Review

Early Barrett's Carcinoma of the Esophagus

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Introduction

Early cancer in Barrett's esophagus (BE) is a special entity in five aspects:

- Chronic gastroesophageal reflux is the pathophysiological origin of the disease.
- It can be diagnosed by endoscopic surveillance of risk groups with reflux and a columnar cell-lined lower esophagus.
- The malignant degeneration to early carcinoma can be traced in genetic alterations.
- It offers much greater chances for cure than advanced carcinomas do.
- It can be treated by limited procedures in case of mucosal stage.

These five aspects will be elucidated under special reference to the histopathology.

Epidemiology

Early esophageal carcinoma used to be rare in Western countries. During the late 1970s, the frequency of early cancer was only 0.75% of all esophageal carcinomas detected during a mass European survey.[1)] The ratio of squamous cell carcinoma (SCC) to adenocarcinoma (AC) was 17:1. Currently, the overall incidence of esophageal AC is rising[2,3)] and in Great Britain now annually totals 6 cases per 100,000 inhabitants. Probably because of intensified surveillance of patients with BE, early AC is now diagnosed more frequently. In recent publications, early cancer accounted for 16%–38% of resected ACs of the esophagus.[4,5)] In parallel with the rising incidence of AC of the esophagus, ACs located at the esophagogastric junction (EGJ) have also been observed more frequently.[6,7)]

BE is considered one of the most important complications of gastroesophageal reflux disease because of its association with AC. The risk for patients with BE to develop an AC is up to 125 times higher than in the normal population.[8,9)]

Figures on the prevalence of BE vary considerably. In 1,128 consecutive patients with reflux symptoms or dyspepsia referred for endoscopy in primary care, the prevalence was 1% in the whole population and 4.4% in the gastroesophageal reflux disease–enriched population.[10)] In a German outpatient study of 6,215 patients with reflux symptoms, the overall prevalence was reported to be 4.9%; however, in those with esophagitis, 8.4% had BE.[11)] The incidence of BE is rising. A study of the general population in the Netherlands showed an incidence of 14.3 per 100,000 persons per year in 1997 and 23.1 per 100,000 persons per year in 2002.[12)] A recent published study showed that approximately a third of the German adult population suffer gastroesophageal reflux.[13)] Furthermore, reports have been made about the rising incidence rates of gastroesophageal reflux in Western industrial nations.[14,15)]

Molecular biology

The development of malignant degeneration of Barrett's epithelium in reflux patients has been extensively studied concerning molecular changes.

The process of changes in the direction of neoplasia is based on a follow-up of several genetic alterations affecting the six cancer hallmarks[16,17)]:

- Self-sufficiency in growth signals. Whittles et al. assessed the balance between apoptosis and proliferation in the development of Barrett's AC. They found a shift in the proliferation to apoptosis ratio with a sig-

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Table 1. The revised Vienna classification of gastrointestinal epithelial neoplasia

Group	Diagnosis	Clinical management
1	Negative for neoplasia	Optional follow-up
2	Indefinite for neoplasia	Follow-up
3	Mucosal low-grade neoplasia Low-grade adenoma Low-grade dysplasia	Endoscopic resection or follow-up
4	Mucosal high-grade neoplasia 4.1 High-grade adenoma/dysplasia 4.2 Noninvasive carcinoma (carcinoma in situ) 4.3 Suspicious for invasive carcinoma 4.4 Intramucosal carcinoma	Endoscopic or surgical local resection
5	Submucosal invasion by carcinoma	Surgical resection

nificant increase of proliferative activity and a decrease of apoptotic activity in the progression from metaplastic to cancerous tissue.[18]

- Insensitivity to antigrowth signals. The inactivation of tumor suppressor genes is one of the most frequent genetic alterations in human malignancies, leading to insensitivity to antigrowth signals. In fact, it has been shown in the progression to esophageal AC that the p16 tumor suppressor gene is significantly inactivated by increased promoter hypermethylation.[19]
- Avoidance of apoptosis. The ability of tumor cells to expand is mainly influenced by the rate of cell attrition. For example, it has been shown in the development of Barrett's AC that an overexpression of antiapoptotic factors like survivin or bcl-2 occurs.[20]
- Limitless replicative potential. To become deathless: in most malignant tumors a stabilization of the telomere length through an increased expression of telomerase is found. This was described in esophageal AC.[21]
- Sustained angiogenesis. Sustained angiogenesis is essential for the development and progression of cancer. Multiple studies have shown that potent angiogenetic factors are overexpressed in the progression from metaplasia to esophageal AC, including cyclooxygenase-2 (Cox-2), a vascular endothelial growth factor receptor (EGFR).[22]
- Invasion and metastasis: distant metastases of primary tumors are the major cause of death in patients with malignant disease. Matrix metalloproteinases (MMPs), enzymes known to be associated with tumor cell invasion, have been shown to be overexpressed in esophageal carcinogenesis.[23]

Histopathology

Precursors of invasive AC are neoplasias in the columnar cell–lined lower esophagus. The histopathological classification differentiates between low-grade and high-grade neoplasia (HGN) according to the Vienna consensus[24,25] (Table 1).

Several seminars have shown sizable differences between Japanese and Western pathologists in the diagnostic differentiation of regenerative changes, dysplasia, and well-differentiated ACs in gastroenterological biopsy material. Lesions that most Western pathologists identify as "dysplasia" are often considered ACs in Japan. A comparison of the biopsy-based diagnoses with those established in resected mucosa, however, reveals appreciable diagnostic inexperience on the part of Western pathologists, with significant discrepancies between their diagnoses based on biopsies and those based on resected material. Against this background, a new classification of epithelial neoplasias of the gastrointestinal tract was drafted on the occasion of the World Congress of Gastroenterology in Vienna in 1998.

Epithelial tumors developing in the digestive tract include intraepithelial neoplasia (adenomas, dysplasia, premalignancy) in the mucosa and invasive lesions classified as intramucosal or submucosal carcinomas. The progression of intraepithelial neoplasia to invasive carcinoma is not invariable, and the delay can be short or long. The Vienna classification of epithelial neoplasia in the mucosa of the esophagus, stomach, and intestines (compatible with the World Health Organization classification) now provides a consensus terminology for Western and Asian specialists. The revised edition of the classification[25] features five distinct groups, and neoplastic intramucosal lesions confirmed by the pathologist are classified into groups 3 and 4; submu-

cosal carcinoma is in group 5 (Table 1).

Group 3 includes premalignant lesions, termed "low-grade noninvasive intraepithelial neoplasia." Group 4 includes premalignant lesions, termed "high-grade noninvasive intraepithelial neoplasia" (subgroups 4-1 and 4-2), and malignant lesions, termed "invasive high-grade intraepithelial neoplasia" or "intramucosal carcinoma" (subgroups 4-3 and 4-4). Low-grade and high-grade dysplasia and adenoma are terms equivalent to low-grade and high-grade noninvasive intraepithelial neoplasia. High-grade intraepithelial lesions have the potential to progress after a short delay into submucosal or advanced carcinoma, as shown in the follow-up of untreated lesions in the gastric mucosa in Japan.[26,27] In summary, all high-grade neoplastic lesions (invasive and noninvasive) are now included in the subdivisions of group 4.

ACs of the esophagus are called early cancer if they are limited to the mucosa or submucosa. However, there are decisive differences concerning frequency of lymph node metastases and long-term prognosis according to the depth of infiltration within these two layers. Therefore the mucosa as well as the submucosa have been divided into thirds: m1, m2, m3, and sm1, sm2, sm3 (Fig. 1).

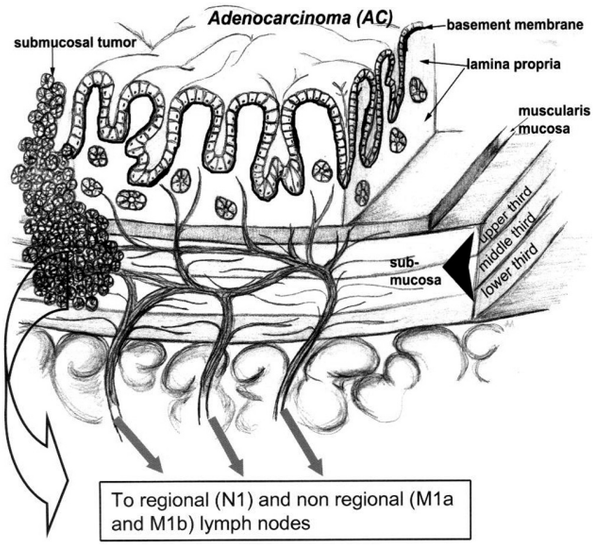

Fig. 1. Schematic representation of the pathological subclassification of superficial esophageal cancer.

Prevention by antireflux surgery or medication

Because the development of BE is based on gastroesophageal reflux, a potential concept would be to stop reflux by surgery and thereby interrupt the mechanisms of malignant degeneration. Another possibility would be to reduce the corrosive agent of the refluxate, especially acid, by medication and to change the pathophysiological process. Neither concept clearly showed success in prospective randomized trials. Our own review of the literature showed a sizable number of ACs after fundoplication, not only after failed antireflux procedures.[28] This result was confirmed by a meta-analysis in 2007.[29] Further ACs in BE under medication with protone pump inhibitors have been reported. The prospective randomized trial of Parrilla comparing medication and fundoplication in the prevention of neoplasia or adenocarcinoma resulted in equal numbers of ACs in both groups.[30] The interpretation without the intention to treat the principle, which means exclusion of nonfunctioning fundoplications, seems unacceptable because a 100% success rate of the surgical principle cannot be awaited. The available data show that if BE already exists, the process of malignant degeneration cannot be definitely interrupted by antireflux surgery or by medication. However, this is different in reflux patients without BE. No report exists that shows a development of BE after effective antireflux surgery.

Lymph node metastasis

During recent years, the correlation between depth of tumor infiltration in mucosa and submucosa and the rate of lymph node metastasis has been examined in detail. Whereas this had already been made quite clear for SCC in analyses presented by Japanese authors, data concerning AC in BE were lacking. Several authors, including those in our own group, have now examined the mucosa and submucosa with the differentiation in thirds (Fig. 1, Table 2). This has nearly always shown no lymph node metastasis in mucosal carcinoma, especially m1 and m2, whereas penetration of the lamina muscularis mucosae causes the onset of lymphatic involvement (Fig. 2). The high rate of lymph node metastases in sm2 or sm3 carcinomas is clear, and in this respect these numbers are not very different from T2 carcinomas. The doubtful zone remains m3 and sm1 because lymph node metastasis can develop in the event of carcinoma infiltration in both layers.[5,33] However, this happens with lesser frequency compared to deeper submucosal layers. Therefore endoscopists currently tend to extend their indication for mucosectomy to the

Table 2. Reports of literature on the frequency of lymph node metastasis in mucosal (m1, m2, m3) and submucosal (sm1, sm2,sm3) adenocarcinomas of the esophagus-differentiating thirds

Authors	Mucosa						Submucosa					
	m1		m2		m3		sm1		sm2		sm3	
	n	% LNM	n	% LNM	n	% LNM	n	% LNM	n	% LNM	n	% LNM
Liu et al., 2005[31]	36	0	–	–	17	12	12	8	–	–	25	36
Westerterp et al., 2005[32]	13	0	18	0	23	4	25	0	23	35	18	67
Bollschweiler et al., 2006[5]	9	0	2	0	3	0	10	20	6	0	10	70

LNM, lymph node metastasis.

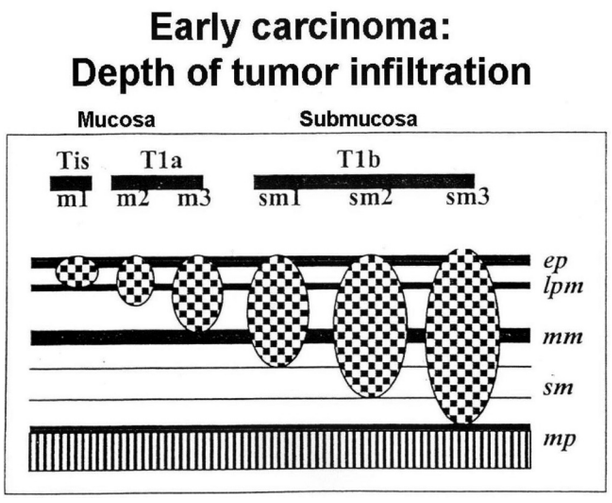

Fig. 2. Mucosa and submucosa in Barrett's esophagus.
Lymphatic channels are reaching the m3 layer, but not the m1 or m2 layers (according Baldus and Bollschweiler).
ep, epithelium; lpm, lamina propria mucosae; mm, muscularis mucosae; sm, submucosa; mp, muscularis propria; ml, ep (Ca in situ); m2, lpm; m3, mm; sml, shallow one-third of sm; sm2, intermediate one-third of sm; sm3, deepest one-third of sm; Tis, m1; T1a, mucosa (m1 + m2 + m3); T1b sm (sm1 + sm2 + sm3).

sm1 layer. This is critical with respect to the exact detection of sm1 limitation by endoscopy or endoscopic ultrasound, as well as the potential of lymphatic infiltration.[34] Further studies on the frequency of lymph node metastasis, especially in m3/sm1 carcinomas, are necessary to clarify this issue. Perhaps risk groups can be defined by such methods as grading, lymphatic or vascular invasion, or molecular markers to identify those carcinomas with a low or high potential of lymphatic metastases.[35] Until now, the penetration of the muscularis mucosae layer still represents the danger of lymph node metastasis and therefore is an indication for surgery.

Several authors have reported a lower rate of lymph node metastasis in AC compared to SCC, especially in the stage of early cancer. However, these opinions were not based on detailed layer-to-layer comparisons of the mucosa or submucosa. If this is performed as in Table 3, it becomes obvious that no differences exist between the histological entities of esophageal cancer. It is even striking how similar the rates of lymph node metastasis are in the sm2 and sm3 layers, especially because these facts are based on a great many patients (Table 3).

This comparison elucidates also that the opinion that early Barrett's carcinoma patients have a better prognosis than early SCC patients can be substantiated only if the mucosal and submucosal layers are differentiated in detail. In our own series, T1 ACs were more in the mucosal stage and infiltrating sm1 and sm2 more than the SCCs, which had less mucosal stages and more sm2 and sm3 infiltration. Because the deeper infiltration leads to more lymph node metastasis, the prognostic effect is then due more to a higher rate of lymphatic infiltration than to the entity AC or SCC as such. Another reason for a more dismal prognosis of T1 SCC patients compared to T1 AC patients is the higher rate of second cancers in SCC.[39]

Mucosectomy

If restricted to the mucosa, Barrett's carcinoma can basically be treated by endoscopic mucosectomy

Table 3. Comparison of the frequency of lymph node metastasis in early squamous cell or adenocarcinomas of the esophagus

	Mucosa		Submucosa					
			sm1		sm2		sm3	
	n	%	n	%	n	%	n	%
SCC[5,35–38]	191	2	68	12	119	28	170	55
AC[5,31,32]	133	2	47	7	29	29	53	53

SCC, squamousmous-cell carcinoma; AC, adenocarcinoma.

because the risk of the lymphatic infiltration is very low (Table 4). However, the prerequisite is complete removal to the depth as well as to the side. The best is en bloc resection. Piecemeal resections have the potential to distribute tumor cells and for the pathologist are very difficult to interpret.[45] In gastric cancer, the negative prognostic effect of piecemeal resection compared to en bloc resection has been shown. Endoscopists argue that incomplete resections at the side are not of disadvantage because secondary removal can be performed. Nevertheless, the high rate of R1 resections seems to be critical. The current publications, however, show very good survival data of patients after an endoscopic mucosectomy for mucosal AC.[46,47]

Another issue is the multifocal development of HGN, or mucosal carcinoma, in BE. This must be ruled out by chromoendoscopy and multiple biopsies prior to mucosectomy.

Table 4. Reports in the literature on the frequency of lymph node metastasis in mucosal adenocarcinomas of the esophagus

Author	Mucosa		
	n	n LNM	% LNM
van Sandick et al., 2000[40]	12	0	0
Hagen et al., 2001[41]	16	0	0
Rice et al., 2001[42]	53	2	4
Stein et al., 2003[43]	27	0	0
Liu et al., 2005[31]	53	2	4
Westerterp et al., 2005[32]	54	1	2
Bollschweiler et al., 2006[5]	26	0	0
Oh et al., 2006[44]	23	1	4
Total	264	6	2

LNM, lymph node metastasis.

Surgery

If mucosal AC in BE is too large for endoscopic mucosectomy or this removal is incomplete, a limited surgical procedure such as distal esophageal resection is possible.[48] This can be performed via a transhiatal or abdomino-thoracic approach.[49–51] The reconstruction is performed via an isoperistaltic jejunal interposition. The best is a vagal sparing technique because the functional advantages of this limited procedure are really beneficial to the patient.[49,51] This has also been an argument for the vagal-sparing esophageal-stripping technique. In patients with pT1a ACs, this operation showed the same long-term results as more radical esophagectomies.[44,52,53] However, this procedure seems to be quite extensive because a large portion of the sound esophagus is removed.

The lymphadenectomy of the limited esophageal resection is inadequate for submucosal cancer because lymph node metastases may be present in a considerable percentage (see above). Therefore the indication for the Merendino procedure or vagal-sparing esophagectomy is questionable. In submucosal cancer, the adequate procedure remains transthoracic en bloc esophagectomy because this shows prognostic advantages compared to limited procedures as transhiatal esophageal resection.[54] Concerning the extent of lymphadenectomy, transhiatal esophagectomy is comparable in a way to Merendino.[55] The question remains if sm1 infiltration could be an indication for limited surgical procedures[56] in well-defined patient groups. These could be those with grading G1 or G2 without lymphangiosis and polypoid tumor growth. Further studies are necessary to identify submucosal ACs, which represent a good indication either for mucosectomy or esophagectomy. This attempt could be supported by biomarkers from molecular biology studies. However, a concrete marker is currently unavailable.

Conclusion

Patients with early Barrett's carcinoma of the esophagus

have good chances for cure especially in case of mucosal stage. This can be detected by endoscopic surveillance of risk groups with gastroesophageal reflux disease and a columnar cell–lined lower esophagus. However the investment of time and costs are very high per detected carcinoma. Biomarkers from biopsies of Barrett's epithelium could predict malignant potential more than just a histological analysis or grade of neoplasia. These molecular biological factors could also be helpful to define the potential of lymphatic metastasis of m3 or sm1 carcinomas to support the choice of therapy. Radical esophagectomy remains the standard treatment in case of deep submucosal infiltration and can still lead to good long-term results in a sizable percentage of patients.

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