Endoscopic Mucosal Resection
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Edited by:

Massimo Conio, MD
Director, Department of Gastroenterology and Digestive Endoscopy
General Hospital
Sanremo (IM), Italy

Peter D. Siersema, MD, PhD
Professor of Gastroenterology
Director, Department of Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands

Alessandro Repici, MD
Director, Unit of Digestive Endoscopy Unit
Istituto Clinico Humanitas
Rozzano (MI), Italy

Thierry Ponchon, MD
Director, Department of Gastroenterology
Hôpital E. Herriot
Lyon, France

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List of Contributors

Pradeep Bhandari  Solent Centre for Digestive Diseases, Portsmouth Hospital
NHS Trust, Portsmouth, UK

Amitabh Chak, MD  Professor of Medicine and Oncology, UH Case Medical
Center, Case Western Reserve School of Medicine, Cleveland, OH, USA

Mihai Ciocirlan  Department of Gastroenterology, Hôpital Edouard Herriot,
Lyon, France

Jan-Willem W. Coebergh  Comprehensive Cancer Centre South, Eindhoven
Cancer Registry, Eindhoven, the Netherlands; Department of Public Health,
Erasmus University Medical Center, Rotterdam, the Netherlands

Sergio Coda  Operative Unit of Diagnostic and Therapeutic Endoscopy, Depart-
ment of General and Specialized Surgery and Organ Transplantation “Paride
Stefanini”, University of Rome “La Sapienza”, Rome, Italy

Salvatore Comunale  Digestive Endoscopy Unit, IRCCS Istituto Clinico Humani-
tas, Milano, Italy

Massimo Conio  Department of Gastroenterology and Digestive Endoscopy,
General Hospital, Sanremo, Italy

Guido Costamagna  Unità Operativa di Endoscopia Digestiva Chirurgica,
Policlinico Universitario ‘A.Gemelli’, Università Cattolica del Sacro Cuore,
Roma, Italy

Giuseppe De Caro  Digestive Endoscopy Unit, IRCCS Istituto Clinico Humani-
tas, Milano, Italy

Christian Ell  Department of Medicine II, HSK Wiesbaden, Teaching Hospital
of the University of Mainz, Germany

Farees T. Farooq, MD, Fellow, Division of Gastroenterology, UH Case Medical
Center, Case Western Reserve School of Medicine, Cleveland, OH, USA
LIST OF CONTRIBUTORS

Rosangela Filiberti  Epidemiology and Biostatistics, National Cancer Research Institute, Genoa, Italy

Paul Fockens  Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Mitsuhiro Fujishiro  The University of Tokyo Graduate School of Medicine, Tokyo, Japan

Liebwin Gossner  Department of Internal Medicine I, Karlsruhe, Teaching Hospital of the University of Freiburg, Germany

Christopher Gostout  Mayo Clinic Division of Gastroenterology and Hepatology, Rochester, MN, USA

Takuji Gotoda  Head of Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

Keiichi Ikeda  Department of Endoscopy, Jikei University School of Medicine, Tokyo, Japan

Hisatomo Ikehara  Endoscopy Division, Shizuoka Cancer Center, Shizuoka, Japan

Naomi Kakushima  Department of Gastroenterology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan

Ralf Kiesslich  Department of Internal Medicine, University of Mainz, Germany

Valery E.P.P. Lemmens  Comprehensive Cancer Centre South, Eindhoven Cancer Registry, Eindhoven, the Netherlands; Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands

Carmelo Luigiano  Digestive Endoscopy Unit, IRCCS Istituto Clinico Humanitas, Milano, Italy

Takahisa Matsuda  Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

Helmut Messmann III  Medical Department, Clinic of Augsburg, Augsburg, Germany

Ichiro Oda  Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan
Maria Antonietta Orengo  Liguria Cancer Registry–Descriptive Epidemiology, National Cancer Research Institute, Genoa, Italy

Thierry Ponchon  Department of Gastroenterology, Hôpital Edouard Herriot, Lyon, France

Alessandro Repici  Digestive Endoscopy Unit, IRCCS Istituto Clinico Humanitas, Milano, Italy

Riccardo Rosati  Mininvasive Surgical Unit, IRCCS Istituto Clinico Humanitas, Milano, Italy

Yutaka Saito  Head of Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

Peter D. Siersema  Department of Gastroenterology and Hepatology, University Medical Center Utrecht, the Netherlands

Paul Swain  Department of Surgical Oncology and Technology, Imperial College, St Mary’s Hospital, London, UK

Kaiyo Takubo  Department of Pathology, Tokyo Metropolitan Hospital, Tokyo, Japan

Michael Vieth  Institute of Pathology, Klinikum Bayreuth, PreuschwitzerStr. 101, Bayreuth, Germany

Chizu Yokoi  Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan
Preface

Writing a book on any endotherapy subject also means accepting the fact that the concepts expressed have a high risk of aging rapidly. This risk is even higher when dealing with a technique which is still in evolution such as EMR. However, there is now a body of consolidated knowledge that can be used to promote a better endoscopy technique for EMR, even for endoscopists who are not familiar with this particular method.

This book is entirely dedicated to EMR, with the special purpose of discussing in detail the practical aspects of this new endotherapy technique. The EMR technique was introduced by Japanese endoscopists, and is now becoming increasingly popular in the West where the majority of endoscopists have no experience with this method. The impact of EMR in the clinical field has been tremendous, and now for a group of patients, when the removal of superficial cancers in the esophagus, stomach, duodenum and colorectum is indicated, open surgery can be avoided.

Up to now, EMR has been reported in journals devoted to endoscopy, such as *Gastrointestinal Endoscopy* or *Endoscopy*. A considerable number of articles have been published in these journals in the last two years on this procedure. Essential information about results and indications or when to apply this technique has been presented. However these articles do not consider the different scenarios in which the technique can be performed. Our book, which analyzes in depth the details of this technique, will likely fill this gap.

The purpose of the current book is to provide a careful step-by-step guide to aid the endoscopist in his daily clinical practice. Methods, details and particularities that are not usually reported in scientific articles have been described. A comprehensive and essential analysis of the literature has been included in each chapter, along with tables, diagrams and photographs to help the reader. All the technical aspects have been explained and clarified with high quality illustrations. Photographs of the available endoscopic devices have also been provided.

We wish to thank all the authors for their contribution to this book. They are all highly experienced endoscopists and well known at the international level. They have been able to condense their knowledge for these pages. A special thank you should also go to Blackwell Publishing for their excellent support.
We wish this book to be thought-provoking and hope that it stimulates new ideas and projects in the arena of therapeutic endoscopy, which has developed significantly over the last 10 years. New materials and accessories have aided the progressive diffusion of EMR and of endoscopic submucosal dissection (ESD), even outside referral centres. We are certain that with the simplification of these methods, EMR and ESD will in the future be performed in most endoscopic departments worldwide.

We hope that this book can represent an important point of reference for those interested in this subject.

Massimo Conio, MD
Peter D. Siersema, MD
Alessandro Repici, MD
Thierry Ponchon, MD
CHAPTER 1

Epidemiology of Gastrointestinal Cancer: (Trends in) Incidence and Mortality from Esophageal, Stomach, and Colorectal Cancer

VALERY E.P.P. LEMMENS AND JAN-WILLEM W. COEBERGH

Introduction

In the past decades, clinically and population-based studies in developed countries have reported increases in the incidence of adenocarcinoma of the esophagus, gastric cardia, and colorectum. This increase was not observed for squamous cell carcinoma of the esophagus and tumors of the non-gastric part of the stomach; the latter showed a clear decrease in incidence. A strong decrease in mortality from stomach cancer and a moderate decrease in mortality from colorectal cancer have been reported in several Western countries, while mortality rates increased for esophageal cancer. In developed countries, colorectal cancer has a higher incidence and mortality than esophageal and stomach cancer, while the opposite is true for less developed countries (Figs 1.1 and 1.2).

In this chapter, we will give an overview of the current incidence and mortality rates of esophageal, stomach, and colorectal cancer, including geographic variations and male–female differences. We will present the most important trends in time, with a more detailed view on trends in histology of esophageal and gastric cancer incidence and trends in subsite distribution of colorectal cancer incidence. We will discuss age-adjusted trends; it is important to bear in mind that even stable incidence rates can mean large increases in absolute numbers of newly diagnosed cancer patients in Western countries, due to the aging of the population.
Methods

Esophageal, stomach, and colorectal cancer were classified according to the International Classification of Disease (ICD, 10th revision): Esophagus (C15), stomach (C16), and colon/rectum (C18–C21).
Incidence

Incidence is the number of new cases arising in a given period in a specified population. Cancer registries collect this information routinely. It can be expressed as an absolute number of cases per year or as a rate per 100 000
persons per year. The latter provides an approximation to the average risk of developing a cancer, which is particularly useful in making comparisons between populations.

**Mortality**

Mortality is the number of deaths occurring in a given period in a specified population. It can be expressed as an absolute number of deaths per year or as a rate per 100,000 persons per year.

**Population**

Estimates of the population of countries (by age and sex) for the year 2000 and 2005 were taken from the United Nations population projections (the 2002 revision). The population figures for the year 2002 were estimated by calculating the annual percentage change by sex and age between the year 2000 and 2005.

**Analyses**

All analyses were carried out using the GLOBCAN software [1]. The GLOBCAN 2002 database has been built up using the huge amount of data available in the Descriptive Epidemiology Group of the International Agency for Research on Cancer.

Incidence data were available from cancer registries. They cover entire national populations, or samples of such populations from selected regions. Cancer registries also provide statistics on cancer survival. With data on incidence, and on survival, we can estimate the prevalence of cancer (persons who are alive with cancer diagnosed within a given number of years of diagnosis). Mortality data by cause are available for many countries through the registration of vital events, although the degree of detail and quality of the data vary considerably. With such data, it is possible to prepare estimates of the numbers of new and prevalent cancer cases and deaths by site, sex, and age group. These are more or less accurate, for different countries, depending on the extent and accuracy of locally available data.

**Age-standardized rate**

All data are presented as standardized rates. An age-standardized rate (ASR) is a summary measure of a rate that a population would have if it had a standard age structure. The most frequently used standard population is the World standard population. The calculated incidence or mortality rate is then called the World age standardized incidence or mortality rate. It is expressed as a rate per 100,000.
Esophageal cancer

The incidence of esophageal cancer in 2002 was particularly high in Western Europe, south-central Asia, eastern Africa, and parts of South America (Figs 1.3 and 1.4). It was lowest in western Africa and in Indonesia. This pattern was equal for both males and females. In the developed countries, the incidence of esophageal cancer was the highest in the United Kingdom, France, Ireland, and Japan, and lowest in Norway, Finland, and Malta (Fig. 1.5). The incidence in males was much larger than in females, this difference was largest in France and Slovakia.

In countries with a high incidence of esophageal cancer, such as Japan and the United Kingdom, the incidence was especially high among elderly people (Fig. 1.6).

There has been a large increase of adenocarcinoma of the esophagus in many developed countries, compared with a decrease of squamous cell carcinoma. Rates of adenocarcinoma have been increasing in the USA, United Kingdom, Scandinavia, France, Switzerland, Denmark, Italy, Slovakia, the Netherlands (restricted to males), Australia, and New Zealand [2–4]. This might be partly due to a diagnostic shift; tumors arising in the cardio-esophageal junction are classified with gastric cardia tumors; an increase in esophageal adenocarcinoma

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Fig. 1.3 Incidence of esophageal cancer in males, 2002, worldwide.

Fig. 1.4  Incidence of esophageal cancer in females, 2002, worldwide.

Fig. 1.5  Incidence of esophageal cancer in 2002, by country and gender.
could appear if tumors at or near the junction were identified increasingly as being esophageal in origin. However, gastric cardia rates would then diminish to a similar extent, which has not occurred. Rates may increase with earlier endoscopy-based diagnosis, but the stage distribution has not changed over time, and survival consistently has been poor, even for patients diagnosed with localized disease. These observations suggest that the increase of adenocarcinoma of the esophagus is real and reflects changes in the prevalence of risk factors [2].

Mortality from esophageal cancer showed the same patterns as the incidence (Figs 1.7, 1.8, and 1.9). Due to the increased incidence and the very limited improvements in survival of people with esophageal cancer, mortality rates have been increasing in most countries.

**Stomach cancer**

The incidence of stomach cancer in 2002 was highest in northern Asia, including China and Japan, eastern Europe, southern Europe, and eastern South America. Lowest rates were found in Africa and Indonesia (Figs 1.10 and 1.11). Among developed countries, rates were by far the highest in Japan, and lowest in the USA (Fig. 1.12). Stomach cancer was more common among males than among females. Already by middle age, in Japan the incidence of stomach cancer is much higher compared to, for example, the USA or Italy (Fig. 1.13).

While there has been a marked decline in distal, intestinal-type gastric cancers (especially among females), the incidence of proximal, diffuse-type
Fig. 1.7  Mortality from esophageal cancer in males, 2002, worldwide.

Fig. 1.8  Mortality from esophageal cancer in females, 2002, worldwide.
Fig. 1.9 Mortality from esophageal cancer, 2002, by country and gender.

Fig. 1.10 Incidence of stomach cancer in males, 2002, worldwide.
Fig. 1.11 Incidence of stomach cancer in females, 2002, worldwide.

Fig. 1.12 Incidence of stomach cancer in 2002, by country and gender.
adenocarcinomas of the gastric cardia has been increasing, particularly in Western countries. Incidence by tumor subsite also varies widely based on geographic location, race, and socio-economic status. Distal gastric cancer predominates in developing countries, among black people, and in lower socio-economic groups, whereas proximal tumors are more common in developed countries, among white people, and in higher socio-economic classes. Diverging trends in the incidence of gastric cancer by tumor location suggest that they may represent two diseases with different etiologies [5].

Over the past few years, gastric cancer mortality has decreased markedly in most areas of the world. However, gastric cancer remains a disease of high mortality, second only to lung cancer as the leading cause of cancer-related death worldwide (Figs 1.14 and 1.15).

Availability of screening for early detection in high-risk areas has led to a decrease in mortality. In Japan, mortality rates for gastric cancer in men have halved since the introduction of screening in the 1970s [5]. Mortality rates in 2002 were lower in Japan than in some eastern European countries (Fig. 1.16).

**Colorectal cancer**

The incidence of colorectal cancer showed a different picture than the incidence of esophageal or stomach cancer. Colorectal cancer is predominantly a cancer
Fig. 1.14  Mortality from stomach cancer in males, 2002, worldwide.

Mortality from stomach cancer: ASR (World) – Male (all ages)

Fig. 1.15  Mortality from stomach cancer in females, 2002, worldwide.

Mortality from stomach cancer: ASR (World – Female (all ages))

GLOBOCAN 2002
of the developed world. It was most common in 2002 in Europe, the USA, and Australia, for both males and females (Figs 1.17 and 1.18). It was somewhat more frequent among males than among females. The highest incidence was found in Germany, Hungary, Japan (especially males), the Czech Republic, and Norway (especially females), while the lowest rates in the Western world were found in the Ukraine and in Greece (Fig. 1.19).

Colorectal cancer in all countries is predominantly a disease of elderly people. While the incidence rates in the USA and Canada have been stable for two decades, incidence is still increasing in many European countries, especially among men. In many countries, a shift toward more proximal tumors has been noted [6–10]. Exposure to changing risk factors is probably the cause of this shift. Also the male-to-female rate ratio progressively increased from the proximal colon to the distal colorectum, and the ratio of proximal-to-distal colorectal cancer gradually increased with advancing age [11].

Colorectal cancer mortality showed the same patterns as colorectal incidence (Figs 1.20 and 1.21). Mortality was highest in Hungary, the Czech Republic, and Slovakia (Fig. 1.22). A favorable pattern in colorectal cancer mortality for both genders was observed in most European countries from the 1990s onward.
Incidence of colorectal cancer: Crude rate – Male (all ages)

Fig. 1.17 Incidence of colorectal cancer in males, 2002, worldwide.

Incidence of colorectal cancer: Crude rate – Female (all ages)

Fig. 1.18 Incidence of colorectal cancer in females, 2002, worldwide.
Fig. 1.19 Incidence of colorectal cancer in 2002, by country and gender.

Fig. 1.20 Mortality from colorectal cancer in males, 2002, worldwide.
Mortality from colorectal cancer in females, 2002, worldwide.

Fig. 1.21 Mortality from colorectal cancer in females, 2002, worldwide.

Fig. 1.22 Mortality from colorectal cancer in 2002, by country and gender.
Lower incidence rates, earlier detection, and improvements in treatment were responsible for this. Colorectal cancer mortality rates were still in the upward direction in some eastern European countries, as well as in some Mediterranean countries. Mortality rates tended to converge, a pattern even clearer when colorectal mortality rates were examined in three broad European regions. Similar mortality rates over recent calendar years have been reached by countries where mortality has been decreasing in recent decades, and in those countries (mainly eastern European and Mediterranean countries) which have experienced a recent leveling-off and decrease [12].

References
CHAPTER 2

Etiological Factors in Gastrointestinal Tumors

ROSANGELA FILIBERTI AND MARIA ANTONIETTA ORENGO

Introduction

The etiology of gastrointestinal cancers is multifactorial, and differences in the exposure to a range of environmental factors account for much of the variation seen in the incidence of these tumors over time and among populations. However, so far it has not been clear to what extent the risk is due to the environment or to genetic factors, and studies are now focusing on the interaction between exogenous factors and individual susceptibility.

This chapter will focus on esophageal, gastric, and colorectal cancers and will give an overall outlook on epidemiologic findings about these pathologies. In Tables 2.1–2.5 a selection of studies on some factors involved in the etiology of these diseases is reported.

Esophageal cancers

The increasing incidence trends observed for adenocarcinomas of the esophagus (EA) in Western countries, associated with stable or declining incidence trends for esophageal squamous cell carcinoma (ESCC), suggest that different risk factors may be associated with these tumors. The improvement of different diagnostic and/or classification criteria, as well as the changes in time of the histological confirmation, can only partially explain the observed trends.

Esophageal squamous cell carcinoma

ESCC often arises from preceding dysplastic lesions in the esophageal epithelium and DNA methylation appears to contribute to the progression of dysplasia–carcinoma sequence [1].
### Table 2.1  Smoking and gastrointestinal tumors.

<table>
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<tr>
<th>Cancer</th>
<th>Author</th>
<th>RR and their 95% confidence intervals</th>
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<tbody>
<tr>
<td>Esophageal AC</td>
<td>Gammon et al., 1997 [23] (C–C)</td>
<td>2.2 (1.4–3.3)</td>
</tr>
<tr>
<td></td>
<td>(293 cancers – 695 controls)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wu et al., 2001 [20] (C–C)</td>
<td>2.8 (1.8–4.3)</td>
</tr>
<tr>
<td></td>
<td>(222 cancers – 1356 controls)</td>
<td></td>
</tr>
<tr>
<td>Esophageal squamous cell carcinoma</td>
<td>Gallus et al., 2003 [84] (C–C)</td>
<td>&lt;20 mg tar: 4.8 (3.1–7.6)</td>
</tr>
<tr>
<td></td>
<td>(395 cancers – 1006 controls)</td>
<td>≥20 mg tar: 5.4 (3.2–9.3)</td>
</tr>
<tr>
<td></td>
<td>Zambon et al., 2000 [2] (C–C)</td>
<td>≥25 cigarettes/day: 7.0 (3.2–15.1)</td>
</tr>
<tr>
<td></td>
<td>(275 cancers – 593 controls)</td>
<td>Smoking for ≥35 years:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.4 (3.3–12.0)</td>
</tr>
<tr>
<td>Cardia AC</td>
<td>Wu et al., 2001 [20] (C–C)</td>
<td>2.12 (1.5–3.1)</td>
</tr>
<tr>
<td></td>
<td>(277 cancers – 1356 controls)</td>
<td></td>
</tr>
<tr>
<td>Distal gastric AC</td>
<td>Wu et al., 2001 [20] (C–C)</td>
<td>1.5 (1.1–2.1)</td>
</tr>
<tr>
<td></td>
<td>(443 cancers – 1356 controls)</td>
<td></td>
</tr>
<tr>
<td>Gastric AC</td>
<td>Sasazuki et al., 2002 [85] (Cohort, 293 cancers)</td>
<td>2.1 (1.2–3.6)</td>
</tr>
<tr>
<td></td>
<td>Fujino et al., 2005 [86] (Cohort, 757 cancers)</td>
<td>1.36 (1.07–1.73)</td>
</tr>
<tr>
<td>Colorectal AC</td>
<td>Verla-Tebit et al., 2006 [62] (C–C)</td>
<td>Smiling ≥30 years: 1.25 (0.90–1.75)</td>
</tr>
<tr>
<td></td>
<td>(540 cancers – 614 controls)</td>
<td>Smoking ≥40 pack-years: 1.92 (1.13–3.28)</td>
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<tr>
<td></td>
<td></td>
<td>Quitting smoking ≥40 years vs. current smokers: 0.46 (0.21–0.98)</td>
</tr>
<tr>
<td></td>
<td>Limburg et al., 2003 [87] (Cohort, 41 836 women – 1118 cancers)</td>
<td>1.17 (1.00–1.36)</td>
</tr>
</tbody>
</table>

AC: adenocarcinoma; C–C: case–control study; RR: relative risk point estimates for smokers vs. non-smokers.

### Table 2.2  Obesity, glycemic profile, physical activity, and gastrointestinal tumors.

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<tr>
<th>Cancer</th>
<th>Author</th>
<th>RR and their 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal AC</td>
<td>Lindblad et al., 2005 [19] (C–C nested) (287 cancers – 10 000 controls)</td>
<td>BMI ≥25 kg/m²: 1.67 (1.22–2.30)</td>
</tr>
<tr>
<td></td>
<td>Engeland et al., 2004 [88] (Cohort, 2245 cancers)</td>
<td>BMI ≥30 kg/m²: 2.58 (1.81–3.68) men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.06 (1.25–3.39) women</td>
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<tr>
<td></td>
<td>Vigen et al., 2006 [89] (C–C) (212 cancers – 1330 controls)</td>
<td>Mean annual activity index: highest vs. lowest quartile: 0.61 (0.38–0.99)</td>
</tr>
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<tr>
<th>Cancer</th>
<th>Author</th>
<th>RR and their 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal AC</td>
<td>Kubo et al., 2006 [90]</td>
<td>BMI &gt; 25 kg/m²:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 (1.7–2.7) men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI &gt; 25 kg/m²:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0 (1.4–2.9) women</td>
</tr>
<tr>
<td>Esophageal squamous cells carcinoma</td>
<td>Engeland et al., 2004 [88]</td>
<td>BMI ≥ 30 kg/m²:</td>
</tr>
<tr>
<td></td>
<td>(Cohort, 2245 cancers)</td>
<td>0.68 (0.5–0.93) men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.43 (0.32–0.59) women</td>
</tr>
<tr>
<td>Cardia AC</td>
<td>Lindblad et al., 2005 [19]</td>
<td>BMI &gt; 25 kg/m²:</td>
</tr>
<tr>
<td></td>
<td>(C–C nested)</td>
<td>1.46 (0.98–2.18)</td>
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<td></td>
<td>Vigen et al., 2006 [89]</td>
<td>Mean annual activity index:</td>
</tr>
<tr>
<td></td>
<td>(C–C)</td>
<td>highest vs. lowest quartile:</td>
</tr>
<tr>
<td></td>
<td>(264 cancers – 1330 controls)</td>
<td>0.76 (0.49–1.18)</td>
</tr>
<tr>
<td>Distal gastric AC</td>
<td>Lindblad et al., 2005 [19]</td>
<td>BMI &gt; 25 kg/m²:</td>
</tr>
<tr>
<td></td>
<td>(C–C nested)</td>
<td>no association</td>
</tr>
<tr>
<td></td>
<td>Vigen et al., 2006 [89]</td>
<td>Mean annual activity index:</td>
</tr>
<tr>
<td></td>
<td>(C–C)</td>
<td>highest vs. lowest quartile:</td>
</tr>
<tr>
<td></td>
<td>(389 cancers – 1330 controls)</td>
<td>0.77 (0.52–1.14)</td>
</tr>
<tr>
<td>Colorectal AC</td>
<td>Engeland et al., 2005 [63]</td>
<td>Height 10 cm increase:</td>
</tr>
<tr>
<td></td>
<td>(Cohort, 47 117 cancers)</td>
<td>1.14 (1.11–1.16) men;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.17 (1.14–1.20) women</td>
</tr>
<tr>
<td></td>
<td>Lin et al., 2004 [91]</td>
<td>BMI = 27–29.9 kg/m²:</td>
</tr>
<tr>
<td></td>
<td>(Cohort, 202 cancers in women)</td>
<td>1.72 (1.12–2.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI ≥ 30 kg/m² vs. BMI &lt; 25 kg/m²:</td>
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<tr>
<td></td>
<td></td>
<td>1.67 (1.08–2.59)</td>
</tr>
<tr>
<td></td>
<td>Franceschi et al., 2001 [92]</td>
<td>GI highest vs. lowest quintile:</td>
</tr>
<tr>
<td></td>
<td>(C–C)</td>
<td>1.71 (1.4–2.0)</td>
</tr>
<tr>
<td></td>
<td>(2953 cancers – 4154 controls)</td>
<td>In obese women: GI</td>
</tr>
<tr>
<td></td>
<td>McCarl et al., 2006 [69]</td>
<td>highest vs. lowest quintile:</td>
</tr>
<tr>
<td></td>
<td>(Cohort, 954 cancers)</td>
<td>1.66 (1.13–2.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GL highest vs. lowest quintile:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.79 (1.19–2.70)</td>
</tr>
<tr>
<td>Rectal AC</td>
<td>Mao et al., 2003 [93] (C–C)</td>
<td>Caloric intake: highest vs. lowest quartile:</td>
</tr>
<tr>
<td></td>
<td>(1447 cancers – 3106 controls)</td>
<td>1.61 (1.12–2.28) men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI ≥ 30 kg/m²:</td>
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<tr>
<td></td>
<td></td>
<td>1.78 (1.36–2.34) men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caloric intake: highest vs. lowest quartile:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.50 (1.00–2.28) women</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI ≥ 30 kg/m²:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.44 (1.06–1.95) women</td>
</tr>
</tbody>
</table>

AC: adenocarcinoma; BMI: body mass index; C–C: case–control study; GI: glycemic index, GL: glycemic load; RR: relative risk point estimates.
In Western areas tobacco and alcohol may be responsible for more than 80% of cases. Forty-five per cent of tumors may be due to elevated alcohol use [2,3]. A case-control performed in northern Italy, in an area where heavy alcohol consumption is common, showed that, when considering exposure intensity, the risk from alcohol was higher than the one from smoking. In addition, the association between high levels of smoking and alcohol consumption increased the risk by 130 times [2].

Table 2.3 Pathological conditions related to esophageal and gastric tumors.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Author</th>
<th>RR and their 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esophageal AC</strong></td>
<td>Wu et al., 2003 [10] (C–C)</td>
<td>GERD: 3.61 (2.49–5.25)</td>
</tr>
<tr>
<td>(222 cancers – 1356 controls)</td>
<td></td>
<td>Hiatal hernia: 5.85 (3.18–10.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GERD + Hiatal hernia: 8.11 (4.75–3.87)</td>
</tr>
<tr>
<td></td>
<td>Farrow et al., 2006 [9] (C–C)</td>
<td>GERD daily symptoms: 5.5 (3.2–9.3)</td>
</tr>
<tr>
<td>(293 cancers – 695 controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ye et al., 2004 [16] (C–C)</td>
<td>Hp CagA+: 0.5 (0.3–0.8)</td>
</tr>
<tr>
<td>(97 cancers – 499 controls)</td>
<td></td>
<td>Gastric atrophy: 1.1 (0.5–2.5)</td>
</tr>
<tr>
<td><strong>Esophageal squamous cell carcinoma</strong></td>
<td>Farrow et al., 2006 [9] (C–C)</td>
<td>GERD: no association</td>
</tr>
<tr>
<td>(221 cancers – 695 controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ye et al., 2004 [16] (C–C)</td>
<td>Hp CagA+: 2.1 (1.1–4.0)</td>
</tr>
<tr>
<td>(85 cancers – 499 controls)</td>
<td></td>
<td>Gastric atrophy: 4.3 (1.9–9.6)</td>
</tr>
<tr>
<td><strong>Cardia AC</strong></td>
<td>Wu et al., 2003 [17] (C–C)</td>
<td>Seropositivity for Hp: 1.26 (0.82–1.94)</td>
</tr>
<tr>
<td>(87 cancers – 356 controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Farrow et al., 2006 [9] (C–C)</td>
<td>GERD: no association</td>
</tr>
<tr>
<td>(261 cancers – 695 controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ye et al., 2004 [16] (C–C)</td>
<td>Hp CagA+: no association</td>
</tr>
<tr>
<td>(133 cancers – 499 controls)</td>
<td></td>
<td>Gastric atrophy: 4.5 (2.5–7.8)</td>
</tr>
<tr>
<td>Kamangar et al., 2006 [34] (C–C)</td>
<td></td>
<td>Hp CagA+: 0.31 (0.11–0.89)</td>
</tr>
<tr>
<td>(61 cancers – 234 controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distal gastric AC</strong></td>
<td>Wu et al., 2003 [10] (C–C)</td>
<td>Seropositivity for Hp: 1.85 (1.03–3.32)</td>
</tr>
<tr>
<td>(127 cancers – 356 controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Farrow et al., 2006 [9] (C–C)</td>
<td>GERD: no association</td>
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<tr>
<td>(368 cancers – 695 controls)</td>
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<tr>
<td></td>
<td>Knekt et al., 2006 [33] (C–C nested)</td>
<td>High IgA: 3.12 (1.97–4.95)</td>
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<tr>
<td>(225 cancers – 435 controls)</td>
<td></td>
<td>High IgG: 2.88 (1.63–5.07)</td>
</tr>
<tr>
<td></td>
<td>High IgA and Ig G, low PGI: 10.9 (4.31–27.7) vs. negative antibody and normal PGI</td>
<td></td>
</tr>
<tr>
<td>Kamangar et al., 2006 [33] (C–C)</td>
<td></td>
<td>Hp CagA+: 7.9 (3.0–20.9)</td>
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<tr>
<td>(173 cancers – 234 controls)</td>
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</tbody>
</table>

AC: adenocarcinoma; C–C: case–controls; GERD: gastroesophageal reflux disease; Hp: helicobacter pylori infection; PGI: serum pepsinogen I; RR: relative risk point estimates.
<table>
<thead>
<tr>
<th>Cancer</th>
<th>Author</th>
<th>RR and their 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal AC</td>
<td>Bahmanyar, 2006 [3] (C–C)</td>
<td>Western diet (high 3rd tertile vs. lowest 1st tertile): 1.6 (0.9–3.1)</td>
</tr>
<tr>
<td></td>
<td>(185 cancers – 815 controls)</td>
<td></td>
</tr>
<tr>
<td>Esophageal squamous cell</td>
<td>Bollscheiwer et al., 2002 [94]</td>
<td>Vit. E intake &gt;13 mg/day: 0.13 (0.1–0.5)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>(C–C)</td>
<td>Vit. C intake &gt;100 mg/day: 0.33 (0.11–0.92)</td>
</tr>
<tr>
<td></td>
<td>(52 cancers – 50 controls)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>De Stefani et al., 2003 [7]</td>
<td>Red meat: 2.4 (1.4–4.2)</td>
</tr>
<tr>
<td></td>
<td>(C–C)</td>
<td>White meat: 0.5 (0.3–0.9)</td>
</tr>
<tr>
<td></td>
<td>(116 cancers – 664 controls)</td>
<td>Fruit: 0.2 (0.1–0.4)</td>
</tr>
<tr>
<td></td>
<td>De Stefani et al., 2005 [4]</td>
<td>Vegetables: 0.7 (0.4–1.2)</td>
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<tr>
<td></td>
<td>(C–C)</td>
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<td></td>
<td>(200 cancers – 400 controls)</td>
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</tr>
<tr>
<td>Cardia AC</td>
<td>Bahmanyar, 2006 [3] (C–C)</td>
<td>Western diet (high 3rd tertile vs. lowest 1st quartile): 1.8 (1.1–2.9)</td>
</tr>
<tr>
<td></td>
<td>(258 cancers – 815 controls)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(C–C)</td>
<td>84 or more alcohol drinks per week vs. light drinkers: 24.5 (11.7–51.0)</td>
</tr>
<tr>
<td></td>
<td>(275 cancers – 593 controls)</td>
<td></td>
</tr>
<tr>
<td>Distal gastric AC</td>
<td>Gonzalez et al., 2006 [31]</td>
<td>Total meat 100 g/day increase: 3.52 (1.96–6.34)</td>
</tr>
<tr>
<td></td>
<td>(Cohort, 330 cancers)</td>
<td>Red meat 50 g/day increase: 1.73 (1.03–2.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Processed meat 50 g/day increase: 2.45 (1.43–4.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total meat + Hp: 5.32 (2.10–13.4)</td>
</tr>
<tr>
<td>Gastric AC</td>
<td>Kobayashi et al., 2002 [95]</td>
<td>Vegetables ≥1 day/week</td>
</tr>
<tr>
<td></td>
<td>(Cohort, 404 cancers)</td>
<td>Yellow vegetables: 0.64 (0.45–0.92)</td>
</tr>
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<td></td>
<td></td>
<td>White vegetables: 0.48 (0.25–0.89)</td>
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<tr>
<td></td>
<td></td>
<td>Fruits ≥1 day/week: 0.70 (0.49–1.0)</td>
</tr>
<tr>
<td></td>
<td>Larsson et al., 2006 [96]</td>
<td>All processed meat:</td>
</tr>
<tr>
<td></td>
<td>(Cohort, 156 cancers)</td>
<td>Highest vs. lowest intake: 1.66 (1.13–2.45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacon or side pork: 1.55 (1.00–2.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-nitrosodimethylamine high quintile vs. lowest: 1.96 (1.08–3.58)</td>
</tr>
</tbody>
</table>

AC: adenocarcinoma; C–C: case–control study; Hp: *Helicobacter pylori* infection; RR: relative risk point estimates; Western diet: high in processed meat, red meat, sweets, high-fat dairy, high-fat gravy.
### Table 2.5  Risk or protective factors and colorectal tumors.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Author</th>
<th>RR and their 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal AC</td>
<td>Norat et al., 2005 [48]</td>
<td>Red and processed meat: &gt;160 g/day vs. &lt;20 g/day: 1.35 (0.96–1.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fish: &gt;80 g/day vs. &lt;10 g/day: 0.69 (0.54–0.88)</td>
</tr>
<tr>
<td></td>
<td>Larsson et al., 2006 [55]</td>
<td>Total calcium: highest quartile vs. lowest quartile: 0.68 (0.51–0.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dairy foods: ≥7 servings/day vs. &lt;2 servings/day: 0.46 (0.30–0.71)</td>
</tr>
<tr>
<td></td>
<td>Lin et al., 2005 [97]</td>
<td>Fruit: highest vs. lowest quintile: 0.79 (0.49–1.27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vegetables: highest vs. lowest quintile: 0.88 (0.56–1.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total fiber: highest vs. lowest quintile: 0.75 (0.48–1.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Legume fiber: highest vs. lowest quintile: 0.60 (0.40–0.91)</td>
</tr>
<tr>
<td></td>
<td>Larsson et al., 2005 [98]</td>
<td>Total fiber: highest vs. lowest quintile: 0.75 (0.48–1.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dietary Folate intake: highest vs. lowest quintile: 0.93 (0.55–1.56) for rectal cancers</td>
</tr>
<tr>
<td></td>
<td>Nichols et al., 2005 [73]</td>
<td>OC users vs. never users: 0.89 (0.75–1.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Premenopausal women vs. postmenopausal women: 0.67 (0.47–0.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recent OC users vs. never users: 0.53 (0.28–1.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Five or more births vs. nulliparous: 0.66 (0.43–1.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women with age at first birth older than the median vs. age at first birth below the median: 0.83 (0.70–0.98)</td>
</tr>
<tr>
<td></td>
<td>Larsson and Wolk, 2006 [99]</td>
<td>Highest vs. lowest intake red meat: 1.28 (1.15–1.42)</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis:</td>
<td>Highest vs. lowest intake processed meat: 1.20 (1.11–1.31)</td>
</tr>
<tr>
<td></td>
<td>Studies on red meat: 7367 cancers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Studies on processed meat: 7903 cancers</td>
<td></td>
</tr>
</tbody>
</table>

AC: adenocarcinoma; C–C: case–control study; OC: oral contraceptives; RR: relative risk point estimates.
Dietary factors are considered important in the prevention of ESCC. A protective effect is attributed to fruit and vegetables and a 40% lower risk is associated with an intake of about five servings/day [4,5]. Protection is conferred partly through an antioxidative mechanism. With regard to nutrients, an inverse association was found for fiber, β-carotene, folate, vitamin C, and vitamin B6 [6]. Foods ingested at high temperature, such as stewed meat, could be a risk factor for ESCC [7]. It could be said that elimination of smoking, reduction of alcohol consumption, and enrichment of the diet with fruit and vegetables would make esophageal cancer a rare disease in Western areas.

**Esophageal adenocarcinoma**

In an analysis of national population-based incidence data from Italy, we found a significant upward trend for EA in males over the age of 60 years. The adenocarcinomas of the junction, conventionally classified by cancer registries as cardia tumors, increased in older males and also in younger females. It is still controversial whether EA and cardia adenocarcinoma represent a unique entity [8].

The etiology of EA is dominated by non-genetic risk factors, but so far the epidemiology of this cancer has not yet been solved and it is still uncertain which factors cause the increasing incidence. Gastroesophageal reflux (GERD) is an established risk factor for EA. The more frequent, more severe, and longer lasting the symptoms of reflux, the greater the risk. The use of medications that relax the lower esophageal sphincter might contribute to increasing the risk facilitating the reflux [9,10].

In recent years, attention has been focused on Barrett’s esophagus (BE) and on the BE-dysplasia-adenocarcinoma sequence. BE is an acquired condition secondary to longstanding GERD [9]. It is present in about 5–10% of patients having endoscopy for reflux symptoms and is more likely to be present in obese people [11]. BE is considered to be a precancerous lesion and a strong risk factor for EA and, to a lesser extent, for cardia adenocarcinoma. Recent studies estimated an incidence of one adenocarcinoma for every 200 to 220 patients with BE per year [12]. People with BE have an excess risk of developing adenocarcinoma 30- to 125-fold relative to the risk of the general population [13]. In the few reported long-term surveillance studies the incidence of EA in high-grade dysplasia patients was 16–26% [12]. Nevertheless, among patients presenting with EA in a previously undiagnosed BE, only about 60% had chronic reflux symptoms. In a study on a Swedish population undergoing endoscopy, BE was present in 2% of participants. Overall, 40% reported reflux symptoms and 15% showed esophagitis. The prevalence of BE was 2% and 1% in people with and without GERD, respectively [14].
Evidence of an inverse relation between *Helicobacter pylori* (* Hp *) infection and risk of EA is getting stronger, suggesting that * Hp * may decrease the risk of EA by 50–80% [15,16], but more studies are warranted to establish these findings [17].

There are few known dietary risk factors. The best established risk exposure is a low intake of fruit, vegetables and fibers and, in particular, of antioxidants [5,6,18]. Other potential dietary risk factors include high intake of dietary fat, dietary cholesterol, and animal protein [6].

There are strong indications that there is a dose dependent association between increasing BMI and risk of EA [19,20]. EA patients and refluxers had a significantly higher BMI than patients with ESCC. The contribution of obesity, as well as of reflux, in explaining the increasing incidence of EA is unclear, because the prevalence trends of these two factors do not match those of EA incidence [21].

Tobacco smoking is a controversial issue and any association with smoking seems to be of moderate importance [22]. In studies in which a significant increase of risk for smokers emerged, it was suggested that the shift in esophageal histology could be mostly due to changes in tobacco constituents [20,23]. Alcohol consumption is not a risk factor, independent of the type of alcoholic beverage consumed [20,24].

Several studies have indicated an anti-tumoral effect with the use of non-steroidal anti-inflammatory drugs (NSAIDs), especially by using selective cyclooxygenase-2 inhibitors [25].

**Gastric adenocarcinoma**

Data from medical literature show that the two major histopathological variants in gastric adenocarcinoma (GA) are associated with a different distribution and different etiologic factors. The diffuse type occurs more often in young patients [26], it is more likely to have a primary genetic etiology and is not associated with intestinal metaplasia [27].

The intestinal type cancers are more frequently sporadic and associated with environmental factors. They may arise from chronic atrophic gastritis, which has a prevalence in gastroscopies of 28% (severe 8%) [28,29]. Gastric carcinogenesis is a continuous process from non-atrophic gastritis to glandular atrophy, to metaplasia and dysplasia, and to adenocarcinoma. Foods rich in salt; smoked or poorly preserved foods; and processed meat can induce atrophic gastritis and generate carcinogenic N-nitroso compounds in the gastric environment [30]. The association with red meat intake seems to be present for non-cardia adenocarcinoma (NCA), especially in people who were * Hp * antibody-positive, but not for cardia adenocarcinoma (CA) [31].
The association between *Hp* infection and GA has been postulated by independent studies indicating that *Hp* plays a dual role in the etiology of different gastric subsites. A prolonged infection with *Hp* (more than 10 years) seems to double the risk of NCA, mainly of intestinal-type [32,33], but is inversely associated with the risk of CA [34]. An increased risk of NCA has also been associated with a history of gastric ulcer [9].

The role of environmental factors in the etiology of GA was suggested in the late 1960s by studies on migrants from a high-incidence country (Japan) to a low-incidence country (Hawaii). According to these surveys, migrants showed the risk rate of their native areas, while their second-generation acquired the risk rate of the host country, thanks to better dietary habits [35]. As a confirmation of this, in Japan, where stomach cancer is still a dominant cancer, a Western-style breakfast showed an inverse association with gastric cancer risk in males [36]. Wheat fiber can neutralize carcinogenic nitrosamines from salivary nitrates [37]. The intake of calcium, vitamin A and C may reduce the N-nitroso compounds concentration [30]. High intakes of fruit and vegetables may reduce the risk by 30–70%; this protective effect seems to be less important for CA [5]. Data on diet can be summarized by the results of a case-control study performed in Uruguay, a country where incidence rates reach high figures. This study confirmed that diets rich in vegetables and fruits and with low amounts of salty (i.e. stewed and processed meat) and starchy foods are recommended for the prevention of gastric cancer [38].

Paralleling esophageal adenocarcinomas, obesity has been considered as another main risk factor for CA in the West, increasing the risk by approximately 50% [19].

Tobacco smoking increases risk of both CA and NCA by two to three times [19,20]. It has been shown that prolonged use of tobacco products is associated with a 1.5 to 2 times increased stomach cancer mortality in men and women [39]. Only a few epidemiologic studies have addressed the role of sex hormones in the etiology of gastric cancer. They have mainly investigated the association with menstrual or reproductive factors, and the results have been contradictory [40,41]. The hypothesis that estrogens may prevent gastric cancer is supported by a nationwide cohort study of men with prostate cancer, that indicated a reduced risk in this cohort exposed to estrogens [42]. Regular, continuing use of NSAIDs was found to be associated with a reduced risk (by about 70%) of stomach cancer [43].

It seems that a number of these factors sometimes play an opposite role in the occurrence of cancers in different gastric subsites, substantiating the hypothesis that cardia and proximal gastric cancer be different entities with respect to distal cancers.
Colorectal adenocarcinoma

Colon carcinogenesis results from a loss of genomic stability that leads to the transformation of normal colonic epithelial cells to colon adenocarcinoma cells. Most colorectal cancers arise from benign and asymptomatic colonic polyps, and some factors influencing the risk for colorectal carcinomas (CRC) are responsible for the occurrence of adenomas. Nevertheless, other evidence suggests that many risk factors for colorectal neoplasia may be important to adenoma formation, but not to dysplasia per se [44,45]. It is estimated that 12% of colon cancers are attributable to the following of a Western-style diet, but dietary factors associated with polyp development may not be the same as those associated with cancer [46]. The evidence is consistent for increases in risk associated with animal fat and red meat consumption [47,48]. However, no evidence of a positive association with the frequency of meat consumption was observed among non-vegetarians and vegetarians [49]. In addition, recently The Women’s Health Initiative Dietary Modification Trial showed that a low-fat dietary pattern intervention did not reduce the risk of CRC in postmenopausal women [50]. The potential risk-reducing benefits of fruit, vegetable, and fiber consumption for colorectal cancer are less clear [51,52]. The beneficial role of most vegetables was confirmed in an Italian study, which showed a more than 20% reduction in the risk of colorectal cancer from the addition of one daily serving [53]. Among nutrients, beta-carotene, ascorbic acid, folate, selenium, magnesium, calcium are thought to contribute to colon cancer prevention, especially in high risk individuals [54,55], but equivocal evidence exists for dietary antioxidants [56].

The role of alcohol is also controversial. In patients with at least one colorectal adenoma an excessive consumption of alcohol increased the likelihood of developing high risk adenomas or colorectal cancer. A meta-analysis of prospective cohort studies showed a 15% increased risk of colon or rectal cancer for an increase of 100 g of alcohol intake per week. This relationship did not differ significantly by anatomical site [57,58]. On the contrary, no increased risk of colorectal cancer was found among alcoholics by Ye et al. [59].

Several studies strongly support the idea that colorectal cancer might be a tobacco-associated disease, assuming that up to one in five tumors in Western countries may be attributable to tobacco use [49,60]. The major effect of smoking could occur in the earlier stages of the formation of adenomas and of development of carcinoma in situ. Alcohol use, tobacco use, and male gender seem to be associated with earlier onset and a distal location of CRC [61]. The risk for colorectal cancer increases with the length of exposure to smoke, and it may be reduced after long-term smoking cessation [62].

An increased risk for CRC has been associated with obesity and low physical activity, which is inversely associated with the risk of having large polyps.
However, so far the available data are inconsistent [63–65]. Glycemic index has been positively associated with approximately three-fold risk of colorectal cancer. The risk may be mostly explained by glycated hemoglobin concentrations and it is possible that the correlation be due to an indirect role of refined carbohydrates, which are considered general indicators of a poor diet [66,67], but data are contradictory [68,69].

Barrett’s esophagus, the main determinant of esophageal adenocarcinoma, has been hypothesized to be an independent risk factor for CRC as well [70]. The protective effect of NSAIDs on CRC was recently questioned by a prospective cohort study from Sturmer et al. [71] showing that regular use of these drugs did not succeed in a substantial risk reduction for CRC.

As in the case of gastric cancer, exogenous female hormones are supposed to play a protective role in CRC, too [72]. This could explain in part the decline of mortality rates for the pathology in many developed countries in women, but not in men. Reproductive factors may have differential roles in colon and rectal cancer etiology [73].

**Familial history and individual susceptibility**

It is proven that some individuals are more prone to develop several pathologies and that an interaction exists between environmental factors and individual susceptibility. It is also possible that in certain cases environmental factors are the main reason for familial clustering of carcinomas and that the expression of familial susceptibility can be modified by adult life risk factors [74].

A positive family history of ESCC or CA has been significantly associated with risk of ESCC and gastric tumors [75], while heredity does not seem to contribute significantly to the occurrence of esophageal cancer according to Lagergren et al. [76]. Familial clustering of both BE and EA occurs, but the influence of genetic factors in the etiology of EA is still debated [77]. Gastric cancer can develop as part of the hereditary non-polyposis colon cancer syndrome, as well as part of the gastrointestinal polyposis syndrome, including familial adenomatous polyposis and Peutz–Jeghers syndrome. It has been estimated that approximately 8% of stomach cancers have an inherited familial component [78]. Associations with family history are weakest for rectal cancer and strongest for proximal colonic cancer. Data among spouses and siblings consistently point to the importance of heritable factors in familial CRC: the risks between siblings were increased particularly for cancer in the right-sided colon [79]. According to Negri et al. [80] a family history of CRC in first-degree relatives increases the risk of both colon and rectal cancer, the association being stronger at younger ages and for the right colon.
A colonoscopy screening program focusing on first-degree relatives of CRC patients showed that 26% of lesions were hyperplastic polyps, 48% were tubular adenomas, 13% were tubulovillous adenomas, 5% were adenomas with high-grade dysplasia, and 7% were adenocarcinomas [81].

The polymorphism of different genes may simultaneously modulate the risk of the tumors and interact with environmental risk factors. Some metabolic pathways, e.g. those involving folate and heterocyclic amines, may be modified by alterations in relevant genes. Polymorphisms of DNA repair genes, and an imbalance between phase I drug metabolism and phase II detoxification may contribute to the development of these diseases. In addition, the expression of key genes in any of these pathways may be lost by inherited or acquired mutation or by hypermethylation. In Table 2.6 some recent studies on the relation between genes and gastrointestinal tumors are reported.

Conclusions

Carcinomas of the esophagus, stomach, and colorectum are somewhat different entities and multiple factors seem to influence the occurrence of these tumors in males or females and at different ages. However, it is certain that a
large number of these cancers may be preventable by following simple recommendations for improving life quality and that few known risk factors account for the majority of tumors. From a public health viewpoint, the impact of a disease depends on the distribution of exposures in the population and on the strength of the association. Table 2.7 reports some studies on the population

Table 2.7  Population attributable risks (%) for some aetiologic factors in gastrointestinal tumors.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Author</th>
<th>Attributable risk</th>
</tr>
</thead>
</table>
| Esophageal AC              | Engel et al., 2003 [82] | Smoke: 40%  
Gastroesophageal reflux: 30%  
Low fruit and vegetable intake: 15%  
Fruit and vegetables: <3 servings/day: 20% |
|                            | Terry et al., 2001 [5]  |                                                                                   |
| Esophageal squamous cell carcinoma | Engel et al., 2003 [82] | Smoke: 57%  
Alcohol: 72%  
Low fruit and vegetable intake: 29%  
Fruit and vegetables: <3 servings/day: 20% |
|                            | Terry et al., 2001 [5]  |                                                                                   |
|                            | Negri et al., 1992 [106] | Smoking: 71%  
Elevated alcohol: 45%  
Low β-carotene: 40%  
for males |
| Cardia AC                  | Engel et al., 2003 [82] | Smoke: 45%  
High body mass index: 19% |
| Distal gastric AC          | Engel et al., 2003 [82] | Smoke: 18%  
History of gastric ulcers: 10%  
Helicobacter pylori +: 10%  
High nitrite intake: 41% |
| Gastric AC                 | Chao et al., 2002 [39]  | Tobacco: 28% men, 14% women  
Low beta-carotene intake: 48%  
High traditional foods intake: 40%  
Low vitamin C intake: 16% |
|                            | La Vecchia et al., 1995 [107] |                                                                                   |
|                            | Sjodahl, 2007 [108]    | Current smoke: 18%  
Family history: 8% |
| Colorectal AC              | La Vecchia et al., 1996 [109] | Low beta-carotene: 39%  
Low vitamin C: 14%  
Low beta-carotene and vitamin C: 43%  
High red meat intake: 17%  
High daily meal frequency: 13%  
Family history of CRC: 4% |
|                            | La Vecchia et al., 1999 [83] | Low vegetable intake: 22%  
Low physical activity: 14%  
High education: 12%  
Family history of CC: 8% |

AC: adenocarcinoma; CC: colon cancer; CRC: colorectal cancer.
attributable risk (PAR) for the study of tumors, i.e. the measure of the proportion of the disease that would have been avoided if all participants were moved to the lowest exposure level with regard the etiologic factors. We can see, for example, that ever smoking, alcohol consumption, and low fruit and vegetable consumption can increase the PAR up to 89% for ESCC, and that ever smoking, high body mass, history of GERD, and low fruit and vegetable consumption account for 79% of EA. Smoking, history of gastric ulcers, high nitrite intake, and \(Hp\) infection may be responsible for about 59% of distal gastric adenocarcinomas [82]. High education, low physical activity, high energy intake, low vegetable intake, high eating frequency, and a family history of colorectal cancer may account for 56% of colon cancers [83]. In general, lifestyles associated with an increased risk of gastrointestinal tumors are those typical of a diet rich in fat and calories, alcohol, tobacco smoking, and with a low intake of vegetable, fruits, and fibers, and a sedentary lifestyle. Generally speaking, we can say that recommendations for improving lifestyle behavior and the quality of the diet, increasing physical activity, and cessation of smoking are consistent with general recommendations for reducing overall cancer risk.

References

1 Ishii T, Murakami J, Notohara K et al. Oesophageal squamous cell cancer may develop within a background of accumulating DNA methylation in normal and dysplastic mucosa. Gut 2006 [Epub ahead of print].


36  CHAPTER 2


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Introduction

Historically, the detection of high-grade intra-epithelial neoplasia (HGIN) and early-stage cancer in the gastrointestinal (GI) tract, i.e. intramucosal (T1m) or submucosal (T1sm) cancer, is mostly performed with videoendoscopy, which is able to detect gross mucosal lesions in the GI tract, such as elevations, ulcerations, and nodularity. More careful and thorough inspection is however needed to detect early lesions.

Detection of these abnormalities has been improved by the development of new endoscopic modalities, particularly with regard to: (a) white light endoscopy, particularly high-resolution endoscopy (HRE), high magnification endoscopy and chromoendoscopy; (b) optical spectroscopy; and (c) endomicroscopy, represented by endocystoscopy and laser confocal microscopy. The pros and cons and results of these techniques in detecting early neoplastic lesions in the GI tract are discussed in Chapter 4: Advances in Endoscopic Imaging of Barrett’s Esophagus.

Although some of these new modalities play a role in staging early neoplastic lesions, the mainstay in the staging process is endoscopic ultrasound (EUS). In this chapter we will discuss the available staging modalities for early cancer of the esophagus, stomach, and colorectum.

Esophagus

The endoscopic diagnosis and staging of esophageal carcinoma is relatively straightforward since patients usually are diagnosed with advanced tumors that are easily recognizable by endoscopy. The true challenge is the detection of early neoplastic lesions of the esophagus. If these lesions are histologically confirmed, the next step is staging with the aim of determining whether an endoscopic resection is feasible.

---

High-resolution endoscopy

In the last two decades, endoscopes with charge-coupled devices (CCD), i.e. electronic endoscopes, have largely replaced fibreoptic endoscopes. The CCDs in a standard videoendoscope used to contain hundred 38000–300 000 pixels. Recently, endoscopes containing CCDs with 600 000 to 1 million pixels have been introduced. These are called high-resolution endoscopes (HRE). High resolution now seem to have become the new standard for endoscopic imaging.

May et al. [1] performed a study in which HRE was used to stage patients with early esophageal adenocarcinoma \( (n=81) \) or squamous cell carcinoma \( (n=19) \). Polypoid, depressed, and excavated configurations and ulcerations were regarded as endoscopic signs with a higher risk of submucosal infiltration. Results were correlated with the histological result obtained by endoscopic mucosal resection (EMR). Overall accuracy of staging with HRE was 83%. Sensitivity for mucosal \( (T1m) \) tumors was higher than 94%, while that for submucosal \( (T1sm) \) tumors was only 56%.

Endoscopic ultrasound

Anatomy of the normal esophageal wall

The GI tract wall comprises four distinct histologic layers, i.e. the mucosa, submucosa, muscularis propria, and adventitia (Fig. 3.1). The innermost layer is the superficial mucosa and is represented as a hyperechoic band by EUS. In reality, this layer represents the initial echo-interface between the ultrasound waves, the GI tract mucosa, and the surrounding fluid. The second hypoechoic layer represents the deep mucosa, including the muscularis mucosae. The third hyperechoic layer corresponds histologically with the submucosa. The fourth hypoechoic layer represents the muscularis propria, whereas the fifth hyperechoic layer is the adventitial layer. The normal esophageal wall measures 3–4 mm in the distal esophagus. Areas of focal thickening are suspicious for the presence of carcinoma.

Distinguishing between \( T1m \) and \( T1sm \) early esophageal cancer

It should be noted that the risk of lymph node metastases increases rapidly with tumors invading the esophageal submucosa \( (T1sm) \) [2]. T1m squamous cell carcinomas have a less than 4% risk of lymph node metastases, but this risk is more than 25% for \( T1sm \) tumors. This is also true for adenocarcinomas, with lymph node metastases in 2% of \( T1m \) and 27% of \( T1sm \) tumors [3].

EMR is an attractive alternative to esophagectomy, particularly for \( T1m \) esophageal cancers, as the risk of dying from metastatic disease (varying between
1.9% and 3.7%) in this situation is lower than that of a surgical procedure. It is known that the mortality due to esophagectomy varies between 3% and 5%, with significant morbidity in 30% of cases, even in expert centers [4].

In addition, EMR is able to give prognostic information, as it allows histological examination of the resected specimen with regard to the depth of infiltration (involvement of the mucosa (T1m) and submucosa (T1sm)), extension of the tumor into the base and lateral margins, degree of infiltration, and, in some cases, invasion of lymphatic vessels and veins. This information is however only available after an EMR has already been performed.

Staging before EMR is clinically important for defining the subgroup of patients that are most likely to be good candidates for an endoscopic therapeutic option. On the other hand, if the histological examination of the EMR specimen shows that the lesion is extending into the submucosa, a surgical resection is still possible. Therefore, EMR can also be considered to be a diagnostic procedure in these situations. Other imaging methods such as EUS are in that case only used to exclude metastatic disease (N or M).

**EUS method**

In general, high-frequency (20–30 MHz) probes are used to determine tumor infiltration into the different layers of the wall of the GI tract, whereas low-frequency (7.5–12.5 MHz) probes are used to detect the presence of metastases in lymph nodes or other organs such as the liver.
The main advantage of evaluating the esophagus with high-frequency EUS probes is the higher resolution of images compared to low-frequency probes. With these high-frequency miniprobes, it is possible to discriminate nine different layers. In this nine-layer concept the first four layers are all mucosal with the fourth layer representing the muscularis mucosae. The miniprobes are 2–3 mm in diameter and can be passed through the working channel of a standard or therapeutic endoscope.

Enlarged peri-esophageal, celiac, and posterior mediastinal lymph nodes are easily detected with EUS. Lymph nodes generally appear darker (‘hypoechoic’) than surrounding fat or soft tissues (Fig. 3.2). Ultrasonographic features suggestive of malignancy include a round (vs. any other) shape, sharply demarcated borders, hypoechogenicity, and an enlarged size (>5–10 mm) [5].

EUS is increasingly combined with fine-needle aspiration (FNA) to confirm metastatic disease in lymph nodes, particularly if the FNA result will affect a clinical decision [6]. Care should be taken not to perform an EUS–FNA procedure through an esophageal tumor because this may lead to false positive results.

**Findings at EUS**

Various studies have reported on T and N staging of early esophageal cancer [1,7–12].

**T stage.** From these studies, it can be concluded that the combined sensitivity of T1 staging is 80% (Table 3.1). Only one small study, including nine patients,
Table 3.1  Reported endoscopic ultrasound (EUS) results on T1 staging in patients with high-grade intra-epithelial neoplasia (HGIN) or early esophageal cancer (EC).

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Biopsy result (n)</th>
<th>Probe (MHz)</th>
<th>Sensitivity T1 (%)</th>
<th>Specificity T1 (%)</th>
<th>Sensitivity T1m (%)</th>
<th>Specificity T1m (%)</th>
<th>PPV T1m (%)</th>
<th>NPV T1m (%)</th>
<th>Sensitivity T1sm (%)</th>
<th>Specificity T1sm (%)</th>
<th>PPV T1sm (%)</th>
<th>NPV T1sm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scotinotis et al. [7]</td>
<td>22</td>
<td>HGIN (10) EC (12)</td>
<td>7.5/12</td>
<td>5/5/12 (100)</td>
<td>16/17 (94)</td>
<td>16/16 (100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May et al. [1]</td>
<td>94</td>
<td>EC (94)</td>
<td>20</td>
<td>75/94 (80)</td>
<td>62/68 (91)</td>
<td>12/25 (48)</td>
<td></td>
<td></td>
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<tr>
<td>Buskens et al. [8]</td>
<td>77</td>
<td>HGIN (13) EC (64)</td>
<td>12/20/30</td>
<td>20/21 (95)</td>
<td>19/24 (79)</td>
<td>19/20 (95)</td>
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<tr>
<td>Larghi et al. [9]</td>
<td>48</td>
<td>HGIN (25) EC (23)</td>
<td>5–20</td>
<td>41/48 (85)</td>
<td>34/40 (85)</td>
<td>7/8 (88)</td>
<td></td>
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<tr>
<td>Waxman et al. [10]</td>
<td>9</td>
<td>HGIN (7) EC (2)</td>
<td>5/12</td>
<td>1/3 (33)</td>
<td>3/4 (75)</td>
<td>12/14 (86)</td>
<td></td>
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<tr>
<td>Pech et al. [11]</td>
<td>100</td>
<td>EC (100)</td>
<td>7.5 + 12.5/20</td>
<td>42/55 (76)</td>
<td>39/44 (89)</td>
<td>3/11 (27)</td>
<td></td>
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<tr>
<td>Shimoyama et al. [12]</td>
<td>20</td>
<td>EC (20)</td>
<td>7.5 + 12–20</td>
<td>Acc.: T1m1-2/m3-sml/sm2–3: 70%</td>
<td>39/47 (83)</td>
<td>3/8 (38)</td>
<td>12/14 (86)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
<td>HGIN (55) EC (315)</td>
<td>159/200 (80)</td>
<td>3/4 (75)</td>
<td>335/152 (89)</td>
<td>3/11 (27)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

NPV: negative predictive value; PPV: positive predictive value.
gave results on specificity of T1 tumors, which was 75% (3/4) [10]. The combined sensitivity of T1m tumors was 89%, while that of T1sm tumors was lower, at 70% (Table 3.1). One study reported the specificity of T1m tumors, which was only 27% in that study [11]. In contrast, the combined specificity of T1sm tumors was 87%. This translated into a high positive predictive value (PPV) of EUS for T1m tumors and a high negative predictive value (NPV) for T1sm tumors, at 83% and 89%, respectively.

The results show that, when EUS is inaccurate, it tends to overstage rather than to understage. This will result in a decision to perform an esophageal resection in these patients, which is in fact not desirable as an EMR would have been sufficient in the majority of these people. Since understaging rarely occurs, very few patients will be treated with an EMR when the preferred approach would have been a surgical resection. In the latter situation, EMR can however be considered to be a diagnostic procedure, which can still be followed by a more invasive (surgical) procedure. The low morbidity and absent mortality add to the use of EMR as a diagnostic method in experienced hands.

N stage. For N staging in early esophageal cancer, EUS is considered to be most important, as the finding of positive peri-esophageal, celiac, and posterior mediastinal lymph nodes means that EMR is no longer indicated, and a surgical resection with or without neoadjuvant chemoradiotherapy is the only treatment option. Cytological proof through EUS–FNA is mandatory.

If the results of the four studies that reported on N staging are taken together (Table 3.2), sensitivities varied between 43% and 100%, whereas results for specificity were less different, varying between 71% and 97%. An issue in these studies is however that it is more difficult to define the gold standard as compared to studies in which T stage is evaluated. In three of four studies, the gold standard was the surgical specimen, whereas in another study the gold standard was follow-up by EUS and CT at 6-month intervals [11].

Computed tomography

A major part of the standardized staging procedure in esophageal cancer is thoracic and abdominal computed tomography (CT) to detect the presence of metastatic disease. EUS has been demonstrated to be superior to CT for T and N staging in patients with esophageal cancer [13]. Pech et al. [11] compared CT chest/abdomen with high-frequency EUS in 100 patients with T1 esophageal cancer. However, CT had no influence on TNM stage in any of these patients.
Table 3.2  Reported endoscopic ultrasound (EUS) results on N staging in patients with high-grade intra-epithelial neoplasia (HGIN) or early esophageal cancer (EC).

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Biopsy result (n)</th>
<th>Probe (MHz)</th>
<th>Sensitivity N stage (%)</th>
<th>Specificity N stage (%)</th>
<th>PPV N stage (%)</th>
<th>NPV N stage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scotiniotis et al. [7]</td>
<td>22</td>
<td>HGD (10) EC (12)</td>
<td>7.5/12</td>
<td>1/1 (100)</td>
<td>17/21 (81)</td>
<td>17/17 (100)</td>
<td></td>
</tr>
<tr>
<td>Buskens et al. [8]</td>
<td>77</td>
<td>HGD (13) EC (64)</td>
<td>12/20/30</td>
<td>8/14 (57)</td>
<td>57/61 (94)</td>
<td>8/14 (57)</td>
<td>57/61 (93)</td>
</tr>
<tr>
<td>Pech et al. [11]</td>
<td>100</td>
<td>EC (100)</td>
<td>7.5 + 12.5/20</td>
<td>75%</td>
<td>97%</td>
<td>75%</td>
<td>98%</td>
</tr>
<tr>
<td>Shimoyama et al. [12]</td>
<td>20</td>
<td>EC (20)</td>
<td>7.5 + 12–20</td>
<td>43% (Acc.: 57%)</td>
<td>71%</td>
<td>60%</td>
<td>56%</td>
</tr>
</tbody>
</table>

HGD: high-grade dysplasia; NPV: negative predictive value; PPV: positive predictive value.
Conclusion

EUS with high- (12–30 MHz) and low- (7.5 MHz) frequency EUS probes is the investigation of choice in patients with early (T1) esophageal cancer to detect more deeply invading tumors and/or metastatic lymph nodes, which would preclude the use of EMR. An endoscopic treatment should mainly be offered if neoplasia is limited to mucosal (T1m1–3) and selected submucosal (T1sm1) tumors without malignant-appearing or demonstrated (by FNA) lymph nodes. There is no additional role for HRE in the staging of these early lesions, whereas a CT should be reserved for patients with more advanced esophageal tumors to detect (distant) metastases.

Stomach

Early gastric cancer is detected by careful endoscopic examination of the stomach and is histologically confirmed by biopsy. For detecting early stage gastric cancer, it is important to realize that subtle changes in color and mucosal pattern may be indicative of an early lesion. It is generally considered to be difficult to diagnose early neoplastic changes in the stomach, at least for Western endoscopists. If an early gastric cancer is found, however, the next step is to determine whether the lesion can be removed by endoscopic means or should be treated with a (partial) gastrectomy.

Videoendoscopy

It would be of clinical value if standard videoendoscopy could predict whether a small gastric lesion, which is suspected to be malignant, is still limited to the mucosa or is already extending into the submucosa of the gastric wall.

Yanai et al. [14] compared staging characteristics of endoscopy, using an Olympus GIF-2T200 endoscope with 100,000–300,000 pixels, and conventional EUS in 59 patients with suspected early gastric cancer, and compared these with the gold standard, an endoscopically or surgically resected specimen. Lesions that protruded from the mucosa with a smooth surface and those with a shallow and smooth surfaced depression were classified as mucosal (endoscopy-mucosal). Lesions considered to exhibit submucosal invasion (endoscopy-submucosal) were those that showed a more uneven base, with an irregularly shaped nodule, or those with folds that were enlarged. Overall accuracy rate in staging invasion depth was similar, i.e. 63% for endoscopy and 71% for EUS. Both endoscopy and EUS tended to overstage lesions, in 46% and 43% of patients, respectively, showing submucosal lesions, which were histologically demonstrated to be mucosal. The errors of endoscopy mainly resulted from inadequate interpretation of the depth of the depression, unevenness of the surface, and ulcerous changes.
Magnification endoscopy

Magnification endoscopy in the stomach is often performed in combination with installation of acetic acid [15,16]. Although five different types of surface patterns could be discriminated, no correlation was found between depth of invasion (mucosa vs. submucosa vs. deeper invasion) and surface pattern. On the other hand, magnification endoscopy was able to determine the extent of horizontal spread of gastric lesions.

Endoscopic ultrasound

Anatomy of the normal gastric wall

On EUS, the normal gastric wall is not different from that of the normal esophagus and is also visualized as having a five-layer architecture. In the stomach, the 5th hyperechoic layer represents the serosa, including the subserosa, and not the adventitia as in the esophagus. Using a high-frequency EUS probe, the fine hypoechoic layer (about 0.2 mm in thickness) between the 2nd and the 3rd hyperechoic layers, which is considered to be the muscularis mucosae, gives information on the depth of invasion of tumors.

Distinguishing between T1m and T1sm early gastric cancer

Similar to the esophagus, the risk of lymph node metastases increases rapidly with tumors invading the gastric submucosa (T1sm). Although the risk of lymph node metastases is low for mucosal lesions, varying between 1.9% and 3.5%, it increases to 14–27% for tumors invading the submucosa [17]. This means that T1m gastric tumors can be considered to be removable by EMR, while a T1sm tumor should be considered to be an indication for partial or total gastrectomy.

EUS method

In general, high-frequency (20–30 MHz) EUS probes are also used in the stomach to determine tumor infiltration into the different layers of the wall of the GI tract, whereas low-frequency (7.5–12.5 MHz) probes are used to detect the presence of metastases in lymph nodes.

Findings at EUS

Five studies have reported on the results of T and N staging of early-stage gastric adenocarcinoma [14,18–21].

T stage. From these studies, it can be concluded that the combined accuracy of T1 staging is 83% (Table 3.3). In more detail, the combined sensitivity of
<table>
<thead>
<tr>
<th>Author</th>
<th>N (Biopsy result)</th>
<th>Probe result (MHz)</th>
<th>Sensitivity T1 (%)</th>
<th>Specificity T1 (%)</th>
<th>Sensitivity T1m (%)</th>
<th>Specificity T1m (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akahoshi et al.</td>
<td>78 GC (78)</td>
<td>7.5/12</td>
<td>52/78 (67)</td>
<td>40/57 (70)</td>
<td>6/13 (46)</td>
<td>6/13 (46)</td>
</tr>
<tr>
<td>Yanai et al.</td>
<td>52 GC (52)</td>
<td>20</td>
<td>37/52 (71)</td>
<td>21/33 (64)</td>
<td>11/17 (65)</td>
<td>11/17 (65)</td>
</tr>
<tr>
<td>Ohashi et al.</td>
<td>49 GC (49)</td>
<td>7.5/12</td>
<td>39/49 (80)</td>
<td>37/38 (97)</td>
<td>2/11 (18)</td>
<td>2/11 (18)</td>
</tr>
<tr>
<td>Yoshida et al.</td>
<td>295 GC (295)</td>
<td>7.5/12</td>
<td>265/295 (90)</td>
<td>246/264 (93)</td>
<td>19/31 (61)</td>
<td>19/31 (61)</td>
</tr>
<tr>
<td>Tsendsuren et al.</td>
<td>12 GC (12)</td>
<td>5/7.5</td>
<td>10/12 (83)</td>
<td>98/128 (77)</td>
<td>98/128 (77)</td>
<td>98/128 (77)</td>
</tr>
<tr>
<td>Total</td>
<td>486 GC (486)</td>
<td>15</td>
<td>403/486 (83)</td>
<td>98/128 (77)</td>
<td>98/128 (77)</td>
<td>98/128 (77)</td>
</tr>
</tbody>
</table>
T1m gastric cancer was 77% (Table 3.3). One study reported the combined sensitivity of T1m plus T1sm1 (tumor invading the first of three layers of the submucosa) gastric cancers and found a sensitivity of 93% (246/264) for EUS [20]. The combined sensitivity of T1sm tumors was only 46%. The sensitivity of T1sm2–3 gastric cancers was somewhat higher, i.e. 61% (19/31) in this study [20]. These results suggest that the distinction between T1m and T1sm early gastric cancer is more difficult than when the cut-off point is set between the first and second layer of the submucosa. Nonetheless, even if invading only the first layer of the T1sm1, a distinction should be made between tumor invasion that is shallower or deeper than 400 µm. In the experience of these authors [20], well-differentiated gastric adenocarcinoma was not associated with lymph node metastases, provided that invasion was shallower than 400 µm into the submucosa.

Akahoshi et al. [18] investigated whether staging accuracy was influenced by endoscopic tumor type, histologic type, and tumor size. The accuracy in determining depth of invasion in relation to endoscopic type was significantly higher for the elevated type (91%) than for the depressed type of early cancer (56%). The staging accuracy classified by histologic type was significantly higher for differentiated (86%) than for undifferentiated (18%) cancer and decreased when tumor size increased.

As stated above, it is technically often difficult to make a distinction between mucosal and submucosal early gastric cancers. Matsumoto et al. [22] evaluated EUS images of the 3rd hyperechoic layer (submucosa) of 75 patients to define EUS features suggestive of submucosal tumor invasion. They found that irregular narrowing (60%), a budding sign (86%), meaning an irregularly bordered low echo break into the 3rd layer within a width of 2 mm below the tumor, or the combination of these features (91%) were predictive for the presence of submucosal invasion when tumorous changes in the 3rd layer exceeded 1 mm in depth.

These results show, as in early esophageal cancer, that EUS tends to overstage rather than to understage. In one study, the percentage of overstaging (false-positive ingrowth into the submucosa) was 43% [14], whereas in another study this was 24% for both early (n=12) and advanced (n=29) gastric cancer [21]. Similar to early esophageal cancer, this will result in a decision to perform a (subtotal) gastrectomy in these patients, which is in fact not desirable as an EMR would have been sufficient in the majority of these people.

**N stage.** For N staging in early gastric cancer, EUS with high-frequency probes is inadequate, with one study reporting accuracy of 80%, but a sensitivity of 17% [18]. In the combined early and advanced gastric cancer series, sensitivity was still only 66% using a low-frequency EUS probe [21] (Table 3.4). Therefore, the presently available catheter probes are unreliable in detecting lymph node
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Biopsy result (n)</th>
<th>Probe (MHz)</th>
<th>Sensitivity N stage (%)</th>
<th>Specificity N stage (%)</th>
<th>PPV N stage</th>
<th>NPV N stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akahoshi et al. [18]</td>
<td>78</td>
<td>GC (78)</td>
<td>15</td>
<td>1/6 (17) (Acc.: 80%)</td>
<td>36/40 (90)</td>
<td>20%</td>
<td>88%</td>
</tr>
<tr>
<td>Tsenduren et al. [21]</td>
<td>41</td>
<td>GC (41), both early (12) and advanced (29) cancer</td>
<td>5/7.5</td>
<td>27/41 (66)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NPV: negative predictive value; PPV: positive predictive value.
metastases in early gastric cancer. The reason is that only perigastric lymph nodes near the lesion can be visualized, while deeper metastatic lymph nodes remain out of reach of these probes.

Conclusion

EUS using small caliber EUS probes can be used to try to discriminate between T1m and T1sm early gastric cancer. However, it is unreliable in detecting lymph nodes (N stage). Various tumor characteristics, for example a depressed tumor type as seen by endoscopy, an undifferentiated adenocarcinoma as seen by histology, and a larger tumor size negatively influence reliability of T staging. For the most optimal staging result, particularly of T stage, EUS should be combined with endoscopy to evaluate the macroscopic tumor type. Magnification endoscopy with dye spraying may play a role in the evaluation of the horizontal spread of the lesion. Endoscopic treatment of early gastric cancer should only be offered if the lesion is limited to the mucosa (T1m1–3) and in selected submucosal (T1sm1) tumors.

Colorectum

It has convincingly been shown that the early detection and endoscopic resection of precursor lesions in the colorectum is able to disrupt the adenoma-carcinoma sequence. Until recently, it was assumed that the majority of these precursor lesions were polypoid structures, which can easily be removed by snare polypectomy. However, as in Japan, flat and depressed non-polypoid colorectal lesions are increasingly being detected in Western patients and these accounted for 38% of all adenomas detected in a recent UK series [23]. Moreover, an anatomical preponderance of flat and depressed adenomas and carcinomas in the right colon has been demonstrated.

EMR is now increasingly being practised for flat and depressed lesions in the colorectum. These lesions are however associated with a higher submucosal invasion rate than polypoid lesions. Lymph nodes metastases have been reported in 15–50% of flat and depressed colorectal lesions invading the submucosal layers 2 + 3 (T1sm2–3). Lymph node metastases in intramucosal (T1m1–2) and focally extending submucosal (T1m3–sm1) cancer are rarely found and can therefore be treated by EMR [24].

Videoendoscopy

As the newer diagnostic endoscopic techniques are relatively time consuming and not generally available in many endoscopy units, it could be a more cost-effective
and convenient approach if the discrimination between flat and depressed type T1m–sm1 and T1sm2–3 cancers could be made by videocolonoscopy.

Saitoh et al. [25] diagnosed and treated 64 depressed-type early CRCs using an Olympus GIF-2T200 endoscope or a Hitachi EVC-400-HM endoscope. When a faint abnormality of the mucosa was suspected by routine colonoscopy, 0.1% indigo carmine solution was sprayed onto the mucosal surface. Colonoscopic findings of T1m–sm1 cancers and more extended submucosal (sm2–3) cancers were compared with confirmed histologic findings. Characteristic colonoscopic findings for T1sm2–3 CRCs were: (1) an expansive appearance, (2) a deep depression surface, (3) an irregular bottom of depression surface, and (4) two or more mucosal folds converging toward the tumor. Using these findings, the invasion depth of depressed-type early CRC could be correctly determined in 58 of 64 lesions (91%).

Magnification endoscopy

Hurlstone et al. [26] used high magnification chromoscopic colonoscopy (HMCC) for discriminating neoplastic from non-neoplastic colorectal lesions, particularly when flat and depressed. Total colonoscopy was performed in 1850 patients using an Olympus C240Z magnifying colonoscope. The detailed non-magnified chromoscopic appearance of all lesions was documented using the macroscopic classification of the Japanese Research Society for Cancer of the Colon and Rectum, after delineating the contour with 0.5% indigo carmine [27]. The magnified surface pit pattern was then further classified according to Kudo’s modified criteria (type I–V) [28]. A total of 1008 flat lesions were identified. Sensitivity and specificity of HMCC in distinguishing between non-neoplastic and neoplastic lesions were 98% and 92%, respectively. However, when using this technique to differentiate non-invasive from invasive neoplastic lesions, sensitivity was poor (50%) with a specificity of 98%. Therefore, HMCC is able to discriminate neoplastic from non-neoplastic lesions, but cannot be used to discriminate invasive from non-invasive neoplastic lesions.

Endoscopic ultrasound

Anatomy of the normal colonic wall

On EUS, the colonic wall is no different from the gastric wall in that it has a five-layered architecture. The 5th hyperechoic layer represents the serosa, including the subserosa, and in the rectum the adventitia. Using a high-resolution EUS probe, the fine hypoechoic layer (about 0.2 mm in thickness) between the 2nd and the 3rd hyperechoic layers in the colon also represents the muscularis mucosae separating the mucosa from the submucosa.
Findings at EUS

Eight studies have reported on the results of T and N staging of early stage colorectal carcinoma [29–36]. The majority of these lesions were flat or depressed early CRCs.

T stage. Taking these studies together, we found that the combined accuracy of T1 staging is 90% (Table 3.5). Only one study reported on the sensitivity of T1m lesions and found this to be 88% [34]. Akasu et al. [30] performed the largest study (309 patients with HGD, or T1/T2 CRC) and made a distinction between T1sm1 and T1sm2–3 tumors. They found that the accuracy of a radial scanning transducer for the former was 96%, whereas this was 97% for tumors invading the deeper submucosa.

N stage. For N staging in early CRC, EUS with high-frequency probes seems inadequate, with a reported accuracy varying between 24% and 89%, and a disappointingly low sensitivity of 9% [31] and 38% [30] in two studies, but a sensitivity of 80% in the most recent study by Hurlstone et al. [36] (Table 3.6). Given the rather superficial scanning capacity of these high-frequency EUS probes, it is not surprising that in the former two studies low sensitivity rates were found. On the other hand, specificity of EUS is high, suggesting that false-positive findings are unlikely.

EUS vs. high magnification chromoscopic colonoscopy

As a consequence of the findings summarized above, it is of particular interest to compare EUS with HMCC. Is one of these staging methods superior to the other or do they both have additional value in staging early CRC?

Both Matsumoto et al. [31] and Hurlstone et al. [36] compared HMCC with high-frequency 20/12 MHz miniprobe EUS. In both studies, it was found that the accuracy for invasive submucosal depth (T1sm2–3) detection was significantly higher with EUS than with HMCC, i.e. 92% vs. 63% [31] and 93% vs. 59% [36], respectively. Negative predictive value for deep invasion was also higher for EUS than for HMCC (91% vs. 54% [31] and 88% and 47% [36], respectively). The accuracy for lymph node metastasis was however surprisingly different between the two studies, 24% for EUS and 72% for HMCC in the study by Matsumoto et al. [31] vs. 85% for EUS and 44% for HMCC in the study by Hurlstone et al. [36]. This is remarkable, but the impressive results for lymph node detection by Hurlstone et al. [36] have not been reported previously and have not been confirmed by others so far (Table 3.6). These two studies provide evidence that high-frequency probe EUS imaging is a more sensitive and more specific tool for establishing invasive depth in T1sm CRC. The results in the study of Matsumoto et al. [31] suggest that HMCC may be predictive for lymph nodes metastasis in early-stage CRC, but further trials are required.
Table 3.5  Reported endoscopic ultrasound (EUS) results on T staging in patients with early colorectal cancer (CRC).

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Biopsy result (n)</th>
<th>Probe (MHz)</th>
<th>Sensitivity T1 (%)</th>
<th>Specificity T1 (%)</th>
<th>Sensitivity T1m (%)</th>
<th>Specificity T1m (%)</th>
<th>Sensitivity T1sm1 (%)</th>
<th>Specificity T1sm1 (%)</th>
<th>Sensitivity T1sm2–3 (%)</th>
<th>Specificity T1sm2–3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saitoh et al.</td>
<td>49</td>
<td>Flat/depressed CRC (49)</td>
<td>20</td>
<td>Acc.: 4/3/49 (88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Akasu et al.</td>
<td>309</td>
<td>Rectal cancer (Tis-T2) (309)</td>
<td>7.5/12</td>
<td></td>
<td>270/274 (99)</td>
<td>(Acc.: 96%)</td>
<td></td>
<td>26/35</td>
<td>261/266</td>
<td>38/43 (88)</td>
<td></td>
</tr>
<tr>
<td>Matsumoto et al.</td>
<td>50</td>
<td>Flat/depressed CRC (50)</td>
<td>12/20</td>
<td>Acc.: 4/5/49 (92)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tseng et al.</td>
<td>10</td>
<td>CRC (T1) (10)</td>
<td>12/10</td>
<td>Acc.: 10/10 (100)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stergiou et al.</td>
<td>33</td>
<td>Adenoma (16) CPRC (T1) (17)</td>
<td>12</td>
<td>Acc.: 3/3/3 (100)</td>
<td></td>
<td></td>
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<tr>
<td>Konishi et al.</td>
<td>125</td>
<td>Villous (35)</td>
<td>7.5</td>
<td>Villous: 18/20 (60)</td>
<td>Villous: ½</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Non-villous (90) (T1/T2)</td>
<td></td>
<td>Acc.: 2/1/35 (60)</td>
<td>Non-villous: 8/2/90 (91)</td>
<td></td>
<td></td>
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<tr>
<td>Hurlstone et al.</td>
<td>48</td>
<td>Flat/depressed CRC (Tis/T1) (48)</td>
<td>12.5</td>
<td>Acc.: 4/8/48 (100)</td>
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<td></td>
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<tr>
<td>Hurlstone et al.</td>
<td>52</td>
<td>Flat/depressed CRC (T1sm1–3) (52)</td>
<td>12.5/20</td>
<td>Acc.: 4/9/52 (94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>676</td>
<td></td>
<td></td>
<td></td>
<td>Acc.: 331/366 (90)</td>
<td></td>
<td></td>
<td>36/41 (88)</td>
<td>279/287 (97)</td>
<td>26/35 (74)</td>
<td>286/294 (97)</td>
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</table>
Table 3.6  Reported endoscopic ultrasound (EUS) results on N staging in patients with early colorectal cancer (CRC).

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Biopsy result (n)</th>
<th>Probe (MHz)</th>
<th>Sensitivity N stage (%)</th>
<th>Specificity N stage (%)</th>
<th>PPV N stage (%)</th>
<th>NPV N stage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akasu et al. [30]</td>
<td>309</td>
<td>Rectal cancer (Tis-T1) (309)</td>
<td>7.5/12</td>
<td>3/8 (38) (Acc.: 89%)</td>
<td>68/72 (94)</td>
<td>3/8 (38)</td>
<td>68/73 (93)</td>
</tr>
<tr>
<td>Matsumoto et al. [31]</td>
<td>50</td>
<td>Flat/depressed CRC (50)</td>
<td>12/20</td>
<td>2/23 (9) (Acc.: 24%)</td>
<td>5/6 (83)</td>
<td></td>
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<tr>
<td>Hurlstone et al. [36]</td>
<td>52</td>
<td>Flat/depressed (T1sm1-3) (52)</td>
<td>12.5/20</td>
<td>8/10 (80) (Acc.: 85%)</td>
<td>15/17 (88)</td>
<td>8/10 (80)</td>
<td>15/17 (88)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>411</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

NPV: negative predictive value; PPV: positive predictive value.
Conclusion

EUS is the preferred method of discriminating between flat and depressed T1m/T1sm1 CRC and T1sm2–3 CRC, however EUS is less reliable in detecting lymph nodes. HMCC can be used to discriminate neoplastic from non-neoplastic lesions. Both procedures provide complementary information with respect to the decision to perform a local or a surgical treatment. It remains to be established whether videoendoscopy plus chromoendoscopy if an abnormality of the mucosa is suspected can replace high magnification endoscopy. For this, additional trials are indicated.

Staging of early-stage neoplastic lesions in the GI tract is a part of the work-up of patients with these disorders as it is able to direct a treatment decision toward a local endoscopic treatment with EMR or more radical surgical therapy. In general, EUS with high-frequency EUS probes is the preferred technique to accurately stage early malignancies in the esophagus, stomach, and colorectum. The role of HRE and high magnification endoscopy lies primarily in detecting these lesions. Both modalities play only a modest role in staging early neoplastic lesions in the GI tract. Finally, EMR is a safe procedure and can, apart from being a therapeutic procedure, also be used as a diagnostic procedure making the staging of early lesions in some cases unnecessary.

References


CHAPTER 4

Advances in Endoscopic Imaging of Barrett’s Esophagus

AMITABH CHAK AND FAREES T. FAROOQ

Introduction

Barrett’s esophagus (BE) is defined by displacement of the squamocolumnar junction proximal to the esophagogastric junction and the presence of metaplastic intestinal-type epithelium in place of the normal esophageal squamous epithelium. As this definition suggests, the diagnosis of BE requires both endoscopic findings and histologic confirmation. It seems intuitive that techniques aimed to improve endoscopic detection or aid in histologic prediction would be beneficial.

The importance of BE is clearly based on the recognition of it as a precursor of esophageal adenocarcinoma. The histologic progression from metaplastic BE to dysplastic BE and subsequently to adenocarcinoma is the rationale for endoscopic screening and surveillance programs. Current surveillance protocols call for periodic endoscopic examination for mucosal abnormalities as well as four-quadrant random biopsies every 1–2 cm within a segment of BE. The limitations of such protocols include sampling error because they sample less than 1% of the affected esophageal surface as well as the monotony and time required to perform biopsies in this fashion. The development of endoscopic imaging modalities that identify intestinal metaplasia and facilitate differentiation of bland Barrett’s epithelium from low-grade and high-grade dysplasia and early adenocarcinoma has been the focus of intense research. The potential merit of such imaging modalities is the possibility of complete examination of a BE segment for dysplasia without the need for biopsy or with the ability to focus biopsies to areas most likely to contain dysplastic epithelium. A number of endoscopic imaging methods have been developed for this purpose over the past two decades. The basis for each method, as well as the
technique, interpretation, and evidence for these imaging modalities, is the focus of this chapter.

**Histopathology in Barrett’s esophagus**

To understand how these novel imaging methods might enhance the ability to identify intestinal metaplasia and dysplasia and to realize their limitations it is necessary to understand the histologic criteria that define Barrett’s esophagus and its dysplastic stages. Normally, the esophagus has a stratified squamous epithelium with a uniformly flat surface. The hallmark of Barrett’s esophagus is specialized intestinal metaplasia, which contains absorptive goblet cells arranged in a villous architecture. Thus, imaging techniques can identify Barrett’s epithelium either by its absorptive nature or by magnifying to a resolution that identifies its villous structure. Low-grade dysplasia is characterized by increased nuclear activity that results in variations in nuclear size, nuclear crowding, and some loss of epithelial polarity. In vivo recognition of low-grade dysplasia requires an image resolution that identifies nuclei or a chemical method that identifies increased nuclear activity. In high-grade dysplasia (HGD) and early cancer, not only is there increased nuclear activity, but the villous architecture is distorted. Therefore, imaging techniques that can identify epithelial architecture are able to resolve these changes.

**Overview of endoscopic imaging for Barrett’s esophagus**

One of the difficulties in identifying dysplastic foci in BE is the large esophageal surface area that must be examined. In general, imaging methods with higher resolution that provide greater tissue detail or histologic information are difficult, if not impossible, to apply in scanning an entire segment of BE. Lower resolution methods can usually be used to image the entire esophagus but are less reliable in distinguishing dysplastic from non-dysplastic epithelium. The ideal imaging technique would have the following characteristics: high sensitivity for dysplasia, moderate specificity not affected by inflammation, the ability to scan a wide area in real time, high inter-observer agreement, ability to localize dysplastic areas for biopsy, and non-prohibitive cost. No single currently available imaging method has all of these criteria or even several of these criteria. However, the development of new endoscopic imaging techniques has opened exciting avenues in the area of Barrett’s research with the potential to improve upon surveillance and treatment strategies that comprise the current standard of care. In the future, we may find that the combination of various imaging methods is the best management algorithm.
Endoscopic imaging methods

Chromoendoscopy

Chromoendoscopy refers to the application of contrast stains to the mucosa at endoscopy such that surface patterns are highlighted. The use of various contrast agents including methylene blue, acetic acid, Lugol’s solution, and indigo carmine has been described extensively in the literature.

Methylene blue (MB) is absorbed by intestinal-type epithelium. Therefore, application of methylene blue in the setting of BE results in staining of Barrett’s epithelium with sparing of non-intestinal columnar and squamous epithelium. Furthermore, dysplastic Barrett’s epithelium stains less than BE without dysplasia due to the paucity of goblet cells in the setting of dysplasia. Therefore, areas of BE with dysplasia may be more evident on chromoendoscopy using MB. The technique of chromoendoscopy using MB involves clearance of surface mucus in the esophagus by flushing with 10% N-acetylcysteine. Subsequently, 0.5% MB is applied to the esophageal mucosa using an endoscopic spray catheter. After a 2-minute staining period, excess MB is cleared by flushing with sterile water. The use of MB has been described extensively in the literature. The results of these studies have been quite variable. Some authors have reported favorable results, some have reported mixed results, and some have reported unfavorable results [1–3]. This variability may be related to the fact that this technique is quite observer dependent and also may reflect some publication bias in the earlier reports.

The methylene blue chromoendoscopy technique has not been adopted widely and recent studies have suggested that methylene blue chromoendoscopy is likely to be of limited benefit in BE surveillance.

Unlike methylene blue, indigo carmine is simply a contrast agent that accentuates mucosal surface patterns. Indigo carmine is applied during endoscopy using a typical endoscopic spray catheter, after clearing of surface mucus with a water, saline, or N-acetylcysteine flush. The use of a cap fitted at the endoscope tip has been described to stabilize high magnification images and image areas of interest. Sharma et al. [4] have investigated the surface patterns in Barrett’s esophagus using magnification chromoendoscopy with Indigo carmine. In their study of 80 patients with BE, three distinct surface patterns were appreciated: ridged/villous, circular, and irregular/distorted. The ridged/villous pattern, which has a cerebriform appearance, and the circular pattern, which has uniform circular or oval areas were observed in non-dysplastic BE and in low-grade dysplasia. The irregular/distorted pattern was observed in HGD with a 100% sensitivity and specificity.
Narrow-band imaging

Conventional videoendoscopes transmit white light from a xenon lamp that passes through a rotating red-green-blue filter. The transmitted light, composed of alternating pulses of red, green, and blue light, illuminates the imaged area, and the wavelengths of visible light waves that strike and are absorbed or reflected by the imaged area are detected by a charge-coupled device (CCD) at the endoscope tip. The light waves detected by the CCD are transmitted to the video processor unit where superimposed red, green, and blue light images are integrated to create the final videoendoscopic image that is detected by the human eye [5]. In narrow-band imaging (NBI), an additional special filter has been incorporated into the endoscope such that imaged tissue is illuminated with narrow band-pass ranges of light in the red, green, and blue spectra. Blue light is disproportionately transmitted whereas other light wavelengths are selectively removed by absorption and/or interference. Red light at a wavelength of 650 nm penetrates tissue more deeply than blue light of 475 nm wavelength. Therefore, blue light is theoretically better for imaging superficial tissue structures in detail than red light or white light which is comprised of the entire visible light spectrum. As a result, the use of NBI allows for higher resolution of superficial tissue structures. In addition, blue light is preferentially absorbed by hemoglobin. Therefore, hemoglobin-containing structures, such as capillaries and luminal blood, are accentuated in the presence of blue light [6–9].

The value of NBI in the evaluation of gastrointestinal mucosal lesions, including colonic polyps and Barrett’s esophagus, has been investigated. Sharma et al. studied the mucosal and vascular patterns in Barrett’s esophagus [8,9]. The study found three distinct mucosal patterns in patients with BE. The ridge/villous pattern, as also identified in their high-magnification chromoendoscopy studies, is characterized by uniformly aligned ridges alternating with a villiform pattern. The ridge/villous pattern is seen as alternating dark and light lines on NBI. The circular pattern is characterized by a uniformly arranged circular mucosal pattern. The irregular/distorted pattern demonstrated ridge and villous pattern irregularity and distortion. Vascular patterns on NBI were characterized as normal (thin, uniformly branching vessels) or abnormal (dilated, corkscrew vessels in non-uniform branching patterns). Using a magnification NBI endoscope fitted with a cap to stabilize a focused imaged area, Sharma et al. found a positive predictive value, sensitivity, and specificity of 93.5%, 86.5%, and 94.7% for the ridge/villous pattern in BE without HGD and 100%, 98.7%, and 95.3% for the irregular/distorted pattern in BE with HGD [9]. The positive predictive value, sensitivity, and specificity of the abnormal vascular pattern for HGD was 94.7%, 100%, and 97.4%. The false-positives
with an abnormal vascular pattern included two areas of low-grade dysplasia. Normal vascular patterns were found in areas of nondysplastic BE, low-grade dysplasia, and intestinal metaplasia of the gastric cardia. Kara et al. [6] also characterized BE based on mucosal and vascular patterns. Their terminology was slightly different from that used by Sharma et al. but essentially described the same findings. In this study, irregular or disrupted mucosal pattern, irregular vascular pattern, and the presence of abnormal blood vessels were independent predictors of HGD ($p < 0.05$). This study also found a new pattern, a flat featureless epithelium with long normal capillaries that also corresponded to non-dysplastic BE.

**Autofluorescence**

Fluorescence is the process in which certain molecules, termed fluorophores, absorb light energy and reach an excited state. From the excited state, fluorophores return to the ground state and, in that process, emit light of a longer wavelength than the light that produced the excited state. Emitted light within the visible light spectrum accounts for the optical phenomenon of fluorescence. The use of fluorescence for imaging may be based on endogenous fluorophores such as nicotinamide adenine dinucleotide (NADH) or collagen or the use of exogenously supplied fluorophores, such as porfimer sodium or the fluorescent dye fluorescein. The exploitation of endogenous fluorophores in biological tissue for imaging is termed autofluorescence [10]. Variations in molecular composition

Fig. 4.1  Barrett’s esophagus with high-grade dysplasia on standard white-light videoendoscopy.
Fig. 4.2 The same area with NBI. An irregular/distorted mucosal pattern is apparent in an area of high-grade dysplasia.

Fig. 4.3 The same area following endoscopic mucosal resection.
and tissue microstructure lead to differences in fluorescence, thereby creating the potential for distinguishing neoplastic from non-neoplastic tissue. Prototype endoscopes that make use of this technology have been developed in recent years. Additional tissue characteristics based on red and green light reflectance have also been incorporated to improve the image production algorithm. The application of the concept of autofluorescence using the endoscope as the source of excitation light waves has been termed light-induced fluorescence endoscopy (LIFE).

Early fiberoptic endoscopy technology that incorporated LIFE found that inflammation as well as dysplasia leads to increased autofluorescence. The autofluorescence signal is also quite weak and difficult to identify, limiting the applicability of this technology for BE surveillance. The use of intravenous or topical fluorophores such as 5-aminolevulinic acid improved the performance of LIFE but still not to a level where it could be applied clinically [11]. Kara et al. [12] compared autofluorescence-targeted biopsies with random four-quadrant biopsies in 50 patients presenting for BE surveillance. Using a fiberoptic endoscope with the LIFE II autofluorescence system (Xillix Corp, British Columbia, Canada), the investigators found that the use of LIFE-targeted biopsies did not improve the detection of HGD and adenocarcinoma over standard white-light endoscopy with the ‘Seattle protocol’.

The value of autofluorescence endoscopy in the detection of dysplasia in Barrett’s esophagus has been improved by the development of new AFI techniques that utilize CCD endoscopes and imaging algorithms that incorporate reflectance. In another study, investigators from Amsterdam used a prototype autofluorescence imaging (AFI) system (Olympus, Inc., Tokyo, Japan) that integrates autofluorescence and red/green reflectance to produce a real-time AFI image in which non-dysplastic Barrett’s esophagus appears green and suspected dysplastic Barrett’s esophagus appears blue/violet [13]. In this initial unblinded pilot study, the investigators compared the rate of detection of HGD in all-comers being evaluated with BE using AFI-guided biopsies and random four-quadrant biopsies. In 60 patients, AFI-guided biopsies increased the detection rate of HGD or adenocarcinoma from 23% to 33%. The positive predictive value of AFI-suspicious areas was 49% while the negative predictive value was 89%.

The same investigators later studied 20 patients with known BE with HGD and identified suspicious areas using AFI and NBI [14]. Biopsies obtained from these areas were used to determine the accuracy of histologic prediction based on AFI. They found that the false-positive rate of AFI for predicting dysplasia was 40%. Additional interpretation of NBI along the AFI reduced false-positivity to 10%.

Thus, similar to NBI, autofluorescence endoscopy is conceptually interesting and shows promise as an adjunctive imaging method. However, the early data show that AFI lacks the sensitivity and specificity to warrant routine use in
Fig. 4.4  Barrett’s esophagus with standard white-light videoendoscopy.

Fig. 4.5  The same area with autofluorescence imaging. Non-dysplastic BE appears green, while high-grade dysplasia appears violet.
guiding endoscopic surveillance [15]. As AFI instruments continue to evolve, these parameters are likely to improve. And, as Kara et al.’s studies suggest, the combination of imaging techniques such as AFI and NBI may ultimately be the most accurate way of detecting dysplastic BE.

**Optical coherence tomography**

Optical coherence tomography (OCT) is an imaging technique that is conceptually analogous to B-mode ultrasound, except that OCT uses light waves rather than sound waves. Light waves derived from a low-coherence light source are delivered to an optical-fiber splitter that sends half of the light to the area to be imaged and the other half to a reference mirror. By a process termed interferometry, the backscattered light from tissue and the time delay between reflected light waves from tissue and the reference mirror are processed [16–18]. The resulting image is a two-dimensional tomogram with a resolution of 1–15 μm and a scanning depth of 1–3 mm. OCT uses optical fiber technology allowing for incorporation into a catheter-probe design that can be passed through an endoscope channel. Although the resolution of OCT is not quite at the level of histopathology, the aim of OCT imaging, in contrast to chromoendoscopy, NBI, and AFI, is to produce images that provide some degree of histologic detail. In this context, OCT can not only differentiate Barrett’s epithelium from squamous epithelium and detect villous/crypt architecture, but it also has the potential to differentiate non-dysplastic BE from dysplastic BE.

Studies in the colon polyp model were initially used to determine the OCT characteristics of dysplasia – loss of tissue organization and reduced light scattering, that have since been applied to the esophagus [19]. Using these criteria in a double-blinded, prospective study of 33 patients with BE, Isenberg et al. [20] found that in detecting dysplasia in BE, OCT had a sensitivity and specificity of 68% and 82%, respectively. Another study by Evans et al. [18] using analogous criteria found that OCT could be used to distinguish BE from non-metaplastic epithelium at the squamocolumnar junction. Currently available endoscopic OCT probes do not yet have the capability of providing images at the nuclear level and are applicable only for research purposes at this time. However, ongoing development of these devices with improved resolution is likely to improve the diagnostic accuracy of OCT in Barrett’s esophagus.

**Confocal endomicroscopy**

As discussed earlier, fluorescence imaging is based on the emitted light from molecules returning from the excited state to ground state. In fluorescence
Fig. 4.6 OCT image of Barrett’s esophagus. Villous surface pattern is apparent.

Fig. 4.7 OCT image of Barrett’s esophagus with high-grade dysplasia characterized by loss of tissue organization. (The thin bright line near the center of the field represents the cap fitted at the endoscope tip.)
imaging an entire area is flooded with light, and a wide area of emitted light is detected. Fluorescence emitted by tissue away from the region of interest interferes with the resolution of the in-focus region. In confocal microscopy, laser light is reflected off a dichromatic mirror to an in-focus tissue plane. Exogenously supplied fluorophores within the imaged specimen emit light, and emitted light of sufficient wavelength is refocused through a pinhole at a conjugate plane to the imaged area. The pinhole aperture at the detector allows out-of-focus emitted light to be rejected whereas light transmitted though the pinhole is detected and processed to produce an ‘optical section’ of one focal plane within the imaged region of interest [21–23]. Scanning over multiple points allows construction of a two-dimensional planar image. The confocal microscope has been miniaturized such that it can be incorporated into the tip of an endoscope.

Confocal endomicroscopic images are of high resolution and allow for subsurface mucosal analysis and in vivo histology. Kiesslich et al. [24] imaged 63 patients with BE following administration of fluorescein. By confocal imaging, intestinal metaplasia was easily demonstrated by the presence of dark goblet cells, and low-grade neoplasia was identifiable by the presence of dark irregularly shaped epithelial cells. In addition subepithelial capillaries were detectable and differed in pattern between non-dysplastic BE and low-grade neoplasia. The accuracy of confocal endomicroscopy in detecting BE and low-grade neoplasia was 96.8% and 97.4%, respectively. Low-grade and high-grade dysplasia and early cancer were not specifically distinguished in this study. Therefore, the ability to distinguish non-dysplastic BE from BE with varying degrees of dysplasia short of early cancer is uncertain.

Endoscopic ultrasound (EUS)

While certainly not a new imaging method, EUS is worthy of mention in the context of BE imaging and endoscopic mucosal resection. EUS is used commonly for the staging of esophageal cancer, but the use of EUS for detection of early cancer in patients with dysplastic BE has not been universally accepted.

EUS in Barrett’s esophagus can be performed using a standard radial-scanning echoendoscope or alternatively using high-frequency catheter probes. Neither method has been shown to be reliable in differentiating BE from BE with dysplasia, as the mucosal thickening seen in dysplasia is mimicked by inflammation in the setting of non-dysplastic BE. Furthermore, the compressability of the esophageal wall layers by the echoendoscope balloon increases the subjectivity of EUS interpretation for this indication. However, EUS may have a role in selecting patients with high-grade dysplasia or early cancer for endoscopic ablative therapy by determining the presence or absence of submucosal invasion and lymph node involvement [25–28].
CHAPTER 4

Fig. 4.8 Confocal endomicroscopic image of squamous epithelium in a patient with chronic gastroesophageal reflux disease showing normal squamous cells outlined faintly by fluorescein and fluorescein in the multiple interpapillary capillary loops. Red blood cells can be seen ‘stacked’ in the blood vessels.

Fig. 4.9 Confocal endomicroscopic image of Barrett’s esophagus in the same patient as Fig. 4.8, showing the villiform intestinal-type epithelium with dark goblet cells after injection of intravenous fluorescein. Note the normal architecture of the glands, abundant lamina propria, intact basement membrane, and orderly arrangement of epithelial cells consistent with absence of dysplasia.
In a study of 25 patients referred for endoscopic therapy of BE with HGD or early cancer, EUS identified submucosal invasion or lymphadenopathy in 20% of patients, thereby altering their management from endoscopic therapy to surgery [27]. The use of EUS and CT staging for 100 patients referred for endoscopic therapy of BE with early cancer identified 23% of the patients as more appropriate for surgery than endoscopic ablation based on tumoral and nodal staging, with EUS far exceeding the sensitivity of CT in detecting advanced disease [26]. The results of these studies suggest that EUS staging should be strongly considered prior to undertaking EMR in a patient who is otherwise a good surgical candidate.

Conclusions
Identification of the ideal endoscopic method for surveillance of Barrett’s esophagus and detection of dysplasia remains an elusive goal. Whether recent advances in endoscopic imaging such as NBI, OCT, and AFI will complement or replace some of the older methods of mucosal enhancement such as chromoendoscopy from a clinically practical standpoint is uncertain. What is clear is that the more sophisticated techniques such as OCT and confocal endomicroscopy which produce higher resolution images inevitably narrow the endoscopic ‘field of view’ making these techniques difficult to use in scanning an entire segment of BE. In the future, combining techniques that can image a large region and then focus in on suspicious areas for targeted biopsies or therapy (e.g. EMR) may be the optimal approach.

Fig. 4.10  EUS of esophagus in BE with high-grade dysplasia.
Acknowledgments

The confocal endomicroscopy images were kindly provided by Marcia Canto, MD. The autofluorescence images were provided courtesy of Michelle Wong Kee Song, MD.

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Summary
Endoscopic mucosal resection (EMR) has gained more and more importance in the treatment of early gastrointestinal neoplasia over the last few years. The choice of the different available techniques depends on the site, the macroscopic type of the tumor, and the personal experience of the endoscopist. The ‘suck and cut’ technique with ligation device or cap should be favored over normal strip biopsy in the upper gastrointestinal tract because of the larger size of the resected specimen and its technical feasibility.

EMR of gastrointestinal lesions is a safe and effective method but should only be performed by experienced endoscopists in high volume centers.

Introduction
The technique of endoscopic mucosal resection (EMR) emerged in the early 1970s. Since then EMR in the gastrointestinal (GI) tract has been used for many years as a diagnostic and therapeutic procedure for early malignancies. Initially intended to allow large biopsy, it actually became an alternative to surgery for the treatment of flat, sessile lesions, including high-grade intraepithelial neoplasia, carcinomas such as mucosal cancer, or superficial submucosal cancer (sm1) with a low risk of spread to lymph nodes. The technique is used especially in the east Asian region, and data concerning EMR for this indication are sparse in Western publications.

In a 1984 publication, Tada et al. [1] for the first time described the use of ‘strip-off biopsy’ as a treatment option in early gastric carcinoma. The first
EMR procedures for early esophageal carcinoma were carried out in the early 1990s, again by Japanese endoscopists [2]. It was only several years later that the first Western research groups published their experience in EMR for esophageal neoplasias [3,4]. This was the start of the triumphant progress of EMR as a therapeutic and diagnostic procedure in the upper and lower gastrointestinal tract. A large number of different EMR techniques was described (see Table 5.1). The original strip biopsy technique advocated by Tada involved only injection and snaring – a submucosal injection is used to form a bleb, which is then cut by snare strangulation. Hirao et al. [5] described a technique involving injection, pre-cutting, and snaring, in which after submucosal injection, the target mucosa is cut with an electrocautery needle-knife, and the isolated mucosa is then captured with a snare wire. Makuuchi [6] later developed an endoscopic esophageal mucosal resection (EEMR) tube method, with which a larger resected specimen can be obtained.

Our own group now has more than 10 years’ experience in EMR treatment for malignant lesions in the upper gastrointestinal tract, with more than 1000 ER procedures. We believe that the method of endoscopic mucosal resection using a cap (EMR-C) or a ligation device (EMR-L) are the simplest techniques for carrying out mucosectomy in any part of the gastrointestinal tract.

Table 5.1  Classification of endoscopic mucosal resection techniques

<table>
<thead>
<tr>
<th>I Without suction</th>
<th>II With suction</th>
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<tbody>
<tr>
<td>2. Lift and cut biopsy, double-snare polypectomy [grasping and snaring] [7,8]</td>
<td>2. np-EEM: endoscopic esophageal mucosectomy under negative-pressure control [injection and snaring using an overtube] [10]</td>
</tr>
<tr>
<td>4. EMR-T: endoscopic mucosal resection using a transparent overtube [snaring using an overtube] [9]*</td>
<td>4. EMR-L: endoscopic mucosal resection using a ligating device [endoscopic variceal ligation and snaring] [12]</td>
</tr>
<tr>
<td></td>
<td>5. Simple suction technique [snaring with a stiff snare] [4]</td>
</tr>
</tbody>
</table>

* These techniques are only available in the esophagus.
Principle

The organs of the GI tract basically consist of two major parts, the muscle layer and the mucosal layer. These two components are attached to each other by the loose connective tissue of the submucosa and can easily be separated. Thus, it is possible to resect the mucosa and submucosa without hurting the muscle layer. As the wall of the GI-tract is only about 4 mm thick, special management is required to avoid perforation. Correct lifting of the mucosa is therefore extremely important. Injecting saline or other liquids into the submucosal layer or mechanical lifting using special instruments, e.g. a ligation device are the easiest and most effective techniques for avoiding muscle involvement. After lifting the mucosa including the target lesion, it can be safely captured, grasped with the snare wire, and resected by electrocauterization.

Prior to EMR of gastrointestinal lesions, especially in the upper GI tract, a carefully done staging by experienced physicians including chromoendoscopy, endosonography with 7.5 MHz-probe and 20 MHz miniprobe, and computed tomography, abdominal ultrasound is crucial.

Different EMR techniques

Strip biopsy

Strip biopsy was first successfully used by Tada to treat early gastric carcinoma [1]. In this technique, a diathermy loop is introduced through the endoscope’s working channel and positioned above a polypoid lesion. The lesion is caught by tightening the loop, and is slowly resected using electric cutting current. This technique can mainly be used in polypoid tumors (type I), as it is not possible to position the loop with flat lesions. Soehendra et al. [4] report successful ER treatment of two early squamous-cell carcinomas. No complications or recurrences were reported. Technically, ER was carried out using a monopolar diathermy–polypectomy loop, without prior injection under the lesion.

However, submucosal injection of a solution can also raise flat or depressed lesions (type II) so that they can be resected (the ‘lift and cut’ technique) – a method that was first described by Rosenberg in 1955 [13]. In addition to extending the range of target lesions in comparison with simple strip biopsy, this procedure also has other advantages. Injecting a solution of saline and epinephrine, for example, into the submucosa raises the early carcinoma, increasing the distance from the muscularis propria and thus reducing the risk of perforation. Since the wall of the entire gastrointestinal tract is only a few millimeters thick, this cushion is a very important safety factor. Another advantage of the injection technique is the reduced risk of hemorrhage due to the
vasoconstriction produced by epinephrine and the compression caused by the injection itself.

The type of injection solution used has not been standardized. The solution most often used is saline with epinephrine or dextrose in various concentrations. We use 10 ml of a 1:100 000 epinephrine–saline solution. The advantage of the epinephrine solution, in comparison with the saline plus dextrose solution also used, is the vasoconstriction caused by the catecholamine and the resulting reduction in the risk of hemorrhage. A disadvantage of the epinephrine–saline mixture is its short disappearance time (3.0 min) in comparison with a 50% dextrose solution (4.7 min) and a 1% rooster comb hyaluronic acid solution (22.1 min). These data were obtained in an animal-experiment study in the porcine esophagus [14]. Hyaluronic acid therefore, is more frequently used for the submucosal injection. After placement of electro-markers, which mark the boundaries of the tumor with a sufficient safety margin, injection under the lesion with a mixture of hyaluronic acid, epinephrine, and indigo carmine follows.

**Suck and cut technique**

The ‘suck-and-cut’ technique is used in the esophagus more frequently than strip biopsy, due to the anatomical conditions, and is also the technique favored by our own group. With a simple strip biopsy, with or without mucosal injection, sufficiently large specimens cannot be obtained in the esophagus, particularly in flat neoplastic lesions. A study by Tanabe et al. [15] demonstrated that endoscopic suck-and-cut mucosectomy in early gastric cancer is more effective than strip biopsy with regard to the largest diameter of the resected specimen, the rate of en-bloc resection, and the complication rate.

In the early 1990s, Inoue and co-workers developed the cap technique, thereby improving the effectiveness of EMR in comparison with simple strip biopsy [16]. In the EMR cap technique (EMR-C), a specially developed transparent plastic cap is attached to the end of the endoscope. After injection under the target lesion, the lesion is sucked into the cap and resected with a diathermy loop that has previously been loaded onto a specially designed groove on the lower edge of the cap. Since injecting underneath early carcinomas often makes it difficult to distinguish them, prior marking of the lesion – e.g. using electrocautery – is recommended.

EMR with a ligation device (EMR-L) is another suction mucosectomy technique. In this method, the target lesion is sucked into the ligation cylinder, and a polyp is created by releasing a rubber band around it. The polyp is then resected at its base, either above or below the rubber band, using a diathermy loop (Fig. 5.1(a)–(e)). In this technique, the endoscope being used for resection
has to be withdrawn again and reintroduced in order to remove the ligation cylinder and introduce the loop. Ligation devices available include, in addition to single-use devices, a reusable ligator [17], with which comparable results can be achieved at reduced cost. The feasibility of this technique was demonstrated in patients with early Barrett’s carcinoma and intraepithelial high-grade neoplasia and was presented by our own research group [18]. Complete remission was achieved in 82.5% of cases. Recent publications have also confirmed

![Fig. 5.1 Endoscopic resection of a mucosal Barrett’s adenocarcinoma with a ligation device: (a) early Barrett’s cancer type IIa seen through the ligation device prior to resection; (b) early Barrett’s type IIa cancer after ligation forming an artificial polyp; (c) resection of the artificial polyp by placing the snare below the rubber band; (d) Resected area after EMB at the cardia: the muscular layer is clearly visible; (e) the resected specimen of 22 mm in diameter pinned on cork.](image-url)
the effectiveness of EMR with the ligation technique in 50 patients with early neoplasia in short-segment Barrett’s esophagus [19,20]. The intermediate results were similarly encouraging (average follow-up period 34 ± 10 months) in 115 patients treated [21].

A study published in 2003 by our research group compared the two suction mucosectomy techniques – the cap technique and the ligation technique – in the resection of early esophageal neoplasias [22]. In this prospective study, 100 consecutive endoscopic mucosal resections were performed in 70 patients with early esophageal cancer. Fifty resections were carried out with the ligation device without prior injection, and 50 resections using the cap technique with prior submucosal injection with a diluted epinephrine–saline solution. The main criteria were the maximum diameter of the resected specimen, the resection area, and the complication rate. No significant differences were observed between the two groups with regard to the maximum diameter of the resected specimens and the resection area after 24h. There was only a slight advantage for the ligation group in patients who had had prior treatment. One minor bleeding incident occurred in each group, but no severe complications were seen.

Furthermore, our own experience with EMR treatment in the suck and cut technique for early squamous-cell carcinoma in 39 patients has now for the first time in a Western country confirmed the promising data presented by Asian researchers [23,24]. Complete remission was achieved in 79% of cases; recurrences or metachronous carcinomas were observed in five. Complications encountered involved mild bleeding, not requiring transfusion, in 3% of cases (three of 94 resections). Similarly good results were presented by Narahara et al. [25]. In 21 patients, successful mucosectomy of a total of 25 mucosal carcinomas was carried out after injection of a saline solution under the lesion. None of the patients had experienced a recurrence after two years.

If the lesion is so large that it is not possible to remove it using a single ‘suck-and-cut’ EMR procedure, then it is also permissible even with malignant lesions to resect the entire lesion using the so-called ‘piecemeal’ method. The long-term results with this method are as good for early gastric cancer, for example, as with en-bloc resections [26]. Endoscopic submucosal dissection (ESD) might offer the chance of entire en-bloc resection of large lesions (see Chapter 11).

In addition to the suck-and-cut mucosectomy and strip biopsy techniques, EMR using a double-channel endoscope has also been reported by several research groups [27]. In this method, a grasping forceps is used to pull the target lesion through a diathermy loop that has been introduced through the second working channel. The lesion is then resected with the loop. Due to the large caliber of the endoscope required, double-channel procedures appear to be very difficult, especially at the esophagogastric junction, and may even be almost impossible in the inverted position in short-segment Barrett’s neoplasia.
Risks and complications of EMR

ER involves certain risks, and should therefore only be carried out by experienced endoscopists. The most frequent complication of EMR is hemorrhage. Arterial bleeding is very rare. By contrast, oozing venous bleeding is not uncommon; it is usually not associated with a drop in hemoglobin, and is easily arrested by injection. Hemorrhage after EMR usually occurs during the first 12–24 h. For this reason, we regularly carry out check-up endoscopies after 24 h following EMR in the upper gastrointestinal tract, and only discharge patients when the findings are unremarkable.

By contrast, hemorrhage following EMR in the colon can appear up to 14 days after resection. According to a Japanese study, the risk of bleeding after ER in the colon is 1.15%, compared with 0.66% with simple polypectomy [28].

After circular ER in the esophagus, colon, or duodenum, scar formation and stenosis can develop during the subsequent months. However, this complication can be satisfactorily treated by bougienage or dilatation.

Perforation is the most serious complication of ER. Depending on the size and location of the lesion, the figures for the frequency of perforation in the upper gastrointestinal tract range from 0.06% to 5% [29]. Perforations in the stomach can usually by treated conservatively by closing the site with metal clips and administering antibiotic treatment and parenteral nutrition. The risk of perforation after ER in the colon is approximately 0.35% – much higher than with simple polypectomy (0.053%) [28].

In experienced hands, ER is a safe method of resecting dysplastic lesions and early carcinomas in the gastrointestinal tract, and it has decisive advantages over other local endoscopic treatment procedures (such as thermal destruction and photodynamic therapy): the histological processing of the resection specimen provides information about the depth of infiltration of the individual wall layers, and whether complete removal with healthy margins has been achieved. This means that even when a patient has an advanced carcinoma that has not been detected before treatment and which is not suitable for local endoscopic therapy, surgical resection can still be carried out.

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Introduction

Most gastrointestinal cancers are diagnosed at an advanced stage, with a poor survival rate despite treatment including major surgery and adjuvant therapy. Superficial cancers have a low risk of lymph node involvement, allowing effective local treatment.

Endoscopic mucosal resection (EMR), is a promising therapeutic option for removal of superficial gastrointestinal tract carcinomas (Table 6.1) [1].

Unlike ablative methods such as photodynamic therapy (PDT) and argon plasma coagulation (APC), EMR permits histologic assessment of the entire specimen.

Until 30 to 40 years ago, most esophageal cancers in developed countries were squamous-cell carcinomas (SCC). Since then, the proportion of esophageal adenocarcinomas (AC), related to gastroesophageal reflux and Barrett’s esophagus (BE) has risen to constitute 46–50% of new cases of esophageal cancer [2]. BE is a complication of long-standing gastroesophageal reflux disease, which is present in about 5–10% of patients undergoing endoscopy for reflux symptoms.

Cancer can develop in patients with BE over several years, through a sequence encompassing non-dysplastic metaplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), and invasive AC. HGD is found in fewer than 5% of patients with BE [3]. Pathological examination showed unrecognized cancers in 38–73% of patients who had surgery for HGD [4]. When HGD is diagnosed, slides should be reviewed by an expert pathologist because there is substantial variation within and between observers.
CHAPTER 6

Classification of early cancers

In the Vienna classification, gastrointestinal neoplastic lesions are defined as non-invasive or invasive. The non-invasive group includes LGD and HGD, where the basement membrane is not infiltrated. Invasive lesions include intramucosal cancers (IMC) and neoplasms infiltrating the submucosa [5].

Risk of lymph node metastases

To better define the risk for lymph node metastases, mucosal (m) and submucosal (sm) layers have each been divided in three sections: m1 (epithelium), m2 (lamina propria), m3 (muscularis mucosae) and sm1 (sm1a, b, c), sm2, and sm3. Nodal metastases were found in 0% of patients with m1 and m2 SCC of the esophagus, 4% with m3, and 26% with sm1 tumors.

The full thickness of the submucosa can be carefully evaluated in surgically resected specimens. This allows a semiquantitative measurement of the depth of the tumor invasion, and the fractioning of the submucosa in three equal layers. Buskens et al. [6] studied 77 esophagectomy specimens containing HGD or T1 carcinoma. Node metastases occurred with 23% sm2, and 69% sm3 tumors, but not in m1, m2, m3, and sm1 lesions. They concluded that m1, m2, m3, and sm1 lesions could be treated endoscopically if the lesion is <30 mm, well-differentiated, and without lymphangitic invasion. This detailed histologic analysis is not possible for specimens obtained with EMR, as it is difficult to entirely resect the submucosa.

The evaluation of EMR specimens can be carried out using a quantitative micrometric measure (µ) of the depth of the invasion, starting from the bottom of the mucosa. The risk of lymph node metastasis is related to a defined cut-off. In the squamocellular cancer (SCC) of the esophagus, when infiltration is

<table>
<thead>
<tr>
<th>Table 6.1 Considerations for endoscopic mucosal resection of a gastrointestinal lesion.</th>
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<tr>
<td><strong>When EMR is suitable</strong></td>
</tr>
<tr>
<td>• Patient with LGD, HGD, or IMC without lymph node involvement</td>
</tr>
<tr>
<td>• Lesion at risk for malignancy or progression</td>
</tr>
<tr>
<td>• Complete resection technically feasible</td>
</tr>
<tr>
<td><strong>Favorable outcomes depend on</strong></td>
</tr>
<tr>
<td>• Complete removal of the lesion</td>
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<tr>
<td>• Absence of synchronous lesions or invasive disease</td>
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</table>

EMR: endoscopic mucosal resection; HGD: high-grade dysplasia; IMC: intramucosal cancer; LGD: low-grade dysplasia.
<200 µm the risk of nodal metastases is low. It increases to 36–47% with deeper invasion.

For BE, a submucosal infiltration of 500 µm has been proposed, as the risk of nodal metastases is low. However, a 20–25% risk of node involvement with submucosal infiltration has been reported [7,8].

Endoscopic mucosal resection techniques

Before performing EMR, in patients with visible mucosal abnormalities, the lesion margins should be identified, to avoid incomplete resection. Chromoendoscopy with methylene blue, or Lugol iodine may show the extent of cancers. Marking the periphery of the lesion with electrocautery helps to determine the area of EMR.

The lesion can be removed ‘en bloc’, or ‘piecemeal’. Piecemeal resection increases the complication rate, histologic assessment of the margins is difficult, and the recurrence risk is higher. The maximum recommended diameter for ‘en bloc’ resection is 20 mm in the esophagus.

Submucosal injection

The gastrointestinal wall has two components, mucosal and muscle layers, attached by a loose connective tissue of submucosa. Injection of a fluid into the submucosa creates a cushion between the lesion and the deeper layers of the gut wall before removal.

Submucosal fluid injection facilitates EMR and avoids thermal damage to the muscularis propria, helping to identify invasive lesions, with sensitivity 100% and specificity 99%. If the lesion does not lift, EMR should not be attempted.

A more durable submucosal fluid cushion may result in safer procedures. Several solutions have been proposed, some of which have been tested only experimentally: normal saline with or without adrenaline, 50% dextrose, glycerol (10% glycerol and 5% fructose), hyaluronic acid, and hydroxypropyl methylcellulose.

The effects of hydroxypropyl methylcellulose were studied in the esophagus of pigs. The mean submucosal fluid cushion duration was 36 min. The authors stated that 0.83% hydroxypropyl methylcellulose was able to create a longer lasting submucosal esophageal cushion, without causing tissue reaction. The leakage of the solution from the needle puncture site was the main cause of short-lasting cushions [9].

In our endoscopic practice, we use normal saline plus adrenaline solution (1/100,000). A small amount of methylene blue is added to the solution to
facilitate visibility in the esophageal wall. Whatever solution is used, it is necessary to avoid repeated needle injections so that the fluid is not dispersed.

**Strip biopsy**

Strip biopsy is the simplest technique as it requires the use of a polypectomy snare. After the submucosal injection, the open snare is placed around a portion of the lesion and gently pressed against the mucosa. Excess air has to be aspirated from the hollow organ to decrease distention and to allow an easy grasp of the targeted lesion. After snare excision, air is again insufflated to visualize the resected area and to allow the residual tissue to be removed. Resections have to be performed until complete removal of the lesion, and exposure of the muscularis propria. A barbed snare can be used to facilitate the grasping of the tissue.

The size of the samples obtained with this procedure ranges between 10 and 15 mm.

Soehendra *et al.* [10] reported the use of a monofilament stainless steel wire (0.4 mm) polypectomy snare to perform esophageal EMR, without submucosal injection.

**Endoscopic mucosal resection ‘cap-assisted’ (EMR-C)**

A transparent plastic cap is preloaded on the endoscope tip. Inside the cap is a gutter which positions the opened polypectomy snare. After submucosal injection, the cap is pressed against the mucosa, the lesion is aspirated into the cap, and resected (Fig. 6.1).

It has been reported that EMR-C is better and safer than standard snare resection. Experimental studies have corroborated this assertion, showing that EMR-C is safer and easier than snare resection. The diathermic injury is less marked, allowing a better histologic assessment of depth and margin involvement.

![Fig. 6.1 EMR-C technique.](image-url)
The major limitation of the EMR-C is that it is impossible to evaluate the amount of tissue that, after the suction, has been grasped with the polypectomy snare. An excessive suction could entrap the muscularis propria, causing a transmural resection. To decrease the risk of perforation it is advisable to sever the grasped tissue after having decreased the aspiration into the cap. This maneuver allows the muscularis propria to retract, returning to its original position.

In our experience results of EMR-C, in terms of width and depth of the resected specimen, are sometimes unpredictable in the lower esophagus, close to the esophagogastric junction. Sometimes, the diameter of the resection is no wider than 10 mm, and resection can involve fibers of the muscularis propria. Caution is advised when the EMR involves the esophagogastric junction. During the aspiration into the cap, a large amount of gastric tissue, which is softer and more mobile, may be captured by the snare or by the rubber, leading to potential complications.

‘Suck and ligate’ technique

EMR can be performed using a standard variceal ligator device. An artificial polyp is created and resection is performed with a polypectomy snare (Fig. 6.2). The diameter of the resected mucosa ranges between 10 and 15 mm [11–12].

When performing this technique, the submucosa injection is not always necessary, as the risk of damaging the muscularis propria is nil [13].

The ligation technique has proved to be more effective than EMR-C in treating recurrences in patients who previously underwent endoscopic treatments. The fibrosis of the scar did not impede placement of the rubber [14].

A randomized study showed no significant difference between the ‘suck and ligate’ technique, without submucosal injection, and EMR-C after injection for

Fig. 6.2  ‘Suck and ligate’ technique.
early esophageal AC or SCC. After EMR, 57% of patients had residual neoplasia at the first follow-up [14].

This method is cumbersome, requiring the repeated introduction of endoscopes. The first endoscope allows the submucosal injection, and the second instrument is placed into the esophagus to release the band. As a standard polypectomy snare cannot be introduced through the operative channel of the instrument, the endoscope is withdrawn and the first endoscope is reintroduced to resect the artificial polyp.

A novel multibanding mucosectomy device (MMD) (Duette®, Cook Ireland Ltd, Limerick, Ireland) has been recently presented (Fig. 6.3). It consists of a modified multi-band variceal ligator and a mini hexagonal polypectomy snare which can be passed through the ligator handle. The lesion is suctioned into the barrel of the ligator and a rubber band is placed on it creating a pseudopolyp. This pseudopolyp is resected using the preloaded snare.

The setup is similar to a standard multiple-band ligator device. Up to six resections per device may be made.

Complications

Despite the advantages of EMR compared to surgery, it must be remembered that it is an invasive technique and complications may occur. However, in the literature, deaths have not been reported. To minimize the risks, only experienced endoscopists should undertake EMR in an appropriate environment.

Early complications include bleeding and perforation. Bleeding has been reported in up to 14% of procedures. Usually it is intraprocedural, but it can occur later than 24 hours following EMR. Epinephrine and hemoclips are useful to control spurring hemorrhage. Bleeding was reported in 4–20% of esophageal

Fig. 6.3 Multibanding mucosectomy device (Duette®).
SCC, in about 10% of patients with lesions in BE, and in 12% of early gastric cancer (EGC) [15–18]. The perforation risk during EMR is 0.1–5% [19].

When EMR involves over three-quarters of the esophageal circumference, stenosis can occur a few weeks later. Mucosal defects longer than 3 cm were also associated with greater severity of the stenosis. This complication has been reported in up to 30% of cases [20–22]. A few sessions of endoscopic dilation can solve the stricture [23].

Indications for esophageal EMR are summarized in Table 6.2 and outcomes in Table 6.3.

**Esophageal squamous-cell cancer**

In Japan EMR is a common therapy for SCC confined within the lamina propria mucosae. EMR is also used for lesions infiltrating the muscularis mucosae, as the survival is comparable with esophagectomy [24]. Indications for EMR of SCC are listed in Table 6.2.

### Table 6.2 Indications for esophageal EMR.

<table>
<thead>
<tr>
<th>Benign epithelial lesions</th>
<th>Hyperplastic-adenomatous polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-stage AC</td>
<td>Well or moderately differentiated SCC–AC</td>
</tr>
<tr>
<td></td>
<td>IIa, IIb, IIC $&lt;20$ mm</td>
</tr>
<tr>
<td></td>
<td>m1 or m2 cancers</td>
</tr>
<tr>
<td>Barrett’s esophagus</td>
<td>HGD–IMC within visible mucosal abnormalities</td>
</tr>
<tr>
<td></td>
<td>Circumferential EMR for endoscopically</td>
</tr>
<tr>
<td></td>
<td>undetectable foci of HGD in SSBE*</td>
</tr>
<tr>
<td></td>
<td>Visible areas of LGD to refine the histologic</td>
</tr>
<tr>
<td></td>
<td>diagnosis</td>
</tr>
</tbody>
</table>


### Table 6.3 EMR outcome in esophageal lesions.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Resection rate (%)</th>
<th>Recurrence (%)</th>
<th>Surgery after EMR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Squamous-cell cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding: 4–20%</td>
<td>64–94</td>
<td>0–10</td>
<td>0–15</td>
</tr>
<tr>
<td>Perforation: 1–5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Barrett’s esophagus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding: 0–33%</td>
<td>60–95</td>
<td>0–31</td>
<td>0–15</td>
</tr>
<tr>
<td>Stenosis: 0–30%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EMR: endoscopic mucosal resection.
Multicentric squamous epithelial dysplasia is common, and chromoendoscopy with Lugol is useful in these patients. Lugol-voiding lesions (LVLs) have been observed in association with synchronous and metachronous multiple esophageal cancer in patients with head and neck cancer. It has been reported that patients with multiple LVLs are at risk of developing local recurrences after EMR [25]. Multiple synchronous lesions have been reported in 26–31% of patients with SCC. Metachronous lesions may also develop [26,27].

Local recurrence after EMR has been reported in 2.4–7.8%, and it has been associated with piecemeal resection [28]. After EMR in patients with superficial SCC, the five-year survival rate is up to 95% [29,30].

M1 and m2 SCC have little likelihood of lymph node metastasis [31]. EMR in 25 patients with superficial (m1) SCC showed no recurrence after a mean follow-up of two years [16].

It has been reported that patients with m3 areas attached or infiltrating the lamina muscularis mucosae showed lymph node or distal metastasis. These patients should be treated with curative surgery.

Few reports have analysed the outcome of EMR in patients with invasive cancer. Shimizu et al. compared 26 patients with SCC invading the muscularis mucosae or the submucosa, treated by EMR, with 44 comparable patients undergoing surgery. Survival was similar in the two groups, 77% vs. 84% [24]. A European group treated 39 SCC patients. Success was obtained in 79% of cases, and local recurrences or metachronous lesions occurred in five (13%). Bleeding (3%) was managed endoscopically. Two patients died because of disease progression [32].

A multimodality approach in patients with SCC invading the submucosa was tried in 18 patients. After EMR, chemo-radiotherapy was given if lymph node involvement was present or suspected. No local recurrences were observed [33].

Barrett’s esophagus

Endoscopic therapy aims to remove the dysplastic BE, allowing restoration of squamous epithelium. Methods used to remove HGD include PDT and APC, as well as EMR (Table 6.4). After these procedures, patients need long-term control of acid reflux with proton pump inhibitors or antireflux surgery.

Patients with visible areas of LGD, should also undergo EMR. There are reports on the natural history of LGD, showing the progression to HGD and AC. Skacel et al. [34] followed 25 patients with LGD (mean follow-up: 26 months) and seven patients (28%) developed HGD, while AC occurred in two of them.

EMR could become a therapeutic alternative to surgical esophagectomy, which involves substantial morbidity, and a mortality rate of 3–5% [20,31].
Table 6.4  Therapeutic options for superficial cancer in Barrett’s esophagus.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pros</th>
<th>Cons</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMR</td>
<td>✓ Histologic assessment</td>
<td>✓ Incomplete treatment of invisible foci of HGD</td>
<td>✓ Favorable in superficial cancer</td>
</tr>
<tr>
<td></td>
<td>✓ Removal of circumferential BE up to 4 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDT</td>
<td>✓ Easy to perform</td>
<td>✓ Lack of adequate histological examination</td>
<td>✓ Favorable in superficial cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✓ Photosensitivity and esophageal stenosis</td>
<td></td>
</tr>
<tr>
<td>Laser</td>
<td>✓ Deep penetration</td>
<td>✓ Lack of adequate histological examination</td>
<td>✓ Few data available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✓ Persistence of buried metaplastic epithelium</td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>✓ Non-contact technique</td>
<td>✓ Lack of adequate histological examination</td>
<td>✓ Few data available</td>
</tr>
<tr>
<td></td>
<td>✓ Easy to perform</td>
<td>✓ Persistence of buried metaplastic epithelium</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>✓ Complete removal of BE</td>
<td>✓ Morbidity and mortality not negligible</td>
<td>✓ Radical treatment</td>
</tr>
<tr>
<td></td>
<td>✓ Histological evaluation of lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>✓ Worsening of quality of life</td>
<td></td>
</tr>
</tbody>
</table>

APC: argon plasma coagulation; BE: Barrett’s esophagus; EMR: endoscopic mucosal resection; HGD: high-grade dysplasia; PDT: photodynamic therapy.
The review of 161 cases who underwent EMR showed a survival rate of 100%, and an overall recurrence rate ranging between 0% and 15.8% [35,36].

The frequency of synchronous cancers undetected by endoscopy and biopsy in patients with long segment of BE (LSBE) is about 50%.

EMR maximizes the histological assessment of the lesion, allowing definition of both its lateral extent and its depth. It changes the pathological stage in many patients. Ablative methods (PDT, APC) prevent any histopathological assessment. Histological reclassification has been reported in up to 75% of patients after EMR, because of biopsy sampling error and observer interpretation (Table 6.5). In a previous chapter of this book, the role of EUS as a staging tool has been discussed. However, several reports have demonstrated that EMR is more accurate than EUS in staging superficial esophageal tumors.

In our experience, we observed a change in histological diagnosis in 26% of patients with BE who underwent EMR [37]. Mino-Kenudson et al. [38] also reported a change in the histologic diagnosis in 37% of the cases.

When HGD is found in short BE tongues (≤30 mm) EMR can remove all the metaplastic epithelium.

The sequential use of EMR to remove the visible areas of HGD, followed by PDT for invisible foci of malignant disease has been proposed in patients with LSBE. Buttar et al. [22] successfully treated 17 non-surgical patients who had superficial esophageal cancer. EMR improved staging in 47% of cases. Stenosis after PDT was recorded in 30% of patients.

After PDT, microscopic remnants of specialized intestinal metaplasia (‘buried Barrett’) can persist under the neosquamous epithelium, making an adequate endoscopic follow-up even more difficult [39]. It has also been shown that genetic abnormalities persist in the residual BE after PDT treatment.

At present, the majority of articles have reported the endoscopic resection of nodular lesions, or mucosal abnormalities, easily detectable at endoscopy.

Circumferential mucosectomy is an attractive option as it would permit the complete removal of the metaplastic epithelium, with an optimal histologic assessment, avoiding the persistence of buried remnants of BE (Figs 6.4(a)–(c)).

Our group was the first to demonstrate the feasibility of circumferential mucosectomy in an animal model [40].

Circumferential EMR was performed in 12 patients with non-visible HGD and/or IMC. The authors removed 30–40 mm in length and three-quarters of the circumference in each session, using a polypectomy snare without submucosal injection. Two strictures were resolved with bougienage. No recurrences were observed during a median nine-month follow-up [21].

In another study, circumferential EMR was carried out in 21 patients with HGD or mucosal cancer. Three patients had residual disease: one underwent surgery, and two, treated with chemo-radiotherapy, were free of disease after
Table 6.5  Selected studies on EMR in high-grade dysplasia or early cancer in Barrett’s esophagus.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Size of lesion cm (mean)</th>
<th>Histology pre-EMR</th>
<th>Histology post-EMR</th>
<th>Complications</th>
<th>Surgery</th>
<th>Follow-up months (mean)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters et al., 2006</td>
<td>33</td>
<td>Median 1.5</td>
<td>9 HGD</td>
<td>22 HGD</td>
<td>Bleeding: 45% (15/33)</td>
<td>5</td>
<td>Median 19</td>
<td>15% (5/33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 HGD/AC</td>
<td>8 EC</td>
<td>Stenosis: 3% (1/33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14 AC</td>
<td>3 no dysplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mino-Kenudson et al.,</td>
<td>18</td>
<td>1.1</td>
<td>10 HGD</td>
<td>2 LGD</td>
<td></td>
<td>1</td>
<td>ND</td>
<td>5% (9/19)</td>
</tr>
<tr>
<td>2005 [38]</td>
<td></td>
<td></td>
<td>7 IMC</td>
<td>5 LGD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 AC</td>
<td>5 HGD</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 IMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 AC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conio et al., 2005</td>
<td>39</td>
<td>1.5</td>
<td>35 HGD</td>
<td>5 LGD</td>
<td>Bleeding: 10% (4/39)</td>
<td>3</td>
<td>Median 35</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 IMC</td>
<td>27 HGD</td>
<td>Stenosis: 3% (1/39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 IMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 SMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giovannini et al.,</td>
<td>21</td>
<td>1.6</td>
<td>12 IMC</td>
<td>12 HGD</td>
<td>Bleeding: 19%</td>
<td>1</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>2004 [41]</td>
<td></td>
<td></td>
<td>9 AC</td>
<td>9 AC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Size of lesion cm (mean)</th>
<th>Histology pre-EMR</th>
<th>Histology post-EMR</th>
<th>Complications</th>
<th>Surgery</th>
<th>Follow-up months (mean)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seewald et al., 2003 [21]</td>
<td>12</td>
<td>ND</td>
<td>3 HGD 2 HGD/IMC 7 IMC</td>
<td>2 BE 1 LGD 5 HGD 4 AC</td>
<td>Bleeding: 33% (4/12) Stenosis: 17% (2/12)</td>
<td>0</td>
<td>Median 9</td>
<td>0</td>
</tr>
<tr>
<td>May et al., 2002 [20]</td>
<td>80</td>
<td>ND</td>
<td>7 HGD 73 EC</td>
<td>11/80 AC</td>
<td>Bleeding: 6% Stenosis: 4%</td>
<td>0</td>
<td>34</td>
<td>30% (24/80)</td>
</tr>
<tr>
<td>Buttar et al., 2001 [22]</td>
<td>17</td>
<td>ND</td>
<td>7 IMC 10 AC</td>
<td>7 IMC 10 AC</td>
<td>Bleeding: 6% (1/17) Stenosis: 0</td>
<td>1</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Nijhawan et al., 2000 [36]</td>
<td>25</td>
<td>ND</td>
<td>2 BE 8 LGD 5 HGD 9 AC 1 other</td>
<td>2 BE 3 LGD 5 HGD 13 AC 2 other</td>
<td>0</td>
<td>2/13 (AC)</td>
<td>14.6</td>
<td>31% (4/13 AC)</td>
</tr>
<tr>
<td>Ell et al., 2000 [35]</td>
<td>35</td>
<td>0.9</td>
<td>3 HGD 32 EC</td>
<td>3 HGD 32 EC</td>
<td>Bleeding: 20% (7/35) ND 12</td>
<td>11% (4/35)</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

18 and 24 months, respectively. Two local recurrences were retreated by EMR. Neosquamous epithelium was observed in 75% of patients [41].

Stepwise radical endoscopic resection has been performed in 37 patients, with a median BE length of 4 cm (range 3–5 cm). APC was used in 34 patients to complete the resection. Complete eradication was achieved in all 37 patients, and no recurrences were detected during a median follow-up of 11 months. The overall complication rate was 2%. One patient suffered esophageal perforation, which was managed conservatively by placing a suction tube and a duodenal feeding tube [42].

Soehendra et al. [43] performed MMD–EMR in ten patients with BE containing HGD and/or IMC. No submucosal injection was performed. In five out of ten patients with circumferential BE (median length: 4 cm; range: 2–9 cm)

Fig. 6.4 Circumferential EMR-C for Barrett’s esophagus. (a) the esophagus before EMR; (b) the complete resection of BE has been performed; (c) the neosquamous epithelium is visible three months later.
complete EMR was performed in one session. Four patients required more sessions (median: three). One patient underwent surgery due to the multifocality of HGD and/or IMC. No immediate complications occurred. Seven patients developed strictures that were managed successfully by weekly bougienage (median sessions: five). The authors conclude that MMD–EMR is safe, but it is associated with a high stricture rate if circumferential EMR is performed in one session.

After the EMR, a double dose of proton pump inhibitors must be given to these patients. The acid suppressive therapy should be started one week before the endoscopic procedure. The anacid environment favors the regrowth of squamous mucosa.

Conclusions

EMR represents an important advance in endoscopic therapy, making it possible to remove early cancers from the esophagus. Randomized control studies comparing EMR with surgery are still lacking. However, the quality of life after EMR is undoubtedly better than after esophagectomy.

Patients need careful evaluation prior to EMR, and only those with superficial lesions and no lymph node involvement should undergo the procedure. EMR is less invasive than surgical resection, and thus morbidity and mortality are lower. Compared to PDT and APC, EMR can more easily remove full thickness mucosa without damaging the underlying muscle and permits histologic evaluation of all the resected mucosa. Improved endoscopic equipment would allow circumferential EMR to be performed as a unique treatment, without other mucosal ablative procedures.

The 'suck and ligate' technique, now performed with the Duette® device, can be more reassuring for endoscopists undertaking this endotherapy technique. However, more data are necessary to establish the safety and effectiveness of this procedure.

Surveillance after EMR is mandatory to detect recurrences at an early stage, which could be easily retreated with EMR. In patients who underwent EMR for SCC, chromoendoscopy with Lugol should be performed. According to the literature and our experience, we would suggest performing endoscopic follow-up one month after EMR, then every three months for the first year, and every six months thereafter.

More training, and exposure, is required for gastroenterologists and trainees to become conversant with this technique. EMR should be performed by competent endoscopists, able to cope with procedural complications. However, more data are needed on the long-term results.
References


Introduction

Application of endoscopic resection (ER) to early gastric cancer (EGC) is limited to lesions with no risk of nodal metastasis. In Japan, many methods of ER have been developed and become popular, probably due to the high incidence of gastric cancer and the fact that more than half of Japanese patients with gastric cancer are diagnosed at an early stage. Empirical indications for endoscopic mucosal resection (EMR) have been considered as differentiated type mucosal cancers without ulcerative findings, 2 cm in size if elevated or 1 cm if depressed or flat. This indication was widely accepted for a long time because of two aspects. First, these lesions have no risk of nodal metastasis; second, the size and shape of these lesions are resectable in a single fragment, by the conventional ER technique of EMR. Recently, remarkable technical advances and acquisition of data about lesions with no risk of nodal metastasis brought us to a new generation of ER – the development of endoscopic submucosal dissection (ESD) and expanding the indication for EGC. In this chapter the indication, techniques and outcomes of various EMR and ESD methods are described.

Expanding indication for endoscopic resection

EGC is defined to a mucosal or submucosal invasive cancer (T1 cancer) irrespective of the presence of nodal metastasis. Lesions indicated for ER should be EGC with no risk of nodal metastasis and ability to be resected in a single fragment. Using a large database of more than 5000 patients with EGC who underwent gastrectomy with D2 lymph node dissection, a criteria of node negative tumors has been defined (Table 7.1)[1]. For the lesions described in Table 7.1, gastrectomy with lymph node dissection would be excessive.
treatment if en bloc resection were possible by ER, and would impair the quality of life afterwards. At present, lesions with preoperative endoscopic diagnosis of differentiated-type intramucosal cancer without ulcer findings, or differentiated-type intramucosal cancer no larger than 3 cm in diameter with ulcer findings, are considered as expanding the indication for ER. Because the margins of undifferentiated-type cancer lesions are often difficult to delineate, and because preoperative diagnosis of minute submucosal invasive cancer is difficult, ER for these lesions should be carefully considered.

Conventional ER methods are technically limited by lesions greater than 2 cm in diameter and by lesions with ulcer findings in respect of en bloc resection. Until the development of ESD, the approach to those lesions was only by piecemeal technique. Visual inspection of the resected site following piecemeal resection is often difficult, particularly if bleeding occurs, which may result in incomplete tumor removal. In addition, it is difficult to achieve a thorough pathologic evaluation from fragmented specimens after piecemeal resection. To facilitate reconstruction after piecemeal resection, and to confirm the completeness of the resection of the entire lesion, marking around the lesion before resection is useful. However, piecemeal resection has been associated with an increased recurrence rate and the inability to assess the specimen fully, which gives rise to uncertainty about the treatment’s efficacy [2]. Therefore, for lesions

<table>
<thead>
<tr>
<th>Expanded criteria for endoscopic mucosal resection</th>
<th>Incidence (no. with metastasis/ total number)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intramucosal cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiated adenocarcinoma, no lymphatic vessel invasion, irrespective of ulcer findings, tumor ≤3 cm</td>
<td>0/1230</td>
<td>0–0.3</td>
</tr>
<tr>
<td><strong>Intramucosal cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiated adenocarcinoma, no lymphatic vessel invasion, without ulcer findings, irrespective of tumor size</td>
<td>0/929</td>
<td>0–0.4</td>
</tr>
<tr>
<td><strong>Intramucosal cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated adenocarcinoma, no lymphatic vessel invasion, without ulcer findings, tumor ≤2 cm</td>
<td>0/141</td>
<td>0–2.6</td>
</tr>
<tr>
<td><strong>Cancer with minute submucosal penetration</strong> (≤500 µm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiated adenocarcinoma, no lymphatic vessel invasion, irrespective of ulcer findings, tumor ≤3 cm</td>
<td>0/145</td>
<td>0–2.5</td>
</tr>
</tbody>
</table>

Table 7.1  Early gastric cancer with no risk of nodal metastasis.
larger than 2 cm in diameter and lesions with ulcer findings, ESD ensures more complete and efficient removal of the tumor in a single fragment.

Techniques and history of EMR

Just cut, or lift and cut technique

Simple polypectomy was first described in Japan in 1968. Protruded tumors with a stalk can be easily resected by polypectomy. For resection of lesions without stalks, endoscopic double-snare polypectomy (EDSP) was devised by Takekoshi in 1988 [3]. EDSP consists of two procedures using a double-channel endoscope; a sessile or depressed lesion is transformed into a subpedunculated shape by being pulled upward by one snare, and then another snare catching the pseudostalk and excising the lesion with high frequency electric current (HFEC).

Inject, lift and cut technique

From the early 1980s to the 1990s, methods using injection solution before resection were reported, including the strip biopsy method by Tada in 1984 [4], and four-point fixation endoscopic mucosal resection by Inatsuchi and colleagues [5].

Strip Biopsy Method. After marking around the lesion with the tip of a standard needle knife, saline with diluted epinephrine (1:100 000) is injected into the submucosal layer under the lesion with an injection needle. A double-channel endoscope is required, and both a snare and a pair of grasping forceps are advanced through the working channels. The forceps are passed through the opened snare to grasp the lesion, and gently pulled back through the opened snare. When the lesion is completely pulled into the snare, the snare is closed and the lesion is resected with HFEC. Small lesions without ulcer findings regardless of shape can be resected with this method, but the location applicable is limited.

Inject, suck and cut technique

In the early 1990s, several EMR techniques using a single-channel endoscope were reported. These techniques are characterized by using suction to capture the lesion. EMR with cap (EMRC) [6], endoscopic aspiration mucosectomy (EAM) [7], and EMR with ligation (EMRL) [8] fall in this group. These techniques are applied to small lesions without ulcer findings regardless of shape, and to lesions located in narrow or angulated areas. They are popular both in Japan and in Western countries for their convenience.
**EMRC method.** A single-channel endoscope with a transparent cap fitted to the tip is used. After marking and injection as described before, a crescent-shaped snare (SD-221L-25; Olympus Co., Tokyo, Japan) is pre-looped into the groove of the rim of the cap. Pre-looping could be done by suctioning the normal mucosa with the cap, together with light pressing of the opened snare to rest along the inside groove of the cap. The lesion is then sucked into the cap, the snare is pushed down onto the base of the aspirated lesion and closed. The suction is released to determine whether the center of the lesion is captured into the snare. The lesion is removed by HFEC and aspirated within the cap. Different-sized caps are available according to the diameter of the endoscope and the size of the target lesion.

**EAM method.** After marking and injection, an aspiration mucosector (Top Co. Ltd, Tokyo, Japan) is attached to the tip of a single-channel endoscope. The lesion is aspirated into the mucosector and a snare is opened to catch the lesion. The lesion is removed by HFEC.

The major difference between EMRC and EAM is that the snare is advanced through the working channel in EMRC, whereas in EAM, it is advanced through an outer sheath, which is preset to the endoscope.

**EMRL method.** After marking, the endoscope is withdrawn to fit a variceal ligation device (MD-48809, Sumitomo Bakelite Co., Tokyo, Japan). After submucosal injection, the lesion is ligated by the rubber band and snared below the rubber band.

The techniques given above are generally known as conventional ER/EMR methods (Figs 7.1(a)–(d)) compared to the following method. Conventional methods are safe, easy and convenient to use for small lesions. For lesions larger than 20 mm in diameter piecemeal resection is frequently performed using these methods because of technical limitations. To overcome technical problems of en bloc resection using conventional EMR methods, the following method has recently been developed.

**Endoscopic submucosal dissection (ESD)**

**Inject, mucosal incision and submucosal dissection technique**

The concept of this method was first reported by Hirao and colleagues in 1988 [9], and was named endoscopic resection with hypertonic saline–epinephrine solution (ERHSE). In this technique, after injection of hypertonic saline and diluted epinephrine, the periphery of the lesion was cut using a needle knife, followed by snaring. However, it has not been popular due to its difficulty and high complication rates.

It became common around 2000, with amelioration of the technique and development of numerous endoscopic equipments. At present, ESD with an
Fig. 7.1 Scheme of conventional endoscopic resection techniques. (a) Strip biopsy; (b) EMR with cap (EMRC); (c) Endoscopic aspiration mucosectomy (EAM); (d) EMR with ligation (EMRL).
insulation-tipped diathermic knife (IT-ESD) [10], EMR with sodium hyaluronate (EMRSH) [11], ER with a hook knife [12], ESD with the tip of an electrosurgical snare (thin type)/a flex knife [13], ER with a triangle-tipped knife by Inoue and colleagues [14], ER with a flush knife by Toyonaga and colleagues [15], and ER with a mucosectome by Kawahara and colleagues [16], have been developed to fall into this group, which is the latest category of ER, known as ESD. ESD requires special electrosurgical knives with an HFEC generator with an automatically controlled system (Endocut mode, Erbotom ICC200, ICC350, VIO300D, ERBE, Tubingen, Germany).

ESD is characterized by three steps – injecting fluid into the submucosa to elevate the lesion from the muscle layer; circumferential cutting of the surrounding mucosa of the lesion; and subsequent dissection of the connective tissue of the submucosa beneath the lesion (Fig. 7.2). It is controversial whether ESD should be included in EMR methods, or whether it is an independent ER technique. Most endoscopists in Japan now consider it as a novel and independent technique, because available outcomes are extremely different from those of conventional EMR methods.

**ESD with IT-knife.** Marking is made around the lesion with a needle knife. (forced coagulation 20 W for ICC 200, swift coagulation 20 W, effect 4 for VIO300D). After injection with saline plus diluted epinephrine and indigo carmine to raise the submucosal layer, a small initial incision is made by a needle knife (Endocut mode 80 W, effect 3 for ICC 200, EndocutQ mode, duration 4, interval 1, effect 1 for VIO300D). The tip of the IT-knife is inserted from the initial incision into the submucosal layer. Circumferential mucosal cutting outside the marking is performed by an IT-knife (Endocut mode 80 W, effect 3 for ICC200, EndocutQ mode, duration 4, interval 1, effect 1 or dry cut mode 50W, effect 4 for VIO300D). The ceramic ball prevents perforation of the knife. After completion of circumferential mucosal cutting, submucosal injection is added. Then, the submucosal layer under the lesion is directly dissected by the IT-knife until removal of the lesion.

**ESD with Flex-knife.** Marking is made around the lesion with the tip of a Flex-knife (soft coagulation mode 50 W for ICC 200, soft coagulation mode 50W, effect 5 for VIO300D). Injection is made with a glycerin solution (Glyceol™, a 10% glycerin with 0.9% NaCl plus 5% fructose solution, Chugai Pharmaceutical Co., Tokyo, Japan) with diluted epinephrine and indigo carmine. For lesions with ulcer findings, 1% 1900 kDa hyaluronic acid preparation is mixed to Glyceol with a ratio of 1:7 to achieve higher and long-lasting submucosal elevation. This special mixture of injection solution was developed through animal models and human studies considering the viscosity, tissue damage effect and lesion-lifting properties of several solutions [17–20]. Mucosal cutting (Endocut mode, 80W, effect 3 for ICC200, EndocutI mode, duration 4, interval 3, effect 3 for VIO300D)
Fig. 7.2  Procedures of endoscopic submucosal dissection. (a) Chromoendoscopy using indigo carmine of an elevated lesion on the anterior wall of the gastric antrum; (b) marking is made around the lesion; (c) submucosal injection is performed to elevate the lesion; (d) after circumferential mucosal cutting, additional submucosal injection is performed followed by submucosal dissection; (e) the lesion is removed in one piece.
and submucosal dissection (forced coagulation mode 40W for ICC200, swift coagulation mode 40W, effect 4 for VIO300D) is performed step by step with the Flex-knife. A transparent attachment to the endoscope is frequently used during submucosal dissection, to achieve better vision and to get under the lesion into the submucosa.

The major advantages of ESD in comparison to other EMR methods are (a) the resected size and shape can be controlled, (b) en bloc resection is possible even for large lesions and difficult locations, and (c) lesions with ulcer findings are also resectable. Thus, ESD has rapidly become popular in Japan, and is applied to large lesions, ulcerative non-lifting lesions, lesions of the esophago-gastric junction [21] and recurrent lesions after previous endoscopic treatment [22]. Its efficacy and safety have also been reported in elderly patients [23]. The disadvantages of ESD are (a) it is time consuming, (b) the high complication rate of bleeding and perforation, and (c) technical difficulty. Available electrosurgical knives and other instruments for each method are provided in Table 7.2 and Fig. 7.3. Various knives and injection solutions have been

<table>
<thead>
<tr>
<th>Method</th>
<th>Electrosurgical devices</th>
<th>Recommended injection solutions</th>
<th>Other instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT-ESD</td>
<td>Insulation-tipped diathermic knife (IT knife, KD-610L, Olympus)</td>
<td>Saline + diluted epinephrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Needle knife (KD-1L-1, Olympus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESD-flex knife</td>
<td>Flex knife (KD-630L, Olympus)</td>
<td>Glyceol* + diluted epinephrine ±</td>
<td>Transparent hood (D-201, Olympus)</td>
</tr>
<tr>
<td></td>
<td>Hook knife (KD-620LR, Olympus)</td>
<td>hyaluronic acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Needle knife (KD-1L-1, Olympus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMRSH</td>
<td>Needle knife (KD-1L-1, Olympus)</td>
<td>Saline + diluted epinephrine +</td>
<td>Small caliber tip transparent (ST) hood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hyaluronic acid</td>
<td>(DH-15GR, 15CR, Fujinon Toshiba ES systems)</td>
</tr>
</tbody>
</table>

*Glyceol: a 10% glycerin with 0.9% NaCl plus 5% fructose solution (Glyceol™, Chugai Pharmaceutical Co., Tokyo, Japan).
Fig. 7.3 Electrosurgical knives used in endoscopic submucosal dissection (ESD). (a) Insulation-tipped diathermic knife (IT-knife); (b) hook-knife; (c) flex-knife; (d) needle knife; (e) triangle-tipped knife (TT-knife); (f) small caliber tip transparent (ST) hood.
developed to lower the high complication rate and technical difficulty compared to EMR. Each ESD method has now achieved excellent outcomes, but they require highly skilled endoscopists, and a suitable training program is needed for this technique to become more widespread. Trainees in ESD should have skills of routine endoscopy and colonoscopy, target biopsy, endoscopic hemostasis techniques and a knowledge of simple EMR techniques. A trainee would gain early proficiency in ESD after 30 cases under the supervision of a mentor [24,25].

Pathological evaluation of the removed specimen

Whether a lesion may be included in the criteria of node-negative tumor is considered before treatment. However, at present, it is impossible to make a definite diagnosis of a tumor regarding depth, histological type and lymphatic vessel invasion before treatment. Therefore, a precise pathological evaluation of the resected specimen is essential, and an en bloc resection of the lesion is desirable in this respect.

After removal, the specimen should be oriented immediately before it is immersed in formalin. Orientation of the specimen is accomplished by fixing the periphery with thin needles on a plate of rubber or wood. The submucosal side of the specimen is faced to the plate. After fixation, the specimen is sectioned serially at 2 mm intervals parallel to a line that includes the closest part between the margin of the specimen and of the tumor, so that both lateral and vertical margins are assessed. The depth of tumor invasion is then evaluated microscopically along with the degree of differentiation and lymphatic or vascular involvement, if any.

After thorough pathological assessment, if the lesion is resected en bloc with negative margins of tumor, and if it fulfills the criteria for node-negative tumors, the treatment is judged as curative resection. For lesions with piecemeal resection but which are being judged as node-negative tumors, or lesions with histologically non-evaluable areas due to artifact or tissue burning, a periodical endoscopic follow-up should be performed to detect residual tumor or local recurrence. On the other hand, for lesions that do not fulfill the criteria of node-negative tumors, additional gastrectomy with nodal dissection should be strongly recommended.

Outcomes of EMR and ESD

The en bloc resection rate and local recurrence of ER reported before and after 2000 are described in Table 7.3. For lesions larger than 20 mm, the en
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bloc resection rate is extremely low among conventional EMR methods, and local recurrence rates are around 10%. Although ESD was considered as a difficult and complicated technique when it was first described, after maturity of the techniques of ESD, en bloc resection rates became greater than 90%, regardless of size, and local recurrence rates became almost zero [26].

Complications of EMR include pain, bleeding, perforation, and stricture. Pain after EMR is mild. Complications of bleeding and perforation among

### Table 7.3 Outcomes of various endoscopic resection methods before and after 2000.

<table>
<thead>
<tr>
<th>Author</th>
<th>Methods</th>
<th>≤10 mm</th>
<th>11–20 mm</th>
<th>≥21 mm</th>
<th>Local recurrence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results before 2000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tada, 1998</td>
<td>Strip biopsy</td>
<td>70 (421/599)</td>
<td>–</td>
<td>11 (63/599)</td>
<td></td>
</tr>
<tr>
<td>Inatsuchi, 1996</td>
<td>Four-point fixation EMR</td>
<td>71 (30/42)</td>
<td>72 (21/29)</td>
<td>14 (2/14)</td>
<td>–</td>
</tr>
<tr>
<td>Takeshita, 1998</td>
<td>EMR-C</td>
<td>80 (44/55)</td>
<td>42 (24/57)</td>
<td>0 (0/9)</td>
<td>1.7 (2/118)</td>
</tr>
<tr>
<td>Torii, 1999</td>
<td>EAM</td>
<td>84 (52/62)</td>
<td>–</td>
<td>4.8 (3/62)</td>
<td></td>
</tr>
<tr>
<td>Hirao, 1998</td>
<td>ERHSE</td>
<td>63 (123/196)</td>
<td>44 (60/136)</td>
<td>19 (7/37)</td>
<td>2.3 (8/349)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>En bloc resection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤20 mm</td>
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</table>

<table>
<thead>
<tr>
<th>Recent results of ESD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishigooka, 2004</td>
</tr>
<tr>
<td>Hamanaka, 2004</td>
</tr>
<tr>
<td>Yahagi, 2004</td>
</tr>
<tr>
<td>Yamamoto, 2002</td>
</tr>
<tr>
<td>Oyama, 2004</td>
</tr>
</tbody>
</table>

EAM: endoscopic aspiration mucosectomy; EMR: endoscopic mucosal resection; EMR-C: EMR with cup; EMRSH: EMR with sodium hyaluronate; ERHSE: endoscopic resection with hypertonic saline-epinephrine solution; ESD: endoscopic submucosal dissection; IT-ESD: with insulation – tipped diathermic knife.
various EMR methods are described in Table 7.4. To prevent post-procedural bleeding, hemostasis of appearing vessels on the artificial ulcer after removing the specimen is essential. Hemostasis is performed by hemostatic forceps (HDB2422/HDB2418, Pentax), coagrasper (FD-410LR, Olympus), hot biopsy forceps, argon plasma coagulation or endoclips. With regard to perforation, recent case series suggest that small perforations immediately recognized can be successfully sealed with endoclips and treated conservatively by nasogastric suction, fasting and antibiotics, without emergency laparotomy [27].

**Table 7.4  Bleeding and perforation rate of various endoscopic resection methods.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Total cases</th>
<th>Bleeding (%)</th>
<th>Perforation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torii, 1995</td>
<td>EAM</td>
<td>24</td>
<td>8.3</td>
<td>4</td>
</tr>
<tr>
<td>Tada, 1998</td>
<td>Strip biopsy</td>
<td>599</td>
<td>1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Chonan, 1998</td>
<td>EMR-C/strip biopsy</td>
<td>123</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Takeshita, 1998</td>
<td>EMR-C</td>
<td>121</td>
<td>14.9</td>
<td>0</td>
</tr>
<tr>
<td>Tanabe, 2002</td>
<td>EAM</td>
<td>206</td>
<td>13</td>
<td>1.5</td>
</tr>
<tr>
<td>Ohkuwa, 2001</td>
<td>Strip biopsy</td>
<td>88</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Ono, 2001</td>
<td>Strip biopsy/IT-ESD</td>
<td>479</td>
<td>–</td>
<td>5</td>
</tr>
</tbody>
</table>

**ESD**

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Total cases</th>
<th>Bleeding (%)</th>
<th>Perforation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirao, 1996</td>
<td>ERHSE</td>
<td>373</td>
<td>6.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Ohkuwa, 2001</td>
<td>IT-ESD</td>
<td>41</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Yamamoto, 2002</td>
<td>EMRSH</td>
<td>70</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Miyamoto, 2002</td>
<td>IT-ESD</td>
<td>123</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Yahagi, 2004</td>
<td>Thin-type snare/flex-knife</td>
<td>59</td>
<td>1.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Oda, 2005</td>
<td>IT-ESD</td>
<td>1033</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

EAM: endoscopic aspiration mucosectomy; EMR-C: endoscopic mucosal resection with cup; EMRSH: endoscopic mucosal resection with sodium hyaluronate; ERHSE: endoscopic resection with hypertonic saline-epinephrine solution; IT-ESD: endoscopic submucosal dissection with insulation-tipped diathermic knife.

Managements after EMR and ESD

Proton pump inhibitors (PPI) are administered to the patients to prevent postoperative bleeding and promote ulcer healing. Recent studies show that the duration of PPI treatment should be at least one week after EMR [28]. Large ulcers after ESD are reported to heal within 8 weeks after resection under antacid treatment [29].
Long-term outcomes after EMR

Long-term outcomes after EMR for small differentiated mucosal EGC less than 20 mm in diameter have been reported as comparable to those after gastrectomy. The disease-specific 5- and 10-year survival rates were 99% and 99% [30]. Long-term outcomes after ESD for lesions within the expanded indication are currently under investigation. On the other hand, endoscopic surveillance should be carried out in patients after EMR not only to detect local recurrence but also to detect metachronous gastric cancer (MGC). A recent study showed that the average time to detect a first MGC was $3.1 \pm 1.7$ years after EMR, and the cumulative three-year incidence was 5.9% [31]. In order to detect MGC at an early stage to perform a successful ER, an annual endoscopic surveillance program may be practical for post-ER patients.

Future perspectives

The advancement of technology in ESD is promising for further application in cancer treatment including esophageal and colorectal lesions. En bloc retrieval of lesions is essential for detailed histopathologic studies, which form the basis for stratification of treatment outcomes and patients’ prognosis. ESD theoretically offers greater histopathological accuracy than conventional EMR methods or piecemeal resection. Although ESD developed at first as a subgroup of EMR, it is an innovative technique that can be applied to any mucosal lesions regardless of size and location, and which is expected to replace surgery. For less invasive surgery, ESD plus laparoscopic regional lymph node dissection has been investigated by Abe and colleagues [32]. Endoscopic full-thickness resection (EFTR) is under development in animal studies, to achieve more complete histological examination of the cancer by Ikeda and colleagues [33]. The field of ER is rapidly progressing, and in the near future, we will be able to completely avoid unnecessary gastrectomy.

References

37 Yamamoto H, Kawata H, Sunada K et al. Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. Gastrointest Endosc 2002; 56: 507–12.
Introduction

Tumors of the ampulla of Vater are rare, accounting for less than 5% of all gastrointestinal tumors. Both benign (adenoma, hemangioma, leiomyoma, lipoma, and neurogenic tumors) and malignant tumors (adenocarcinoma, carcinoid tumors, signet-ring cell tumors, and choriocarcinoma) are well described. The most common lesions are tubulovillous adenomas and adenocarcinoma [1–3]. Although benign, ampullary adenomas have the potential to undergo malignant transformation, similar to the adenoma-carcinoma sequence in the colon and elsewhere in the gastrointestinal (GI) tract [4,5]. Ampullary adenomas may occur sporadically or in association with familial polyposis syndromes such as familial adenomatous polyposis (FAP) (Fig. 8.1). Such patients have a lifetime risk of up to 90% of developing ampullary and periampullary tumors [6,7]. Periampullary lesions involve the papilla and extend onto the surrounding duodenum to within 2 cm of the papilla (Fig. 8.2). Both ampullary and periampullary lesions are commonly grouped together and most often referred to as ampullary adenomas, as in this chapter [8]. The excision of adenomatous ampullary lesions is considered to prevent the eventual development of adenocarcinoma.

Benign ampullary lesions may be treated by surgical transduodenal ampullectomy. This involves complete en bloc excision of the ampulla of Vater together with a portion of healthy periampullary duodenal mucosa. The common bile duct and main pancreatic duct are then reinserted into the duodenal wall by two separate anastomoses. Pancreaticoduodenectomy (so-called Whipple’s procedure or pylorus-preserving pancreaticoduodenectomy) remains the most commonly performed surgical procedure for large lesions, lesions with high grade dysplasia, and invasive neoplasms. However, pancreatic surgery is associated with increased morbidity and reported mortality rates between 1% and 9%, even in referral centers [7,9–15].
Endoscopic resection offers non-invasive management of benign ampullary neoplastic lesions. It is technically similar to polypectomy or mucosectomy, and involves excision (en bloc or piecemeal) of the Papilla of Vater which includes the overlying mucosa and submucosa of the ampulla of Vater, together with part of the sphincter of Oddi and the distal common bile duct and main pancreatic duct. Endoscopic snare resection is limited by the extent of tumor invasion into the bile or pancreatic ducts, or infiltration into the duodenal wall. Because of the low cost, minimal or no hospitalization, lack of a need for general anesthesia and low morbidity, endoscopic snare resection is advocated as first-line treatment for the management of benign, non-invasive ampullary neoplasms. However, despite widespread use in clinical practice, the indications, technique, and limitations of endoscopic resection vary between centers [16].

**Indications for endoscopic snare resection**

Over the past decade, there have been several retrospective reports on the technique of endoscopic snare resection with few published, prospective, randomized controlled studies [17]. For this reason, variations exist, even among experts, both for endoscopic technique and indications [3,18–28]. Endoscopic resection may be considered an alternative to surgical excision in patients with benign ampullary tumors, whereas invasive lesions should always be treated by surgical excision, unless short-term palliation for advanced malignancies is
intended. Endoscopic resection may be considered to be curative if histological examination of the resected specimen shows the excision margins to be free of tumor and without any evidence of invasive carcinoma [29]. The morphologic characteristics of an ampullary lesion may be helpful in predicting whether the lesion is likely to be malignant or benign. The majority of ampullary and periampullary tumors are diagnosed when they are advanced lesions. An attempt at endoscopic resection should, therefore, only be considered for small (e.g. ≤2 cm) or early lesions without evidence of deep invasion or tumor infiltration (Fig. 8.3). Submucosal invasion is associated with a high risk of lymph node metastases, and in such cases, endoscopic resection should not be attempted [12,30,31]. Published surgical studies reporting on the risk of lymph node metastasis associated with ampullary lesions, grouped together adenomatous lesions with in situ carcinoma, intramucosal carcinoma, and carcinoma with
submucosal invasion as T1 lesions. For tumors limited to the ampulla of Vater (T1 according to the TNM classification), the rate of lymph node metastasis is reported to be between 0% and 22% [2,9,12,30,31]. Adenomas (low- and high-grade dysplasia) and carcinomas limited to the epithelium (in situ carcinoma) have a low risk of lymph node metastasis [32]. Lamina propria invasion (intramucosal carcinoma) is considered by some authors to be invasive carcinoma due to the rich mucosal lymphatic network in the ampullary area [33,34]. However, there is only scanty data on this particular issue in the scientific literature [16]. In general, submucosal invasion is considered to be a relative contra-indication to endoscopic resection [35], however, in patients with multiple comorbidities who are unfit for surgery, and those with very small, well-differentiated adenocarcinomas or small neuroendocrine tumors, endoscopic resection may be appropriate [30,36].

**Indications for endoscopic resection in patients with FAP**

In patients with FAP, endoscopic resection is controversial. Patients with FAP have a lifelong risk of developing periampullary adenomas necessitating...
regular, lifelong, endoscopic follow-up [6,37]. Patients with FAP have a high rate of recurrence following endoscopic resection. Ampullary adenomas in FAP progress slowly and may not become malignant [38–42]. Local recurrence following endoscopic resection is reported to be higher for lesions associated with familial polyposis syndromes as opposed to sporadic lesions [22]. For this reason, a less invasive approach has been considered by some authors for the endoscopic management of ampullary adenomas in FAP. Lifelong surveillance of the ampullary area can be facilitated after snare resection. Some authors advocate performing endoscopic papillectomy only in patients with adenomas showing high-grade dysplasia or in situ carcinoma, and repeated endoscopic surveillance and biopsy for the vast majority of patients [43].

Pre-operative staging: diagnosis of ampullary tumors and criteria for identifying invasive lesions

Duodenoscopy and ERCP

Ampullary neoplasms are readily diagnosed during ERCP. The macroscopic appearance of the papilla of Vater at duodenoscopy may predict whether the lesion is invasive or non-invasive. Macroscopic features suggesting malignancy include mucosal ulceration, spontaneous bleeding, induration or friability, and ill-defined or infiltrating margins [20,25]. In addition, the presence of duodenal infiltration can be assessed by grasping the base of the lesion with a snare and moving it back and forth. Lesions which are mobile are likely to be superficial and confined to the mucosal layer of the duodenum. Some authors consider the size of the lesion to be important when deciding whether to perform endoscopic resection [20,23,24]. Large lesions may be resected depending on the experience and expertise of the endoscopist.

In some cases, when the adenoma arises from the intra-ampullary epithelium, the whole papilla and overlying duodenal hood may be enlarged and bulging or protruding. The ERCP may identify extension of the neoplasm into the biliary or pancreatic duct prohibiting complete endoscopic excision (Fig. 8.4). In other cases, the ampullary lesion has a polypoid appearance without invasion into the biliary- and pancreatic-ducts. In such cases, endoscopic resection is not technically difficult, even with large neoplastic lesions, which can require a piecemeal excision.

In early cases, the adenoma arises from the intestinal-type mucosa involving the papilla of Vater. Papillary adenomas occurring in patients affected by FAP belong to this specific group of lesions. In such cases, the adenoma tends to spread inferiorly, in a ‘goatee’ distribution and in time, laterally along the duodenal mucosa. Endoscopic resection in these presentations will additionally
Fig 8.4  (a) A large ‘bulging’ ampullary adenoma suspicious for extensive involvement of the actual ampulla; (b) ERCP demonstrates actual invasion of the adenoma into both the common bile duct (CBD) and the pancreatic duct (PD). (c) EUS demonstrating the same extension of the adenoma into the CBD and PD.
require piecemeal mucosectomy of the periamputal tissues as well as supplemental argon plasma coagulation of residual tissues for complete eradication of the lesion. Large lesions in excess of 2 cm are technically more difficult to resect. The risk of malignant transformation increases with the size of the lesion. Some authors advocate endoscopic resection for lesions with intraductal extension of up to 1 cm, in patients who are unfit for surgery [21]. A carefully performed ERCP with attention to the pancreatic and common bile duct anatomy up to the ampulla is critical. Histological confirmation is also essential since some normal papillas may appear to be polypoid. ERCP allows biopsies to be taken from the papilla and with cannulation, from the ampullary segment of the common bile duct or pancreatic duct. However, endoscopic biopsies cannot reliably exclude an invasive adenoma. False-negative results from endoscopic biopsies have been described in 25–60% of patients with carcinoma and diagnostic accuracy rates of 58–74% in reported series [2, 44–47]. Malignant foci are reported to occur in up to 15% or more of ampullary adenomas. Surgery has been advocated by some when endoscopic biopsies reveal high-grade dysplasia within an adenoma because of the risk of sampling error [46]. If the tumor arises from inside the ampulla of Vater it may not be completely visible at duodenoscopy. In such cases, an endoscopic sphinctero-tomy
is necessary to expose the lesion and allow biopsies to be taken under direct visual control [48]. Because of the low accuracy rates of diagnostic endoscopic biopsies, some authors suggest obtaining a minimum number of six biopsies from the lesion in order to identify those patients in whom a surgical resection is more appropriate [20].

Endoscopic ultrasonography (EUS)

EUS is useful for tumor staging and assessing lymph node involvement and is advocated for large lesions and bulging intra-ampullary lesions [49]. EUS can accurately demonstrate extension of an ampullary lesion into the duodenal wall (T2) or into the pancreas (T3 or T4). Fine-needle aspiration biopsy (FNA) allows assessment of peri-lesional lymph nodes. EUS is not considered mandatory when planning endoscopic resection of small lesions [25,49–58].

Invasion of the muscularis mucosa and submucosal invasion can be determined with reasonable accuracy using intraductal ultrasound (IDUS). This technique involves the use of ultrasonic miniprobes inserted directly into the common bile duct or pancreatic duct [59].

EUS is a recommended technique for the staging of advanced neoplasms of the ampulla of Vater, especially prior to surgery. For early lesions, endoscopic snare resection followed by histological analysis of the resected specimen remains an accurate and effective method for evaluating curative endoscopic resection or the need for additional surgery.

Technique of endoscopic resection

Endoscopic snare resection of ampullary adenomas should be performed with the intent of completely excising all of the involved tissues. Although a relatively straightforward technique in expert hands, a number of different ‘tricks’ and variations in technique have been described to improve success rates of endoscopic resection and minimize complication rates. However, there is little if any prospective data on the efficacy of the various techniques that have been described in the literature.

Endoscopic retrograde cholangio-pancreatography (ERCP)

The endoscopic resection should be performed during ERCP. The addition of a few drops of methylene blue to the contrast agent used for cholangiography, helps to make it easier to identify the orifice of both the bile duct and pancreatic duct after snare excision. Theoretically, this may help to reduce the risk of post-ERCP pancreatitis by allowing quicker and safer cannulation.
of the bile and pancreatic duct, avoiding repeated cannulation and trauma to the main pancreatic duct.

**Lifting of the lesion**

Isolating the primary ampullary lesion by means of an injected submucosal fluid cushion (SFC) has been advocated by some endoscopists in order to reduce the risk of endoscopic perforation and bleeding after endoscopic papillectomy. If a ‘non-lifting sign’, or failure to lift the lesion away from the underlying submucosa, occurs, this may indicate an invasive lesion [23–25]. Endoscopic resection can be safely and even preferably performed without a SFC [20–22, 26, 60]. The SFC will allow excision of the mucosal component of the ampullary adenoma leaving behind an intact sphincter of Oddi and underlying ampullary area with the attendant portions of the common bile duct and pancreatic duct. This can actually complicate the procedure by making subsequent cannulation of either the common bile duct or pancreatic duct technically very difficult. In case of lesions arising from within the ampulla of Vater, the SFC will interfere with en bloc resection [16, 61]. An SFC may be useful for small lesions limited to and arising from a very flat papilla and when there is lateral (periampullary) spread of the lesion along the duodenal mucosa adjacent to the ampulla. Sometimes, the inferiorly spreading ‘goatee’ of neoplastic tissue on the lower part of the papilla and its frenulum can be resected safely by means of a pre-excision SFC. The inferior and laterally spreading components of the larger lesions are well suited to piecemeal snare-type EMR assisted by an SFC after the main or primary component of the ampullary lesion is removed by unassisted snare resection.

**Resection of the ampullary lesion**

Endoscopic resection is performed by snaring and removing the neoplasm and ampullary tissues down to the level of the muscularis propria [20]. Some endoscopists advocate performing a circumferential incision around the ampulla using a needle knife prior to endoscopic snare resection. This technique may facilitate accurate placement of the snare but entails risk and would require a SFC for added safety against perforation [23].

A variety of snares, including specially designed snares, may be used [17, 62] (Fig. 8.5). In our unit a specially designed snare is used which is of monofilament construction, more flexible, and wider than standard snares to allow the snare to be accurately ‘draped’ around the lesion, preferably top down or from a proximal to distal approach. After the snare is tightened, the lesion is lifted up as it is excised under greater visual control. No more than 2 cm of tissue should be ensnared and excised in order to avoid a major complication such as
perforation and bleeding. Larger lesions and especially those requiring palliation should be resected in a piecemeal fashion. There is no prospective data in the literature comparing success rates for en bloc versus piecemeal resection of ampullary tumors. In our experience the former method has most consistently allowed complete resection. En bloc resection does allow for more accurate histological evaluation of completeness of resection and depth of tumor invasion. Theoretically, en bloc resection may potentially reduce the risk of tumor seeding post-resection although this remains to be determined. En bloc resection may also be associated with less thermal injury to the ampullary area, and thus potentially a reduced risk of post-procedure pancreatitis [63,64]. In contrast, some experts advocate performing piecemeal resection in order to reduce the risk of perforation and bleeding [24]. It is recommended that en bloc resection should always be performed when possible to reduce the risk of local recurrence. When en bloc resection is not possible then residual adenomatous tissue should be excised piecemeal during the same procedure [16,18,20–23, 27,28,60].

There is some debate as to the best method for snaring and grasping an ampullary lesion. The majority of endoscopists advocate ensnaring the lesion top down as mentioned above, from the proximal to the distal or caudal side of the lesion. The apex of the snare is accurately placed at the superior margin of the ampulla and the snare slowly closed while advancing the outer sheath of the snare so as to impact and then grasp the entire base of the ampulla [25]. This maneuver is critical. There are no established recommendations as to the
power output or type of electro-surgical current. Some experts use a blended current whereas others recommend using a pure cutting current [16].

Additional thermal ablation

Any residual adenomatous tissue after attempted en bloc resection should be removed by either additional piecemeal snare resection or in some cases, additional thermal ablation may be necessary when snare resection is impossible, particularly for small fragments of residual tumor. Ablative thermal modalities include argon plasma coagulation, monopolar or multipolar electro-coagulation, and neodymium–yttrium aluminum garnet (Nd:YAG) laser. The preferred technique is largely dependent on equipment availability, local expertise, and personal preference of the endoscopist. Argon plasma coagulation has become a favored expeditious method for supplemental ablation of residual tissue. Thermal ablation should only be used as an adjunct to snare excision and not as a primary treatment. When thermal ablation is used for primary treatment of adenomas, specimens for histopathologic evaluation cannot be obtained and thus, the presence of cancer may be overlooked [16]. Primary thermal ablation can also result in obstruction of both the common bile duct and pancreatic ducts due to thermally induced edema and complications due to transient obstruction such as jaundice, cholangitis, and pancreatitis [8,26].

Pancreatic sphincterotomy and stenting

Acute pancreatitis is one of the most common and potentially severe, life-threatening complications. Pancreatitis is thought to occur as a result of edema and thermal injury to the pancreatic duct. Endoscopic pancreatic sphincterotomy and temporary pancreatic stent placement will maintain patency of the pancreatic duct and, thus, may reduce the risk of pancreatitis. There is some controversy over whether or not to stent the pancreatic duct after papillectomy. Some endoscopists advocate placing a pancreatic stent in all patients [23], whereas others advocate pancreatic stenting only [18,24,28,60] if there is delayed drainage of injected contrast [20,25,26]. Results from published trials have been inconclusive [17,26,65]. There has been only one published randomized study assessing the effects of pancreatic stenting on the incidence of pancreatitis after endoscopic papillectomy. This study was terminated early because of the high incidence of acute pancreatitis in patients who did not receive prophylactic pancreatic stenting (33%) [17]. The resultant small numbers of patients enrolled (n = 19) makes it difficult to draw definite conclusions [66].

Some authors prefer to use small, three or five French pancreatic stents without a proximal flap because of their tendency to migrate spontaneously
There has been some concern that larger diameter pancreatic stents may cause epithelial damage to the pancreatic duct [68–70]. However, the placement of a 3-Fr pancreatic stent can be difficult, requiring special expertise in handling very small guide-wires (0.018 in.), and until reasonable prospective data are available, larger stents (5–8.5-Fr diameter) are recommended [67]. Some endoscopists recommend leaving a pancreatic stent in place for at least one to two months before removal. Stenting, despite pancreatic sphincterotomy, will protect the pancreatic duct orifice during supplemental endoscopic resection or thermal ablation of any residual tumor [24].

The duration of stenting is unknown. The stents need only be left in place for several days to a week at most. In our experience at Mayo, stents are removed, if not spontaneously expelled, after one week. In patients who are available the day after the procedure, stent position is checked fluoroscopically and if still present, it is then extracted without sequelae [17].

Pancreatic sphincterotomy performed immediately after snare excision is recommended with or without pancreatic stenting. If there is immediate flow of pancreatic juice, instilled contrast promptly drains out, or air is seen within the pancreatic duct on fluoroscopy, then pancreatic stenting may be optional. Insertion of a naso-pancreatic drain for 24–48 h may be an alternative to pancreatic stenting. Pancreatic sphincterotomy, most importantly, may reduce the risk of subsequent, delayed fibrosis and stricturing of the pancreatic duct orifice [26].

**Biliary sphincterotomy and stenting**

In some cases, poor biliary drainage may be observed after papillectomy. In such cases, biliary drainage will be improved by performing biliary sphincterotomy either with or without subsequent biliary stenting. In general, biliary sphincterotomy is technically easier to perform than pancreatic sphincterotomy after resection. If there is incomplete drainage of bile and contrast after biliary sphincterotomy, then a large diameter biliary stent (10-Fr) should be placed and left for one to three months until repeat ERCP to identify any residual polyp and additional endoscopic therapy are planned [20]. There is little evidence for the role of endoscopic biliary sphincterotomy or stenting. Acute cholangitis rarely occurs immediately [16]. Biliary sphincterotomy may reduce the risk of infrequently occurring fibrosis and stenosis of the biliary orifice, which has been reported to occur in up to 10% of patients [16]. Both biliary and pancreatic sphincterotomy will open the ampullary bed and facilitate future surveillance of this area, especially in patients with FAP, who may require supplemental treatment which can easily be performed with minimal risk for complications.
Outcomes

The success rate for endoscopic resection ranges between 74% and 92% (Fig. 8.6). The recurrence rate is reported to be between 0% and 33% [18–28,60]. The majority of published series involve small numbers of patients. Furthermore, it is difficult to compare and analyze the results of published series because of the retrospective nature of the studies with differences in the patient populations studied, indications for endoscopic papillectomy, differences in endoscopic technique, and histological data. Even the definition of ‘success’ varies from one study to another. Some authors consider the technical success of endoscopic resection whereas others report on the absence of local recurrence at long-term follow-up after resection. In addition, difficulty arises as to the definition of ‘local recurrence’ or ‘residual adenoma’ where there is biopsy-proven adenomatous tissue at endoscopic follow-up [16]. The majority of local recurrences are visible during the endoscopic follow-up, and can be easily treated endoscopically by additional snare excision or thermal treatment. Endoscopic treatment is minimally invasive and can be repeated indefinitely.

Adenomatous recurrence is more common in patients with FAP who are significantly younger and with smaller lesions compared to patients affected by sporadic tumors [22]. Other factors which may predict success rate at
Complications

The majority of complications following endoscopic papillectomy occur immediately. These are usually mild, requiring only medical or endoscopic treatment. The most common immediate complications are bleeding from the site of the papillectomy and acute pancreatitis; more rarely acute cholangitis and perforation may occur [16]. Mild self-limited bleeding is not uncommon immediately after resection. This might receive supplemental endoscopic therapy and should not be considered as a complication. The reported complication rate following endoscopic papillectomy varies between 10% and 58% (average rate 23%) [16–28,43,60]. The most common adverse event is bleeding, which may occur in up to 10% of procedures. Usually it is similar to the bleeding after endoscopic sphincterotomy, and may be managed by endoscopic measures such as the use of endoscopic hemostatic clips, epinephrine injection, or thermal coagulation. Acute pancreatitis occurs in up to 9% of patients, but in most cases is usually mild and treated conservatively. Retroperitoneal perforation is a rare complication of endoscopic papillectomy and is reported to occur in less than 1% of cases [16]. Too large a resection, or repeated free-hand attempts at pancreatic duct cannulation may increase the risk of retroperitoneal perforation. In most cases, these can be treated conservatively except where there are signs of sepsis, which requires surgical drainage via a posterior laparostomy [71].

Delayed complications are rare and are usually due to subsequent fibrosis and scarring at the site of the papillectomy causing stenosis of either the biliary and/or pancreatic duct orifice. In such cases, endoscopic therapy, with balloon dilatation of the duct orifice, is usually successful. Mortality following endoscopic papillectomy is rare with a reported incidence of up to 0.4% [16].

Surveillance after ESP

Currently, there are no recommended guidelines on the optimal time interval for surveillance following endoscopic resection. However, all patients should be followed up regularly to determine whether or not resection is complete, and to identify and treat any areas of local recurrence. The timing between endoscopic resection and the first follow-up examination to some extent depends on the personal preferences of the endoscopist performing the resection, the success rate of complete excision, and histological analysis of the excised specimen. In patients where a piecemeal resection has been performed,
when the resection margins of the lesion are involved by tumor, or in cases of adenoma with high-grade dysplasia or invasive carcinoma, repeat examination should be performed early at one to three months post-resection. In contrast, in patients with adenoma with low-grade dysplasia and en bloc complete excision with histological evidence of tumor-free margins, follow-up examination may be delayed six to twelve months post-resection [22].

Endoscopic resection is considered complete when there is no visible residual adenoma or recurrence after a follow-up examination with biopsy. In cases of incomplete tumor excision, repeated endoscopic excision (with snare or biopsies forceps) or thermal ablation (argon plasma coagulation) should be performed at 2–3 month intervals until any residual tumor tissue has been completely ablated [22]. In contrast, for lesions which are completely excised following initial resection, surveillance endoscopy and multiple biopsies should be performed at six to twelve monthly intervals for a minimum of two years [22]. In patients with sporadic adenomas, the risk of local recurrence after two years is extremely low and in such cases some authors would advocate only repeating endoscopic examinations if clinically indicated [20]. Others, however, would recommend continued regular surveillance at yearly intervals [20,21,23,28,60,64]. In our experience at Mayo, patients with sporadic adenomas will have surveillance continued for five years. In contrast, in patients with FAP who have no evidence of local recurrence, the ampullary region should undergo periodic lifelong endoscopic surveillance at established intervals, along with biopsy, which can be as long as three years in the presence of complete eradication that has been histologically proven [22].

**Video legend**

Two video segments are presented with similar-sized lesions in a patient with FAP and a sporadic adenoma. The lesions are 1–1.5 cm in size. In the first video there is a classic ‘goatee’ extension of the adenoma inferiorly below the adenomatous area and enlarged papilla of Vater. The ERCP cholangiogram is shown prior to snare resection. This demonstrates an uninvolved distal common bile duct. Snare excision is performed using a specialized ampullectomy snare positioned in a ‘top down’ fashion. After the main component of the adenoma is excised, a biliary sphincterotomy is performed followed by placement of a 5-French single pigtail pancreatic stent for prophylaxis from pancreatitis. Supplemental cautery is performed using an 0.035 inch fistulatome. In the second video, the accurate placement of the snare is emphasized, lifting the ensnared lesion upward to examine the positioning of the monofilament snare wire. Post-excision ERCP and biliary sphincterotomy is also demonstrated through an intact residual biliary component of the sphincter of Oddi.
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References

Introduction

The removal of colon polyps is the commonest therapeutic maneuver in the large bowel. The technique for small or large polyps is basically the same with repetitive but similar action required for larger polyps. Open access endoscopy and screening programs have been recently introduced in Western countries and have led to the detection of an increased number of lesions in the early stages of neoplastic transformation. Unfortunately polyps larger than 3 cm, involving more than one-third of circumference or two haustral folds or with a flat/depressed morphology are more challenging to remove with the standard polypectomy technique and usually require a different endoscopic approach, which has been named endoscopic mucosal resection (EMR). EMR is now an established technique that tremendously extends the ability to remove in a minimally invasive way colonic lesions that would otherwise require surgical or ablative therapies. One more important advantage of EMR over standard polypectomy is that EMR has the potential to provide en bloc resection specimens for histopathologic analysis. The plane of resection during EMR is typically the middle-to-deep submucosal layer as compared with standard polypectomy which normally provides a resection at a mucosal level.

This chapter will review current data regarding the technique and patient selection as well as complications and outcomes of endoscopic mucosal resection for colonic lesions.
Concepts of early colorectal cancer

Early colorectal cancer is defined by the Japanese rule as being limited to the mucosa or invading only to the submucosa, regardless of the presence or absence of lymph node metastases [1].

From an endoscopic point of view, in the colon, neoplastic lesions are called ‘superficial’ at endoscopy when the endoscopic appearance suggests either a small cancer or a non-invasive neoplastic lesion (dysplasia/adenoma). If invasive, ‘superficial’ tumors correspond to the T1 stage of the TNM classification, in which invasion is limited to the mucosa and submucosa. ‘Superficial’ tumors are typically non-obstructive, usually are asymptomatic, and often are detected as an incidental finding or by screening [2].

The macroscopic classification system provided by the Japanese Research Society for Cancer of the Colon and Rectum (JRSC) divides the gross appearances of early colorectal neoplasms into three categories: protruded or polypoid, flat elevated, and depressed [3]. The Paris classification [4] is an extension of the previously used Japanese Classification of Colorectal Carcinoma. These classifications serve as useful guides to distinguish lesions amenable to endoscopic therapy.

The polypoid type consists of the pedunculated or semipedunculated (type 0–Ip) and sessile (0–Is) morphology. The non-polypoid type comprises slightly elevated (0–IIa), completely flat (0–IIb), and slightly depressed (without ulcer) (0–IIc) lesions. Excavated or ulcerated superficial lesions (type 0–III) are practically non-existent in the colon, and this type of lesion is described primarily in gastric cancer.

However, these classifications are still poorly standardized, leading to significant differences in the interpretation and definition of non-polypoid colonic lesions with problems in interobserver agreement and substantial differences between Western and Japanese experiences [5] and even from endoscopists of the same area.

The original description of a flat neoplasm by Muto et al. [6] in 1985 is of a lesion slightly elevated above the mucosa with a reddish surface and/or a central depression that is seen after the lumen has been adequately inflated. An alternative definition describes these lesions as mucosal elevations with a flat or partially rounded surface where the height is less than half its diameter [7] or histologically as those in which the thickness of the lesion is less than twice that of the adjacent normal colonic mucosa [8]. The depressed-type colon cancer was first described in 1977 [9,10] by Japanese authors. The occurrence of this lesion is now widely accepted and is reported throughout the world with an increasing incidence even in Western countries.
Recognition of depression is very important because depressed lesions are often associated with invasive cancer even when they are very small. The depressed-type colorectal cancers either can be absolutely depressed or accompanied by a slightly elevated margin [9]. Some lesions with depression are elevated as a result of submucosal invasion and proliferation of the tumor cells [10]. Such lesions must not be mistaken for ordinary elevated neoplasms because they are quite different from each other in biological behavior.

Chromoscopy is useful for confirming flat and depressed colorectal lesions, for determining their lateral extent, and for clarifying their gross configuration; this is useful especially in determining the presence or absence of depression within the lesions.

There is some confusion about the depressed and flat lesions. Lesions that are called flat adenomas are not absolutely flat, but often are elevated slightly. It is true that some adenomas appear to have a depression and resemble depressed-type early cancers; the depression in a true depressed lesion is rather extensive and clearly demarcated. In contrast, the depression in flat elevated adenomas actually is an ill-defined pseudodepression with only a thorny or groove-like appearance [11]. Depressed lesions are not part of flat adenomas but should be regarded as a different entity, because the latter almost invariably are benign. Invasive rates in flat elevated adenomas are slightly lower than but not remarkably different from those in protruded polyps [7]. Flat lesions are usually benign or only focally malignant and grow very slowly, not becoming invasive until they are rather large. In contrast, depressed lesions apparently grow rather rapidly, advancing at an early stage [12] and most of the time are not suitable for endoscopic resection. The depressed-type lesions are reported not to have K-ras point mutation, although their genetic alterations are not clear [13] and it is certain that they arise without adenoma-carcinoma sequence [14].

In addition to the Japanese macroscopic classification of early neoplastic lesion, flat adenomas are further classified according to their size. Laterally spreading tumors are defined as those flat adenomas larger than 10 mm in diameter which extend circumferentially rather than vertically [15]. This category is further divided into a granular type, which is composed of fine granules, and a non-granular type (Fig. 9.1(a),(b)), which is devoid of apparent nodules or granules and seems to have higher incidence of cancer with submucosal invasion [16].

The role of EMR in the treatment of early cancer of the colon is becoming more and more well defined, following the guidelines of the Japanese Society of Digestive Endoscopy inclusion criteria, which are: adenoma and small well-differentiated carcinoma; confined to the mucosa or cancer with minimal invasion to submucosa; and without any invasion to lymphatic channels or vessels [17].
Fig. 9.1  Laterally spreading tumor of the right colon, before (a), and after (b) chromoscopy with indigocarmine.
Endoscopic diagnosis and staging of early colorectal cancers

Early colorectal cancers are usually without symptoms and their identification depends on the knowledge of their endoscopic morphology. In many cases high-grade dysplasia and adenocarcinoma are not identifiable during an endoscopic session, and for this reason the endoscopists should use additional technology to increase the sensitivity of the endoscopic investigation.

The evolution in the last years of technology applied to endoscopy have increased the possibility of detection and characterization of lesions of gastrointestinal mucosa.

The ability to magnify endoscopic images in real time by using magnification endoscopy permits the identification of microscopic lesions of the mucosa that cannot be seen with standard endoscopy.

A role of a combination of chromoendoscopy with indigocarmine and magnification endoscopy in the colon has been suggested for the diagnosis of flat and depressed lesions, identification of dysplasia, discrimination among polyp types, and assessing completeness of EMR.

With magnification, the openings of colonic crypts are referred to as pits, and the specific arrangement of the openings of the glands in various kinds of lesions is called the ‘pit pattern’, which shows strong correlation with the histopathological appearance [18].

Kudo has also proposed a classification of the fine surface structure of the mucosa, as well as that of small lesions, into pit pattern types I to V after vital staining especially with indigo carmine [19,20]. One of the most important challenges of endoscopic pit pattern diagnosis remains the differential diagnosis between non-neoplastic and neoplastic lesions.

Lesions with type I and II pit patterns obviate any necessity for endoscopic resection because of their negativity for neoplasia. Lesions with type III (small), IIII (large), or IV pit patterns could be treated endoscopically because they are probably adenomatous but not invasive. Lesions with type V (non-structural) pit pattern should be treated surgically because they are invasive and may have nodal metastases. Lesions with type VI (irregular) pit pattern include a number of lesions from benign adenoma to invasive carcinoma; these kind of lesions are first treated endoscopically, and additional surgical colectomy and lymph node dissection are considered after the histological analysis of the biopsy specimen; non-invasive or minimally invasive (sm 1a) lesions without vessels infiltration can be only observed [21]. The ability to distinguish neoplastic from non-neoplastic lesions has been reported with a sensitivity and a specificity of more than 90% [22].

The potential of EUS evaluation before colonic EMR remains controversial.

High-frequency-miniprobe ultrasound (HFUP) has the ability to distinguish the colorectal mucosa as a nine-layered structure and hence provide an in vivo
staging tool. In a prospective study Harada et al. [23] determined the utility of endoscopic ultrasonography in colonic EMR by using a 15 MHz miniprobe to assess submucosal invasion in 35 patients who were considered for endoscopic therapy. EUS resulted in suboptimal measuring of the precise depth of submucosal involvement. It was able to clearly distinguish shallow from deep invasion and thus determine suitability for EMR (86% accuracy). Ninety-two per cent of cancers thought to be unresectable on EUS were unresectable, whereas only 70% of cancers that were thought to be superficial were in fact resectable. Thus, EUS has better predictive value for deep, unresectable lesions.

Similarly, Hizawa et al. concluded that EUS could not be relied upon to determine the appropriate treatment for early colorectal cancer [24]. The reported accuracy of the invasion depth diagnosis from the largest series by Saitoh et al. was around 80% [25].

Due to these conflicting results EUS is not currently used before EMR for colonic lesions in many centers.

A simple and cheap method to evaluate the submucosal infiltration of early colonic neoplasms is ‘the non-lifting sign’ that has been proposed by Uno et al. [26]. Fluid is injected beneath the lesion at endoscopy. For those lesions with invasion into the deeper layers of the submucosa, the desmoplastic response prevents injected fluid from infiltrating underneath the tumor, so that the neighboring normal mucosa elevates but the lesion itself does not, resulting in the ‘non-lifting sign’. When the sign is negative, the lesion is elevated and suitable for immediate endoscopic mucosal resection (EMR).

Lesions that show the non-lifting sign are not suitable for EMR, and should be tattooed with India ink to aid identification at surgery as small flat cancers may not be palpable at laparotomy [27].

Placement of tattoos above and below the lesion are recommended to aid localization by both the surgeon and the histopathologist.

Narrow band imaging (NBI) is a high-resolution endoscopic procedure that enhances the structure of the mucosal surface without the injection of any substances.

NBI enables better visualization of the mucosal patterns because blue light allows for optimal superficial imaging; moreover NBI reveals the superficial vasculature because of absorption of the blue light by haemoglobin (Fig. 9.2(a),(b)).

Machida et al., in a pilot study performed between November 2001 and August 2002, enlisted 34 patients (22 men and 12 women) who were being followed up in an endoscopic surveillance program [28]. The detected lesions were each investigated three times, first by conventional colonoscopy, next by NBI colonoscopy and lastly, by chromoendoscopy using 0.2% indigo carmine dye. A total of 43 colorectal lesions were evaluated in the 34 patients. Compared with conventional colonoscopy, the pit pattern observed during
Fig. 9.2 Flat adenoma of the left colon (a), same image after NBI (b).
magnifying colonoscopy was better visualized by NBI ($p < 0.001$). The accuracy of endoscopic diagnosis compared with the histological findings was 79.1% for conventional endoscopy, in contrast to NBI colonoscopy (93.4%). NBI colonoscopy had a sensitivity of 100% and a specificity of 75% in the differentiation of neoplastic and non-neoplastic lesion [28].

Optical coherence tomography (OCT) is an emerging medical imaging technology that relies on the backscattering of light to obtain cross-sectional images of tissue.

This method is similar to ultrasonography but it uses light waves rather than acoustical waves. OCT permits the visualization in real time of the mucosa, the muscularis mucosae, and the superficial layer of submucosa.

Cho et al. [29] found that due to interference, the probe provided little benefit in imaging neoplastic lesions, but interesting views of the superficial colonic wall were obtained in patients with telangiectasia and ischemic colitis.

Confocal laser endoscopy is a technique that uses a confocal laser with a wavelength of 488 nanometers. With this method it is possible to visualize single cells and glands of the superficial epithelium, using fluorescein sodium as a contrast agent.

Fluorescein was used for the prospective component of the initial study, in which 42 patients with indications for screening or surveillance colonoscopy after previous polypectomy underwent colonoscopy. A total of 13,020 confocal images from 390 different locations were compared with the histological data from 1038 biopsies. With the newly developed confocal pattern classification, it was possible to predict the presence of neoplastic changes with a high degree of accuracy: sensitivity 97.4%, specificity 99.4%, accuracy 99.2% [30].

Techniques of EMR for early colorectal lesions

Endoscopic mucosal resection is a major advancement in endoscopy. In contrast to what is currently believed by the majority of endoscopists, mucosectomy was not invented in Japan. It was originally described by Deyle et al. [31] as early as 1973, and has been sophisticated and widely used by many others, especially Japanese endoscopists, since then.

The achievement of a proper position in front of the polyp is a crucial issue to success with the EMR of colonic lesions. It is often considerably easier to pass the scope far beyond the polyp, even to the cecum and attempt EMR during the withdrawal phase of the examination; as the scope is withdrawn, the loops are removed and the polyp, which proved difficult to position during intubation, may be quite easily approached. Once the colonoscope has been straightened, the ability to torque the instrument and freely use dial controls is restored, permitting the examiner to precisely maneuver the devices around the target lesions.
An alternative technique for removal of lesions located on the far side of a fold is to perform a U-turn maneuver. This can be accomplished in the cecum, proximal ascending colon, and occasionally in the transverse colon. It is more difficult to resect a polyp in a U-turn mode because the tip deflection responses are opposite to those usually expected. In such a case a narrow caliber endoscope such as a therapeutic gastroscope or a variable stiffness pediatric scope may permit easier polypectomy. The major attribute of these small caliber scopes is that they have a tighter bending radius of the tip than does a standard colonoscope.

Submucosal injection is a major step in performing colorectal EMR. A variety of solutions have been used to create a submucosal cushion including normal (physiologic) saline (NSS), hypertonic saline (3%), hypertonic glucose (D50), glycerol solutions, and diluted epinephrine solution (1:10 000). Most practitioners use NSS. Interest in other agents is in an effort to prolong the 'pillow-effect' and decrease the risk of bleeding, transmural burn syndrome, and perforation (Fig. 9.3(a)–(e)).

There are still insufficient data to identify the ideal solution even on the base of a cost-effectiveness evaluation.

If a more viscous solution such as hyaluronic acid must be injected it may be very helpful to use a large channel needle 21 or 20 gauge. The needle should be directed adjacent to the base of the lesion at a 45° to the bowel wall in order to correctly penetrate just below the lesion and inject the solution into the submucosal layer beneath the lesion. If no cushion is observed, the needle may be too superficial or too deep and needs to be adjusted accordingly. Only the submucosal layer will expand with fluid injection.

When injecting around the circumference of a lesion, or for lesions draped over a fold, it is advantageous to inject at the far aspect of the lesion first to maintain or enhance its visualization. Injecting directly through the lesion should be avoided when possible because it carries the theoretical risk of contributing to metastasis even though up to now there has been no reported case of malignant cells spreading due to submucosal injection.

Whatever is the selected technique of EMR, either a blended current or pure coagulation current could be used. Unfortunately no previous studies have reported comparative data to support one or the other mode when performing EMR. A comparison of blended versus continuous coagulation current for pedunculated colorectal polyps failed to show a statistically significant difference in the incidence of major complications such as bleeding, transmural burn, and perforation [32]. The timing of major bleeding, however, was significantly different: all of the major hemorrhages were immediate when blended current was used; all were delayed (2–8 days) when pure coagulation current was used. Our group and some others suggest that a combination of blended and coagulation current may be safely used for colonic EMR because the
Fig. 9.3  A small flat adenoma with central depression (a), after chromoendoscopy (b), lifted with saline (c) and resected (d and e).
introduction of a saline pillow protects against transmural injury, whereas the risk of acute and delayed bleeding is diminished [33–35].

Once the lesion has been raised, a snare is applied over the lesion and closed. Applying suction as the snare is closed helps in retaining the mucosa within the snare. Once the lesion is caught in the snare, the snare is relaxed slightly to
allow the submucosa to retract and minimize the risk of perforation. In some situations it can be useful to follow the suggestion of Soehendra et al. who favor the use of a 0.4 mm monofilament stainless steel wire snare which is pressed firmly against the mucosa to entrap the lesion [36]. A number of braided and barbed snares are now commercially available in different sizes and shapes and can be helpful when removing flat colonic lesions.

The technique described above is also known as submucosal-injection polypectomy or lift and cut mucosal resection and is the most frequently used way of removing early colonic neoplasms regardless of the morphology and the size. For lesions larger than 25 mm, piecemeal resection is invariably required. In the case of piecemeal mucosal resection by using the lift and cut technique, when a portion of a sessile polyp is resected, one edge of the reopened snare can be placed in the divot created by the previous resection so that the same maneuver is repeated on the adjacent portion of polyp, continuing in this manner until resection is complete. In some instances, it may be necessary to change from a jumbo or standard snare to a minisnare to successfully remove smaller fragments at the border of the lesion.

Lesions draped over mucosal folds, extending in a circumferential manner or flat and larger than 30 mm can be a difficult challenge. Additional EMR techniques such as the use of a cap may be required to successfully proceed with endoscopic resection of these lesions. Although most upper gastrointestinal...
EMRs in Japan are carried out using the ‘suction cap’, this technique has proved less popular for colonic EMR.

This is probably due to the perception that the risk of perforation may be greater in the colon than in the stomach. The use of a cap does not increase the difficulty of colonoscopy; it can improve diagnostic yield and can allow more precise targeting of polyps [37].

Nevertheless, considerable skill is required to control suction so as not to aspirate the full thickness of the colonic wall and avoid strangulating the mucosa with the snare too near the base of the created bleb [33,38].

Sadahiro et al. [39] demonstrated, using colorectal cancer surgical specimens, that a cap with a height of 7 mm is more suitable for the colon, while either a 7 mm cap or a 10 mm cap could be used in the rectum.

In our experience and in other reported experiences the cap-mucosectomy technique in the colon may add a significant advantage in removing lesions behind mucosal folds, both increasing the visual field and improving the ability to focus the target lesion during resection maneuvers [38,40].

The inject, lift, and cut technique is another modality of performing EMR which uses a double-channeled endoscope. First the lesion is lifted with submucosal injection as described earlier. A snare is then passed through one channel and a forceps through the other. The forceps are used to grasp and lift the lesion allowing it to be ensnared. The use of a double-channel scope in the colon is challenging because of its rigidity, and using the two devices at the same time may be very complicated in the colon where the available operative lumen is much smaller than in the stomach where the technique has been originally described. We have found this technique difficult to perform and not very beneficial and the reported use for colonic lesions is very scarce in the literature. To improve access to mucosal lesions, the use of two endoscopes inserted in parallel has been proposed. One endoscope is then used to lift and manipulate the lesion while the other is used to resect the mucosa with a better ability to identify the dissection line and properly to control the devices used for the endoscopic procedures [41].

**Endoscopic submucosal dissection for colonic lesions**

For the curative treatment of mucosal colonic lesions, the most important issue is the completeness of the resection. This task can be difficult to achieve in large sessile polyps and residual tumor may be left behind, leading to local recurrence. Conventional techniques of EMR such as the cap assisted, strip biopsy, with ligating device etc., are thought to be inadequate for en bloc resection of large colonic lesions. The multiple fragments that result from this piecemeal resection make the histopathologic evaluation of the completeness of polyp removal difficult.
Therefore, en bloc resection with an adequate tumor cell-negative margin is considered a more desirable outcome. The technical limitations in endoscopic treatment of large colonic lesions can sometimes be overcome by a device enabling the performance of en bloc resection, thus allowing the acquisition of a single large specimen for the correct evaluation of the resection margins.

In 1995 Hosokawa and Yoshida [42] developed a new device for EMR: the insulated-tip electrosurgical knife (It-knife) which has a ceramic bulb at the tip to prevent injury to deeper layers of the GI tract. It was reported that EMR with an It-knife made it possible to perform en bloc resections of large early stage gastric cancers with a reduction in the recurrence rate [43,44].

Subsequently a number of different knives with specific technical peculiarities, such as the hook-knife or the flex-knife have been introduced in clinical practice by Japanese endoscopists with extensive experience in submucosal dissection of early gastric cancer [45].

As for standard colonic EMR, formation of a good submucosal cushion of the targeted mucosa is one of the most important elements for a successful ESD. Because the colonic wall is thinner than the gastric wall, it is more difficult to inject sodium hyaluronate solution or other viscous substances into the appropriate submucosal layer of the colon. To avoid injections of sodium hyaluronate into the wrong layer, pre-injections of small amounts of normal saline into the submucosal layer are useful. By mixing a small amount of indigo carmine dye or methylene blue into the injected solution, the injected area of the sodium can be distinguished much more easily from the non-injected area even after pre-injections of normal saline.

As previously described by a Korean group [46], we are testing in animal studies the possibility of injecting fibrin glue that is able to create a stable and thick cushion and provide an excellent hemostatic effect which can be useful for preventing both intraprocedural and delayed bleeding [47]. Unlike ESD of early gastric cancer, marking placement can be omitted for ESD of colonic neoplastic lesions in the majority of cases because the margins of the lesions are clearly visible even after submucosal injections especially if chromoendoscopy with indigo carmine has been performed prior to resection.

After a sufficient protrusion of the mucosa is produced, a small mucosal incision with a needle knife is created in the two opposite areas of the tumor and thereafter the circumferential mucosal incision with a knife can be performed safely. A cylindric transparent hood, 8 mm in length, or a standard transparent cap, attached to the endoscope tip are also very helpful for the safety of mucosal incision by reducing unintentional movements of the colonic wall toward the needle knife. But this technique is more demanding and is only sporadically used for resection of non-gastric lesions such as large colonic neoplasms [48–50].
The main reasons for the difficulty are the inability to use countertraction for good visualization of the targeted tissue.

With regard to endoscopic submucosal dissection (ESD) into the stomach, scope retroflexion in the colon is one of the most required maneuvers to approach large lesions and especially those located behind folds, on the proximal end of tight turns or involving more than two-thirds of the circumference.

In order to facilitate retroflexion, especially in the left colon, we use a therapeutic gastroscopy whose flexibility is greater than a standard colonoscope and allowed to easily retroflex in all the colonic segments. A potential alternative to the therapeutic gastroscopy can be a pediatric colonoscope with a short bending section [51], designed to improve therapeutic access in the colon.

Working with the scope retroflexed in the colon does not negatively affect in any instance the ability to maneuver the devices required to complete the submucosal incision including the use of clips or argon plasma coagulation probes.

For the submucosal dissection, a forced coagulation mode of 25 W is selected. The submucosal dissection is progressively performed by advancing the submucosal dissection while sliding the tip of the endoscope with a hood under the dissected mucosa. Effective control of bleeding during the procedure is a key element for a successful ESD. We think that intraprocedural bleeding must be promptly controlled whenever it occurs regardless of its severity. An endoscopic field which is dirty with fresh blood or clots makes it difficult to identify the submucosal resection plane as well as the lesion margin.

During submucosal dissection blood vessels can be recognized during the submucosal incision because it is performed under direct visualization of the tissue. When blood vessels are recognized, the output mode is changed to the argon plasma coagulation mode. Because the voltage of the argon plasma coagulation mode is higher than the coagulation mode, small blood vessels can be cut without bleeding.

Bleeding can also be prevented or stopped by using hemostatic forceps. The generator is set to soft coagulation mode (50–80 W) for hemostatic forceps which are used to pinch a blood vessel precisely, retract it, and coagulate with a minimal contact area.

Perforation is a major concern as a possible complication of ESD. Perforation during ESD using sodium hyaluronate can be minimized by sufficiently thickening the submucosa by proper injection of sodium hyaluronate and careful selection of the layer for incision.

In our experience, the increased risk of wall perforation is due also to the reduced room of colonic lumen and the variety of angles and folds in the colon which make the proper control of knife movements very difficult as it may be challenging to control the depth and the direction of the cut at the same time. The risk can be further increased when the lesion is infiltrating the submucosa and injection cannot adequately create a submucosal cushion. For this reason
careful inspection of the submucosal layer during its dissection is required to identify submucosal tissue or irregularities compatible with deep neoplastic invasion.

When a perforation is made during the procedure, it is usually small and recognized immediately; therefore, it can be closed with endoscopic clip placements and can be managed conservatively [35].

Outcome

Endoscopic mucosal resection (EMR) represents a major therapeutic advance in the management of early cancer of the upper and lower gastrointestinal tract. In the colon, lymph node metastasis occurs only after penetration of the submucosa and is directly correlated to the depth of submucosal penetration by the tumor [52]. This supports the therapeutic effectiveness of endoscopic removal of polyps and flat lesions when confined to the mucosa, regardless of their size.

Various studies have been published on the safety and therapeutic potential of EMR for colonic tumors since the first data were reported by Tata et al. in 1984 [53].

Yokota et al. in their series involving 137 flat lesions resected by EMR achieved a complete removal in 87% with complication rates of 0.7% and 0.4% for perforation and bleeding, respectively [54]. Bergmann and Beger used EMR for 71 lesions of sizes ranging from 10 to 50 mm [55]. They encountered one case of bleeding which was treated endoscopically and one case of perforation treated by surgery. At 18 months follow-up local recurrence was observed in two cases. Similar results in terms of technical success (98.1%), complication rate (9.6%), and recurrence rate (15%) have been recently reported by a French group in 50 patients affected by advanced sessile adenoma and early-stage colorectal carcinoma [56].

Sometimes en bloc resection of large sessile polyps is not possible and endoscopic piecemeal mucosal resection is performed. Iishi et al. [57] reported from their study on 42 large polyps that with intense follow-up program piecemeal resection can also be safe and effective.

The proportion of piecemeal vs. en bloc resection seems to be directly correlated with the diameter of the lesions. In a recent paper, despite the use of a long-lasting solution for submucosal injection, the rate of en bloc resection decreased from 85.9% in the case of lesions between 10 mm and 19 mm to 23.1% for lesions between 20 mm and 29 mm [58]. In the study by Su et al., piecemeal resection was invariably required for all colonic flat lesions larger than 30 mm [59].

The appearance of carcinoma after removal of adenomatous polyps is rare. In only one study, published by Walsh et al. [60], carcinoma was reported to have occurred in 5% of patients during follow-up.
Less extensive data have been published on the use of EMR-C for colonic lesions because its application in the colon remains controversial while EMR-C has been used extensively to treat early-stage esophageal and gastric cancers. Tada et al. [37] used EMR-C in the colon and achieved full thickness resection of the mucosal layer and a third of the submucosal layer.

In a paper from our group, the EMR-C technique was used with minimal complications in 46 patients [38]. The lack of perforation in these studies can be attributed to the large volume of fluid injected submucosally and the judicious application of suction with the cap. Resection of 10.8% of the polyps was complicated by bleeding, usually larger polyps. In all cases, bleeding was intra procedural and was easily controlled by endoscopic techniques. Post-polypectomy syndrome with fever and abdominal pain occurred in a few patients.

In the Bergmann series, the EMR-C technique was successfully used only if snare resection was not feasible [55]. It has been suggested that full suction should not be used during EMR-C to avoid grasping of the muscularis propria [60].

Sometimes it may be very challenging to access the target area for EMR when neoplastic disease had migrated proximally beyond the forward-viewing field of the endoscope.

A prospective technical endoscopic evaluation of retroflexion EMR using cap-assisted dissection as a method of luminal ‘salvage’ therapy was conducted in patients referred to a tertiary endoscopy unit, in whom colonic lesions had been assessed as unresectable using conventional forward-viewing EMR at the index colonoscopy, who were therefore candidates for direct surgical resection. All 68 patients fulfilling the criteria were successfully treated with success rate, complications, and mid-term recurrence comparable to a previous study of colonic EMR [61]. Retroflexion EMR with a cap may therefore offer ‘salvage’ endoluminal therapy in patients in whom surgical resection would otherwise have been required.

Overall, whatever the technique used, the two most frequently reported major complications are perforation (0–5%) and bleeding (0.5–6%) and both may be potentially controlled with endoscopic methods and very rarely require surgical treatment (11,62–64).

Removal of large sessile lesions is technically demanding and often requires up to two hours. The length and the difficulty of the procedure are increased by the need to reintroduce the colonoscope to retrieve fragments of lesions after a piecemeal resection in the colorectum. The complete ablation of large adenoma may require from one to five endoscopic sessions. In most recent studies, all lesions are reported as being removed in a single session [11]. When feasible, this eliminates the discomfort and the inconvenience of repeated procedures.

Follow-up is essential because of the risk of recurrence. Aggressive surveillance seems justified, because it has been shown, in an animal model, that residual tumor has a high regrowth rate [65].
Surveillance is devoted to allowing detection of early regrowth, which is more easily treated by APC or standard polypectomy [38]. Therefore, rigorous follow-up is necessary to detect recurrence. However, the strategy for follow-up is unclear at present. Re-examination between one and three months seems mandatory after resection of an early-stage carcinoma. Follow-up colonoscopy should be done at least every three to six months during the first two years after EMR. Some authors have recommended colonoscopy only at one year after en bloc resection, due to the lower risk of recurrence compared with piecemeal resection. However, we prefer to carry out a scrupulous surveillance after endoscopic treatment of an early carcinoma (Fig. 9.4).

The recurrence rate after EMR of sessile colorectal polyps ranges from 0% to 40%, but it is difficult to compare the different series because of wide variations in polyp size and length of follow-up. It is likely that patients with larger adenomas are at higher risk for the development of new polyps [66–68]. In our experience, there is a tendency toward an increased risk of recurrence after EMR for polyps larger than 35 mm [35,38].

When remnants of adenoma remain after EMR, APC has been used to reduce the frequency of residual adenoma by 50% [69]. In the study by Zlatanic et al., [70] the recurrence rate after EMR without APC was 100%, as compared with less than 50% of those treated with complementary APC.

Regula et al. [71] completely eradicated polyps in 90% of cases when EMR was combined with APC. Others have found APC to be useful, when required, to complete the eradication of adenomatous tissue [72].

**Fig 9.4** Huge scarring area after en bloc resection for a 3 cm large flat adenoma of the rectum.
Nevertheless, in the most recent current studies, EMR has allowed adequate histopathologic assessment of the early colonic neoplasia in all patients, including the identification of invasive cancer [11,12,38]. If EMR is performed properly and all fragments of the polyp are retrieved, the risk of missing a cancer seems negligible.

For this reason, we do not recommend forceps biopsy specimens when a colonic lesion is discovered, provided it is considered, by macroscopic criteria, amenable to EMR.

There are qualitative and quantitative histological features by which nodal involvement may be predicted. A recent study suggested that for tumors without unfavorable histological features such as poor differentiation, vascular invasion, tumor budding, and extensive submucosal invasion (i.e. depth of over 2000 µm from muscularis mucosae or maximum tumor width in the submucosa over 4000 µm), endoscopic resection alone may be considered adequate [73]. Kikuchi et al. [74] assessed the risk of recurrence in 17 patients with early stage colorectal cancer infiltrating the upper third of the submucosa. After EMR, there was no local recurrence or lymph node metastasis in any patient. The endoscopic appearance and the characteristics of colonic lesions can usually predict the feasibility and advisability of EMR.

However, if deeper submucosal infiltration is detected in the resection specimens, surgery should be recommended unless operation is precluded by other factors, such as advanced age and/or comorbid disorders.

In conclusion, the ability to retrieve a large resected specimen after EMR allows thorough histopathologic assessment, which can have a significant impact on patient management. The results of the literature data demonstrate that surgery can be avoided for many patients when large colonic lesions are removed by EMR.

**Surgical considerations**

The use of a laparoscope might be of help in treating colonic polyps or early colonic cancers. Most colonic polyps can be removed during colonoscopy using endoscopic polypectomy. In some patients, however, endoscopic polypectomy or EMR is not possible or is unsafe due to location, size, tortuosity of the colon, adhesions, or complexity of the lesion. In such cases colonoscopic polypectomy or EMR of benign lesions can be performed under laparoscopic guidance.

For laparoscopy-assisted endoscopic polypectomy or EMR, surgeons and monitors are placed according to the segment of colon where the polyp is expected. A 10 mm trocar is inserted for introduction of the videoscope, and two additional trocars are inserted to facilitate the use of additional instruments. The bowel segment is mobilized and the bowel proximal to the
The EMR for colorectal lesions is clamped using an atraumatic grasper to prevent distension of the proximal bowel during colonoscopy. This is done because a distended large and small bowel limits laparoscopic visibility.

The colonoscopy should be performed with a minimum of insufflation. Laparoscopic instruments can be used to straighten the bowel to facilitate the advancement of the endoscope. If the lesion is identified, the laparoscopist can present the base of the lesion with laparoscopic graspers for easier snaring by the colonoscopist. When the endoscopic removal of the entire lesion is completed, the extraluminal bowel wall is inspected laparoscopically for signs of transmural involvement of the bowel, either by cautery or by perforation. In case of any suspicion, the defect can be oversewn laparoscopically using seromuscular sutures.

If laparoscopic-assisted colonoscopic polypectomy fails to remove the lesion, alternatives are laparoscopic wedge resection of the polyp or exteriorisation of the affected segment of bowel through a minilaparotomy in order to remove the polyp via colotomy.

The success rate for avoiding a formal bowel resection varies between 67% and 100%. Prohm et al. [75] studied six patients with polyps in such unfavorable positions in the rectosigmoid or splenic flexure that they were considered to be more suitable for an open or laparoscopic removal. The polyp-containing segment of the colon was mobilized laparoscopically and stretched as much as possible to facilitate endoscopic polypectomy. No complications occurred. Segmental colectomy was avoided in a series of 12 cases out of 36 patients with problematic adenomas not suitable for endoscopic polypectomy [76]. In another 16 consecutive patients only 40% of the adenomas could be removed by polypectomy under laparoscopic assistance [77].

The removed lesion should undergo immediate frozen section analysis. In the case of malignancy, a laparoscopic bowel resection can be performed immediately according to standard oncological principles.

References


Le Picard P, Vacher B, Pouliquen X. Laparoscopy assisted polypectomy or how to be helped by laparoscopy to prevent colectomy in benign polyps considered to be unresectable by colonscopy. *Ann Chir* 1997; 51: 986–9.
Introduction

First, one has to note that the term ‘endoscopic mucosal resection’ is wrong in respect of anatomical structures because not only the mucosal layer but also preferably most of the submucosal layer should be removed endoscopically in the case of early neoplasia in the gastrointestinal (GI) tract. Therefore, in this chapter the more correct term ‘endoscopic resection’ (ER) is used. The diagnosis of early cancer in the GI tract has become very important since new endoscopic techniques nowadays allow local endoscopic resections instead of surgical procedures in selected cases. The advantage of surgery is the removal of potentially involved regional lymph nodes. But on the other hand it is known that many patients with early carcinoma will never develop metastases. Patients need to be selected by assessment of high and low risk criteria to offer a local therapy instead of a surgical procedure. Therefore, histopathological evaluation of the resection specimen is very important. In the different parts of the GI tract such as the esophagus, stomach, and colon the risk of lymph node involvement is variable [1–4]. The lowest frequency is given for early colon adenocarcinomas compared to other locations in the GI tract. There are several endoscopic techniques used throughout the GI tract that are described in various chapters of this book.

Gross description and work-up of endoscopic resections

Prior to sending an endoscopic resection specimen to a pathologist some requirements are necessary to achieve the best possible quality of the specimen. From our own experience we know that if you want to preserve fresh material...
the best method to freeze specimens in liquid nitrogen is to embed them completely in ‘OCT Cryocompound’ (e.g. Leica, Wetzlar, Germany) prior to freezing the specimen. This minimizes freezing artefacts and even allows such specimens to be shipped worldwide in transport containers for liquid nitrogen (e.g. GT series, Air liquide, Kornwestheim, Germany). In the Institute of Pathology, specimens are taken out and one slice is cut from the middle of the specimen without letting the specimen warm up. One frozen section should be performed from this slice to document the content of this material. The remaining specimen will be fixed in formalin as with all ordinary specimens. The advantage of this method is the fresh material that can be used for further analysis. The disadvantage is that specimens cannot be orientated so that the closest margin can be recognized and the specimen orientated respectively.

In respect of quality it is better to receive specimens fixed in formalin. Prior to fixation, specimens in formalin needles should be used either to fix the specimen on cork or on a piece of thick paper. It is very important not to create tension on the specimen because formalin leads to shrinking in about 20% of endoscopic specimens (through fixation small biopsies shrink about 50%). The specimen should be fixed very loosely on the piece of cork in order to take shrinkage into account and avoid tension artefacts due to formalin.

In the Institute of Pathology the specimen is orientated in a manner that the closest margin to the neoplasia can be detected. We use a microscope for reverse light to orientate the specimen at a 20-fold magnification and if this is not possible, to orientate at a 90-fold magnification. Normally, neoplasias show structural changes of the surface such as erosions, marked gyration, polypoid structures, and irregular folds. The vast majority of specimens can be orientated on the basis of these changes. After orientation it might be useful to mark the basal margin with black ink or latex colors but this is open to discussion because it is probably not necessary if the specimen has not been orientated by the endoscopists in a way that a certain clockwise recognition of the resection margins can be achieved.

After orientation and marking of the margins (especially in those cases in which the endoscopist has given the exact clockwise orientation of the resection margins) the specimen needs to be cut into slices (each about 1–1.5 mm thick). In order to receive the best quality (especially if recuts are necessary) do not place more than two slices into one cassette (the optimum would be a single slice only).

The technique of gross description of endoscopic resection specimens does not vary throughout the GI tract but through histological grading. Every specimen has a three-dimensional size; areas of squamous epithelium and irregular areas on the surface should be reported. Line drawings or photographs are helpful.
Technique

The different techniques of endoscopic resection have so far not been evaluated in randomized controlled trials. The reported series were predominately performed in a small number of highly selected patients with relatively short follow-up periods. It is therefore difficult to compare the efficacy and safety between the various methods. The lift and cut technique and the suck and ligate technique were recently investigated in patients with Barrett’s high-grade dysplasia or mucosal cancer [5,6]. Endoscopic mucosal resection with cap (EMR-C) has been extensively studied in patients with early squamous carcinoma of the esophagus [7,8].

Endoscopic submucosal dissection (ESD) is a technique developed with the primary aim of obtaining one-piece resection even in large lesions. This procedure involves circumferential cutting of the mucosa surrounding the tumor followed by dissection of the submucosa beneath the lesion [9–13]. The advantage of ESD is that it provides a single specimen which allows a correct histological statement including the resection margins. Additionally the one-piece resection has been proposed as a gold standard of EMR as it reduces the risk of tumor recurrences [14], but this is controversial because in the hands of experienced groups it has been shown that the piecemeal technique also gives an excellent outcome [15]. The disadvantages of the piecemeal technique that have been discussed, i.e. that it is difficult to recognize complete removal histologically, plays a minor role in early neoplasia because remaining nests of neoplasia can also be recognized endoscopically and can be excluded by biopptic control or complete ablation of questionable areas (especially in Barrett’s neoplasia).

As well as new endoscopic techniques it should be noted that new molecular methods still do not answer the questions about what is still regenerative and what is already neoplasia, and what is still high-grade intraepithelial neoplasia and what is already invasive carcinoma. The histological diagnosis by an experienced pathologist is still the gold standard in recognition and grading of neoplasia.

In 2000 the World Health Organization (WHO) [16] recommended that the term ‘dysplasia’ should not be used any more but that ‘intraepithelial neoplasia’ should be used instead throughout the gastrointestinal tract. The term ‘high-grade intraepithelial neoplasia’ replaces and includes ‘high-grade dysplasia’ and ‘carcinoma in situ’. Because of the uncritical use of the term ‘dysplasia’, quite often regenerative changes were mixed up with early neoplastic changes and sometimes the term dysplasia was also used by some authors to indicate early carcinomas [17]. This led to overdiagnosis and underdiagnosis of regenerative and neoplastic lesions with concomitant confusion of endoscopists due to lack of matching of endoscopical and
histological diagnosis. The world record for low-grade dysplasia is nearly 70% within a consecutive series of patients with Barrett’s esophagus [18] (see Table 10.1). Obviously in such series overdiagnosis of regenerative changes led to confusion in the literature since most of these authors concluded that low-grade dysplasia does progress to Barrett’s carcinoma in a small fraction only so it is no surprise if series are corrupted by overestimation of regenerative changes.

According to the WHO classification invasive adenocarcinoma is diagnosed whenever the tumor invades into the lamina propria or the submucosal layer in the case of colon carcinoma, which leads to different ‘artificial’ definitions of carcinoma in the upper and lower GI tract. In the upper GI tract the entity of mucosal carcinoma is existing whereas in the colon the diagnosis of carcinoma is only made if the submucosal layer has been invaded. From a biological point of view this artificial border makes little sense because cytological and histological criteria mean that all mutations and changes in the affected cell populations can already be recognized on the mucosal level. On the other hand, in the colon, lymph node metastases never develop if the lesion is limited to the mucosa.

### Squamous cell carcinoma of the esophagus

Early squamous cell cancer of the esophagus is divided into mucosal (m1–3) and submucosal (sm1–3) carcinoma. This has been adapted from the Japanese classification of early neoplasia of the esophagus [19]. Instead of the term ‘carcinoma in situ’ pT1 m1 is used. Infiltration of the tunica propria is labeled as pT1 m2 tumor and invasion into the muscularis mucosa is named pT1 m3 (see Table 10.2). The more invasive the carcinoma, the higher the risk of lymph node metastasis. The decision in favor of a surgical procedure or local

<table>
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<th>Author</th>
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<th>Frequency of low-grade dysplasia (%)</th>
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<td>Schnell et al.</td>
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endoscopical therapy mainly depends on the risk of lymph node metastasis that should be lesser than the risk of the surgical procedure [20].

Due to uncertainties between bioptic diagnosis and diagnosis on resection specimens, the Vienna classification was introduced in 1998 at the World Congress of Gastroenterology [21,22]. The Vienna classification groups diagnoses together in five groups in conjunction with a clinical consequence. This leads to a subsequent loosening of the WHO classification of tumors. Fortunately this is without any consequence since cases with high-grade intraepithelial neoplasia and very early (mucosal) carcinoma need the same clinical treatment, and thus a further subdivision has no clinical consequence.

### Adenocarcinoma of the distal esophagus

Up until now the morphogenesis of Barrett’s mucosa (specialized intestinal metaplasia) is still unsolved. Furthermore, discrepancies between clear segments or tongues of columnar epithelium in the distal esophagus diagnosed endoscopically and the absence of histological confirmation of a Barrett’s diagnosis [23] is a confusing issue between gastroenterologists and pathologists. At least it is known that patients with Barrett’s esophagus have an up to 30 times elevated risk of developing Barrett’s adenocarcinoma compared to a normal population [24]. The individual risk ranges between 0.5% and 1% per year [25] and varies regionally, with higher rates in Scotland compared to other parts of the world [26].

For Barrett’s adenocarcinoma it is very important to carry out a risk stratification for the development of regional lymph node metastasis before undertaking further therapy. For the low risk group the following criteria have been established: well or moderately differentiated; no lymphatic vessel permeation; mucosal carcinoma; and size less than 2 cm. All other cases probably have to be regarded as belonging to a high risk group for the development/existence of lymph node metastasis [27]. Whether or not the biological behavior at the front

<table>
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<th>Depth of infiltration</th>
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<tr>
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</table>

m: mucosal; sm: submucosal.

Table 10.2  Risk of lymph node metastasis in early squamous cell carcinoma of the esophagus (modified after [20]).
of the invasion needs to be included into such a risk stratification (Stolte, personal communication) should be discussed. Up until now Barrett’s neoplasia has been somewhat roughly divided into a mucosal and submucosal type (sm1–3) (Table 10.3), similar to gastric carcinoma. Sm1 level is defined as infiltration lesser than 500 µm in Western countries, whereas in Japan sm1 infiltration is defined as invasion within 200 µm. Very problematic in this respect is the fact that columnar epithelium in the distal esophagus always show a double layer of muscularis mucosae [28]. Thus it is difficult to describe the depth of infiltration in relation to the muscularis mucosae. Our group therefore proposed a new division of the mucosa into different layers (m1–4) (see Fig. 10.1).

Even old cases from the archives can be subclassified. A first analysis of the frequency of presence or absence of lymphatic vessel permeation showed a strong relation to the depth of infiltration (see Table 10.4). These results derive from local endoscopic resection specimens published recently [29].

**Difficulties in the distinction between high-grade dysplasia and mucosal carcinoma is well documented through the recent version of the WHO classification (Fig. 1.25, p. 23) where a clear invasive adenocarcinoma is depicted but the footnote below the photograph declares that this is ‘high-grade intraepithelial neoplasia’ in Barrett’s esophagus [16].**

The question of whether an adenocarcinoma at the gastroesophageal junction derives from the cardia mucosa or on the base of Barrett’s mucosa is sometimes difficult to decide. It becomes more probable that Barrett’s adenocarcinoma is present when ‘regular’ Barrett’s mucosa is confirmed close to the carcinoma. The WHO classification proposed to diagnose all adenocarcinomas reaching

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**Table 10.3 Frequency of lymph node metastasis in early Barrett’s adenocarcinoma subdivided between mucosal (pT1m) and submucosal (pT1sm) type (modified after [49,50]).**

<table>
<thead>
<tr>
<th>Year</th>
<th>pT1m</th>
<th>pT1sm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>N+ (%)</td>
</tr>
<tr>
<td>Rice [52]</td>
<td>1997</td>
<td>29</td>
</tr>
<tr>
<td>Hölscher [53]</td>
<td>1997</td>
<td>10</td>
</tr>
<tr>
<td>Ruol [54]</td>
<td>1997</td>
<td>4</td>
</tr>
<tr>
<td>van Sandvick [55]</td>
<td>2000</td>
<td>12</td>
</tr>
<tr>
<td>Stein [56]</td>
<td>2000</td>
<td>38</td>
</tr>
<tr>
<td>Buskens [57]</td>
<td>2004</td>
<td>33</td>
</tr>
<tr>
<td>Westerterp [58]</td>
<td>2005</td>
<td>54</td>
</tr>
<tr>
<td>Liu [59]</td>
<td>2005</td>
<td>42</td>
</tr>
<tr>
<td>Stein [60]</td>
<td>2005</td>
<td>70</td>
</tr>
<tr>
<td>Bollschweiler [61]</td>
<td>2006</td>
<td>14</td>
</tr>
<tr>
<td>DeMeester [62]</td>
<td>2006</td>
<td>78</td>
</tr>
</tbody>
</table>

* Mucosal and sm-1 tumors were analysed together as pT1m.
In any case, an etiological diagnosis should preferably always be given. The term ‘cardia’ should be avoided since no overall and clear anatomic nor histological definition of this region is known. Instead, the term ‘proximal gastric carcinoma’ should be used. In the case of involvement of the gastroesophageal junction the tumor should be designated as a tumor of the gastroesophageal junction. Squamous cell carcinomas are always excluded [16].

**Gastric carcinoma**

In 1984 Takaheshi and Iwama [30] showed through three-dimensional reconstruction that lateral fusion and anastomosis with neighboring glands are the
first signs of early invasion into the tunica propria. The diagnosis of mucosal carcinoma is possible even without the presence of single tumor cells that are frequently seen in poorly differentiated carcinomas but not in well-differentiated carcinomas.

Worldwide differences in the diagnostic criteria of mucosal carcinomas mostly apply to bioptic diagnoses but not to (endoscopic) resection specimens and are probably just a sign of uncertainty [21,22,31,32] rather than an expression of Japanese or Western viewpoints. Furthermore, due to forensic reasons some pathologists prefer the term ‘high-grade intraepithelial neoplasia’ rather than adenocarcinoma.

In the literature, follow-up studies on high-grade intraepithelial neoplasia up until the development of invasive gastric adenocarcinoma [32–38] show that within a few months invasive carcinoma is present. This could have led to the speculation that all these cases of carcinoma were already present at the time of bioptic diagnosis but uncertainty led to the histological diagnosis of high-grade dysplasia (intraepithelial neoplasia).

Gastric carcinomas are subdivided into carcinomas of the mucosal layer (m-type) and submucosal layer (sm1–3) (see Table 10.5).

### Colon carcinoma

According to national cancer registries colon cancer is by far the most common GI cancer in Europe; the second most common is gastric cancer, and the third most frequent are neoplasms of the esophagus. National data from the German cancer registry show that colon cancer is almost three times more frequent than gastric cancer, and esophageal cancer sums up to less than 10% of the cases of colon cancer [39,40]. Therefore, endoscopic techniques are widely used for colon neoplasms. Fortunately most cases with intraepithelial neoplasia (adenoma) as a precursor for invasive carcinoma are resected. For the decision about endoscopic resection versus surgical treatment, histology needs to distinguish between high and low risk criteria for the presence of regional lymph
node metastasis (see Table 10.6). Low risk criteria are: depth of infiltration confined to the upper third (1000 µm) or middle third of the submucosal layer; well or moderately differentiated: absence of lymphatic vessel permeation; and absence or slight tumor cell budding at the front of invasion [41]. Poor differentation, infiltration into the lower third of the submucosal layer (sm3), incomplete resection, presence of lymphatic vessel permeation, and moderate or marked budding of tumor cells are considered as high risk criteria. Venous invasion need not be considered as a risk factor for lymph node metastasis, but for distant hematogenous metastasis that cannot be influenced by surgical treatment. On the other hand it can be discussed that cases with venous invasion might represent cases with higher concomitant risk for lymphatic permeation. But in general, venous invasion is not a factor influencing high or low risk assessment.

Summary
Endoscopic resection techniques for early neoplasms of the gastrointestinal tract need an exact description of the depth of infiltration before the decision is taken about whether to use endoscopic therapy or surgical therapy and before grouping patients into low risk or high risk groups. Histologically, subdivision of the mucosa in early esophageal neoplasms does make sense since the risk of lymph node metastasis increases with the depth of infiltration. Differences between squamous cell carcinoma and adenocarcinoma of the esophagus should be noted.

The distinction of high-grade intraepithelial neoplasia and mucosal carcinoma is almost without further clinical consequence since the diagnosis of high-grade intraepithelial neoplasia should (after clinical staging) at least lead to diagnostic endoscopic resection. The final histological diagnosis could then be made on the resection specimen. Diagnosis of low-grade intraepithelial neoplasia should not be mixed up with regenerative changes. Worldwide criteria on biopsy specimens for intraepithelial neoplasia and invasive carcinoma should be improved further.
Table 10.6  Risk of lymph node metastasis in colon adenocarcinoma subdivided into cases with low and high risk criteria (modified after [41]).

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>N+ high risk (%)</th>
<th>N+ low risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanaka et al., 1995 [63]</td>
<td>65</td>
<td>5/42 (11.9)</td>
<td>1/23 (4.3)</td>
</tr>
<tr>
<td>Kikuchi et al., 1995 [64]</td>
<td>182</td>
<td>9/36 (25)</td>
<td>4/146 (2.7)</td>
</tr>
<tr>
<td>Nivatvongs et al., 1991 [65]</td>
<td>151</td>
<td>13/113 (11.5)</td>
<td>0/38</td>
</tr>
<tr>
<td>Jung et al., 1988 [66]</td>
<td>87</td>
<td>1/17 (5.8)</td>
<td>0/70</td>
</tr>
<tr>
<td>Hackelsberger et al., 1995 [67]</td>
<td>86</td>
<td>1/45 (2.2)</td>
<td>1/41 (2.4)</td>
</tr>
<tr>
<td>Huddy et al., 1993 [68]</td>
<td>27</td>
<td>3/17 (17.6)</td>
<td>0/10</td>
</tr>
<tr>
<td>Christie et al., 1988 [69]</td>
<td>101</td>
<td>1/55 (1.8)</td>
<td>0/46</td>
</tr>
<tr>
<td>Coverlizza et al., 1989 [70]</td>
<td>81</td>
<td>5/14 (35.7)</td>
<td>0/67</td>
</tr>
<tr>
<td>Morson et al., 1984 [71]</td>
<td>60</td>
<td>0/14</td>
<td>0/46</td>
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<td>60</td>
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<td>2/42 (5)</td>
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<tr>
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<td>80</td>
<td>3/31 (9.6)</td>
<td>0/49</td>
</tr>
<tr>
<td>Hase et al., 1995 [77]</td>
<td>79</td>
<td>11/47 (23.4)</td>
<td>0/32</td>
</tr>
<tr>
<td>Masaki et al., 2000 [78]</td>
<td>57</td>
<td>2/19 (10.5)</td>
<td>0/38</td>
</tr>
<tr>
<td>Schmitt, 2001 [79]</td>
<td>162</td>
<td>17/79 (21.5)</td>
<td>1/83 (1.25)</td>
</tr>
<tr>
<td>Moreira et al., 1992 [80]</td>
<td>24</td>
<td>1/13 (7.7)</td>
<td>0/11</td>
</tr>
</tbody>
</table>

References


Principles

Endoscopic mucosal resection (EMR) is used as a diagnostic and therapeutic tool for epithelial lesions of the digestive tract (benign, early stage and advanced adenocarcinoma) as well as for subepithelial lesions. EMR cannot be considered as a definitive diagnostic tool or a definitive treatment, but the major component of a therapy which requires a strict follow-up of the patients.

Benign epithelial lesions

Treatment of benign epithelial lesions is motivated by the risk of already existing malignant foci in the lesion or by the risk of malignant development in time or when lesions are clinically manifest. The prototypes of these lesions are adenomas.

Early stage epithelial cancer

EMR appeared first as a diagnostic tool and is used currently as a curative therapy for early digestive cancer. Therapeutic EMR should have a cost-benefit ratio superior to any other treatment option, usually surgery.

(a) Curative intent EMR (standard indications)

With standard indications, the risk of distant metastases is zero and EMR may be considered curative. Endoscopic follow-up looks for residual tissue in order to confirm that all identifiable neoplastic tissues were removed and detects neoplastic tissue in a curable stage as local recurrence and/or metachronous lesions. Risk factors must be identified in order to better target the follow-up protocol and allow risk modification strategies.
At present there is no randomized controlled study between a non-follow-up policy and/or between different follow-up timetables. With the exception of colorectal epithelial lesions, follow-up frequency was empirically chosen.

(b) Best cost-efficacy EMR (extended indications)
EMR indications may be extended thus increasing the risk of distant metastases. In this instance, EMR may be the best therapeutic option for patients with high surgical morbidity and mortality. In addition to endoscopic follow-up, an extra digestive follow-up may be indicated to look for these distant metastases. The goal is to find them in curable stages by other therapeutic measures: surgery, chemo-radiotherapy, and so on.

Advanced epithelial cancer
EMR for such lesions is performed with palliative intent, in order to achieve better quality of life. Patients are followed up using clinical and biological parameters.

Esophagus

Early stage adenocarcinoma and high-grade dysplasia (HGD) on Barrett’s esophagus
High-grade dysplasia and early mucosal adenocarcinoma are considered standard indications.

Literature survey

Distant recurrences
In surgical series, for mucosal lesions, the risk of distant metastasis was from 0% to 2%. In EMR series, there were no distant metastases when high-grade dysplasia or early adenocarcinomas limited to the mucosa were considered as indications.

Residual tissue
Residual tissue has not been regarded as a failure of EMR, as the lesion may be removed in one or multiple sessions.

Local recurrence
In published series, local recurrence rate was about 7% after 33 months, while after circumferential Barrett resection by EMR was 0–11%. All local recurrences were treatable by repeated EMR.
Risk factors for local recurrence included resection completeness which depends on the lesion size, technique and number of EMR pieces.

**Metachronous lesions**
Metachronous lesions occurred in 3–5% after 25–33 months respectively. That means that when a first area of high-grade dysplasia has appeared and has been treated, the risk that a second dysplastic areas appears is higher than during the follow-up of a nondysplastic Barrett. Furthermore, this second area could have been missed initially. There were no metachronous lesions when the entire Barrett mucosa was resected [1,2].

**Follow-up technique and schedules**
Follow-up with endoscopy plus biopsies of all visible lesions has been systematically performed. Some series included high resolution endoscopy, systematic biopsies of the EMR site, four quadrant biopsies of the Barrett mucosa and Lugol chromoscopy if the Barrett mucosa has been removed to verify squamous re-epithelialization [1,2].

In these series, the follow-up was organized at one month, every three months during the first year then every six months or less frequent with a 3-, 6-, and 12-month schedule, then yearly. The follow-up was continued for five years.

Extra digestive surveillance was proposed – transabdominal ultrasonography, endoscopic ultrasound (EUS) and CT scan every three to six months at least during the first year or as long as the follow-up continued.

**Risk groups**
No risk groups were identified for local recurrence or metachronous lesions.

**Risk modification**
Removing all Barrett mucosa may protect against local recurrence or metachronous lesions. However, the only two studies published did not confirm this hypothesis, as the first study by Seewald et al. [1] did not have any local recurrence or metachronous lesion, after a median follow-up of nine months, while in the second study by Giovannini et al. [2], there were two local recurrences in 18 patients after a median follow-up of 18 months.

Inadequate acid suppression post-EMR does not predict local recurrence.

**Summary of evidence and recommendations**
Early one- to three- month follow-up and repeated EMR is recommended until there is complete local remission. When a complete local remission is obtained, follow-up is done at three and six months during the first year and between
6 and 12 months after the first year. There is no evidence that shorter intervals would be of benefit as all detected lesions were in curable stages by repeated EMR.

Until there is definite proof of risk modification, surveillance of patients with complete ablation of Barrett mucosa is to be done. For patients with Barrett’s esophagus, an 1-cm interval four quadrant biopsy protocol at every follow-up ensures detection of metachronous lesions. Chromoscopy is to be performed in order to better target the biopsies.

Even if there are no distant recurrences in EMR series at present and the risk is estimated to be near zero from surgical series, we find that extra-digestive follow-up is necessary, at least in patients with m3/sm lesions, especially using EUS.

Early stage squamous-cell carcinoma and squamous-cell dysplasia

Therapeutic curative EMR may be indicated for squamous cell dysplasia or carcinoma limited to the epithelium or lamina propria (m1, m2), when the risk of distant metastases is zero. Extended indications may include m3 and sm1 lesions.

Literature survey

Distant recurrences
The risk of distant recurrences is zero for carcinoma limited to m1 and m2; 8% for m3 and sm1.

Distant recurrences usually caused the death of the patients: there was one pulmonary metastasis in 82 patients with mucosal and submucosal carcinomas [3], two pulmonary and mediastinal lymph node metastases in 26 patients with m3 and sm1 carcinomas [4], two lymph node metastases in 62 patients with high-grade dysplasia and mucosal carcinomas [5], two out of three lymph node metastases in 62 patients with mucosal and sm1 carcinomas, initially treated by chemo-radiotherapy but with subsequent relapse [6].

Residual tissue
Residual tissue was either considered a signal that EMR should be repeated or it was reported together with local recurrences.

Local recurrence
Local recurrence rate varied from 0% to 31%, depending on parietal invasion.

Risk factors for local recurrences were heterogeneous Lugol staining pattern or multiple synchronous lesions [5,7,8]. Features that influence resection
completeness such as piecemeal resection or large lesion diameter were also risk factors. More invasive lesions had increased risk for local recurrence.

Local recurrences were usually treatable by repeated EMR/laser/argon plasma coagulation (APC) or surgery/chemo-radiotherapy in a few cases of submucosal involvement. Local recurrences rarely caused the death of the patient: two advanced carcinomas of eight local recurrences considered unsuitable for treatment due to concomitant comorbidities [7], one invasive carcinoma out of 14 local recurrences treated by radiotherapy complicated by perforation [6].

**Metachronous lesions**
The incidence of metachronous lesions varied from 0% to 20%, all curable by repeated EMR.

Lugol chromoscopy scattered pattern was a risk factor for metachronous lesion development.

**Follow-up technique and schedules**
Early follow-up was performed at day one to four post-EMR to check for residual tissue; if found, this was treated by laser/APC [5,6] or EMR sessions were scheduled at one- to three-month intervals. After complete local remission, follow-up continued at three to six months during the first year then at 6–12 months, with Lugol and biopsies.

Two studies with six-month screening intervals during the first year and then annually, found that sometimes local recurrences were advanced and caused the death of the patients [6,7]. On the other hand one study with smaller follow-up intervals – at three months during the first year then at six months – found that all local recurrences were curable by EMR [5].

Extra-esophageal follow-up was proposed to look for distant recurrences by CT scan, ultrasound and endoscopic ultrasound yearly or at six months during the first two years then annually. This was mostly ineffective: either there were no distant recurrences or these were not curable and caused death when found – seven of eight distant recurrences from four series with 232 patients (only three treated by chemo-radiotherapy with two relapses and death) [3–6]. In one paper, a lymph node metastasis untreatable by chemo-radiotherapy was diagnosed after more than one year since the last follow-up, due to non-compliance of the patient [4].

**Risk groups**
Stratified extra-esophageal surveillance was applied by Esaki *et al.* [6] for patients with significant risk of distant metastases (patients with m3 or sm1 carcinoma).
Risk modification
Soon after EMR, APC/laser was used to treat residual tissue [6], but it did not significantly decrease the rate of local recurrence. Chemo-radiotherapy post-EMR was proposed not only for deep submucosal but also for m3/sm1 carcinomas, with no recurrence or distant metastasis.

Summary of evidence and recommendations
Post-EMR early APC/laser application is not useful for local recurrence prevention. Endoscopic follow-up with Lugol is mandatory because it can detect most local recurrences and all metachronous lesions in early curable stages by EMR. Shorter follow-up intervals are probably better (every three months during first year and every six months afterwards) as it may prevent development of advanced local recurrences.

Extra-esophageal screening does not seem to detect distant metastases in treatable stages. Shorter than one-year interval for extra-esophageal screening (especially with EUS) would probably be cost-effective and is recommended for patients with more invasive lesions (m3, sm1) who have positive distant metastasis risk.

Stomach

Early stage gastric adenocarcinoma

Literature survey

Distant recurrence
With standard indications the distant recurrence incidence was 0% in most of the studies. The estimated risk is 0.36%, which is acceptable as the mortality from surgery is higher, at 0.5% [9].

Residual tissue
Residual tissue after EMR was reported from 0% and 18%. After complete resection, the incidence of residual tissue was 0%.

Local recurrence
Local recurrence depends on resection completeness, which depends on the lesion size, EMR technique (EMR versus endoscopic submucosal dissection) and the number of resection pieces. Larger lesions resected by conventional EMR in multiple pieces have a higher frequency of incomplete or non-evaluable
resections which lead to a higher rate of local recurrence. En bloc resection was complete in 81% of cases with 2% local recurrence, piecemeal resection in four pieces or more was complete in 17% of cases with 24% recurrence rate. The recurrence frequency varied from 0% to 2% for complete resection, 13% for non-evaluable lateral margin, and 37% for positive lateral margin.

**Metachronous lesions**

The risk of metachronous lesions after EMR may be higher than after surgery because a larger gastric surface remains. On the other hand, after Billroth-type surgery the alkaline pH will promote the formation of N-nitroso carcinogens in the stomach. The five years post-surgery cumulative prevalence rate was 2.4%.

After EMR the metachronous frequency was reported from 3.5% in 23 months to 14% in 36 months.

Metachronous lesions were usually found at the same one-third of the stomach, usually at the distal two-thirds; were differentiated; with the same macroscopic aspect and a smaller size than the initial lesion.

Most metachronous lesions were in early stages, curable by repeated EMR or surgery in the few cases with submucosal involvement or undifferentiated. Metachronous lesions were not fatal.

Micro-satellite instability (MSI) was a risk factor. Older age, presence of synchronous lesions and *Helicobacter pylori* infection were all risk factors in one study and without influence in another. Male sex was not a risk factor in two studies.

**Follow-up technique and schedules**

Standard endoscopy plus indigo carmine was used. Examinations were performed in the first one to two weeks to check for residual tissue. Follow-up was carried out at one, two and/or three months after EMR then at six month intervals within the first year, or not at all. After the first year, the examinations were done yearly or every six months for the first two years.

After surgery for early gastric cancer, there was a difference in patients with less than two years surveillance intervals versus patients with longer than two year intervals. Although the total number of metachronous cancers was not significantly different, the number of advanced metachronous cancers was significantly higher in the longer interval follow-up group.

Follow-up intervals used after EMR were, on average, annual. It might be thought that after EMR, shorter screening intervals could prevent development of submucosal cancers, but this may not always be true as one submucosal lesion appeared nine months after EMR [10]. On the contrary, as the differentiation rate does not depend on the size and extension of the lesion, there is no reason to believe that shorter screening intervals would prevent the development
of poorly differentiated lesions as one case was found six months after a normal endoscopic examination [11].

Compliance is essential. One patient lost to follow-up was diagnosed with advanced cancer diagnosed more than 11 years after the EMR [12].

Risk groups
Patients with early gastric cancer with MSI may benefit from higher follow-up frequency.

Using closer follow-up intervals for patients with extended indications would not detect recurrent lesions in curable stages. This is sustained by the fact that in one study, four years after the EMR, a case of poorly differentiated early gastric cancer led to development of local, distant recurrence and death, which were not prevented by additional EMR, laser and a close six-month follow-up [13].

Risk modification
Although disputed, Helicobacter pylori infection should be looked for and eradicated.

Summary of evidence and recommendations
Early second look endoscopy is needed to look for residual tissue, even for complete en bloc resection.

The follow-up should be adapted to the resection completeness and also to the presence of risk factors for metachronous lesions. Optimal follow-up should be done at one, three and six months during the first year, then yearly.

Surgery is needed for a small proportion of early gastric cancers found through follow-up – poorly differentiated or with submucosal involvement. After surgery patient prognosis is unaffected and there is a 99% specific survival rate.

Extra-esophageal surveillance with EUS may be recommended, in a similar manner to the post-EMR follow-up for early esophageal cancers.

Ampulla and duodenum
Apart from adenomas and adenocarcinomas, other histological types of ampullary tumors are rare, their treatment by EMR is performed in a case-by-case manner and their post-EMR surveillance is not standardized. Because of the low negative predictive value of ampullary biopsies showing adenoma, EMR is primary diagnostic.
Duodenal non-ampullary lesions are also rare. Adenomas are the most frequent histological type and other than that, there may be hamartomas, Brunner's glands, inflammatory polyps and other rare lesions (leiomyoma, lipoma, lymphangioma, carcinoid tumor, neurofibroma).

Adenomas and adenocarcinomas may be familial adenomatous polyposis (FAP) associated or sporadic.

Literature survey

Distant recurrence
EMR with curative intent may be performed for sporadic or FAP-associated ampullary adenomas and adenocarcinomas with zero risk of lymph node metastasis (mucosal adenocarcinoma not extending beyond the sphincter of Oddi). For ampullary lesions, after EMR, if the lesion has a lymph node metastasis risk of more than zero, surgery is to be done (Whipple resection).

Residual tissue
If the risk of lymph node metastasis is zero, a systematic follow-up for residual tissue is performed at one to three months after EMR. Expected residual tissue rate is 0–26% of cases of EMR for ampullary lesions. If residual tissue is found, EMR is repeated until complete resection.

Local recurrence
Local recurrence rate varies from 4% for sporadic to 23% for FAP-related ampullary lesions [14]. For sporadic duodenal adenomas, local recurrences may be detected in 25% of cases, all treatable by repeated EMR.

Follow-up technique and schedules
In patients with FAP, guidelines have been published for endoscopic surveillance after colectomy [15]. This should be done every two to three years at the level of duodenum and proximal jejunum with an axial and lateral view endoscope plus chromoscopy with indigo carmine. Anomalies are graded according to Spiegelman stage [16]. In stage IV surgical resection should be discussed. In cases of duodenal or ampullary adenomas more than 10 mm or high-grade dysplasia EMR may be considered.

After EMR for sporadic duodenal adenomas different policies have been proposed: either at 1, 6 and 12 months during the first year then annually for at least 5–10 years, or every six months during the first two years and after that only when clinically indicated.
Risk modification
APC application after EMR for ampullary lesions non-significantly lowers the recurrence risk [14].

Summary of evidence and recommendations
For FAP-related duodenal or ampullary adenomas and adenocarcinomas with zero risk of distant metastasis, after complete resection follow-up is to be done yearly, at closer intervals than recommended before EMR. For sporadic ampullary adenomas, in the absence of comparative data, our opinion is that after six months surveillance during the first year, a consecutive annual surveillance may be a more safe approach.

When patients are poor candidates for surgery, EMR has a palliative intent and a palliative stent placement may be proposed, with control examinations afterward only when clinically indicated.

Colon and rectum
Benign colorectal lesions consist mainly of adenomas and hyperplastic polyps, while malignant lesions are mainly adenocarcinomas.

Literature survey

Risk groups
For adenomas, high-magnification endoscopy might predict resection completeness after EMR, with sensitivity of 80% and specificity of 97% [17].

Risk modification
Also, for adenomas, APC of the resection margins after apparent complete resection decreases the risk of local recurrence.

Celecoxib reduces metachronous recurrence of colorectal adenomas in the three years after their resection, but its use increases the risk of cardiovascular events. Moreover in a decision analysis, surveillance colonoscopy was more cost-effective than celecoxib.

Summary of evidence and recommendations
Guidelines regarding post-polypectomy surveillance [18] are also applicable post-EMR. An initial one- to three-month colonoscopy to check for residual tissue is recommended. Patients are stratified according to their risk for metachronous advanced adenomas, depending on histology, the number of
adenomas, size and resection type. After complete resection, surveillance colon-
oscopv is to be done:
• 10 years after EMR of hyperplastic polyps
• Five to ten years after EMR in the case of one to two small tubular adenomas
  with low-grade dysplasia
• Three years after EMR for 3–10 adenomas or size larger than 10 mm, or
  villous, or with high-grade dysplasia (provided that the resection was
  en bloc)
• Less than three years for more than 10 adenomas (screening for familial
  polyposis syndromes is also necessary in this case)
• Sessile adenomas removed piecemeal at 1, 3 and 5 years.

In polyposis syndromes, EMR indication is to be discussed and if performed,
surveillance is to be done according to the specific disease guideline, but essen-
tially more frequently than for sporadic lesions [19].

Follow-up colonoscopy should be performed more frequently after EMR for
lateral spreading tumors. Recurrence rate in these lesions was 17% in two
years, eight of ten recurrences were retreated by EMR. Colonoscopy at three
and six months during the first year is recommended and then after one, three
and five years (similar to large sessile adenomas). APC at the resection margins
may reduce the risk of local recurrence.

Guidelines for post-cancer resection surveillance [20] are also valid for
post-EMR. An initial one- to three-month colonoscopy to check for residual
tissue is needed. After complete local resection, colonoscopy surveillance is
performed at 1, 3, and 5 years.

For rectal lesions more frequent examinations may be performed every three
to six months during the first two to three years. EUS may be used for lymph
node metastasis surveillance.

Chromoendoscopy and magnification endoscopy are not essential to screening
and surveillance.

Subepithelial lesions

Literature survey

EMR of subepithelial lesions is mainly performed with a diagnostic purpose, as
an alternative to the classical ‘surveillance or surgery.’ It can provide a histo-
logical specimen for diagnosis, significantly more frequent than with biopsy or
fine needle aspiration. Noninvasive imaging techniques such as endoscopic
ultrasound are essential in the pre-EMR staging, but alone cannot establish
diagnosis on the basis of the image characteristics.
In the series published in the literature, the authors followed up the patients early after EMR to verify healing, then every six months during the first year and yearly afterwards or from the start at every two or three months. No recurrences were detected for benign lesions.

Malignant lesions or with malignant potential such as gastrointestinal stromal tumors (GIST), carcinoid or lymphomas are managed according to their etiology.

The malignant potential of GIST depends on its mitotic index which cannot be appreciated on biopsy fragments, but only on resected specimens. EMR is purely diagnostic in GIST lesions (it provides specimen for diagnostic and mitotic index calculation), even in R0 resection or in low-grade mitotic index. Surgery is indicated in every GIST case.

For carcinoid lesions, there have been case reports of lesions treated by EMR in various locations of the digestive tract. Adequate assessment according to published guidelines is mandatory [21]. Series of small gastric and rectal carcinoid tumors resected by EMR have been published. There have been no reports of recurrence after EMR for rectal carcinoid in a follow-up of three years. Type-1 gastric carcinoids which are smaller than 10 mm may be treated by EMR.

Summary of evidence and recommendations

Benign lesions (lipoma, fibroma, leiomyoma, etc.) do not need follow-up.

For GIST lesions, as EMR is purely diagnostic, there is no post-EMR follow-up policy. Follow-up after surgery includes CT scan every six months for five years.

Although there have been no recurrences after EMR for rectal carcinoids, intensive follow-up – yearly chest X-ray, abdominal CT scan, colonoscopy and EUS – is recommended, due to the unpredictable nature of these lesions.

After EMR for gastric carcinoids, follow-up after EMR is warranted, but there is no established schedule. A six month follow-up interval is recommended.

References


Clinical results

Early esophageal cancer and tumors of the esophagogastric junction

Endoscopic submucosal dissection (ESD) in the esophagus and esophagogastric junction is more difficult due to the narrow lumen, and is associated with higher complication rates (e.g. perforation rate) compared to ESD in the stomach. Therefore up to now only limited data have been available in this area because many groups first start with ESD in the stomach. Nevertheless the aim for endoscopic treatment of early tumors in the esophagus and esophagogastric junction are similar: R0 resection of the tumors to avoid local recurrences. The EMR method for treatment of early esophageal cancer and tumors of the esophagogastric junction is safe but has its limitations. The mean resected specimen size is about 15–16 mm using either the cap or ligation technique [1]. Therefore for larger lesions piecemeal resection is performed, however en bloc resection is only possible in 23–57% and the local recurrence rate varies between 7.8% and 20% [2,3]. In the esophagus the indication for ESD or EMR depends on the histology of the esophageal cancer, since the risk for lymph node metastases in squamous cell cancer is different from Barrett’s adenocarcinoma. The Japanese Esophagus Association decided that the indication for EMR or ESD should be restricted to tumors involving the superficial epithelial layer m1 (carcinoma in situ) or the proper mucosal layer (m2) in patients with squamous cell cancer of the esophagus [4]. In contrast, in patients with adenocarcinoma of a Barrett’s esophagus all types of mucosal cancer (m1–3) and even invasion of the superficial submucosa up to 200 µm (sm1) local resection is allowed since lymph node metastases are quite rare in this situation [5].
Since ESD is very popular in Japan and squamous cell cancer of the esophagus is more frequent compared to Barrett’s esophagus adenocarcinoma, it is conclusive that the first series on ESD and esophageal cancer has been reported from a Japanese group who treated 102 patients with squamous cell cancer of the esophagus [6]. The median size of the resected specimen and cancer was 32 mm (range 8–76 mm) and 28 mm (range 4–64 mm), respectively. The en bloc resection rate was 95% (95 of 102) and the local recurrence rate was 0% (0 of 102) after a mean follow-up of 21 months (range 3–54 months). There were no perforations, but six cases of mediastinal emphysema (6%) were observed and treated conservatively. Seven patients required balloon dilation due to stenosis. The mucosa defect was 80% of the circumference in these cases.

Fujishiro et al. recently reported on 43 patients with 58 esophageal squamous cell neoplasms [7]. The rate of en bloc resection was 100% (58/58) and the en bloc resection with tumor-free lateral/basal margins (R0 resection) was 78% (45/58). There was no evidence of significant bleeding, but perforation occurred in four cases (6.9%). In all cases this complication was managed conservatively after endoscopic closure of the perforation. In nine cases (16%) ESD was associated with esophageal stricture requiring balloon dilatation. Of 40 lesions occurring in 31 patients fulfilling the criteria of node negative tumors (mean follow-up of 17 months) one lesion resected by en bloc resection with non-evaluable tumor-free lateral margins (Rx [lateral] resection) recurred locally six months after ESD, which was treated successfully by a second ESD.

Up to now no larger series on ESD and treatment of Barrett’s adenocarcinoma have been available. Kakushima et al. recently published their experience on ESD in tumors of the esophagogastric junction [8]. Thirty lesions with an average diameter of 22.4 mm were resected. The size of the specimens were on average 40.6 mm in diameter and en bloc resection (R0) was possible in 97% (29/30). Perforation occurred in one case and was managed conservatively by rotatable clips and antibiotics for three days. Local recurrence was not observed during follow-up (mean 16.6 months, range 6–31 months).

Early gastric cancer

Gastrectomy with lymph node dissection has provided an excellent therapeutic outcome for patients with early gastric cancer, with a five-year survival rate of 96%. The prevalence of lymph node metastases associated with intramucosal- and submucosal-invading gastric cancer was reported as approximately 1–3% and 11–20%, respectively [9]. Because of its risks and the negative effect on the quality of life that gastrectomy has, endoscopic treatment of early gastric cancer has meanwhile an accepted standard in Japan and is becoming more attractive in the Western world as well. Similar to
esophageal cancer the risk of positive lymph nodes depends on the penetration depth of the tumor. According to the *Gastric Cancer Treatment Guidelines* (GL) published by the Japanese Gastric Cancer Association in 2001, the indications for EMR of EGC are restricted to a non-ulcerated, differentiated-type mucosal carcinoma measuring \( \leq 2\text{cm} \) [10]. Submucosal invasion, ulceration, and undifferentiated type are important risk factors for lymph node metastasis as shown in large surgical studies [11]. Using ESD as a novel approach to resect larger specimens in one piece the size of the tumor is no longer limited to 2 cm in diameter. Furthermore Gotoda analysed more than 5000 patients who underwent gastrectomy with R2-level lymph node dissection and found further criteria to extend the indication for endoscopic treatment of gastric cancer [12]. Table 12.1 shows different criteria and the risk for lymph node metastases.

Meanwhile ESD is performed in many centers in Japan since it offers the advantage of R0- en bloc resection and reduces the risk for recurrences compared to EMR.

The technique and especially the equipment are still changing, which demonstrates that ESD in its present form can still be improved. Meanwhile quite a lot of knives (insulated-tip knife, flex-knife, triangle-knife, and hook-knife) have been developed and many centers prefer their ‘own knife’ for ESD. The first large series came from the National Cancer Center Hospital, where the IT-knife was developed. In the first series on 41 patients complete resection of the tumors was dependent on the tumor size: one-piece resection rates were 82% (14/17) for lesions \( \leq 10\text{mm} \), 75% (12/16) for those between 11 and 20 mm and 14% (1/7) for those of \( \geq 20\text{mm} \) [13]. In their following series they could improve their complete en bloc resection rates for lesions \( \geq 20\text{mm} \) to 76% (22/29), demonstrating that ESD needs a special learning curve [14]. Rösch et al.

Table 12.1 Early gastric cancer with no risk of lymph node metastases [12].

<table>
<thead>
<tr>
<th>Incidence (no. with metastases/total number)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramucosal G1/G2; LO,VO; ulcer +/-; &lt;3 cm</td>
<td>0/1230; 0% 0–0.3</td>
</tr>
<tr>
<td>Intramucosal G1/G2; LO,VO; ulcer-; irrespective of tumor size</td>
<td>0/929; 0% 0–0.4</td>
</tr>
<tr>
<td>Intramucosal ( \geq \text{G3}; \text{LO,VO}; \text{ulcer-}; &lt;3\text{cm} )</td>
<td>0/256; 0% 0–2.6</td>
</tr>
<tr>
<td>Submucosal (Sm1) G1/G2; LO,VO; ulcer-; &lt;3 cm</td>
<td>0/145; 0% 0–2.5</td>
</tr>
</tbody>
</table>

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Table 12.1 Early gastric cancer with no risk of lymph node metastases [12].

<table>
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<tr>
<th>Incidence (no. with metastases/total number)</th>
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<tr>
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<td>Submucosal (Sm1) G1/G2; LO,VO; ulcer-; &lt;3 cm</td>
<td>0/145; 0% 0–2.5</td>
</tr>
</tbody>
</table>
also had initially disappointing results with complete resection rates of only 25% in a series of 24 mucosa lesions [15]. Recent data from Ono using the IT knife demonstrated a complete resection in one piece in 96% (471/488) [16]. Watanabe compared the ESD with historical data of conventional EMR. The complete en bloc resection rates were significantly higher in the ESD group compared to the EMR group, however the procedure was more time consuming for lesions larger than 10 mm [17].

The most important factor for successful en bloc resection is the experience of the endoscopist. It is not associated with tumor location/site, tumor size, specimen size, or ulceration within the tumor [18]. In this study, in 9% en bloc resection by ESD failed. The multivariate analysis showed that the second-half period of the procedure was responsible for the success. Finally in cases with recurrent early gastric cancer after prior EMR it was possible to treat those patients more effectively with ESD than with EMR. Among 46 patients who underwent ESD, 41 (89.1%) en bloc resections were achieved but in none of the 18 cases who were retreated by conventional EMR. One specimen out of 41 (2.4%) cases treated by ESD was not evaluable, compared to 10 lesions of 23 piecemeal resections (p<0.0001) [19].

The two major complications of ESD are bleeding and perforation. Bleeding is the most common complication, occurring in up to 8% of patients undergoing standard EMR and in up to 7% of patients undergoing ESD [20]. During ESD, immediate minor bleeding is not uncommon but can be successfully treated by grasping and coagulation of the bleeding vessels using hot biopsy forceps. Delayed bleeding is commonly found after ESD, but is strongly dependent on the location and size of the tumor [21]. Perforation during EMR is rare but occurs more often during ESD (4%), but in most cases endoscopic clipping of the defect is possible.

Colorectal neoplasia

The experience with ESD in the colorectum is limited. Yamamoto reported on a case of a large villous tumor of the sigmoid which was treated by ESD using a hyaluronic acid and a small-caliber-tip transparent hood. The resected specimen was an intra-mucosal well-differentiated adenocarcinoma with a 70 × 55 mm diameter [22] and another case of a 40-mm flat-elevated tumor in the rectum [23]. Recently, Fujishiro reported on a larger series of rectal epithelial neoplasia treated by ESD: 35 consecutive patients were treated with ESD. The rates of en bloc resection and en bloc plus R0 resection were 88.6% (31 of 35) and 62.9% (22 of 35), respectively. No major bleeding requiring blood transfusion occurred, but two patients suffered from perforation (5.7%), and were managed conservatively. In three patients with sm2 or deeper infiltration, surgery
was performed. The remaining 32 patients were free of recurrence during a mean follow-up of 36 months (range 12–60 months) [24].

Submucosal tumors

ESD has the potential to enucleate submucosal tumors in a R0 situation. While Rösch et al. [15] reported disappointing data on 14 patients with submucosal tumors and 36% R0 resection, Park et al. [25] could enucleate 14 of 15 tumors completely. The median procedure time in the series from Park was 35 min (8–160 min) and the median size 2 × 1.7 cm. The largest lesion located in the esophagus measured 6 × 3 cm. Histopathologic diagnosis included leiomyoma (9), GIST (4), stromal tumor of unknown malignant potential (1), and glomus tumor (1). One perforation occurred in a patient with a 2.5 cm tumor in the anterior wall of the stomach but could be managed by clip application. En bloc endoscopic enucleation of submucosal tumors by using an insulated-tip electrosurgical knife appears to be safer, easier, and less time consuming compared with previously described methods.

Conclusion

ESD is a novel technique that allows en bloc resection of large mucosal/submucosal tumors in the stomach, esophagus, and colon. The advantage of this technique is the low recurrence rate after endoscopic treatment, however there are also some disadvantages. The procedure is only safe in experienced hands since the complication rate of bleeding and especially perforation is higher compared to conventional EMR. Therefore the procedure needs a relative long learning curve and is time consuming. Improvement of the technical equipment will overcome the disadvantages in the near future.

References

Introduction

Endoscopic resection (ER) has been accepted as a less invasive local resection in early cancers of the gastrointestinal tract, with a negligible risk of lymph node metastasis [1–3]. This allows less invasive treatments and therefore improves the quality of life of the patients when compared with surgery. The method of ER varies from polypectomy and conventional endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD) [4–14]. EMR procedures include inject and cut, strip biopsy, EMR with a cap-fitted panendoscope (EMR-C), endoscopic aspiration mucosectomy (EAM), and EMR with a ligating device (EMRL). ESD is a new method of ER developed for achieving one-piece resection, especially in the stomach.

In this chapter, we describe ER for early cancers of the gastrointestinal tract especially focusing on technical points of ESD for early gastric cancer (EGC).

Stomach

EMR and ESD are established alternative treatments to surgery for EGC in Japan [15]. The general criteria for EMR in EGC proposed by the Japanese Gastric Cancer Association includes: (1) differentiated adenocarcinoma; (2) intramucosal cancer; (3) lesion less than 20 mm in size; and (4) without ulcer finding [16]. Lesions that meet all of the above criteria have a negligible risk of lymph node metastasis and have a reasonable tumor size that will allow one-piece resection by conventional EMR. Recently, based on the risk of lymph node metastasis in
EGC obtained from a large number of surgical cases, expanded histological criteria for ER in EGC have been reported (Table 13.1) [17]. These include lesions of more than 20 mm in size and ulcerative lesions which were originally resected by surgery. By expanding the criteria for EMR as suggested above, the need for gastrectomy in EGC can be reduced, as these patients could be treated by EMR. However, it is difficult to resect large and ulcerative lesions by conventional EMR techniques so a new technique of endoscopic submucosal dissection (ESD) has been developed [9–15].

The primary aim of the ESD technique is to obtain one-piece resection during ER. Despite requiring significant additional technical skill and a longer procedure time [18,19], these ESD techniques are rapidly gaining popularity in Japan, primarily because of the ability to remove large EGC lesions en bloc. ESD utilizes a direct dissection of the submucosa with a modified needle knife. ESD with an insulation-tipped (IT) diathermic knife (see Chapter 7, Fig. 7.3(a)), developed at the National Cancer Center Hospital, was the first of these techniques [9–11,20]. The concept of ESD with an IT knife was initially proposed and modified to make ERHSE, usually performed by a surgeon, easier and safer to perform by an endoscopist. Other endoscopic devices for the ESD procedure, a hook-knife (Chapter 7, Fig. 7.3(b)) [13], a flex-knife (Fig. 7.3(c)) [14], and a needle knife in a small cap technique [12], have also been described. The processes of ESD differ depending on endoscopic devices such as IT knife, hook-knife, flex knife, and so on.

We describe in particular the established ESD technique with IT knife for en bloc resection and comment on the set-up of the high-frequency electric surgical unit (Table 13.2). The process of ESD consists of three steps: (1) identification of the lesion margin and marking with the needle knife (Fig. 13.1(a)); (2) the mucosa is then lifted up by submucosal fluid injection followed by a circumferential incision (Fig. 13.1(b)); and (3) Submucosal dissection under the lesion is performed with the IT knife (Fig. 13.1(c)–(f)).

### Table 13.1 Expanded histological criteria for curative endoscopic resection.

| 1. Differentiated adenocarcinoma | and |
| 2. No lymphatic or venous invasion | and |
| 3. Intramucosal cancer regardless of tumor size without ulcer finding | or |
| Intramucosal cancer ≤30 mm in size with ulcer finding | or |
| Minute submucosal cancer (sm1) ≤30 mm in size | and |
| 4. Tumor-free margin |
Table 13.2 Set-up of high-frequency electric surgical unit of ESD with IT knife for early gastric cancer.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Device</th>
<th>Mode</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) ICC200; ERBE Corp., Tubingen, Germany</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marking</td>
<td>Needle knife</td>
<td>Forced coag</td>
<td>20 W</td>
</tr>
<tr>
<td>Precutting</td>
<td>Needle knife</td>
<td>ENDO CUT</td>
<td>Effect 3, 80 W</td>
</tr>
<tr>
<td>Mucosal incision</td>
<td>IT knife</td>
<td>ENDO CUT</td>
<td>Effect 3, 80 W</td>
</tr>
<tr>
<td>Submucosal dissection</td>
<td>IT knife</td>
<td>ENDO CUT</td>
<td>Effect 3, 80 W</td>
</tr>
<tr>
<td></td>
<td>Needle knife</td>
<td>Forced coag</td>
<td>50 W</td>
</tr>
<tr>
<td>Endoscopic hemostasis</td>
<td>IT knife</td>
<td>Forced coag</td>
<td>50 W</td>
</tr>
<tr>
<td></td>
<td>Needle knife</td>
<td>ENDO CUT</td>
<td>Effect 3, 80 W</td>
</tr>
<tr>
<td></td>
<td>Hot biopsy</td>
<td>Soft coag</td>
<td>80 W</td>
</tr>
<tr>
<td></td>
<td>Coagrasper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) VIO300D; ERBE Corp., Tubingen, Germany</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marking</td>
<td>Needle knife</td>
<td>Swift coag</td>
<td>Effect 2, 50 W</td>
</tr>
<tr>
<td>Precutting</td>
<td>Needle knife</td>
<td>ENDO CUT I</td>
<td>Effect 2, CUT duration 3, CUT interval 1</td>
</tr>
<tr>
<td>Mucosal incision</td>
<td>IT knife</td>
<td>ENDO CUT I or Q</td>
<td>Effect 2, CUT duration 3, CUT interval 1</td>
</tr>
<tr>
<td></td>
<td>Needle knife</td>
<td>DRY CUT</td>
<td>Effect 4, 50 W</td>
</tr>
<tr>
<td>Submucosal dissection</td>
<td>IT knife</td>
<td>DRY CUT</td>
<td>Effect 4, 50 W</td>
</tr>
<tr>
<td></td>
<td>Needle knife</td>
<td>ENDO CUT I</td>
<td>Effect 2, CUT duration 3, CUT interval 1</td>
</tr>
<tr>
<td></td>
<td>DRY CUT</td>
<td>Swift coag</td>
<td>Effect 5, 50 W</td>
</tr>
<tr>
<td>Endoscopic hemostasis</td>
<td>IT knife</td>
<td>Swift coag</td>
<td>Effect 5, 50 W</td>
</tr>
<tr>
<td></td>
<td>Needle knife</td>
<td>ENDO CUT I</td>
<td>Effect 2, CUT duration 3, CUT interval 1</td>
</tr>
<tr>
<td></td>
<td>Hot biopsy</td>
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</tr>
<tr>
<td></td>
<td>Coagrasper</td>
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</tbody>
</table>

Needle knife (KD-1L-1; Olympus Medical Systems Corp., Tokyo, Japan); IT knife (KD-610L; Olympus Medical Systems Corp., Tokyo, Japan); Hot biopsy forceps (Radial Jaw; Boston Scientific Corp., Natick, Mass.); Coagrasper (FD-410LR; Olympus Medical Systems Corp., Tokyo, Japan).
Fig. 13.1 Process of ESD: (a) Marking of the periphery of the lesion; (b) Submucosal fluid injection and mucosal incision; (c)–(e) Submucosal dissection; (f) Mucosal defect of resected site.
Marking of the periphery of the lesion is begun by using a standard needle knife with 50W of forced coagulation mode (ICC200; ERBE Corp., Tubingen, Germany).

After injection of normal saline mixed with epinephrine and indigo carmine to raise the submucosal layer, a small initial incision is made by a standard needle knife with 80W of endocut mode with effect 3 (ICC200; ERBE Corp., Tubingen, Germany) for insertion of the tip of the IT knife into the submucosal layer. We usually use dilute 1 mg of epinephrine and 1–4 ml of 0.4% indigo carmine solution with 200 ml of normal saline. The concentration of epinephrine for ESD is lower than that for EMR, because we sometimes need a lot of injection solution during ESD. The use of fluid solution mixed with indigo carmine for submucosal injection is effective to distinguish the white muscularis propria from the blue submucosal layer during following submucosal dissection (Fig. 13.1(d)). The concentration of indigo carmine solution depends on operator preference. Then circumferential mucosal cutting at the periphery of the marking dots is performed by an IT knife with 80W of endocut mode with effect 3 (ICC200; ERBE Corp., Tubingen, Germany).

After completion of the circumferential cutting, normal saline is injected again submucosally. With the same IT knife, the submucosal layer under the lesion is directly dissected using a lateral movement. Complete endoscopic submucosal dissection can achieve a large one-piece resection without size limitation. Finally, the resected specimen is retrieved with grasping forceps.

More tips

Marking of the periphery of the lesion with a stronger press and too much coagulation by the needle knife may sometimes cause a minor perforation. Marking with other devices such as argon plasma coagulation (APC), hook knife, or flex knife is also useful to prevent a minor perforation.

A first incision by needle knife should be located on the far point on the TV monitor, because following mucosal incision using an IT knife is performed from the far side to near side. For example, the first incision should be located on a distal side of the lesion when located on the gastric antrum (Fig. 13.2(a)). On the other hand it should be on a proximal side of the lesion when located on the gastric body, because we need a retroflex view (Fig. 13.2(b)). A superficial initial incision should not be done, because it makes it difficult following mucosal incision by IT knife.

The IT knife should be placed from a tangential position not from a vertical position to get an adequate depth of mucosal incision (Fig. 13.3).
Fig. 13.2 Location of first incision by needle knife: (a) Distal side of the lesion when it is located on the gastric antrum; (b) proximal side of the lesion when it is located on the gastric body.
4 Because submucosal dissection using an IT knife is performed from the far side to the near side on the TV monitor, it is easy to do it lengthwise but difficult to do it widthwise. Therefore we would start with submucosal dissection lengthwise from the far side, make a hole at the near side, and then continue to dissect widthwise, hanging the IT knife on the hole (Fig. 13.1(c),(d)). The perforation induced by ESD usually occurs during the process of submucosal dissection and not during circumferential incision. The potential mechanisms of perforation induced by ESD are submucosal dissection with less space in the submucosal layer and misunderstanding of the gastric wall curve. The fluid solution mixed with indigo carmine for submucosal injection can be injected into the submucosa at any time to raise and confirm the submucosal layer. It is important to cut tangentially to the submucosal layer to avoid perforation. The use of transparent attachment of the scope is useful to recognize the gastric wall curve. It is also useful to get counter-traction for easier dissection.

**Esophagus**

Squamous cell carcinoma (SCC) of the esophagus that is confined to m1 and m2 is a definite indication for ER. Nodal metastases were found in 0% of patients with m1 and m2 SCC of the esophagus, 8% with m3, and 30% with sm1 tumors [21]. Following EMR in patients with superficial SCC, the five-year survival rate is up to 95% [22,23]. EMR in 25 patients with superficial m1 SCC showed no recurrence after a mean follow-up of two years [24]. It has been reported that patients with m3 areas infiltrating the muscularis mucosa (MM) showed lymph node or distal metastasis. These patients should be
treated with curative surgery [25]. Few reports have analyzed the outcome of EMR in patients with invasive cancer. Shimizu et al. compared 26 patients with SCC invading the MM or the submucosa, treated by EMR, with 44 comparable patients undergoing surgery. Survival was similar in the two groups: 77% vs. 84% [26]. Esophageal stenosis developed after endoscopic mucosal resection in 13 lesions (6.0%). During the follow-up period (median 26 months), no patient died of esophageal cancer. Recently, an expansion of the indications for EMR in patients with superficial esophageal carcinoma m3 or sm1 has been proposed in Japan [27]. Multiple synchronous lesions have been reported in 26–31% of patients with SCC [28]. We should also be careful with metachronous lesions. The application of ESD for esophageal SCC has been reported with promising results [29].

**Colorectum**

EMR and ESD are being successfully used for early-stage colon cancers, flat adenomas, large superficial colorectal tumors, and rectal carcinoids [30,31]. Lymph node metastasis in T1 colorectal carcinoma occurs only after infiltration of the submucosa and is correlated to the depth of submucosal penetration by the tumor. This supports the therapeutic effectiveness of endoscopic removal of polyps and flat lesions when confined to the mucosa, regardless of their size [32]. Some authors prefer snare excision without cap. Of 57 patients with sessile polyps (SP) and early cancers of 10–50 mm, complications occurred in 2 patients [33]. Published studies show a recurrence rate following EMR ranging from 0% to 40% [34,35]. Combined APC reduced the recurrence rate by 50% [36,37]. In another report, APC did not reduce the recurrence rate compared to polypectomy alone [38]. EMR was performed for 139 SP in 136 patients by snare polypectomy, with or without cap. Median lesion diameter was 20 mm in the right colon and 30 mm in the remaining bowel. Bleeding occurred in 11%. Invasive carcinoma was found in 17 SP, and surgery was performed in 10 of these. After a median 12 months, local recurrence was detected in 22% of polyps with no invasive cancer, and in none of the patients with alonocarcinoma who did not undergo surgery [39]. Of EMR in 24 patients with 30 large colorectal polyps (median size 20 mm), 22 lesions were resected en bloc while 8 were resected piecemeal. Histologically the lesions were predominantly adenomatous polyps. An incidental focus of ADC was found in seven lesions. Histologically complete excision was achieved in 10 lesions. Bleeding occurred during two EMRs. There was no case of bowel perforation. Median follow-up period was 21 months. None of the patients diagnosed with ADC showed any evidence of recurrence [40].
Colorectal laterally spreading tumors (LSTs), classified in granular and non-granular type, are defined as lesions larger than 10 mm in diameter, with a low vertical axis, extending along the luminal wall. They are best removed by ESD as they sometimes invade deeply into the submucosal layer. For en bloc resection of flat lesions >20 mm, conventional EMR is inadequate because incomplete removal and local recurrence are frequently observed. When analyzing the endoscopic features of 257 LSTs in order to assess which features correlated with the depth of invasion, unevenness of nodules, presence of large nodules, size, histological type, and presence of depression in the tumor were significantly associated with depth of invasion. When LSTs showed even nodules without depression, or uneven nodules without depression and less than 3 mm in diameter, the risk of massive submucosal invasion was 0% (0/121) and 3.7% (3/82) respectively. When LSTs meet the above endoscopic criteria, ESD should be the first-line treatment because of the low risk of submucosal invasion [41]. In a recent study, LSTs non-granular type (LST-NG) showed a higher frequency of submucosal invasion than granular (LST-G) (14% versus 7%). Presence of a large nodule in LST-G type was associated with higher submucosal invasion while pit pattern (invasive), sclerous wall change, and larger size were significantly associated with higher sm invasion in LST-NG type. In LST-G type with sm invasion, sm penetration occurred under the largest nodules and depressed areas. Therefore, for LST-G type, endoscopic piecemeal resection with the area including the large nodule resected first is advisable. In contrast, LST-NG type should be removed by ESD en bloc because of the higher potential of sm invasion compared with LST-G type [31,42]. We need some improvements for ESD in the colorectum because of its technical difficulty and the risk of perforation. As an injection solution a mixed solution with glycerol and sodium hyaluronate acid should be used to keep better lifting. The newly developed B-knife results in a safer ESD, because the electric current is localized to the needle tip [31]. CO₂ insufflation instead of air insufflation is used for safer ESD and for reducing patient discomfort [43]. In a recent prospective study in Italy, the IT knife was used for EMR of large colorectal polyps (>3 cm) unsuitable for standard polypectomy [44]. The results of this pilot study showed that the likelihood of complete en bloc resection of mucosal lesions is improved by this new approach compared with previous studies on colonic EMR, even for lesions located in difficult positions or larger than 30 mm. En bloc resection was achieved in 55.1% of the lesions and in the other cases piecemeal resection was used. Thirteen patients had low-grade dysplasia, fifteen had high-grade dysplasia, and one had a tumor invading the submucosa and was admitted to surgery. Complications occurred in four patients (13.7%), all managed conservatively. Local recurrence was detected in five patients (17.8%) and was treated by APC and snare
polypectomy. No further recurrence was observed over the median follow-up period of 15.7 months.

Conclusion

For all gastrointestinal cancers, prognosis correlates with stage of the disease at diagnosis. With the discovery of these early lesions, EMR and ESD could be used with increasing frequency, avoiding surgery with its relatively high mortality and morbidity. In conclusion, the EMR and ESD techniques, if performed with the right indications and with expertise, should be considered as an elective treatment modality for early gastrointestinal cancers.

References


Introduction

Endoscopic resection has been accepted as a less invasive treatment for gastrointestinal (GI) tumors which have a negligible risk of lymph node metastasis [1–5]. It should be safe, effective, and applicable to a variety of clinical situations. However, there is a risk of complications related to endoscopic resection, which include bleeding, perforation, and stricture formation.

As the number of patients who undergo endoscopic resection increases, the number of complications may increase. The number of patients with early gastric cancer who undergo endoscopic resection is increasing in Japan, because the indications are expanded and the techniques are improving. The general indications of endoscopic resection for early gastric cancer proposed by the Japanese Gastric Cancer Association includes: (1) differentiated adenocarcinoma; (2) intramucosal cancer; (3) ≤20 mm in size; and (4) without ulcer findings [6]. Early gastric cancer which can be treated under these criteria is limited to small tumors without ulcer findings, allowing one-piece resection by conventional endoscopic mucosal resection (EMR) [7–10]. Recently the indications for endoscopic resection for early gastric cancer have been expanded, based on the risks of lymph node metastasis in early gastric cancer obtained from a large number of surgical cases [6,11]. The expanded indications include lesions ≥20 mm and ulcerative lesions which were originally resected by surgery. The new technique of endoscopic submucosal dissection (ESD) has been developed to obtain one-piece resection during endoscopic resection for even large and ulcerative lesions [12–17].
In other GI tumors, as the improvement of diagnostic techniques such as chromoendoscopy, high magnification endoscopy, and narrow band imaging can facilitate early detection, the number of patients who undergo endoscopic resection may increase.

Consequently, physicians must be able to treat patients who have complications related to endoscopic resection. In this chapter, we describe how to cope with complications throughout the gastrointestinal tract.

**Stomach**

**Perforation**

*Incidence*

Perforation is uncommon with EMR techniques [18], but in ESD has been reported as about 4% of gastric wall perforations [17]. We have reported the rate of gastric perforation according to lesion location, size, and ulcer finding (Table 14.1) [17,19]. The rates of gastric perforation in the upper and middle third of the stomach, especially the greater curvature of the gastric body, are higher than in the lower third of the stomach, probably because the gastric wall in these locations is comparatively thin. The endoscopic procedure for lesions on the upper and middle third of the stomach had to be achieved with a retroflexed view, compared to that of a straight view for the lesions on the lower third of the stomach. The rates of gastric perforation in larger lesions and ulcerative lesions are higher than in smaller lesions and non-ulcerative lesions.

<table>
<thead>
<tr>
<th>Table 14.1</th>
<th>Relationship between gastric wall perforation induced by ESD and lesion location, size, and ulcer finding [17].</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perforation</strong></td>
<td><strong>Location</strong></td>
</tr>
<tr>
<td></td>
<td>U</td>
</tr>
<tr>
<td></td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>L</td>
</tr>
<tr>
<td></td>
<td>Size (mm)</td>
</tr>
<tr>
<td></td>
<td>≤20</td>
</tr>
<tr>
<td></td>
<td>21–30</td>
</tr>
<tr>
<td></td>
<td>≥31</td>
</tr>
<tr>
<td></td>
<td>Ulcer finding</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>

U: upper third; M: middle third; L: lower third.
Prevention
The potential mechanisms of perforation induced by EMR and proposed techniques to avoid it are reported as follows: (1) Inadequate amount of submucosal injection and/or excessively large snare being used; (2) consequently, when the snare is closed, excessive tissue will be grasped. One way of detecting this problem is to move the snare back and forth. If the muscularis propria is entrapped, the whole wall, as opposed to only the lesion, may be seen to move; and (3) slightly loosening the grasp of the snare while tenting the mucosa into the lumen and toward the endoscope may help to release potentially entrapped muscularis propria. Alternating forward and backward movements of the snare are also often performed to avoid entrapment of the muscularis propria. The closed snare then captures a smaller amount of tissue. If there is still uncertainty about whether there is entrapment of the muscularis propria, the loop is fully opened, and repeat snaring with or without repeat submucosal injection is performed [3].

The perforation induced by ESD usually occurs a process of submucosal dissection not of circumferential incision. The potential mechanisms of perforation induced by ESD are submucosal dissection with less space in the submucosal layer and misunderstanding of the gastric wall curve. Figure. 14.1 shows a moment of preparation. The IT knife goes to the muscle layer. To avoid this, adequate space in the submucosal layer between the muscularis propria and the mucosal layer is indispensable. For that purpose, an adequate amount of submucosal injection is necessary. To keep lifting the mucosa for a longer period, the use of sodium hyaluronate, Glyceol, or a mixture of sodium hyaluronate and

Fig. 14.1 The potential mechanism of perforation induced by ESD is misunderstanding of the gastric wall curve during submucosal dissection.
Glyceol for submucosal injection has been reported as effective [15,20–23]. Special knives such as an insulation-tipped (IT) knife (KD-610L; Olympus Medical Systems Corp., Tokyo, Japan), Hook knife (KD-620-L; Olympus Medical Systems Corp., Tokyo, Japan), and Flex knife (KD-630L; Olympus Medical Systems Corp., Tokyo, Japan) are useful to keep the space from the muscularis propria (see Chapter 7, Fig. 7.3(a)–(c)). We can make the space by the ceramic ball of the tip of the IT knife, by the pulling hook knife and by the thick tip of the sheath of the flex knife. The use of fluid solution mixed with indigo carmine for submucosal injection is effective for recognizing the gastric wall curve. We can distinguish the white muscularis propria from the blue submucosal layer (Fig. 14.2). The use of transparent attachment of the scope is also useful. We can recognize the gastric wall curve by lifting the mucosal layer using the attachment.

**Management**

**Endoscopic closure.** In the past, when gastric perforation occurred during endoscopic resection, emergency surgery was usually performed and the merits of the resection were lost [19]. Endoscopic closure of a perforation by using clips after snare excision of a gastric leiomyoma, was first reported by Binmoeller et al. [24] in 1993. The metallic clips were originally developed for hemostatic purposes [25].
We also used a non-surgical treatment such as endoscopic closure with endoclips as a less invasive method of the treatment of gastric perforations after endoscopic resection and reported that it proved useful [19]. The results of 116 patients with gastric perforation during endoscopic resections for early gastric cancer are shown in Fig. 14.3. The initial four patients, who underwent endoscopic resection from 1987 to 1993 were treated by emergent surgery. In 110 patients (98.2%) among the remaining 112 patients, endoscopic closure was possible and the clinical courses of the patients were favorable under anti-biotic therapy with a second-generation cephalosporin.

Two methods of endoscopic closure are reported: a ‘single-closure method’ and an ‘omental-patch method’ using endoclips with a right-angled hook (HX-600-090 or HX-610-090; Olympus Medical Systems Corp., Tokyo, Japan) [19]. A single-closure method is done to treat small defects. The knack for the single-closure method is to start clipping from the edge of the hole not from the center. A perforation hole induced by ESD is smaller and move lined compared to that of a strip biopsy, so a single-closure method can be applied to treat perforations caused by ESD. The knack for closure of defects by ESD is to make enough space for clipping, because perforation by ESD usually occurs in the process of submucosal dissection. An omental-patch method is performed for comparatively larger defects by using either the greater omentum or the lesser omentum as a patch [19].

**Peritoneal tap.** Vital signs such as blood pressure, oxygen saturation, and electrocardiograms must continuously be checked during these endoscopic procedures. If abdominal fullness because of air leakage from the perforated lesion is severe, breathing deterioration or neurogenic shock can occur. To prevent
these complications when gastric perforation occurs, frequent abdominal palpation is recommended to check the degree of abdominal fullness with air. If severe abdominal fullness is noted, decompression of the pneumoperitoneum must be performed with a 14- or 16-gauge puncture needle with side slits. Before puncture, we tested with a 23-gauge needle syringe filled with local anesthetic [19].

Management after endoscopic closure. The management after successful endoscopic closure is shown in Table 14.2. Patients are treated with a nasogastric tube for one day, antibiotics for two days, and start eating after one to two days of fasting [19].

Bleeding

Incidence

Procedure-related bleeding is one of the most common complications. The rates of bleeding have been reported as 1.2–20.5%, which probably vary according to the definition [8,17,18,26–28].

Procedure-related bleeding can be subdivided into immediate bleeding during procedure and delayed bleeding after the procedure from the point of view of time, although there are a few reports in which bleeding was investigated with the definition as immediate and delayed bleeding. Immediate bleeding is not generally frequent with EMR techniques. On the other hand, it is quite common with ESD techniques, and the management for it is indispensable to completion of ESD. We estimated immediate bleeding in terms of a difference in hemoglobin (Hb) level between pre-procedure and next-day values and a diminution of ≥2 g/dl in Hb level was defined as significant. Evidence of immediate bleeding was found in 7% [17]. The rates of it in the upper and the middle third of the stomach are higher than in the lower third of the stomach (Table 14.3), probably because the diameter of submucosal arteries in the upper and the middle third of the stomach are significantly larger than that for arteries in the lower third of the stomach.

The rate of delayed bleeding after EMR reported from various institutions is 5.3% [28]. Delayed bleeding after ESD was reported as 6% [17]. The rates of it in the lower and the middle third of the stomach are higher than in the upper

<table>
<thead>
<tr>
<th>Methods</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drip infusion</td>
<td>2–3</td>
</tr>
<tr>
<td>Nasogastric tube</td>
<td>1</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>2</td>
</tr>
<tr>
<td>Fasting</td>
<td>2</td>
</tr>
<tr>
<td>Admission period</td>
<td>4–7</td>
</tr>
</tbody>
</table>

Table 14.2  Management after endoscopic clipping for gastric perforation [19].
### Table 14.3  Relationship between immediate bleeding during gastric endoscopic submucosal dissection and lesion location, size, and ulcer finding [17].

<table>
<thead>
<tr>
<th>Location</th>
<th>Diminution of Hb level (≥2 g/dl)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>8% (14/176)</td>
<td>0.01</td>
</tr>
<tr>
<td>M</td>
<td>8% (35/431)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>L</td>
<td>3% (14/426)</td>
<td></td>
</tr>
<tr>
<td>Size (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>4% (32/719)</td>
<td>0.065</td>
</tr>
<tr>
<td>21–30</td>
<td>8% (14/176)</td>
<td></td>
</tr>
<tr>
<td>≥31</td>
<td>12% (17/138)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ulcer finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7% (17/243)</td>
<td>0.504</td>
</tr>
<tr>
<td>Negative</td>
<td>6% (46/790)</td>
<td></td>
</tr>
</tbody>
</table>

U: upper third; M: middle third; L: lower third.
* Immediate bleeding was estimated in terms of a difference of Hb level between pre-procedure and next-day values.

### Table 14.4  Relationship between delayed bleeding after gastric endoscopic submucosal dissection and lesion location, size, ulcer finding, and time since procedure [17].

<table>
<thead>
<tr>
<th>Location</th>
<th>Delayed bleeding</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>1% (1/176)</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>6% (27/431)</td>
<td>0.001</td>
</tr>
<tr>
<td>L</td>
<td>6% (31/426)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Size (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>5% (35/719)</td>
<td></td>
</tr>
<tr>
<td>21–30</td>
<td>7% (13/176)</td>
<td>0.1838</td>
</tr>
<tr>
<td>≥31</td>
<td>8% (11/138)</td>
<td>0.1385</td>
</tr>
<tr>
<td>Ulcer finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>5% (13/243)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>6% (46/790)</td>
<td>0.7811</td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24 h</td>
<td>76% (45/59)</td>
<td></td>
</tr>
<tr>
<td>2–7 days</td>
<td>12% (7/59)</td>
<td></td>
</tr>
<tr>
<td>8–15 days</td>
<td>12% (7/59)</td>
<td></td>
</tr>
</tbody>
</table>

U: upper third; M: middle third; L: lower third.

third of the stomach (Table 14.4), again probably because the diameter of submucosal arteries in the upper and the middle third of the stomach were significantly larger than that for arteries in the lower third of the stomach. The reason for the latter remains unclear but antral peristaltic activity may contribute to this to some extent. It is also speculated that this increase in the risk of bleeding from lesions of the lower third of the stomach could be due to the fact
that intra-operative bleeding in this group of lesions is low, and therefore needs less intra-operative hemostatic treatment compared to vessels in the lesions of the upper third of the stomach. This lack of intra-operative intervention may contribute toward the risk of delayed bleeding.

Management

Acid suppressing drug. In general, proton pump inhibitors are used for acid suppressing for two months. Their use is based on the observation that the stability of a blood clot is reduced in an acid environment. Thus a pH greater than 6 is necessary for platelet aggregation while clot lysis occurs when the pH falls below 6. There are no convincing data to support the use of H2 receptor antagonists, and these drugs do not reliably or consistently increase gastric pH to 6 [29].

Endoscopic treatment modality. Endoscopic treatment modalities for GI tract bleeding are divided into cautery, injection methods, and mechanical therapy. Cautery devices include heat probes, argon plasma coagulation (APC), and electrocautery forceps, and so on. The method of action of injection therapy is primary tamponade because of volume effect, with some agents having a secondary pharmacologic effect. The types of the solution include normal saline with epinephrine (of which the main mechanism is tamponade), hypertonic sodium chloride with epinephrine (which has both primary tamponade and secondary direct tissue injury and thrombosis), and ethanol (of which the main mechanism is direct tissue injury and thrombosis). The mechanical therapy refers to the implantation of a device that causes physical tamponade of a bleeding site. Currently, the only mechanical therapies widely available are endoscopically placed clips and band ligation devices. Endoscopic clips are usually placed over a bleeding site (e.g. visible vessel) and left in place. Endoscopic band ligation devices, commonly used in variceal bleeding, have also been used to treat nonvariceal causes of bleeding and involve the placement of elastic bands over tissue to produce mechanical compression and tamponade.

Hemostasis for immediate bleeding. Cautery is used for hemostasis against immediate bleeding during endoscopic resection, because clips disturb the following resection. We usually use electrocautery using different devices according to the degree of bleeding. Minor oozing bleeding can be controlled by cautery using a cutting device such as a needle knife, IT knife, Hook knife, or Flex knife. Electro-Surgical Unit (ESU) is set up as 50 W of Forced coagulation mode (ICC200; ERBE Corp., Tubingen, Germany) or 50 W, Effect 5 of Swift coagulation mode (VIO 300D; ERBE Corp., Tubingen, Germany) for this cautery. It is necessary to pre-coagulate for prevention of bleeding using a
cutting device with the same setting of ESU, when vessels are found. Cautery using hemostatic forceps such as Coagrasper (FD-410LR; Olympus Medical Systems Corp., Tokyo, Japan) or hot biopsy forceps (Radial Jaw; Boston Scientific Corp., Natick, Mass.) are suitable for massive bleeding. ESU is set up as 80W of Soft coagulation mode (ICC200; ERBE Corp., Tubingen, Germany) or 80W, Effect 5 of Soft coagulation mode (VIO 300D; ERBE Corp., Tubingen, Germany) for this cautery. The knack for hemostasis is to find the exact bleeding point by water flash and take aim at it.

Hemostasis for delayed bleeding. All sorts of the abovementioned endoscopic treatment modalities can be used in combination or on their own for hemostasis against delayed bleeding after endoscopic resection. We use different modalities according to the period of bleeding. In the early days of delayed bleeding, the artificial ulcer floor is still soft with less granulation tissue, so endoscopic clips or electrocautery using hemostatic forceps can be applied. In the latter days of delayed bleeding, the artificial ulcer floor is getting hard with granulation tissue, so injection method using a solution that has direct tissue injury and thrombosis is preferred. In our series, 76% of patients bled within 24 hours and the remaining 24% bled between 2 and 15 days after the procedure (Table 14.4) [17].

Stenosis

Incidence
Bleeding and perforation remain major complications. Stenosis after endoscopic resection for lesions located near cardia or the pylorus is an important late complication, as it results in severe dysphagia. A total of 2011 early gastric cancers resected by ESD between 2000 and 2005 were reviewed at our institution. These were located at the upper third of the stomach in 326 lesions, the middle third in 887 lesions, and the lower third in 798 lesions. The resections in which mucosal defects included squamo-columnar junction (SCJ resection) were found in 41 of the 326 upper third lesions. The resections in which mucosal defects included pylorus ring (pylorus resection) were found in 115 of the 798 lower third lesions. Significant stenosis was defined as present when a standard 11 mm diameter endoscope (GIF Q240, Q230, Q200, Olympus Medical Systems Corp., Tokyo, Japan) could not be passed through the stricture. Significant stenosis developed in seven (17%) of the 41 SCJ resections and eight (7%) of the 115 pylorus resections after ESD (Tables 14.5 and 14.6). There was a significant relationship between degree of luminal circumferential mucosal defect and the development of significant stenosis. There
was no stenosis in the 34 SCJ resections and 97 pylorus resections in which mucosal defects after ESD were less than three-quarters of the luminal circumference. On the other hand, all (100%) of the seven SCJ resections in which mucosal defects after ESD were over three-quarters of the luminal circumference developed stenosis, and eight (44%) of the 18 pylorus resections after ESD over three-quarters of the luminal circumference developed stenosis.

Bleeding and perforation are complications that usually occur during endoscopic resection or within 24 h of the procedure and thus treatment is usually immediate. In contrast, stenosis manifests a few weeks after endoscopic resection during the healing process. In our series, the median period between ESD and the first endoscopic dilatation was 22 days in the patients with significant stenosis in SCJ resections and 30 days in the pylorus resections.

Management
If a patient with significant stenosis complains of dysphagia, endoscopic dilatation is performed with a 15–18 mm balloon dilator (CRE Wireguided

<table>
<thead>
<tr>
<th>Grade of circumferential mucosal defect</th>
<th>Stenosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>–1/2</td>
<td>0% (0/81)</td>
<td></td>
</tr>
<tr>
<td>1/2–3/4</td>
<td>0% (0/16)</td>
<td></td>
</tr>
<tr>
<td>3/4–</td>
<td>44% (8/18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>7% (8/115)</td>
<td></td>
</tr>
</tbody>
</table>

*Pylorus resection was defined as resection in which mucosal defects included pylorus ring.

<table>
<thead>
<tr>
<th>Grade of circumferential mucosal defect</th>
<th>Stenosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>–1/2</td>
<td>0% (0/28)</td>
<td></td>
</tr>
<tr>
<td>1/2–3/4</td>
<td>0% (0/6)</td>
<td></td>
</tr>
<tr>
<td>3/4–</td>
<td>100% (7/7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>17% (7/41)</td>
<td></td>
</tr>
</tbody>
</table>

*SCJ resection was defined as resection in which mucosal defects included squamo-columnar junction.
Balloon Dilatation Catheter; Boston Scientific Corp., Natick, Mass.). Dilation is continued until dysphagia resolves. In our series, dysphagia and significant stenosis fully resolved in all patients in response to repeated balloon dilatation. The median frequencies of repeated balloon dilatation were five times in the patients with significant stenosis in SCJ resections and nine times in the pylorus resections. The median periods of repeated balloon dilatation were 42 days in the patients with significant stenosis in SCJ resections and 52 days in the pylorus resections.

Colon

Most therapeutic colonoscopies are done in the outpatient clinic without hospital admission excluding endoscopic resection for large tumors. Familiarity with the endoscopic findings, symptoms and signs of complications, and treatment of complications is a prerequisite for performance of colonoscopic polypectomy and mucosal resection.

Perforation

During therapeutic colonoscopy, perforation is the most serious accidental disorder and requires rapid and appropriate management [30–33]. The rate of perforations due to therapeutic colonoscopies has varied from 0.1% to 0.85%, while mortality has ranged from 0.01% to 0.34% [30–37]. Taku et al. [37] reported the rate of perforation according to the methods of therapeutic colonoscopies. The overall rate of occurrence of perforation was 0.15% (23/15 160). Perforation rate for EMR (0.58%) showed a significantly higher rate ($p < 0.0001$) than that for hot biopsy and polypectomy. The rate for ESD (14%) showed a markedly higher rate ($p < 0.0001$) than that for other standard procedures.

Generally, surgery is the first choice of treatment, because it is difficult to manage chemical or bacterial peritonitis due to intraperitoneal leakage of intestinal fluid containing chemical substances such as digestive enzymes, and fecal fluid containing large amounts of bacteria via the perforated site [30–39]. Patients who developed sepsis and died of peritonitis due to delayed initiation of surgery have also been reported [40]. However, recent reports have suggested the usefulness of endoscopic clipping to prevent leakage of intestinal contents in patients with perforation associated with endoscopic treatment [37,40–46]. Taku et al. [37] have reported the indications for endoscopic clipping for perforations during therapeutic colonoscopy as follows: (1) The dimension of the defect is less than 10 mm; (2) adequate bowel preparation was performed; and (3) the patient is in a stable condition after immediate perforation.
Bleeding

Bleeding is the most common complication associated with therapeutic colonoscopies including hot biopsy, snare polypectomy, and endoscopic mucosal resection. The reported incidence varies according to the definition of bleeding, and the size and type of lesions resected. The overall risk is approximately 1–2% for snare polypectomy [47]. Rosen et al. [48] reported an 0.4% risk of bleeding requiring hospital admission in a retrospective study involving 4721 patients who had polypectomies. Nivatvongs reported 10 episodes of bleeding requiring blood transfusions among 1172 patients [49]. Binmoeller et al. [50] reported a 24% risk of bleeding in a series of 176 large (>3 cm) polypectomies. Most of these hemorrhages occurred during the procedure, and all were successfully treated by endoscopic methods.

Bleeding can occur immediately after the procedure or can be delayed. Immediate bleeding after endoscopic removal is usually a slow ooze, and arterial bleeding is rarely encountered. Almost all of the immediate bleeding could be managed endoscopically with an injection of saline containing epinephrine or by hemoclips, and so on. On the other hand, delayed bleeding is important because of the necessity of repeated colonoscopy or hospitalization. Fu et al. [51] have reported the risk factor and clinical course of delayed bleeding after endoscopic resection. The size of the removed lesions was a significant risk factor of delayed bleeding.

A variety of techniques are useful. These include application of the endoclip or endoloop, use of APC, injection of diluted epinephrine, cauterization using monopolar or bipolar instruments, and repeat application of the snare or hot-forceps biopsy to grasp the remnant stalk of pedunculated polyp [47,52]. In cases of delayed bleeding, we typically would purge the bowel using 4 to 6L of polyethylene glycol solution within three hours, immediately followed by a colonoscopy [47]. On the other hand, Rex and colleagues have reported successful colonoscopic treatment of delayed post-polypectomy bleeding without prior bowel purge [53].

Esophagus

Perforation

The reported rates of perforation induced by EMR in the esophagus are 1.4–2.5% [54,55]. Although there are few reports of perforations caused by endoscopic resection in the esophagus, esophageal perforations caused by balloon dilation are described; the management of such cases is highly controversial. Some surgeons
recommend early surgical treatment [56–58], whereas others recommend consideration of conservative therapy [59–61]. Shimizu et al. [55] have reported three cases of successful closures of esophageal perforations after EMR with endoscopically applied clips. In their opinion, closure of esophageal perforations from EMR by endoscopic clip application is appropriate therapy if the perforation is recognized immediately and is not larger than 1–1.5 cm in shortest diameter. When this method of treatment is used, the patient must be observed for an extended period of time, with particular attention to signs of a transition from localized inflammation to generalized mediastinitis.

Bleeding

Kodama et al. [62] have described a bleeding rate (1.5%, 6/396) of EMR for patients with superficial esophageal cancer in the survey of Japanese institutions.

A variety of techniques are useful for bleeding of esophageal EMR. These include application of the endoclip, use of APC and cauterization using monopolar or bipolar instruments.

Stenosis

Esophageal stenosis after endoscopic resection is an important late complication, as it results in severe dysphagia. In particular, large mucosal defects are more likely to lead to stricture formation in the esophagus because the lumen is much narrower than in the stomach and the colon. Esophageal stenosis developed after EMR has been described by Katada et al. [63]. Significant stenosis was defined as present when a standard 11 mm diameter endoscope (GIF Q240, Q230, Q200, Olympus Optical Co. Ltd., Tokyo, Japan) could not be passed through the stricture. It was found in 13 (6.0%) of 216 superficial esophageal lesions. In all these cases endoscopic mucosal resection resulted in a mucosal defect that involved over three-quarters of the luminal circumference. There was a significant relationship between degree of luminal circumferential mucosal defect and the development of significant stenosis. There was no stenosis in the 197 resections with mucosal defects involving less than three-quarters of the luminal circumference. On the other hand, 13 (68%) of the 19 resections involving over three-quarters of the luminal circumference developed stenosis. There was also a significant relationship between longitudinal length of the mucosal defect and the development of esophageal stenosis. The esophageal stenosis was more frequent in the subgroup of patients with mucosal defects involving over three-quarters of the circumference, those with
a mucosal defect over 30 mm long (10/10; 100%) compared to those with a mucosal defect less than 30 mm long (3/9; 33%).

All patients with esophageal stenosis experienced dysphagia and all therefore required endoscopic balloon dilatation. The dysphagia fully resolved in all patients with esophageal stenosis in response to repeated balloon dilatation. A total of 85 balloon dilatations were performed (median 5 per patient, range 1–15). In the subgroup of patients with mucosal defects involving over three-quarters of the circumference, those with a mucosal defect over 30 mm long required more frequent balloon dilatation (mean 8 [4.3] times), and the stenosis was of longer duration (mean 16 [17.7] months) than those with defects 30 mm or less in length (respectively, 1 [0.6] times and 2 [1.9] months).

References


Introduction

The advent of endoscopic submucosal dissection (ESD) has expanded the indications for the endoscopic treatment of early gastric cancer and has enabled en bloc resection of larger lesions than before. However, in order to accomplish ESD in safety from beginning to end when a complete en bloc specimen is removed for histological analysis, a skilled and meticulous technique is needed. From the risk management point of view, various devices and scopes for ESD have been developed to facilitate the difficult procedures of ESD and to minimize complication rates.

First, this chapter describes a new ESD technique using two newly developed therapeutic endoscopes, and then endoscopic full-thickness resection (EFTR) is presented as a potential future technique to treat early gastrointestinal cancer.

Endoscope development

Multibending endoscope (‘M-scope’)

The multibending endoscope, the ‘M-scope’ (XGIF-2T240M; Olympus Medical Systems, Tokyo, Japan; Fig. 15.1(a),(b)) has two independently bending segments: the proximal section can be deflected in one plane (up/down); the distal section can be deflected in two planes (up/down, right/left), similar to a conventional gastrointestinal (GI) endoscope [1]. A combined operation of these segments allows operators to obtain a variety of visual fields, to selectively approach or recede from the lesions, and to obtain en face views, which may
be difficult to obtain with conventional endoscopes. Downward bending of the proximal section and upward bending of the distal section allows frontal viewing of lesions located on the lesser curvature. On the other hand, upward bending of the proximal section and downward bending of the distal section provides a frontal view of the lesion on a greater curvature.
Robotics endoscope (‘R-scope’)

A new therapeutic endoscope, the ‘R-scope’ (XGIF-2TQ240R; Olympus Medical Systems, Tokyo, Japan; Fig. 15.2(a),(b) is equipped with a multibending system and has two independently movable instrument channels: one can move a grasping forceps vertically for lesion countertraction; the other can swing a cutting knife horizontally for dissection. Moreover, this new endoscope is equipped with a water-jet system for maintaining clear views even in hemorrhagic areas. Our study of ESD using the R-scope [2] demonstrated efficacy with minimal complications and has significantly shortened operation times when compared to conventional ESD.
Next steps toward the future

Endoscopic suturing technique

In order to minimize the complication rates in ESD, ideally it would be better to close the defect after resection. However at the moment there is no commercially available endoscopic device capable of suturing the gastrointestinal wall closed. There are several methods currently used to close the defect after EMR or ESD endoscopically. These include clip application [3] and clip application with subsequent endoloop placement to close the gap between the edges of a perforation.

The next paragraph describes two prototypes for the endoscopic suturing technique.

Eagle Claw

The ‘Eagle Claw’ is a complex flexible endoscopic sewing machine with an unusual action. Although most surgical stitches, whether placed at open surgery or at laparoscopy, are delivered using a curved needle, this is the first flexible endoscopic sewing device that attempts to solve the difficulties of sewing using a curved needle. The proximal end of the thread is passed through a thread lock which is tightened using a pushing catheter passed through a channel in the device once the two stitches have been placed. This device has not yet been used in patients [4]. Pham AV et al. [5] have used this device for the closure of colon perforation in pigs and they reported good results. Another application of this device for a new endoscopic therapy such as NOTES is expected in future.

The next paragraph presents the new sewing method that has been developed by our group and might be useful for closing defects following ESD.

New sewing method using T-tags on thread and a locking and cutting device

This new sewing device has been developed and tested [6]. It has also been called a tissue approximation system or TAS. It is not yet commercially available although it is likely to become so in a few months time once it has FDA clearance and a CE mark. This device places a T-tag on a thread into tissue using a 20-gauge needle. Knots are tied by using a thread locking system. The suturing and knot locking can be accomplished through a 2.8 mm accessory channel in a conventional gastroscope (or colonoscope) and has also been used under endoscopic ultrasound guidance.

Endoscopic full-thickness resection (EFTR)

An effective and reliable endoscopic suturing device would allow full-thickness resection of the gastric wall for the treatment of early-stage cancer (Fig. 15.3).
Endoscopic full-thickness resection would allow complete histopathological examination of the cancer and allow less invasive removal of more deeply penetrating cancers, which have not spread to the serosal surface [7]. We have described a method using an endoscopic variceal ligation (EVL) device [8] without prior injection of saline, and a bidirectional cutter without prior injection of saline. We have also reported a method of circumferential full-thickness excision with subsequent closure using an experimental bidirectional cutter [9]. The T-fastener method described above was applied in these studies to close the defect. They gave good results and were safe in studies on pigs.

Fig. 15.3  Full-thickness resection method with sutured closure.
Endoscopic mucosal resection device for Barrett’s esophagus

We have described an experimental endoscopic resection device for Barrett’s esophagus, which has an action similar to a potato peeler. The abnormal mucosa is sucked into a sling in an overtube, a small gauge needle is passed subcutaneously, and saline is used to separate the deep muscle from the submucosa and mucosa. A curved wire is used to slice long linear strips off the esophagus (Figs 15.4, 15.5, and 15.6).

Fig. 15.4  Experimental Barrett’s resection device.

Fig. 15.5  Esophageal resection specimen.
Perspectives for the future

There is room for improvement in EMR, ESD and full-thickness resection. Better ways to elevate and maintain a plane between the mucosa and submucosa under the lesion being resected would help. Better endoscopic control during cutting would be very useful – it is very easy to perforate the stomach and even easier to perforate the colon using needle knives. There is room for improvement in hemostasis and the development of bipolar forceps and more effective clips which can compress larger vessels and can be rotated, opened and closed on the vessel before firing are desirable and are likely to be available shortly. Because needle knives are relatively imprecise and because snares in end-caps can only take relatively small circular pieces of tissue, thus preventing en bloc resection, alternative approaches are needed. If EMR can only be performed safely and effectively by very skilled and experienced endoscopists who take a very long time per patient for endoscopy then it seems likely that there is room for innovation to make this less invasive surgical treatment of cancer easier, quicker and safer for less-skilled operators.

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