjehpour M, Overholt BF, Haydek JM, Lee SG. Results of photodynamic therapy for ablation of dysplasia and early cancer in Barrett's esophagus and effect of oral steroids on stricture formation. Am J Gastroenterol. 2000;95(9):2177–84.
21. Overholt BF, Lightdale CJ, Wang KK, et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointest Endosc. 2005;62:488–98.
22. Pech O, Gossner L, May A, et al. Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. Gastrointest Endosc. 2005;62(1):24–30.
23. Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc. 2007;66(3):460–8.
24. Dunn JM, Mackenzie GD, Banks MR, et al. A randomised controlled trial of ALA vs. Photofrin photodynamic therapy for high-grade dysplasia arising in Barrett's oesophagus. Lasers Med Sci. 2013;28(3):707–15.
25. Ertan A, Zaheer I, Correa AM, et al. Photodynamic therapy vs radiofrequency ablation for Barrett's dysplasia: efficacy, safety and cost-comparison. World J Gastroenterol. 2013;19:7106–13.
26. David WJ, Qumseya BJ, Qumsiyeh Y, et al. Comparison of endoscopic treatment modalities for Barrett's neoplasia. Gastrointest Endosc. 2015;82(5):793–803.e3.
27. Wang KK, Nijhawan PK. Complications of photodynamic therapy in gastrointestinal disease. Gastrointest Endosc Clin N Am. 2000;10:487–95.
28. Ganapathy A, Prasad MD, Kenneth K, Wang MD. Predictors of stricture formation after photodynamic therapy for high-grade dysplasia in Barrett's esophagus. Gastrointest Endosc. 2007;65(1):60–6.

29. Overholt B, Panjehpour M, Tefftellar E, et al. Photodynamic therapy for treatment of early adenocarcinoma in Barrett's esophagus. Gastrointest Endosc. 1993;39:73–6.
30. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. Gastroenterology. 2016;111(7):1077.
31. Weusten B, Bisschops R, Coron E. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017;49(2):191–8.

Cryotherapy for Barrett's Esophagus

14

Nico Pagano, Raffaele Manta, and Giuseppe Galloro

14.1 Introduction

Cryotherapy (also referred to as cryoablation) is a technique that uses freezing to destroy malignant tissues.

Cryotherapy has been applied in the treatment of various neoplastic diseases, as prostate, kidney, liver, and endobronchial cancers [1–8].

In the gastrointestinal tract, to date, the evidence shows a good efficacy and safety profile, but no high-level evidence supports the application of cryotherapy in the treatment of Barrett esophagus. There are ongoing trials evaluating the optimization of devices, technique, treatment schedule, and follow-up.

New evidence is about to come in the next future and there is the need for trials comparing different therapeutic options such as cryotherapy, mucosectomy, or radiofrequency ablation in the treatment of Barrett esophagus.

N. Pagano (✉)
Gastroenterology and Digestive Endoscopy Unit, Department of Medical and Surgical Sciences (DIMEC), University Alma Mater Bologna, Italy—School of Medicine, Bologna, Italy

R. Manta
Gastroenterology and Digestive Endoscopy Unit, NOCSAE Hospital of Modena, Modena, Italy

G. Galloro
Surgical Digestive Endoscopy Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II—School of Medicine, Naples, Italy
e-mail: giuseppe.galloro@unina.it

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_14

14.2 Physical Principles and Technical Consideration

Cryotherapy causes rapid intracellular and extracellular freezing, with a direct effect on cell membrane protein denaturation, producing cell necrosis. Freezing causes also a cessation of vascular supply. Apoptosis and immune toxicity occur in areas of sub-lethal injury. The duration and intensity of freezing is directly related to tissue necrosis but the vascular flow, melting the ice, increases the damage. This latter part of the process causes variability in the extension of the necrosis, determining the difficulty in the optimization of dosimetry [9, 10].

Endoscopic cryotherapy can be performed with three different systems, all approved by the US Food and Drug Administration for clinical use. The cryotherapy system can be based on delivery of liquid nitrogen (Liquid Nitrogen Cryotherapy or LNC) or carbon dioxide (CO_2C). Lately a cryoballoon focal ablation system has been developed (CbFAS). The freezing of the tissue is caused by liquid nitrogen evaporation or by CO_2 gas expansion. The nitrogen based system delivers the energy through a polymer coated catheter (CSA Medical, Lexington, MA, USA). The LNC is performed positioning the catheter tip at a distance of 1–2 cm from the target area. The application of energy causes a hemi-circumferential freeze zone. The dosing of LNC has not yet been standardized. In most of the series, a 10–20 s application with subsequent 45 s of pause for reperfusion has been used. In the same session, the cycle is generally repeated 2–4 times and treatments are scheduled every 4–8 weeks.

The second type of cryotherapy device (Polar Wand, GI Supply, Camp Hill, PA, USA) uses CO_2. The first clinical application was for the treatment of bleeding GAVE (Gastric Antral Vascular Ectasia) and radiation proctitis. It has also been used for the treatment of BE. At present the device is no more commercially available. The CO_2 is released by a flexible thin catheter. During the treatment, the catheter is placed close to mucosa. Several cycles of freezing and reperfusion are done every single session. In porcine model, it was calculated that a single application of 15 s of cryotherapy using the CO_2 based system causes a tissue injury with a depth of 1.2–2.5 mm. In patients an application of 15 s for 6–8 cycles has been used, with no cases of transmural injury. Treatments are generally repeated every 4–8 weeks until eradication is achieved [11, 12].

In both LN or CO_2 based system, a certain amount of gas is produced during the treatment, thus requiring orogastric decompression by the placement of a tube.

The last cryotherapy system is the CbFAS (C2 Therapeutics, Redwood, CA, USA), introduced in 2011. The nitrogen is maintained in liquid state by a heat system. The tissue contact causes the conversion of the liquid to gas with a subsequent rapid decrease of the temperature, inflating and cooling the balloon. The delivery system consists of an oval shaped 3.7-mm disposable balloon catheter which measures 30 mm in length. The balloon is transparent, so the ablation can be performed under endoscopic guidance. The mucosa which is in contact with the balloon surface freezes within a range of 2 cm.

The cryogen dose measured in seconds of application is preset in the system, making the procedure smoother, and it is currently of 10 s each site according to the results of dosimetry studies.

In the balloon system, the gas does not enter the gastrointestinal lumen, obviating the need for decompression. A software keeps the balloon pressure stable during the ablation with a maximum of 3.5 psi.

A single application per site without cycles seems sufficient for complete ablation of the Barrett epithelium. This might result in a shortening of the procedure time, thus improving the efficiency [13, 14].

14.3 Clinical Results

Endoscopic cryotherapy has been applied to BE treatment since 2005 when a clinical study described a small series of patients in which complete eradication of intestinal metaplasia was obtained in all the patients and sustained at 6 months in 78% of the cases. Since then, multiple studies have been published about the treatment of BE with cryotherapy in populations of naïve or recurrent BE with encouraging results [15].

In a cohort study by Dumot and colleagues published in 2009, 30 patients with BE and high-grade dysplasia or mucosal adenocarcinoma were included. All patients were excluded from surgery for clinical reasons. The cryotherapy treatment determined a downgrade of the dysplasia in 80% of patients with mucosal adenocarcinoma and 68% of patients with HGD. The mean follow-up was 12 months [16].

In 2010, a large study was published by Shaheen and colleagues, collecting patients from nine academic and community centers. The design was retrospective with the inclusion of 98 subjects with BE and HGD that underwent LNC. Only 60 patients completed the treatment. Of these, 58 (97%) had complete eradication of the dysplasia (CE-D), and 87% had complete eradication of the intestinal metaplasia (CE-IM) [17].

Ghorbani and colleagues enrolled prospectively, in a multicenter registry, patients with BE and LGD or HGD. Patients were treated by LN-cryotherapy with intervals of 2–3 months. The results were published in 2015. Eighty of the 96 subjects (83%) completed treatment and were followed for 2 years. The eradication rate was 91% for LGD with 61% of CE-IM. Patients with HGD had 81% of CE-D and 65% of CE-IM [18].

Cryotherapy has been applied in the treatment of Barrett esophagus after failed RFA treatment with good results [19].

In the treatment of BE after EMR for adenocarcinoma complete IM eradication was achieved in 70% of the patients but 4% developed invasive adenocarcinoma during follow-up [20].

Data published on efficacy of CO_2C are limited to one single-center retrospective cohort study by Canto and colleagues. In this study, 64 patients with dysplastic BE (only 20 naive) were treated. The mean follow-up was 4.2 years. At 1 year, there was an overall complete response rate of 77% for cancer and 89% for dysplasia [21, 22].

The results of balloon cryotherapy (CbFAS) are promising [23].

Clinical trials studying the efficacy of the CbFAS for the ablation of dysplastic BE are ongoing in Europe and the USA. A multicenter trial found a complete

squamous epithelium regeneration after a single dose delivered for 10 s in all the subjects treated. Preliminary data from a single-center prospective clinical trial are promising with complete eradication of intestinal metaplasia of 71% and 95% of complete dysplasia eradication at 1 year [24].

Sustained dysplasia and intestinal metaplasia eradication is the main goal of every Barrett esophagus treatment. Few clinical trials explored long-term results of cryotherapy in Barrett esophagus treatment using the liquid nitrogen system.

No long-term studies are available for the CbFAS system.

Complete eradication of dysplasia was reported in 94% at 3 years and 88% at 5 years, and complete intestinal metaplasia eradication in 75% of patients at 5 years.

Recurrent BE neoplasia was detected by Gosain and colleagues in patients with baseline high-grade dysplasia after treatment with cryotherapy. In 19% of patients who completed treatment, a recurrence of HGD occurred in a median follow-up time of 6 months. In the 5-year study by Greenwald and colleagues, the incidence rate of dysplasia was 4% and the incidence rate of HGD/ADK was 1.4% per person-year after complete metaplasia eradication in a cohort followed up for a 5-year period.

Intestinal metaplasia relapses in up to 41% of the cases, usually in distal parts of the esophagus [25, 26, 27, 28].

The safety profile for cryotherapy, according to data published, is very good. The rate of severe adverse event is less than 3%. The most commonly reported severe adverse events are perforation and bleeding. Symptomatic post-treatment strictures with the need for dilation occur in less than 9% of the cases. Post-ablation severe pain is quite rare, and has been reported in less than 10% of treated patients [15].

Dumot and colleagues reported a gastric perforation in a Marfan syndrome patient and lip ulcer. Shaheen and colleagues reported 1 progression to adenocarcinoma out of 60 treated patients [16, 17, 18].

Data on balloon cryoablation are too limited to describe a safety profile. In the trials published to date no major adverse events have been reported. Minor mucosal trauma due to balloon pressure was reported in some patients but without clinical consequences. At present, no strictures have been reported after treatment. Also, the post-ablation pain seems to be rare, transient, and self-limiting, not requiring medications. Although the number of treated patients is low in balloon cryoablation, it seems to be a trend toward lower rate of stricture formation. In published and preliminary data, only one patient required endoscopic dilation [23, 24].

Conclusions

Cryotherapy is a new weapon in the treatment of Barrett esophagus and initial results are promising. There are a number of issues that need to be addressed in ongoing and future clinical trials before the technique is ready for prime time. The correct technique and the best equipment has yet to be determined. Also, the long-term results are to be evaluated before introducing cryotherapy in clinical practice [29, 30, 31]. Surely, thanks to technical and scientific development, Barrett esophagus treatment is becoming a multi-modal therapy.

References

1. Cho S, Kang SH. Current status of cryotherapy for prostate and kidney cancer. Korean J Urol. 2014;55(12):780–8.
2. Schuld J, Richter S, Kollmar O. The role of cryosurgery in the treatment of colorectal liver metastases: a matched-pair analysis of cryotherapy vs, liver resection. Hepato-Gastroenterology. 2014;61(129):192–6.
3. Awad T, Thorlund K, Gluud C. Cryotherapy for hepatocellular carcinoma. Cochrane Database Syst Rev. 2009;4:CD007611.
4. Tay KJ, Polascik TJ. Focal cryotherapy for localized prostate cancer. Arch Esp Urol. 2016;69(6):317–26.
5. Lee SH, Choi WJ, Sung SW, et al. Endoscopic cryotherapy of lung and bronchial tumors: a systematic review. Korean J Intern Med. 2011;26(2):137–44.
6. Rodriguez-Faba O, Palou J, Rosales A, et al. Prospective study of ultrasound-guided percutaneous renal cryotherapy: case selection as an optimization factor for a technique. Actas Urol Esp. 2015;39(1):8–12.
7. Mohammed A, Miller S, Douglas-Moore J, et al. Cryotherapy and its applications in the management of urologic malignancies: a review of its use in prostate and renal cancers. Urol Oncol. 2014;32(1):39.e19–27.
8. Santesso N, Mustafa RA, Wiercioch W, et al. Systematic reviews and metaanalyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. Int J Gynaecol Obstet. 2016;132(3):266–71.
9. Baust JG, Gage AA, Robilottto AT, et al. The pathophysiology of thermoablation: optimizing cryoablation. Curr Opin Urol. 2009;19(2):127–32.
10. Baust JG, Gage AA, Clarke D, et al. Cryosurgery–a putative approach to molecular-based optimization. Cryobiology. 2004;48(2):190–204.
11. Johnston CM, Schoenfeld LP, Mysore JV, et al. Endoscopic spray cryotherapy: a new technique for mucosal ablation in the esophagus. Gastrointest Endosc. 1999;50(1):86–92.
12. Pasricha PJ, Hill S, Wadwa KS, et al. Endoscopic cryotherapy: experimental results and first clinical use. Gastrointest Endosc. 1999;49(5):627–31.
13. Friedland S, Triadafilopoulos G. A novel device for ablation of abnormal esophageal mucosa (with video). Gastrointest Endosc. 2011;74(1):182–8.
14. Greenwald BD, Dumot JA, Horwhat JD, et al. Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. Dis Esophagus. 2010;23(1):13–9.
15. Johnston MH, Eastone JA, Horwhat JD, et al. Cryoablation of Barrett's esophagus: a pilot study. Gastrointest Endosc. 2005;62(6):842–8.
16. Dumot JA, Vargo JJ 2nd, Falk GW, et al. An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. Gastrointest Endosc. 2009;70(4):635–44.
17. Shaheen NJ, Greenwald BD, Peery AF, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc. 2010;71(4):680–5.
18. Ghorbani S, Tsai FC, Greenwald BD, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's dysplasia: results of the National Cryospray Registry. Dis Esophagus. 2016;29(3):241–7.
19. Trindade AJ, Inamdar S, Kothari S, Berkowitz J, McKinley M, Kaul V. Feasibility of liquid nitrogen cryotherapy after failed radiofrequency ablation for Barrett's esophagus. Dig Endosc. 2017;29(6):680–5.
20. Trindade AJ, Pleskow DK, Sengupta N, Kothari S, Inamdar S, Joshua Berkowitz MD, Kaul V. Efficacy of liquid nitrogen cryotherapy for Barrett's esophagus after endoscopic resection of intramucosal cancer: a multicenter study. J Gastroenterol Hepatol. 2018;33(2):461–5.
21. Canto MI, Shin EJ, Khashab MA, et al. Safety and efficacy of carbon dioxide cryotherapy for treatment of neoplastic Barrett's esophagus. Endoscopy. 2015;47(7):591.

22. Canto M, Shin EJ, Khashab M, et al. Multifocal nitrous oxide cryoballoon ablation with or without endoscopic mucosal resection (EMR) for treatment of neoplastic Barrett's esophagus: preliminary results of a prospective clinical trial in treatment-naive and previously ablated patients. Gastrointest Endosc. 2016;83(55):AB159.
23. Kunzli HT, Scholvinck DW, Meijer SL, et al. Efficacy of the cryoballoon focal ablation system for the eradication of dysplastic Barrett's esophagus islands. Endoscopy. 2017;49(2):169–75.
24. Scholvinck DW, Kunzli HT, Kestens C, et al. Treatment of Barrett's esophagus with a novel focal cryoablation device: a safety and feasibility study. Endoscopy. 2015;47(12):1106–12.
25. Ramay FH, Cui Q, Greenwald BD. Outcomes after liquid nitrogen spray cryotherapy in Barrett's esophagus associated high-grade dysplasia and intramucosal adenocarcinoma: 5-year follow-up. Gastrointest Endosc. 2017;86(4):626–32.
26. Gosain S, Mercer K, Twaddell WS, et al. Liquid nitrogen spray cryotherapy in Barrett's esophagus with high-grade dysplasia: long-term results. Gastrointest Endosc. 2013;78(2):260–5.
27. Barthel JS, Kucera S, Harris C, et al. Cryoablation of persistent Barrett's epithelium after definitive chemoradiation therapy for esophageal adenocarcinoma. Gastrointest Endosc. 2011;74(1):51–7.
28. Sengupta N, Ketwaroo GA, Bak DM, Kedar V, Chuttani R, Berzin TM, et al. Salvage cryotherapy after failed radiofrequency ablation for Barrett's esophagus-related dysplasia is safe and effective. Gastrointest Endosc. 2015;82(3):443–8.
29. Hamade N, Sharma P. Ablation therapy for Barrett's esophagus: new rules for changing times. Curr Gastroenterol Rep. 2017;19:48.
30. Das KK, Falk GW. Long-term outcomes for cryotherapy in Barrett's esophagus with high-grade dysplasia: just cracking the ice. Gastrointest Endosc. 2017;86(4):633–5.
31. Canto MI. Cryotherapy for Barrett's esophagus. Gastrointest Endosc Clin N Am. 2017;27:503–13.

Endoscopic Resections: EMR and ESD

15

Seiichiro Abe, Filippo Catalano, and Yutaka Saito

15.1 Introduction

Historically, radical esophagectomy was the standard of care for the management of esophageal cancer including high-grade dysplasia (HGD) and early esophageal adenocarcinoma (EAC) associated with Barrett's esophagus. However, esophageal surgery is associated with major morbidity and high mortality rates [1–4]. Endotherapy is minimally invasive treatment option for early gastrointestinal cancer including Barrett's adenocarcinoma, which allows for curative resection for the lesion without risk of lymph node metastasis while preserving organ function. Endoscopic resection emerged as a less invasive alternative for treatment of superficial esophageal cancer and is currently the gold standard. Endotherapy for Barrett's adenocarcinoma is generally divided into endoscopic resection and ablation by the use of thermal therapy or cryogens. Particularly, the former allows for removal of visible lesions, which serves to provide accurate histologic staging (distinguishing dysplasia and mucosal adenocarcinoma from submucosal adenocarcinoma) and determine subsequent management of the patient. This chapter presents an overview of indication, technique, and treatment outcomes of endoscopic resection for esophageal dysplasia and adenocarcinoma associated with Barrett's esophagus.

S. Abe · Y. Saito (✉)
Digestive Endoscopy Unit, Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan
e-mail: seabe@ncc.go.jp; ytsaito@ncc.go.jp

F. Catalano
Emergency Surgical Endoscopy Unit, Piastra Endoscopica, Polo Confortini, Ospedale Borgo Trento, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy
e-mail: filippo.catalano@aovr.veneto.it

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_15

15.2 Criteria for Curative Endoscopic Resection

Curability of endoscopic resection is generally determined by completeness of the primary tumor removal and nil possibility of lymph node metastasis. The endoscopically resected specimen allows for optimal histological staging including the depth of invasion, which provides further strategy for patients.

A recent systematic review by Dunber et al. revealed that no metastases were found in 524 patients with HGD, whereas 26 of the 1350 patients with intramucosal carcinoma had positive lymph nodes (1.93%, 95% CI 1.19–2.66%) [5]. Manner et al. retrospectively analyzed 72 patients who had a proven maximum invasion depth of SM1 (<500 μm) [6]. The rate of lymph node metastasis was 2% (1/49) in the low-risk group (well- or moderately differentiated tumor grade and absence of tumor invasion into lymphatics or blood vessels) and 9% (2/23) in the high-risk group (other than low-risk group). Although the treatment strategy for patients with a T1b is controversial, endoscopic resection might be considered for the low-risk group because risk of lymph node metastasis could be lower than the mortality rate of esophagectomy.

Given the evidence, American College of Gastroenterology (ACG) clinical guidelines stated as follows: (1) Endoscopic therapy is the preferred therapeutic approach, being both effective and well tolerated in patients with T1a esophageal adenocarcinoma. (2) Endoscopic therapy may be an alternative strategy to esophagectomy, especially in those with SM1 with low risk of metastasis although consultation with multidisciplinary surgical oncology team should occur before embarking on endoscopic therapy [7]. Similarly, ESGE position statement determined that the optimal treatment strategy in patients with T1b EAC depended on histopathological characteristics of the endoscopic resection specimen, and endoscopic resection might be a valid alternative to surgery and was recommended in patients who were borderline fit for surgery, if the endoscopic resection specimen met all of aforementioned criteria [8]. However, experience in Europe is limited above all in relation to the not yet completely appropriate preparation of endoscopist and pathologists who deal with this topic. Recently, a multicenter retrospective study from Japan demonstrated that no metastasis was detected in patients who had lesions without lymphovascular involvement, a poorly differentiated component with invasion into the deep muscularis mucosa (0/88) and superficial submucosa (≤500 μm) 30 mm or less in size (0/32) [9].

In summary, additional surgery can be avoided if the resected specimen showed HGD, T1a EAC, or selected T1b EAC (well- or moderately differentiated EAC, SM1 (<500 μm) in depth without lymph node metastasis or positive deep margin, strictly ≤30 mm in size). Additional surgery should be considered given the risk of lymph node metastasis if the histology doesn't meet the criteria.

15.3 Preoperative Diagnosis for Endoscopic Resection

In general, endoscopic resection is local treatment and thus indicated for the gastrointestinal cancer which has negligible risk of lymph node metastasis. In addition, minimal risk of lymph node metastasis for endoscopic resection is acceptable if the

mortality of surgery exceeds its risk. Thus, careful patient selection by accurate staging is essential to embark on curative endoscopic therapy. Preoperative endoscopic staging for gastrointestinal neoplasms is commonly performed based on careful inspection of the target lesion, histological diagnosis with forceps biopsy, and the depth diagnosis using conventional endoscopy and endoscopic ultrasound (EUS).

In terms of endoscopic appearance, Oda et al. found that mucosal esophagogastric junction adenocarcinoma was significantly smaller than submucosal invasive lesions. Non-polypoid type without mixed type (0-IIa, 0-IIb, or 0-IIc) lesions had a significantly lower risk for SM invasion compared to polypoid type (0-I) and mixed type (0-IIa + IIc or 0-IIc + IIa) lesions. In the polypoid type lesions, the risk for SM invasion was significantly lower for the pedunculated subtype (0-Ip) than for the sessile subtype (0-Is) lesions. Although this study included non-Barrett adenocarcinoma and didn't subclassify SM1 and SM2 in depth, this simple determination of endoscopic macroscopic type may be useful in depth diagnosis [10].

Preoperative both random/targeted biopsy and endoscopic ultrasound (EUS) are performed in addition to endoscopic assessment of the target lesion. In the West, a recently published meta-analysis reported that EUS detected advanced disease in only a minority of patients with HGD or early EAC and therefore was considered of limited utility [11]. In addition, endoscopic forceps biopsy correlated with EMR findings in only 50% of patients [12]. Thus, the Western guidelines recommend that irrespective of the endoscopic forceps biopsy results, all visible lesions associated with Barrett's esophagus should be removed by means of endoscopic resection techniques, generally EMR in order to obtain optimal histopathological staging [7, 8, 12].

15.4 Endoscopic Mucosal Resection (EMR)

EMR is currently the most commonly available treatment of BE associated neoplasia particularly in the West, because of technically easy and simple procedure. The principle of technique is mainly based on the creation of a "cushion" by submucosal injection of a saline solution or other materials which allow the detachment of neoplastic lesion from muscularis propria. Following technique is snare application for the flat target in the BE with use of some devices.

EMR is performed in order to remove visible early neoplastic lesion in Barrett's Esophagus as possible alternative to surgery with a low related procedure morbidity (0–14% risk of bleeding and 1.8% perforation risk with no death) [13–15]. In addition, EMR plays an important role of precise histological assessment, because it can change diagnosis in approximately 30% of BE in comparison with pre EMR biopsy [16].

Two main technique for carrying out EMR are present in literature reports: cap assisted mucosectomy (EMR-C) and multiband mucosectomy (MBM) (Fig. 15.1). A randomized controlled trial comparing between EMR-C and MBM demonstrated that the cap technique with submucosa injection and the ligation technique without submucosa injection were similar with respect to efficacy and safety for endoscopic resection of early stage esophageal adenocarcinoma [14].

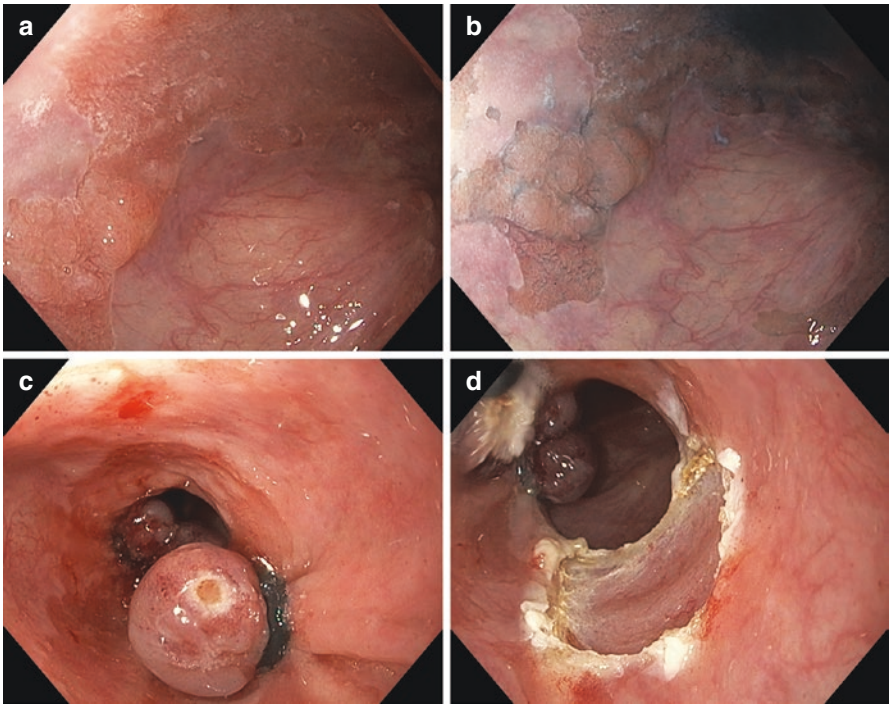

Fig. 15.1 A band-assisted EMR. (**a**) White light endoscopy demonstrated a flat elevated lesion on the left side of long-segment Barrett's esophagus. (**b**) Chromoendoscopy with indigo carmine spraying visualized the margin of the lesion. (**c**) A band was ligated around the lesion following suction. (**d**) The resected specimen histologically revealed high-grade dysplasia, 5 mm in size

It is considered safe and effective with complete remission in 98% of patients after 40 months of follow-up [17]. However, EMR can only achieve en bloc resection of lesions smaller than 15–20 mm due to the limited size of snare, and one of the risk factors most frequently associated with recurrence is piecemeal resection [18]. However, ablation therapy is generally scheduled for the background BE in order to treat the residual tumor and intestinal metaplasia. Actually it seems EMR for any visible lesions plus eradication of residual metaplastic mucosa is safe and efficacious so the need for esophagectomy has been eliminated for high-grade dysplasia and greatly reduced for mucosal cancer [19].

15.5 Endoscopic Submucosal Dissection (ESD)

Endoscopic submucosal dissection can provide en bloc resection and thus a more complete understanding of the lateral margins of a lesion regardless of the size and location of gastrointestinal cancer. This technique was firstly introduced in early gastric cancer and then applied to colorectal cancer and esophageal squamous cell

carcinoma [20–22]. Esophageal ESD is technically challenging due to the following reasons: (1) The narrow lumen of the esophagus makes gravity counter traction less effective. (2) The resected specimen retracts distally making it difficult to maintain good traction and orientation. (3) The thin wall of the esophagus increases the risk of perforation. Some items mentioned below should be used for safe procedure.

15.5.1 Items for Safe and Effective Esophageal ESD

First, distal endocap is essential to stabilize the operation field against respiratory movements; it helps us to access the submucosal plane facilitating the submucosal dissection.

Second, high viscous injection solution is strongly recommended to safe and efficient ESD because esophageal wall is very thin compared with that of stomach. In Asia, sodium hyaluronate 0.4% (MucoUp; Boston scientific, Tokyo, Japan) is widely used, with the disadvantage of being expensive [23]. Glycerol (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) has also been used in Japan, with the advantages of being inexpensive and producing a long-lasting lift [24]. In the West, hydroxyethyl starch (Voluven, Fresenius/Hospira, Germany) and 0.4% hydroxypropyl methylcellulose has been typically used [25, 26]. Recently, a polymer- and methylene blue-containing solution (Eleview™, Cosmo Technologies Ltd., Dublin, Ireland) was approved by the Food and Drug Administration (FDA) for submucosal lift of lesions in the upper and lower gastrointestinal tract. A blinded randomized controlled trial in an ex-vivo porcine model comparing different submucosal injection solutions demonstrated the superior long-lasting lifting effect of Eleview and Volven to the submucosal injection fluids available in the West [27].

Third, CO_2 insufflation can be rapidly absorbed allowing for the reduction of patient's abdominal fullness and pain in addition to minimal air leak in case of perforation [28]. Moreover, monitored anesthesia care and deep sedation is preferred for esophageal ESD [29]. General anesthesia can be considered for less-experienced endoscopists, because of the long procedure times, and the risk of aspiration of secretions or blood. In addition, positive pressure of mediastinum in general anesthesia can help minimize air leak in case of perforation.

15.5.2 Technical Tips and Tricks of ESD of Visible Lesions Associated with Barrett's Esophagus (Fig. 15.2)

The following technical tips and tricks are recommended to perform the advanced procedure safely.

(a) *Marking*
Appropriate identification, mapping, and demarcation of the lesion is mandatory before starting ESD. Circumferential marking should be carefully performed. The tip of a needle-type or argon plasma coagulation can be used to

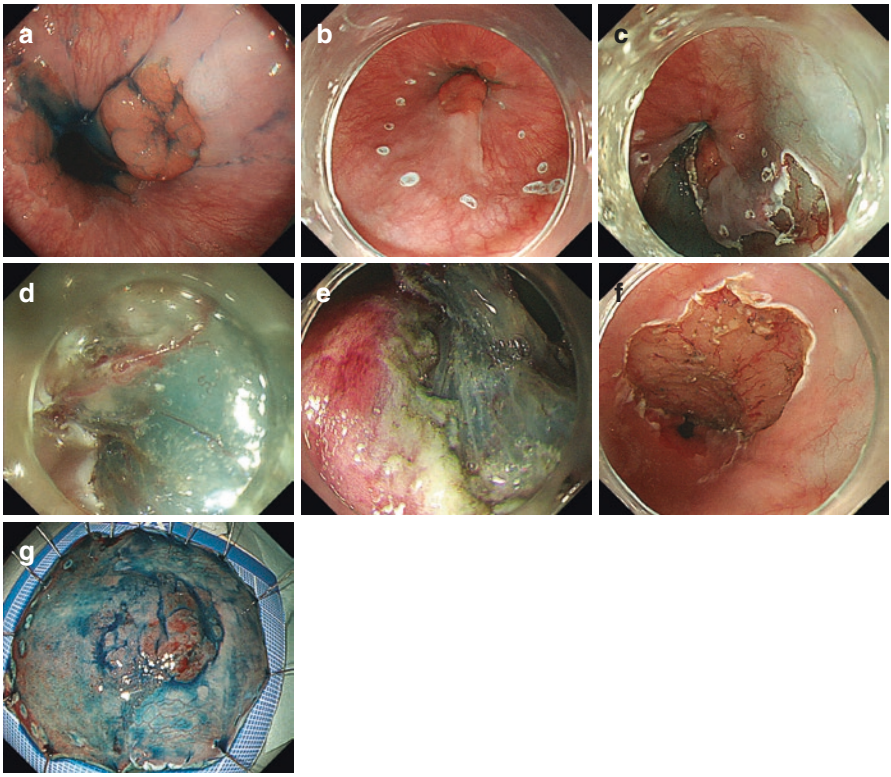

Fig. 15.2 A standard ESD of Barrett's adenocarcinoma. (**a**) Flat elevated lesion was seen on the right side of esophagogastric junction. (**b**) Marking. (**c**) Partial mucosal incision of the left side. (**d**) Identification of submucosal plane to dissect with the use of endocap. (**e**) Submucosal dissection by retroflexed approach. (**f**) Mucosal defect after ESD. (**g**) The resected specimen histologically revealed well-differentiated tubular adenocarcinoma, 16 mm, T1a-LPM, ly(−), v(−), pHM0, pVM0

sharply and clearly mark at 3–5 mm from the edge of the lesion. Soft coagulation mode (effect 5, 80 W in VIO 300D (ERBE Tuebingen, Germany) or 50 W in ESG100 (Olympus)) or forced APC mode (effect 3, 30 W) is recommended to avoid perforation of the thin wall of the esophagus (Fig. 15.2a, b).

(b) *Submucosal Injection*
As mentioned, high viscous injection solution allows for safe and efficient ESD. These lifting solutions can be easily injected to muscle layer when injected deeply, it is essential to make sure good submucosal elevation by normal saline prior to the high viscous solutions.

(c) *Mucosal incision*
In esophageal ESD, partial circumferential incision is preferred to prevent the escape of fluid from the submucosal layer. Additionally, it is very important to firstly incise muscularis mucosa to expose the lucent submucosal plane following enough submucosal lifting (Fig. 15.2c). Suction of the air makes submucosal cushion thicker and helps perform safe and effective mucosal incision.

The oral and anal incisions are made first. A retrograde approach is often required for part of the resection when the lesion is located on or near the EGJ (Fig. 15.2e). Mucosal incision along the left lateral border mucosal lesion is then performed allowing the lesion to retract away from the water pool on the gravity dependent side. Circumferential incision of the right lateral wall is then completed when approximately three-fourths of the lesion had been dissected.

(d) *Submucosal dissection*
After enough exposure of the submucosal layer of the proximal side, the lesion is then lifted with injection of a lifting solution. The submucosa can be dissected with a needle-type device or IT knife nano (KD-612 L/U; Olympus) by hooking and cutting the submucosa. It is important to enter the submucosa with the use of the tip of endocap for direct visualization of submucosa, allowing for safe submucosal dissection avoiding perforation. Similarly to mucosal incision, submucosal dissection should be started from the left side allowing the lesion to retract away from the water pool on the gravity dependent side when performed in left lateral position (Fig. 15.2d).

15.5.3 Current Technical Innovation of ESD

In esophageal ESD, it is generally difficult to keep good tissue traction during the procedure, particularly for the distal side in a large lesion. Recently clip line traction method is commonly used for submucosal dissection in ESD of esophageal squamous cell carcinoma [30]. A catheter was inserted through an accessory channel of the endoscope, with an endoclip attached to the catheter. The loaded clip was left half-open. A length of commercial line was tied directly to the arm of the endoclip. Subsequently, the endoclip with line was placed in the accessory channel to enable reinsertion of the endoscope into the stomach, followed by re-exposure of the endoclip and anchoring to backside of the proximal side of the mucosal flap for per-oral traction (Fig. 15.3g). It allows for improved exposure of submucosa allowing easier identification of the edges of exposed submucosa to direct dissection (Fig. 15.3h). One prospective study showed clip line traction contributed to significantly shorten the procedure time in ESD of esophageal squamous cell carcinoma [31].

In addition, submucosal tunneling method is proposed to keep nice visualization of submucosal layer and submucosal fluid cushion. This technique allows for safe ESD procedure shortening time [32]. It can be performed with use of IT knife nano device even for large esophageal Barrett's adenocarcinoma involving complete luminal circumference (Fig. 15.3e). Although these techniques were originally developed in ESD of esophageal squamous cell carcinoma, both are applicable for ESD of Barrett's adenocarcinoma.

15.5.4 Short- and Long-Term Outcomes of ESD

Although most of the paper regarding ESD in Barrett's adenocarcinoma and HGD consisted of small case series reporting single center experience, a recent

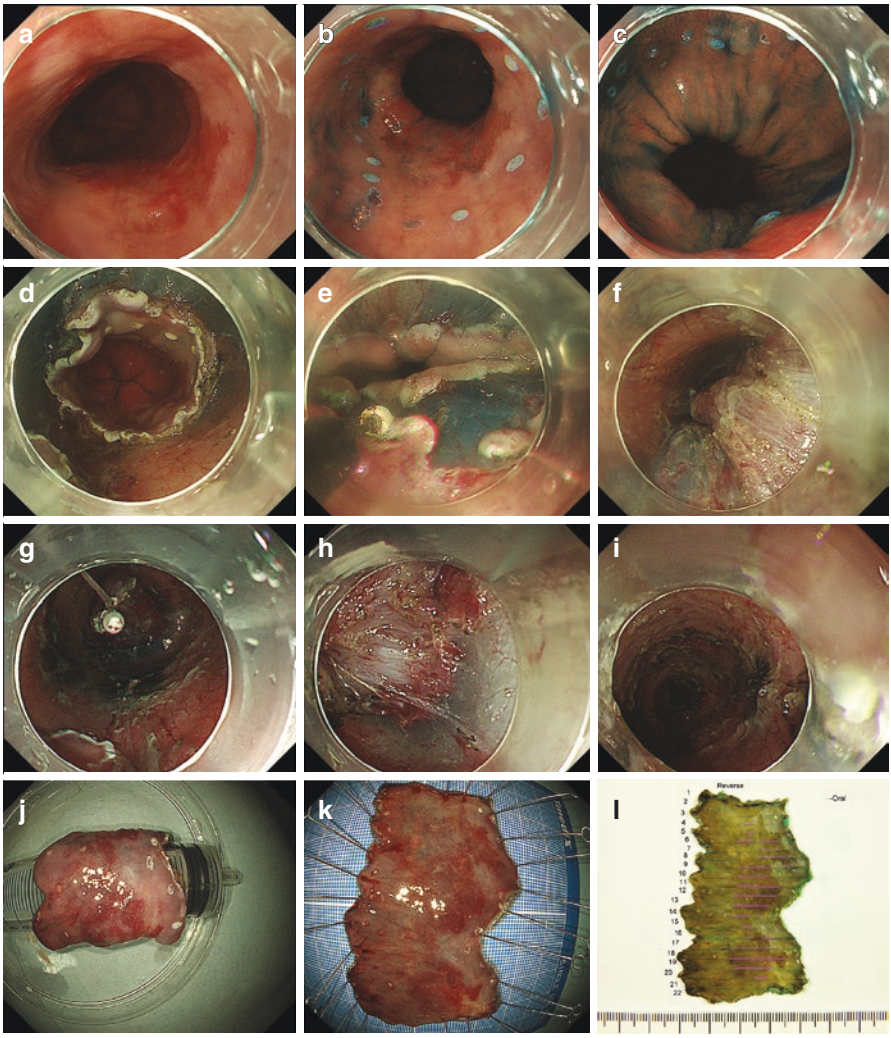

Fig. 15.3 An extensive ESD with the use of innovative techniques. (**a**) Large flat elevated lesion involving almost complete luminal circumference. (**b**) Marking of the proximal side. (**c**) Marking of the distal side. (**d**) Circumferential mucosal incision of the proximal side. (**e**) Circumferential mucosal incision of the distal side. (**f**) Tunneling dissection of the left side. (**g**) Clip line traction technique. (**h**) Well-visualized submucosa with tissue retraction by clip-line traction. (**i**) Mucosal defect after complete Barrett excision. (**j**) A syringe shaped specimen. (**k**) The opened specimen (**l**) The resected specimen histologically revealed moderately to well-differentiated tubular adenocarcinoma, 52 mm, T1a-MM, ly(−), v(−), pHM0, pVM0

meta-analysis evaluated the safety and efficacy of ESD in the treatment of early BE neoplasia [33]. It included 11 studies, of which 10 were cohort studies and 1 was a randomized controlled trial. Seven studies were from Europe, three from Asia, and one from the United States. Mean lesion size was 27 mm (20.9–33.1) and average

procedure time was 107.5 min (86.4–128.5). The pooled en bloc resection rate was 92.9% (95%CI, 90.3–95.2%), while the R0 and curative resection rates were 74.5% (95%CI, 66.3–81.9%) and 64.9% (95%CI, 55.7–73.6%), respectively. This meta-analysis reported highly favorable outcomes and safety profiles, comparable to those in gastric and colorectal ESD. Interestingly, this study found significant heterogeneity in R0 and curative resection rates [33]. Variation has been attributed to whether both HGD and Barrett's adenocarcinoma were included, differences including lesion location and length of Barrett's esophagus between the East and West, or infiltrated lateral margins that were not evident before endoscopic resection.

Two recent multicenter analyses demonstrated the efficacy and safety of ESD in the West for resection of BE associated HGD and EAC. The multicenter retrospective analysis from five academic tertiary referral centers in the United States reported en bloc and curative resection rates of 96% and 70%, respectively. Post-ESD bleeding was noted in 6% of the patients, perforation in 2.1%, and esophageal strictures in 15% [34]. The European multicenter study which included large (≥2 cm), nodular or fibrotic lesions similarly revealed the en bloc resection rate of 90.8% and curative resection rate of 65.8%. The learning curve portraying en bloc resection revealed that it plateaued after 30 procedures. Post-ESD was 1.4%, perforation 0%, and stricture 2.1% [35]. These findings highlight the potential role of ESD for the assessment and management of neoplastic lesions associated with Barrett's esophagus, and provide reassurance on the safety of ESD when performed by experts in high-volume centers.

15.6 Comparison Between EMR and ESD

In recent years also thanks to the use of ESD, some works have appeared in the literature that demonstrate the superiority of this technique compared to the traditional EMR in terms of en bloc resection and reducing the risk of local recurrence [36]. Indeed, a randomized controlled trial by Terheggen et al. demonstrated that R0 resection was achieved more frequently with ESD (59% vs 12%) [37]. However, this study didn't show any clinical advantage of ESD over EMR in terms of need for surgery, neoplasia remission or recurrence. Thus, although a compelling argument can be made regarding the theoretical advantages of en bloc resection made possible by ESD, this has not translated into clinically meaningful benefits to date. However, this RCT had short follow-up period and it is still unclear if the higher R0 resection rates achieved by ESD might translate into lower rates of neoplasia recurrence over longer periods of time. Therefore, further prospective studies with longer follow-up periods are warranted to conclude the clinical questions.

Conclusions

EMR is currently the most commonly available treatment of BE associated neoplasia because of technically easy and simple procedure. Although en bloc

resection rate and R0 resection rate were inferior to that of ESD, the following ablation therapy is generally scheduled for the remaining Barrett's esophagus in order to achieve complete eradication of intestinal metaplasia. This multimodality strategy is applied in the Western country where the neoplasia is mainly seen in the long-segment Barrett esophagus.

On the other hand, ESD allows for higher en bloc resection rate compared with that of EMR and it is widely spread in the East. Although there are still some clinical issues such as technical difficulty, long-time procedure, and financial reimbursement, it has been gradually accepted in the West. If patients have short-segment, non-circumferential areas of BE-related neoplasia, ESD will provide better clinical outcomes.

It is essential to understand the differences in endoscopic treatment strategies in the East and the West, and the method of endoscopic resection should be determined considering the length of Barrett esophagus, lesion location, availability of subsequent ablation therapy, and the skill and experience of ESD.

References

1. Seder CW, Raymond DP, Wright CD, Gaissert HA, Chang AC, Clinton S, et al. The Society of Thoracic Surgeons General Thoracic Surgery Database 2017 Update on Outcomes and Quality. Ann Thorac Surg. 2017;103(5):1378–83.
2. Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two thousand transhiatal esophagectomies: changing trends, lessons learned. Ann Surg. 2007;246(3):363–72; discussion 72–4.
3. McCulloch P, Ward J, Tekkis PP, ASCOT group of surgeons, British Oesophago-Gastric Cancer Group. Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. BMJ. 2003;327(7425):1192–7.
4. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349(22):2117–27.
5. Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. Am J Gastroenterol. 2012;107(6):850–62; quiz 63.
6. Manner H, Pech O, Heldmann Y, May A, Pohl J, Behrens A, et al. Efficacy, safety, and long-term results of endoscopic treatment for early stage adenocarcinoma of the esophagus with low-risk sm1 invasion. Clin Gastroenterol Hepatol. 2013;11(6):630–5; quiz e45
7. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG Clinical Guideline: diagnosis and management of Barrett's Esophagus. Am J Gastroenterol. 2016;111(1):30–50; quiz 1.
8. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau JM, Esteban JM, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017;49(2):191–8.
9. Ishihara R, Oyama T, Abe S, Takahashi H, Ono H, Fujisaki J, et al. Risk of metastasis in adenocarcinoma of the esophagus: a multicenter retrospective study in a Japanese population. J Gastroenterol. 2016;52(7):800–8.
10. Oda I, Abe S, Kusano C, Suzuki H, Nonaka S, Yoshinaga S, et al. Correlation between endoscopic macroscopic type and invasion depth for early esophagogastric junction adenocarcinomas. Gastric Cancer. 2011;14(1):22–7.
11. Qumseya BJ, Brown J, Abraham M, White D, Wolfsen H, Gupta N, et al. Diagnostic performance of EUS in predicting advanced cancer among patients with Barrett's esophagus and

high-grade dysplasia/early adenocarcinoma: systematic review and meta-analysis. Gastrointest Endosc. 2015;81(4):865–74. e2
12. Thota PN, Sada A, Sanaka MR, Jang S, Lopez R, Goldblum JR, et al. Correlation between endoscopic forceps biopsies and endoscopic mucosal resection with endoscopic ultrasound in patients with Barrett's esophagus with high-grade dysplasia and early cancer. Surg Endosc. 2017;31(3):1336–41.
13. Ell C, May A, Gossner L, Pech O, Gunter E, Mayer G, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology. 2000;118(4):670–7.
14. May A, Gossner L, Behrens A, Kohnen R, Vieth M, Stolte M, et al. A prospective randomized trial of two different endoscopic resection techniques for early stage cancer of the esophagus. Gastrointest Endosc. 2003;58(2):167–75.
15. Nijhawan PK, Wang KK. Endoscopic mucosal resection for lesions with endoscopic features suggestive of malignancy and high-grade dysplasia within Barrett's esophagus. Gastrointest Endosc. 2000;52(3):328–32.
16. Wani S, Abrams J, Edmundowicz SA, Gaddam S, Hovis CE, Green D, et al. Endoscopic mucosal resection results in change of histologic diagnosis in Barrett's esophagus patients with visible and flat neoplasia: a multicenter cohort study. Dig Dis Sci. 2013;58(6):1703–9.
17. Bahin FF, Jayanna M, Hourigan LF, Lord RV, Whiteman D, Williams SJ, et al. Long-term outcomes of a primary complete endoscopic resection strategy for short-segment Barrett's esophagus with high-grade dysplasia and/or early esophageal adenocarcinoma. Gastrointest Endosc. 2016;83(1):68–77.
18. Pech O, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut. 2008;57(9):1200–6.
19. Lada MJ, Watson TJ, Shakoor A, Nieman DR, Han M, Tschoner A, et al. Eliminating a need for esophagectomy: endoscopic treatment of Barrett esophagus with early esophageal neoplasia. Semin Thorac Cardiovasc Surg. 2014;26(4):274–84.
20. Gotoda T. Endoscopic resection of early gastric cancer. Gastric Cancer. 2007;10:1):1–11.
21. Saito Y, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, et al. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc. 2010;72(6):1217–25.
22. Oyama T, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, et al. Endoscopic submucosal dissection of early esophageal cancer. Clin Gastroenterol Hepatol. 2005;7 Suppl 1:S67–70.
23. Yamamoto H, Yahagi N, Oyama T, Gotoda T, Doi T, Hirasaki S, et al. Usefulness and safety of 0.4% sodium hyaluronate solution as a submucosal fluid "cushion" in endoscopic resection for gastric neoplasms: a prospective multicenter trial. Gastrointest Endosc. 2008;67(6):830–9.
24. Uraoka T, Saito Y, Yamamoto K, Fujii T. Submucosal injection solution for gastrointestinal tract endoscopic mucosal resection and endoscopic submucosal dissection. Drug Des Devel Ther. 2009;2:131–8.
25. Draganov PV, Gotoda T, Chavalitdhamrong D, Wallace MB. Techniques of endoscopic submucosal dissection: application for the Western endoscopist? Gastrointest Endosc. 2013;78(5):677–88.
26. Arantes V, Albuquerque W, Benfica E, Duarte DL, Lima D, Vilela S, et al. Submucosal injection of 0.4% hydroxypropyl methylcellulose facilitates endoscopic mucosal resection of early gastrointestinal tumors. J Clin Gastroenterol. 2010;44(9):615–9.
27. Mehta N, Strong AT, Franco M, Stevens T, Chahal P, Jang S, et al. Optimal injection solution for endoscopic submucosal dissection: a randomized controlled trial of Western solutions in a porcine model. Dig Endosc. 2017;30(3):347–53.
28. Nonaka S, Saito Y, Takisawa H, Kim Y, Kikuchi T, Oda I. Safety of carbon dioxide insufflation for upper gastrointestinal tract endoscopic treatment of patients under deep sedation. Surg Endosc. 2010;24(7):1638–45.

29. Nonaka S, Kawaguchi Y, Oda I, Nakamura J, Sato C, Kinjo Y, et al. Safety and effectiveness of propofol-based monitored anesthesia care without intubation during endoscopic submucosal dissection for early gastric and esophageal cancers. Dig Endosc. 2015;27(6):665–73.
30. Oyama T. Counter traction makes endoscopic submucosal dissection easier. Clin Endosc. 2012;45(4):375–8.
31. Koike Y, Hirasawa D, Fujita N, Maeda Y, Ohira T, Harada Y, et al. Usefulness of the thread-traction method in esophageal endoscopic submucosal dissection: randomized controlled trial. Dig Endosc. 2015;27(3):303–9.
32. Huang R, Cai H, Zhao X, Lu X, Liu M, Lv W, et al. Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal squamous cell carcinoma: a propensity score matching analysis. Gastrointest Endosc. 2017;86(5):831–8.
33. Yang D, Zou F, Xiong S, Forde JJ, Wang Y, Draganov PV. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. Gastrointest Endosc. 2017;87(6):1383–93.
34. Yang D, Coman RM, Kahaleh M, Waxman I, Wang AY, Sethi A, et al. Endoscopic submucosal dissection for Barrett's early neoplasia: a multicenter study in the United States. Gastrointest Endosc. 2017;86(4):600–7.
35. Subramaniam S, Chedgy F, Longcroft-Wheaton G, Kandiah K, Maselli R, Seewald S, et al. Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Gastrointest Endosc. 2017;86(4):608–18.
36. Guo HM, Zhang XQ, Chen M, Huang SL, Zou XP. Endoscopic submucosal dissection vs endoscopic mucosal resection for superficial esophageal cancer. World J Gastroenterol. 2014;20(18):5540–7.
37. Terheggen G, Horn EM, Vieth M, Gabbert H, Enderle M, Neugebauer A, et al. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. Gut. 2017;66(5):783–93.

Radiofrequency Ablation of Barrett's Esophagus

16

Jason Samarasena, David Lee, and Kenneth J. Chang

16.1 Introduction

In the modern era, radiofrequency ablation (RFA) of Barrett's esophagus (BE) has become a widespread and, in many cases, preferred modality for ablative treatment of Barrett's esophagus. Its advantages in terms of ease of use and proven efficacy for ablation of BE tissue have contributed to its general acceptance among gastroenterologists.

Prior to the advent of RFA, various ablative modalities had been explored for the treatment of BE, including multipolar electrocoagulation (MPEC), laser photoablation, and argon plasma coagulation (APC). Such modalities had significant shortcomings, primarily related to the operator-dependent nature of the procedure, leading to uneven treatment, especially over long-segment BE. This would result in suboptimal ablation of some areas and overtreatment of other areas, potentially risking complications of deep tissue injury, such as perforation or stricture.

Ganz et al. [1] first described success in ablation of porcine esophageal epithelium using a balloon-based bipolar radiofrequency (RF) electrode. It was found during this study that radiofrequency electrodes could effectively ablate porcine esophageal epithelium to the level of the muscularis mucosa without injury to the submucosal layer, provided there was close control of the energy density delivered to the tissue. Interestingly, it was found during this trial that the depth of ablation achieved seemed to be linearly related to the energy density delivered, and did not correspond to the power delivered.

In an early human trial [2], 13 patients with esophageal adenocarcinoma scheduled for esophagectomy had RFA performed on non-tumor-bearing esophageal epithelium just prior to surgical esophagectomy. This trial demonstrated that complete

J. Samarasena · D. Lee · K. J. Chang (✉)
Division of Gastroenterology and Hepatology, H. H. Chao Comprehensive Digestive Disease Center, University of California, Irvine Medical Center, Orange, CA, USA
e-mail: kchang@uci.edu

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_16

epithelial removal without submucosal injury could be achieved with two ablations at 10 J/cm^2, or with one or two ablations at 12 J/cm^2. Ablations at 8 J/cm^2, either one or two sessions, or one ablation session at 10 J/cm^2 was found to only partially ablate the epithelium.

Given such promising preliminary results, the pivotal AIM trial was conducted and what followed was a vast number of high quality randomized clinical trials producing a supportive body of literature that is unrivaled by any endoscopic device today.

16.2 Indications

Current guidelines [3, 4] regarding the management of BE recommend complete ablation whenever dysplasia is detected within a Barrett's segment. In cases of high-grade dysplasia (HGD) or endoscopically resectable esophageal adenocarcinoma (EAC), endoscopic resection may be carried out first, such as via endoscopic mucosal resection (EMR) technique, followed by ablation in separate staged sessions. In cases of confirmed low-grade dysplasia (LGD), RFA of BE has been demonstrated [5] to reduce progression to HGD and EAC, and has become the recommended ablative strategy [3].

16.3 Equipment

Currently, the most widely used system for radiofrequency ablation of BE is the Barrx system (Medtronic, Minneapolis, MN). This system consists of a high-power radiofrequency (RF) energy generator, a selection of balloon catheters for circumferential ablation, and a series of focal catheters for segmental ablation.

The energy generator (Fig. 16.1) is a bipolar radiofrequency energy generator that is capable of automated, pressure-regulated air inflation of the catheters, followed by rapid delivery of a set RF energy density (J/cm^2) at a set power level to the ablation catheter electrode. Its current iteration is able to adjust to both circumferential and focal catheters, changing the default settings to match the catheter, and is able to recommend ablation catheter sizing and track the number of ablations performed.

The original Barrx 360 ablation catheters (Fig. 16.2) consisted of a series of single-use ablation balloon catheters. The balloon catheters' diameters came in five sizes: 18, 22, 25, 28, and 31 mm. The ablation electrode arrays were 3 cm in length, and consisted of a series of electrodes arranged circumferentially in a series of 60 rings around the balloon, alternating in polarity. The catheter itself was 165 cm in length and 7 mm in diameter.

The appropriate size of catheter was selected by first using a soft sizing balloon (Fig. 16.3), which the RF generator inflates to a set pressure. The average inner diameter of the esophagus measured across the length of the sizing balloon was then displayed on the RF generator.

Fig. 16.1 The Barrx Flex RFA energy generator

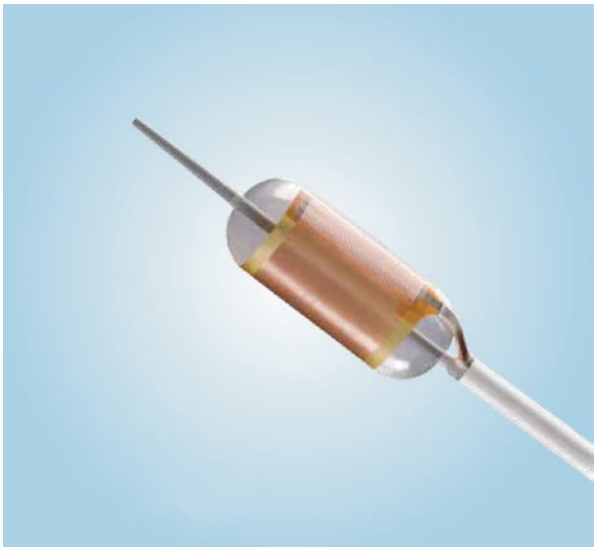

Fig. 16.2 Barrx 360 ablation catheter

Fig. 16.3 Barrx 360 soft sizing balloon

More recently, the Barrx 360 Express balloon catheter has been released. This is an automated sizing balloon that self-adjusts to the appropriate inner diameter of the esophagus, thereby eliminating the need for the sizing balloon. The Express balloon can self-adjust to a diameter between 18 and 31 mm, and has an electrode length of 4 cm (Fig. 16.4).

For the treatment of any residual focal areas of BE, a variety of focal ablation catheters are available, including the Barrx 90 (Fig. 16.5), Barrx 60 (Fig. 16.6), Barrx Ultra-Long (Fig. 16.7), and Barrx Channel RFA endoscopic catheter (Fig. 16.8). The first three focal ablation catheters all attach to the distal tip of a flexible endoscope. They have an articulating hinge that allows for side-to-side and front-to-back movement for better positioning. The Barrx Channel RFA catheter is a through-the-scope device that can be passed through the working channel of an endoscope, and has flexible ablation electrode "wings" which can unfurl once it has exited the channel.

Fig. 16.4 Barrx 360 Express RFA balloon catheter

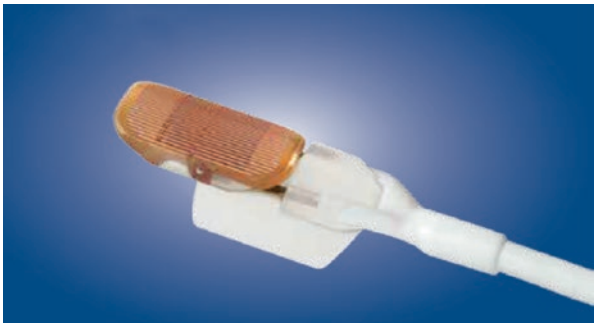

Fig. 16.5 Barrx 90 RFA focal ablation catheter

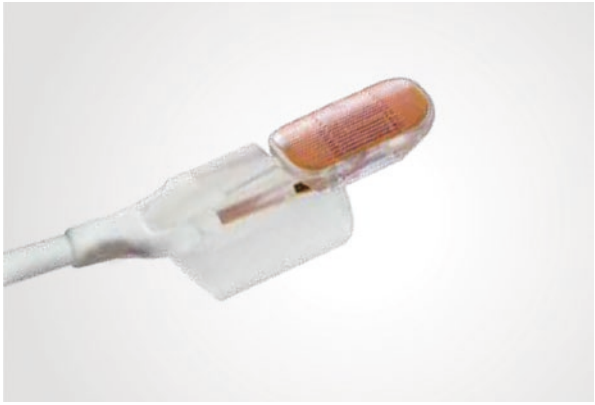

Fig. 16.6 Barrx 60 RFA focal ablation catheter

Fig. 16.7 Barrx Ultra-Long RFA focal ablation catheter

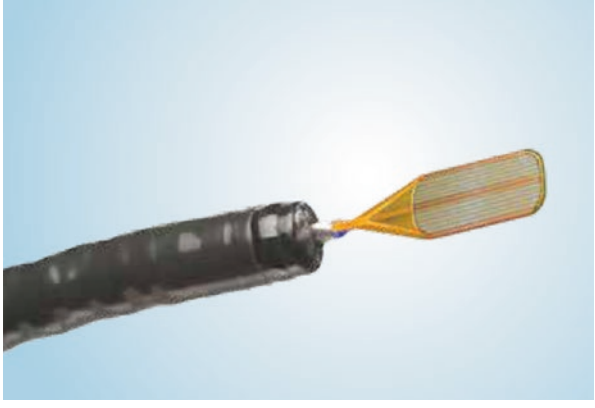

Fig. 16.8 Barrx Channel RFA endoscopic ablation catheter

16.4 Technique

The procedure of RFA ablation starts with a diagnostic esophagogastroduodenoscopy (EGD) procedure, with careful examination of the segment of BE to assess whether there are any interval changes, especially in the form of nodularity or other mucosal irregularity to suggest a new focus of HGD or EAC. Assuming no such lesions are found, the location of landmarks are then noted, including the location of the top of gastric folds, the location of the furthest circumferential extent of Barrett's, and the length of any mucosal "tongues" of Barrett's that may extend beyond the circumferential BE segment.

At this point, the esophageal mucosa is lavaged to clear the mucosa of any excess mucus that could impair contact of mucosa with the ablation catheter. Conventionally, this lavage was performed with a solution of 1% acetylcysteine. However, a subsequent study [6] examined a simplified procedure which eliminated this spray step and found no significant difference in endpoints compared to water spray alone. Therefore, many centers have eliminated the use of acetylcysteine solution, opting for thorough lavage with the water jet of the endoscope instead.

At this point, for circumferential ablation, a guidewire is passed through the working channel of the endoscope, and the endoscope is removed, leaving the guidewire in place. If the original Barrx 360 system is being used, the sizing balloon is connected to the RF generator and passed over the guidewire, using the 1-cm markings on the catheter to advance the sizing balloon such that the distal tip of the balloon is 6 cm above the proximal end of circumferential BE. The footswitch is activated, inflating the balloon to a standardized pressure of 4.3 psi (0.3 atm). After this cycle, the catheter is advanced by 1 cm, and the process repeated to resize the inner diameter of the esophagus. This cycle is repeated, advancing the catheter by 1 cm each time, until the catheter enters the stomach or hiatal hernia. This can be detected by a large increase in the size of the inflated sizing balloon. The sizing balloon is then removed, leaving the guidewire in place.

Using these measurements, the appropriate Barrx 360 ablation catheter can be chosen. The diameter of the ablation balloon chosen should be smaller than the narrowest esophageal diameter measured. Special attention should be paid to those patients who have scarring from prior endoscopic mucosal resection (EMR) or other areas of focal narrowing, as the sizing balloon will often overestimate the diameter of the esophagus at these focal points. In those cases, it may be prudent to step down to a catheter one size smaller.

The ablation balloon catheter is then connected to the RF generator and passed over the guidewire into the esophagus. An endoscope is also advanced into the esophagus alongside the guidewire and ablation catheter to allow for

direct endoscopic visualization. The ablation catheter is advanced until the proximal end of the electrode is 1 cm above the proximal extent of circumferential BE. The inflation footswitch is activated and the balloon catheter is automatically inflated to 3 psi. The energy footswitch is then activated to apply one session of RF energy to the electrode. The balloon will automatically deflate following this. The catheter is then advanced distally, allowing for a small amount of overlap (5–10 mm) with the previously ablated segment, and another ablation is performed. This continues until the entire length of circumferential BE has been treated once. The guidewire, ablation catheter, and endoscope are all removed at this point.

Following this, a clear plastic cap is attached to the distal end of an endoscope, and the scope is reintroduced into the esophagus. The rim of the cap is then used to scrape off the ablated tissue from the esophageal wall, and the water jet allows for clearing the esophagus to visualize the remnant mucosa.

After cleaning, the guidewire is replaced through the endoscope, and the ablation catheter is reintroduced over the guidewire. The endoscope, with cap removed, is then readvanced into the esophagus, and another ablation session performed, such that the entire length of BE has received a total of two ablations.

Of note, a trial [6] of a simplified RFA procedure for Barrett's, which essentially consists of two back-to-back ablation sessions, eliminating the step of device removal and cleaning/scraping of the esophageal mucosa, demonstrated similar efficacy as the standard procedure.

Following this initial treatment session, the patient gets brought back in 3 months for a repeat endoscopy. During this session, repeat circumferential treatment may be performed if necessary, such as if there is a residual segment of circumferential BE or multiple tongues/islands of BE. For more focal lesions, focal treatment is pursued.

For focal treatment of BE, the Barrx 90 focal ablation catheter has been the conventional catheter of choice. This device is attached to the distal tip of a standard endoscope, such that the device appears at the 12 o'clock position on the monitor, and the endoscope-device assembly is passed into the esophagus. The focal segment of Barrett's is positioned at the 12 o'clock position, and the Barrx 90 catheter brought into contact with the BE mucosa. The foot pedal is activated for one ablation session, immediately followed by a second ablation session.

Of note, there exists some controversy in regard to the optimal settings for the focal ablation catheter. In the USA, per standard protocol, the RF generator settings for the Barrx 90 catheter delivers 10 J/cm^2 per ablation for non-dysplastic BE, and 12 J/cm^2 per ablation for LGD and HGD. In Europe, the conventional settings for focal ablation is set to 15 J/cm^2 per ablation [7].

The tip of the Barrx 90 catheter is then used to scrape off the ablated tissue, and the endoscope is removed to allow for cleaning of the catheter tip. The endoscope-device assembly is then reintroduced into the esophagus, and another session of two ablations repeated over the same area.

A simplified version of the standard focal ablation technique has been developed and tested. In a randomized trial [8], three back-to-back ablation sessions of 15 J/cm^2 each were performed. This demonstrated non-inferiority to the standard technique of two double sessions with cleaning in between. However, in a retrospective study [9], there seemed to be higher rates of significant stenoses in the simplified focal ablation group. It has therefore been suggested that if a simplified technique is used, the energy density should be reduced from 15 to 12 J/cm^2 per treatment.

The other focal ablation catheters, such as the Barrx 60, the Channel RFA device, and the Ultra-Long, use similar techniques. The Barrx 60 catheter is 15 mm long and 10 mm wide, with an electrode surface area 60% (hence the name) of the Barrx 90 catheter. The Barrx 60 catheter is typically most useful in areas of short tongues or small islands of BE, difficult anatomy, or strictures [10].

Settings for the Ultra-Long catheter and the Channel RFA devices have not been studied as extensively as the Barrx 90 catheter, and the settings for these devices are typically extrapolated as being similar to the Barrx 90 catheter.

With either focal or circumferential device, our goal is to see a "chamois" colored appearance to the mucosa after the ablation (Fig. 16.9). This beige brown appearance is usually void of oozing and bleeding and often has a shiny look. In some disease locations of certain BE patients this appearance is achieved after one focal treatment, and in others it may require more than two. For example, with the Ultra-Long catheter, our experience is that two ablations followed by cleaning and an additional two ablations often are not necessary to achieve the chamois

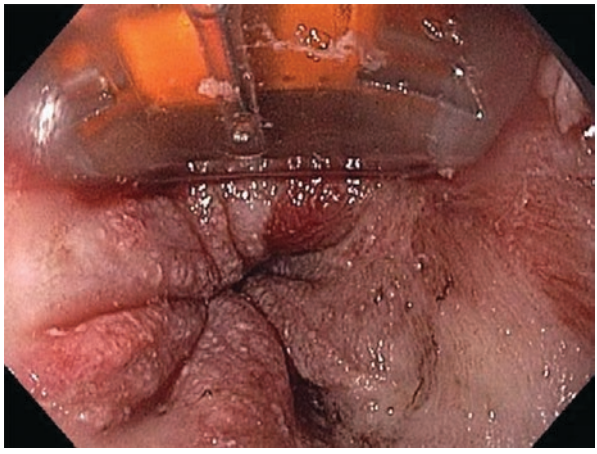

Fig. 16.9 Endoscopic view of Barrx 90 RFA focal ablation catheter within esophagus with post-treatment "chamois" effect

appearance and less energy treatments (single ablation-clean-single ablation) can reach the desired goal.

16.5 Post-procedure

Immediately following RFA treatment, the patient is monitored for a period in the endoscopy center. If the patient is doing well, and the procedure itself was otherwise uncomplicated, the patient can be discharged home after this monitoring period. The patient goes home with prescriptions for high dose acid suppression, including twice daily proton pump inhibitor (PPI) therapy. We also prescribe sucralfate oral suspension four times a day for at least 1 month post-procedure. A limited supply of acetaminophen/hydrocodone liquid is prescribed to be taken as needed for pain. Viscous lidocaine has also been used successfully for analgesia.

The patient is directed to follow a liquid diet for 24 h, with self-titration of diet up to a soft diet then back to a normal diet as tolerated.

If the patient experiences significant postoperative chest pain or fever, we have a low threshold for admitting the patient for overnight observation, albeit this is a very rare event. This allows for closer monitoring, as well as inpatient pain control. If the pain persists, a chest X-ray is checked to evaluate for pneumomediastinum or other such complications, followed by either a barium esophagram or a computed tomography (CT) scan of the chest if X-ray findings are concerning. Typically, though, symptoms will improve during the observation stay and no further intervention is required.

16.6 Efficacy

Several studies have demonstrated that RFA can safely and effectively ablate BE. This has been demonstrated in small pilot studies [11, 12], as well as a larger, multicenter trials [13, 14]. Additionally, it has been demonstrated that effective RFA can be performed not just in academic and tertiary care centers, but community-based practices as well [15, 16].

The early AIM [17] and AIM-II [18] trials demonstrated that BE can effectively be eradicated via RFA even at long-term follow-up. The AIM trial was the first large, multicenter trial to examine RFA of BE to evaluate whether complete remission of intestinal metaplasia (CR-IM) could be achieved. This initial trial was performed on 70 patients with non-dysplastic Barrett's esophagus and found that CR-IM could be achieved in 69% of patients at 12-month follow-up, and 97% of patients at 30-month follow-up with additional focal RFA therapy. This trial was followed up by the AIM-II trial [18], which extended the initial follow-up period from 30 months to 5 years and found that CR-IM could be achieved in 92% of patients at 5-year follow-up, and that additional focal RFA therapy could convert the

remaining failures to CR-IM with a single session. This was followed by the AIM-Dysplasia trial [13], which was a pivotal trial in the acceptance of RFA as a viable treatment strategy for BE with dysplasia. This was a large, multicenter, randomized, sham-controlled trial of 127 patients over 19 sites in the United States which demonstrated RFA was associated with a high rate of complete eradication of dysplasia (90.5% in patients with low-grade dysplasia, 81.0% in those with high-grade dysplasia) and a lower risk of disease progression (3.6% vs. 16.3% in sham group) and fewer cancers (1.2% vs. 9.3% in sham group). Subsequent follow-up data at 3 years [19] and 5 years [20] have demonstrated that this eradication is durable, with low rates of recurrence.

Since the AIM series of trials, there have been multiple further trials that have demonstrated efficacy of RFA in BE, specifically focusing on those patients with LGD. The Surveillance vs. Radiofrequency Ablation (SURF) trial was a multicenter, randomized, controlled trial which demonstrated that ablation reduced the risk of progression to HGD or EAC by 25.0% (1.5% vs. 26.5% for control) and the risk of progression to EAC alone by 7.4% (1.5% vs. 8.8% for control).

A recent meta-analysis and systematic review [21] estimated a 10.9% absolute risk reduction (12.6% to 1.7%) by pursuing a strategy of RFA of BE with LGD, rather than following with surveillance EGD procedures. This translates to a number needed to treat with RFA to prevent one case of disease progression to HGD/EAC at 9.2.

16.7 Adverse Events

A mild degree of chest discomfort is not uncommon following an RFA treatment session. In one trial [13], it was reported that patients were reporting a median discomfort level of 23 out of a 100-point visual-analogue scale on the day after the procedure. This is sometimes associated with a degree of nausea. However, by day 8, the chest discomfort score had returned to 0.

More serious side effects have been noted, including hemorrhage, severe chest pain requiring hospitalization, stricture, and perforation. In a meta-analysis [22], stricture was found to be the most common adverse event, at about 5%, followed by pain (3%) and bleeding (1%). Typically, strictures can be resolved with endoscopic dilation therapy, with the median number of sessions required estimated between 1 and 3 dilation sessions [5, 13, 15]. The rate of perforation following RFA appears to be low, and primarily a risk for those patients who underwent EMR prior to RFA, with one meta-analysis reporting a 0.2% risk of perforation under these circumstances [23].

16.8 Cost-Effectiveness Analysis

Several studies have addressed the question of whether RFA of BE is a cost-effective management strategy.

In one study [24], a Markov model was developed to compare three strategies: endoscopic surveillance with surgery once EAC was detected; endoscopic surveillance with RFA when HGD was detected; and initial RFA followed by endoscopic surveillance. In patients with HGD, initial RFA was found to be more cost-effective than endoscopic surveillance. In patients with LGD, the incremental cost-effectiveness ratio (ICER) for pursuing the initial RFA strategy rather than surveillance with RFA of HGD strategy was found to be $18,231 per quality-adjusted life-year (QALY). This assumes an annual progression rate from LGD to EAC of 0.5%.

In another analysis [25] performed by the National Institute for Health and Clinical Excellence (NICE) in the UK, RFA was deemed to be cost-effective in comparison to no surveillance. By this analysis, cost-effectiveness estimates were around £25,000 per QALY gained.

16.9 Buried Barrett's

Notable mention should be made of the phenomenon known as buried Barrett's, which describes residual BE that gets hidden underneath neosquamous epithelium that develops following RFA therapy. The significance of buried Barrett's following RFA remains controversial. This is, in part, due to the fact that there seems to be a certain rate of buried Barrett's that seems to exist at baseline even prior to any ablative therapies. In one systematic review [26], it was found that this baseline buried Barrett's prevalence ranged from 0 to 28%. Following RFA, buried Barrett's was only found in 0.9% of patients. This suggests that buried Barrett's is a rare phenomenon, and that RFA is able to adequately eradicate all Barrett's epithelium.

Conclusions

Within the past decade, radiofrequency ablation of Barrett's esophagus has become a viable and widely available strategy for the eradication of BE. It has been shown to be a safe and effective strategy for eradication of BE and is overall well-tolerated. The eradication also seems durable to at least 5-year follow-up. Given this, RFA is an invaluable tool to the modern practicing gastroenterologist.

References

1. Ganz RA, Utley DS, Stern RA, Jackson J, Batts KP, Termin P. Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: a phased evaluation in the porcine and in the human esophagus. Gastrointest Endosc. 2004;60(6):1002–10.
2. Dunkin BJ, Martinez J, Bejarano PA, et al. Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device. Surg Endosc. 2006;20(1):125–30.
3. Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111(1):30–50; quiz 51.
4. American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011;140(3):1084–91.

5. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. 2014;311(12):1209–17.
6. van Vilsteren FG, Phoa KN, Alvarez Herrero L, et al. Circumferential balloon-based radiofrequency ablation of Barrett's esophagus with dysplasia can be simplified, yet efficacy maintained, by omitting the cleaning phase. Clin Gastroenterol Hepatol. 2013;11(5):491–98.e1.
7. Belghazi K, Cipollone I, Bergman JJ, Pouw RE. Current controversies in radiofrequency ablation therapy for Barrett's esophagus. Curr Treat Options Gastroenterol. 2016;14(1):1–18.
8. van Vilsteren FG, Phoa KN, Alvarez Herrero L, et al. A simplified regimen for focal radiofrequency ablation of Barrett's mucosa: a randomized multicenter trial comparing two ablation regimens. Gastrointest Endosc. 2013;78(1):30–8.
9. Kunzli HT, Scholvinck DW, Phoa KN, et al. Simplified protocol for focal radiofrequency ablation using the HALO90 device: short-term efficacy and safety in patients with dysplastic Barrett's esophagus. Endoscopy. 2015;47(7):592–7.
10. Allen B, Kapoor N, Willert R, McEwan H, Fullarton G, Penman I. Endoscopic ablation of Barrett's neoplasia with a new focal radiofrequency device: initial experience with the Halo60. Endoscopy. 2012;44(7):707–10.
11. Gondrie JJ, Pouw RE, Sondermeijer CM, et al. Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients. Endoscopy. 2008;40(5):359–69.
12. Gondrie JJ, Pouw RE, Sondermeijer CM, et al. Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. Endoscopy. 2008;40(5):370–9.
13. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009;360(22):2277–88.
14. Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol. 2010;8(1):23–9.
15. Lyday WD, Corbett FS, Kuperman DA, et al. Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry. Endoscopy. 2010;42(4):272–8.
16. Ganz RA, Overholt BF, Sharma VK, et al. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. Multicenter Registry. Gastrointest Endosc. 2008;68(1):35–40.
17. Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. Gastrointest Endosc. 2008;68(5):867–76.
18. Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy. 2010;42(10):781–9.
19. Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology. 2011;141(2):460–8.
20. Cotton CC, Wolf WA, Overholt BF, et al. Late recurrence of Barrett's esophagus after complete eradication of intestinal metaplasia is rare: final report from ablation in intestinal metaplasia containing dysplasia trial. Gastroenterology. 2017;153(3):681–688.e2.
21. Qumseya BJ, Wani S, Gendy S, Harnke B, Bergman JJ, Wolfsen H. Disease progression in Barrett's low-grade dysplasia with radiofrequency ablation compared with surveillance: systematic review and meta-analysis. Am J Gastroenterol. 2017;112(6):849–65.
22. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(10):1245–55.

23. Desai M, Saligram S, Gupta N, et al. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis. Gastrointest Endosc. 2017;85(3):482–495.e4.
24. Hur C, Choi SE, Rubenstein JH, et al. The cost effectiveness of radiofrequency ablation for Barrett's esophagus. Gastroenterology. 2012;143(3):567–75.
25. Barrett's oesophagus: ablative therapy for the treatment of Barrett's oesophagus. London. 2010.
26. Gray NA, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. Am J Gastroenterol. 2011;106(11):1899–908; quiz 1909.

17 What We Have to Do After the Treatment of Metaplasia or Dysplasia in Barrett's Esophagus? Protocols and Timing of Follow-Up in the Treated Patient

Jose-Miguel Esteban

17.1 Introduction

Barrett's esophagus (BE) is a precursor of esophageal adenocarcinoma. Malignant degeneration of BE occurs typically through a multistep transition from non-dysplastic intestinal metaplasia (NDBE) to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and finally invasive adenocarcinoma.

Regular endoscopic surveillance is therefore recommended in patients with BE, although its benefits and adherence to this is currently under debate [1]. Endoscopic therapy is a first-line therapeutic option for treatment of Barrett's esophagus (BE) and intraepithelial neoplasia [1–3]. There are tissue acquiring and tissue damaging modalities for therapy and are often used in concert. Professional practice guidelines support the use of these endoscopic options, including endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA), for treatment of BE containing HGD [1, 2].

The presence of HGD and intramucosal adenocarcinoma (ADC) is an established indication for endoscopic therapy by means of endoscopic resection, radiofrequency ablation (RFA), or a combination of both techniques [1]. Any visible lesion in the Barrett segment should be resected for assessment of its histopathological characteristics [4]. In case further endoscopic treatment is indicated, additional endoscopic resection and/or RFA of the remaining flat Barrett segment is recommended because the risk of metachronous lesions is estimated to be up to 30% [5, 6]. When HGD or intramucosal ADC is present, the present guidelines recommend to eradicate the whole BE. For this reason RFA and EMR are often used in the same patient until eradication.

J.-M. Esteban
Endoscopy Unit, Hospital Clínico San Carlos, Madrid, Spain

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_17

17.2 Endoscopic Therapies of Barrett's

Controlled prospective trials demonstrate the ability of RFA to offer remission of dysplasia in a majority of treated patients and to reduce the rate of progression to cancer, during reported follow-up [7]. RFA is typically combined with focal EMR of visible lesions, and this hybrid method has produced high (>90%) rates of eradication and a durable response up to 5 years post-treatment [8–12]. There is also emerging data that hybrid therapy in patients with LGD can decrease rates of progression to HGD and IMC by up to 25% with an acceptable safety profile when compared to optimal surveillance alone [13]. Endoscopic eradication therapy is also the procedure of choice for patients with confirmed LGD [1, 2].

However, endoscopic therapy may require multiple treatment sessions over a number of months to achieve the desired therapeutic outcome (typically, eradication of all intestinal metaplasia). We also need to consider the rate of recurrence of BE after eradication.

Endoscopic factors which predict the response to therapy have been identified. Persistence of acid reflux, despite pharmacologic gastric acid suppression; hiatal hernia size; and initial BE segment length are associated with an incomplete response to RFA [14]. Patients with long segments of columnar epithelium and large hiatal hernias may therefore require an increased number of RFA treatment sessions to achieve desired outcomes [15].

Moreover, successful endoscopic therapy, with endoscopic and histopathologic eradication of dysplasia and/or intestinal metaplasia, does not alter predisposition to gastroesophageal reflux and does not eliminate the need for continued endoscopic surveillance. Recurrence of BE has been reported in extended follow-up after RFA [9, 11]. Such data led to the concept of endoscopic therapy offering "remission," rather than "cure," of BE [16]. In patients with BE which had any kind of neoplasia before and is in remission after treatment, it is mandatory to control acid exposure of distal esophagus and the neosquamous mucosa. But this is another issue that is not clear.

17.3 Surveillance After Endoscopic Therapy

The long-term durability of complete eradication of intestinal metaplasia (CEIM) has not been well characterized, so the frequency and duration of surveillance are unclear. Research to date has consistently demonstrated low rates of recurrence after CEIM [7, 8, 11, 17]. However, discontinuing surveillance remains a contentious area, in large part because follow-up of BE patients in most prior studies is only 1–2 years [7, 8, 11], leaving the long-term risk of recurrence and progression of BE in doubt. Cotton et al. [18] recruited participants from the AIM Dysplasia Trial and collected data on BE recurrence (defined as intestinal metaplasia in the tubular esophagus) and dysplastic BE recurrence among patients who achieved CEIM. One hundred and ten (92%) achieved CEIM. Over 401 person-years of follow-up (mean, 3.6 years per patient; range, 0.2–5.8 years), 35 of 110 (32%) patients

had recurrence of BE or dysplasia, and 19 (17%) had dysplasia recurrence. The incidence rate of BE recurrence was 10.8 per 100 person-years overall (95% CI, 7.8–15.0); 8.3 per 100 person-years among patients with baseline low-grade dysplasia (95% CI, 4.9–14.0), and 13.5 per 100 person-years among patients with baseline high-grade dysplasia (95% CI 8.8–20.7). The incidence rate of dysplasia recurrence was 5.2 per 100 person-years overall (95% CI 3.3–8.2); 3.3 per 100 person-years among patients with baseline low-grade dysplasia (95% CI 1.5–7.2), and 7.3 per 100 person-years among patients with baseline high-grade dysplasia (95% CI 4.2–12.5). Neither BE nor dysplasia recurred at a constant rate. There was a greater probability of recurrence in the first year following CEIM than in the following 4 years combined. So they found BE to recur after CEIM by RFA in almost one-third of patients with baseline dysplastic disease; most recurrences occurred during the first year after CEIM. However, patients who achieved CEIM and remained BE free at 1 year after RFA had a low risk of BE recurrence. They did not identify any BE or dysplasia recurrence after 4 years of surveillance. Phoa et al. [9] looked at remission of neoplastic lesions 5 years following focal EMR and serial RFA in a 54-patient cohort using EUS and neosquamous resection to detect recurrence. They showed that 90% sustained complete eradication of neoplasia and intestinal metaplasia, with both neoplastic recurrences occurring near the 5-year cutoff.

17.4 Surveillance Strategies

Even though most experts agree that surveillance is beneficial following endoscopic treatment of neoplastic BE, there are deficiencies in the current surveillance process that cast doubt on our ability to reliably detect recurrence and progression of disease [19]. First there is a lack of standardization in terminology when discussing disease recurrence. Often times, intestinal metaplasia is found incidentally on random biopsy of neosquamous epithelium following circumferential RFA of high-grade lesions, and its implication on prognosis and the need for more sesions of RFA treatment is uncertain [7, 20, 21]. When such areas are found and touched up, it is unclear if this constitutes residual metaplasia that was insufficiently treated, if it represents true recurrence of the parent lesion, or if it is a metachronous lesion that may be genetically independent with unknown malignant potential [19].

Surveillance in patients after endoscopic treatment looks controversial. The strategy in these patients depends on many issues. We need to consider different aspects: the worst status of the BE prior therapy and if there is any BE after therapy and the type of BE (NDBE, LGD, or HGD). Also we should consider if acid exposure of distal esophagus is controlled.

We also need to consider that in these groups of patients surveillance endoscopies should be performed in an optical way. Surveillance endoscopies for BE are predominantly performed in community hospitals; however, most experts advocate for the surveillance of BE related neoplasia should be centralized in expert centers.

Forty-eight endoscopists in the United States with expertise in BE endotherapy based on high-impact publications and national reputation filled an electronic survey

aimed to define expert practice patterns regarding follow-up after endoscopic treatment of BE with HGD and IMC [22]. The survey inquires about post-BE endotherapy follow-up practices. Of 48 expert endoscopists, 42 completed the survey. After successful treatment of BE with HGD or IMC, all experts perform surveillance upper endoscopy, most commonly at 3-month intervals in the first post-treatment year, every 6 months during the second year, and annually thereafter. None of the experts perform surveillance EUS after treatment of HGD, and only 19% perform EUS after treatment of IMC. After cancer eradication, only 36% of experts refer patients for CT, and 24% refer patients for positron emission tomography. Thirty-eight percent of experts refer patients for a surgical opinion when IMC extends into the muscularis mucosa; 100% refer when IMC extends into submucosa.

17.5 Publications Regarding Protocols and Timing for Surveillance

The type of protocol and timing of follow-up in these patients are not well established yet. Different groups had published some recommendations. There are national groups in Europe with established recommendations, and recently the European Society of Gastrointestinal Endoscopy (ESGE) published the "Endoscopic management of Barrett's esophagus: Position Statement" [2]. The American College of Gastroenterology [1] also published some recommendations for surveillance after endoscopic therapy.

The British Society of Gastroenterology (BSG) [23] establish that Endoscopic follow-up is recommended after endoscopic therapy of Barrett's neoplasia, with biopsies taken from the GOJ and within the extent of the previous Barrett's esophagus with an Evidence grade III. German recommendations [24] states that *"After successful eradication of neoplasia and BE, surveillance endoscopies should be performed after 3 months, afterwards every 6 months up to 2 years and yearly thereafter."*

The ESGE position statement [2] don't say anything regarding what to do in patients with any kind of dysplastic Barrett's after being treated with endoscopic therapy.

The American Gastroenterological Association (AGA) Medical Position Statement [4] confirms that the goal of endoscopic eradication therapy is the elimination of all Barrett's epithelium to prevent neoplastic progression. Complete eradication appears to be more effective than therapy that removes only a localized area of dysplasia in Barrett's epithelium. (**Quality of Evidence: Low).** The second goal of eradication therapy is to achieve reversion to normal-appearing squamous epithelium within the entire length of the esophagus without islands of buried intestinal metaplasia. RFA can lead to reversion of the metaplastic mucosa to normal-appearing squamous epithelium in a high proportion of subjects at any stage of Barrett's esophagus. The data to date show that reversion to squamous epithelium can persist for up to 5 years. **Quality of Evidence: High.** But they also didn't establish which kind of protocol should be recommended for surveillance in these group of patients.

The American Society of Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee [25] don't confirm any kind of recommendation.

The ACG gives these recommendations [1]:

1. Following successful endoscopic therapy and complete elimination of intestinal metaplasia (CEIM), endoscopic surveillance should be continued to detect recurrent IM and/or dysplasia (strong recommendation, low level of evidence).
2. Endoscopic surveillance following CEIM, for patients with HGD or IMC before ablation, is recommended every 3 months for the first year following CEIM, every 6 months in the second year, and annually thereafter (conditional recommendation, low level of evidence).
3. In patients with LGD before ablation, endoscopic surveillance is recommended every 6 months in the first year following CEIM, and annually thereafter (conditional recommendation, low level of evidence).
4. During endoscopic surveillance after CEIM, careful inspection of the tubular esophagus and gastroesophageal junction (in antegrade and retrograde views) should be performed with high-resolution white light imaging and narrow band imaging to detect mucosal abnormalities that may reflect recurrent IM and/or dysplasia (strong recommendation, low level of evidence).
5. Treatment of recurrent metaplasia and/or dysplasia should follow guidelines for the treatment of metaplasia/dysplasia in BE before ablation (strong recommendation, low level of evidence).
6. Following CEIM, the goal of medical antireflux therapy should be control of reflux as determined by absence of frequent reflux symptoms (more than once a week) and/or esophagitis on endoscopic examination (conditional recommendation, very low level of evidence).

17.6 Protocols and Timing of Follow-Up in the Treated Patient Recommendations

The protocol differs between groups because there are not many publications and also the evidence is really low. We need to consider these factors: The worst Barrett's status prior starting the treatment and if the eradication of Barrett's was complete or not (in terms of eradication of the whole intestinal metaplasia (IM)). Those cases were there are any kind of dysplasia we don't consider as "already" treated patients and we should recommend to continue with therapy until dysplasia is completely removed.

17.6.1 Patients Treated with Prior Non-dysplastic Barrett's

Guidelines only consider treatment in these patients as an option. We consider that eradication don't change the follow-up. When complete eradication of IM and BE, follow-up should be continued. Acid exposure of distal esophagus must be

controlled because if not BE can appear again. This is the most important factor. We consider ESGE Position Statement [2] as a valid option considering the prior status before therapy: Surveillance intervals for non-dysplastic BE should be stratified according to the length of the Barrett's segment. Maximum extent of BE ≥1 cm, and <3 cm: 5 years. Maximum extent of BE ≥3 cm: 3 years.

We also consider that when a patient reach 6 years of surveillance endoscopy since eradication and has no previous evidence of IM, no subsequent surveillance endoscopies should be performed.

In those cases where there is still any kind of NDBE, we consider that follow-up endoscopy should be performed every 3 years.

17.6.2 Patients with Prior LGD BE

In these group of patients, eradication of BE is the preferred option to avoid cancer. In those cases that IM is completely eradicated, follow-up should be considered. It's mandatory that like in the rest of patients the acid exposure of distal esophagus must be controlled with medication or surgery (fundoplication). We strongly recommend continuing the follow-up in this group of patients in this way:

– At 6 months, then at 12, 24, 36, 60 months and then once more time 96 months since eradication. We also consider that when a patient reach 8 years of surveillance endoscopy since eradication and has no previous evidence of IM, no subsequent surveillance endoscopies should be performed.

17.6.3 Patients with Prior HGD or Intramucosal Cancer

This is the high-risk group where the estimated proportion of patients without recurrence of neoplasia is lower than in the other groups. Eradication is mandatory, and since years ago endoscopic treatment is the preferred method instead of surgery. After treatment it is also necessary to control acid reflux with PPIs or fundoplication. We consider that in this group follow-up endoscopies should be performed:

– At 6, 12, 18, 24, 36, 60 months and then each 18 months until reach 120 months since eradication. We also consider that when a patient reach 10 years of surveillance endoscopy since eradication or is older than 80 years old and has no previous evidence of IM, no subsequent surveillance endoscopies should be performed.

17.7 Special Considerations

Despite its high rate of dysplasia eradication, there remain concerns about durability of response and recurrence patterns following hybrid endotherapy [9, 11, 26, 27]. Multiple studies have demonstrated that recurrence of intestinal metaplasia and

progression to cancer still happen in the post-treatment period [28–31]. One meta-analysis quotes recurrence rates of 11% following endotherapy with complete eradication of neoplastic lesions [32]. Most gastroenterologists agree with continued surveillance, but there still remains significant variability among endoscopic follow-up in practice due to both patient and physician factors [22, 33, 34].

Different factors provide challenges to the standard of targeted and four quadrant biopsies [19]. The cost-effectiveness of post-ablation surveillance and new imaging technologies to detect buried intestinal metaplasia are also items gaining attention in the literature, as the financial burden of healthcare continues to grow [7, 35, 36]. All of these reasons highlight the need for evidence-based protocols to guide surveillance in the post-treatment period [19].

Routine endoscopy with white light endoscopy (WLE) can be insufficient for the study of these patients. The use of Narrow Band Imaging (NBI) has limited sensitivity and specificity (sensitivity 65–71%, specificity 37–46%) for detecting biopsy-confirmed intestinal metaplasia [37]. It could be considered in the follow-up protocol to use WLE and any kind of virtual filters (*NBI, Iscan,* or *FICE*). But the rate of detection will not be excellent.

Buried intestinal metaplasia following ablation techniques has become recognized as an increasingly common phenomenon that may be underestimated by studies using pinch biopsies for surveillance. A systematic review of buried metaplasia following RFA yielded positive findings in only 0.9% of specimens on follow-up biopsy, a rate much lower than for prior ablative techniques [26]. Neosquamous epithelium may also be more fibrous and limit the ability to achieve adequate biopsy depth.

Volumetric laser endomicroscopy (VLE) is a second-generation optical coherence tomography which provides high-resolution (10 μm) real-time images to evaluate esophageal tissue microstructure up to 3 mm depth [38]. Benjamin et al. [39] presented their initial experience with VLE by NvisionVLETM Imaging System (Cambridge, MA) in patients with Barrett's esophagus (BE). VLE has a potential role in identifying abnormal areas which are otherwise not visible on white light endoscopy (WLE) and also in identifying buried BE in post-ablation surveillance of patients with BE. Normal esophageal squamous mucosa is seen by VLE as a layered horizontal architecture without glands in the epithelium [40]. In intestinal metaplasia, VLE shows loss of layered architecture with no surface pits, crypts, or glands. Dysplasia is suspected if there is complete effacement with surface intensity greater than subsurface intensity or if there is partial effacement with greater than five atypical glands. Homogeneous scattering is suggestive of high-grade dysplasia (HGD) or cancer. They conclude that VLE has a potential role in post-ablation surveillance of BE as it detected areas of BE that were not identified on WLE and four quadrant surveillance biopsies.

17.8 Summary

Surveillance after endoscopic therapies of BE with prior ND, LGD, HGD, or intramucosal ADC is necessary. However the type of protocol differs from different experts and there is not any optimal way for surveillance. We consider that when

any kind of dysplasia is present and endoscopic therapy is recommended for BE eradication, these patients should be controlled in a special protocol in the best way to identify any alteration. Acid exposure of distal esophagus should be controlled. Depending on what were the worst status of Barrett's before endoscopic treatment, we need to do the follow-up in a different way.

References

1. Shaheen NJ, Falk GW, Iyer PG, et al. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111:30–50.
2. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau JM, Esteban JM, Hassan C, Pech O, Repici A, Bergman J, di Pietro M. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) position statement. Endoscopy. 2017;49(2):191–8. https://doi.org/10.1055/s-0042-122140.
3. Cassani L, Slaughter JC, Yachimski P. Adherence to therapy for Barrett's esophagus-associated neoplasia. United European Gastroenterol J. 2016;4(1):42–8.
4. Moss A, Bourke MJ, Hourigan LF, et al. Endoscopic resection for Barrett's high-grade dysplasia and early esophageal adenocarcinoma: an essential staging procedure with long-term therapeutic benefit. Am J Gastroenterol. 2010;105:1276–83.
5. American Gastroenterological Association, Spechler SJ, Sharma P, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011;140:1084–91.
6. May A, Gossner L, Pech O, et al. Local endoscopic therapy for intraepithelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. Eur J Gastroenterol Hepatol. 2002;14:1085–91.
7. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009;360:2277–88.
8. Shaheen NJ, Overholt BF, Sampliner RE, Wolfsen HC, Wang KK, Fleischer DE, Sharma VK, Eisen GM, Fennerty MB, Hunter JG, Bronner MP, Goldblum JR, Bennett AE, Mashimo H, Rothstein RI, Gordon SR, Edmundowicz SA, Madanick RD, Peery AF, Muthusamy VR, Chang KJ, Kimmey MB, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Dumot JA, Falk GW, Galanko JA, Jobe BA, Hawes RH, Hoffman BJ, Sharma P, Chak A, Lightdale CJ. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology. 2011;141:460–8. https://doi.org/10.1053/j.gastro.2011.04.061.
9. Orman ES, Kim HP, Bulsiewicz WJ, Cotton CC, Dellon ES, Spacek MB, Chen X, Madanick RD, Pasricha S, Shaheen NJ. Intestinal metaplasia recurs infrequently in patients successfully treated for Barrett's esophagus with radiofrequency ablation. Am J Gastroenterol. 2013;108:187–95; quiz 196. https://doi.org/10.1038/ajg.2012.413.
10. Phoa KN, Pouw RE, van Vilsteren FG, Sondermeijer CM, Ten Kate FJ, Visser M, Meijer SL, van Berge Henegouwen MI, Weusten BL, Schoon EJ, Mallant-Hent RC, Bergman JJ. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. Gastroenterology. 2013;145:96–104. https://doi.org/10.1053/j.gastro.2013.03.046.
11. Pouw RE, Wirths K, Eisendrath P, Sondermeijer CM, Ten Kate FJ, Fockens P, Devière J, Neuhaus H, Bergman JJ. Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol. 2010;8:23–9. https://doi.org/10.1016/j.cgh.2009.07.003.
12. Gupta M, Iyer PG, Lutzke L, Gorospe EC, Abrams JA, Falk GW, Ginsberg GG, Rustgi AK, Lightdale CJ, Wang TC, Fudman DI, Poneros JM, Wang KK. Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's

esophagus: results from a US Multicenter Consortium. Gastroenterology. 2013;145:79–86.e1. https://doi.org/10.1053/j.gastro.2013.03.008.
13. Phoa KN, van Vilsteren FG, Weusten BL, Bisschops R, Schoon EJ, Ragunath K, Fullarton G, Di Pietro M, Ravi N, Visser M, Offerhaus GJ, Seldenrijk CA, Meijer SL, ten Kate FJ, Tijssen JG, Bergman JJ. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. 2014;311:1209–17. https://doi.org/10.1001/jama.2014.2511.
14. Krishnan K, Pandolfino JE, Kahrilas PJ, et al. Increased risk for persistent intestinal metaplasia in patients with Barrett's esophagus and uncontrolled reflux exposure before radiofrequency ablation. Gastroenterology. 2012;143:576–81.
15. Korst RJ, Santana-Joseph S, Rutledge JR, et al. Effect of hiatal hernia size and columnar segment length on the success of radiofrequency ablation for Barrett's esophagus: a single-center, phase II clinical trial. J Thorac Cardiovasc Surg. 2011;142:1168–73.
16. Inadomi JM. Time to burn? Endoscopic ablation for Barrett's esophagus. Gastroenterology. 2011;141:417–9.
17. Wolf WA, Pasricha S, Cotton C, et al. Incidence of esophageal adenocarcinoma and causes of mortality after radiofrequency ablation of Barrett's esophagus. Gastroenterology. 2015;149:1752–61.
18. Cotton CC, Sampliner RE, et al. Late recurrence of Barrett's esophagus after complete eradication of intestinal metaplasia is rare: final report from ablation in intestinal metaplasia containing dysplasia trial. Gastroenterology. 2017;153(3):681–8.
19. Stier HW, Konda VJ, Hart J, Waxman I. Post-ablation surveillance in Barrett's esophagus: a review of the literature. World J Gastroenterol. 2016;22(17):4297–306.
20. Pouw RE, Visser M, Odze RD, Sondermeijer CM, ten Kate FJ, Weusten BL, Bergman JJ. Pseudo-buried Barrett's post radiofrequency ablation for Barrett's esophagus, with or without prior endoscopic resection. Endoscopy. 2014;46:105–9.
21. Odze RD, Lauwers GY. Histopathology of Barrett's esophagus after ablation and endoscopic mucosal resection therapy. Endoscopy. 2008;40:1008–15.
22. Bedi AO, Kwon RS, Rubenstein JH, et al. A survey of expert follow-up practices after successful endoscopic eradication therapy for Barrett's esophagus with high-grade dysplasia and intramucosal adenocarcinoma. Gastrointest Endosc. 2013;78(5):696–701. https://doi.org/10.1016/j.gie.2013.04.196.
23. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology (BSG) guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014;63:7–42.
24. Koop H, Fuchs KH, Labenz J, et al. S2k guideline: gastroesophageal reflux disease guided by the German Society of Gastroenterology AWMF register no. 021-013. Z Gastroenterol. 2014;52:1299–346.
25. Evans JA, Early DS, Fukami N, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc. 2012;76(6):1087–94.
26. Gray NA, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. Am J Gastroenterol. 2011;106:1899–908; quiz 1909. https://doi.org/10.1038/ajg.2011.255.
27. Corley DA. Can you stop surveillance after radiofrequency ablation of Barrett's esophagus? A glass half full. Gastroenterology. 2013;145:39–42. https://doi.org/10.1053/j.gastro.2013.05.039.
28. Gorospe EC, Sun G, Wang KK. Endpoints for radiofrequency ablation in Barrett's dysplasia. Am J Gastroenterol. 2013;108:197–9. https://doi.org/10.1038/ajg.2012.415.
29. Titi M, Overhiser A, Ulusarac O, Falk GW, Chak A, Wang K, Sharma P. Development of subsquamous high-grade dysplasia and adenocarcinoma after successful radiofrequency ablation of Barrett's esophagus. Gastroenterology. 2012;143:564–566.e1. https://doi.org/10.1053/j.gastro.2012.04.051.
30. Chennat J, Ross AS, Konda VJ, Lin S, Noffsinger A, Hart J, Waxman I. Advanced pathology under squamous epithelium on initial EMR specimens in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma: implications for surveillance and

endotherapy management. Gastrointest Endosc. 2009;70:417–21. https://doi.org/10.1016/j.gie.2009.01.047.
31. Zeki SS, Haidry R, Graham TA, Rodriguez-Justo M, Novelli M, Hoare J, Dunn J, Wright NA, Lovat LB, McDonald SA. Clonal selection and persistence in dysplastic Barrett's esophagus and intramucosal cancers after failed radiofrequency ablation. Am J Gastroenterol. 2013;108:1584–92. https://doi.org/10.1038/ajg.2013.238.
32. Wu J, Pan YM, Wang TT, Gao DJ, Hu B. Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis. Gastrointest Endosc. 2014;79:233–241.e2. https://doi.org/10.1016/j.gie.2013.08.005.
33. Bennett C, Vakil N, Bergman J, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. Gastroenterology. 2012;143:336–46. https://doi.org/10.1053/j.gastro.2012.04.032.
34. Hinojosa-Lindsey M, Arney J, Heberlig S, Kramer JR, Street RL, El-Serag HB, Naik AD. Patients' intuitive judgments about surveillance endoscopy in Barrett's esophagus: a review and application to models of decision-making. Dis Esophagus. 2013;26:682–9. https://doi.org/10.1111/dote.12028.
35. Vaccaro BJ, Gonzalez S, Poneros JM, Stevens PD, Capiak KM, Lightdale CJ, Abrams JA. Detection of intestinal metaplasia after successful eradication of Barrett's esophagus with radiofrequency ablation. Dig Dis Sci. 2011;56:1996–2000. https://doi.org/10.1007/s10620-011-1680-4.
36. Inadomi JM, Somsouk M, Madanick RD, Thomas JP, Shaheen NJ. A cost-utility analysis of ablative therapy for Barrett's esophagus. Gastroenterology. 2009;136:2101–2114.e1-6. https://doi.org/10.1053/j.gastro.2009.02.062.
37. Alvarez Herrero L, Curvers WL, Bisschops R, Kara MA, Schoon EJ, ten Kate FJ, Visser M, Weusten BL, Bergman JJ. Narrow band imaging does not reliably predict residual intestinal metaplasia after radiofrequency ablation at the neo-squamo columnar junction. Endoscopy. 2014;46:98–104. https://doi.org/10.1055/s-0033-1344986.
38. Vakoc BJ, Shishko M, Yun SH, et al. Comprehensive esophageal microscopy by using optical frequency-domain imaging (with video). Gastrointest Endosc. 2007;65:898–905.
39. Benjamin T, Shakya S, Thota PN. Feasibility of volumetric laser endomicroscopy in Barrett's esophagus with dysplasia and in post-ablation surveillance. J Gastrointestin Liver Dis. 2016;25(3):407–8.
40. Trindade AJ, George BJ, Berkowitz J, Sejpal DV, Mckinley MJ. Volumetric laser endomicroscopy can target neoplasia not detected by conventional endoscopic measures in long segment Barrett's esophagus. Endosc Int Open. 2016;4:E318–22. https://doi.org/10.1055/s-0042-101409.

18 Is There a Role for the Surgeon in the Therapeutic Management of Barrett's Esophagus?

Uberto Fumagalli Romario and Paul Magnus Schneider

18.1 Introduction

Gastroesophageal reflux disease (GERD) is an evidence-based major risk factor for the development of Barrett's esophagus (BE) and esophageal adenocarcinoma (EA) [1, 2]. Individuals suffering from at least weekly symptoms for at least 20 years had a 9.3-fold risk (odds ratio, OR) for EA in a meta-analysis of case-control studies, whereas those with severe symptoms for at least 20 years had a 44-fold risk for EA [2, 3]. Barrett's esophagus is an intermediate step in the sequence from esophagitis to cancer and a clear risk factor for disease progression. Intestinal metaplasia develops in about 10% of patients with GERD during 5 years following initial diagnosis, and this risk is associated with the severity of reflux. These numbers have been recently confirmed in the PRO-GERD study where 9.7% out of 2721 patients with GERD developed BE during 5-year follow-up predominantly within the group of patients with C or D esophagitis [4]. The risk of patients with BE for EA development has been estimated to be around 0.38% per year, and is clearly higher than the 0.07% risk for patients without intestinal metaplasia [5]. In addition, annual cancer transition rates for various lengths of BE were recently estimated to be 0.22% for long segment, 0.03% for short segment, and 0.01% for ultrashort segment BE [6]. Duodeno-gastro-esophageal reflux is increased in BE [7], and bile acids induce BE in rats [8].

Antireflux surgery (ARS) may offer more complete reflux inhibition than does medical treatment, because surgery also mechanically prevents duodeno-gastro-esophageal reflux (bile and pancreatic juice reflux). Medical treatment with PPI is

U. F. Romario (✉)
General Surgery 2 Unit, ASST Spedali Civili, Brescia, Italy

P. M. Schneider
Department of Visceral, Thoracic, and Vascular Surgery,
City of Zurich-Triemli Hospital, Zurich, Switzerland

Department of Visceral, Thoracic, and specialized Tumor Surgery,
Visceral Oncology Tumor Center, Hirslanden Medical Center, Zurich, Switzerland

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_18

also influenced by dosage and patient's compliance. Theoretically, ARS could reduce the risk of progression for patients with BE to EA or even lead to a regression of BE and/or dysplasia. In addition, ARS could be useful in combination with ablation techniques to prevent Barrett's recurrence.

18.2 Does BE Regress After ARS and/or Does ARS Reduce the Cancer Risk in BE?

Gastroesophageal reflux disease (GERD) is a major risk factor for esophageal adenocarcinoma (EA) with recurrent symptomatic GERD leading to an eightfold increased risk [2]. GERD is the mechanism of the neoplastic process leading to esophagitis, Barrett's esophagus and progression with dysplastic changes and eventually EA [9, 10].

As stated before, antireflux surgery may offer a more complete reflux inhibition than does medical treatment due to mechanical prevention of duodeno-gastroesophageal reflux (bile reflux).

Several studies comparing patients with BE treated either with PPI or ARS have demonstrated an increased risk for the progression to low grade dysplasia (LGD) in the medical therapy group. Other series even demonstrated a regression of BE after ARS. Beyond that, some studies showed that ARS lowered the risk for progression of dysplasia [11–24].

In the series by Oeberg et al. from 2005 [25], the risk of progression of intestinal metaplasia (IM) to dysplasia was 2.3 times less following ARS as compared to PPI treatment. Development of high grade dysplasia (HGD) or cancer was significantly higher in 94 patients treated with PPI (7.4%) as compared to 46 patients submitted to ARS (0%) after a median follow-up of 5.8 years. ARS appeared as the single factor associated with the reduced progression risk.

Regression of BE after ARS has been demonstrated in a higher proportion of patients treated with surgery than medical therapy. Gurski and colleagues from DeMeester's group [26] reported, in a retrospective analysis a 36.4% regression rate among 77 patients with BE submitted to ARS compared to 7.1% in 14 medically treated patients. Furthermore, regression from LGD to IM and from IM to normal squamous epithelium was 68% and 21.2% following ARS. In multivariate analysis, ARS and short segment BE (SSBE) were significantly associated with regression.

Similar results have been reported by Rossi et al. [27] in a non-randomized comparison between two groups of patients with LGD treated either with ARS or PPI. After a 12-month follow-up, regression from LGD to IM was significantly higher in the ARS group (94% vs. 63%). ARS was the only independent factor associated with remission of LGD being 16 times more likely following ARS.

The results of all these studies have been criticized since they are retrospective or non-randomized studies and suffer from various biases including patient selection adding to a low level of evidence. Furthermore, it is difficult to interpret the reported regressions from LGD to IM due to inter-observer variability of diagnosis of LGD [28].

Additional data for the protective effect of ARS on carcinogenesis might come from gene expression studies: COX-2 gene expression increases during carcinogenesis from BE to EA [29], but COX-2 and interleukin-8 levels normalize after ARS, indicating the presence of a genetic mechanism for the regression from LGD to non-dysplastic IM [30, 31].

From the accumulated literature on ARS and Barrett's regression, it appears that regression from IM mainly occurs in SSBE with a regression rate inversely related to the length of IM [12, 32]. In Oelschlager's series, regression from BE to normal squamous mucosa was reported in 55% of 54 patients with SSBE and no patient with long segment BE (LSBE) [11]. Similar results have been reported by Csendes and colleagues who described a regression from IM to cardiac mucosa in 60.8% of patients with SSBE 39–56 months following ARS [22].

A significantly lower regression rate for LSBE after ARS could be a consequence of frequent large hiatal hernias and a severe malfunction of the lower esophageal sphincter (LES) in patients with LSBE [33]. In addition, these patients have a higher incidence of hernia recurrence or failure of ARS [12].

In 2007, Chang et al. published a systematic review on the probability of progression/regression of BE with ARS or medical treatment. The probability of regression was 15.4% in the ARS group and 1.9% in medical patients with a regression from LGD to IM in 4% of ARS-treated patients and 0% of medically treated patients [34]. No significant difference was found in terms of progression from BE to LGD or HGD which was 2.9% in ARS vs. 6.8% among medical patients ($p = 0.054$).

A study published after that review suggests a benefit in terms of IM reversal in short segment BE for antireflux surgery over medical therapy, whereas neither therapy modality affects long segment BE [35].

Previous publications including a recent systematic review have failed to demonstrate a clear consistent benefit of antireflux surgery in reducing the risk of esophageal adenocarcinoma compared to medical therapy [36, 37]. However these publications have been limited by small sample sizes with low numbers of esophageal adenocarcinoma in the long-term follow-up categories, and poorly defined control populations specifically regarding the severity of reflux [36].

These inconsistent results could be due to a relatively high failure rate of laparoscopic fundoplication to control reflux in 17.7% of patients as recently shown in a nationwide population-based Swedish cohort study in 2655 patients who underwent laparoscopic ARS [38].

It appeared that patients with BE after ARS have a higher chance of regression from non-dysplastic IM to normal squamous epithelium in comparison to patients treated with PPI. However, no clear protective effect of ARS on the development of cancer was found. The reduction of cancer risk in this meta-analysis was shown to be associated with the type of study and was found in case series and uncontrolled studies. In controlled studies, this risk however, was not statistically significant.

Data on a possible protective effect of ARS on the development of EA were searched for in a population-based retrospective cohort study. A large Swedish population-based retrospective cohort study from 2001 in more than 10,000 patients after ARS did not show a risk reduction for the development of EA following ARS [39].

It is interesting to note that ARS patients who developed an EA had a higher chance for failed fundoplication with recurrent or persistent reflux [40].

A recent meta-analysis comprising ten studies analyzed the incidence of EA following ARS compared with medically treated patients with GERD with or without BE including the general background population [36]. The results of this study indicate that the incidence rate ratio (IRR) for EA is generally lower among patients treated with ARS. Limiting this analysis to the seven studies considering the effect of ARS or medical therapy in patients with BE, there is a statistically significant risk reduction for EA in the surgical group. No difference of IRR is reported comparing the effect of ARS on the development of EA in patients without Barrett's metaplasia. It appears therefore that patients with BE have a decreased risk for EA after ARS even if the risk is still higher than within the general population.

The prevalence of BE in patients submitted to ARS is higher than in the general population and IM does not regress in all operated patients. We should also expect that some operated patients may have a recurrent GERD, a condition that increases the risk of cancer in comparison to the general population. This is in line with the observation that in up to 20% of patients with BE submitted to ARS there is still an abnormal esophageal acid exposure [40–42]. In the series reported by O'Riordan et al. [17], 2 out of 58 patients with BE treated with ARS progressed to LGD while two other patients developed an EA 4 and 7 years after surgery. All four patients had a pathological esophageal acid exposure. Similar data have been reported [19] in a retrospective study on 75 patients with BE followed for a long period after ARS: progression of non-dysplastic IM to HGD was 7 times higher among patients with failed fundoplication.

The main factor proposed to contribute to the development of EAC after antireflux surgery is persistent postoperative reflux due to failed antireflux surgery. The prevalence of abnormal postoperative acid reflux has ranged from 15% to 41% [17, 43]. At a median follow-up of 8.9 years after antireflux surgery in BE patients, progression to HGD or EAC was more frequent in patients with a disrupted fundoplication (27%) than in those with an intact fundoplication (3%). The progression rate from BE to HGD or EAC was 2.6% per patient-year in those with a disrupted fundoplication compared to 0.36% in those with an intact plication [19].

Interestingly, the results of the English national population-based cohort study have been presented at the Annual Meeting of the European Surgical Association in Trieste 2018 by Markar and colleagues [44]. The Hospital Episode Statistics (HES) database was used to identify all patients in England aged over 50 years diagnosed with GERD with or without Barrett's esophagus from 2000 to 2012. Among 580,293 included patients with GERD and 22,901 with BE, 9753 and 432 underwent ARS, respectively. In GERD patients, ARS reduced the risk of esophageal cancer (HR = 0.74; 95%CI 0.58–0.96). In Barrett's esophagus patients, the corresponding HR was 0.44 (95% CI 0.06-3.04). ARS was associated with decreased point estimates of esophageal cancer in patients with GERD (0% vs. 0.6%; $P = 0.15$) and Barrett's esophagus (HR = 0.80; 95%CI 0.24–2.66), but these were not statistically significant. The authors conclude that ARS may be associated with a reduced risk of esophageal cancer risk however, ARS remains primarily an operation for symptomatic relief.

Patients with BE undergoing ARS appear to also have a change in the molecular environment which might help to explain the apparent risk reduction for EA after ARS: ARS induces a significantly higher reduction of activated NF-kappaB, p50 and p65 subunits, interleukin (IL)-1alpha, and IL-1beta in comparison to medical treatment [45]. These patients also seem to have a reduction of mucosal gene methylation [46]. Data on the efficacy of ARS in molecular stabilization of BE come from a study from Spain [47], where 45 patients randomly assigned to ARS or medical therapy were followed for at least 5 years. Three biomarkers (Ki67, p53, and apoptotic index) were analyzed in endoscopic biopsies. Cellular proliferation (percentage of Ki-67 positive cells) and expression of p53 remained stable in surgical patients, but increased significantly under medical treatment ($p = 0.041$). Apoptotic index increased after surgery and decreased under medical therapy. These data from a small series point towards a protective effect of ARS in BE. Interestingly, patients in the medical arm maintain these alterations independent of the efficacy in the control of esophageal acid exposure. It is hypothesized that in patients treated with PPI, biliopancreatic reflux, if present as a potential key factor in the malignant progression of BE [43], might still damage the esophageal mucosa [43, 45, 48].

In conclusion, patients with BE after effective ARS have a higher chance of regression from non-dysplastic IM to normal squamous epithelium in short segment Barrett's esophagus compared to patients treated with PPI. However, no clear protective effect of ARS on the development of cancer has been found.

18.3 Which Type of Surgery for Short and Long Segment Barrett's Esophagus?

Regression of BE depends on the type of surgery. As discussed before, ARS may induce regression of IM in up to 30% of patients with SSBE, while regression in patients with LSBE is ineffective. There might be a need for a more radical procedure such as adding a duodenal diverting procedure (vagotomy, antrectomy, and Roux-en-Y) to fundoplication [49]. A study from Chile [49] demonstrated that 50% of patients with LSBE treated with fundoplication still have esophagitis and IM with progression towards dysplasia in 5% of patients. More than 60% of similar patients submitted to duodenal diversion had an endoscopic regression of metaplasia at 3 and 5 years follow-up.

The efficacy of diverting surgery on BE has also been reported in obese patients with BE submitted to Roux-en-Y gastric bypass. In this group of patients, regression of BE was obtained in 42.9% of patients 1 year after gastric bypass [50].

Similar data have been reported in another study on 2144 obese patients treated with bariatric procedures [51]: 1681 had a Roux-en-Y gastric bypass. Among them, 19 patients (0.9%) had BE. Eleven of them who had either SSBE (nine patients) or LSBE (two patients) all had a reduction of the extent of BE, and a complete regression was noted in three patients with SSBE (three patients) and one with LSBE.

Whereas it is generally accepted that ARS surgery in obese patients should not consist of a fundoplication but a bariatric procedure, the role of duodenal diverting procedures in combination with ARS for patients with Barrett's esophagus is currently unclear and it is unlikely that such a complex procedure will gain widespread acceptance.

18.4 Role of ARS to Prevent BE Recurrence Following Endoscopic Ablation Procedures

As extensively discussed in another chapter of this book, radiofrequency ablation (RFA) of BE can induce squamous re-epithelization of the esophagus in a substantial proportion of patients. BE can be eradicated in more than 80% of patients with IM and more than 70% of patients with LGD.

On the contrary, approximately 40% of patients experience a recurrence of BE after morphologic complete eradication within 24 months of follow-up. Even more serious is the 8% progression rate to EA [52–55]. A recent meta-analysis reported a lower but still substantial 13% recurrence rate of BE after eradication [56].

Since ARS seems to reduce the risk of progression from IM towards EA, it appears logical to add ARS to any ablation procedure. This approach has been reported to be safe [57]. ARS does not seem to render RFA more difficult. In a study of 5537 patients undergoing RFA, 301 (5.4%) had a previous fundoplication. No significant difference was noted in this group of patients in terms of complications of RFA, rate of eradication of IM or dysplasia, or number of RFA courses [58].

A recent prospective study [59] compared 47 patients with complete BE eradication after RFA who were then treated either with medical antireflux therapy (25 patients) or with ARS (22 patients with Nissen fundoplication synchronous or after RFA). After a 2 years follow-up, recurrence of BE was reported in 20% of patients in the medical group as compared to 9.1% of the ARS group. In patients submitted to ARS, BE reappeared after a longer time elapse in comparison to medically treated patients, and the risk of recurrence was directly related to pretreatment severity of reflux, presence of LSBE and large hiatal hernias. This suggests that patients with LSBE and large hiatal hernia are good candidates for ARS following eradication of BE.

Similar results were obtained in another study comparing these two treatment modalities after RFA [60].

Still, these data come from small groups of patients and contrasting results were also reported. In a study from Finland, the incidence of Barrett's recurrence after ARS in patients with complete eradication of intestinal metaplasia with the NDyag laser was significant (5 out of 15 patients) after a median follow-up of 7.6 years [61].

Recently, the results of a retrospective study on 49 patients with BE and dysplasia undergoing RFA and endoscopic mucosal resection (EMR), if needed, followed by a Nissen fundoplication were published [62]. A complete remission of IM was obtained in 26 patients. Four patients (15%) had a recurrence within a mean follow-up of 26 months. Sixteen patients had a regression from dysplasia to metaplasia. In

this group, no progression was observed during the 2 years follow-up. Among seven patients with persistence of dysplasia after RFA and EMR treated with ARS and further ablative procedures, four patients had a remission of metaplasia (57%), two had regression from dysplasia to metaplasia (29%), and one had persistence of LGD. Patients in this subgroup had a more severe disease, long lasting GERD, LSBE, higher BMI, and large hiatal hernias. Again patients with these characteristics might benefit from ARS after ablation of BE ± dysplasia for symptom control and risk reduction of progression.

Reluctance for this strategy may come from retrospective studies showing that a higher risk for postoperative complications has been reported in patients submitted to esophagectomy for EA after ARS [63, 64]. Both studies however, suffer from many biases including too long time periods [63] and open transhiatal resections [64].

In conclusion, it appears that patients at high risk for BE progression (i.e., *severe GERD, LSBE, large hiatal hernia) treated with RFA should be considered candidates for ARS.*

References

1. Anderson LA, Watson RG, Murphy SJ, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. World J Gastroenterol. 2007;13:1585–94.
2. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340:825–31.
3. Cook MB, Corley DA, Murray LJ, et al. Gastroesophageal reflux in relation to adenocarcinomas of the esophagus: a pooled analysis from the Barrett's and esophageal adenocarcinoma consortium (BEACON). PLoS One. 2014;9:e103508.
4. Malfertheiner P, Nocon M, Vieth M, et al. Evolution of gastro-oesophageal reflux disease over 5 years under routine medical care the ProGERD study. Aliment Pharmacol Ther. 2012;35:154–64.
5. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst. 2011;103:1049–57.
6. Pohl H, Pech O, Arash H, et al. Length of Barrett's oesophagus and cancer risk: implications from a large sample of patients with early oesophageal adenocarcinoma. Gut. 2016;65:196–201.
7. Hak NG, Mostafa M, Salah T, et al. Acid and bile reflux in erosive reflux disease, non-erosive reflux disease and Barrett's esophagus. Hepato-Gastroenterology. 2008;55:442–7.
8. Sun D, Wang X, Gai Z, et al. Bile acids but not acidic acids induce Barrett's esophagus. Int J Clin Exp Pathol. 2015;8:1384–92.
9. Fitzgerald RC, Abdalla S, Onwuegbusi BA, et al. Inflammatory gradient in Barrett's oesophagus: implications for disease complications. Gut. 2002;51:316–22.
10. Fitzgerald RC. Barrett's oesophagus and oesophageal adenocarcinoma: how does acid interfere with cell proliferation and differentiation? Gut. 2005;54(Suppl 1):i21–6.
11. Oelschlager BK, Barreca M, Chang L, et al. Clinical and pathologic response of Barrett's oesophagus to laparoscopic antireflux surgery. Ann Surg. 2003;238:458–64.
12. Hofstetter WL, Peters JH, DeMeester TR, et al. Long-term outcome of antireflux surgery in patients with Barrett's esophagus. Ann Surg. 2011;234:532–8; discussion 538-9
13. Abbas EA, Deschamps C, Cassivi SD, et al. Barrett's esophagus: the role of laparoscopic fundoplication. Ann Thorac Surg. 2004;77:393–6.
14. Biertho L, Dallemagne B, Dewandre JM, et al. Laparoscopic treatment of Barrett's esophagus: long-term results. Surg Endosc. 2007;21:11–5.

15. Desai KM, Soper NJ, Frisella MM, et al. Efficacy of laparoscopic antireflux surgery in patients with Barrett's esophagus. Am J Surg. 2003;186:652–9.
16. Marano S, Mattacchione S, Luongo B, et al. Two-year subjective, objective, quality of life, and endoscopic follow-up after laparoscopic Nissen-Rossetti in patients with columnar-lined esophagus. Surg Laparosc Endosc Percutan Tech. 2013;23:292–8.
17. O'Riordan JM, Byrne PJ, Ravi N, et al. Long-term clinical and pathologic response of Barrett's esophagus after antireflux surgery. Am J Surg. 2004;188:27–33.
18. Simonka Z, Paszt A, Abraham S, et al. The effects of laparoscopic Nissen fundoplication on Barrett's esophagus: long-term results. Scand J Gastroenterol. 2012;47:13–21.
19. Zehetner J, deMeester SR, Ayazi S, et al. Long-term follow-up after antireflux surgery in patients with Barrett's esophagus. J Gastrointest Surg. 2010;14:1483–91.
20. Ozmen V, Oran ES, Gorgun E, et al. Histologic and clinical outcome after laparoscopic Nissen fundoplication for gastroesophageal reflux disease and Barrett's esophagus. Surg Endosc. 2006;20:226–9.
21. Zaninotto G, Cassaro M, Pennelli G, et al. Barrett's epithelium after antireflux surgery. J Gastrointest Surg. 2005;9:1253–60.
22. Csendes A, Braghetto I, Burdiles P, et al. Late results of the surgical treatment of 125 patients with short-segment Barrett esophagus. Arch Surg. 2009;144:921–7.
23. Mabrut JY, Baulieux J, Adham M, et al. Impact of antireflux operation on columnar lined esophagus. J Am Coll Surg. 2003;196:60–7.
24. Bowers SP, Mattar SG, Smith CD, Waring JP, Hunter JG. Clinical and histologic follow-up after antireflux surgery for Barrett's esophagus. J Gastrointest Surg. 2002;6:532–8; discussion 39
25. Oeberg S, Wenner J, Johansson J, et al. Barrett esophagus: risk factors for progression to dysplasia and adenocarcinoma. Ann Surg. 2005;242:49–54.
26. Gurski RR, Peters JH, Hagen JA, et al. Barrett's esophagus can and does regress after antireflux surgery: a study of prevalence and predictive features. J Am Coll Surg. 2003;196:706–12.
27. Rossi M, Barreca M, de Bortoli N, et al. Efficacy of Nissen fundoplication versus medical therapy in the regression of low grade dysplasia in patients with Barrett esophagus. A prospective study. Ann Surg. 2006;243:58–63.
28. Vennalaganti P, Kanakadandi V, Goldblum JR, et al. Discordance among pathologists in the United States and Europe in diagnosis of low-grade dysplasia for patients with Barrett's esophagus. Gastroenterology. 2017;152:564–70.
29. Kuramochi H, Vallbohmer D, Uchida K, et al. Quantitative, tissue-specific analysis of cyclooxygenase gene expression in the pathogenesis of Barrett's adenocarcinoma. J Gastrointest Surg. 2004;8:1007–16; discussion 1016-7.
30. Vallbohmer D, DeMeester SR, Oh DS, et al. Antireflux surgery normalizes cyclooxygenase-2 expression in squamous epithelium of the distal oesophagus. Am J Gastroenterol. 2006;101:1458–66.
31. Oh DS, DeMeester SR, Vallbohmer D, et al. Reduction of interleukin 8 gene expression in reflux esophagitis and Barrett's oesophagus with antireflux surgery. Arch Surg. 2007;142:554–9; discussion 559–60.
32. Low DE, Levine DS, Dail DH, Kozarek RA. Histological and anatomic changes in Barrett's oesophagus after antireflux surgery. Am J Gastroenterol. 1999;94:80–5.
33. Oberg S, DeMeester TR, Peters JH, et al. The extent of Barrett's oesophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. J Thorac Cardiovasc Surg. 1999;117:572–80.
34. Chang EY, Morris CD, Seltman AK, et al. The effect of antireflux surgery on esophageal carcinogenesis in patients with Barrett oesophagus: a systematic review. Ann Surg. 2007;246:11–21.
35. Zaninotto G, Parente P, Salvador R, et al. Long-term follow-up of Barrett's epithelium: medical versus antireflux surgical therapy. J Gastrointest Surg. 2012;16:7–14.
36. Maret-Ouda J, Konings P, Lagergren J, Brusselaers N. Antireflux surgery and risk of esophageal adenocarcinoma: a systematic review and meta-analysis. Ann Surg. 2016;263:251–7.

37. Lagergren J, Ye W, Lagergren P, Lu Y. The risk of esophageal adenocarcinoma after antireflux surgery. Gastroenterology. 2010;138:1297–301.
38. Maret-Ouda J, Wahlin K, El-Serag HB, Lagergren J. Association between laparoscopic antireflux surgery and recurrence of gastroesophageal reflux. JAMA. 2017;318:939–46.
39. Ye W, Chow WH, Lagergren J, et al. Risk of adenocarcinomas of the oesophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. Gastroenterology. 2001;121:1286–93.
40. Lagergren J, Viklund P. Is esophageal adenocarcinoma occurring late after antireflux surgery due to persistent postoperative reflux? World J Surg. 2007;31:465–9.
41. Tran T, Spechler SJ, Richardson P, et al. Fundoplication and the risk of esophageal cancer in gastroesophageal reflux disease: a veterans affairs cohort study. Am J Gastroenterol. 2005;100:1002–8.
42. Lofdahl HE, Lu Y, Lagergren P, et al. Risk factors for esophageal adenocarcinoma after antireflux surgery. Ann Surg. 2013;257:579–82.
43. Parrilla P, Martinez de Haro LF, Ortiz A, et al. Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. Ann Surg. 2003;237:291–8.
44. Markar SR, Arhi C, Leusink A, et al. The influence of antireflux surgery on esophageal cancer risk in England – National population-based cohort study. 2018 Paper presented at the Annual Meeting of the European Surgical Association, Trieste 2018.
45. Babar M, Ennis D, Abdel-Latif M, et al. Differential molecular changes in patients with asymptomatic long-segment Barrett's esophagus treated by antireflux surgery or medical therapy. Am J Surg. 2010;199:137–43.
46. Smith E, Kelly JJ, Ruskiewicz AR, et al. The effect of long-term control of reflux by fundoplication on aberrant deoxyribonucleic acid methylation in patients with Barrett esophagus. Ann Surg. 2010;252:63–9.
47. Martinez de Haro LF, Ortiz A, Parrilla P, et al. Long-term follow-up of malignancy biomarkers in patients with Barrett's esophagus undergoing medical or surgical treatment. Ann Surg. 2012;255:916–21.
48. Stein HJ, Kauer WK, Feussner H. Bile reflux in benign and malignant Barrett's esophagus: effect of medical acid suppression and Nissen fundoplication. J Gastrointest Surg. 1998;2:333–41.
49. Braghetto I, Korn O, Valladares H, et al. Laparoscopic surgical treatment for patients with shortand long-segment Barrett's esophagus: which technique in which patient? Int Surg. 2011;96:95–103.
50. Andrew B, Alley JB, Aguilar CE, Fanelli RD. Barrett's esophagus before and after Roux-en-Y gastric bypass for severe obesity. Surg Endosc. 2018;32:930–6.
51. Gorodner V, Buxhoeveden R, Clemente G, et al. Barrett's esophagus after Roux-en-Y gastric bypass: does regression occur? Surg Endosc. 2017;31:1849–54.
52. Haidry RJ, Dunn JM, Butt MA, et al. Radiofrequency ablation and endoscopic mucosal resection for dysplastic Barrett's esophagus and early esophageal adenocarcinoma: outcomes of the UK National Halo RFA Registry. Gastroenterology. 2013;145:87–95.
53. Gupta M, Iyer PG, Lutzke L, et al. Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's esophagus: results from a US Multicenter Consortium. Gastroenterology. 2013;145:79–86.
54. Guarner-Argente C, Buoncristiano T, Furth EE, Falk GW, Ginsberg GG. Long-term outcomes of patients with Barrett's esophagus and high-grade dysplasia or early cancer treated with endoluminal therapies with intention to complete eradication. Gastrointest Endosc. 2013;77:190–9.
55. Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology. 2011;141:460–8.
56. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11:1245–55.

57. dos Santos RS, Bizekis C, Ebright M, et al. Radiofrequency ablation for Barrett's esophagus and low-grade dysplasia in combination with an antireflux procedure: a new paradigm. J Thorac Cardiovasc Surg. 2010;139:713–6.
58. Shaheen NJ, Kim HP, Bulsiewicz WJ, et al. Prior fundoplication does not improve safety or efficacy outcomes of radiofrequency ablation: results from the U.S. RFA Registry. Gastrointest Surg. 2013;17:21–9.
59. Skrobić O, Simić A, Radovanović N, et al. Significance of Nissen fundoplication after endoscopic radiofrequency ablation of Barrett's esophagus. Surg Endosc. 2016;30:3802–7.
60. O'Connell K, Velanovich V. Effects of Nissen fundoplication on endoscopic endoluminal radiofrequency ablation of Barrett's esophagus. Surg Endosc. 2011;25:830–4.
61. Kauttu T, Räsänen J, Krogerus L, et al. Long-term results of ablation with antireflux surgery for Barrett's esophagus: a clinical and molecular biologic study. Surg Endosc. 2012;26:1892–7.
62. Johnson CS, Louie BE, Wille A, et al. The durability of endoscopic therapy for treatment of Barrett's metaplasia, dysplasia, and mucosal cancer after Nissen fundoplication. J Gastrointest Surg. 2015;19:799–805.
63. Shen KR, Harrison-Phipps KM, Cassivi SD, et al. Esophagectomy after antireflux surgery. J Thorac Cardiovasc Surg. 2010;139:969–75.
64. Chang AC, Lee JS, Sawicki KT, Pickens A, Orringer MB. Outcomes after esophagectomy in patients with prior antireflux or hiatal hernia surgery. Ann Thorac Surg. 2010;4:1015–21.

19 Early Adenocarcinoma of Barrett's Esophagus in the East and the West: Is This an Endoscopic or a Surgical Problem?

Takuji Gotoda and Antonello Trecca

19.1 Important Background

In the West, the incidence of esophageal adenocarcinoma has been increasing rapidly in the last few decades [1, 2].The risk factors for this cancer include male sex, Caucasian, hiatal hernia, gastroesophageal reflux disease (GERD), obesity, and cigarette smoking [3, 4]. In addition, recurrent heartburn/regurgitation and obesity are appreciably stronger risk factors for early-onset esophageal adenocarcinoma relative to older age categories [5–7]. Esophagogastric junction (EGJ) adenocarcinoma is classified according to the Siewert system (Fig. 19.1) based on tumor epicenters: type I, 5 to 1 cm above the EGJ; type II, 1 cm above to 2 cm below the EGJ; and type III, 2 to 5 cm below the EGJ, and Siewert type II tumors are considered as true cardiac carcinomas arising from the EGJ epithelium [8]. Thus, the term of esophageal adenocarcinoma clinically used in the West is almost equal to Siewert type I as same as adenocarcinoma developed from long-segment Barrett's esophagus. Actually, EGJ adenocarcinoma has risen significantly since the early 1970s in the USA [9, 10].

In many European countries, cardia cancer was coded just in that period but a consensus on its definition was established only at the end of the 1990s. The real incidence of the disease in the period between 1989 and 1994 in Sweden could have been overestimated of 45% or underestimated of 15% in comparison with the Swedish Cancer Registry [11]**.** However, a more recent study in the USA showed that the incidence of EGJ adenocarcinoma had plateaued during the early 1990s [12].

T. Gotoda
Division of Gastroenterology and Hepatology, Department of Medicine,
Nihon University School of Medicine, Tokyo, Japan

A. Trecca (✉)
Gastroenterology and Operative Endoscopic Units, I-Salus Project Group, Rome, Italy

G. Galloro (ed.), *Revisiting Barrett's Esophagus*,
https://doi.org/10.1007/978-3-319-92093-1_19

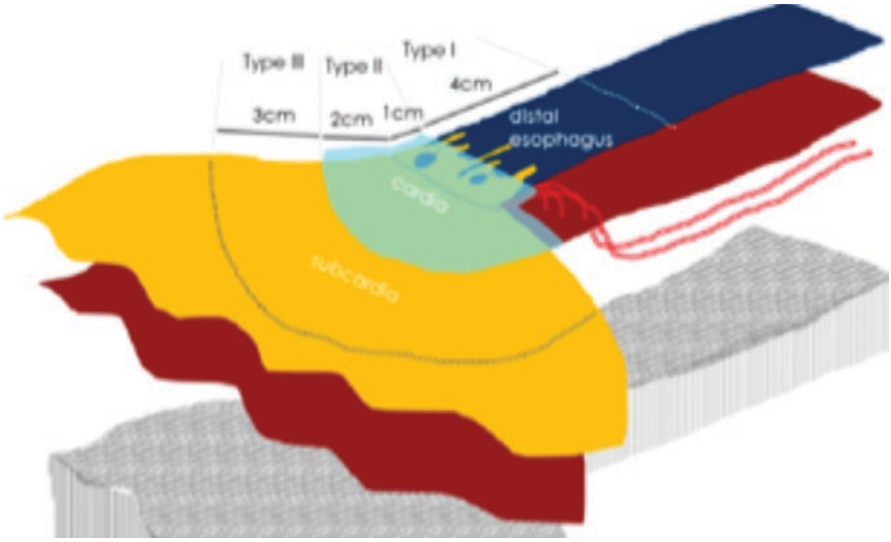

Fig. 19.1 Siewert classification of adenocarcinoma of the esophagogastric junction (EGJ). Type I, adenocarcinoma of the distal esophagus; type II, true carcinoma of the cardia; type III, adenocarcinoma of the subcardia

Table 19.1 Demographic data of gastric adenocarcinoma in the East

	EGJ	Elsewhere	*P*-value
No. of patients	520	6415	
Male/female ratio	4.1	1.95	<0.001
Age, med	62	61	
Age, range	23–88	16–93	

In Asian countries, although squamous cell type remains the most common type of esophageal cancer, it is suggested that the incidence of esophageal adenocarcinoma will increase with recent changes to a westernized dietary lifestyle. However, esophageal adenocarcinoma in Asia means EGJ adenocarcinoma classified into Siewert type II. A previous report revealed that the ratio of EGJ adenocarcinomas among gastrointestinal neoplasms is 4% in Japan [13]. Another report showed that the overall proportion of EGJ adenocarcinoma cases among those of gastric cancer has been gradually increasing from 2.3% in 1962–1965 to 10.0% in 2001–2005 (Table 19.1, Fig. 19.2) [14]. Siewert type II tumors have also increased from 28.5% in 1962–1965 to 57.3% in 2001–2005 among patients with resected EGJ adenocarcinoma, whereas the proportion of Siewert type I tumors has remained at 1% and the incidence of Siewert type III tumors has declined during the past four decades. In Western countries, the decrease in the incidence of esophageal squamous cell cancer and noncardia gastric cancer parallels a concomitant increase in the incidence of distal esophageal adenocarcinoma and EGJ/cardia cancer. So far upper gastrointestinal tumors are decreasing overall, but concentrating around gastrointestinal junction [15]. European Prospective Investigation into Cancer and Nutrition (EPIC) study showed that cardia adenocarcinoma represent 29.4% of all gastric

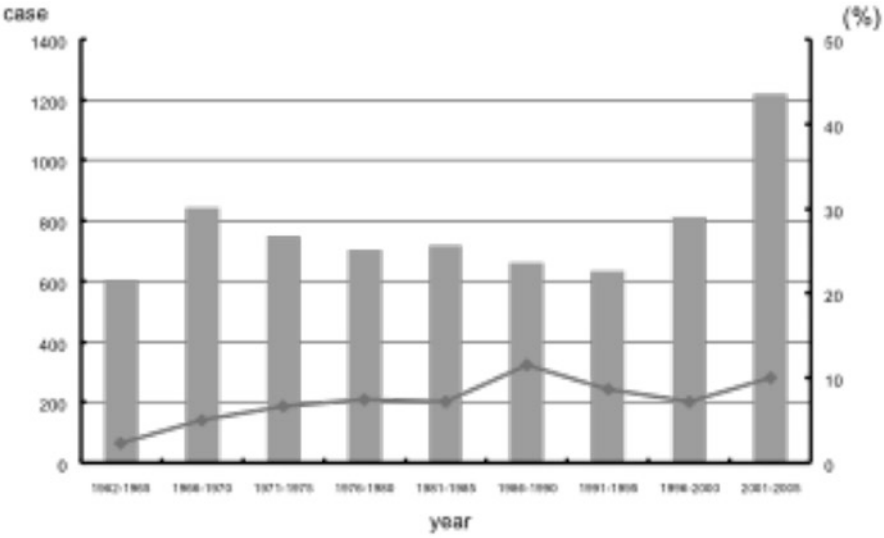

Fig. 19.2 Changing rate in EGJ adenocarcinoma among all gastric adenocarcinoma. Bar, no. of gastric adenocarcinoma; line, proportion of EGJ adenocarcinoma among all gastric adenocarcinoma

adenocarcinoma in Europe with a higher proportion in Northern countries (35%) than in Mediterranean countries (18%) [16].

In addition, some studies suggest that EGJ adenocarcinoma has two distinct etiologies: one arising from chronic gastritis similar to distal gastric cancer, and the other related to GERD similar to esophageal adenocarcinoma including Barrett's adenocarcinoma [17, 18]. A wide range of stimulants to the mucosa, including reflux of acid, bile acid, and other substances, as well as *Helicobacter pylori* (*H. pylori*), cause inflammatory deformations, intestinal metaplasia, and hybrid mucosa [19]. This, along with the complex involvement of multiple types of glandular epithelia, can be the background for the development of EGJ adenocarcinoma [20]. The presence of *H. pylori* and the degree of atrophic gastritis using serological markers reported that there may be two etiologies for EGJ adenocarcinoma, related to *H. pylori*-associated atrophic gastritis (resembling non-cardiac gastric adenocarcinoma) and resembling esophageal adenocarcinoma related to non-atrophic gastric mucosa and gastroesophageal reflux disease (GERD) [17, 21]. In recent years, nitric oxide stress localized in the EGJ has been suggested to contribute to carcinogenesis in EGJ adenocarcinoma [22]. GERD is reportedly an important risk factor for EGJ adenocarcinoma, as it is for esophageal adenocarcinoma in the broad sense [23]. In addition, a report on short-segment Barrett's esophagus (Fig. 19.3) found no significant difference in genomic change from long-segment Barrett's esophagus [24]. Thus, it is expected that at least some EGJ adenocarcinoma cases have the same carcinogenic pathway as esophageal adenocarcinoma (Fig. 19.4) [25]. Thus, when we discuss about esophageal adenocarcinoma, we should know that different definitions causing possible confusion are used in each region.

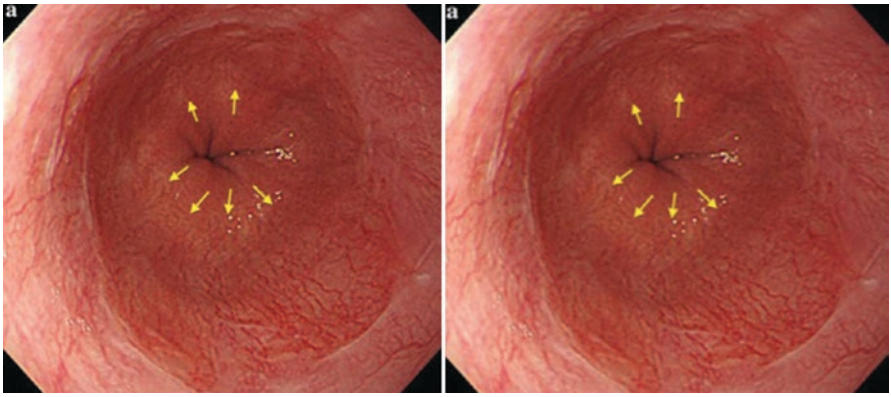

Fig. 19.3 Endoscopic images of the landmark (palisade vessels) on the esophagogastric junction. (**a**) Small longitudinal vessels named "palisade vessels" can be observed in the lower esophagus across the squamocolumnar junction with the patient in deep inhalation. The end of the palisade vessels and gastric folds can be identified above the columnar epithelium. (**b**) Without adequate inhalation, the end of the palisade vessels cannot be recognized clearly

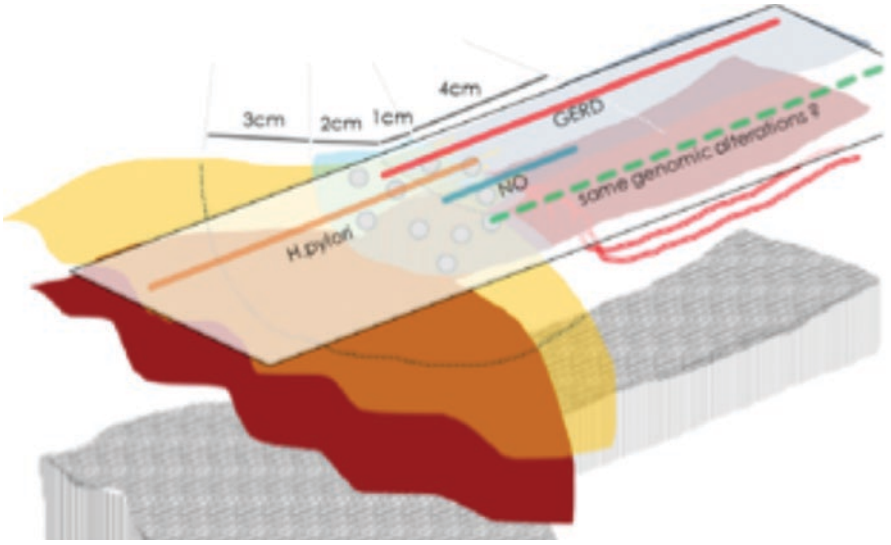

Fig. 19.4 Schema indicating the presumed etiology of adenocarcinoma in the esophagogastric junction (EGJ) zone and surrounding area. Multiple etiologies have been proposed for adenocarcinoma in the EGJ zone, and although some of these are common to esophageal adenocarcinoma, separate etiologies and genetic changes within the EGJ zone, further subdivided by the EGJ line, remain unclear. *GERD* gastroesophageal reflux disease, *NO* nitric oxide

19.2 Early Adenocarcinoma of Barrett Esophagus in the East

19.2.1 Endoscopic Diagnosis and Treatment

According to a recent report, endoscopic resection was carried out in over half of cases with esophageal adenocarcinomas, including EGJ adenocarcinomas, which were confined to the submucosa. Endoscopic screening and precise diagnosis may contribute to detection at an early stage. However, the Japanese treatment guidelines for both esophageal and gastric cancer are unclear concerning the role of endoscopic resection for Siewert type II tumors (true EGJ adenocarcinomas) [26]. Thus far, most reported studies of feasible endoscopic resection for Siewert type II tumors were based on the gastric cancer guidelines [27]. Among 53 consecutive patients with superficial EGJ adenocarcinoma who underwent endoscopic submucosal dissection (ESD: Fig. 19.5), the 5-year overall, recurrence-free, and cause-specific survival rates in the 53 patients were 94.2%, 92.3%, and 96.1%, respectively (Fig. 19.6) [28, 29]. En bloc, R0, and curative resection rates were 100%, 79%, and 68%, respectively. In 36 patients with curative resection, the cause-specific survival rate was 100% and no recurrence or metastases were detected. In 17 patients with non-curative resection, recurrence was found in three patients (17%); two of the three patients died of their disease while one patient received chemotherapy.

All were retrospective single-center studies with a relatively small number of cases. Recently, a multicenter retrospective study in Japan suggested that mucosal and submucosal cancers (1–500 lm invasion) without risk factors, such as lymphovascular involvement, a poorly differentiated component, and tumor size of >30 mm, have a low incidence of metastasis and may be good candidates for endoscopic resection in patients with esophageal adenocarcinomas including EGJ adenocarcinomas (Table 19.2) [30, 31]. However, a well-designed prospective multicenter trial using the same definition of EGJ adenocarcinoma is warranted.

Curative endoscopic resection for EGJ adenocarcinoma can be problematic if there is subsquamous carcinoma extension. Modalities such as conventional white-light endoscopy [32], magnifying endoscopy with narrow-band imaging after acetic acid spraying [33], and optical coherence tomography [34] can be used to detect the oral extension of buried glands underneath the squamous epithelium. The subsquamous carcinoma extension was less than 1 cm in most reported studies [35], therefore, ESD with a 1-cm safety margin can be suggested for such cases, but not if the extension is beyond 1 cm [36, 37].

19.2.2 Surgical Treatment

In order to clarify to what extent resection and lymphadenectomy are reasonable in EGJ cancer of ≤4 cm in diameter (defined as cancer, either adenocarcinoma or

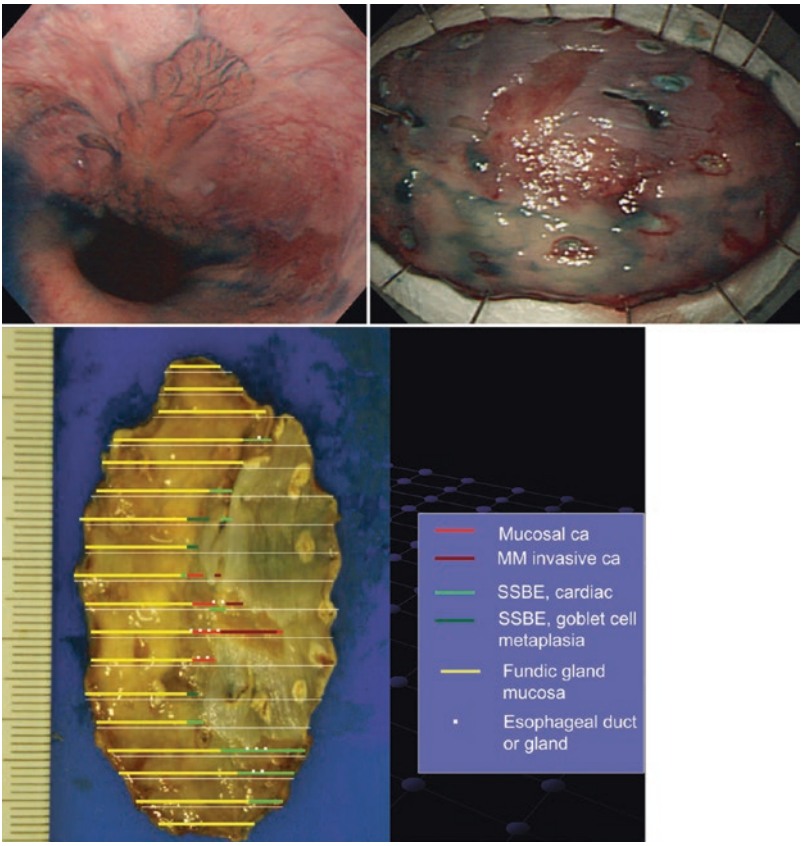

Fig. 19.5 Endoscopic submucosal dissection (ESD) for superficial EGJ adenocarcinoma. (**a**) Superficial EGJ adenocarcinoma identified on 2 O'clock. (**b**) Resected material pined on the board for precise pathological assessment. (**c**) Result of pathological evaluation; 0-IIc pT1a (*MM* muscularis mucosa) well-differentiated adenocarcinoma negative lymphovascular involvement

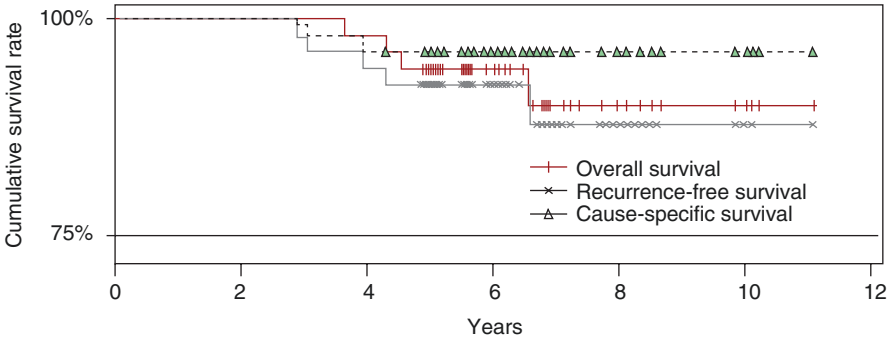

Fig. 19.6 Endoscopic submucosal dissection (ESD) for superficial EGJ adenocarcinoma: cumulative overall, recurrence-free, and cause-specific survival curves for 53 patients

Table 19.2 Multivariate analysis of risk factors for metastasis from esophageal adenocarcinoma: a multicenter retrospective study in a Japanese population

	Odds ratio	95 % CI	*p* value
Lesions size (mm)			0.001
≤30 mm	1	1.63–5.97	
30 mm<	3.12		
Macroscopic appearance			0.10
Flat type	1	0.91–3.18	
Protruding type	1.70		
Invasion depth of cancer			0.25
DMM	1	0.22–1.49	
SM	0.57		
Lymphovascular involvement			<0.001
Negative	1	3.12–12.32	
Positive	6.20		
Infiltrative growth pattern			0.13
a	1	0.80–5.64	
b or c	2.12		
Poorly differentiated component			<0.001
Negative	1	1.92–7.10	
Positive	3.69		

CI confidence interval, *DMM* deep muscularis mucosa, *SM* submucosa

squamous cell carcinoma with its center located within 2 cm of the EGJ), the Japanese Gastric Cancer Association and Japan Esophageal Society have joined forces to conduct a nationwide surveillance in 3177 patients from 273 institutions who had surgery between 2001 and 2010. As a result of this collaborative effort, a new algorithm in the extent of lymphadenectomy for EGJ cancer was constructed based on tumor location, histology, and T-categories (Fig. 19.7) [38]. Another important observation was that perigastric lymph node stations numbered 4a, 4sb, 4d, 5, and 6 were considered as non-beneficial to dissect [39–41].

19.3 Early Adenocarcinoma of Barrett Esophagus in the West

19.3.1 Endoscopic Diagnosis and Treatment

In western countries, much attention has been paid to the study of Barrett Esophagus due to a higher incidence of the disease and its evolutive progression to indefinite dysplasia, low-grade and high-grade dysplasia with a rate of less than 0.5 per 100 patient-year for non-dysplastic BE, up to 10 times higher in presence of low-grade and 60 times higher in high-grade dysplasia [42]. This is in contrast with a general incidence of the disease of around 2%, so far the latest guidelines by the Delphi Consensus for management of Barrett's Esophagus (BOBCAT) stressed the importance to identify patients at higher risk of progression [43]. A multivariate analysis

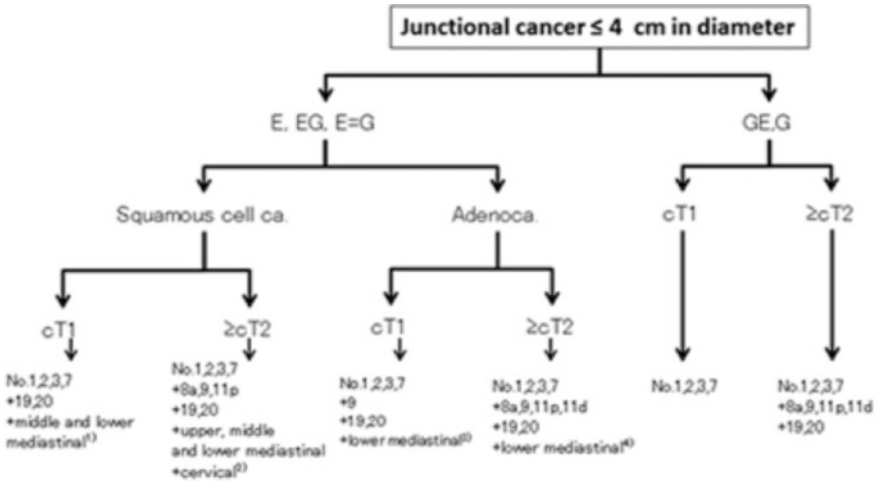

Fig. 19.7 Algorithm showing the tentative standard in the extent of lymphadenectomy for junctional cancer based on the tumor location, histology, and T-categories

conducted in a multicenter cohort study showed that length of BE of more than 6–7 cm was a significant predictor of progression to high-grade dysplasia and esophageal adenocarcinoma with a relative risk of 1.11 per cm increase in length [44]. The parameter of length was highly considered in the West and for this reason a distinction was outlined between two variants of BE, short and long with the former defined as columnar metaplastic glands extending less than 3 cm (but more than 2 cm) into the distal esophagus (Fig. 19.8) [45]. This distinction is not adopted in the East where SSBE is included in BE, being a possible factor explaining the actual difference in the incidence of this disease in eastern countries. Endoscopic detection of any subtle change of the mucosa such as nodularity, erosion, or depression plays a fundamental role in the identification of high-risk patients or patients with high-grade dysplasia or early cancer (Figs. 19.9, 19.10, and 19.11). This approach is much more adopted in the eastern countries where the detection of early gastric cancer already prompts Japanese authors to identify the majority of this disease at an earlier stage. On the other hand, the surveillance of the disease together with the introduction of advanced imaging helped western endoscopists to find preneoplastic or early neoplastic cases, thus improving the early detection. In the West, the traditional treatment was based on esophagectomy with lymph node dissection whose morbidity and mortality rate are very high ranging from 20% to 50% and from 2% to 10%, respectively [46]. On the basis of these findings, endoscopic therapies have gained acceptance and are endorsed in the society guidelines. They include endoscopic mucosal resection (EMR) of visible abnormalities followed by ablation to eradicate Barrett's epithelium with subsequent surveillance. The place for endoscopic treatment is limited to

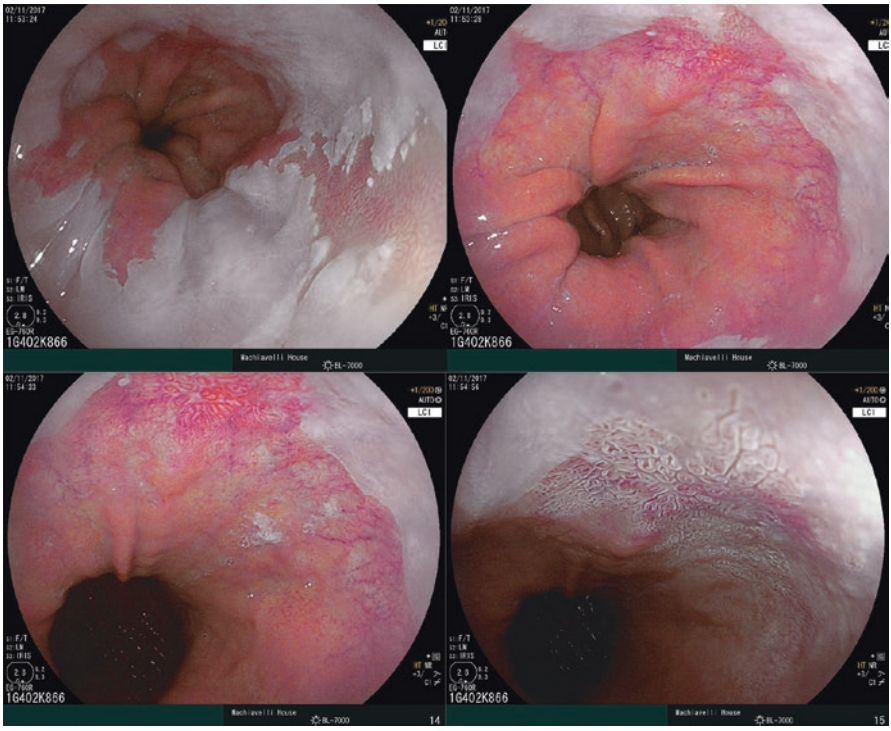

Fig. 19.8 A case of SSBE visible with the enhancement of BLI (Blue Laser Imaging-Fujinon system)

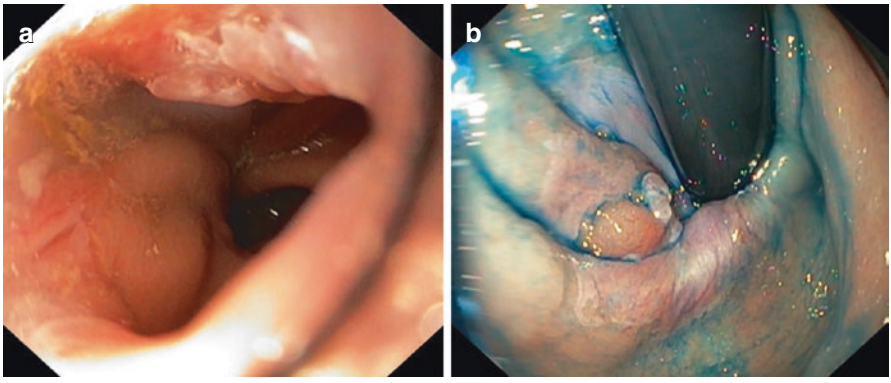

Fig. 19.9 (**a**) White-light endoscopy showing mucosal change on Barrett's Esophagus (slightly elevated lesion with irregular surface) at the anterograde view. (**b**) Chromoendoscopy with indigo carmine 0.4% clearly shows the borders of the lesion in the retrograde view

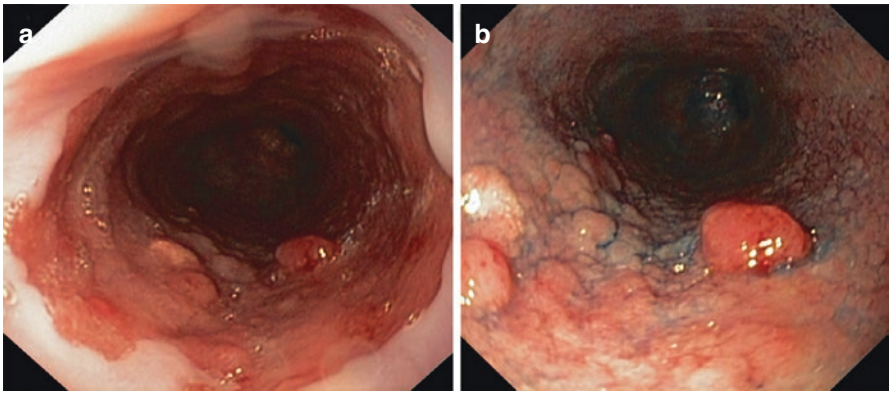

Fig. 19.10 (**a**) White-light endoscopy showing long Barrett's esophagus with nodular changes. (**b**) Chromoendoscopy with indigo carmine 0.4% highlighted the surface of the lesions

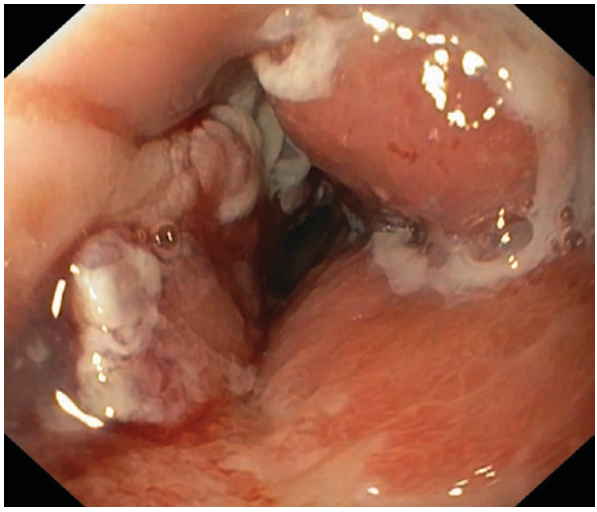

Fig. 19.11 A patient 75 years old with an advanced adenocarcinoma occurred in Barrett's esophagus. The patient had refused surveillance

patients with cancer limited to the mucosa with a very low risk of lymph node metastasis (0–2%), while in case of submucosal cancer or poorly differentiated cancer, size >2 cm and lymphatic or venous infiltration, the patient should be referred to surgery due to the high risk of lymph node metastasis (around 20%) [47]. A large population study based on the Surveillance Epidemiology and End Results (SEER) database compared the outcomes of endoscopic eradication therapies with esophagectomy in 2016 patients with early esophageal cancers demonstrating comparable 2-year and 5-year esophageal cancer-specific survival rates [48]. In order to better identify patients suitable to endoscopic treatment in the eastern experience, esophageal mucosa was further divided into three layers: m1 indicates the involvement of the epithelium, m2 the invasion of the lamina propria, and m3 the invasion of muscular mucosa which can be accurately identified only after obtaining a satisfactory surgical

or endoscopic specimen. The accurate endoscopic methodology in studying early precursors prompts Japanese authors to stress the importance of en bloc resection particularly when dealing with early lesions and the multifocal nature of Barrett's neoplasia. A recent meta-analysis on type I cancers reported that 5% of m3 patients are N positive, although in 90% of the cases only one node is involved. Surgery might be advised in m3 cases [49]. Another recent review on Siewert I stressed the importance of moderately or poorly differentiated cancers (G2-3) and lymphovascular invasion in T1m cancers [50]. Data on Siewert II are very few and they are often included in the Siewert I because they are considered as Barrett esophagus adenocarcinomas. Indications for treatment are similar to those discussed for Siewert I. The identification of the type III is even much more difficult mainly for its late diagnosis as an advanced cancer particularly in western countries where they resemble gastric cancer of the upper third. Concerning the endoscopic treatment we have to underline, once more, the importance of the en bloc resection because it represents the unique opportunity to obtain an accurate histological examination able to select the best treatment for the patient. Endoscopic Mucosal Resection can guarantee en bloc resection only in case of lesions with a diameter of no more than 15 mm. For this reason Japanese authors introduced in the clinical practice another technique, Endoscopic Submucosal Dissection which allows the en bloc resection of lesions irrespective of size, facilitates histological interpretation and reduces recurrence rates [51]. ESD guidelines from the European Society of Gastrointestinal Endoscopy recommend EMR as the mainstay of treatment for Barrett's neoplasia but also advice consideration of ESD for lesions >15 mm, poorly lifting lesions because of scarring and lesions suspicious of Sm invasive cancers [52–56]. A multicenter European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST) demonstrates the technical feasibility and safety of ESD in western setting for resection of complex Barrett's neoplasia (diameter more than 2 cm, poor lifting sign, lesions with sm invasion). A total of 143 lesions were included in the study with a R0 resection rate of 79% similar to other published series (39–85%). Even with limitations due to retrospective design and different sample sizes of the three centers, the authors refer a plateau for en bloc resection after 30 performed procedures [57].

19.3.2 Surgical Treatment

On the other hand, the concept of R0 surgery is gaining attention because it represents the mainstay of cancer treatment in order to reduce recurrence and improve survival [58]. Avoiding positive margins is a key step also in the treatment of EGJ cancers. Margins that can be involved are both longitudinal (proximal and distal) and circumferential. Five centimeter in vivo margins both proximally and distally seem appropriate for all Siewert types. In Siewert I cancers and probably in type II, a wider proximal margin is advisable and normally achievable. In Siewert III cancers, a wider proximal margin is probably unnecessary and thus, if a 5 cm proximal margin can be obtained from the abdomen, a thoracic approach would not be required [59, 60].

19.4 Discussion

The numbers of cases from the three countries are still comparatively low compared with those of Western countries. In addition, there are no data on EGJ adenocarcinoma from cancer registries in most Asian countries. EGJ adenocarcinoma encompasses cardia cancer and lower esophageal adenocarcinoma, including Barrett's adenocarcinoma. In Western countries, most EGJ adenocarcinomas have characteristics similar to those of esophageal adenocarcinomas, in contrast to Asian countries where most have characteristics similar to those of distal gastric cancers [61].The reason for the above difference between the West and East may be the more frequent incidence of *H. pylori*-related gastric cancers and ethnicity factors in the East. The variable prevalence of GERD, obesity, and *H. pylori* infection, and the pattern of gastric atrophy (corpus- or antrum-predominant) may explain the observed differences in incidence and time trends. In Japan, histological curability criteria for endoscopic resection cases have not been established. Endoscopic resection is a minimally invasive treatment for EGJ adenocarcinoma, but it is only indicated for those with a negligible risk of lymph node metastasis. Thus, it is important to carry out endoscopy in high-risk patients (e.g., patients with obesity, heartburn, or regurgitation) to detect early-stage cancers. International collaborative studies would be helpful to clarify differences in the clinicopathological characteristics and for improving the detection rate and the clinical outcome in EGJ adenocarcinomas [62].

References

1. Thrift AP, Whiteman DC. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. Ann Oncol. 2012;23(12):3155–62.
2. Drahos J, Wu M, Anderson WF, et al. Regional variations in esophageal cancer rates by census region in the United States, 1999–2008. PLoS One. 2013;8(7):e67913.
3. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825–31.
4. Lubin JH, Cook MB, Pandeya N, et al. The importance of exposure rate on odds ratios by cigarette smoking and alcohol consumption for esophageal adenocarcinoma and squamous cell carcinoma in the Barrett's esophagus and esophageal adenocarcinoma consortium. Cancer Epidemiol. 2012;36(3):306–16.
5. Hoyo C, Cook MB, Kamangar F, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the international BEACON consortium. Int J Epidemiol. 2012;41(6):1706–18.
6. Pohl H, Wrobel K, Bojarski C, et al. Risk factors in the development of esophageal adenocarcinoma. Am J Gastroenterol. 2013;108(2):200–7.
7. Drahos J, Xiao Q, Risch HA, et al. Age-specific risk factor profiles of adenocarcinomas of the esophagus: a pooled analysis from the international BEACON consortium. Int J Cancer. 2016;138(1):55–64.
8. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg. 1998;85(11):1457–9.
9. Blot WJ, Devesa SS, Kneller RW, et al. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA. 1991;265(10):1287–9.
10. Hansson LE, Sparen P, Nyren O. Increasing incidence of carcinoma of the gastric cardia in Sweden from 1970 to 1985. Br J Surg. 1993;80(3):374–7.

11. Ekstrom AM, Signorello MB, Hansson LE, et al. Evaluating gastric cancer misclassification: a potential explanation for the raise in cardia cancer incidence. J Natl Cancer Inst. 1999;91(9):786–90.
12. Wayman J, Forman D, Griffin SM. Monitoring the changing pattern of esophagogastric cancer: data from a UK regional cancer registry. Cancer Causes Control. 2001;12(10):943–9.
13. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. Semin Radiat Oncol. 2013;23(1):3–9.
14. Kusano C, Gotoda T, Khor CJ, et al. Changing trends in the proportion of adenocarcinoma of the esophagogastric junction in a large tertiary referral center in Japan. J Gastroenterol Hepatol. 2008;23(11):1662–5.
15. Jankowski JA, Harrison RF, Perry I, et al. Barrett's neoplasia. Lancet. 2000;356(9247):2079–85.
16. Carneiro F, Moutinho C, Pera G, et al. Pathology findings and validation of gastric and esophageal cancer cases in a European cohort (EPIC/EUR-GAST). Scand J Gastroenterol. 2007;42(5):618–27.
17. Derakhshan MH, Malekzadeh R, Watabe H, et al. Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. Gut. 2008;57(3):298–305.
18. Horii T, Koike T, Abe Y, et al. Two distinct types of cancer of different origin may be mixed in gastroesophageal junction adenocarcinomas in Japan: evidence from direct evaluation of gastric acid secretion. Scand J Gastroenterol. 2011;46(6):710–9.
19. Glickman JN, Chen YY, Wang HH, et al. Phenotypic characteristics of a distinctive multilayered epithelium suggests that it is a precursor in the development of Barrett's esophagus. Am J Surg Pathol. 2001;25(5):569–78.
20. Goldblum JR. Inflammation and intestinal metaplasia of the gastric cardia: Helicobacter pylori, gastroesophageal reflux disease, or both. Dig Dis. 2000;18(1):14–9.
21. Hansen S, Vollset SE, Derakhshan MH, et al. Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and Helicobacter pylori status. Gut. 2007;56(7):918–25.
22. Iijima K, Shimosegawa T. Gastric carditis: is it a histological response to high concentrations of luminal nitric oxide? World J Gastroenterol. 2006;12(36):5767–71.
23. Crane SJ, Locke GR 3rd, Harmsen WS, et al. Subsite-specific risk factors for esophageal and gastric adenocarcinoma. Am J Gastroenterol. 2007;102(8):1596–602.
24. Nobukawa B, Abraham SC, Gill J, et al. Clinicopathologic and molecular analysis of high-grade dysplasia and early adeno- carcinoma in short- versus long-segment Barrett esophagus. Hum Pathol. 2001;32(4):447–54.
25. Ichihara S, Uedo N, Gotoda T. Considering the esophagogastric junction as a 'zone'. Dig Endosc. 2017;29(Suppl 2):3–10.
26. Kuwano H, Nishimura Y, Oyama T, et al. Guidelines for diagnosis and treatment of carcinoma of the esophagus April 2012 edited by the Japan Esophageal Society. Esophagus. 2015;12:1–30.
27. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer. 2017;20:1–19.
28. Yoshinaga S, Gotoda T, Kusano C, et al. Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. Gastrointest Endosc. 2008;67(2):202–9.
29. Hirasawa K, Kokawa A, Oka H, et al. Superficial adenocarcinoma of the esophagogastric junction: long-term results of endoscopic submucosal dissection. Gastrointest Endosc. 2010;72(5):960–6.
30. Yamada M, Oda I, Nonaka S, et al. Long-term outcome of endoscopic resection of superficial adenocarcinoma of the esophagogastric junction. Endoscopy. 2013;45(12):992–6.
31. Ishihara R, Oyama T, Abe S, et al. Risk of metastasis in adenocarcinoma of the esophagus: a multicenter retrospective study in a Japanese population. J Gastroenterol. 2017;52(7):800–8.
32. Goda K, Singh R, Oda I, et al. Current status of endoscopic diagnosis and treatment of superficial Barrett's adenocarcinoma in Asia-Pacific region. Dig Endosc. 2013;25(Suppl 2):146–50.

33. Yamagata T, Hirasawa D, Fujita N, et al. Efficacy of acetic acid- spraying method in diagnosing extension of Barrett's cancer under the squamous epithelium. Dig Endosc. 2012;24(5):309–14.
34. Hatta W, Uno K, Koike T, et al. Feasibility of optical coherence tomography for the evaluation of Barrett's mucosa buried underneath esophageal squamous epithelium. Dig Endosc. 2016;28(1):427–33.
35. Chennat J, Ross AS, Konda VJ, et al. Advanced pathology under squamous epithelium on initial EMR specimens in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma: implications for surveillance and endotherapy management. Gastrointest Endosc. 2009;70(3):417–21.
36. Nagami Y, Machida H, Shiba M, et al. Clinical efficacy of endoscopic submucosal dissection for adenocarcinomas of the esophagogastric junction. Endosc Int Open. 2014;2(1):E15–20.
37. Tokioka S, Umegaki E, Takeuchi N, et al. A case of the Barrett's adenocarcinoma with intramucosal spread extending. Gastroenterol Endosc. 2010;52(1):402–11.
38. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011;14:101–12.
39. Yamashita H, Katai H, Morita S, et al. Optimal extent of lymph node dissection for Siewert type II esophagogastric junction carcinoma. Ann Surg. 2011;254(2):274–80.
40. Fujitani K, Miyashiro I, Mikata S, et al. Pattern of abdominal nodal spread and optimal abdominal lymphadenectomy for advanced Siewert type II adenocarcinoma of the cardia: results of a multicenter study. Gastric Cancer. 2013;16(3):301–8.
41. Mine S, Sano T, Hiki N, et al. Lymphadenectomy around the left renal vein in Siewert type II adenocarcinoma of the oesophagogastric junction. Br J Surg. 2013;100(2):261–6.
42. Gilbert W, Luna RA, Harrison VL, Hunter JC. Barrett's esophagus: a review of the literature. J Gastrointest Surg. 2011;15(5):708–18.
43. Sikkema M, Looman CV, Steyerberg EW, et al. Predictors for neoplastic progression in patients with Barrett's esophagus: a prospective cohort study. Am J Gastroenterol. 2011;106(7):1231–8.
44. Hillman LC, Chiragakis L, Clarke AC, et al. Barrett's esophagus: macroscopic markers and the prediction of dysplasia and adenocarcinoma. J Gastroenterol Hepatol. 2003;18(5):526–33.
45. Bahin FF, Jayanna M, Hourigan LF, et al. Long-term outcomes of a primary complete endoscopic resection strategy for short segment Barrett's esophagus with high-grade dysplasia and/or early esophageal adenocarcinoma. Gastrointest Endosc. 2016;83(1):68–77.
46. Dumbar KB, Spechler SJ. The risk of lymph node metastases in patients with high grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systemic review. Am J Gastroenterol. 2012;107(6):850–63.
47. Luna RA, Gilbert E, Hunter JG. High-grade dysplasia and intarmucosal adenocarcinoma in Barrett's esophagus: the role of esophagectomy in the era of endoscopic eradication therapy. Curr Opin Gastroenterol. 2012;28(4):362–9.
48. Pech O, Behrens A, May A, et al. Long term results and risk factors analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut. 2008;57(9):1200–6.
49. Sgourakis G, Gockel I, Lang H. Endoscopic and surgical resection of T1a/T1b esophageal neoplasms: a systemic review. World J Gastroenterol. 2013;19(9):1424–37.
50. Prasad GA, Wu TT, Wigle D, et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. Gastroenterology. 2009;137(3):815–23.
51. Yang D, Zou F, Xiong S, et al. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. Gastrointest Endosc. 2018;87(6):1383–93.
52. Ma MX, Bourke MJ. Endoscopic submucosal dissection in the west: current status and future directions. Dig Endosc. 2017;30:310. https://doi.org/10.1111/den.12960.
53. Chevaux JB, Psvaux H, Jouret-Mourin A, et al. Clinical outcome in patients treated with endoscopic submucosal dissection for superficial Barrett's neoplasia. Endoscopy. 2015;47(3):103–12.
54. Probst A, Aust D, Markl B, et al. Early esophageal cancer in Europe: endoscopic treatment by endoscopic submucosal dissection. Endoscopy. 2015;47(3):113–21.

55. Terheggen G, Horn EM, Vieth M, et al. A randomized trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. Gut. 2017;66(5):783–93.
56. Moss A, Bourke MJ, Hourigan LF, et al. Endoscopic resection for Barrett's high grade dysplasia and early esophageal adenocarcinoma: an essential staging procedure with long term therapeutic benefit. Am J Gastroenterol. 2010;105(6):1276–83.
57. Subramaniam S, Chedgy F, Longcroft-Wheaton G, et al. Complex early Barrett's neoplasia at 3 western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Gastrointest Endosc. 2017;86(4):608–18.
58. Zehtner J, Demeester SR, Hagen J, et al. Endoscopic resection and ablation versus esophagectomy for high grade dysplasia and intramucosal adenocarcinoma. J Thorac Cardiovasc Surg. 2011;141(1):39–47.
59. Ngamruengphong S, Wolfsen HC, Wallace MB. Survival of patients with superficial esophageal adenocarcinoma following endoscopic treatment vs surgery. Clin Gastroenterol Hepatol. 2013;11(11):1424–e81.
60. Raziee HR, Cardoso R, Seevaratnam R, et al. Systematic review of the predictors of positive margins in gastric cancer surgery and the effect on survival. Gastric Cancer. 2012;15(Suppl 1):S116–24.
61. Kamada T, Kurose H, Yamanaka Y, et al. Relationship between gastroesophageal junction adenocarcinoma and Helicobacter pylori infection in Japan. Digestion. 2012;85(4):256–60.
62. Kusano C, Gotoda T, Kaltenbach T, et al. Differences in the endoscopic detection rates of Barrett's esophagus using the Japanese and western criteria: a pilot study. Esophagus. 2016;13(2):25–9.